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2016 Environ. Res. Lett. 11 074014

(http://iopscience.iop.org/1748-9326/11/7/074014)

Environmental Research Letters

LETTER

Combined atmospheric oxidant capacity and increased levels of exhaled nitric oxide

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Keywords: nitrogen dioxide, ozone, combined oxidant capacity, fractional exhaled nitric oxide, panel study

OPEN ACCESS

RECEIVED
26 January 2016

REVISED
19 June 2016

ACCEPTED FOR PUBLICATION
27 June 2016

PUBLISHED
11 July 2016

Abstract

Nitrogen dioxide and ozone are two interrelated oxidative pollutants in the atmosphere. Few studies have evaluated the health effects of combined oxidant capacity (O_x). We investigated the short-term effects of O_x on fractional exhaled nitric oxide (FeNO), a well-established biomarker for airway inflammation, in a group of chronic obstructive pulmonary disease patients. Real-time concentrations of O_x were obtained by calculating directly the sum of nitrogen dioxide and ozone. Linear mixed-effect models were applied to explore the acute effects of O_x on FeNO levels. Short-term exposure to O_x was significantly associated with elevated FeNO. This effect was strongest in the first 24 h after exposure, and was robust to the adjustment of $PM_{2.5}$. A 10 $\mu g\ m^{-3}$ increase in 24 h average concentrations of O_x was associated with 4.28% (95% confidence interval: 1.19%, 7.37%) increase in FeNO. The effect estimates were statistically significant only among males, elders, and those with body mass index $\geqslant$24 $kg\ m^{-2}$, a comorbidity, higher educational attainment, or moderate airflow limitation. This analysis demonstrated an independent effect of O_x on respiratory inflammation, and suggested that a single metric O_x might serve as a preferable indicator of atmospheric oxidative capacity in further air pollution epidemiological studies.

Introduction

Nitrogen dioxide (NO_2) and ozone (O_3) are commonly known as oxidative and irritant atmospheric pollutants. Previous epidemiological studies have reported their significant associations with adverse respiratory outcomes (Bell *et al* 2005, Samoli *et al* 2006, Chen *et al* 2012b). The inhalation of NO_2 and O_3 may lead to airway inflammation and high responsiveness due to their strong oxidizing properties, which mainly contribute to their hazardous effects on the human respiratory system (Dadvand *et al* 2014).

Epidemiological studies typically evaluated the associations between NO_2 or O_3 and a health outcome using single-pollutant or bi-pollutant regression models (Chen *et al* 2012b, Peng *et al* 2013). However, the explanation of the epidemiological findings was problematic due to the inextricably chemical conjunction between O_3 and NO_x (=NO + NO_2) (Clapp and Jenkin 2001). They can also interchange over a timescale from minutes to days dependent on a number of factors such as photochemical reactions (Ghazali *et al* 2010). Furthermore, any resultant reduction in NO_2 is invariably but not linearly accompanied by an increase in O_3 (Clapp and Jenkin 2001). Consequently, the existing epidemiological results of NO_2 and O_3 were largely limited by the complex collinearity and confounding from each other.

The term 'combined atmospheric oxidant capacity' (O_x) was naturally developed by denoting O_x as the sum of NO_2 and O_3 because the sum and its oxidizability was largely constant in a certain timescale (Clapp and Jenkin 2001). Few studies have assessed the

use of O_x in exploring the association between air pollution and heath endpoints. Only two time-series studies have considered O_x in the associations with daily hospital admissions for respiratory diseases (Chardon *et al* 2007) and with daily all-cause mortality (Williams *et al* 2014). However, bias was inevitable in the two investigations because of the ecological nature in design. Besides, it was unknown whether the associations remained when the potentially confounding effects of $PM_{2.5}$ were controlled. Furthermore, the underlying mechanisms were also not clear about the observed associations of O_x exposure with respiratory hospital admissions and mortality.

We therefore designed a longitudinal panel study to explore the effects of O_x on respiratory inflammation in a group of patients with chronic obstructive pulmonary disease (COPD) in Shanghai, China. Respiratory inflammation was evaluated using fractional exhaled nitric oxide (FeNO), a non-invasive biomarker commonly used in previous studies (Liu *et al* 2009, 2011, Malerba *et al* 2014).

Material and methods

Study design

In this study, we initially recruited 30 retired COPD patients from a central urban community (1.9 km^2 in area) in Shanghai, China. The inclusion criteria included: (1) doctor-diagnosed COPD based on the results of spirometry; (2) local residents who lived in this Community for at least 3 years; and (3) retirees aged more than 40 years. We excluded those who were currently active or passive smokers (at home); consumed any alcohol; had severe comorbidities or inflammatory diseases; and had received antibiotic treatments during the past month. We further excluded those patients with unstable and severe COPD in this study to reduce the influence of respiratory medication on our results. Subjects who took anti-inflammatory medications during follow-ups would be excluded from final analyses.

From 27th May to 5th July, 2014, we scheduled six repeated follow-ups every week. The subjects were randomly divided into three subgroups and were invited to participate in FeNO examinations on Tuesday, Thursday or Saturday, respectively at the Community Health Service Center. For each patient, examinations were scheduled at the same time (1:30 p.m. to 2:30 p.m.) on the same day of the week to control for potential circadian rhythms and day-of-week variations in FeNO levels (Spanier *et al* 2008). Self-administered questionnaires were applied to collect individual baseline information including residential address, age, gender, height, weight, educational status, duration of COPD and chronic comorbidities. Spirometry was performed at baseline to assess the severity of airflow limitation in these COPD patients, according to the Global initiative for Chronic Obstructive Lung Disease guidelines (Vestbo *et al* 2013). These subjects were also asked to record any COPD symptoms and medications, and whether they left the central urban areas of Shanghai during the entire study period. This study was approved by the Institutional Review Board of the School of Public Health, Fudan University. Written consent forms were obtained from all subjects.

FeNO measurements

FeNO levels were measured with a portable NIOX MINO machine (Aerocrine AB, Solna, Sweden) according to the standardized procedures issued by the American Thoracic Society and the European Respiratory Society (Dweik *et al* 2011). Briefly, subjects were asked to avoid eating and drinking for at least 1 h before examinations. They were instructed to inhale from the machine as fully as they can and then exhale into the machine for 10 s without a break. A visible indicator was shown during exhalation to help subjects maintain a constant flow rate of 50 ml s^{-1}. At last, the results would display automatically after a 90 s interval. The quality control was autonomically performed and it would not display a reading once the subject exhaled below or above the required speed of flow rate.

Environmental data

We obtained the hourly data on NO_2 and O_3 from a nearby government-controlled monitoring station that was approximately 3 km away from this community. This station was not in the direct vicinity of major air pollution sources including traffic. We calculated O_x as the sum of real-time concentrations on NO_2 and O_3. In order to allow for the adjustment of potential confounding of other environmental variables, we also collected the hourly concentrations of particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) from the same fixed-site station and weather data (mean temperature and mean relative humidity) from a meteorological station that was 5 km away from the community. The concentrations of $PM_{2.5}$, NO_2 and O_3 were measured using the methods based on tapered element oscillating microbalance, chemiluminescence and ultraviolet absorption, respectively.

Statistical analysis

Environmental and individual health data were linked by the time of physical examinations. FeNO levels were natural log-transformed before statistical analyses because they were approximately right-skewed distributed.

We applied linear mixed-effect models to examine the associations between air pollutants and FeNO. In the basic model, FeNO was a dependent term, and O_x was introduced as an independent fixed-effect term. Several covariates were also incorporated as fixed-effect terms: (1) an indicator variable for 'week' to adjust for any unknown weekly time trends in FeNO

Table 1. Summary statistics of FeNO measurements, 24 h average air pollution levels and meteorological conditions.

Variables	Mean	SD	Min	P25	Median	P75	Max
FeNO (ppb)	24.4	23.2	5.0	12	17.0	23.0	122.0
NO_2 ($\mu g\ m^{-3}$)	47.2	13.2	28.3	36.7	42.9	59.2	70.0
O_3 ($\mu g\ m^{-3}$)	82.4	30.4	29.9	62.5	75.9	103.7	143.5
O_x ($\mu g\ m^{-3}$)	129.6	34.0	89.9	109.5	117.4	150.1	211.2
$PM_{2.5}$ ($\mu g\ m^{-3}$)	56.1	30.8	11.9	35.2	47.0	61.7	147.3
Temperature (°C)	23.8	1.6	21.5	22.2	23.3	25.5	27.2
Relative humidity (%)	71.7	12.7	43.0	66.0	72.0	83.0	90.0

Abbreviations: SD, standard deviations; FeNO, fractional exhaled nitric oxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; $O_x = NO_2 + O_3$.

levels; (2) an indicator variable for 'day of the week' to exclude any unknown variations in FeNO levels within a week; (3) mean temperature and relative humidity on the concurrent day to adjust for the confounding effects of meteorological conditions; and (4) individual characteristics, including age, sex, body mass index. We did not further adjust for educational attainment, duration of COPD and prevalence of a chronic comorbidity (hypertension, coronary heart disease, diabetes,) because the model fit statistic was not further improved, characterized by smaller Akaike information criterion (AIC) (Akaike 1973). At last, we included a random intercept for each subject to account for the autocorrelations among repeated FeNO measurements.

To fully explore the time windows for the short-term effects of O_x on FeNO, we evaluated the models using multiple lag periods of O_x exposure preceding FeNO measurements, i.e., single lags of 0–6 h (h), 7–12 h, 13–24 h, 0–24 h (0 d), 25–48 h (1 d) and 49–72 h (2 d). We did not explore lags longer than 72 h because most previous studies found that the short-term effects of air pollution on respiratory outcomes were limited in the first 3 days after exposure (Dominici *et al* 2006, Williams *et al* 2014, Chen *et al* 2015).

To compare the individual effects of NO_2 and O_3 with combined O_x, we fitted the same models as described above for NO_2 and O_3, and further evaluated the mode fit based on the AIC statistic (Akaike 1973).

As a sensitivity analysis, we fitted two-pollutant models to evaluate whether the effects of O_x were sensitive to the adjustment of $PM_{2.5}$, another source of atmospheric oxidative activity.

At last, in order to explore the potential effect modification of individual characteristics, we further performed stratification analyses by sex, age (<65 and $\geqslant 65$), BMI (<24 and $\geqslant 24\ kg\ m^{-2}$), educational status (low: illiteracy, primary school and junior middle school; high: senior middle school and above), presence of comorbidities (hypertension, coronary heart disease or diabetes) and severity of COPD (mild and moderate).

Statistical tests were two-sided, and the effects of p-values $\leqslant 0.05$ were considered to be statistically significant. All analyses were performed in R software (Version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria) with the 'lme4' package. The effect estimates were presented as the percent change and their 95% confidence intervals (95% CI) associated with a 10 $\mu g\ m^{-3}$ increase of air pollutant concentrations.

Results

Descriptive statistics

Two subjects were excluded from the analysis because they took anti-inflammatory medications during follow-ups. The descriptive statistics on individual characteristics of the remaining 28 subjects were shown in a previous publication of this project (Chen *et al* 2015). According to the results from self-administered questionnaires, they did not go out of the central urban area of Shanghai, have an exacerbation of COPD or take anti-COPD medication during the study period. Based on the results of spirometry at baseline, there were 12 mild and 16 moderate COPD patients.

Table 1 shows the summary statistics of FeNO measurements, 24 h averages of air pollutant concentrations and meteorological variables preceding each follow-up visit. In total, we obtained 168 valid measurements of FeNO. The mean level of FeNO is 24.4 ppb with apparent variations (standard deviation: 23.2 ppb). During the study period, the averaged 24 h mean concentrations for NO_2, O_3, O_x and $PM_{2.5}$ are 47.2 $\mu g\ m^{-3}$, 82.4 $\mu g\ m^{-3}$, 129.6 $\mu g\ m^{-3}$ and 56.1 $\mu g\ m^{-3}$, respectively. The daily mean temperature and relative humidity are 23.8 °C and 71.7%, respectively. There are no missing data in our study.

Table 2 shows the spearman correlation coefficients among environmental variables. Generally, the 24 h average concentrations of O_x are more strongly correlated with O_3 than with NO_2. O_x is moderately positively correlated with $PM_{2.5}$, moderately positively correlated with temperature and weakly negatively correlated with relative humidity. There were moderate or strong correlations of FeNO ($r = 0.44$–0.92) among the subgroups with male sex, older age, higher

Table 2. Spearman correlation coefficients among environmental variables.

	NO_2	O_3	O_x	$PM_{2.5}$	Temperature
NO_2	1				
O_3	−0.06	1			
O_x	0.26[a]	0.90[a]	1		
$PM_{2.5}$	0.70[a]	0.45[a]	0.65[a]	1	
Temperature	0.46[a]	0.41[a]	0.53[a]	0.65[a]	1
Humidity	−0.23[a]	−0.67[a]	−0.71[a]	−0.68[a]	−0.58[a]

[a] $p < 0.05$.

Table 3. Percent changes in FeNO (mean and 95% confidence interval) associated with a 10 $\mu g\ m^{-3}$ increase in O_x using different lag structures, with or without adjustment of $PM_{2.5}$.

Lag structure	Without adjustment	Adjustment
0–6 h	2.51 (−0.30, 5.32)	3.74 (0.84, 6.64)[a]
7–12 h	2.86 (−0.39, 6.11)	4.00 (0.38, 7.64)[a]
13–24 h	3.09 (0.72, 5.46)[a]	2.76 (0.29, 5.23)[a]
0 d	4.28 (1.19, 7.37)[a]	4.27 (1.16, 7.39)[a]
1 d	2.44 (−0.52, 5.42)	3.19 (−3.02, 9.44)
2 d	−1.50 (−6.23, 3.25)	−1.51 (−6.84, 3.84)

Abbreviations: FeNO, fractional exhaled nitric oxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; $O_x = NO_2 + O_3$.
[a] $p < 0.05$.

BMI, the prevalence of comorbidity and higher educational status.

Regression results

Table 3 provides the associations between O_x and FeNO using different lag periods. The associations are statistically significant within the first 24 h after exposure with the strongest effects occurring in the sub-period of 13–24 h. Then, the associations attenuate substantially and turn to be non-significant from lag 0 d to 2 d. For example, FeNO increase by 4.28% (95%CI: 1.19%, 7.37%) corresponding to a 10 $\mu g\ m^{-3}$ increase in 24 h average concentrations of O_x.

Table 3 also shows the results of sensitivity analyses after adjusting for $PM_{2.5}$. In comparison with the unadjusted results, the adjusted estimate increases and turned to be statistically significant within the first 12 h after exposure; it is quite similar using the 24 h averaged exposure; it remains non-significant on lag 1 or 2 days.

The effects of O_3 and NO_2 are not statistically significant at almost all lags using single-pollutant models, but increase substantially and become significant in the first 24 h when adjusting for each other (table 4). The AIC values obtained in single-pollutant models with O_x is smaller than with NO_2 and O_3 (i.e., 139.6 versus 143.4 and 143.4, respectively, for 24 h averages). The values are also obviously lower than those obtained in two-pollutant models with NO_2 and O_3.

Figure 1 illustrates the effects of 24 h average O_x on FeNO levels in different subgroups. The effect estimates were statistically significant only among males, elders, and those with body mass index $\geqslant$24 kg m^{-2}, a comorbidity, higher educational attainment, or moderate airflow limitation.

Discussion

In this panel study among COPD patients, we found significant evidence of positive associations between short-term exposure to O_x and increased levels of FeNO in Shanghai, China. This effect was strongest in the first 24 h after exposure, and robust to the adjustment of $PM_{2.5}$. Furthermore, males, elders, and those with body mass index $\geqslant$24 kg m^{-2}, a comorbidity, higher educational attainment, or moderate airflow limitation were more susceptible. To our best knowledge, this analysis was the first epidemiological study to investigate the impact of combined atmospheric oxidant capacity on FeNO, a well-established indicator of respiratory inflammation.

Oxidative stress was believed to be one of the main pathways through which air pollutants affect human health (Brook *et al* 2010). Oxidative activity of air pollutants can lead to the generation of reactive oxygen species upon the interaction with epithelial cells and macrophages, resulting in systematic inflammatory responses and oxidative injuries. NO_2 and O_3 were both key oxidative gaseous pollutants. Their strong chemical interrelationship that vary in direction and magnitude by different spatial-temporal scales made it difficult to separate their individual effects (Williams *et al* 2014). O_x is thus introduced in atmospheric chemistry to represent the combined oxidative capacity of NO_2 and O_3. It has the advantage of characterizing well the combined oxidative stress on the exposed population from simultaneous exposure to the two pollutants. This seems to be supported by our findings that the use of O_x could generate stronger or more precise risk estimates as well as better model fit than O_3 or NO_2.

Another support for the use of O_x as a single metric for airborne oxidative capacity may originate from the problems associated with single- or two- pollutant models. A number of previous studies have found the significant associations between short-term exposure to photochemical pollutants (NO_2 and O_3) and respiratory outcomes, but only a few of them considered NO_2 and O_3 jointly (Saez *et al* 2002, Gryparis

Table 4. Percent changes in FeNO (mean and 95% confidence interval) associated with a 10 $\mu g\ m^{-3}$ increase in O_3 and NO_2 in single- or two- pollutant models.

	O_3		NO_2	
Lag	—	$+NO_2$	—	$+O_3$
0–6 h	2.38 (−1.81, 6.60)	0.40 (−4.29, 5.11)	6.16 (0.34, 12.02)[a]	5.89 (−0.78, 12.60)
7–12 h	1.00 (−1.21, 3.22)	4.88 (1.05, 8.73)[a]	1.39 (−3.48, 6.28)	10.30 (1.86, 18.81)[a]
13–24 h	1.78 (−0.16, 3.73)	4.55 (1.91, 7.19)[a]	2.00 (−4.18, 8.21)	12.10 (3.85, 20.41)[a]
25–48 h	2.70 (−0.89, 6.30)	2.24 (−1.60, 6.09)	5.08 (−3.7, 13.95)	3.19 (−6.13, 12.60)
49–72 h	−2.14 (−7.32, 3.07)	−2.21 (−7.67, 3.27)	0.47 (−5.80, 6.78)	−0.31 (−6.87, 6.30)
0 d	2.69 (−0.15, 5.54)	4.38 (1.31, 7.45)[a]	4.56 (−2.58, 11.76)	9.40 (1.78, 17.08)[a]
0–1 d	2.90 (−0.41, 6.22)	3.46 (0.15, 6.78)[a]	7.10 (−2.44, 16.73)	8.88 (−0.60, 18.46)
0–2 d	5.80 (−0.38, 12.03)	5.18 (−1.47, 11.87)	5.83 (−4.34, 16.11)	2.84 (−7.90, 13.70)

Abbreviations: FeNO, fractional exhaled nitric oxide; NO_2, nitrogen dioxide; O_3, ozone.
[a] $P < 0.05$.

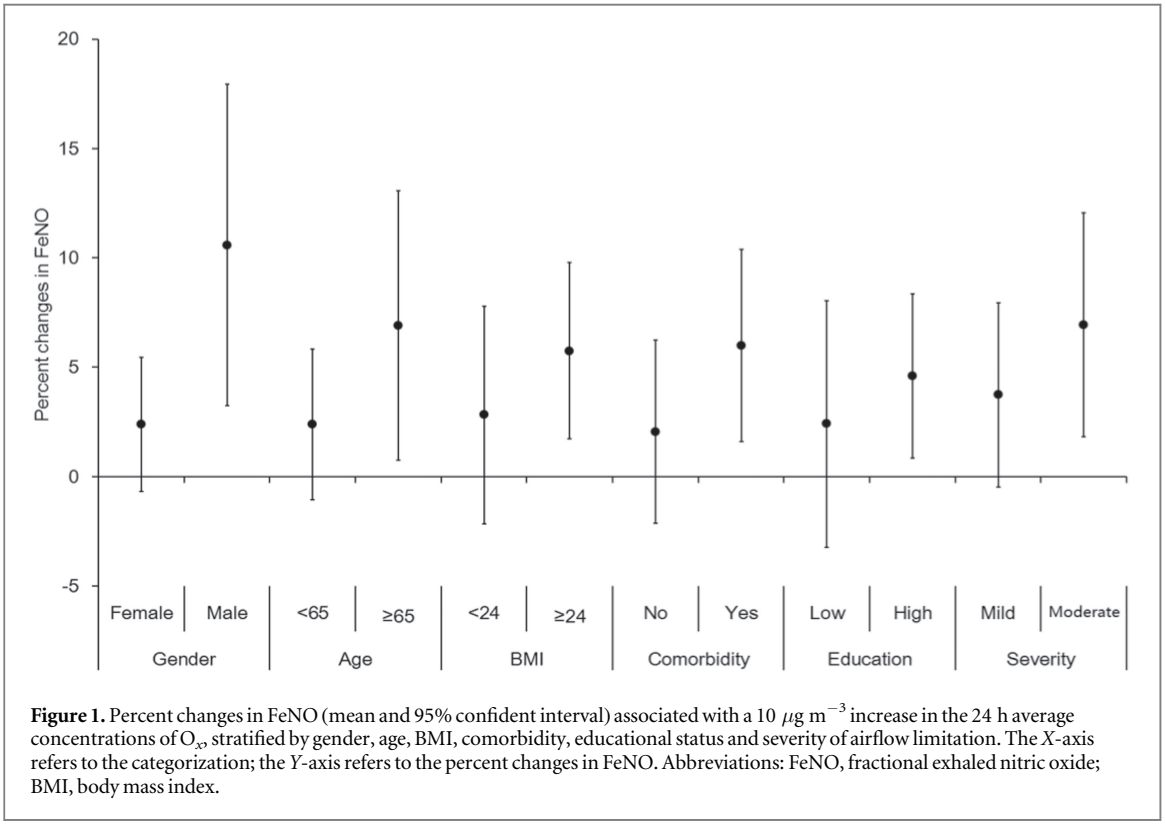

Figure 1. Percent changes in FeNO (mean and 95% confident interval) associated with a 10 $\mu g\ m^{-3}$ increase in the 24 h average concentrations of O_x, stratified by gender, age, BMI, comorbidity, educational status and severity of airflow limitation. The *X*-axis refers to the categorization; the *Y*-axis refers to the percent changes in FeNO. Abbreviations: FeNO, fractional exhaled nitric oxide; BMI, body mass index.

et al 2004, Samoli *et al* 2006). We reported larger increases in both risk estimates when the two pollutants were assessed simultaneously in bi-pollutant models than in single-pollutant models. The larger effect estimates was consistent with a previous investigation based on daily mortality (Williams *et al* 2014). However, interpretation of the results from two-pollutant models was problematic because of the different magnitude of exposure measurement errors and uncertain linear assumptions about the concentration-response functions (Kim *et al* 2007, Baxter *et al* 2010). Besides, double-counting in risk estimates may also occur when evaluating NO_2 and O_3 separately or jointly.

Atmospheric oxidative agents mainly comprised particulate matter, NO_2 and O_3. PM oxidative potential has also been recognized in several cell assays and epidemiological studies (Delfino *et al* 2013, Liu *et al* 2014, Kelly and Fussell 2015). However, few previous studies have evaluated whether the observed effects of O_x were dependent on the simultaneous exposure to $PM_{2.5}$. In this study, the association between O_x and FeNO was robust to the adjustment of $PM_{2.5}$, suggesting the oxidative effects of O_x on respiratory system might be independent of $PM_{2.5}$. Nevertheless, confirming the independent effects of O_x requires additional investigations.

We reported a significant increase of 4.18% in FeNO levels associated with a 10 $\mu g\ m^{-3}$ elevation in O_x among COPD patients. FeNO is a well-established biomarker of respiratory inflammation in both clinical practice and epidemiological studies (Lin *et al* 2011,

Malerba *et al* 2014). FeNO is predominantly produced in airway epithelial cells by inducible nitrogen monoxide synthase. This synthase can be activated by proinflammatory cytokines, reactive oxygen species or hypomethylation of the synthase gene, which may be stimulated by the inhalation of exogenous oxidants (Chen *et al* 2015). Elevated FeNO levels corresponded to higher levels of inflammatory response, which played important roles in the development and exacerbation of COPD. Our findings on FeNO supported previous epidemiological results on the associations between O_x (including NO_2, O_3) and daily mortality (Chardon *et al* 2007, Williams *et al* 2014).

Few previous studies have examined the modifications by age, sex, BMI, educational, comorbidities and disease severity in the O_x-mediated health effects. In this study, high responsiveness among males may be explained by the reduced exposure measurement error due to more outdoor activities, or simply by the incomparable statistical power between the male and female group. The susceptibility of elders may be due to their relatively frail physique, airway hyper-responsiveness and higher prevalence of chronic comorbidities (Chen *et al* 2012a). Obese people may have a chronic inflammation state, and a higher prevalence of chronic comorbidities (Li *et al* 2016), thus they are sensitive to the inflammatory response triggered by O_x (Lu *et al* 2013). Higher effects in subjects with high educational attainment might be explained by higher average BMI than those with low educational attainment (e.g. 24 kg m^{-2} versus 23 kg m^{-2} in this study). The larger effects observed in those having worse airflow capacity and in those with comorbidity might be due to their intrinsic vulnerability to external toxics.

This study has several strengths. First, this was a longitudinal panel study which allowed us to control for potential individual confounders including age, sex, BMI (Olin *et al* 2006). Second, COPD patients who were sensitive to air pollution were recruited in this study. Third, FeNO were repeatedly measured at the same daytime once a week within 6 weeks to avoid any unknown time-varying patterns, such as the diurnal rhythm and inherent seasonality (Spanier *et al* 2008).

The limitations of our study should be also addressed. First, as in most of previous studies, exposure measurement errors are still inevitable because we obtained data from a nearby fixed-site monitor rather than personal measurements. However, we did not think that the errors had led to substantial bias on our findings because the distance between the fixed-site monitor and the community was reasonable (about 3 km) and all the subjects were retirees who may share similar time-location patterns. Second, the sample size in our study is relatively small, which may add uncertainty to our results on main analyses and stratification analyses. Third, the generalizability of our results is limited because our subjects are COPD patients and most of them are females.

In summary, this analysis demonstrated an independent effect of O_x on respiratory inflammation among COPD patients. Our results also suggested that a single metric O_x might serve as a preferable indicator of atmospheric oxidative capacity in further air pollution epidemiological studies. Further work is still needed to confirm our findings using larger sample size and more health outcomes.

Acknowledgments

The study was supported by the Public Welfare Research Program of National Health and Family Planning Commission of China (201502003 and 201402022), National Natural Science Foundation of China (81502774 and 81502775), and China Medical Board Collaborating Program (13-152).

Conflict of interest

The authors declared no conflicts of interests.

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