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Ambient Carbon Monoxide and Daily Mortality: A Global Time-Series Study in 337 cities

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Abstract:	Background Epidemiological evidence on short-term association between ambient carbon monoxide (CO) and mortality is inconclusive and limited to single cities, regions, or countries. Generalization of results from previous studies is challenged by potential publication bias and different modeling approaches. We, therefore, assessed the association between short-term exposure to ambient CO and daily mortality in a multi-city multi-country setting. Methods We collected daily data on air pollution, meteorology, and total mortality from 337 cities in 18 countries or regions. We first estimated city-specific associations using confounder-adjusted generalized additive models with a quasi-Poisson distribution; then, we pooled the estimates, accounting for their statistical uncertainty, using a random-effects multilevel meta-analytical model. We also assessed the overall shape of the exposure-response curve and evaluated the possibility of a threshold below which health is not impacted. Findings Overall, a 1 mg/m 3 increase in the average CO concentration of the previous day was associated with a 0·91% (95% confidence interval [95% CI]: 0·32%, 1·50%) increase in daily total mortality. The pooled exposure-response curve showed a continuously elevated mortality risk with increasing CO concentrations, suggesting no threshold. Larger mortality risk estimates were found at daily CO levels below 1 mg/m 3 and persisted at concentrations as low as below 0·2 mg/m 3 . Interpretation This international study is by far the largest epidemiological investigation on short-term CO-related mortality. We found significant associations between ambient CO and daily mortality, even at levels well below current air quality guidelines. Funding EU Horizon 2020, UK Medical Research Council and Natural Environment Research Council.

Ambient Carbon Monoxide and Daily Mortality: A Global Time-Series Study in 337 cities

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Abstract *(not exceeding 250 words)*

Background

Epidemiological evidence on short-term association between ambient carbon monoxide (CO) and mortality is inconclusive and limited to single cities, regions, or countries. Generalization of results from previous studies is challenged by potential publication bias and different modeling approaches. We, therefore, assessed the association between short-term exposure to ambient CO and daily mortality in a multi-city multi-country setting.

Methods

We collected daily data on air pollution, meteorology, and total mortality from 337 cities in 18 countries or regions. We first estimated city-specific associations using confounder-adjusted generalized additive models with a quasi-Poisson distribution; then, we pooled the estimates, accounting for their statistical uncertainty, using a random-effects multilevel meta-analytical model. We also assessed the overall shape of the exposure-response curve and evaluated the possibility of a threshold below which health is not impacted.

Findings

Overall, a 1 mg/m^3 increase in the average CO concentration of the previous day was associated with a 0·91% (95% confidence interval [95% CI]: 0·32%, 1·50%) increase in daily total mortality. The pooled exposure-response curve showed a continuously elevated mortality risk with increasing CO concentrations, suggesting no threshold. Larger mortality risk estimates were found at daily CO levels below 1 mg/m^3 and persisted at concentrations as low as below 0·2 mg/m^3.

Interpretation

This international study is by far the largest epidemiological investigation on short-term CO-related mortality. We found significant associations between ambient CO and daily mortality, even at levels well below current air quality guidelines.

Funding

EU Horizon 2020, UK Medical Research Council and Natural Environment Research Council.

Research in context

Evidence before this study

We searched the literature without any language restriction from PubMed up to December 31, 2019, using the following search terms: "carbon monoxide," "mortality" or "death*," "daily," and "short-term" or "acute." Then we screened the abstracts and full texts to select relevant articles. Our literature review showed that epidemiological evidence is inconsistent. As previous studies were mainly from single cities, regions, or countries, also the generalizability of the reported short-term associations between carbon monoxide (CO) and mortality is limited. Moreover, whether a potential threshold exists in the CO-mortality relationship remains unclear.

Added value of this study

To our knowledge, this is the first global study of the risk of mortality associated with short-term exposure to ambient CO. Findings indicate adverse health effects of ambient CO levels, even below the current air quality guidelines. This large multi-country study applied the same analytical method for data from 337 cities, thus avoiding potential publication bias. Significant mortality risk estimates were found at daily concentrations below 0·2 mg/m^3. We also addressed the overall shape of the exposure-response function and found no evidence for a threshold value below which ambient exposure to CO did not affect total mortality.

Implications of all the available evidence

Our study provides evidence on the positive association of daily mortality with short-term exposure to ambient CO at levels below the current air quality guidelines. These findings suggest that global and national air quality guidelines for carbon monoxide may need to be revisited.

Introduction

Carbon monoxide (CO) is formed by incomplete combustion of fossil fuels and is ubiquitously found in ambient air. Adverse health effects of exposure to high levels of CO, such as accidental poisoning, are well documented.[1,2] Epidemiological studies using time-series designs have also reported that exposure to ambient (low) CO concentrations could be associated with mortality and morbidity.[3-9] However, epidemiological evidence from single-city studies remains inconclusive, with significant associations reported for some cities such as Montreal,[6] Sao Paulo,[7] and Seoul,[10] but not for others such as London,[11] Amsterdam,[12] or Chiang Mai.[13] Further, a few multicity studies have been conducted, but they were mostly focusing on a single region or country,[3,5,8,9,14] thus limiting the generalizability of the reported associations. Furthermore, previous studies applied different modeling choices, making it difficult to estimate a globally representative short-term CO-mortality association.

In 1971, the U.S. Environmental Protection Agency (EPA) initially established the health-based National Ambient Air Quality Standard (NAAQS) for the daily maximum 8-h average CO concentration at 9 ppm (~10 mg/m^3)[15], which is equivalent to approximately 7 mg/m^3 for the daily 24-h average CO. The NAAQS for CO was retained for the past five decades. The same limit value (10 mg/m^3 for maximum 8-h average) is also applied in European Air Quality Guidelines (AQG). In China, a lower limit value of 4 mg/m^3 was promulgated in the Chinese Ambient Air Quality Standards (CAAQS) for 24-h average CO. In 2005, the World Health Organization (WHO) published the latest edition of AQG, which did not include recommendations for ambient CO. Since then, substantial new evidence on the adverse health effects of ambient CO has emerged,[15] leading to an ongoing review and update of the WHO AQG to reevaluate CO as an ambient air pollutant.[16]

A key issue in setting AQG for CO is whether a threshold exists in the CO exposure-response relationship below which health is not impacted. Very limited epidemiological research has examined the existence of a potential threshold for CO at concentrations below existing guidelines. A previous time-series study found very weak evidence for a potential threshold at 0·5 mg/m^3 for the maximum 8-h average in the CO-mortality association in 19 European cities.[3] Another multicity research in the U.S. reported a significantly increased risk in hospitalization admission for cardiovascular diseases for 1-h average ambient CO below 1 ppm (~1·15 mg/m^3), and a linear exposure-response curve, indicating no evidence for a threshold.[4] Two additional studies from China also found no evidence for an apparent threshold value in the association between 24-h average CO and cardiovascular mortality.[5,8] However, these findings are difficult to synthesize because of different CO exposure metrics, health outcomes, and modeling approaches.

Here, we conducted a global time-series analysis to assess the association between short-term exposure to ambient CO and daily mortality within the Multi-Country Multi-City (MCC) Collaborative

Research Network,[17,18] including data from 337 cities within 18 countries. This network allowed a comprehensive and standardized analytical approach to examine and compare the association at the global, regional, and country level. We also evaluated the shape of the exposure-response curve and examined potential thresholds at low levels.

Methods

Data collection

We obtained data on daily mortality, air pollution, and mean temperature for 344 cities across 18 countries or regions with available data on CO from the database of the MCC Collaborative Research Network (http://mccstudy.lshtm.ac.uk/), covering various periods ranging from 1979 to 2016. This dataset has been applied in previous publications on the association between daily mortality and ambient particular matter and ozone pollution.[19,20] Data on daily mortality were collected from local health authorities in each country. Mortality was represented by daily counts of deaths due to non-external causes (International Classification of Diseases, 9th Revision codes 0-799 or 10th Revision codes A00-R99) or all-cause deaths when data on the non-external causes were not available. For each city, we derived daily 24-h average concentrations of CO, particulate matter with an aerodynamic diameter $\leq$ 10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and daily maximum 8-h average ozone (O_3) concentrations from urban and sub-urban air quality monitoring stations. In the MCC dataset, CO were collected using the 24-h average metric and then harmonized using the unit of mg/m^3. We excluded seven cities due to limited periods (less than two years) with both CO and mortality, resulting in a total number of 337 cities in the final analysis. The geographical distribution of the studied cities and the corresponding annual mean CO concentrations in each city can be found in Figure 1. A detailed description of the data collection has been described in the Supplementary material Text S1.

Statistical analysis

We used a two-stage analytic framework to estimate the association between short-term exposure to ambient CO and daily mortality. In the first stage, we applied generalized additive models with a quasi-Poisson distribution to evaluate the city-specific associations between CO and mortality. Consistent with previous studies,[19,21] the following confounders were included in the city-specific models: (1) a penalized cubic spline with seven degrees of freedom (df) per year to control the long-term time trend and seasonal variations; (2) an indicator variable for day of the week to account for within week variations; and (3) two separate natural cubic splines for low and high temperatures, which account for different lag structures in heat- and cold-related mortality while reducing concurvity between the two splines.[21] The temperature terms were defined as the average temperature on the previous six days (lag 1-6) only for days on which temperature was below the city-specific median value, and the average temperature on the current and previous day (lag 0-1) only for days on which the temperature was higher than the city-specific median

temperature. Different lag patterns in the association between CO and mortality were also explored using single lag days from lag 0 (current day) to lag 4 (previous three days) and cumulative lag days for lag 0-1 (average of the current and the previous day).

In the second stage, we pooled city-specific estimates using a random-effects multilevel meta-analytical model that accounts for variations in risk across two nested groups (cities and countries).[22] We assessed the heterogeneity using I^2 statistic and Cochran Q-test. We evaluated the statistical significance of the risk estimates across countries using a likelihood ratio test of the meta-analytical model and another model without the nested group of countries. We then calculated the city-specific and country-specific estimates of the CO-mortality associations using the best linear unbiased predictions (BLUPs) at each level (city/country) from the fitted random-effects meta-analytical model. BLUPs can borrow information from the pooled associations within the same hierarchical level, thus providing more accurate estimates than the first-stage estimates in locations with small daily mortality counts or short time-series.

In addition, we fitted two-pollutant models to adjust for potential confounding of co-pollutants (i.e., PM_{10}, NO_2, SO_2, and O_3) with the same lag as CO. For each pair of pollutants, the number of cities reduced due to data availability. To compare with estimates from two-pollutant models, we calculated the estimates for CO from single-pollutant models using the same days with both pollutants available within the same reduced number of cities, which were denoted as the estimates without adjustment for co-pollutants. The association of CO with mortality was considered robust if the pooled effect estimates with and without adjustment for co-pollutants were not statistically significantly different. We tested the statistical significance of differences between the risk estimates in single-pollutant and two-pollutant models by calculating the z score as $(\hat{E}_1 - \hat{E}_2)/\sqrt{(S\hat{E}_1)^2 + (S\hat{E}_2)^2}$, where $\hat{E}_1$ and $\hat{E}_2$ are the natural logarithms of risk estimates, and $S\hat{E}_1$ and $S\hat{E}_2$ are their respective standard errors calculated from the widths of 95% Confidence Intervals (CIs).

To assess the overall shape of the association between CO and mortality at the global level, we estimated the exposure-response curve following an approach that was used in previous studies.[19,23] Briefly, we applied a B-spline term with two knots at the average 25th and 75th percentiles of CO concentration distributions, which were first averaged across cities within a country, and then averaged across all countries.

To evaluate whether a threshold exists in the CO-mortality relationship, we performed a subset analysis, which was applied in previous studies.[24,25] This approach only includes days that meet a certain air quality threshold in each city (i.e., only days with concentrations at or below that threshold), and then varies that possible threshold. Based on the sample sizes and distribution of CO concentrations across all

countries (Table 1), we explored thresholds ranging from 0·2 to 1·0 mg/m^3 with an increment of 0·2 mg/m^3, and from 1·0 to 4·0 mg/m^3 with an increase of 0·5 mg/m^3.

We conducted several sensitivity analyses to examine the robustness of the results, including using different dfs for time trend (5-10 per year), additionally adjusting for relative humidity in 230 cities with available information, restricting the analysis to 311 cities with data after the year 2000, and restricting the analysis to 315 cities with at least three years (1,095 days) of complete time-series data, which excluded all cities in China and Italy. In assessing the overall exposure-response curve, we also placed different knots at the average 30th and 70th percentiles of CO concentration distributions. Moreover, we restricted the subset analysis to 114 cities with at least one year of data for CO concentration at or below 0·2 mg/m^3. Furthermore, we compared the difference between using all-cause and non-external mortality as the outcome in 70 cities with both all-cause and non-external mortality. Finally, we applied alternative temperature control approaches: (1) using alternative lag days for low and high temperatures (lag 1-3 and lag 0-1, lag 0-5 and lag 0, and lag 0-3 and lag 0 for low and high temperatures, respectively); (2) a natural cubic spline term of moving average temperatures (lag 0-1, lag 0-3, and lag 0-7) with six dfs; and (3) a distributed lag nonlinear term (DLNM) using a quadratic B-spline for temperature with three internal knots at 10th, 75th, and 90th percentile of city-specific temperature distributions, and a natural cubic spline for lag with seven, 14, or 21 days, with four dfs for the lag structure. We compared these lag patterns using generalized cross-validation scores.[19]

All analyses were conducted with R, version 3·6·0 (R Foundation for Statistical Computing, Vienna, Austria), using the mgcv and the mixmeta packages in the first and second stage analyses, respectively. Risk estimates are presented as percent increase (together with 95% confidence intervals [95% CI]) of daily mortality per 1 mg/m^3 increase of CO. To facilitate comparison with other studies and guidelines that used the maximum 8-h average concentration, a conversion factor of 3:2 was applied to convert the maximum 8-h average to 24-h average concentrations.[15]

Role of the funding source

The funders of this study had no role in the study design, in the collection, analysis, or interpretation of the data, or in drafting the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 summarizes the environmental and mortality data in each country. This analysis included a total of 40,090,407 deaths in 337 cities, covering an average period of 16 years in 18 countries. The annual city-specific mean concentrations of CO in all 337 cities were below 2·3 mg/m^3 (Figure 1), with the highest levels in some cities in the US and the lowest levels in some cities in the US, Romania, Spain,

UK, and Canada. Only 28 cities had an average of 0·2% of days with CO above 7 mg/m^3 (equivalent to NAAQS), 24 of which were in the US. Table S1 reports country-specific summaries of the other air pollutants and Table S2 and S3 describe city-specific summary statistics of data. In general, CO was moderately to highly correlated with PM_{10}, NO_2, and SO_2, but had weak and negative correlations with O_3 and daily mean temperature. The mean Pearson correlation coefficients between CO and co-pollutants were 0·40 for PM_{10}, 0·58 for NO_2, 0·37 for SO_2, -0·16 for O_3, and -0·23 for temperature. Country-specific correlation coefficients are summarized in Figure S1.

The previous day's (lag 1) exposure to ambient CO generated the smallest mean generalized cross-validation scores and the largest risk estimate across different lag days (Figure 2). Therefore, we used lag 1 for further analyses. Overall, an increase of 1 mg/m^3 in CO at the previous day was associated with a 0·91% (95% CI: 0·32%, 1·50%) increase in daily mortality in 337 cities (Figure 3). We observed some heterogeneity across country- and city-specific estimates (I^2 of 41·4%, Cochran Q-test p-value < 0·001). Likelihood ratio test showed significant heterogeneity across countries (p-value < 0·001). The country-specific estimates of the percentage change in daily mortality, per 1 mg/m^3 increase in CO concentration, ranged from 3·09% (95% CI: 2·15%, 4·04%) for South Korea to -0·92% (95% CI: -1·90%, 0·08%) for Taiwan. Positive and significant effect estimates were also observed in Canada (1·71%), Chile (1·26%), Italy (2·11%), Spain (2·17%), Thailand (1·35%), and the US (0·92%).

Figure 4 shows the pooled exposure-response curve of CO and mortality. No apparent threshold below which CO does not affect daily mortality was found from the curve. The curve also suggests an association with mortality for levels below 1 mg/m^3.

When restricting the analysis to days when CO concentrations were below a certain value (i.e., subset analysis), risk estimates remained positive and significant, further suggesting no thresholds in the CO-mortality association (Figure 5). When the potential threshold decreased from 4·0 to 1·5 mg/m^3, risk estimates remained similar and consistent with the main analysis. For example, when restricting the analysis to days with CO concentrations below 2 mg/m^3, a 1 mg/m^3 increase in CO was associated with an increase of 1·01% (95% CI: 0·40%, 1·62%) in daily mortality. When the potential threshold decreased from 1·5 to 0·2 mg/m^3, risk estimates increased and remained significant, albeit the 95% CIs increased due to declining sample sizes from 337 to 114 cities.

In two-pollutant models, the magnitude of the association between CO and mortality decreased after adjustment for PM_{10}, NO_2, and SO_2, but remained similar after adjustment for O_3 (Table 2). No significant differences in effect estimates were observed before and after adjustment for co-pollutants, except for NO_2 (p-value for difference = 0·006). In 290 cities with both CO and NO_2 data, the percent change per 1 mg/m^3 increase in CO concentration decreased significantly from 0·83% (95% CI: 0·24%, 1·42%) to -0·20% (95% CI: -0·64%, 0·24%) after adjustment for NO_2. Figure S2 compared the city-specific effect

297 estimates for CO, with and without adjustment for co-pollutants, and also indicated that city-specific
298 effect estimates were sensitive to adjustment for NO_2.
299 Our results remained robust when: a) using 5 to 10 dfs per year for the time trend adjustment, b)
300 adjusting for relative humidity, c) using at least three years of complete time-series data, d) restricting
301 data after the year 2000, and e) comparing all-cause with non-external mortality (Table S4). The use of
302 alternative temperature control approaches did not substantially change the estimated effect and the
303 choice of temperature adjustment in the main model yielded the smallest mean generalized cross-
304 validation scores (Table S5). Using alternative knots generated similar shape of the exposure-response
305 curve (Figure S3). Restricting data to 114 cities with at least one year of CO at or below 0·2 mg/m^3, the
306 subset analysis resulted in a similar pattern as using all cities that suggested no threshold in the CO-
307 mortality association (Figure S4).

308 **Discussion**

309 To the best of our knowledge, this research is by far the largest epidemiological study to investigate the
310 association between ambient CO pollution and daily mortality. We analyzed data from 337 cities in 18
311 countries, including more than 40 million deaths and covering a wide range of populations from different
312 regions of the world. We found a significant association between short-term exposure to CO and daily
313 mortality, with no evidence for a threshold value. This global study could provide comprehensive
314 evidence on the health effects of ambient CO pollution to inform the adequacy of current AQG, both
315 globally and regionally.
316 Overall, we found an increase of 0·91% (95% CI: 0·32%, 1·50%) in total mortality per 1 mg/m^3
317 increase in 24-h average ambient CO at the previous day (lag1). Consistently, two earlier national time-
318 series studies also observed the strongest association at lag day 1, with a slightly lower mortality increase
319 of 0·40% in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) of 82 U.S. cities[9] and
320 0·58% in 12 Canadian cities[14]. For the same increase in CO concentration on the current and previous day
321 (lag0-1), the increase in total mortality was 1·81% in 19 European cities in the Air Pollution and Health:
322 A European Approach (APHEA-2) project,[23] which was higher compared to 0.69 % in our study using the
323 same CO metric (Figure 2).
324 We observed some regional differences in the CO-mortality associations across countries (Figure 3).
325 Large mortality risk estimates (> 2% increase) were observed in South Korea, Spain, and Italy, whereas
326 null or negative (although not significant) associations were found in Sweden and Taiwan. This
327 variability across countries could be due to differences in air pollution levels, exposure assessment
328 accuracies, population susceptibility, basic health status, and sample sizes. Notably, most of the countries
329 with negative central estimates or null associations had only a limited number of cities included: Romania
330 (n=2), Sweden (n=1), and Taiwan (n=2), except for the UK (n=30). On the contrary, countries with a

large number of cities generally had significant positive associations such as Canada (n=24), Spain (n=45), Thailand (n=19), and the U.S. (n=156). Thus, the failure to detect the CO-mortality associations in some countries using time-series regressions of mortality counts might be in part due to small sample sizes within these countries.[26] Unlike the imprecise association that we observed for 3 Chinese cities, a recent study using 272 Chinese cities found a significant association between lag0-1 CO and cardiovascular mortality.[8] This discrepancy suggests that future studies with increased sample sizes within each country are warranted to explore the between-country differences in the CO-mortality associations.

The current ambient air quality standard for maximum 8-h average CO is 10 mg/m^3 (about 7 mg/m^3 for 24-h average) in the U.S. and Europe, which is the same as the one established in 2010 by the WHO indoor air quality guideline.[27] A more stringent guideline for 24-h average CO (4 mg/m^3) is implemented in China. In this study, all 337 cities had low levels of CO, with annual mean concentrations below 2 mg/m^3 (Figure 1) and the 99th percentiles of all cities were below 4 mg/m^3 (Table 1). However, when restricting CO concentrations below 4 mg/m^3, we still observed a significant association between short-term exposure to CO and total mortality (Figure 5). This association remained similar for CO concentrations below 4 to 1·5 mg/m^3 but elevated when restricting CO concentrations below 1 to 0·2 mg/m^3. The pooled exposure-response curve also showed no threshold below which CO was not associated with daily mortality (Figure 4). In accordance with our findings, previous multicity studies also found weak or no evidence for a threshold in the associations of CO with total or cardiovascular mortality in Europe [3] and China.[5,8] Our results suggest that current ambient AQG for CO in the U.S., Europe, and China are not sufficient enough to protect public health and should be updated. Thus, reductions in ambient CO levels, even in cities meeting the current AQG, should yield important health benefits.

Emission of ambient CO are mainly from incomplete combustion of fuels from vehicles, whereas the contribution from natural sources is generally smaller (e.g., 0·15 mg/m^3 in the U.S.).[15] This primary source of CO makes it challenging to disentangle the health effects of CO and other combustion-related co-pollutants. In this study, the CO mortality risk estimates attenuated but remained positive after adjustment for PM_{10} and SO_2 (Table 2). The association was reduced to null after adjustment for NO_2, which also results from traffic emissions and is widely used as a surrogate for traffic-related air pollution.[28] Consistently, previous multicity studies also found reduced mortality risk estimates for CO after including NO_2 in the model.[3,8,9,14] This sensitivity to adjustment for NO_2 might be because: (1) CO and NO_2 share common anthropogenic sources such as traffic; (2) CO and NO_2 are usually moderately to highly correlated; and (3) NO_2 might serve as a better surrogate for traffic-related exposure compared to low level concentrations of CO, which has decreasing relative contributions from traffic emissions for the past decades.[15,28]

Although the underlying mechanisms have not been fully delineated, it is biologically plausible that short-term exposure to low levels of ambient CO is associated with increased daily mortality. Epidemiological studies have provided evidence of a link between ambient CO exposure and blood markers of inflammation and coagulation, including increased levels of C-reactive protein, intercellular adhesion molecule-1, and fibrinogen[29,30] and decreases in prothrombin time (hypercoagulability)[31]. Short-term exposure to CO pollution may also lead to high blood pressure among women[32] and impaired lung function in asthmatic children seen as reductions in forced vital capacity and forced expiratory volume in one second[33]. Consistently, toxicological studies reported that exposure to CO concentrations mimicking air pollution could aggravate cardiac dysfunction in rats[34] and alter iron homeostasis in lung epithelial cells[35].

A major strength of this study is that we used an extensive dataset with large statistical power and applied a standardized analytical approach to cities across different countries and regions, which can provide robust results and avoid potential publication bias. Furthermore, we found no evidence of a threshold value in CO concentration, below which no effect occurs on daily mortality. The CO-mortality association persists at levels (<0·2 mg/m^3) well below the current WHO indoor AQG and the outdoor guidelines in the U.S., Europe, and China. Our findings could provide timely evidence for the update of the WHO and national AQG.

Several limitations should also be acknowledged in this study. First, our results cannot be interpreted as fully global representative estimates due to the lack of or insufficient coverage in Africa, the Middle East, and Latin America. We also note that our findings should be interpreted as the pooled estimates in the 337 studied cities and not as the total impacts of the 18 countries. Second, exposure measurement errors are inevitable since we only used fixed monitoring sites for air pollution. Despite the spatial variability in ambient CO concentrations, risk estimates from time-series designs may not be biased if levels at different locations have good temporal correlations.[15] Finally, we were unable to fully disentangle the health effects of ambient CO exposure from other combustion-related air pollutants. Thus, we cannot rule out the possibility that the observed associations might reflect the effects of traffic-related air pollution mixture. The question of whether CO is independently affecting mortality or serve as an indicator of the combustion-related pollutants warrants further investigation.

In conclusion, this multi-country time-series analysis provides evidence that exposure to ambient CO, despite its lower levels than current air quality guidelines, may still pose a public health threat. We demonstrated that short-term exposure to ambient CO was associated with increased daily mortality, with no evidence for a threshold value. Our findings suggest that the ongoing revision of WHO air quality guidelines, as well as future updates of national air quality guidelines in the U.S., Europe, and China, should consider revisiting the guideline for ambient CO.

Contributors

KC, AG, and AS contributed to the concept and design of this study. KC conducted the statistical analysis and drafted the manuscript. SB, KW, MS, AMVC, AG, and AS contributed to the development of statistical methods. FS prepared and cleaned the data. SB, KW, AMVC, YG, ST, EL, PMC, NVO, JJ, NR, VH, MS, MH, YH, BN, JM, HK, WL, AT, CI, BF, CÅ, MSR, YLG, BYC, SL, AZ, JS, MLB, HK, AG, and AS provided the data, contributed to the interpretation of results and reviewed the paper.

Declaration of interest

We declare no competing interests.

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References

1. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med* 1998; **339**(22): 1603-8.
2. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning - a public health perspective. *Toxicology* 2000; **145**(1): 1-14.
3. Samoli E, Touloumi G, Schwartz J, et al. Short-term effects of carbon monoxide on mortality: an analysis within the APHEA project. *Environ Health Perspect* 2007; **115**(11): 1578-83.
4. Bell Michelle L, Peng Roger D, Dominici F, Samet Jonathan M. Emergency hospital admissions for cardiovascular diseases and ambient Llevels of carbon monoxide. *Circulation* 2009; **120**(11): 949-55.
5. Chen R, Pan G, Zhang Y, et al. Ambient carbon monoxide and daily mortality in three Chinese cities: The China Air Pollution and Health Effects Study (CAPES). *Science of The Total Environment* 2011; **409**(23): 4923-8.
6. Goldberg MS, Burnett RT, Stieb DM, et al. Associations between ambient air pollution and daily mortality among elderly persons in Montreal, Quebec. *Sci Total Environ* 2013; **463-464**: 931-42.
7. Costa AF, Hoek G, Brunekreef B, Ponce de Leon AC. Air pollution and deaths among elderly residents of Sao Paulo, Brazil: an analysis of mortality displacement. *Environ Health Perspect* 2017; **125**(3): 349-54.
8. Liu C, Yin P, Chen R, et al. Ambient carbon monoxide and cardiovascular mortality: a nationwide time-series analysis in 272 cities in China. *The Lancet Planetary Health* 2018; **2**(1): e12-e8.
9. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. Mortality among residents of 90 cities. Revised Analyses of Time-Series Studies of Air Pollution and Health. Boston, MA: Health Effects Institute; 2003.
10. Hong YC, Lee JT, Kim H, Ha EH, Schwartz J, Christiani DC. Effects of air pollutants on acute stroke mortality. *Environ Health Perspect* 2002; **110**(2): 187-91.
11. Atkinson RW, Analitis A, Samoli E, et al. Short-term exposure to traffic-related air pollution and daily mortality in London, UK. *J Expo Sci Environ Epidemiol* 2016; **26**(2): 125-32.
12. Verhoeff AP, Hoek G, Schwartz J, van Wijnen JH. Air pollution and daily mortality in Amsterdam. *Epidemiology* 1996; **7**(3): 225-30.
13. Pothirat C, Chaiwong W, Liwsrisakun C, et al. Acute effects of air pollutants on daily mortality and hospitalizations due to cardiovascular and respiratory diseases. *J Thorac Dis* 2019; **11**(7): 3070-83.
14. Burnett RT, Stieb D, Brook JR, et al. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Arch Environ Health* 2004; **59**(5): 228-36.
15. U.S. Environmental Protection Agency. Integrated Science Assessment (ISA) for Carbon Monoxide. Research Triangle Park, NC: U.S. EPA Office of Research and Development, 2010.
16. World Health Organization. WHO expert consultation: available evidence for the future update of the WHO global air quality guidelines (AQGs). Geneva, Switzerland, 2016.
17. Gasparrini A, Guo YM, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; **386**(9991): 369-75.
18. Guo Y, Gasparrini A, Armstrong B, et al. Global variation in the effects of ambient temperature on mortality: A systematic evaluation. *Epidemiology* 2014; **25**(6): 781-9.
19. Liu C, Chen R, Sera F, et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019; **381**(8): 705-15.
20. Vicedo-Cabrera AM, Sera F, Liu C, et al. Short term association between ozone and mortality: global two stage time series study in 406 locations in 20 countries. *BMJ* 2020; **368**: m108.
21. Stafoggia M, Samoli E, Alessandrini E, et al. Short-term associations between fine and coarse particulate matter and hospitalizations in Southern Europe: results from the MED-PARTICLES project. *Environ Health Perspect* 2013; **121**(9): 1026.
22. Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. *Stat Med* 2019; **38**(29): 5429-44.

23. Samoli E, Analitis A, Touloumi G, et al. Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. *Environ Health Perspect* 2005; **113**(1): 88-95.
24. Bell ML, Peng RD, Dominici F. The exposure-response curve for ozone and risk of mortality and the adequacy of current ozone regulations. *Environ Health Perspect* 2006; **114**(4): 532-6.
25. Chen K, Zhou L, Chen X, Bi J, Kinney PL. Acute effect of ozone exposure on daily mortality in seven cities of Jiangsu Province, China: No clear evidence for threshold. *Environ Res* 2017; **155**: 235-41.
26. Armstrong BG, Gasparrini A, Tobias A, Sera F. Sample size issues in time series regressions of counts on environmental exposures. *BMC Med Res Methodol* 2020; **20**(1): 15.
27. World Health Organization. WHO guidelines for indoor air quality: selected pollutants. Geneva, Switzerland, 2010.
28. HEI Panel on the Health Effects of Traffic-Related Air Pollution. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. Boston, Massachusetts: Health Effects Institute; 2010.
29. Bind M-A, Baccarelli A, Zanobetti A, et al. Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigene-environment interactions in an elderly cohort. *Epidemiology* 2012; **23**(2): 332-40.
30. Rückerl R, Hampel R, Breitner S, et al. Associations between ambient air pollution and blood markers of inflammation and coagulation/fibrinolysis in susceptible populations. *Environ Int* 2014; **70**: 32-49.
31. Baccarelli A, Zanobetti A, Martinelli I, et al. Effects of exposure to air pollution on blood coagulation. *J Thromb Haemost* 2007; **5**(2): 252-60.
32. Männistö T, Mendola P, Liu D, Leishear K, Sherman S, Laughon SK. Acute air pollution exposure and blood pressure at delivery among women with and without hypertension. *Am J Hypertens* 2014; **28**(1): 58-72.
33. Ierodiakonou D, Zanobetti A, Coull BA, et al. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. *J Allergy Clin Immunol* 2016; **137**(2): 390-9.
34. Reboul C, Boissiere J, Andre L, et al. Carbon monoxide pollution aggravates ischemic heart failure through oxidative stress pathway. *Sci Rep* 2017; **7**: 39715.
35. Ghio AJ, Stonehuerner JG, Dailey LA, et al. Carbon monoxide reversibly alters iron homeostasis and respiratory epithelial cell function. *Am J Respir Cell Mol Biol* 2008; **38**(6): 715-23.

Table 1. Summary statistics of daily data on deaths, air pollutants, and temperature.

	Cities (N)	Period	Deaths	CO (mg/m^3)			Temperature (°C)
				1^{st} percentile	Median (IQR)	99^{th} percentile	Median (IQR)
Australia	2	2000-2009	279,410	0	0·38 (0·25; 0·63)	1·88	18·1 (14·5; 22·2)
Canada	24	2000-2015	1,759,125	0	0·32 (0·23; 0·48)	1·39	8·1 (0; 15·8)
China	3	2013-2015	246,246	0·35	0·95 (0·73; 1·24)	4·16	19·9 (11·3; 25·6)
Chile	3	2004-2014	282,232	0·01	0·57 (0·34; 1·06)	3·49	13·4 (10·3; 17·1)
Finland	1	1994-2014	153,308	0·11	0·25 (0·19; 0·35)	0·95	5·9 (0; 13·8)
Germany	12	1993-2015	1,897,704	0·05	0·40 (0·27; 0·63)	1·79	10·4 (4·7; 15·8)
Italy	12	2013-2015	212,494	0·14	0·57 (0·33; 0·99)	2·23	16·1 (10·6; 21·7)
Japan	6	1979-2009	3,112,302	0·18	0·68 (0·48; 0·99)	2·63	15·6 (8·1; 22·3)
South Korea	7	1999-2015	1,661,559	0·27	0·61 (0·48; 0·82)	1·85	15·1 (5·9; 22·0)
Portugal	2	1995-2012	559,147	0·02	0·27 (0·19; 0·40)	1·09	16·3 (12·8; 19·9)
Romania	7	2008-2016	242,014	0·01	0·17 (0·08; 0·39)	2·72	12·3 (4·9; 19·8)
Spain	45	2003-2014	1,306,694	0·04	0·36 (0·25; 0·51)	1·25	15·7 (10·4; 21·2)
Switzerland	4	1995-2013	150,003	0·20	0·50 (0·40; 0·90)	2·60	11·0 (4·9; 16·8)
Sweden	1	1990-2010	194,239	0·31	0·92 (0·65; 1·45)	3·48	6·7 (1·1; 13·6)
Thailand	19	1999-2008	758,133	0·13	0·63 (0·42; 0·92)	1·99	28·0 (26·5; 29·2)
Taiwan	3	1996-2014	1,113,099	0·26	0·70 (0·53; 0·93)	1·91	25·1 (20·4; 28·0)
UK	30	1990-2016	3,543,977	0·07	0·33 (0·21; 0·53)	1·71	10·6 (6·7; 14·8)
USA	156	1985-2006	22,618,721	0·06	0·87 (0·56; 1·32)	3·93	15·2 (7·1; 22·2)

IQR: Interquartile range

Table 2. Overall percent increase of mortality per 1 mg/m^3 increase in CO at lag day 1 with and without adjustment for co-pollutants.

Models	N. of cities with at least 2 years data	Without co-pollutant	With co-pollutant	P-value for difference
Single pollutant model of CO	337	0·91 (0·32, 1·50)	-	-
$+PM_{10}$	271	0·95 (0·30, 1·61)	0·38 (-0·28, 1·03)	0·223
$+NO_2$	290	0·83 (0·24, 1·42)	-0·20 (-0·64, 0·24)	0·006
$+SO_2$	297	0·78 (0·10, 1·45)	0·44 (-0·23, 1·11)	0·487
$+O_3$	249	1·20 (0·34, 2·07)	1·45 (0·67, 2·23)	0·676

Note: All models were adjusted for time trend, day of the week effect, and temperature. Same lag days were applied to CO and co-pollutants.

Figure Legends

Figure 1. Map of the city-specific annual mean CO concentrations of 337 cities included in the analysis.

Figure 2. Overall percent increase in daily mortality per 1 mg/m^3 increase in CO at different lag days in 337 cities in 18 countries.

Figure 3. Overall and country-specific percent increase in daily mortality per 1 mg/m^3 increase in CO at lag 1 day in 337 cities.

Figure 4. Pooled exposure-response curve between CO (lag1) and daily mortality. The y axis represents the percentage change in daily mortality at a certain CO concentration compared with the median concentration. The x axis represents CO concentration from the 1st to 99th percentiles of CO concentrations across all cities. Shaded area represents the 95% confidence intervals.

Figure 5. Overall percent increase in daily mortality per 0·1 mg/m^3 increase in CO at lag 1 day by varying hypothetical thresholds using the subset analysis. Cities with at least 1 year of data (365 days) with CO below the threshold were used in this analysis. The italicized number in the bracket represents the number of cities included in each threshold analysis.

Figure 1

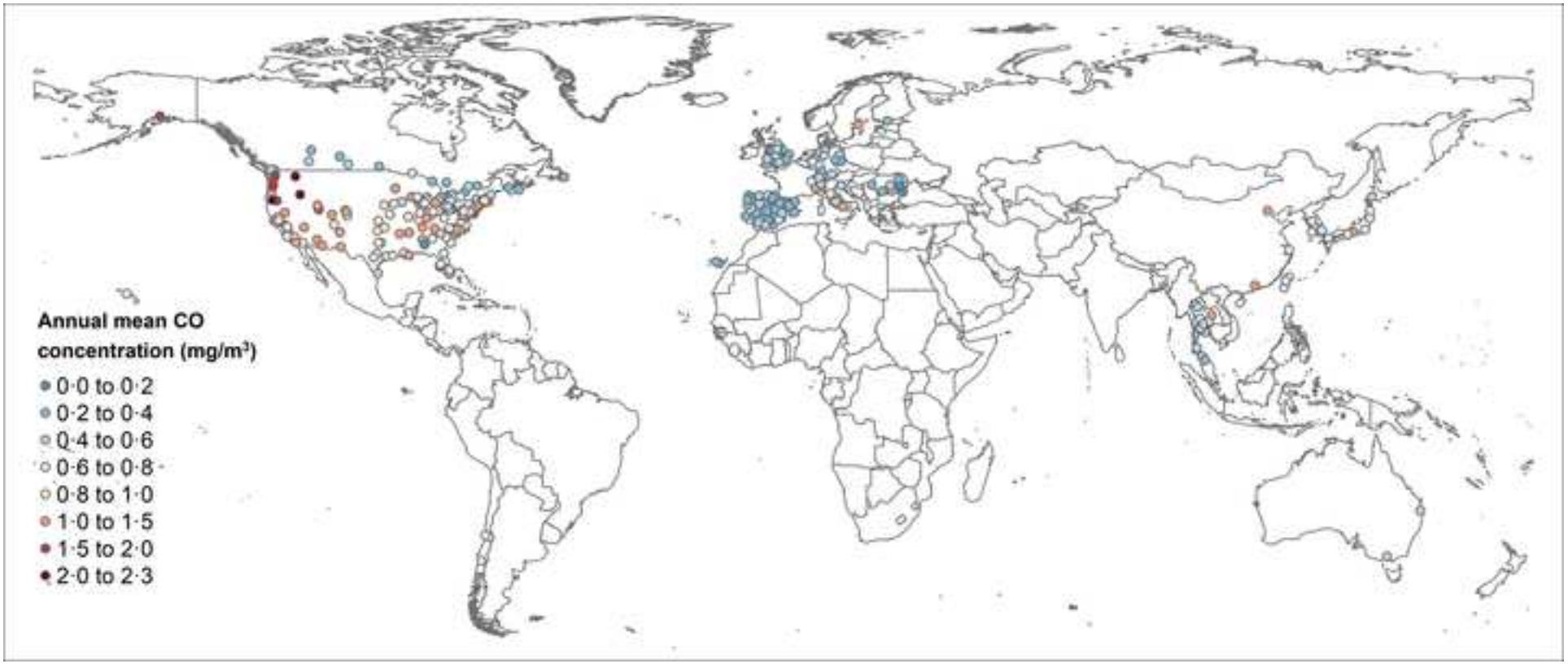

Figure 2

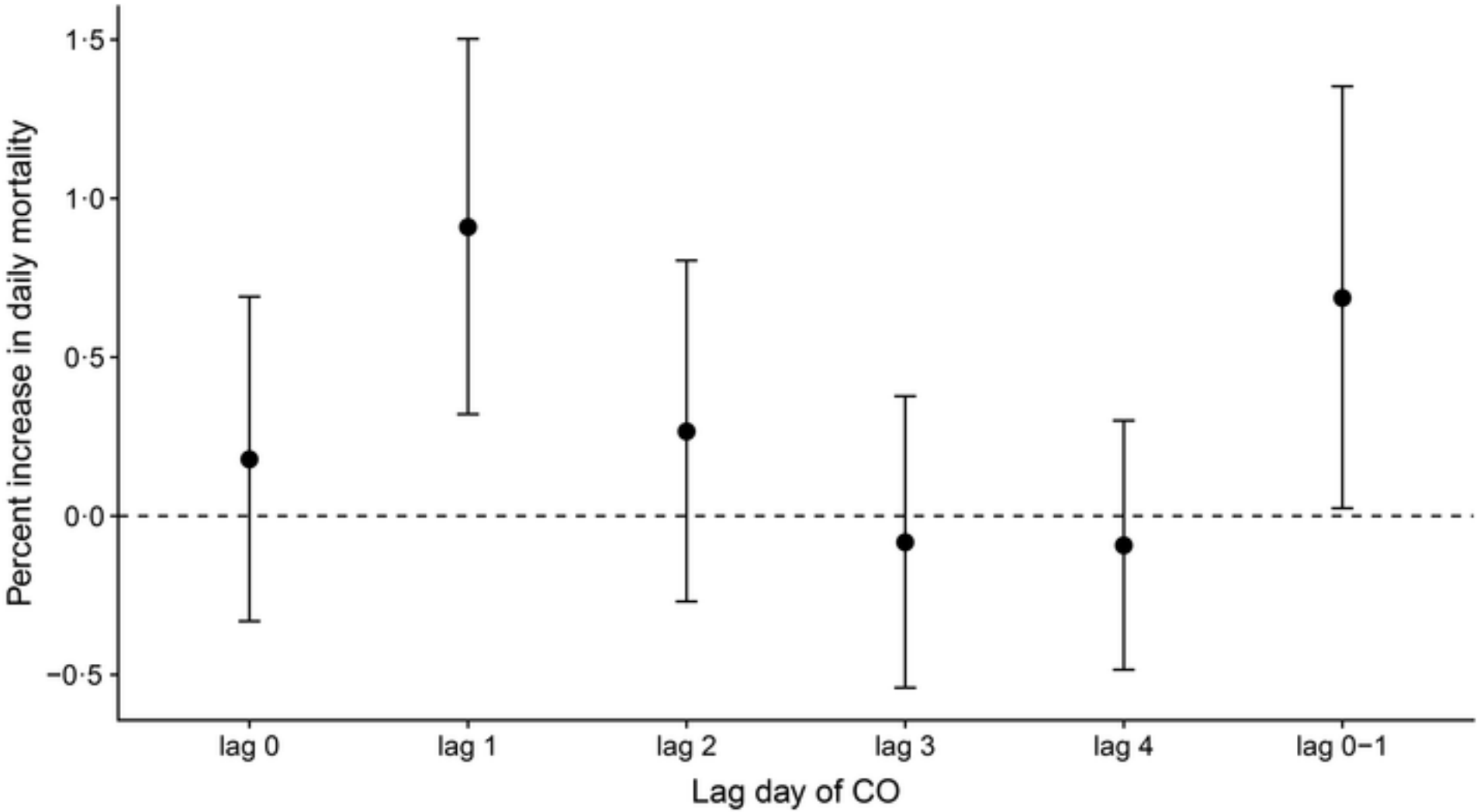

Figure 3

Click here to access/download;Figure;Fig3.Country_overall_perctincrease_lag1CO_massimotemp.

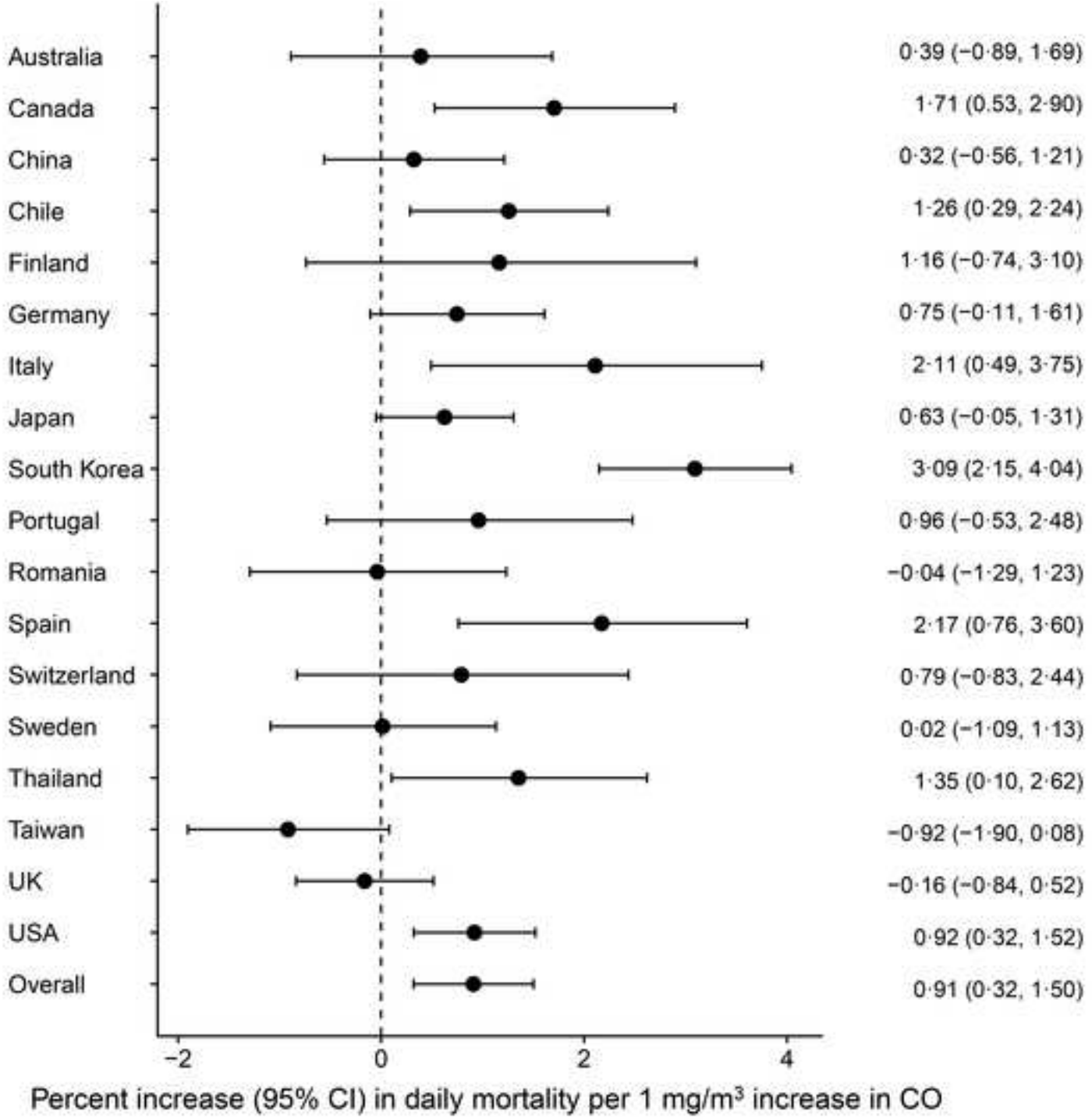

Figure 4

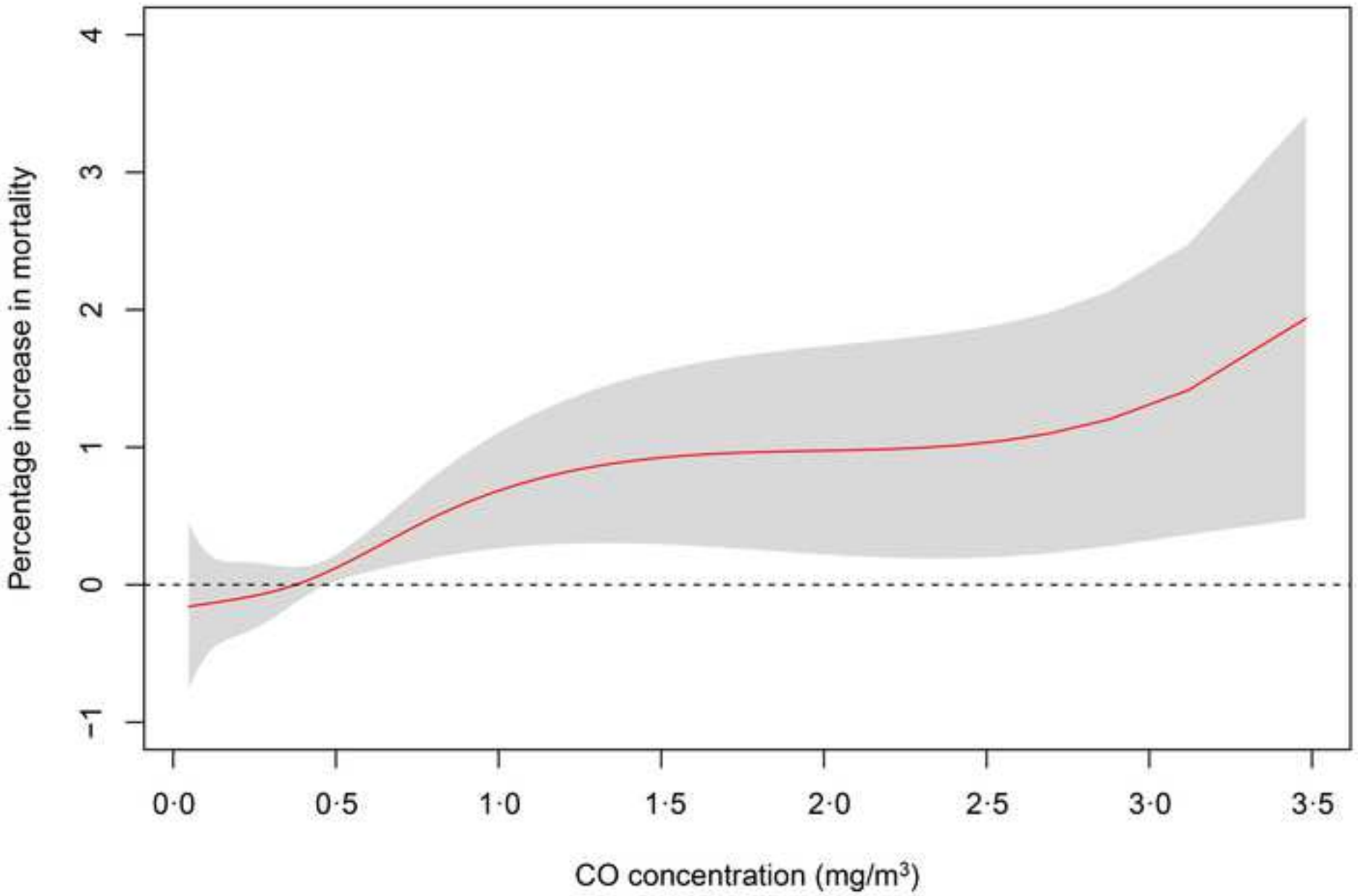

Figure 5

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