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Respiratory effects of particulate air pollution episodes in former smokers with and without chronic obstructive pulmonary disease: a panel study

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Abstract

Background: Air pollution is associated with adverse health effects in individuals with chronic obstructive pulmonary disease (COPD). It is uncertain if and how individuals with COPD differ from former smokers without airflow obstruction in their response to naturally occurring episodes of particulate air pollution. We hypothesized that episodic temperature inversions with high particulate matter (PM) air pollution during the winter would be associated with increased pulmonary inflammation and oxidative stress, increased respiratory symptoms, and decreased lung function in individuals with COPD compared to controls.

Methods: We conducted a panel study of former smokers, 16 with moderate-to-severe COPD and 12 without airflow obstruction as controls. We measured biomarkers (nitrite/nitrate (NOx), 8-isoprostane) in exhaled breath condensate (EBC), spirometry, and respiratory symptoms during periods of low and high $PM_{2.5}$ (PM < 2.5 microns in diameter). We compared differences between pollution and clean air days within the COPD and control groups using linear mixed effect models.

Results: High $PM_{2.5}$ levels were associated with increased EBC NOx in participants with COPD (mean ratio 3.16, $p = 0.007$), but not in controls (mean ratio 0.49, $p = 0.23$, difference between groups $p = 0.01$). Respiratory symptoms significantly increased on pollution days in COPD participants but not in controls. We did not detect a difference in pulmonary function or EBC 8-isoprostane.

Conclusions: Former smokers with COPD have a distinctive response to particulate air pollution episodes compared to former smokers without airflow obstruction, with increased airway inflammation and respiratory symptoms.

Keywords: Air pollution, Chronic obstructive pulmonary disease, Exhaled breath condensate, Particulate matter, Airway inflammation

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Background

Exposure to air pollution is associated with adverse health effects in individuals with chronic obstructive pulmonary disease (COPD). Long-term exposure to elevated concentrations of ambient air pollution is associated with decreased lung function [1, 2] and increased mortality [3], and may be associated with increased prevalence of COPD [4–7]. Among individuals with COPD, short-term exposure to elevated levels of outdoor air pollution is associated with increased respiratory symptoms [8], decreased lung function [9–12], increased acute exacerbations of COPD [13–15], and increased daily mortality [16–18]. Thus, episodes of air pollution exposure represent significant stress episodes for individuals with COPD. However, it is unclear whether the response to particulate air pollution differs between former smokers with COPD and those without airflow obstruction.

The pathophysiologic mechanisms resulting in these clinical effects are poorly defined, but are likely similar to the underlying pathophysiology of COPD itself, and involve oxidative stress and local inflammation in the lung. Multiple components of outdoor air pollution are sources of oxidative stress, which may induce lung damage [19, 20]. We postulate that these mechanisms may result in a fundamentally different response to outdoor air pollution episodes in individuals with COPD compared to those without lung disease.

Exhaled breath condensate (EBC) is a noninvasive method of sampling the airway lining fluid to analyze changes in the local pulmonary environment that has shown promise for identifying biomarkers indicating pulmonary inflammation and oxidative stress. Multiple markers of oxidative stress and inflammation are increased in EBC of COPD patients, including nitrite + nitrate (NOx) [21–23] and 8-isoprostane [24–26]. Exposure to high levels of ambient air pollution is also associated with increased markers of pulmonary inflammation and oxidative stress. In healthy adults, decreased air pollution during the Beijing Olympics was associated with decreased EBC NOx and 8-isoprostane [27]. In one study of adults with chronic respiratory disease, exposure to ambient coarse particle air pollution was associated with increased EBC NOx [28]. It has not yet been demonstrated if increased levels of $PM_{2.5}$ (particulate matter less than 2.5 microns in diameter) are associated with increased EBC biomarkers of inflammation and oxidative stress in patients with moderate to severe COPD or if the response to air pollution episodes differs between individuals with COPD and controls without COPD.

The Salt Lake Valley in Utah experiences wintertime temperature inversions resulting in multi-day periods of intense fine particulate matter air pollution with levels of $PM_{2.5}$ exceeding the Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS). These relatively predictable air pollution episodes provide an opportunity to investigate the impact of naturally occurring elevated ambient PM on individuals with COPD compared to appropriate controls.

We aimed to determine if former smokers with and without airway obstruction differed in their response to naturally occurring PM air pollution episodes. We hypothesized that episodic exposure to high PM air pollution during temperature inversions would be associated with increased pulmonary inflammation and oxidative stress, indicated by increased EBC biomarkers, increased respiratory symptoms, and decreased lung function, and that this response would be exaggerated in individuals with COPD compared to former smokers without COPD.

Methods

We conducted a prospective observational study comparing characteristics of EBC biomarkers, spirometry, and respiratory symptoms in COPD and control subjects under naturally occurring conditions of good and poor air quality. All participants were adults aged 40-85 living in the Salt Lake Valley in Utah. The COPD group consisted of former smokers with moderate or severe COPD, defined by FEV1/FVC below the lower limit of normal and FEV1 < 70 % predicted for age and height [29]. The control group consisted of former smokers without chronic lung disease, airflow obstruction, or emphysema on CT imaging. Inclusion and exclusion criteria are summarized in Table 1. An acute exacerbation of COPD was defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD [30]. Subjects were recruited from the community, the Pulmonary Clinic and Pulmonary Function Test Lab of the University of Utah, and the Lung Health Research Center at the University of Utah. Approval was obtained from the University of Utah Institutional Review Board.

The study took place over a 4 month period in the winter December 2012 – March 2013. Participants completed a baseline questionnaire regarding residential history, exposure to smoke, pollution, or occupational exposures, and disease history.

Participants were evaluated both during periods of good air quality and in "triggered visits" initiated during periods of poor air quality based on measurements of $PM_{2.5}$ updated hourly from the Salt Lake City Hawthorne Station, which is the controlling monitor for the Salt Lake basin [31]. Good air quality days were defined by a $PM_{2.5}$ level ≤ 15.4 μg / m3. Poor air quality days were defined by a 24 h average $PM_{2.5}$ level ≥ 35.5 μg / m^3 ("red alert" days) or 24 average $PM_{2.5}$ level ≥ 25.5 μg / m^3 ("yellow action"

Table 1 Inclusion and exclusion criteria

Inclusion criteria		Exclusion criteria
COPD Group	Control Group	All Groups
Former smoker	Former smoker	Active smoking
≥10 pack year smoking history, quit at least 3 months prior to enrollment	≥10 pack year smoking history, quit at least 3 months prior to enrollment	Any significant pulmonary disease other than COPD which would limit the interpretability of the pulmonary function measures
Age 40-85	Age 40-85	
Moderate or severe COPD:	Spirometry without evidence of airflow obstruction	COPD exacerbation[a] in the prior six weeks
FEV1/FVC below the lower limit of normal and FEV1 < 70 % predicted for age and height	No evidence of emphysema on CT imaging, if previously obtained	Currently taking ≥10 mg a day of prednisone or equivalent systemic corticosteroid
		Inability to perform exhaled breath condensate, spirometry, or complete respiratory symptom questionnaire
		Pregnant or intending to become pregnant

[a] An acute exacerbation of COPD was defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD [30]

days) with peak $PM_{2.5}$ exceeding 35.5 μg / m^3 [31]. We incorporated at least a 1 day lag for testing on poor air quality days based on the 1 3 day lag-effect for pulmonary symptoms and lung function seen in prior studies with particulate pollution [10, 11]. Participants were contacted and asked to come to the study center during periods of poor air quality, based on measurements from the Utah Department of Environmental Quality, Division of Air Quality, following the first day of the temperature inversion (lag 1 day). Testing on good air quality days occurred after a minimum of 4 days of consecutive good air quality after a period of poor air quality to incorporate the lag effect from particulate pollution.

Testing at each visit included EBC collection for biomarker analysis, spirometry, and completion of a respiratory symptom questionnaire. EBC was used to measure NOx and 8-isoprostane as biomarkers of oxidative stress and inflammation. EBC was collected at each visit using the R-tube [32] according to standard protocol with tidal breathing x 10 min. Approximately 1 – 2 mL condensate fluid was collected from each participant. Samples were divided into 200 μl aliquots and frozen at -80° F. EBC NOx was measured using the colorimetric Griess enzymatic reaction with Total Nitric Oxide and Nitrate/Nitrite Parameter Assay Kit (R&D Systems). 8-isoprostane was measured by ELISA using Cell Biolab OxiSelect™ 8-iso-Prostaglandin F2a ELISA Kit. Spirometry without bronchodilator was conducted at each study visit according to ATS criteria. Subjects continued all home medications prior to testing except they were asked to hold short-acting beta agonists for 4 h prior to spirometry if able.

Respiratory symptoms were assessed using a questionnaire that asked about change from baseline in eight symptoms over the preceding few days: shortness of breath, sputum thickness or color, amount of sputum, cough, wheeze, chest tightness, nasal congestion or discharge, and feeling of activity limitation due to lung condition. For each symptom the participant indicated one of the following with numerical score in parentheses: Symptoms have decreased (0), symptoms are the same (1), symptoms have increased a little (2), symptoms have increased a lot (3), or I don't know / I don't experience this symptom. Symptoms were analyzed as the total aggregate score obtained by adding the individual symptom scores.

Statistical methods, data analysis and interpretation

The primary outcomes were 8-isoprostane and NOx in exhaled breath condensate. Secondary outcomes included FEV1, FVC, and respiratory symptoms.

Baseline characteristics were summarized for the COPD and control cohorts. 8-isoprostane and NOx were found to be positively skewed, and were log transformed prior to subsequent statistical analyses. Baseline characteristics were compared between the COPD and former-smoker control groups using 2-sample t-tests for quantitative variables.

The lung function, inflammatory, and oxidative stress outcomes were analyzed using separate linear mixed effect models with random effects for each patient and a fixed effect to distinguish between pollution and clean air days to estimate the mean differences between pollution and clean air days within the COPD and former smoker groups, respectively. We then applied a mixed model including both the COPD and control groups with random effects for each individual and fixed effects to designate the COPD and control groups, the pollution vs. clean air assessments, and the interaction between

the two fixed effect terms to estimate the difference in estimated pollution effect vs. clean air day effects between the COPD and control groups. We applied mixed effects models in order to incorporate all available lung function, inflammatory, and oxidative stress measurements in a statistically efficient manner even when the numbers of visits differed between the pollution and clean air days [33]. The model for the FVC incorporated different residual variances for the COPD and control groups as a likelihood ratio test indicated a significantly higher level of variability for the COPD group. The aggregate symptom score was analyzed using the same mixed effects models used for the quantitative outcomes. Frequencies and proportions of patients experiencing a worsening of symptoms on at least one pollution day and on at least one clean air day were also summarized.

The analyses of this observational study were interpreted as exploratory, and results were regarded as statistically significant using a 2-sided significance level of 0.05, without adjustment for multiple comparisons. All analyses were performed used SAS 9.2 (SAS 9.2, SAS Inc., N.C., USA).

Results

Study subjects and observed air quality

We enrolled 16 former smokers with moderate to severe COPD (5 with moderate and 11 with severe airflow obstruction) and 12 former smoker controls without airflow obstruction based on an FEV1/FVC greater than the lower limit of normal. Baseline characteristics are shown in Table 2. The COPD group had greater mean pack-years smoking history, and fewer years since quitting smoking. As might be anticipated, the COPD group had airflow obstruction on spirometry and demonstrated lower mean FEV1, FVC, and FEV1/FVC.

Mean maximum pollutant levels were calculated averaging testing day and one day prior. Mean (±SD) peak 24 h $PM_{2.5}$ was 6.35 (±2.06) $\mu g/m^3$ on clean air testing days, and 48.13 (±13.26) $\mu g/m^3$ during pollution testing days. Fig. 1 shows the trends of 24-h $PM_{2.5}$ in Salt Lake County during the winter of 2012-2013. Peak levels of other criteria pollutants remained well below the EPA NAAQS during the period of our study. Mean (±SD) peak levels of 8-h ozone, 1-h nitrogen dioxide (NO_2), 1-h sulfur dioxide (SO_2), and 1-h carbon monoxide (CO) were 0.035 (±0.008) ppm, 0.037 (±0.008) ppm, 0.97 (±0.37) ppb, and 0.88 (±0.39) ppm, respectively, on clean air testing days and 0.019 (±0.009) ppm, 0.056 (±0.006) ppm, 3.17 (±1.43) ppb, and 1.29 (±0.47) ppm, respectively, on pollution testing days. Of the COPD participants, 6 had one visit and 10 had two visits on poor air quality days, and 12 had one visit and 1 had two visits on good air quality days. Of the former smoker controls, 6 had one visit and 6 had two visits on poor air quality days, and 11 had one visit on good air quality days. The minimum observed interval between a PM pollution episode and clean air testing was 7 days. Follow-up time period between testing visits ranged from 15 to 91 days.

Exhaled breath condensate parameters

We found evidence of pollution-related increases in airway inflammation in EBC from subjects with COPD but not in EBC from controls. PM air pollution was associated

Table 2 Baseline characteristics

	COPD [57.2 % ($n = 16$)]	Control [42.9 % ($n = 12$)]	*P* value
Male [%(n)]	81.3 (13)	50.0 (6)	0.11
Smoking history [mean ± SD]			
Smoking (pack-years)	71.2 ± 24.1	40.1 ± 15.5	<0.001
Years since quitting smoking	8.9 ± 8.0	21.2 ± 9.0	<0.001
Spirometry [mean ± SD]			
FEV1 (L)	1.1 ± 0.5	2.5 ± 0.4	<0.001
FVC (L)	3.0 ± 0.9	3.4 ± 0.7	0.18
FEV1/FVC %	38.7 ± 11.4	74.7 ± 8.1	<0.001
FEV1 % predicted	39.1 ± 16.6	86.5 ± 9.1	<0.001
FVC % predicted	74.6 ± 17.1	90.8 ± 12.5	<0.001
Inhaled Medications [%(n)]			
Taking inhaled corticosteroid	81.3 (13)	0	<0.001
Taking inhaled long acting anticholinergic	75.0 (12)	7.7 (1)	<0.001
Taking inhaled long acting beta agonist	81.3 (13)	0	<0.001
Taking inhaled short acting beta agonist	81.3 (13)	0	<0.001

P-values for comparisons between the COPD and Controls were computed using t-tests for continuous variables and Fisher exact tests for categorical variables (gender, history of antibiotics, and use of inhaled medications

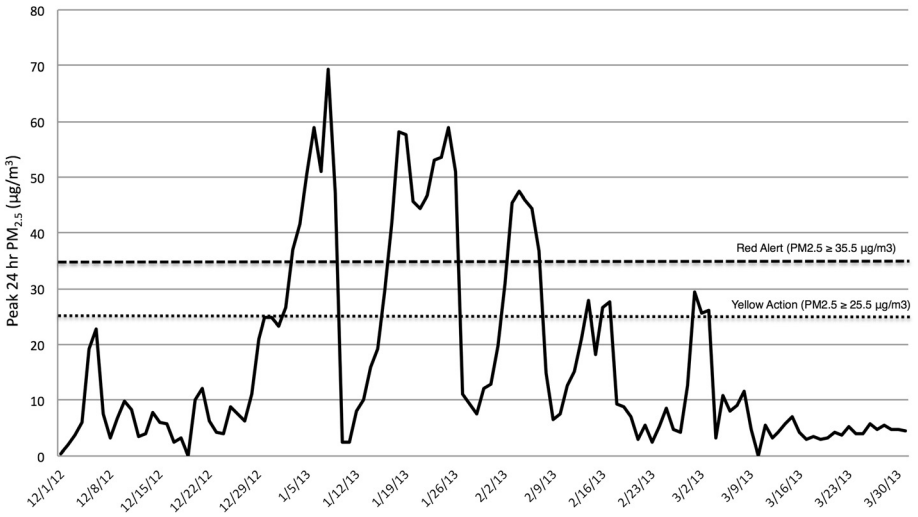

Fig. 1 24-h average $PM_{2.5}$ in Salt Lake Valley, UT during Winter 2012-2013. Dashed lines indicate the level of 24-h average $PM_{2.5}$ designated as "Red Alert" and "Yellow Action" days by the Utah Division of Air Quality. "Red Alert" days are defined by a 24 h average $PM_{2.5}$ level ≥ 35.5 μg / m^3, which is the value which exceeds the National Ambient Air Quality Standards (NAAQS). "Yellow Action" days are defined by a 24 average $PM_{2.5}$ level ≥ 25.5 μg / m^3. Poor air quality testing days included those with 24 h average $PM_{2.5}$ level ≥ 35.5 μg / m^3, or 24 average $PM_{2.5}$ level ≥ 25.5 μg / m^3 with peak $PM_{2.5}$ ≥ 35.5 μg / m^3

with increased EBC NOx in participants with COPD (ratio of geometric means for pollution vs. clean air days 3.16, 95 % CI 1.41-7.04, $p = 0.007$) but not in control participants (ratio of geometric means 0.49, 95 % CI 0.14-1.65, $p = 0.23$) (Fig. 2, Table 3). The pollution effect on EBC NOx differed significantly between the COPD and control groups ($p = 0.01$) (Table 4). Conversely, PM pollution days were not significantly associated with changes in EBC 8-isoprostane in either group.

Clinical parameters

Respiratory symptoms were increased on PM pollution days compared with clean air days in COPD patients (difference in aggregate symptom score 3.47, CI 1.01 to 5.93, $p = 0.008$) but not in control subjects (difference in aggregate symptom score 2.02, CI -0.92 to 4.95, $p = 0.16$) Table 3). The pollution effects did not differ between the two groups ($p = 0.45$) (Table 4). The increase in aggregate symptom score in the COPD group appeared to be due to increases in all respiratory symptoms (Table 5). We did not detect a significant difference in pulmonary function between pollution and clean air days in the two groups (Figs. 3 and 4, Table 3).

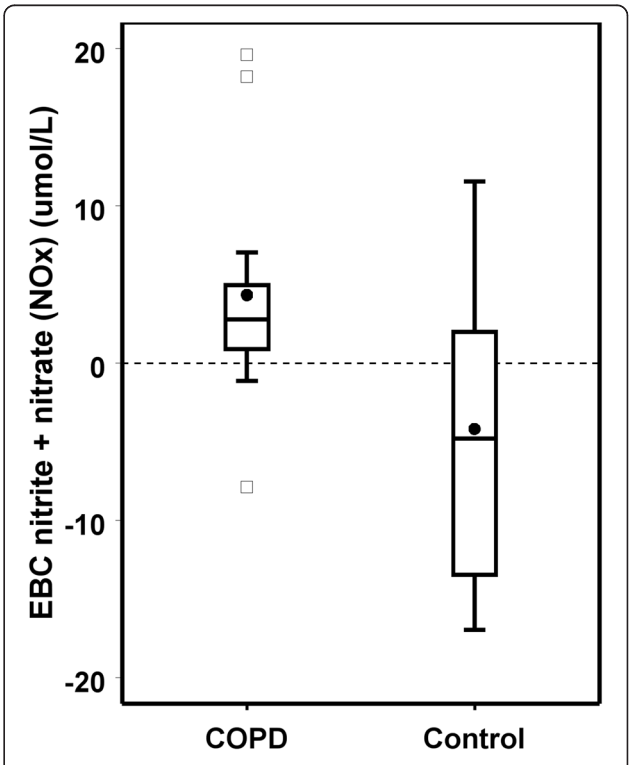

Fig. 2 Change in exhaled breath condensate (EBC) nitrite + nitrate (NOx) between pollution and clean air testing days. The value on the Y axis is the difference between pollution and clean air testing days. Schematic box-and-whiskers plots define values as the following: Interior boxes display 25th percentile, median, 75th percentile and mean (filled circle). Whiskers extend to most extreme data values within 1.5 IQR (interquartile range) from 25th and 75th percentiles. More extreme data values are indicated by open squares

Discussion

We found that in individuals with moderate to severe COPD, but not in former smokers without COPD, exposure to episodes of PM pollution was associated with an increase in NOx in exhaled breath condensate. Additionally, in the COPD group, respiratory symptoms

Table 3 Comparison of variables on pollution vs. clean air quality days

Variable	Group	Estimate[a]	95 % CI	*P* value
Nitrite + nitrate (NOx)	COPD	3.15	(1.41, 7.04)	0.007
	Control	0.49	(0.14, 1.65)	0.23
8-Isoprostane	COPD	0.44	(0.05, 3.61)	0.43
	Control	2.34	(0.18, 29.73)	0.49
FEV1 (L)	COPD	0.01	(-0.10, 0.12)	0.85
	Control	0.01	(-0.10, 0.11)	0.90
FVC (L)	COPD	−0.17	(-0.37, 0.03)	0.09
	Control	−0.01	(-0.12, 0.09)	0.80
Aggregate symptom score	COPD	3.47	(1.01, 5.93)	0.008
	Control	2.02	(-0.92, 4.95)	0.16

[a] Displayed are estimated ratios of geometric mean levels (with 95 % CIs and p-values) of 8-isoprostane and NOx between pollution and clean air days, as well as estimated mean differences (with 95 % CIs and p-values) in FEV1, FVC, and aggregate symptom score between pollution and clean air days in a) COPD patients and b) Control group participants

were increased during periods of elevated PM pollution compared with clean air days. We did not detect a change in pulmonary function in response to these pollution events. These findings support the hypothesis that environmental PM air pollution exposure results in increases in airway inflammation in individuals with COPD, which may translate into increased respiratory symptoms. This response may be a reflection of the underlying process resulting in COPD in these individuals.

To our knowledge, this study is the first to demonstrate an association of short-term air pollution exposure with increased EBC biomarkers of inflammation and increased respiratory symptoms in people with moderate to severe COPD in comparison to former smokers without COPD. In other studies, short term exposure to ambient air pollution has been associated with increased EBC markers of inflammation and oxidative stress in adults with more broadly defined chronic respiratory disease [28], healthy adults [27], and children with asthma [34, 35]. EBC is attractive as a window to the local environment in the peripheral lung because it is noninvasive and easily repeated. A number of different biomarkers have been described in EBC. We focused on total EBC concentrations of NOx and 8-isoprostane as validated measures of inflammation and local oxidative stress in the airways. Similar to the findings of Manney et al. [28] and Huang et al. [27], we detected an increase in EBC NOx in association with episodes of poor air quality. Unlike Huang et al., we did not detect a difference in 8-isoprostane, which may reflect a different pathophysiologic mechanism in individuals with COPD compared with healthy adults. This difference could be due to the much higher levels of ambient PM2.5 experienced in Beijing compared with Salt Lake Valley, or due to different composition of PM air pollution in Salt Lake Valley which consists of a greater proportion of nitrates compared with other areas [36]. These hypotheses warrant further investigation. Despite this difference in particulate composition, NOx in EBC is a marker of inflammation in the lung and is not simply a measure of increased nitrate in the ambient air, supported by the observation that control EBC NOx was not increased even during periods of significant pollution.

There are several important features of this pilot study. The predictable wide swings in ambient PM2.5 levels to well above the EPA National Ambient Air Quality Standards that occur in the Salt Lake Valley during wintertime temperature inversions offer a unique natural laboratory to study the effects of short-term air pollution exposure. Our measurement of biomarkers in exhaled breath condensate, in conjunction with respiratory symptoms and lung function, offers insight into the pathophysiology of observed clinical associations. Increased NOx in exhaled breath condensate suggests that exposure to particulate matter activates inflammatory pathways in the airways, and that this may be the mechanism for changes in respiratory health observed in numerous prior studies.

A key aspect of this study was the selection of former smokers for both the COPD and control groups. This choice avoided confounding effects of current cigarette use on parameters in EBC. It is known that acute exposure to cigarette smoke can induce oxidative stress in the lungs, reflected in changes in EBC parameters. However, these acute changes resolve quickly [26, 37]. All of our

Table 4 Comparison of estimated effects of pollution vs. clean air days between COPD and Control subjects

Variable	Estimate COPD vs Control	95 % CI	*P* value
EBC nitrite + nitrate (NOx)	6.34	(1.53, 26.17)	0.01
EBC 8-isoprostane	0.19	(0.01, 4.44)	0.29
FEV1 (L)	0.00	(-0.15, 0.16)	0.96
FVC (L)	−0.16	(-0.40, 0.08)	0.19
Aggregate symptom score	1.41	(-2.36, 5.18)	0.45

Displayed are the ratios of the geometric means (for 8-isoprostane and NOx) and the difference in the estimated pollution effects (for FEV1, FVC, and symptom score) which compare the estimated pollution effects between the COPD patients and Controls

Table 5 Percent of patients reporting worsening symptoms on pollution or clean air visits

	Control		COPD	
	Pollution days	Clean air days	Pollution days	Clean air days
Symptoms	% (n)	% (n)	% (n)	% (n)
Nasal congestion discharge	50.0 (6)	45.4 (5)	68.8 (11)	30.8 (4)
Activity limitation	25.0 (3)	0.0 (0)	62.5 (10)	30.8 (4)
Chest tightness	33.3 (4)	9.1 (1)	43.8 (7)	7.7 (1)
Cough	66.7 (8)	36.4 (4)	56.2 (9)	15.4 (2)
Shortness of breath	41.7 (5)	9.1 (1)	62.5 (10)	23.1 (3)
Sputum thickness	41.7 (5)	9.1 (1)	50.0 (8)	15.4 (2)
Sputum amount	41.7 (5)	18.2 (2)	56.2 (9)	30.8 (4)
Wheeze	0.0 (0)	9.1 (1)	37.5 (6)	15.4 (2)

Displayed are the number and percent of patients reporting worsening symptoms on at least one polluted air day and on at least one clean air day for the Control and COPD groups

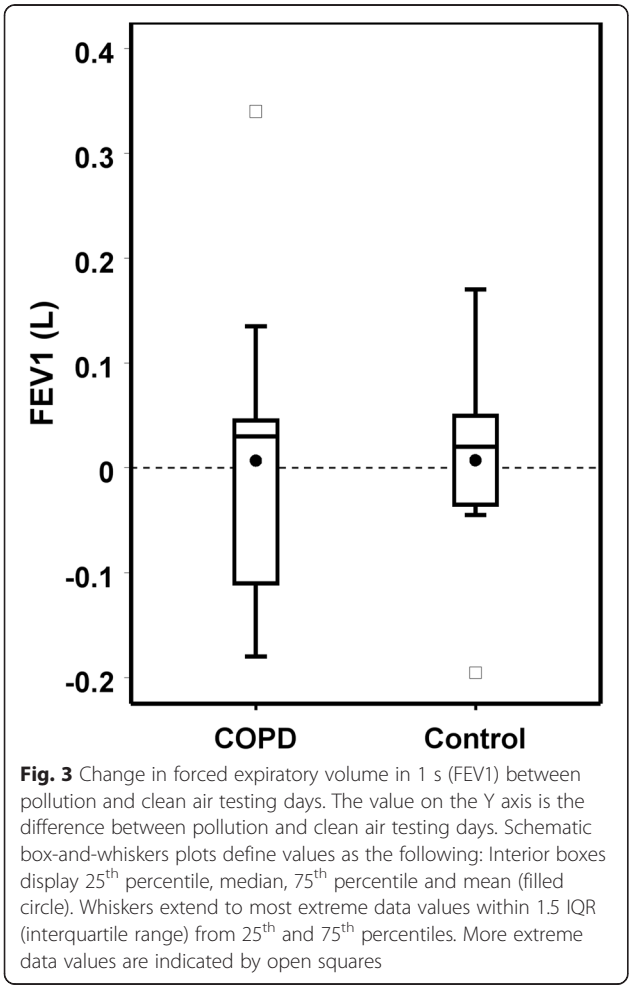

Fig. 3 Change in forced expiratory volume in 1 s (FEV1) between pollution and clean air testing days. The value on the Y axis is the difference between pollution and clean air testing days. Schematic box-and-whiskers plots define values as the following: Interior boxes display 25th percentile, median, 75th percentile and mean (filled circle). Whiskers extend to most extreme data values within 1.5 IQR (interquartile range) from 25th and 75th percentiles. More extreme data values are indicated by open squares

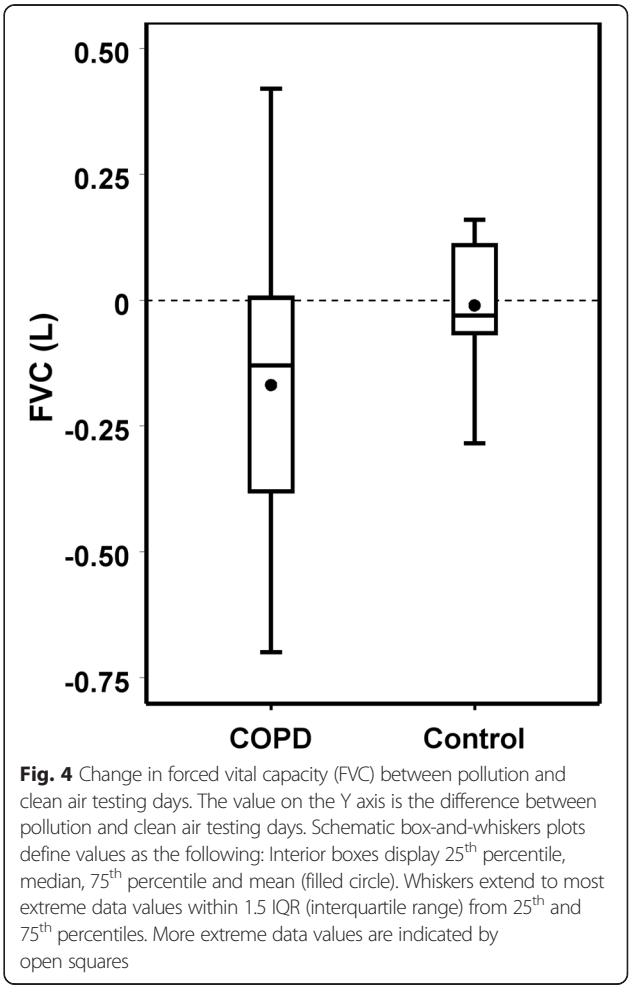

Fig. 4 Change in forced vital capacity (FVC) between pollution and clean air testing days. The value on the Y axis is the difference between pollution and clean air testing days. Schematic box-and-whiskers plots define values as the following: Interior boxes display 25th percentile, median, 75th percentile and mean (filled circle). Whiskers extend to most extreme data values within 1.5 IQR (interquartile range) from 25th and 75th percentiles. More extreme data values are indicated by open squares

subjects had stopped smoking at least 3 months prior to entry into this study; most had stopped smoking far longer than this. Studying former smokers also offered an opportunity to compare responses to air pollution between smokers who had developed COPD and those who had not. It remains unclear why only a minority of smokers develop clinically significant airflow obstruction. We found significant differences in airway inflammation induced by air pollution episodes between former smokers who had developed COPD and former smokers without airflow obstruction. Whether these differences in response to inhaled toxins are a reflection of the differing extent of tobacco smoke exposure between the two groups, host characteristics contributing to susceptibility to developing COPD, or are a consequence of the disease process will be the subject of further investigation.

Our results support the findings of prior studies showing an association of short term air pollution exposure with increased respiratory symptoms [8] in individuals with COPD. Recent work has shown decreased lung function in healthy adults exposed to moderate levels of air pollution [38]. However, in this study we were not able to detect a significant difference in lung function perhaps because our study may have been too small to detect smaller lung function changes. Additionally, exhaled breath NOx and respiratory symptoms may be more sensitive indicators of particulate effects than pulmonary function.

There are several limitations to this study. We studied a small number of Caucasian, middle and older aged adults in a single small geographic area. Due to the small sample size, confidence limits for comparisons of comparisons of pollution vs. clean air days were wide, reflecting limited statistical power, and we are not able to rule out undetected effects in cases where comparisons were not statistically significant. The mixed effects analyses applied in this study were able to incorporate all available information from patients who had different numbers of measurements on pollution and clean air days, but the imbalances in the numbers of visits between the two types of days further limited statistical power. The control and COPD groups differed in extent of smoking history, therefore we cannot exclude an effect of smoking history alone on the differing response to particulate air pollution. Personal pollution exposure was estimated based on average PM2.5 level from a central measuring station in the valley, rather than by personal monitoring. This is an imperfect measurement of individual exposure due to individual variability in time spent indoors and geographical variations in ambient pollutant levels. Many individuals with COPD spend less time outdoors during periods of poor air quality, thus our results likely underestimate the true effect of exposure to high PM2.5 levels. We did not assess for association with specific levels of PM2.5, but rather extremes above the EPA National Ambient Air Quality Standards, excluding days with PM2.5 in the low moderate range. Similarly, we did not specifically address other criteria pollutants, temperature or other weather effects which could have also had an effect on airway inflammation. However, peak levels of other criteria pollutants remained well below the EPA NAAQS during the period of our study. The geography of the Salt Lake valley and the pattern of weather inversions results in relatively homogenous PM pollution exposure for those living in this valley. EPA thresholds are defined based on ambient particulate pollution levels found to have health effects in epidemiologic studies, suggesting that these levels are indicative of overall exposure, despite variation in time spent in doors or out of doors. PM2.5 is the primary air pollutant during the wintertime inversions and our indicators do reflect the real-life conditions experienced by residents in the Salt Lake Valley.

We speculate that episodes of short-term elevated ambient air pollution may function as informative stress tests for these individuals. Beyond the possibility that the changes in airway inflammation associated with pollution episodes might be an indication of the potential for these episodes to provoke acute exacerbations of COPD in susceptible individuals, they may also reflect the vulnerability of COPD subjects to ongoing airway inflammation in response to other nonspecific triggers. Exuberant responses to relatively modest inflammatory stimuli such as air pollution events may be a key feature in the pathobiology of COPD. Future larger studies may be able to identify a subsets of individuals with COPD who have exaggerated response to air pollution events. This may help us understand why some patients with COPD are more susceptible to exacerbations or experience more rapid decline in pulmonary function with their disease. It may also provide insights into targets to interrupt this progression.

Conclusions

In summary, the results of this study provide insight into the mechanisms involved in the relationship between air pollution and respiratory disease. We found that former smokers with airflow obstruction, but not those without, developed airway inflammation and respiratory symptoms in association with PM air pollution episodes. Air pollution induced inflammation may impact progression of COPD or development of acute exacerbations of COPD.

Abbreviations

COPD: Chronic obstructive pulmonary disease; $PM_{2.5}$: Particulate matter less than 2.5 microns in diameter; NOx: Nitrite + nitrate; EBC: Exhaled breath condensate; EPA: Environmental Protection Agency; NAAQS: National Ambient Air Quality Standards; SD: Standard deviation; NO_2: Nitrogen dioxide; SO_2: Sulfur dioxide; CO: Carbon monoxide.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
The study was conceived by CP, AS, MBS, RK and RP. It was conducted by CP, AS, PC, SW, HH, and JB. Data were analyzed by HW and TG. The manuscript was prepared by CP, HW, TG, and RP. Critical revision of the manuscript was provided by HW, TG, MBS, and RK. CP and RP were responsible for the overall content of the manuscript as guarantors. All authors read and approved the final manuscript.

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