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Long-term exposure to particulate matter and COPD mortality: Insights from causal inference methods based on a large population cohort in southern China

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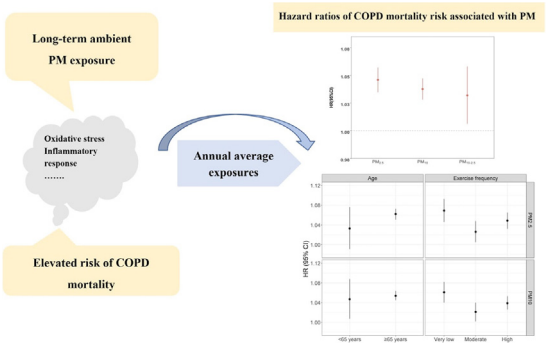
HIGHLIGHTS

- Casual links were identified between the long-term PM exposure and COPD mortality.
- A 3.2–4.6 % excess COPD mortality was attributed to a 1-μg/m^3 increase in PM levels.
- The elderly were more vulnerable while the moderate exercise was protective.
- Participants generally at low PM exposures tended to be more susceptible.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Evidence of the association between long-term exposure to particulate matter (PM) and chronic obstructive pulmonary disease (COPD) mortality from large population-based cohort study is limited and often suffers from residual confounding issues with traditional statistical methods. We hereby assessed the casual relationship between long-term PM ($PM_{2.5}$, PM_{10} and $PM_{10-2.5}$) exposure and COPD mortality in a large cohort of Chinese adults using state-of-the-art causal inference approaches.

Methods: A total of 580,757 participants in southern China were enrolled in a prospective cohort study from 2009 to 2015 and followed up until December 2020. Exposures to PM at each residential address were obtained from the Long-term Gap-free High-resolution Air Pollutant Concentration dataset. Marginal structural Cox models were used to investigate the association between COPD mortality and annual average exposure levels of PM exposure.

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Results: During an average follow-up of 8.0 years, 2250 COPD-related deaths occurred. Under a set of causal inference assumptions, the hazard ratio (HR) for COPD mortality was estimated to be 1.046 (95 % confidence interval: 1.034–1057), 1.037 (1.028–1.047), and 1.032 (1.006–1.058) for each 1-μg/m^3 increase in annual average concentrations of $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ respectively. Additionally, the detrimental effects appeared to be more pronounced among the elderly (age ≥ 65) and inactive participants. The effect estimates of $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ tend to be greater among participants who were generally exposed to PM_{10} concentrations below 70 μg/m^3 than that among the general population.

Conclusion: Our results support causal links between long-term PM exposure and COPD mortality, highlighting the urgency for more effective strategies to reduce PM exposure, with particular attention on protecting potentially vulnerable groups.

1. Introduction

Globally, chronic obstructive pulmonary disease (COPD) is one of the leading causes of death, affecting approximately 10 % of the world's adult population (GBD 2017 Causes of Death Collaborators, 2018; Adeloye et al., 2015). According to the World Health Organization, the number of deaths due to COPD was estimated to be over 3 million worldwide annually (World Health Organization: Chronic respiratory diseases, 2022). In China, COPD is one of the five most common causes of death with 99.9 million adults suffering from COPD in 2015 (Wang et al., 2018).

Ambient air pollutants are well-documented environmental risk factors, among which particulate matter (PM) is one of the dominant and was estimated to be responsible for 27.1 % of COPD mortality in 2015 (Cohen et al., 2017). Most previous studies assessed the short-term effects of PM exposure on human health and were usually based on monitoring data. Recent studies also considered the long-term effect of PM exposures which generally were based on cohorts. For instance, a recent meta-analysis of 11 studies reported a positive association between $PM_{2.5}$ (PM with aerodynamic diameters ≤2.5 μm) exposure and COPD mortality (Chen and Hoek, 2020). Compared with the assessment of short-term associations, evaluation of the long-term adverse impact of PM exposure on COPD health would be of a greater public health significance.

However, relevant studies on the long-term impact of PM exposure on COPD mortality showed inconclusive results (Chen and Hoek, 2020). Some studies reported significant associations (Carey et al., 2013; Chen et al., 2017; Pinault et al., 2016; Pinault et al., 2017; Turner et al., 2016; Yin et al., 2017) whereas others did not detect any significant signals (Gan et al., 2013; Crouse et al., 2015; Hart et al., 2011; Katanoda et al., 2011; Lepeule et al., 2012; Wong et al., 2015; Yang et al., 2018). Furthermore, the majority of studies were conducted in settings with $PM_{2.5}$ concentration under 15 μg/m^3, the findings from which may not be generalized to highly polluted settings. The rest of studies either were limited in the generalizability of findings as they only covered certain subgroup of the population such as older adults (Wong et al., 2015; Yang et al., 2018), men (Yin et al., 2017) or age > 40 years (Katanoda et al., 2011), or suffer from decreased statistical power with limited number of participants identified with outcomes of interest (i.e., 46 (0.12 %)) (Chen et al., 2017). Therefore, more comprehensive and reliable evidence from a large cohort of the general Chinese population is needed to better understand the effect of long-term exposure to ambient PM on COPD mortality in China.

Existing studies generally used traditional association assessment which is straightforward but suffers from the bias by the impact of residual confounders (Robinson and Jewell, 1991; Bind, 2019). In the latest decades, an alternative set of approaches, state-of-the-art causal inference methods, have been proposed to address this issue by mimicking randomized controlled trials based on the observational data (Cole and Hernán, 2008; Robins et al., 2000). With causal inference methods, effect estimates are more reliable and are considered to represent the risk of COPD mortality that could be specifically attributed to a specific exposure. However, such evidence is limited among existing studies.

To address these important knowledge gaps, we performed causal inference analysis to investigate the association between long-term exposure to $PM_{2.5}$, PM_{10} (PM with aerodynamic diameters ≤10 μm), and $PM_{10–2.5}$ (PM with aerodynamic diameters between 2.5 and 10 μm) and the risk of COPD mortality using a community-based cohort of 0.6 million residents in southern China. Potential modification effects of individual characteristics and lifestyle factors were also examined.

2. Materials and methods

2.1. Study design and population

As a part of the Major Projects of Science Research for the 11th and 12th Five-year Plans of China, a prospective study of over 5 million participants was originally established to investigate the prevalence of hepatitis B virus and hepatitis B virus carriers in southern China as well as test prevention strategies at the community level (Ruan et al., 2019). In this study, we focused on the Guangzhou sub-cohort where we recruited 654,115 participants from 35 randomly selected communities from January 2009 and December 2015, and confirmed the COPD death and census status with the Death Registry operated by the Guangzhou Center for Disease Control and Prevention (Guangzhou CDC). Baseline information was collected by well-trained nurses. Information on demographic characteristics and lifestyle factors was collected by a computer-based questionnaire in face-to-face interviews. Physical examinations were conducted following a standard protocol.

Demographic characteristics and lifestyle factors assessed in the present study were sex, age (years), ethnicity (i.e., Han and minority), marital status (i.e., never married, married, widowed and divorce), education (i.e., illiterate or semiliterate, primary school, secondary school, high school and college or above), medical insurance (i.e., medical insurance for urban workers, medical insurance for urban residents, the new rural cooperative medical insurance, and others), smoking status (i.e., never, ever and current), alcohol consumption (i.e., never and ever), exercise frequency (i.e., very low, low, moderate and high), and body mass index (BMI). This study was approved by the IRB Committee at Sun Yat-sen University (No. L2017030) and all participants provided written, informed consent before participation.

2.2. Outcome definition

Follow-up duration was defined as the time from enrollment to the event of interest, death or the end of the present study on 31st December 2020. Causes of diseases and deaths were coded according to the 10th revision of the International Classification of Diseases (ICD-10). The causes of death up to December 31, 2020 were obtained through record linkage with the Death Registry of the Guangzhou CDC. If death certificates were not issued by a medical institution, the causes of death were verified by Guangzhou CDC by cross-checking past medical history. In the present study, the primary outcome was the COPD mortality (ICD-10: J40-J44, J47).

2.3. Assessment of PM and relevant environmental exposures

Annual average $PM_{2.5}$ and PM_{10} concentrations at a spatial resolution of one kilometer were obtained from the Long-term Gap-free High-resolution Air Pollutant concentration dataset (https://zenodo.org/record/5655807#.

Yn-chlhBypo, accessed data: August 11, 2022). Specifically, based on the data fusion method of tensor-flow, the multi-modal aerosol data from different sources were integrated, and finally a gap-free daily aerosol optical depth (AOD) dataset at one-kilometer resolution in China from 2000 to 2020 was generated. Other auxiliary data were also upscaled to one kilometer resolution as well, including aerosol components, the normalized difference vegetation index (NDVI), eleven meteorological factors, land cover information, the digital elevation model, and population. Then an ensemble learning approach was established for estimation of $PM_{2.5}$ and PM_{10} concentrations using the full-coverage AOD and other auxiliary data as predictors, with ground-level monitored $PM_{2.5}$ and PM_{10} concentrations as the outcome. Finally, to further improve the accuracy of PM data after 2014, ground measured $PM_{2.5}$ and PM_{10} concentrations were fused with grid-based PM estimations. $PM_{2.5}$ and PM_{10} estimations showed satisfactory validation against the ground measurements, with r - values of 0.95 and 0.94 and RMSEs of 12.03 and 19.56 $\mu g/m^3$. Details on data collection and modeling processes have been reported elsewhere (Bai et al., 2022). Annual average exposures of $PM_{2.5}$ and PM_{10} for each participant were estimated during the follow-up period according to the corresponding residential address, as the primary exposure variable in this study.

Since the existing evidence showed that greenness and night-time lights were associated with COPD (Yang et al., 2021; Okuliarova et al., 2020; Al-Naggar and Anil, 2016), we also considered land-use variables, including NDVI and visible infrared imaging radiometer suite night-time lights (VNL) as possible confounders. NDVI, Moderate Resolution Imaging Spectroradiometer (MODIS)—MOD13Q1 (Collection 6) Terra composite NDVI data (at 16 days interval and 250 m spatial resolution) during the study period (2009–2020) were downloaded from the LPDAAC (Land Processing Distributed Active Archive Center (https://lpdaac.usgs.gov). The VNL data was obtained from version 2 visible infrared imaging radiometer suite nighttime lights (V.2 VNL) annual composites (Elvidge et al., 2021). The annual average value of land-use variables within the radial buffer (500 m) surrounding the residential address were assigned for each participant.

2.4. Statistical analysis

Marginal structural Cox proportional hazards model with IPWs were used to estimate the risk of COPD mortality associated with each 1 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ concentrations. The annual average exposure of PM was commonly used in literature to represent the long-term PM exposure (Carey et al., 2013; Wu et al., 2020). Our study further displayed that PM concentrations changed with a decreasing trend over time during follow-up. Therefore, we included the PM concentration as a

Table 1
Characteristics for the study participants from 2009 to 2015[a].

Characteristic	Overall	Overall COPD deaths	Control group	*P*-value
Number of participants	580,757	2250	578,507	
Demographics				
Age, mean (SD), years	48.33 (17.55)	78.84 (8.63)	48.21 (17.47)	<0.001
Sex, (men %)	275,676 (47.47)	1525 (67.78)	274,151 (47.39)	<0.001
Ethnic, (minority %)	10,953 (1.89)	8 (0.36)	10,945 (1.89)	<0.001
Education (%)				<0.001
Illiterate or semiliterate	6603 (1.14)	152 (6.76)	6451 (1.11)	
Primary school	67,247 (11.58)	778 (34.58)	66,469 (11.49)	
Second school	131,394 (22.62)	567 (25.20)	130,827 (22.61)	
High school	266,467 (45.88)	669 (29.73)	265,798 (45.95)	
College or above	109,046 (18.78)	84 (3.73)	108,962 (18.84)	
Marital status (%)				<0.001
Never married	108,424 (18.67)	145 (6.44)	108,279 (18.72)	
Married	448,138 (77.16)	1678 (74.58)	446,460 (77.17)	
Widowed	17,262 (2.97)	395 (17.56)	16,867 (2.92)	
Divorce	6933 (1.20)	32 (1.42)	6901 (1.19)	
Medical insurance (%)				<0.001
Medical insurance for urban workers	354,396 (61.02)	1382 (61.42)	353,014 (61.02)	
Medical insurance for urban residents	164,213 (28.28)	771 (34.27)	163,442 (28.25)	
The new rural cooperative medical insurance	6439 (1.11)	3 (0.13)	6436 (1.11)	
Others	55,709 (9.59)	94 (4.18)	55,615 (9.62)	
BMI, mean (SD), kg/m^2	22.07 (2.45)	21.87 (2.73)	22.07 (2.45)	0.01
Lifestyle behaviors				
Smoking status (%)				<0.001
Never	505,385 (87.02)	1770 (78.67)	503,615 (87.05)	
Ever	6716 (1.16)	135 (6.00)	6581 (1.14)	
Current	68,656 (11.82)	345 (15.33)	68,311 (11.81)	
Alcohol consumption (%)				0.04
Never	515,205 (88.71)	1964 (88.29)	513,241 (88.72)	
Ever	65,552 (11.29)	286 (11.71)	65,266 (11.28)	
Exercise frequency (%)				0.03
Very low	322,225 (55.48)	1251 (55.60)	320,974 (55.48)	
Low	73,103 (12.59)	302 (13.42)	72,801 (12.58)	
Moderate	68,835 (11.85)	222 (9.87)	68,613 (11.86)	
High	116,594 (20.08)	475 (21.11)	116,119 (20.08)	
Land-use variables				
NDVI (500), mean (SD)	0.213 (0.040)	0.209 (0.038)	0.214 (0.040)	<0.001
VNL, mean (SD), $nW/cm^2/sr$	81.64 (3.36)	82.02 (3.11)	81.64 (3.36)	<0.001
PM espouses (2009–2020)				
$PM_{2.5}$, mean (SD), $\mu g/m^3$	37.34 (0.91)	37.40 (0.85)	37.34 (0.91)	<0.001
PM_{10}, mean (SD), $\mu g/m^3$	62.05 (1.68)	62.11 (1.54)	62.05 (1.68)	0.07
$PM_{10-2.5}$, mean (SD), $\mu g/m^3$	24.710 (0.87)	24.705 (0.80)	24.710 (0.87)	0.60

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, stand deviation; BMI, body mass index; NDVI, normalized difference vegetation index; VNL, visible infrared imaging radiometer suite night-time lights; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 um; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{10-2.5}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated.

time-varying variable. We fitted marginal structural Cox models with time-varying covariates (annual average PM concentrations and NDVI). Confounders were identified using a directed acyclic graph (DAG) (Supplementary Fig. 1), including the demographic factors (age, sex, ethnic group, marital status, medical insurance, and education level), lifestyle behavior (smoking status, and exercise frequency), and a land-use variable (NDVI). Generalized variance-inflation factor (GIF) was performed to identify the collinearity between the variables, and GVIF >10 was considered to indicate multicollinearity (Kim, 2019). In our study, GIFs were all <2, indicating no multicollinearity among the variables.

The basic concept of marginal structural Cox models was to construct a weighted pseudo-population by mimicking a randomized controlled trial, where confounding effects were supposed to be balanced across exposure groups and the effect estimates would have causal implications. The process of constructing matched pseudo-population was described in section Supplementary statistical methods section. In the present study, we developed three weighting methods based on a linear model (LM), a generalized estimating equation (GEE) or a gradient boosting machine learning approach (ML) (Chen and Guestrin, 2016), respectively. We checked the covariate balance on the weighted pseudo-population through average absolute correlation (AC) (Wu et al., 2020), with values of <0.1 indicating high quality in mimicking randomized experiments. In the final model, due to the optimal balance of confounders (Supplementary Fig. 2), the GEE- IPWs method was used to estimate HR for COPD mortality outcomes per 1 μg/m^3 increase in PM concentrations. For comparison, we also fitted Cox models using annual PM concentrations and NDVI as the time-varying variables.

Overall, we developed the following four models: 1) Model 0 was a crude model under conventional Cox proportional hazards model. 2) Model 1: model 0 adjusted for age. 3) Model 2: additionally adjusted for sex, ethnicity, education, marital status, medical insurance, exercise frequency and NDVI (500 m) based on model 1. 4) Model 3: refitted with the marginal structural Cox proportional hazards model based on the same co-variates in the model 2. The results of the Model 3 were reported as main results in the present study.

Results from the final model (i.e., model 3) were also stratified by sex, age, ethnicity, marital status, education, and exercise frequency. Missing data for confounding variables were imputed via multiple imputations using a chained equation (van Buuren and Groothuis-Oudshoorn, 2011). Given that China is a highly polluted region, to assess the potential influence of low-concentration exposure on COPD mortality, we further restricted the analysis to participants with annual PM_{10} concentration below the WHO interim target 1 of 70 μg/m^3 (n = 281,317) (WHO global air quality guidelines, 2021).

To assess the robustness of our findings, we conducted multiple sensitivity analyses. First, we further adjusted the main models by using more covariates (temperature and relative humidity) that have not been included in the final model. Second, we used different buffer sizes (i.e., 250 m and 1000 m) for the estimation of NDVI exposure. Third, we performed complete case analysis (individuals who did not have any missing data that required imputation) to assess whether the results remained unchanged. Fourth, we examined the associations between long-term PM exposure and outcomes using three different marginal structural Cox models. Furthermore, we calculated the E-value to evaluate the robustness of our results against potential unmeasured confounding. A larger E-value suggests that the findings are less likely to be overridden by unmeasured confounding (Haneuse et al., 2019). All statistical analyses were conducted using R (version 4.1.3). Two-sided *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics and PM concentrations

Among the 654,115 participants recruited from 2009 to 2015 at baseline, 72,330 had ages below 18 years and 1028 had unknown vital status and these individuals were excluded, leaving 580,757 participants [mean (standard deviation (SD)) age = 48.3 (17.6) years; 275,676 (47.5 %) men] in the present study. During an average follow-up period of 8.0 years (SD = 1.8), 2250 deaths occurred from COPD.

Table 1 shows that participants who died from COPD tended to be older, men, Han ethnicity, more likely to be current smokers, ever drinkers, and widowed compared with other participants. They also had less education, higher prevalence of medical insurance for urban residents, lower BMI, higher VNL exposure and lower NDVI exposure (*P* from 0.04 to <0.001). The characteristics of the participants included in complete case analysis were shown in the Supplementary Table 1. As shown in Fig. 1, annul average $PM_{2.5}$ and PM_{10} concentrations declined from 2009 to 2020. The average concentrations of $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ over the entire study was 37.34 μg/m^3 (SD = 0.91), 62.05 μg/m^3 (SD = 1.68), and 24.71 μg/m^3 (SD = 0.87), respectively. In general, participants who died from COPD had been exposed to higher concentrations of $PM_{2.5}$ than those who did not (37.40 μg/m^3 vs 37.34 μg/m^3, $P < 0.001$) with annual average differences ranging from 0.028 to 0.194 (Supplementary Fig. 3).

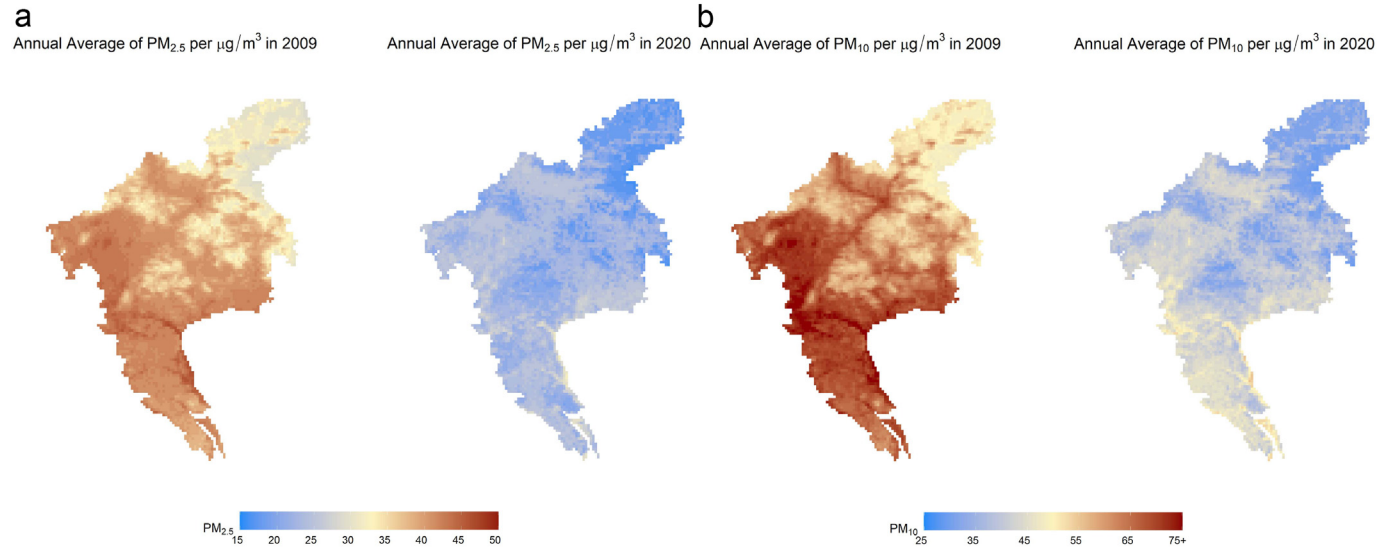

Fig. 1. Annual average particulate matter concentrations in the southern China for 2009 and 2020.
Note: (a) particulate matter with an aerodynamic diameter ≤ 2.5 μm; (b) particulate matter with an aerodynamic diameter ≤ 10 μm.

3.2. Association between PM exposure and COPD mortality

Fig. 2 shows that, after adjusting for potential confounders, the HR for COPD mortality was 1.046 (95 % confidence interval (CI): 1.034–1.057), 1.037 (95 % CI: 1.028–1.047), and 1.032 (95 % CI: 1.006–1.058) for per each 1-μg/m^3 increase in the concentrations of $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$, respectively. Similar results were found in the fully adjusted conventional regression models. The HR (95 % CI) of COPD mortality was 1.050 (1.040–1.061), 1.043 (1.033–1.053), and 1.030 (1.009–1.051) for per each 1-μg/m^3 increase in $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ concentrations, respectively, under the fully adjusted conventional Cox regression.

3.3. Stratified analyses

Results of the stratified analysis showed that participants aged over 65 years tended to be more vulnerable to the adverse effects of COPD (Table 2) due to $PM_{2.5}$ and PM_{10}. The effect estimates for $PM_{10–2.5}$ tended to be consistent across different subgroups. According to the significant signals, the effect estimates for $PM_{2.5}$ and PM_{10} with COPD mortality appeared to be greater among the older (≥65) participants (HR: 1.062, 95 % CI: 1.051–1.073 and HR: 1.054, 95 % CI: 1.045–1.064), compared with the younger (<65) ones (HR: 1.033, 95 % CI: 0.991–1.076 and HR: 1.047, 95 % CI: 1.007–1.088). Moreover, women tended to show stronger effects of $PM_{2.5}$ on COPD mortality (HR: 1.068, 95 % CI: 1.049–1.088) than men (HR: 1.033, 95 % CI: 1.019–1.047), with the *P* value being borderline significant.

Regarding the association of exercise with COPD mortality, participants with low frequency of exercise (HR: 1.069, 95 % CI: 1.046–1.093) tended to be more vulnerable to the impact of $PM_{2.5}$ than those doing moderate frequency of exercise (HR: 1.026, 95 % CI: 1.005–1.048). Similar trends were found for the PM_{10}-COPD mortality association. However, we did not observe significant differences in the associations between PM and COPD mortality across different groups of marital status, education level and smoking status.

The associations between long-term exposure to PM and COPD mortality among participants who experienced low PM_{10} concentration throughout the follow-up period are shown in Supplementary Fig. 5 (Supplementary Fig. 4, Supplementary Table 2). Each 1 μg/m^3 increase in $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ concentrations was associated with a higher risk of mortality from COPD (HR: 1.049, 95 % CI:1.033–1.065, HR: 1.055, 95 % CI: 1.040–1.071, HR: 1.075, 95 % CI: 1.032–1.120, respectively). The estimated risk of COPD mortality appeared to be stronger among participants who were generally exposed to lower levels of PM_{10} during the follow-up period than that among the general population.

3.4. Sensitivity analysis

Sensitivity analyses showed similar results when additionally adjusted for annual average temperature and relatively humidity or using different sizes of NDVI buffers (i.e., 250 m and 1000 m) (Supplementary Table 3). Results were also consistent across different datasets (i.e., complete data before and after imputation, Supplementary Table 4) and across different methods of developing IPW (i.e., LM, ML and GEE, Supplementary Table 5). Furthermore, our results were shown to be robust when accounting for the presence of unmeasured confounding bias using E values (Supplementary Table 6).

4. Discussion

In this large cohort study of 0.6 million participants in southern China, long-term exposure to ambient PM was associated with higher risks of COPD mortality using causal analysis methods. Furthermore, our results showed that the elderly were more vulnerable, whereas those with

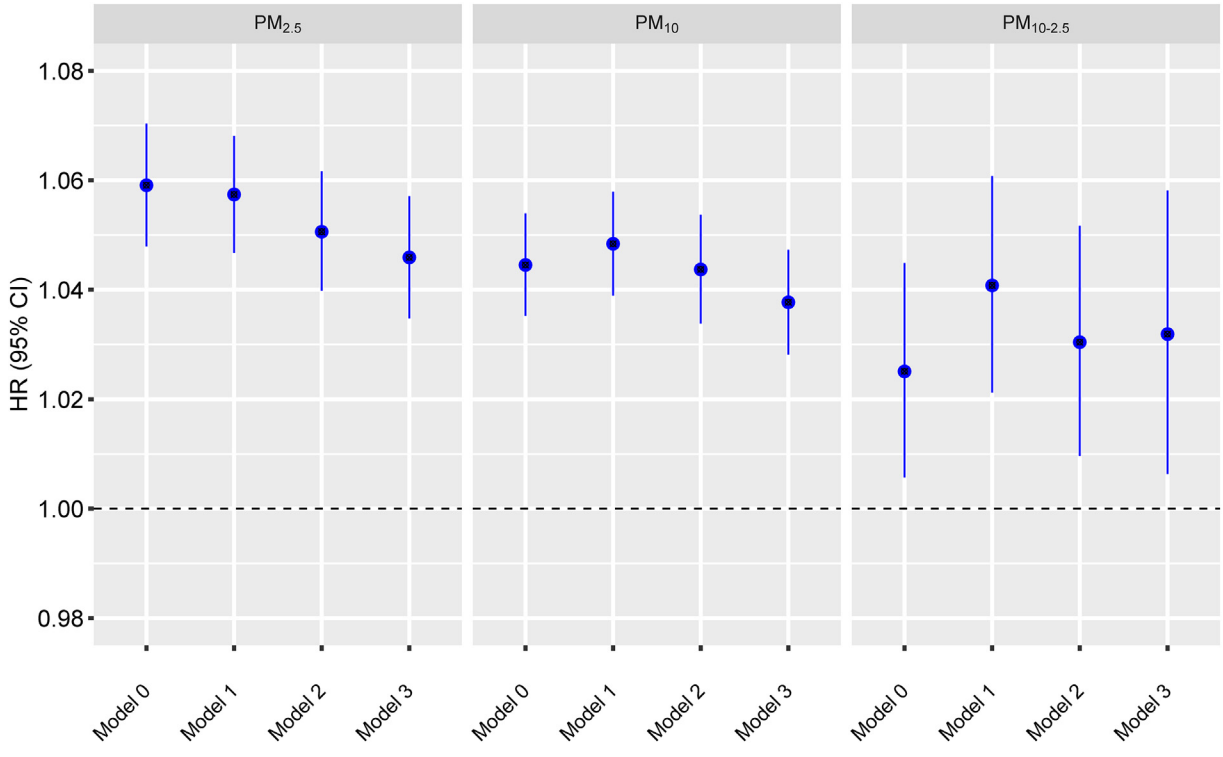

Fig. 2. Hazard ratio and 95 % confidence interval of COPD mortality risk associated with each 1-μg/m^3 in long-term exposure to ambient particulate matter under two different statistical approaches (traditional approach and causal inference approach).
Note: 1) Model 0 was a crude model under conventional Cox proportional hazards model. 2) Model 1: model 0 adjusted for age. 3) Model 2: additionally adjusted for sex, ethnicity, education, marital status, medical insurance, smoking status, exercise frequency, and normalized difference vegetation index (500 m) based on model 1. 4) Model 3: refitted with the marginal structural Cox proportional hazards model based on the same co-variates in the model 2.
Abbreviations: HR, hazard ratio; CI, confidence interval; PM, particulate matter; COPD, chronic obstructive pulmonary disease; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{10–2.5}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm.

Table 2
Hazard ratios and 95 % confidence interval of COPD mortality risk associated with each 1-μg/m^3 in long-term exposure to ambient particulate matter, stratified by demographic and lifestyle factors.

	$PM_{2.5}$		PM_{10}		$PM_{10-2.5}$	
Effect modifiers	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age						
<65 years	1.033 (0.991–1.076)	Ref.	1.047 (1.007–1.088)	Ref.	1.143 (1.037–1.260)	Ref.
≥65 years	1.062 (1.051–1.073)	0.005	1.054 (1.045–1.064)	0.01	1.042 (1.017–1.067)	0.60
Sex						
Men	1.033 (1.019–1.047)	Ref.	1.028 (1.017–1.040)	Ref.	1.040 (1.006–1.075)	Ref.
Women	1.068 (1.049–1.088)	0.08	1.052 (1.035–1.069)	0.33	1.014 (0.976–1.054)	0.35
Marital status						
Never married	1.010 (0.966–1.057)	Ref.	1.026 (0.985–1.069)	Ref.	1.168 (1.041–1.311)	Ref.
Married	1.048 (1.035–1.060)	0.81	1.040 (1.029–1.051)	0.58	1.038 (1.009–1.068)	0.31
Widowed/Divorce	1.055 (1.030–1.080)	0.74	1.040 (1.019–1.062)	0.29	1.003 (0.956–1.051)	0.06
Education						
Primary school and below	1.043 (1.026–1.061)	Ref.	1.034 (1.019–1.049)	Ref.	1.034 (0.993–1.077)	Ref.
Second and high school	1.035 (1.020–1.049)	0.30	1.023 (1.011–1.035)	0.19	1.004 (0.973–1.036)	0.35
College degree or above	1.093 (1.041–1.148)	0.40	1.079 (1.037–1.122)	0.50	1.016 (0.903–1.142)	0.76
Smoking status						
Never	1.047 (1.035–1.060)	Ref.	1.039 (1.028–1.050)	Ref.	1.041 (1.013–1.069)	Ref.
Ever	1.017 (0.975–1.061)	0.97	1.013 (0.979–1.049)	0.95	1.014 (0.913–1.126)	0.81
Current	1.057 (1.027–1.087)	0.15	1.048 (1.022–1.074)	0.16	1.027 (0.960–1.099)	0.69
Exercise frequency						
Very low	1.069 (1.046–1.093)	Ref.	1.061 (1.040–1.082)	Ref.	1.049 (0.995–1.105)	Ref.
Moderate[a]	1.026 (1.005–1.048)	0.01	1.021 (1.002–1.040)	0.02	1.023 (0.967–1.082)	0.46
High	1.049 (1.032–1.065)	0.39	1.039 (1.026–1.053)	0.33	1.024 (0.992–1.058)	0.36

Note: The effects were estimated under causal inference model with adjustment for age, sex, ethnicity, education, marital status, medical insurance, smoking status, exercise frequency and normalized difference vegetation index (500 m). All stratified estimates were adjusted for the remaining covariates.
Abbreviations: HR, hazard ratios CI, confidence interval; COPD, chronic obstructive pulmonary disease; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{10-2.5}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm.
[a] The group of low exercise frequency was combined into the group of moderate exercise frequency due to sample size limit in the stratified analysis.

moderate exercise were less vulnerable to PM related COPD mortality. We also found that participants who were generally exposed to lower PM_{10} levels tended to be at a greater risk of COPD mortality than general participants for the same incremental increase in PM exposures. The robustness of our findings was then confirmed with multiple sensitivity analyses. To the best of our knowledge, the current study is one of the largest cohort studies to date reporting the association between long-term ambient PM exposure and the risk of COPD mortality using causal analysis methods.

4.1. The effect of long-term PM exposure on COPD mortality

Our results showed higher risks of COPD mortality attributable to greater exposure to ambient PM concentrations. Previous studies on the associations between different size PM fractions and COPD mortality showed inconclusive results. For example, a recent meta-analysis suggested a significantly higher risk of COPD mortality associated with a greater $PM_{2.5}$ exposure, which is consistent with our finding of the adverse impact of long-term $PM_{2.5}$ exposure on COPD mortality (Chen and Hoek, 2020). However, non-significant association was found between PM_{10} exposure and COPD mortality in this meta-analysis. Of them, two studies conducted in China and England respectively, showed that elevated PM_{10} was associated with the risk of COPD mortality (Chen et al., 2017; Hansell et al., 2016), while the other three found non-significant association (Carey et al., 2013; Katanoda et al., 2011; Hart et al., 2011). The discrepancies might be due to diversity in methodologies (e.g., variation of sample size across different studies), PM compositions and concentrations, and the adjustment of confounding factors. Based on a distinct casual inference approach and a large population cohort, our findings add additional credible evidence to the literature.

The mechanisms underlying the detrimental effects of PM pollution on COPD mortality may be due to the inflammatory response and oxidative stress, as well as the disruption of the coagulation cascade, which may lead to decrements in lung function and airway hyperreactivity (Pompilio and Bonaventura, 2020; Schraufnagel et al., 2019). Furthermore, PM may also be involved in both DNA-damaging and inflammation-signaling pathways (e.g., genotoxicity and cell and tissue proliferation) (Knaapen et al., 2004). Notably, the biological pathways between PM pollution and COPD mortality might vary by particle size. Smaller particles are more likely to translocate into the circulatory system and tissues as they could enter the lung alveolar region more easily, while larger particles are often settled in the upper respiratory tract (Yin et al., 2020). It was consistent of and supported by our findings of the greater effect estimates for $PM_{2.5}$ compared with PM_{10}.

4.2. The effects by sociodemographic features

Moreover, our findings indicated that the elderly and women had a greater risk of COPD mortality from PM exposure than their counterparts. Our findings were supported by existing evidence (Hu et al., 2018; Yang et al., 2012; Gouveia and Fletcher, 2000). The increased susceptibility among the elderly may be due to the fact that these people usually are suffering from preexisting diseases and more advanced COPD, particularly among who continue to smoke. In terms of the gender disparity, a possible explanation for the increased vulnerability among women is that women usually have smaller airways and a greater airway reactivity (Yunginger et al., 1992). Thus, they tend to suffer from a stronger physiological response to air pollutants. Taken together, evidence from previous studies as well as the present one suggests that individuals, especially women and older people, may have more benefit from effective protective measures against ambient PM.

Additionally, our results indicated a lower risk of COPD mortality attributable to PM exposure among the individuals with moderate exercise compared with those who had very low exercise level. Our findings were consistent with a European study showing that physical activity might

counterbalance the detrimental effect of black carbon on lung function (Laeremans et al., 2018). Another cohort study also showed that physical activity might protect against the adverse vascular effects of air pollution in low pollution settings (Endes et al., 2017). Meanwhile, in the present study, a non-significant association of PM exposure with the risk of COPD mortality was found in those with high exercise frequency. Further studies are needed to validate whether the health benefits of higher levels of exercise outweigh the potential harmful effects due to exposure to air pollution during exercise.

4.3. A greater risk among low-exposure participants

An interesting finding is that the effects of PM_{10} and $PM_{10-2.5}$ exposure on COPD mortality were more pronounced in participants who generally were exposed to PM_{10} concentrations below the WHO interim target 1 of 70 μg/m^3 during the follow-up period than that in the general population. Consistent with our findings, one cohort study in the U.S. showed that the estimated HRs were larger for Medicare enrollees that were always exposed to $PM_{2.5}$ levels lower than 12 μg/m^3 than the entire group of Medicare enrollees (Wu et al., 2020). Another cohort study in the U.S. showed that the risk of death associated with an increase of 10 μg/m^3 in $PM_{2.5}$ was 1.136 (1.131–1.141) among participants with $PM_{2.5}$ exposures generally lower than 12 μg/m^3 which was greater than the estimate for the entire population which was 1.073 (1.071–1.075) (Di et al., 2017). This study was focused on multiple PM exposures and our finding of the higher risk among the low-PM_{10} exposure participants suggested that although lower PM concentration usually represents a smaller health impact, residents in areas with PM concentration below the current WHO target may have a greater vulnerability probably due to decreased adaptation. Therefore, residents in low PM areas should also be protected and more comprehensive preventive programs should be developed. However, more data are needed to confirm these findings.

4.4. Strengths and limitations

To the best of our knowledge, this study is one of the first that investigated the relationship between the long-term PM exposure and COPD mortality based on a large cohort of general Chinese population in one of the most PM polluted areas of the country. The evidence regarding the links between long-term exposure to PM and COPD mortality are limited and controversial. Therefore, this study helps to clarify the role of PM in affecting COPD mortality rates. The study covers participants with diverse social demographic backgrounds that increased the generalizability of our findings. The huge sample size ensured a sufficient statistical power to detect modest associations and comprehensively assess the vulnerability of different subgroups. In addition, using the state-of-the-art causal inference approaches, we reduce the residual confounding issues inherent with the traditional methods and provided strong evidence of the causal link between the long-term PM exposure and COPD mortality, which is of great importance for establishing long-term health based guidelines in reducing PM pollution.

Nevertheless, some potential limitations should be acknowledged. First, we used grid-level PM simulations where participants in the same community may be assigned the same value of PM concentration, which likely resulted in exposure misclassification. However, this misclassification error is likely a combination of Berkson and classical error, resulting in a bias toward the null and would underestimate the effects (Zhang et al., 2018). Second, similar to previous studies (Chen et al., 2017; Katanoda et al., 2011), although we included important individual confounders, we may have missed the confounding of spatial variability factors due to data limit. Although the established E-values indicated a good robustness of our results against the potential residual confounders, future studies considering spatial variability factors are still warranted. Third, our results might be affected by the missing data. However, we imputed the missing covariates by multiple imputation, conducted a sensitivity analysis and found their impact was subtle. Finally, our data were restricted to a single city of Guangzhou. Therefore, the individual exposure to PM may show small differences among the cohort. This difference may also lead to the underestimate of effects due to Berkson error (Zhang et al., 2018). Moreover, Guangzhou is the fourth largest city across China, with an area of >7000 km^2 and roughly 7 times that of Hong Kong (Wong et al., 2015) and 6 times that of Rome (Badaloni et al., 2017) where reliable results were still observed.

5. Conclusions

Our results support likely causal links between long-term PM exposure and COPD mortality among the Chinese population. The increase in the risk of COPD mortality seems to be more pronounced among participants with certain characteristics such as elderly, inactive participants, as well as those who generally were exposed to low PM levels. Therefore, more comprehensive preventive programs should be developed, with particular attention on protecting potentially vulnerable groups.

CRediT authorship contribution statement

Ying Wang: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Zhicheng Du:** Conceptualization, Methodology, Software, Writing - review & editing. **Yuqin Zhang:** Conceptualization, Methodology, Software, Writing - original draft. **Shirui Chen:** Methodology, Software, Writing - review & editing. **Shao Lin:** Methodology, Writing - review & editing. **Shao Lin:** Conceptualization, Writing - review & editing. **Philip K. Hopke:** Conceptualization, Writing - review & editing. **David Q. Rich:** Conceptualization, Writing - review & editing. **Kai Zhang:** Conceptualization, Writing - review & editing. **Xiaobo X. Romeiko:** Methodology, Validation, Writing - review & editing. **Xinlei Deng:** Conceptualization, Methodology, Software, Validation. **Yanji Qu:** Conceptualization, Methodology, Software, Validation. **Yu Liu:** Conceptualization, Validation, Formal analysis, Investigation, Data curation. **Ziqiang Lin:** Conceptualization, Writing - review & editing. **Shuming Zhu:** Conceptualization, Software, Data curation. **Wangjian Zhang:** Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Funding acquisition, Resources, Supervision, Project administration. **Yuantao Hao:** Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Funding acquisition, Resources, Supervision, Project administration. All authors read and approved the final manuscript.

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Data availability statement

Data are available upon reasonable request.

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.

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Appendix A. Supplementary data

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