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Long-term $PM_{2.5}$ exposure in association with chronic respiratory diseases morbidity: A cohort study in Northern China

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.114025.

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Abstract

Several literatures have examined the risk of chronic respiratory diseases in association with short-term ambient $PM_{2.5}$ exposure in China. However, little evidence has examined the chronic impacts of $PM_{2.5}$ exposure on morbidity of chronic respiratory diseases in cohorts from high pollution countries. Our study aims to investigate the associations. Based on a retrospective cohort among adults in northern China, a Cox regression model with time-varying $PM_{2.5}$ exposure and a concentration-response (C-R) curve model were performed to access the relationships between incidence of chronic respiratory diseases and long-term $PM_{2.5}$ exposure during a mean follow-up time of 9.8 years. Individual annual average $PM_{2.5}$ estimates were obtained from a satellite-based model with high resolution. The incident date of a chronic respiratory disease was identified according to self-reported physician diagnosis time and/or intake of medication for treatment. Among 38,047 urban subjects analyzed in all-cause chronic respiratory disease cohort, 482 developed new cases. In CB (38,369), asthma (38,783), and COPD (38,921) cohorts, the onsets were 276, 89, and 14, respectively. After multivariable adjustment, hazard ratio and 95% confidence interval for morbidity of all-cause chronic respiratory disease, CB, asthma, and COPD were 1.15 (1.01, 1.31), 1.20 (1.00, 1.42), 0.76 (0.55, 1.04), and 0.66 (0.29, 1.47) with each 10 $\mu g/m^3$ increment in $PM_{2.5}$, respectively. Stronger effect estimates were suggested in alcohol drinkers across stratified analyses. Additionally, the shape of C-R curve showed an increasing linear relationship before 75.00 $\mu g/m^3$ concentrations of $PM_{2.5}$ for new-onset all-cause chronic respiratory disease, and leveled off at higher levels. These findings indicated that long-term exposure to high-level $PM_{2.5}$ increased the risks of incident chronic respiratory diseases in China. Further evidence of C-R curves is warranted to clarify the associations of adverse chronic respiratory outcomes involving air pollution.

Keywords

Satellite-based model; $PM_{2.5}$; Cohort study; Chronic respiratory diseases; Incidence; China

1. Introduction

Over the past few decades, the global burden of chronic respiratory diseases remains a sustainable global concern. During 1990 and 2017, disability-adjusted life-years (DALYs) counts of chronic respiratory diseases significantly increased (GBD Chronic Respiratory Disease Collaborators, 2020). As the Global Burden of Disease Study reported, in 2017, chronic respiratory diseases caused almost 3.91 million deaths, accounting for approximately 7% of total deaths globally (GBD, 2017 Causes of Death Collaborators., 2018; Li et al., 2020b). In 2016, 9% of the all-cause non-communication disease mortality was attributed to chronic respiratory diseases with an estimated number of 0.87 million in China (Guan et al., 2016; Li et al., 2020b; Mokoena et al., 2019).

The development of urbanization and industrialization brings severe air pollution and poor air quality problems, causing over 7 million premature deaths each year worldwide (World

Health Organization, 2019), especially ambient $PM_{2.5}$. $PM_{2.5}$ is widely deposited in the lung and constitutes about 96% of particles existing in human pulmonary parenchyma (Churg and Brauer, 1997), contributing to 4.8 million deaths in 2015 (Cohen et al., 2017). Ambient $PM_{2.5}$ pollution is still a major global health issue.

Nowadays, several epidemiological studies have demonstrated that being exposed to daily $PM_{2.5}$ was positively related to the acute risk of hospitalizations or emergency room visits of chronic respiratory diseases such as chronic bronchitis (CB), asthma, and chronic obstructive pulmonary disease (COPD) (Chi et al., 2019; Dominici et al., 2006; Lin et al., 2020; Wang et al., 2019; Yao et al., 2020; Zuo et al., 2019). However, the evidence on morbidity of chronic respiratory diseases related to long-term exposure to $PM_{2.5}$ was mostly obtained from North American and European settings, and the annual concentrations of $PM_{2.5}$ pollution in these countries were commonly under 35 $\mu g/m^3$ (Atkinson et al., 2015; Carey et al., 2016; Doiron et al., 2021; Fisher et al., 2016; Gan et al., 2013; Guo et al., 2018; Hooper et al., 2018; Weichenthal et al., 2017; Young et al., 2014). Yet, the studies derived from longitudinal cohorts with relatively high pollution exposure such as in China was scarce. It was mainly related to the fact that China did not have available $PM_{2.5}$ ground-based monitoring data until 2013. Currently, combining the historical $PM_{2.5}$ estimates assessed by a satellite-based spatiotemporal model, some nationwide studies have reported the harmful impacts of lung cancer incidence attributable to long-term $PM_{2.5}$ exposure among Chinese (Guo et al., 2020; Li et al., 2020a), but we still lacked the accurate evidence on prolonged $PM_{2.5}$ exposure related to the risks of other chronic respiratory diseases.

To our best knowledge, due to large emissions of traffic engines, fugitive dusts, smokes or soot associated with coal and/or biofuel combustion, the accumulated concentrations of $PM_{2.5}$ in China remain much higher compared with that in other western countries (Cao et al., 2018; Ebisu and Bell, 2012; Pandey et al., 2013; Wang et al., 2017; Wu et al., 2013). Additionally, dominate elements on the surface of $PM_{2.5}$ are various in different regions, which may stimulate different toxic effects (Cao et al., 2005; Kioumourtzoglou et al., 2015; Zhang et al., 2013). Therefore, the estimated effects of $PM_{2.5}$ on chronic respiratory outcomes obtained from developed regions with relatively low levels may not directly extended to those in China.

Herein, based on a cohort with urban adults in northern China, this study is intended to investigate the impacts of $PM_{2.5}$ pollution on chronic respiratory diseases by using evaluated $PM_{2.5}$ data from satellite-inversion model during 2000–2009.

2. Methods

2.1. Study area and population

39, 054 adults in this retrospective study were recruited from four cities in northern China: Rizhao, Taiyuan, Shenyang, and Tianjin. A published article has provided the complete information of geography and location of environment monitoring sites in these cities (Yan et al., 2020; Zhang et al., 2014). Briefly, Tianjin, as one of the earliest industrial cities in China, comprises a population of 12.3 million in 2009 and located southeast of Beijing. Shenyang is the capital city of Liaoning Province and has major industries including steel

manufacturing, nonferrous metals, machinery, coke-related industries, and electric power generation. Taiyuan, known for the largest coal-producing area in China, lies on the eastern edge of the Loess Plateau. As an emerging coastal city, Rizhao is located on the west coast of the Yellow China Sea with a 2.7 million population in 2009. The $PM_{2.5}$ pollution in these four cities can partially cover the wide range of $PM_{2.5}$ pollution levels in northern urban China. The study participants based-on community were recruited from above four cities in 2009. Firstly, according to geographical and population sizes of each city, one, two, five, and seven environmental monitoring stations were identified in Rizhao, Taiyuan, Shenyang, and Tianjin, respectively. Secondly, all apartment buildings or street blocks as small neighborhoods within a radius of 1 km around the local environmental monitoring stations of each city were selected and those small neighborhoods including 500–700 urban residents were numbered to form a sampling frame. The samples of each neighborhood were randomly drawn until a desired number of approximately 10,000 participants in each city were recruited. The eligible participants included that (1) candidates were born before January 1, 1975; (2) they had already resided in the defined sites since January 1, 1998; and (3) they were able to be contacted for the information of age, sex, years of residence details from local neighborhood offices and survey questionnaire. After obtaining the information on age, sex, and residential addresses from local neighborhood offices, the trained interviewers contacted the participants to retrospectively collect their basic socio-demographic, lifestyle and medical information in 1998, and the disease and/or medical conditions during the period from 1998 to 2009 with a standardized questionnaire, establishing a retrospective cohort in northern China. The baseline information was basic information in 1998, and the cohort was followed once in 2009. Initially, a total of 39,054 participants completed the cohort investigation. Because the data of satellite-derived $PM_{2.5}$ exposure were available since 2000, we excluded 113 deceased individuals before 2000. Besides, participants suffering from chronic respiratory diseases before January 1st, 2000 and those missing information of diagnosis were further excluded at the baseline, with a sample size of 38,047, 38,369, 38,783 and 38,921 participants were eligible for the analysis on the occurrence of all-cause chronic respiratory disease, CB, asthma, and COPD related to $PM_{2.5}$, respectively.

The ethical committee of the coordinating center of Tianjin Medical University approved this study. All participants signed informed consents before the investigation started.

2.2. Health data acquirement and Assessment of chronic respiratory diseases

In the current study, the data on characteristics of demography, status of diseases, drug usage, and lifestyle habits during the follow-up period from baseline to 2009 were obtained by local neighborhood offices and/or trained investigators through a uniformed questionnaire. For decedents, we collected information from their family members recalling. Smoking status was divided into yes (current and former smokers) or no (never smoke) by asking subjects (1) whether he/she smoked ≥ 1 cigarette a day for one year; (2) whether he/she was a former or current smoker at the baseline survey. Alcohol intake was classified into “yes” or “no” according to self-reported intake of alcohol once or more times per week in the last year or not. Passive smoke status was divided into “yes” or “no” according to whether a resident was exposed to second-hand smoke at least 6 months or not. Physical

activity was assigned as “yes” or “no” based on whether participants had one or more leisure physical activities one week or not. Disease related-data were collected by asking individuals whether he/she or their families suffered chronic respiratory diseases. If yes, the information on (1) physician diagnosed time from at least a three-class hospital; (2) and/or whether they took treatment measures were also obtained through self-reporting.

According to the International Classification of Diseases-tenth revision, the defined all-cause chronic respiratory disease (J40-J47) was coded, including CB (J40-J42), COPD (J44), asthma (J45-J46), and other chronic respiratory diseases (J43 and J47). The definition of incident date was based on self-reported physician diagnosed time from at least a three-class hospital, and/or intake of medication for treating these respiratory diseases since diagnosis, which was usually used previously (Camargo et al., 1999; Fisher et al., 2016).

$PM_{2.5}$ exposure data were available after 2000. Considering the time consistency of $PM_{2.5}$ exposure and population survey, the follow-up started at January 1st, 2000 (baseline date), and the basic data in 1998 were used as the baseline information of all participants in this study. The end time was the date of chronic respiratory diseases occurrence, the date of death or the end of follow-up, when an ending event appeared firstly. Follow-up time was calculated from baseline time to end time. For the morbidity of all-cause chronic respiratory disease, CB, asthma and COPD, the follow-up time was calculated respectively.

2.3. Assessment of ambient pollution exposure

In the present study, because the monitoring stations did not measure $PM_{2.5}$ levels in mainland China before 2013, the ambient $PM_{2.5}$ concentrations were evaluated by the spatiotemporal model based on satellite in this study, with high spatial resolution of 1 km × 1 km. The details of the model, and assessments of personal $PM_{2.5}$ exposure have been reported previously (Liang et al., 2020; Xiao et al., 2018).

In brief, the Aerosol Optical Depth (AOD) product obtained from NASA was retrieved by the Multi-Angle Implementation of Atmospheric Correction (MAIAC) algorithm, which was employed to calculate $PM_{2.5}$ exposure estimates at 1 km × 1 km spatial resolution. To minimize the bias induced by cloud cover, we filled the missing AOD values by a multiple imputation method and then we use random forest and extreme gradient boosting models to combine with land use information, meteorology, road information, air pollution emissions indicators, and population density data for prediction of $PM_{2.5}$ levels. What’s more, the accuracy of $PM_{2.5}$ pollution estimates were assessed from two aspects. For data available from ground $PM_{2.5}$ measurements from the China Environmental Monitoring Center (i.e., data after 2013), a random 10-fold cross-validation R^2 was calculated (R^2 =0.93 at monthly level and R^2 = 0.95 at annual level). For those that couldn’t be obtained from national ground observations in mainland China (i.e., data during 2000–2012), the predictions of $PM_{2.5}$ were compared with the available $PM_{2.5}$ ground measurements from Hong Kong, Taiwan, the US Embassy, with R^2 of 0.80 and a root mean squared error of 8.90 $\mu g/m^3$ at the annual level.

As a published article reported (Yang et al., 2021), individual pollution exposure was calculated via combining with the latitude and longitude coded by each resident’s address

and satellite-based $PM_{2.5}$ data. Accounting for the temporal variations of $PM_{2.5}$ during 2000–2009, the annual mean $PM_{2.5}$ levels were calculated as a time-varying exposure, which is time-varying $PM_{2.5}$ exposure on 1-calendar year scale, and they were assigned to each participant who was alive or not suffering chronic respiratory diseases in that year during the follow-up period based on the individual coded address.

Till now, satellite-driven techniques are preferred methods to predict long-term $PM_{2.5}$ concentrations in China given their high accuracy and extensive temporal coverage. In this study, high-resolution $PM_{2.5}$ concentration estimates with 1 km × 1 km would provide more accurate exposure gradients within population clusters. This model has been widely applied in the published studies on historical $PM_{2.5}$ exposure levels with human health (Li et al., 2020a; Liang et al., 2020; Lin et al., 2021; Yang et al., 2021).

Annual average gaseous pollutants levels in each city were acquired from the database in the China National Environmental Monitoring Center (CNEMC), the methods of ambient pollutants measurement and individual exposure estimates were described in detail in previous literature (Zhang et al., 2014; Yan et al., 2020). Briefly, the data were derived from the monitoring stations (seven in Tianjin, five in Shenyang, two in Taiyuan, and one in Rizhao) in CNEMC, which were collected by the local government agency. The daily average levels of NO_2 ($\mu g/m^3$) and SO_2 ($\mu g/m^3$) were measured using chemiluminescence, and ultraviolet fluorescence, respectively. Because CNEMC didn't have ground monitoring data of O_3 before 2013 in mainland of China, O_3 was not considered in this study. Based on daily monitoring data of the nearest monitoring stations, we calculated annual (2000–2009) average concentrations, from which the concentration of NO_2 and SO_2 exposure to individuals was estimated during the follow-up time.

2.4. Statistical analyses

Characteristics of study subjects at baseline were displayed as numbers (percentages) for categorical variables and mean ± standard derivations for continuous variables. Given that the annual mean $PM_{2.5}$ levels changed over the follow-up period, we used a Cox proportional hazards model with time-varying $PM_{2.5}$ exposure on 1-year scale to assess the relationships between long-term $PM_{2.5}$ pollution and onset of each chronic respiratory disease. $PM_{2.5}$ levels were introduced in analyses as continuous variable. As well, $PM_{2.5}$ were categorized into four groups according to quartiles, and reported hazard ratio (HR) for top 3 quartile groups compared with Q1 (Quartile 1) group as well. All analyses were performed by introducing certain risk factors gradually in adjustment models. The basic model is a crude model without introducing other covariates. Age, gender, and BMI were adjusted for Model 1; Model 2 was additionally adjusted for individual monthly income, and education level. In Model 3, smoking status, passive smoking, physical activity, drink status, and family history of related chronic respiratory diseases (All-cause respiratory disease: all chronic respiratory diseases; CB: CB; Asthma: asthma; COPD: COPD) were also taken into account. Finally, city was added as a covariate for adjustment in Model 4. Apart from single-pollutant models, considering that gas pollutants and $PM_{2.5}$ might have co-effects on incidence of chronic respiratory disease, two-pollutant models were further performed to evaluate the influences of multiple air pollution exposures on chronic respiratory diseases

morbidity. The combinations of the double-pollutant model were $PM_{2.5}$-NO_2 and $PM_{2.5}$-SO_2 models.

Stratified analyses were performed to assess the effect modifications of each potential covariate on $PM_{2.5}$-related chronic respiratory diseases. We also introduced a cross-product term to examine the statistical interactions between time-varying $PM_{2.5}$ exposure and baseline confounders in the Cox proportional hazards model.

We further performed concentration-response (C-R) curves using restricted cubic spline functions with 4 degrees of freedom (df) after adjusting for potential confounders in Model 4 for morbidity of all-cause chronic respiratory disease linked-to prolonged exposure to $PM_{2.5}$.

To test robustness, several sensitivity analyses were carried out. Firstly, due to recall bias, the diagnosed time of respiratory diseases might not be precise, a logistic regression model was performed to examine the impacts of the mean annual concentrations of $PM_{2.5}$ on the chronic respiratory diseases during the follow-up from 2000 to 2009. Secondly, occupational particulate matter (PM) may influence the main effect estimates potentially, so we restricted the subjects who were free of occupational PM exposure at baseline. Thirdly, considering that the confounding effects were derived from burning of household biofuels, study participants cooking with biofuels in the baseline were excluded.

All the statistical analyses were conducted via SAS (version 9.4) and R (version 4.1.1) software. The statistic significant test was two sided and *P*-value was below 0.05 across all analyses.

3. Results

3.1. Descriptive characteristics of the study populations

During the follow-up, there were 482 incident cases of all-cause chronic respiratory disease (372,509 person-years of follow-up), 276 onset of CB (376,507 person-years of follow-up), 89 new cases of asthma (381,129 person-years of follow-up), and 14 (382,936 person-years of follow-up) new COPD incidents. Table 1 showed the characteristics at the baseline of the study populations investigated in four cities for the cohort of all-cause chronic respiratory disease. The average age of participants was 43.87 ± 13.62 years old and the mean BMI was 22.63 ± 2.95 kg/m^3 at baseline. The proportion of gender is approximately equal. More than half of the overall subjects had a personal monthly income ≥ 500 CNY, more than one-quarter were smokers, and about one-fifth were alcohol drinkers. Furthermore, the baseline demographic characteristics of cohort population for other chronic respiratory diseases (CB, asthma, and COPD) were similar to those of all-cause respiratory disease, which were showed in Table S1-S3 in Supplementary Materials.

3.2. $PM_{2.5}$ exposure in association with incidence of chronic respiratory diseases

Among the original cohort of 39,054 participants without exclusion of any chronic respiratory disease at baseline, the time-varying trends of annual $PM_{2.5}$ concentrations in four cities were displayed in Fig. 1. For the entire cohort, the average concentration of annual-mean $PM_{2.5}$ exposure from 2000 to 2009 was 66.51 $\mu g/m^3$. The lowest level

appeared in Rizhao and it was 41.44 μg/m^3. By contrast, Tianjin was the highest with 96.75 μg/m^3. Furthermore, we calculated the mean annual $PM_{2.5}$ level in the cohort of each chronic respiratory disease (approximately as same as 66.51 μg/m^3), which was revealed in Fig. S1. Besides, the variations of $PM_{2.5}$ concentrations by city were displayed in Fig. S2.

As illustrated in Table 2, $PM_{2.5}$ attributed increased risks of all-cause respiratory disease, and CB incidence in both crude and multivariable-adjusted models. The hazard ratio (HR) for occurrence of all-cause respiratory disease and CB were 1.15 (95% confidence interval [CI]: 1.01, 1.31) and 1.20 (95% CI: 1.00, 1.42) per 10 μg/m^3 increment of $PM_{2.5}$ after multiple covariates were adjusted for. Additionally, after the $PM_{2.5}$ concentrations were categorized based on quartiles, higher risks of all-cause chronic respiratory disease morbidity were observed with HR of 2.11 (95% CI: 1.50, 2.97), 2.03 (95% CI: 1.40, 2.94), and 3.13 (95% CI: 1.90, 5.16) for the Q2, Q3, and Q4 group, respectively, compared with the Q1 as reference (Table S4). The estimate results in CB analyses also revealed consistent significant trends. By contrast, no significant associations of $PM_{2.5}$ with the onset of asthma and COPD were reported in any analyses.

In double-pollutant models (Table S5), the effect estimates of $PM_{2.5}$ levels on all-cause chronic respiratory disease were enhanced after adjustment for NO_2 or SO_2 exposure levels. Similar increasing risk relationships were also observed for the $PM_{2.5}$ levels linked to CB after NO_2 or SO_2 levels were controlled. Overall, the results of these two-pollutant analyses were consistent with that in the single-$PM_{2.5}$ models.

Fig. 2 illustrated the shape of C-R curve of $PM_{2.5}$ and the onset of all-cause chronic respiratory disease after adjustment for multi-confounders. The curve of all-cause chronic respiratory disease showed no evidence of a threshold, with a steeply increasing linear pattern at the concentration range from approximately 40.00 to 75.00 μg/m^3, and no increase in risks at the levels over 80.00 μg/m^3.

3.3. Stratified subgroups

In this study, a pooled stratified Cox proportional hazards analysis was carried out to detect the possible modification for the risks of incident chronic respiratory diseases associated with prolonged $PM_{2.5}$ exposure by the selected characteristics in Model 4. Stronger effect estimates were observed in residents younger than 60 years old, males, the participants with lower education levels, smokers, and alcohol drinkers. However, only significant interaction of subgroups with $PM_{2.5}$ exposure was reported in alcohol drinking status among the cohorts of all-cause chronic respiratory disease and cohort. For instance, the HR was 1.52 (95% CI: 1.21, 1.91) and 1.79 (95% CI: 1.31, 2.44) per 10 μg/m^3 increase in $PM_{2.5}$ among drinkers in all-cause chronic respiratory disease cohort and CB cohort, respectively. But no appreciable differences were revealed in the subgroups classified by other characteristics for all diseases. These results were illustrated in Table 3. Besides, the results of two-pollutant stratified models were summarized in Table S6-S7, and the results of all chronic respiratory diseases with ambient $PM_{2.5}$ exposure were similar to those from each single-$PM_{2.5}$ model.

3.4. Sensitivity analyses

In the sensitivity analyses, the results of the logistic regression analysis resembled to those displayed from the main analyses, the corresponding odds ratio (OR) were 1.15 (95% CI: 1.01, 1.31), 1.19 (95% CI: 1.00, 1.42), 0.76 (95% CI: 0.55, 1.04) and 0.65 (95% CI: 0.29, 1.46) for the incidence of all-cause respiratory disease, CB, asthma, and COPD, respectively (Table S8). In addition, after excluding participants who are exposed to occupational PM or use biofuels for cooking at the baseline, we found similar effect estimates of $PM_{2.5}$ on occurrence of studied chronic respiratory diseases, and the corresponding HR were outlined in Table S9-S10. Overall, in most sensitivity analyses, no substantial changes were revealed in estimations of the relationship between long-term $PM_{2.5}$ exposure and the occurrence of chronic respiratory diseases.

4. Discussion

This cohort study conducted in northern China reported significant associations between the risk of incident all-cause chronic respiratory disease, and CB linked to long-term ambient $PM_{2.5}$ exposure with high levels. The corresponding HR were up to 1.15 (95% CI: 1.01, 1.31), and 1.20 (95% CI: 1.00, 1.42), respectively. These results suggested the significance of exploring the adverse respiratory outcomes affected by air particles and jointly with certain covariates effects in the following directions.

4.1. Chronic respiratory diseases

Prior literatures have demonstrated the deleterious impacts on chronic respiratory diseases when people were exposed to ambient $PM_{2.5}$ for a short time. For instance, two meta-analyses reported that short-term $PM_{2.5}$ exposure elevated 1.4% (95% CI: 0.7%, 2.1%) or 0.33% (95% CI: 0.21%, 0.46%) risk of COPD acute exacerbation or hospitalizations in China (Li et al., 2016; Wang et al., 2019). Furthermore, similar findings were obtained for the associations between $PM_{2.5}$ exposure and hospital visits of CB, asthma, and COPD in China, with the strongest effects of 1.104 (95% CI: 1.032, 1.176) on CB at lag4, 1.072 (95% CI: 1.024, 1.119) on asthma at lag5 and 1.091 (95% CI: 1.047, 1.135) on COPD at lag 3 (Chi et al., 2019; Lin et al., 2020; Tian et al., 2018), separately. There was no analysis for multiple diseases classified by northern and southern regions in China in the same research, while the levels of $PM_{2.5}$ pollution in northern areas were the most severe (He et al., 2017). The biological mechanism underlying $PM_{2.5}$-caused respiratory morbidity remains evolving. It's well known that the common ones involve the oxidative stress pathway and free radical reaction, triggering an inflammation cascade such as chronic airway inflammation, with the inflammatory cytokine receptors increasing. (Danesh Yazdi et al., 2019; Gowers et al., 2012; Grievink et al., 2000; Li et al., 2018). Another proposed mechanism reported that PM particles could interact with airway wall, resulting in the structural changes and remodeling (Churg et al., 2003; Gowers et al., 2012). These changes subsequently cause chronic airflow obstruction. Given that chronic airflow limitation is a major pathogeneses factor of chronic respiratory diseases (Kirkham and Barnes, 2013; Li et al., 2018), it can be assumed that $PM_{2.5}$ may result in chronic respiratory diseases occurrence and development (Kirkham and Barnes, 2013). However, according to previous epidemiologic literature exploring the risks of long-term exposure to $PM_{2.5}$ in association with chronic respiratory diseases, most of

them focused on the prevalent outcome (Cai et al., 2014; Doiron et al., 2021; Hooper et al., 2018). Whether $PM_{2.5}$ contributes to the incidence of chronic respiratory diseases remains scarce and controversial (Schikowski et al., 2014). This is the first longitudinal study that provide evidence for the impacts of prolonged exposure to air $PM_{2.5}$ on incident chronic respiratory diseases in northern China. To diminish the influence of confounding as much as possible, demographics, BMI, lifestyle habits, family history of related disease, and city were adjusted in final model, and the analyses were conducted after the exclusion of subjects exposed to occupational PM or biofuels. The stable and significant positive association from each analysis confirmed the hypothesis mentioned above.

4.2. CB

In this study, a positive association was obtained between incident CB and chronic exposure to ambient $PM_{2.5}$. The HR was 1.20 (95% CI: 1.00, 1.42) in the final adjusted model, which was similar to the results presented from some prior literatures. For example, a combined analysis of cross-sectional data in two large Europeans (654,835) from ESCAPE study revealed the adverse impact of prolonged $PM_{2.5}$ exposure on wheezing with OR up to 1.16 (95% CI: 1.11, 1.21) per 5 $\mu g/m^3$ (Doiron et al., 2017). What's more, another investigation conducted in 39,844 American women found that CB increased by 1.18 (95% CI: 1.04, 1.34) per 4.4 $\mu g/m^3$ increment in $PM_{2.5}$ concentrations among never smokers (Hooper et al., 2018). However, the $PM_{2.5}$ levels were only assessed in the period of 1 or 2 years from these two studies, which may ignore and mask the temporal impacts of long-term $PM_{2.5}$ concentrations on CB morbidity. Additionally, all of them were performed in western countries, and the annual average concentrations of $PM_{2.5}$ pollution in these places were often lower than 35 $\mu g/m^3$. Apart from these positive results, a cohort study from Netherland also reported no significant link between $PM_{2.5}$ and incident CB. The possible reason is that in this study, pollution data were evaluated in 2010 monitoring data. By contrast, CB incident information was collected from 2014 to 2017. The bias may be attributed to different accumulated concentrations of $PM_{2.5}$ caused by long time interval (4–7 years). In special, the annual mean $PM_{2.5}$ concentrations generally decreased during the follow-up years. As such, almost 10-year long-term moving average satellite-inversion data of time-varying $PM_{2.5}$ level were distributed to subjects in a Cox regression model in the present article, which modified above limitations and provided more robust association results (Doiron et al., 2021).

4.3. Asthma

When it comes up to asthma, data on the impact of ambient $PM_{2.5}$ were limited. In an analysis of 1057,722 participants from the Canadian cohort, an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ was linked to an elevated risk of asthma onset with the HR of 1.03 (95% CI: 1.00, 1.10) (Weichenthal et al., 2017). The longitudinal data from ESCAPE cohorts across six European districts indicated positive but nonsignificant associations of PM exposure with incident asthma, with the effect estimate up to 1.08 (95% CI: 0.77, 1.51) for $PM_{2.5}$ per 10 $\mu g/m^3$ increment (Jacquemin et al., 2015) and the consistent result was reported among 23,704 American females (HR=1.66, 95% CI: 0.97, 2.86) per 10 $\mu g/m^3$ increment (Young et al., 2014). In our study, when "city" was additionally adjusted for in model 4, the effect estimate was null-significant in asthma analysis with 0.76 (95% CI: 0.55, 1.04) per 10

μg/m^3 increase of $PM_{2.5}$. The heterogeneity in the associations between $PM_{2.5}$ and asthma morbidity in distinct settings might be partially attributable to the differences in regional $PM_{2.5}$ compositions (Ge et al., 2020; Li et al., 2019; Rosa et al., 2016; Siddique et al., 2020; Wang et al., 2014a, 2014b; Xu et al., 2016). To our best knowledge, PM exists in nature as a complex with chemicals, heavy metals, and biological substances attached (Pandey et al., 2013). As we know, over 20% of global total PAHs emissions in 2014 were contributed to China (Wang et al., 2014a). Another investigation observed that 16 $PM_{2.5}$-associated polycyclic aromatic hydrocarbons (PAHs) in Zhengzhou were higher than those in certain cities of Korea and USA, which appeared to cause different asthma symptoms (Liu et al., 2016; Wang et al., 2014b). What's more, due to the inconsistent development of economics and medical conditions in different cities, the incident rates of asthma distributed slightly differently among four cities in our study, which may explain the difference of the results between Model 4 and other models. These above results suggested that it's necessary to carry out studies on the associations of ambient $PM_{2.5}$ components, socioeconomics and medical conditions with incidence of asthma in the future direction.

4.4. COPD

Our study indicated null relationship between $PM_{2.5}$ exposure and onset of COPD, and the HR was 0.66 (95% CI: 0.29, 1.47) with a 10 μg/m^3 increment in $PM_{2.5}$. After the potential risks such as occupational PM exposure, the burning of biomass and fossil fuels were eliminated in sensitive analyses, the main results seemed no changes in direction of associations. These findings only indicated possible trend of inverse associations, but not real inverse associations, which agreed with those from certain prior literatures. An English (Atkinson et al., 2015) and a Canadian cohort study (Gan et al., 2013) found that the HR linked to incidence of COPD were 1.05 (95% CI: 0.98, 1.13) for $PM_{2.5}$ with each 10 μg/m^3 increment and 1.02 (95% CI: 0.98, 1.07) with a 1.58 μg/m^3 increase in $PM_{2.5}$, separately. But the average levels of $PM_{2.5}$ pollution (range from 4.1 to 12.9 μg/m^3) in these two works was much lower than that (66.51 μg/m^3) in our research. A US nurses' Health Study containing 121,701 nurses revealed the HR of incident COPD was 0.93 (95% CI: 0.66, 1.31) per 10 μg/m^3 increment of $PM_{2.5}$, however, the study was only recruited females for investigation (Fisher et al., 2016).

Despite the above irrelevant results, whether chronic exposure to air pollution is linked to increased morbidity of COPD is inconclusive. Several articles have documented the evidence for potential adverse impacts of $PM_{2.5}$ on COPD. A meta-analysis analyzed a positive association of long-term exposure to $PM_{2.5}$ with the COPD incidence by combining six prospective cohort studies (Park et al., 2021). Among European subjects, chronic $PM_{2.5}$ exposure was related to the elevated emergency room visits (ERVs), hospital admissions or outpatient visits of COPD with the HR up to 1.17 (95% CI: 1.06, 1.29) (Liu et al., 2021). In a Canadian cohort with Toronto residents, $PM_{2.5}$ affected COPD morbidity and the HR was 1.06 (95% CI: 1.04, 1.08) per 3.2 μg/m^3 increase in $PM_{2.5}$ (Weichenthal et al., 2017). Furthermore, there were two Asian cohort articles containing Korean elders and Taiwan individuals exposed to relatively high-settings revealed significant positive relationships of COPD development with $PM_{2.5}$ levels in the adjusted HR (Guo et al., 2018; Han et al., 2020). The possible explanations for the inconsistent results compared with ours is that most

of the above articles identified new-onset COPD by using records of hospital admission, which may capture more COPD incidence than the reals because hospital admissions may incorporate acute exacerbation of previously diagnosed as COPD cases, leading to the overestimated effect values. To provide more comparable evaluations, standard for defining incident of COPD in further literatures should be uniformed. What's more, the subjects from Korean and European works were the elderly with more sensitivity to air pollution than other residents (Ferreira et al., 2016), causing bias of overestimated effect values. These differed results also may be attributed to the adjustment of confounding factors (whether adjusted for other air pollutants, smoking habits or not), the difference of racial distinction, the evaluation methods of pollutants and the identification of COPD morbidity. In addition, considering short-term air pollution exposure was significantly associated with acute exacerbation of COPD, and high correlation was observed in short- and long-term exposure (Schikowski et al., 2014), it's difficult to explore the single chronic effect of air pollution on COPD. Last, it's worth noting that long-term follow-up time interval (9.8 years) might contribute to survival bias. As a result, the number of new COPD cases in the study period may be less than real incidents. For instance, in this study, only 14 individuals were new cases of COPD, and the incidence of COPD was 0.04%. The limited sample size may lead to underestimated effect estimates in this study. Herein, it implies that more studies should be conducted to assess the COPD morbidity attributable to ambient air pollution. In addition, future research directions can target to the effects of air pollution on COPD symptom classifications.

4.5. C-R curves

Although the C-R curve in this study showed no evidence of a threshold for all-cause respiratory disease, and disagreed with the shape in previous literature studied on respiratory admissions for short-term exposure to $PM_{2.5}$ (Yao et al., 2020), generally, the incident risk of all-cause respiratory disease was observed under high $PM_{2.5}$ exposure ranges in both articles. In this study, the risk revealed when $PM_{2.5}$ was over 63.00 μg/m^3 level, and it exceeded the annual average threshold for the air $PM_{2.5}$ exposure levels set by WHO (5 μg/m^3) (World Health Organization, 2021). We also found that after $PM_{2.5}$ level was more than 80 μg/m^3, the curve showed a slightly downward trend, which suggested that the following researches should provide more comprehensive and credible evidence on the shape of curve among residents who are exposed to high $PM_{2.5}$ pollution levels. Notably, the annual average concentrations of $PM_{2.5}$ among four cities in northern China was 66.51 μg/m^3, which was about 2–16 times higher than those of western countries (4.10 μg/m^3-26.91 μg/m^3) (Atkinson et al., 2015; Carey et al., 2016; Fisher et al., 2016; Gan et al., 2013; Weichenthal et al., 2017). Due to the heavier $PM_{2.5}$ pollution in northern China compared with western countries, we were unable to determine the C-R curve in the relatively lower $PM_{2.5}$ level ranges. These findings suggested that more comprehensive and valid data of cohorts are needed to explore the influence pattern of air pollution on chronic respiratory diseases morbidity, and hence provide the basis and directions in evaluation of the respiratory damages induced by air pollutions, ascertainment of threshold level, and prevention for chronic respiratory damages.

4.6. Effect modification

As to the effect modification, no significant difference was obtained from the relationships between $PM_{2.5}$ exposure and incident chronic respiratory diseases by most characteristics (e.g., age, gender, education level, and personal behavior habits). However, interestingly, we found alcohol drinkers were more sensitive to the ambient $PM_{2.5}$ in all-cause respiratory disease cohort and CB cohort than non-alcoholic drinkers. The similar trend was also observed by Li et al. and colleges based on China-PAR project, though null interactions were observed of $PM_{2.5}$ exposure with drinking status (Li et al., 2020a). Yet, the role of alcohol drinking status in this process remains unclear, which is a topic that requires further research and verification.

4.7. Strengths and Limitations

This study has several strengths. It is a large cohort study based on Chinese adults with a long period of almost 10-year follow-up to access the relationship and the C-R curves between prolonged ambient $PM_{2.5}$ exposure and onset of chronic respiratory diseases. To our best knowledge, the information from the C-R plot plays an important role in public health assessment for the prevention of diseases. **Besides,** almost 40 thousand residents' epidemiological information were collected in four cities, where data of $PM_{2.5}$ pollution levels represented the broad range of northern China. **What's more,** compared with the exposure assessment such us monitoring station or land-use regression model in part of the prior analysis, the estimate of individual $PM_{2.5}$ exposure in our study was derived from high resolution (1 km × 1 km) through an ensemble machine-learning spatiotemporal. **In addition,** among diverse risk factors, smoking is the most important one for respiratory diseases development but little articles eliminate the effects of second-hand smokers. This is the first study that considered passive smoking status as an adjustment variable. An increasing number of epidemiological and biological evidence showed that second-hand smoke exists as a major risk factor of respiratory diseases in never smokers. It would irritate the airways, cause or worsen asthmatic diseases and allergies (Braun et al., 2020; Kim et al., 2018). As such, it's recommended that more researches should attach on the modification of second-hand smoke. Finally, air pollutants exist as complex mixture in nature, some literatures also indicated that gas pollutants such as NO_2, O_3, and SO_2 may have adverse impact on chronic respiratory diseases (Doiron et al., 2019; Park et al., 2021; Saygın et al., 2017; Zhang et al., 2018), and the impacts of ambient $PM_{2.5}$ exposure on chronic respiratory diseases might be affected by gas pollutants exposure. Thus, we conducted bi-pollutant models such as $PM_{2.5}$-NO_2 and $PM_{2.5}$-SO_2 to evaluate the impacts of multi-pollutant exposure on chronic respiratory outcomes. Analysis of the above data provided rare but valuable evidence of unfavorable impacts on all-cause respiratory diseases, CB, and asthma morbidity influenced by long-term $PM_{2.5}$ exposure in China.

Despite these strengths, some limitations should be noticed. Firstly, the design of a retrospective cohort study caused the bias of recall for certain self-reported contents, inducing exercise, lifestyle habits, etc. Further study directions could target to the risk influences of prolonged air pollution exposure on incident chronic respiratory diseases collected from hospital admissions. Secondly, the effects induced by $PM_{2.5}$ may differ in different districts of China because of the various attachments of $PM_{2.5}$. Nevertheless,

we are unable to carry out the related analyses due to the lack of data on mixture compositions of $PM_{2.5}$ (Wang et al., 2014a, 2014b; Zhu et al., 2018). More specific respiratory damages involved to particulate components should be assessed in the future. Thirdly, due to the lack data of O_3 levels before 2013 in mainland China, $PM_{2.5}$-O_3 model was not conducted in this study. Further studies are needed to explore the impacts of the mixed effects of $PM_{2.5}$ and O_3 exposure on chronic respiratory outcomes. Fourthly, lifestyles such as smoking and drinking status may be potential risk factors for chronic respiratory diseases, but we lack time scale data of these covariates, and they were not analyzed as time-varying covariates, which is one of the limitations in our study. More researches needed to evaluate the confounding effects of time-varying lifestyles on the incidence of chronic respiratory diseases linked to prolonged $PM_{2.5}$ exposure in the future. Additionally, an increasing number of researches have indicated that certain common biomarker known as C-reactive protein (CRP) was associated with respiratory diseases development, but it was not available in the current study (Lock-Johansson et al., 2014). Therefore, to provide more comprehensive and powerful results, the information of common and possible biomarkers at the baseline survey should be provided in the following studies. Finally, cautions should be treated to the results. Indoor fuel contamination might be the potential risk factor of adverse respiratory outcomes (Chan et al., 2019). Yet, it was not considered as a confounder because the lack of indoor pollutants' data in our study. Future directions target to independent but comprehensive multi-center studies with uniformed participants' characteristics, complete disease-related information, and more accurate methods of air pollution estimation.

5. Conclusions

In conclusion, we found that prolonged exposure to $PM_{2.5}$ pollution at high levels was a risk factor contributing to the increased morbidity of chronic respiratory diseases among adults in northern China. The evidence provided the local governments a better prospect to regulate and formulate the strategies on $PM_{2.5}$ pollution emissions for prevention from unfavorable outcomes of chronic respiratory diseases in China.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data that has been used is confidential.

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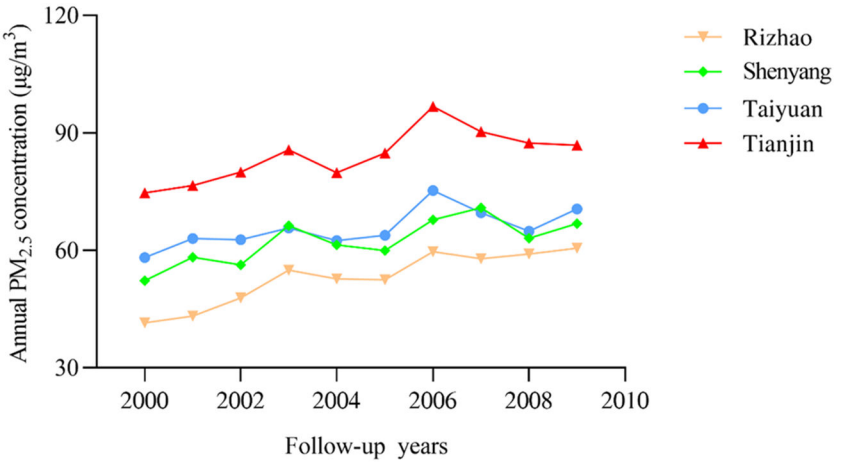

Fig. 1.

The temporal trends for average annual concentrations of $PM_{2.5}$ ($\mu g/m^3$) during the period from 2000 to 2009 across the four cities in northern China.

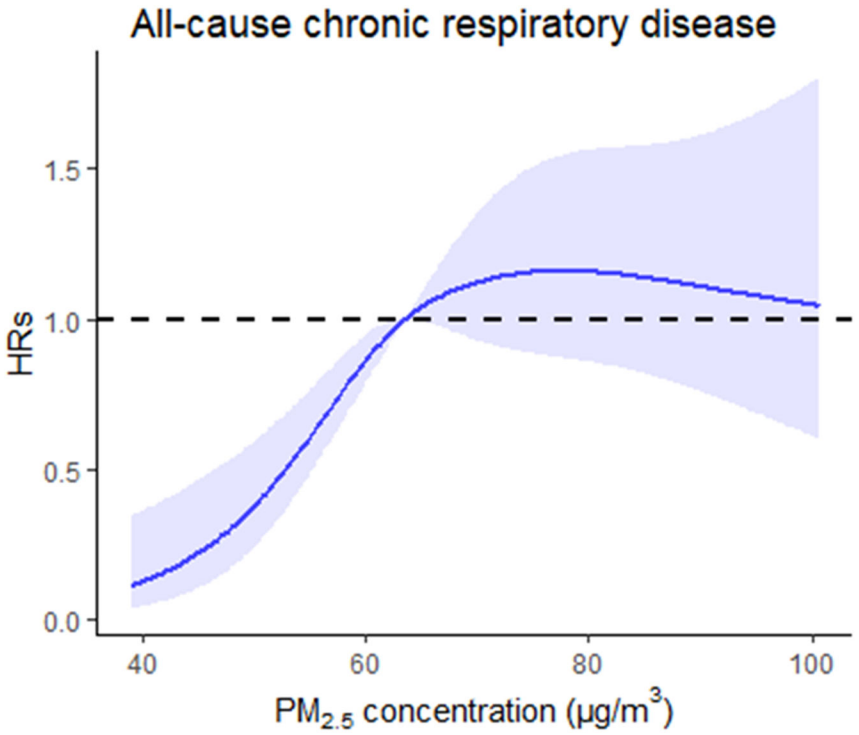

Fig. 2.

The concentration-response curve for the association between long-term $PM_{2.5}$ exposure and morbidity of all-cause chronic respiratory disease. The X-axis is the average concentration of $PM_{2.5}$ in the cohort study. The Y-axis is the log relative risk. The solid line represents the mean risk estimate, and the dotted lines represent the 95% confidence intervals.

Table 1

Baseline characteristics of all-cause chronic respiratory disease cohort by cities.

Characteristic	Rizhao	Shenyang	Taiyuan	Tianjin	Total
Total numbers (%)	9277	9542	9821	9407	38047
Gender (%)					
Male	4879 (52.59)	4613 (48.34)	4883 (49.72)	4530 (48.16)	18905 (49.69)
Female	4398 (47.41)	4929 (51.66)	4938 (50.28)	4877 (51.84)	19142 (50.31)
Age (years)	38.38 ± 12.39	46.85 ± 14.26	44.33 ± 13.79	45.76 ± 12.33	43.87 ± 13.62
BMI (kg/m2)	22.34 ± 2.51	22.38 ± 3.36	22.86 ± 2.65	22.93 ± 3.16	22.63 ± 2.95
Monthly income (%)					
< 500 CNY	4482 (48.31)	4703 (49.29)	3609 (36.75)	4448 (47.28)	17242 (45.32)
≥ 500 CNY	4795 (51.69)	4839 (50.61)	6212 (63.25)	4959 (52.72)	20805 (54.68)
Education (%)					
< High school	6557 (70.68)	5693 (59.66)	4754 (48.41)	4487 (47.70)	21491 (56.49)
≥ High school	2506 (27.01)	3849 (40.34)	5067 (51.59)	4860 (51.66)	16282 (42.79)
Smoking status (%)					
No	7412 (79.90)	6608 (69.25)	7123 (72.53)	6387 (67.90)	27530 (72.36)
Yes	1865 (20.10)	2934 (30.75)	2698 (27.47)	3020 (32.10)	10517 (27.64)
Alcohol intake (%)					
No	7295 (78.64)	7615 (79.81)	8055 (82.02)	7411 (78.78)	30376 (79.84)
Yes	1982 (21.36)	1927 (20.19)	1766 (17.98)	1996 (21.22)	7671 (20.16)
Exercise status (%)					
No	4437 (47.83)	5500 (57.64)	4979 (50.70)	4128 (43.88)	19044 (50.05)
Yes	4839 (52.16)	4041 (42.35)	4835 (49.20)	5268 (56.12)	18983 (49.89)
Passive smoking status (%)					
No	7376 (79.51)	5745 (60.21)	5302 (53.99)	4740 (50.39)	23163 (60.88)
Yes	1892 (20.39)	3539 (37.09)	4411 (44.91)	4482 (47.65)	14324 (37.65)
Family history of all-cause chronic respiratory disease (%)					
No	9202 (99.19)	9439 (98.92)	9704 (98.81)	9220 (98.01)	37154 (97.65)
Yes	27 (0.29)	112 (1.17)	3 (0.03)	187 (1.99)	79 (0.21)
New cases of all-cause chronic respiratory disease (%)	75 (0.81)	103 (1.08)	117 (1.19)	187 (1.99)	482 (1.27)

The values are presented as percentages (%) or means ± standard.

Table 2

Adjusted HR (95% CI) for the incidence of chronic respiratory diseases in relation to each 10 μg/m^3 increase in $PM_{2.5}$.

Baseline variable adjusted for	HR (95% CI) for incidence of chronic respiratory diseases			
	All-cause respiratory disease	CB	Asthma	COPD
Crude model	1.30 (1.21, 1.39)	1.15 (1.05, 1.26)	1.48 (1.27, 1.73)	0.95 (0.63, 1.44)
Model 1	1.27 (1.18, 1.36)	1.12 (1.02, 1.23)	1.45 (1.24, 1.70)	0.83 (0.53, 1.31)
Model 2	1.28 (1.19, 1.37)	1.14 (1.03, 1.25)	1.45 (1.23, 1.70)	0.82 (0.51, 1.32)
Model 3	1.20 (1.12, 1.29)	1.09 (1.00, 1.20)	1.35 (1.15, 1.60)	0.86 (0.54, 1.38)
Model 4	1.15 (1.01, 1.31)	1.20 (1.00, 1.42)	0.76 (0.55, 1.04)	0.66 (0.29, 1.47)

Abbreviations: HR, hazard ratio; CI, confidence interval; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease;

Crude model: adjusted no factors associated with respiratory disease and $PM_{2.5}$. **Model 1**: adjusted for gender (male and female), age (continuous variable), and BMI (continuous variable). **Model 2**: adjusted for Model 1 plus education level (below high school or high school or above), personal income (< 500 CNY or ≥ 500 CNY per month). **Model 3**: adjusted for Model 2 plus smoking status (yes or no), passive smoking status (yes or no), alcohol consumption (yes or no), physical activity (yes or no) and family history of related chronic respiratory diseases (yes or no). **Model 4**: adjusted for Model 3 + city (Rizhao, Shenyang, Taiyuan, and Tianjin).

Table 3

Estimated HR for the incidence of chronic respiratory diseases per 10 μg/m^3 increase of $PM_{2.5}$ by stratified Cox proportional hazards models.

Characteristics	All-cause chronic respiratory disease				CB			
	No. of onset	HRs	95% CI	$P_{interaction}$ value	No. of onset	HRs	95% CI	$P_{interaction}$ value
Age	482			0.35	276			0.19
< 60	303	1.31	1.11–1.54		178	1.32	1.06–1.64	
≥ 60	179	1.04	0.83–1.29		98	1.08	0.80–1.45	
Gender				0.77				0.92
Male	300	1.27	1.08–1.50		166	1.32	1.06–1.65	
Female	182	1.09	0.88–1.35		110	1.03	0.78–1.36	
Education level				0.43				0.76
< High school	287	1.23	1.04–1.46		171	1.37	1.09–1.71	
≥ High school	194	1.02	0.83–1.26		104	0.95	0.72–1.26	
Monthly income				0.22				0.68
< 500 CNY	188	1.15	0.93–1.43		108	1.28	0.96–1.70	
≥ 500 CNY	294	1.14	0.96–1.34		168	1.15	0.92–1.43	
Smoking status				0.28				0.16
No	246	1.08	0.90–1.30		144	1.07	0.84–1.36	
Yes	236	1.23	1.02–1.50		132	1.37	1.06–1.76	
Passive smoking status				0.44				0.38
No	234	1.09	0.90–1.31		147	1.16	0.91–1.47	
Yes	242	1.22	1.01–1.46		127	1.02	1.00–1.03	
Alcohol intake				< 0.001				< 0.001
No	310	0.99	0.84–1.17		181	0.98	0.79–1.22	
Yes	172	1.52	1.21–1.91		95	1.79	1.31–2.44	
Physical activity				0.34				0.60
No	310	1.13	0.91–1.40		106	1.11	0.83–1.49	
Yes	172	1.14	0.97–1.35		170	1.23	0.99–1.52	

Abbreviations: HR, hazard ratio; CI, confidence interval; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease.

Covariates: adjusted for age, sex, BMI, smoking status (yes or no), education level (below high school or high school or higher), personal income (< 500 CNY and ≥ 500 CNY per month), smoking status (yes or no), passive smoking status (yes or no), alcohol intake (yes or no), physical activity (yes or no), family history of related chronic respiratory diseases (yes or no), and city (Rizhao, Shenyang, Taiyuan, and Tianjin).

*P*interaction values are the interaction results between $PM_{2.5}$ and the variables.