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Short-Term Association between Sulfur Dioxide and Mortality: A Multicountry Analysis in 399 Cities

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Background: Epidemiological evidence on the health risks of sulfur dioxide (SO_2) is more limited compared with other pollutants, and doubts remain on several aspects, such as the form of the exposure–response relationship, the potential role of copollutants, as well as the actual risk at low concentrations and possible temporal variation in risks.

Objectives: Our aim was to assess the short-term association between exposure to SO_2 and daily mortality in a large multilocation data set, using advanced study designs and statistical techniques.

Methods: The analysis included 43,729,018 deaths that occurred in 399 cities within 23 countries between 1980 and 2018. A two-stage design was applied to assess the association between the daily concentration of SO_2 and mortality counts, including first-stage time-series regressions and second-stage multilevel random-effect meta-analyses. Secondary analyses assessed the exposure–response shape and the lag structure using spline terms and distributed lag models, respectively, and temporal variations in risk using a longitudinal meta-regression. Bi-pollutant models were applied to examine confounding effects of particulate matter with an aerodynamic diameter of $\leq$10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), ozone, nitrogen dioxide, and carbon monoxide. Associations were reported as relative risks (RRs) and fractions of excess deaths.

Results: The average daily concentration of SO_2 across the 399 cities was 11.7 $\mu g/m^3$, with 4.7% of days above the World Health Organization (WHO) guideline limit (40 $\mu g/m^3$, 24-h average), although the exceedances occurred predominantly in specific locations. Exposure levels decreased considerably during the study period, from an average concentration of 19.0 $\mu g/m^3$ in 1980–1989 to 6.3 $\mu g/m^3$ in 2010–2018. For all locations combined, a 10-$\mu g/m^3$ increase in daily SO_2 was associated with an RR of mortality of 1.0045 [95% confidence interval (CI): 1.0019, 1.0070], with the risk being stable over time but with substantial between-country heterogeneity. Short-term exposure to SO_2 was associated with an excess mortality fraction of 0.50% [95% empirical CI (eCI): 0.42%, 0.57%] in the 399 cities, although decreasing from 0.74% (0.61%, 0.85%) in 1980–1989 to 0.37% (0.27%, 0.47%) in 2010–2018. There was some evidence of nonlinearity, with a steep exposure–response relationship at low concentrations and the risk attenuating at higher levels. The relevant lag window was 0–3 d. Significant positive associations remained after controlling for other pollutants.

Discussion: The analysis revealed independent mortality risks associated with short-term exposure to SO_2, with no evidence of a threshold. Levels below the current WHO guidelines for 24-h averages were still associated with substantial excess mortality, indicating the potential benefits of stricter air quality standards. https://doi.org/10.1289/EHP11112

Introduction

Sulfur dioxide (SO_2) is an important air pollutant linked with increased health risks.[1,2] It originates largely from the combustion of fossil fuels to generate electricity and transportation.[1,3,4] SO_2 is also released during industrial processes, mainly the production of metals, such as copper, and other chemical plants, or from emissions from fuel combustion in shipping, whereas a very small percentage occurs naturally from volcanoes and fissures. In many

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developed nations, the desulfurization of cars and power plants has dramatically reduced emissions and the related population exposure, but the same cannot be said of many developing countries, where levels remain relatively very high.[2] In 2005, the World Health Organization (WHO) published their recommendation for air quality standards, stating that the average SO_2 concentration over a 24-h period should not exceed 20 $\mu g/m^3$ or 500 $\mu g/m^3$ over 10 min.[5] The WHO guidelines were revised in 2021, with the 24-h limit increased to 40 $\mu g/m^3$ following a new criterion based on the distribution of daily SO_2 concentrations and the corresponding limit of annual averages.[6]

Short-term mortality risks of SO_2 have been assessed in several ecological studies primarily based on time-series data. Early multicity studies were conducted in Europe,[7,8] the United States,[9] and East Asia.[10] More recently, large investigations were performed in China, where the SO_2 concentrations far exceed those of most high-income countries.[11,12] A recent meta-analysis of 67 eligible studies systematically reviewed the evidence and provided pooled estimates of the association.[13] When restricting the unit of analysis to 24-h averages of SO_2, a 10-μg/m3 increment of SO_2 was associated with an increase of 0.59% (95% CI: 0.46%, 0.71%) in all-cause mortality. The association remained when controlling for particulate matter (PM), but not for nitrogen dioxide (NO_2) or ozone (O_3). Moreover, there was no evidence of an exposure threshold below which no risk can be assumed.[13]

However, several gaps in knowledge still exist, as discussed in a comprehensive report from the U.S. Environmental Protection Agency (EPA).[14] In addition to the uncertainty regarding the potential confounding effects from copollutants mentioned above, limited evidence is available on other aspects of the short-term association between exposure to SO_2 and mortality risks. For instance, there is no conclusive evidence on the shape of the exposure–response relationships and possible nonlinearities or about the presence of more complex temporal dependencies and lagged associations. Further, it is still unclear whether results from studies from China are generalizable elsewhere, or if the risk shows geographical heterogeneity. More importantly, the published analyses assessed the association at relatively high exposure ranges. It is unclear to what extent the risk can be extrapolated at lower concentrations, for instance, below current air quality guidelines. This information is critical for revising air quality limits using evidence-based processes.

In this contribution, we address these limitations and present results from an investigation of the short-term mortality risks associated with SO_2 exposure using data from 399 cities in 23 countries across the globe. The analysis used advanced study designs and statistical methods to characterize the associations of interest, whereas the large database and broad exposure contrasts offered enough statistical power to assess geographical variations and risks at low exposure levels.

Methods

Data Collection

The data were collected within the Multi-Country Multi-City (MCC) Collaborative Research Network, an international collaboration investigating environmental stressors and their impacts on human health.[15] The MCC database has been used in previous publications that evaluated associations between air pollutants and mortality.[15–20] Mortality data were gathered from the local health authorities and were represented as daily counts of all causes [*International Classification of Diseases, Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* (ICD-9),[21] codes 0–799], if available, or nonexternal [*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10),[22] codes A00–R99] deaths. Nonexternal causes of death exclude intentional and unintentional injury, poisoning (including drug overdose), and complications of medical or surgical care.

The data set also contains 24-h average city-level concentrations of SO_2, NO_2, O_3, carbon monoxide (CO), and PM with an aerodynamic diameter of $\leq$10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), in addition to daily temperature. All pollutants were harmonized using the unit of micrograms per meter cubed, except CO, which was harmonized with milligrams per meter cubed. The country-specific data sets generally include all the major cities; however, this analysis was restricted to the 399 locations within 23 countries with SO_2 data available and at least 365 d of measurement. The United States of America (USA) was divided into nine regions to account for the large heterogeneity in SO_2 values, for a total of 31 areas. The geographical location of each city and the mean SO_2 concentrations are displayed in Figure 1. Detailed information on data collection is reported in the Supplemental Material, "Information on country-specific datasets."

Statistical Methods

Main Model

We applied a two-stage procedure to analyze the short-term association between SO_2 and mortality. In the first stage, we performed city-specific time-series analyses using a quasi-Poisson generalized linear model with distributed lag terms.[23,24] The city-specific model included an indicator for the day of the week to account for within-week variation and a natural spline function with 7 degrees of freedom per year to control for long-term trends and seasonal variations. Air temperature was modeled with a distributed lag nonlinear model (DLNM), composed of a quadratic B-spline with three knots placed at the 10th, 75th, and 90th percentiles for the exposure–response and a step function with strata lags of 0 and 1–3 d for the lag–response. In the main model, SO_2 was modeled assuming a linear exposure–response relationship of the moving average computed over lag 0–3 d.

In the second stage, we combined the city-specific estimates using a multilevel random-effect meta-analysis fitted with restricted maximum likelihood (REML) and nested random effects defined by city and country.[25] The pooled estimate represents the global average SO_2-mortality association, whereas city and country-specific estimates were derived as best linear unbiased predictions (BLUPs) at the corresponding aggregation level. The BLUPs use information from pooled associations to make more accurate location-specific estimates by borrowing information from the whole sample, especially for cities/countries with higher uncertainty, while at the same time accounting for heterogeneity in risks.[25,26] All estimates are reported as the relative risk (RR) for a 10-μg/m3 increase in SO_2, with corresponding 95% confidence intervals (CIs). Heterogeneity was reported as I^2 statistics and tested with the Cochran's Q test.[25–27]

Secondary Analyses

We performed a series of secondary analyses. First, we explored potential nonlinear exposure–response shapes and more complex lag structures of the SO_2–mortality relationship, extending the model first using a quintic polynomial, and then using a distributed lag model (DLM) with a natural spline with knots at lag 1 and 3 plus an intercept over lag 0–7 d. The polynomial parameterization was adopted to decrease the sensitivity of the estimates to different ranges of SO_2 concentrations because polynomial terms are not local and are, instead, defined across the whole variable range. In both extensions, city-specific estimates of the multiparameter associations were pooled using a multivariate multilevel meta-analysis.[28]

Second, we evaluated possible changes in risk over time by subsetting the city-specific data and performing the first-stage

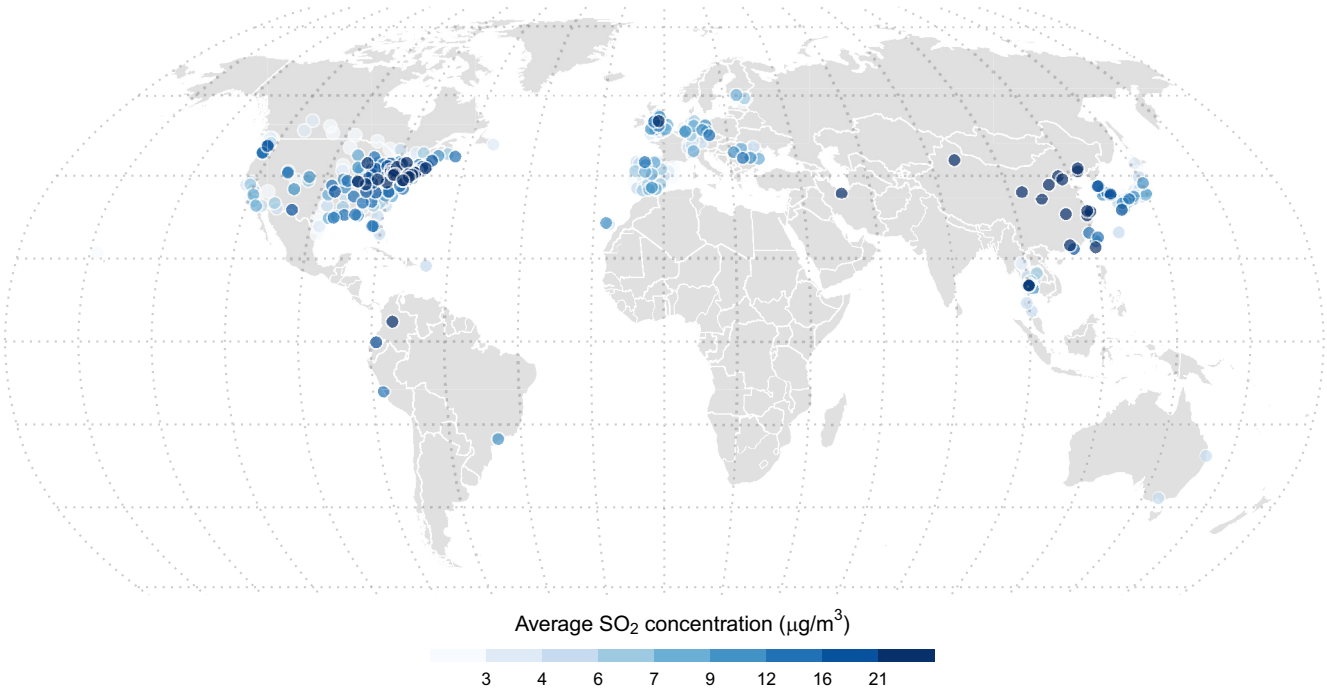

Figure 1. Geographical location of the 399 urban areas and related average annual concentrations of SO_2 (in $\mu g/m^3$) within the study period 1980–2018. Data can be found in Table S1. Note: SO_2, sulfur dioxide.

model in multiple subperiods, splitting the time series into ~5-y intervals. City and period-specific estimates were pooled in a longitudinal multilevel meta-regression using time (defined as the mid-year of each subperiod) as a continuous fixed-effect term.[28]

Third, we assessed the potential confounding effect of other pollutants in bi-pollutant models, where PM_{10}, $PM_{2.5}$, O_3 (8-h daily maximum), NO_2, and CO entered the model linearly, using a moving average of lag 0–3 d. These choices were informed by previous studies.[12,29,30] Only one other pollutant was controlled for at a time because of the high correlation between pollutants.[14,31] These models were fitted both with and without adjustment in the subset of cities, providing measurements for both pollutants. Information on the levels of copollutants across cities and countries has been provided in previous articles.[16–20]

Computation of Excess Mortality

Finally, using the main model, we computed the excess mortality associated in the short term with exposure to SO_2 in each city, using a previously described method.[32] Briefly, the cumulative RR within lag 0–3 was applied to compute the excess daily deaths, adopting a forward perspective using the standard formula $(1 - exp\,(-\beta_j(x_{jt} - c)_+)) \times d_{jt}$ for continuous exposure, as in previous analyses.[17] In the formula, β_j represents the log-RR for a unit increase in SO_2, defined as the country-specific BLUP for city j, and x_{jt} and d_{jt} are the corresponding SO_2 levels at day t and the average daily mortality in the same and next 3 d, respectively. The term $(x_{jt} - c)_+$ represents the exceedance in SO_2 concentration above a limit c. We used $c = 0$ and $c = 40$ to compute the burden attributable to short-term exposure to SO_2 in total and above the WHO guideline, respectively. The results are reported as fraction of excess deaths, both in total and for levels below the WHO guideline, together with 95% empirical CIs (eCIs).

All analyses were conducted in R (version 4.2.2; R Development Core Team), using the *dlnm* and *mixmeta* packages. The R code for the original analysis and for performing a reproducible example using simulated data is available in a GitHub repository (https://github.com/gasparrini/MCC-SO2).

Results

Descriptive Analysis

The analysis included 43,729,018 deaths across 399 cities, in 23 countries (separating the USA into nine regions), with an average period of 14.5 y. Table 1 shows the total deaths, number of cities, period of analysis, and levels of SO_2 across cities in each country. The list of cities, together with basic information on study periods and SO_2 exposure levels, is provided in Table S1. The SO_2 exposure was widely heterogeneous both within and between countries, with an average across cities of 11.7 $\mu g/m^3$ and an average 5th–95th percentile range of 2.6–29.3 $\mu g/m^3$ (see the map in Figure 1 for the geographical distribution). The highest mean concentrations were found in cities of China and Iran (50.1 and 98.9 $\mu g/m^3$, respectively), and the lowest concentrations were in Portugal and Estonia (2.6 and 3.5 $\mu g/m^3$, respectively). Across the whole set of cities and periods, 4.7% of days registered concentrations higher than the WHO limits of 40 $\mu g/m^3$.[6]

Figure 2 displays the distribution of city-specific average SO_2 concentrations over the years, revealing a strong attenuation in exposure levels within the study period, although the comparison should account for the different sample of cities/countries contributing to each interval. Actual figures of SO_2 levels and percentage exceedances of WHO limits aggregated by decade are reported in Table S2. Results show that the average daily concentration decreased from 19.0 $\mu g/m^3$ in 1980–1989 to 6.3 $\mu g/m^3$ in 2010–2018, and the corresponding percentage of days >40 $\mu g/m^3$ from 11.7% to 1.3%.

Association between SO_2 and Mortality

The risk associations estimated from the main model using a linear exposure–response relationship and a moving average of lag 0–3 are illustrated in Figure 3, with the pooled RR and related country-specific BLUPs (see Table S3 for the numeric data). On average

Table 1. Descriptive statistics reported by country (with the United States separated into nine regions): number of cities, total days, and deaths in the time series, distribution of sulfur dioxide (SO_2) across cities, and percentage of days with SO_2 concentrations >40 μg/m^3.

Country	Cities (*n*)	Period	City-days (*n*)	Deaths (*n*)	Average mean and 5th–95th percentile range of SO_2 (μg/m^3)	Percentage of days >40 μg/m^3 (%)[a]
Canada	24	2000–2015	109,953	1,741,439	5.6 (0.3–17.7)	1.1
USA-Central	30	1985–2006	216,457	3,724,610	19.6 (3.5–49.0)	9.9
USA-NE Central	14	1985–2006	76,137	1,518,119	10.2 (1.0–29.2)	2.4
USA-Northeast	42	1985–2006	291,202	6,912,465	19.8 (3.6–49.8)	10.2
USA-Northwest	5	1985–2006	19,994	394,004	14.6 (3.8–32.3)	2.3
USA-NW Central	2	1985–2006	10,894	69,007	2.8 (0.2–9.7)	0.4
USA-South	17	1985–2006	105,338	1,513,772	8.7 (0.9–26.1)	2.7
USA-Southeast	29	1985–2006	173,040	2,945,570	9.5 (1.5–25.9)	2.2
USA-Southwest	9	1985–2006	50,766	794,800	8.0 (0.8–22.6)	1.6
USA-West	15	1985–2006	81,604	3,367,343	5.0 (0.2–16.9)	0.2
Puerto Rico	1	2009–2016	2,877	26,161	4.6 (0.0–9.4)	0.7
Brazil	1	1997–2011	5,076	909,305	12.3 (4.0–26.3)	0.6
Colombia	1	1998–2013	5,800	423,344	20.9 (5.3–41.6)	6.4
Ecuador	1	2014–2018	1,819	44,369	16.7 (8.0–26.0)	0.2
Peru	1	2010–2014	1,489	148,775	12.8 (3.4–27.8)	0.1
Estonia	4	2002–2018	18,239	96,455	2.6 (0.2–10.1)	0.6
Finland	1	1994–2014	7,663	153,166	9.1 (2.1–25.9)	1.0
UK	31	1990–2016	157,489	3,823,644	8.6 (0.5–23.6)	1.9
Czech Republic	1	1994–2009	5,835	213,706	14.6 (2.0–55.7)	8.6
Germany	12	1993–2015	70,542	2,098,705	7.9 (1.9–23.8)	2.0
Romania	8	2008–2016	14,964	221,816	8.4 (3.2–17.7)	0.4
Switzerland	4	1995–2013	24,229	151,898	5.6 (0.7–16.9)	0.2
Portugal	6	1995–2018	28,860	847,377	3.5 (0.5–9.9)	0.3
Spain	48	2002–2014	197,008	1,480,869	5.5 (2.6–10.4)	0.1
Iran	1	2002–2015	5,025	683,739	98.9 (17.0–279.1)	70.7
China	15	1996–2015	23,139	1,181,405	50.1 (14.8–124.2)	45.8
Japan	46	1980–2015	133,940	4,382,591	6.0 (2.2–12.6)	0.3
South Korea	7	1999–2015	42,979	1,658,788	15.5 (7.5–29.1)	1.3
Thailand	18	1999–2008	52,980	722,911	10.1 (3.0–20.7)	2.3
Taiwan	3	1994–2014	22,981	1,208,118	15.4 (6.1–32.1)	3.6
Australia	2	2000–2009	6,609	270,751	5.1 (0.8–18.8)	0.8
All MCC countries[b]	399	1980–2018	1,964,928	43,729,018	11.7 (2.6–29.3)	4.7

Note: The analysis includes data from 399 cities within the study period 1980–2018 from the Multi-Country Multi-City (MCC) Collaborative Research Network.
[a]Current limit of daily concentration of SO_2 in the World Health Organization guidelines.[6]
[b]Data shown represents the statistics for all the areas included above.

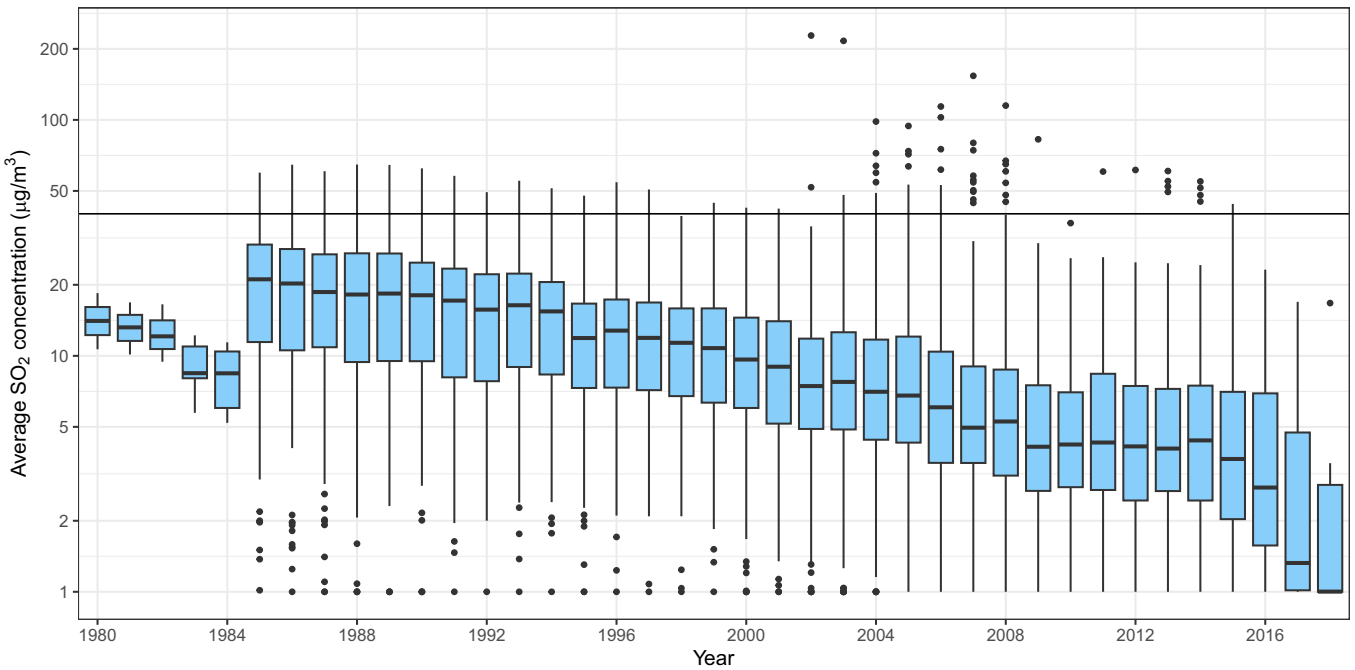

Figure 2. Box plot of the distribution of the average concentration of SO_2 (in μg/m^3) across cities for each year. The horizontal line identifies the current limit of daily concentration of SO_2 in the WHO guidelines (40 μg/m^3). The *y*-axis is represented in a logarithmic scale. The analysis includes data from 399 cities within the study period 1980–2018. Note that a different set of countries contributes to each study period (see Table 1 for details). Note: SO_2, sulfur dioxide; WHO, World Health Organization.

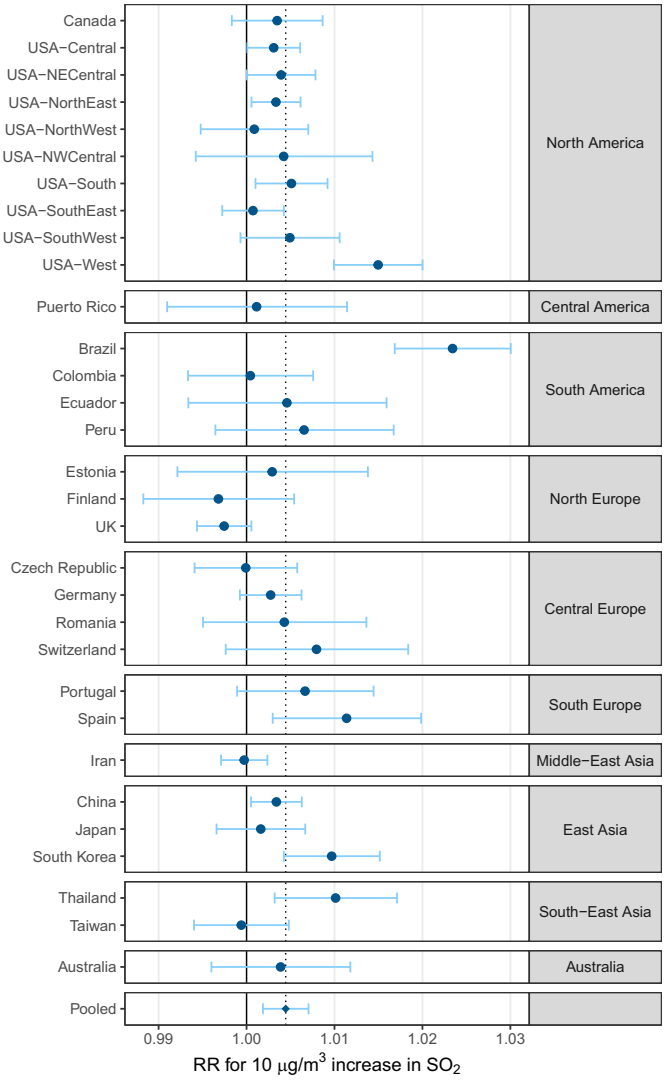

Figure 3. Country-specific and pooled relative risks (RRs, with 95% CIs) for mortality corresponding to a 10-$\mu g/m^3$ increase in SO_2 over lag 0–3 d. The analysis includes data from 399 cities within the study period 1980–2018. Data can be found in Table S3. Note: CI, confidence interval; SO_2, sulfur dioxide.

across all cities and countries, each 10-$\mu g/m^3$ increase of SO_2 was associated with an RR of mortality of 1.0045 (95% CI: 1.0019, 1.0070). Although country-specific estimates were less precise, there is evidence of substantial heterogeneity ($I^2 = 45.8\%$, Cochran Q $p < 0.001$), with the RRs ranging from 0.9968 (95% CI: 0.9883, 1.0054) in Finland to 1.0234 (95% CI: 1.0168, 1.0300) in Brazil, and a few nonsignificant negative estimates.

Exposure and Lag–Response Relationships

Results from secondary analyses are displayed in Figure 4. Figure 4A shows the estimate of the pooled SO_2-mortality relationship from the flexible model allowing nonlinear exposure–response associations. The graph is augmented with the estimated log-linear relationship from the main model and a bar representing the number of cities with SO_2 measurements within the related exposure range. The figure indicates some evidence of nonlinearity, with a steep increase in risk and an attenuation at high concentrations. It is unclear if this supralinear shape resulted from lower risks at high SO_2 exposures or if it is attributable to a different sample of countries contributing at various ranges, given that only 23.3% of cities

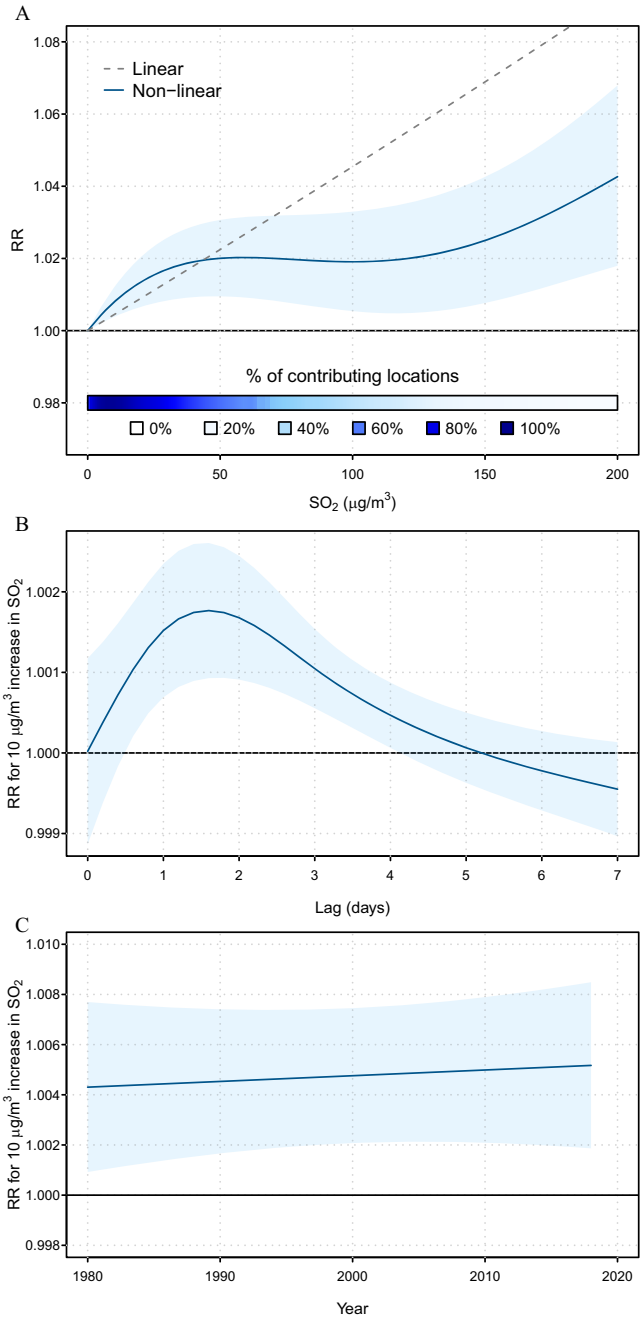

Figure 4. Secondary analysis on the short-term association between SO_2 (per 10-$\mu g/m^3$ increase) and mortality. (A) Pooled exposure–response curve obtained using a linear term (dashed line) and a quintic polynomial (continuous line, with 95% confidence intervals), with a bar representing the percentage of studies contributing to the specific exposure range. (B) Pooled lag–response curve obtained using a natural spline with knots at lags 1 and 3, plus intercept. (C) Analysis of temporal variation of the pooled relative risk (RR) associated with a 10-$\mu g/m^3$ increase in SO_2 over lag 0–3 d. Shaded areas represent the 95% confidence intervals. The analysis includes data from 399 cities within the study period 1980–2018. Summary data on city-specific exposure distributions can be found in Table S1. Note: SO_2, sulfur dioxide.

were exposed to levels $>150\ \mu g/m^3$. In any case, the nonlinear parameterization confirms the evidence of mortality risks for exposures below the WHO limit of $40\ \mu g/m^3$. A comparison of country-specific exposure–response relationships (as BLUPs) estimated using the linear and nonlinear models is presented in Figure

Table 2. Relative risk with 95% confidence interval) [RR (95% CI)] associated with a 10-μg/m^3 increase in sulfur dioxide (SO_2, in μg/m^3) over lag 0–3 d with and without adjustment for each copollutant in selected cities with both measurements within the study period 1980–2018.

		RR ± 95% CI	
Copollutant	Cities (*n*)	Without adjustment	With adjustment
PM_{10}	265	1.0045 (1.0017, 1.0074)	1.0028 (1.0004, 1.0052)
$PM_{2.5}$	217	1.0028 (1.0005, 1.0050)	1.0056 (1.0028, 1.0084)
O_3 8h	309	1.0044 (1.0023, 1.0065)	1.0040 (1.0017, 1.0062)
NO_2	358	1.0046 (1.0019, 1.0073)	1.0032 (1.0012, 1.0052)
CO	302	1.0038 (1.0016, 1.0060)	1.0036 (1.0023, 1.0048)

Note: Number of cities included in the bi-pollutant models are reported in Table S4. CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm.

S1. The results of the second modeling extension with the application of a DLM over lag 0–7 to assess the lag structure are displayed in Figure 4B. The graph suggests no risk of same-day exposure to SO_2, with the risk then increasing in the next 3–4 d. This analysis indicated that the main model with the moving average of lag 0–3 can capture these lagged associations and can provide valid estimates of the association.

Analysis of Temporal Variation in Risk

The extension of the two-stage design for assessing potential temporal changes in risk involved the analysis by subperiod and the pooling of estimates using time as a continuous meta-predictor. The results are reported in Figure 4C, which shows the pooled mortality RR for a 10-μg/m^3 increase in SO_2 along the years predicted from the longitudinal meta-analytical model. The graph suggests little evidence of variation in time in the short-term association, with a *p*-value of the time term equal to 0.67.

Bi-Pollutant Analysis

Results from bi-pollutant analyses are provided in Table 2, with information on the number of cities contributing to the analysis of each copollutant provided in Table S4. The comparison suggests that an independent risk associated with SO_2 remained even after adjustment for each of the five other pollutants, although with some variations indicative of partial confounding. Specifically, the estimated risks seemed to attenuate after controlling for PM_{10} and NO_2, whereas they increased when including $PM_{2.5}$ in the model. Results were only negligibly affected by control for O_3 and CO.

Excess Mortality

Finally, Table 3 depicts the excess mortality fraction associated with SO_2 exposure computed from the main model, assuming a linear relationship both by decade and within the whole study period of each area. Overall across the 399 cities, SO_2 was found to be associated with an excess increase of 0.50% (95% eCI: 0.42%, 0.57%) of the total deaths. This fraction showed a strong decrease in time and variation across regions, consistent with the reduction in SO_2 levels and the geographical variation in risk described above. Specifically, the excess mortality overall decreased from 0.74% (0.61%, 0.85%) in 1980–1989 to 0.37% (0.27%, 0.47%) in 2010–2018. The corresponding quota of excess deaths attributable to levels <40 μg/m^3 is shown in Table S5, indicating that 93.8% of the excess was due to exposures below the WHO limits on average across the study period.

Table 3. Excess mortality fraction with 95% empirical confidence interval [% (95% eCI)] attributable to short-term exposure to sulfur dioxide (SO_2, per 10 μg/m^3) by country (separating the USA into nine regions) and decade.

Country/region	1980–1989	1990–1999	2000–2009	2010–2019	Full period
Canada	—	—	0.24 (0.12, 0.37)	0.11 (0.05, 0.17)	0.19 (0.10, 0.29)
USA-Central	0.82 (0.56, 1.05)	0.57 (0.40, 0.73)	0.40 (0.28, 0.51)	—	0.58 (0.40, 0.73)
USA-NE Central	0.71 (0.28, 1.16)	0.50 (0.19, 0.82)	0.35 (0.12, 0.58)	—	0.50 (0.19, 0.82)
USA-Northeast	1.09 (0.79, 1.36)	0.77 (0.56, 0.97)	0.55 (0.40, 0.70)	—	0.78 (0.57, 0.98)
USA-Northwest	0.15 (−0.52, 0.80)	0.15 (−0.48, 0.73)	0.06 (−0.32, 0.39)	—	0.13 (−0.46, 0.67)
USA-NW Central	0.20 (−0.28, 0.65)	0.22 (−0.31, 0.72)	0.08 (−0.11, 0.25)	—	0.16 (−0.22, 0.53)
USA-South	0.63 (0.45, 0.83)	0.49 (0.35, 0.64)	0.33 (0.22, 0.44)	—	0.47 (0.33, 0.61)
USA-Southeast	0.11 (−0.06, 0.26)	0.07 (−0.02, 0.17)	0.05 (−0.01, 0.11)	—	0.07 (−0.02, 0.15)
USA-Southwest	0.55 (0.21, 0.88)	0.47 (0.18, 0.74)	0.26 (0.09, 0.43)	—	0.40 (0.16, 0.63)
USA-West	1.07 (0.86, 1.29)	0.80 (0.66, 0.94)	0.76 (0.64, 0.88)	—	0.84 (0.70, 0.99)
Puerto Rico	—	—	0.04 (−0.32, 0.40)	0.05 (−0.41, 0.50)	0.05 (−0.40, 0.49)
Brazil	—	3.75 (2.69, 4.70)	2.85 (2.04, 3.57)	1.69 (1.21, 2.12)	2.87 (2.05, 3.60)
Colombia	—	0.14 (−2.02, 2.26)	0.10 (−1.55, 1.73)	0.03 (−0.49, 0.56)	0.09 (−1.32, 1.47)
Ecuador	—	—	—	0.76 (−1.07, 2.55)	0.76 (−1.07, 2.55)
Peru	—	—	—	0.83 (−0.41, 2.17)	0.83 (−0.41, 2.17)
Estonia	—	—	0.08 (−0.12, 0.28)	0.05 (−0.05, 0.14)	0.06 (−0.07, 0.19)
Finland	—	−0.35 (−1.25, 0.59)	−0.28 (−1.00, 0.47)	−0.27 (−0.98, 0.46)	−0.29 (−1.07, 0.50)
UK	—	−0.46 (−0.79, −0.14)	−0.14 (−0.21, −0.08)	−0.06 (−0.10, −0.02)	−0.24 (−0.39, −0.09)
Czech Republic	—	−0.03 (−1.65, 1.69)	−0.01 (−0.36, 0.38)	—	−0.01 (−0.88, 0.91)
Germany	—	0.38 (0.16, 0.59)	0.15 (0.07, 0.22)	0.09 (0.02, 0.15)	0.24 (0.11, 0.35)
Romania	—	—	0.54 (−0.27, 1.31)	0.39 (−0.13, 0.89)	0.42 (−0.16, 0.98)
Switzerland	—	0.82 (0.15, 1.57)	0.41 (0.14, 0.71)	0.21 (0.07, 0.36)	0.48 (0.13, 0.86)
Portugal	—	0.42 (0.04, 0.81)	0.27 (0.07, 0.46)	0.11 (0.04, 0.18)	0.24 (0.06, 0.40)
Spain	—	—	0.82 (0.60, 1.04)	0.60 (0.46, 0.74)	0.73 (0.55, 0.92)
Iran	—	—	−0.37 (−4.30, 3.31)	−0.13 (−1.45, 1.16)	−0.26 (−3.02, 2.35)
China	—	0.58 (0.11, 1.07)	1.55 (1.12, 1.98)	1.68 (0.79, 2.55)	1.48 (1.04, 1.95)
Japan	0.17 (−0.18, 0.51)	0.11 (−0.10, 0.31)	0.06 (−0.04, 0.16)	0.11 (0.02, 0.19)	0.11 (−0.05, 0.25)
South Korea	—	2.32 (1.72, 2.91)	1.49 (1.09, 1.88)	1.37 (1.00, 1.74)	1.49 (1.09, 1.88)
Thailand	—	1.21 (0.80, 1.61)	1.07 (0.74, 1.40)	—	1.08 (0.75, 1.41)
Taiwan	—	−0.13 (−0.87, 0.53)	−0.08 (−0.54, 0.35)	−0.06 (−0.42, 0.27)	−0.09 (−0.59, 0.37)
Australia	—	—	0.20 (−0.10, 0.50)	—	0.20 (−0.10, 0.50)
All MCC countries	0.74 (0.61, 0.85)	0.46 (0.38, 0.53)	0.50 (0.40, 0.60)	0.37 (0.27, 0.47)	0.50 (0.42, 0.57)

Note: The analysis includes data from the Multi-Country Multi-City (MCC) Collaborative Research Network for 399 cities within the study period 1980–2018. Estimates based on the main model assuming a linear exposure–response relationship and a moving average of lag 0–3 d. —, not applicable.

Discussion

To our knowledge, this study represents the most extensive epidemiological assessment of the short-term mortality risks associated with exposure to SO_2, investigating the relationship using a large database that includes almost 44 million deaths from 399 cities in 23 countries across 5 continents. We found an overall increased short-term risk, with an RR = 1.0045 (95% CI: 1.0019, 1.0070) per 10-$\mu g/m^3$ increase in SO_2, although with evidence of heterogeneity across countries and cities. This translated to an annual excess corresponding to 0.5% of the total mortality on average across the study period. Stratified by decades, the analysis indicates a strong decrease in the health impacts, in line with the reduction in the concentration levels of SO_2 although this result should be interpreted with caution given the differential temporal coverage across countries. The application of more flexible models suggested some evidence of nonlinearity, with steeper RR estimates at low exposure levels, and a complex lag structure with the maximal risk arising 1–3 d after exposure. Independent associations were still measurable even after controlling for copollutants, and there was no evidence that the risk associated with a given exposure level had changed over time.

This study provides an essential contribution to the literature on the mortality risks associated with short-term SO_2 exposure. The pooled RR estimates are consistent with previous epidemiological studies, although slightly lower when compared with figures published in the multicity studies and the meta-analysis described in the introduction.[7–13] The difference can be due to the selection of locations, which in our study represent a broader sample and a wider geographical area. Our results strengthen the evidence on the association of short-term SO_2 exposure with total mortality, which was determined as suggestive but not sufficient to infer a causal relationship in the U.S. EPA report mentioned above.[14] One of the main reasons described in the report for such a conclusion was the limited knowledge about the potential confounding by other pollutants. Our analysis confirms that risk estimates were somewhat sensitive to control for copollutants but that there was still strong evidence of the association when PM_{10}, $PM_{2.5}$, O_3, NO_2, and CO were each included in the model. In addition, our contribution addresses other knowledge gaps on the association, such as the shape of the exposure–response relationship, the lag patterns, and possible temporal variations in risks.

There are several biological pathways and mechanisms through which SO_2 can lead to higher mortality risks. The body of evidence from animal, experimental, and epidemiological studies is deemed sufficient to suggest a causal relationship between exposure and effects on the respiratory system.[13] Specifically, short-term exposure to SO_2 is known to induce neural reflex responses, release of inflammatory mediators, and modulation of allergic inflammation, leading to several end points that include bronchoconstriction and increased airway responsiveness.[33] The impacts are known to be more severe in susceptible individuals, such as those with asthma.[34] Previous studies have also assessed potential risks for cardiovascular outcomes. SO_2 was shown to cause drops in measures of baroreflex sensitivity and cardiac vagal control, as well as increases in plasma fibrinogen, oxidative stress, and blood viscosity in young adults.[35] However, the body of evidence is not sufficient and consistent enough to establish a causal relationship.[14]

Another important result of this study is the evidence of the potential public health benefits achievable with more stringent air quality policies. As stated above, we found that short-term exposure to SO_2 was associated with an excess risk of mortality. Although the impact has decreased in time consistent with the reduction in concentration levels, exposure to SO_2 was still linked with a considerable number of excess deaths in recent years. More importantly, the majority of the additional deaths were linked with exposures sustained on days in which SO_2 levels were at or below the current daily WHO threshold, which was recently increased from 20 to 40 $\mu g/m^3$. These results, in line with previous multicountry studies on other pollutants,[16–20] indicate the presence of a considerable risk even at low exposure ranges that is also associated with a substantial health burden in countries that comply with the current WHO guidelines. These results therefore support the efforts to enforce national and international policy guidelines and to consider the opportunity to revise the limits downward.

An important aspect of this assessment is the application of state-of-the-art study design and statistical methods on a large multicountry database. Given the large sample of locations covering such a wide geographic area, we were able to obtain consistent evidence using a uniform model of a short-term association between exposure to SO_2 and all-cause mortality. The use of advanced analytical techniques applied in the first stage, including time-series regression and distributed lag models, allows a nuanced characterization of complex exposure–lag–response relationships. Similarly, the analysis of hundreds of locations and the use of extended meta-analytical techniques provide both pooled and city- and country-specific estimates and offer a comprehensive geographical and temporal comparison across various regions of the globe.

Some limitations must be acknowledged. First, although we were able to provide risk summaries across four inhabited continents, our results should not be considered truly global estimates given that some areas, such as Africa, South America, and the Middle East, were underrepresented or not assessed. Moreover, the study was restricted to urban populations, with several countries represented by a small number of cities, and therefore it cannot be entirely representative of the risks across whole populations. Notably, although the assessment offers a consistent comparison of risks across locations and found important differences in risks and impacts across countries, we did not attempt to characterize such heterogeneity. Part of this variability can be due to systemic differences concerning measurements from atmospheric monitors (type of station, proximity to the study area), study area boundaries, temporal coverage, and data processing, whereas the other part can be related to actual differences in susceptibility. This will be a topic for future research. In addition, the extension using polynomial terms indicates a degree of nonlinearity in the exposure–response relationship. However, it is challenging to disentangle to what extent this is due to heterogeneous risks in areas with high exposure ranges, and the main results are therefore reported from a model assuming a linear association. Further research on the shape of the exposure–response relationship and the risk at high SO_2 levels is needed. Furthermore, although we assessed potential confounding effects in bi-pollutant models, we did not extend the analysis to evaluate possible synergistic effects between SO_2 and other pollutants. Finally, the study was conducted using aggregated time-series data, preventing a more refined analysis of potential biological mechanisms and differential susceptibility patterns at the individual level.

Conclusions

This large multicountry study provides evidence of an independent short-term association between exposure to SO_2 and all-cause mortality. The assessment indicates that even if current air quality guidelines for SO_2 were enforced, many deaths would still occur, and additional health benefits could be attained by further lowering existing limits. These findings have important implications for the design of future health and environmental policy actions. More generally, they can contribute to the design and implementation of mitigation strategies to reduce the environmental risks and impacts on health in the context of climate change.

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