Ambient carbon monoxide and daily mortality: a global time-series study in 337 cities

Kai Chen, Susanne Breitner, Kathrin Wolf, Massimo Stafoggia, Francesco Sera, Ana M Vicedo-Cabrera, Yuming Guo, Shilu Tong, Eric Lavigne, Patricia Matus, Nicolás Valdés, Haidong Kan, Jouni J K Jaakkola, Niilo R I Ryti, Veronika Huber, Matteo Scortichini, Masahiro Hashizume, Yasushi Honda, Baltazar Nunes, Joana Madureira, Iulian Horia Holobâcă, Simona Fratianni, Ho Kim, Whanhee Lee, Aurelio Tobias, Carmen Íñiguez, Bertil Forsberg, Christofer Åström, Martina S Ragettli, Yue-Liang Leon Guo, Bing-Yu Chen, Shanshan Li, Ai Milojevic, Antonella Zanobetti, Joel Schwartz, Michelle L Bell, Antonio Gasparrini, Alexandra Schneider**

Summary

Background Epidemiological evidence on short-term association between ambient carbon monoxide (CO) and mortality is inconclusive and limited to single cities, regions, or countries. Generalisation of results from previous studies is hindered by potential publication bias and different modelling approaches. We therefore assessed the association between short-term exposure to ambient CO and daily mortality in a multicity, multicountry setting.

Methods We collected daily data on air pollution, meteorology, and total mortality from 337 cities in 18 countries or regions, covering various periods from 1979 to 2016. All included cities had at least 2 years of both CO and mortality data. We estimated city-specific associations using confounder-adjusted generalised additive models with a quasi-Poisson distribution, and then 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 affected.

Findings Overall, a 1 mg/m³ increase in the average CO concentration of the previous day was associated with a 0·91% (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. The exposure–response curve was steeper at daily CO levels lower than 1 mg/m³, indicating greater risk of mortality per increment in CO exposure, and persisted at daily concentrations as low as 0·6 mg/m³ or less. The association remained similar after adjustment for ozone but was attenuated after adjustment for particulate matter or sulphur dioxide, or even reduced to null after adjustment for nitrogen dioxide.

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. Further studies are warranted to disentangle its independent effect from other traffic-related pollutants.

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

Copyright © 2021 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

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 low levels of ambient CO 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] São Paulo,[7] Tokyo,[10] and Seoul,[11] but not for others such as London,[12] Amsterdam,[13] or Chiang Mai.[14] A few multicity studies have been done, but they were mostly focused on a single region or country,[3,5,8,9,15] thus limiting the generalisability of the reported associations. Furthermore, previous studies have applied different modelling choices, making it difficult to estimate a globally representative association between short-term CO exposure and mortality.

In 1971, the US Environmental Protection Agency established the health-based National Ambient Air Quality Standard (NAAQS) for the daily maximum 8-h average CO concentration at 9 parts per million (ppm; approximately 10 mg/m³),[16] which is equivalent to approximately 7 mg/m³ for the daily 24-h average CO. The NAAQS for CO has been retained for the past five decades. The same limit value (10 mg/m³ for maximum 8-h average) is also applied in the European air quality guidelines. In China, a lower limit value of 4 mg/m³ for 24-h average CO was promulgated in the Chinese Ambient Air Quality Standards. In 2005, WHO published the latest edition of their air quality guidelines,

Lancet Planet Health 2021; 5: e191–99

See **Comment** page 177

*Senior authors and contributed equally

Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA (K Chen PhD); **Institute of Epidemiology, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg, Germany** (S Breitner PhD, K Wolf PhD, A Schneider PhD); **Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany** (S Breitner); **Department of Epidemiology, Lazio Regional Health Service, Rome, Italy** (M Stafoggia PhD, M Scortichini MSc); **Department of Public Health, Environments and Society** (F Sera MSc, A Milojevic PhD, Prof A Gasparrini PhD), **Centre for Statistical Methodology** (Prof A Gasparrini), **and Centre on Climate Change and Planetary Health** (Prof A Gasparrini), **London School of Hygiene & Tropical Medicine, London, UK; Department of Statistics, Computer Science and Applications "G. Parenti", University of Florence, Florence, Italy** (F Sera); **Institute of Social and Preventive Medicine** (A M Vicedo-Cabrera PhD) **and Oeschger Center for Climate Change Research** (A M Vicedo-Cabrera), **University of Bern, Bern, Switzerland; Climate, Air Quality Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof Y Guo PhD, S Li PhD); **Shanghai Children's Medical**

Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Prof S Tong PhD); School of Public Health, Institute of Environment and Population Health, Anhui Medical University, Hefei, China (Prof S Tong); School of Public Health and Social Work, Queensland University of Technology, Brisbane, QLD, Australia (Prof S Tong); Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China (Prof S Tong); Air Health Science Division, Health Canada, Ottawa, ON, Canada (Prof E Lavigne PhD); School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada (Prof E Lavigne); Department of Public Health (P Matus PhD) and Faculty of Nursing and Midwifery (N Valdés MSc), Universidad de los Andes, Santiago, Chile; School of Public Health, Key Lab of Public Health Safety of the Ministry of Education and Key Lab of Health Technology Assessment of the Ministry of Health (Prof H Kan PhD) and Shanghai Key Laboratory of Atmospheric Particle Pollution and Prevention (LAP3) (Prof H Kan), Fudan University, Shanghai, China; Center for Environmental and Respiratory Health Research (CERH), University of Oulu, Oulu, Finland (Prof J J K Jaakkola PhD, N R I Ryti PhD); Biocenter Oulu, University of Oulu, Oulu, Finland (Prof J J K Jaakkola, N R I Ryti); Finnish Meteorological Institute, Helsinki, Finland (Prof J J K Jaakkola); Department of Physical, Chemical and Natural Systems, Universidad Pablo de Olavide, Seville, Spain (V Huber PhD); Potsdam Institute for Climate Impact Research, Potsdam, Germany (V Huber); Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (Prof M Hashizume PhD); Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan (Prof Y Honda PhD); Department of Epidemiology, Instituto Nacional de Saúde Dr Ricardo Jorge, Lisbon, Portugal (B Nunes PhD); Centro de Investigação em Saúde

Research in context

Evidence before this study

We searched PubMed without any language restrictions for articles published from inception up to Dec 31, 2019, using the following search terms: "carbon monoxide", "mortality" or "death*", "daily", and "short-term" or "acute." After screening abstracts and full texts, our literature review showed that epidemiological evidence is inconsistent. As previous studies were mainly from single cities, regions, or countries, there is little generalisability of reported short-term associations between carbon monoxide (CO) and mortality. Moreover, whether a potential threshold exists in the relationship between CO exposure and mortality 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 multicountry 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 of less than 0·6 mg/m³. 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. This association was attenuated with other traffic-related pollutants such as nitrogen dioxide. These findings suggest that global and national air quality guidelines for CO might need to be revisited and, in addition to single pollutant standards, policies should also address traffic-related air pollution mixtures.

which did not include recommendations for ambient CO. Since then, substantial new evidence on the adverse health effects of ambient CO has emerged,[16] leading to an ongoing review and update of the WHO air quality guidelines to re-evaluate CO as an ambient air pollutant.[17]

A key issue in setting an air quality guideline for CO is whether a threshold exists in the CO exposure–response relationship below which health is not affected. Very little 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/m³ for the maximum 8-h average in the CO–mortality association in 19 European cities.[3] Another multicity study in the USA reported a significantly increased risk in hospital admission for cardiovascular diseases for 1-h average ambient CO of less than 1 ppm (approximately 1·15 mg/m³), and a linear exposure–response curve, indicating no evidence for a threshold.[4] Two additional studies from China also found no evidence for a threshold value in the association between 24-h average CO and cardiovascular mortality.[5,8] However, these findings are difficult to synthesise because of different CO exposure metrics, health outcomes, and modelling approaches.

Here, we did 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,[18,19] including data from 337 cities within 18 countries. This network allowed a comprehensive and standardised 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, covering various periods ranging from 1979 to 2016. This dataset has been used in previous publications on the association between daily mortality and ambient particulate matter and ozone pollution.[20,21] 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 codes 0–799 [9th revision] or codes A00–R99 [10th revision]), or by all-cause deaths when data on non-external causes were not available. For each city, we derived daily 24-h average concentrations of CO, PM_{10}, nitrogen dioxide (NO_2), and sulphur dioxide (SO_2) and daily maximum 8-h average ozone (O_3) concentrations from urban and suburban air quality monitoring stations. In the MCC dataset, CO concentrations were collected using the 24-h average metric and then harmonised using the mg/m³ unit, which corresponded to the metric and unit applied by the 2010 WHO indoor air quality guidelines.[22] We excluded seven cities that had short periods (<2 years) with both CO and mortality data, resulting in 337 cities being included 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 the appendix (p 26). Data collection by country is described in detail in the appendix (pp 2–5).

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 generalised additive models with a quasi-Poisson distribution to evaluate the city-specific associations between CO and mortality. Consistent with previous studies,[20,23] the following confounders were included in the city-specific models: (1) a cubic regression spline with 7 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-related and cold-related mortality while reducing concurvity between the two splines.[23] Temperature terms were defined as the average temperature on the previous 6 days (lag 1–6) for days of low temperature (ie, below the city-specific median value) or as the average temperature on the current and previous day (lag 0–1) for days of high temperature (ie, 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 4 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).[24] We assessed heterogeneity using the I^2 statistic and Cochran's 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 or 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. To further explore potential effect modifications by economic and climatic characteristics, we fitted separate meta-regression models with the gross domestic product (GDP) per capita, latitude, and annual mean temperature of cities.

We also fitted two-pollutant models to adjust for potential confounding of co-pollutants (ie, 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 estimates without adjustment for co-pollutants.

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 used in previous studies.[20,25] 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 did a subset analysis, as applied in previous studies.[26,27] This approach only includes days that meet a certain air quality cutoff value in each city (ie, only days with concentrations below that threshold), and then varies that value. Based on the sample sizes and distribution of CO concentrations across all countries included in the study, we explored cutoff values ranging from 0·6 mg/m³ to 1·0 mg/m³ with increments of 0·2 mg/m³, and from 1·0 mg/m³ to 4·0 mg/m³ with increments of 0·5 mg/m³. Cities with at least 1 year of data (365 days, not necessarily consecutive) with CO below the cutoff value were used in this analysis.

We did several sensitivity analyses to examine the robustness of the results, including using different df for time trend (5–10 df per year), additionally adjusting for relative humidity in the 230 cities with available humidity data, restricting the analysis to 311 cities with data after the year 2000, and restricting the analysis to 315 cities with at least 3 years (1095 days, not necessarily consecutive) 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. 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 data. Finally, we applied alternative temperature control approaches: (1) using alternative lag days for low and high temperatures (lag 1–3 for low with lag 0–1 for high, lag 0–5 for low with lag 0 for high, and lag 0–3 for low with lag 0 for high); (2) a natural cubic spline term of moving average temperatures (lag 0–1, lag 0–3, and lag 0–7) with 6 df; and (3) a distributed lag non-linear term using a quadratic B-spline for temperature with three internal knots at the tenth, 75th, and 90th percentiles of city-specific temperature distributions, and a natural cubic spline for lag with 7, 14, or 21 days, with 3 df for the lag structure. We compared these lag patterns using generalised cross-validation scores.[20]

All analyses were done with R (version 3.6.0), using the mgcv package in the first-stage analysis and the mixmeta package in the second-stage analysis. Risk estimates are presented as percentage increases (together with 95% CIs) of daily mortality per 1 mg/m³ increase of CO. To facilitate comparison with other studies and guidelines that used the maximum 8-h average concentration, a conversion factor of 2/3 was applied to convert the maximum 8-h average to 24-h average concentrations.[16]

Pública, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Lisbon, Portugal (B Nunes); **Department of Enviromental Health, Instituto Nacional de Saúde Dr Ricardo Jorge, Porto, Portugal** (J Madureira PhD); **EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal** (J Madureira); **Faculty of Geography, Babes-Bolay University, Cluj-Napoca, Romania** (I H Holobâcă PhD); **Department of Earth Sciences, University of Torino, Turin, Italy** (S Fratianni PhD*); **Graduate School of Public Health, Seoul National University, Seoul, South Korea** (Prof H Kim PhD, W Lee PhD); **Institute of Environmental Assessment and Water Research, Spanish Council for Scientific Research, Barcelona, Spain** (A Tobias PhD); **School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan** (A Tobias); **Department of Statistics and Computational Research, University of Valencia, Valencia, Spain; Ciberesp, Madrid, Spain** (C Íñiguez PhD); **Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden** (Prof B Forsberg PhD, C Åström PhD); **Swiss Tropical and Public Health Institute, Basel, Switzerland** (M S Ragettli PhD); **University of Basel, Basel, Switzerland** (M S Ragettli); **Environmental and Occupational Medicine, National Taiwan University and NTU Hospital, Taipei, Taiwan** (Prof Y-L L Guo PhD); **National Institute of Environmental Health Science, National Health Research Institutes, Zhunan, Taiwan** (Prof Y-L L Guo, B-Y Chen PhD); **Department of Environmental Health, Harvard T H Chan School of Public Health, Boston, MA, USA** (A Zanobetti PhD, Prof J Schwartz PhD); **School of the Environment, Yale University, New Haven, CT, USA** (Prof M L Bell PhD)

*Dr Fratianni died in September, 2020

Correspondence to:
Dr Kai Chen, Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, 06520, USA
kai.chen@yale.edu

For more on the **MCC Collaborative Research Network** see http://mccstudy.lshtm.ac.uk

See Online for appendix

	Cities	Period	Deaths	CO (mg/m³)			Median temperature (°C)
				1st percentile	Median	99th percentile	
Australia	2	2000–09	279 410	0·00	0·38 (0·25–0·63)	1·88	18·1 (14·5–22·2)
Canada	24	2000–15	1 759 125	0·00	0·32 (0·23–0·48)	1·39	8·1 (0·0–15·8)
Chile	3	2004–14	282 232	0·01	0·57 (0·34–1·06)	3·49	13·4 (10·3–17·1)
China	3	2013–15	246 246	0·35	0·95 (0·73–1·24)	4·16	19·9 (11·3–25·6)
Finland	1	1994–2014	153 308	0·11	0·25 (0·19–0·35)	0·95	5·9 (0·0–13·8)
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	2013–15	212 494	0·14	0·57 (0·33–0·99)	2·23	16·1 (10·6–21·7)
Japan	6	1979–09	3 112 302	0·18	0·68 (0·48–0·99)	2·63	15·6 (8·1–22·3)
Portugal	2	1995–2012	559 147	0·02	0·27 (0·19–0·40)	1·09	16·3 (12·8–19·9)
Romania	7	2008–16	242 014	0·01	0·17 (0·08–0·39)	2·72	12·3 (4·9–19·8)
South Korea	7	1999–2015	1 661 559	0·27	0·61 (0·48–0·82)	1·85	15·1 (5·9–22·0)
Spain	45	2003–14	1 306 694	0·04	0·36 (0·25–0·51)	1·25	15·7 (10·4–21·2)
Sweden	1	1990–2010	194 239	0·31	0·92 (0·65–1·45)	3·48	6·7 (1·1–13·6)
Switzerland	4	1995–2013	150 003	0·20	0·50 (0·40–0·90)	2·60	11·0 (4·9–16·8)
Taiwan	3	1996–2014	1 113 099	0·26	0·70 (0·53–0·93)	1·91	25·1 (20·4–28·0)
Thailand	19	1999–2008	758 133	0·13	0·63 (0·42–0·92)	1·99	28·0 (26·5–29·2)
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)

Data in parentheses are IQRs. CO=carbon monoxide.

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

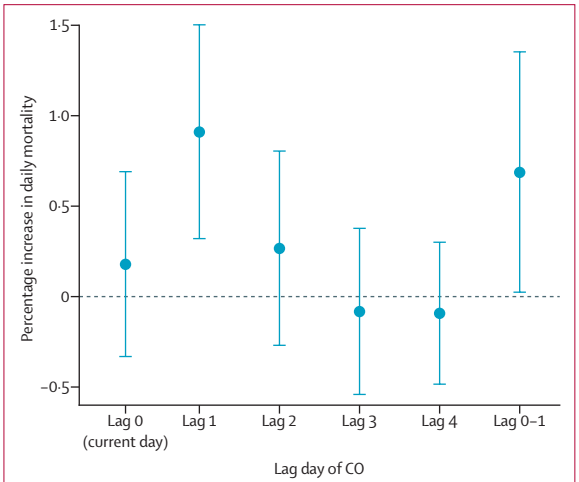

Figure 1: **Overall percentage increase in daily mortality per 1 mg/m³ increase in CO at different lags in 337 cities in 18 countries**

Whiskers show 95% CIs. CO=carbon monoxide.

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.

Results

This analysis included a total of 40 090 407 deaths in 337 cities, covering an average period of 16 years in 18 countries (table 1). The annual city-specific mean concentrations of CO in all 337 cities was less than 2·3 mg/m³ (appendix p 26), with the highest levels in some cities in the USA and the lowest levels in some cities in the USA, Romania, Spain, the UK, and Canada. Only 28 cities had an average of 0·2% of days with CO higher than 7 mg/m³ (equivalent to NAAQS), 24 of which were in the USA. Country-specific summaries of the other air pollutants are shown in the appendix (p 9), alongside city-specific summary statistics (appendix pp 10–22). 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 summarised in the appendix (p 27).

The previous day's (lag 1) exposure to ambient CO generated the largest risk estimate across different lag days (figure 1). Therefore, we used lag 1 for further analyses. Overall, an increase of 1 mg/m³ in CO on the previous day was associated with a 0·91% (95% CI 0·32 to 1·50) increase in daily mortality in the 337 cities (figure 2). We observed some heterogeneity across country-specific and city-specific estimates (I^2=41·4%; Cochran's Q-test p<0·0001). The likelihood ratio test showed significant heterogeneity across countries (p<0·0001). Country-specific estimates of the percentage change in daily mortality, per 1 mg/m³ increase in CO concentration, ranged from 3·09% (2·15 to 4·04) for South Korea to –0·92% (–1·90 to 0·08) for Taiwan. Positive and significant effect estimates were also

observed in Canada, Chile, Italy, Spain, Thailand, and the USA (figure 2). There was no significant effect modification by GDP per capita, latitude, and annual mean temperature of cities (appendix p 25).

When considering the pooled exposure–response curve of CO and mortality, no apparent threshold below which CO does not affect daily mortality was found (figure 3). The curve also suggests an association with mortality for levels below 1 mg/m³.

When restricting the analysis to days when CO concentrations were below a certain cutoff value (ie, subset analysis), risk estimates remained positive and significant, further suggesting no thresholds in the CO–mortality association (figure 4). When the cutoff value decreased from 4·0 mg/m³ to 1·5 mg/m³, risk estimates remained similar and consistent with the main analysis. For example, when restricting the analysis to days with CO concentrations of less than 2 mg/m³, a 1 mg/m³ increase in CO was associated with a 1·01% (0·40–1·62) increase in daily mortality. When the cutoff value decreased from 1·5 mg/m³ to 0·6 mg/m³, risk estimates, corresponding to the increased gradient in figure 3, increased and remained significant, although the 95% CIs increased due to declining sample sizes from 87% to 45% of days of observations.

In the two-pollutant models, the magnitude of the association between CO and mortality decreased and became non-significant after adjustment for PM_{10}, NO_2, and SO_2, but remained similar after adjustment for O_3 (table 2). In 290 cities with both CO and NO_2 data, the percentage change per 1 mg/m³ increase in CO concentration decreased significantly after adjustment for NO_2. When comparing city-specific effect estimates for CO, with and without adjustment for co-pollutants, estimates appear to be sensitive to adjustment for NO_2 (appendix p 28). In addition, the effect estimate with adjustment for PM_{10} was 60% smaller than that without adjustment for PM_{10} (table 2).

Our results remained robust when using 5–10 df per year for the time trend adjustment, adjusting for relative humidity, when using at least 3 years of complete time-series data, when restricting data after the year 2000, and when comparing all-cause with non-external mortality (appendix p 23). The use of alternative temperature control approaches did not substantially change the estimated effect (appendix p 24). Finally, using alternative knots generated a similar shape of the exposure–response curve (appendix p 29).

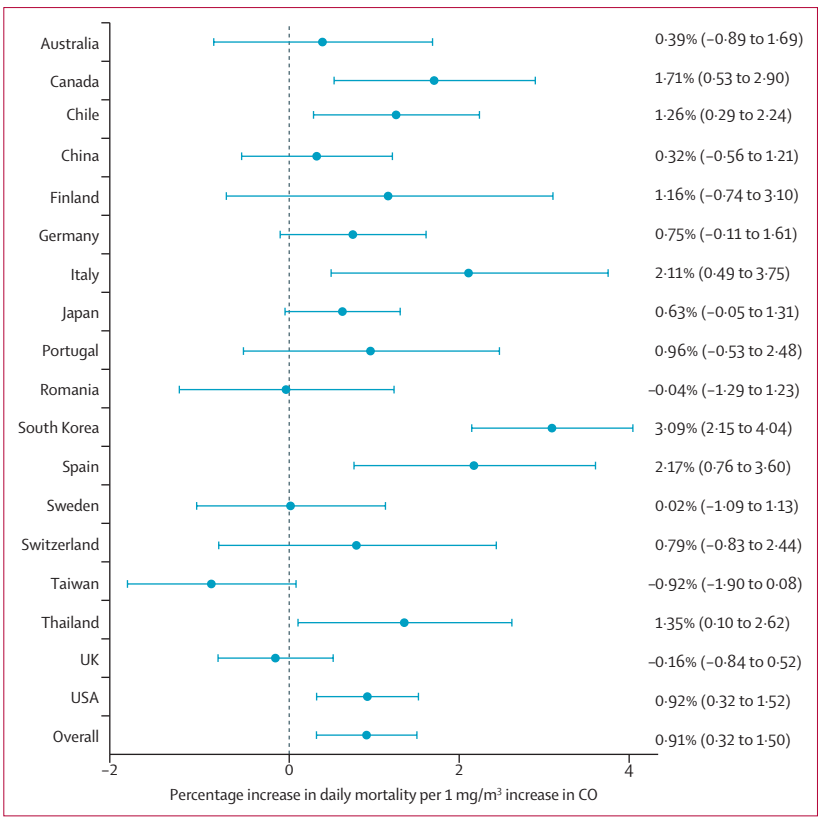

Figure 2: **Overall and country-specific percentage increase in daily mortality per 1 mg/m³ increase in CO (at lag 1 day) in 337 cities**
Whiskers show 95% CIs. CO=carbon monoxide.

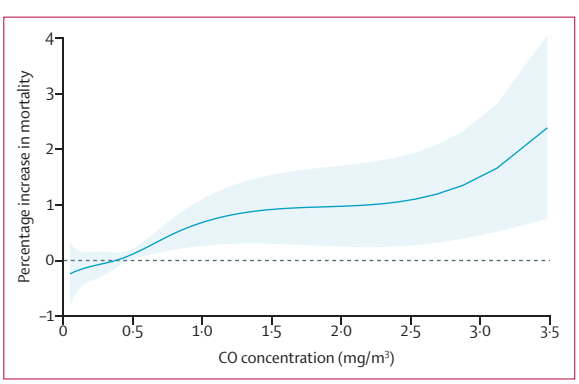

Figure 3: **Pooled exposure–response curve between CO (at lag 1 day) and daily mortality**
The *y*-axis represents the percentage change in daily mortality at a certain CO concentration compared with the median concentration. The *x*-axis represents CO concentration from the first to 99th percentiles of CO concentrations across all cities. The shaded area represents 95% CIs. CO=carbon monoxide.

Discussion

To the best of our knowledge, this research is by far the largest epidemiological study to investigate the association between ambient CO pollution and daily mortality. We analysed data from 337 cities in 18 countries, including more than 40 million deaths and covering a wide range of populations from different regions of the world. We found a significant association between short-term exposure to CO and daily mortality, with no evidence for a threshold value. This global study could provide comprehensive evidence on the health effects of ambient CO pollution to inform the adequacy of current air quality guidelines, both globally and regionally.

Overall, we found an increase of 0·91% (95% CI 0·32–1·50) in total mortality per 1 mg/m³ increase in

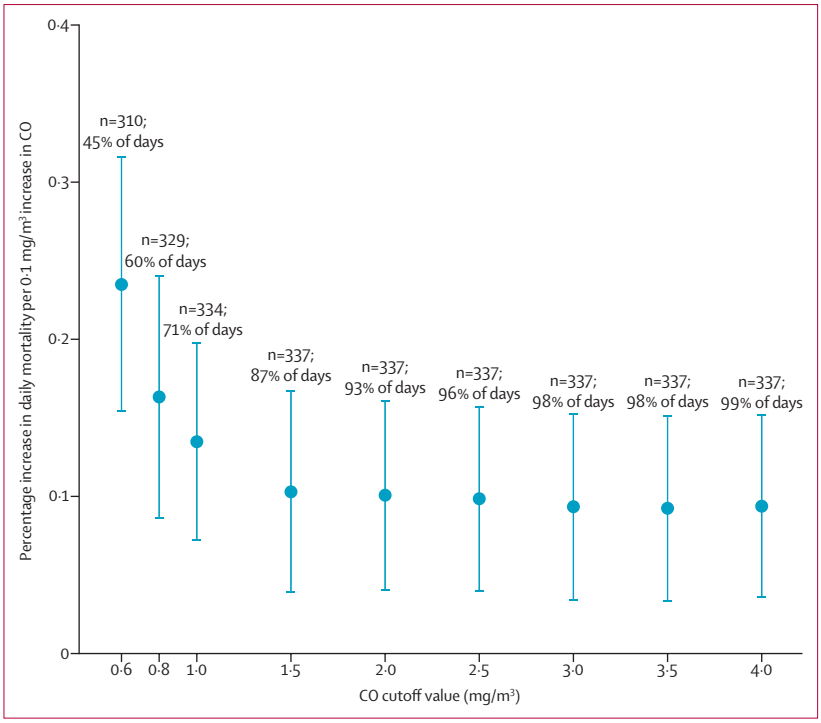

Figure 4: **Overall percentage increase in daily mortality per 0·1 mg/m³ increase in CO (at lag 1 day) by varying cutoff values**

Cities with at least 365 days of data with CO below the threshold were included. The number of cities (n) and the percentage of observation days included in each threshold analysis are shown. Whiskers show 95% CIs. CO=carbon monoxide.

	Cities with at least 2 years of data	Without co-pollutant	With co-pollutant
CO only	337	0·91% (0·32 to 1·50)	..
CO + PM_{10}	271	0·95% (0·30 to 1·61)	0·38% (–0·28 to 1·03)
CO + NO_2	290	0·83% (0·24 to 1·42)	–0·20% (–0·64 to 0·24)
CO + SO_2	297	0·78% (0·10 to 1·45)	0·44% (–0·23 to 1·11)
CO + O_3	249	1·20% (0·34 to 2·07)	1·45% (0·67 to 2·23)

All models were adjusted for time trend, day of the week effect, and temperature. Same lag days were applied to CO and co-pollutants. CO=carbon monoxide. NO_2=nitrogen dioxide. SO_2=sulphur dioxide. O_3=ozone.

Table 2: **Overall percentage increase of mortality per 1 mg/m³ increase in CO (at lag 1 day), with and without adjustment for co-pollutants**

24-h average ambient CO on the previous day (lag 1). Two previous national time-series studies also observed the strongest association at lag day 1, with a slightly lower mortality increase of 0·40% in 82 US cities[9] and 0·58% in 12 Canadian cities.[15] For the same increase in CO concentration on the current and previous day (lag 0–1), the increase in total mortality was 1·81% in 19 European cities,[25] which was higher than our estimate of 0·69% using the same CO metric.

We observed some regional differences in the CO–mortality associations across countries. Large mortality risk estimates (>2% increase) were observed in South Korea, Spain, and Italy, whereas null or negative (although not significant) associations were found in several countries such as Sweden and Taiwan. This variability across countries could be due to differences in air pollution levels, exposure assessment accuracies, population susceptibility, basic health status, and sample sizes. Notably, most of the countries with negative central estimates or null associations had a small number of cities included—Romania (n=2), Sweden (n=1), and Taiwan (n=3)—with the exception of 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 USA (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.[28] Although South Korea and Taiwan are geographically close to each other and economically comparable, we observed a significant positive effect in South Korea but a non-significant negative effect in Taiwan. Previous studies have also reported significant CO-related total mortality in South Korea[29,30] but not in Taiwan.[31–33] We did not find that economic (GDP per capita) or climatic (latitude and annual mean temperature) characteristics significantly modify the CO–mortality relationship (appendix p 25), suggesting that the different findings in South Korea and Taiwan might be due to the smaller sample size in Taiwan or other factors. Unlike the imprecise association that we observed for the three Chinese cities with available data, a recent study using 272 Chinese cities found a significant association between CO at lag 0–1 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 CO–mortality associations.

The current ambient air quality standard for maximum 8-h average CO is 10 mg/m³ (about 7 mg/m³ for 24-h average) in the USA and Europe, which is the same as the one established in 2010 by the WHO indoor air quality guideline.[22] A more stringent guideline for 24-h average CO (4 mg/m³) is implemented in China. In this study, all 337 cities had low levels of CO, with annual mean concentrations of less than 2·3 mg/m³ and 99th percentiles all less than 7 mg/m³ (appendix pp 10–17, 26). However, when restricting CO concentrations to less than 4 mg/m³, we still observed a significant association between short-term exposure to CO and total mortality. This association remained similar when CO concentrations were restricted to less than 4 mg/m³ down to less than 1·5 mg/m³, but increased when restricting CO concentrations to less than 1 mg/m³ down to less than 0·6 mg/m³. The pooled exposure–response curve also showed no threshold below which CO was not

associated with daily mortality, albeit with imprecise estimates for concentrations less than 0·4 mg/m³. In accordance with our findings, previous multicity studies have also found weak or no evidence for a threshold in associations of CO with total or cardiovascular mortality in Europe[3] and China.[5,8] Our results suggest that current ambient air quality guidelines for CO in the USA, 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 air quality guideline, could yield important health benefits.

Emissions of ambient CO are mainly from incomplete combustion of fuels from vehicles, whereas the contribution from natural sources is generally smaller (eg, 0·15 mg/m³ in the USA).[16] 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 were attenuated but remained positive after adjustment for PM_{10} and SO_2, although non-significant. 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.[34] Consistently, previous multicity studies have also found reduced mortality risk estimates for CO after including NO_2 in the model.[3,8,9,15] This sensitivity to adjustment for NO_2 might be because CO and NO_2 share common anthropogenic sources such as traffic, CO and NO_2 are usually moderately to highly correlated, and NO_2 might serve as a better surrogate for traffic-related exposure compared with low-level concentrations of CO, which has decreasing relative contributions from traffic emissions for the past decades.[16,34]

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[35,36] and decreases in prothrombin time (hypercoagulability).[37] Short-term exposure to CO pollution might also lead to high blood pressure among women[38] and impaired lung function in asthmatic children, presenting as reductions in forced vital capacity and forced expiratory volume in 1 s.[39] Consistently, toxicological studies have reported that exposure to CO concentrations mimicking air pollution could aggravate cardiac dysfunction in rats[40] and alter iron homoeostasis in lung epithelial cells.[41]

A major strength of this study is that we used an extensive dataset with large statistical power and applied a standardised 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/m³) well below the current WHO indoor air quality guidelines and the outdoor guidelines in the USA, Europe, and China. Our findings could provide timely evidence for the update of the WHO and national air quality guidelines.

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 of the 337 studied cities; thus, our estimates are more representative of the urban population of the 18 included countries, not necessarily of the countries as a whole. Second, exposure measurement errors are inevitable since we only used fixed monitoring sites for air pollution. Although we cannot ascertain how well the exposure time series capture the real day-to-day variations, we collected the air pollution time-series data using multiple monitors in the related area of each city, following standard procedures of air pollution time-series analyses. Despite the spatial variability in ambient CO concentrations, risk estimates from time-series designs might not be biased if levels at different locations have good temporal correlations.[16] Previous studies have observed high temporal correlations for air pollutants measured at multiple monitors within the same city or region.[42,43] Third, our country-specific estimates from BLUP might not fully account for sampling uncertainty in the presence of small data, for which estimates of random-effects (co)variance parameters are very uncertain. However, this is likely to cause negligible biases in a large sample of cities and countries used in this analysis. 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 serves as an indicator of combustion-related pollutants warrants further investigation.

In conclusion, this multicountry time-series analysis provides evidence that exposure to ambient CO, despite its lower levels than current air quality guidelines, might still pose a public health threat. We showed that short-term exposure to ambient CO was associated with increased daily mortality, with no evidence for a threshold value. This association appeared to be independent of exposure to O_3, but not to NO_2 or PM_{10}. Our findings suggest that the ongoing revision of WHO air quality guidelines, as well as future updates of national air quality guidelines in the USA, Europe, and China, should consider revisiting the guidelines for ambient CO.

Contributors

YG, MH, and AG set up the collaborative network. KC, AG, and AS contributed to the concept and design of this study. KC did the statistical

analysis and drafted the manuscript. SB, KW, MSt, AMV-C, AG, and AS contributed to the development of statistical methods. FS prepared and cleaned the data. KC, FS, and AG have directly accessed and verified the underlying data. SB, KW, AMV-C, YG, ST, EL, PMC, NVO, JJKJ, NRIR, VH, MSc, MH, YH, BN, JM, HKi, WL, AT, CÍ, BF, CÅ, MSR, Y-LLG, B-YC, SL, AZ, JS, MLB, HKa, AG, AS, IHH, SF, and AM provided the data, contributed to the interpretation of results, and reviewed the paper. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data were collected within the MCC Collaborative Research Network under a data sharing agreement and cannot be made publicly available. Researchers can refer to MCC participants, who are listed as coauthors of this Article, for information on accessing the data for each country.

Acknowledgments

This study was supported by the European Union's Horizon 2020 Project Exhaustion (grant ID 820655), UK Medical Research Council (MR/R013349/1), and UK Natural Environment Research Council (NE/R009384/1). JM was supported by the Fundação para a Ciência e a Tecnologia through the scholarship SFRH/ BPD/115112/2016. VH received funding from the Spanish Ministry of Economy, Industry and Competitiveness (PCIN-2017-046), and the German Federal Ministry of Education and Research (01LS1201A2). YG was supported by a Career Development Fellowship of the Australian National Health and Medical Research Council (APP1163693). SL was supported by an Early Career Fellowship of the Australian National Health and Medical Research Council (APP1109193). ST was supported by the Shanghai Municipal Science and Technology Commission (grant 18411951600).

References

1 Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med* 1998; **339:** 1603–08.

2 Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning—a public health perspective. *Toxicology* 2000; **145:** 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:** 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:** 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). *Sci Total Environ* 2011; **409:** 4923–28.

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:** 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. *Lancet Planet Health* 2018; **2:** e12–18.

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 Honda Y, Nitta H, Ono M. Low level carbon monoxide and mortality of persons aged 65 or older in Tokyo, Japan, 1976–1990. *J Health Sci* 2003; **49:** 454–58.

11 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:** 187–91.

12 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:** 125–32.

13 Verhoeff AP, Hoek G, Schwartz J, van Wijnen JH. Air pollution and daily mortality in Amsterdam. *Epidemiology* 1996; **7:** 225–30.

14 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:** 3070–83.

15 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:** 228–36.

16 US Environmental Protection Agency. Integrated Science Assessment (ISA) for carbon monoxide. Research Triangle Park, NC: US EPA Office of Research and Development, 2010.

17 WHO. WHO expert consultation: available evidence for the future update of the WHO global air quality guidelines (AQGs). Geneva: World Health Organization, 2016.

18 Gasparrini A, Guo YM, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; **386:** 369–75.

19 Guo Y, Gasparrini A, Armstrong B, et al. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. *Epidemiology* 2014; **25:** 781–89.

20 Liu C, Chen R, Sera F, et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019; **381:** 705–15.

21 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.

22 WHO. WHO guidelines for indoor air quality: selected pollutants. Geneva: World Health Organization, 2010.

23 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:** 1026.

24 Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. *Stat Med* 2019; **38:** 5429–44.

25 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:** 88–95.

26 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:** 532–36.

27 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.

28 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:** 15.

29 Son J-Y, Cho Y-S, Kim Y-S, Lee J-T, Kim Y-J. An analysis of air pollution effect in urban area related to Asian dust on all-cause and cause-specific mortality in Seoul, Korea, 2000–2006. *Korean J Environ Health Sci* 2009; **35:** 249–58.

30 Son J-Y, Lee J-T, 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:** 227–34.

31 Yang CY, Chang CC, Chuang HY, Tsai SS, Wu TN, Ho CK. Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. *Environ Int* 2004; **30:** 519–23.

32 Tsai S-S, Huang C-H, Goggins W, Wu T-N, Yang C-Y. Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. *J Toxicol Environ Health A* 2003; **66:** 1341–49.

33 Tsai D-H, Wang J-L, Chuang K-J, Chan C-C. Traffic-related air pollution and cardiovascular mortality in central Taiwan. *Sci Total Environ* 2010; **408:** 1818–23.

34 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, MA: Health Effects Institute, 2010.

35 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:** 332–40.

36 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.

37 Baccarelli A, Zanobetti A, Martinelli I, et al. Effects of exposure to air pollution on blood coagulation. *J Thromb Haemost* 2007; **5:** 252–60.

38 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:** 58–72.

39 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:** 390–99.

40 Reboul C, Boissiere J, Andre L, et al. Carbon monoxide pollution aggravates ischemic heart failure through oxidative stress pathway. *Sci Rep* 2017; **7:** 39715.

41 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:** 715–23.

42 Ito K, Thurston GD, Silverman RA. Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. *J Expo Sci Environ Epidemiol* 2007; **17** (suppl 2): S45–60.

43 Ito K, De Leon S, Thurston GD, Nádas A, Lippmann M. Monitor-to-monitor temporal correlation of air pollution in the contiguous US. *J Expo Sci Environ Epidemiol* 2005; **15:** 172–84.