ORIGINAL ARTICLE

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

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Abstract

Rationale: The associations between ambient coarse particulate matter ($PM_{2.5–10}$) and daily mortality are not fully understood on 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, and 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 PM. A two-stage time-series analytic approach was applied, with overdispersed generalized linear models and multilevel meta-analysis. We fitted two-pollutant models to test the independent effect of $PM_{2.5–10}$ from copollutants (fine PM, 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 $\mu g/m^3$ 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 copollutants 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 $PM_{2.5–10}$.

Keywords: air pollution; $PM_{2.5-10}$; mortality; multicenter study; time-series study

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 fewer investigations on the associations

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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 whereas PM_{10} and $PM_{2.5}$ are both regulated through the Air Quality Guidelines 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 U.S. Environmental Protection Agency had initially proposed a unique standard for $PM_{2.5–10}$ under the National Ambient Air Quality Standards in 2003 (9), but this initiative failed because of the inadequate available epidemiological evidence on the health effects of this pollutant.

Over the past 2 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 and colleagues extended this work in 2014 by incorporating new studies and summarizing results from multipollutant 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 of the lag structure, the shape of the

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: Evidence on the short-term association between ambient coarse particulate matter ($PM_{2.5–10}$) and mortality remains to be determined on 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 modeling approaches were used, leading to heterogeneous and incomparable results.

What This Study Adds to the Field: This global study in 205 cities found that each 10 μg/m3 increase in $PM_{2.5–10}$ 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 copollutants. The concentration–response relationships had no discernable thresholds with steeper slopes in lower concentrations, suggesting the need to set a unique daily standard for $PM_{2.5–10}$.

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

The MCC Network (Multi-City Multi-Country Collaborative Research Network; https://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 are independent of copollutants and pooled the exposure–response 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 in the online supplement. Mortality data were obtained from local authorities within each country/region. Causes of death were classified according to the ninth or 10th version of the International Classification of Diseases (ICD) codes, where available. In each location, mortality is represented by daily counts of either nonexternal causes (ICD-10, codes A00–R99) or, when 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).

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 the 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 on the basis of 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 seven degrees of freedom per year to control for unmeasured temporal trends and indicator variables for the day of the week. The temperature was adjusted using a natural spline function with 6 degrees of freedom and relative humidity using the same spline function with 3 degrees of freedom in cities in which 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 to 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, and 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 for $PM_{2.5–10}$ mortality associations at both concentrations (19). We computed global, country/region, and city-specific estimates with 95% confidence intervals (CIs) as percent change in daily mortality per 10 $\mu g/m^3$ 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 copollutants ($PM_{2.5}$, 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 in which we first combined the effect estimates derived from single and two-pollutant models, assigned a binary variable to each estimate (with or without a copollutant adjustment), and then performed a likelihood ratio test to examine the difference between estimates with and without the adjustment of copollutants. Countries or regions with unavailable copollutants data were excluded accordingly. Furthermore, we conducted

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

Country/Region	Cities, *n*	Period	Number of Deaths (in Thousands)*			Median (interquartile range)	
			Total	Cardiovascular	Respiratory	$PM_{2.5–10}$ (μg/m^3)	Temperature (°C)
Australia	3	1988–2009	1,178	NA	NA	11.7 (8.6 to 15.4)	18.1 (14.7 to 21.2)
Canada	11	1986–2011	1,758.7	615.1	139.9	8.9 (5.1 to 14.1)	7.5 (−0.3 to 15.2)
Chile	4	2006–2014	325.5	NA	NA	24.8 (17 to 35)	13.4 (10.3 to 17.3)
China	4	2005–2008	276.5	124.4	42.5	32.5 (16.9 to 57.0)	16.2 (6.3 to 23.6)
Estonia	3	1997–2015	49.8	NA	NA	5.6 (3.2 to 9.4)	5.9 (−0.3 to 13.6)
Finland	1	1994–2014	153.3	57.4	9.7	2.0 (1.1 to 3.9)	5.9 (0 to 13.8)
Germany	11	1993–2015	2,876.4	NA	NA	5.9 (3.8 to 8.5)	10.5 (4.8 to 15.9)
Greece	1	2001–2010	288	136.2	28.8	12.5 (8 to 19.2)	17.9 (12.9 to 24.9)
Japan	46	2011–2015	1,874.5	493.8	294.7	4.9 (2.9 to 7.6)	16.1 (7.6 to 22.7)
Mexico	3	1998–2014	2,167.6	573.9	214	32.0 (22.4 to 42.7)	20.3 (17.5 to 22.5)
Norway	1	1969–2016	263.4	109.6	27.2	8.5 (5.4 to 13.9)	4.5 (−1.3 to 11.7)
Portugal	3	1980–2018	1,012.6	401.4	88.8	8.3 (5.4 to 13.2)	15.6 (11.5 to 21)
Romania	2	1994–2016	127.9	NA	NA	12.8 (7.4 to 19.7)	12 (4.1 to 19.4)
South Africa	5	1997–2013	1,231.2	193.5	166.6	26.6 (14.9 to 44.3)	17.5 (12.8 to 20.5)
Spain	15	1990–2014	1,757.3	587.4	203.9	12.9 (9.6 to 17.2)	14.9 (10.5 to 20.2)
Sweden	1	1990–2010	201.2	91.3	15.9	5.3 (3.3 to 8.5)	6.8 (1.2 to 13.9)
Switzerland	4	1995–2013	167.9	64.3	10.6	6.9 (4.5 to 10.2)	10.9 (4.6 to 16.7)
Taiwan	3	1994–2014	1,209.6	269.4	116.5	22.3 (15.9 to 30.6)	24.9 (20.4 to 28)
United Kingdom	24	1990–2016	4,610.3	1,683.3	681.3	5.3 (3.4 to 7.7)	10.4 (6.5 to 14.6)
United States	60	1973–2006	18,305.2	6,827.8	1,593.5	11.5 (6.9 to 17.4)	14.4 (7.2 to 21.4)
Pooled	205	1969–2018	39,834.9	12,228.9	3,634	26.6 (19.4 to 35.7)	13.9 (7.4 to 19.9)

Definition of abbreviation: $PM_{2.5-10}$ = coarse particulate matter; NA = no available data.
*Mortality data from cardiovascular and respiratory diseases were not available in Australia, Chile, Estonia, Germany, and Romania.

regional analyses, with regions identified by strata of gross domestic product (GDP) per capita and WHO classification (Table E1), including the Western Pacific Region, the American Region, and the European Region. We also investigated potential effect modifiers (i.e., long-term degrees 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 exposure–response relationship curve using a meta-smoothing approach applied in previous studies (20, 21), modeling $PM_{2.5–10}$ as a nonlinear term through a natural spline function with knots at 25th and 75th percentiles of the exposure range of each location.

We conducted several sensitivity analyses to test the robustness of our estimates, including alternative choices for controlling for temperature, adjustment for relative humidity, and seasonal differences modeled through an interaction with an indicator of the warm/cold season (March to August vs. 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/region's time period).

We conducted all statistical analyses in R software (Version 3.3.1), using the *stats* and *dlnm* 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 nonexternal 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, whereas 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 annual mean temperature was 13.9°C (25–75% percentiles: 7.4–19.9°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 associations across city-specific estimates, with an I^2 statistic of 43.16%

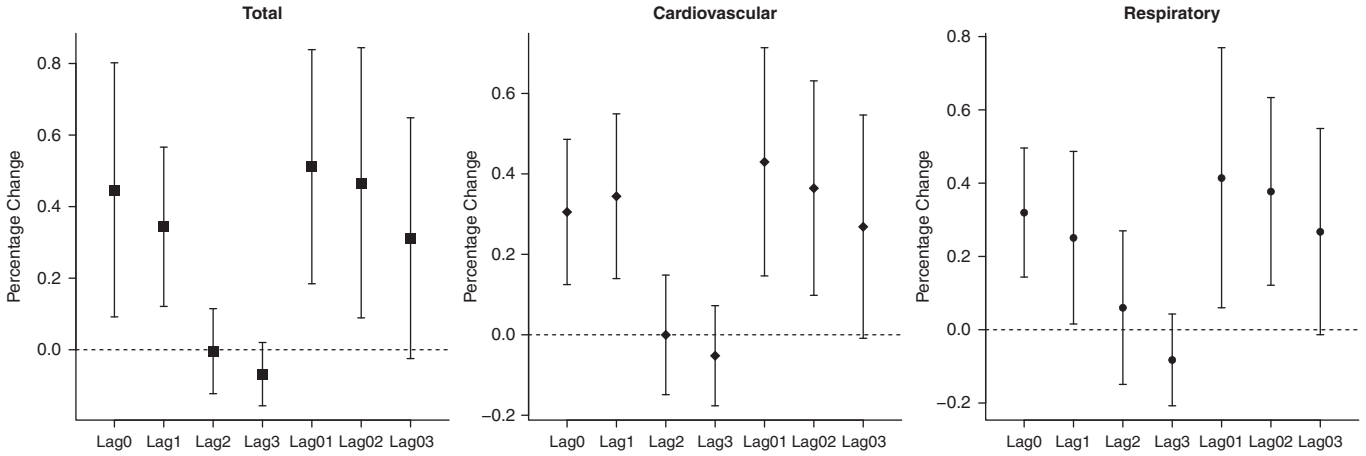

Figure 1. Percent changes (mean and 95% confidence intervals) in total, cardiovascular, and respiratory mortality were associated with a 10 $\mu g/m^3$ increase in ambient coarse particulate matter ($PM_{2.5–10}$) on different lag days. Lag 0, the present day; lag 1, the previous day; lag 2, the previous 2 days; lag 3, the previous 3 days; 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.

and a Cochran Q test *P* value < 0.001. Across 205 cities, a 10 $\mu g/m^3$ increase in $PM_{2.5–10}$ concentration was associated with an increase of 0.51% (95% CI, 0.18–0.84%) in total mortality; whereas 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 $\mu g/m^3$ 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 exposure–response relationship curves for $PM_{2.5–10}$ concentrations and three mortality endpoints modeled with flexible spline functions. The curves indicate increased risks, with much steeper slopes at concentrations less than 15 $\mu g/m^3$, then attenuating at exposure ranges lower than 60 $\mu g/m^3$, and eventually leveling off with wider CIs afterward. 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 copollutants, 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 European Region with an average increment of 0.54% in total mortality per 10 $\mu g/m^3$ increase of $PM_{2.5–10}$ concentrations and was lowest in the American Region (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 concentrations of air pollutants, temperature, relative humidity, GDP per capita, WHO region, or latitude 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, whereas larger estimates were generated with longer lags (Table E4). The quasi Akaike information criterion 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 a seasonal difference in the $PM_{2.5–10}$ mortality association (*P* value = 0.895), although the estimate in the cold season (0.49% [95% CI, 0.26–0.60%]) was smaller than that in the warm season (0.88% [95% CI, 0.40–1.37%]). Finally, the estimates for all three mortality outcomes did not vary substantially in the 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 exposure–response relationships between $PM_{2.5–10}$ and mortality across different regions worldwide using flexible nonlinear 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 and colleagues, which summarized 19 studies on $PM_{2.5–10}$, mostly from North

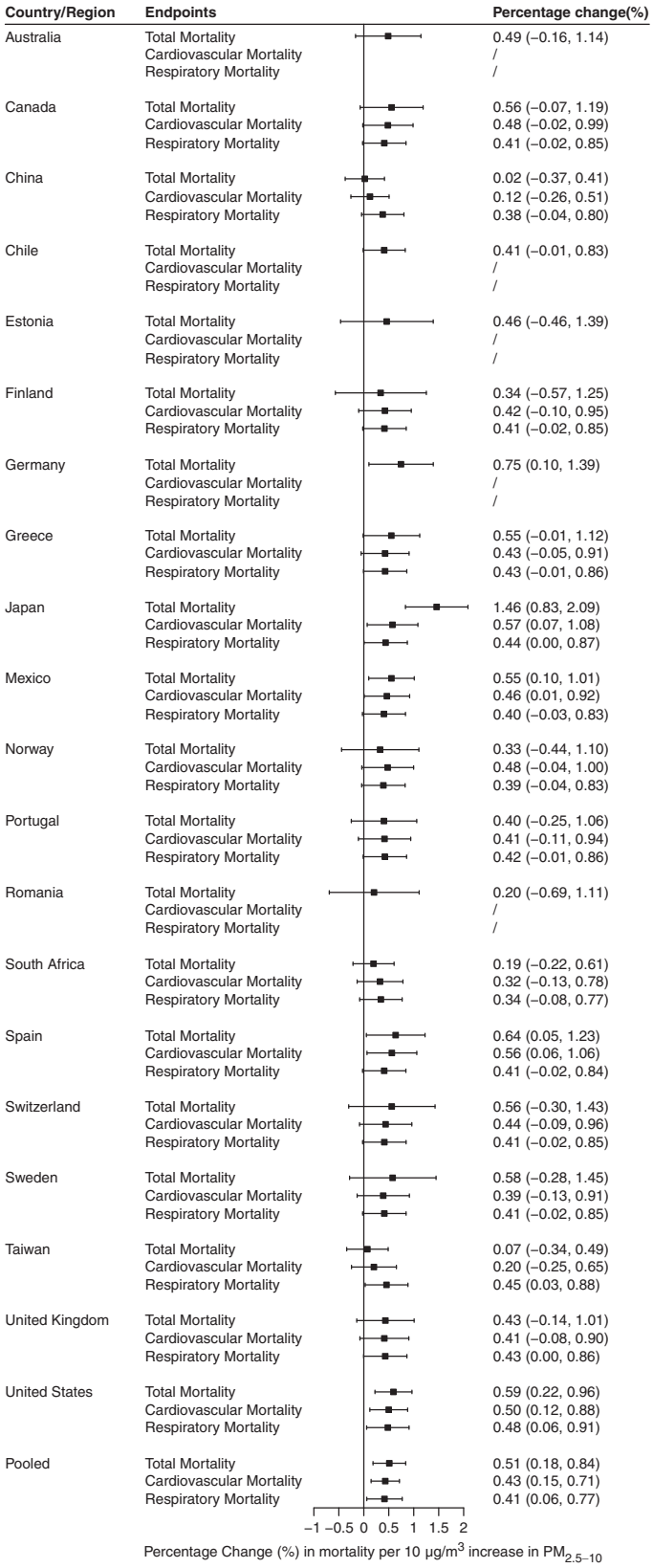

Figure 2. Percent changes (mean and 95% confidence intervals) in total, cardiovascular, and respiratory mortality associated with a 10 $\mu g/m^3$ increase in ambient coarse particulate matter ($PM_{2.5–10}$) on lag 0–1 day in each country/region. Data on cause-specific mortality were not available in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

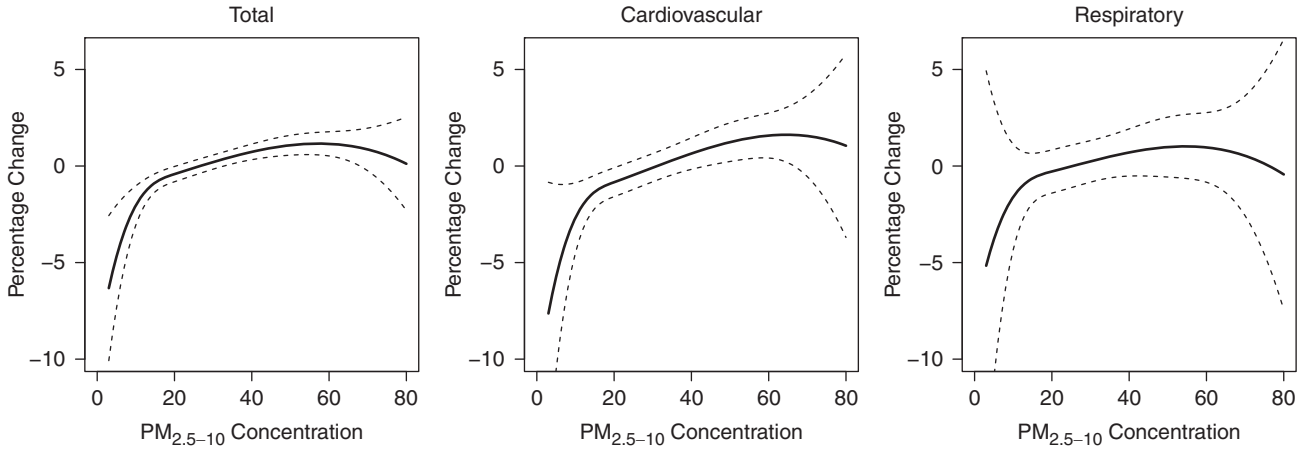

Figure 3. Exposure–response curves for ambient coarse particulate matter ($PM_{2.5–10}$) exposure (lag 0–1 day, μg/m^3) and total, cardiovascular, and respiratory mortality. The solid line indicates the pooled mean effect, and the dashed lines indicate the 95% confidence intervals. The vertical scale 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.

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 μg/m^3 increase in $PM_{2.5–10}$, a time-series study in 47 cities in the United States estimated a 0.47% (95% CI, 0.21–0.73%) increase in all-cause mortality (22). A national study in 272 cities in China observed a 0.23% (95% CI, 0.13–0.33%) increase in nonaccidental mortality (23). Another multicity study in 11 cities in Asia reported a marginally significant estimate of 0.39% (95% CI: −0.02% to 0.81%) for all-cause mortality (24). In contrast, a 10-city study in the European Mediterranean region found a positive but statistically nonsignificant association with an increase of 0.30% (95% CI, −0.10% to 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 on the basis of $PM_{2.5}$ or gaseous pollutants rather than coarse particles. For example, Deguen and colleagues reported that chronic exposure to higher air pollution concentrations was associated with a larger risk of all-cause mortality in relation to short-term NO_2 exposure in Paris (26). Ou and colleagues found that low socioeconomic status enhanced the short-term effects of PM_{10} on mortality in Hong Kong (27). Chen and colleagues observed stronger $PM_{2.5}$ mortality associations in cities with higher annual temperatures in China (17). These heterogeneous epidemiological findings may be because of 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 and colleagues, 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

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

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)	

Definition of abbreviations: CO = carbon monoxide; n = number of cities with available data; $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; $PM_{2.5–10}$ = coarse particulate matter; NO_2 = nitrogen dioxide; O_3 = ozone; SO_2 = sulfur dioxide.
**P* value for the difference was calculated by assigning a binary variable (indicating with or without adjustment for a copollutant) 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 not statistically significant between-group differences.

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 nonsignificant estimates can be explained by other factors, such as the small study sample and the increased uncertainty because of 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 research 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 exposure–response 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 exposure–response 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 to establish a unique air quality guideline or standard for a 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 of cardiac dysfunction (such as increased blood pressure and decreased heart rate variability), reduced pulmonary function, and perturbation in circulating cytokines (34–36). Although 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.

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 exposure–response 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 were obtained from Europe, North America, and East Asia. Although some countries with high $PM_{2.5–10}$ concentrations 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 concentrations 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 with monitoring $PM_{2.5–10}$ directly (40). However, we postulate that such measurement errors would largely be nondifferential as these concentrations were derived from collocated monitors that were designed to reflect the urban general degree 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 location because of different contributions of sources such as transport and agriculture. These differences could explain the 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 exposure–response curves were all positive and increasing without obvious thresholds, suggesting potential health benefits for the 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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