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

Maximilian Schwarz, Annette Peters, Massimo Stafoggia, Francesca de'Donato, Francesco Sera, Michelle L Bell, Yuming Guo, Yasushi Honda, Veronika Huber, Jouni J K Jaakkola, Aleš Urban, Ana Maria Vicedo-Cabrera, Pierre Masselot, Eric Lavigne, Souzana Achilleos, Jan Kyselý, Evangelia Samoli, Masahiro Hashizume, Chris Fook Sheng Ng, Susana das Neves Pereira da Silva, Joana Madureira, Rebecca M Garland, Aurelio Tobias, Ben Armstrong, Joel Schwartz, Antonio Gasparrini, Alexandra Schneider*, Susanne Breitner*, on behalf of the MCC Collaborative Research Network

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.

Funding None.

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

Institute of Meteorology, Helsinki, Finland (Prof J J K Jaakkola); Faculty of Environmental Sciences, Czech University of Life Sciences, Prague, Czech Republic (A Urban PhD, J Kyselý PhD); Institute of Atmospheric Physics, Czech Academy of Sciences, Prague, Czech Republic (A Urban, J Kyselý); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (A M Vicedo-Cabrera PhD); Oeschger Center for Climate Change Research, University of Bern, Bern, Switzerland (A M Vicedo-Cabrera); Environment & Health Modelling Lab, Department of Public Health, Environments and Society, London School of Hygiene & Tropical Medicine, London, UK (P Masselot PhD, Prof A Gasparrini PhD); School of Epidemiology & Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada (Prof E Lavigne PhD); Environmental Health Science and Research Bureau, Health Canada, Ottawa, ON, Canada (Prof E Lavigne); Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus (S Achilleos PhD); Department of Hygiene, Epidemiology and Medical Statistics, National and Kapodistrian University of Athens, Greece (Prof E Samoli PhD); Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (Prof M Hashizume PhD); School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan (C Fook Sheng Ng PhD); Department of Epidemiology, Instituto Nacional de Saúde Dr Ricardo Jorge, Lisbon, Portugal (S das Neves Pereira da Silva MSc); Department of Environmental Health, Instituto Nacional de Saúde Dr Ricardo Jorge, Porto, Portugal (J Madureira PhD); Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal (J Madureira); Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal (J Madureira); Department of Geography, Geoinformatics and Meteorology, University of Pretoria, Pretoria, South Africa (R M Garland PhD); Institute of

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

Environmental Assessment and Water Research, Spanish Council for Scientific Research, Barcelona, Spain (A Tobias PhD); Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, UK (Prof B Armstrong PhD)

Correspondence to:
Maximilian Schwarz, Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
maximilian.schwarz@helmholtz-munich.de

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

See Online for appendix

	NO₂				PM₁₀				PM₂.₅			
	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 multi-variable 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).

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: $r_s \geq 0·7$) and moderately with NO_2 ($r_s \geq 0·40$ 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
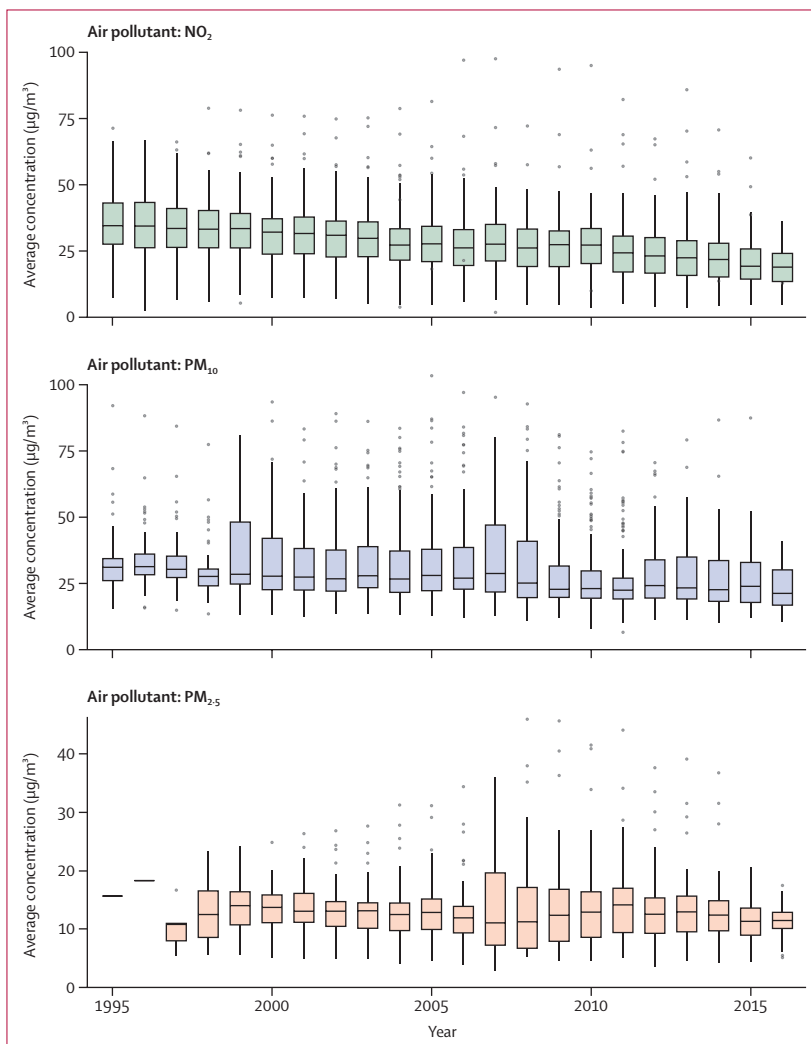
Figure 1: Yearly boxplots across cities of 24 h average concentrations of NO_2, PM_{10}, and $PM_{2.5}$
Only one city contributed $PM_{2.5}$ data in 1995 and 1996. NO_2=nitrogen dioxide. PM_{10}=particulate matter with diameters ≤10 μm. $PM_{2.5}$=particulate matter with diameters ≤2·5 μm.

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).
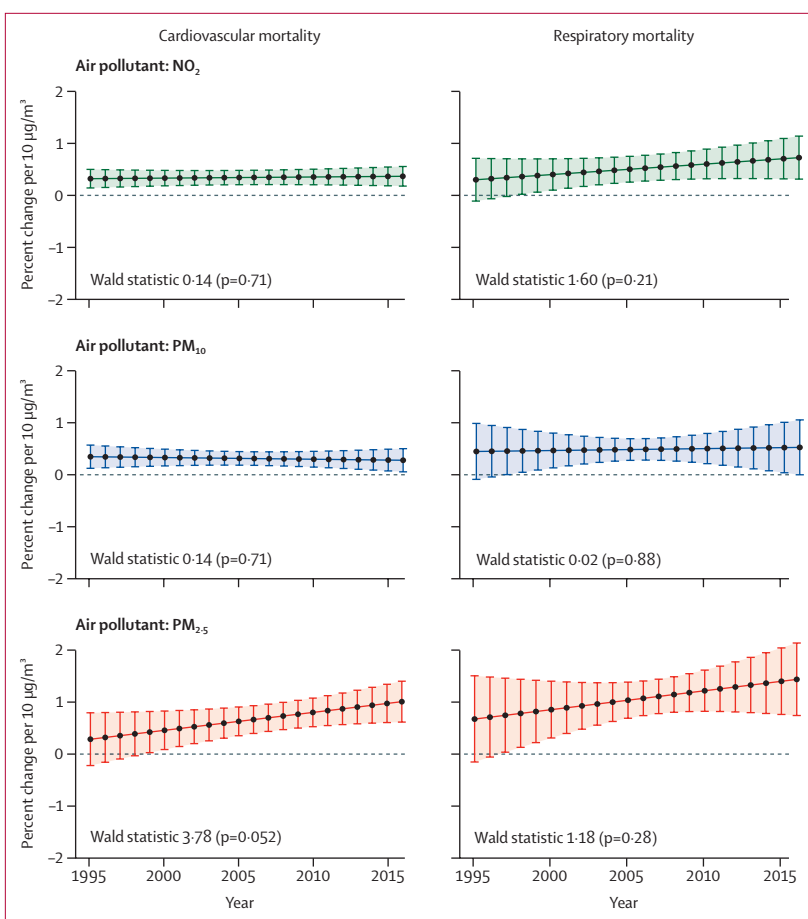
Figure 2: Pooled percent change in cardiovascular and respiratory mortality by NO$_2$, PM$_{10}$, and PM$_{2.5}$ over the study period (1995–2016)
Percent change in daily cardiovascular (left column) and respiratory (right column) mortality per 10 µg/m³ increase in NO$_2$ (first row, at lag 1), PM$_{10}$ (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
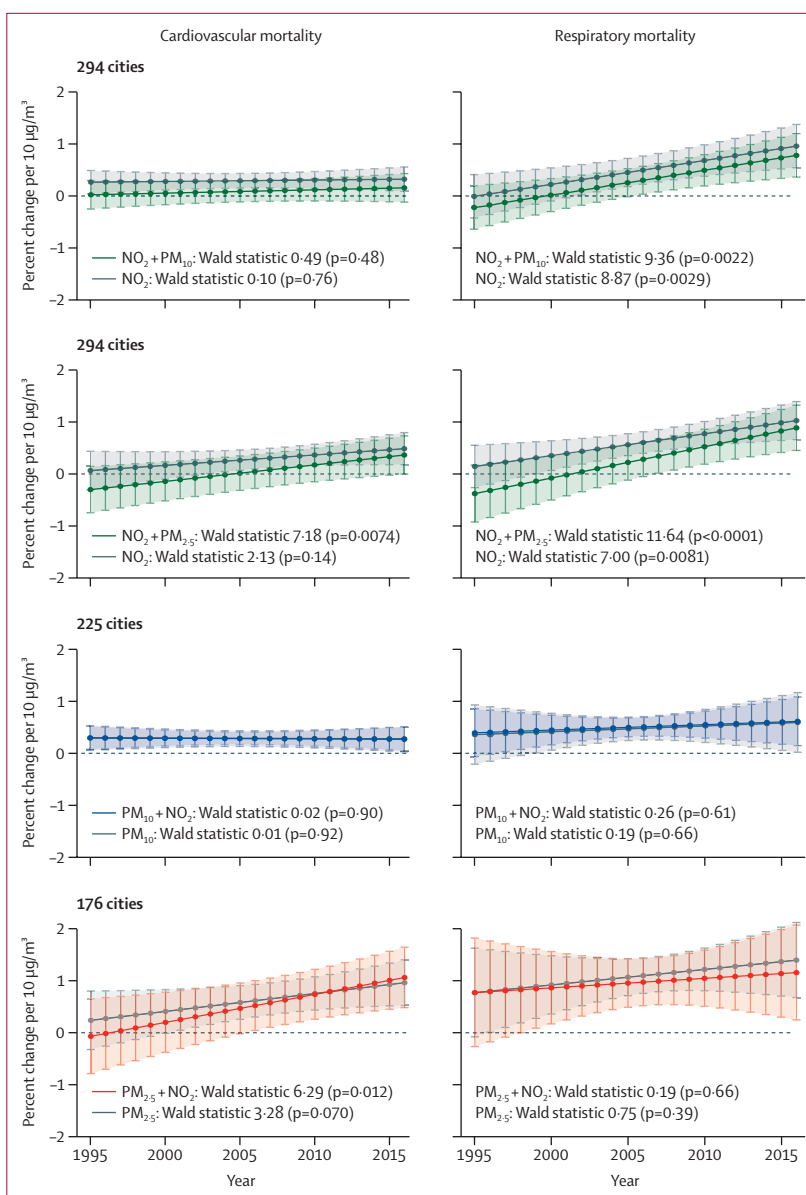
Figure 3: **Pooled percent change in cardiovascular and respiratory mortality by NO_2, PM_{10}, and $PM_{2.5}$ over the study period (1995–2016) using two-pollutant models**
Percent change in daily cardiovascular (left column) and respiratory (right column) mortality per 10 µg/m³ increase in NO_2 (first 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.

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.

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.

MCC Collaborative Research Network
Haidong Kan (Department of Environmental Health, School of Public Health, Fudan University, Shanghai, China), Samuel Osorio (Department of Environmental Health, University of São Paulo, São Paulo, Brazil), Hans Orru and Ene Indermitte (Department of Family Medicine and Public Health, University of Tartu, Tartu, Estonia), Marek Maasikmets (Estonian Environmental Research Centre, Tallinn, Estonia), Niilo Ryti (Center for Environmental and Respiratory Health Research [CERH], University of Oulu, Oulu, Finland), Mathilde Pascal (Santé Publique France, Department of Environmental Health, French National Public Health Agency, Saint Maurice, France), Klea Katsouyanni and Antonis Analitis (Department of Hygiene, Epidemiology and Medical Statistics, National and Kapodistrian University of Athens, Athens, Greece), Alireza Entezari (Faculty of Geography and Environmental Sciences, Hakim Sabzevari University, Sabzevar, Iran), Fatemeh Mayvaneh (Institute of Landscape Ecology, Climatology Research Group, University of Münster, Münster, Germany), Yoonhee Kim (Department of Global Environmental Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan), Barrak Alahmad and Antonella Zanobetti (Department of Environmental Health, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA), Magali Hurtado Diaz and Eunice Elizabeth Félix Arellano (Department of Environmental Health, National Institute of Public Health, Cuernavaca, Morelos, Mexico), Shilpa Rao and Alfonso Diz-Lois Palomares (Norwegian Institute of Public Health, Oslo, Norway), Noah Scovronick (Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA), Fiorella Acquaotta (Department of Earth Sciences, University of Turin, Turin, Italy), Ho Kim (Graduate School of Public Health, Seoul National University, Seoul, South Korea), Whanhee Lee (School of Biomedical Convergence Engineering, College of Information and Biomedical Engineering, Pusan National University, Yangsan, South Korea), Carmen Íñiguez (Department of Statistics and Computational Research, Universitat de València, València, Spain), Bertil Forsberg (Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden), Martina S Ragettli (Swiss Tropical and Public Health Institute, Basel, Switzerland), Yue Leon Guo (Environmental and Occupational Medicine, National Taiwan University [NTU], College of Medicine and NTU Hospital, Taipei, Taiwan), Shih-Chun Pan (National Institute of Environmental Health Science, National Health Research Institutes, Zhunan, Taiwan), Shanshan Li (School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia).

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