# 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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## Summary

**Background** Ambient air pollution, including particulate matter (such as $PM_{10}$ and $PM_{2·5}$) and nitrogen dioxide ($NO_2$), has been linked to increases in mortality. Whether populations' vulnerability to these pollutants has changed over time is unclear, and studies on this topic do not include multicountry analysis. We evaluated whether changes in exposure to air pollutants were associated with changes in mortality effect estimates over time.

**Methods** We extracted cause-specific mortality and air pollution data collected between 1995 and 2016 from the Multi-Country Multi-City (MCC) Collaborative Research Network database. We applied a two-stage approach to analyse 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** Over 21·6 million cardiovascular and 7·7 million respiratory deaths in 380 cities across 24 countries over the study period were included in the analysis. 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% (0·55 to 1·16) in 2012 with a 10 μg/m³ increase in $PM_{2·5}$. Two-pollutant models generally showed similar results to single-pollutant models for PM fractions and indicated temporal differences for $NO_2$.

**Interpretation** Although air pollution levels decreased during the study period, the effect sizes per unit increase in air pollution concentration have not changed. This observation might be due to the composition, toxicity, and sources of air pollution, as well as other factors, such as socioeconomic determinants or changes in population distribution and susceptibility.

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## Introduction

Ambient air pollution, especially particulate matter ($PM_{2·5}$ and $PM_{10}$), is a major environmental risk factor contributing to the global mortality burden[1] and also substantially impacting the economy.[2] Epidemiological studies have extensively studied the associations between air pollution and adverse health effects 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 its related health burden worldwide.[11] However, air pollutants such as $PM_{2·5}$ and nitrogen dioxide ($NO_2$) have been associated with mortality risk 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 (eg, 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 behaviour or temporal shifts in the underlying population distribution (eg, longer life expectancy, ageing populations, and increased prevalence of chronic

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## Research in context

### Evidence before this study

In the past, ambient air pollution has been associated with mortality. However, it remains unclear whether changes in exposure concentrations over time are associated with changes in mortality effects. We searched PubMed with the following terms: "air pollution" AND ("$NO_2$" OR "$PM_{10}$" OR "$PM_{2·5}$") AND "mortality" AND ("temporal variation" OR "temporal variability" OR "temporal*"), with no language restrictions, for studies published between Jan 1, 2013, and May 31, 2024. Studies covering a period of 5 years or more and investigating temporal variations in short-term effects of three air pollutants ($PM_{10}$, $PM_{2·5}$, and $NO_2$) on cardiovascular and respiratory mortality were reviewed. Previous epidemiological studies have 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 geographical location, population demographics, socioeconomic factors, and statistical methods.

### Added value of this study

This pooled analysis comprises data from 380 cities across 24 countries and provides global risk estimates of the associations between short-term exposures to three commonly studied air pollutants and mortality over 22 years (1995–2016). To our knowledge, this is the first study to apply a comprehensive and standardised analytical framework to a global dataset of cities to reduce bias and increase the comparability of results. We found no significant temporal changes in effect estimates for the association between $NO_2$ and $PM_{10}$ and mortality, although exposure concentrations have decreased over the past decades. A borderline significant temporal change in the effect estimate for $PM_{2·5}$ and cardiovascular mortality was seen. The effects might vary by different factors such as geographical region and co-pollutant adjustment, although the overall heterogeneity between cities or countries was moderate.

### Implications of all the available evidence

These results suggest that reductions in air pollution concentrations during the study period did not necessarily lead to a change in the association between air pollution and mortality or to a reduction in the slope of the exposure–response function. These findings are consistent with a linear or supralinear relationship when high air pollution concentrations were included, indicating that larger health benefits of air pollution mitigation might be achieved at lower levels of air pollution. Influencing factors such as the sources and composition of pollutants, social and economic determinants, human behaviour, and changes in population distribution warrant further research. Given the stable risk over time, adapting and expanding public health policies might be necessary to attribute the risk of air pollution accurately, especially at low concentrations, where mitigation measures are successful.

diseases) could further contribute to changes 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 or detriments of different emissions scenarios, which is particularly relevant for studies of co-impacts (also called co-benefits) for air quality and climate change mitigation policies.[13]

To date, there have been no large multicountry studies on temporal variations of short-term air pollution effects; only single-country studies have explicitly addressed this research question. In general, although the concentrations of particulate matter (PM) and $NO_2$ have decreased, studies have reported inconclusive results regarding the temporal trend in their effect estimates per unit increase in air pollution concentration.[14–20] Studies from Japan, China, Switzerland, South Korea, Greece, and Italy have 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 cardiovascular or respiratory mortality. However, comparability between studies and the overall generalisability are limited because different geographical regions and populations were analysed, including locally prevailing air pollutant mixtures and different statistical approaches. In addition, potential non-linearity in the relationship between exposure and response might give the impression of a change in risk following a change in air pollution concentration.

Therefore, with this study, we aimed to examine temporal variations in ambient $NO_2$, $PM_{10}$, and $PM_{2·5}$ exposure concentrations using the large international Multi-Country Multi-City (MCC) Collaborative Research Network database. We hypothesised 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. Furthermore, we assessed potential heterogeneity factors, such as the geographical region according to the WHO classification.

## Methods

### Data sources and selection of urban areas

We retrieved data from the MCC database, which has been previously analysed and described in more detail.[7,8,21] We defined the study period between Jan 1, 1995, and Dec 31, 2016, because data before and after these years were scarce (eg, data from only one country), and excluded cities without available air pollution data. Mortality data were obtained as daily counts from local authorities in

each city and were classified according to 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 h average $NO_2$, $PM_{10}$, and $PM_{2·5}$ concentrations measured by local reference or 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 Organisation 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 (eg, temperature range).

We made further constraints to the original data to improve data quality regarding the analysis of temporal variations: first, we removed individual years in cities with less than two-thirds of available data for those years; second, we only included cities with a minimum of 5 years of valid air pollution data; and finally, we excluded cities with more than 50% missing outcome data. A detailed description of the data collection per country can be found in the appendix (pp 1–6).

## Statistical analysis

We used a two-stage modelling framework to analyse 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 of 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 (df) per year for time trends; indicator terms for day of week; a natural spline of the 4-day moving average concentrations using six df for temperature; and a natural spline using three df for same day relative humidity levels. We 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

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For the **MCC Collaborative Research Network** see https://mccstudy.lshtm.ac.uk

See **Online** for appendix

| | $NO_2$ | | | | $PM_{10}$ | | | | $PM_{2·5}$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cities (n) | Period | Cardiovascular deaths (n) | Respiratory deaths (n) | Cities (n) | Period | Cardiovascular deaths (n) | Respiratory deaths (n) | Cities (n) | Period | Cardiovascular deaths (n) | Respiratory deaths (n) |
| Canada | 25 | 1995–2015 | 826 003 | 224 702 | 7 | 2000–11 | 153 068 | 40 410 | 25 | 1997–2015 | 673 436 | 187 688 |
| China | 2 | 1996–2008 | 76 689 | 44 549 | 2 | 1996–2008 | 76 689 | 44 549 | .. | .. | .. | .. |
| Colombia | 1 | 1998–2013 | 123 780 | 46 328 | 1 | 2002–13 | 95 588 | 36 514 | .. | .. | .. | .. |
| Cyprus | 4 | 2010–16 | 12 607 | 2879 | 5 | 2005–16 | 22 263 | 4666 | 2 | 2010–16 | 4804 | 1139 |
| Czech Republic | 1 | 1995–2009 | 102 835 | 9094 | 1 | 1995–2009 | 102 835 | 9094 | .. | .. | .. | |
| Estonia | 4 | 2003–16 | 42 485 | 2824 | 4 | 2003–16 | 42 485 | 2824 | 3 | 2009–16 | 10 917 | 718 |
| Finland | 1 | 1995–2014 | 54 366 | 9226 | 1 | 1995–2014 | 54 366 | 9226 | 1 | 1995–2014 | 54 366 | 9226 |
| France | 18 | 2000–15 | 255 222 | 66 657 | 18 | 2007–15 | 234 413 | 62 250 | 15 | 2007–15 | 200 895 | 53 136 |
| Greece | 1 | 2001–10 | 136 194 | 28 771 | 1 | 2001–10 | 136 194 | 28 771 | .. | .. | .. | .. |
| Iran | 1 | 2002–15 | 316 976 | 52 649 | 1 | 2002–15 | 316 976 | 52 649 | .. | .. | .. | .. |
| Japan | 44 | 1995–2016 | 1 176 249 | 625 020 | 40 | 1995–2016 | 1 114 447 | 588 611 | 26 | 2001–16 | 610 505 | 346 247 |
| Kuwait | .. | .. | .. | .. | 1 | 2010–16 | 15 962 | 3170 | .. | .. | .. | .. |
| Mexico | .. | .. | .. | .. | 6 | 2000–12 | 492 867 | 185 735 | 2 | 2004–12 | 269 157 | 96 373 |
| Norway | .. | .. | .. | .. | 1 | 2000–16 | 23 503 | 7152 | 1 | 2000–16 | 23 503 | 7152 |
| Portugal | 6 | 1995–2016 | 297 057 | 87 784 | 5 | 1999–2016 | 238 172 | 73 264 | 3 | 2004–16 | 106 124 | 30 614 |
| South Africa | .. | .. | .. | .. | 2 | 2004–13 | 62 203 | 48 086 | 1 | 2007–13 | 14 721 | 13 713 |
| South Korea | 7 | 1999–2015 | 389 590 | 106 209 | 7 | 1999–2015 | 389 590 | 106 209 | .. | .. | .. | .. |
| Spain | 48 | 2001–14 | 516 250 | 191 989 | 34 | 2001–14 | 376 387 | 146 017 | 2 | 2004–14 | 87 540 | 38 337 |
| Sweden | 1 | 1995–2010 | 66 455 | 11 697 | 1 | 1995–2010 | 66 434 | 11 695 | 1 | 2001–10 | 37 873 | 6707 |
| Switzerland | 8 | 1995–2013 | 90 744 | 16 015 | 8 | 1995–2013 | 86 906 | 15 382 | 4 | 1998–2009 | 39 568 | 6394 |
| Taiwan | 3 | 1995–2014 | 257 553 | 113 269 | 3 | 1995–2014 | 257 553 | 113 269 | 3 | 2007–14 | 117 402 | 58 942 |
| Thailand | 16 | 1999–2008 | 150 329 | 99 509 | 16 | 1999–2008 | 151 824 | 100 179 | .. | .. | .. | .. |
| UK | 33 | 1995–2016 | 1 309 605 | 580 669 | 30 | 1995–2016 | 1 235 377 | 547 036 | 28 | 1998–2016 | 577 277 | 277 262 |
| USA | 114 | 1995–2006 | 3 768 420 | 1 134 984 | 54 | 1995–2006 | 1 336 061 | 424 075 | 77 | 1999–2006 | 1 725 612 | 533 461 |
| Total | 338 | 1995–2016 | 9 969 409 | 3 454 824 | 249 | 1995–2016 | 7 082 163 | 2 660 833 | 194 | 1995–2016 | 4 553 700 | 1 667 109 |

$NO_2$=nitrogen dioxide. $PM_{10}$=particulate matter with diameters ≤10 μm. $PM_{2·5}$=particulate matter with diameters ≤2·5 μm.

***Table 1:*** **Total death counts due to cardiovascular and respiratory causes by country and air pollutant**

heterogeneity. All results are presented as percent change in daily mortality and 95% CI per 10 μg/m³ increase in the air pollutant concentration.

The temporal variation in mortality effect estimates was assessed following the general modelling strategy described above, 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] On the basis of 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, 2002–08, and 2009–16) separately. In the first stage, we calculated city-specific interactions per period, followed by the general modelling procedure without the longitudinal meta-regression (second stage) to obtain an overall pooled estimate for each period.

In addition, we carried out several exploratory secondary analyses. First, we replaced the linear term with a non-linear term of time in the longitudinal analysis. Second, 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 modelling procedure. Third, we applied a multivariable meta-regression analysis that involved a set of nine meta-predictors (WHO 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 population aged 65 years and older) 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 (eg, changing model parameters, confounding variables, or further restrictions to the dataset).

All statistical analyses were performed in R software (version 4.1.2), using the packages *mgcv* (first stage), *mixmeta* (second stage), and *ggplot2* (visualisation). 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).

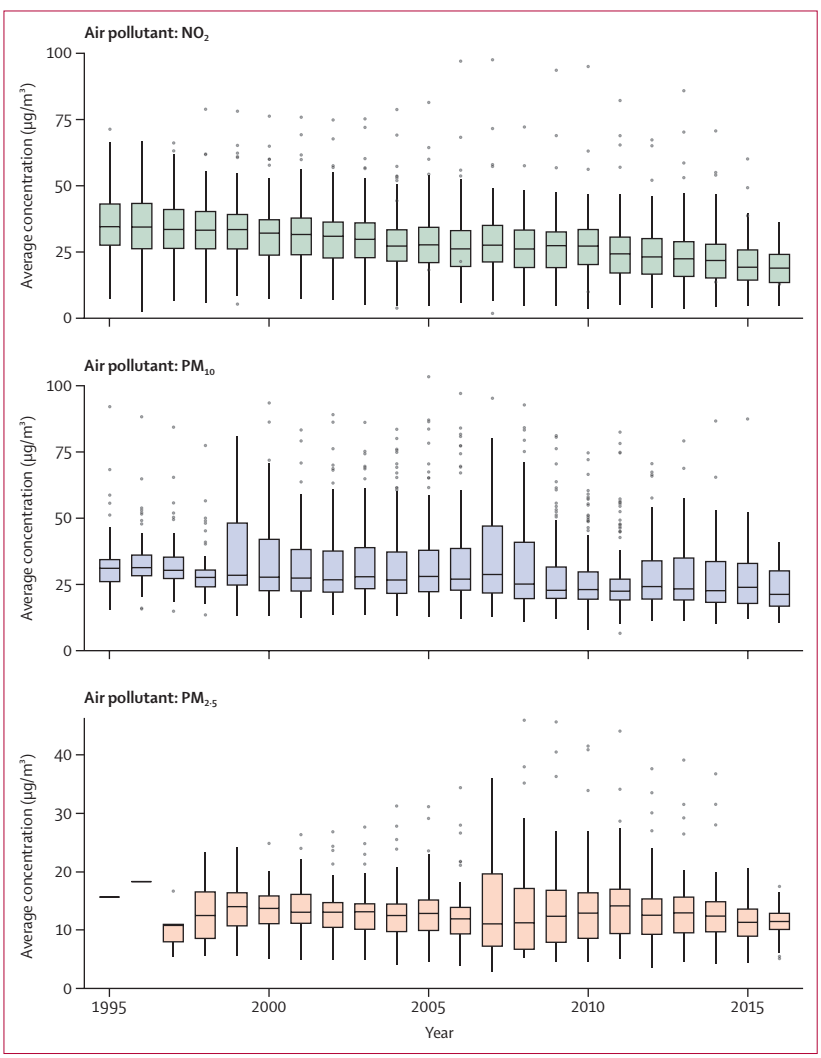


*Figure 1:* **Yearly boxplots across cities of 24 h average concentrations of $NO_2$, $PM_{10}$, and $PM_{2·5}$**
Only one city contributed $PM_{2·5}$ data in 1995 and 1996. $NO_2$=nitrogen dioxide. $PM_{10}$=particulate matter with diameters ≤10 μm. $PM_{2·5}$=particulate matter with diameters ≤2·5 μm.


### Role of the funding source

There was no funding source for this study.


## Results

We analysed 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-specific and country-specific data or geographical distribution, can be found in the appendix (pp 12–32, 37). Median concentrations of $NO_2$, $PM_{10}$, and $PM_{2·5}$ were 25·6 μg/m³ (IQR 18·7–34·4), 27·6 μg/m³ (19·9–38·4), and 11·5 μg/m³ (7·9–16·9), respectively, and showed high heterogeneity within and between countries (appendix pp 12–14). During the study period, substantial reductions in $NO_2$ and $PM_{10}$ concentrations were observed; decreases in $PM_{2·5}$ concentrations were more modest (figure 1; appendix p 38). PM fractions correlated highly with each other (mean correlations over all cities: $r_S$ ≥0·7) and moderately with $NO_2$ ($r_S$ ≥0·40 and $r_S$ <0·70; appendix pp 7–8, 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=0·052; figure 2; table 2). A 10 μg/m³ 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 in 0·61% (0·34 to 0·89) and 0·85% (0·55 to 1·16) higher risks 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<0·0001) 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 sub-periods indicated overall similar 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 both the single-pollutant and two-pollutant models. The associations remained nearly unchanged when $NO_2$ was added to the $PM_{10}$ or $PM_{2·5}$ models, although $PM_{2·5}$+$NO_2$ showed temporal differences. However, it should be noted that the underlying number of cities was reduced in these analyses to allow for 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 was strongest in the region of the Americas and was slightly stronger in the Western Pacific region than the European 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 (categorised 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).

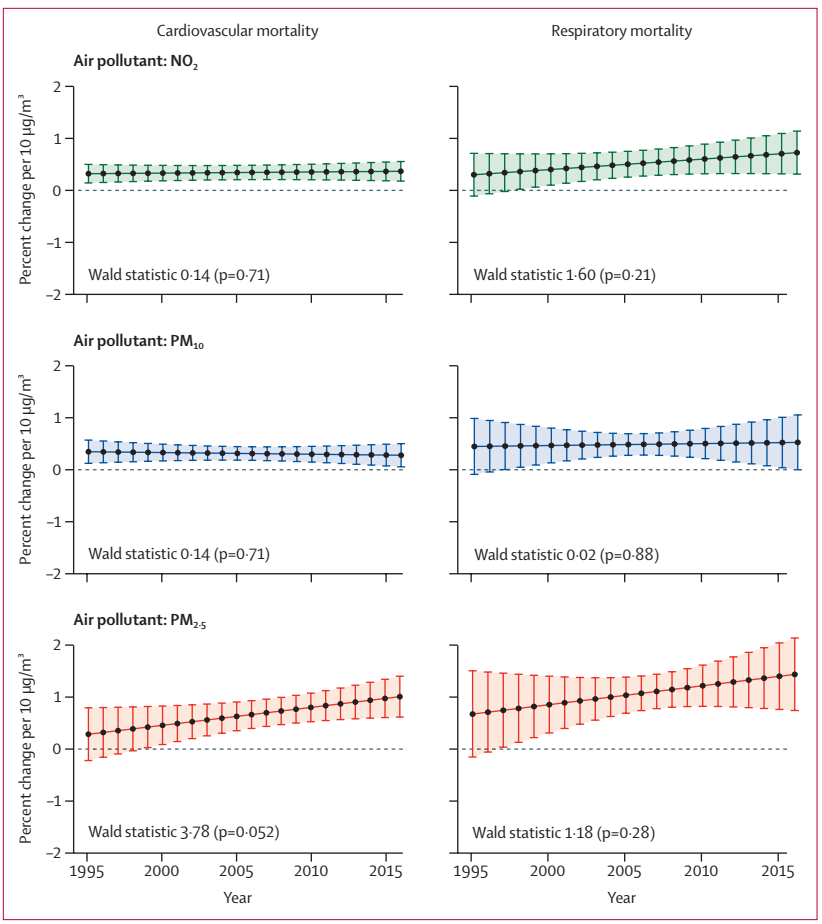


***Figure 2:*** **Pooled percent change in cardiovascular and respiratory mortality by $NO_2$, $PM_{10}$, and $PM_{2·5}$ over the study period (1995–2016)**

Percent change in daily cardiovascular (left column) and respiratory (right column) mortality per 10 μg/m³ increase in $NO_2$ (first row, at lag 1), $PM_{10}$ (second row, at lag 0–1), and $PM_{2·5}$ (third row, at lag 0–1) over the study period (1995–2016), calculated by pooled longitudinal meta-regression using time as a linear term. Shaded areas show 95% CIs. The p value of the corresponding Wald test indicates a significant difference of the model with the linear term for time compared with a model without the linear time term. $NO_2$=nitrogen dioxide. $PM_{10}$=particulate matter with diameters ≤10 μm. $PM_{2·5}$=particulate matter with diameters ≤2·5 μm.

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 cardiorespiratory mortality, but no changes were observed for $PM_{10}$ or $NO_2$ (appendix pp 34–36).

## Discussion

The findings from this multicountry, multicity analysis indicate that there were no significant temporal changes in the associations between $PM_{10}$, $PM_{2·5}$, or $NO_2$ and cardiorespiratory mortality during the study period. 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

| | Temporal variation analysis by longitudinal meta-regression | | | Temporal variation analysis by period | | |
|---|---|---|---|---|---|---|
| | At midyear period 1 (1998) | At midyear period 2 (2005) | At midyear period 3 (2012) | Period 1 (1995–2001) | Period 2 (2002–08) | Period 3 (2009–16) |
| **Cardiovascular mortality** | | | | | | |
| $NO_2$ | 0·34% (0·18 to 0·49) | 0·35% (0·21 to 0·49) | 0·37% (0·21 to 0·53) | 0·35% (0·16 to 0·54) | 0·37% (0·25 to 0·49) | 0·35% (0·17 to 0·52) |
| $PM_{10}$ | 0·34% (0·16 to 0·52) | 0·32% (0·19 to 0·45) | 0·29% (0·12 to 0·47) | 0·23% (0·02 to 0·44) | 0·32% (0·19 to 0·44) | 0·16% (0·01 to 0·32) |
| $PM_{2·5}$ | 0·37% (–0·05 to 0·80) | 0·61% (0·34 to 0·89) | 0·85% (0·55 to 1·16) | 0·39% (–0·06 to 0·85) | 0·59% (0·22 to 0·97) | 0·50% (0·02 to 1·03) |
| **Respiratory mortality** | | | | | | |
| $NO_2$ | 0·37% (0·03 to 0·71) | 0·51% (0·27 to 0·76) | 0·65% (0·33 to 0·98) | 0·39% (–0·01 to 0·78) | 0·55% (0·24 to 0·86) | 0·36% (0·12 to 0·59) |
| $PM_{10}$ | 0·47% (0·06 to 0·88) | 0·50% (0·29 to 0·71) | 0·52% (0·16 to 0·89) | 0·33% (–0·05 to 0·71) | 0·46% (0·18 to 0·74) | 0·35% (0·07 to 0·63) |
| $PM_{2·5}$ | 0·79% (0·13 to 1·44) | 1·04% (0·69 to 1·39) | 1·30% (0·81 to 1·78) | 0·67% (0·02 to 1·32) | 1·13% (0·68 to 1·59) | 1·18% (0·70 to 1·65) |

Models were adjusted for main model covariates using multilevel random-effects meta-analysis. None of the longitudinal models indicated a significant temporal difference using a Wald test comparing the model with and without a time term, and none of the results showed significant heterogeneity. The results of the longitudinal meta-regression analyses are presented for selected years of the entire study period 1995–2016 (for better comparability, the midyear of each period of the period-specific analysis is presented). The results are based on the following city numbers: for the longitudinal meta-regression analysis of $NO_2$ exposure: 338; for analysis of $PM_{10}$ exposure: 249; for analysis of $PM_{2·5}$ exposure: 194; and for the analysis by three subperiods—$NO_2$: 237, 287, 158; $PM_{10}$: 154, 203, 124; $PM_{2·5}$: 104, 131, 53. $NO_2$=nitrogen dioxide. $PM_{10}$=particulate matter with diameters ≤10 μm. $PM_{2·5}$=particulate matter with diameters ≤2·5 μm.

***Table 2:*** **Pooled percent change in daily cause-specific mortality (95% CI) per 10 μg/m³ increase in air pollutants using the temporal variation analyses by longitudinal meta-regression analysis and by study period**

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 to 2015.[15,19] Both studies found slightly increasing associations between $PM_{2·5}$ or $PM_{10}$ exposure and cardiovascular and respiratory mortality over time, although Choi and colleagues[19] reported a decrease in the effects of $PM_{10}$ during the latest period of the study (2011–15). Our country-specific analysis of seven South Korean cities indicated only slight increases in the $PM_{10}$ effects on cardiorespiratory 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 and colleagues reported a slight decrease in the association between $NO_2$ and respiratory mortality, especially among people aged 65 years or older. 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 (eg, 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 (1977–80), which is not included in our analysis and might have contributed to the different results. In addition, Nishikawa and colleagues reported increased associations with respiratory mortality in the most recent periods and observed no temporal changes when examining gaseous pollutants, which is consistent with our findings.[20]

In recent decades, air pollution concentrations have generally declined in most regions, particularly in North America (USA and Canada) and Europe.[3,5,26] However, our analyses indicate that, on average, a substantial number of days still exceeded the current 24 h WHO air quality standards (appendix pp 12–32). In addition, some regions showed opposite trends, with increasing air pollution levels,[11] some of which could 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; data not shown). In addition, we identified the WHO regions as a potential factor that might have contributed substantially to this variability. We observed higher estimates in the regions of the Americas compared with Europe, as well as in regions with higher gross domestic product per capita or wider temperature

ranges. Liu and colleagues previously reported similar heterogeneity in PM effects on total mortality.[7] Possible contributors to these variations include susceptibility and health behaviour of the population, lower air pollution concentrations, different lengths of study periods or different local climate patterns.[7] In future research, it will be important to disentangle the co-impacts or 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 and colleagues[28] 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. We found no evidence contradicting our linear model assumptions (data not shown), although we cannot completely rule out the possibility of non-linearity (eg, a supralinear relationship with steeper slopes at low concentrations and flatter or continuous slopes at high concentrations might 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, for example, 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 multicountry, multicity study[31] investigated the differential health effects of $PM_{2·5}$ composition and examined yearly differences in $PM_{2·5}$ components between regions and over time. Although some countries had relatively stable $PM_{2·5}$ compositions, others showed slight changes and a wide temporal variability (eg, reduction of sulphate content in the UK).[31] In addition, the authors reported a greater proportion of nitrate in northern and central European countries and sulphate 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 might have contributed to different associations over time. However, given the remaining issues of co-pollutant models (eg, 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. Furthermore, 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 and colleagues,[31] a changing exposure mix or composition might have contributed to our findings. In addition, changing demographics (eg, children or older people), health behaviours (eg, using face masks, air purifiers, or spending more time outdoors), or population vulnerabilities (eg, chronic diseases) might be among the factors driving changes over time.

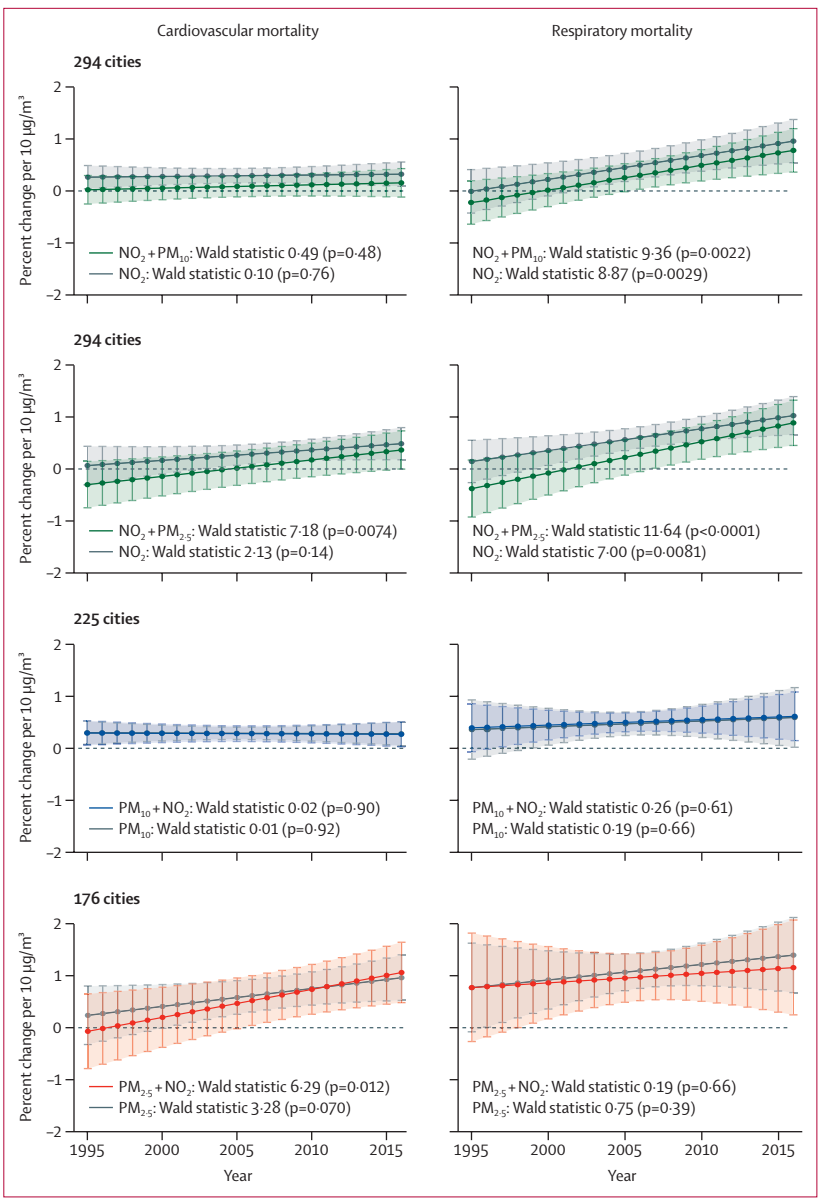


***Figure 3:*** **Pooled percent change in cardiovascular and respiratory mortality by $NO_2$, $PM_{10}$, and $PM_{2·5}$ over the study period (1995–2016) using two-pollutant models**

Percent change in daily cardiovascular (left column) and respiratory (right column) mortality per 10 µg/m³ increase in $NO_2$ (first two rows, at lag 1), $PM_{10}$ (third row, at lag 0–1), and $PM_{2·5}$ (fourth row, at lag 0–1) over the study period 1995–2016, calculated by pooled two-pollutant longitudinal meta-regression using time as a linear term (coloured lines). Grey lines show single-pollutant models (restricted dataset including both pollutants). Shaded areas show 95% CIs. The p value of the corresponding Wald test indicates a significant difference of the model with the linear term for time compared with a model without the linear time term; $NO_2$ models were adjusted for additional PM fractions, PM models for $NO_2$. $NO_2$=nitrogen dioxide. $PM_{10}$=particulate matter with diameters ≤10 µm. $PM_{2·5}$=particulate matter with diameters ≤2·5 µm.

In summary, the complexity of a changing environment over time emphasises 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 multicountry, multicity study specifically designed to examine differences in air pollution effects over time. The large sample size provides good statistical power and stability to analyse effects even for cause-specific mortality endpoints. We applied comprehensive and standardised state-of-the-art analytical methods to account for city-specific 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, limitations should be acknowledged. First, although our final dataset included 380 cities in 24 countries worldwide, some regions, such as the Middle East, Latin America, and Africa, were under-represented, and thus generalisations 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, extrapolating the results to an entire country might be 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, some cities and countries contributed data at different time points during the study period, and 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 (eg, sulphate or nitrate content) or different PM subfractions (eg, ultrafine particles), which might be key factors in toxicity and overall health risks associated with PM. Fourth, the study relied on city-level time-series data without more detailed analysis at the individual level (eg, age or biological sex). Furthermore, the potential for exposure measurement error over past decades (eg, relocation of monitoring stations) or the ecological fallacy of drawing individual-level conclusions from aggregated data could have impacted the results; however, visual inspection of the individual time series (data not shown) suggested these effects to be marginal. Finally, we only analysed the primary coded cardiovascular and respiratory mortality endpoints. However, air pollution exposure is also related to non-fatal disease endpoints, such as temporal changes in hospitalisations.[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 observation 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 standardised and multicountry analyses, enhanced data quality and accessibility, and the exploration of underlying factors that might drive temporal trends in the associations between air pollution and cardiorespiratory mortality, such as geographical or sociodemographic factors. These are particularly important to support mitigation measures to allow WHO's updated air quality targets to be reached.

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**Contributors**

MSc, SB, AS, FdD, MSt, AG, and FS were involved in the design of the study. MSc and SB accessed and verified the data, performed the analyses, drafted an internal summary report to circulate preliminary results and figures, 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 country-specific air pollution and mortality data. All authors had full access to all the data in the study, contributed to the interpretation and visualisation of the results, read the manuscript, and had final responsibility for the decision to submit for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

The mortality data analysed in this study are not publicly available due to restrictions imposed by data usage agreements with the respective data providers of the included countries.

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