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Fine particles matter components and interstitial lung disease in rheumatoid arthritis

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Tweetable abstract: Interstitial lung disease (ILD) in rheumatoid arthritis is associated with long-term exposure to ambient fine particles matter ($PM_{2.5}$). Among the major $PM_{2.5}$ chemical components, ammonium contributed the most to the ILD risk.

Abstract

Exposure to ambient fine particulate matter ($PM_{2.5}$) is a risk factor for pulmonary and systemic autoimmune diseases, however evidence on which $PM_{2.5}$ chemical components are more harmful is still scant. Our goal is to investigate potential associations between $PM_{2.5}$ components and interstitial lung disease (ILD) onset in rheumatoid arthritis (RA).

New-onset RA subjects identified from a United States health care insurance database (MarketScan) were followed for new onset of RA associated ILD (RA-ILD) from 2011 to 2018. Annual ambient $PM_{2.5}$ concentrations of its chemical components (i.e. sulfate, nitrate, ammonium, organic matter, black carbon, mineral dust, and sea salt) were estimated by combining satellite retrievals with chemical transport modelling and refined by geographically weighted regression. Exposures from 2006 up to one year before ILD onset or end of study were assigned to subjects based on their metropolitan division or core-based statistical area codes. A novel time-to-event quantile-based g(generalized)-computation approach was used to estimate potential associations between RA-ILD onset and the exposure mixture of all seven $PM_{2.5}$ chemical components adjusting for age, sex, and prior chronic obstructive pulmonary disease (as a proxy for smoking).

We followed 280,516 new-onset RA patients and detected 2194 RA-ILD cases across 1,394,385 person-years. The adjusted hazard ratio for RA-ILD onset was 1.54 (95% confidence interval 1.47-1.63) per every decile increase in all seven exposures. Ammonium, mineral dust, and black carbon contributed more to ILD risk than the other $PM_{2.5}$ components.

In conclusion, exposure to elements of $PM_{2.5}$, particularly ammonium, increases ILD risk in RA.

Keywords: rheumatoid arthritis, interstitial lung disease, fine particles matter components, quantile-based g-computation, MarketScan database.

Abbreviations

AIC: Akaike information criterion

CBSA: core-based statistical area

CI: confidence interval

COPD: chronic obstructive pulmonary disease

HR: hazard ratio

ICD-9/10-CM: International Classification of Disease, Ninth/tenth Revision, Clinical Modifications

ILD: interstitial lung disease

$PM_{2.5}$: fine particulate matter with an aerodynamic diameter <2.5 μg/m^3

PM_{10}: particulate matter with an aerodynamic diameter <10 μg/m^3

RA: rheumatoid arthritis

RA-ILD: RA-associated ILD

US: United States

WQS: weighted quantile sum

Introduction

Rheumatoid arthritis (RA) is a potentially disabling systemic autoimmune disorder that affects up to 80 million people world-wide [1]. Interstitial lung disease (ILD) is a severe extraarticular RA manifestation that contributes greatly to morbidity and mortality [2,3]. Although it is increasingly recognized that fine particulate matter ($PM_{2.5}$) in air pollution is an environmental risk factor associated with some pulmonary and systemic autoimmune diseases [4,5], knowledge about a potential association between ambient $PM_{2.5}$ and ILD in RA (RA-ILD) is scant. As well, ambient $PM_{2.5}$ is composed of different chemical components (e.g. organic matter, black carbon, mineral dust, and mineral salt) [6]. A few studies suggested that individual chemical components of $PM_{2.5}$ may be more closely related to adverse health effects than aggregated $PM_{2.5}$ [7,8]. Ambient air pollution has been linked to subclinical ILD in the non-RA setting [9]. However, for many diseases including RA-ILD, it remains unclear which $PM_{2.5}$ chemical components are the most harmful.

People are usually exposed to multiple air pollutants and chemical components simultaneously [10]. Concentrations of these different air pollutants or chemical compositions are often correlated in space, since they share common sources (e.g. industries and road traffic) [11]. Given this correlation, studies of the health effects of multiple $PM_{2.5}$ chemical compositions do not lend themselves well to a common parametric regression approach (e.g. a multi-exposure Cox proportional hazards model) due to the potential problem of collinearity.

G-computation belongs to the G-method family of ‘generalized’ models which provide consistent estimates of contrasts (e.g. differences and ratios) of average potential outcomes under a less restrictive set of identification conditions than standard parametric regression methods. Quantile-based g-computation [10] represents a novel way to investigate the joint health effects

of multiple exposures. Compared to other methods for assessing joint effects of multiple inter-correlated exposures, e.g. Bayesian kernel machine regression [12] and weighted quantile sum (WQS) regression [13] (Carrico et al., 2015), quantile-based g-computation is much more efficient, which is beneficial in analyzing datasets with a large number of subjects and multiple exposure variables and covariates [10]. More importantly, current Bayesian kernel machine regression and WQS regression methods apply only to cross-sectional studies. By contrast, quantile-based g-computation can be used to fit time-to-event models to estimate marginal hazard ratios (HRs) for exposure mixtures. Therefore, in this study we used quantile-based g-computation in conjunction with conventional Cox proportional hazards models to investigate associations between RA-ILD onset and long-term exposure to a mixture of $PM_{2.5}$ chemical components, based on a general-population cohort using administrative health data from the United States (US).

Methods

study cohort

Our analyses were based on the Truven Health MarketScan Commercial Claims Database, which curates non-nominal longitudinal health claims (related to physician visits, emergency room encounters, hospitalizations, and prescription drug dispensations) from all US health care insurance agencies willing to provide data. MarketScan has been used to estimate the prevalence of RA and ILD-RA [14]. The database records at least one diagnosis code for each physician billing claim and up to four diagnostic codes for each hospitalization, coded using the International Classification of Disease, Ninth/tenth Revision, Clinical Modifications (ICD-9/10-CM) classification system. Besides standard demographic variables (e.g. age and sex), the database contains a geographic code for each enrollee, as either a metropolitan division or core-

based statistical area (CBSA) code. A CBSA is a US geographic area that consists of one or more counties with an urban center of at least 10,000 people. A metropolitan division is constituted by subdividing one of the 11 largest Metropolitan Statistical Areas (e.g. Chicago-Naperville-Elgin, Los Angeles-Long Beach-Anaheim, and New York-Newark-Jeresy City). In the MarketScan database, people living in rural areas (i.e. not residing in a CBSA or metropolitan division) have no indicator of their geographic location, and thus could not be included in our analyses.

New-onset RA subjects, defined by at least two physician billing claims with an RA diagnostic code (i.e. ICD-10 M05 or M06) within two years or at least one relevant hospitalization diagnostic code, were identified in the MarketScan database from January 1, 2011 to December 31, 2018. Subjects were followed until ILD onset (at least two physician claims with relevant diagnostic codes of ICD-10 M05.1 or J84.1, at least one month apart), death, or end of study (i.e. December 31, 2018). Subjects with incident ILD before RA diagnosis were excluded. Additionally, we adjusted for ICD codes (ICD-10 J41-J44.x) related to chronic obstructive pulmonary disease (COPD) for two reasons. First, COPD is a potential confounder in our analyses since it is associated with air pollution and because COPD may sometimes be mistaken for ILD within administrative coding [15]. Second, smoking is associated with ILD [16], and could be an effect-modifier in the relationship between ILD and air pollution. However, smoking status is limited in MarketScan commercial claims data; instead, COPD has been used by investigators as a proxy for smoking, given COPD's strong association with tobacco use [17].

Exposure variables

The annual $PM_{2.5}$ chemical composition products (V4.NA.03 version) for 2006 to 2017 were obtained from the Atmospheric Composition Analysis Group (available from https://sites.wustl.edu/acag/datasets/surface-pm2-5/?, last accessed: June 29, 2021). Concentrations of overall $PM_{2.5}$, sulfate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt in the products were estimated by combining satellite retrievals of aerosol optical depth with GEOS-Chem chemical transport model calculations to relate aerosol optical depth with $PM_{2.5}$ composition. Ground-based measurements were then incorporated using a geographically weighted regression to provide a spatially continuous dataset at approximately a 1 km × 1 km resolution over North America [18]. In more detail, the geographically weighted regression was used to predict the bias of $PM_{2.5}$ and its components compared to ground-based measurements using predictor variables related to simulated composition, as well as land surface cover and local elevation features [18]. The overall cross-validated agreement (coefficients of variation) of the resultant all-composition $PM_{2.5}$, sulfate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt to the in situ measurements for 2000-2016 are 0.70, 0.96, 0.86, 0.90, 0.59, 0.57, 0.60, and 0.80, respectively, over North America [18]. The average ambient $PM_{2.5}$ and its chemical composition concentrations from 2006 to one year before ILD onset or end of study for each metropolitan division area or CBSA were calculated based on the gridded $PM_{2.5}$ chemical composition products and assigned to each subject. The spatial variations of overall $PM_{2.5}$ and its seven components for 2006 are shown by Figure S1. Similar spatial variations of the air pollutants can be seen for the other 11 years (i.e. 2007-2017).

Similar to others [19, 20], we considered the role of ozone, another common ambient air pollutant in our models. Ozone is a powerful oxidant and toxic air pollutant [21]. County-level daily ambient ozone concentrations were retrieved from the Centers for Disease Control and Prevention (Available from www.data.cdc.gov, last accessed: June 2, 2021). These ground-based daily measurements were averaged for each year between 2006-2017, aggregated to each metropolitan division area or CBSA, and assigned to each subject as was done for $PM_{2.5}$ and its compositions.

Statistical methods

First, the risk of RA-ILD onset after RA diagnosis was assessed using single-exposure Cox proportional hazard models for overall $PM_{2.5}$, the seven $PM_{2.5}$ chemical compositions, and ozone exposures separately, adjusting for age (in years), sex, and co-existence of baseline COPD (at time of RA). Many previous studies have demonstrated that in North America (where $PM_{2.5}$ and its chemical composition levels are relatively low), the relationships between the $PM_{2.5}$ or its chemical composition concentration and hazard ratios (HRs) are nearly linear [20,22]. Hence, we did not categorize the continuous exposure variables to avoid unnecessary loss of information [23].

Next, we used the quantile-based g-computation to estimate the marginal HR and 95% confidence interval (CI) for the exposure mixture of the seven individual $PM_{2.5}$ chemical composition exposures, adjusting for the same covariates as those in the above Cox proportional hazard models. The quantile-based g-computation approach was developed by combining WQS [13] and g-computation [24]. To address potential collinearity, the WQS method transforms each continuous exposure of interest (X) into an ordinal variable (X^q) and combines the ordinal

exposure variables into a mixed-effect index (*S*) to estimate the overall effect of increasing each exposure by one quantile using Equation 1:

$$S = \sum_{i=1}^{n} w_i X_i^q \quad (1)$$

in which *i* denotes an exposure, *n* represents the number of exposures of interest, *q* is the number of quantiles of each exposure variable (10 in this study), and *w* is the weight for an exposure. All weights are forced to sum to 1 and have the same sign or be equal to zero. Considering that nonlinear effects of exposure variables would be examined in this study (see the following two paragraphs), we selected a relatively large value of *q* (i.e. 10) as per the suggestion of the developers of the quantile-based g-computation approach [25]. Under the directional homogeneity of the weights, the WQS regression model is expressed by Equation 2:

$$Y = \beta_0 + \psi S + \beta_1^T Z \quad (2)$$

where *Y* denotes the health outcome (i.e. the binary outcome of ILD onset in this study), β_0 is the model intercept, *Z* is a vector of potential confounders or effect modifiers (i.e. age, sex, and co-existence of COPD in this study), β_1 represents the coefficient vector of the covariates, and ψ is the coefficient of the mixed-effect index. The coefficients of each ordinal exposure, *w*, in the index (usually called index weights) are obtained by the maximizing likelihood method and are used to quantify the magnitudes of effects of individual exposures on the health outcome [13]. Although WQS regression has been widely applied [e.g. 26-28], the assumption of directional homogeneity in WQS may lead to estimation biases and lack of convergence [10].

When the sample size is large, the WQS regression can be treated as a generalized linear model [13]. Variables in a generalized linear model do not need to adhere to directional homogeneity and generalized linear regression is often used to assess the effects of complex exposures in observational datasets [29]. G-computation (or g-formula) is usually used to

estimate causal effects and can be fitted by generalized linear model [30]. If the directional homogeneity assumption holds true, a quantile-based g-computation model is equivalent to a WQS model; otherwise, the coefficient of the mixed-effect index (i.e. logarithm of the odds ratio or HR of the exposure mixture regarding the outcome) is estimated by the standard g-computation algorithm. Thus, quantile-based g-computation can be treated as a generalization and extension of WQS, which eliminates the restriction of directional homogeneity [10]. Similar to the WQS regression, the index weights that are generated in quantile-based g-computation provide an estimation of the relative magnitude of associations regarding individual exposures and the outcome. However, this holds only if associations are in the same (positive or negative) direction. The index weights may go in either direction, suggesting that some exposures may have a positive association, while others a negative association, with the studied outcome.

The quantile-based g-computation uses Cox proportional hazards as the underlying model for time-to-event analysis to yield estimates of the effect of increasing all exposures by one quantile. The quantile-based g-computation can be extended to consider potential nonlinear effects of variables. In our preliminary assessment, we tried to use spline functions to model the nonlinear effects for each of the exposure variables, and the mixed-effect index was developed by Equation 3:

$$S = \sum_{i=1}^{n} w_i f(X_i^q) \qquad (3)$$

where $f(\cdot)$ is a spline function with a degree of two [25]. Comparing the Akaike information criterion (AIC) values [10], we found that the simple linear combination of the exposure variables (i.e. Equation 1) provided a better fit (i.e. with a lower AIC) and avoided over-fitting, compared to the use of the spline non-linear function. Thus, we selected the linear additive strategy to structure the mixture effect index in the quantile-based g-computation model.

Mathematical formulation details on the quantile-based g-computation approach have been elaborately demonstrated by Keil et al. [10]. Our specific quantile-based g-computation model was fitted by "qgcomp" package in the R statistical computing environment (version 4.0.4). The code of fitting a quantile-based g-computation model for the primary analysis can be seen in Supporting materials.

We repeated the above quantile-based g-computation analysis by adding ozone as an additional exposure variable. We also conducted a sensitivity analysis of the Cox proportional hazard models and the quantile-based g-computation models, excluding subjects with COPD (again, as a means of addressing heavy tobacco use-which was unmeasured in our dataset and outcome ascertainment error related to COPD-which can mimic ILD). We conducted more sensitivity analyses of the quantile-based g-computation models that stratified subjects by sex and age (i.e. ≤52 and >52 years old, 52 being the mean age of the first ILD diagnosis of the RA patients).

Given that our follow-up period was relatively short (eight years) and ambient $PM_{2.5}$ levels were relatively stable in the contiguous US over the period [18], we did not adopt time-varying exposures, so that the quantile-based g-computation models were more efficiently fitted. To explore whether this simplified assignment of exposure variables might generate large measurement biases, we performed Kendall's Tau tests in an attempt to detect any calendar-year trends in any of the $PM_{2.5}$ components in any metropolitan division or CBSA over time.

Results

We identified 280,516 new-onset RA patients (75.6% female) from 401 different CBSA or metropolitan division areas. Distribution of the 280,516 RA patients is shown by Figure 1. The mean area of the 401 CBSA or metropolitan divisions is 2636 km^2 with a standard deviation of 3588 km^2. Among the RA patients, 2,194 (74.5% female) developed ILD over a median follow-up of 0.48 (interquartile range 1.17) years for a total of 1,394,385 person-years (incidence of 3.2 cases per 1000 patient-years). The mean age at RA onset was 50.3 (standard deviation 11.0) years. RA patients were exposed to overall $PM_{2.5}$ concentrations ranging from 3.0 $\mu g/m^3$ to 12.4 $\mu g/m^3$. Detailed participant characteristics and exposures for subgroups of each covariate are exhibited in Table 1. The distribution of population weighted $PM_{2.5}$, $PM_{2.5}$ compositions, and ozone exposures are shown in Table 2. Concentrations of the $PM_{2.5}$ compositions were significantly inter-correlated and particularly, concentrations of mineral dust and sea salt were negatively correlated with those of the other $PM_{2.5}$ chemical components (Table S1).

[Figure 1 about here]

The single-pollutant Cox proportional hazards models (controlling for demographics but not concomitant air pollution exposure) showed that ambient overall $PM_{2.5}$ and ozone exposures were both associated with RA-ILD onset. In these partially adjusted models, most $PM_{2.5}$ chemical components had positive associations with RA-ILD onset, but mineral dust had a negative association with RA-ILD, and sea salt had no clear association. The risk of developing RA-ILD increased with age (Table 3). Similar results were obtained by removing COPD subjects from the single-pollutant Cox proportional hazards models (see Tables S2).

Using quantile-based g-computation, we observed a significantly increased risk of RA-ILD onset with every decile increase in all seven $PM_{2.5}$ composition exposures (HR 1.54, 95% CI 1.47-1.63). This HR increased significantly after including ozone in the quantile-based g-computation model (Table 4). Ammonium (index weight: 0.59), mineral dust (0.15), black carbon (0.14), ozone (0.09), and sea-salt (0.03) had positive effects on RA-ILD while nitrate (0.57), organic matter (0.31), and sulfate (0.12) had negative effects. The negative index weights suggest that the $PM_{2.5}$ components of nitrate, organic matter, and sulfate are not correlated with RA-ILD. Results from sensitivity analyses with COPD subjects removed were similar (Table 4).

With the sex or age subgroups, similar positive associations between the mixture of $PM_{2.5}$ component exposures and RA-ILD and index weights (i.e. in positive direction index weight of ammonium larger than those of mineral dust, black carbon, ozone, and sea-salt, and in negative direction index weight of nitrate larger than those of organic matter and sulfate) can be observed. (Table S3).

The Kendall's Tau tests showed that only 34.7% of the 401 CBSA or metropolitan division areas had more than two (of the seven) $PM_{2.5}$ component concentrations time-series with statistically significant calendar-year trends ($p<0.01$).

Discussion

A few studies have demonstrated that long-term exposures to nitrogen dioxide, ozone, and particulate matter with an aerodynamic diameter <10 $\mu g/m^3$ (PM_{10}) were associated with the increased risk of ILD or idiopathic pulmonary fibrosis (IPF, the most common form of ILD) in the general population [31-33], although clear associations between overall $PM_{2.5}$ and ILD/IPF was not clearly demonstrated in studies from Taiwan [31], North Italy [32], and Pennsylvania and New Jersey [33]. In our study, we observed a significant positive association between $PM_{2.5}$

exposure and RA-ILD incidence. More importantly, we quantified differential effects of $PM_{2.5}$ chemical compositions on RA-ILD onset and found that ammonium had the largest positive index weight among the seven $PM_{2.5}$ chemical constituents (Table 4). This finding complements other work suggesting that the health effects of $PM_{2.5}$ may not be entirely related to its total concentration, but also to the characteristics of its chemical constituents [34]. The composition of ambient $PM_{2.5}$ may vary greatly across different countries/areas, which should be taken into account when interpreting any study of its effects on health; a failure to demonstrate associations between a composite measure like total ambient $PM_{2.5}$ and a particular outcome does not exclude the possibility that a component of $PM_{2.5}$ may indeed be a culprit.

Many studies have demonstrated harmful effects of mineral dust on respiratory health [35] however, a significant negative association between mineral dust exposure and RA-ILD onset was seen with our single-exposure Cox model. This may have been due to confounding since the concentration of mineral dust in ambient $PM_{2.5}$ was negatively associated with most of the other $PM_{2.5}$ chemical components in the metropolitan statistical areas of the US (including ammonium). Clearly, single pollutant Cox model cannot capture the real effect of PM components.

With the quantile-based g-computation approach, we observed the second largest weight index for mineral dust, preceded only by ammonium (Table 4). There is strong biologic plausibility for both ammonia and mineral dust as potential triggers for RA-ILD, since both are very strong triggers of pulmonary inflammation. [36,37]. In the current study, we observed negative index weights from nitrate, organic matter, and sulfate. Setting a negative direction for the effects of these three exposure variables ensured convergence of the quantile-based g-computation regression [10], but it does not necessarily indicate that nitrate, organic matter, and

sulfate are significantly associated with RA-ILD. In the quantile-based g-computation, index weights are fixed (i.e. no confidence interval can be generated) [10], which is a shortcoming of the method, since statistical significance cannot be estimated. Considering there were already eight exposures (seven $PM_{2.5}$ chemical compositions + ozone) in our quantile-based g-computation model, further adding interaction terms might induce over-fitting [10]. Future exploration of interactions between individual $PM_{2.5}$ chemical compositions may be possible, using a non-parametric Bayesian procedure and high-performance computers [12].

In this study, we assigned air pollution estimates to subjects based on their CBSA or metropolitan division codes, since we did not have access to postal codes or census tract, unlike other studies [19,20,28]. While potential misclassification of exposure is a limitation, we expect this to be non-differential, meaning that our estimates would have tended to be biased towards the null instead of finding any association. Assigning exposures based on residential postal code or census tract may also be misleading since people are typically mobile in their cities as they engage in work and other activities [38]. Thus, a CBSA or metropolitan division area's average concentration of air pollution may be closer to a person's actual exposure than the concentration at the centroid point of the person's residential postal code. Additionally, unlike Pope et al. [39] in which air pollution exposures were assigned at the metropolitan statistical area level, we assigned $PM_{2.5}$ exposures to subjects living in the 11 largest metropolitan statistical areas based on their metropolitan division area codes, which can reduce the exposure misclassification error generated by the over-large metropolitan areas.

Since only one third of the CBSA or metropolitan division areas had more than two (of the seven) $PM_{2.5}$ component concentrations time-series with statistically significant calendar-year trends. Thus, we believe our time-fixed exposure approach is reasonable. However, our study

was limited to residents in urban areas, and thus results may not be generalizable to individuals living in rural areas. Also, we could not obtain reliable data regarding concentrations of other gaseous air pollutants (e.g. nitrogen dioxide and sulfur dioxide) for the US during our study period. Additionally, variables such as race/ethnicity, income and education are unavailable in the Commercial Claims dataset. Given that Americans with commercial health insurance may be more likely to have middle or high incomes, our results may not be generalizable to low-income populations.

Although use of a large population-based database is a strength, use of billing code diagnoses have imperfect specificity for ILD ascertainment, which could result in a non-differential misclassification of the outcome. This could be a contributor to the relatively wide confidence intervals for some of our HR estimates. Another potential limitation is that MarketScan subjects are no longer identifiable after they change insurance status; thus, it is possible that some subjects actually had prevalent RA instead of true incident RA, and a few might have already had prevalent ILD.

In conclusion, we identified positive associations between a mixture of individual $PM_{2.5}$ chemical compositions and RA-ILD onset and quantified specific effects of individual chemical compositions on RA-ILD using quantile-based g-computation. Our findings lend weight to the argument that some components of $PM_{2.5}$ (e.g. ammonium and mineral dust) are of greater concern than others, and that greater public health benefits may be gained by controlling emissions of more toxic components. It seems increasingly clear that efficient use of nitrogen fertilizers and keeping more nitrogen and ammonium in soil are critical ways to limit $PM_{2.5}$ levels in atmosphere and curb the burden of many chronic diseases, potentially including RA-ILD [40].

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Figure captions

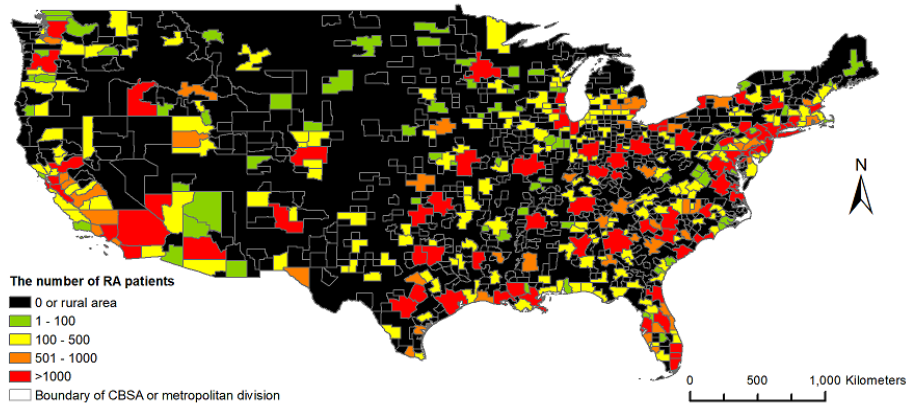


Figure 1. Distribution of identified new-onset rheumatoid arthritis (RA) patients. CBSA: core-based statistical area. Note: these are absolute numbers not rates, and do not account for variations between states in terms of age, MarketScan enrolment, or other factors.

Table 1. Participant characteristics and exposures for subgroups of each covariate in the study cohort.

Covariate	Sub-group	Number of ILD (%)	Person-years	Overall $PM_{2.5}$ ($\mu g/m^3$)	BC ($\mu g/m^3$)	DUST ($\mu g/m^3$)	NH4 ($\mu g/m^3$)	NO3 ($\mu g/m^3$)	OM ($\mu g/m^3$)	SO4 ($\mu g/m^3$)	SS ($\mu g/m^3$)	Ozone (ppb)
Sex	Male	564 (0.8)	342464	8.30	0.71	0.64	0.76	0.94	2.88	2.00	0.37	39.37
	Female	1630 (0.8)	1052876	8.31	0.71	0.67	0.74	0.93	2.89	2.00	0.37	39.47
Age	≤52	860 (0.6)	675557	8.31	0.71	0.68	0.74	0.92	2.89	1.99	0.37	39.53
	>52	1334 (0.9)	719782	8.31	0.71	0.65	0.75	0.93	2.89	2.00	0.37	39.38
COPD	No	121 (1.5)	37302	8.55	0.74	0.64	0.78	0.95	2.98	2.11	0.36	39.41
	Yes	2073 (0.8)	1358037	8.30	0.71	0.66	0.75	0.93	2.89	2.00	0.37	39.45

Table 2. Distribution of population weighted concentrations of ambient $PM_{2.5}$ and its major chemical compositions over the 401 core-based statistical areas and metropolitan division areas in the United States for 2006-2017. (Unit of $PM_{2.5}$ and its compositions: $\mu g/m^3$, unit of ozone: ppb)

Exposure variable	Min	Decile									Max
		10%	20%	30%	40%	50%	60%	70%	80%	90%	
$PM_{2.5}$	3.01	6.10	7.15	7.65	8.39	8.68	8.98	9.21	9.68	10.30	12.40
Ammonium	0.10	0.31	0.47	0.59	0.68	0.75	0.84	0.92	1.02	1.16	1.86
Black carbon	0.22	0.43	0.54	0.59	0.67	0.72	0.79	0.80	0.87	0.94	1.43
Mineral dust	0.11	0.27	0.35	0.41	0.48	0.54	0.66	0.78	0.92	1.22	4.29
Nitrate	0.06	0.37	0.45	0.54	0.60	0.79	0.98	1.10	1.43	1.81	2.65
Organic matter	1.04	2.01	2.35	2.52	2.72	2.92	3.03	3.20	3.38	3.69	5.03
Sea salt	0.00	0.11	0.15	0.18	0.21	0.24	0.29	0.41	0.63	0.78	2.91
Sulfate	0.28	0.85	1.50	1.83	2.01	2.18	2.27	2.40	2.61	2.77	4.32
Ozone	28.66	35.80	37.32	38.19	38.67	39.35	40.00	40.68	41.46	42.47	51.12

Table 3. Hazard ratios (95% confidence intervals) from the single-pollutant Cox proportional hazards models for time to RA-associated ILD onset, per 0.1 μg/m^3 (1 μg/m^3) increase in the $PM_{2.5}$ composition (overall $PM_{2.5}$) and 1 ppb increase in ozone, adjusting for age (in year), sex (male as reference), and co-existence of chronic obstructive pulmonary disease (COPD).

Exposure	Exposure variable	age	sex	COPD
Overall $PM_{2.5}$	1.50 (1.45-1.55)	1.02 (1.01-1.02)	0.96 (0.87-1.06)	1.76 (1.46-2.11)
Ammonium	1.38 (1.36-1.40)	1.02 (1.01-1.02)	0.99 (0.90-1.09)	1.73 (1.43-2.08)
Black carbon	1.26 (1.23-1.28)	1.02 (1.01-1.02)	0.96 (0.87-1.06)	1.79 (1.49-2.15)
Mineral dust	0.97 (0.96-0.98)	1.02 (1.01-1.02)	0.97 (0.88-1.07)	1.86 (1.55-2.24)
Nitrate	1.01 (1.01-1.02)	1.02 (1.01-1.02)	0.96 (0.86-1.06)	1.86 (1.54-2.34)
Organic	1.01 (1.01-1.02)	1.02 (1.01-1.02)	0.96 (0.87-1.05)	1.85 (1.54-2.23)
Sea salt	1.00 (0.98-1.01)	1.02 (1.01-1.02)	0.96 (0.87-1.06)	1.87 (1.55-2.24)
Sulfate	1.17 (1.16-1.18)	1.02 (1.01-1.02)	0.97 (0.88-1.07)	1.71 (1.43-2.07)
Ozone	1.03 (1.01-1.04)	1.01 (1.01-1.02)	0.96 (0.87-1.06)	1.87 (1.55-2.45)

Table 4. Adjusted HR (95% CI) and index weights from the quantile-based g-computation models for time to RA-ILD onset with an increase in all exposures by one decile. The number of overall subjects is 280,516, of which 7835 are with COPD. Note: the positive and negative weights should not be compared with each other. The weights are only compatible with other weights in the same (i.e. positive or negative) direction.

COPD subjects	Ozone exposure	HR (95% CI)	Index weight							
			NH4	DUST	BC	ozone	SS	NO3	OM	SO4
Included	Excluded	1.54 (1.47-1.63)	0.66	0.18	0.16	-	0.00	-0.61	-0.27	-0.12
Included	Included	2.21 (2.08-2.34)	0.59	0.15	0.14	0.09	0.03	-0.57	-0.31	-0.12
Excluded	Excluded	1.63 (1.55-1.72)	0.66	0.18	0.15	-	0.01	-0.61	-0.27	-0.12
Excluded	Included	2.30 (2.16-2.45)	0.59	0.15	0.13	0.09	0.04	-0.58	-0.31	-0.11

BC: black carbon, DUST: mineral dust, NH4: ammonium, NO3: nitrate, OM: organic matter, SO4, sulfate, SS: sea salt.

Fine particles matter components and interstitial lung disease in rheumatoid arthritis

Supporting Materials

Table S1. Spearman correlation coefficients of concentrations between any two of $PM_{2.5}$ compositions. All p-values <0.001.

	BC	**DUST**	**NH4**	**NO3**	**OM**	**SO4**	**SS**
BC	1.00	-0.13	0.59	0.28	0.88	0.80	-0.16
DUST		1.00	-0.40	-0.34	-0.07	-0.14	0.09
NH4			1.00	0.85	0.40	0.60	-0.24
NO3				1.00	0.17	0.21	-0.17
OM					1.00	0.66	-0.10
SO4						1.00	-0.07
SS							1.00

BC: black carbon, DUST: mineral dust, NH4: ammonium, NO3: nitrate, OM: organic matter, SO4, sulfate, SS: sea salt.

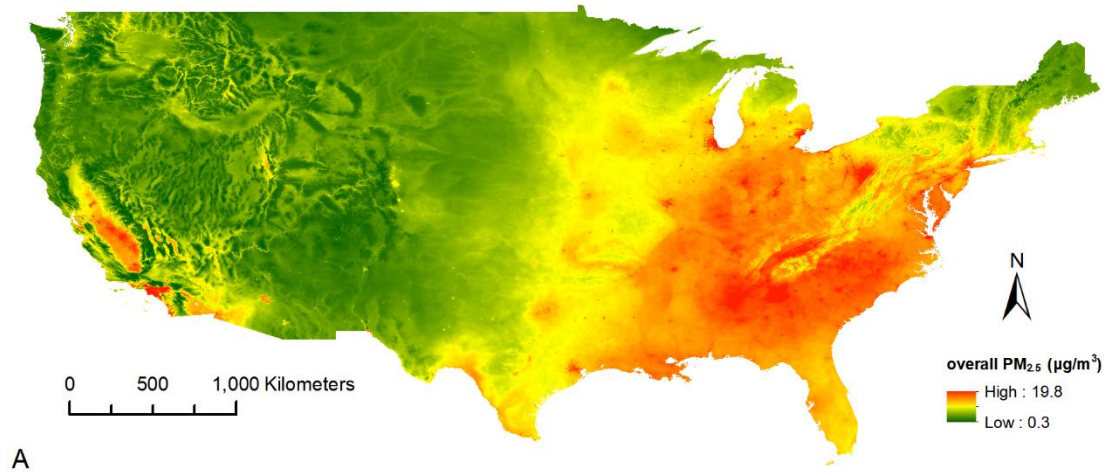
Table S2. Hazard ratios (95% confidence interval) from the single-pollutant Cox proportional hazards models for time to RA-associated ILD onset, per 0.1 $\mu g/m^3$ (1 $\mu g/m^3$) increase in the $PM_{2.5}$ composition (overall $PM_{2.5}$) and 1 ppb increase in ozone with chronic obstructive pulmonary disease (COPD) subjects removed, adjusting for age (in year) and sex (male as reference).

Exposure variable	**Exposure variable**	**age**	**sex**
Overall $PM_{2.5}$	1.50 (1.45-1.56)	1.02 (1.01-1.02)	0.97 (0.87-1.07)
Ammonium	1.39 (1.36-1.41)	1.02 (1.01-1.02)	1.00 (0.91-1.11)
Black carbon	1.26 (1.23-1.28)	1.02 (1.01-1.02)	0.97 (0.87-1.07)
Mineral dust	0.97 (0.96-0.98)	1.02 (1.01-1.02)	0.98 (0.89-1.08)
Nitrate	1.01 (1.01-1.02)	1.02 (1.01-1.02)	0.98 (0.88-1.08)
Organic matter	1.01 (1.01-1.02)	1.02 (1.01-1.02)	0.97 (0.88-1.07)
Sea salt	1.00 (0.98-1.01)	1.02 (1.01-1.02)	0.97 (0.88-1.07)
Sulfate	1.17 (1.16-1.18)	1.01 (1.01-1.02)	0.98 (0.89-1.09)
Ozone	1.03 (1.01-1.04)	1.01 (1.01-1.02)	0.97 (0.88-1.07)

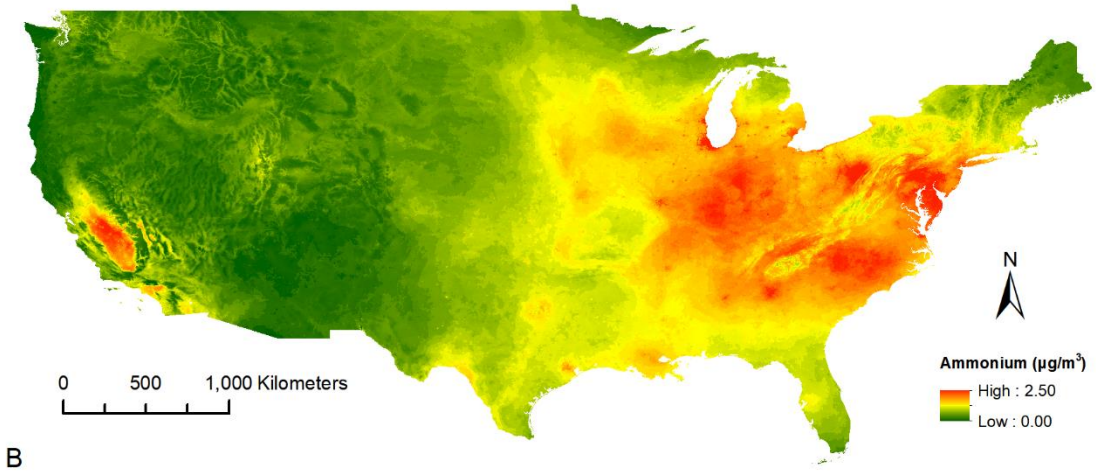
Table S3. Adjusted HR (95% CI) and index weights from the quantile-based g-computation models for time to RA-ILD onset with an increase in all exposures by one decile, using sub-samples stratified by sex or age. Note: the positive and negative weights should not be compared with each other. The weights are only compatible with other weights in the same (i.e. positive or negative) direction.

Sub-group	COPD subjects	HR (95% CI)	Index weight							
			NH4	DUST	BC	ozone	SS	NO3	OM	SO4
Male	Included	1.27 (1.16-1.63)	0.73	0.11	0.13	-	0.02	-0.62	-0.24	-0.14
Male	Included	1.81 (2.03-1.62)	0.65	0.10	0.11	0.09	0.05	-0.58	-0.27	-0.15
Male	Excluded	1.33 (1.22-1.46)	0.71	0.14	0.13	-	0.02	-0.62	-0.25	-0.13
Male	Excluded	1.73 (2.16-2.45)	0.59	0.15	0.13	0.09	0.04	-0.58	-0.31	-0.11
Female	Included	1.69 (1.59-1.80)	0.64	0.19	0.17	-	0.01	-0.61	-0.29	-0.10
Female	Included	2.44 (2.28-2.62)	0.57	0.15	0.14	0.09	0.04	-0.57	-0.32	-0.11
Female	Excluded	1.71 (1.61-1.81)	0.64	0.19	0.17	-	0.01	-0.60	-0.29	-0.11
Female	Excluded	2.45 (2.28-2.63)	0.57	0.15	0.14	0.09	0.04	-0.57	-0.33	-0.11
Age ≤52	Included	1.72 (1.58-1.87)	0.66	0.19	0.15	-	0.00	-0.60	-0.30	-0.10
Age ≤52	Included	2.50 (2.27-2.75)	0.59	0.16	0.13	0.08	0.03	-0.55	-0.34	-0.11
Age ≤52	Excluded	1.73 (1.59-1.88)	0.60	0.19	0.15	-	0.00	-0.60	-0.30	-0.10
Age ≤52	Excluded	2.53 (2.29-2.79)	0.59	0.16	0.13	0.09	0.03	-0.56	-0.33	-0.11
Age >52	Included	1.52 (1.42-1.61)	0.68	0.18	0.13	-	0.00	-0.67	-0.26	-0.07
Age >52	Included	2.27 (2.10-2.45)	0.58	0.15	0.12	0.10	0.04	-0.62	-0.30	-0.08
Age >52	Excluded	1.55 (1.45-1.65)	0.67	0.19	0.14	-	0.00	-0.66	-0.27	-0.07
Age >52	Excluded	2.34 (2.16-2.54)	0.58	0.15	0.12	0.11	0.04	-0.61	-0.31	-0.08

BC: black carbon, DUST: mineral dust, NH4: ammonium, NO3: nitrate, OM: organic matter, SO4, sulfate, SS: sea salt.


N
0 500 1,000 Kilometers
overall PM2.5 (µg/m3)
High : 19.8
Low : 0.3

A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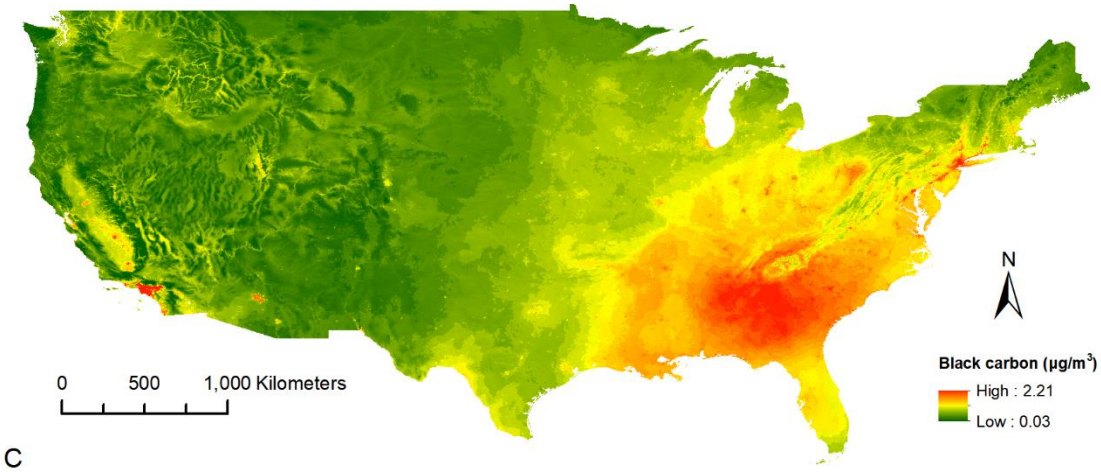
Ammonium (µg/m3)
High : 2.50
Low : 0.00

B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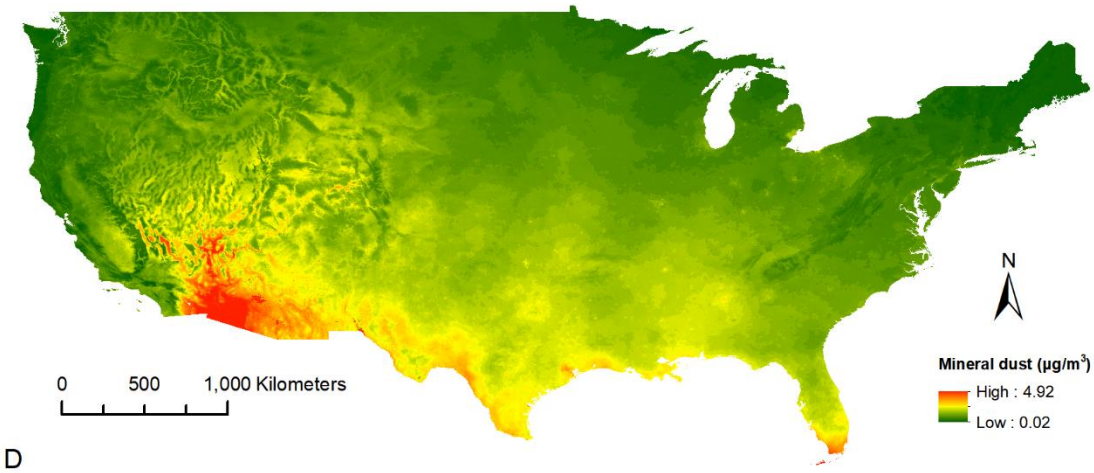
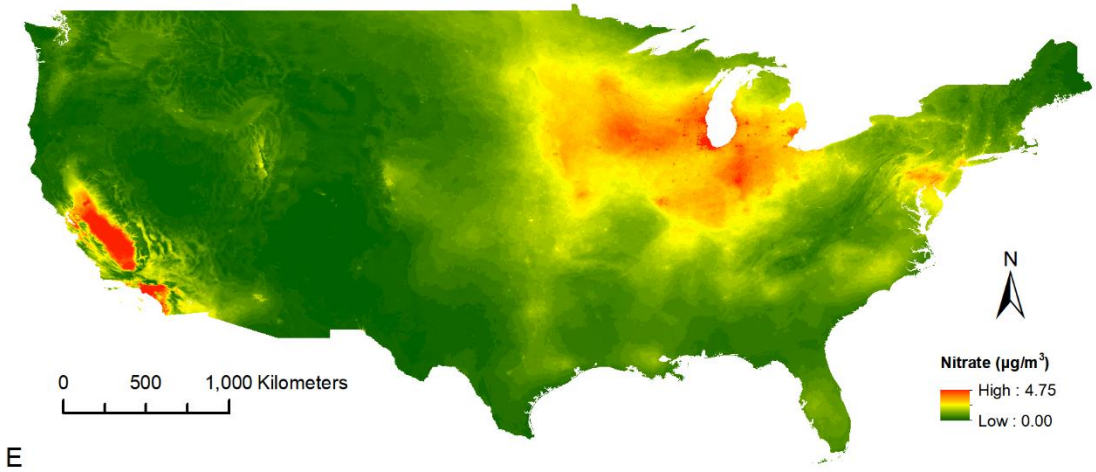
Black carbon (µg/m3)
High : 2.21
Low : 0.03

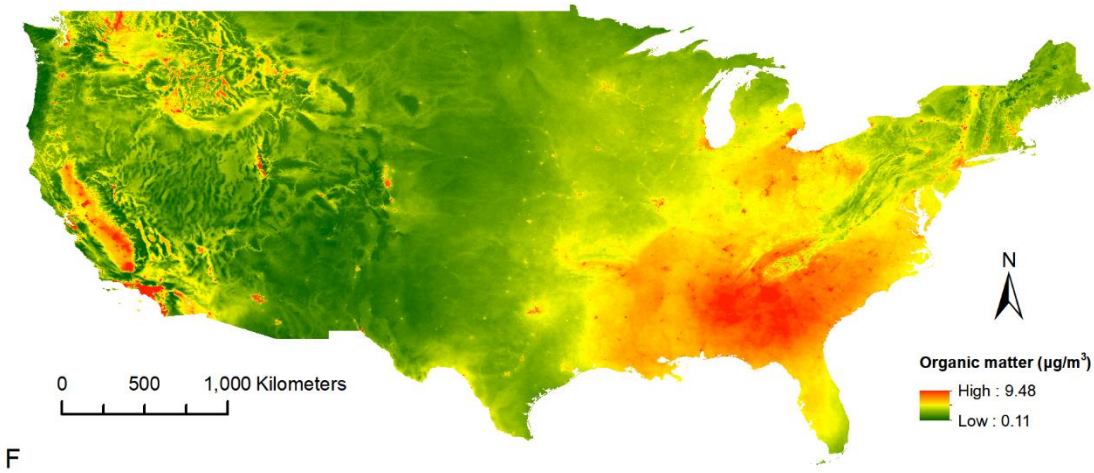
C


N
0 500 1,000 Kilometers
Mineral dust (µg/m3)
High : 4.92
Low : 0.02

D


N
0 500 1,000 Kilometers
Nitrate (µg/m3)
High : 4.75
Low : 0.00

E


N
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Organic matter (µg/m3)
High : 9.48
Low : 0.11

F

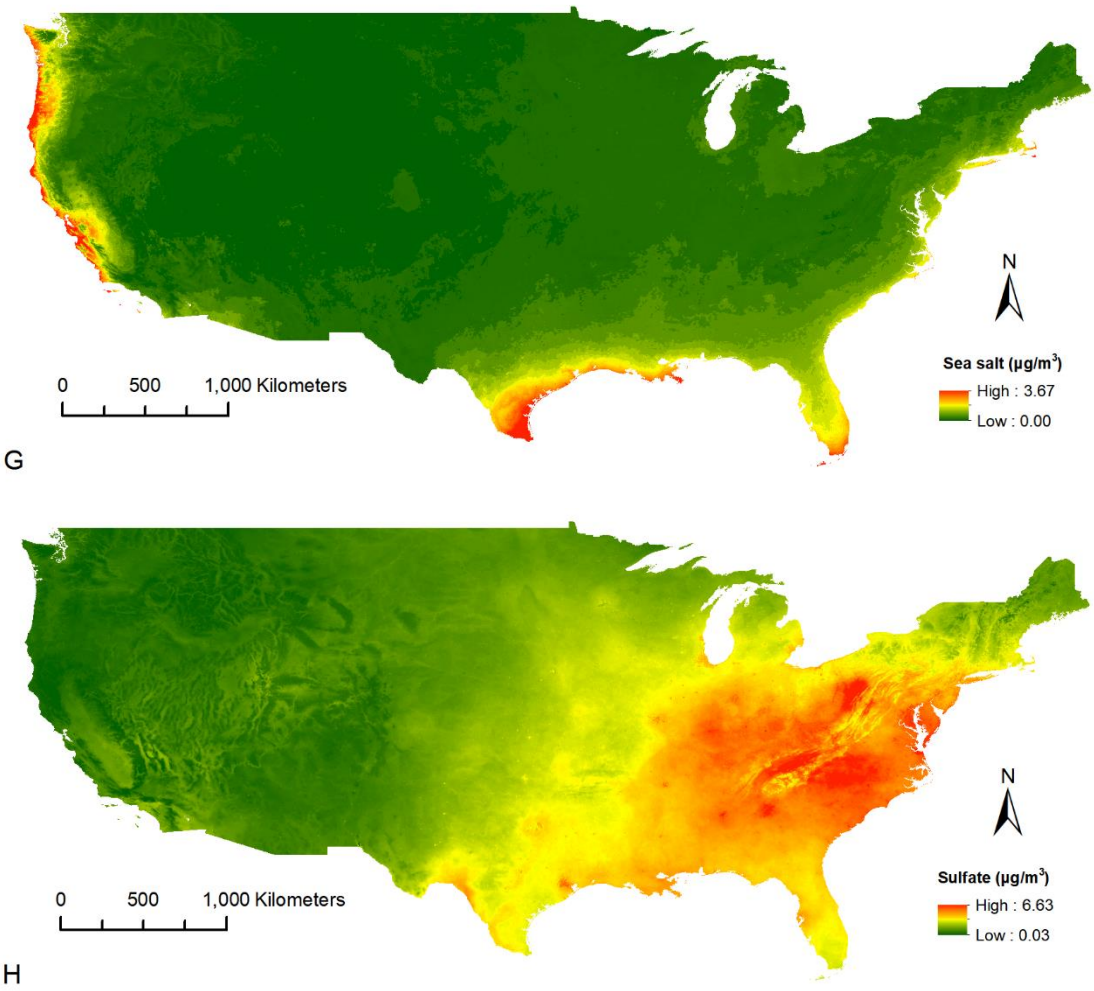

Figure S1. Concentrations of overall $PM_{2.5}$ (A), ammonium (B), black carbon (C), mineral dust (D), nitrate (E), organic matter (F), sea salt (G), and sulfate (H) over the contiguous United States for 2006.

Sample code of fitting a quantile-based g-computation model for the primary analysis

```
library(survival)

library(qgcomp)

setwd("D:/MarketScan/EI") #set the path to the folder saving analysis data

df <- read.csv("RA_ILD_PM_ozone_PMcompositions.csv") #read the dataset to R

Xnm <- c('BC','DUST','NH4','NO3','OM','SO4','SS') #define exposure variables

#Xnm <- c('BC','DUST','NH4','NO3','OM','SO4','SS','ozone_exposure') #use it when ozone is considered as an additional exposure variable

#fit a quantile-based g-computation model, in which "Time" denote the number of follow-up dates,

#"status" is a bindary variable representing ILD incident.

#"q" is the number of quantiles of each exposure variable.

qc.survfit <- qgcomp.cox.noboot(survival::Surv(Time, status) ~ .,expnms=Xnm,

                                data=df[,c(Xnm, 'Age','Sex','Time', 'status')],q=10)

a<-summary(qc.survfit1)

b<-a$coefficents

exp(b[1]) #Hazard ratio

#cacluate 95% confidence interval

CI_lower<-exp(b[1]-1.96*b[2])

CI_upper<-exp(b[1]+1.96*b[2])
```