Coarse Particulate Air Pollution and Daily Mortality: A Global Study in 205 Cities

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At a Glance

What is the current scientific knowledge on this subject?

• Evidence on the short-term association between ambient coarse particulate matter (PM2.5-10) and mortality remains to be determined at a global scale, and a unique air quality guideline is absent.

• Previous studies were mainly conducted in a small number of locations or regions, and different study designs and/or modelling approaches were used, leading to heterogeneous and incomparable results.

What does this study add to the field?

• This global study in 205 cities found that each 10 μg/m3 increase in PM2.5-10 concentrations on lag 0-1 day was significantly associated with increased risk of total (0.51%), cardiovascular (0.43%), and respiratory (0.41%) mortality, even with adjustment for fine particulate matter and other co-pollutants.

• The concentration-response relationships had no discernable thresholds with steeper slopes in lower concentrations, suggesting the need to set a unique daily standard for PM2.5-10.

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Abstract

Rationale: The associations between ambient coarse particulate matter ($PM_{2.5-10}$) and daily mortality is not fully understood at a global scale.

Objectives: To evaluate the short-term associations between $PM_{2.5-10}$ and total, cardiovascular, and respiratory mortality across multiple countries/regions worldwide.

Methods: We collected daily mortality (total, cardiovascular, respiratory) and air pollution data from 205 cities in 20 countries/regions. Concentrations of $PM_{2.5-10}$ were computed as the difference between inhalable and fine particulate matter. A two-stage time-series analytic approach was applied, with over-dispersed generalized linear models and multilevel meta-analysis. We fitted two-pollutant models to test the independent effect of $PM_{2.5-10}$ from co-pollutants (fine particulate matter, nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide). Exposure–response relationship curves were pooled and regional analyses were conducted.

Measurements and Main Results: A 10 μg/m^3 increase in $PM_{2.5-10}$ concentration on lag 0–1 day was associated with increments of 0.51% (95% confidence interval [CI]: 0.18%, 0.84%), 0.43% (95%CI: 0.15%, 0.71%) and 0.41% (95%CI: 0.06%, 0.77%) in total, cardiovascular, and respiratory mortality, respectively. The associations varied by country and region. These associations were robust to adjustment by all co-pollutants in two-pollutant models, especially for $PM_{2.5}$. The exposure–response curves for total, cardiovascular, and respiratory mortality were positive, with steeper slopes at lower exposure ranges and without discernible thresholds.

Conclusions: This study provides novel global evidence on the robust and independent associations between short-term exposure to ambient $PM_{2.5-10}$ and total, cardiovascular and respiratory mortality, suggesting the need to establish a unique guideline or regulatory limit for daily concentrations of $PM_{2.5-10}$.

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Introduction

Ambient particulate matter (PM) has been reported to induce adverse impacts on human health, including mortality and morbidity from all causes and major cardiopulmonary diseases (1-3). One categorization of PM is by aerodynamic sizes of particles, including inhalable particles (PM_{10}), fine particles ($PM_{2.5}$), and coarse particles ($PM_{2.5-10}$). Different from $PM_{2.5}$, $PM_{2.5-10}$ is usually formed by mechanical grinding and resuspension of solid material (4). The differences in composition and deposition sites suggest that $PM_{2.5}$ and $PM_{2.5-10}$ may have different impacts on human health. Compared with studies on PM_{10} or $PM_{2.5}$ (5-7), there are less investigations on the associations between $PM_{2.5-10}$ and human health, for which evidence remains inconclusive and needs further assessment by large-scale studies. One plausible reason for the sparser scientific literature is the fact that while PM_{10} and $PM_{2.5}$ are both regulated through the Air Quality Guidelines (AQGs) recommended by the World Health Organization (WHO) and national and international concentration limits (8), no such regulatory framework exists for $PM_{2.5-10}$. The Environmental Protection Agency (EPA) of the United States had initially proposed a unique standard for $PM_{2.5-10}$ under the National Ambient Air Quality Standards (NAAQS) in 2003 (9), but this initiative failed due to the inadequate available epidemiological evidence on the health effects of this pollutant.

Over the past two decades, an increasing number of epidemiological and experimental studies have examined health endpoints related to $PM_{2.5-10}$. For example, an early review in 2005 by Brunekreef and colleagues suggested associations with increased morbidity and mortality for short-term but not long-term exposures to $PM_{2.5-10}$, and the estimates were found to be quite sensitive to mutual adjustment of $PM_{2.5}$ (10). Ada et al. extended this work in 2014 by incorporating new studies and summarizing results from multi-pollutant models (11). This updated review indicated that the associations between short-term exposures to $PM_{2.5-10}$ and mortality could not be fully explained by confounding by $PM_{2.5}$. Additional research is therefore required to better understand the relationship between exposure to $PM_{2.5-10}$ and health risks, as well as several gaps in knowledge. First, many of the studies examined mortality from all causes, and there is a need to assess the associations of $PM_{2.5-10}$ with mortality from specific causes, such as cardiopulmonary diseases. Second, critical knowledge on the lag structure, the

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shape of exposure–response relationship curve, and the independence of the association from co-pollutants need further investigations. Third, the existing evidence was based on analysis at the city, country, or regional level, creating challenges for interpreting and integrating results from different study areas and analytical approaches. Large-scale studies covering multiple countries and regions are warranted to increase the statistical power and generalizability of results.

The Multi-City Multi-Country (MCC) Collaborative Research Network (http://mccstudy.lshtm.ac.uk/) is an international partnership that aims to integrate the evidence on health risks of environmental factors across the globe. The MCC Network has gathered the largest epidemiological database in this research area, which will be used in this study to investigate associations between short-term exposure to $PM_{2.5-10}$ and mortality from major causes across multiple countries and regions worldwide. This study also tested whether the associations of $PM_{2.5-10}$ with daily mortality is independent of co-pollutants, and pooled the exposure–response (E–R) relationships across countries and regions.

Methods

Data Collection

We collected mortality data and environmental records in time series format from the MCC database. Detailed information has been provided in previous publications (12, 13). The current analysis was limited to locations with available data on $PM_{2.5-10}$, eventually including a total of 205 cities located in 20 countries (Table 1). The geographic distribution of these cities, and the corresponding averaged annual-mean $PM_{2.5-10}$ concentrations are shown in Figure E1. Mortality data was obtained from local authorities within each country/region. Causes of death were classified according to the 9th or 10th version of the International Classification of Diseases (ICD) codes, where available. In each location, mortality is represented by daily counts of either non-external causes (ICD-10, codes A00-R99) or, where not available, all-cause mortality. We also collected mortality data from two major causes in 15 countries (Table 1): cardiovascular disease (ICD-10, codes I00-I99) and respiratory disease (ICD-10, codes J00-J99) (14).

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Daily concentrations of PM_{10}, $PM_{2.5}$, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ground-level ozone (O_3), and carbon monoxide (CO), were obtained from fixed-site monitoring stations and averaged at the city level. Concentrations of $PM_{2.5-10}$ were computed as the difference between PM_{10} and $PM_{2.5}$. We also collected daily data on weather variables, represented by daily mean temperature and daily mean relative humidity from local meteorological bureau or other government or scientific authorities (13). Overall, the percentages of missing daily observations for all-cause mortality, $PM_{2.5-10}$ and temperature were 0.20%, 10.02% and 2.10%, respectively. Detailed information on missing data is summarized in the online supplement (Table E7).

Statistical Analysis

The associations of $PM_{2.5-10}$ with daily total, cardiovascular, and respiratory mortality were analyzed using the same protocol for all locations, based on a two-stage analytic framework used in previous multicenter studies of the MCC Network (5, 15, 16).

In the first stage, we estimated city-specific associations using a time series *quasi*-Poisson generalized linear regression model with a natural cubic spline function of time with 7 degrees of freedom (*df*) per year to control for unmeasured temporal trends, and indicator variables for day of the week. Temperature was adjusted using a natural spline function with 6 *df*, and relative humidity using the same spline function with 3 *df* in cities where such data were available. We *a priori* selected the moving average of the present-day and previous 3 days (lag 0-3) to adjust for temperature, accordingly with previous studies (5, 17). We empirically examined different lag structures using concentrations at single lag days from 0 to 3 days, and moving average concentrations from the present day to the previous 1 to 3 days (i.e., lag 0–1, reflecting exposure on the same and previous day, lag 0–2, lag 0–3) to identify the most appropriate lags for the main model (5, 18).

In the second stage, we used a multilevel meta-analysis to pool the city-specific associations (19). Briefly, this model allows for more complex random-effects structures that account for the hierarchical structure of the data, namely cities nested within countries, and provides estimates of the empirical best linear unbiased prediction (BLUPs) for $PM_{2.5-10}$–mortality associations at both levels (19). We

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computed global, country, and city-specific estimates with 95% confidence intervals (CIs) as percent change in daily mortality per 10 μg/m^3 increase in $PM_{2.5-10}$ concentrations. Potential heterogeneity across cities was assessed via Cochran Q tests and *I*-squared (I^2) statistics.

We extended the main models to assess specific features of the association. First, we fitted two-pollutant models by adjusting for co-pollutants ($PM_{2.5}$, NO_2, SO_2, O_3, and CO). We then assessed the independence and robustness of the associations of $PM_{2.5-10}$ by comparing the estimates with and without control for the other pollutants. A significance test on the difference was produced via a meta-analytical model where we first combined the effect estimates derived from single and two-pollutant models, assigned a binary variable to each estimate (with or without a co-pollutant adjustment), and then performed a likelihood ratio test to examine the difference between estimates with and without the adjustment of co-pollutants. Countries or regions with unavailable co-pollutants data were excluded accordingly. Furthermore, we conducted regional analyses, with regions identified by strata of gross domestic product (GDP) per capita and WHO classification (Table E1), including the Western Pacific Region (WPRO), the American Region (AMRO), and the European Region (EURO). We also investigated potential effect modifiers (i.e., long-term levels of air pollution, temperature and relative humidity, and latitude of locations) on the associations between ambient $PM_{2.5-10}$ and total mortality using a meta-regression analysis. Finally, we pooled the E–R relationship curve using a meta-smoothing approach applied in previous studies (20, 21), modelling $PM_{2.5-10}$ as a nonlinear term through a natural spline function with knots at 25th and 75th percentiles of each location's exposure range.

We conducted several sensitivity analyses to test the robustness of our estimates, including alternative choices for controlling for temperature, adjustment for relative humidity, seasonal differences modelled through an interaction with an indicator of warm/cold season (March to August versus September to next February for the northern hemisphere, and vice versa for the southern hemisphere), and comparing the associations within different time periods with a cut point at the year 2000 (around the median year of each country's time period).

We conducted all statistical analyses in R software (Version 3.3.1), using the *stats* and *dlnm*

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packages for fitting first-stage models and the *mixmeta* package for performing multilevel meta-analyses. We presented the percent change of mortality for a 10 μg/m^3 increase in $PM_{2.5-10}$ concentrations. *P*-values < 0.05 were considered statistically significant in all statistical analyses.

Results

Descriptive Statistics

This analysis included 39.8 million deaths for total or non-external causes from 205 cities in the study period from 1969 to 2018, and included 12.2 million and 3.6 million deaths from cardiovascular and respiratory diseases in 180 cities (Table 1), respectively. Cardiovascular deaths accounted for 30.6% of total deaths among all countries, ranging from 15.7% in South Africa to 47.3% in Greece; while respiratory deaths accounted for 9.0%, ranging from 6.3% in Switzerland to 15.7% in Japan. On average, the median annual mean concentration of $PM_{2.5-10}$ across 205 cities was 26.6 μg/m^3 (25th–75th percentiles: 19.4 μg/m^3–35.7 μg/m^3). The median of annual mean temperature was 13.9°C (25%–75% percentiles: 7.4°C–19.9°C). A detailed summary of the exposure data is provided in Table E2. $PM_{2.5-10}$ was weakly correlated with $PM_{2.5}$ (Spearman correlation coefficient r_s = 0.28), NO_2 (r_s = 0.21), SO_2 (r_s = 0.19), O_3 (r_s = 0.18), and CO (r_s = 0.18). On average, $PM_{2.5-10}$ was moderately correlated with mean temperature (r_s = 0.33) and negatively correlated with relative humidity (r_s = -0.32).

Regression Results

Figure 1 illustrates the estimated pooled associations between $PM_{2.5-10}$ and total, cardiovascular and respiratory mortality on different lag days. The associations with the three mortality outcomes were all present at lag 0 day (same day), attenuated at lag 1 day, and then lost statistical significance from lag 2 day on. The same pattern is also present for grouped lags, from lag 0–1 day to lag 0–3 day. Among these lags, the lag 0–1 day generated the strongest associations for all three endpoints, and was used as the main choice for summarizing associations with $PM_{2.5-10}$ in subsequent analyses.

Figure 2 displays the pooled estimates on the associations of $PM_{2.5-10}$ (lag 0–1) with total, cardiovascular and respiratory mortality. Moderate heterogeneity was found in $PM_{2.5-10}$–mortality

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associations across city-specific estimates, with an I^2 statistics of 43.16% and a Cochran Q test *p*-value < 0.001. Across 205 cities, a 10 μg/m^3 increase in $PM_{2.5-10}$ concentration was associated with an increase of 0.51% (95%CI: 0.18%, 0.84%) in total mortality; while across 180 cities, the corresponding increases were 0.43% (95%CI: 0.15%, 0.71%) and 0.41% (95%CI: 0.06%, 0.77%) for cardiovascular and respiratory mortality, respectively. The associations of $PM_{2.5-10}$ with total mortality were all positive among the 20 countries or regions, but the magnitude differed, with the percentage change ranging from 0.02% to 1.45% for total mortality per 10 μg/m^3 increase in $PM_{2.5-10}$. Country/region-specific estimates were more uncertain for cause-specific associations, although generally indicating an increased risk.

Figure 3 shows the E–R relationship curves for $PM_{2.5-10}$ concentrations and three mortality endpoints modelled with flexible spline functions. The curves indicate increased risks, with much steeper slopes at concentrations less than 15 μg/m^3, then attenuating at exposure ranges lower than 60 μg/m^3, and eventually levelling off with wider confidence intervals afterwards. No obvious thresholds were observed, indicating positive associations even at low exposure ranges.

In two-pollutant models (Table 2), the associations of $PM_{2.5-10}$ with total mortality were generally robust to the adjustment for co-pollutants, with no evidence of differences between models with and without adjustment (*p*-values > 0.05). We observed a small increase in effect estimates with adjustment for SO_2 and CO, whereas there was a small decrease in estimates when adjusting for NO_2 and O_3. The effect estimates decreased by 34% (*p*-value = 0.151) when adjusting for $PM_{2.5}$, but the $PM_{2.5-10}$–mortality association was still positive and statistically significant.

In regional analyses (Table E3), the magnitude of $PM_{2.5-10}$–mortality association was highest in the EURO with an average increment of 0.54% in total mortality per 10 μg/m^3 increase of $PM_{2.5-10}$ concentrations, and was lowest in the AMRO (corresponding estimate: 0.18%). The associations did not vary significantly by GDP per capita (*p*-value for difference = 0.192), with estimates of 0.32% (0.02%, 0.61%), 0.60% (0.25%, 0.95%), and 0.60% (0.28%, 0.92%) corresponding to low-, medium-, and high-GDP areas, respectively. Furthermore, no significant effect modification was observed by annual levels of air pollutants, temperature, relative humidity, GDP per capita, WHO region, or latitude

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of locations.

In sensitivity analyses, compared with main models, the estimates for the $PM_{2.5-10}$–mortality associations were generally smaller when adjusting for temperature with shorter lag structures, while larger estimates were generated with longer lags (Table E4). The qAIC statistic for the model adjusting for lag 0–3 temperature was the smallest, indicating the best goodness of fit for our main model. The associations of $PM_{2.5-10}$ with total, cardiovascular, and respiratory mortality were similar between models with or without adjustment of relative humidity (Table E5). We found no evidence of seasonal difference in the $PM_{2.5-10}$–mortality association (*p*-value =0.895), although the estimate in cold season [0.49% (95% CI: 0.26%, 0.60%)] was smaller than that in warm season [0.88% (95%CI: 0.40%, 1.37%)]. Finally, the estimates for all three mortality outcomes did not vary substantially in periods before and after the year 2000 (Table E6).

Discussion

To the best of our knowledge, this is the most extensive epidemiological investigation to date on the effect of short-term exposure to ambient $PM_{2.5-10}$ on mortality. We observed positive and significant associations of $PM_{2.5-10}$ with daily total, cardiovascular and respiratory mortality, and these associations remained statistically significant after adjusting for $PM_{2.5}$ and gaseous pollutants. Notably, for the first time, we pooled the E–R relationships between $PM_{2.5-10}$ and mortality across different regions worldwide using flexible non-linear functions. The curves were positive and increasing with no obvious thresholds, and demonstrated a much steeper slope at lower ranges. These findings indicate the need to establish an independent air quality guideline or standard for $PM_{2.5-10}$.

Among the 205 cities examined, the association with total mortality increased by 0.51% (95%CI: 0.18%, 0.84%) for a 10 $\mu g/m^3$ increase in $PM_{2.5-10}$ concentrations. The magnitude of the association is comparable with the result from a systematic review by Adar et al., which summarized 19 studies on $PM_{2.5-10}$ mostly from North America and Europe, and yielded a pooled estimate of 0.60% (95%CI: 0.30%, 0.80%) for total mortality (11). Our estimate is generally larger than previous national or regional studies. For a 10 $\mu g/m^3$ increase in $PM_{2.5-10}$, a time-series study in 47 cities of the United States

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estimated a 0.47% (95%CI: 0.21%, 0.73%) increase in all-cause mortality (22). A national study in 272 cities of China observed a 0.23% (95%CI: 0.13%, 0.33%) increase in non-accidental mortality (23). Another multicity study in 11 cities of Asia reported a marginally significant estimate of 0.39% (95%CI: -0.02%, 0.81%) for all-cause mortality (24). In contrast, a 10-city study in the European Mediterranean region found a positive but statistically non-significant association with an increase of 0.30% (95%CI: -0.10%, 0.69%) for all-cause mortality (25). The differences in previous findings do not necessarily reflect the diverse health impacts of $PM_{2.5-10}$. Rather, the coverage of regions and periods, population characteristics, exposure patterns, and even stochastic variability may contribute to the heterogeneity of previous findings. Our meta-regression analysis showed no significant effect modification by city-level factors on the $PM_{2.5-10}$–mortality association. Some of these results differ from previous findings in regional studies, although those earlier studies were primarily based on $PM_{2.5}$ or gaseous pollutants rather than coarse particles. For example, Deguen et al. reported that chronic exposure to higher air pollution levels was associated with larger risk of all-cause mortality in relation to short-term NO_2 exposure in Paris (26). Ou et al. found that low socioeconomic status enhanced short-term effects of PM_{10} on mortality in Hong Kong (27). Chen et al. observed stronger $PM_{2.5}$–mortality associations in cities with higher annual temperatures in China (17). These heterogeneous epidemiological findings may be due to the different locations and air pollutants examined, as well as the differences in composition and toxicity of coarse particles. Notably, our study used a uniform analytic framework and covered multiple regions worldwide, providing robust and consistent evidence on the association between $PM_{2.5-10}$ and daily mortality.

There is a crucial knowledge gap on whether $PM_{2.5-10}$ exposure could trigger health effects independently from $PM_{2.5}$, and whether it serves as a proxy for other air pollutants (9). In the systematic review by Adar et al., the associations between $PM_{2.5-10}$ concentration and mortality were sensitive to the adjustment of $PM_{2.5}$ in two-pollutant models, with the association weakened and became statistically insignificant in all scenarios (11). The lack of robust association was interpreted as potential confounding from $PM_{2.5}$ in the $PM_{2.5-10}$–mortality association. However, the observed non-significant estimates can be explained by other factors, such as the small study sample and the increased uncertainty

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due to between-study heterogeneity. In our analysis, the $PM_{2.5-10}$–mortality association decreased after adjusting for $PM_{2.5}$, but the association remained positive and statistically significant. In addition, the estimates were unaffected by control for gaseous pollutants. This global analysis demonstrated stable estimates of $PM_{2.5-10}$ when adjusting for $PM_{2.5}$ and gaseous pollutants, providing strong support to the hypothesis of an independent effect. Nevertheless, additional researches in more locations, on more health endpoints, with finer exposure assessment and with more sophisticated statistical techniques are encouraged to clarify the possible independent health effects of $PM_{2.5-10}$.

Quantifying the E–R relationship is crucial for bridging scientific evidence with policymakers. Compared with previous studies on short-term $PM_{2.5-10}$ exposure, our analysis had a much larger sample covering broader spatial areas, and for the first time it allowed us to pool E–R relationships for $PM_{2.5-10}$ exposure with total, cardiovascular and respiratory mortality. The curves had steeper slopes at lower concentrations, and kept increasing without obvious thresholds. This evidence highlights the need of establishing a unique air quality guideline or standard for daily concentration of ambient $PM_{2.5-10}$, considering the current absence of any regulatory framework for this specific pollutant.

Sources, compositions, and deposition mechanisms of particulate matter determine their toxicity (28). The primary contributors to $PM_{2.5-10}$ include crustal elements, metals from suspended road dust, and organic debris, which were basically generated from mechanic grinding and solid resuspension (29). However, coarse particles may also adsorb endotoxin, pesticides, and other toxic material (30, 31). Its high biological compositions and rich content of heavy metals may adversely impact health (9). Multiple toxicological studies and controlled human exposure studies reported that $PM_{2.5-10}$ may induce inflammatory effects, blood coagulation, and alterations in autonomic tone (32, 33). Although epidemiological explorations for $PM_{2.5-10}$ with subclinical markers are relatively sparse, there is still certain evidence on cardiac dysfunction (such as increased blood pressure and decreased heart rate variability), reduced pulmonary function, and perturbation in circulating cytokines (34-36). While the smallest particles in the size range of 2.5 to 10 μm can be deposited in the lungs, most are deposited in the conducting airways. Given the above reasons, a unique air quality regulation limit needs to be considered for this size fraction of particles.

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This study has several advantages. First, the analysis included 205 cities from 20 countries or regions, and this large study sample ensured higher statistical power and wider generalizability of the findings. Second, we examined the associations of $PM_{2.5-10}$ with cardiovascular and respiratory mortality, providing important information about its impacts on specific diseases. Third, we adopted a uniform analytical protocol across different regions and populations, which facilitates the integration and comparison of the results. Fourth, we pooled global E–R relationship curves for $PM_{2.5-10}$ and mortality within a wide concentration range, providing support for setting a unique air quality standard for $PM_{2.5-10}$.

Potential limitations of the current study should be acknowledged. First, most of the data included in this analysis was obtained from Europe, North America and East Asia. Although some countries with high $PM_{2.5-10}$ levels were included, such as China, Mexico and South Africa, the current results can be influenced by the selected locations and the absence or sparseness of data from West Asia, Africa, and Latin America, where the levels of wind-blown dust are high. The dust-originated $PM_{2.5-10}$ may differ from anthropogenic $PM_{2.5-10}$ in terms of toxicity and health effects (37). Thus, the extrapolation of our results to other areas should be performed with caution. Second, this time-series analysis was inherently an ecological study that used averaged $PM_{2.5-10}$ measurements as a proxy for population exposure. Results of such aggregate-level analysis lead to the correct point estimates in the absence of classical measurement error, but with an inflation of the uncertainty (38, 39). Third, as in most previous studies, we calculated the difference between PM_{10} and $PM_{2.5}$ as $PM_{2.5-10}$. This indirect approach may be affected by measurement errors of both PM_{10} and $PM_{2.5}$, compared to monitoring $PM_{2.5-10}$ directly (40). However, we postulate that such measurement errors would largely be non-differential as these concentrations were derived from collocated monitors that were designed to reflect the urban general level of air pollution (39). Future studies that use direct measures of $PM_{2.5-10}$ or rely on exposure assessment methodology with high spatial resolution are needed to alleviate these uncertainties. Fourth, missing data was inevitable in such a global study with a prolonged time span, but their amount was relatively small for both exposure and health data, and its influence on our estimates should be negligible. Finally, the characteristics of particles, including compositions and size fractions, may vary substantially by

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locations due to different contributions of sources such as transport and agriculture. These differences could explain heterogeneity of city-specific results and increase the uncertainty when pooling effect estimates for $PM_{2.5-10}$.

Conclusions

This time-series analysis provided supportive evidence on the independent associations of short-term exposure to $PM_{2.5-10}$ with increased risks for total, cardiovascular, and respiratory mortality across many regions of the globe. The associations remained robust after adjusting for $PM_{2.5}$, and gaseous pollutants, implying the necessity of setting a unique air quality guideline or regulation limit for ambient $PM_{2.5-10}$. The E–R curves were all positive and increasing without obvious thresholds, suggesting potential health benefits for continued reduction of ambient $PM_{2.5-10}$. Our findings may be helpful for future policymaking and public health actions against particulate air pollution.

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Figure Legends

Figure 1. Percent changes (mean and 95% confidence intervals) in total, cardiovascular, and respiratory mortality associated with a 10 μg/m^3 increase in $PM_{2.5-10}$ on different lag days. Lag 0, the present day; lag 1, the previous day; lag 2, the previous 2 day; lag 3, the previous 3 day; lag 0–1, moving average of the present and the previous day; lag 0–2, moving average of the present and the previous 2 days; lag 0–3, moving average of the present and the previous 3 days.

Figure 2. Percent changes (mean and 95% confidence intervals) in total, cardiovascular and respiratory mortality associated with a 10 μg/m^3 increase in $PM_{2.5-10}$ on lag 0–1 day in each country/region. Data on cause-specific mortality were not available in Australia, Chile, Estonia, Germany, and Romani, thus relevant estimates were not presented.

Figure 3. Exposure–response curves for $PM_{2.5-10}$ exposure (lag 0–1 day, μg/m^3) and total, cardiovascular, and respiratory mortality. The solid line indicates the pooled mean effect, and the dashed lines indicate the 95% confidence intervals. The vertical scale can be interpreted as the relative change of the mean effect of $PM_{2.5-10}$ on mortality; the fraction of the curve below zero denotes a smaller estimate compared with the mean effect.

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Table 1. Mortality and environmental data in 205 cities of 20 countries/regions.

Country /Region	No. of Cities	Period	Number of deaths (in thousands) *			Median (interquartile range)	
			Total	Cardiovascular	Respiratory	$PM_{2.5-10}$ (μg/m^3)	Temperature (℃)
Australia	3	1988–2009	1178	NA	NA	11.7 [8.6–15.4]	18.1 [14.7–21.2]
Canada	11	1986–2011	1758.7	615.1	139.9	8.9 [5.1–14.1]	7.5 [–0.3–15.2]
Chile	4	2006–2014	325.5	NA	NA	24.8 [17–35]	13.4 [10.3–17.3]
China	4	2005–2008	276.5	124.4	42.5	32.5 [16.9–57.0]	16.2 [6.3–23.6]
Estonia	3	1997–2015	49.8	NA	NA	5.6 [3.2–9.4]	5.9 [–0.3–13.6]
Finland	1	1994–2014	153.3	57.4	9.7	2.0 [1.1–3.9]	5.9 [0–13.8]
Germany	11	1993–2015	2876.4	NA	NA	5.9 [3.8–8.5]	10.5 [4.8–15.9]
Greece	1	2001–2010	288	136.2	28.8	12.5 [8–19.2]	17.9 [12.9–24.9]
Japan	46	2011–2015	1874.5	493.8	294.7	4.9 [2.9–7.6]	16.1 [7.6–22.7]
Mexico	3	1998–2014	2167.6	573.9	214	32.0 [22.4–42.7]	20.3 [17.5–22.5]
Norway	1	1969–2016	263.4	109.6	27.2	8.5 [5.4–13.9]	4.5 [–1.3–11.7]
Portugal	3	1980–2018	1012.6	401.4	88.8	8.3 [5.4–13.2]	15.6 [11.5–21]
Romania	2	1994–2016	127.9	NA	NA	12.8 [7.4–19.7]	12 [4.1–19.4]
South Africa	5	1997–2013	1231.2	193.5	166.6	26.6 [14.9–44.3]	17.5 [12.8–20.5]
Spain	15	1990–2014	1757.3	587.4	203.9	12.9 [9.6–17.2]	14.9 [10.5–20.2]
Sweden	1	1990–2010	201.2	91.3	15.9	5.3 [3.3–8.5]	6.8 [1.2–13.9]
Switzerland	4	1995–2013	167.9	64.3	10.6	6.9 [4.5–10.2]	10.9 [4.6–16.7]
Taiwan	3	1994–2014	1209.6	269.4	116.5	22.3 [15.9–30.6]	24.9 [20.4–28]
United Kingdom	24	1990–2016	4610.3	1683.3	681.3	5.3 [3.4–7.7]	10.4 [6.5–14.6]
United States	60	1973–2006	18305.2	6827.8	1593.5	11.5 [6.9–17.4]	14.4 [7.2–21.4]

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Pooled	205	1969–2018	39834.9	12228.9	3634	26.6 [19.4–35.7]	13.9 [7.4–19.9]

Abbreviations: $PM_{2.5-10}$, coarse particulate matter.

Notes: *Mortality data from cardiovascular and respiratory diseases were not available in Australia, Chile, Estonia, Germany, and Romania.

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Table 2. Percent changes (mean and 95% confidence interval) in total mortality associated with a 10 μg/m^3 increase in $PM_{2.5-10}$ on lag 0–1 day, with and without adjustment for co-pollutants.

Models	N	Estimates	*P*-values
Single-pollutant	202	0.50 (0.17, 0.83)	0.151
+ $PM_{2.5}$		0.33 (0.09, 0.56)	
Single-pollutant	172	0.48 (0.06, 0.90)	0.492
+ NO_2		0.47 (0.11, 0.85)	
Single-pollutant	158	0.48 (0.02, 0.94)	0.441
+SO_2		0.52 (0.10, 0.94)	
Single-pollutant	164	0.49 (0.01, 0.97)	0.420
+O_3		0.46 (0.01, 0.92)	
Single-pollutant	107	0.54 (0.19, 0.89)	0.639
+CO		0.62 (0.31, 0.94)	

Abbreviations: $PM_{2.5-10}$, coarse particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; CO, carbon monoxide.

Notes: N, number of cities with available data.

* *P*-value for difference was calculated by assigning a binary variable (indicating with or without adjustment for a co-pollutant) to each estimate, and then likelihood ratio tests were used to test differences in estimates between single- and two-pollutant models. *P*-values > 0.05 were considered as no statistically significant between-group differences.

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Figure 1

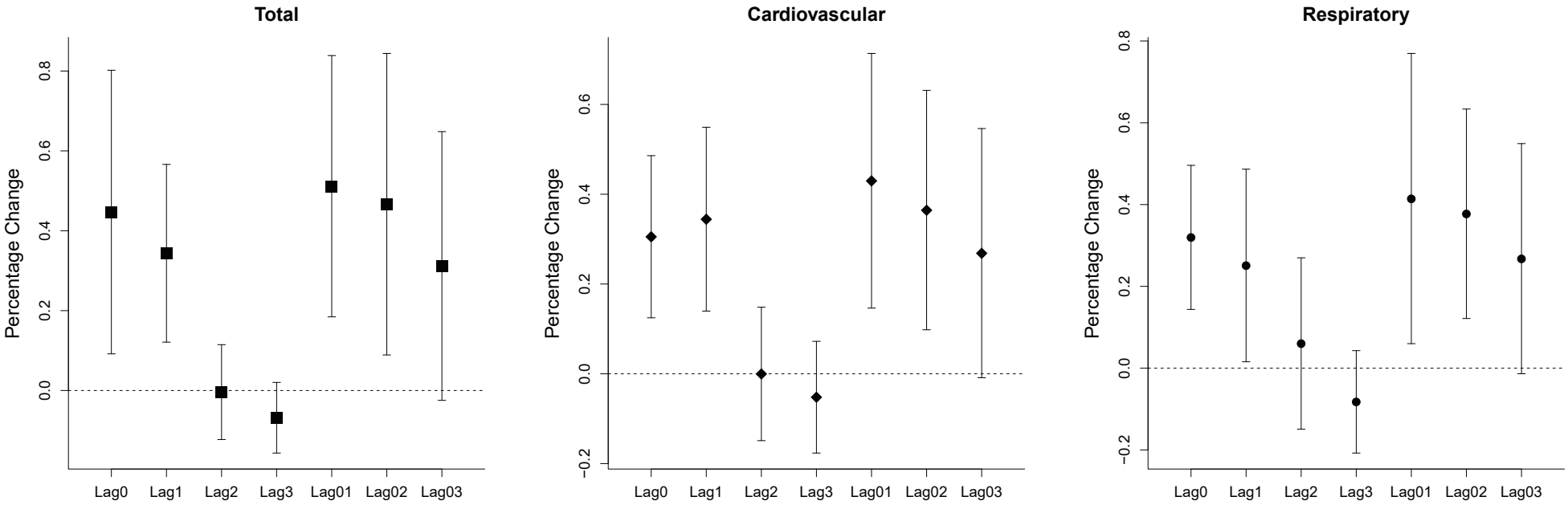

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Figure 2

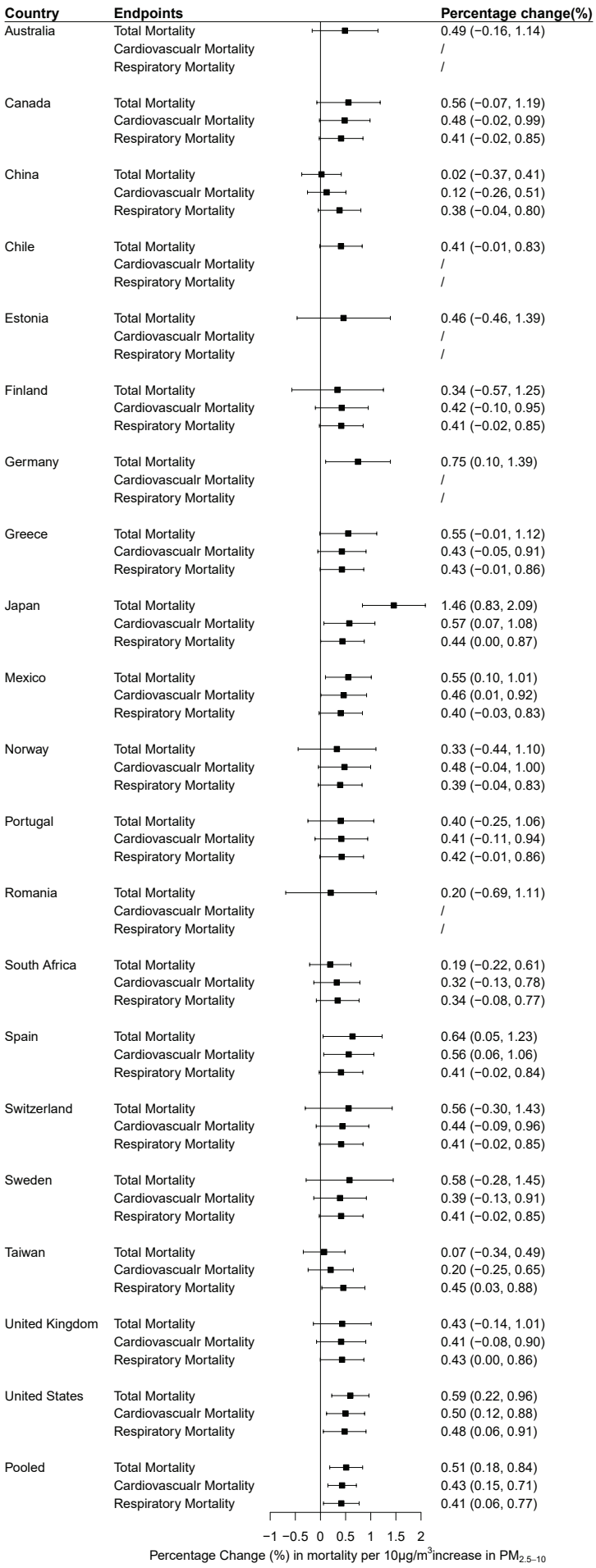

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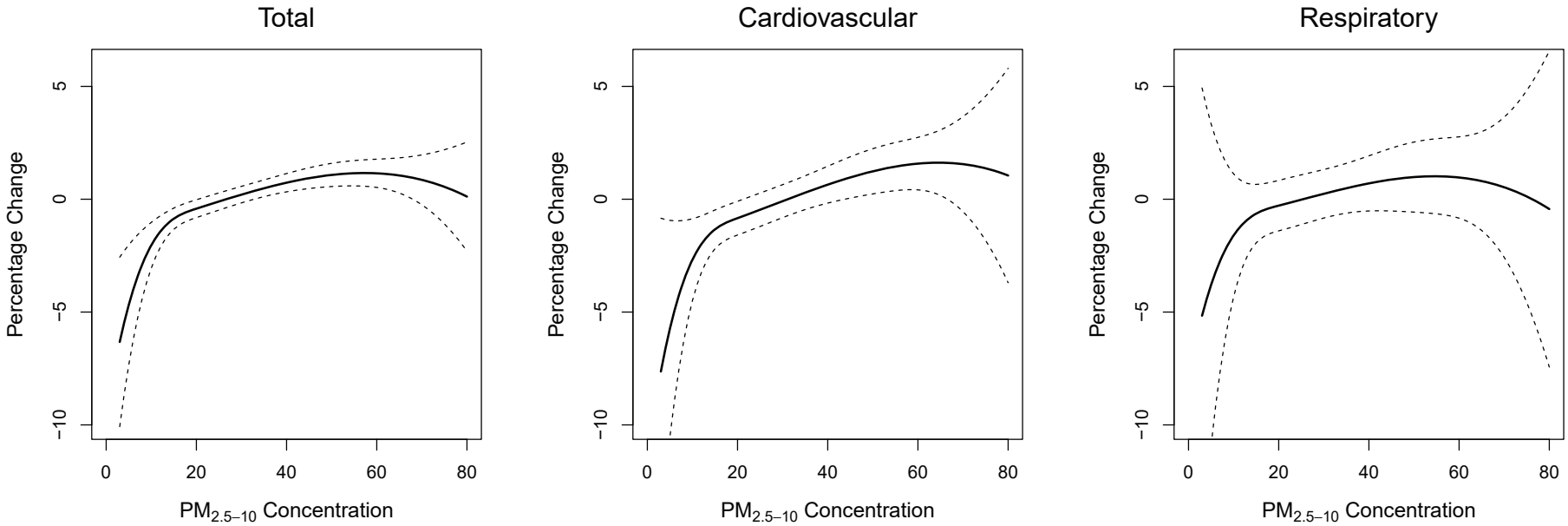
Figure 3



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Online Supplements

Coarse Particulate Air Pollution and Daily Mortality: A Global Study in 205 Cities

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increase in $PM_{2.5-10}$ (lag 0-1) for different time periods.

Table E7. Summary statistics on missing rates of health and exposure data at the country/region level.

Figure E1. Geographic distributions of the 205 cities within the 20 countries included in the analysis, and the corresponding annual mean $PM_{2.5-10}$ concentrations ($\mu g/m^3$).

References

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1. Supplemental Methods

1.1 Health and exposure data

We obtained mortality data from the Multi-City Multi-Country (MCC) database, which has been described in previous publications (1, 2). The current analysis was limited to locations with available data on $PM_{2.5-10}$, which included a total of 205 cities in 20 countries and/or regions with different study periods, including Australia (3 cities, 1988–2009), Canada (11 cities, 1986–2011), Chile (4 cities, 2006–2014), China (4 cities, 2005–2008), Estonia (3 cities, 1997–2015), Finland (1 city, 1994–2014), Germany (11 cities, 1993–2015), Greece (1 city, 2001–2010), Japan (46 cities, 2011–2015), Mexico (3 cities, 1998–2014), Norway (1 city, 1969–2016), Portugal (3 cities, 1980–2018), Romania (2 cities, 1994–2016), South Africa (5 cities, 1997–2013), Spain (15 cities, 1990–2014), Sweden (1 city, 1990–2010), Switzerland (4 cities, 1995–2013), Taiwan (3 cities, 1994–2014), United Kingdom (24 cities, 1990–2016), and United States (60 cities, 1973–2006). Concentrations of $PM_{2.5-10}$ were computed as the difference between PM_{10} and $PM_{2.5}$. Mortality data were obtained from local authorities within each country/ region. Causes of death were classified according to the 9th or 10th version of International Classification of Diseases (ICD) codes, wherever available. In each location, mortality is represented by daily counts of either non-external causes or, where not available, all-cause only (ICD-9: 0-799; ICD-10: A0-R99). We also collected mortality data for two main causes: cardiovascular disease (ICD-10, codes I00-I99) and respiratory disease (ICD-10, codes J00-J99) (3). Mortality from non-external causes were not available in Canada, Chile, Estonia, Germany, Greece, Japan, Portugal, Mexico, Romania, South Africa, Sweden, and United States. Deaths from cardiovascular and respiratory diseases were recorded in 180 cities from 15 countries, and were not available in Australia, Brazil, Chile,

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Estonia, Germany, and Romania (Table 1).

Daily data of other gaseous pollutants, including inhalable nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2) and carbon monoxide (CO), were also obtained where available, to adjust for potential confounding by co-pollutants. There were 172 cities with NO_2 data, 164 cities with O_3 data, 158 cities with SO_2 data, and 107 cities with CO data. In brief, measurements for air pollutants were obtained from fixed-site monitoring networks operated in the same standard by local authorities. The majority of monitors were located in urban areas, and daily time-series of $PM_{2.5}$ and PM_{10} was derived from one or more monitoring stations in each city; when more than one monitor, an average daily measurement was derived. Only those cities with daily measurements reporting above 75% of hourly data, in more than 300 days of a year, and with a coverage over a 3-year period were included. The overall missing rate for total mortality, $PM_{2.5-10}$ and temperature time-series was 0.20%, 10.02% and 2.10%, respectively. A detailed summary of missing rates for health and exposure data was provided in Table E7.

1.2 Lag structure

We selected and compared a list of lag structures for $PM_{2.5-10}$ and temperature that were reported in previous studies (2, 4-6). The lags of $PM_{2.5-10}$ include: 1) lag 0, the present day; 2) lag 1, the previous day; 3) lag 2, the day before lag 1; 4) lag 3, the day before lag 2; and 5) lag 0–1, the two-day moving average of the present day and the previous day; 6) lag 0–2, the three-day moving average of the present day and the previous two days; 7) lag 0–3, the four-day moving average of the present day and the previous three days

For temperature, we tested the traditional single lag days and moving averages, including 1) lag 0,

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the present day; 2) lag 0 and lag 1, separate terms of the present and previous day; 3) lag 0–3, the 4–day moving average of the present and previous 3 days; 4) lag 0 and lag 1–3, separate terms of the present day and the average of the previous 3 days; 5) lag 0–7, the moving average of the present and previous 7 days; 6) lag 0–14, the moving average of the present and previous 14 days, and 7) lag 0–21, the moving average of the present and previous 21 days (Table E4).

1.3 Heterogeneity and effect modification analyses

We explored potential effect modifiers on the associations between $PM_{2.5-10}$ and total mortality based on the main models. First, we conducted separate analyses by regions classified by the World Health Organization (WHO) (Table E1), which include Western-Pacific Region (WPRO), Regional Office for the Americas (AMRO), and Regional Office for Europe (EURO), and Regional Office for Africa (ROA). Then, the statistical significance for differences among groups were determined by likelihood ratio tests. Second, using the aforementioned approach, we conducted additional analyses by regions in terms of Gross Domestic Product (GDP) per capita at country/region level (Table E1). Third, we assessed potential effect modification in the $PM_{2.5-10}$-mortality associations by including annual-mean levels of all air pollutants and temperature, relative humidity, latitude of locations, region (WHO and GDP), and GDP per capita in meta-regression models all together.

2. Supplemental Results

2.1 Descriptive Statistics

Figure E1 illustrates the locations of cities included in present analysis and the average values of annual mean concentrations of $PM_{2.5-10}$ during the periods with available $PM_{2.5-10}$ ground measurements

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at city level. Table E1 summarizes the descriptive statistics of environmental data. The summary of missing rates for health and exposure data is provided in Table E7.

2.2 Heterogeneity, regional analyses, and effect modifications

Among all cities, heterogeneity was found in the $PM_{2.5-10}$-mortality association across city-specific estimates, with I^2 statistics of 43.16%, and Cochran Q *p*-value < 0.001.

In regional analyses (Table E3), the $PM_{2.5-10}$-mortality association was highest in the EURO with an average increment of 0.54% in total mortality per 10 μg/m^3 increase of $PM_{2.5-10}$ concentrations, and was lowest in the AMRO (corresponding estimate: 0.18%). The associations did not vary by GDP (*p*-value=0.192), with estimates of 0.32% (0.02%, 0.61%), 0.60% (0.25%, 0.95%), and 0.60% (0.28%, 0.92%) corresponding to low, medium, and high GDP areas, respectively. There was no significant effect modification by annual levels of air pollutants, temperature, relative humidity, GDP, WHO region and latitude of locations. Table E6 lists the results for different time-periods, and no significant difference was observed.

2.3 The impact of missing values

There were two types of missing data in the current study: one was caused by complete unavailability of measurements for certain variables in a city/country; and the other was caused by a small number of missing values scattered during the study time period of each city.

For the first type of missing data, the NAs in Table E2 denote lack of co-pollutant or relative humidity data in corresponding countries/regions, which are determined by the data availability in different countries/regions. Regarding to this kind of missingness, countries or regions with unavailable

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co-pollutants data were excluded accordingly; therefore, the number of countries/regions in Table 2 varied by co-pollutants. We did not control relative humidity in cities without such data, and a sensitivity analysis was conducted to test influence of this missing information on results (Table E5).

For the second type of missing data, there were also some missing values for air pollutant measurements in certain periods of consecutive days, which were mainly caused by data logging errors or abnormal operations of the monitoring equipment. This kind of missing is likely to be independent from any other predictors and especially the outcome. Multiple imputation or other imputation methods has been used to handle the issue of missing values in previous studies with small sample size, but it is unfeasible and not cost-effective in this large multi-location studies across dozens of countries. We thereby provided a summary of missing rates of mortality and exposure data at the country level (Table E7). The overall missing rates for total mortality, $PM_{2.5\text{-}10}$ and temperature were 0.20%, 10.02% and 2.10%, respectively. Thus, this amount of missingness is unlikely to produce appreciable influences on our estimates in main models.

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3. Supplemental Tables

Table E1. Summary of the locations, GDP, and region specification of the 20 countries/regions included in this analysis.

Country/Region	Cities	GDP per capita	WHO region	GDP region
Australia	3	54066	WPRO	2
Canada	11	45148	AMRO	2
China	4	8879	WPRO	1
Chile	4	14999	AMRO	1
Estonia	3	20388	EURO	1
Finland	1	46316	EURO	2
Germany	11	44349	EURO	2
Greece	1	18930	EURO	1
Japan	46	38386	WPRO	1
Mexico	3	9278	AMRO	1
Norway	1	75496	AMRO	3
Portugal	3	21490	EURO	1
Romania	2	10807	EURO	1
South Africa	5	6132	ROA	1
Spain	15	28170	EURO	1
Switzerland	4	80449	EURO	3
Sweden	1	53791	EURO	2
Taiwan	3	24283	WPRO	1
United Kingdom	24	40361	EURO	2
United States	60	59957	AMRO	3

Abbreviations: GDP, Gross Domestic Product; WHO, World Health Organization.

Notes: Regions by GDP: Regions classified by GDP per capita in 2017 according to World Bank (data.worldbank.org). Regions by WHO: classified by the World Health Organization, including the Western Pacific Region (Western-Pacific Regional Office, WPRO), the American Region (Regional Office for America, AMRO), the European Region (Regional Office for Europe, EURO), and the African Region (Regional Office for Africa, ROA)

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Table E2. Descriptive statistics of annual-mean concentration (median, 25%-75% percentiles) of coarse particulate matter ($PM_{2.5-10}$), weather conditions and other air pollutants in each country/region throughout the study period.

Country /Region	$PM_{2.5-10}$ (μg/m^3)	$PM_{2.5}$ (μg/m^3)	NO_2 (μg/m^3)	O_3 (μg/m^3)	SO_2 (μg/m^3)	CO (mg/m^3)	Temperature (℃)	Humidity (%)
Australia	11.7 [8.6-15.4]	6 [4.3-8.4]	21.4 [14.1-27.9]	3.3 [1.4-5.7]	29.9 [22.1-37.9]	0.4 [0.2-0.7]	18.1 [14.7-21.2]	70.1 [62.5-77.2]
Canada	8.9 [5.1-14.1]	6.7 [4.3-10.2]	27.5 [19.6-37.4]	3.5 [1.7-6.5]	36.9 [24.8-50.1]	0.4 [0.3-0.5]	7.5 [-0.3-15.2]	73.5 [64.8-82.1]
Chile	24.8 [17-35]	20.8 [12.7-40.2]	21.6 [13.9-32.4]	NA	25.2 [13.8-33.7]	0.6 [0.3-1.1]	13.4 [10.3-17.3]	NA
China	32.5 [16.9-57]	92.8 [61.9-134.7]	44.8 [33.8-58]	34.6 [23.1-60.3]	NA	NA	16.2 [6.3-23.6]	65.5 [53-77.2]
Estonia	5.6 [3.2-9.4]	6.6 [3.8-10.6]	8.2 [5.6-12.4]	1.5 [0.7-3.9]	51 [38.7-64.2]	NA	5.9 [-0.3-13.6]	83.7 [74-90.7]
Finland	2 [1.1-3.9]	12.6 [7.4-21.7]	6.8 [4.3-11.7]	6.2 [3.5-11.6]	51.3 [40-63]	0.3 [0.2-0.3]	5.9 [0-13.8]	79.2 [67.8-87.7]
Germany	5.9 [3.8-8.5]	12 [8-18.8]	29.5 [21.8-38.2]	4.5 [2.9-8.3]	38.5 [21.2-54.9]	0.4 [0.3-0.6]	10.5 [4.8-15.9]	NA
Greece	12.5 [8-19.2]	20.3 [15-26.4]	50.2 [39.6-61.6]	NA	75.1 [52.8-97.5]	1.8 [1.3-2.6]	17.9 [12.9-24.9]	66 [54-75.4]
Japan	4.9 [2.9-7.6]	12.6 [8.3-18.2]	17 [12.3-23.7]	5 [3.6-7.3]	56.3 [41.3-72.3]	NA	16.1 [7.6-22.7]	69.7 [60.7-77.9]
Mexico	32 [22.4-42.7]	25.1 [18.8-32.9]	NA	NA	124.8 [96-156.8]	NA	20.3 [17.5-22.5]	58.3 [45.2-70.6]
Norway	8.5 [5.4-13.9]	9.4 [6.9-12.8]	NA	NA	42.6 [30.5-54.5]	NA	4.5 [-1.3-11.7]	NA
Portugal	8.3 [5.4-13.2]	8.2 [5.4-12.8]	12.2 [8.1-17.9]	1.3 [0.9-2.4]	55.8 [43-68]	0.3 [0.2-0.4]	15.6 [11.5-21]	NA
Romania	12.8 [7.4-19.7]	15.5 [10.1-23.3]	23.9 [17.8-33.1]	10.7 [7.6-15.2]	38.1 [25.5-52]	0.2 [0.1-0.3]	12 [4.1-19.4]	75.7 [65.3-86.3]
South Africa	26.6 [14.9-44.3]	27.3 [18.6-39.8]	NA	NA	76.6 [59-99]	NA	17.5 [12.8-20.5]	NA
Spain	12.9 [9.6-17.2]	10.2 [7.2-14.5]	29.2 [22.2-37.6]	5.9 [4.4-7.9]	48.4 [35.1-60.1]	0.3 [0.3-0.4]	14.9 [10.5-20.2]	NA
Sweden	5.3 [3.3-8.5]	6.6 [4.7-9.5]	26.8 [20-34.8]	NA	61.9 [48.9-76]	0.9 [0.6-1.5]	6.8 [1.2-13.9]	79.6 [68.4-87.6]
Switzerland	6.9 [4.5-10.2]	16.2 [10.6-24.7]	35.2 [25.7-46.1]	3.8 [1.8-7.5]	73.2 [44.5-100.6]	0.6 [0.4-0.9]	10.9 [4.6-16.7]	75.6 [66.3-83.3]
Taiwan	22.3 [15.9-30.6]	32.3 [20.6-44.6]	42.2 [31.6-54.7]	13.4 [9.6-18.7]	65 [44.5-91.6]	0.7 [0.6-0.9]	24.9 [20.4-28]	75.3 [70.3-80.2]
United Kingdom	5.3 [3.4-7.7]	9.6 [6.8-14.9]	28.5 [20.2-38.9]	5.7 [2.8-10.3]	39.9 [27.3-52.4]	0.4 [0.2-0.5]	10.4 [6.5-14.6]	NA
United States	11.5 [6.9-17.4]	10.9 [7.5-16]	32.2 [23.6-42.9]	11.3 [6.5-18.9]	50.1 [34.6-66]	1 [0.7-1.4]	14.4 [7.2-21.4]	64.2 [53.9-74.5]
Pooled	26.6 [19.4-35.7]	24.8 [17.5-35]	13.6 [9.2-20.2]	50.6 [35.6-66.1]	7.6 [4.7-12.4]	0.7 [0.5-1.0]	13.9 [7.4-19.9]	68.1 [58.4-77.3]

Abbreviations: $PM_{2.5-10}$, coarse particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; CO, carbon monoxide.

Notes: NA denotes lack of specific variables in corresponding countries/regions.

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Table E3. Percentage change (mean and 95% confidence intervals) in total mortality associated with a 10 μg/m^3 increase in $PM_{2.5-10}$ stratified by WHO/GDP regions and *p*-values for testing difference among regions.

Classifications	Regions	Estimates	*P*-values*
WHO	AMRO	0.18 (-0.27, 0.64)	0.031
	WPRO	0.37 (-0.09, 0.84)	
	EURO[#]	0.54 (0.09, 0.99)	
GDP	1	0.32 (0.02, 0.61)	0.192
	2	0.60 (0.25, 0.95)	
	3	0.60 (0.28, 0.92)	

Abbreviations as in Table E1.

Notes:

* *P*-values were obtained by likelihood ratio tests comparing the fit of a meta-regression model with the region variable to the simple meta-analysis model. *P*-values < 0.05 were considered statistically significant for regional differences.

[#] As South Africa is the only country in ROA, it was classified in EURO for the region-specific analysis.

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Table E4. Percentage changes in total mortality associated with a 10 μg/m^3 increase in $PM_{2.5-10}$ (lag 0-1), with different modelling approaches to control for temperature.

Lags of temperature	Estimates (95%CI)	qAIC
Lag 0	0.15 (0.00, 0.29)	1951796
Lag 0+1	0.14 (0.02, 0.26)	1951055
Lag 0+1–3	0.14 (0.04, 0.23)	1948415
Lag 0–3	0.51 (0.18, 0.84)	1943723
Lag 0–7,	0.85 (0.46, 1.25)	1947343
Lag 0–14	0.93 (0.50, 1.37)	1944701
Lag 0–21	0.87 (0.42, 1.31)	1956128

Notes: Lag 0, the present day; Lag 0+1, the present and the previous day; Lag 0+1–3, the present day and the mean of the previous 3 days; Lag 0–3, moving average of the present day and the previous 3 days; Lag 0–7, moving average of the present day and the previous 7 days; Lag 0–14, moving average of the present day and the previous 14 days; Lag 0–21, moving average of the present day and the previous 21 days.

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Table E5. Percentage change (pooled estimate and 95% confidence intervals) in total mortality per 10 μg/m^3 increase in $PM_{2.5-10}$ (lag 0-1), with and without adjustment of relative humidity.

Endpoints	Adjustments	N	Estimates	P*
Total	RH adjusted	169	0.51 (0.44 to 0.59)	0.440
	RH unadjusted		0.54 (0.47 to 0.61)	
Cardiovascular	RH adjusted	159	0.44 (0.32 to 0.56)	0.757
	RH unadjusted		0.46 (0.34 to 0.58)	
Respiratory	RH adjusted	159	0.63 (0.53 to 0.73)	0.668
	RH unadjusted		0.67 (0.57 to 0.76)	

Abbreviations: RH, relative humidity.

* *P*-values for difference were calculated by evaluating a binary variable (with and without adjusting for humidity) in likelihood ratio tests with both model estimates. *P*-values < 0.05 were considered statistically significant for differences.

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Table E6. Percentage change (pooled estimate and 95% confidence intervals) in mortality per 10 μg/m^3 increase in $PM_{2.5-10}$ (lag 0-1) for different time periods.

Mortality endpoints	Time periods	N	Estimates	P*
Total	Before 2000 (included)	69	0.67 (0.17, 1.18)	0.588
	After 2000		0.53 (0.11, 0.95)	
Cardiovascular	Before 2000 (included)	65	0.49 (-0.24, 1.23)	0.846
	After 2000		0.60 (-0.14, 1.33)	
Respiratory	Before 2000 (included)	61	0.82 (-0.48, 2.15)	0.587
	After 2000		0.31 (-0.99, 1.63)	

Notes: * *P*-values for difference were calculated by evaluating a binary variable (before or after the year 2000) in likelihood ratio tests with both model estimates. *P*-values < 0.05 were considered statistically significant for differences.

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Table E7. Summary statistics on missing rates of health and exposure data at the country/region level.

Country /Region	Total	Cardiovascular	Respiratory	$PM_{2.5-10}$ ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	NO_2 ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)	O_3 ($\mu g/m^3$)	CO (mg/m^3)	Temp (℃)	Humidity (%)
Australia	NA	NA	NA	5.13%	2.92%	4.00%	3.82%	3.11%	1.64%	0.00%	0.00%
Canada	0.61%	0.45%	1.44%	11.33%	1.71%	4.11%	2.57%	2.68%	3.18%	0.65%	0.06%
Chile	NA	NA	NA	10.79%	8.62%	10.89%	NA	14.11%	11.18%	9.98%	NA
China	0.36%	0.00%	0.00%	20.78%	2.27%	0.89%	0.89%	NA	NA	0.00%	0.00%
Estonia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Finland	0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	4.97%	5.03%
Germany	NA	NA	NA	5.99%	1.78%	5.06%	6.90%	3.88%	4.23%	0.01%	NA
Greece	0.00%	0.00%	0.00%	NA	NA	NA	NA	NA	NA	NA	NA
Japan	0.00%	0.00%	0.00%	6.79%	0.60%	0.81%	3.14%	1.15%	NA	0.05%	0.13%
Mexico	0.00%	0.00%	0.00%	NA	NA	NA	NA	NA	NA	NA	NA
Norway	0.90%	1.36%	0.82%	0.90%	0.76%	NA	NA	3.45%	NA	0.00%	NA
Portugal	0.13%	0.92%	1.83%	8.62%	6.07%	13.85%	17.14%	2.98%	1.16%	7.61%	NA
Romania	NA	NA	NA	28.70%	18.14%	46.95%	34.84%	13.60%	31.91%	0.00%	0.00%
South Africa	0.00%	0.00%	0.00%	18.10%	11.95%	NA	NA	NA	NA	6.97%	NA
Spain	0.00%	0.00%	0.00%	3.58%	2.19%	4.03%	3.64%	2.52%	6.99%	0.07%	NA
Sweden	0.00%	0.00%	0.00%	NA	NA	NA	NA	NA	NA	NA	NA
Switzerland	0.00%	0.00%	0.00%	NA	NA	NA	NA	NA	NA	NA	NA
Taiwan	0.02%	0.00%	0.00%	0.02%	0.02%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%
United Kingdom	0.00%	0.00%	0.00%	10.00%	5.46%	11.84%	10.54%	12.88%	5.56%	0.00%	NA
United States	1.03%	1.03%	1.03%	19.51%	9.34%	9.77%	4.16%	21.26%	4.43%	1.25%	5.38%
Pooled	0.20%	0.25%	0.34%	10.02%	4.79%	8.63%	7.30%	6.28%	6.39%	2.10%	1.33%

Abbreviations as in Table E2.

Notes: NA denotes lack of specific variables in corresponding countries/regions.

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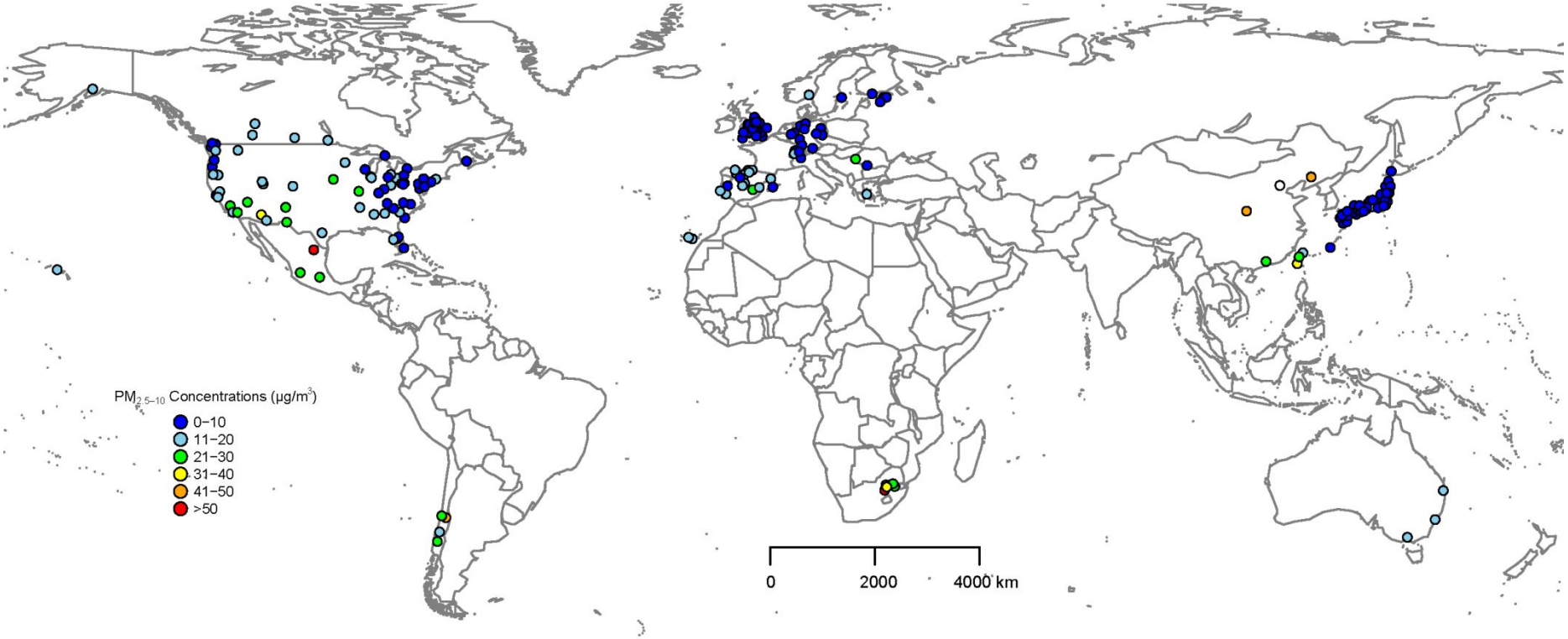

Figure E1. Geographic distributions of the 205 cities within the 20 countries included in the analysis, and the corresponding annual mean $PM_{2.5-10}$ concentrations (µg/m³).

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