Ambient Carbon Monoxide and the Risk of Hospitalization Due to Chronic Obstructive Pulmonary Disease

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Data from recent experimental and clinical studies have indicated that lower concentrations of inhaled carbon monoxide might have beneficial antiinflammatory effects. Inhaled carbon monoxide has the potential to be a therapeutic agent for chronic obstructive pulmonary diseases (COPD). However, population-based epidemiologic studies of environmentally relevant carbon monoxide exposure have generated mixed findings. We conducted a time-series study in Hong Kong to estimate the association of short-term exposure to ambient carbon monoxide with emergency hospitalizations for COPD. We collected daily emergency hospital admission data and air pollution data from January 2001 to December 2007. We used log-linear Poisson models to estimate the associations between daily hospital admissions for COPD and the average daily concentrations of carbon monoxide while controlling for the traffic-related copollutants nitrogen dioxide and particulate matter with an aerodynamic diameter less than 2.5 μm. Results showed that ambient carbon monoxide was negatively associated with the risk of hospitalizations for COPD. After adjustment for levels nitrogen dioxide or particulate matter with an aerodynamic diameter less than 2.5 μm, the negative associations of carbon monoxide with COPD hospitalizations became stronger. The risk estimates were similar for female and male subjects. In conclusion, short-term exposure to ambient carbon monoxide was associated with a decreased risk of hospitalization for COPD, which suggests that carbon monoxide exposure provides some acute protection against exacerbation of COPD.

Chronic obstructive pulmonary disease (COPD), which is a leading cause of morbidity and mortality worldwide (1), is characterized by airflow limitation that is not fully reversible. COPD currently has no cure, and one main objective of therapy for COPD is to reduce the rates of morbidity associated with exacerbations, namely episodes of increased dyspnea and cough and changes in the amount and character of sputum (2). Patients with moderate-to-severe airflow obstruction typically have 1–3 episodes per year (3). In addition to bacterial and viral infections, air pollution is an environmental trigger that exacerbates COPD because of complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution and that leads to an increase in the inflammatory burden (2). Many epidemiologic studies on the association have linked air pollution to increased rates of COPD exacerbations and emergency hospital admissions (4–6). The specific effect of carbon monoxide on COPD, however, has seldom been reported.

The few epidemiologic studies that did examine the association of ambient carbon monoxide with hospital admissions for COPD yielded mixed results (7–9). Moreover, the lack of copollutant models has contributed to the inability to disentangle the effects attributed to carbon monoxide from those of the larger complex air pollution mix (particularly motor vehicle emissions), and this creates uncertainty in interpreting the results observed in the epidemiologic studies.
On the other hand, beneficial antiinflammatory effects under certain circumstances have been suggested in recent experimental and clinical studies (11, 12). The first human pilot study on the association of carbon monoxide with COPD indicated that inhalation of carbon monoxide at a concentration of 100–125 ppm by patients with COPD was feasible and led to reduction of sputum eosinophils and improvement of responsiveness to methacholine (13).

We conducted a time-series study to estimate the association between short-term exposure to ambient carbon monoxide and the risk of hospitalization for COPD in Hong Kong. Given the strong role of traffic as a source of carbon monoxide, we investigated whether associations between carbon monoxide and COPD hospitalizations were robust after adjustment for the traffic-related pollutants particulate matter with an aerodynamic diameter less than 2.5 μm (PM$_{2.5}$) and nitrogen dioxide.

**METHODS**

**Hospitalization data**

Daily data on emergency hospital admissions in Hong Kong were collected from January 1, 2001, to December 31, 2007. The hospitals that were included were publicly funded hospitals that provide 24-hour accident and emergency services and comprise 90% of hospital beds in Hong Kong (14). Patient data captured from the computerized medical record system included age, date of admission, source of admission, hospital, residential address, and principal diagnosis on discharge coded using the *International Classification of Diseases, Ninth Revision*. The codes for COPD were 491, 492, and 496. We constructed daily time series of COPD hospitalization for male and female subjects separately.

**Pollutant and metrology data**

Data on air pollution levels between January 1, 2001, and December 31, 2007, were obtained from the Environmental Protection Department of Hong Kong. The Environmental Protection Department has continuously monitored hourly ambient air pollution levels at 11 background monitoring stations since 1983. Carbon monoxide has been monitored in background stations in 3 districts: Tsuen Wan, which is an urban residential area; Tung Chung, which is a new town; and Tap Mum, which is a rural area (Figure 1). Daily 24-hour average concentrations across these 3 background stations were calculated for carbon monoxide and for the traffic-related copollutants PM$_{2.5}$ and nitrogen dioxide. Sensitivity analyses were performed using daily 1-hour maximum carbon monoxide levels. Meteorological data on daily average temperature and humidity were obtained from the Hong Kong Observatory for the same study period.

![Figure 1. Locations of the 3 background air monitoring stations included in the present analysis, Hong Kong, China, 2001–2007. The whole territory of Hong Kong is approximately 40 km by 30 km in linear dimensions. TC, Tung Chung; TM, Tap Mum, TW, Tsuen Wan.](image-url)
Statistical methods

The risk of emergency hospitalization associated with inhalation of carbon monoxide was estimated using a log-linear overdispersed Poisson time-series model. To reduce the problems associated with multiple testing and model-selection strategies, we followed some previous time-series studies to select a priori the model specification and degree of freedom (df) for the time trend and other meteorological variables (15, 16). We used 8 df per year for the time trend, 3 df for the same-day temperature, 3 df for the average of lag 1 through 3 daytime temperature, and 3 df for the same-day humidity. Day of the week and public holidays were also included in the model as dummy variables. The sensitivity of the key findings were assessed in terms of the degrees of freedom in the smooth function of time to adjust for seasonal and long-term trends, the lag of exposure to carbon monoxide, and the degrees of freedom in the smoothers of temperature and humidity. We also compared the main results with those from alternative analytical methods, such as case-crossover analysis (17) and generalized additive modeling methods, which aim to minimize the partial autocorrelation function of residuals (18).

In single-day lag models, we examined 0-, 1-, and 2-day lag relationships. We also used a constrained (second-degree polynomial) distributed lag model using the dlnm package (version 1.6.3) in R (R Foundation for Statistical Computing, Vienna, Austria) that was developed by Gasparrini (19) to examine the association of cumulative exposure from lag 0 to lag 2 days (lag 02) with hospitalizations for COPD. As traffic is one major source of carbon monoxide, we investigated whether associations between carbon monoxide and emergency hospitalizations were sensitive to adjustment for the traffic-related pollutants PM$_{2.5}$ and nitrogen dioxide in 2-pollutant models in which copollutants were included simultaneously at the same lag. Models were fitted for both the female and male populations. In order to justify the assumption of linearity between the logarithm of emergency hospital admissions and pollutant concentrations, we applied second-degree polynomial models to examine variation in the exposure-response relation across the exposure range. The data were analyzed using the statistical software R, version 3.0.3 (20), and the mgcv package (21). The excess risk estimates are presented as the percent change in daily hospital admissions per each interquartile-range increment increase in carbon monoxide concentrations.

RESULTS

Table 1 provides descriptive statistics on pollution, weather, and hospitalization data. Carbon monoxide concentrations were low during the study period, with a daily average of 0.6 ppm and a 1-hour maximum of 0.8 ppm in background stations; the WHO 8-hour air quality guideline for carbon monoxide is 8.7 ppm. Carbon monoxide concentrations were moderately correlated with both nitrogen dioxide and PM$_{2.5}$ levels; the correlation coefficients were 0.57 and 0.59, respectively. From January 1, 2001, to December 31, 2007, a total of 117,329 hospital admissions for COPD through emergency departments were recorded, with a daily average of 57 admissions. The mean age of the COPD patients was 80.7 years for female subjects and 74.2 years for male subjects.

Table 2 shows the percentage change in total emergency hospital admissions for COPD per each interquartile-range increment increase in pollutant concentration at lag 0, 1, 2 and 02 days in single-pollutant and 2-pollutant models. The former 3 were risk estimates for the single days of lag 0, 1, and 2, respectively, whereas lag 02 was an estimate of the association of cumulative exposure of from lag 0 to lag 2 days

<table>
<thead>
<tr>
<th>Table 1. Distribution of Air Pollution Concentrations, Weather Factors, and Emergency Hospital Admissions for Chronic Obstructive Pulmonary Disease, Hong Kong, 2001–2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Air pollution</td>
</tr>
<tr>
<td>24-Hour mean carbon monoxide level, ppm</td>
</tr>
<tr>
<td>1-Hour maximum carbon monoxide level, ppm</td>
</tr>
<tr>
<td>PM$_{2.5}$, µg/m$^3$</td>
</tr>
<tr>
<td>Nitrogen dioxide, µg/m$^3$</td>
</tr>
<tr>
<td>Weather</td>
</tr>
<tr>
<td>Temperature, °C</td>
</tr>
<tr>
<td>Humidity, %</td>
</tr>
<tr>
<td>Sex of subjects admitted for COPD</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm; SD, standard deviation.
with hospitalization for COPD. Both nitrogen dioxide and PM$_{2.5}$ were associated with higher risks of COPD hospitalizations. The risk estimates for carbon monoxide, however, were negative for all 3 single-day lags, and the lag 1 day carbon monoxide was associated with the largest COPD risk reduction. For the cumulative risk estimates of the distributed lag of 0–2 days, one interquartile-range increment increase in background carbon monoxide (0.4 ppm) was associated with −1.8% (95% confidence interval: −3.1, −0.4) change in COPD hospitalizations according to the single-pollutant model; the negative association became stronger when we adjusted for nitrogen dioxide or PM$_{2.5}$ in the 2-pollutant models. Sensitivity analysis found that the risk estimates for carbon monoxide were largely robust to the degree of adjustment for seasonality and trend, model specifications for weather variables, the lag of carbon monoxide exposure, and the usage of other carbon monoxide measurement (1-hour maximum; Table 3). The results from these a priori models were also comparable to those from case-crossover analyses and those from generalized additive models chosen by minimizing the partial autocorrelation function of residuals.

Exposure to the 2 copollutants (PM$_{2.5}$ and nitrogen dioxide) was associated with an increased risk of COPD hospitalization. One interquartile-range increment increase in PM$_{2.5}$ (31.1 µg/m$^3$) corresponded to a 5.4% (95% confidence interval: 3.9, 6.9) increase in COPD hospitalizations according to the single-pollutant model; the risk estimate was robust to adjustment for carbon monoxide or nitrogen dioxide. One interquartile-range increment increase in nitrogen dioxide (24.2 µg/m$^3$) corresponded to a 4.2% (95% confidence

### Table 2. Percentage Change in Total Emergency Hospital Admissions for Chronic Obstructive Pulmonary Disease per Each Interquartile-Range Increment Increase in 24-Hour Daily Mean Concentrations of Pollutants in Single-Pollutant and 2-Pollutant Models*, Hong Kong, 2001–2007

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Lag 0</th>
<th>Lag 1</th>
<th>Lag 2</th>
<th>Lag 02$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
<td>% Change</td>
<td>95% CI</td>
</tr>
<tr>
<td>Carbon monoxide only</td>
<td>−1.4</td>
<td>−2.4, −0.3</td>
<td>−1.6</td>
<td>−2.6, −0.5</td>
</tr>
<tr>
<td>Carbon monoxide with nitrogen dioxide</td>
<td>−3.3</td>
<td>−4.5, −2.1</td>
<td>−4.4</td>
<td>−5.6, −3.2</td>
</tr>
<tr>
<td>Carbon monoxide with PM$_{2.5}$ only</td>
<td>−3.3</td>
<td>−4.5, −2.1</td>
<td>−3.0</td>
<td>−4.2, −1.8</td>
</tr>
<tr>
<td>PM$_{2.5}$ only</td>
<td>1.8</td>
<td>0.6, 3.0</td>
<td>3.1</td>
<td>2.0, 4.3</td>
</tr>
<tr>
<td>PM$_{2.5}$ with carbon monoxide</td>
<td>3.9</td>
<td>2.5, 5.4</td>
<td>5.7</td>
<td>4.4, 7.1</td>
</tr>
<tr>
<td>PM$_{2.5}$ with nitrogen dioxide</td>
<td>0.7</td>
<td>−0.9, 2.2</td>
<td>4.1</td>
<td>2.6, 5.6</td>
</tr>
<tr>
<td>Nitrogen dioxide only</td>
<td>2.1</td>
<td>0.9, 3.2</td>
<td>1.3</td>
<td>0.2, 2.4</td>
</tr>
<tr>
<td>Nitrogen dioxide with carbon monoxide</td>
<td>4.0</td>
<td>2.7, 5.4</td>
<td>2.9</td>
<td>1.6, 4.2</td>
</tr>
<tr>
<td>Nitrogen dioxide with PM$_{2.5}$ only</td>
<td>1.6</td>
<td>0.2, 3.1</td>
<td>−1.4</td>
<td>−2.8, 0.1</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm.

$^a$ The 24-hour mean concentrations of carbon monoxide were used.

$^b$ Cumulative risk distributed from lag 0 to lag 2 days.

### Table 3. Percentage Change in Total Emergency Hospital Admissions for Chronic Obstructive Pulmonary Disease per Each Interquartile-Range Increment Increase in 1-Hour Daily Maximum Carbon Monoxide Concentrations in Single-Pollutant and 2-Pollutant Models*, Hong Kong, 2001–2007

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Lag 0</th>
<th>Lag 1</th>
<th>Lag 2</th>
<th>Lag 02$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
<td>% Change</td>
<td>95% CI</td>
</tr>
<tr>
<td>Carbon monoxide only</td>
<td>−1.0</td>
<td>−1.9, −0.1</td>
<td>−1.5</td>
<td>−2.4, −0.6</td>
</tr>
<tr>
<td>Carbon monoxide with nitrogen dioxide</td>
<td>−2.5</td>
<td>−3.5, −1.4</td>
<td>−3.8</td>
<td>−4.9, −2.8</td>
</tr>
<tr>
<td>Carbon monoxide with PM$_{2.5}$ only</td>
<td>−2.8</td>
<td>−3.9, −1.8</td>
<td>−3.1</td>
<td>−4.2, −2.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm.

$^a$ The 1-hour maximum concentrations of carbon monoxide were used.

$^b$ Cumulative risk distributed from lag 0 to lag 2 days.
interval: 2.7, 5.7) increase in COPD hospitalizations according to the single-pollutant model; the risk estimate was robust to adjustment for carbon monoxide but was attenuated to null after adjustment for PM$_{2.5}$.

Figure 2 shows the percentage change in emergency hospital admissions for COPD per interquartile-range increment increase in pollutant concentrations at distributed lags of 0–2 days in single-pollutant and 2-pollutant models, Hong Kong, China, 2001–2007. The results for the 2 sexes were compared. The points indicate central estimates. CO, carbon monoxide; NO$_2$, nitrogen dioxide; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm. Bars, 95% confidence intervals.

Figure 3 shows the second-degree polynomial exposure-response curves for daily average pollutant concentration at distributed lags of 0–2 days and risk of emergency hospital admissions for COPD in single-pollutant and 2-pollutant models. The exposure-response curves for carbon monoxide and COPD hospitalizations were approximately linear in all the single-pollutant and 2-pollutant models; the downward slope was steeper when we adjusted for PM$_{2.5}$ or nitrogen dioxide. In both sexes, exposure to the 2 copollutants was associated with increased risks of COPD hospitalizations except that the risk estimates for nitrogen dioxide became statistically insignificant after adjustment for PM$_{2.5}$ levels.

Figure 2. Percentage change in emergency hospital admissions for chronic obstructive pulmonary disease per interquartile-range increment increase in pollutant concentrations at distributed lags of 0–2 days in single-pollutant and 2-pollutant models, Hong Kong, China, 2001–2007. The results for the 2 sexes were compared. The points indicate central estimates. CO, carbon monoxide; NO$_2$, nitrogen dioxide; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm. Bars, 95% confidence intervals.
we adjusted for carbon monoxide. The upward slope for the exposure-response curve of nitrogen dioxide and COPD hospitalizations was substantially reduced when we adjusted for PM$_{2.5}$.

DISCUSSION

To our knowledge, this was the first population-based study to demonstrate the negative association between ambient carbon monoxide and hospital admissions for COPD. After adjustment for nitrogen dioxide or PM$_{2.5}$, the negative associations of carbon monoxide with hospitalization for COPD became stronger. The risk estimates were similar between female and male subjects, although the uncertainties of the risk estimates were larger for the former than for the latter. The risk estimates for PM$_{2.5}$ were robust to adjustment for carbon monoxide or nitrogen dioxide, whereas those for nitrogen dioxide were attenuated to null after adjustment for PM$_{2.5}$.

When examining the association of ambient carbon monoxide with COPD hospitalizations, we considered confounding by other traffic-related pollutants. After adjustment for nitrogen dioxide or PM$_{2.5}$, the negative associations of carbon monoxide with COPD became stronger. Many of the

Figure 3. Second-degree polynomial exposure-response curves for daily average pollutant concentrations at distributed lags of 0–2 days and risk of emergency hospital admissions for chronic obstructive pulmonary disease in single-pollutant and 2-pollutant models, Hong Kong, China, 2001–2007. The solid line represents central estimates; the dashed lines represent 95% confidence intervals. CO, carbon monoxide; NO$_2$, nitrogen dioxide; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm.
earlier epidemiologic studies that showed the adverse effects of carbon monoxide did not adjust for the confounding effect of copollutants. In the studies that evaluated multipollutant models, positive associations between carbon monoxide concentrations and respiratory outcomes did not persist after adjustment for nitrogen dioxide or PM$_{10}$ (9, 15, 22, 23). In a time-series study conducted in Vancouver, Canada (9), ambient carbon monoxide was associated with an increase in the number of hospital admissions for COPD in single-pollutant models, whereas the risk estimates for carbon monoxide were attenuated to null after adjustment for nitrogen dioxide or PM. In New York City, carbon monoxide was shown to increase emergency department visits for asthma in single-pollutant models, but the risk estimate for carbon monoxide became negative once nitrogen dioxide was included in the model (15). These results may reflect the actual differences in health effects of the corresponding pollutants, but it is difficult to differentiate between such factors in multipollutant models. In the present study, carbon monoxide was negatively associated with COPD hospitalizations in both single-pollutant and multipollutant models, which made it more likely that the negative risk estimates reflected the actual beneficial effects of carbon monoxide.

The negative association between carbon monoxide and COPD hospitalizations appeared to be similar in male and female subjects, although the uncertainties of the risk estimates were larger for female subjects than for male subjects. Carbon monoxide exposure profiles might also differ between the sexes. The present study focused on only outdoor carbon monoxide concentrations; however, indoor carbon monoxide also contributes to personal exposure. Carbon monoxide is produced indoors by combustion sources (cooking and heating) and is also introduced through the infiltration of carbon monoxide from outdoor air into the indoor environment. Tobacco smoke can be another major source of indoor exposure. In Hong Kong, the smoking prevalence has been substantially lower in female subjects than in male subjects. Although the carbon monoxide exposure profiles may differ between sexes, there is no biological evidence that carbon monoxide disproportionately affects either sex (10).

Exposure to the copollutant PM$_{2.5}$ was associated with an increased risk of hospitalization for COPD. The risk estimates for PM$_{2.5}$ were robust to adjustment for carbon monoxide or nitrogen dioxide, whereas those for nitrogen dioxide were attenuated to null after adjustment for PM$_{2.5}$. As noted by Sint et al. (24), there is compelling evidence that ambient air pollution particles can exacerbate preexisting COPD, resulting in increased morbidity and mortality. In Hong Kong, we have also demonstrated the association between short-term exposure to PM$_{2.5}$ and hospitalizations for COPD (25). The effect of nitrogen dioxide on COPD hospitalizations, however, is uncertain according to a review from the US Environmental Protection Agency (10). Although many studies observed positive associations between nitrogen dioxide concentrations and hospitalizations for all respiratory diseases and asthma, the limited evidence does not support a relationship between COPD hospitalizations and ambient nitrogen dioxide levels.

The short-term beneficial effects of ambient carbon monoxide on COPD exacerbations are biologically plausible. COPD is an inflammatory disease. The antiinflammatory effects of exogenous carbon monoxide have been suggested in recent experimental and clinical studies (11, 12, 26). The first human pilot study of the effect of carbon monoxide on COPD indicated that inhalation of carbon monoxide at a concentration of 100–125 ppm by COPD patients was feasible and led to trends in reduction of sputum eosinophils and improvement of responsiveness to methacholine (13). The antimicrobial effects have also been extensively reviewed in the literature (27–29). Carbon monoxide administered exogenously via carbon monoxide—releasing molecules was able to kill bacteria (28). Inhalation of carbon monoxide resulted in preservation of organ function and improved survival in rodents who had previously been treated with endotoxin (30). In a recent time-series study of respiratory tract infections in Hong Kong, we showed that short-term exposure to ambient carbon monoxide was associated with a decreased risk of hospital admission for respiratory tract infections, suggesting some acute protection from exposure to low levels of ambient carbon monoxide (31). The decreased risk of airway infection associated with exposure to ambient carbon monoxide might in turn reduce the risk of COPD exacerbations and hospitalizations.

The dose-response curves of the relationship between carbon monoxide and COPD hospitalizations were essentially linear at the ambient levels of the 0.1–2.1 ppm, much lower than the carbon monoxide levels administered in experimental investigations (approximately 50 ppm) (10, 11). Although the 1-hourly maximum carbon monoxide concentration was 3.2 ppm in the present study, for microenvironments that are in or near vehicles, the actual carbon monoxide exposure levels can be much higher than the monitoring station measurements. Moreover, there have been experimental data that suggested that inhaled carbon monoxide levels as low as 10 ppm can protect rats against lethal endotoxemia and induce antioxidant defenses in bovine pulmonary artery endothelial cells. In a rat model of lipopolysaccharide-induced multiorgan failure, exposure to a low concentration of carbon monoxide (10 ppm) for only 1 hour imparted a potent defense against lethal endotoxemia and effectively inhibited the inflammatory response (32). Exposure of bovine pulmonary artery endothelial cells to carbon monoxide concentrations of 100 ppm for more than 1 hour caused cell death, whereas preconditioning of these endothelial cells with 10 ppm of carbon monoxide enabled them to resist the detrimental effects of exposure to concentrations of 100 ppm (33). Those authors hypothesized that low concentrations of carbon monoxide may cause nonlethal oxidative stress and thus induce antioxidant defenses in endothelial cells.

Given the ecological design of the present study, caution should be exercised when inferring cause-effect relations between low levels of environmental carbon monoxide exposure and COPD hospitalizations. Misclassifications in health outcomes and carbon monoxide exposures were likely. We used the International Classification of Diseases, Ninth Revision codes as the operational definition of COPD. These administrative codes might include a heterogeneous group of hospitalizations with differing risks, diagnoses, and concomitant conditions. Although the misclassification might not cause any differential bias, it warrants caution in the interpretation of
negative associations between exposure to environmental carbon monoxide and COPD. Merely modeling the associations between air pollution and health is not adequate because the association between an exposure and an outcome may not equal the causal effect, even after adjustments to the model for covariates. We cannot rule out the possibility of residual confounding by an unmeasured factor. Based on aggregated measures of exposure and health outcomes, the time-series findings in the current study were subject to ecological fallacy. The preliminary hypothesis of carbon monoxide protection against COPD exacerbation can be further tested by investigations, such as intensive longitudinal studies of symptoms in a cohort of patients with COPD who undergo personal monitoring of carbon monoxide exposures. Exposure misclassification was also likely because carbon monoxide concentrations are spatially heterogeneous within a city, and the small number of fixed monitoring stations might not be representative enough of the general population exposure. Moreover, the effect of prolonged carbon monoxide exposure on COPD is unknown. In the present time-series study, we examined the association of short-term exposure to ambient carbon monoxide with only emergency hospital admissions for COPD, not with scheduled outpatient clinic visits. The present study design allows us to infer only the acute effects, not the long-term effects, which need to be examined in experimental studies or epidemiologic designs, such as cohort or case-control studies.

In conclusion, we found that low levels of environmental carbon monoxide were associated with a reduced risk of hospitalization for COPD. This association could be due to residual confounding by an unmeasured factor, and the ecological design of this study warrants caution in inferring cause-effect relations. Nevertheless, the hypothesis that ambient carbon monoxide protects against COPD exacerbations should be further tested in longitudinal cohort studies because such a mechanism is possible based on experimental studies of systemic inflammation and could underlie the observed association of carbon monoxide exposure with lower risk of COPD hospitalizations. However, although this is an interesting etiological possibility, caution should be exercised from a public-health perspective. Even if the beneficial effects of ambient carbon monoxide are confirmed for a segment of COPD patients, there may be detrimental effects on other subpopulations or other health end points, and there is the complication that carbon monoxide is coemitted with a number of other air pollutants.

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Conflict of interest: none declared.

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