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Association of mortality and combined oxidative capacity of ozone and nitrogen dioxide

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Ozone (O_3) and nitrogen dioxide (NO_2) are two common gaseous pollutants that both possess oxidizing properties with consequences for human health and have an inextricable chemical relationship that could have distinct public health impacts when considered in combination. We examined the short-term associations of the combined oxidative capacity of O_3 and NO_2 (represented by Ox^{wt}, the average of O_3 and NO_2 concentrations weighted by their standard electrode potential) with total, cardiovascular and respiratory mortality in 380 cities across 23 countries or regions between 1985 and 2020. Over 2 days (LAG01), a 10-ppb increase in Ox^{wt} concentration was associated with an increase of 0.82% (95% confidence interval (CI): 0.55%, 1.10%) in total mortality, 1.09% (95% CI: 0.83%, 1.35%) in cardiovascular mortality and 0.88% (95% CI: 0.31%, 1.45%) in respiratory mortality. We also observed variations in this association by geographic region and study period. More deaths were attributable to Ox^{wt} than to either O_3 or NO_2 but fewer than the sum of the two. Thus, Ox^{wt} might be a valuable indicator for use in public health efforts to capture the combined effects of O_3 and NO_2.

Air pollution has been linked to an increased risk of mortality and has been ranked as the second-leading risk factor for death worldwide[1]. This conclusion is largely based on epidemiological studies that associated the mass concentrations of pollutants with mortality[1]. In contrast, relatively few studies have examined how the chemical characteristics of pollutants affect human health. Both epidemiological and toxicological investigations have revealed that the damage caused by air pollutants to humans is primarily initiated by oxidative stress, which is characterized by the overproduction of reactive oxygen species[2,3]. Therefore, the oxidative capacity of a certain air pollutant or the atmospheric oxidation capacity (AOC) might play an important role in the health effects of air pollution. In this context, researchers have proposed the oxidative potential of particulate matter (PM), the capacity to oxidize target molecules through the production of redox species. This oxidative potential is largely associated with anthropogenic emissions, particularly secondary organic aerosols and metals[4,5]. Epidemiological evidence has suggested that the oxidative potential of PM may be a more health-relevant exposure metric than conventional mass concentration when evaluating the acute effect of PM on cardiorespiratory health[6–8].

In addition to PM, gaseous pollutants may also prompt oxidative stress through their oxidative capacity. Ozone (O_3) and nitrogen dioxide (NO_2) are common oxidizing gaseous air pollutants. They have an inextricable chemical relationship, as NO_2 is one of the precursors for O_3 formation, and an increase in NO_2 is always accompanied by an increase in nitrogen monoxide (NO), which in turn acts to quench O_3 (ref. 9). A noteworthy point is that these reactions occur rapidly and constantly interchange O_3 and NO_2 quickly, accompanied by a constant release and depletion of atmospheric oxidants (for example, O_3, hydroxyl and nitrate radicals), which thereby affects the AOC. A substantial body of epidemiological evidence has demonstrated that exposure to O_3 or NO_2 was independently associated with adverse health outcomes, including increased short-term mortality and morbidity[10–13]. However, most of these studies typically estimated the effects of one pollutant at a time, either O_3 or NO_2, without accounting for the inextricable chemical relationship between them.

Combining O_3 and NO_2 would be a suitable and valuable way to account for the dynamic equilibrium in their chemical relationships. To address this issue, two metrics Ox^{wt} (the average concentration of O_3 and NO_2 weighted by their standard electrode potentials) and Ox (the

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Table 1 | Mortality and Ox^{wt} data in 380 cities of 23 countries or regions

Country/region	Geographic region	n [a]	Period	Deaths (in thousands)			Ox^{wt} (in ppb) [b]
				Total	CVD	RES	
Canada	North America	25	1987–2015	3,443	1,151	293	18.6 (14.8, 22.9)
USA	North America	136	1985–2006	20,243	7,008	1,939	22.9 (17.8, 28.8)
Brazil	South America	1	1997–2011	910	NA	NA	42.0 (30.8, 55.3)
Chile	South America	2	2004–2014	230	NA	NA	14.7 (11.4, 18.3)
Colombia	South America	1	1998–2013	426	124	46	13.6 (11.1, 16.8)
Ecuador	South America	1	2014–2018	45	11	6	11.7 (10.0, 13.9)
Peru	South America	1	2010–2014	172	NA	NA	9.7 (8.2, 11.2)
France	Western Europe	18	2000–2015	1,054	255	67	27.1 (21.7, 33.4)
Germany	Western Europe	12	1993–2015	3,095	NA	NA	18.0 (13.6, 23.0)
UK	Western Europe	33	1990–2016	4,376	1,534	657	19.0 (15.7, 22.6)
Finland	Northern Europe	1	1994–2014	153	57	10	18.7 (15.2, 22.6)
Cyprus	Southern Europe	5	2010–2019	51	18	5	24.6 (20.8, 28.4)
Portugal	Southern Europe	6	1999–2018	868	267	99	22.4 (18.0, 27.0)
Romania	Southern Europe	6	2008–2016	316	NA	NA	18.4 (13.7, 23.8)
Spain	Southern Europe	47	2004–2014	1,277	402	153	21.9 (17.9, 25.9)
China	East Asia	3	2013–2015	246	102	31	43.4 (33.8, 56.7)
Japan	East Asia	46	2011–2015	1,865	491	293	22.3 (17.9, 27.5)
South Korea	East Asia	7	1999–2015	1,662	390	106	22.2 (18.6, 27.1)
Taiwan	East Asia	3	1994–2014	1,210	269	117	29.0 (22.1, 39.4)
Thailand	Southeast Asia	18	1999–2008	804	158	105	14.7 (10.4, 21.0)
Iran	West Asia	1	2002–2015	696	317	53	28.5 (21.6, 37.3)
Israel	West Asia	4	2000–2020	401	NA	NA	26.7 (22.9, 30.7)
Australia	Australia	3	2000–2009	514	NA	NA	14.1 (11.7, 16.5)
Pooled	Pooled	380	1985–2020	44,058	12,556	3,978	21.3 (16.6, 26.7)

[a]The number of cities. [b]Ox^{wt} was presented as median and inter-quartile range. Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide; CVD, cardiovascular disease; RES, respiratory disease; NA, not available.

sum concentration of O_3 and NO_2) have been developed. The former metric considers the different oxidative strengths of O_3 and NO_2, with O_3 being the stronger oxidant, whereas the latter treats both gases as equivalent. From the perspective of atmospheric chemistry, Ox^{wt} and Ox can be viewed as indirect reflections of AOC[14], although they are not direct measures of AOC. In addition to their chemical properties, the shared biological effects of O_3 and NO_2 further support the rationale for combining them, as epidemiological and toxicological studies have reported that both O_3 and NO_2 could cause oxidative stress[3,15,16]. To date, only a few studies have examined the associations of the combined oxidative capacity of O_3 and NO_2 with mortality or morbidity[17–20], and nearly all of them have focused on short-term exposure[17–19]. For example, Williams et al. found that every 10-parts-per-billion (ppb) increase in Ox concentrations in London was significantly associated with a 1.30% increase in daily mortality[17]. Faustini et al. reported a 1.93% increase in daily natural mortality for every 10-ppb increase in Ox^{wt} concentration in Rome[18]. However, most existing studies were limited to a single city or country, posing a challenge in comparing these results due to different modelling approaches and potential publication bias.

Therefore, this Article aimed to examine the short-term association between the combined oxidative capacity of O_3 and NO_2 and mortality across multiple countries or regions globally, using data from the Multi-City Multi-Country (MCC) Collaborative Research Network. To accomplish this objective, we employed a standardized analytical framework based on state-of-the-art epidemiological methodologies to flexibly estimate concentration–response associations and to pool the results across countries.

Results

Descriptive statistics on death and exposure

The analysis included a total of 380 cities across 23 countries or regions (Supplementary Fig. 1) and covered the period from 1985 to 2020, although the years of analysis differed by country or region due to data availability. The study recorded approximately 44 million deaths from all causes, among which, 12.6 million were due to cardiovascular diseases and 4.0 million were due to respiratory diseases (Table 1). Cardiovascular deaths accounted for 28.5% of total deaths across all countries or regions (N = 23), ranging from 19.7% in Thailand to 45.5% in Iran, while respiratory deaths accounted for 9.0% of total deaths, ranging from 6.4% in France to 15.7% in Japan.

The median of the 380 cities' annual mean Ox^{wt} concentrations was 21.3 ppb, with an inter-quartile range of 16.6 ppb to 26.7 ppb. The highest level of Ox^{wt} was observed in China (median = 43.4 ppb), while the lowest level was observed in Peru (median = 9.7 ppb). Although the temporal variations in Ox^{wt} levels varied by country or region, annual mean concentrations remained nearly constant in most countries over the study period, except for large fluctuations in Brazil and Iran and notable declines in the Taiwan region and Peru (Supplementary Fig. 2). During the same period, O_3 concentrations increased slightly while NO_2 concentrations decreased modestly (Supplementary Fig. 2). In most countries, particularly those farther from the equator, Ox^{wt} levels displayed a clear seasonal pattern, being higher during warm seasons and lower during cool seasons (Supplementary Fig. 3). The median values of annual mean Ox, O_3 and NO_2 concentrations for 380 cities were 39.9 ppb, 24.4 ppb and 14.7 ppb, respectively (Supplementary Table 1).

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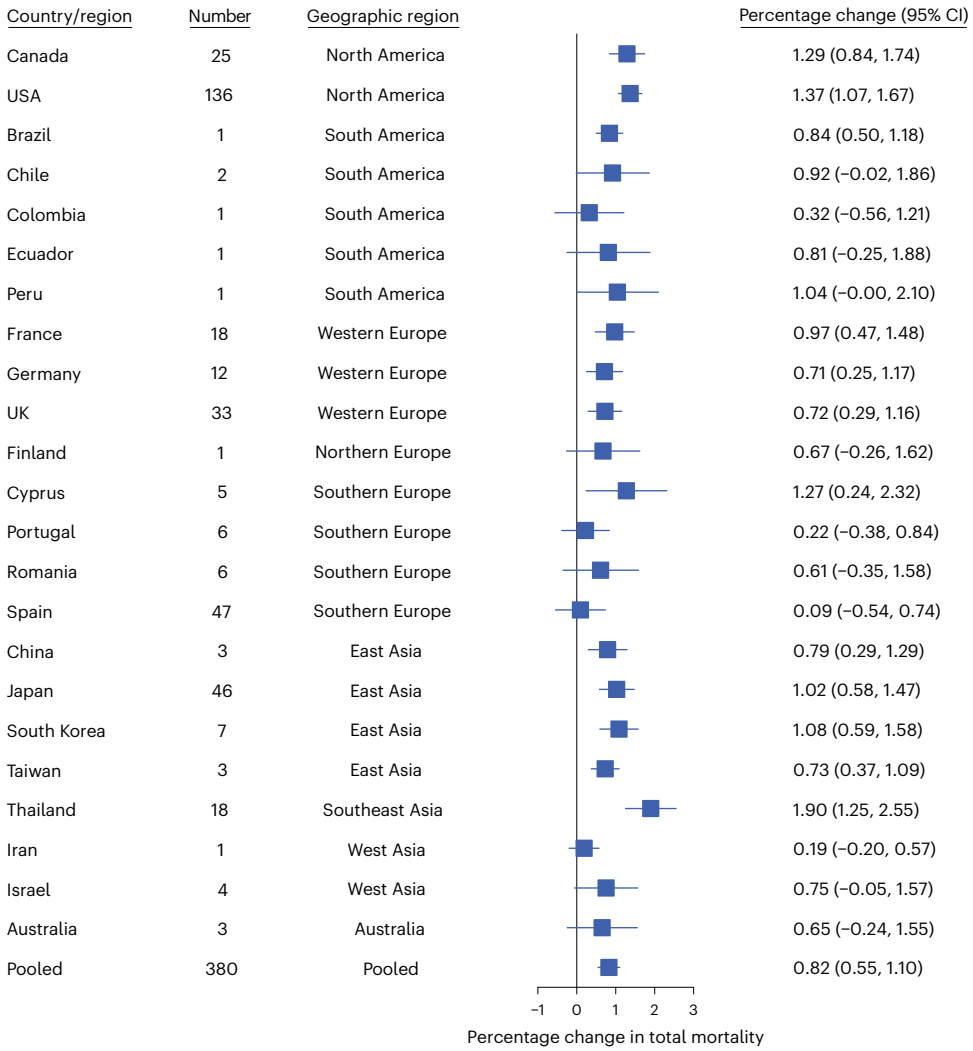

Fig. 1 | Associations betwen Ox^{wt} and daily total mortality. Results are expressed as percentage changes and 95% confidence intervals in total mortality associated with a 10-ppb increase in Ox^{wt} concentration over lag 0–1 days. Number refers to the number of cities. The blue squares represent point estimates, and the lines represent their 95% confidence intervals. Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide; CI, confidence interval.

Associations between Ox^{wt} and mortality

In the 380 cities, a 10-ppb increase in Ox^{wt} concentration over lag 0–1 days (LAG01) was associated with a 0.82% (95% confidence interval (CI): 0.55%, 1.10%) increase in total mortality (Fig. 1). The country-specific estimates showed a substantial variation, with the percentage changes in total mortality ranging from 0.09% (95% CI: −0.54%, 0.74%) in Spain to 1.97% (95% CI: 1.25%, 2.55%) in Thailand per 10-ppb increase in Ox^{wt} concentrations. The estimates for countries with only a few cities were less stable and exhibited wider CIs. The associations between Ox^{wt} and total mortality showed significant heterogeneity, with an I^2 statistic of 45.0% ($Q = 688$, $P < 0.0001$). For the 351 cities with available data, the corresponding increases were 1.09% (95% CI: 0.83%, 1.35%) for cardiovascular mortality and 0.88% (95% CI: 0.31%, 1.45%) for respiratory mortality (Table 2). The estimates were less heterogeneous for the associations with cardiovascular ($I^2 = 21.0\%$, $Q = 437$, $P = 0.0006$) and respiratory ($I^2 = 10.4\%$, $Q = 388$, $P = 0.067$) mortality.

As shown in Fig. 2, the magnitude of the association between Ox^{wt} and total mortality decreases as the lag increases, with the estimate highest at lag 0 days, attenuating gradually to the null by lag 5 days. The curve for the association with cardiovascular mortality flattens slightly over lag 0 to 1 days and thereafter decreases sharply. In contrast, the curve for the association with respiratory mortality rises and peaks within 2 days of exposure and then declines, suggesting a delayed effect of Ox^{wt} on respiratory mortality. The concentration–response curves for total, cardiovascular and respiratory mortality were positive and almost linear (Fig. 3). No clear threshold was evident for any of the three curves within the current concentration range, although wider CIs were observed at higher concentrations.

Overall, the associations between Ox^{wt} and total mortality varied by geographic region and study period (Supplementary Table 2). During the same study period, the associations of Ox^{wt} with total mortality were slightly weaker in western Europe than in North America. From 2010 to 2020, when data were available for most countries or regions, the effects of Ox^{wt} were relatively weaker in North America and western Europe while relatively stronger in East Asia and South America. The association between Ox^{wt} and total mortality remained consistently insignificant in southern Europe, although data were not scarce in this geographic region. When comparing high- and low-exposure cities within the same country or region, slightly stronger associations were generally observed in high-exposure cities, particularly in countries with larger numbers of cities included, although this pattern was not entirely consistent (Supplementary Table 3). Similarly, seasonal comparisons revealed marginally stronger associations during warm seasons in most countries, especially those with more cities and marked seasonal variation (Supplementary Table 4). However, at the global level, neither the differences by exposure level nor those by season reached statistical significance.

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Table 2 | Percentage changes and 95% confidence intervals in cardiovascular and respiratory mortality associated with a 10-ppb increase in Ox^{wt} concentration over lag 0–1 days

Country/ Region	Geographic region	Cardiovascular	Respiratory
Canada	North America	1.20 (0.69, 1.71)	1.63 (0.48, 2.79)
USA	North America	1.26 (0.93, 1.58)	1.33 (0.65, 2.02)
Colombia	South America	0.96 (0.32, 1.59)	0.53 (−1.02, 2.11)
Ecuador	South America	1.09 (0.44, 1.74)	0.90 (−0.74, 2.56)
France	Western Europe	1.08 (0.52, 1.64)	0.58 (−0.72, 1.89)
UK	Western Europe	1.26 (0.77, 1.75)	1.13 (0.17, 2.09)
Finland	Northern Europe	1.01 (0.37, 1.65)	0.74 (−0.87, 2.37)
Cyprus	Southern Europe	1.14 (0.49, 1.79)	1.05 (−0.58, 2.71)
Portugal	Southern Europe	1.10 (0.45, 1.75)	0.68 (−0.64, 2.02)
Spain	Southern Europe	0.97 (0.37, 1.57)	−0.04 (−1.39, 1.33)
China	East Asia	1.04 (0.52, 1.56)	0.83 (−0.28, 1.95)
Japan	East Asia	1.22 (0.69, 1.75)	0.50 (−0.46, 1.48)
South Korea	East Asia	1.19 (0.62, 1.75)	1.33 (0.05, 2.63)
Taiwan	East Asia	1.16 (0.70, 1.62)	0.79 (−0.10, 1.69)
Thailand	Southeast Asia	1.21 (0.60, 1.82)	2.00 (0.67, 3.33)
Iran	West Asia	0.58 (0.17, 1.00)	0.05 (−0.95, 1.07)
Pooled	Pooled	1.09 (0.83, 1.35)	0.88 (0.31, 1.45)

Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide.

The results of sensitivity analyses are presented in Supplementary Table 5. Among the 157 cities with complete data for all air pollutants, the associations between Ox^{wt} and total mortality remained statistically significant after adjusting for fine PM ($PM_{2.5}$), sulfur dioxide (SO_2) and carbon monoxide (CO). However, the magnitude of the associations decreased by approximately 13% when $PM_{2.5}$ was included in the model. In terms of meteorological confounders, the associations were similar regardless of whether relative humidity was adjusted for. Similarly, using different approaches to control for ambient temperature did not substantially alter the results, although the estimate was slightly attenuated from 0.82% to 0.62% after employing a more complex temperature model. Furthermore, increasing the degree of freedom (df) for the time trend from 7 to 10 per year had no meaningful impact on the estimates, indicating that the choice of 7 df per year was sufficient to control for the impacts of the time trend. Finally, when the analysis was restricted to cities with at least one year of consecutive data, the association remained largely unchanged, suggesting that missing data patterns did not considerably affect the findings.

Comparisons across exposure metrics and statistical models

Compared with Ox, Ox^{wt} showed a slightly weaker association with total mortality, corresponding to a 0.83% (95% CI: 0.55%, 1.11%) increase per inter-quartile range increase in Ox^{wt} concentration, versus 1.00% (95% CI: 0.73%, 1.27%) for Ox (Table 3). Moreover, the effect size of Ox^{wt} fell between those of its individual components, being larger than the separate effect of O_3 but smaller than the separate effect of NO_2. Nevertheless, in terms of model fit, the single-pollutant model for Ox^{wt} yielded lower median and sum of the Akaike information criterion (AIC) values than the single-pollutant models for Ox, O_3 and NO_2, indicating superior performance. In the two-pollutant model including both O_3 and NO_2, the effects of both pollutants were augmented.

To further evaluate their impacts on public health, we estimated the number of deaths attributable to each pollutant. In the 380 cities, exposure to Ox^{wt} was associated with a total of 1,054,622 attributable deaths. The population-attributable fraction of total mortality due to Ox^{wt} remained relatively stable over the study period in most countries or regions (Supplementary Fig. 4). In contrast, using the risk estimates from the single-pollutant model, the attributable deaths were 380,562 for O_3 and 834,356 for NO_2. Notably, the sum of these separate estimates exceeded the deaths attributable to Ox^{wt}.

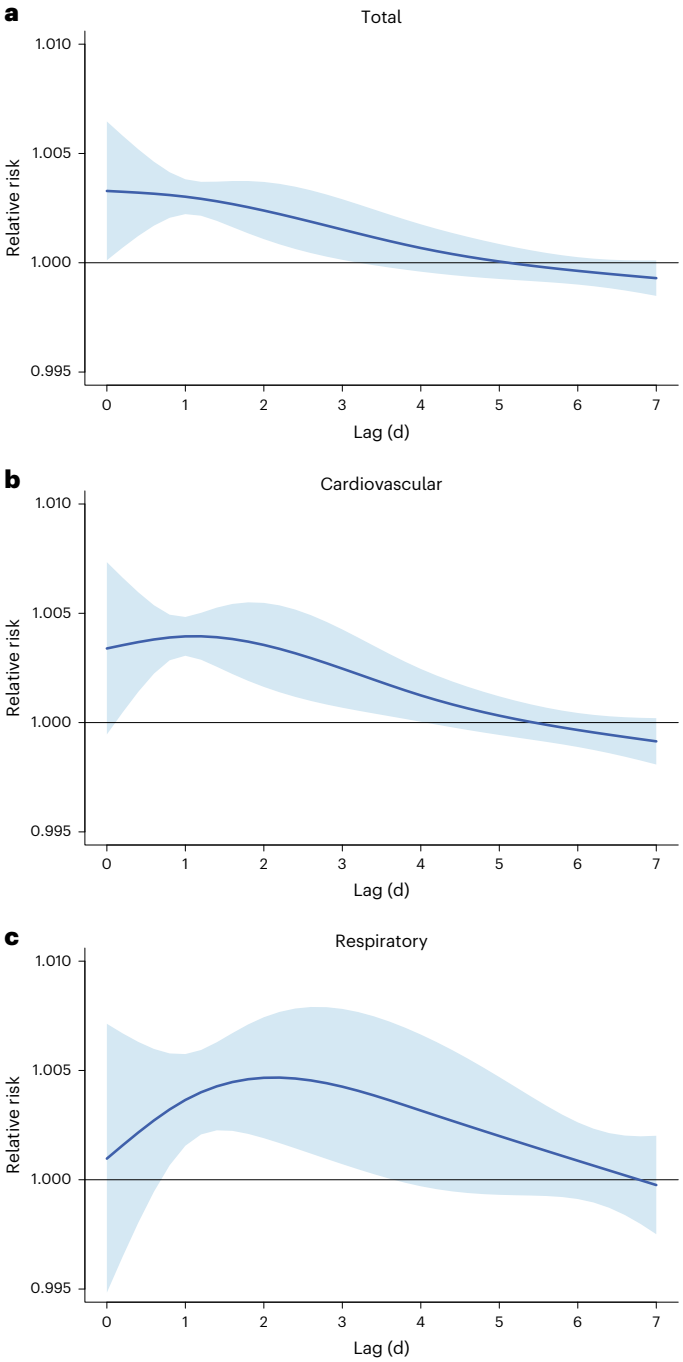

Fig. 2 | Lag patterns for the associations between Ox^{wt} and daily mortality. **a**–**c**, Pooled lag–response curves for the short-term associations between Ox^{wt} and total (**a**), cardiovascular (**b**) and respiratory (**c**) mortality. The dark blue lines represent the point estimates, and the light blue areas represent their 95% confidence intervals. Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide.

Discussion

This global epidemiological investigation provides, to the best of our knowledge, an unprecedented scale for examining the association between the combined oxidative capacity of O_3 and NO_2 and mortality.

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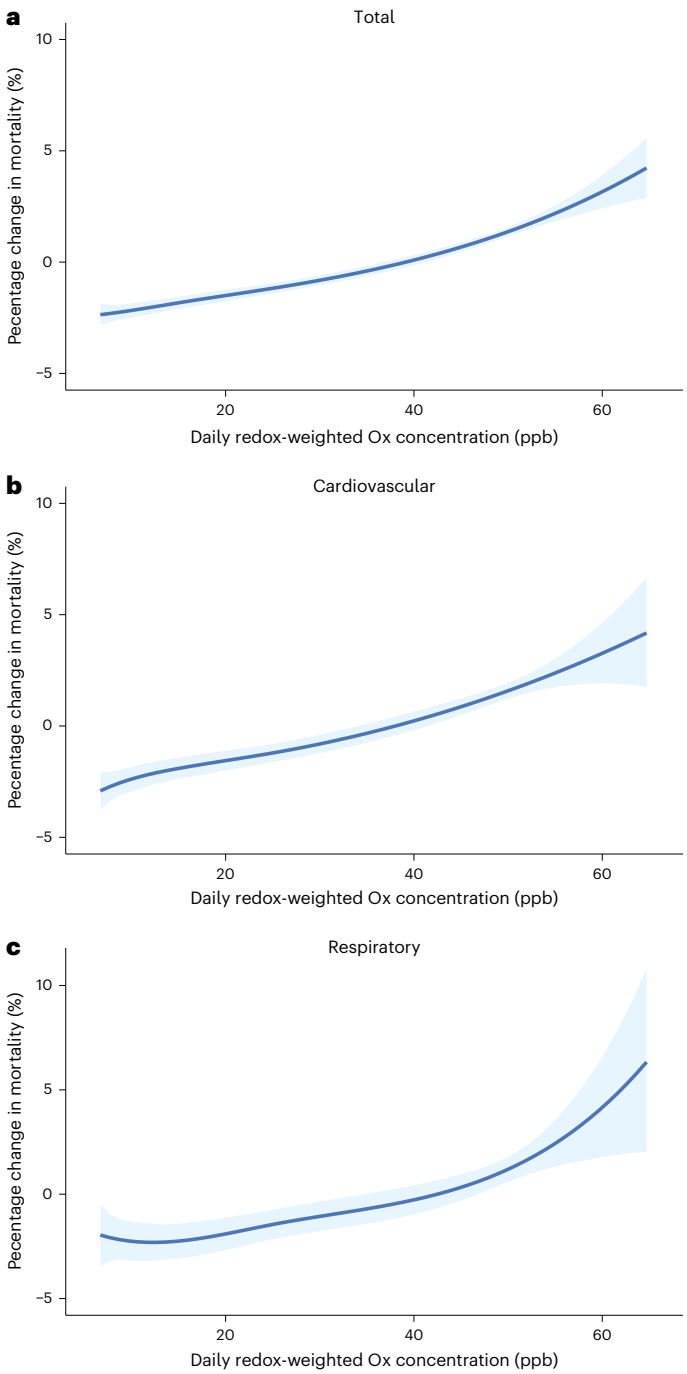

Fig. 3 | Concentration-response relationships between Ox^{wt} and daily mortality. a–**c**, Pooled concentration–response curves for the associations between Ox^{wt} concentration and total (**a**), cardiovascular (**b**) and respiratory (**c**) mortality over lag 0–1 days. The dark blue lines represent the mean percentage changes in mortality, and the light blue areas represent their 95% confidence intervals. Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide.

The application of a uniform analytical protocol to data from 380 cities across 23 countries or regions enhances the statistical power of our study, improves the generalizability of the findings and facilitates the integration and comparison of the results. In this study, we found that Ox^{wt} exposure was associated with increased risks of total, cardiovascular and respiratory mortality. The effect estimate of Ox^{wt} was relatively smaller than that of Ox and intermediate between those of O_3 and NO_2 individually. Correspondingly, the number of deaths attributable to Ox^{wt} was smaller than the sum of deaths attributable to O_3 and NO_2 separately. Notably, this study provides a global synthesis of concentration–response relationships between Ox^{wt} and mortality, indicating near-linear positive associations with no apparent threshold.

On the basis of such a global representative database, we found that a 10-ppb increase in Ox^{wt} concentration was significantly associated with a 0.82% increase in daily total mortality. Although this finding was consistent with the direction of previous studies[18,21], our effect estimates were smaller in magnitude. For example, earlier studies reported that every 10-ppb increase in Ox^{wt} concentration was associated with a 1.93% increase in natural mortality in Rome[18] and with a 1.77% increase in natural mortality in a Chinese province[21]. From an atmospheric chemistry perspective, although Ox^{wt} is not a direct measure of AOC, it was recognized as a surrogate reflecting the intensity of atmospheric oxidation processes[14]. In this context, our findings extend beyond the traditionally perceived health hazards associated with the increasing concentrations of one pollutant. To some extent, our results can be interpreted as an integrated adverse effect of high AOC, which is characterized by complex chemical reactions and the production of multiple harmful species[22]. It implies that future air quality management strategies should not only target the mass concentrations of specific air pollutants but also consider measures to mitigate the overall oxidative potential of the atmosphere, which may offer an additional pathway for public health protection. However, it should be noted that our study was limited to the combined oxidative capacity of O_3 and NO_2 and did not include the oxidative potential of PM due to the lack of relevant data.

The associations between Ox^{wt} concentration and total mortality exhibited spatial heterogeneity across countries or regions. Consistent with the APHENA study[23], we found a slightly weaker association in western Europe than in North America, possibly due to minor differences in Ox^{wt} levels. A similar pattern was also observed at the country level. For example, within North America, Canada had lower Ox^{wt} levels and smaller health impacts than the USA. However, between 2010 and 2020, the effects of Ox^{wt} were relatively smaller in East Asia than South America, despite East Asia having higher Ox^{wt} levels than South America, suggesting that differences in Ox^{wt} levels alone cannot fully explain the spatial heterogeneity. This speculation was further reinforced by our stratified analysis, which revealed that although cities with higher Ox^{wt} levels exhibited slightly stronger associations, the differences by exposure level were not statistically significant at the global level. Another notable finding was that southern Europe showed no significant association between Ox^{wt} and total mortality, even though the Ox^{wt} levels were not low in this region. Due to the lack of individual-level data, it is difficult to identify the precise reasons underlying the complex spatial heterogeneity. The insensitivity of southern Europeans to air pollution may be partly explained by their high antioxidant intake from the Mediterranean diet, which have been demonstrated to mitigate the systemic oxidative stress and inflammation induced by air pollution[24,25]. Moreover, differences in air pollution mixtures (for example, sources and PM oxidative potential), socio-economic status, access to healthcare and prevalence of comorbidities should also be considered when interpreting this heterogeneity. Further research is needed to specifically investigate these potential effect modifiers. Due to varying time frames across cities, we were unable to directly assess how the Ox^{wt}–mortality association may have changed over time. However, it is clear that emission reduction strategies may alter the distributions of O_3 and NO_2, thereby changing the intensity and composition of the oxidative mixtures. In this context, examining the temporal trends in health effects per unit change in pollutant concentrations is crucial for dynamically adjusting emissions reduction strategies. Additionally, this study did not provide strong evidence for a distinct seasonal pattern in the associations, suggesting that the adverse effects of Ox^{wt} may persist throughout the year.

In the present study, we also examined the associations of Ox^{wt} with deaths from two main causes, that is, cardiovascular diseases and respiratory diseases. Our findings suggested that Ox^{wt} had a slightly

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Table 3 | Associations of Ox^{wt}, Ox, O_3 and NO_2 with total mortality over lag 0–1 days and their attributable deaths in the 380 cities

Model	Exposure	% Change per 10 ppb[a]	% Change per IQR[b]	Attributable deaths	Median of AIC	Sum of AIC
Single-pollutant model	Ox^{wt}	0.82 (0.55, 1.10)	0.83 (0.55, 1.11)	1,054,622 (666,137; 1,439,113)	19,222.76	9,176,545
Single-pollutant model	Ox	0.62 (0.45, 0.78)	1.00 (0.73, 1.27)	1,403,871 (960,109; 1,842,422)	19,222.84	9,176,976
Single-pollutant model	O_3	0.24 (0.09, 0.40)	0.41 (0.15, 0.68)	380,562 (131,792; 627,664)	20,254.48	9,663,417
Single-pollutant model	NO_2	0.82 (0.60, 1.05)	1.01 (0.73, 1.28)	834,356 (563,814; 1,102,800)	21,280.68	9,934,527
Two-pollutant model	O_3	0.39 (0.25, 0.54)	0.67 (0.43, 0.91)	510,250 (272,175; 746,799)	19,223.43	9,176,965
Two-pollutant model	NO_2	0.91 (0.66, 1.17)	1.12 (0.80, 1.43)	915,281 (609,149; 1,218,734)	19,223.43	9,176,965

[a]The results were expressed as percentage changes and their 95% confidence intervals in total mortality per 10-ppb increase in pollutant concentration. [b]The results were expressed as percentage changes and their 95% confidence intervals in total mortality per inter-quartile range increase in pollutant concentration. Abbreviations: Ox^{wt}, the redox-weighted average concentration of ozone and nitrogen dioxide; Ox, the sum concentration of ozone and nitrogen dioxide; O_3, ozone; NO_2, nitrogen dioxide; IQR, inter-quartile range; AIC, Akaike Information Criterion.

larger impact on cardiovascular mortality (1.09% per 10-ppb) than respiratory mortality (0.88% per 10-ppb), which was consistent with previous findings[18]. In addition, a few epidemiological studies have demonstrated their effects on the incidence of cardiovascular and respiratory diseases. For example, investigators previously found that Ox^{wt} exposure was associated with a higher incidence of chronic obstructive pulmonary disease[26], acute upper respiratory infection[19], congestive heart failure[27], acute myocardial infarction[27], atrial fibrillation[28] and stroke[28]. Moreover, several publications also provided evidence on the subclinical effects of Ox^{wt}, including airway inflammation[29], increased blood pressure[30] and decreased arteriolar diameter[31], suggesting biological plausibility for the effects of Ox^{wt} on cardiovascular and respiratory mortality. Similar to previous studies[32], we found a delayed effect of Ox^{wt} on respiratory mortality but not on cardiovascular mortality, which were consistent with the underlying pathophysiology of each group of diseases. Cardiovascular deaths are typically caused by acute events such as heart attacks or strokes that disrupt blood flow or electrical conduction, leading to death within minutes to hours. Key mechanisms include acute coronary thrombosis, plaque rupture, endothelial dysfunction and conduction abnormalities[33,34]. In contrast, respiratory deaths generally progress more slowly, resulting from impaired gas exchange due to mucus plugging, bronchospasm, inflammation, thickened septa and consolidation[35,36].

Our findings suggest that Ox^{wt} may be valuable as a promising exposure indicator in health risk assessment and management. Although the effect estimate for Ox^{wt} was slightly lower than that for Ox, the model employing Ox^{wt} achieved a lower AIC value, indicating that Ox^{wt} could more accurately explain variations in total mortality than Ox. Moreover, a key advantage of Ox^{wt} is that it differentially weights the contributions of O_3 and NO_2, making it a more rational measure of total oxidizing capacity, which is critical for inducing oxidative stress. Thus, from both statistical and biological perspectives, Ox^{wt} could serve as a more health-relevant exposure metric. In addition, we found that the effect of Ox^{wt} was larger than the estimates of O_3, one of the important atmospheric oxidants and the models fitted better. This finding was similar to previous time series studies[17,21], providing supportive evidence that individual pollutants cannot separately characterize the effects of AOC. When quantifying these effects in terms of attributable deaths, we found that the number of deaths attributable to Ox^{wt} was greater than the number of deaths attributable to either O_3 or NO_2 but less than the sum of the two. This suggests that calculating the mortality burdens for O_3 and NO_2 separately and then adding the two together might result in double counting. When using a two-pollutant model to solve this problem, new issues would arise, such as multicollinearity and difficulties for policymakers in interpreting the results. Collectively, the use of Ox^{wt} for health impact assessment is appealing to policymakers because it simplifies calculations and seems to avoid possible double counting. In this sense, the single indicator may become one of the key tools for air quality control and environmental health management in the future.

However, we must also acknowledge the limitations of the current study. First, the majority of the data included were obtained from Europe, North America and East Asia. Consequently, the results may not fully represent other regions such as West Asia, Africa and South America due to uncertainties in Ox^{wt} exposure, socio-economic status and genetic background. For China, only three cities were included, which may not fully capture the spatial heterogeneity in air pollution and its health effects across the country. This limitation should be taken into account when interpreting the findings on regional heterogeneity. Moreover, all data in this study were for cities and the results do not represent rural areas. Second, the use of city-level data to estimate Ox^{wt} exposure may lead to non-differential exposure misclassification, as it does not account for within-city heterogeneity in concentrations or individual exposure levels. Such misclassification typically, but not always, biases effect estimates towards the null and increases their uncertainty[37]. To improve accuracy, future studies should employ more refined exposure assessment methods, such as satellite-derived pollutant data or high-resolution spatial-temporal modelling, which would better account for within-city gradients or personal exposure. Third, this study was limited to the combined oxidative capacity of O_3 and NO_2 and did not consider the oxidative potential of PM. However, we believe the omission of PM oxidative potential does not significantly confound our results, given its distinct seasonal distribution from Ox^{wt} (suggesting a low correlation) and the lack of evidence for an independent association with mortality[38–40]. Despite this, previous studies indicated that exposure to high PM oxidative potential can amplify the acute health effects of oxidizing gases[41]. Therefore, failing to adjust for it may lead to an underestimation of the Ox^{wt} effect, especially in regions where PM oxidative potential is high.

In summary, our findings provide evidence that Ox^{wt} is associated with increased risks of total, cardiovascular and respiratory mortality and further reveal that Ox^{wt} may be a valuable indicator to capture the effects of the combined oxidative capacity of O_3 and NO_2. This time series analysis also sheds new light on studying the hazards of air pollution beyond a single pollutant or beyond a pollutant's mass concentration.

Methods

Data collection

Data on death counts and environmental factors were obtained from the MCC database (https://mccstudy.lshtm.ac.uk/)[42,43], and the analytical protocol has been approved by the MCC Collaborative Research Network. Our analysis was restricted to cities with both 24-hour average O_3 and NO_2 data and with a cumulative total of at least 365 days of data for the primary variables, which were allowed to be distributed across multiple years. Finally, a total of 380 cities in 23 countries or regions were included in the analysis.

Death data were initially obtained from the local authorities in each country. The causes of death were coded in accordance with the available International Classification of Diseases, either the 9th

or 10th Revision (ICD-9 or ICD-10). In the present study, we defined total mortality as the daily count of deaths due to any cause in Canada, Chile, Colombia, Cyprus, Ecuador, Finland, France, Germany, Israel, Japan, South Korea, Peru, Portugal, Romania, Taiwan region, the UK and the USA, or the daily count of deaths due to non-external causes in Australia, Brazil, China, Iran, Spain and Thailand. Additionally, we collected death data for two major causes, that is, cardiovascular diseases (ICD-9: 390-459; ICD-10: I00-I99) and respiratory diseases (ICD-9: 460–519; ICD-10: J00-J99).

Air pollution data were obtained on a city level from daily measurements of one or more monitors of the national or regional networks. When multiple monitors were available in one city, we computed the average of measurements from all monitors to represent the city-specific daily level of each pollutant. We derived daily time series of 24-hour average exposure data, including O_3, NO_2, $PM_{2.5}$, SO_2, CO, ambient temperature and relative humidity. No extreme air pollution events were excluded to ensure the data accurately represent real-world conditions. The units for O_3 and NO_2 were converted to ppb before being used to estimate their combined oxidative potential. Considering that O_3 is a stronger oxidant than NO_2, we calculated Ox^{wt} as the average concentration of O_3 and NO_2 weighted by their standard electrode potentials ($E°$), a thermodynamic measure of oxidizing power, using the following equation[44]:

$$Ox^{wt} = \frac{E^{\circ}_{O_3} \times C_{O_3} + E^{\circ}_{NO_2} \times C_{NO_2}}{E^{\circ}_{O_3} + E^{\circ}_{NO_2}}$$

where C_{O_3} and C_{NO_2} refer to the 24-hour average concentrations of O_3 and NO_2, respectively, on the same day; the $E^{\circ}_{O_3}$ and $E^{\circ}_{NO_2}$ are their standard electrode potentials in aqueous solution at 25 °C, which are 2.075 volt and 1.07 volt, respectively[44]; the Ox^{wt} (in ppb) denotes their redox-weighted oxidative capacity. We also calculated the sum of the 24-h average concentrations of O_3 and NO_2 as another metric of the combined oxidative capacity, denoted as Ox.

Statistical analysis

As in previous multi-centre time series studies[13,42], we utilized a two-stage analytic approach to evaluate the associations of Ox^{wt} concentrations with total, cardiovascular and respiratory mortality. In the first stage, city-specific associations were estimated using a generalized linear model with quasi-Poisson family due to the over-dispersed distribution of the death data[10,11], as follows:

$$\log(Y_{ji}) = \text{cross.basis}(X_{ji}) + \text{ns}(\text{time}, \text{df} = 7 \text{ per year}) + \text{DOW}_i + \text{ns}(\text{Temp}_{ji}, \text{df} = 6)$$

where Y_{ji} is the count of deaths in city j on day i and X_{ji} is the level of Ox^{wt} in city j on day i. The lagged effects of Ox^{wt} were estimated using a distributed lag model, in which a linear function was used for the exposure–response dimension and a strata function was used for the lag–response dimension to calculate the moving averages over lag 0–1 days (LAG01) of Ox^{wt}. This model employed a natural cubic spline to control for the underlying nonlinear temporal trend in mortality. On the basis of model fit diagnostics and prior knowledge[10,11], seven df per year were set within the range of 5 to 9 to avoid over-smoothing or over-fitting. The model also included an indicator of day of the week to account for short-term weekly variations. Given the well-established nonlinear associations between temperature and mortality, a natural cubic spline with six df for average temperature from the day of death to the previous day (LAG01) was used to control for its nonlinear impact, which was consistent with previous studies[11,42]. In the second stage, we combined the estimates of city-specific associations through a multilevel random effect meta-analysis[45], as follows.

$$\beta_{kj} = \beta_0 + b_k + b_{kj} + \epsilon_{kj}$$

$$b_k \sim N\left(0, \tau^2_{\text{country}}\right), b_{kj} \sim N\left(0, \tau^2_{\text{city}}\right), \epsilon_{kj} \sim N\left(0, s^2_{kj}\right)$$

where β_{kj} is the estimated coefficient from the first stage for the city j nested in the country or region k; β_0 is the pooled estimate; b_k and b_{kj} are the random effects at the country or region level and the city level, respectively; and ϵ_{kj} is the error term for the city j nested in the country or region k. This methodology defines the random effect at the city and country level to account for the nested structure of the data and derives the best linear unbiased predictions for the associations at both levels. By borrowing information across units within the same hierarchical level, best linear unbiased predictions could enhance the estimates' accuracy and stability, particularly for cities or countries with limited data[45]. The pooled estimate represents the global average association, and country-specific associations were obtained as the best linear unbiased predictions at the country level. All estimates were reported as the percentage changes and their 95% CIs in daily mortality per 10-ppb increase in Ox^{wt} concentrations. Cochran Q tests and I^2 statistics were used to assess potential heterogeneity[46].

Following the two-stage framework, we performed a set of additional analyses to investigate specific features of the associations. First, to examine heterogeneity, we conducted regional analyses by grouping cities based on their geographical distribution and further restricted the analyses to three periods, that is, 1990–1999, 2000–2009 and 2010–2020. In addition, considering the differences in economic conditions and mortality patterns, we conducted a stratified analysis within each country or region based on city-specific average Ox^{wt} concentrations. This stratified analysis was restricted to countries or regions with at least two cities, exposure levels were categorized as low or high relative to the country-specific median. We also stratified the analysis by warm and cold seasons, which were defined based on the five consecutive months with the highest and lowest moving average of temperature, respectively. Second, we replaced the strata function with a natural spline function in the distributed lag model, with two knots at lag 1 and 3 days over a lag of 0–7 days plus intercept, to explore more complex lag structures of the Ox^{wt}–mortality associations. Third, we used a distributed lag nonlinear model for Ox^{wt} to flexibly estimate the potential nonlinear associations between Ox^{wt} and total, cardiovascular and respiratory mortality as in previous studies[42,47]. The distributed lag nonlinear model has an advantage of simultaneously representing nonlinear exposure–response dependencies and delayed effects. In short, we applied a B-spline function for the exposure–response dimension with two knots at the 25th and the 75th percentiles of the daily mean Ox^{wt} concentrations across all cities and a strata function for the lag–response dimension to calculate the moving averages over lag 0–1 days of Ox^{wt}.

We conducted multiple sensitivity analyses. First, we fitted three two-pollutant models by including $PM_{2.5}$, SO_2 and CO, one at a time, into the main model to assess whether the associations of Ox^{wt} were confounded by other air pollutants. To ensure comparability across these models, the analysis was limited to those cities with data available for all involved air pollutants. Second, because the evidence for the acute effect of relative humidity on mortality is less established than that for temperature, we used two methods, either a linear term or a natural cubic spline function with 3 df (refs. 11,42), to adjust for the potential linear and nonlinear effects of relative humidity (LAG01). Third, we applied two additional approaches to control for the impacts of temperature. One was to change the df of the natural cubic spline for temperature from 6 in the main model to 3. The other was to construct a cross-basis matrix for temperature by using a distributed lag nonlinear model, where a quadratic b-spline with internal knots at the 10th, 75th, 90th percentiles was used in the exposure–response dimension, and a natural spline with three equally spaced internal knots over 7 days was used in the lag–response dimension. Fourth, we alternated the df for the time trend from 7 per year to 10 per year. Fifth, we restricted our analysis within cities having at least 365 consecutive day data to examine whether our results were influenced by missing data patterns.

In addition, we compared the effects of the combined oxidative capacity using different exposure metrics or models. We first constructed single-pollutant models by adding either O_3 or NO_2 and then fitted a two-pollutant model with both O_3 and NO_2. We also compared the effect estimates of Ox and Ox^{wt} on mortality. The specifications of these models were consistent with the main model and the goodness-of-fit of these models was evaluated by calculating AIC values[48]. Given the different distributions of these pollutants, the results were expressed as a percentage change in daily mortality per inter-quartile range increase in the concentrations of a corresponding air pollutant. To quantify the health impacts of these exposures, we calculated the number of deaths contributable to Ox^{wt}, Ox, O_3 and NO_2 exposure. For each city and year, we calculated attributable deaths using the following equation:

$$AD_{kjy} = \frac{\exp(\beta_k \times C_{kj}) - 1}{\exp(\beta_k \times C_{kj})} \times D_{kjy}$$

where β_k represents to the best linear unbiased prediction (per 1-ppb increase in exposure) for the country or region k (refs. 10,49); C_{kj} denotes the annual concentration of the exposure in city j within country or region k; and D_{kjy} is the total number of deaths in city j within country or region k in year y. Then, we summed the attributable deaths across all 380 cities over the entire study period to obtain the total attributable deaths. Furthermore, we computed the proportion of attributable deaths to total deaths for each country using these estimates, that is, the population-attributable fraction. All statistical analyses were performed using R software (version 4.1.2), and all tests were two sided.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Both exposure and mortality data have been collected within the MCC (Multi-Country Multi-City) Collaborative Research Network (https://mccstudy.lshtm.ac.uk/) under a data sharing agreement and cannot be made publicly available. Researchers can refer to MCC participants listed as co-authors for information on accessing the data for each country.

Code availability

The main code used in this study is publicly available via Zenodo at https://doi.org/10.5281/zenodo.20019197 (ref. 50).

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	None.
Data analysis	R software (version 4.1.2) was used to analyze data.

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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☐ Behavioural & social sciences ☒ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is a time series study involving 380 cities across 23 countries or regions between 1985 and 2020, including approximately 44 million deaths from all causes. The analytical protocol has been approved by the MCC Collaborative Research Network.
Research sample	The research sample of this study is general population in the involved cities. However, this study does not involve individual-level data.
Sampling strategy	Based on data availability.
Data collection	Data used in this study were collected by collaborators within the Multi-Country Multi-City Collaborative Research Network under a data sharing agreement.
Timing and spatial scale	The study covers the period from 1985 to 2020, but the time period varies by country or region. Deaths were collected on a daily basis for each city.
Data exclusions	Our analysis was restricted to cities with both 24-hour average O3 and NO2 data and with at least 365 days of data for the primary variables. Finally, a total of 380 cities in 23 countries or regions were included in the analysis.
Reproducibility	All data were reviewed by the Multi-City Collaborative Research Network.
Randomization	N/A
Blinding	N/A

Did the study involve field work? ☐ Yes ☒ No

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.