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Vicedo-Cabrera, AM; Sera, F; Liu, C; Armstrong, B; Milojevic, A; Guo, Y; Tong, S; Lavigne, E; Kyselý, J; Urban, A; +32 more... Orru, H; Indermitte, E; Pascal, M; Huber, V; Schneider, A; Katsouyanni, K; Samoli, E; Stafoggia, M; Scortichini, M; Hashizume, M; Honda, Y; Fook Sheng Ng, C; Hurtado-Diaz, M; Cruz, J; Silva, S; Madureira, J; Scovronick, N; Garland, RM; Kim, H; Tobias, A; Íñiguez, C; Forsberg, B; Åström, C; Ragettli, MS; Röösli, M; Guo, Y-L; Chen, B-Y; Zanobetti, A; Schwartz, j; Bell, ML; Haidong, K; Gasparrini, A; (2019) Short-term association between ozone and mortality: a global study in 406 locations in 20 countries. BMJ. ISSN 1468-5833 https://researchonline.lshtm.ac.uk/id/eprint/4655527 (In Press)

Title: Short-term association between ozone and mortality: a global two-stage time-series study in 406 locations in 20 countries.

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Summary boxes

What is already known on this topic

- Evidence on the short-term association between ground-level ozone and mortality has been obtained in a large number of studies. These investigations have been mostly performed in a relatively small number of locations, in limited geographical areas, and using various designs and modelling approaches.
- While most of the studies found positive associations, results are heterogeneous, and a critical comparison across different countries and regions is made difficult by the limited statistical power and the differences across studies mentioned above.
- Estimates of the association are usually reported as relative risk, a summary measure that does not quantify the actual health impact and makes it difficult to evaluate comparative health benefits of different regulatory limits.

What this study adds

- This large multi-country study found increased mortality risks associated to ozone exposure across locations and countries, with an average 0.18% per 10 μg/m^3, reinforcing the evidence of a potential causal association.
- The application of state-of-the-art study designs and analytical methods allows a consistent comparison across regions and populations, with evidence of heterogeneous associations.
- Risk estimates were translated in measures of excess mortality, and it was found that more than 6 thousand deaths per year, corresponding to 0.20% of the total mortality, would have been avoided in the 406 cities studied if countries had implemented stricter air quality standards compliant with WHO guideline. Substantial annual excess deaths above this threshold were found in main cities such as Valley of Mexico with 694 per year, 211 in Los Angeles, 170 in Tokyo or 128 in Toronto.
- Moreover, smaller but still substantial mortality impacts were found below WHO guideline, supporting the WHO initiative of encouraging countries to revisit current air quality guidelines and enforcing stronger emission restrictions to meet these recommendations.

Abstract

Objective: To assess short-term mortality risks and excess mortality associated to exposure to ozone in a multi-city multi-country setting.

Design: Two-stage time-series analysis with quasi-Poisson time series regression and multilevel meta-analysis.

Setting and population: daily time series data from 406 cities within 20 countries in overlapping periods between 1985 and 2015, collected in the Multi-City Multi-Country (MCC) Collaborative Research Network.

Main Outcome(s) and Measure(s): Daily total mortality (all or non-external causes only).

Results: On average, a 10-μg/m^3 increase in ozone during the current and previous day was associated with a relative risk of mortality of 1.0018 (95% CI, 1.0012 to 1.0024). We found some heterogeneity across countries, ranging from estimates above 1.0020 in the United Kingdom, South Africa, Estonia and Canada to associations below 1.0008 in Mexico and Spain. Exposure to ozone above maximum background levels (70 μg/m^3) accounted for short-term excess mortality of 0.26% (95% CI, 0.24 to 0.28) on average across the 406 cities. The impact remained substantial (0.20% (95% CI, 0.18 to 0.22)) when restricting to days above the WHO guideline (100 μg/m^3), corresponding to a total of 6,262 deaths per year (95% CI, 1,413 to 11,065). Above more lenient thresholds, excess mortality amounted to 0.14%, 0.09% and 0.05% corresponding to the European, American and Chinese air quality standards (AQSs), respectively.

Conclusions: This multi-country study represents the largest assessment to date on short-term ozone-related mortality. For the first time, this study reports health impacts quantified as excess mortality across countries and various exposure ranges. In particular, results suggest that a substantial reduction in mortality would be potentially achieved under stricter AQS. These findings have relevance for the implementation of efficient clean air interventions and mitigation strategies designed within national and international climate policies.

Print abstract

Study question: What is the short-term mortality risk associated with exposure to ozone and the corresponding excess mortality at exposure levels above current air quality standards?

Methods: A two-stage time-series analysis with quasi-Poisson time series regression and multilevel meta-analysis was performed using daily data from 406 cities within 20 countries in overlapping periods between 1985 and 2015, collected by the Multi-City Multi-Country Collaborative Research Network.

Study answer and limitations: overall, mortality risk increased by 0.18% per 10-μg/m^3 increase in ambient ozone, which translated into 0.26% excess mortality in days with exposure to ozone above maximum background levels (70 μg/m^3). The impact remained substantial (0.20% (95% CI, 0.18 to 0.22)) when restricting to days above the WHO guideline (100 μg/m^3), corresponding to a total of 6,262 deaths per year (95% CI, 1,413 to 11,065) in the selected cities. Findings cannot be considered truly global estimates, as some geographical areas or countries are under-represented. There could be some systematic differences in the collected data between countries. This study did not aim at assessing cause-specific mortality association or sources of heterogeneity across estimates. Excess mortality estimates refer to transient impact measures and not to the mortality burden or person-years of life lost attributed to long-term ozone exposure.

What this study adds: our study suggests that ozone-related health impacts can be largely preventable by attaining effective AQSs in line with the WHO guideline.

Funding, competing interests and data sharing: This work was primarily supported by the Medical Research Council-UK (Grants ID: MR/M022625/1 and MR/R013349/1) and by the Natural Environment Research Council UK (Grant ID: NE/R009384/1). Other individual grants also supported this work. Ethical approval was not required. No additional data is available.

*Include Figure 3

Introduction

Ground-level ozone is a highly reactive, oxidative gas commonly found in urban and suburban environments mostly derived from anthropogenic emissions. The exposure to this pollutant has been associated to adverse health outcomes, including increased short-term mortality and morbidity, in numerous epidemiological studies and reported in several reviews from important health and environmental agencies worldwide.[1–4] Evidence on health impacts related to ozone exposure has important implications in climate change research, as ozone levels are predicted to increase as global warming progresses.[5]

Short-term ozone-mortality associations have been widely assessed in several multi-location time series studies in Europe, US, Canada, Latin-America and Asia.[2,6–8] The general methodological framework consists of pooling location-specific estimated risks, accounting for potential heterogeneity in the magnitude of the effect and uncertainty. In addition, the increased statistical power of multi-location analyses allows for the exploration of potentially complex features of the association (*i.e.*, non-linearity, delayed effects and harvesting, or differential risks by season).[9–11] However, previous multi-location studies included a small number of cities/countries, have generally a limited geographical scope, and applied heterogeneous analytical approaches and modelling choices, making it difficult to draw a consistent and comprehensive picture across different regions of the world.

While ozone-mortality associations have been widely assessed, results are rarely reported in terms of health impacts, for instance as excess deaths.[12] Available figures are mostly derived from long-term exposure metrics and risks estimated in specific subgroups, which are usually extrapolated to the general population.[13,14] Quantification of air-pollution-health burdens can be extremely useful for the design of efficient public health interventions, including the definition, assessment, and review of air quality standards (AQS). Current AQS greatly vary between countries, and only a few of them meet the stricter World Health Organization (WHO) recommendations.[15] The comparison between health impacts above different AQSs can provide valuable insights into potential public health benefits achieved by strengthening current clean air policies. Although a few studies attempted to address this issue, a widespread evaluation across several countries, which would help identifying more affected areas with a greater need for intervention, is still lacking.[16,17]

We aim to address these gaps in knowledge through a comprehensive assessment of mortality associated with short-term exposure to ozone, using the largest epidemiological dataset ever collected for this purpose, including data from 406 cities within 20 countries from multiple geographical regions. We first assessed ozone-mortality associations using advanced statistical techniques for multi-location time-series analysis. Next, we explored potential complexities of the association, namely non-linearity, mortality displacement and seasonality. Finally, we quantified the ozone-associated mortality impacts for specific concentrations ranges consistent with the current AQS levels, and then we compared estimates across countries.

Methods

Data collection

Data for 434 locations across the 20 countries were initially extracted from the database of the Multi-city Multi-country (MCC) Collaborative Research Network (http://mccstudy.lshtm.ac.uk/). These include location-specific daily mortality counts and environmental measures (weather and air pollutants) in largely overlapping periods, ranging from 1st of January 1985 to 31st December 2015. For each location, we derived daily time series of ozone (maximum 8-hour average), particulate matter with an aerodynamic diameter less than or equal to 10µm (PM_{10}, µg/m^3, 24-hour average), particulate matter with an aerodynamic diameter less than or equal to 2.5µm ($PM_{2.5}$, µg/m^3, 24-hour average), nitrogen dioxide (NO_2, 24-hour average), total mortality, mean temperature (°C) and relative humidity (%). Mortality was represented by all-cause deaths in Canada, Czech Republic, Estonia, France, Germany, Greece, Italy, Japan, Mexico, Portugal, South Africa, South Korea, Sweden, Taiwan, UK, and US, while deaths due to non-external causes (e.g. excluding self-intentional harm, poisoning) were used in Australia, China, Spain and Switzerland (see the eMethods 1 for the specific ICD used in each country). City-specific air pollution series were derived from daily measurements of one or more monitors of the national or regional network. When more than one monitor were available, daily level of each pollutant (24h-average of 8-hour maximum) was computed as the average across monitors of the city, consistent with previous multi-city studies.[2] We excluded 28 cities due to either poor quality data or limited periods (less than 3 years), with a final number of 406 locations included in the final analysis (detailed description of the data, exposure assessment, and exclusion criteria are provided in eMethods 1).

Statistical analysis

The general statistical framework applied here is an extension of the classical two-stage design,[6] and it incorporates complex multi-parameter associations, hierarchical pooling methods, and the computation of impact measures.[18–20] In brief, city-specific ozone-mortality risks were firstly estimated from separate time-series regression models, and then pooled in the second stage through a meta-analysis. In a final step, impact estimates, expressed as excess mortality fractions associated with ozone, were derived from the pooled country-specific risks and city-specific exposure series. Using this general statistical framework, a set of additional and sensitivity analyses were performed to investigate specific features of the association. The following sub-sections provide a more detailed description of each step and sub-analyses. We did all analysis with R software (version 3.5.2) using the packages *dlnm* and *mixmeta*.

Main analysis

In the first stage, we performed city-specific time-series analyses using generalized linear models with quasi-Poisson family. In this type of regression models, a quasi-likelihood is applied to properly scale the standard deviation of the coefficients proportionally to the potential overdispersion. This phenomenon is very common in this type of data, when the variability is larger than that expected under the assumption of a Poisson distribution. Short-term ozone-mortality associations were assessed using unconstrained distributed lag linear models (DLMs).[11,21] These model accounts for delayed effects of time-varying exposures, and quantify net effects over a pre-defined lag period.[20] For the main model, we selected lag 0-1, estimating cumulative associations with the same and previous day's exposures. The regression model included a natural spline of time with 7 degrees of freedom (df) per year, selected based on a quasi-likelihood version of the Akaike Information Criterion (q-AIC) between 4, 6, 7, 8, 10 df, and indicator variables for the day of the week, in order to control for long-term, seasonal, and weekly variations in risk. Unlike in most previous studies on ozone, we applied a stricter control for temperature by using distributed lag non-linear models (DLNMs), an extension of DLMs for modelling complex non-linear and lagged association. Following modelling choices applied in published analyses, we modelled the net temperature-mortality association over lag 0-21 (see details in eMethods 2).[22]

In the second stage, city-specific estimates were then pooled through a multilevel meta-analysis. This novel meta-analytical model defines more complex random-effects that can account for variations in risk across two nested grouping levels, represented by cities within countries.[19] This approach allowed the derivation of improved estimates of ozone-mortality associations at both city and country level, defined as best linear unbiased predictions (BLUPs). BLUPs borrow information across units within the same hierarchical level, and can provide more accurate estimates especially in locations with small daily mortality counts or short series. We tested the presence of heterogeneity and reported it using multilevel extensions of Cochran Q test and I^2 statistic.[23] Association estimates, expressed as relative risk (RR) of mortality per 10 µg/m^3 increase of ozone and 95% confidence interval (CI), were derived for each country from the corresponding BLUPs.

Ozone-mortality risk estimates were then translated into impact measures, represented by excess mortality, following a method described elsewhere.[18] In brief, for each city we computed the daily number of deaths attributable to ozone (or daily excess deaths) using the corresponding risk estimate associated with the level of ozone in each day. Regarding the latter, country-specific BLUPs, instead of the city-specific estimates, were used to avoid imbalances due to selection of cities and periods within each country. City-specific estimates were reported as annual average number of excess deaths and 95% CI, so allowing for a proper comparison between locations with different length of study period. Then, country-specific impacts were represented by excess mortality fractions (%) computed as the sum of the city-specific daily excess deaths divided by the total mortality for each country. Fractions were used instead of number of excess deaths, as these are not comparable across countries given its dependency on the denominator (i.e. total mortality) which at the same time depends on the number of locations included. Although there is no evidence of a “safe” threshold, we computed associated deaths only for days with ozone above 70 µg/m^3, as in previous health impact assessments.[4] This counterfactual scenario of 70 µg/m^3 was considered because ozone levels below this threshold could be mostly attributed to non-anthropogenic sources. A counterfactual scenario defined at 0 µg/m^3 would not be appropriate either as it is not realistic given the ubiquitous presence of low levels of ozone derived from natural sources. Mortality impacts were also disaggregated into contributions for exposure ranges above and between current AQS: 100 µg/m^3 (WHO), 120 µg/m^3 (EU directive), 140 µg/m^3 (National Ambient Air Quality Standard (NAAQS) in the US, approximately 0.070 parts-per-million) and 160 µg/m^3 (Chinese Ambient Air Quality Standard (CAAQS) level 2).[15]

Additional complexities and sensitivity analyses

A series of additional sub-analyses were performed to explore more complex features of the association, such as potential non-linearity, lagged effects, and seasonal differences. First, exposure-response functions were modelled with a non-linear function consisting of a cubic B-spline with internal knots at 50 and 60 µg/m^3 of ozone. Second, delayed risks and potential mortality displacement were assessed by extending the lag dimension of the DLM up to 30 days. Lag-response associations were modelled using a natural cubic spline with three internal knots placed at equally-spaced lag values in the log scale. Third, seasonal differences were assessed through interaction models between an indicator of season and the DLM of ozone, as described elsewhere.[24] We derived the ozone-mortality risk for the warm season (June to August in Northern Hemisphere, December, January and February in Southern Hemisphere) and cold seasons (the remaining months).

Modelling choices in the main model and extensions described above where assessed and compared through q-AIC and multivariate extensions of the Wald test. As sensitivity analyses, we first assessed changes in control for time trends, and the potential confounding from other air pollutants ($PM_{10,}$ $PM_{2.5}$ and NO_2) and relative humidity by including each of these terms separately in the model. We then assessed the exclusion of a subset of US cities with summer-only data which were included in the main analysis, and then different modelling approaches to control for temperature. See eMethods 1 and 2 for a description of the modelling details.

Patient and public involvement

This was a multinational collaboration using aggregated city-level mortality and environmental data. Patients and members of the public did not contribute to the steering committee, design or other areas of the study, which involved complex research methods and analysis. Dissemination of the findings will be carried out through press releases by the research institutions of the contributing authors.

Results

Table 1 provides a summary description of the data included for each country. We analysed a total number of 45,165,171 deaths in the 406 cities, with an average time series of 13 years. Figure 1 shows a widely heterogeneous pattern in ozone levels, reported as average annual mean, across cities between and within country. For example, lower levels were registered in the Australian cities and cities in Northern Europe, while higher annual averages were found in some cities in the central area of US, Mexico and Taiwan. Country-specific descriptive summaries of the other air pollutants and humidity are provided in eTable1, and the corresponding city-specific descriptive results are reported in eTable 2.

On average, each 10-$\mu g/m^3$ increase in ozone was associated with an overall RR of mortality of 1.0018 (95%CI, 1.0012 to 1.0024) (Figure 2). Some heterogeneity was found across country and city-specific risks (I^2 of 29.8%, Cochran Q p-value <0.001). Larger risk estimates were found in the United Kingdom (UK) (1.0035 (95%CI, 1.0024 to 1.0046)), South Africa (1.0027 (95%CI, 1.0013 to 1.0042)), Estonia (1.0023 (95% CI, 1.0006 to 1.0040)) and Canada (1.0023 (95%CI, 1.0013 to 1.0032)), while Australia, China, Czech Republic, France, Germany, Italy, Japan, South Korea Sweden, Switzerland and the US reported similar risks ranging between 1.0014 and 1.0020. Lower and imprecise associations were estimated for Greece (1.0011 (95%CI, 0.9995 to 1.0028)), Mexico (1.0008 (95%CI, (1.000 to 1.0015)), Portugal (1.0011 (95%CI, 0.9997 to 1.0026)), Spain (1.0006 (95%CI, 0.9992 to 1.0019)) and Taiwan (1.0010 (95%CI, 0.9999 to 1.0021)). The corresponding figures with the RRs for an increase in 10 parts-per-billion (ppb) of ozone are provided in eFigure 1.

Figure 3 depicts the excess mortality fractions above WHO guideline and its distribution across intervals between the other AQSs for each country, while eTable 3 and eTable 4 report the corresponding figures for excess fractions for total ozone (above 70 μg/m^3) and above and between AQS. Table 2 shows fractions and annual number of excess deaths associated with ozone for the total range of exposure and above WHO guideline for a selection of the main cities in each country and overall across the 406 locations. Total mortality associated with ozone above 70 μg/m^3 accounted for 0.26% of deaths (95%CI, 0.24 to 0.28), which translates into 8,203 annual excess deaths (95% CI, 3,525 to 12,840) across the 406 locations studied (Table 2). A substantial residual excess mortality of 0.20% (95%CI, 0.18 to 0.22) corresponding to 6,262 (95% CI, 1,413 to 11,065) annual excess deaths remained when restricting to days with levels above the WHO recommendation of 100 μg/m^3. As shown in Figure 3, this proportion varied greatly by country, with considerably larger fractions in Mexico (0.52% (95%CI, 0.14 to 0.92)) and Taiwan (0.37% (95%CI, 0.08 to 0.64)). Mortality excess around 0.20% were estimated in Canada, China, Italy, Japan, South Africa, Switzerland and USA, while France, Germany, South Korea and UK reported smaller percentages, ranging between 0.14% and 0.05%. Imprecise or almost null estimates were found in Czech Republic, Estonia, Greece, Portugal, Spain and Sweden. Overall mortality fractions above more lenient AQSs (i.e. EU, NAAQS and CAAQS) decreased progressively to 0.14%, 0.09% and 0.05%, respectively (eTable 3). Only Mexico reported a considerably higher fraction of 0.35% above the highest AQS of 160 μg/m^3, although highly uncertain (black bar in Figure 3). Note that null excess deaths were found in Australia, as daily exposure levels were all below 70 μg/m^3. A similar pattern was found across estimates for the main cities in each country (Table 2). A substantial number of annual excess deaths were associated to ozone levels above WHO guideline, namely 694 (95% CI, 22 to 1,317) in Valley of Mexico, 211 (95% CI: 112 to 307) in Los Angeles, 170 (95% CI, 40 to 304) in Tokyo, 128 (95% CI, 59 to 197) in Toronto, 82 (95% CI, 19 to 148) in Johannesburg, 48 (95% CI, 0 to 96) in Paris and 37 (95% CI, 15 to 57) in London (Table 2). eTable 5 shows the corresponding estimates for the 406 cities.

Additional analyses suggested no evidence of non-linearity in the concentration-response association (according to q-AIC) (eFigure 2). The assessment of the lagged associations confirmed an immediate ozone-mortality association during the first week (eFigure 1). However, lag-specific estimates below 1 were found after the second week which resulted in a slightly lower overall cumulative association of 1.0015 (95% CI, 0.9991 to 1.0032) when considering the delayed effects over the first 30 days after the exposure. Finally, no evidence of seasonal differences in ozone-mortality association were found (warm season: 1.0012 (95% CI, 1.000 to 1.0026); cold season 1.0015% (95% CI, 1.0006 to 1.0024), Wald test p-value = 0.37).

Results from sensitivity analyses suggest that risk estimates of the main analysis were robust to the different modelling choices related to the control for time trends and adjustment by the three air pollutants and humidity (eTable 6). However, ozone-mortality risk estimates seemed to be sensitive to the approach to control for temperature (eFigure 3). We found larger ozone-mortality association estimates using less stringent control, although q-AIC values suggested that the model with DLNM of temperature (main model) provided the best fit.

Discussion

Principal findings

To the best of our knowledge, this is the largest epidemiological investigation on short-term ozone-mortality associations to date, including almost 50 million deaths from 406 cities in 20 countries from different regions across the world. Given its large sample size and wide geographical coverage, we were able to obtain consistent evidence of an association between short-term exposure to ozone and total mortality. In addition, we provided for the first time ozone-related impact estimates, quantified as excess mortality, across different AQS, countries and cities, providing evidence with important public health implications.

On average, we found an overall short-term ozone-mortality association of 1.0018 (95%CI, 1.0012 to 1.0024) per 10-μg/m^3 increase. This evidence is supported by previous epidemiological and experimental studies suggesting several patho-physiological mechanisms (e.g. systemic inflammation, haemostatic alterations).[25,26] Larger associations were found in previous multi-country studies, including a subset of countries investigated here (e.g. RR of 1.0022 in APHEA, 1.0026 in APHENA, per 10-μg/m^3 increase),[11,21] or other single-country studies (e.g. RR of 1.0025 in the US (originally 1.0052 per 10-ppb increase), and China, and 1.015 in Italy).[27–29] Differences in the definition of the exposure variable (e.g. moving average, single lag) and modelling approach could explain these discrepancies in the magnitude of the association. For example, compared to previous studies, we applied a stronger control for temperature (i.e. DLNMs), fully accounting for non-linearity and lagged temperature-mortality associations.[22] In fact, results from sensitivity analyses are consistent with previous findings showing that ozone-mortality risk estimates were very sensitive to the modelling strategy to control for temperature, reporting larger risks when using simpler approaches (eFigure 3).[27] Moreover, one of the novelties of the applied statistical framework is the use of multilevel meta-analytical models in the second stage, properly accounting for heterogeneity across cities and countries.

Our results revealed important differences in the ozone-mortality association across countries. For example, while some areas such as UK, South Africa, Canada and Estonia reported the largest risk estimates above 1.0020, smaller and/or imprecise estimates below 1.0011 were found in Greece, Mexico, Spain and Taiwan. This unclear pattern would suggest that, while several community-level factors have been proposed as potential modifiers in single-country studies (e.g. population characteristics), these might not fully characterise between-country differences.[30] Future multi-country studies are needed to provide further evidence on the factors defining the level of vulnerability of the population to air pollution.

This study also provides valuable evidence on the potential public health benefits of stricter clean air policies. In particular, we found that 0.20% excess mortality, which translates into more than 6 thousand deaths per year, related to short-term exposure to ozone would have been avoided if ambient levels were below WHO recommendation of 100 μg/m^3 in the 406 cities included in the study. Recent reviews found that the vast majority of current AQSs are not compliant with the WHO air quality recommendations,[15] and that 80% of the world population in urban areas are exposed to air pollution levels above this threshold.[31] Moreover, an additional 0.06% of excess deaths is associated with ozone levels between 70 and 100 μg/m^3. These findings support the WHO initiative of encouraging countries to revisit current AQSs and enforce stronger emission restrictions and other public health interventions to meet their recommendations. Additionally, our results have important implications for healthcare practice. Apart from the implementation of clean air policies, individual strategies to reduce the personal exposure to air pollutants are also desirable.[32] In this regard, clinicians play an important role in providing counselling to patients with potentially a higher susceptibility to adverse health outcomes related to air pollution. For instance, professionals can advise sensitive individuals to stay indoors or avoid doing exercise during episodes of elevated ambient ozone.

Previous studies showed that important health benefits could be achieved if reductions of ozone levels are reached.[9,13,16] However, this is the first multi-country study comparing excess mortality estimates across AQSs and countries, providing additional insights on specific areas with more urgent need of further interventions. For example, we found that 0.52% of total mortality in Mexico was associated to ozone above WHO limit, the largest mortality fraction amongst the studied countries. This is due to the high ozone levels registered in the Mexican cities, especially above 160 $\mu g/m^3$ limit, which is close to its current AQS of 156 $\mu g/m^3$. This means that attaining the current lenient standards would prevent a substantial proportion of ozone-related deaths in this country. In contrast, results for the UK show a lower mortality fraction, despite the strongest ozone-mortality association, due to the lower ozone levels registered in this country.

Strengths and limitations of the study

We were able to efficiently explore additional complexities of the association by taking advantage of the large statistical power and advanced statistical techniques. First, our results support the conclusions of previous studies on a generally linear concentration-response functions, with no indication of threshold.[9,27] Second, we found evidence of a potential mortality displacement in the third and fourth week after the exposure. A similar lag pattern was previously observed.[10,11] However, potential mechanisms explaining this delayed and sustained pattern remain unclear. Finally, we found no evidence of seasonal differences in the ozone-mortality association. Previous multi-site studies have provided conflicting results, with larger risks in cold seasons in Asia,[27] and in warm season in US and Europe.[6] Further analyses are warranted to characterize different patterns across regions.

This study presents some limitations. First, our results should not be considered truly global estimates, since several areas of the world such as South America, Africa and Middle East, are unrepresented or not assessed. In addition, the reported nationwide results may not be representative of the true impacts for some countries with a limited number of cities included in the study (e.g. Sweden, Czech Republic, China). In particular, the estimated number of total excess deaths attributed to ozone should be interpreted as the sum of impacts in the 406 observed locations, and not as total estimates across the 20 countries. It should be noted that while excess fractions could be considered proper representations of the impacts for each country, the total excess number of deaths for each country is highly dependent on the total mortality considered in the study, that is the number of locations included in each country. There could also be systematic differences between countries concerning the characteristics of monitors (type, proximity to the study area), study area boundaries, temporal coverage, data processing prior to the data collection and in the collection of mortality data (e.g. case ascertainment, codification). However, we ensured that the provided data fulfilled a minimum set of requirements in terms of quality, similar definition of the 8-hour maximum metric and location of the monitor (i.e. within the study area or close enough to ensure its representativeness). Risks and impact estimates were only reported for total mortality (i.e. deaths due to all or non-external causes) and we did not seek to identify the sources of heterogeneity of the results across countries. We acknowledge that the applied approach prevents us from understanding the potential mechanisms and/or differential susceptibility of the population, together with contextual differences across locations. Further studies are warranted to clarify this complex research question including for example cause-specific mortality and morbidity, and more complex two-stage analyses. Finally, it is worth noting that although small the risk estimates apply to the whole population, thus translating into substantial mortality impacts as shown in our estimates of excess mortality. To the same token, due to the nature of the study design (i.e. time series analysis) the obtained excess mortality estimates refer to transient impact measures and not to the mortality burden or person-years of life lost attributed to chronic ozone exposure.[33]

Conclusions

This large multi-country study provided robust evidence on the short-term association between ozone and mortality. We also demonstrated that clean air policies with the enactment of AQSs can constitute essential public health tools to minimize the health burden. In particular, our results clearly suggest that ozone-related health impacts can be largely preventable by attaining effective AQSs in line with the WHO guideline. Moreover, interventions to further reduce ozone pollution would provide additional health benefits, even in regions that meet current regulatory standards and guidelines. These findings have important implications for the design of future public health actions, in particular, for example in relation to the implementation of mitigation strategies to reduce the impacts of climate change.

Figure legends

Figure 1. Map showing the geographical distribution of the city-specific average annual means of ozone (maximum 8-hour average) of the 469 MCC cities.

Figure 2. Overall and country-specific short-term ozone-mortality association, expressed as relative risk (RR) per 10-μg/m^3 increase in ozone (maximum 8-hour average) (lag 01).

Figure 3. Overall and country-specific excess mortality (%) associated to ozone by specific ranges defined between thresholds consistent with current air quality standards. (No excess mortality associated to ozone were found in Australia, as daily ozone levels were below the maximum background level set up at 70 μg/m^3).

* 100 μg/m^3, World Health Organization guideline (WHO); 120 μg/m^3, European Directive; 140 μg/m^3 (approximately 0.070ppm); National Ambient Air Quality Standard in the US (NAAQS); 160 μg/m^3 Chinese Ambient Air Quality Standard (CAAQS).

Authors' contributions

*AG and HK are both senior authors and contribute equally to this work.

AG, YG, MH, and BA set up the collaborative network. AMVC, AG, FS and HK designed the study. AMVC coordinated the work, and took the lead in drafting the manuscript and interpreting the results. AG and FS developed the statistical methods. AMVC conducted the statistical analysis. BA, AH, FS, AG, KK, ES, MS, AT, CI, VH, AS, JS, NS, RG, EL provided substantial scientific input in interpreting the results and drafting the manuscript. CL, AM, YG, ST, EL, JK, AU, HO, EI, MP, VH, AS, KK, ES, MS, MS, MH, YH, CFSN, MH, JC, SS, JM, NS, RG, HK, AT, CI, BF, CA, MSR, MR, YLLG, BYC, AZ, JS, MB, HK provided the data, and contributed to the interpretation of the results and to the submitted version of the manuscript.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted

Conflict of interest statements

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

This work was primarily supported by the Medical Research Council-UK (Grants ID: MR/M022625/1 and MR/R013349/1) and by the Natural Environment Research Council UK (Grant ID: NE/R009384/1). The following individual grants also supported this work: HaK was supported by the National Natural Science Foundation of China (91843302 and 91643205), and China Medical Board Collaborating Program (Grant 16-250). JM was supported by the Fundação para a Ciência e a Tecnologia (FCT) through the scholarship SFRH/BPD/115112/2016. VH was supported by the Spanish Ministry of Economy, Industry and Competitiveness (MINECO, Grant ID: PCIN-2017-046) and the German Federal Ministry of Education and Research (BMBF, Grant ID: 01LS1201A2). AU and JK were supported by the Czech Science Foundation (no. 18-22125S). HO and EI were supported by the Estonian Ministry of Education and Research grant IUT34-17. AT was supported by the Japanese Society for the Promotion of Science (JSPS) Invitational Fellowships for Research in Japan (S18149). YG was supported by the Career Development Fellowship of the Australian National Health and Medical Research Council (APP1107107 & APP1163693). ST was supported by the Science and Technology Commission of Shanghai Municipality [18411951600]. HoK was supported by the Global Research Lab (#K21004000001-10A0500-0710) through the National Research Foundation of Korea and by the Future Planning and Korea Ministry of Environment as the “Climate Change Correspondence R&D Program” (2013001310002). RMG was supported by a CSIR Parliamentary Grant. NS is supported by the NIEHS-funded HERCULES Center (P30ES019776)

This publication was developed under Assistance Agreement No. RD835871 awarded by the U.S. Environmental Protection Agency to Yale University (Michelle L. Bell). It has not been formally reviewed by EPA. The views expressed in this document are solely those of the authors of the publication and do not necessarily reflect those of the Agency. EPA does not endorse any products or commercial services mentioned in this publication.

Ethical approval

It was not required.

Data sharing

Data have been collected within the MCC Collaborative Research Network (http://mccstudy.lshtm.ac.uk/) under a data sharing agreement, and cannot be made publicly available. Researcher can refer to MCC participants listed as co-authors for info on accessing the data for each country. The R code for the analysis is available from the corresponding author.

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Acknowledgements

The authors would like to thank Meltem Kutlar (Swiss Tropical and Public Health Institute, Basel; University of Basel, Basel, Switzerland), responsible of the LUDOK database (funded by Swiss Federal Office for the Environment) for her support during the literature review.

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Table 1. Description of the environmental and mortality data.

	Locations (N)	**Period (range)**	**Total deaths (N)**	**Daily deaths (Median (IQR))**	**Ozone (Median (IQR))**	**Mean temperature (Median (IQR))**
Australia	3	2000-2009	513,527	49.3 (43.7; 55.7)	31.2 (24.2; 38.6)	18.3 (14.8; 21.5)
Canada	26	1986-2011	2,914,630	12.8 (10.5; 15.3)	69.2 (53.9; 88.4)	7.3 (-1.0; 15.7)
China	3	1996-2015	780,655	87.3 (71.7; 140.3)	49.3 (27.8; 77.5)	20.4 (13.0; 25.7)
Czech Republic	1	1994-2009	214,062	36.0 (32.0; 41.0)	69.3 (47.4; 95.0)	9.2 (2.5; 15.3)
Estonia	4	2002-2015	80,043	5.0 (3.5; 6.5)	48.9 (36.7; 61.8)	6.0 (0.2; 13.6)
France	18	2000-2010	1,197,555	16.3 (13.7; 19.1)	67.8 (46.8; 87.4)	12.7 (7.6; 17.9)
Germany	12	1993-2015	3,099,176	30.4 (26.4; 34.8)	57.1 (35.8; 79.2)	10.5 (4.8; 15.9)
Greece	1	2001-2010	287,969	78.0 (70.0; 87.0)	75.1 (52.8; 97.5)	17.9 (12.9; 24.9)
Italy	9	2006-2015	373,421	15.1 (12.6; 17.9)	74.1 (50.5; 97.0)	15.8 (10.2; 22.1)
Japan	45	2011-2015	1,856,232	22.3 (19.1; 25.7)	78.5 (62.4; 98.4)	16.1 (7.5; 22.7)
Mexico	7	2000-2012	2,018,313	61.0 (53.7; 69.4)	108.9 (85.1; 135)	18.6 (15.9; 20.5)
Portugal	2	1997-2012	536,958	47.0 (41.0; 54.0)	64.2 (50.2; 79.2)	16.1 (12.5; 19.6)
South Africa	5	2004-2013	924,478	58.4 (48.8; 67.0)	69.5 (52.9; 89.5)	18.3 (14.2; 21.2)
South Korea	7	1999-2015	1,662,199	38.3 (34.0; 42.7)	59.5 (42.7; 81.9)	15.1 (5.8; 22.1)
Spain	48	2004-2014	1,294,162	6.7 (5.1; 8.4)	70.0 (53.9; 84.7)	15.3 (10.3; 21.1)
Sweden	1	1990-2010	201,197	26.0 (22.0; 30.0)	61.9 (48.9; 76.0)	6.8 (1.2; 13.9)
Switzerland	8	1995-2013	230,587	4.2 (2.9; 5.6)	72.8 (47.0; 98.1)	10.7 (4.4; 16.5)
Taiwan	3	2008-2014	443,680	57.0 (51.0; 63.7)	109.1 (82.1; 138.6)	24.8 (20; 28.2)
UK	15	1993-2006	2,073,285	28.4 (24.5; 32.9)	51.6 (36.7; 65.2)	10.4 (6.5; 14.6)
USA	188	1985-2006	24,463,042	16.3 (13.6; 19.3)	80.1 (58.9; 104.0)	14.9 (7.5; 21.9)

Ozone: daily maximum 8-hour mean, $\mu g/m^3$. Mean temperature, ˚C. IQR: interquartile range. N: number. Mortality: deaths due to non-external causes (Australia, China, Spain, Switzerland (including accidents)) or to all-cause mortality (the remaining countries). Detailed description of the data provided in eMethods 1. Country-specific summaries of other air pollutants and relative humidity are provided in eTable 1. City-specific descriptive summaries reported in eTable 2.

Table 2. Excess mortality associated to ozone for the total (above 70 µg/m^3) and above WHO guideline of 100 µg/m^3 in the main cities of each participating country and overall estimates for the 406 cities.

Country	**City**	**Total (Above 70 µg/m^3)***		**Above WHO Guideline (100 µg/m^3)**	
		Excess fraction (%, 95% CI)	**Annual excess deaths (N, 95% CI)**	**Excess fraction (%, 95% CI)**	**Annual excess deaths (N, 95% CI)**
*Australia***	Sydney	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Canada	Toronto	0.59 (0.34 to 0.85)	159 (90 to 228)	0.48 (0.22 to 0.73)	128 (59 to 197)
China	Shanghai	0.32 (0.04 to 0.57)	117 (15 to 209)	0.27 (-0.01 to 0.53)	99 (-4 to 195)
Czech Republic	Prague	0.27 (0.02 to 0.48)	38 (3 to 69)	0.20 (-0.06 to 0.44)	29 (-9 to 63)
Estonia	Tallinn	0.01 (0.00 to 0.02)	1 (0 to 1)	0.00 (-0.01 to 0.01)	0 (-1 to 1)
France	Paris	0.15 (0.05 to 0.26)	70 (24 to 119)	0.11 (0.00 to 0.21)	48 (0 to 96)
Germany	Berlin	0.12 (0.04 to 0.20)	46 (14 to 74)	0.08 (-0.01 to 0.17)	30 (-3 to 62)
Greece	Athens	0.16 (-0.07 to 0.41)	52 (-23 to 132)	0.11 (-0.13 to 0.37)	35 (-42 to 117)
Italy	Rome	0.27 (0.05 to 0.52)	69 (13 to 132)	0.19 (-0.05 to 0.44)	48 (-12 to 111)
Japan	Tokyo	0.27 (0.14 to 0.40)	249 (127 to 371)	0.18 (0.04 to 0.32)	170 (40 to 304)
Mexico	Valley of Mexico	0.73 (0.04 to 1.38)	707 (39 to 1,339)	0.72 (0.02 to 1.36)	694 (22 to 1,317)
Portugal	Lisbon	0.09 (-0.03 to 0.2)	20 (-6 to 45)	0.04 (-0.09 to 0.17)	9 (-20 to 39)
South Africa	City of Johannesburg	0.32 (0.15 to 0.49)	121 (59 to 187)	0.22 (0.05 to 0.39)	82 (19 to 148)
South Korea	Seoul	0.10 (0.03 to 0.17)	41 (13 to 71)	0.06 (-0.01 to 0.14)	27 (-3 to 58)
Spain	Madrid	0.03 (-0.04 to 0.11)	9 (-12 to 31)	0.01 (-0.07 to 0.10)	3 (-21 to 27)
Sweden	Stockholm	0.10 (0.02 to 0.18)	10 (2 to 18)	0.03 (-0.07 to 0.13)	3 (-7 to 13)
Switzerland	Zurich	0.31 (0.05 to 0.54)	13 (2 to 22)	0.23 (-0.02 to 0.48)	10 (-1 to 20)
Taiwan	Taipei	0.34 (-0.05 to 0.72)	131 (-21 to 276)	0.28 (-0.11 to 0.67)	109 (-43 to 258)
UK	London	0.10 (0.07 to 0.12)	63 (44 to 81)	0.06 (0.02 to 0.09)	37 (15 to 57)
USA	Los Angeles	0.41 (0.24 to 0.57)	242 (142 to 335)	0.36 (0.19 to 0.52)	211 (112 to 307)
20 MCC countries	406 MCC cities	0.26 (0.24 to 0.28)	8,203 (3,525 to 12,840)	0.20 (0.18 to 0.22)	6,262 (1,413 to 11,065)

*Total refers to ozone-related deaths when levels above 70 µg/m^3 (defined as maximum background levels).
**No excess mortality associated to ozone were found in Australia, as daily ozone levels were below the maximum background level set up at 70 µg/m^3.
WHO: World Health Organization. N: number.