All-cause, cardiovascular, and respiratory mortality and wildfire-related ozone: a multicountry two-stage time series analysis

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Summary

Background Wildfire activity is an important source of tropospheric ozone (O_3) pollution. However, no study to date has systematically examined the associations of wildfire-related O_3 exposure with mortality globally.

Methods We did a multicountry two-stage time series analysis. From the Multi-City Multi-Country (MCC) Collaborative Research Network, data on daily all-cause, cardiovascular, and respiratory deaths were obtained from 749 locations in 43 countries or areas, representing overlapping periods from Jan 1, 2000, to Dec 31, 2016. We estimated the daily concentration of wildfire-related O_3 in study locations using a chemical transport model, and then calibrated and downscaled O_3 estimates to a resolution of 0·25°×0·25° (approximately 28 km² at the equator). Using a random-effects meta-analysis, we examined the associations of short-term wildfire-related O_3 exposure (lag period of 0–2 days) with daily mortality, first at the location level and then pooled at the country, regional, and global levels. Annual excess mortality fraction in each location attributable to wildfire-related O_3 was calculated with pooled effect estimates and used to obtain excess mortality fractions at country, regional, and global levels.

Findings Between 2000 and 2016, the highest maximum daily wildfire-related O_3 concentrations (≥30 μg/m³) were observed in locations in South America, central America, and southeastern Asia, and the country of South Africa. Across all locations, an increase of 1 μg/m³ in the mean daily concentration of wildfire-related O_3 during lag 0–2 days was associated with increases of 0·55% (95% CI 0·29 to 0·80) in daily all-cause mortality, 0·44% (–0·10 to 0·99) in daily cardiovascular mortality, and 0·82% (0·18 to 1·47) in daily respiratory mortality. The associations of daily mortality rates with wildfire-related O_3 exposure showed substantial geographical heterogeneity at the country and regional levels. Across all locations, estimated annual excess mortality fractions of 0·58% (95% CI 0·31 to 0·85; 31 606 deaths [95% CI 17 038 to 46 027]) for all-cause mortality, 0·41% (–0·10 to 0·91; 5249 [–1244 to 11 620]) for cardiovascular mortality, and 0·86% (0·18 to 1·51; 4657 [999 to 8206]) for respiratory mortality were attributable to short-term exposure to wildfire-related O_3.

Interpretation In this study, we observed an increase in all-cause and respiratory mortality associated with short-term wildfire-related O_3 exposure. Effective risk and smoke management strategies should be implemented to protect the public from the impacts of wildfires.

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Introduction

In the past few decades, wildfire occurrence has increased worldwide, with widened geographical extent and prolonged fire seasons.[1] In recent years, many locations globally have had unprecedented wildfires, including Australia, Brazil, northern California (USA), Canada, and the Mediterranean region of Europe, causing substantial economic loss and health impacts.[2–6] For example, the total economic cost due to wildfires in California during 2018 was estimated to be US$148·5 billion (95% CI 126·1–192·9), accounting for approximately 1·5% of annual gross domestic product (GDP) in the state.[7] Due to rapid climate change and population growth, the occurrence and related health burden of wildfires are expected to increase in the future.[8]

Both wildfires and planned or controlled fires are categorised as landscape fires, with wildfires comprising the predominant share (approximately 95%) of such occurrences.[1] Wildfire smoke is a chemically complex mixture of contaminants that are hazardous to human health, including particulate matter, ozone (O_3), and other toxic gaseous pollutants.[9] A growing body of scientific literature has examined the health impacts from wildfire-related air pollutants. However, the majority of previous

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Research in context

Evidence before this study

Unprecedented wildfires have been occurring in many locations globally. Air pollution from wildfires has become a considerable public health concern, given the various adverse effects on health. According to previous research, air pollution from wildfire sources is significantly linked to an increased risk of death. To ascertain the latest evidence from Jan 1, 2000, to June 25, 2023, we did a systematic search on Google Scholar, Web of Science, and PubMed, using the following terms: ("wildfire" or "bushfire" or "fire") and ("ozone" or "O_3") and ("mortal*" or "fatal*" or "death*" or "dead*"). The language of publications was restricted to English and Chinese. Our search yielded a small number of studies investigating the impact of wildfire-related O_3 exposure on mortality. These studies showed statistically significant links between O_3 from wildfires and increased hospital admissions or mortality. However, the current evidence largely originates from localised or regional studies, with a notable absence of comprehensive assessments across regions globally.

Added value of this study

To our knowledge, this study is the first to systematically evaluate the associations of short-term wildfire-related O_3 exposure with daily mortality across various regions and populations globally. We collected daily counts of all-cause, cardiovascular, and respiratory deaths from up to 749 locations in 43 countries or areas between 2000 and 2016. The daily concentration of O_3 from wildfire sources in study locations was estimated with a 3D GEOS-Chem model. We first examined the associations of short-term wildfire-related O_3 exposure with daily mortality at the location level, and then pooled results at the country, regional, and global levels via a random-effects meta-analysis. Across all locations, we found that short-term exposure to wildfire-related O_3 was associated with significant percentage increases in daily all-cause and respiratory mortality. No such significant increase was found for daily cardiovascular mortality.

Implications of all the available evidence

Based on multicountry assessment of exposure, this study presents epidemiological evidence showing an excess of deaths linked to short-term exposure to wildfire-related O_3. Effective risk management is required from policy makers and public health experts, involving actions to reduce exposure to wildfires.

studies have focused on fine particulate matter ($PM_{2.5}$), with little knowledge about the health effects of O_3 from wildfire sources.[10]

O_3 is a highly reactive and oxidative gaseous pollutant that shows various toxic effects. Both short-term and long-term O_3 exposure has been linked to a number of adverse health effects, including respiratory and cardiovascular mortality and morbidity.[11] Wildfire activity is an important source of tropospheric O_3. Wildfires can contribute to tropospheric O_3 by releasing a large amount of O_3 precursors, such as nitrogen oxides (NO_x) and volatile organic compounds, which form O_3 by reacting in the presence of sunlight.[12,13]

Existing studies on the adverse health effects of wildfire-related O_3 have either been challenged by accurate population exposure assessment or restricted to single location or country.[14–16] To the best of our knowledge, no previous study has assessed the health effects or health burden of wildfire-related O_3 comprehensively across different populations and geographical regions globally. To fill these research gaps, we systematically analysed the associations between short-term exposure to wildfire-related O_3 and daily all-cause, cardiovascular, and respiratory mortality across various regions and populations worldwide, based on data from the established Multi-City Multi-Country (MCC) Collaborative Research Network. The MCC Network comprises international research teams collaborating on a programme dedicated to generating epidemiological evidence on associations between weather and health.

Methods

Study design and data collection

We did a multicountry two-stage time series analysis to examine the associations between wildfire-related O_3 exposure and mortality. Time-series mortality data were collected from the database of the established MCC Network on Jan 15, 2021, at which time the database covered 750 locations (location refers to city or county) in 43 countries or areas. Based on data from the MCC Network, we have previously examined the excess mortality associated with urban air pollution and ambient temperature.[17,18] Daily counts of deaths from all causes, cardiovascular causes (International Classification of Diseases, 10th Revision [ICD-10] codes I00–I99), and respiratory causes (ICD-10 codes J00–J99) were collected from each location in overlapping periods from Jan 1, 2000, to Dec 31, 2016, with the extraction of cardiovascular and respiratory causes based on the underlying cause (the primary reason leading to death). Cardiovascular disease refers to a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism. In places where mortality data were unavailable for all causes, non-external cause mortality data (ICD-10 codes A0–R99) were used instead. The availability of all-cause mortality data (or non-external cause mortality data) was a prerequisite for inclusion, resulting in the inclusion of 749 locations in the 43 countries or areas. In addition, daily data on mean

temperature (°C) and relative humidity (%) and GDP per capita (US$) were collected for each location from the MCC Network database, as in our previous study.[18]

Procedures

We estimated population-weighted exposure to wildfire-related O_3. As wildfires constitute most landscape fires worldwide, and distinguishing between wildfires and non-wildfires presents challenges with current satellite detection methods,[1] the prevailing approach involves the use of landscape fire exposure as a surrogate metric for wildfire exposure, as exemplified by initiatives such as the *Lancet* Countdown reports.[19,20] The approach for estimation of daily wildfire-related O_3 concentration has been reported previously.[1] In brief, daily wildfire-related O_3 concentration across study locations was estimated with the 3D GEOS-Chem model (version 12.0.0). The model simulates tropospheric O_3 concentration based on the O_3–NO_x–hydrocarbon–aerosol chemical mechanisms for each global grid cell (2·0°×2·5° spatial resolution; about 220 km×280 km at the equator).[21,22] O_3 photolysis rates were computed based on the Fast-JXv7.0 scheme.[23] Dry deposition of O_3 was computed based on a multiple-resistance model.[24] The fire emission data were from the Global Fire Emissions Database (version 4.1 with small fires, GFED4.1s),[25] in which the amount of biomass burned has been calculated with use of satellite-based burn area and active fire information.[26] In this study, daily O_3 perturbations caused by fires were calculated as the difference between simulations with and without fire emissions for each day and global grid cell from 2000 to 2016.

As no ground-level measurements were available specifically for wildfire-related O_3 concentration, the GEOS-Chem-derived wildfire-related O_3 concentration was validated, adjusted, and downscaled via a three-step approach, which is shown in detail in appendix 1 (pp 2–4). In brief, daily concentration of ambient O_3 from all sources derived from the GEOS-Chem model was compared with ground monitoring data from 6851 stations in 58 countries and areas (sources of ground monitoring data reported previously[27]), and their difference was applied to calibrate wildfire-related O_3 concentration derived from the GEOS-Chem model. According to results of ten-fold cross-validation, the GEOS-Chem-derived O_3 concentration from all sources explained 80% of the variability of ground measurements globally (R^2=80%), and the continent-specific results ranged from 43% to 82% (appendix 1 p 4). With use of the validated and adjusted model, daily concentration of wildfire-related O_3 was estimated in each of the 749 locations at 0·25°×0·25° spatial resolution (approximately 28 km² at the equator). For locations with multiple grid cells, the mean value of all cells that included each location was used.

We sourced annual population counts spanning from Jan 1, 2000, to Dec 31, 2016, for every 1 km×1 km grid through the WorldPop project.[28] These population data were subsequently aggregated to a spatial resolution of 0·25°×0·25° to align with the daily wildfire-related O_3 data. To compute population-weighted mean daily wildfire-related O_3 exposure, we calculated the exposure by calculating the mean of the values of all 0·25°×0·25° grids that were fully or partially within the community boundaries. The community boundary information was obtained from OpenStreetMap (version 0.7.56). In this calculation, we weighted each grid's contribution based on its specific population count, multiplied by the proportion (0–100%) of the grid's area intersecting with the community.

Statistical analysis

We present the maximum, mean, and IQR of daily concentrations of population-weighted wildfire-related O_3 exposure for each study location during the study period, and the monthly mean of the maximum daily wildfire-related O_3 concentrations.

The associations of short-term exposure to O_3 from wildfire sources with daily mortality were first examined at each location with consideration of potential lag effects, and then the results were pooled at country, regional, and global levels. To examine the relationship of wildfire-related O_3 exposure with all-cause, cardiovascular, and respiratory mortality separately, a location-specific quasi-Poisson regression model was fitted to the time series, as follows:

$$\log(D_{ij}) = bs(O_{3ij}) + \text{ns}(\text{time}, 8/\text{year}) + \text{ns}(TEMP_{ij}, 3) + dow_j$$

where D_{ij} is count of deaths in location i on day j, and $bs(O_{3ij})$ is the concentration of O_3 from wildfire sources fitted with use of a constrained distributed lag model, which can flexibly examine both the exposure–response relationship and lag effect (where *bs* is a function in the model that is used to generate the basis matrices for the two dimensions of predictor and lag).[29] According to the quasi-likelihood version of the Akaike information criterion (qAIC) for various lag times (appendix 1 p 5), we considered the cumulative effects (mean concentration) of wildfire-related O_3 on the current day and previous 2 days of exposure (lag 0–2 days), which is also consistent with our previous work.[30] In the model, ns(time, 8/year) is a time variable fitted with a natural cubic spline (with 8 degrees of freedom per year) to account for the long-term time trends and seasonality;[17] ns($TEMP_{ij}$, 3) is mean temperature during lag 0–2 days fitted with a natural cubic spline (with 3 degrees of freedom).[31] The selections of degrees of freedom for natural cubic splines of time and lag times for temperature were also based on the qAIC information. A range of potential degrees of freedom and lag days were considered and the ones with the smallest qAIC value were selected (appendix 1 pp 5–6). dow is day of the week, numbered from 1 to 7 (1 being Monday). In the model, the association between variability of O_3 concentration and that of counts of

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For **WorldPop** see https://www.worldpop.org/

For **OpenStreetMap** see https://www.openstreetmap.org/

For the **GEOS-Chem model** see http://wiki.seas.harvard.edu/geos-chem/

For the **Global Fire Emissions Database** see https://www.globalfiredata.org/

See **Online** for appendix 1

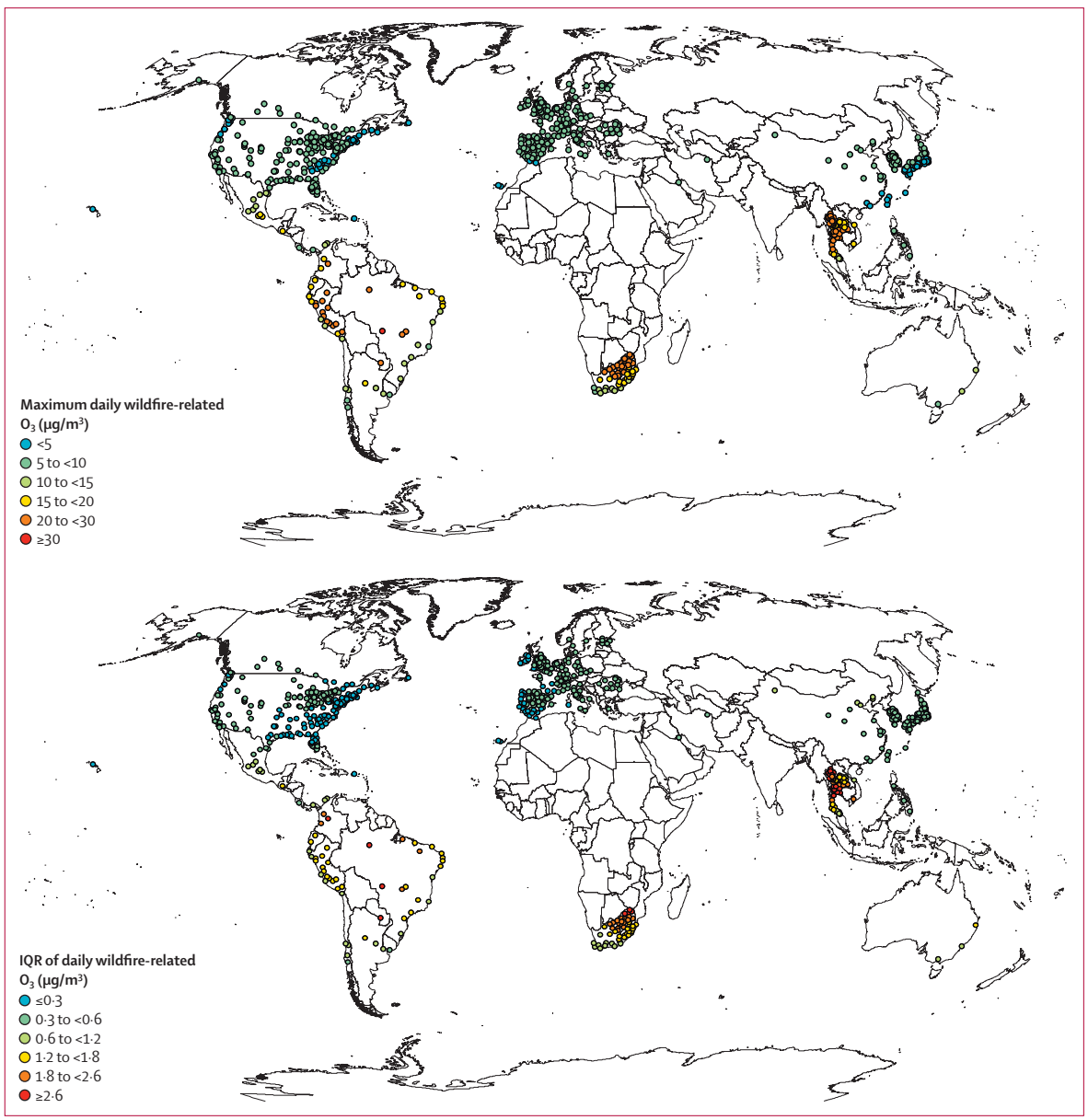

Figure 1: **Maximum values and IQRs of daily concentrations (μg/m³) of wildfire-related O_3 in 749 locations during 2000–16**
Some datapoints overlap with others; the values for all locations are provided in appendix 2. The equator (0°) and the tropics (Tropic of Cancer and Tropic of Capricorn, 23·6°) are shown. IQR is shown as the difference between quartile 1 and quartile 3. O_3=ozone.

deaths over time (per day) was examined for the whole study period.

The second-stage analysis pooled location-specific effect estimates at the country, regional, and global levels via a random-effect meta-analysis, which accounted for both within-location and between-location variabilities in effect estimates.[32] Considering that the number of locations was small in some countries or areas and the mortality data did not cover the whole study period in some countries, we used the best linear unbiased predictions at this stage and set location as the random-effect term.[33] This approach has been shown to provide estimates for countries accurately and robustly, especially for those with a small number of locations and short series of mortality data, as it uses information across units at the same hierarchical level.[33] To examine the variations of the O_3–mortality association in different geographical regions and economic zones, location-specific results were also pooled for UN regions (based on the 22 geographical subregions of the UN geoscheme; some subregions had no locations and some subregions were combined due to small numbers of locations, resulting in a total of 11 regions; appendix 1 pp 7–8) and four economic zones according to location-specific GDP

For the **UN geoscheme** see https://unstats.un.org/unsd/methodology/m49

per capita, using the same regions and GDP groups as in our previous study.[30]

In this study, the O_3–mortality associations were expressed as percentage change in daily mortality (%) with 95% CIs per 1 μg/m³ increase in the concentration of O_3 from wildfire sources. Annual excess mortality fraction in each location attributable to acute effects of wildfire-related O_3 was calculated with use of the pooled effect estimates (% and 95% CI). Annual excess deaths for all-cause, cardiovascular, and respiratory causes were first calculated for each location separately, considering both the current-day and lag effects of wildfire-related O_3. Then, the sum of reported deaths in all locations was divided by the sum of excess deaths to derive the excess mortality fraction at the country, regional, and global levels. Details on the calculation of excess mortality fraction are shown in appendix 1 (p 4).

The associations between daily concentrations of non-wildfire-related O_3 and daily mortality were also examined, and excess mortality fractions attributable to non-wildfire O_3 exposure were calculated, with the same methods as those used for wildfire-related O_3. The daily concentration of O_3 from other sources was estimated as the difference between GEOS-Chem-derived O_3 from all sources and that from wildfires.

A series of sensitivity analyses was done to examine the robustness of results. In addition to controlling for time, temperature, and day of the week, we further controlled for wildfire-related $PM_{2·5}$, O_3 from other sources, and $PM_{2·5}$ from all sources (mean daily concentrations for lag 0–2 days). The estimation of GEOS-Chem-derived daily $PM_{2·5}$ from wildfire sources and all sources has been reported previously.[30] In addition, as data on relative ambient humidity were not available for 235 of 749 locations, a sensitivity analysis was done by further controlling for relative humidity in locations with available data. In another analysis, the degrees of freedom for temperature and relative humidity were changed to 4, 5, and 6 to test the robustness of the results. A two-sample test was used to examine the differences in effect estimates of the main models and these alternative models.[34]

We did all statistical analyses using R (version 4.2.2) and the dlnm and mixmeta packages. We interpreted the statistical significance of effect estimates of wildfire-related O_3 based on 95% CIs, and the difference between two effect estimates in the sensitivity analyses based on p values.

Role of the funding source

There was no funding source for this study.

Results

A summary of study locations, study periods, and mortality data is presented in appendix 1 (pp 7–8). Among the 749 locations in 43 countries or areas across six continents (excluding Antarctica) with all-cause mortality data (160 [21·4%] of 749 with non-external cause mortality data only), 629 (84·0%) locations had available cardiovascular mortality data, and 647 (86·4%) locations had available respiratory mortality data. In

	All-cause mortality	Cardiovascular mortality	Respiratory mortality
Argentina	−0·23% (−1·44 to 0·99)	NA	NA
Australia	<0·01% (−5·87 to 6·24)	NA	NA
Brazil	0·06% (−0·22 to 0·34)	NA	NA
Canada	1·56% (0·50 to 2·63)	0·09% (−0·58 to 0·76)	0·50% (−2·16 to 3·23)
Chile	1·82% (−2·84 to 6·71)	NA	NA
China	−0·68% (−2·13 to 0·79)	0·72% (0·47 to 0·97)	0·48% (−0·18 to 1·15)
Colombia	0·64% (−0·61 to 1·92)	0·45% (−0·48 to 1·39)	−0·97% (−2·34 to 0·41)
Costa Rica	1·13% (0·46 to 1·80)*	−0·04% (−23·40 to 30·46)*	2·19% (−12·66 to 19·57)*
Czech Republic	0·76% (−0·62 to 2·15)	0·47% (−2·64 to 3·68)	1·93% (−3·27 to 7·41)
Ecuador	0·77% (0·15 to 1·40)	1·71% (0·48 to 2·95)	−0·39% (−1·15 to 0·37)
Estonia	0·76% (−2·82 to 4·47)	NA	NA
Finland	3·23% (2·67 to 3·79)*	4·96% (−9·43 to 21·63)*	6·40% (4·49 to 8·35)*
France	0·39% (−1·18 to 1·99)	NA	−3·79% (−8·34 to 0·98)
Germany	−0·21% (−1·00 to 0·59)	NA	NA
Greece	0·98% (0·40 to 1·55)*	1·54% (−0·79 to 3·93)*	0·20% (−4·83 to 5·50)*
Guatemala	−0·04% (−1·21 to 1·14)*	NA	NA
Iran	1·75% (−11·20 to 16·59)*	3·34% (0·79 to 5·95)*	−4·96% (−6·08 to −3·84)*
Ireland	1·18% (−0·51 to 2·90)	3·12% (−0·77 to 7·17)	2·97% (−3·92 to 10·35)
Italy	−0·89% (−3·03 to 1·29)	NA	NA
Japan	0·41% (0·08 to 0·73)	1·11% (0·46 to 1·76)	0·72% (0·13 to 1·32)
Kuwait	−5·04% (−9·71 to −0·13)*	−5·82% (−15·52 to 4·99)*	−0·85% (−24·39 to 30·01)*
Mexico	−0·09% (−0·69 to 0·51)	−0·54% (−2·04 to 0·98)	1·15% (−2·79 to 5·25)
Moldova	7·23% (−0·64 to 15·74)	NA	NA
Netherlands	−0·90% (−2·94 to 1·18)	NA	NA
Norway	4·78% (1·49 to 8·18)*	4·38% (−7·02 to 17·19)*	1·43% (−14·08 to 19·73)*
Panama	−1·81% (−7·43 to 4·15)*	0·29% (−9·48 to 11·11)*	−9·87% (−19·10 to 0·42)*
Paraguay	−0·09% (−3·36 to 3·29)*	−0·31% (−6·16 to 5·90)*	0·81% (−9·99 to 12·91)*
Peru	−0·09% (−0·38 to 0·19)	NA	NA
Philippines	0·22% (−1·05 to 1·51)	−0·27% (−1·34 to 0·82)	−3·13% (−4·77 to −1·46)
Portugal	−0·87% (−1·58 to −0·15)	−1·67% (−6·69 to 3·61)	3·53% (−0·73 to 7·97)
Puerto Rico	0·93% (0·34 to 1·52)*	NA	NA
Romania	1·27% (0·15 to 2·40)	NA	NA
South Africa	0·12% (−0·04 to 0·27)	−0·06% (−0·44 to 0·34)	−0·30% (−0·72 to 0·13)
South Korea	0·43% (−0·31 to 1·18)	1·32% (−0·30 to 2·97)	0·66% (−0·93 to 2·29)
Spain	−0·13% (−1·11 to 0·85)	−1·39% (−3·01 to 0·26)	−2·04% (−4·58 to 0·57)
Sweden	−0·10% (−0·71 to 0·52)	−1·32% (−3·53 to 0·94)	4·59% (0·38 to 8·96)
Switzerland	−1·26% (−3·41 to 0·94)	−0·23% (−6·76 to 6·77)	−3·85% (−13·48 to 6·85)
Taiwan	1·02% (−3·15 to 5·37)	0·90% (−5·24 to 7·45)	1·99% (−6·59 to 11·37)
Thailand	0·57% (0·36 to 0·77)	0·45% (−0·01 to 0·91)	1·05% (0·54 to 1·57)
UK	1·30% (0·59 to 2·02)	0·34% (−0·95 to 1·64)	1·57% (−0·25 to 3·42)
Uruguay	0·38% (−2·97 to 3·86)*	NA	NA
USA	0·82% (0·14 to 1·51)	0·70% (−0·54 to 1·96)	1·49% (0·14 to 2·85)
Viet Nam	0·36% (−0·58 to 1·32)	0·40% (−4·14 to 5·16)	1·72% (−0·12 to 3·60)

Numbers in parentheses are 95% CIs. The main models were controlled for a time variable, ambient temperature, and day of the week at the first stage (location level), and included location as the random-effect term at the second stage (country or area level). For countries or areas with only one location, location-specific effect estimates were used to present the country or area-level results. NA=not available. *Location-specific estimates.

Table 1: **Percentage change in mortality per 1 μg/m³ increase in mean daily concentration of wildfire-related ozone during lag 0–2 days in 43 countries or areas**

	All-cause mortality	Cardiovascular mortality	Respiratory mortality
Region			
Australia	<0·01% (–5·87 to 6·24)	NA	NA
Central America	0·05% (–0·47 to 0·58)	–0·53% (–1·98 to 0·95)	0·25% (–3·71 to 4·38)
Central Europe	0·77% (–0·28 to 1·82)	0·11% (–4·44 to 4·89)	–3·09% (–7·07 to 1·07)
Eastern Asia	0·20% (–0·22 to 0·64)	1·15% (0·42 to 1·89)	0·77% (0·03 to 1·51)
Western Asia	–4·25% (–8·67 to 0·39)	0·21% (–8·01 to 9·17)	–4·96% (–6·07 to –3·83)
Northern America	0·89% (0·27 to 1·52)	0·70% (–0·45 to 1·85)	1·43% (0·19 to 2·69)
Northern Europe	1·22% (0·60 to 1·84)	0·51% (–0·68 to 1·71)	1·85% (0·19 to 3·54)
Southern Africa	0·12% (–0·04 to 0·27)	–0·06% (–0·44 to 0·34)	–0·30% (–0·72 to 0·13)
South America	0·21% (–0·29 to 0·73)	0·87% (0·05 to 1·68)	–0·52% (–1·18 to 0·15)
Southern Europe	–0·37% (–1·21 to 0·48)	–1·32% (–2·86 to 0·24)	–1·66% (–4·01 to 0·74)
Southeastern Asia	0·53% (0·33 to 0·73)	0·34% (–0·10 to 0·78)	0·74% (0·16 to 1·32)
Location-specific GDP per capita, US$			
<10 000	0·37% (0·06 to 0·68)	0·35% (0·09 to 0·60)	0·19% (–0·34 to 0·73)
10 000–19 999	0·19% (–0·38 to 0·76)	–0·26% (–1·37 to 0·86)	–0·76% (–2·33 to 0·84)
20 000–29 999	1·38% (0·55 to 2·22)	0·76% (–0·40 to 1·93)	1·25% (–0·94 to 3·49)
≥30 000	0·66% (0·24 to 1·08)	0·66% (–0·20 to 1·54)	1·03% (0·06 to 2·01)

Pooled estimates are presented, with 95% CIs in parentheses. The main models were adjusted for a time variable, ambient temperature, and day of the week at the first stage (location level), and included location as the random-effect term at the second stage (regional level). GDP=gross domestic product. NA=not available.

Table 2: **Percentage change in mortality per 1 μg/m³ increase in mean daily concentration of wildfire-related ozone during lag 0–2 days for different regions and GDP levels**

total, 65·62 million deaths from all causes, 15·11 million deaths from cardiovascular causes, and 6·84 million deaths from respiratory causes were recorded in these locations between Jan 1, 2000, and Dec 31, 2016, over a median study period of 13 years (IQR 7–16). The maximum daily wildfire-related O_3 concentrations in all locations during 2000–16 are shown in figure 1 and appendix 2. Regions with locations with the highest maximum daily wildfire-related O_3 (≥30 μg/m³) were South America, central America, and southeastern Asia; the top three locations with the highest concentrations were Cuiaba (Brazil), Ucayali (Peru), and Guatemala. Locations in Thailand, such as Chanthaburi, and South Africa, such as Vhembe, also showed high maximum daily wildfire-related O_3 (≥30 μg/m³). The lowest concentrations (<5 μg/m³) were observed in locations northern America, eastern Asia, and central and southern Europe; the top three locations with the lowest concentrations were Kuwait, Phoenix (USA), and Las Vegas (USA; figure 1, appendix 2). Locations situated close to the equator in the tropical region and within subtropical regions, such as those in South America, southeastern Asia, and South Africa, showed the highest maximum daily wildfire-related O_3 concentrations. Conversely, areas at high latitudes, including eastern Asia, northern America, and central, southern, and northern Europe, consistently reported the lowest concentrations. Among the 749 locations, 734 (98·0%) had an IQR of daily wildfire-related O_3 concentration of less than 3 μg/m³ (figure 1). The peak months of daily wildfire-related O_3 were January to May for locations in the northern hemisphere, and July to October for those in the southern hemisphere (appendix 1 p 9). Mean concentrations of wildfire-related O_3 in all locations are shown in appendix 1 (p 14) and appendix 2.

See Online for appendix 2

Across all locations, an increase of 1 μg/m³ in the mean daily concentration of wildfire-related O_3 during lag 0–2 days was associated with increases of 0·55% (95% CI 0·29 to 0·80) in daily all-cause mortality, 0·44% (–0·10 to 0·99) in daily cardiovascular mortality, and 0·82% (0·18 to 1·47) in daily respiratory mortality. For O_3 from non-wildfire sources, the associated increases in mortality were 0·08% (0·07 to 0·10), 0·07% (0·04 to 0·10), and 0·09% (0·05 to 0·13) for the three causes, respectively. Estimates of the percentage change in daily mortality rates associated with wildfire-related O_3 showed substantial geographical heterogeneity at the country or area level. The country-specific estimates ranged from –5·04% (–9·71 to –0·13; for Kuwait) to 7·23% (–0·64 to 15·74; for Moldova) for all-cause mortality, from –5·82% (–15·52 to 4·99; for Kuwait) to 4·96% (–9·43 to 21·63; for Finland) for cardiovascular mortality, and from –9·87% (–19·10 to 0·42; for Panama) to 6·40% (4·49 to 8·35; for Finland) for respiratory mortality; table 1). For pooled results by regions, the highest estimates of percentage change in mortality were observed in northern Europe, eastern Asia, southeastern Asia, and northern America, and the lowest in western Asia and southern Europe (table 2). In addition, the highest estimates were in locations with a GDP per capita of $20 000 or higher, whereas the lowest estimates were in locations with a GDP per capita of $10 000–19 999 (table 2).

Based on the pooled associations of all locations, an estimated 31 606 (95% CI 17 038 to 46 027) excess all-cause deaths, 5249 (–1244 to 11 620) cardiovascular deaths, and 4657 (999 to 8206) respiratory deaths annually were attributable to short-term exposure to wildfire-related O_3 for lag 0–2 days, corresponding to annual excess mortality fractions of 0·58% (95% CI 0·31 to 0·85), 0·41% (–0·10 to 0·91), and 0·86% (0·18 to 1·51), respectively (figure 2). For O_3 from non-wildfire sources, the excess mortality fractions were 2·96% (2·40 to 3·52), 2·35% (1·33 to 3·36), and 3·10% (1·66 to 4·52) for the three causes, respectively. The country or area-specific results for short-term wildfire-related O_3 exposure showed substantial variations, with annual excess mortality fractions ranging from 0·27% (0·15 to 0·39; Taiwan) to 2·23% (1·21 to 3·32; Ecuador) for all-cause mortality, from 0·24% (–0·06 to 0·53; Kuwait) to 0·92% (–0·22 to 2·02; China) for cardiovascular mortality, and from 0·44% (0·09 to 0·78; Canada) to 2·14% (0·46 to 3·72; China) for respiratory mortality (figure 2). The highest excess mortality fractions were observed in southern Africa (ie, South Africa), South America, and locations with the lowest GDP levels (<$10 000 per capita), whereas the lowest

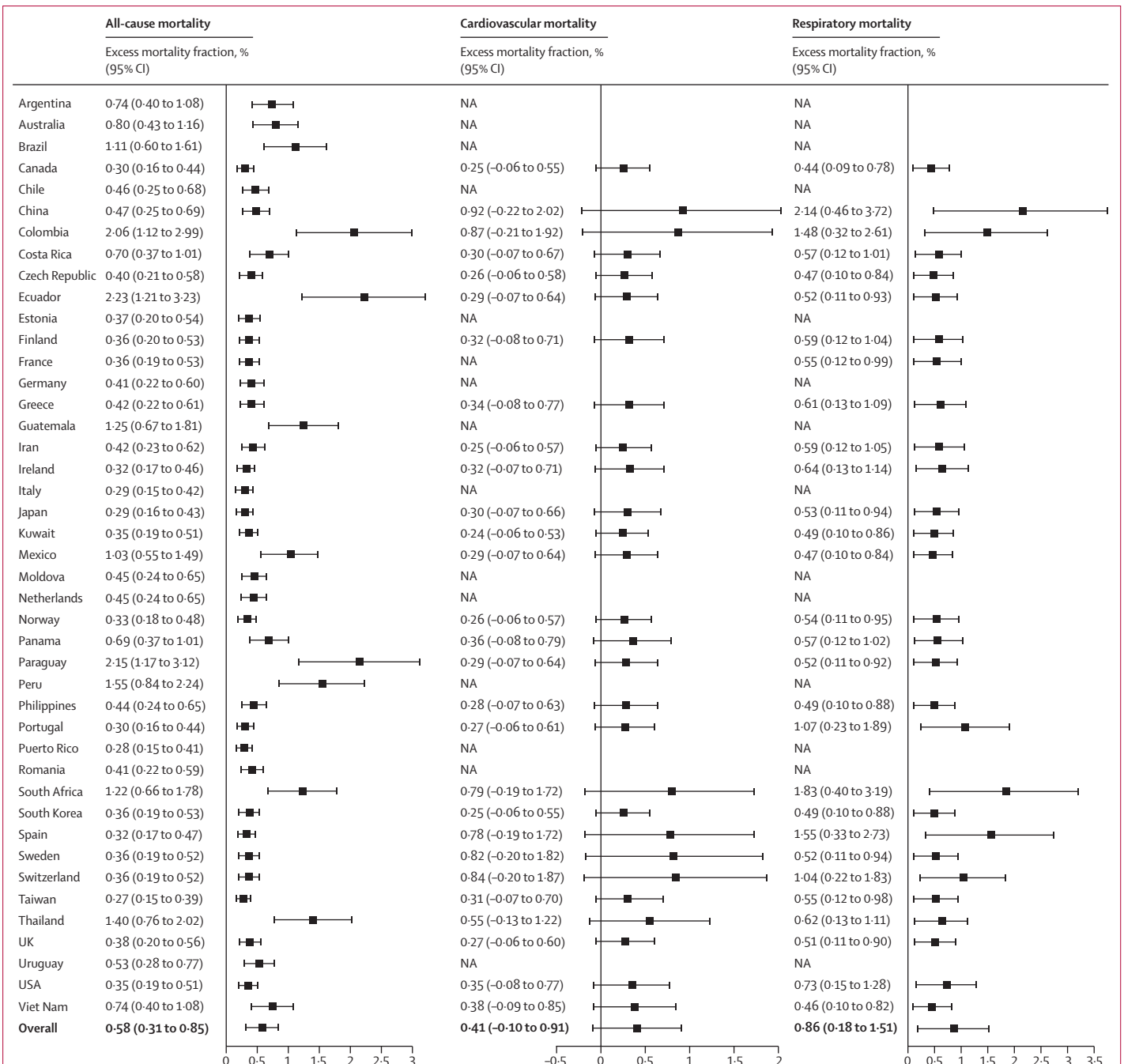

Figure 2: **Annual excess mortality fractions due to exposure to wildfire-related O_3 for lag 0–2 days in 43 countries or areas**
Annual excess mortality fraction in each location was calculated using the pooled effect estimates and mean daily concentration of wildfire-related O_3 for lag 0–2 days. The sum of reported deaths was divided by the sum of excess deaths across all locations to derive the excess mortality fraction at the global level. O_3=ozone. NA=not available.

excess mortality fractions were observed in central and northern Europe, eastern and western Asia, northern America, and locations with high GDP levels (≥$20 000 GDP per capita; appendix 1 p 9). The corresponding numbers of excess annual deaths in different countries and regions and by GDP levels are shown in appendix 1 (pp 10–12).

Sensitivity analyses indicated that, in addition to controlling for time, temperature, and day of the week, controlling for wildfire-related $PM_{2·5}$, ambient O_3 from other sources, and $PM_{2·5}$ from all sources did not significantly change the pooled estimates (figure 3), with the p values all greater than 0·1 for differences with the main model estimates (appendix 1 p 13). The pooled

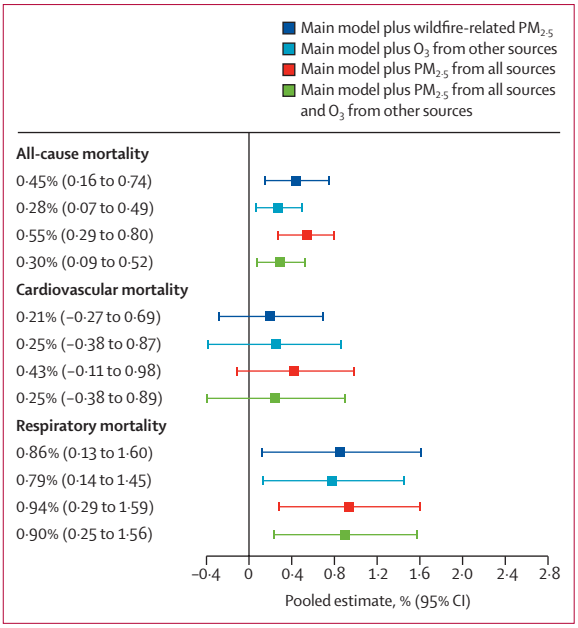

Figure 3: **Pooled percentage change in mortality per 1 μg/m³ increase in wildfire-related O_3 during lag 0–2 days by controlling wildfire-related $PM_{2·5}$, O_3 from other sources, and $PM_{2·5}$ from all sources**
The main models adjusted for a time variable, ambient temperature, and day of the week at the first stage and included location as the random-effect term at the second stage. O_3=ozone.

effect estimates were robust to different degrees of freedom (3 to 6) for meteorological variables (temperature and relative humidity; appendix 1 p 13). Controlling for both ambient temperature and relative humidity did not significantly change the pooled effect estimates (appendix 1 p 15).

Discussion

Our study findings underscore the substantial impact of short-term exposure to O_3 from wildfire sources, which we found to be associated with increased all-cause and respiratory mortality. However, the association with cardiovascular mortality did not reach statistical significance. The estimated mortality burden attributable to wildfire-related O_3 exposure showed notable geographical disparities, which were particularly pronounced in South America and the country of South Africa, where wildfires have been frequent in recent years.[1] Our study, encompassing a large dataset spanning many geographical regions and diverse sociodemographic conditions, provides strong evidence of a link between excess mortality and O_3 pollution from wildfires.

Currently, evidence on the adverse health effects of wildfire-related O_3 is scarce, but some local studies have indicated its adverse health impacts. One study reported significantly increased risk of emergency hospital visits for asthma (relative risk per 10 μg/m³ increase in O_3 concentration: 1·050 [95% CI 1·022–1·078)] during active wildfire periods in northern California in 2008.[14] One study in Victoria, Australia, during the 2002–03 bushfire season showed a significant association between O_3 pollution and increased hospital admissions (relative risk per IQR increase in O_3 concentration: 1·027 [95% CI 1·001–1·053]).[35] However, another study that examined the health impacts of long-distance O_3 transport in rural and remote areas of Portugal during fire seasons reported null results for the associations of O_3 peaks with hospital admissions for respiratory illnesses.[36]

The oxidative stress caused by inhalation of O_3 is the most widely studied pathway on the health effects of O_3, which subsequently leads to respiratory cell injury and changed cell signalling.[11] Other pathways related to the respiratory effects of O_3 include the stimulation of neural reflexes, changes in epithelial barrier function, and immune disruption,[37,38] among others. Currently, evidence for the cardiovascular effects of O_3 is insufficient and inconclusive. Experimental and epidemiological studies indicated that initiation of inflammation, increased vascular oxidative stress, altered heart rate, and decreased heart rate variability were all linked to exposure to O_3.[39,40] However, epidemiological studies in the UK and USA reported no significant link between short-term O_3 exposure and cardiovascular hospital admission.[41,42] A controlled human exposure research study also found no significant correlation between short-term O_3 exposure and changes in stroke volume or left ventricular ejection time.[43] In our study, the absence of a significant association between exposure to O_3 from wildfire sources and cardiovascular mortality might also be due to uncertainties in the pooled estimates, potentially caused by the cardiovascular mortality dataset including the least locations (appendix 1 pp 7–8). The pooled results across four economic levels highlight the potential impact of economic prosperity on wildfire-related health risks. Economically disadvantaged regions, such as southern Africa (ie, South Africa) and South America, showed the highest excess mortality fractions, whereas regions with higher GDP levels, such as central and northern Europe and northern America, showed the lowest excess mortality fractions. In addition to economic prosperity, this trend is influenced by regional wildfire frequency.

The health burden of wildfire-related O_3 might be largely underestimated. Existing studies have primarily focused on short-term health effects, and the long-term health effects and underlying biological mechanisms remain largely unknown.[44] Furthermore, evidence on the health effects of wildfire smoke is insufficient, with research limited to all-cause mortality effects and cardiovascular and respiratory effects. To address these critical evidence gaps, future research efforts should prioritise investigating the intricate relationship between wildfire smoke and various health outcomes. This prioritisation is particularly vital in vulnerable populations, including children, older people, patients with comorbidities, outdoor workers, and racial or ethnic minority subpopulations. Additionally, a comprehensive understanding of the interaction effects between wildfire smoke and other environmental factors,

such as high ambient temperature, is paramount.[10] Such insights are likely to be crucial in informing the development of effective public health interventions aimed at mitigating the adverse health effects associated with wildfire-related O_3 exposure.

Wildfire smoke poses acute respiratory risks due to its high concentration of particulate matter and volatile organic compounds, whereas O_3 contributes to cardiovascular events and exacerbates respiratory illnesses, often synergistically amplifying health effects when combined with other pollutants.[45] Meanwhile, the psychological stress induced by wildfires can exacerbate mental health issues, potentially affecting a wide population range.[46] Understanding all of these impacts is crucial for developing targeted public health interventions aimed at mitigating the diverse health risks associated with wildfires. In particular, the adverse effects of wildfire-related O_3 to public health should be of high concern. Although wildfires only occur in specific locations worldwide, O_3 generated during wildfires can extend as far as 1000 km, and most personal actions (eg, wearing a face mask) cannot help to reduce individual exposure.[10] Furthermore, amplified health effects of wildfire particulate matter has been observed with exposure to both O_3 and high temperature during fire seasons.[47] To minimise O_3 exposure during wildfires, comprehensive risk management strategies are essential, and should use exposure estimates and health data to guide interventions. Coordinated efforts need to be made alongside fuel and smoke management initiatives.[48] Government agencies and communities should be equipped with wildfire forecasting tools and tailored prevention strategies to mitigate O_3-related health risks effectively. Integrating O_3 reduction measures with existing strategies to limit smoke exposure ensures a holistic approach to safeguarding public health during wildfire events.

To our knowledge, this study is the first to systematically evaluate the associations between wildfire-related O_3 exposure and daily mortality across various locations and populations globally. The spatial and temporal characteristics of wildfire smoke can be accurately captured by exposure assessment with the GEOS-Chem model.[49] Furthermore, many studies have assessed the short-term health effects of air pollution via a two-stage analytic approach.[17,50] In the first stage, both the conventional exposure–response association and the additional lag response association are defined in the distributed lag model.[17] In the second stage, random-effects meta-analysis evaluates variability in effect estimates both within and between cities.[51] Via meta-analysis, we obtained more robust and plausible results than from individual studies conducted in one city. In addition, this study considered cardiovascular and respiratory effects of wildfire-related O_3, which can facilitate the calculation of overall attributable burden.

Some limitations with our study need to be noted. Although this study has considered various populations and regions, the pooled mortality risk cannot be interpreted as representative at the global level, as the study locations are not evenly distributed in each continent (eg, many more locations in the Americas than Africa) and most of them were from urban areas.[17] With use of the GEOS-Chem model and various spatiotemporal predictors, we were able to estimate the concentration of wildfire-related O_3 in each location, but there were predictive errors (R^2=80% for GEOS-Chem-derived daily O_3 concentrations from all sources). Although this value indicates high predictive ability of the GEOS-Chem model in capturing wildfire-related O_3, there remains capacity for improvement in future iterations. Enhancements in predictive accuracy can be achieved by collecting more individual-level data (eg, age and gender) and location-specific data (eg, vegetation type and topographical features) on predictors, thereby refining exposure assessment methods. As a further limitation, this study only used time series mortality data. With individual-level information on participants (eg, sex, age, and behavioural factors), researchers could pinpoint vulnerable populations more accurately than in the current analysis, enabling targeted interventions and resource allocation to mitigate the health effects of wildfires effectively.

Based on multicountry exposure assessment, our study highlights the excess of all-cause and respiratory deaths linked to short-term O_3 exposure from wildfires. Urgent action is required from policy makers and public health experts to implement effective risk management strategies amid the escalating wildfire frequency and intensity driven by climate change. These strategies should include establishing early warning systems and robust disease prevention approaches. Our findings emphasise the need to integrate wildfire-related O_3 exposure into ongoing fire smoke research and smoke prevention activities, to guide the development of comprehensive strategies for mitigating the adverse health effects of wildfires.

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Contributors

YG and SL conceived and designed the study. GC did statistical analyses and wrote the manuscript. XY helped with the exposure assessment of wildfire-related ozone. Other coauthors collected the data for each country and reviewed the manuscript. YG, SL and GC have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data used in this study were collected by collaborators within the MCC Network under a data sharing agreement (http://mccstudy.lshtm.ac.uk/). The data cannot be made available publicly. Researchers can contact the corresponding authors (Yuming Guo, yuming.guo@monash.edu; and Shanshan Li, shanshan.li@monash.edu) for information on accessing the data used for this study and for the R code.

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