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Differential mortality risks associated with PM2.5 components: a multi-country, multi-city study

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Data accessibility: The computer code is freely available on the first author's github page (https://github.com/PierreMasselot/Paper--2022--Epidemiology--PM2.5_components). The mortality data have been obtained through a restricted data use agreement with each national institute and are therefore not available for public dissemination.

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Abstract

Background. The association between fine particulate matter ($PM_{2.5}$) and mortality widely differs between as well as within countries. Differences in $PM_{2.5}$ composition can play a role in modifying the effect estimates, but there is little evidence about which components have higher impacts on mortality.

Methods. We applied a two-stage analysis on data collected from 210 locations in 16 countries. In the first stage, we estimated location-specific relative risks (RR) for mortality associated with daily total $PM_{2.5}$ through time series regression analysis. We then pooled these estimates in a meta-regression model that included city-specific logratio-transformed proportions of seven $PM_{2.5}$ components as well as meta-predictors derived from city-specific socio-economic and environmental indicators.

Results. We found associations between RR and several $PM_{2.5}$ components. Increasing the ammonium (NH_4^+) proportion from 1% to 22%, while keeping a relative average proportion of other components, increased the RR from 1.0063 (95%CI: 1.0030-1.0097) to 1.0102 (95%CI:1.0070-1.0135). Conversely, an increase in nitrate (NO_3^-) from 1% to 71% resulted in a reduced RR, from 1.0100 (95%CI: 1.0067-1.0133) to 1.0037 (95%CI: 0.9998- 1.0077). Differences in composition explained a substantial part of the heterogeneity in $PM_{2.5}$ risk.

Conclusions. These findings contribute to the identification of more hazardous emission sources. Further work is needed to understand the health impacts of $PM_{2.5}$ components and sources given the overlapping sources and correlations among many components.

Introduction

Particulate matter (PM) is a major environmental risk factor to which the Global Burden of Diseases attributed between 4.1 and 5 million deaths worldwide in 2017.[1] In particular, evidence on short-term associations between exposure to fine particulate matter ($PM_{2.5}$) and total and cause-specific mortality are well established,[2,3] although with some heterogeneity both between[4] and within countries.[5,6]

A potentially key factor explaining such geographic differences is the variation in the chemical composition of $PM_{2.5}$, mostly related to different sources. $PM_{2.5}$ is a complex chemical mixture of various liquid droplets and solid particles varying in size, chemical composition, and other factors.[7,8] Some components are naturally present in the atmosphere, whereas others emanate from anthropogenic activities, either as direct emissions (primary components) or after chemical reactions in the atmosphere (secondary components). The proportions of the components vary substantially across locations,[9] and some components may be more harmful to health than others. The present study focuses on a comprehensive classification of the main chemical components of $PM_{2.5}$ that are sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), the three of them forming the group of secondary inorganic aerosols, as well as black carbon (BC), organic carbon (OC), mineral dust, and sea salt.[10] SO_4^{2-} and NO_3^- originate from the oxidation of sulphur and nitrogen oxides, whose sources include fossil fuel combustion (e.g. coil, gas, and oil) as well as volcanoes. The third secondary inorganic aerosol, NH_4^+, originates mainly from fertilizer use and livestock.[11] Organic components, OC and BC, are emitted by all types of combustion, the former being more associated with residential sources such as biofuel and wildfire,[9,12] while the latter is often related to transportation emissions.[13] Mineral dust contains coarser particles transported from deserts,[14,15] as well as street and road dust and industrially emitted particles such as metals and cement.[16,17] Finally, sea salt originates from sea spray and is thus more prominent in coastal areas.[10]

Many of the components described above have been previously studied, either alone such as BC[18,19] and mineral dust,[14,15] or together as effect modifiers.[20,21] Nonetheless, results widely vary among studies with important heterogeneity found in meta-analyses.[22] This may be due in part to the difficulty of modelling compositions data, as well as limitations in disentangling component-specific effects from analyses performed in single locations or countries with relatively homogeneous composition of PM.

The objective of the present study is to identify and compare the all-cause mortality risks associated with the main chemical components of $PM_{2.5}$, takindg advantage of statistical methodologies for compositional data analysis methods and a large international database gathered within the Multi-Country Multi-City (MCC) Collaborative Research Network.

Methods

Data

The data consists of city-level daily time series of all-cause mortality, measured $PM_{2.5}$ concentrations and temperature, as well as estimated annual $PM_{2.5}$ composition and socio-economic indicators from the MCC database. We selected the cities with at least 1 full year of available data, and then restricted the analysis to 1999-2017, the period with available $PM_{2.5}$ composition data (see below) and the 4 previous years, allowing more stable estimates for some countries such as the US. The final dataset includes 210 urban areas in 16 countries. Table 1 summarizes data for each represented country. Details are provided in eAppendix A; http://links.lww.com/EDE/B889.

For each city, we extracted the average annual $PM_{2.5}$ components mass concentration estimates for the period 2003-2017 from a global reconstruction model.[10] We then divided each component by the sum of all seven components to obtain relative composition and computed the average composition across the whole period. Details are given in eAppendix A; http://links.lww.com/EDE/B889. We also gathered the proportion of people aged 65 years and older, the gross domestic product per capita, the total buit-up area, the average and range of temperature as well as the greenness. Details about specific measures and years covered by each variable are given in eAppendix B (eTable 1; http://links.lww.com/EDE/B889).

Statistical analysis

The statistical analysis followed a two-stage design, first estimating a relative risk (RR) associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ at the city level, and then modeling the heterogeneity of these RRs in a meta-regression model. The analysis was entirely performed using the R software version 4.1.0[23] with additional packages dlnm,[24] mixmeta,[25] compositions,[26] and zCompositions.[27]

First-stage modeling

At the city level, we performed a time series analysis with a quasi-Poisson regression model consistently with a previously published study.[4] Briefly, total $PM_{2.5}$ mass entered the model linearly as a 2-day moving average to account for both same-day and one-day delayed effects. We accounted for confounding by mean air temperature using a cubic B-spline of its 4-day moving average with knots at the 10th, 75th, and 90th percentiles. Finally, the model also included a factor for day-of-week to account for weekly cycles in mortality and a natural spline of time with seven degrees of freedom per year to account for seasonal effects and long-term trends.

Definition of transformed components

The compositional nature and sum-to-one constraint of the components means that they are necessarily correlated and cannot be used directly as predictors in a meta-regression model. We therefore applied a compositional data methodology based on the additive logratio approach of Aitchison,[28–30] which consists in transforming the compositional dataset $x_1, \dots, x_D$ into $D-1$ new variables:

$$z_k = \log\left(\frac{x_k}{x_D}\right) \tag{1}$$

for $k = 1, \dots, D-1$, using the D^{th} component as the baseline comparison. This transformation allows removing the sum-to-one constraint while retaining the relative information of all components [31]. Classical statistical analyses can then be performed on the z_k variables. Note that the final results are insensitive to the chosen baseline component x_D in equation (1).[32]

Second-stage modeling

The second stage consisted of a two-level random-effects meta-regression[25] of the first-stage RR using the additive log ratio-transformed $PM_{2.5}$ components as meta-predictors:

$$\log(RR_{ij}) = \beta_0 + \sum_{k=1}^{6} \beta_k \log\left(\frac{x_{ijk}}{x_{ij7}}\right) + \gamma_1 PC_{ij1} + \gamma_2 PC_{ij2} + \omega_j + \xi_{ij} + \epsilon_{ij} \tag{2}$$

where $\log(RR_{ij})$ is the coefficient associated with a 10 $\mu g/m^3$ increase of $PM_{2.5}$ obtained in the first stage of the analysis, for city i of country j. x_{ijk} represents the proportion of $PM_{2.5}$ component $k = 1, \dots, 7$ from the average annual $PM_{2.5}$ mass for city i of country j. We accounted for potential confounding from the socio-economic and large-scale environmental variables given above by including their first two principal components (PC_{ij1} and PC_{ij2}) in the meta-regression model, which represented 67% of this dataset's variance (eFigure 1 in eAppendix B; http://links.lww.com/EDE/B889). Random effects were added at the country and city level (ω_j

and ξ_{ij} respectively), allowing to control for confounding due to spatial differences such as climatology or country-specific policies. Finally, the ϵ_{ij} component represents city level residual error. Model (2) was fitted by restricted maximum likelihood.

We reported the compositional mean of $PM_{2.5}$ components for each country. We also reported the city and country-level best linear unbiased predictions (BLUPs) of RRs from the meta-regression model described above.[25,33] The reported RR represent the ratio of predicted mortality for a 10 $\mu g/m^3$ increase of $PM_{2.5}$ compared to its baseline, consistently with recent investigations.[2,4,34] Finally, we also checked the residuals to ensure that there is no apparent bias, heteroscedasticity, or departure from normality (see eAppendix C; http://links.lww.com/EDE/B889).

To interpret the results of the meta-regression model in Equation (2), we reported the relative excess risk (RER) as the ratio of predicted RRs[35] associated with a doubling of the relative proportion of each component. In addition, we predicted the RR for a range of values of each component x_j. We then interpreted results for each component by comparing predicted RR at their lowest and largest observed values to underscore the full scale of effect modification. When reporting RR and RER associated to specific components, the sub-composition of other components is kept constant under the sum-to-one constraint.

Effect modification assessment

To assess how much effect modification is brought by variation in the $PM_{2.5}$ components in the full model (2), we also performed a meta-analysis without any meta-predictors (the “null” model), and another one with only the principal components (PC) of confounding indicators (the “PC-only” model). For each of the three models, we computed the Cochran Q and I^2 which respectively test the presence of heterogeneity and quantify its proportion between locations unexplained by the second-stage meta-regression model.[25,36] To decide whether the drop in Q and

I^2 between two nested models is significant, Wald tests were also conducted.[37] These tests assessed whether the γ_l coefficients for the PC-only model and the β_k coefficients for the full model can be considered non-null (see equation 2).

Results

Descriptive statistics

Table 1 reports summary statistics of the mortality and pollution data aggregated per country. A total of almost 15 million deaths were included in the study overall. Figure 1 shows the world map with all the cities included in the study and their average observed $PM_{2.5}$. The highest levels of $PM_{2.5}$ were observed in China, Chile, and Mexico. Northern countries (i.e., Sweden and Canada) as well as Australia showed the lowest $PM_{2.5}$ levels.

Figure 2 displays the mean $PM_{2.5}$ composition in each country. Some countries show stable compositions through the years while others reveal widely variable distributions. The wider variability is observed in Australia and Mediterranean countries, widely affected by mineral dust, a component that can represent a significant part of $PM_{2.5}$ in one year and be almost absent the next one. Mineral dust particles are usually coarser than other components, thus representing a higher proportion of the total mass. Overall, the two components representing the largest fraction of $PM_{2.5}$ are generally SO_4^{2-} and NO_3^-, both linked to the burning of fossil fuel. NO_3^- is more represented in European countries except for Mediterranean ones, while SO_4^{2-} is widely present in hotter countries. OC represents a large part of the composition in Nordic countries since it is linked to both wildfires and residential wood burning. BC and NH_4^+ are overall lower components of the $PM_{2.5}$ composition. Sea salt represents a visible part of total $PM_{2.5}$ mass only in mostly seaside countries, notably Portugal and the UK. Note that sea salt is also present in coastal locations of many other countries such as the US, although it is not visible in Figure 2 due to the large number of inland locations.

City-specific relative risks

The RRs for each city are reported in Figure 1 and range from 0.995 in Valladolid (Spain) to 1.021 in Sendai (Japan), corresponding to mortality changes of -0.5% and 2.1% in association with a 10 $\mu g/m^3$ increase of $PM_{2.5}$, respectively. Predicted RRs above 1 are found for 202 cities among the 210 considered in the analysis. The highest RRs are found in North America, Mexico, and Japan, as well as specific locations in Europe such as Greece. In contrast, lower predicted RRs are found in Spain and Finland. eAppendix C; http://links.lww.com/EDE/B889 provides insight on the location-specific residuals from the second-stage meta-regression.

Effect modification by $PM_{2.5}$ composition

Figure 3A reports the RER associated with a doubling of the relative proportion of each component. Specifically, we found a positive effect modification of NH_4^+, suggesting that the RR of $PM_{2.5}$ increased by 0.08% as NH_4^+ doubled. RRs also increased with SO_4^{2-} but with important uncertainty as shown by the wide confidence interval. Conversely, an increase in NO_3^- was associated with decreased RR of $PM_{2.5}$ by around 0.08% for both components. Finally, Figure 3A indicated no effect modification from carbonaceous components (BC and OC), and a slightly negative effect by sea salt and mineral dust although with important uncertainty.

Figure 3B shows the predicted RRs for $PM_{2.5}$ within observed ranges of each component, while keeping the relative proportions of other components constant and accounting for the sum-to-one constraint. A more direct comparison of the predicted curves along with ternary representations are shown in eAppendix D; http://links.lww.com/EDE/B889. The logit form of reported curves stems from the additive logratio transformation applied to the components before the meta-regression model (see Equation 2) with the slope corresponding to the RER reported in Figure 3A. While all components were associated with positive mortality risks, results showed substantial variations depending on their proportions.

Observed proportions of NH_4^+ ranged from 0 to 22% with respective predicted RR of 1.0063 (95%CI: 1.0030-1.0097) and 1.0102 (95%CI:1.0070-1.0135), while keeping relative average of other components constant. RRs also increased with SO_4^{2-}, from 1.0066 (95%CI: 0.9992-1.0140) to 1.0092 (95%CI: 1.0035-1.0148) for respective proportions of 6 and 99%. Conversely, an increase in the proportion of NO_3^- from 1 to 71% was associated with a decrease in the RRs from 1.0100 (95%CI: 1.0067-1.0133) to 1.0037 (95%CI: 0.9998- 1.0077). The RR curve was flat for carbonaceous components (BC and OC), with a constant estimated effect of $PM_{2.5}$ around 1.0080 independently of these components relative proportions. Finally, a slight decrease was seen from 1.0055 (95%CI: 0.9995-1.0115) to 1.0047 (0.9975-1.0120) for sea salt and from 1.0067 (95%CI: 1.0027-1.0108) to 1.0005 (95%CI: 0.9982- 1.0119) for mineral dust, although with wide confidence intervals.

Table 2 reports the assessment of the effect modification by composition. It indicates that including the components as meta-predictors reduced residual heterogeneity in the meta-regression model. The Q statistics dropped from 473 in the socio-economic and environment PC-only model to 313 in the full model, with a drop in I^2 from 56% to 36%. A Wald test on composition variable coefficients had a p-value of about 0.004, indicating that the composition explains part of the heterogeneity. Table 2 also shows that the PC-only model results in a negligible drop in residual heterogeneity compared to the null model. Even though the Wald p-value is close to the nominal 5%, principal components in the PC-only and full models were associated with approximately null coefficients.

Discussion

This study provides original evidence that the mortality risks associated with exposure to $PM_{2.5}$ varies depending on the chemical composition of the particulate matter. All the results indicate that the heterogeneity in risk to $PM_{2.5}$ is in large part explained by its composition. While all the components are associated with positive relative risks for mortality, changes in their proportion modifies the predicted risk. Although the effect modification is illustrated by comparing RRs at the lowest and largest values of each component, we acknowledge such changes in the composition are not representative of achievable policy results.

We found higher RR associated with $PM_{2.5}$ for cities with a larger part of NH_4^+ in the mix, but a decrease of the RR when the part of NO_3^- increases. Surprisingly, we found no effect modification associated with carbonaceous components (BC and OC) and mineral DUST, while there was important uncertainty about the role of SO_4^{2-} and sea salt proportions. This uncertainty was probably linked to the extreme variability of the former and the rarity of the latter.

The most interesting result is about the role of ammonium (NH_4^+) in enhancing the harmful effects of $PM_{2.5}$. This is a component that has received less attention than others such as BC, OC, and SO_4^{2-}, although it is one of the three secondary inorganic aerosols. Recently published studies reviewed by the authors have not identified any previous evidence on potential effect modification of NH_4^+ [20,21,38–41]. However, a Canadian cohort study identified NH_4^+ as the component with the highest coefficient in a model that included all components and total $PM_{2.5}$ concentration.[42] Interestingly, this is the only previous study we are aware of that used a strategy similar to the compositional data approach considered in this contribution. Few studies focusing on the concentration of components rather than their effect modification have reported a positive association between mortality and NH_4^+ levels, although the analyses included many other components.[43–46] Besides, confounding by total $PM_{2.5}$ concentration is rarely accounted for in these studies. Some studies also linked agriculture, responsible for the largest part of NH_4^+, as the most adverse source in Europe and parts of Asia.[47]

NH_4^+ shows important co-variation with the two other secondary inorganic components (see eFigure 7; http://links.lww.com/EDE/B889). Indeed, NH_4^+ is typically found as ammonium sulfate or ammonium nitrate within $PM_{2.5}$ and likely varies strongly with SO_4^{2-} in some communities and NO_3^- or organics in others. The effect modifications found for SO_4^{2-} and NO_3^-, positive for the former and negative for the latter, suggest that ammonium sulfate may be the more harmful of the two. Further investigation is nonetheless needed to disentangle the health effects of ammonium nitrate and ammonium sulfate. Evidence on their toxicology is so far inconclusive,[48] although secondary inorganic components have been linked to the hypothalamus–pituitary–adrenal axis, increasing cardiometabolic risks.[49] It also cannot be ruled out that the apparent adverse effect might be due to interaction effects with other most harmful components.[50] Overall, NH_4^+ is also the component most closely correlated with the total $PM_{2.5}$ mass in our dataset (see eTable 2). It has been suggested that ammonia, the main precursor of NH_4^+, is a major driver of $PM_{2.5}$, at least in some countries.[51–53]

The other important result of our analysis is the observed reduction in RRs for high proportions of nitrate (NO_3^-) in the composition of $PM_{2.5}$. Indeed, NO_3^- represents a large part of the total concentration in northern and central European countries (Estonia, Finland, Germany, Switzerland, Sweden, and the UK, see Figure 2), which are areas displaying weaker associations between $PM_{2.5}$ and mortality.[4] NO_3^- is a secondary product of nitrogen oxides emissions, emitted by gas and oil burning, and is thus mainly related to traffic. Note that in the data used here, NO_3^- shows a high variation value with BC (see eFigure 7; http://links.lww.com/EDE/B889); specifically, when it increases, NO_3^- tends to replace BC. Both are usually considered traffic-related components, NO_3^- being mainly related to oil and gas combustion while BC also includes all biofuel combustion.[9] Previous research on sources suggests that traffic is the source most consistently associated with health impacts[7,54] and with the highest toxicologic evidence.[55] Since our results indicate lower risks associated with NO_3^- compared to BC, further work is needed to explore the implications of mitigation strategies focusing more heavily on BC emissions compared to NO_3^- precursors.

The strengths of this study lie in both the data used, with a large number of cities across multiple countries, and the methods applied. It takes advantage of a large international database from the MCC network to evaluate how $PM_{2.5}$ composition affects its association with all-cause mortality. We observed wide heterogeneity in the composition between locations, allowing the comparison of different compositional patterns. The study uses state-of-the-art statistical methods, including the recently proposed mixed-effects meta-analysis two-stage framework[25] and compositional data analysis. The mixed-effect framework allows consideration of several levels of heterogeneity as part of meta-analysis, which in our study are country and city level. This captures structural differences, as well as climatic or environmental conditions that may modify the association between $PM_{2.5}$ and all-cause mortality. Compositional data analysis provides a rigorous framework to analyze the role of different constituents of $PM_{2.5}$. Such data structures are prone to spurious results and misinterpretations if not analyzed properly, as already observed by Pearson.[56] In the present case, compositional data analysis seems successful in reducing confounding by total $PM_{2.5}$ mass as illustrated by the low correlation on the relative scale shown in eTable 2; http://links.lww.com/EDE/B889.

Although the wide range of locations available is a strength of the study, it is limited regarding spatial representativeness. Available data were more heavily weighted to high-income countries (North America, Europe, and Japan), which means that some types of compositions might not be well represented. Further work should focus on gathering and analyzing data from lower-income countries. A second limitation is related to the measurement of total $PM_{2.5}$ that differs across locations. A part of this uncertainty is nonetheless captured by the country-level random effects added to the model. The composition data we used are derived from remote sensing rather than station measurements, providing a consistent measure of the compositions across locations. However, this also means that this dataset is estimated rather than measured, meaning that some level of error and uncertainty in the reconstruction is expected. The difference between estimates and actual composition may vary by region and components due to complex interactions between diverse emission sources as well as uncertainties in the models generating the data.[10] Important uncertainty is associated with mineral dust, which also contains industrial metals. The other shortcoming of the considered dataset is the lack of data on specific components such as metals that have been previously linked to adverse mortality outcomes.[22]

The analysis performed here relies on the underlying assumption that the composition of $PM_{2.5}$ and its association with mortality have stayed roughly constant during the past 20 years. This assumption allows extending city-specific time series for more stable first-stage risk estimation, while considering a limited number of meta-predictor in the second-stage. Figure 2 suggests that this is a reasonable assumption with few exceptions (UK and Greece). However, if the chemical composition of $PM_{2.5}$ impacts the health, the effects of $PM_{2.5}$ over time are likely to change following the evolution of chemical composition; this issue warrants further research. The first-stage analysis also assumes linearity of the dose–response relationship between $PM_{2.5}$ and mortality, although some studies suggest it might be slightly supralinear.[4] A potential extension of our approach would be to account for temporal differences, both as a long-term trend and as a seasonal pattern by using monthly data, as well as to account for potentially nonlinear first-stage associations. However, these would require longer time-series than what is available for many countries in the MCC dataset, and it poses non-trivial methodologic problems. These extensions can be the topic of future research.

Although our model assessments suggest that the results reported above are robust to confounding by either socio-economic indicators or specific regional effects, and the residual analysis does not show obvious patterns that may have been missed by the model either, some residual confounding is still possible. Humidity is not addressed in the first stage because of the lack of data in many MCC locations. Removing the variable from every location allows more consistency in the first-stage estimates, increasing the power of the second stage meta-regression. The city-specific socio-economic and large-scale environmental indicators that have been introduced in the second stage model only represent a fraction of city-specific characteristics that may affect vulnerability to $PM_{2.5}$, and are limited to a few years. Additional work, is needed to gather a larger list of standardized city-specific characteristics in order to better explore socio-economic indicators in more detail than the variables used here.

The main message of the present paper is that we estimate that $PM_{2.5}$ composition played an important role in the observed heterogeneity of mortality risk linked to air pollution, which necessitated appropriate analytical methods. We estimate that the most harmful component was ammonium, while we did not identify effect modification from the widely studied black carbon and organic carbon components. At the same time, a substantial decrease in the health risk was associated with higher proportions of nitrates. These results also suggest the need for studies of ammonium nitrate and ammonium sulfate to disentangle the effects of these components.

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Figure Legends

Figure 1: Locations used in the study with their mean $PM_{2.5}$ concentration and best linear unbiased predictions (BLUPs) of relative risks (RRs) per 10 $\boldsymbol{\mu g/m^3}$ increase in $PM_{2.5}$.

Figure 2: Annual geometrical mean of the $PM_{2.5}$ composition in each country.

Figure 3: Effect modification from each $PM_{2.5}$ component. A: relative excess risk (RER) associated to doubling the relative proportion of each component with 95% confidence interval. B: predicted relative risks (RRs) for different values of each component while keeping the other constituents constant. The predicted RR is associated with an increase of $10 \mu g/m^3$ in $PM_{2.5}$. Thick lines indicate the range of observed values for each component, while thin dashed lines indicate extrapolations. Colored bands represent 95% confidence regions.

Table 1: Description of first-stage data aggregated per country

Country	Cities	Data period[a]	Total mortality	Mean $PM_{2.5}$ (10 – 90 percentiles) in μg/m^3
Australia	3	2000-2009	388 122	7.0 (3.2 – 11.9)
Canada	19	1999-2015	1 824 857	8.0 (2.7 – 15.0)
Chile	4	2008-2014	293 477	32.1 (8.8 – 59.7)
China	3	2013-2015	248 716	61.2 (19.9 – 120.4)
Estonia	1	2008-2015	8 226	9.6 (2.1 – 19.4)
Finland	1	1999-2014	117 610	16.8 (4.8 – 34.4)
Germany	11	2004-2015	1 303 058	14.3 (5.4 - 25.4)
Greece	1	2007-2010	118 034	21.9 (11.5 – 34.0)
Japan	36	2011-2015	1 292 348	14.3 (5.5 – 25.5)
Mexico	3	2003-2012	1 148 573	27.0 (14.0 – 41.3)
Portugal	1	2004-2017	315 615	12.5 (4.9 – 23.2)
Spain	15	2004-2014	410 043	13.2 (5.0 - 24.0)
Sweden	1	2001-2010	90 670	8.2 (3.6 - 14.4)
Switzerland	4	1999-2013	128 779	19.3 (6.7 - 35.8)
UK	25	1999-2016	1 589 098	12.3 (4.8 - 23.4)
USA	82	1999-2006	5 494 039	13.0 (5.0 - 23.4)

[a] For the first stage only. It may slightly vary within countries because of missing values.

Table 2: Measures of residual heterogeneity for second-stage meta-analysis specification.

	Cochran Q	I^2 (%)	Wald statistic[a]	p-value[a]
Full model	312.6	36.0	19.0	0.0041
PC-only	472.6	56.4	6.8	0.0337
Null model	500.9	58.5	-	-

[a] Wald statistic and associated p-value test nested hypotheses compared to the model on the line below. PC=principal components.

Figure 1

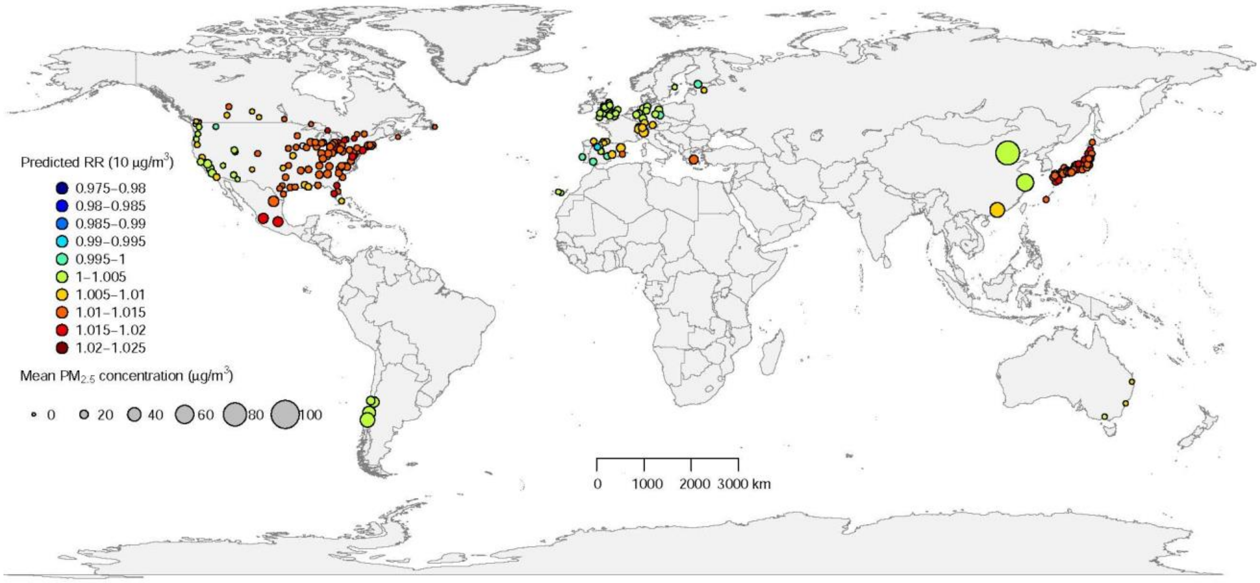
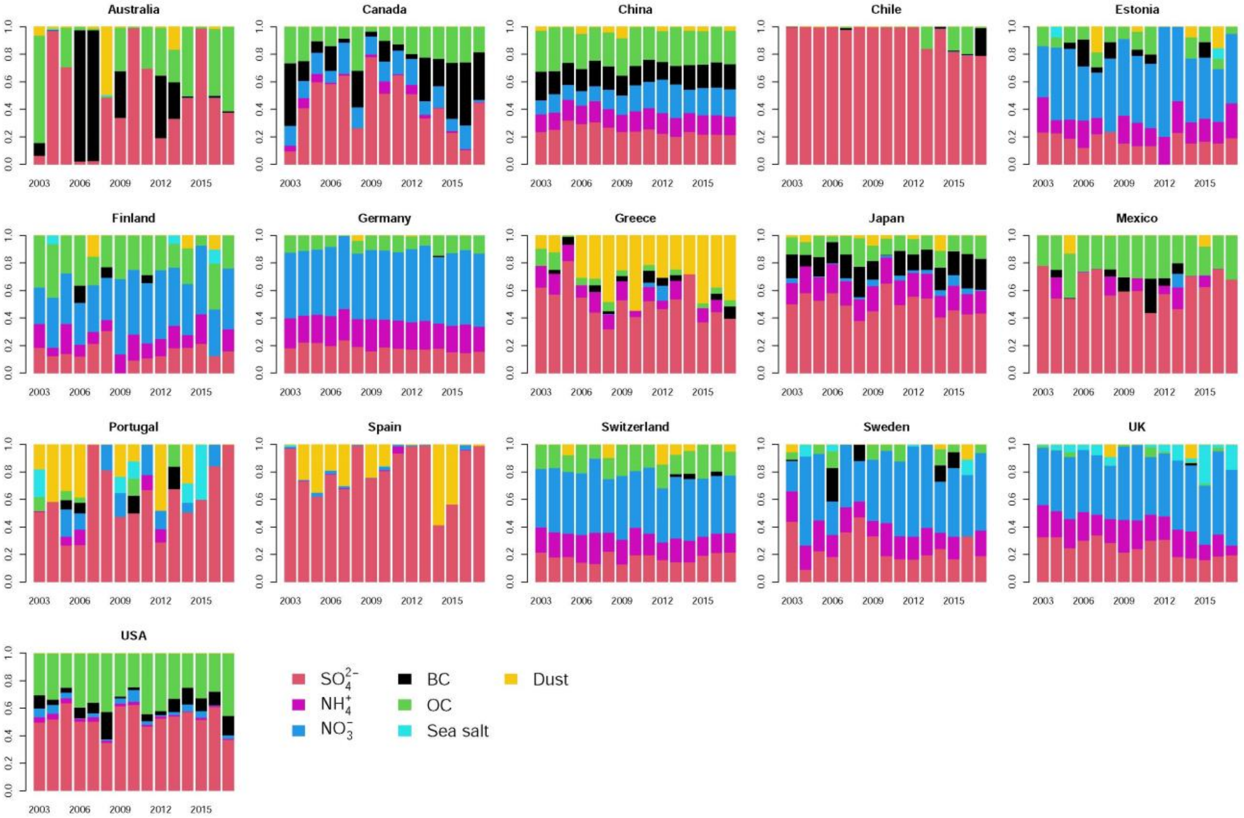
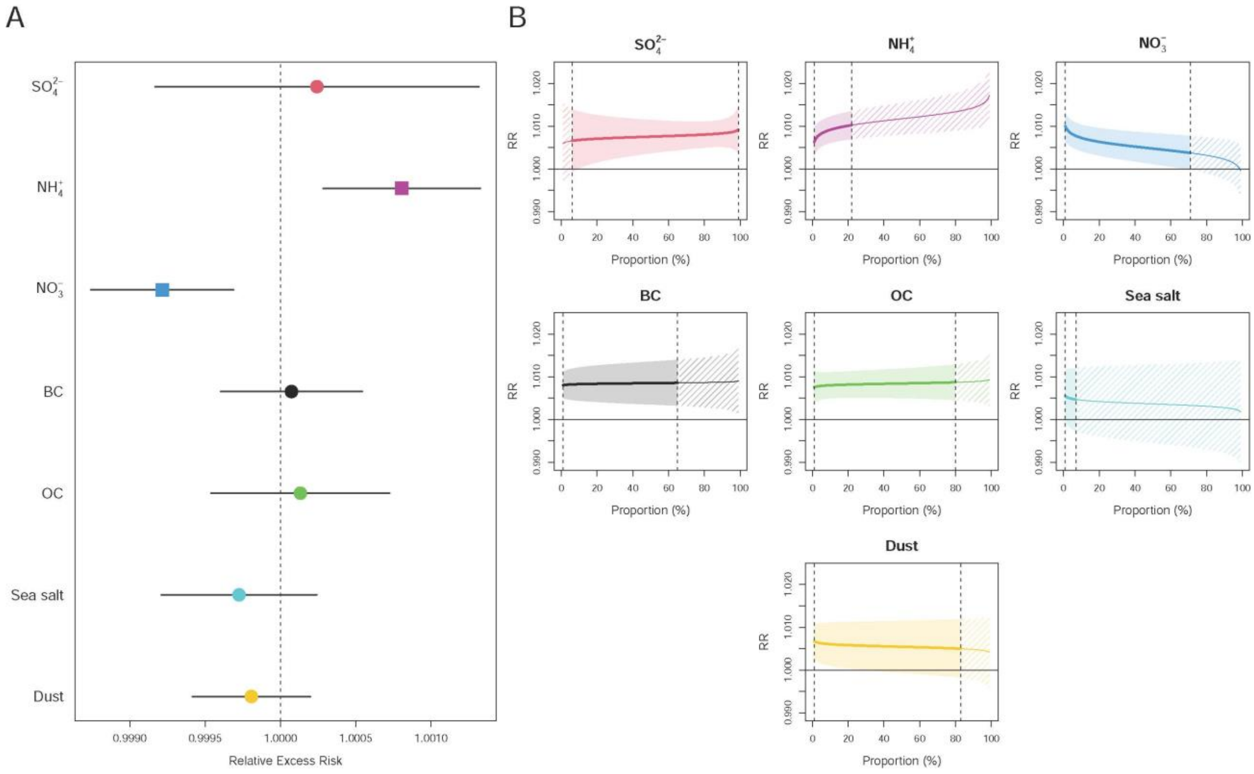

Predicted RR (10 μg/m^3)
0.975–0.98
0.98–0.985
0.985–0.99
0.99–0.995
0.995–1
1–1.005
1.005–1.01
1.01–1.015
1.015–1.02
1.02–1.025
Mean PM$_{2.5}$ concentration (μg/m^3)
0
20
40
60
80
100
0
1000
2000
3000 km

Figure 2



Australia
Canada
China
Chile
Estonia
Finland
Germany
Greece
Japan
Mexico
Portugal
Spain
Switzerland
Sweden
UK
USA
0.0
0.2
0.4
0.6
0.8
1.0
2003
2006
2009
2012
2015
SO_4^{2-}
NH_4^+
NO_3^-
BC
OC
Sea salt
Dust

Figure 3


A
SO_4^{2-}
NH_4^+
NO_3^-
BC
OC
Sea salt
Dust
0.9990
0.9995
1.0000
1.0005
1.0010
Relative Excess Risk
B
SO_4^{2-}
NH_4^+
NO_3^-
BC
OC
Sea salt
Dust
RR
0.990
1.000
1.010
1.020
0
20
40
60
80
100
Proportion (%)