Environmental Pollution 208 (2016) 294–298

Contents lists available at ScienceDirect

Environmental Pollution

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

# Ambient carbon monoxide associated with alleviated respiratory inflammation in healthy young adults

Zhuohui Zhao [a], Renjie Chen [a, b], Zhijing Lin [a], Jing Cai [a, b], Yingying Yang [a], Dandan Yang [c], Dan Norback [d], Haidong Kan [a, b, *]

[a] *School of Public Health, Key Lab of Public Health Safety of the Ministry of Education, Key Lab of Health Technology Assessment of the Ministry of Health, Fudan University, Shanghai, China*

[b] *Shanghai Key Laboratory of Atmospheric Particle Pollution and Prevention (LAP3), Fudan University, Shanghai, China*

[c] *Shanghai Key Laboratory of Meteorology and Health, Shanghai, China*

[d] *Department of Environmental and Occupational Medicine, Uppsala University, Uppsala, Sweden*

A R T I C L E I N F O

*Article history:*
Received 19 May 2015
Received in revised form
8 July 2015
Accepted 18 July 2015
Available online 15 August 2015

*Keywords:*
Air pollution
Carbon monoxide
Respiratory inflammation
Panel study

A B S T R A C T

There is increasing controversy on whether acute exposure to ambient carbon monoxide (CO) is hazardous on respiratory health. We therefore performed a longitudinal panel study to evaluate the acute effects of ambient CO on fractional exhaled nitric oxide (FeNO), a well-established biomarker of airway inflammation. We completed 4–6 rounds of health examinations among 75 healthy young adults during April to June in 2013 in Shanghai, China. We applied the linear mixed-effect model to investigate the short-term associations between CO and FeNO. CO exposure during 2–72 h preceding health tests was significantly associated with decreased FeNO levels. For example, an interquartile range increase (0.3 mg/$m^3$) of 2-h CO exposure corresponded to 10.6% decrease in FeNO. This association remained when controlling for the concomitant exposure to co-pollutants. This study provided support that short-term exposure to ambient CO might be related with reduced levels of FeNO, a biomarker of lower airway inflammation.



## 1. Introduction

Carbon monoxide (CO) has been widely regarded as a hazardous air pollutant, and was thus regulated in Air Quality Guidelines issued by the World Health Organization and air quality standards in many countries. A number of epidemiological literature have consistently linked short-term exposure to ambient CO with increased risks of all-cause and cardiovascular outcomes (mortality, hospitalization, etc.), but less consistent evidence was reported on the hazardous respiratory effects (Bell et al., 2009; Chen et al., 2011; Samoli et al., 2007). The overall adverse health effects of CO have been well established for cardiovascular and central nervous system usually at a blood carboxyhemoglobin (COHb) level ≥2.4%, corresponding to CO exposure level of 10–15 ppm. Recently, however, there is increasing controversy on whether acute exposure to ambient CO, usually at a low level, is hazardous on respiratory health. For example, three ecological time-series studies in Hong Kong and Shanghai, China reported reduced risks of respiratory disease hospitalizations in association with an acute CO exposure (Cai et al., 2015; Tian et al., 2014, 2013), suggesting that ambient CO might be an agent related with lower risks of respiratory diseases or symptoms.

Experimental evidence has suggested that both endogenous and exogenous CO at low levels may have anti-inflammatory effects under certain circumstances (Durante et al., 2006; Otterbein, 2009; Ryter et al., 2006). Fractional exhaled nitric oxide (FeNO) is a well-established biomarker of respiratory inflammation in both clinical practice and epidemiological studies (Adamkiewicz et al., 2004; Dales et al., 2008; Dweik et al., 2011; Liu et al., 2009). However, the epidemiological evidence linking ambient CO and FeNO was scarce and inconsistent (Delfino et al., 2010; Huang et al., 2012; Miranda et al., 2012).

Therefore, we conducted a longitudinal panel study in a group of young healthy adults in Shanghai, China to examine the short-term effects of ambient CO on FeNO.

* Corresponding author. P.O. Box 249, 130 Dong-An Road, Shanghai 200032, China.
*E-mail address:* haidongkan@gmail.com (H. Kan).

http://dx.doi.org/10.1016/j.envpol.2015.07.029
0269-7491/

## 2. Methods

### 2.1. Study design and subjects

The study was performed in a panel of healthy college students during the period of April to June in 2013 in the Fenglin campus of Fudan University, which is located in the central urban area of Shanghai, China. For each subject, the level of FeNO was repeatedly measured at the same time (10–11 a.m. or 2–3 p.m.) on the same day of the week (between Monday and Friday) in order to control for possible circadian rhythm and day-of-week effects. If the subject missed the examination, another measurement was arranged in the next week. This study was approved by the Institutional Review Board at School of Public Health, Fudan University. All written consents were obtained from the participating subjects.

We recruited 75 healthy college students aged 18 years or above who normally lived in the Fenglin campus. Those who had a history of tobacco smoking, alcohol drinking and chronic cardiorespiratory diseases (allergic or non-allergic asthma, bronchitis, etc.) were excluded. Data on individual basic characteristics, such as age, gender, height, weight, were collected during the first visit. Study subjects were also asked to record physical activity level, medication use, acute diseases or symptoms, and the time-location information during the study period.

### 2.2. FeNO measurement

The FeNO levels were measured online by a portable NIOXMINO machine (Aerocrine AB, Solna, Sweden) using the standardized procedures issued by American Thoracic Society (ATS) and European Respiratory Society (ERS) (Anonymous, 2005). Food, beverage, intense exercises were not allowed at least within 1 h before the FeNO measurements. The detailed procedure for FeNO measurement was previously reported (Zhao et al., 2013). Briefly, subjects were required to sit, rinse the mouth twice by drinkable pure water, and then empty theirs lungs by complete expiration. After that, they inhaled NO-free air (by using an NO-scrubber attached with the instrument) to the lung capacity through a disposable filter attached in the machine. Finally, they exhaled the air through the machine at an exhalation rate of 50 ± 5 ml/s. The standard mode of 10 s exhalation time was used in all tests. Maximum 5 repeated tests with 10 min rest between were allowed for subjects who could not successfully complete the test at the first time. The sensor in the device was replaced periodically according to the manufacture's guide.

### 2.3. Exposure assessment

The hourly concentrations of CO and co-pollutants including sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), particulate matter with an aerodynamic meter less than 2.5 μm ($PM_{2.5}$) and particulate matter with an aerodynamic meter less than 10 μm ($PM_{10}$) were measured by a state-controlled fixed-site monitoring station, which was 3.5 km away from the campus. The standard automated continuous monitoring system was applied in the monitoring of these air pollutants. The non-dispersive infrared absorption method was used for the measurement of CO. The differential optical absorption spectroscopy method and the tapered element oscillating microbalance method were used for $SO_2$/$NO_2$ and $PM_{2.5}$/$PM_{10}$, respectively. All monitoring instruments and data reporting system were strictly and regularly validated according to the national standards. The daily mean temperature and relative humidity data were collected from a nearby meteorological station (less than 1 km away from this campus).

### 2.4. Statistical analyses

The FeNO data were approximately log-normal distributed and were thus log-transformed before statistical analyses. Linear mixed-effect models were applied in analyzing the short-term effects of CO on FeNO. CO was entered in the model as a fixed-effect term. Potential confounders were also introduced into the models as fixed-effect terms, including age, gender, body mass index (BMI), temperature, relative humidity, day of week, time of day (binary terms for morning and afternoon) and an indicator of month. Random intercept for subjects was incorporated to account for intra-individual correlations between repeated measurements of FeNO. Moving average CO concentrations in multiple periods up to 72 h preceding the FeNO measurements were introduced into the model one at a time. The moving average of temperature and relative humidity on the current day and previous day was used in all models.

We performed two sensitivity analyses. First, we fit two-pollutant models to assess the stability of CO's effects after controlling for the concomitant exposure to other pollutants. Second, we evaluated the effects of co-pollutants using the same single-pollutant models with CO.

All statistical tests were two-sided, and p-values of $\leq$0.05 were considered statistically significant. All analyses were conducted using SPSS 16.0 software. The results were presented as percent change of FeNO per an interquartile range (IQR) increase in lag-specific air pollutant concentrations.

## 3. Results

### 3.1. Descriptive statistics

We completed 6 follow-ups for 42 subjects and 4 for 33 subjects. For these participants, the average age was 24.5 ± 1.9 years; girls accounted for 65.3% (n = 49); the mean BMI was 22.1 ± 3.0 kg/m$^2$. In total, we obtained 384 measurements of FeNO, 48 of which were considered as invalid in this analysis because of catching cold, experiencing infection or having 20% or above of their time going out of the campus. Therefore, there were totally 336 effective measurements of FeNO. As shown in Table 1, the geometric mean of FeNO was 12.4 ppb. Older subjects (aged 25–29), males and overweight subjects (BMI $\geq$ 24.0 kg/m$^2$) had higher FeNO levels.

During the whole follow-up period, the daily average CO concentration ranged from 0.35 mg/m$^3$ to 1.22 mg/m$^3$ with a mean of 0.77 mg/m$^3$. The air pollutant concentrations at different time lags were summarized in Table 2. There were weak and positive correlations between CO and co-pollutants with *Pearson* correlation coefficient varying between 0.02 and 0.47, but the correlation

**Table 1**
The descriptive statistics of individual characteristics and FeNO levels.

| | Subjects | Measurements | FeNO levels (ppb) | | | |
|---|---|---|---|---|---|---|
| | n (%) | n | Mean ± SD | GM | Median | Range |
| Total | 75 (100) | 336 | 15.3 ± 1.5 | 12.4 | 11.5 | 5–149 |
| **Age (years)** | | | | | | |
| 20–24 | 37 (49.3) | 180 | 12.9 ± 6.7 | 11.6 | 11 | 5–47 |
| 25–29 | 38 (50.7) | 156 | 18.2 ± 2.1 | 13.4 | 12 | 5–149 |
| **Gender** | | | | | | |
| Male | 26 (34.7) | 123 | 17.6 ± 1.5 | 13.9 | 12 | 5–87 |
| Female | 49 (65.3) | 213 | 14.1 ± 1.5 | 11.6 | 11 | 5–149 |
| **BMI (kg/m$^2$)** | | | | | | |
| <24 | 62 (82.7) | 276 | 15.1 ± 1.6 | 12.0 | 11 | 5–149 |
| ≥24 | 13 (17.3) | 60 | 16.5 ± 9.9 | 14.3 | 13 | 6–47 |

Abbreviations: FeNO, fractional exhaled nitric oxide; SD, standard deviation; GM, geometric mean; BMI, body mass index.