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Association between Long-Term Exposure to $PM_{2.5}$ Inorganic Chemical Compositions and Cardiopulmonary Mortality: A 22-Year Cohort Study in Northern China

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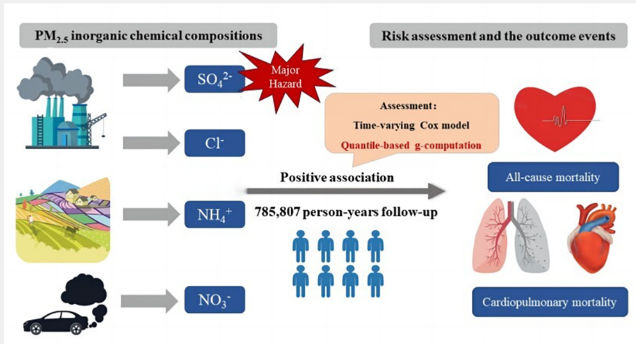

ABSTRACT: Particulate matter with diameters ≤2.5 μm ($PM_{2.5}$) has been identified as a significant air pollutant contributing to premature mortality. Nevertheless, the specific compositions within $PM_{2.5}$ that play the most crucial role remain unclear, especially in areas with high pollution concentrations. This study aims to investigate the individual and joint mortality risks associated with $PM_{2.5}$ inorganic chemical compositions and identify primary contributors. In 1998, we conducted a prospective cohort study in four northern Chinese cities (Tianjin, Shenyang, Taiyuan, and Rizhao). Satellite-based machine learning models calculated $PM_{2.5}$ inorganic chemical compositions, including sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), and chloride (Cl^-). A time-varying Cox proportional hazards model was applied to analyze associations between these compositions and cardiorespiratory mortality, encompassing nonaccidental causes, cardiovascular diseases (CVDs), nonmalignant respiratory diseases (RDs), and lung cancer. The quantile-based g-computation model evaluated joint exposure effects and relative contributions of the compositions. Stratified analysis was used to identify vulnerable subpopulations. During 785,807 person-years of follow-up, 5812 (15.5%) deaths occurred from nonaccidental causes, including 2932 (7.8%) from all CVDs, 479 (1.3%) from nonmalignant RDs, and 552 (1.4%) from lung cancer. Every interquartile range (IQR) increase in SO_4^{2-} was associated with mortality from nonaccidental causes (hazard ratio: 1.860; 95% confidence interval: 1.809, 1.911), CVDs (1.909; 1.836, 1.985), nonmalignant RDs (2.178; 1.975, 2.403), and lung cancer (1.773; 1.624, 1.937). In the joint exposure model, a simultaneous rise of one IQR in all four compositions increased the risk of cardiorespiratory mortality by at least 36.3%, with long-term exposure to SO_4^{2-} contributing the most to nonaccidental and cardiopulmonary deaths. Individuals with higher incomes and lower education levels were found to be more vulnerable. Long-term exposure to higher levels of $PM_{2.5}$ inorganic compositions was associated with significantly increased cardiopulmonary mortality, with SO_4^{2-} potentially being the primary contributor. These findings offer insights into how $PM_{2.5}$ sources impact health, aiding the development of more effective governance measures.

KEYWORDS: *$PM_{2.5}$ inorganic chemical compositions, mortality, cohort study, cardiorespiratory disease, joint association*

■ INTRODUCTION

It is widely acknowledged that exposure to ambient air pollution poses a risk to human health. In 2020, over 81% of China's population resided in areas where concentrations of particulate matter (PM) with diameters ≤2.5 μm ($PM_{2.5}$) exceeded the World Health Organization's (WHO) Interim Target 1.[1] It is well-known that long-term exposure to $PM_{2.5}$ is associated with increased morbidity and mortality from a variety of diseases.[2−5] $PM_{2.5}$ originates from various environmental sources, encompassing transportation, industrial emissions, agricultural activities, and desert dust. Each of these sources can emit $PM_{2.5}$ particles with distinct physical and chemical properties.[6] Despite our better understanding of the sources of $PM_{2.5}$, the chemical composition of $PM_{2.5}$ shows great spatial and temporal variations due to factors such as economic development, population density, topography, climate change, and government policies.[7,8] $PM_{2.5}$ chemical compositions include organic

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matter, black carbon, sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), chloride (Cl^-), mineral dust, and trace elements, among others. In this study, we specifically concentrate on inorganic chemical compositions, including SO_4^{2-}, NO_3^-, NH_4^+, and Cl^-. In January 2013, China suffered severe haze pollution, affecting a large area of the country and approximately 800 million people.[9] The formation of secondary inorganic aerosols (SIAs) compositions, including SO_4^{2-}, NO_3^-, and NH_4^+, is a primary contributor to severe haze pollution.[9,10] Different compositions of $PM_{2.5}$ affect human health in different ways.[11,12] Recent studies have indicated that carbonaceous aerosols derived from agricultural biomass burning and forest fires, ultrafine particles from vehicle exhaust, and fine particles contributing to severe haze exhibit high levels of toxicity.[13−16]

In general, the high concentrations of these four compositions are concentrated in the North China Plain. The source of SO_4^{2-} is mainly coal combustion, while transportation and industrial emissions contribute greatly to NO_x.[17] NH_4^+ is mainly agricultural emissions, and Cl^- is an important composition of sea salt aerosols, which are also affected by anthropogenic activities such as coal and biomass burning and industrial processes.[18] Addressing these sources could lead to substantial socio-economic benefits by effectively controlling $PM_{2.5}$ at its origin.

Investigating the potential toxicity of the compositions and identifying the primary sources of health risks may be a more effective approach to reducing the disease burden associated with $PM_{2.5}$.[19] However, the majority of earlier studies examined the compositions of $PM_{2.5}$ and their impacts on health only using the single pollution model, and the results were inconsistent. Inconsistent results may be attributed primarily to differences in exposure ranges, time spent outdoors, access to health care, differences in demographics and biometrics, and differences in confounders and statistical models.[2,20] Moreover, these studies primarily focused on regions in developed areas. For instance, the American Cancer Society reported an association between sulfate and total cardiopulmonary deaths.[21] In a cohort of male U.S. military veterans, mixed results were found, with significant associations between the elements carbon, nickel, and nitrate with all-cause mortality, but not sulfate.[22] In general, studies on the relationship between $PM_{2.5}$ compositions and health effects have not reached a consensus.

The follow-up cohort was established in a highly polluted area in northern China. Previous studies explored the associations between long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, SO_2, and NO_2) and cardiopulmonary mortality.[23−25] A strong positive correlation between air pollution and cardiovascular mortality was identified, with $PM_{2.5}$ emerging as the most significant contributor.[25] The present study aims to build upon prior research by investigating the impact of $PM_{2.5}$ inorganic chemical compositions on cardiopulmonary mortality. Our objectives include examining the relationship between inorganic chemical compositions and cardiopulmonary mortality using both single and multiple pollution models, as well as exploring vulnerable subpopulations and identifying the main contributors of these compositions.

■ MATERIALS AND METHODS

Study Setting and Population

The study spanned 22 years, from January 1998 to December 2019, and was conducted in four representative northern cities in China: Tianjin, located in the Beijing−Tianjin−Hebei (BTH) region; Shenyang, the capital of Liaoning Province; Taiyuan, the capital of Shanxi Province; and Rizhao, a newly developed port city in northern China.[25] Figure S1 illustrates the geographical locations of these cities. These cities represent a diverse range of sources and levels of air pollution in China. The survey included individuals born before January 1, 1975, who had been residents of the selected region since January 1998. According to the study design, our cohort comprised approximately 10,000 participants from each city. The population size was selected based on the count and geographic dispersion of environmental monitoring stations in each city, varying from 1 in the smallest city, Rizhao, to 7 in the largest city, Tianjin. More specifically, within a 1 km radius of a monitoring station, we randomly designated neighborhoods comprising apartment buildings and blocks. In a designated vicinity surrounding each environmental monitoring station, neighborhoods were numbered to establish sampling frames. Samples were then randomly chosen from these frames until the desired sample size was attained. Each neighborhood consisted of approximately 500 to 700 households.[24]

Baseline (1998) and follow-up (2009) data on socio-demographic information, residential address, lifestyle factors, occupational exposure to particulate matter, and physical activity levels were collected from participants using standard questionnaires administered by trained interviewers. Of the initial 39,054 participants in the baseline survey, 1576 (4%) were eliminated due to missing information, and 36 were excluded within a year due to death, focusing on long-term effects. A total of 37,442 individuals were included in the final analysis. Figure S2 provides details of the population screening process. The majority of residents (81.2%) did not change their place of residence between January 1998 and the follow-up survey, while the rest moved within the city and registered their move. The Ethics Committee of the Tianjin Medical University Coordination Centre approved the study. Written informed consents were obtained from all participants.

Definition of Mortality Outcomes

Each participant was followed up until December 31, 2019 or the date of death. The Center for Disease Control and Prevention (CDC) staff and the relatives of the dead subjects each filled out a questionnaire to provide information about the deceased, including the time, place, and cause of death. Subsequently, we crosschecked the information. Four mortality outcomes-nonaccidental causes (ICD-10: A00-R99), cardiovascular disease (ICD-10: I10-I70), nonmalignant RDs (ICD-10: J00-J99), and lung cancer (ICD-10: C34) were chosen to encode and define mortality outcomes according to the 10th Revision of the International Classification of Diseases (ICD-10). Information on relevant deaths was collected by trained interviewers, and revisions to ICD-10 were considered during follow-up.

Exposure Assessment

Daily averages of different inorganic chemical compositions were separated from 2000 to 2019, while other satellite remote sensing products related to surface cover, topography, and population density were also used.[8] The sources and changes of $PM_{2.5}$ inorganic chemical compositions were so complicated that we separated the compositions of $PM_{2.5}$ using a deep learning model with more powerful functions and stronger data mining ability, namely the deep forest model.[26] We incorporated the spatiotemporal heterogeneity of air pollutants into our models to improve their capabilities.[27] Finally, the four dimensional-spatiotemporal deep forest (4D-STDF) model was used to estimate daily $PM_{2.5}$ chemical composition at a spatial resolution of 1 km in China by integrating measurements of $PM_{2.5}$ species from a high-density observation network, satellite $PM_{2.5}$ retrievals, atmospheric reanalyses, and model simulations.[8] Cross-validation results illustrate the reliability of SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- estimates, with high cross-validated coefficients of determination ($CV\text{-}R^2$) with ground-based observations of 0.74, 0.75, 0.71, and 0.66, respectively.[8] Monitoring station data and satellite inversion data for the inorganic chemical composition of $PM_{2.5}$ for the years 1998−1999 were not available, so the natural spline function of the available data for other years was used for prediction.[28] A 1 km buffer around the geocoded residential address was used as the primary buffer to quantify the annual environmental exposure to air pollutants for each participant between 1998 and 2019.

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Environ. Health 2024, 2, 530−540

Table 1. Baseline Characteristics of the Participants from the Four-City Cohort in Northern China by the Status (Alive or Dead) from 1998 to 2019[a]

Variable		Total (N = 37,442)	Followed-up (N = 31,630)	Dead[b] (N = 5812)
Mean ± SD				
Age at baseline (years)[c]		43.50 (13.40)	43.00 (13.20)	46.20 (14.10)
BMI (kg/m^2)[c]		22.60 (2.95)	22.60 (2.96)	22.90 (2.92)
N (%)				
Gender[c]	Male	18,456 (49.3)	15,250 (48.2)	3206 (55.2)
	Female	18,986 (50.7)	16,380 (51.8)	2606 (44.8)
Education level[c]	<High school	21,476 (57.4)	17,801 (56.3)	3675 (63.2)
	≥High school	15,966 (42.6)	13,829 (43.7)	2137 (36.8)
Income level per month[c]	<1500 CNY	35,115 (93.8)	29,770 (94.1)	5345 (92.0)
	≥1500 CNY	2327 (6.2)	1860 (5.9)	467 (8.0)
Marital status[c]	Married	34,455 (92.0)	29,187 (92.3)	5268 (90.6)
	Single/separated/divorced	2987 (8.0)	2443 (7.7)	544 (9.4)
Smoking status[c]	Never	27,124 (72.4)	23,133 (73.1)	3991 (68.7)
	Former	989 (2.6)	815 (2.6)	174 (3.0)
	Current	9329 (24.9)	7682 (24.3)	1647 (28.3)
Occupational exposure[c]		2705 (7.2)	2197 (7.0)	508 (8.7)
Alcohol intake[c]		7558 (20.2)	6266 (19.8)	1292 (22.2)
Exercise		18,880 (50.4)	15,918 (50.3)	2962 (51.0)
City[c]	Rizhao	9060 (24.2)	8474 (26.8)	586 (10.0)
	Shenyang	9378 (25.0)	8447 (26.7)	931 (16.0)
	Taiyuan	9700 (25.9)	6613 (20.9)	3087 (53.1)
	Tianjin	9304 (24.8)	8096 (25.6)	1208 (20.8)

[a]Abbreviations: SD, standard deviation; BMI, body mass index. [b]Mortality from all nonaccidental causes. [c]$P < 0.05$ for the difference between alive and dead groups.

Meteorological factors were obtained from the ECMWF reanalysis v5 (ERA5), a fifth-generation atmospheric reanalysis data set produced by the Copernicus Climate Change Service. ERA5 provides data on several atmospheric, terrestrial, and oceanic climate variables from 1950 to the present. The resolution is about 0.25 degrees (approximately 28 km). The data are generated using the latest assimilation techniques that allow model data to be combined with observations from around the world to produce the best estimates of the state of the atmosphere.[29,30]

ERA5 data have a high degree of reliability and are used in climate, environment, and health studies.[31−33] In this study, we used the ECMWF-recommended Python script to retrieve ERA5 day-by-day data from the Copernicus Climate Database from January 1, 1998, to December 31, 2019, including 2-m temperature, 2-m dew temperature, surface pressure, and u and v components of the 10-m wind.

Since relative humidity was not directly available, relative humidity was calculated from 2-m temperature and 2-m dew temperature using the formula: $\mathrm{RH} = \mathrm{es}(T_\mathrm{d}) \times 100/\mathrm{es}(T)$. $\mathrm{es}(T) = 6.11 \times e^{[17.67 \times (T - 273.15)/(T - 273.15 + 243.5)]}$. In addition, we interpolated the grid points to the study points based on matching the home address to the ERA5 grid points using linear interpolation. Annual mean $PM_{2.5}$ inorganic chemical composition exposure and meteorological factors from 1998 to 2019 were quantified for each subject. to facilitate our treatment of time-dependent covariates. Long-term exposure for each subject was determined as the annual mean of air pollution at the date of death or end of follow-up.[25,34]

Statistical Analysis

Descriptive analysis involved calculating the mean and standard deviation (SD) for normally distributed continuous variables. Group differences were assessed using t tests, while categorical variables were analyzed using percentages (%) and compared between groups using the Chi-square test. The correlation relationships between $PM_{2.5}$ inorganic chemical compositions were examined using the Spearman rank test. To explore the association of $PM_{2.5}$ compositions with multiple mortality outcomes, a time-varying Cox proportional risk model was employed in the primary analysis. This model was adjusted for covariates, including baseline age (in years), gender (female vs male), body mass index (BMI, kg/m^2), education level (<high school vs ≥high school), monthly income level (<1500 CNY/month vs ≥1500 CNY/month), occupational exposure (self-reported workplace dust or smoke exposure, yes vs no), physical activity (active vs inactive), marital status (married vs single/separated/divorced), current smoking (yes vs no), and alcohol consumption (yes vs no). Calendar years served as the time scale in this model, and $PM_{2.5}$ inorganic chemical compositions, income, BMI, exercise, smoking, and alcohol use were included as time-dependent variables. The follow-up period extended from January 1, 1998, to December 31, 2019, or the date of death of the participants. Results were presented with hazard ratios (HR) and 95% confidence intervals (95% CI) for nonaccidental mortality, cardiovascular diseases (CVDs), nonmalignant respiratory diseases (RDs), and lung cancer. Following established conventions,[35,36] we reported results using a per interquartile range (IQR) increase.

Constituent residual modeling was employed to investigate changes in each composition independently of $PM_{2.5}$. This involved constructing linear regression models with the composition concentration as the dependent variable and $PM_{2.5}$ levels as the independent variable. The resulting residuals were then utilized as proxy exposure variables for inclusion in the model. This approach enables us to estimate the effects of elevated composition while controlling for other inorganic chemical compositions of $PM_{2.5}$.[37]

Quantile g-computation was further used to investigate the relationship between joint exposure to $PM_{2.5}$ inorganic chemical compositions and multiple mortalities, as well as the relative contribution of each composition.[38] In contrast to the conventional multipollutant model of Weighted Quantile Sum (WQS) regression, this method integrates its estimator and g-computation in an edge structure model. This model can incorporate nonlinearity in joint exposures, overcome one-way assumptions, and allow Cox proportional hazard models to serve as the basis for time-to-event analysis.[38] It is worth noting that by focusing on the effects of the mixture as a whole, the model is not necessarily strongly influenced by exposure correlations.[38] We adjusted the model for the same confounding factors as in the main model and used the simultaneous rise of all four pollutants by one interquartile spacing as the main outcome of the joint exposure.

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Environ. Health 2024, 2, 530−540

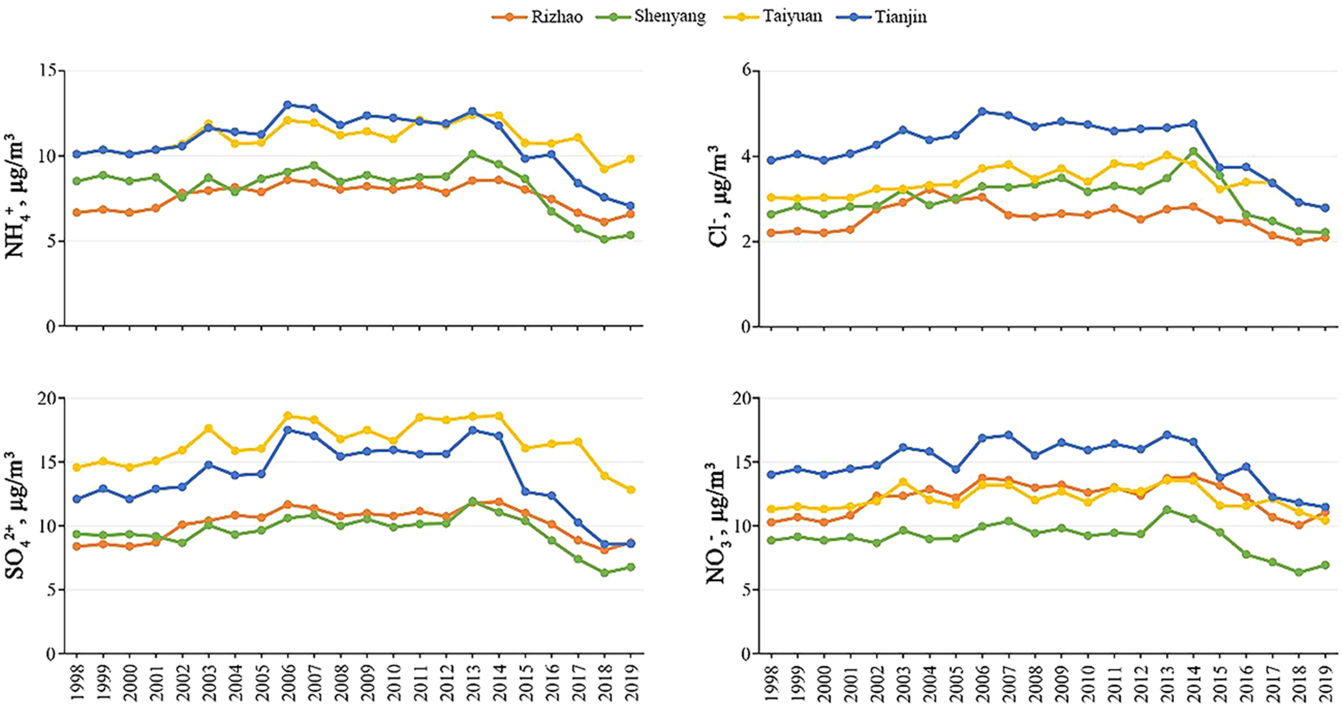

Figure 1. Average annual exposure (μg/m³) to $PM_{2.5}$ inorganic chemicals (NH_4^+, NO_3^-, SO_4^{2-}, and Cl^-) for participants in four cities from 1998 to 2019. Abbreviations: $PM_{2.5}$, particle with aerodynamic diameter ≤2.5μm; NH_4^+, ammonium salt; NO_3^-, nitrate; SO_4^{2-}, sulfate; Cl^-, chloride.

To characterize the exposure-response relationship of $PM_{2.5}$ inorganic chemical compositions to multiple causes of death, we used the restricted cubic spline (RCS) function. To fit the exposure-response curves, we selected the optimal value of knots based on the Akaike Information Criterion (AIC). The median concentration was chosen as the reference point for HR = 1, and the same confounding variables as the main model were also included.

To explore vulnerable populations, we conducted a stratification analysis of age (<60 years old vs ≥60 years old), gender (male vs female), education level (<high school vs ≥high school), and income level (<1500 CNY/month vs ≥1500 CNY/month) and used multiplicative interaction to examine how various compositions affected populations at risk. Additionally, we conducted a series of sensitivity analyses to verify the stability of our results. First, we constructed a variety of models: Model 1 (Crude), adjusted for age and gender; Model 2, additionally adjusted for individual socioeconomic status (SES), including level of education, income, and marital status; and Model 3, additionally adjusted for BMI and exercise level. Second, to test the correctness of our data filling for pollutants during the years 1998−1999, we interpolated it using a variety of imputation functions. Third, the average annual temperature and average annual relative humidity were further adjusted on Model 3. Finally, we repeated the analyses with air pollution at the city-level to investigate possible bias due to the potential movement of study participants within the city.

All statistical analyses were conducted in R v4.3.0 (R Development Core Team). A two-tailed *P*-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents the key characteristics of respondents from four cities in northern China. The cohort included a total of 37,442 participants, with a baseline age of 43.50 years old (SD: 13.40). The baseline mean BMI was 22.60 kg/m² (SD: 2.95). The gender distribution was balanced, with 50.70% of participants being female. At baseline, 24.9% and 20.2% of participants reported smoking and drinking habits, respectively. Over the follow-up period of 785,807 person-years, 5812 deaths (15.5%) occurred from nonaccidental causes.

Among these deaths, 2932 were attributed to cardiovascular diseases (CVDs), 552 to lung cancer, and 479 to nonmalignant respiratory diseases (RDs). Factors associated with an increased risk of death included being male, older, single/separated/divorced, a smoker or drinker, having occupational exposure to PM, lower education, higher BMI, and higher income levels.

Figure 1 illustrated the trends in individual exposure to $PM_{2.5}$ inorganic chemical concentrations in participants from four cities in northern China from 1998 to 2019. The overall variation trend of NH_4^+, NO_3^-, SO_4^{2-}, and Cl^- appears to be similar. The interquartile concentrations (IQR) of the four inorganic chemical components of $PM_{2.5}$ are as follows: NH_4^+ at 2.93 μg/m³, NO_3^- at 3.44 μg/m³, SO_4^{2-} at 5.49 μg/m³, and Cl^- at 1.00 μg/m³ (Table S1). Figure S3 reveals a moderate to high correlation between $PM_{2.5}$ and its compositions, with correlation coefficients ranging from 0.66 to 0.94.

In the time-varying Cox model, we identified consistent and positive associations between inorganic chemical compositions and cardiopulmonary mortality. For example, a per IQR (5.49 μg/m³) increase in SO_4^{2-} was associated with higher mortality from nonaccidental causes (HR: 1.860; 95% CI: 1.809, 1.911), cardiovascular diseases (CVDs) (1.909; 1.836, 1.985), non-malignant respiratory diseases (RDs) (2.178; 1.975, 2.403), and lung cancer (1.773; 1.624, 1.937). Similar significant effects were observed for other compositions in Table 2. Nonetheless, NO_3^- exhibited insignificant or feeble association with cardiovascular and respiratory mortality. When the residual is introduced to the model as an independent variable, the findings demonstrate that the effects of NH_4^+, SO_4^{2-}, and Cl^- are comparable to those observed in the main study (Table S2).

Table 3 revealed that joint exposure to four compositions had a relatively stronger impact on the human body and exhibited the most serious harm to nonmalignant RDs. HR values of joint exposure to four inorganic compositions were 1.374 (95% CI: 1.318,1.433), 1.395 (95% CI: 1.313, 1.482), 1.553 (95% CI:

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Environ. Health 2024, 2, 530−540

Table 2. Associations of Per IQR Increase in NH_4^+, NO_3^-, SO_4^{2-}, and Cl^- with Mortality from Nonaccidental Causes, CVDs, Nonmalignant RDs, and Lung Cancer with Time-Varying Cox Model Adjustment (*N* = 37,442)[a]

	HR (95% CI)			
Compositions	Nonaccidental causes	CVDs	Nonmalignant RDs	Lung cancer
NH_4^+	1.789 (1.739, 1.841)	1.825 (1.753, 1.900)	2.129 (1.923, 2.357)	1.699 (1.550, 1.863)
NO_3^-	1.032 (1.003, 1.061)	1.036 (0.996, 1.078)	1.106 (1.004, 1.218)	0.992 (0.908, 1.084)
SO_4^{2-}	1.860 (1.809, 1.911)	1.909 (1.836, 1.985)	2.178 (1.975, 2.403)	1.773 (1.624, 1.937)
Cl^-	1.493 (1.446, 1.541)	1.515 (1.448, 1.585)	1.621 (1.445, 1.818)	1.478 (1.333, 1.639)

[a]Abbreviations: $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm; IQR, interquartile range; NH_4^+, ammonium salt; NO_3^-, nitrate; SO_4^{2-}, sulfate; Cl^-, chloride; CVDs, cardiovascular diseases; RDs, respiratory diseases; CI, confidence interval; HR, hazard ratio; and BMI, body mass index. Adjusted for age, gender, BMI, level of education, income, occupational exposure, physical exercise, status of marital, smoking, and drinking. Estimates are presented as HRs and 95% CIs based on IQR increases in NH_4^+ (2.93 μg/m³), NO_3^- (3.44 μg/m³), SO_4^{2-} (5.49 μg/m³), and Cl^- (1.00 μg/m³).

Table 3. Adjusted Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) of Nonaccidental Causes, CVDs, Nonmalignant RDs, and Lung Cancer Incidence Associated with Air Pollution in a Multi-pollutant Model[a]

Mortality cause	Compositions	Proportion	HR (95% CI)	*P*
Nonaccidental causes	SO_4^{2-}	0.70	1.374 (1.318, 1.433)	<0.001
	NH_4^+	0.25		
	Cl^-	0.05		
	NO_3^-	−1.00		
CVDs	SO_4^{2-}	0.75	1.395 (1.313, 1.482)	<0.001
	NH_4^+	0.22		
	Cl^-	0.03		
	NO_3^-	−1.00		
Nonmalignant RDs	SO_4^{2-}	0.46	1.553 (1.298, 1.858)	<0.001
	Cl^-	0.31		
	NH_4^+	0.23		
	NO_3^-	−1.00		
Lung cancer	SO_4^{2-}	0.70	1.363 (1.169, 1.589)	<0.001
	NH_4^+	0.30		
	NO_3^-	−0.72		
	Cl^-	−0.28		

[a]Abbreviations: HR, hazard ratio; CI, confidence interval; CVDs, cardiovascular diseases; RDs, respiratory diseases; NH_4^+, ammonium salt; NO_3^-, nitrate; SO_4^{2-}, sulfate; Cl^-, chloride, BMI, body mass index. Adjusted for age, gender, BMI, level of education, income, occupational exposure, physical exercise, status of marital, smoking, and drinking.

1.298, 1.858), and 1.363 (95% CI: 1.169, 1.589) for nonaccidental causes, CVDs, nonmalignant RDs, and lung cancer, respectively. It is found that SO_4^{2-} is always the most serious composition in the human body, followed by NH_4^+ and Cl^-. It was observed that SO_4^{2-} consistently exhibited the most significant impact on the human body, followed by NH_4^+ and Cl^-. Notably, there were variations in the contributions of NH_4^+ and Cl^- to nonmalignant RDs and lung cancer in Figure S4.

Figure S5 depicted the results of the restricted cubic spline (RCS) and the bar chart of the pollutant frequency distribution. The associations between $PM_{2.5}$ and compositions with cardiopulmonary mortality were generally nonlinear. Interestingly, the exposure-response curves of the four compositions showed different shapes. SO_4^{2-} and NH_4^+ exhibited a J and S shape, respectively.

Figure 2 and Table S3 present the results of stratified analysis by gender, age, education, and income. SO_4^{2-} and NH_4^+ exhibit more significant effects on individuals under 60 years of age, while NO_3^- has the opposite effect. Concerning the effect modification by gender, Cl^- has a more significant impact on women. In general, individuals with lower education and higher incomes appear to be more vulnerable to inorganic chemical compositions.

Additionally, we conducted a sensitivity analysis. First, we performed sensitivity analyses using multiple models for the above analysis (Tables S4 and S5). Furthermore, to verify the reliability of our data filling, we applied different interpolation functions to fill the pollution data again and conducted related analyses (Table S6). After adjusting for mean annual temperature and mean annual humidity, similar effects to those of the main model were observed, with an increase in the effect value of NO_3^- (Table S7). However, in the models using city-level air pollutants, the impact estimates changed slightly (Table S8).

■ DISCUSSION

In this population-based cohort study, we delved into the effects of long-term exposure to the inorganic chemical composition of $PM_{2.5}$ on cardiorespiratory mortality. Through 785,807 person-years of follow-up, we identified the main risk contributors and vulnerable populations. Inorganic chemical compositions were consistently associated with significantly increased risks of cardiorespiratory mortality, with SO_4^{2-} emerging as the primary contributor. Notably, individuals with higher incomes and lower education levels appeared to be more vulnerable to the elevated mortality risks associated with $PM_{2.5}$ inorganic chemical compositions.

To the best of our knowledge, this study represents one of the largest and longest cohort investigations comprehensively assessing the association between $PM_{2.5}$ inorganic chemical compositions and various cardiopulmonary mortality outcomes in a developing region. Notably, we placed increased emphasis on inorganic chemical compositions, crucial components of haze, and underscored the significance of source management. Furthermore, the application of a joint exposure model in our study provides a more realistic approximation of human exposure, enhancing the robustness of our findings.

In eastern China, the four main inorganic chemical compositions typically constitute 58.1% of $PM_{2.5}$, with SIA accounting for a substantial portion at 54.2%. Notably, SO_4^{2-} holds the highest contribution at 20.5%, especially in regions with high temperatures and strong radiation emitted by coal-fired power plants, fostering the chemical conversion of SO_2 to SO_4^{2-}.[39] NO_3^- comprises 19.8% of total $PM_{2.5}$ and is predominantly distributed over economically developed urban agglomerations, such as the BTH region. Sulfuric and nitric acid particles are formed through the oxidation of SO_2 and NO_x, leading to the creation of acid rain. Additionally, sulfate aerosols play a role in climate change by affecting atmospheric transport and climate responses.[8] The annual NH_4^+ fraction, constituting 13.9%, displays relatively weak seasonality, possibly attributed to higher NH_3 emissions from agricultural sources. NH_4^+ increases

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Environ. Health 2024, 2, 530−540

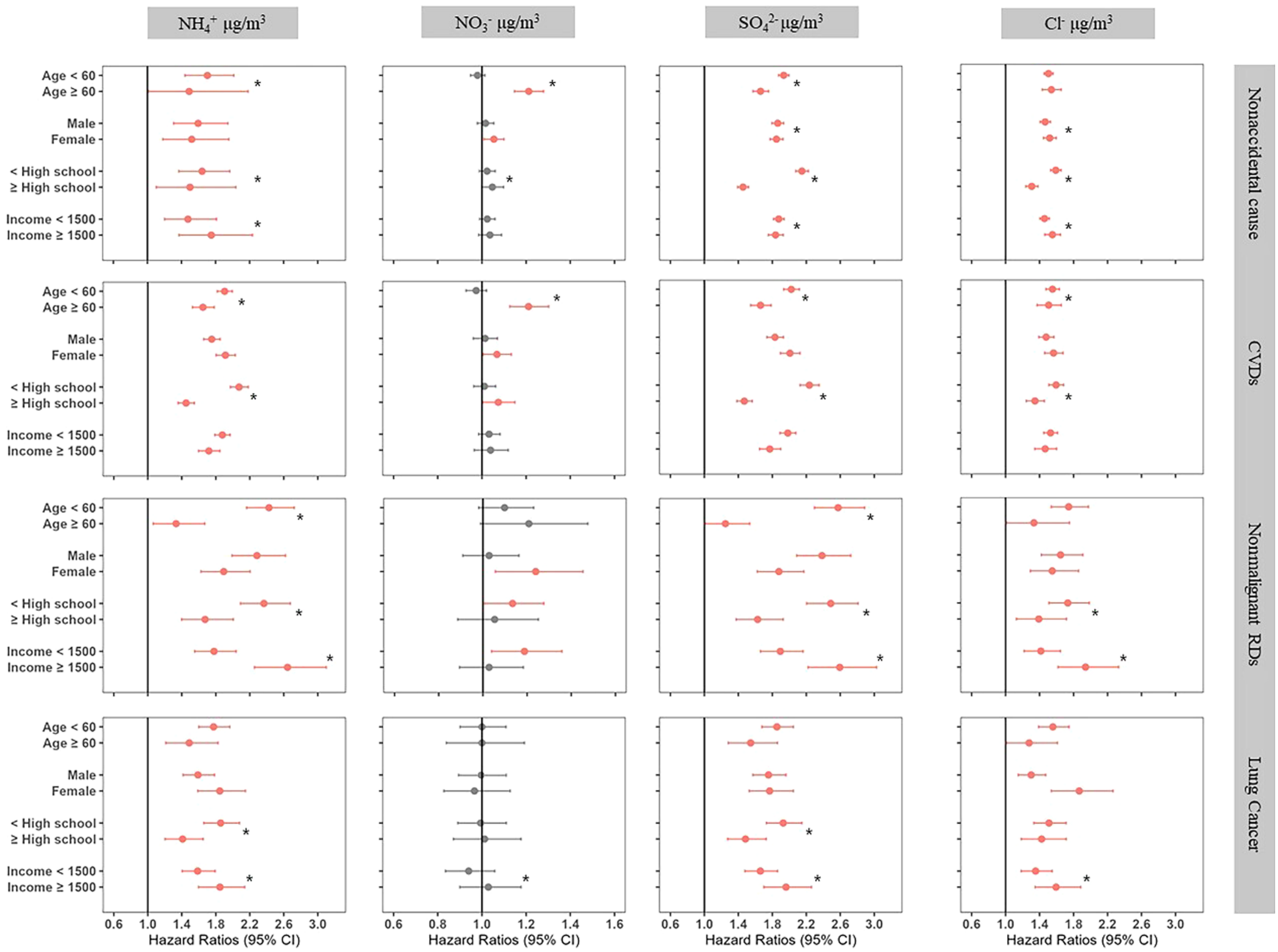

Figure 2. Association of per IQR increase in NH_4^+, NO_3^-, SO_4^{2-}, and Cl^- with mortality from nonaccidental causes, CVDs, nonmalignant RDs, and lung cancer, stratified by age, gender, education, and income level (N = 37,442). Abbreviations: IQR, interquartile range; NH_4^+, ammonium salt; NO_3^-, nitrate; SO_4^{2-}, sulfate; Cl^-, chloride; CVDs, cardiovascular diseases; RDs, respiratory diseases; HR, hazard ratio; CI, confidence interval. Estimates are presented as HRs and 95% CIs based on IQR increases in NH_4^+ (2.93 $\mu g/m^3$), NO_3^- (3.44 $\mu g/m^3$), SO_4^{2-} (5.49 $\mu g/m^3$), and Cl^- (1.00 $\mu g/m^3$). *Interaction is statistically significant (P < 0.05).

the frequency of hazy weather.[10] Conversely, annual and seasonal Cl^- to $PM_{2.5}$ ratios are much smaller (average = 3.0−4.6%) than those of the other three inorganic species, with elevated Cl^- concentrations localized primarily in heavily industrialized zones like BTH,[8] where its production affects the growth of aerosol particles, atmospheric chemistry, and air quality for $PM_{2.5}$ and ozone.[40,41] As depicted in Figure 1, there was a notable decline in the mass of the inorganic compositions from 2013 to 2019, partly attributable to China's environmental policies. The Clean Air Action Plan (2013−2017) led to a substantial reduction in the inorganic compositions of $PM_{2.5}$, particularly SO_4^{2-} and NO_3^-, with SO_2 and NO_x emissions falling by 59% and 21%, respectively.[17,42] However, the rate of decrease began to taper off during the Blue Sky Defense Campaign (2018−2020). After 2018, the decrease in SO_4^{2-} concentration was primarily observed in central Shanxi, a change mainly attributed to the implementation of the clean heating policy.[43,44]

Several studies have confirmed that desert dust is associated with increased mortality from a variety of circulatory and respiratory diseases,[45−47] and $PM_{2.5}$, the main component of desert dust, is a growing concern. The association between $PM_{2.5}$ and cardiovascular mortality was demonstrated in our previous study, where a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with higher nonaccidental mortality (HR 1.20; 95% CI: 1.17−1.23).[25] Three general population cohort studies in mainland China with an average follow-up of 15 years indicated that the HRs of all-cause/nonaccidental death were 1.08−1.11 for every 10 $\mu g/m^3$ rise in $PM_{2.5}$, which is consistent with our findings.[2,5,48] In comparison, we obtained higher HR values. Differences in population backgrounds, survey areas, and pollution concentrations may have contributed to this result. The current research, however, delves into the impact of $PM_{2.5}$ inorganic chemical compositions, yielding novel and intriguing results. The association between $PM_{2.5}$ inorganic chemical compositions and multiple cardiopulmonary mortalities demonstrated a significant effect on various causes of death, evident in both the single pollutant time-varying Cox model and the quantile-based g-computation model. Notably, in the joint exposure model, the detrimental impact of SO_4^{2-} on human health consistently occupied the forefront. Comparing our findings with previous large-scale cohort studies in Denmark and China, which linked SIA to total and cardiopulmonary mortality,[49,50] we observed relatively higher HR values. This

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Environ. Health 2024, 2, 530−540

variance may be attributed to differences in population backgrounds, modeling strategies, and exposure settings. Additionally, our choice of estimation model for SIA concentration could contribute to these differences. In line with our study, the US Medicare cohort study also suggested that NO_3^- and lung cancer were insignificantly associated.[51] This finding may be related to study design, population characteristics, outdoor exposure time, and government control of traffic pollution.[2]

Previous evidence on the biological mechanisms of exposure to $PM_{2.5}$ inorganic chemical compositions and cardiopulmonary mortality is limited. Exposure to SO_4^{2-}, NH_4^+, and NO_3^- activates the hypothalamic-pituitary-adrenal axis, which may have effects on the cardiovascular system.[52] SO_4^{2-} provides an acidic environment that promotes the solubility and bioavailability of metals in $PM_{2.5}$, which in turn leads to the production of reactive oxygen species, leading to oxidative stress as well as inflammatory responses.[53] Previous studies have shown that NO_3^- exposure is associated with tumor necrosis factor-α (TNF-α),[54] and TNF-α elevated levels may be associated with myocardial infarction, the formation and progression of atherosclerosis, and negative cardiac remodeling.[55] In addition, some progress has been made in animal studies, which can lead to the infiltration of lung inflammatory cells, the thickening of the tube wall, and the collapse of the alveoli.[56]

In large cohort studies conducted in China and the United States, exposure-response curves for $PM_{2.5}$ compositions and various mortality were similarly found to be nonlinear.[35,57] It is crucial to acknowledge the influence of regional selection, individual preventive measures in high-concentration environments, and differences in sample sizes across populations exposed to varying component concentrations. The exposure−response curves for the four compositions were not consistent, which we believe may be related to the susceptibility of the population, the toxicological characteristics of the exposed components, and regional differences.[57]

Moreover, stratified analyses and interactive analyses were employed to pinpoint sensitive subpopulations. Notably, we observed that SO_4^{2-} and NH_4^+ had a more pronounced effect on individuals with lower education levels and higher income groups. However, existing evidence on subgroups categorized by education or income levels has been limited. Consistent with our study, higher exposure concentrations were observed in more affluent areas.[58] In our study, the median exposure concentration of SO_4^{2-} was 11.76 $\mu g/m^3$ in higher income populations compared to 11.48 $\mu g/m^3$ within lower income populations. This may be due to complex socio-economic factors, methods of deriving exposure concentrations, population distribution, modeling techniques, and population characteristics.[25] Besides, individuals with lower education levels may have comparatively lower safeguards against the detrimental effects of air pollution. This underscores the importance of considering socio-economic factors in understanding the vulnerabilities of different subpopulations.

This study boasts several notable strengths. First, we assembled a substantial sample size encompassing four cities in northern China, undertaking a comprehensive follow-up of 785,807 person-years within this cohort. This duration coincided with a pivotal period for environmental governance policies in China. Second, our model incorporated adjustments for multiple confounding factors, including BMI, education level, income, occupational exposure, physical activity, marital status, smoking, and alcohol consumption. Additionally, the utilization of a time-varying multipollutant model allowed us to account for collinearity and explore potential additive or synergic effects among air pollutants when analyzing joint exposure to $PM_{2.5}$ inorganic chemical compositions. Lastly, through stratified analyses, we successfully identified vulnerable subpopulations for different causes of death under distinct pollutant exposures, providing valuable insights to enhance the effectiveness of protective measures for these susceptible groups.

Despite its strengths, our study is not without limitations. First, there is the potential for recall bias and self-report bias in collecting information on death and covariates, which may introduce misclassification of covariates and outcomes. Second, the lack of satellite data availability compelled us to fill in compositions for the years 1998−1999. Finally, improvements in healthcare, enhanced death reporting accuracy, and the reduction of air pollution levels since 2013 in China during our study period might have contributed to an overestimation of the harmful effects of air pollution. However, it is important to note that this error is likely to be nondifferential, typically reducing the precision of estimates and leading to an underestimation of effects.

■ CONCLUSIONS

In summary, this study provides evidence of a strong negative impact on cardiopulmonary health due to long-term exposure to inorganic chemical compositions. Among these compositions, SO_4^{2-} emerged as the most significant contributor to the elevated risk of death, followed by NH_4^+ and Cl^-. Our findings present novel evidence on the risks of cardiorespiratory mortality associated with prolonged exposure to inorganic chemical compounds. This scientific basis can guide policymakers in addressing the root causes of ambient air pollution for effective public health interventions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00020.

Concentration parameters of pollutants; results for constituent residual model; results of stratified analysis; sensitivity analysis findings; spatial distribution of participants; inclusion and exclusion criteria for participants; correlation among pollutants; graphs depicting pollutant weights; and results of RCS models (PDF)

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Author Contributions

[††]H.S., X.C., W.H., and J.W. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. N.T. and G.D. had full access to all the data in the study and had final responsibility for the decision to submit for publication. Designed the study: N.T. and G.D. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: H.S. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis:

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Notes

The authors declare no competing financial interest.

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Environ. Health 2024, 2, 530−540