



Early View

Original article

Personal exposure to air pollution and respiratory health of COPD patients in London

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Take home message: Significant adverse associations were found between the respiratory health of COPD patients and their personal exposure to gaseous pollutants measured using portable sensors over 6 months. No significant associations were found for particulate pollutants.

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Personal exposure to air pollution and respiratory health of COPD patients in London

Abstract

Previous studies have investigated the effects of air pollution on chronic obstructive pulmonary disease (COPD) patients using either fixed site measurements or a limited number of personal measurements, usually for one pollutant and a short time period. These limitations may introduce bias and distort the epidemiological associations as they do not account for all the potential sources or the temporal variability of pollution.

We used detailed information on individuals' exposure to various pollutants measured at fine spatio-temporal scale to obtain more reliable effect estimates. A panel of 115 patients was followed up for an average continuous period of 128 days carrying a personal monitor specifically designed for this project that measured temperature, PM₁₀, PM_{2.5}, NO₂, NO, CO and O₃ at one-minute time resolution. Each patient recorded daily information on respiratory symptoms and measured peak expiratory flow (PEF). A pulmonologist combined related data to define a binary variable denoting an "exacerbation". The exposure-response associations were assessed with mixed-effects models.

We found that gaseous pollutants were associated with a deterioration in patients' health. We observed an increase of 16.4% (95% confidence interval: 8.6-24.6%), 9.4% (5.4-13.6%) and 7.6% (3.0-12.4%) in the odds of exacerbation for an interquartile range increase in NO₂, NO and CO respectively. Similar results were obtained for cough and sputum. O₃ was found to have adverse associations with PEF and breathlessness. No association was observed between particles and any outcome.

Our findings suggest that, when considering total personal exposure to air pollutants, mainly the gaseous pollutants affect COPD patients' health.

Keywords: COPD, exacerbations, personal exposure, air pollution, monitor

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, with prediction of further increases unless urgent action is taken to reduce the underlying risk factors.[1,2] COPD patients are at risk of acute episodes of deterioration – 'exacerbations' – typically defined as a sudden worsening of respiratory symptoms. COPD exacerbations are the second commonest cause of adult emergency medical hospital admission in the UK and are associated with increased mortality and decreased quality of life.[3]

COPD hospitalisations and mortality increase in periods of high air pollution and air pollutants at levels even within current guidelines may increase exacerbation risk.[4-6] Pollutants may trigger airway inflammation, thus leading to an exacerbation, or may increase susceptibility to viral/bacterial infection, increasing severity and frequency of episodes.[7] The impact of extremes of, or rapid changes in air pollution are not well characterised due, in part, to insufficiently detailed individual environmental exposure estimates in studies.[8]

Human exposure to environmental stress in urban environments depends on a range of influencing factors, such as activity, surroundings, geography, proximity to source and meteorology. An individual's level of exposure is constantly changing as they go about their daily lives and move through the environment. Traditionally, short-term exposure assessments of epidemiological studies are based on fixed monitoring locations, which cannot accurately be used to describe human exposure that comprises of indoor- and outdoor-generated pollution without many assumptions, which may introduce bias.[9] Active mobile sensors have been used in 'snapshot' studies of exposure in micro-environments such as transport modes or indoors.[10] They have also been used to measure exposure in panel studies.[11] However, in each case monitoring periods were limited to a small number of hours or days and the number of subjects were small. Advances in measurement, materials and computing technologies mean that practical limitations are becoming less restrictive, presenting new opportunities for personal exposure assessment.[12] This development creates the potential for associations between environmental exposure and acute health outcomes to be assessed within large pre-selected panels or cohorts in usual daily environments, rather than in chamber or small panel studies. Furthermore, these sensors can now be deployed over much longer periods of time, allowing the capture of associations within a patient's normal daily routine and across seasons when behaviours may change.

The COPE study (<http://erg.ic.ac.uk/research/home/projects/COPE-Characterisation-of-COPD-Exacerbations-using-Environmental-Exposure-Modelling.html>) aimed to characterise associations between personal air pollution exposure and lung function, COPD symptoms and exacerbations within a cohort of 115 COPD patients. For the first time, direct personal exposure measurements were utilised for multiple pollutants, rather than proxy measurements or models, through the deployment of multi-parameter personal sensors to all patients for up to six months each. By extending the period of personal exposure monitoring, infrequent health signals and symptoms could be investigated under a broad range of conditions and activities.

Methods

A full study protocol for exposure data collection is available in Moore et al. (2016).[13] A description of the study recruitment methodology and outcomes is described in Quint et al. (2018).[14] Key details are described here.

Participant sample

In total, 130 ex-smoking COPD patients were recruited through the Clinical Practice Research Datalink (CPRD) within Greater London, of whom 115 provided exposure and health data; 15 patients who took part in the study for less than two weeks were excluded. Patients were selected for recruitment based on prior medical history, and not housebound. Upon recruitment, patients filled out a basic questionnaire including type of residence, cooking and heating fuel, car ownership and presence of smokers in the household and were provided with a personal air quality monitor (PAM). A research physiotherapist trained participants in the use of a peak flow meter (PFM) and diary card at recruitment, followed up with a monthly telephone call. This level of interaction minimised dropout rates and maximised valid data capture and diary card use.

The personal air quality monitor

The PAM was designed, manufactured and tested specifically for the study. It is an autonomous unit that incorporates multiple sensors for activity and for physical and chemical parameters. The time resolution of the measurements was set at 20 seconds. Gaseous pollutants (nitrogen dioxide (NO₂), ozone (O₃), nitric oxide (NO) and carbon monoxide (CO)) were quantified with electrochemical sensors. Masses of particles with aerodynamic diameter less than 2.5µm and 10µm (PM_{2.5} and PM₁₀ respectively) were derived from particle counts taken by an Optical Particle Counter. The PAM also recorded temperature, humidity, noise levels, 3D accelerometry and GPS position. Measurements were aggregated to 1-minute means and stored in a relational database. A description of the operation and performance of the PAM is described in Chatzidiakou et al. (2019).[15]

All sensors were calibrated in the winter and summer season, before and after the deployment to participants in outdoor co-locations with reference instruments. The root mean square error was less than 4 ppb for NO, NO₂ and O₃, 0.03 ppm for CO and 9 µg/m³ and 2 µg/m³ in winter and summer respectively for particles.

No interaction with the unit was required by the participant, other than to place it in its charger each night. Patients were asked to wear the PAM continuously for six months whenever they left their home. When at home, the PAM was placed within their living room.

Health outcomes

Each evening, the participants filled out a diary card indicating any worsening of symptoms, any change in medication, including the use of oral steroids or antibiotics, and disrupted sleep patterns.[16] The diary card also asked whether the patient had left their home at any point and whether they had taken the PAM. Additionally, patients recorded their daily peak expiratory flow (PEF) using the PFM at the same time each day.

Upon completion of the fieldwork, diary cards were verified by a respiratory clinician and daily 'exacerbation' events noted. Exacerbation was defined as a sustained worsening of symptoms (breathless, cough, sputum volume or colour) for at least 2 days beyond normal variation.[17] A change in treatment, or healthcare utilisation without symptoms recording was also considered.

The confirmation of each participant exacerbation was determined initially via telephone conversation follow up and then again during clinic visit, based on what was written on the diary card. Exacerbations were then re-confirmed by independent review of diary data by AL and JQ followed by a discussion of discrepancies in clinical opinion. Index of Multiple Deprivation (IMD) rank was assigned to each patient based on their home post code cross referenced against 2015 UK census data¹.

Statistical analysis

Pollutant concentrations were aggregated to daily means (CO, NO, NO₂, PM_{2.5} and PM₁₀) or daily maximum 8-hour mean (O₃). We applied a predefined mixed-effects models analysis.[18] PEF measurements were analysed using linear regression, while the occurrence of exacerbation and daily symptoms, coded as binary variables,

¹ Ministry of Housing, Communities and Local Government. English indices of deprivation 2015. <http://imd-by-postcode.opendatacommunities.org/imd/2015> accessed December 2019.

were examined by logistic regression. Random intercept models were used providing conditional estimates on the expected change in the health outcomes, taking into account the correlation between each participant's repeated measurements.[19] Our core models were of the following form:

$$\text{Outcome} = \text{Air Pollution} + \text{Age} + \text{Sex} + \text{COPD Severity}$$

where *Air Pollution* refers to that individual's daily exposure to each of the pollutants alternatively. To account for potential confounding effects, the full model included IMD as an indicator of the participants' socio-economic status, and a binary variable for inhaled corticosteroids (ICS) medication use. A restricted cubic spline of time with four degrees of freedom was introduced to account for potential long-term patterns in the data. Temperature was also included as a natural spline with three degrees of freedom.

To quantify the potential prolonged effects of air pollution on patients' health, we assessed the effect estimates of lag 1, 2, 3 days and, also, the average lag 0-3. Two-pollutant models were also fitted with all pairwise combinations of pollutants except PM_{2.5}-PM₁₀, as the former is a subset of the latter, to account for the potential synergistic or confounding effects between pollutants. As sensitivity analyses, the full models were fitted excluding those person-days that patients left their home without taking their PAM. We investigated potential effect modification by season and COPD severity. For the former, we fit the full models in four categories, i.e. winter, spring, summer and autumn, while for the latter we included an interaction term coded into two categories, i.e. mild/moderate and severe/very severe. Finally, we carried out a comparison of the effect estimates yielded when ambient measurements from a central monitor were used as the exposure metrics.

The regression estimates were expressed as change in the expected PEF or as odds ratios (OR) for exacerbation and symptoms for a unit increase in all pollutants except CO for which it was a 0.01 ppm increase. Estimates per inter-quartile range are also reported. Missing data were excluded from the analysis. STATA 15 was used for all analyses.

Ethics

The Research Ethics Committee for Camden & Islington provided ethical approval for the study. Approval was also been granted by NHS Research & Development and the use of clinical practice research datalink (CPRD) GOLD data was approved by the CPRD Independent Scientific Advisory Committee.

Results

Descriptive statistics

Mean age at recruitment was 70.5 years, while the majority of patients (73%) suffered from moderate or severe COPD (Table 1). All patients reported their primary address to be within Greater London.

Table 1 - Summary statistics of peak expiratory flow (PEF), person-days recorded with symptoms according to patients' diaries and baseline characteristics from questionnaire. PEF is the maximum of three measurements per day. *As defined by airflow obstruction. n: number of occurrences in categorical variables.

Variable	Mean (SD) or n (%)
Health Outcomes (14,740 person-days)	
Peak Expiratory Flow (L/min) – Mean (SD)	249 (108)
Exacerbation (Yes) – n (%)	2,245 (15.2)
Breathlessness (Yes) – n (%)	2,650 (18.0)
Cough (Yes) – n (%)	2,285 (15.5)
Sleep disturbance (Yes) – n (%)	1,528 (10.4)
Sputum (Yes) – n (%)	1,227 (8.3)
Wheeze (Yes) – n (%)	1,470 (10.0)
Baseline Characteristics (115 participants)	
Sex (Females) – n (%)	54 (47.0)
Age (years) – Mean (SD)	70.5 (8.1)
COPD severity* – n (%)	
Mild	19 (16.5)
Moderate	52 (45.2)
Severe	32 (27.8)
Very severe	12 (10.5)
Index of multiple deprivation (IMD Rank) – Mean (SD)	16528.2 (8233.4)
Medication Use: Inhaled corticosteroids (Yes) – n (%)	80 (69.6)
Number of days each participant goes out per two weeks (0,1,...,14) – Mean (SD)	10.5 (3.2)
Car ownership (Yes) – n (%)	73 (63.5)
House type – n (%)	
Flat	47 (40.9)
(semi-) Detached	37 (32.2)
Other	31 (27.0)
Cooking – n (%)	
Gas	44 (38.3)
Electric	48 (41.7)
Gas hob, electric oven	20 (17.4)
Other including wood-burning	3 (1.6)

Our database included 14,740 person-days from May 2015 to October 2017, with a mean/median follow-up of 128/145 days respectively per participant (minimum/maximum: 14/208). An exacerbation was observed in 15% of the person-days, breathlessness in 18%, cough in 16% sleep disturbance and wheeze in 10% and sputum in 8%. The most common cause of data loss was participant withdrawal from the study. Other reasons included periods of participant vacation away from home, PAM malfunction, failure to charge PAM, and failure to record health data.

Mean (SD) 24-hour average personal exposure measurements were 13.8 (6.3) ppb for NO₂, 9.0 (6.5) ppb for NO, 0.2 (0.1) ppm for CO, 15.8 (18.0) µg/m³ for PM_{2.5} and 16.8 (20.6) µg/m³ for PM₁₀ while the mean 8-hour maximum for O₃ was 6.5 (5.3) ppb (Table 2). Seasonal differences were observed in pollutants' concentrations (supplementary material Table S2). Temperature was relatively stable across the cohort, reflecting the fact that most participants spent most of their time inside temperature-controlled buildings.

Table 2 - Descriptive statistics for personal measurements of air pollution and temperature, expressed as 24-hour averages, except for O₃ which is 8-hour maximum. N obs: number of valid observations.

Exposure	N obs	Mean (SD)	25 th %ile	Median	75 th %ile	Between-patient SD	Within-patient SD	Capture rate ^a
PM _{2.5} (µg/m ³)	13657	16 (18)	7	11	18	10	16	91%
PM ₁₀ (µg/m ³)	13585	17 (21)	7	12	19	13	18	90%
NO ₂ (ppb)	14739	14 (6)	10	12	15	4	5	100%
NO (ppb)	14629	9 (11)	3	5	10	6	10	99%
O ₃ (ppb)	14739	6 (5)	3	5	8	3	5	100%
CO (ppm)	14522	0.21 (0.10)	0.15	0.18	0.23	0.04	0.10	98%
Temperature (°C)	14739	21 (2)	20	21	22	2	2	100%

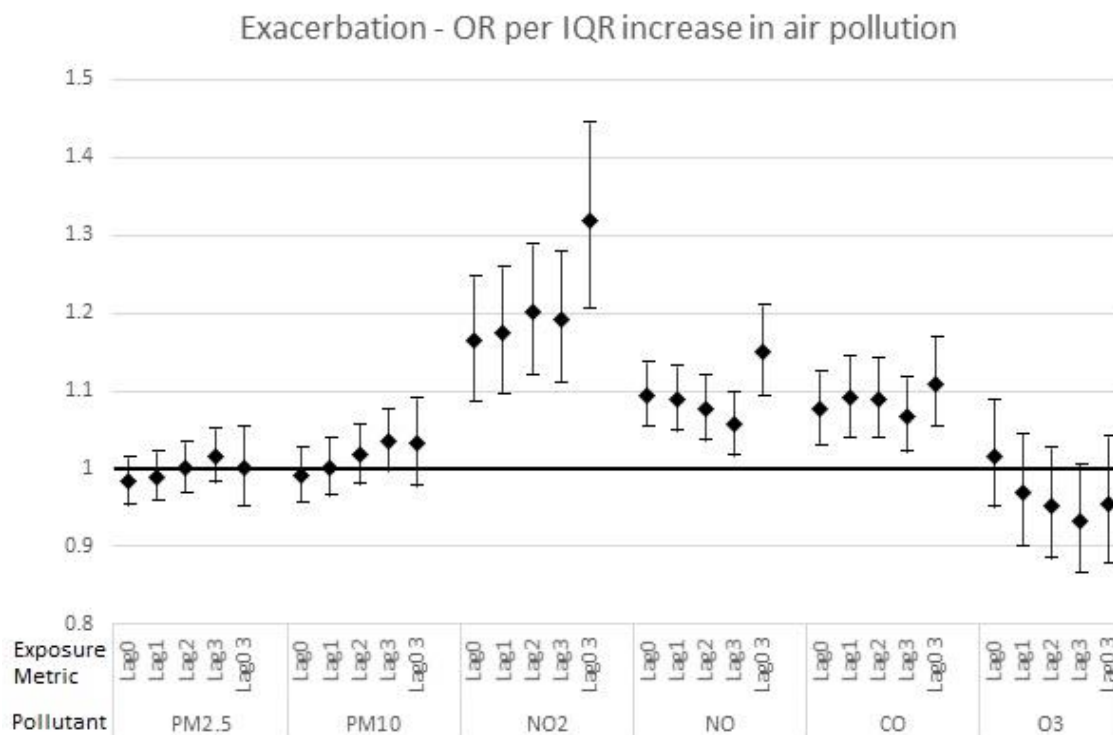
^a Mean value of the number of valid observations over the number of theoretical observations per participant across cohort (N obs / N theoretical).

All pairwise correlation coefficients between air pollutants were relatively low (<0.4) except for PM_{2.5} and PM₁₀, which was 0.8 (supplementary material Table S1). The number of person-days that people left their house without taking the PAM was 4,083 (28% of total person-days).

Epidemiological analysis:

In our analysis for occurrence of an exacerbation, gaseous pollutants were found to be associated with deterioration of COPD patients' health, increasing the odds (95% confidence interval) of an exacerbation by 16.4% (8.6,24.6%), 9.4% (5.4,13.6%) and 7.6% (3.0,12.4%) per IQR increase in NO₂, NO and CO respectively (Figure 1). No significant associations were observed for particles in the main or sensitivity analyses that covered the whole study period except for a marginal association for lag 3, i.e. 3.6% (0.0,7.6%) per IQR increase. No significant, but consistently negative associations were observed for O₃ in the fully adjusted models.

Figure 1 - Odds ratio (OR) with 95% CI for the occurrence of exacerbation associated with an interquartile (IQR) increase on the same (Lag0) or previous (Lag1, Lag2, Lag3) days or the average of the same and three previous days (Lag03) for each pollutant. Random intercept models adjusted for age, sex, COPD severity, Index of Multiple Deprivation (IMD) rank, inhaled corticosteroids (ICS) medication use, temperature and time. IQRs: $PM_{2.5} = 10.8 \mu\text{g}/\text{m}^3$, $PM_{10} = 12.0 \mu\text{g}/\text{m}^3$, $NO_2 = 5.2 \text{ ppb}$,



$NO = 7.2 \text{ ppb}$, $CO = 0.08 \text{ ppm}$, $O_3 = 5.0 \text{ ppb}$.

When lung function was considered with PEF as an indicator, few associations were found to be significant (Table 3). We observed an adverse effect of O_3 , i.e. 0.5 L/min decrease for an IQR increase of the pollutant, and a protective effect for NO which was consistent in the lagged exposure-response analysis.

Table 3 - Associations between personal exposure to air pollutants and peak expiratory flow (PEF) in main and sensitivity analyses. In bold are the statistically significant estimates.

	Estimated change in PEF (L/min) with 95% CI per interquartile range increase (unless otherwise stated)							
	Core ^a	Full ^b		Lag1 Full	Lag2 Full	Lag3 Full	Lag03 Full	Took monitor ^c
		per unit change	per IQR change					
PM_{2.5}	-0.045 (-0.306, 0.217)	0.004 (-0.021, 0.028)	0.038 (-0.226, 0.302)	0.055 (-0.212, 0.322)	-0.031 (-0.297, 0.235)	-0.045 (-0.310, 0.220)	0.095 (-0.321, 0.511)	-0.080 (-0.379, 0.219)
PM₁₀	-0.085 (-0.354, 0.184)	-0.003 (-0.026, 0.019)	-0.038 (-0.309, 0.233)	0.022 (-0.252, 0.296)	-0.077 (-0.351, 0.196)	-0.019 (-0.290, 0.252)	0.030 (-0.370, 0.431)	-0.057 (-0.366, 0.252)
NO₂	-0.267 (-0.684, 0.150)	0.011 (-0.072, 0.094)	0.057 (-0.375, 0.490)	-0.146 (-0.583, 0.291)	-0.108 (-0.550, 0.333)	0.338 (-0.104, 0.780)	-0.012 (-0.571, 0.546)	0.254 (-0.244, 0.751)

NO	0.185 (-0.103, 0.473)	0.048 (0.008, 0.089)	0.347 (0.055, 0.639)	0.341 (0.042, 0.640)	0.323 (0.021, 0.626)	0.371 (0.068, 0.675)	0.561 (0.163, 0.960)	0.330 (-0.004, 0.663)
CO	-0.189 (-0.525, 0.147)	-0.007 (-0.047, 0.033) ^d	-0.058 (-0.397, 0.282)	-0.251 (-0.608, 0.107)	-0.153 (-0.506, 0.200)	-0.112 (-0.463, 0.239)	-0.262 (-0.696, 0.172)	0.057 (-0.334, 0.448)
O₃	-0.134 (-0.543, 0.275)	-0.103 (-0.192, - 0.013)	-0.517 (-0.969, -0.066)	-0.438 (-0.905, 0.029)	-0.221 (-0.684, 0.243)	-0.339 (-0.799, 0.122)	-0.372 (-0.869, 0.124)	-0.195 (-0.693, 0.304)

^a Includes: age, sex, COPD severity and each pollutant's same day (Lag0) personal measurement.

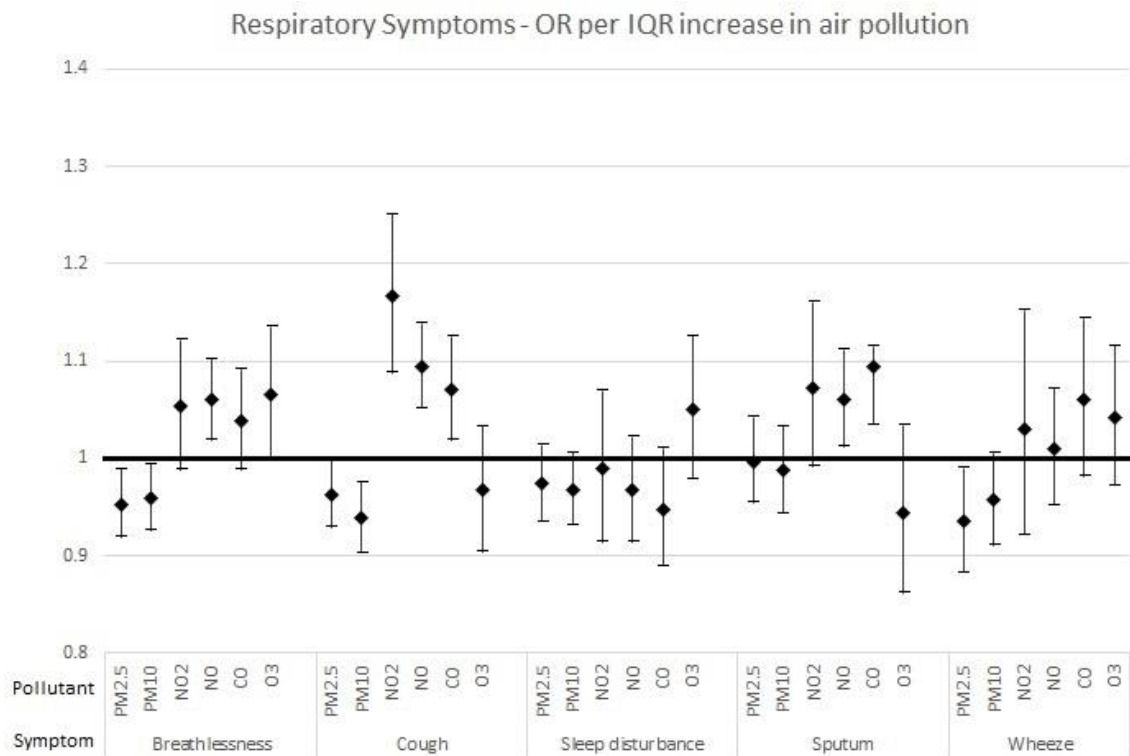
^b Core model plus Index of Multiple Deprivation (IMD) rank, inhaled corticosteroids (ICS) medication use, temperature and time. IQRs: PM_{2.5} = 10.8 µg/m³, PM₁₀ = 12.0 µg/m³, NO₂ = 5.2 ppb, NO = 7.2 ppb, CO = 0.08 ppm, O₃ = 5.0 ppb.

^c Excluding those person-days that participants left their house and forgot to take the portable monitor.

^d Per 0.01 ppm increase.

For the self-reported respiratory symptoms, generally gaseous pollutants were found to have negative impact on participants' health (Figure 2). In particular, breathlessness was associated with NO (OR=1.060, 95%CI (1.019,1.102) per IQR) and O₃ (OR=1.065 (1.000,1.135) per IQR); cough with NO₂ (OR=1.167 (1.088,1.251) per IQR), NO (OR=1.094 (1.052,1.139) per IQR) and CO (OR=1.071 (1.019,1.125) per IQR); and sputum with NO (OR=1.060 (1.012,1.112) per IQR) and CO (OR=1.094 (1.035,1.115) per IQR). However, particles were negatively associated with breathlessness, cough and wheeze. Sleep disturbance was not associated with any pollutant.

Figure 2 - Odds ratio (OR) with 95% CI for the occurrence respiratory symptoms associated with an IQR increase on the same (Lag0) for each pollutant. Random intercept models adjusted for age, sex, COPD severity, Index of Multiple Deprivation (IMD) rank, inhaled corticosteroids (ICS) medication use, temperature and time. IQRs: PM_{2.5} = 10.8 µg/m³, PM₁₀ = 12.0 µg/m³, NO₂ = 5.2 ppb, NO = 7.2 ppb, CO = 0.08 ppm, O₃ = 5.0 ppb.



ppb, CO = 0.08 ppm, O₃ = 5.0 ppb.

We observed significant relationships in the winter period sub-group analysis; 0.5% (0.1,0.9%), 0.8% (0.2,1.3%) and 3.0% (0.1,5.8%) decreased risk of exacerbation for a unit increase in PM_{2.5}, PM₁₀ and NO₂, but also negative (adverse) association for NO and a strong negative (adverse) association for O₃ with OR of 1.009 (1.001,1.017) and 1.149 (1.074,1.229) per unit respectively (Table 4). Particles were found to be statistically significantly associated with a decrease in PEF in the summer period, i.e. -0.122 (-0.186,-0.058) and -0.063 L/min (-0.113,-0.014) per unit increase in PM_{2.5} and PM₁₀. Ozone was positively and PM_{2.5} was negatively associated with exacerbation in spring. All the other associations were not statistically significant.

Table 4 – Season-specific estimates for the associations between personal exposure to air pollutants and peak expiratory flow and exacerbation. In bold are the statistically significant estimates.

	Estimated change in PEF (L/min) or OR for exacerbation with 95% CI by season per unit increase ^a							
	Spring (n=4,495)		Summer (n=4,507)		Autumn (n=2,769)		Winter (n=2,969)	
	PEF	Exacerbation	PEF	Exacerbation	PEF	Exacerbation	PEF	Exacerbation
PM_{2.5}	-0.011 (-0.059, 0.037)	0.986 (0.975 , 0.997)	-0.122 (-0.186 , 0.058)	1.010 (1.000 , 1.021)	0.012 (-0.041, 0.065)	1.000 (0.994, 1.005)	0.018 (-0.018, 0.053)	0.995 (0.990 , 0.999)
PM₁₀	-0.003 (-0.042, 0.035)	1.001 (0.993, 1.010)	-0.063 (-0.113 , 0.014)	1.006 (0.998, 1.015)	0.006 (-0.048, 0.060)	1.000 (0.994, 1.005)	0.011 (-0.027, 0.049)	0.992 (0.987 , 0.998)
NO₂	-0.119 (-0.248, 0.011)	1.008 (0.982, 1.034)	0.059 (-0.156, 0.275)	1.024 (0.976, 1.074)	-0.115 (-0.368, 0.138)	1.003 (0.964, 1.043)	0.063 (-0.092, 0.218)	0.970 (0.942 , 0.999)
NO	0.034 (-0.136, 0.205)	1.000 (0.970, 1.031)	-0.027 (-0.171, 0.117)	1.030 (0.988, 1.073)	0.002 (-0.084, 0.088)	1.002 (0.990, 1.014)	-0.006 (-0.058, 0.046)	1.009 (1.001 , 1.017)
CO^b	-0.009 (-0.082, 0.064)	0.996 (0.982, 1.011)	0.052 (-0.031, 0.135)	1.001 (0.985, 1.018)	-0.096 (-0.209, 0.016)	1.005 (0.988, 1.022)	-0.012 (-0.074, 0.050)	1.007 (0.995, 1.018)
O₃	0.009 (-0.113, 0.132)	1.028 (1.004 , 1.052)	0.035 (-0.099, 0.169)	1.016 (0.987, 1.045)	-0.169 (-0.515, 0.177)	0.969 (0.913, 1.029)	0.008 (-0.411, 0.427)	1.149 (1.074 , 1.229)

^a Models adjusted for age, sex, COPD severity, Index of Multiple Deprivation (IMD) rank, inhaled corticosteroids (ICS) medication use, temperature and time.

^b Per 0.01 ppm increase.

When we restricted the analysis to person-days in which the patients went outside their home and took the monitor with them (Table 3 and supplementary material Figure S1), only the positive (protective) association between NO on PEF became not statistically significant, and there was a slight decrease in the odds ratios of exacerbation for NO₂, NO and CO, which did not affect the statistical significance of the estimates.

Two-pollutant models analysis showed that the statistical significance of the estimates for all pollutants did not change when we adjusted for any of the other co-pollutants except for the effect of O₃ on exacerbations which turned null after

adjustment (Table 5). the OR of exacerbation for NO₂, NO and CO decreased in two-pollutant models, showing a potential confounding effect between these gaseous pollutants. The negative association of O₃ and PEF remained unchanged. When we performed season-specific two-pollutant models analysis, findings for each season were almost identical to Table 4 (results not shown).

Effect modification by COPD severity was observed for the NO₂- and CO-PEF associations, and the NO-, CO- and O₃-exacerbation associations (supplementary material Table S6). Except for the latter, all these significant interaction terms were found to support adverse effects for the Mild\Moderate severity group and protective effects for the Severe\Very severe group. However, not all associations were statistically significant. When ambient measurements were used as exposure metrics, we found that statistically significant associations between exacerbations and personal exposure to NO and CO turned null while the NO₂ OR remained practically the same (supplementary material Table S7). For PEF, we observed some changes in the statistical significance of the estimates (PM_{2.5} and NO₂ effects were significant in the models with ambient concentrations, NO with personal exposures), however all the effects were contrary to the expected direction (i.e. more exposure to ambient PM_{2.5} and NO₂ was associated with an increase in PEF). The O₃ association was almost doubled.

Table 5 - Two-pollutant models for the associations between personal exposure to air pollutants and peak expiratory flow and exacerbation. In bold are the statistically significant estimates.

	Estimated change in PEF (L/min) or OR for exacerbation with 95% CI per IQR increase ^a							
Outcome	Effect of	Unadjusted	PM _{2.5} adjusted	PM ₁₀ adjusted	NO ₂ adjusted	NO adjusted	CO adjusted	O ₃ adjusted
PEF	PM _{2.5}	0.038 (-0.226, 0.302)	-	-	0.036 (-0.228, 0.300)	-0.010 (-0.275, 0.256)	0.041 (-0.226, 0.307)	0.033 (-0.231, 0.297)
	PM ₁₀	-0.038 (-0.309, 0.233)	-	-	-0.040 (-0.311, 0.232)	-0.077 (-0.349, 0.195)	-0.039 (-0.312, 0.234)	-0.039 (-0.310, 0.232)
	NO ₂	0.057 (-0.375, 0.490)	0.063 (-0.378, 0.505)	0.080 (-0.363, 0.523)	-	-0.087 (-0.537, 0.364)	0.063 (-0.390, 0.517)	0.022 (-0.412, 0.456)
	NO	0.347 (0.055, 0.639)	0.429 (0.116, 0.742)	0.438 (0.126, 0.750)	0.360 (0.061, 0.659)	-	0.402 (0.095, 0.709)	0.339 (0.047, 0.630)
	CO	-0.058 (-0.397, 0.282)	-0.036 (-0.428, 0.356)	-0.013 (-0.406, 0.380)	-0.070 (-0.420, 0.281)	-0.202 (-0.560, 0.155)	-	-0.097 (-0.438, 0.245)
	O ₃	-0.517 (-0.969, -0.066)	-0.551 (-1.015, -0.087)	-0.551 (-1.018, -0.083)	-0.516 (-0.968, -0.063)	-0.498 (-0.950, -0.046)	-0.528 (-0.985, -0.071)	-
Exacerbation	PM _{2.5}	0.983 (0.953, 1.014)	-	-	0.982 (0.951, 1.013)	0.975 (0.944, 1.006)	0.977 (0.946, 1.008)	0.983 (0.953, 1.015)
	PM ₁₀	0.992 (0.957, 1.028)	-	-	0.994 (0.958, 1.030)	0.984 (0.949, 1.021)	0.985 (0.950, 1.022)	0.992 (0.957, 1.029)
	NO ₂	1.164 (1.086, 1.246)	1.158 (1.080, 1.242)	1.157 (1.079, 1.240)	-	1.126 (1.048, 1.210)	1.138 (1.060, 1.221)	1.167 (1.089, 1.250)
	NO	1.094 (1.054, 1.136)	1.084 (1.043, 1.128)	1.082 (1.040, 1.125)	1.077 (1.036, 1.119)	-	1.080 (1.038, 1.124)	1.095 (1.055, 1.137)
	CO	1.076 (1.030, 1.124)	1.067 (1.018, 1.118)	1.065 (1.016, 1.116)	1.055 (1.011, 1.101)	1.044 (1.000, 1.090)	-	1.079 (1.033, 1.128)
	O ₃	1.017 (0.950, 1.089)	1.036 (0.967, 1.110)	1.037 (0.968, 1.111)	1.031 (0.964, 1.103)	1.026 (0.959, 1.098)	1.042 (0.973, 1.114)	-

^a Models adjusted for age, sex, COPD severity, Index of Multiple Deprivation (IMD) rank, inhaled corticosteroids (ICS) medication use, temperature and time. IQRs: PM_{2.5} = 10.8 µg/m³, PM₁₀ = 12.0 µg/m³, NO₂ = 5.2 ppb, NO = 7.2 ppb, CO = 0.08 ppm, O₃ = 5.0 ppb.

Discussion

Improving our knowledge on the associations between environmental stress and COPD symptoms and exacerbations has the potential to facilitate better patient care by predicting when patients are at increased risk of exacerbation. These associations could also be used to warn patients of periods of high risk and prevent exacerbations as a result, improving quality of life and reducing mortality.

In this study we investigated associations between COPD patients' respiratory health and their personal exposure to air pollution, including ambient (outdoor) and indoor environments. A unique database for 115 participants followed intensively for up to six months was utilised. Personal exposures to various air pollutants, along with health data and information about potential confounders, were collected, resulting in more than 14,700 person-days of observations. We observed consistent positive (adverse) associations between respiratory symptoms, i.e. exacerbations, breathlessness, cough and sputum, and gaseous pollutants such as NO₂, NO, CO. O₃ was negatively associated with PEF. Particulate matter was not found to have associations with any adverse effects on patients' health.

We assessed the robustness of our findings with various sensitivity analyses. We fitted two-pollutant models to account for the potential confounding effect between pollutants, we excluded from the analysis person-days that the patients went out without their monitor, and we checked whether season was an effect modifier. A large positive O₃-exacerbation association in winter can be explained by a combination of uniformly low winter-time ozone concentrations indoors [20] and inverse relationship with NO through titration.[21] Additionally, some apparently protective effects were observed for particles and NO₂ during the same season. These findings could not be explained by two-pollutant models, in which the estimates remained unchanged.

We also compared the health effect estimates when ambient (central monitor) measurements were used instead of personal exposures. Some differences were observed in the estimates, both qualitatively and quantitatively, but we expected this might be the case. Epidemiological studies typically use central monitoring site data or, more commonly in recent years, ambient models to estimate an individual's personal exposure to ambient air pollution, whereas we measured total personal exposure directly. Therefore, one must be cautious in the interpretation of this comparison - one method assesses the impact of ambient air pollution exposure, the other total air pollution exposure. Furthermore, such studies use ambient concentrations as a proxy for personal exposure. In most cases, this will represent an overestimate because less than 100% of ambient pollution typically infiltrates into buildings, where we spend most of our time. Therefore, a unit increase represents that proxy measure, whereas, personal measurements are not a proxy. Thus, one cannot directly compare epidemiological estimates per unit increase using the two methods, and we, therefore, expressed associations per IQR increase in this study. We are currently developing statistical methods to allow a direct comparison of exposure methods, including separation of indoor and outdoor source exposures, which will facilitate estimates of bias and the value of absolute versus proxy measures of exposure. It should be noted that our subjects were relatively old, had a chronic respiratory condition and probably spent more time at home compared to other groups of the same population.

Despite that, our findings are in close agreement with Peacock et al. who conducted a large panel study with COPD patients in London.[22] Results were similar for the associations between matching pollutants and health outcomes, although their study only assessed exposure to ambient pollutants. Similarly, absence of significant associations between particle mass and PEF has been reported in other studies with COPD patients.[23-25] Chamber studies, which measure absolute exposure, may be more appropriate for comparison with our results. In the two 'Oxford Street' natural chamber studies,[11,26] consistent adverse associations in asthma and COPD patients were found between respiratory functions and ultrafine particles – a pollutant not measured in our study – but not PM_{2.5}. Laboratory chamber study results are mixed for all pollutants.[27-29]

The COPE study benefited from the plethora of personal exposure and health outcome measurements obtained from a relatively large number of participants. Similar personal exposure studies previously have either focused on one or two pollutants only[30,31] and/or limited their follow-up to a few days or weeks.[24,32] Using monitors designed specifically for this study, we have been able to collect measurements for six different pollutants. In addition, we reached a median follow-up of 145 days per participant, covering a long, representative period of mixed seasons.

However, the main strength of the COPE study is the collection of sustained personal exposure measurements which, even though it was a demanding task for the patients, had high levels of compliance. Anecdotal evidence suggests that this is because COPD patients are used to long-term clinical monitoring and could see direct benefit to themselves. Previous studies have used datasets of similar size, but instead of personal exposures they used ambient measurements of pollution.[22,33] This exposure metric can differ substantially from the actual exposures of the patients for multiple reasons, including exposure to both ambient and indoor sources of pollution, variable infiltration factors of buildings, the time-activity patterns of the individuals, the concentrations in different micro-environments and spatial aggregation.[34] Thus, they may have resulted in biased epidemiological estimates due to exposure measurement error.[35,36,37] In this study, we collected personal exposure data to accurately represent the quality of air that the participant's breathed, rather than a proxy estimate.

Our study is subject to some limitations. Firstly, the COPE study was conducted in London, which, even though it is a highly ethnically diverse metropolitan city, cannot provide a representative sample of the COPD patients worldwide. Despite this, they seem to be in agreement with some studies from other locations using different methodologies.[25,32,38]

Because of the length and the demands of this study, some participants did not always carry the monitor when they left the house. However, our results were unchanged by restricting our analysis to those that did take the monitor out. It should be noted that COPD patients are less mobile and more used to carrying/using medical equipment than other population groups.

Finally, we have performed many ancillary analyses, some of which may have resulted in statistically significant associations by chance. However, finding consistent associations for gaseous pollutants for various health outcomes, makes this unlikely. On the other hand, we observed some unexpected negative associations between PM exposures and respiratory symptoms which were difficult

to explain biologically. A potential reason might be the use of total personal exposure as the metric of interest, as, even though it reflects what patients actually breathe, indoor- and outdoor-generated pollution comprise different sources, composition and behaviours.[34] False-positive associations might be the result of treating pollution from different sources equally, without accounting for potentially different health effects.[39] This issue, along with the impact of mobility in the exposure estimates, will be further investigated by separating total personal exposure into indoor- and outdoor-generated pollution and re-applying the models in future work. This partition is very important for policy making as regulations and mitigation actions for indoor pollution are very different from those for ambient air due to their contrasting sources, i.e., traffic, industrial and agricultural emissions versus domestic cooking, heating and cleaning emissions. Such partitioning will also facilitate identification of dominant sources of each pollutant in the indoor and outdoor environment.[15]

Conclusions

This study demonstrated that it is feasible to gather robust multi-pollutant personal exposure measurements over extended periods in a cohort of COPD patients. By utilising personal measurements total exposure can be assessed at unprecedented detail. Significant associations were found between an individual's exposure to gaseous pollutants and their respiratory health, but not particulate pollutants. While this finding is important in confirming links between personal pollutant exposure and patient health, further work is required to identify which sources drive this association and whether these operate indoors or outdoors.

Additional information

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Table S1 – Pearson correlation coefficients between any pair of personal exposure to air pollutants based on 14,740 person-days of follow-up. All exposures are expressed as 24-hour means, except for O₃ which is 8-hour maximum.

	PM_{2.5}	PM₁₀	NO₂	NO	CO	O₃
PM_{2.5}	1					
PM₁₀	0.816	1				
NO₂	0.110	0.118	1			
NO	0.235	0.152	0.212	1		
CO	0.213	0.165	0.241	0.399	1	
O₃	-0.086	-0.031	0.067	-0.145	-0.157	1

All results are statistically significant at significance level of <0.001.

Table S2 - Descriptive statistics for personal exposure to air pollution, expressed as 24-hour averages, except for O3 which is 8-hour maximum by season. N: number of valid measurements.

Personal Exposure	Season	N	Mean	SD	25 th %ile	Median	75 th %ile
PM_{2.5} (µg/m³)	Spring	4,223	15.0	13.4	7.6	11.5	17.6
	Summer	4,152	10.4	10.3	5.6	8.1	11.9
	Autumn	2,517	17.7	20.7	8.8	13.3	19.4
	Winter	2,765	23.5	25.8	11.1	17.0	26.8
PM₁₀ (µg/m³)	Spring	4,200	16.9	21.3	6.1	11.5	18.5
	Summer	4,103	11.2	14.0	4.3	8.6	13.5
	Autumn	2,517	18.4	20.5	10.1	14.2	20.2
	Winter	2,765	23.6	25.1	11.3	17.3	26.9
NO₂ (ppb)	Spring	4,495	14.6	6.7	10.5	13.0	16.3
	Summer	4,506	11.7	3.4	9.4	10.7	13.0
	Autumn	2,769	13.8	5.5	10.6	12.6	15.3
	Winter	2,969	15.8	8.5	11.2	13.7	17.3
NO (ppb)	Spring	4,456	6.1	4.8	3.0	4.7	7.3
	Summer	4,463	4.5	5.2	2.3	3.5	5.2
	Autumn	2,753	12.6	13.1	4.6	8.6	16.2
	Winter	2,957	16.9	17.0	6.0	11.5	21.4
O₃ (ppb)	Spring	4,495	6.6	5.4	3.7	5.4	8.3
	Summer	4,506	8.5	6.0	4.7	7.0	10.6
	Autumn	2,769	5.0	4.1	2.5	4.0	6.1
	Winter	2,969	4.5	3.4	2.2	3.4	5.7
CO (ppm)	Spring	4,425	0.19	0.09	0.15	0.17	0.21
	Summer	4,429	0.18	0.07	0.14	0.16	0.19
	Autumn	2,724	0.23	0.09	0.17	0.21	0.26
	Winter	2,944	0.25	0.14	0.18	0.23	0.30

Table S3 - Descriptive statistics for ambient measurements of air pollution as measured from the nearest monitor of the London Air Quality Network (LAQN), expressed as 24-hour averages, except for O₃ which is 8-hour maximum. N obs: number of valid observations.

Exposure	N obs	Mean	SD	25th %ile	Median	75th %ile
PM_{2.5} (µg/m³)	13,646	12.4	10.4	6.3	8.7	14.3
PM₁₀ (µg/m³)	13,596	19.1	11.1	12.0	15.4	22.7
NO₂ (ppb)	14,739	17.2	9.3	10.6	15.6	21.5
NO (ppb)	14,630	11.0	26.6	1.7	3.1	7.3
O₃ (ppb)	14,647	29.4	12.3	22.1	0.16	0.21
CO (ppm)	14,289	0.20	0.14	0.13	30.3	37.0

The measurements are from the nearest monitor of the London Air Quality Network (<http://www.londonair.org.uk/LondonAir/Default.aspx>).

Table S4 - Associations between personal exposure to air pollutants and exacerbation in main and sensitivity analyses. In bold are the statistically significant estimates.

	OR for exacerbation with 95% CI per interquartile range increase (except otherwise stated)							
	Core ^a	Full ^b		Lag1 Full	Lag2 Full	Lag3 Full	Lag03 Full	Took monitor ^c
		per unit change	per IQR change					
PM _{2.5}	0.998 (0.967, 1.029)	0.998 (0.995, 1.001)	0.983 (0.953, 1.014)	0.990 (0.959, 1.022)	1.001 (0.969, 1.034)	1.016 (0.982, 1.051)	1.001 (0.952, 1.054)	0.978 (0.944, 1.014)
PM ₁₀	1.008 (0.973, 1.044)	0.999 (0.996, 1.002)	0.992 (0.957, 1.028)	1.002 (0.965, 1.040)	1.018 (0.980, 1.057)	1.036 (0.997, 1.076)	1.032 (0.977, 1.090)	0.983 (0.943, 1.025)
NO ₂	1.227 (1.149, 1.311)	1.029 (1.016, 1.043)	1.164 (1.086, 1.246)	1.175 (1.096, 1.259)	1.201 (1.120, 1.288)	1.192 (1.111, 1.279)	1.319 (1.206, 1.444)	1.156 (1.071, 1.248)
NO	1.119 (1.079, 1.161)	1.013 (1.007, 1.018)	1.094 (1.054, 1.136)	1.089 (1.048, 1.132)	1.077 (1.036, 1.120)	1.057 (1.017, 1.099)	1.150 (1.093, 1.210)	1.076 (1.032, 1.122)
CO	1.014 (0.966, 1.046)	1.009 (1.003, 1.014)^d	1.076 (1.030, 1.124)	1.091 (1.040, 1.145)	1.090 (1.040, 1.142)	1.068 (1.021, 1.117)	1.110 (1.055, 1.169)	1.061 (1.009, 1.117)
O ₃	0.918 (0.861, 0.979)	1.003 (0.990, 1.017)	1.017 (0.950, 1.089)	0.970 (0.900, 1.045)	0.953 (0.885, 1.026)	0.933 (0.866, 1.005)	0.956 (0.878, 1.041)	1.032 (0.957, 1.112)

^aIncludes: age, sex, COPD severity and each pollutant's same day (Lag0) personal measurement.

^bCore model plus IMD rank, ICS medication use, temperature and time.

^cExcluding those person-days that participants left their house and forgot to take the portable monitor.

^dPer 0.01 ppm increase.

Figure S1 - Estimated change in PEF (L/min) associated with an IQR increase on the same (Lag0) or previous (Lag1, Lag2, Lag3) days or the average of the same and three previous days (Lag03) for personal exposure to each pollutant. Random intercept models adjusted for age, sex, COPD severity, IMD rank, ICS medication use, temperature and time.

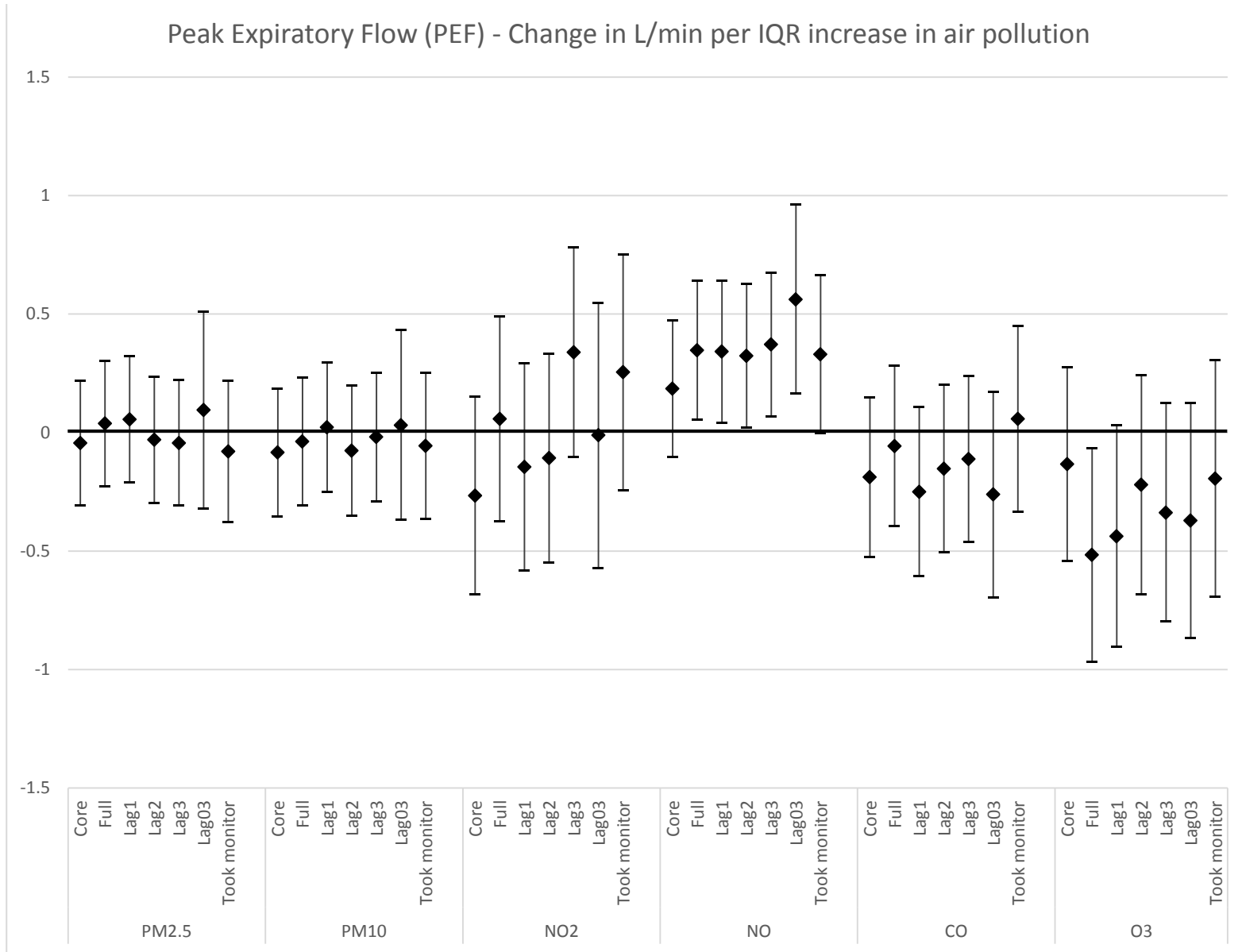


Table S5 - Associations between personal exposure to air pollutants and various respiratory symptoms. In bold are the statistically significant estimates.

	OR for respiratory symptoms with 95% CI ^a									
	Breathlessness		Cough		Sleep disturbance		Sputum		Wheeze	
	per unit change	per IQR change	per unit change	per IQR change	per unit change	per IQR change	per unit change	per IQR change	per unit change	per IQR change
PM_{2.5}	0.996 (0.992, 0.999)	0.953 (0.919, 0.989)	0.996 (0.993, 1.000)	0.963 (0.929, 0.998)	0.998 (0.994, 1.001)	0.974 (0.935, 1.014)	1.000 (0.996, 1.004)	0.997 (0.955, 1.042)	0.994 (0.989, 0.999)	0.935 (0.883, 0.990)
PM₁₀	0.997 (0.994, 0.999)	0.959 (0.926, 0.994)	0.995 (0.992, 0.998)	0.939 (0.903, 0.976)	0.997 (0.994, 1.001)	0.968 (0.932, 1.006)	0.999 (0.995, 1.003)	0.988 (0.944, 1.033)	0.996 (0.992, 1.000)	0.957 (0.911, 1.005)
NO₂	1.010 (0.998, 1.022)	1.053 (0.988, 1.122)	1.030 (1.016, 1.044)	1.167 (1.088, 1.251)	0.998 (0.983, 1.013)	0.989 (0.914, 1.069)	1.014 (0.999, 1.029)	1.073 (0.992, 1.161)	1.006 (0.985, 1.027)	1.030 (0.922, 1.152)
NO	1.008 (1.003, 1.014)	1.060 (1.019, 1.102)	1.013 (1.007, 1.018)	1.094 (1.052, 1.139)	0.995 (0.988, 1.003)	0.967 (0.914, 1.022)	1.008 (1.002, 1.015)	1.060 (1.012, 1.112)	1.001 (0.993, 1.010)	1.010 (0.952, 1.072)
CO	1.004 (0.999, 1.010) ^b	1.038 (0.988, 1.091)	1.008 (1.002, 1.014) ^b	1.071 (1.019, 1.125)	0.994 (0.986, 1.001) ^b	0.948 (0.890, 1.010)	1.011 (1.004, 1.017) ^b	1.094 (1.035, 1.115)	1.007 (0.998, 1.016) ^b	1.060 (0.982, 1.144)
O₃	1.013 (1.000, 1.025)	1.065 (1.000, 1.135)	0.993 (0.980, 1.007)	0.967 (0.904, 1.033)	1.010 (0.996, 1.024)	1.050 (0.979, 1.126)	0.989 (0.971, 1.007)	0.944 (0.862, 1.034)	1.008 (0.994, 1.022)	1.042 (0.972, 1.116)

^aModels adjusted for age, sex, COPD severity, IMD rank, ICS medication use, temperature and time.

^bPer 0.01 ppm increase.

Table S6 –Associations between personal exposure to air pollutants and peak expiratory flow and exacerbation by COPD severity. In bold are the statistically significant interaction term at the 0.05 level.

	Estimated change in PEF (L/min) or OR for exacerbation with 95% CI by COPD severity per unit increase ^a			
	PEF		Exacerbation	
	Mild or Moderate COPD	Severe or Very severe COPD	Mild or Moderate COPD	Severe or Very severe COPD
PM_{2.5}	0.006 (-0.022, 0.034)	-0.004 (-0.054, 0.046)	0.998 (0.995, 1.001)	1.000 (0.994, 1.006)
PM₁₀	-0.002 (-0.028, 0.024)	-0.007 (-0.051, 0.037)	0.998 (0.995, 1.002)	1.002 (0.996, 1.008)
NO₂	-0.090 (-0.189, 0.010)	0.229 (0.084, 0.374)	1.037 (1.019, 1.055)	1.020 (1.001, 1.040)
NO	0.029 (-0.019, 0.076)	0.099 (0.023, 0.175)	1.025 (1.018, 1.032)	0.990 (0.980, 1.000)
CO	-0.034 (-0.079, 0.012)^b	0.086 (0.012, 0.017)^b	1.018 (1.010, 1.025)^b	0.993 (0.983, 1.002)^b
O₃	-0.099 (-0.206, 0.009)	-0.110 (-0.253, 0.031)	0.933 (0.911, 0.955)	1.051 (1.033, 1.070)

^aModels adjusted for age, sex, COPD severity, IMD rank, ICS medication use, temperature and time.

^bPer 0.01 ppm increase.

Table S7 - Associations between air pollutants and peak expiratory flow and exacerbation using personal exposures or ambient measurements as measured from the nearest monitor as exposure metrics. In bold are the statistically significant estimates.

	PEF – Change per IQR increase (95% CI) ^a		Exacerbation – OR per IQR increase (95% CI) ^a	
	Ambient ^b	Personal ^c	Ambient ^b	Personal ^c
PM_{2.5}	0.327 (0.001, 0.654)	0.038 (-0.226, 0.302)	1.017 (0.975, 1.061)	0.983 (0.953, 1.014)
PM₁₀	0.329 (-0.077, 0.734)	-0.038 (-0.309, 0.233)	1.032 (0.979, 1.088)	0.992 (0.957, 1.028)
NO₂	0.669 (0.156, 1.182)	0.057 (-0.375, 0.490)	1.159 (1.084, 1.240)	1.164 (1.086, 1.246)
NO	0.074 (-0.014, 0.162)	0.347 (0.055, 0.639)	1.007 (0.996, 1.018)	1.094 (1.054, 1.136)
CO	0.195 (-0.059, 0.449)	-0.058 (-0.397, 0.282)	1.027 (0.994, 1.061)	1.076 (1.030, 1.124)
O₃	-1.019 (-1.591, -0.447)	-0.517 (-0.969, -0.066)	0.973 (0.900, 1.052)	1.017 (0.950, 1.089)

^aModels adjusted for age, sex, COPD severity, IMD rank, ICS medication use, temperature and time.

^bAmbient measurements IQRs: PM_{2.5} = 8.0 µg/m³, PM₁₀ = 10.7 µg/m³, NO₂ = 10.9 ppb, NO = 5.6 ppb, CO = 0.08 ppm, O₃ = 15.0 ppb.

^cPersonal exposures IQRs: PM_{2.5} = 10.8 µg/m³, PM₁₀ = 12.0 µg/m³, NO₂ = 5.2 ppb, NO = 7.2 ppb, CO = 0.08 ppm, O₃ = 5.0 ppb.