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<th><strong>Title</strong></th>
<th>Ambient carbon monoxide and the risk of hospitalization due to chronic obstructive pulmonary disease</th>
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<tr>
<td><strong>Author(s)</strong></td>
<td>Tian, L; Ho, KF; Wang, T; Qiu, H; Pun, VC; Chan, CS; Louie, PKK; Yu, ITS</td>
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<tr>
<td><strong>Citation</strong></td>
<td>American Journal of Epidemiology, 2014, v. 180 n. 12, p. 1159-1167</td>
</tr>
<tr>
<td><strong>Issued Date</strong></td>
<td>2014</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10722/207836">http://hdl.handle.net/10722/207836</a></td>
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<tr>
<td><strong>Rights</strong></td>
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</table>
Ambient Carbon Monoxide Associated with Reduced Risk of COPD Hospitalizations

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Short Title: Ambient CO and Reduced Risk of COPD

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The authors declare we have no actual or potential competing financial interests.

Funding support: None

Word Count: 190 (Abstract), 3136 (main text)

Abbreviations:
CO: carbon monoxide; COPD: chronic obstructive pulmonary diseases; df: degree of freedom; ER: Excess risk; IQR, interquartile range; NO2, nitrogen dioxide; PM2.5, particulate matter with aerodynamic diameter less than 2.5 microns.

Acknowledgement
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Author’s contributions to the study: LWT, KFH and ITY defined the research theme. LWT, KFH, WT, HQ and VCP analyzed the data, interpreted the results and wrote the paper. JCC and PKL co-worked on associated data collection and their interpretation.

Authors thank the Environmental Protection Department of the Hong Kong Special Administrative Region for supplying the air monitoring data; Hospital Authority for providing the hospital admission data and Hong Kong Observatory for providing weather data for this study.
Abstract

Recent experimental and clinical studies suggested that inhaled carbon monoxide at lower concentrations may have beneficial anti-inflammatory effects. Inhaled carbon monoxide has the potential to be as a therapeutic agent for chronic obstructive pulmonary diseases (COPD). Population-based epidemiological studies of environmentally relevant carbon monoxide exposure, however, generated mixed findings. We conducted a time series study in Hong Kong to estimate the short-term association of 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 daily average concentrations of carbon monoxide, controlling for other traffic related co-pollutants: nitrogen dioxide and PM$_{2.5}$. Results showed that ambient carbon monoxide was negatively associated with the risk of COPD hospitalizations. After adjustment for nitrogen dioxide or PM$_{2.5}$, the negative associations of carbon monoxide with COPD became stronger. The risk estimates were similar between females and males. In conclusion, short-term exposure to ambient carbon monoxide was associated with decreased risk of hospitalizations for COPD, suggesting some acute protection of carbon monoxide exposure against COPD exacerbations.

Key Words: Carbon Monoxide, Chronic obstructive pulmonary disease, Time series study
INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality worldwide (1), is a disease state characterized by airflow limitation that is not fully reversible. COPD has no cure yet and one main objective of therapy for COPD is to reduce the morbidity associated with exacerbations, episodes of increased dyspnea and cough and change in the amount and character of sputum (2). Patients with moderate to severe airflow obstruction have one to three episodes per year (3). Besides bacterial or viral infections, air pollution is an environmental trigger for acute exacerbation of COPD, which result from complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution and lead to an increase in the inflammatory burden (2). Many epidemiological studies linked air pollution to increased COPD exacerbations and emergency hospital admissions (4–6). The particular effect of carbon monoxide (CO) on COPD, however, was seldom reported.

The few epidemiological studies that did examine the ambient carbon monoxide on COPD admissions 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 the larger complex air pollution mix (particularly motor vehicle emissions), and this creates uncertainty in interpreting the results observed in the epidemiological studies (10). On the other hand, beneficial anti-inflammatory effects under certain circumstances have been suggested by recent experimental and clinical studies (11,12). The first human pilot study on the effect of carbon monoxide in COPD indicated that inhalation of 100–125 ppm carbon monoxide by COPD patients was feasible and led to trends in 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 risk of COPD hospitalizations in Hong Kong. Given the strong role of traffic as a source for carbon monoxide, we investigated whether associations between carbon monoxide and COPD hospitalizations were robust to adjustment by traffic-related pollutants PM$_{2.5}$ or nitrogen dioxide.
METHODS

Hospitalization data
Daily emergency hospital admission data in Hong Kong were collected from January 1, 2001 to December 31, 2007. The hospitals included for compilation of hospital admissions were publicly funded hospitals that provide 24-hour accident and emergency services and cover 90% of hospital beds for Hong Kong residents (14). Patient data captured from the computerized medical record system include age, date of admission, source of admission, hospital, residential address and principal diagnosis on discharge coded with the 9th revision of the international classification of diseases (ICD-9). The codes of the 9th revision of the international classification of diseases for COPD were: 491, 492 and 496. Daily time series of COPD hospitalization were constructed for males and females respectively.

Pollutant and meteorology data
Air pollution data between January 1, 2001 and December 31, 2007 were obtained from the Environmental Protection Department (EPD) of Hong Kong. EPD has continuously monitored hourly ambient air pollution levels at 11 background monitoring stations since 1983. But the carbon monoxide has been monitored in 3 background stations: Tsuen Wan (TW) in the urban residential area, Tung Chung (TC) in the new town and Tap Mum (TM) in the rural area (see Figure 1). Daily 24-hr average concentrations across these three background stations were calculated for carbon monoxide and traffic related co-pollutants PM$_{2.5}$ and nitrogen dioxide, respectively. Sensitivity analyses were performed by using daily 1-hour maximum for 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 here.)

Statistical methods
Risk of emergency hospitalization associated with carbon monoxide was estimated in 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 model specification and the degree of freedom (df) for
time trend and other meteorological variables (15,16). We used 8 degrees of freedom (df) per year for time trend, 3 df for the same-day temperature, 3 df for the average of lag 1 through 3 day temperature, and 3 df for the same-day humidity. Day of 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 the generalized additive modeling methods that 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 employed a constrained (second-degree polynomial) distributed lag model using ‘dlnm’ (version 1.6.3), an R package developed by Gasparrini et al. (19), to examine the association of cumulative exposure from lag 0 to lag 2 days (lag 02 thereafter) with COPD hospitalizations. As traffic is one major source of carbon monoxide, we investigated whether associations between carbon monoxide and emergency hospitalizations were sensitive to the adjustment for traffic-related pollutants PM$_{2.5}$ and nitrogen dioxide, respectively, in two-pollutant models where co-pollutants were included simultaneously at the same lag. Models were fit for the female and male populations, respectively. 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 (ER) estimates are presented as the percent change in daily hospital admissions per interquartile range (IQR) increment of carbon monoxide concentrations.

**RESULTS**

(Table 1 here.)

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 1-hour maximum of 0.8 ppm in background stations, compared with the
WHO 8-hour air quality guideline for carbon monoxide: 8.7 ppm. Carbon monoxide concentrations were moderately correlated with both nitrogen dioxide and PM$_{2.5}$; the correlation coefficients were 0.57 and 0.59, respectively. From 1 January 2001 to 31 December 2007, a total of 117,329 hospital admissions through accident and emergency were recorded for COPD, which had daily admissions of 57 on average. The mean age of the COPD patients was 80.7 for females and 74.2 for males.

(Table 2 here.)

Table 2 shows the percentage change in total emergency hospital admissions for COPD per IQR increment in pollutant concentration at lag 0, 1, 2 and 02 days in single pollutant and two-pollutant models. The former three were risk estimates for the single days of lag 0, 1, and 2, respectively, while the last one for lag 02 was to estimate the association of cumulative exposure of from lag 0 to lag 2 days with COPD hospitalizations. Both nitrogen dioxide and PM$_{2.5}$ were associated with increased risks of COPD hospitalizations. The risk estimates for carbon monoxide, however, were negative for all three 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 to 2 days, one IQR increment in background carbon monoxide (0.4 ppm) was associated with -1.8% (95% CI, -3.1 to -0.4) change in COPD hospitalizations according to the single-pollutant model; the negative association became stronger when nitrogen dioxide or PM$_{2.5}$ was adjusted for in two-pollutant models, respectively. Sensitivity analysis found that the risk estimates of 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 generalized additive models chosen by minimizing the partial autocorrelation function of residuals.

The two copollutants (PM$_{2.5}$ and nitrogen dioxide) were associated with increased risks of COPD hospitalizations. One IQR increment in PM$_{2.5}$ (31.1 μg/m$^3$) corresponded to 5.4% (95% CI, 3.9 to 6.9) increase in COPD hospitalizations according to the single-pollutant model; the risk estimate was robust to adjustment by carbon monoxide or nitrogen dioxide. One IQR increment in nitrogen dioxide (24.2 μg/m$^3$) corresponded to 4.2% (95% CI, 2.7 to 5.7) increase in COPD hospitalizations according to the single-
pollutant model; the risk estimate was robust to adjustment by carbon monoxide, but attenuated to null after adjustment for PM$_{2.5}$.

(Figure 2 here.)

Figure 2 shows the percentage change in emergency hospital admissions for COPD per IQR increment in pollutant concentrations at distributed lags of 0 to 2 days in single pollutant models and two-pollutant models, respectively. The risk estimates were similar among females and males although the uncertainties of the risk estimates were larger for females than for males; one underlying factor could be the smaller number of COPD admissions among females (11 cases per day on average) than males (46 per day). Negative associations were found between carbon monoxide concentrations and COPD; the negative associations became stronger when PM$_{2.5}$ or nitrogen dioxide was adjusted for. In both genders, the two copollutants (PM$_{2.5}$ and nitrogen dioxide) were associated with increased risks of COPD hospitalizations except that the risk estimates for nitrogen dioxide turned statistically insignificant after adjustment for PM$_{2.5}$.

(Figure 3 here.)

Figure 3 shows the second-degree polynomial exposure-response curves for daily average pollutant concentration at distributed lags of 0 to 2 days and risk of emergency hospital admissions for COPD in single-pollutant models and two-pollutant models. The exposure-response curves for carbon monoxide and COPD hospitalizations were approximately linear in all the single- and two-pollutant models; the downward slope was steeper when PM$_{2.5}$ or nitrogen dioxide was adjusted for. The exposure-response curves for PM$_{2.5}$ and COPD hospitalizations were linear in all the single- and two-pollutant models; the upward slope appeared steeper when carbon monoxide was adjusted for. The upward slope for the exposure-response curve of nitrogen dioxide and COPD hospitalizations was substantially reduced when PM$_{2.5}$ was adjusted for.

**DISCUSSION**

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 COPD became stronger. The risk estimates were similar between females and males although
the uncertainties of the risk estimates were larger for females than for males. The risk estimates for PM$_{2.5}$ were robust to adjustment by 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 earlier epidemiological studies showing the adverse effects of carbon monoxide did not adjust for the confounding effect of co-pollutants. In the studies that evaluated multi-pollutant models, positive associations between carbon monoxide concentrations and respiratory outcomes did not persist when adjusted by 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 increased COPD hospital admissions in single-pollutant models whereas the risk estimates for carbon monoxide were attenuated to null when adjusting for nitrogen dioxide or PM. In New York City, carbon monoxide was shown to increase asthma emergency department visits in single-pollutant models but the risk estimate for carbon monoxide was turned 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 such factors in multi-pollutant models. In the present study, carbon monoxide was negatively associated with COPD hospitalizations in both single- and multi-pollutant models, which made it more likely that the negative risk estimates reflect the actual beneficial effects of carbon monoxide.

The negative association between carbon monoxide and COPD hospitalizations appeared to be similar in males and females although the uncertainties of the risk estimates were larger for females than for males. Carbon monoxide exposure profiles might also differ between males and females. The current study focused on only outdoor carbon monoxide concentrations whereas 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 females than in males. Although the carbon monoxide exposure
profiles may differ between genders, there is no biological evidence that carbon monoxide disproportionately affect males or females (10).

The copollutant PM$_{2.5}$ was associated with increased risk of COPD hospitalizations. The risk estimates for PM$_{2.5}$ were robust to adjustment by carbon monoxide or nitrogen dioxide whereas those for nitrogen dioxide were attenuated to null after adjustment for PM$_{2.5}$. As reviewed 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 of short-term exposure to PM$_{2.5}$ and COPD hospitalizations (25). The effect of nitrogen dioxide on COPD hospitalizations, however, is uncertain according to the USEPA review (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 against COPD exacerbations are biologically plausible. COPD is an inflammatory disease. The anti-inflammatory effects of exogenous carbon monoxide has been suggested in recent experimental and clinical studies (11,12,26). The first human pilot study on the effect of carbon monoxide in COPD indicated that inhalation of 100–125 ppm carbon monoxide 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). Exogenous administration of carbon monoxide, via carbon monoxide -releasing molecules (CORMs), was able to kill bacteria (28). Inhaled carbon monoxide resulted in preservation of organ function and improved survival of rodents previously treated with endotoxin (30). In a recent time-series study of respiratory tract infections (RTI) in Hong Kong, we have shown that short-term exposure to ambient carbon monoxide was associated with decreased risk of hospital admissions for RTI, suggesting some acute protection of low ambient carbon monoxide exposure (31). The decreased risk of airway infection associated with 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 to 2.1 ppm, much lower than the carbon monoxide levels administered in experimental investigations (around 50 ppm) (10,11). Although the one-hour daily maximum of carbon monoxide concentration was 3.2 ppm in the current 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 to suggest 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 (LPS)-induced multiorgan failure, exposure to a low concentration of carbon monoxide at 10 ppm for only 1 h imparted a potent defense against lethal endotoxemia and effectively inhibited the inflammatory response (32). Exposure of bovine pulmonary artery endothelial cells to 100 ppm carbon monoxide for more than 1 h caused cell death, whereas preconditioning of these endothelial cells with 10 ppm carbon monoxide enabled them to resist the detrimental effects of 100 ppm carbon monoxide exposure (33). These 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 in inferring cause-effect relations between low environmental carbon monoxide exposure and COPD hospitalizations. Misclassifications in health outcomes and carbon monoxide exposures were both likely. We used the 9th revision of the international classification of diseases codes as the operational definition of COPD. These administrative codes might include a heterogeneous group of hospitalizations with differing risks, diagnoses and co-morbidities. Although the misclassification might not cause any differential bias, it warrants caution in the interpretation of negative associations between 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 model adjustments 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 the carbon monoxide protection against COPD exacerbation can be further tested by
investigations such as intensive longitudinal studies of symptoms in a cohort of COPD patients with 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 current time series study, we examined only the short-term association of ambient carbon monoxide with emergency admissions of COPD, but not with scheduled outpatient clinic visits. The current study design only allows us to infer about the acute effects but not the long-term effects which needs to be examined by experimental studies or epidemiological designs such as cohort or case-control studies.

In conclusion, we found low environmental carbon monoxide associated with reduced risk of daily COPD hospitalizations. 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 can 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, while 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 endpoints, and there is the complication that carbon monoxide is co- emitted with a number of other air pollutants.
REFERENCES


Table 1: Distribution of Air Pollution Concentrations, Weather Factors, and Emergency Hospital Admissions for COPD in Hong Kong, 2001-2007

<table>
<thead>
<tr>
<th>Variables</th>
<th>Days</th>
<th>Mean</th>
<th>SD</th>
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<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>Max</th>
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<td></td>
<td></td>
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<tr>
<td>CO (ppm, 24-h mean)</td>
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<td>0.2</td>
<td>0.1</td>
<td>0.4</td>
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<td>0.8</td>
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<tr>
<td>CO (ppm, 1-h max)</td>
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<td>0.8</td>
<td>0.4</td>
<td>0.1</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
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<td>2556</td>
<td>37.6</td>
<td>22.3</td>
<td>6.8</td>
<td>19.4</td>
<td>33.2</td>
<td>50.5</td>
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<td>NO$_2$ ($\mu$ g/m$^3$)</td>
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<td>39.3</td>
<td>51.8</td>
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<td>Temperature (°C)</td>
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<td>14</td>
<td>17</td>
<td>48</td>
<td>56</td>
<td>66</td>
<td>117</td>
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Abbreviation: COPD, chronic obstructive pulmonary diseases; CO, carbon monoxide; NO$_2$, nitrogen dioxide; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 microns; SD, standard deviation; x%, x$^{th}$ percentile; Min, minimum; Max, maximum.
Table 2: Percentage change in total emergency hospital admissions for COPD per IQR increment in 24-hour daily mean concentrations of pollutant at Lag 0, 1, 2 and 02 days in single pollutant and two-pollutant models 

<table>
<thead>
<tr>
<th>Pollutants</th>
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<th>Lag1</th>
<th>Lag2</th>
<th>Lag02</th>
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<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
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<td>95% CI</td>
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<td>-1.6</td>
<td>-2.6, -0.5</td>
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<td>-4.4</td>
<td>-5.6, -3.2</td>
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<tr>
<td>CO with PM₂.₅</td>
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<td>-4.5, -2.1</td>
<td>-3.0</td>
<td>-4.2, -1.8</td>
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<td>PM₂.₅ with CO</td>
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<td>PM₂.₅ with NO₂</td>
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<td>-0.9, 2.2</td>
<td>4.1</td>
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<td>0.9, 3.2</td>
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<td>0.2, 2.4</td>
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<td>NO₂ with CO</td>
<td>4.0</td>
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<td>NO₂ with PM₂.₅</td>
<td>1.6</td>
<td>0.2, 3.1</td>
<td>-1.4</td>
<td>-2.8, 0.1</td>
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Abbreviations: CI: confidence interval; CO: carbon monoxide; IQR: interquartile range.

a: 24-hour mean concentrations of CO was used;
b: Lag02, cumulative risk distributed from lag 0 to lag 2 days.

Table 3: Percentage change in total emergency hospital admissions for COPD per IQR increment in one-hour daily maximum of CO concentrations at Lag 0, 1, 2 and 02 days in single pollutant and two-pollutant models 

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>Lag0</th>
<th>Lag1</th>
<th>Lag2</th>
<th>Lag02</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
<td>% Change</td>
<td>95% CI</td>
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<tr>
<td>CO only</td>
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<td>-1.9, -1.5</td>
<td>-2.4, -0.2</td>
<td>-1.2, 0.7</td>
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<td>CO with NO₂</td>
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<td>CO with PM₂.₅</td>
<td>-2.8</td>
<td>-3.9, -3.1</td>
<td>-4.2, -2.2</td>
<td>-3.3, -4.6</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; CO: carbon monoxide; IQR: interquartile range.

a: 1-hour maximum concentrations of CO was used;
b: Lag02, cumulative risk distributed from lag 0 to lag 2 days.
Figures:

Figure 1. Locations of the three background air monitoring stations included for the present analysis, Hong Kong, China, 2001-2007. The whole territory of Hong Kong is about 40 km by 30 km in linear dimensions. TW, Tsuen Wan; TC, Tung Chung; TM, Tap Mum.
Figure 2. Percentage change in emergency hospital admissions for COPD per IQR increment in pollutant concentrations at distributed lags of 0 to 2 days in single pollutant models and two-pollutant models, respectively. The results for the two genders were compared. The points indicate central estimates; horizontal lines, 95% confidence intervals.
Figure 3. Second-degree polynomial exposure-response curves for daily average pollutant concentration at distributed lags of 0 to 2 days and risk of emergency hospital admissions for COPD in single-pollutant models and two-pollutant models. The solid line represents central estimates; the dashed lines represent 95% confidence intervals.