Temporal variations in the short-term effects of ambient air pollution on cardiovascular and respiratory mortality: a pooled analysis of 380 urban areas over a 22-year period

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RESEARCH IN CONTEXT

Evidence before this study. We conducted a literature search in PubMed without restrictions by language, including the following search terms: "air pollution" AND ("NO_2" OR "PM_{10}" OR "$PM_{2·5}$") AND "mortality" AND ("temporal variation" OR "temporal variability" OR "temporal*"). In addition, we restricted the publication date between January 1, 2013, and May 31, 2024, and included studies with a length of the respective study period of five or more years that investigated temporal variations in short-term effects of these air pollutants on cardio-respiratory mortality. The search revealed that previous epidemiological studies reported inconsistent associations over time and were mainly conducted in single cities or countries. In addition, these studies have shown substantial heterogeneity in factors such as geographic location, population demographics, socioeconomic factors, and statistical methods.

Added value of this study. This study of 380 cities across 24 countries provides global risk estimates of how the associations between short-term exposures to three commonly studied air pollutants and mortality have changed over 22 years. To our knowledge, this is the first study to apply a comprehensive and standardized analytical framework for a global set of cities to reduce bias and increase the comparability of results. Overall, the effect estimates for nitrogen dioxide (NO_2) and particulate matter with a diameter ≤10 µm (PM_{10}) and mortality did not exhibit a significant temporal change, although exposure concentrations have decreased over the past decades. However, a borderline significant temporal change in the effect estimate for particulate matter with a diameter ≤2·5 µm ($PM_{2·5}$) and cardiovascular mortality was seen. The effects may vary by different factors such as geographic region and co-pollutant adjustment, although the overall heterogeneity was rather moderate.

Implications of all the available evidence. The results suggest that a reduction in air pollution concentrations does not necessarily lead to a change in the association between air pollution and mortality or a reduction in the slope of the exposure-response function. This finding is consistent with a linear or supra-linear relationship when high air pollution concentrations were included, indicating that larger health benefits of air pollution mitigation may be achieved at lower levels of air pollution. Influencing factors such as the sources and composition of pollutants, social and economic determinants, but also human behavior and changes in population distribution warrant further research. Given the stable risk over time, it may be necessary to adapt and expand public health policies to attribute the risk of air pollution accurately, especially at low concentrations where mitigation measures are successful.

ABSTRACT

BACKGROUND. Ambient air pollution, including particulate matter (PM) with diameters ≤10 µm (PM_{10}) or ≤2·5 µm ($PM_{2·5}$) and nitrogen dioxide (NO_2), has been linked to mortality. It is unclear whether populations' vulnerability to these pollutants has changed over time, and studies lack multi-country analyses. We therefore evaluated whether changes in exposure were associated with changes in mortality effect estimates over time.

METHODS. We examined over 21·6 million cardiovascular and 7·7 million respiratory deaths in 380 cities across 24 countries between 1995 and 2016. We applied a two-stage approach to analyze the short-term effects of NO_2, PM_{10}, and $PM_{2·5}$ on cause-specific mortality using city-specific time series regression analyses and multilevel random-effects meta-analysis. We assessed changes over time using a longitudinal meta-regression with time as a linear fixed term and explored potential sources of heterogeneity and two-pollutant models.

FINDINGS. All three air pollutants showed decreasing concentrations over time. The pooled results suggested no significant temporal change in the effect estimates per unit exposure of PM_{10}, $PM_{2·5}$, or NO_2 and mortality. However, the risk of cardiovascular mortality increased from 0·37% (95%CI: -0·05% to 0·80%) in 1998 to 0·85% (95%CI: 0·55% to 1·16%) in 2012 with a 10 µg/m^3 increase in $PM_{2·5}$. Two-pollutant models generally showed comparable results for PM fractions and indicated temporal differences for NO_2.

INTERPRETATION. Although air pollution levels have decreased, the effect sizes per unit increase have not changed. This might be due to the composition and toxicity, air pollution sources, but also other factors, such as socioeconomic determinants, or changes in population distribution and susceptibility.

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INTRODUCTION

Ambient air pollution, especially particulate matter (PM) with diameters of 2.5 µm or 10 µm or less ($PM_{2.5}$ and PM_{10}, respectively), is a major environmental risk factor affecting the global mortality burden[1] and also significantly impacting the economy.[2] Epidemiological studies have extensively studied associations over the past decades, providing evidence of increased morbidity[3-5] and mortality[3,5-8] through various physiological pathways, including subclinical alterations.[9,10] These research efforts led to the implementation of evidence-based recommendations and legal public health policies, such as reference and target values, to reduce ambient air pollution levels and the related health burden in societies.[11] However, $PM_{2\cdot5}$ and nitrogen dioxide (NO_2) have been associated with mortality even at low exposure concentrations near or below the recommended target levels.[12]

Epidemiological short-term studies used to propose these recommended levels have mostly assumed a constant health risk over time, and potential temporal trends in associations were less often explicitly examined; thus, the legislative decisions based on those studies were made under this assumption. Furthermore, not considering temporal variations, e.g., in absolute exposure concentration or exposure mixture, limits the accurate representation of the health burden and could mask the positive impacts of technological improvements and past public health policies. In addition, changes in human behavior and/or temporal shifts in the underlying population distribution (e.g., epidemiological transition towards increasing life expectancy, aging populations, and chronic diseases) could contribute further to shifts in effect estimates by different exposure-response functions for subpopulations. Finally, understanding the temporal trends of air pollution effects is necessary to accurately estimate the future health benefits/detriments of different emissions scenarios. This is particularly relevant for studies of co-impacts ("co-benefits") for air quality and climate change mitigation policies.[13]

To date, large multi-country studies on temporal variations of short-term air pollution effects are still lacking; only single-country studies have explicitly addressed this research question. In general, although the concentrations of PM and NO_2 have decreased, studies reported inconclusive results regarding the temporal trend in their effect estimates per unit increase in air pollution.[14-20] Studies from Japan, China, Switzerland, South Korea, Greece, and Italy reported mixed results showing either an increase[14,15,17-20], a decrease[14,19,20], or no temporal trend[16,20] in the effect estimates between PM fractions or NO_2 and cardio-respiratory mortality. However, the comparability between studies, as well as the overall generalizability, is limited because different geographic regions and populations were analyzed, including locally prevailing air pollutant mixtures and different statistical approaches. In addition, a potential non-linearity in the

relationship between exposure and response may give the illusion of a change in risk following a change in air pollution concentration.

Therefore, this study aimed to examine temporal variations of ambient NO_2, PM_{10}, and $PM_{2.5}$ exposure concentrations using the large international Multi-Country Multi-City (MCC) Collaborative Research Network database over 22 years between 1995 and 2016. We hypothesized that changes over time also changed the associations between air pollution and mortality during the study period. In addition, we investigated temporal variations in the cause-specific mortality effect size estimates over the same period in two ways and evaluated the interdependencies of co-pollutants. Further, we assessed potential heterogeneity factors, such as the geographic region according to the World Health Organization classification.

METHODS

Data sources and selection of urban areas

We retrieved data from the MCC database, which has been previously analyzed and described in more detail (homepage: https://mccstudy.lshtm.ac.uk).[7,8,21] We *a priori* defined the study period between January 1, 1995 and December 31, 2016 because of limited available data before and after these years and excluded cities without available air pollution data from the dataset. Mortality data were obtained as daily counts from local authorities in each city and were classified according to the International Classification of Diseases, 10th Revision (ICD-10). In each city, we collected daily death counts due to cardiovascular (ICD-10 codes I00-I99) and respiratory (ICD-10 codes J00-J99) diseases. Air pollution data included 24-hour average NO_2, PM_{10}, and $PM_{2.5}$ concentrations measured by local reference/regulatory air quality monitoring stations. In addition, city-wide averages were calculated for cities with multiple monitoring stations, and city-specific daily averages of air temperature and relative humidity were also included in the dataset. Subsequently, each mortality case was linked to the exposure data at the city level. We incorporated additional indicators from the Organization for Economic Co-operation and Development Regional and Metropolitan Database[22], such as population density or gross domestic product per capita, and calculated climate variables based on location-specific distributions (e.g., temperature range).

We made further constraints to the original data to improve data quality regarding the analysis of temporal variations: 1) We removed city years with less than two-thirds of available data for that year. 2) We included cities with a minimum of five years of valid air pollution data. 3) We excluded cities with more

than 50% missing outcome data. The geographic distribution can be found in the appendix, with a more detailed description of the data collection per country (appendix pp. 1-6).

Statistical analysis

We used a two-stage modeling framework to analyze the associations between daily air pollution concentrations and cause-specific mortality.[23] In the first stage, we obtained city-specific risk estimates using a linear quasi-Poisson regression model. To be consistent with previous MCC analyses on PM fractions[7] and NO_2[8], we controlled for similar confounder models: long-term trends and seasonality, day of the week, temperature, and relative humidity. We used a natural spline with seven degrees of freedom per year for time trends, indicator terms for day of week, a natural spline of the four-day moving average concentrations using six degrees of freedom for temperature, and a natural spline using three degrees of freedom for same day relative humidity levels and present the results of lag 1 for NO_2 and lag 0-1 for PM fractions.[7,8] In the second stage, we pooled the city-specific results using a multilevel random-effects meta-analysis that accounted for variation in effect estimates by nested random terms of cities and countries.[24] The corresponding I^2 statistics and p-values (Cochran's Q test) were reported as measures of heterogeneity. All results are presented as percent change in daily mortality and 95% confidence intervals (CI) per 10 $\mu g/m^3$ increase in the air pollutant concentration.

The temporal variation in mortality effect estimates was assessed following the general modeling strategy, with further modifications to the design. For each city, we calculated yearly effect estimates (first stage) and pooled the yearly and city-specific results using a longitudinal multilevel meta-regression with time as a linear fixed term (second stage).[23,25] Based on the model results, we predicted the estimates over the study period and tested for the presence of a temporal difference by comparing the model with and without the linear term for time using a Wald-Test. As an alternative approach, we compared the effect estimates for three subperiods (1995-2001, 2002-2008, 2009-2016) separately. In the first stage, we calculated city-specific interactions per period, followed by the general modeling procedure without the longitudinal meta-regression (second stage) to obtain an overall pooled estimate for each period.

On an exploratory basis, we carried out several secondary analyses: 1) we replaced the linear term with a non-linear term of time in the longitudinal analysis; 2) we considered two-pollutant models to assess the potential confounding of co-pollutants by adding another primary pollutant as a second linear term in the main model. Therefore, we restricted our two-pollutant analysis to cities with data for both pollutants and followed the general modeling procedure; 3) we applied a multivariable meta-regression analysis that involved a set of nine meta-predictors (World Health Organization regions, gross domestic product per

capita, Köppen climate zones, average temperature and temperature range, average air pollution concentration, total population, population density, and proportion of old population) to investigate causes of heterogeneity affecting the longitudinal meta-regression results. In brief, we used a stepwise forward selection based on the Akaike information criterion to identify models that described most of the heterogeneity and reported the stratified results if the meta-predictor significantly improved the model fit.

We conducted a series of sensitivity analyses to assess the robustness of our findings (e.g., changing model parameters, confounding variables, or further restrictions to the dataset).

All statistical analyses were performed in R software, version 4.1.2 (R Foundation for Statistical Computing), using the packages *mgcv* (first stage), *mixmeta* (second stage), and *ggplot2* (visualization). Results with a p-value less than 0·05 were considered statistically significant.

A more detailed description of data collection and the statistical analysis can be found in the appendix (pp. 7-11).

ROLE OF THE FUNDING SOURCE

The funders of the study had no role in study design, data collection, data analysis, data interpretation, drafting of the manuscript, or the decision to submit the manuscript.

RESULTS

We analyzed more than 21·6 million cardiovascular and 7·7 million respiratory deaths in 380 cities across 24 countries worldwide over an average study period of 12·2 years (Table 1). More detailed information, such as city- and country-specific data or geographic distribution, can be found in the appendix (pp. 12-32; p. 37). Median concentrations (Interquartile range) of NO_2, PM_{10}, and $PM_{2·5}$ were 25·6 μg/m^3 (18·7-34·4), 27·6 μg/m^3 (19·9-38·4), and 11·5 μg/m^3 (7·9-16·9), respectively, and exhibited high heterogeneity within and between countries (appendix pp. 12-14). During the study period, there was a substantial reduction in NO_2 and PM_{10} concentrations, whereas $PM_{2·5}$ showed smaller decreases in concentrations (Figure 1; appendix p. 38). PM fractions were highly correlated (mean correlations over all cities, $r_S \geq 0·7$) with each other and moderately correlated with NO_2 ($r_S \geq 0·40$ and $r_S < 0·70$, appendix p. 33). Over time,

correlations between PM_{10} and $PM_{2·5}$ have increased and remained relatively stable for NO_2. However, some countries have shown changing correlations (data not shown).

In the pooled longitudinal analyses, no significant change in the effect estimates for NO_2 and PM_{10} was observed over the years (Figure 2). In contrast, we observed a borderline significant temporal difference for $PM_{2·5}$ and cardiovascular mortality (p = 0·05) (Figure 2; Table 2). A 10 μg/m^3 increase in $PM_{2·5}$ resulted in a 0·37% (95% CI: -0·05% to 0·80%) higher risk of cardiovascular mortality in 1998 and 0·61% (95% CI: 0·34% to 0·89%), and 0·85% (95% CI: 0·55% to 1·16%) in 2005 and 2012, respectively (Figure 2; Table 2). The regression slopes ranged from -0·003%/per year for cardiovascular mortality and PM_{10} to 0·036%/per year for respiratory mortality and $PM_{2·5}$. The country-specific results (appendix pp. 39-44) showed evidence of (moderate) heterogeneity (highest for respiratory mortality and PM_{10}: I^2 = 20·40%, p = 0·00) and different patterns between countries.

When a non-linear term replaced the linear term for time in the pooled longitudinal analyses, the overall pattern remained similar. However, temporal differences were observed for respiratory mortality and NO_2 and PM_{10} (appendix p. 45). An alternative assessment of temporal variation by separately comparing the three subperiods indicated overall comparable results of no major change in the mortality risk over time (Table 2; appendix p. 46).

Including PM size fractions in the NO_2 models generally showed an increasing trend for the NO_2 effect estimates for cardiovascular and respiratory mortality (Figure 3). A significant temporal trend for mortality was observed over the study period (cardiovascular mortality: NO_2+$PM_{2·5}$; respiratory mortality: NO_2+PM_{10} and NO_2+$PM_{2·5}$). However, these associations were observed in the single- and two-pollutant models. The associations remained nearly unchanged when NO_2 was added to the PM_{10} or $PM_{2·5}$ models, although $PM_{2.5}$+NO_2 showing temporal differences. However, it should be noted that the underlying number of cities has been reduced due to the simultaneous availability of both pollutants.

The results of the exploratory meta-regression models can be found in the appendix (p. 47). The association between $PM_{2·5}$ and cardiovascular mortality exhibited higher levels in the region of the Americas and a slight increase in the Western Pacific Region (appendix p. 47). For the association between NO_2 and respiratory mortality, a medium or higher gross domestic product per capita or temperature range (categorized in terciles: low, medium, high) indicated increased risks. However, none of the other meta-predictors significantly improved the models.

We observed robust positive pooled associations with cardiovascular and respiratory mortality for all three air pollutants over the entire study period, when examining associations without a temporal component in the analysis (appendix p. 48).

The results of the sensitivity analyses can be found in the appendix (pp. 34-36). In general, the results show stable findings for further data or city exclusions, changes in the statistical models, or temperature adjustment (appendix pp. 34-36). The exclusion of outliers in air pollution data showed increasing temporal trends in the association between $PM_{2·5}$ and cardio-respiratory mortality, but no changes were observed for PM_{10} or NO_2 (appendix pp. 34-36).

DISCUSSION

This multi-country, multi-city study provides evidence that there have been no significant temporal changes in the associations between PM_{10}, $PM_{2·5}$, or NO_2 and cardio-respiratory mortality. However, a tendency of a temporal increase in the effect estimate was found for $PM_{2·5}$ and cardiovascular mortality. Including a second pollutant in the main model showed no major changes for the PM fractions, although the effect estimates tended to increase over time for NO_2. The evaluation of spatial heterogeneity using nine explanatory meta-predictors indicated larger effect estimates in the Americas, as well as in regions with medium or high gross domestic product per capita or temperature range levels, with overall moderate heterogeneity.

Until now, most analyses of temporal variations in the effects of air pollution on mortality have been limited to individual countries or even cities. For example, two studies conducted in Seoul, South Korea, examined temporal trends from 1998-2015.[15,19] Both studies found slightly increasing associations between $PM_{2·5}$ or PM_{10} exposure and cardio-respiratory mortality over time, although Choi et al. (2018) reported a decrease in the effects of PM_{10} during the latest period (2011-2015).[19] Our country-specific analysis of seven South Korean cities indicated only slight increases in the PM_{10} effects on cardio-respiratory mortality over time. A time-series study in Switzerland over 16 years (1995-2010) found a significantly increasing trend for PM_{10} and cardiovascular mortality.[14] Also, Perez et al. (2015) reported a slight decrease in the association between NO_2 and respiratory mortality, especially among older people (65y+). Our findings differ from these results as we found no significant differences for either PM_{10} or NO_2 effects over time, indicating relatively stable effect sizes. Moreover, our country-specific estimates suggest a slight decreasing non-significant trend for NO_2 and cardiovascular mortality in Switzerland. However, the analyses might not be directly comparable because of differences in the included cities (eight major cities

vs. 21 Swiss cantons) and statistical methods. A single-city study conducted in Rome, Italy, for the period 1998-2014 reported no consistent trends over time in the effects of NO_2, PM_{10}, and $PM_{2·5}$ on non-accidental mortality. However, the strongest associations were seen in the most recent periods, except for NO_2. Furthermore, the results remained constant when additional meta-regressors (e.g., temperature) were included in the models.[16] Finally, a recent study conducted in ten Japanese cities found evidence of a negative linear trend for suspended PM and cardiovascular mortality over 39 years (1977-2015), contrary to our country-specific findings.[20] However, the authors found the highest estimates in the earliest period (1977-1980), which is not included in our analysis and may have contributed to the different results. In addition, Nishikawa et al. (2023) reported increased associations with respiratory mortality in the most recent periods and observed no temporal changes when examining gaseous pollutants, consistent with our findings.[20]

In recent decades, air pollution concentrations have generally declined in most regions, particularly North America and Europe.[3,5,26] However, our analyses indicate that, on average, 690 (17·3%), 886 (31·9%), and 2,286 (49·0%) days still exceeded the current 24-hour World Health Organization air quality standards for PM_{10}, $PM_{2·5}$, and NO_2, respectively. In addition, some regions showed opposite trends, with increasing air pollution levels[11], some of which may be attributed to wildfires.[27] Therefore, in our secondary analyses, we aimed to examine spatial heterogeneity and dependencies of multiple pollutants. Our models indicated low spatial heterogeneity ranging from 10·39% ($PM_{2·5}$ and respiratory mortality) to 20·40% (PM_{10} and respiratory mortality). In addition, we identified the World Health Organization regions as a potential factor that may have contributed significantly to this variability. We observed higher estimates in the regions of the Americas compared to Europe, as well as in regions with higher gross domestic product per capita or wider temperature ranges. Liu et al. (2019) previously reported similar heterogeneity in PM effects on total mortality.[7] Possible contributors to these variations include susceptibility and health behavior of the population, lower air pollution concentrations in North America, different lengths of study periods or different local climate patterns.[7] In future research, it will be important to disentangle the co-impacts/co-benefits of air quality and climate change mitigation policies, along with the health benefits and harms of different emission scenarios in the context of climate change and rising global temperatures.[13]

Breitner et al. (2009) discussed two competing factors contributing to changes in association with changes in exposure concentration: 1) alterations in the effect estimate due to a non-linear exposure-response relationship, or 2) a linear exposure-response relationship but the measured pollutant marks changes in the exposure mixture or source composition.[28] We found no evidence contradicting our linear model

assumptions (data not shown), although we cannot completely rule out the possibility of non-linearity (e.g., a supra-linear relationship with steeper slopes at low concentrations and flatter/continuous slopes at high concentrations may indicate changes, particularly in low pollution settings[29]). Furthermore, technological advancements, such as particle filters or new combustion engine technologies, could reduce PM mass from, e.g., diesel engines[30], but not necessarily gaseous emissions. Moreover, PM consists of several components that have changed over time, contributing to the decrease in $PM_{2.5}$ concentrations.[5] A multi-country, multi-city study investigated the differential health effects of $PM_{2.5}$ composition and examined yearly differences in $PM_{2.5}$ components between regions and over time. While some countries showed relatively stable $PM_{2.5}$ compositions, others exhibited slight changes and a wide temporal variability (e.g., reduction of sulfate (SO_4^{2-}) content in the UK).[31] In addition, the authors reported a greater proportion of nitrate in Northern and Central European countries and SO_4^{2-} in countries with higher temperatures, which are the two largest contributors to $PM_{2.5}$, and are linked to fossil fuel combustion.[31] The reported relative risks indicated an increasing mortality risk for all components, although changes in the proportion modified the risk.[31] We also observed changing correlations between PM fractions and NO_2, which may have contributed to different associations over time. However, given the remaining issues of co-pollutant models (e.g., multicollinearity, differentiation of direct effects of one pollutant in the presence of others) and different PM compositions, the interpretation of the results is not straightforward. Further, we cannot rule out the presence of residual confounding because air pollution is a complex mixture of different pollutants and components.

However, considering changes in $PM_{2.5}$ composition over time and its associations with mortality, as reported by Masselot at al. (2022), a changing exposure mix or composition may have contributed to our findings. In addition, changing demographics (e.g., children or older people), health behaviors (e.g., using face masks, air purifiers, or spending more time outdoors), or population vulnerabilities (e.g., chronic diseases) may be among the factors driving changes over time.

In summary, the complexity of a changing environment over time emphasizes the need for further analyses of temporal variations across multiple countries and cities with a unified analytical approach to explain observed differences and further verify our findings. Future research should include more spatially and temporally resolved meta-predictors and chemical composition data in the context of changing populations and complex exposure-response relationships.

To our knowledge, this is the first multi-country, multi-city study specifically designed to examine differences in air pollution effects over time. The large sample size provides good statistical power and stability to analyze effects even for cause-specific mortality endpoints. We applied comprehensive and

standardized state-of-the-art analytical methods to account for city- and country-specific differences. We thoroughly constrained our dataset to increase internal validity and comparability across cities and time periods and were able to validate previous findings with this dataset.

However, it is important to acknowledge several limitations. First, although our final dataset included 380 cities in 24 countries worldwide, some regions, such as the Middle East, Latin America, and Africa, were underrepresented, and thus generalizations should be made with caution. Second, the spatial resolution and representativeness of data collected from fixed monitoring stations might be limited, which could result in exposure misclassification. Additionally, it should be noted that extrapolating the results to an entire country is inaccurate because some countries provided data from only one city. Moreover, numerous cities had exposure settings that were primarily urban or suburban, which could differ from rural areas in terms of chemical composition. In addition, it is important to consider that certain cities and countries contributed at different time points during the study period, and that changes in population numbers were not considered due to data unavailability or sparse data on an annual basis. Third, more detailed exposure information was unavailable, such as the chemical composition of PM (e.g., sulfate or nitrate content) or different PM sub-fractions (e.g., ultrafine particles), which may be key factors in toxicity and overall PM risk. Fourth, the study relied on city-level time-series data without more detailed analysis at the individual level (e.g., age or biological sex). Furthermore, the potential for exposure measurement error over past decades (e.g., relocation of monitoring stations) or the ecological fallacy could have impacted the results; however, visual inspection of the individual time series (data not shown) suggested this to be marginal. Finally, we only analyzed the primary coded cardiovascular and respiratory mortality endpoints. However, air pollution exposure is also related to non-fatal disease endpoints. For example, it has been associated with temporal changes in hospitalizations.[13] A more detailed investigation was beyond the scope of this paper and warrants further research.

In conclusion, this study provides evidence that although air pollution levels have decreased over a 22-year period, the related effects on mortality have not changed. This might be due to the overall toxicity of the air pollution mix and their sources, differences in socioeconomic factors, or changes in population distribution or susceptibility. Future research is required to understand how temporal variations in these factors influence the health impacts of air pollution. Research efforts would benefit from more standardized and multi-country analyses, enhanced data quality and accessibility, and the exploration of underlying factors that may drive temporal trends in the associations between air pollution and cardio-respiratory mortality, such as geographical or sociodemographic factors. These are particularly important

to support mitigation measures to allow reaching the updated World Health Organization air quality guidelines.

DECLARATION OF INTEREST. The authors report no conflicts of interest.

Author contributions. MSc, SBr, AS, FdD, MSt, AG, and FS were involved in the design of the study. MSc and SBr accessed and verified the data, performed the analyses, drafted an internal summary report to circulate preliminary results and visualizations, and wrote the first version of the manuscript. AS, FdD, MSt, FS, and AG provided assistance with the methodological framework, and the rest of the MCC Collaborative Research Network provided the country-specific air pollution and mortality data. All authors had access to all the included data, contributed to the interpretation and visualization of the results, read the manuscript, and approved the final version. The decision to submit the manuscript was made by MSc and SBr following consultation with all authors.

Data sharing: The mortality data is not publicly available due to restrictions imposed by data usage agreements with the respective data providers of the included countries.

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Figure 1. Yearly boxplots across cities of 24-hour average concentrations (in $\mu g/m^3$) of NO_2 (green, top panel), PM_{10} (blue, middle panel), and $PM_{2\cdot5}$ (red, bottom panel). Note: Only one city contributed $PM_{2\cdot5}$ data in 1995 and 1996.

Figure 2. Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 $\mu g/m^3$ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2\cdot5}$ (bottom panel, at lag 01) over the study period 1995-2016. The figure represents the results of the pooled longitudinal meta-regression using time as a linear term. The p-value of the corresponding Wald-Test indicates a significant difference of the model with the linear term for time compared to a model without the linear time term.

Figure 3. Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 $\mu g/m^3$ increase in NO_2 (top two panels, at lag1), PM_{10} (second panel from below, at lag01), and $PM_{2\cdot5}$ (bottom panel, at lag 01) over the study period 1995-2016. The colored graphs represent the results of the pooled two-pollutant longitudinal meta-regression using time as a linear term. The black graphs represent the single-pollutant models (restricted dataset including both pollutants). The p-value of the corresponding Wald-Test indicates a significant difference of the model with the linear term for time compared to a model without the linear time term; NO_2 models were adjusted for additional PM fractions, PM models for NO_2.