Ambient carbon monoxide and cause-specific years of life lost: a nationwide time-series analysis in China

Yu Wang

Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Jie Li

National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention

Lijun Wang

National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention

Peng Yin (✉ yinpeng@ncncd.chinacdc.cn)

National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention <https://orcid.org/0000-0002-5515-2824>

Yun Lin

Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Maigeng Zhou

National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention

Research

Keywords: Carbon monoxide, Cardiopulmonary disease, Years of life lost, Time-series analysis, China

Posted Date: February 18th, 2020

DOI: <https://doi.org/10.21203/rs.2.23864/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Ambient carbon monoxide (CO) has been evaluated the effect on public health, mainly linked with mortality and morbidity. Little evidence is available regarding the relation between CO and years of life lost (YLL).

Methods: Using data from 49 major cities in China from 2013 to 2017, we applied generalized additive models and random effects meta-analyses to explore the effects of CO on YLL from various diseases. In addition, stratified analyses were performed to estimate the effect modification of demographic factors.

Results: A 1-mg/m³ increase of CO concentrations (lagged over 0–3 d), was associated with 24.1 (95% confidence interval [CI], 14.7, 33.5), 11.5 (6.4, 16.6), 0.9 (-0.5, 2.2), 3.4 (1.3, 5.5), 5.3 (2.5, 8.1), 0.8 (0.0, 1.6) increments in daily YLL from non-accidental causes, cardiovascular diseases, respiratory diseases, coronary heart disease, stroke and chronic obstructive pulmonary disease, respectively. These associations were robust to the adjustment of co-pollutants and varied substantially by geography and demographic characteristics. Associations were stronger in the elder people (≥ 75 years), males and those with low education attainment, than younger people, females and high educated populations.

Conclusions: This nationwide analysis showed significant and positive associations between short-term ambient CO exposure and cause-specific YLL, and modified by geography and demographic characteristics. These findings may have significant public health implications for the reduction of CO-attributed disease burden in China.

Background

Air pollution has become one of the most important global environmental problems. The Global Burden of Disease 2017 study (GBD 2017) reported 4.9 million global deaths and 1.2 million deaths in China were attributed to air pollution [1]. Along with the rapid development of industrialization and urbanization in recent decades, the problem of air pollution is gradually emerging in China. It could be caused by the increase of coal consumption, automobile exhaust, emissions of power plants, and so on. In most urban communities, carbon monoxide (CO) is a key component among the complex air pollutants, which plays an important role in air quality as, which mainly comes from transportation or industry. However, existing studies on the air pollutants health effect, including GBD study focus mainly on other air pollutant like particulate matter.

In China, several previous studies have shown that ambient CO has a statistically significant adverse effect on human health, could increase cause-specific mortality [2, 3] and morbidity [4, 5]. However, assessing the CO-related effect on human health with the mortality data, implicitly ignore the unequal weights to the deaths of young people and elderly. This might fail to fully consider the air pollution related burden of diseases occurring at distinct age [6, 7]. From a public health perspective, the years of life lost (YLL) of elderly are less than that of young population, as the life expectancy is longer among young people. Therefore, YLL provides more informative and precise information than counts of death for

assessing air pollution related premature death [6, 7]. However, the available evidence is limited on the association between air pollution and YLL in China, especially for ambient CO. Some single city studies assessed the effect of certain air pollutants on YLL from various diseases in China, like Beijing [6, 7], Guangzhou [8] and Ningbo [8]. However, as far as we know, no nationwide studies have examined the ambient CO effect on YLL in China yet. In addition, the association between ambient CO and YLL may vary geographically or be modified by demographic characteristics like age, sex and education level. The single city research may not be a good representative of the air pollutants impact on the burden of disease among Chinese population.

In order to facilitate the evidence-based public health policy making and resource allocation, our study evaluated the ambient CO-associated effects on YLL from various diseases in addition to death counts in 49 cities throughout China, besides, modifications by regional and demographic characteristics was observed as well.

Methods

Research setting and period

In our study, the research area were cities chosen based on population size, mortality data availability and the geographical distribution of each city. Finally, there were 49 large cities in China included in our study, which dispersed into 29 provincial administrative regions covering 642 districts representing 430 million population. The economic and regional areas of China can be basically reflected by the geographical distribution of the 49 cities. Considering the environmental and health data accessibility of each city, we determine the study period of 5 years from 2013 to 2017. Finally, our research setting were clustered into 6 regions according to climate, geography and culture in China: Northeast, North, East, Middle-South, Southwest, and Northwest [10], as shown in Fig. 1.

Data on air pollutants and meteorological data

The daily 24-hour average CO concentration of each 49 cities were collected by all the monitoring sites, covering the period between Jan 1st 2013 to 31st Dec 2017. These monitoring sites cover all districts and shall not be close to the main traffic road or industrial emission source, which monitor and collect concentrations of CO to the National Urban Air Quality Real-time Publishing Platform (<http://106.37.208.233:20035/>). All air pollutants concentration measurements and calculation were performed in accordance with China's National Air Quality Control standards (GB3095-2012), over all monitoring sites, and can reflect the whole city air pollution levels.

Additionally, to adjust the impacts of the co-pollutants exposure, we obtained the daily concentrations of other five major air pollutants, including fine particulate matter with a diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and $\leq 10 \mu\text{m}$ (PM_{10}), sulphur dioxide (SO_2), and nitrogen dioxide (NO_2), and maximum 8-hour average concentrations of ozone (O_3). The daily meteorological data were obtained for each cities, including

temperature, relative humidity and atmospheric pressure from the China Meteorological Data Sharing Service System (<http://data.cma.cn/>), to allow for the adjustment of weather conditions.

YLL data

Mortality data were obtained from the database of Chinese Center for Disease Control and Prevention covering all districts in each city, between 1st January 2013 and 31st December 2017. All deaths were registered residents from each 49 cities, comprised the date of mortality, cause of mortality, gender, age, education attainment. All death cases were extracted and diagnosed according to the International Classification of Diseases, 10th revision (ICD-10, WHO 2016), and divided into non-accidental causes (Total; codes A00-R99), cardiovascular diseases (CVD; codes I00-I99), coronary heart diseases (CHD, I20-I25), stroke (I60-I69), respiratory diseases (RD; codes J00-J98) and chronic obstructive pulmonary disease (COPD, J41-J44) as reported previously [10, 11].

Then the YLL of each cases were generated with the life expectancy [12] and daily death data. We finally calculated the daily YLL number of different causes of death, different genders, different ages, different education levels, and from different regions. In the rest of this paper, YLL caused by non-accidental death were called total YLL. In addition, the daily YLL were further stratified into several strata by gender (male and female), age bands (5–64 y, 65–74 y and ≥ 75 y), and educational attainment level (low: 0–8 years; high: ≥ 9 years). Deaths under the age of 5-years were excluded from our analysis as few mortality data were recorded in this age group.

Statistical analysis

Daily YLL numbers, CO concentrations, and meteorological variables were linked in each day and in each city. Then we applied a two-stage analytic approach to obtain effects of ambient CO on daily cause-specific YLL, on regional- and national-average levels.

In the first stage, we performed time-series analyses with generalized additive models (GAM) to estimated city-specific associations. Gaussian was selected as the family function for GAM, because daily YLL as the dependent variable in the models was normally distributed in each cities [8, 9]. A natural cubic smooth function of calendar time with 7 degrees of freedom (df) per year was used based on previous studies [8, 9], to account for the unmeasured long-term trends and seasonality of daily YLL. To allow for controlling potential non-linear and lagged confounding effects of meteorological factors, we also chose natural smooth functions of 4-day moving average temperature with 6 df, 4-day moving average relative humidity with 3 df [2], and 3 df for atmospheric pressure on the current day [8]. Day of the week was also included in the basic models as categorical variables to exclude the day effect within a week on death.

In the second stage, random-effects meta-analyses were established to pool the estimates at city level, to estimates at regional- and national-level [8]. Potentially delayed and cumulative associations were evaluated by the exploration of CO effects lag pattern: We included the single lags of 1, 2 and 3 days (1, 2, 3 day before the current day) and moving average of lag01 to lag04 (average of the current day and previous 1, 2, 3, 4 days) in the main model to generate the national-average estimates.

Then we explored the potential modification on the associations between CO and total YLL and cause-specific YLL, by regions of China and demographic characteristics, including age groups, gender and education attainment level. Subgroup analyses were conducted, using the concentrations of CO on current day (lag0) and the lag day with the greatest estimated effect on YLL in the main analyses (national-average level). The between-group estimated effects differences were examined by the 95% confidence interval (CI) as shown below:

$$(Q_1 - Q_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2} ,$$

where Q_1 and Q_2 are the estimates of different groups (e.g., elders and young), and SE_1 and SE_2 are their respective standard errors.

To evaluate the robustness of the results, sensitivity analyses were conducted as follows: (1) two-pollutant models to allow the adjustment of PM_{2.5}, PM₁₀, NO₂, SO₂ and O₃; (2) models with different df values (5–10 per year) for calendar time (2) using different df values for temperature (7–9) and relative humidity (4–6).

All statistical analyses were conducted in R software, version 3.5.0, (R Foundation for Statistical Computing), using the package of “mgcv” for main models, and packages of “rmeta” for random-effect models which merge the data to generate the average estimates. The estimated results were presented as changes and their 95% CIs in YLL (years) due to total causes or specific diseases, per 1-mg/m³ increase in daily CO level. The estimations were considered statistically significant as P-values were ≤ 0.05. The ethic approval and informed consent were waived, as only aggregated non-identifiable data were used and no subjects would be contacted throughout the present study.

Results

Summary statistics

The descriptive statistics in this analysis were summarized in Table 1. The daily average of YLL was 1473.7 years for total causes, 623.9 years for CVD and 131.2 years for RD. Detailed summary statistics of data on total YLL by 6 major regions can be found in Table S1 (Additional file 1). The average of annual mean CO concentration across 49 cities was 1.1 mg/m³ (range, 0.6–2.2 mg/m³), which was below the limit of Chinese Ambient Air Quality Standards (CAAQS) implemented in 2016 (<https://cleanairasia.org/node8163/>) (daily mean < 4 mg/m³). The annual mean CO concentration was highest in North cities (1.6 mg/m³) while lowest in east and northeast cities (0.9 mg/m³). Concentrations variation in CO was higher in Middle-South cities (IQRs: 0.5) than cities in other regions (IQRs: 0.2–0.3). There were marked differences in co-pollutant concentrations across these cities and regions. Climatic

conditions also varied among the cities (annual mean temperature range, 3.6–22.0 °C; humidity range, 43.7–88.1%; and atmospheric pressure range, 660.9–1016.5).

Nationwide-average modeling results

As shown in Fig. 1, the associations between CO concentrations and YLL from total causes, CVD, CHD and stroke were positive and statistically significant in a nationwide-average level on different lag days, while the associations were only statistically significant on lag0 and lag01 between CO and YLL from RD and COPD. For single lag days, the total YLL increases associated with CO decreased from the current day to lag3, becoming statistically insignificant on lag3. In addition, Fig. 1 depicted that the national-average effects of CO on cause-specific YLL were strongest for moving average over 4 days (lag03) for all outcomes other than RD. Therefore, we subsequently conducted the next analyses mainly on the current day (lag0) and cumulative effects of CO on lag03.

Regional-average modeling results

Table 2 showed the national-average and six regional-average increase of YLL associated with 1-mg/m³ increase of ambient CO concentrations on both lag0 and lag03. For all outcomes other than RD, the estimated associations were statistically significant on lag03, a 1-mg/m³ increase in CO concentration corresponded to 24.1 (95% CI: 14.7, 33.5), 11.5 (95% CI: 6.4, 16.6), 3.4 (95% CI: 1.3, 5.5), 5.3 (95% CI: 2.5, 8.1) and 0.8 (95% CI: 0.0, 1.6) increase in YLL from total causes, CVD, CHD, stroke and COPD, respectively. The YLL due to RD increased significantly with 1.1 (95% CI: 0.3, 2.0) per 1-mg/m³ increase of CO at lag0. Generally, we observed statistically significant and positive associations between ambient CO and YLL due to total causes in the Northeast China, East China and Middle-South China, and YLL due to CVD in the East China. Except the Northwest China and Southwest China, statistically significant relationships between CO and YLL could be observed on other lagged days in other regions (Table S2 in Additional file 1).

Subgroup modeling results

Table 3 presented the subgroups estimates of total YLL and cause-specific YLL by age, gender, and educational level, associated with ambient CO (lag03) at the national-average level. For total YLL, the estimated effect was stronger in specific subgroups (male sex, age ≥ 75 years, and low level education attainment), although differences were not significant among females and males. Generally, we found statistically significant between-group difference of effect estimates for education attainment groups and age groups. For example, a 1 mg/m³ increase in CO concentration on lag03, was related to increments of 23.0 (95% CI: 14.3, 31.6) total YLL for population with low education attainment level, while only with increments of 1.5 (95% CI: -1.9, 4.9) for population with high education attainment level.

Sensitivity analysis

In the sensitivity analysis, we examined the associations of CO and YLL in different two-pollutant models (Table 4). Generally, we found the effects of CO on YLL from total causes, CVD, CHD and stroke were not substantially affected by the adjustments of the other five air pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂ and O₃),

though they were attenuated appreciably when adjusted $PM_{2.5}$ and PM_{10} . The estimates of the associations between CO and YLL for total causes and CVD in the models with alternative df value for time trend (5–10 per year), temperature (7–9), and relative humidity (4–6) still remained statistically significant and stable (Table S3).

Discussion

In this national time series study, we found that ambient CO pollutant, was significantly and positively associated with daily YLL from total non-accidental causes, overall CVD, CHD, stroke, overall RD and COPD, even at levels below the current CAAQS, in 49 Chinese cities from 2013–2017. The estimated effects of CO on YLL by individual-level were stronger for elders and people with low education attainment level. In addition, the CO-associated effects on YLL were stable by sensitive analyses including two-pollutant models. To the best of our knowledge, it is the first nationwide study systematically explored the impacts of short-term exposure to CO pollution on YLL due to all non-accidental diseases and different cardiopulmonary diseases, in China.

Previously, it has been well documented in China, that ambient CO is associated with cause-specific mortality including total non-accidental death [3, 14], overall RD death [3, 15], overall CVD death [2, 3, 14] and some specific CVD death [2]. However, we still need the studies estimating the effect of CO on YLL, which could provide both novel and accurate indicators into the impact of ambient CO on human health, and be meaningful in both resource allocation and policy making of public health. In China, some single-city studies [7–9] observed the association of YLL with some other air pollutants, like NO_2 , SO_2 , O_3 and particle pollutants. One study examined the effects of ambient $PM_{2.5}$, PM_{10} , SO_2 and NO_2 on total non-accidental YLL in Beijing, China [7] and they found 15.8, 15.8, 16.2 and 15.1 years increases of YLL, associated with an IQR increase of concentration in $PM_{2.5}$, PM_{10} , SO_2 , and NO_2 , respectively in Beijing during 2004–2008, and the impacts of air pollution appeared short-term and only lasted for two days (lag01).

In our study, we found the greatest effect of CO was on the lag03 for moving average days, and it can last for about 3 days (lag2) for total non-accidental YLL. For YLL from CVD, the CO effect can last for 3 days (lag2) and the greatest increase of CVD YLL related to CO was also on lag03 in our study. This lag pattern is similar with the nationwide study exploring the effect of ambient CO on the death due to CVD in China [2]. The study in Yichang (a city in Central China) [2] found estimated effects for CO were greater for the moving averages with longer lag days, and the strongest effect of CO was at lag 06 on the cause-specific outpatient visit which can reflect the acute health effects. Unlike other air pollutants, CO concentrations were mainly at a low level in the 49 cities of China (mean, 1.1, range, 0.6–2.2 mg/m^3), so the effect from CO may need more time to cumulative harm, leading to the morbidity or mortality of the population [4, 16].

In our study, we also estimated a significant CO-related increase of YLL due to some specific CVD, like CHD and stroke. In Guangzhou (a city in South China), a significant and positive relation was found

between air pollution (NO_2 , SO_2 and PM_{10}) and YLL due to overall CVD, and CVD subtype including stroke and ischemic heart disease [8]. Compared with the studies on CO and CVD, studies on the association between CO and mortality from RD were limited and showed mixed results. The first multi-city study concentrating on short-term effect of ambient CO in Chinese population by time series analyses was conducted in the Pearl River Delta of China, and found that 0.5-ppm increase in CO concentration in the lag 1–2 (average of previous 1 and 2 days) was related to 3.72% (95% CI, 1.71–5.76%) increases in excessive risks of respiratory mortality [3]. On the contrary, some other studies showed positive, but not statistically significant association between CO and RD mortality [14, 17]. In our study, we found a slight increase of YLL from RD and COPD related to CO on lag0. As the estimated CO-related increase of RD and COPD YLL were not statistically significant on most lag days in the regional-level analyses, we should be cautious about whether CO will increase the YLL of RD and COPD.

In line with the findings of previous studies on the CO-related mortality in 272 cities in China [2] and 19 European cities [18], we observed that the associations remained statistically significant and positive after the adjustment of the other five air pollutants in our study. Some single-city studies found the significant and positive estimations were attenuated to null after controlling for exposure to other air pollutants [14, 19]. It may be due to small sample sizes of a single city, different air pollution components or population characteristics. Comparing effect estimates for ambient CO in both single- and two-pollutant models can observe the more independent effect of ambient CO pollution after adjusting the effect of other air pollutants.

Identifying vulnerable subgroups is essential for resource allocation to reduce CO-related public health impact. Consistent with previous researches, we found much higher vulnerability to CO among males, elders, and those with low education level [14, 17]. However, the health effects of CO pollution could be significantly modified by age, but not by gender [14, 17] after the test of between-subgroup differences. As for the larger CO effect of less-educated populations, it may directly reflect the environmental health inequalities and inequities which were associated with socioeconomic status, like higher prevalence of preexisting diseases, higher level or frequency of exposure and co-exposure (with household and occupational sources), less affordable health care resources and so on [20].

We can't find the statistically significant associations between CO and YLL from total causes and CVD in the west regions of China (Northwest China and Southwest China). The differences of CO-related effects across the two regions may due to complex factors, like the population susceptibility, variation of air pollutant concentration, quality of YLL data and so on. It may mainly be caused by the small number daily counts of mortality in Northwest China and Southwest China. Besides, the previous study suggested that the adverse effects of CO might not vary substantially by geography in China [2].

Many studies have shown the mechanism and physiological responses to CO poisoning [21, 22]. CO is an odorless, colorless, tasteless, and a nearly ubiquitous gas that could occupy hemoglobin ahead of oxygen with an affinity more than 200 times that of oxygen. Therefore, the process of supplying oxygen to tissues can be interfered when people get CO poisoning [21, 22]. The evidence on the organism

reactivity to a low concentration of ambient CO is still insufficient and unclear. Results of the exposure studies have indicated that patients with atherosclerotic CVD may be affected and exacerbated myocardial ischemia by the presence of carboxyhemoglobin owing to the exposure to ambient CO, even at low concentrations [23]. Previous epidemiological and experimental studies have demonstrated that exposure to ambient CO could bring about an increased risk of CVD by several plausible mechanistic pathways, like a systemic inflammatory response, process of reactive oxygen species generation, and interruption of the terminal oxidase of the electron transport chain, acute increased blood pressure, a propensity for arrhythmias, plasma fibrinogen changes, or increased blood viscosity [24–26].

Although the annual-average concentration of CO (1.1 mg/m^3 , range, $0.6\text{--}2.2 \text{ mg/m}^3$) was below the CAAQS in China (4 mg/m^3), and was comparable with the level of CO concentration in many European cities [18], it still increased the YLL from many causes. As shown in the previous study in 272 cities of China, no apparent lower threshold was found for the short-term effect of CO on CVD mortality [2]. CO is an almost ubiquitous product of incomplete combustion of carbon-containing fuels, and there are various sources of CO pollution, like motor vehicles, engines on motorboats, coal combustion, tobacco smoking, and so on. In the recent three decades, with the rapid development of economic, urbanization and industrialization in China, air pollutants, especially CO warrant further investigation.

Our study had several strengths. First of all, our study is the first nationwide study observing the association between ambient CO and cause-specific YLL. Compared with mortality risk that ignore the inequality due to different age of death, YLL quantifying premature deaths can be better reflecting the burden of CO pollution. Secondly, we selected the top principal causes of death that ranked high in China [27], to see the whole picture of CO-related YLL. Thirdly, we used the largest death database of 49 major cities in China with good internal consistency in data collection in developing countries, which had reliable external representativeness for our findings. Finally, this investigation also provided evidence regarding the population susceptibility to CO pollution, and public health improvement steps can be efficiently developed. Additionally, the modification by geographical region and regional-level characteristics was also investigated, including climatic, geographical, and socioeconomic characteristics.

The present study was also subject to several limitations. Firstly, as a studies using time series methods, we used aggregated levels of air pollutants as surrogates for individual, so that exposure misclassification was inevitable. Nevertheless, these errors are supposed to be random and may not bias the estimated effects [28]. Secondly, we cannot rule out the potential diagnostic or coding errors for death causes, though most death data used for YLL calculation in the present study was under strict quality control. Finally, there may be other unknown and unmeasured factors, for example, we did not control for smoking or obesity related to CVD, because this information was unavailable. However, such factors are not related to air pollution levels because the distribution of such fixed factors does not vary from day to day. We, therefore, assume that the results would have been only marginally affected because the effects are short term, and the time-series method controls for both long-term and fixed-term factors [29].

Conclusion

Conclusively, the present nationwide study provided a comprehensive picture of associations between short-term exposure to CO pollution and YLL due to all non-accidental or cause-specific causes in China. These findings of vulnerability on city-level and individual-level characteristics can be meaningful to improve clinical and public health practices, and have implications for policy making on environmental and social perspectives to reduce the disease burden associated with CO pollution, even at a low concentration.

Abbreviations

GBD: Global Burden of Disease study; CO: carbon monoxide; YLL: years of life lost; PM_{2.5}: particulate matter with a diameter of 2.5 µm or less; PM₁₀: particulate matter with a diameter of 10 µm or less; SO₂: sulphur dioxide; NO₂: nitrogen dioxide; O₃: ozone; Total: non-accidental causes; CVD: cardiovascular diseases; CHD: coronary heart disease; RED: respiratory diseases; COPD: chronic obstructive pulmonary disease; GAM: generalized additive models; df: degrees of freedom; 95%CI: 95% confidence interval; CAAQS: Chinese Ambient Air Quality Standards;

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Yu Wang: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. Jie Li: Data curation, Conceptualization, Investigation, Formal analysis. Lijun Wang: Conceptualization, Investigation, Visualization. Yun Lin: Investigation. Peng Yin: Methodology, Investigation, Supervision, Resources, Writing-review & editing, Project administration. Maigeng Zhou: Conceptualization, Investigation, Resources.

Funding

This study was funded by Project Management Office of the Cause and Control of Atmospheric Heavy Pollution (DQGG0401-01).

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to no permission but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. GBD 2017 Risk Factor Collaborators. 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* 2018, 392(10159):1923-1994.
2. Liu C, Yin P, Chen R, Meng X, Wang L, Niu Y, et al. Ambient carbon monoxide and cardiovascular mortality: a nationwide time-series analysis in 272 cities in China. *Lancet Planet Health* 2018, 2(1):e12-e18.
3. Tao Y, Zhong L, Huang X, Lu SE, Li Y, Dai L, et al. Acute mortality effects of carbon monoxide in the Pearl River Delta of China. *SCI TOTAL ENVIRON* 2011, 410-411:34-40.
4. Wang Y, Yao C, Xu C, Zeng X, Zhou M, Lin Y, et al. Carbon monoxide and risk of outpatient visits due to cause-specific diseases: a time-series study in Yichang, China. *Environ Health* 2019, 18(1):36.
5. Tian Y, Liu H, Zhao Z, Xiang X, Li M, Juan J, et al. Association between ambient air pollution and daily hospital admissions for ischemic stroke: A nationwide time-series analysis. *PLOS MED* 2018, 15(10):e1002668.
6. Rabl A. Interpretation of air pollution mortality: number of deaths or years of life lost? *J Air Waste Manag Assoc* 2003, 53(1):41-50.
7. Guo Y, Li S, Tian Z, Pan X, Zhang J, Williams G. The burden of air pollution on years of life lost in Beijing, China, 2004-08: retrospective regression analysis of daily deaths. *BMJ* 2013, 347:f7139.

8. Yang J, Ou CQ, Song YF, Li L, Chen PY, Liu QY. Estimating years of life lost from cardiovascular mortality related to air pollution in Guangzhou, China. *SCI TOTAL ENVIRON* 2016, 573:1566-1572.
9. Huang J, Li G, Xu G, Qian X, Zhao Y, Pan X, et al. The burden of ozone pollution on years of life lost from chronic obstructive pulmonary disease in a city of Yangtze River Delta, China. *ENVIRON POLLUT* 2018, 242(Pt B):1266-1273.
10. Chen R, Yin P, Meng X, Liu C, Wang L, Xu X, et al. Fine Particulate Air Pollution and Daily Mortality. A Nationwide Analysis in 272 Chinese Cities. *Am J Respir Crit Care Med* 2017, 196(1):73-81.
11. Yin P, Chen R, Wang L, Meng X, Liu C, Niu Y, et al. Ambient Ozone Pollution and Daily Mortality: A Nationwide Study in 272 Chinese Cities. *Environ Health Perspect* 2017, 125(11):117006.
12. WHO (World Health Organization). 2016. "International Statistical Classification of Diseases and Related Health Problems, 10th Revision. <https://icd.who.int/browse10/2016/en> [accessed 29 October 2019].
13. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, et al. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. *N Engl J Med* 2019, 381(8):705-715.
14. Chen R, Pan G, Kan H, Tan J, Song W, Wu Z, et al. Ambient air pollution and daily mortality in Anshan, China: a time-stratified case-crossover analysis. *SCI TOTAL ENVIRON* 2010, 408(24):6086-6091.
15. Yang Y, Cao Y, Li W, Li R, Wang M, Wu Z, et al. Multi-site time series analysis of acute effects of multiple air pollutants on respiratory mortality: a population-based study in Beijing, China. *SCI TOTAL ENVIRON* 2015, 508:178-187.
16. Orazzo F, Nespoli L, Ito K, Tassinari D, Giardina D, Funis M, et al. Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. *Environ Health Perspect* 2009, 117(11):1780-1785.
17. Son JY, Lee JT, Kim H, Yi O, Bell ML. Susceptibility to air pollution effects on mortality in Seoul, Korea: a case-crossover analysis of individual-level effect modifiers. *J Expo Sci Environ Epidemiol* 2012, 22(3):227-234.
18. Samoli E, Touloumi G, Schwartz J, Anderson HR, Schindler C, Forsberg B, et al. Short-term effects of carbon monoxide on mortality: an analysis within the APHEA project. *Environ Health Perspect* 2007, 115(11):1578-1583.
19. Tsai SS, Huang CH, Goggins WB, Wu TN, Yang CY. Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. *J Toxicol Environ Health A* 2003, 66(14):1341-1349.
20. Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N, et al. Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: The Public Health and Air Pollution in Asia (PAPA) Study. *Environ Health Perspect* 2008, 116(9):1183-1188.
21. Kalay N, Ozdogru I, Cetinkaya Y, Eryol NK, Dogan A, Gul I, et al. Cardiovascular effects of carbon monoxide poisoning. *AM J CARDIOL* 2007, 99(3):322-324.
22. Garg J, Krishnamoorthy P, Palaniswamy C, Khera S, Ahmad H, Jain D, et al. Cardiovascular Abnormalities in Carbon Monoxide Poisoning. *AM J THER* 2018, 25(3):e339-e348.

23. Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, et al. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989, 321(21):1426-1432.
24. Wang W, Tian L, Li Y, Wang X, Xia F, Li L, et al. Effects of hydrogen-rich saline on rats with acute carbon monoxide poisoning. *J EMERG MED* 2013, 44(1):107-115.
25. Piantadosi CA. Carbon monoxide, reactive oxygen signaling, and oxidative stress. *Free Radic Biol Med* 2008, 45(5):562-569.
26. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *CIRCULATION* 2004, 109(21):2655-2671.
27. Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, et al. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. *LANCET* 2016, 387(10015):251-272.
28. Chen R, Yin P, Wang L, Liu C, Niu Y, Wang W, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. *BMJ* 2018, 363:k4306.
29. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *INT J EPIDEMIOL* 2013, 42(4):1187-1195.

Tables

Table 1 Summary statistics on YLL, air pollutants, and weather conditions in 49 cities in China								
	Mean (SD)	MIN	P25	Median	P75	MAX	Range	IQR
Annual-average daily YLL								
Total	1473.7(1060.5)	49.8	936.6	1396.9	1770.9	7174.0	7124.2	834.3
CVD	623.9(410.2)	16.6	401.4	543.7	766.3	2486.3	2469.7	364.9
CHD	231.2(167.9)	1.6	104.7	195.6	325.2	686.7	685.1	220.5
Stroke	294.2(203.3)	10.5	200.6	263.4	377.5	1292.7	1282.2	176.9
RD	131.2(160.7)	5.1	68.5	92.1	149.8	1094.4	1089.3	81.3
COPD	87.0(133.0)	1.2	38.9	49.6	89.8	890.1	888.8	50.9
Annual CO concentrations, mg/m ³								
Nationwide	1.1(0.4)	0.6	0.9	1.0	1.3	2.2	1.6	0.4
Northeast	0.9(0.2)	0.7	0.8	0.9	1.0	1.1	0.4	0.2
North	1.6(0.4)	1.2	1.5	1.5	1.8	2.2	1.0	0.3
East	0.9(0.2)	0.6	0.8	0.9	1.0	1.5	0.8	0.2
Middle-South	1.3(0.3)	1.0	1.1	1.1	1.6	1.9	0.9	0.5
Northwest	1.4(0.2)	1.1	1.3	1.4	1.5	1.7	0.6	0.2
Southwest	1.0(0.1)	0.8	0.9	1.0	1.1	1.1	0.3	0.2
Annual-average co-pollutant concentrations, µg/m ³								
PM _{2.5}	58.1(16.8)	23.9	48.2	55.7	68.4	103.7	79.8	20.2
PM ₁₀	99.7(30.1)	51.9	77.6	97.6	113.9	187.8	135.9	36.3
NO ₂	39.4(9.7)	21.2	32.1	37.9	48.5	60.6	39.4	16.4
SO ₂	26.8(14.1)	7.4	16.9	22.8	33.0	60.8	53.5	16.1
O ₃	87.2(12.2)	61.0	79.3	87.2	96.3	114.4	53.4	17.0
Annual-average weather conditions								
Mean temperature	14.4(4.8)	3.6	12.2	15.8	17.3	22.0	18.3	5.1
Relative humidity	66.8(9.4)	43.7	60.0	67.8	75.4	81.1	37.4	15.4
Air pressure	971.7(75.3)	660.9	977.7	1002.7	1010.4	1016.5	355.6	32.7

Abbreviations: YLL, years of life lost; SD, standard deviation; MIN, min minimal; P25, the 25th percentile; P75, the 75th percentile; MAX, maximal; IQR, interquartile range; Total: non-accidental causes; CVD: cardiovascular diseases; CHD: coronary heart disease; RD: respiratory diseases; COPD: chronic obstructive pulmonary disease.

Table 3 National-average increase in daily YLL per 1-mg/m³ increase concentrations of CO on lag03 in subgroups

Subgroups	Total	CVD	RD	CHD	Stroke	COPD
Age groups (years)						
5–64	6.4 (1.6, 11.3)	2.5 (-0.2, 5.1)	0.2 (-0.4, 0.8)	0.6 (-0.5, 1.8)	1.5 (-0.1, 3.1)	0.4 (-0.1, 0.9)
65–74	5.2 (2.7, 7.8)*	3.3 (1.6, 5.0)	0.1 (-0.6, 0.9)	0.9 (0.2, 1.6)	1.4 (0.3, 2.4)	0.2 (-0.0, 0.5)
>75	9.3 (6.3, 12.4)*	5.7 (3.7, 7.7)	0.1 (-0.3, 0.6)	1.8 (0.9, 2.6)	2.3 (1.2, 3.4)	0.2 (-0.3, 0.7)
Gender groups						
Male	13.5 (7.3, 19.6)	5.9 (2.5, 9.2)	0.4 (-0.2, 1.1)	1.3 (-0.1, 2.7)	3.3 (1.4, 5.1)	0.3 (-0.2, 0.9)
Female	10.2 (5.3, 15.1)	5.5 (2.8, 8.1)	0.5 (-0.4, 1.4)	2.0 (0.9, 3.2)	1.7 (0.3, 3.1)	0.5 (-0.0, 1.0)
Education attainment groups						
¹ Low level	23.0 (14.3, 31.6)*	11.1 (6.4, 15.8)*	0.4 (-0.4, 1.1)	3.7 (1.7, 5.6)*	4.8 (2.2, 7.3)*	0.7 (-0.0, 1.5)
² High level	1.5 (-1.9, 4.9)*	0.1 (-1.4, 1.6)*	1.1 (-0.2, 2.5)	-0.3 (-1.0, 0.4)*	0.4 (-0.4, 1.1)*	-0.0 (-0.2, 0.1)

Note: *The difference between different subgroups was significant ($p < 0.05$); ¹low level education attainment groups were population with <9 years spent in education; ¹high level education attainment groups were population with ≥ 9 years spent in education.

Abbreviations: YLL, years of life lost; Total: non-accidental diseases; CVD: cardiovascular diseases; CHD:

Table 2 National- and regional-average increase (95% CI) in daily YLL of 1-mg/m ³ increase in CO							
	Nationwide	Northeast	North	East China	Middle-South	Northwest	Southwest
Lag0							
Total	14.7 (8.8, 20.5)	25.8 (5.1, 46.5)	8.9 (-2.0, 19.8)	19.7 (9.7, 29.6)	14.2 (-0.7, 29.2)	5.8 (-1.3, 12.9)	33.9 (-14.2, 82.0)
CVD	5.5 (2.4, 8.5)	8.3 (-1.1, 17.7)	5.1 (-2.4, 12.6)	7.2 (2.8, 11.6)	4.2 (-6.6, 15.0)	0.5 (-3.6, 4.7)	16.9 (-5.1, 38.9)
CHD	0.7 (-0.4, 1.7)	-1.3 (-6.9, 4.4)	1.6 (-1.1, 4.3)	-0.4 (-2.7, 1.9)	1.6 (-2.0, 5.2)	-0.3 (-2.0, 1.4)	5.7 (-1.1, 12.5)
Stroke	3.5 (1.7, 5.3)	6.9 (1.0, 12.8)	2.6 (-1.1, 6.2)	6.0 (2.8, 9.2)	1.5 (-4.4, 7.4)	0.6 (-1.4, 2.7)	7.0 (-6.4, 20.3)
RED	1.1 (0.3, 2.0)	2.0 (-1.5, 5.5)	0.1 (-1.2, 1.4)	1.4 (-0.3, 3.0)	1.2 (-1.7, 4.0)	1.3 (-0.2, 2.8)	8.2 (-3.4, 19.8)
COPD	0.7 (0.2, 1.3)	1.2 (-0.8, 3.2)	0.5 (-0.6, 1.7)	0.9 (-0.2, 1.9)	0.8 (-0.8, 2.4)	0.4 (-0.6, 1.5)	6.0 (-2.5, 14.5)
Lag03							
Total	24.1 (14.7, 33.5)	45.9 (8.8, 83.0)	19.7 (-1.9, 41.4)	32.4 (18.6, 46.3)	29.3 (6.1, 52.4)	6.1 (-4.4, 16.6)	22.3 (-42.1, 86.6)
CVD	11.5 (6.4, 16.6)	19.0 (-1.1, 39.1)	12.2 (-2.4, 26.8)	16.3 (8.3, 24.3)	12.5 (-2.3, 27.3)	2.2 (-4.7, 9.0)	8.4 (-18.2, 35.0)
CHD	3.4 (1.3, 5.5)	4.3 (-5.0, 13.5)	3.5 (-1.6, 8.7)	4.0 (-1.4, 9.4)	5.7 (-0.1, 11.5)	0.6 (-1.8, 3.1)	7.8 (-2.7, 18.3)
Stroke	5.3 (2.5, 8.1)	11.1 (-1.6, 23.8)	5.4 (-2.1, 12.9)	7.8 (3.8, 11.9)	5.2 (-2.6, 13.0)	1.5 (-2.8, 5.9)	0.6 (-14.6, 15.8)
RED	0.9 (-0.5, 2.2)	-1.7 (-7.1, 3.8)	-0.1 (-2.2, 2.1)	2.3 (-0.2, 4.8)	1.5 (-3.4, 6.4)	1.2 (-1.2, 3.6)	6.4 (-8.2, 21.1)
COPD	0.8 (0.0, 1.6)	1.3 (-1.4, 3.9)	0.0 (-1.5, 1.6)	2.0 (0.4, 3.7)	1.1 (-1.1, 3.2)	0.4 (-1.8, 2.5)	4.6 (-5.2, 14.4)
Abbreviations: YLL, years of life lost; Total: non-accidental causes; CVD: cardiovascular diseases; CHD: coronary heart disease; RED: respiratory diseases; COPD: chronic obstructive pulmonary disease.							

coronary heart disease; RD: respiratory diseases; COPD: chronic obstructive pulmonary disease.

Table 4 National-average increase in daily YLL per 1-mg/m ³ CO increase on lag03, using two-pollutant models				
	Total	CVD	CHD	Stroke
Carbon monoxide	24.1 (14.7, 33.5)	11.5 (6.4, 16.6)	3.4 (1.3, 5.5)	5.3 (2.5, 8.1)
Adjusted for PM _{2.5}	15.6 (6.5, 24.6)	7.8 (2.8, 12.9)	3.0 (0.8, 5.1)	3.0 (0.3, 5.7)
Adjusted for PM ₁₀	15.0 (6.2, 23.9)	7.9 (3.0, 12.7)	3.0 (0.9, 5.1)	3.1 (0.4, 5.8)
Adjusted for NO ₂	23.1 (13.6, 32.5)	11.3 (6.2, 16.4)	3.7 (1.5, 5.9)	4.9 (2.2, 7.6)
Adjusted for SO ₂	16.2 (7.4, 25.0)	9.2 (4.6, 13.9)	3.5 (1.4, 5.6)	3.4 (1.0, 5.8)
Adjusted for O ₃	20.9 (11.5, 30.4)	10.2 (5.1, 15.3)	3.2 (1.0, 5.3)	4.6 (1.8, 7.4)
Abbreviations: YLL, years of life lost; Total: non-accidental diseases; CVD: cardiovascular diseases; CHD: coronary heart disease.				

Figures

Figure 1

The location of study cities and the major regions in China Note: The location of study cities were represented by blue dots; the major regions of China were represented by different color blocks. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 2

National-average increase in daily YLL from different causes of 1-mg/m³ increase in CO in China
 Abbreviations: YLL, years of life lost; Total: non-accidental causes; CVD: cardiovascular diseases; CHD: coronary heart disease; RD: respiratory diseases; COPD: chronic obstructive pulmonary disease. Note: The X-axis is the lag days from lag0 to lag3, and the moving average lag days from lag01 to lag 04; The Y-axis is the national-average increase of daily YLL; the points indicate central estimates; Bars, 95% confidence intervals; Statistically significant effects are marked in red bars (P < .05), and blue bars are not statistically significant.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfiles1.docx](#)