Environmental Research 212 (2022) 113379

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Associations between outdoor air pollution, ambient temperature and fraction of exhaled nitric oxide (FeNO) in university students in northern China - A panel study

Zefei Zhang [a,b], Huilin Zhang [b], Liu Yang [b], Xingyi Chen [b], Dan Norbäck [b,c,*], Xin Zhang [a,b,**]

[a] *Guangdong Key Laboratory of Environmental Catalysis and Health Risk Control, School of Environmental Science and Engineering, Institute of Environmental Health and Pollution Control, Guangdong University of Technology, Guangzhou, China*
[b] *Institute of Environmental Science, Shanxi Laboratory for Yellow River, Shanxi University, Taiyuan, China*
[c] *Department of Medical Sciences, Uppsala University, Uppsala, Sweden*

ARTICLE INFO

Keywords:
FeNO
Air pollution
Panel study
University students
PM2.5
China

ABSTRACT

Background: Northern China has severe air pollution, especially in winter. Fractional exhaled nitric oxide (FeNO) is an established biomarker of airway inflammation.
Aim: To study associations between ambient temperature, air pollution and FeNO in university students in northern China.
Methods: We performed a panel study in 67 university students without asthma diagnosis in the city of Taiyuan. FeNO was measured 6 times, over one heating season. Outdoor PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3 were measured at a fixed location in the campus. SO_2, NO_2 and O_3 were measured 7 days (24 h/day) before the FeNO test. $PM_{2.5}$ and PM_{10} were measured at different lag times (lag 1 day to lag 7 days). Temperature and carbon monoxide (CO) data were collected from a nearby monitoring station (lag 7). Linear mixed models were applied to study associations between exposure and FeNO, adjusting for gender, age, current smoking, height and furry pet or pollen allergy.
Results: The overall geometric mean (GM) of FeNO was 17.2 ppb. GM of FeNO was lowest (12.9 ppb) in January and highest (20.0 ppb) in April. The range of lag 7 pollution was 105.0–339.0 $\mu g/m^3$ for PM_{10}, 72.0–180.0 $\mu g/m^3$ for $PM_{2.5}$, 36.0–347.0 $\mu g/m^3$ for SO_2, 26.0–69.0 $\mu g/m^3$ for NO_2, 31.0–163.0 $\mu g/m^3$ for O_3 and 0.93–3.14 mg/m^3 for CO. The lag 7 temperature ranged from −4.5 to 20.1 °C. FeNO was consistently higher at higher outdoor temperature ($p < 0.001$). In multi-pollutant models with temperature adjustment, PM_{10}, $PM_{2.5}$ and SO_2 were associated with FeNO (all p-values <0.001). In contrast, CO was negatively associated (protective) with FeNO ($p < 0.001$). Associations between exposure and FeNO were similar in men and women.
Conclusion: PM_{10}, $PM_{2.5}$ and SO_2 and outdoor temperature can be associated with airway inflammation, measured as FeNO, in young adults in northern China while CO could be negatively associated with FeNO.

1. Introduction

Outdoor air pollution contributes substantially to disease development in many countries. The global burden of disease study from 2017 concluded that globally, over half of all deaths caused by outdoor air pollution (4.2 million deaths per year) are deaths from respiratory diseases (Stanaway et al., 2018). Asthma is a common respiratory disease, with a prevalence of 6–12% in adults in developed countries (Lundback et al., 2016). Asthma has increased globally, especially in the younger generation (Asher et al., 2006). China has severe problems with outdoor air pollution causing chronic respiratory illnesses (Lu et al., 2015; Guan et al., 2016) and childhood asthma has increased in China in the past decades (Li et al., 2020). Asthma is an inflammatory respiratory disease and airway inflammation is one possible mechanism behind respiratory effects of outdoor air pollution (Delfino et al., 2013).

Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker of T-helper 2 (TH2) driven airway inflammation and can be used as a biomarker of ongoing asthma (Alving and Malinovschi, 2010; Dweik

---

* Corresponding author. Institute of Environmental Science, Shanxi University, Taiyuan, China.
** Corresponding author. Institute of Environmental Science, Shanxi University, Taiyuan, China.
E-mail addresses: dan.norback@medsci.uu.se (D. Norbäck), xinzhang0051@sxu.edu.cn (X. Zhang).

https://doi.org/10.1016/j.envres.2022.113379
Received 6 October 2021; Received in revised form 31 March 2022; Accepted 25 April 2022

et al., 2011). Demographic variables influencing FeNO include gender, age, height, smoking and immediate type allergies (Alving and Malinovschi, 2010; Dweik et al., 2011). Panel studies measuring short-term changes of respiratory health biomarkers are suitable to understand the mechanisms behind respiratory health effects of air pollution. One recent meta-analysis of panel studies on associations between FeNO and outdoor air pollution (PM_{10}, $PM_{2.5}$, black carbon (BC), SO_2, NO_2 and O_3) was published recently (Chen et al., 2020). The review included 27 panel studies and combined risk estimates for children, adults, healthy subjects and subjects with chronic diseases. Only seven of the included panel studies were on healthy adults or adults from the general population. All seven studies found significant associations between outdoor $PM_{2.5}$ and FeNO (Adar et al., 2007; Adamkiewicz et al., 2004; Fan et al., 2018; Gong et al., 2014; Zhang et al., 2016, 2019; Zhao et al., 2016). However, only one of the studies reported significant associations between FeNO and PM_{10}, SO_2 and NO_2 in healthy adults (Zhao et al., 2016). Moreover, only one included study found an association between O_3 and FeNO in healthy adults (Day et al., 2017). Carbon dioxide (CO) was not included in the review, but panel studies on associations between CO and FeNO have found different results. Two studies found a positive association between CO and FeNO Zhang et al., 2013a, b; Yao et al., 2021) while another study found a negative (protective) effect of CO on FeNO (Zhao et al., 2016). Thus, there is a need for more panel studies on associations between outdoor air pollution and FeNO in healthy adults, especially for other types of pollutants than $PM_{2.5}$.

Taiyuan, the capital of Shanxi Province, has previously been one of the most heavily polluted cities in China, due to coal burning in the cold season (Xia et al., 2013). Despite this coal-related air pollution, we found lower FeNO levels in school children in Taiyuan as compared to Shanghai in a cross-sectional study (Zhao et al., 2013). However, in another cross-sectional study we found an association between $PM_{2.5}$ inside and outside day care centers in Taiyuan and FeNO in pre-school children (Zhang et al., 2018). Thus, there is a need for more studies on ambient air pollutants and FeNO in this area. We have performed a panel study on associations between different types of outdoor air pollutants and FeNO in university students in Taiyuan. The main aim was to investigate associations between different air pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3 and CO) and FeNO over one heating season (from early autumn 2014 to early spring 2015). We recruited university students without diagnosed asthma but with elevated FeNO ($>$20 ppb) in a health survey performed in the previous heating season (2013).

2. Materials and methods

2.1. Study design and participants

The panel study was performed at Shanxi University, located in the southern urban area of Taiyuan, China. In order to capture individual sensitive to effects of air pollution on FeNO, we selected students with slightly elevated FeNO in a health survey performed in the heating season the year before our panel study started. However, we excluded students with diagnosed asthma to get a more homogeneous study population.

In November–December 2013, a total of 357 students participated in a health survey, collecting data on gender, age, height, current smoker, allergies, diagnosed asthma, asthmatic symptoms and FeNO. For the panel study, we excluded students with doctor diagnosed asthma, age$<$18 years, FeNO $\leq$ 20 ppb and those who lived outside the campus. Finally, there were 67 eligible student joining the panel study in 2014–2015. The panel study included FeNO measurements and outdoor air pollution measurements once per month (totally 6 times, here called waves), in September, November and December 2014 and January, March and April 2015. The heating season in Taiyuan starts 1st November and end on 31st March. The FeNO measurements were performed in one or two consecutive days in each month (one test per month for each student). February 2015 and March 2015 had no FeNO measurements because most students were away from the university on a longer holiday (Chinese Spring Festival). In each wave, FeNO was always measured at same time in the morning (8:30 a.m. to 11:00 a.m.). The study was approved by the Medical Ethics Committee at Shanxi University. All participants gave written informed consent.

2.2. FeNO measurement

FeNO was measured by NIOX MINO (Aerocrine AB, Solna, Sweden) according to international guidelines (ATS and ERS, 2005) as in previous investigations (e.g. Zhao et al., 2013). Briefly, participants exhaled completely, inhaled NO-free air through the NIOX MINO and then exhaled at a steady flow rate of 50 ± 5 mL/s for 10 s. FeNO was expressed as part per billion (ppb). Food, beverage, medication, smoking and physical exercise were avoided the hour before the FeNO test. All measurements were performed using the same instrument and by the same staff. In each wave, most FeNO measurements were performed the same day but for logistic reasons, a few students were tested the next day.

2.3. Exposure assessment for the health study

The outdoor concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3 were measured at a fixed location on the rooftop of a university building (about 12 m above ground), within 1.0 km distance from the dormitories where the students lived. The concentrations of PM_{10} and $PM_{2.5}$ were measured with 1-min resolution by a direct reading instrument (DUSTTRAK II Aerosol monitors, TSI Incorporated). This instrument was calibrated for $PM_{2.5}$ and PM_{10} against a fixed governmental monitoring station before each sampling wave. This monitoring station used the b-Ray absorption method to measure PM_{10} and $PM_{2.5}$. For $PM_{2.5}$ and PM_{10}, we calculated different lag times (from lag 1 day to lag 7 days). The pollutants SO_2, NO_2 and O_3 were measured by diffusion samplers. The sampling time was 7 consecutive days (24 h/d) prior to the day when the FeNO testing was started in the particular wave (lag 7 days). The diffusion samplers were produced and analyzed by the Swedish Environmental Research Institute (IVL) in Gothenburg. After sampling, the diffusion samplers were collected and stored in a refrigerator at about -4 °C until analysis. Daily average concentration of CO was obtained from a nearest governmental monitoring station located about 2.5 km from the campus. The concentration of CO was measured by the non-dispersive infrared absorption method, consistent with the State Environmental Protection Agency of China. Moreover, daily mean temperature was obtained from the China Meteorological Administration (http://data.cma.cn). The weekly means of CO concentration and temperature were calculated by averaging 7 day mean values (lag 7).

2.4. Seasonal variation of air pollution data from nearest monitoring station

In order to study seasonal variation of air pollution in the area, we collected weekly mean air pollution data for each pollutant (PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO) from the nearest governmental monitoring station. This monitoring station used the tapered element oscillating microbalance method to measure $PM_{2.5}$ and PM_{10}. Differential optical absorption spectroscopy was used for SO_2, NO_2 and O_3. The concentration of CO was measured by the non-dispersive infrared absorption method. All monitoring instruments and data reporting system were strictly and regularly validated according to the State Environmental Protection Agency of China. Data was collected for each week, from the beginning to the end of the study period (September 1, 2014 to April 30, 2015).

2.5. Statistical analysis

Since FeNO has an approximately log-normal distribution it is common to use log transformed data in FeNO studies (e.g. Lim et al., 2016; Norbäck et al., 2017; Prapamontol et al., 2021). We used log-transformed FeNO data (10-logarithm) in the models. Linear mixed models were applied to analyze associations between air pollution, outdoor temperature and FeNO, and the identity number of each participant was incorporated (random intercept models) to account for the repeated measurements of FeNO. Linear mixed models are suitable when the dependent variable is a continuous variable and exposure data is on group level and personal factors are on individual level. It can handle repeated measurements, and missing data for some individuals at some data collection waves.

We used STATA for the linear mixed models. The command for linear mixed models in STATA is: mixed y ×1 x2 etc. || grouplevel:

Where y is the dependent variable, x1, x2 etc. are the independent variables and group level is individual in our study.

Below is the general formula for linear mixed model regression equations:

$Y_{it} = A_0 + B_i + A_1X_1 + \ldots \ldots + A_nX_n + \beta Pollutants + \gamma_{it}$

Y_{it} means that the FeNO level of the i-th subject at t (time).

A_0 means that the total intercept in equations.

B_i means that the random intercept of the i-th subject.

X_1-X_n means that the covariate.

A_1-A_n means that the regression coefficient of X_1-X_n

β means that the regression coefficient of pollutants.

γ_{it} means that the residual error of the i-th subject at t (time)

We used three types of linear mixed models. Model I was a one pollutant model including adjustment for five potential confounders (gender, age, height, current smoking, pollen or furry pet allergy). In model II, outdoor temperature was added to Model I. Moreover, we analyzed correlations between temperature and the different pollutants by Kendal Tau beta rank correlation test. Then we constructed two multi-pollutant models, one for $PM_{2.5}$ and other significant pollutants and another model for PM_{10} and other significant pollutants. In addition, we created two-pollutant models for selected air pollutants. Finally, we stratified the multi-pollutant models by gender. The statistical analysis was performed by SPSS (v24.0, SPSS Inc, Chicago, USA) and STATA 15.1 (for linear mixed models). All statistical analysis used two-tailed tests and a five percent level of significance. The results were presented as antilog-beta values with 95% confidence interval (95% CI).

3. Results

3.1. Descriptive statistics

Data on the health survey population (n = 357) is given in Table S1 and data on the participants in the panel study (n = 67) is given in Table 1. For the health survey population, investigated in 2013, the geometric mean of FeNO was 15.5 ± 1.5 ppb; 63.9% were women, the mean age was 21.2 ± 2.2 years, 4.8% were current smokers, 0.8% had physician diagnosed asthma, and 6.4% had pollen or furry pet allergy (Table S1). Among the participants in the health survey, 84 students fulfilled the inclusion criteria and 67 (79.8%) agreed to join the panel study. For these 67 participants, the mean age was 22.3 ± 1.6 years, 52.2% were women, 6.0% were current smokers and 6.0% had pollen or furry pet allergy. Few used antibiotics (6%) and 19.4% reported wheeze, 35.8% dry cough and 17.9% rhinitis symptoms in the last 12 months (Table 1).

All 67 participants fulfilled the study, but a total of 19 FeNO measurements were missing due to illness, holidays, or for other reasons. Therefore, there were totally 383 FeNO measurements. Mean FeNO level by month is given in Table 2. The geometric mean of FeNO was 22.2 ppb in September 2014, 19.7 in October 2014, 21.1 ppb in November 2014, 14.9 ppb in December 2014, 14.6 ppb in January 2015 and 21.2 ppb in April 2015. Mean weekly air pollution data is given in Table 3 (lag 7 days). The range of seven days mean data (one mean per month) was $105.0–339.0\ \mu g/m^3$ for PM_{10}, $72.0–180.0\ \mu g/m^3$ for $PM_{2.5}$, $36.0–347.0\ \mu g/m^3$ for SO_2, $26.0–69.0\ \mu g/m^3$ for NO_2, $31.0–163.0\ \mu g/m^3$ for O_3 and $0.93–3.14\ mg/m^3$ for CO. The seven day mean data for outdoor temperature and relative humidity (RH) ranged from −4.5 to 20.1 °C and 35.9–73.3%, respectively.

Table 1
Descriptive data for participants in the panel study started in September 2014 (N = 67).

	Participants[a]
Age (years)	
Mean ± SD (min - max)	22.3 ± 1.6 (19.0–26.0)
Height (cm)	
Mean ± SD (min - max)	168.2 ± 6.7 (152.0–182.0)
Gender [N (%)]	
Man	32 (47.8)
Woman	35 (52.2)
Current smoker [N (%)]	4 (6.0)
Physician diagnosed asthma [N (%)]	0 (0)
Allergy to pollen [N (%)]	3 (4.5)
Allergy to furry pets [N (%)]	1 (1.5)
Pollen or furry pet allergy [N (%)]	4 (6.0)
Intake of antibiotics [N (%)]	4 (6.0)
Wheeze last 12 months [N (%)]	13 (19.4)
Dry cough last 12 months [N (%)]	24 (35.8)
Rhinitis last 12 months [N (%)]	12 (17.9)

Abbreviation: FeNO, fractional exhaled nitric oxide; GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

[a] Students without diagnosed asthma and with FeNO >20 ppb in a previous health survey in November–December 2013 (inclusion criteria to join the panel study).

For $PM_{2.5}$ and PM_{10}, we calculated different lag times (lag 1 day to lag 7 days), Data on lag 1 to lag 6 for these pollutants is given in Table 4. Mean concentration of $PM_{2.5}$ and PM_{10} was similar for all lag times but the range (min-max) was somewhat larger for shorter lag times.

Correlations between ambient air pollutants and outdoor temperature and RH are presented in Table 5. Many exposure variables were correlated. The strongest positive correlations were between the PM_{10} and $PM_{2.5}$ (Kendal Tau beta 0.746), between SO_2 and CO (Kendal Tau beta 0.693) and between temperature and O_3 (Kendal Tau beta 0.600). The strongest negative correlations were between temperature and SO_2 (Kendal Tau beta −0.742), between O_3 and CO (Kendal Tau beta −0.701), between O_3 and SO_2 (Kendal Tau beta −0.594). Temperature and RH were positively correlated (Kendal Tau beta 0.554) and there was a positive correlation between RH and NO_2 (Kendal Tau beta 0.704). All other correlations were weak (Kendal Tau beta absolute value below 0.5).

3.2. Seasonal variation of air pollution in the area

Weekly mean air pollution data for the five pollutants during the study period (September 1, 2014 to April 30, 2015), measured at the nearest monitoring station, is presented in figures S1-S5. The weeks when the FeNO panel study were performed are indicated by red text. There were no clear seasonal trends for PM_{10} or $PM_{2.5}$or NO_2. In contrast, SO_2 showed a clear seasonal trend with the highest values in mid-winter. The seasonal trend for CO was similar as for SO_2 (highest values in mid-winter). Ozone showed an opposite seasonal trend, with the lowest levels in mid-winter.

3.3. Associations between FeNO and ambient air pollutants

Associations between temperature, ambient air pollutants and FeNO in single-pollutant models are given in Table 6. In Model I, we adjusted for five demographic co-variates (gender, age, current smoker, height and pollen or furry pet allergy). Temperature, PM_{10}, $PM_{2.5}$, NO_2 and O_3 were positively while SO_2 and CO were negatively associated with FeNO ($p < 0.05$). After further adjustment for outdoor temperature (Model II),

Table 2

Descriptive statistics for FeNO levels by month (one FeNO test each month for each student)[a].

FeNO (ppb)	Total	September	October	November	December	January	April
N	383	66	66	66	61	63	61
Mean ± SD	19.0 ± 8.6	22.2 ± 10.5	19.7 ± 7.3	21.1 ± 8.3	14.9 ± 6.1	14.6 ± 7.8	21.2 ± 7.9
GM ± GSD	17.2 ± 1.6	19.9 ± 1.6	18.4 ± 1.4	19.7 ± 1.4	13.6 ± 1.6	12.9 ± 1.6	20.0 ± 1.4
Min - max	5.0–54.0	8.0–54.0	8.0–39.0	9.0–50.0	5.0–34.0	5.0–49.0	10.0–51.0

Abbreviation: FeNO, fractional exhaled nitric oxide; SD, standard deviation; GM, geometric mean; GSD, geometric standard deviation.

[a] Data collection was performed during a 1–2 days period each month).

Table 3

Weekly means of ambient air pollutants by month (one 7 days period per month)[a].

	September	October	November	December	January	April
PM_{10} ($\mu g/m^3$)	129.0	339.0	181.0	162.0	105.0	208.0
$PM_{2.5}$ ($\mu g/m^3$)	83.0	180.0	118.0	142.0	72.0	128.0
SO_2 ($\mu g/m^3$)	43.0	71.0	192.0	236.0	347.0	36.0
NO_2 ($\mu g/m^3$)	42.0	69.0	40.0	26.0	38.0	34.0
O_3 ($\mu g/m^3$)	163.0	63.0	83.0	67.0	31.0	115.0
CO (mg/m^3)	1.07	2.05	1.44	1.89	3.14	0.93
Temperature (°C)	20.1	10.9	2.9	−4.5	−2.3	13.2
RH (%)	73.3	67.9	56.6	35.9	42.6	42.1

Outdoor PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3 were measured by the research group outside the dormitory.

Outdoor temperature and CO were obtained from the nearest monitoring station.

[a] Air pollutants and temperature were measured 7 days (24 h per day) before the FeNO testing took place (lag 7 days).

Table 4

Descriptive data for PM10 and PM2.5 at different time windows (lag 1-lag 6).

	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6
PM_{10} ($\mu g/m^3$)						
Mean ± SD	192.2 ± 86.0	189.0 ± 79.2	184.6 ± 74.5	182.1 ± 68.1	182.7 ± 64.3	182.8 ± 61.4
Min-max	52.0–381.5	66.0–381.0	62.8–373.0	66.0–359.6	67.2–337.0	68.9–325.9
$PM_{2.5}$ ($\mu g/m^3$)						
Mean ± SD	109.5 ± 57.4	105.7 ± 51.3	101.5 ± 45.5	98.7 ± 40.2	98.3 ± 38.1	97.7 ± 36.8
Min-max	25.5–237.5	22.0–219.3	20.2–203.5	24.2–197.4	26.5–179.8	29.6–180.4

Table 5

Kendal-Tau beta rank correlation coefficients for ambient air pollutants and outdoor climate.

	PM_{10}	$PM_{2.5}$	SO_2	NO_2	O_3	CO	Temp	RH
PM_{10}	–	–	–	–	–	–	–	–
$PM_{2.5}$	0.746**	–	–	–	–	–	–	–
SO_2	- 0.451**	- 0.198**	–	–	–	–	–	–
NO_2	0.211**	- 0.043	- 0.211**	–	–	–	–	–
O_3	0.045	- 0.208**	- 0.594**	0.068	–	–	–	–
CO	- 0.212**	- 0.028	0.693**	0.031	- 0.701**	–	–	–
Temp	0.194**	- 0.060	- 0.742**	0.468**	0.600**	- 0.460**	–	–
RH	0.140**	- 0.063	- 0.370**	0.704**	0.248**	- 0.085*	0.554**	–

**p-value <0.01.

NO_2 and O_3 were no longer associated with FeNO and thus these two pollutants were not included in the multi-pollutant models.

Table 7 gives associations between $PM_{2.5}$ and PM_{10} and FeNO for lag times shorter than 7 day (from lag 1 to lag 6). For $PM_{2.5}$ there was a significant association for lag 6, only. For PM_{10} there were significant associations for lag 4 and lag 6. For shorter lag times, there were no significant associations between FeNO and $PM_{2.5}$ or PM_{10}.

Table 8 shows associations between temperature, ambient air pollutants and FeNO calculated by multi-pollutant models, in the total material and stratified by gender. The main models included the five demographic co-variates and temperature, $PM_{2.5}$, SO_2 and CO. To analyze associations for PM_{10}, we replaced $PM_{2.5}$ by PM_{10} in the models. Temperature, PM_{10}, $PM_{2.5}$ and SO_2 were positively associated with FeNO (all p-values<0.001) and CO was negatively associated with FeNO ($p < 0.001$). All associations in the multi-pollutant models were similar in men and women (Table 8).

To understand why the association between SO_2 and FeNO changed from negative to positive association when adjusting for two other pollutants ($PM_{2.5}$ and CO), we calculated associations between air pollution and FeNO in two-pollutant models for SO_2 and $PM_{2.5}$ or CO, adjusting for gender, age, height, current smoker, pollen or furry pet allergy and outdoor temperature (data shown in text only). In a model with SO_2 and $PM_{2.5}$, the association between SO_2 and FeNO was negative (antilog beta 0.84; 95% CI 0.74–0.95; $p = 0.005$). In a model with SO_2 and CO, there were no association between SO_2 and FeNO (antilog beta 1.00; 95% CI 0.92–1.08; $p = 0.99$).

4. Discussion

In our panel study, we found that outdoor temperature, PM_{10}, $PM_{2.5}$ and SO_2 were associated with increased FeNO in university students in northern China while there was a negative (protective) association for

Table 6

Associations between outdoor air pollutants and FeNO levels by single-pollutant models.

	Model I		Model II	
	Antilog β (95% CI)	p-value	Antilog β (95% CI)	p-value
PM_{10} (per 100 μg/m^3)	1.10 (1.05–1.15)	<0.001	1.04 (1.00–1.09)	0.052
$PM_{2.5}$ (per 100 μg/m^3)	1.12 (1.01–1.24)	0.024	1.12 (1.02–1.22)	0.016
SO_2 (per 100 μg/m^3)	0.87 (0.85–0.90)	<0.001	0.89 (0.83–0.95)	<0.001
NO_2 (per 100 μg/m^3)	1.55 (1.19–2.02)	0.001	1.00 (0.77–1.31)	0.993
O_3 (per 100 μg/m^3)	1.36 (1.26–1.47)	<0.001	1.11 (0.98–1.27)	0.100
CO (per mg/m^3)	0.81 (0.78–0.84)	<0.001	0.85 (0.81–0.90)	<0.001
Temperature (per 10 °C)	1.18 (1.14–1.23)	<0.001	1.18 (1.14–1.23)	<0.001

Antilog β (95% CI) by linear mixed models.

Model I - adjustment for gender, age, height, current smoker, pollen or furry pet allergy (one exposure per model).

Model II - adjustment for gender, age, height, current smoker, pollen or furry pet allergy and temperature (one exposure per model).

The concentrations of pollutants and temperature were measured for 7 days (24 h a day), once per month.

Table 7

Associations between PM10 and PM2.5 at different time windows (lag 1-lag 6) and FeNO levels by single-pollutant models.

	Model I		Model II	
	Antilog β (95% CI)	p-Values	Antilog β (95% CI)	p-Values
PM_{10} (per 100 μg/m^3)				
Lag1	0.93 (0.27–1.65)	0.24	1.10 (0.31–1.72)	0.26
Lag2	1.52 (0.79–2.37)	0.37	1.53 (0.83–0.95)	0.36
Lag3	1.34 (0.52–2.15)	0.41	1.35 (0.67–2.11)	0.59
Lag4	1.06 (1.00–1.47)	0.05	1.11 (1.08–1.27)	0.04
Lag5	1.21 (0.80–1.64)	0.67	1.22 (0.81–1.69)	0.66
Lag6	1.38 (1.17–1.53)	<0.001	1.29 (1.14–1.36)	0.002
$PM_{2.5}$ (per 100 μg/m^3)				
Lag1	1.15 (0.58–2.26)	0.19	1.24 (0.74–2.66)	0.29
Lag2	1.17 (0.36–3.84)	0.23	1.22 (0.41–3.94)	0.18
Lag3	0.90 (0.20–4.09)	0.94	1.01 (0.41–3.88)	0.65
Lag4	1.21 (0.80–1.84)	0.33	1.11 (0.91–1.94)	0.38
Lag5	1.31 (0.70–2.44)	0.27	1.22 (0.88–2.23)	0.43
Lag6	1.52 (1.15–2.23)	0.02	1.22 (1.03–1.46)	0.05

Antilog β (95% CI) by linear mixed models.

Model I - adjustment for gender, age, height, current smoker, pollen or furry pet allergy (one exposure per model).

Model II - adjustment for gender, age, height, current smoker, pollen or furry pet allergy and temperature (one exposure per model).

CO. These associations were observed in multi-pollutant models with mutual adjustment for temperature and other significant air pollutants.

The study population consisted of university students recruited from the environmental research program at a major university in the city of Taiyuan. In Taiyuan, air pollution from coal burning increase drastically when the heating season starts in November. The inclusion criteria was that they should not have diagnosed asthma but should have elevated FeNO (>20 ppb) in a health suvey performed the year before the panel study was done. The prevalence of wheeze was 19.4% and the prevalence of dry cough 35.8%, suggesting that some of the students had respiratory symptoms without an asthma diagnosis. Previous studies have demonstrated that the prevalence of diagnosed asthma was low in this city (Zhang et al., 2013a, b). Moreover, our previous study found that FeNO levels in school children in Taiyuan were low as compared to Shanghai, a more developed city (Zhao et al., 2013).

Data from the nearest monitoring station demonstrated different seasonal patterns for different air pollutants. SO_2 and CO followed the same pattern, with the highest levels in the coldest months. The pollutant O_3 followed an opposite pattern with the lowest levels in the coldest months. In contrast, NO_2, $PM_{2.5}$ and PM_{10} had no clear seasonal variation. It can be assumed that SO_2 and CO mainly comes from coal combustion for heating in winter, and that NO_2 mainly comes from traffic air pollution. In the city of Taiyuan, there has been measures taken to reduce air pollution from coal combustion and outdoor SO_2 concentration have been reduced substantially in the last decades (Zhang et al., 2014). Outdoor PM_{10} decreased substantially from 2000 to 2012, but from 2012 to 2017, outdoor PM_{10} increased (but not up to previous levels) (Zhang et al., 2019, 2020). This information on PM_{10} trends, as well as the lack of a clear seasonal trend for PM_{10} and $PM_{2.5}$ in our own data, suggests that nowadays PM air pollution in Taiyuan has different sources. These sources could be construction work, traffic exhaust, re-suspension of road dust, coal combustion in industries or power plants, or photochemical reactions in the air.

We found a consistent association between outdoor temperature (range −4.5 to 20.1 °C) and FeNO, and the magnitude of this association increased when adjusting for the effect of air pollution. In the final model, an increase of temperature by 10 °C was associated with an 80% increase of FeNO (antilog beta 1.80). The reason for the observed temperature association is unclear, but could be due to increased levels of indoor or outdoor allergens or other bioaerosols at higher outdoor temperature. We did not include outdoor RH in the models because temperature and RH were positively correlated, and moreover because there is no data from other studies indicating that FeNO is influenced by outdoor RH. Many previous panel studies on FeNO and air pollution adjusted for ambient temperature but did not report FeNO associations for temperature. However, a panel study from Shanghai in diabetic patients found that FeNO was lowest when the ambient temperature was 23–25 C. At temperatures below 23 °C (min value was 10 °C), FeNO increased (Li et al., 2017). Since Shanghai has a different climate (a warmer costal climate), more studies are needed from northern China on seasonal variations of FeNO.

We found that $PM_{2.5}$ was associated with FeNO. Our results agrees with results from other panel studies in healthy adults in China (Fan et al., 2018; Gong et al., 2014; Zhang et al., 2016, 2019; Zhao et al., 2016) and USA (Adar et al., 2007; Adamkiewicz et al., 2004) as well as the conclusion from a recent review on air pollution and FeNO (Chen et al., 2020). However, our study is one of few studies on this topic in healthy adults in northern China. One previous study in 20 healthy males in Beijing reported that outdoor $PM_{2.5}$ increased FeNO and the effect of $PM_{2.5}$ on FeNO was enhanced by physical exercise (Chen et al., 2018). Moreover, we found that PM_{10} was associated with FeNO, and significant associations were found for lag 4, lag 6 and lag 7. This agrees with the results from a previous panel study in university students in Shanghai (Zhao et al., 2016), but our study is one of few panel studies on associations between outdoor PM_{10} and FeNO in a healthy adult population. We found a higher risk estimate for $PM_{2.5}$ (84% increase of FeNO per 10 μg/m^3) as compared to PM_{10} (22% increase of FeNO per 10 μg/m^3) suggesting that the fine particles can have a stronger effect on FeNO.

We found that SO_2 was positively associated with FeNO in the final models with mutual adjustment for outdoor temperature and other ambient air pollutants ($PM_{2.5}$ and CO). Monitoring station data showed that SO_2 and CO followed a similar seasonal time pattern, with the highest concentrations in the coldest part of the winter. These two pollutants had relatively high positive correlation which makes it difficult to separate their effects in a panel study. In Taiyuan, these pollutants comes mainly from coal combustion in winter. The risk estimate for SO_2 (70% increase of FeNO per 10 μg/m^3) was similar as for $PM_{2.5}$. Our result concerning SO_2 and FeNO is in agreement with conclusions from the panel study review (Chen et al., 2020) but the review only included one panel study on SO_2 and FeNO in heathy adults (Zhao et al., 2016).

Table 8
Associations between outdoor air pollutants, temperature and FeNO levels by multi-pollutant models, stratified by gender.

Multi-pollutant models						
	Total		Man		Woman	
	Antilog β (95% CI)	p-Values	Antilog β (95% CI)	p-Values	Antilog β (95% CI)	p-Values
PM_{10} (per 100 $\mu g/m^3$)	1.22 (1.13–1.32)	<0.001	1.22 (1.10–1.36)	<0.001	1.22 (1.09–1.36)	<0.001
$PM_{2.5}$ (per 100 $\mu g/m^3$)	1.84 (1.43–2.36)	<0.001	1.80 (1.27–2.55)	0.001	1.87 (1.31–2.67)	0.001
SO_2 (per 100 $\mu g/m^3$)	1.70 (1.35–2.15)	<0.001	1.68 (1.21–2.33)	0.002	1.72 (1.25–2.39)	0.001
CO (per mg/m^3)	0.70 (0.63–0.77)	<0.001	0.68 (0.58–0.78)	<0.001	0.72 (0.62–0.83)	<0.001
Temperature (per 10 °C)	1.80 (1.43–2.27)	<0.001	1.82 (1.32–2.51)	<0.001	1.79 (1.30–2.47)	<0.001

Antilog β (95% CI) by linear mixed models.
The main model for total material included gender, age, height, current smoker, pollen or furry pet allergy, temperature, $PM_{2.5}$, SO_2 and CO (main model used for associations with $PM_{2.5}$, SO_2, CO and temperature).
For PM_{10} associations, $PM_{2.5}$ was replaced by PM_{10} in the model.
In gender stratified models, gender was excluded from the models.
The concentrations of pollutants and temperature were measured for 7 days (24 h a day) once per month.

Another panel study in healthy adults, performed before and after the Olympic games in Beijing in 2008, also found an association between SO_2 and FeNO (Huang et al., 2012). An experimental study in mice demonstrated that inhaled SO_2 can be transformed to sulfurous acid, generating reactive oxygen species (ROS) causing inflammation by oxidative stress (Meng et al., 2003). Thus, our study adds evidence that SO_2 can cause respiratory inflammation, measured as FeNO, in healthy young adults.

We found a consistent negative (protective) association between CO and FeNO. Few panel studies exist on associations between CO and FeNO, and results are inconsistent (Guo et al., 2018; Huang et al., 2012; Zhao et al., 2016). Guo et al. (2018) did not find any association between CO and FeNO in patients with respiratory diseases (Guo et al., 2018). The Beijing Olympic game study found that CO was positively associated with FeNO in healthy adults (Huang et al., 2012). However, a panel study in university students in Shanghai found similar results as in our study, that outdoor CO was negatively associated with FeNO (Zhao et al., 2016). This article discuss a possible biological mechanism that could explain a protective effect of CO on FeNO, linked to interaction between exogenous CO and endogenous CO and NO on a cellular level (Zhao et al., 2016). FeNO is mainly produced in epithelial cells by inducible NO synthase (iNOS) induced by proinflammatory cytokines involved in inflammatory diseases. A hypothetical CO and NO gas cycle has been postulated in which the level of endogenous NO, produced mainly by NO-producing enzyme-nitric oxide synthase (e.g. iNOS), is intermediated by endogenous CO and CO producing enzyme-heme oxygenase 1 levels, respectively (Otterbein, 2009; Otterbein et al., 2000). There is some evidence that exogenous CO may affect CO-mediated physiological responses (Otterbein, 2009). Although mechanisms behind a possible protective effect of CO on FeNO is unclear, our study supports the findings by the Shanghai panel study (Zhao et al., 2016) but further studies are needed on this topic.

Ours study has some strengths. It is a panel study, a stronger study design than a cross-sectional study. Moreover, we controlled for relevant demographic variables, outdoor temperature and used multi-pollutant models. Finally, most of the ambient air pollutants (except CO) were measured by the research group in the campus area where the students had classes and had their dormitories. This enabled us to capture air pollution from local pollution sources that could be missed in data from the nearest monitoring station. We collected health data once per month and performed exposure measurements in one week per month only, but these data collection periods were well spread over the study period from September to April.

The study has some limitations. We used a fixed site monitoring strategy which could lead to some error as compared to measuring personal exposure. However, we excluded students living outside the campus area, and measured air pollution in the campus, near the dormitories where the students lived. Thus, we could expect that the exposure misclassification from the fixed site strategy was a non-differential misclassification. Non-differential means that the exposure misclassification does not lead to a biased risk estimate. However, since the students spend most of their time indoors, where they are partly protected from outdoor air pollution and temperature, outdoor measurements can overestimate their true exposure to outdoor air pollution and coldness in heating season. Average room temperature in the heating season inside the student dormitories was 18.6 C (range 14.6–22.5) (Xin Zhang, personal communication).

Another limitation was that we had no questions on current medication or current respiratory infections, we only had a question on current use of antibiotics. However, the subjects were healthy university students without an asthma diagnose. Thus it is unlikely that they used anti-inflammatory asthma medication, which could lower FeNO. The issue on respiratory infections and FeNO is complex. According to a review on FeNO, rhinovirus infections can increase FeNO but syncytial virus and influenza virus infections can slightly reduce FeNO and there is no evidence that bacterial airway infections influence FeNO (Alving and Malinovschi, 2010). Moreover, antibiotic use in itself should not affect FeNO.

FeNO can be influenced by short term variation of air pollution levels. We measured some pollutants by diffusion samplers which needed to sample at least 7 days. Thus for these pollutants we only have lag 7 data. For $PM_{2.5}$ and PM_{10}, we used direct reading instruments and could test FeNO associations for different lag times (from lag 1 to lag 7). We found the strongest associations for lag 7 (one week average) but found some significant associations for lag 4 (PM_{10}) and lag 6 ($PM_{2.5}$ and PM_{10}) as well. We could have missed some associations by not analyzing shorter lag times for SO_2, NO_2, ozone or CO but our results concerning $PM_{2.5}$ and PM_{10} suggests that in this study lag 7 could have the strongest association with FeNO. This is different from the results from a previous panel study in Shanghai university students. In this study, the strongest associations between air pollution and FeNO were found for lag times between 6 and 48 h (different for different types of air pollution) (Zhao et al., 2016).

Another limitation is the relatively small study population, which could have reduced the statistical power, but observed associations were all highly significant ($p < 0.001$) in the multi-pollutant models. However, the strong correlations between some ambient air pollutants, especially between PM_{10} and $PM_{2.5}$, and between SO_2 and CO limited the possibility to separate health effects of different pollutants. Moreover, since heating season has more air pollution in northern China, it can be difficult to differentiate between effects from ambient temperature and some types of air pollution. Finally, since the study was performed in healthy college students in one city, the external validity is limited.

In conclusion, outdoor exposure to PM_{10}, $PM_{2.5}$ and SO_2 in a polluted city in northern China can be associated with airway inflammation, measured as FeNO, in healthy young adults. It is possible that outdoor CO can reduce FeNO, but this protective association needs to be confirmed in further experimental studies. Moreover, FeNO can be lower when the outdoor temperature is lower.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The study had funding from National Key Research and Development Project of China (2019YFC1804500), Swedish Research Council (2017–05845), Swedish Research Council for a sustainable development FORMAS (348-2011-7402), National Natural Science Foundation of China (42177419), and Shanxi One Hundred Excellent Experts Project (nr 9).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113379.

References

Adamkiewicz, G., Ebelt, S., Syring, M., Slater, J., Speizer, F.E., Schwartz, J., et al., 2004. Association between air pollution exposure and exhaled nitric oxide in an elderly population. Thorax 59, 204–209.

Adar, S.D., Adamkiewicz, G., Gold, D.R., Schwartz, J., Coull, B.A., Suh, H., 2007. Ambient and microenvironmental particles and exhaled nitric oxide before and after a group bus trip. Environ. Health Perspect. 115, 507–512.

Alving, K., Malinovschi, A., 2010. Basic aspects of exhaled nitric oxide. Eur. Respir. Monagr. 49, 1–31.

Asher, M.I., et al., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368, 733–743.

ATS/ERS, 2005. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am. J. Respir. Crit. Care Med. 171, 912–930.

Chen, X.L., Liu, F.F., Niu, Z.P., et al., 2020. The association between short-term exposure to ambient air pollution and fractional exhaled nitric oxide level: a systematic review and meta-analysis of panel studies. Environ. Pollut. 265, 114833.

Chen, X., Chen, W., Wang, Y.W., et al., 2018. Responses of healthy young males to fine-particle exposure are modified by exercise habits: a panel study. Environ. Health 17, 88.

Day, D.B., Xiang, J., Mo, J., Li, F., Chung, M., Gong, J., et al., 2017. Association of ozone exposure with cardiorespiratory pathophysiologic mechanisms in healthy adults. JAMA Intern. Med. 177, 1344–1353.

Delfino, R.J., Staimer, N., Tjoa, T., Gillen, D.L., Schauer, J.J., Shafer, M.M., 2013. Airway inflammation and oxidative potential of air pollutant particles in a pediatric asthma panel. J. Expo. Sci. Environ. Epidemiol. 23, 466–473.

Dweik, R.A., Boggs, P.B., Erzurum, S.C., Irvin, C.G., Leigh, M.W., Lundberg, J.O., Olin, A. C., Plummer, A.L., Taylor, D.R., 2011. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels for Clinical Applications. Am. J. Respir. Crit. Care Med. 184, 602–615. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications.

Fan, Z., Pun, V.C., Chen, X.C., Hong, Q., Tian, L., Ho, S.S., et al., 2018. Personal exposure to fine particles (pm2.5) and respiratory inflammation of common residents in Hong Kong. Environ. Res. 164, 24–31.

Gong, J., Zhu, T., Kipen, H., Wang, G., Hu, M., Guo, Q., et al., 2014. Comparisons of ultrafine and fine particles in their associations with biomarkers reflecting physiological pathways. Environ. Sci. Technol. 48, 5264–5273.

Guan, W.J., Zheng, X.Y., Chung, K.F., Zhong, N.S., 2016. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. Lancet 388, 1939–1951.

Guo, H., Yang, W., Jiang, L., Lyu, Y., Cheng, T., Gao, B., et al., 2018. Association of short-term exposure to ambient air pollutants with exhaled nitric oxide in hospitalized patients with respiratory-system diseases. Ecotoxicol. Environ. Saf. 168 (JAN), 394–400.

Huang, W., Wang, G., Lu, S.E., Kipen, H., Wang, Y., Hu, M., Lin, W., Rich, D., Ohman Strickland, P., Diehl, S.R., Zhu, P., Tong, J., Gong, J., Zhu, T., Zhang, J., 2012. Inflammatory and oxidative stress responses of healthy young adults to changes in air quality during the Beijing olympics. Am. J. Respir. Crit. Care Med. 186, 1150–1159.

Li, H., Bai, H., Yang, C., Chen, R., Wang, C., Zhao, Z., et al., 2017. Acute effects of ambient temperature and particulate air pollution on fractional exhaled nitric oxide: a panel study among diabetic patients in shanghai, China. J. Epidemiol. 27, 584–589.

Li, X., Song, P., Zhu, Y., et al., 2020. The disease burden of childhood asthma in China: a systematic review and meta-analysis. J. Glob. Health 10, 010801.

Lim, F.L., Hashim, Z., Md Said, S., Than, L.T., Hashim, J.H., Norbäck, D., 2016. Fractional exhaled nitric oxide (FeNO) among office workers in an academic institution Malaysia - associations with asthma, allergies and office environment. J. Asthma 53, 353–361.

Lu, F., et al., 2015. Systematic review and meta-analysis of the adverse health effects of ambient PM2.5 and PM10 pollution in the Chinese population. Environ. Res. 136, 196–204.

Lundback, B., Backman, H., Lotvall, J., Ronmark, E., 2016. Is asthma prevalence still increasing? Expet Rev. Respir. Med. 10, 39–51.

Meng, Z.Q., Qin, G.H., Zhang, B., Geng, H., Bai, Q.L., Bai, W., et al., 2003. Oxidative damage of sulfur dioxide inhalation on lungs and hearts of mice. Environ. Res. 93 (3), 285–292.

Norbäck, D., Hashim, J.H., Hashim, Z., Cai, G.H., Sooria, V., Ismail, S.A., Wieslander, G., 2017. Respiratory symptoms and fractional exhaled nitric oxide (FeNO) among students in Penang, Malaysia in relation to signs of dampness at school and fungal DNA in school dust. Sci. Total Environ. 577, 148–154.

Otterbein, L.E., 2009. The evolution of carbon monoxide into medicine. Respir. Care 54, 925–932.

Otterbein, L.E., Bach, F.H., Alam, J., Soares, M., Tao Lu, H., Wysk, M., Davis, R.J., Flavell, R.A., Choi, A.M., 2000. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. Nat. Med. 6, 422e428.

Prapamontol, T., Norbäck, D., Thongjan, N., Suwannarin, N., Somsunun, K., Ponsawansong, P., et al., 2021. Fractional exhaled nitric oxide (FeNO) in students in northern Thailand: associations with respiratory symptoms, diagnosed allergy and the home environment. J. Asthma 1–9 (online publication).

Stanaway, J.D., Afshin, A., Gakidou, E., Lim, S.S., Abate, D., Abate, K.H., et al., 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet 392, 1923–1994.

Xia, Z., Duan, X., Tao, S., et al., 2013. Pollution level, inhalation exposure and lung cancer risk of ambient atmospheric polycyclic aromatic hydrocarbons (PAHs) in Taiyuan, China. Environ. Pollut. 173, 150–156.

Yao, Y., Chen, X., Wang, Q., et al., 2021. Susceptibility of individuals with chronic obstructive pulmonary disease to respiratory inflammation associated with short-term exposure to ambient air pollution. Sci. Total Environ. 766, 142639.

Zhang, J., Zhu, T., Kipen, H., et al., 2013a. Cardiorespiratory biomarkers response in healthy young adults to drastic air quality changes surrounding the 2008 Beijing Olympics. Res. Rep. Health Eff. Inst. 174, 5–174.

Zhang, Q., Wang, W., Niu, Y., Xia, Y., Lei, X., Huo, J., et al., 2019. The effects of fine particulate matter constituents on exhaled nitric oxide and DNA methylation in the arginase-nitric oxide synthase pathway. Environ. Int. 131, 105019.

Zhang, X., Staimer, N., Gillen, D.L., Tjoa, T., Schauer, J.J., Shafer, M.M., et al., 2016. Associations of oxidative stress and inflammatory biomarkers with chemically -characterized air pollutant exposures in an elderly cohort. Environ. Res. 150, 306–319.

Zhang, X., Fan, Q., Bai, X., Li, T., et al., 2018. Levels of fractional exhaled nitric oxide in children in relation to air pollution in Chinese day care centres. Int. J. Tubercul. Lung Dis. 22 (7), 813–819.

Zhang, Y.P., Li, B.Z., Huang, C., Yang, X., Qian, H., Deng, Q.H., Zhao, Z.H., Li, A.G., Zhao, J.N., Zhang, X., Qu, F., Hu, Y., Yang, Q., Wang, J., Zhang, M., Wang, F., Zheng, X.H., Lu, C., Liu, Z.J., Sun, Y.X., Mo, J.H., Zhao, Y.L., Liu, W., Wang, T.T., Norbäck, D., Bornehag, C.G., Sundell, J., 2013b. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. Chin. Sci. Bull. 58, 4182–4189.

Zhang, X., Li, F., Zhang, L., Zhao, Z.H., Norback, D., 2014. Longitudinal study of sick building syndrome (SBS) among pupils in relation to SO_2, NO_2, O_3 and PM_{10} in schools in China. PLoS One 9, e112933.

Zhang, X., Bai, X., Li, C.H., Li, T., Wang, R.H., Zhao, Z.H., Norback, D., 2020. Elemental composition of ambient air particles in Taiyuan, China: evaluation of lifetime cancer and non-cancer risks. Hum. Ecol. Risk Assess. 26, 1391–1406.

Zhao, Z., Chen, R., Lin, Z., Cai, J., Yang, Y., Yang, D., et al., 2016. Ambient carbon monoxide associated with alleviated respiratory inflammation in healthy young adults. Environ. Pollut. 208, 294–298.

Zhao, Z., Huang, C., Zhang, X., Xu, F., Kan, H., Song, W., Wieslander, G., Norback, D., 2013. Fractional exhaled nitric oxide in Chinese children with asthma and allergies - a two-city study. Respir. Med. 107, 161–171.