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Estimating causal links of long-term exposure to particulate matters with all-cause mortality in South China

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ABSTRACT

Background: The association between long-term particulate matter (PM) exposure and all-cause mortality has been well-documented. However, evidence is still limited from high-exposed cohorts, especially for PM_1 which is smaller while more toxic than other commonly investigated particles. We aimed to examine the potential casual links of long-term PMs exposure with all-cause mortality in high-exposed areas.

Methods: A total of 580,757 participants in southern China were enrolled during 2009–2015 and followed up to 2020. The annual average concentration of PM_1, $PM_{2.5}$, and PM_{10} at 1 km^2 spatial resolution was assessed for each residential address through validated spatiotemporal models. We used marginal structural Cox models to estimate the PM-mortality associations which were further stratified by sociodemographic, lifestyle factors and general exposure levels.

Results: 37,578 deaths were totally identified during averagely 8.0 years of follow-up. Increased exposure to all 3 PM size fractions were significantly associated with increased risk of all-cause mortality, with hazard ratios (HRs) of 1.042 (95 % confidence interval (CI): 1.037–1.046), 1.031 (95 % CI: 1.028–1.033), and 1.029 (95 % CI: 1.027–1.031) per 1 $\mu g/m^3$ increase in PM_1, $PM_{2.5}$, and PM_{10} concentrations, respectively. We observed greater effect estimates among the elderly (age $\geq$ 65 years), unmarried participants, and those with low education attainment. Additionally, the effect of PM_1, $PM_{2.5}$, and PM_{10} tend to be higher in the low-exposure group than in the general population.

Conclusions: We provided comprehensive evidence for the potential causal links between long-term PM exposure and all-cause mortality, and suggested stronger links for PM_1 compared to large particles and among certain vulnerable subgroups.

1. Introduction

Air pollution is well acknowledged to be a major public health threat (Schraufnagel et al., 2019), of which particulate matter (PM) impose the most serious health hazard, contributing to approximately 4.14 million deaths worldwide in 2019 (GBD 2019 Risk Factors Collaborators, 2020). In China, PM pollution is the fourth leading risk factor for mortality in 2017, which is estimated to be responsible for 0.85 million deaths nationwide (GBD 2017 Risk Factor Collaborators, 2018; Yin et al., 2020; Zhou et al., 2019).

Previous studies assessed the long-term effects of PM exposure on all-cause mortality. For example, a recent *meta*-analysis suggested each 10-

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μg/m^3 increase in $PM_{2.5}$ (PM with aerodynamic diameters ≤ 2.5 μm) was associated with 8 % higher risk of mortality (Chen and Hoek, 2020). However, existing studies were mainly from western countries where the PM levels and composition, as well as the sociodemographic was substantially different from those in high-polluted areas such as China. The evidence on the long-term impact of PM exposure on mortality was still limited in China with only several cohort studies being identified, which either focused on selected populations (e.g. men (Zhou et al., 2014), elderly (Li et al., 2018; Wong et al., 2015; Yang et al., 2018), tuberculosis patients (Peng et al., 2017)) or reported small number of outcome events (e.g. 256 (2.57 %) (Zhang et al., 2011) or 1,353 (3.46 %) (Chen et al., 2016)). Moreover, these limited studies generally focused on the impact of $PM_{2.5}$ or PM_{10} (PM with aerodynamic diameters ≤ 10 μm), leaving significant gaps in our understanding of the impact of smaller particles. PM_1 (PM with aerodynamic diameters ≤ 1 μm) is a major component of $PM_{2.5}$ but is considered to be more toxic due to the smaller size and higher surface area, allowing particles to easily penetrate deep into the lungs, metastasize to essentially all organs, and rapidly enter blood vessels and cells (Chen et al., 2018; Valavanidis et al., 2008). However, evidence on the long-term effect of PM_1 exposure on mortality in China is even more limited.

Last but not least, most existing evidence was based on traditional association analysis. Effect estimates from traditional approaches may be biased due to unmeasured confounding factors (Bind, 2019). The recently-developed causal inference methods were considered to be able to address this issue by simulating the randomized controlled trials and making exposures independent from other predictors of outcome, thus, providing causal clue based on the observational data (Wang et al., 2016; Wu et al., 2020). For example, a study in the U.S. using a robust causal model with inverse probability weights (IPWs) showed that a decrease in $PM_{2.5}$ by 10-μg/m^3 led to a 6–7 % lower risk of mortality (Wu et al., 2020). Another study in the U.S. using IPWs reported that each 10-μg/m^3 increase in $PM_{2.5}$ concentrations could increase 11.7 % risk of mortality (Higbee et al., 2020). With causal inference methods, effect estimates are more reliable and are considered to represent the risk that could be specifically attributed to PM exposure. However, such evidence is still limited among existing studies.

To address these knowledge gaps, our study aimed to quantify the causal links between long-term PM (PM_1, $PM_{2.5}$, and PM_{10}) exposure and all-cause mortality using a causal inference approach, based on a large general population cohort of 0.6 million participants in South China. We also identified the potential modification effect of demographic characteristics and lifestyle factors.

2. Materials and methods

2.1. Study design and population

Our analysis was based on data collected by the Major Projects of Science Research for the 11th (2006–2010) and 12th (2012–2017) five-year plans of China, a prospective study of over 5 million participants (Ruan et al., 2019). Based on the accessibility of outcome data, we conducted the present study in the Guangzhou cohort which covered 35 communities randomly selected based on sociodemographic characteristics. Totally, 654,115 participants were recruited through a thorough survey of those selected communities between January 2009 and December 2015.The study was approved by the institutional review board (IRB) at Sun Yat-sen University and all participants gave written, informed consent before participation. Of the 654,115 participants at baseline, 72,330 under 18 years old and 12,326 lost in follow-up with unknown vital status were excluded, leaving 580,757 participants (305,081 women and 275,676 men) aged 61.21 ± 6.85 years (mean ± standard deviation (SD)) in the present analysis. Information on the death obtained from the Death Registry of the Guangzhou Center for Disease Control and Prevention. The outcome of this study was the all-cause mortality as well as the time from the enrollment to the date of death or the end of follow-up (December 31, 2020).

Beefily, baseline information was collected using face-to-face interview by well-trained nurses. Information on demographic characteristics and lifestyle factors was collected by a computer-based questionnaire, and physical examinations were done following a standard protocol. Demographic characteristics and lifestyle factors assessed in the present study included sex, age, ethnicity, marital status, education, medical insurance, smoking, drinking, exercise frequency, and body mass index (BMI).

2.2. Assessment of PM and relevant environmental exposures

Annual concentrations of PM at 1 km^2 spatial resolution were obtained from the ChinaHighAirPollutants (CHAP) dataset. The concentrations were estimated by validated spatiotemporal models. These models showed a high predictive ability with R^2 values of 77 %, 92 %, and 90 % and root mean square errors of 14.6 μg /m^3, 10.76 μg /m^3, and 21.12 μg /m^3 for the daily estimations of PM_1, $PM_{2.5}$, and PM_{10}, respectively. The details of modeling processes have been reported in previous studies (Wei et al., 2019a, 2019b, 2020, 2021a, 2021b). Annual average concentrations of PM were assigned to each participant according to the corresponding residential address, as the primary exposure in this study.

In addition, we considered greenness as a potential confounder (Twohig-Bennett and Jones, 2018). Normalized difference vegetation index (NDVI), an indicator of individual greenness exposure level, was downloaded for the period of 2009–2020 from LPDAAC (Land Processing Distributed Active Archive Center) (Huete et al., 2002). The annual average exposure of NDVI within the radial buffer (500 m) surrounding the residential address were assessed for each participant.

2.3. Statistical analysis

We used marginal structural models to assess the risk of mortality with each 1 μg/m^3 increase in PM (PM_1, $PM_{2.5}$, and PM_{10}) concentrations. The method is based on IPWs followed by time-varying Cox proportional hazards models to addressed the temporal variation in PMs exposure, as descried previously (Wu et al., 2020).The basic idea of IPW was to create a pseudo population by mimicking a randomized controlled trial, in which possible confounding effects were effectively balanced (Cole and Hernan, 2008). In this framework, the generalized propensity scores (GPS) were first computed by regressing the exposure against the potential confounders, followed by the development of the stabilized IPW of the exposure based on the inverse of GPS to weigh the observations (Robins et al., 2000). In addition, we considered three weighting methods based on a linear model (LM), a generalized estimating equation (GEE) or a gradient boosting machine learning (ML), respectively (Chen and Guestrin, 2016). Although the percent of IPW exceeding 10 was < 0.01 %, to improve covariate balance, we trimmed those large weights to 10 as commonly used in previous studies (Austin, 2011; Wu et al., 2020). We checked the covariate balance on the weighted pseudo-population through average absolute correlation (AC), with values < 0.1 indicating a good balance of confounders.

Considering the time-dependent exposure variables, including annual PM concentrations and NDVI, we specifically fitted marginal structural Cox models with time-varying covariates. Potential confounders were identified by a directed acyclic graph (Fig. S1) (Tennant et al., 2021). We used the model with GEE weighting method as the final model according to the optimal balance of confounders achieved with this method (Fig. S2).

The study utilized a sequential modeling strategy. Model 0 was the crude model without any adjustment. Model 1 adjusted for age at baseline under the Cox proportional hazard model, and model 2 additionally adjusted for sex, ethnicity, education, marital status, medical insurance, smoking, exercise frequency and NDVI (500 m). Model 3: model 2 refitted with the causal inference approach. Model 3 was the

primary model for the current study.

Furthermore, we conducted stratification analysis among predefined subgroups, including demographic variables and lifestyle factors. The interactions were assessed by including the product term of PM and stratification factors in the main model. The *P*-values of the product terms were used to identify the potential interactions. Furthermore, previous studies also suggested that, within the same area, the group generally exposed to a lower exposure tended to have a greater vulnerability, probably due to less acclimation (Danesh et al., 2021; Di et al., 2017; Wu et al., 2020). To assess the potential influence of the long-term low-concentration exposure on human vulnerability in the study areas, we further restricted the analysis to participants with annual PM (PM_1, $PM_{2.5}$ and PM_{10}) concentrations generally below the third quartile of the entire cohort throughout the study period. We imputed missing data for confounding variables using the multiple imputations by chained equations (MICE), which was an established method for missing imputation and widely used in literature (van Buuren, 2007; White et al., 2011). In this study, the method was implemented via the mice package in R (van Buuren and Groothuis-Oudshoorn, 2011).

The sensitivity analysis was conducted to verify the robustness of our estimates. 1)To evaluate the influence of missing data imputation, the analysis was also done using the complete dataset before imputation. 2) We compared the main results estimated using three different marginal structural Cox models. 3) We developed additional marginal structural Cox models with NDVI averaged across buffers of different sizes (i.e., 250 m and 1000 m). 4) We further calculated the E-value to evaluate the robustness of our results against potential unmeasured confounding, with a larger E-value representing that our findings were less likely to be overridden by unmeasured confounding (VanderWeele and Ding, 2017). All statistical analyses were conducted using R software (version 4.1.3).

3. Results

3.1. Participant characteristics

During an average of 8.0 years (with 4,753,965 person-years) of follow-up, 37,578 deaths occurred. Table 1 shows that participants who died tended to be older (72.39 years vs 46.66 years), and more likely to be men (54.51 % vs 46.98 %), Han people (99.31 % vs 98.03 %), widowed (13.65 % vs 2.23 %), current smokers (13.99 % vs 11.67 %), ever alcohol users (12.24 % vs 11.22 %) than the control group (all $P < 0.001$). They also had lower education (29.35 % vs 10.35 %), higher frequency of exercise (23.37 % vs 19.85 %), higher BMI (22.26 kg/m^2 vs 22.05 kg/m^2), and lower exposed to NDVI (500 m) (0.210 vs 0.214) (all $P < 0.001$). Annul average concentrations of PM_1, $PM_{2.5}$ and PM_{10} declined from 2009 to 2020 (Table 2). The various sizes of PMs were strongly correlated with each other, with the correlation coefficient all greater than 0.9. In addition, the descriptive statistics for the complete dataset were shown in Table S1.

Table 1
Characteristics for the study participants from 2009 to 2015*.

Characteristic	Overall	All-cause deaths	Control group	*P*-value
Number of participants	580,757	37,578	543,179	
Demographics				
Age, mean ± SD, years	48.33 ± 17.55	72.39 ± 13.27	46.66 ± 16.56	<0.001
Sex, (men %)	275,676 (47.47)	20,484 (54.51)	255,192 (46.98)	<0.001
Ethnic, (minority %)	10,953 (1.89)	258 (0.69)	10,695 (1.97)	<0.001
Education (%)				<0.001
Illiterate or semiliterate	6603 (1.14)	1870 (4.98)	4733 (0.87)	
Primary school	67,247 (11.58)	11,030 (29.35)	56,217 (10.35)	
Second school	131,394 (22.62)	9639 (25.65)	121,755 (22.42)	
High school	266,467 (45.88)	12,904 (34.34)	253,563 (46.68)	
College or above	109,046 (18.78)	2135 (5.68)	106,911 (19.68)	
Marital status (%)				<0.001
Never married	108,424 (18.67)	3570 (6.84)	105,854 (19.49)	
Married	448,138 (77.16)	29,310 (78.00)	418,828 (77.11)	
Widowed	17,262 (2.97)	5128 (13.65)	12,134 (2.23)	
Divorce	6933 (1.20)	570 (1.52)	6363 (1.17)	
Medical insurance (%)				<0.001
Medical insurance for urban workers	354,396 (61.02)	23,370 (62.19)	331,026 (60.94)	
Medical insurance for urban residents	164,213 (28.28)	11,888 (31.64)	152,325 (28.04)	
The new rural cooperative medical insurance	6439 (1.11)	100 (0.27)	6399 (1.17)	
Others	55,709 (9.59)	2220 (5.90)	53,489 (9.85)	
Lifestyle behaviors				
Smoking status (%)				<0.001
Never	505,385 (87.02)	31,039 (82.60)	474,346 (87.33)	
Ever	6716 (1.16)	1282 (3.41)	5434 (1.00)	
Current	68,656 (11.82)	5257 (13.99)	63,399 (11.67)	
Alcohol consumption (%)				<0.001
Never	515,205 (88.71)	32979 (87.76)	482,226 (88.78)	
Ever	65,552 (11.29)	4599 (12.24)	60,953 (11.22)	
Exercise frequency (%)				<0.001
Very low	322,225 (55.48)	20,011 (53.25)	302,214 (55.64)	
Low	73,103 (12.59)	4926 (13.11)	68,177 (12.55)	
Moderate	68,835 (11.85)	3859 (10.27)	64,976 (11.96)	
High	116,594 (20.08)	8782 (23.37)	107,812 (19.85)	
BMI, mean ± SD, kg/m^2	22.07 ± 2.45	22.26 ± 2.66	22.05 ± 2.44	<0.001
NDVI (500), mean ± SD	0.214 ± 0.04	0.210 ± 0.04	0.214 ± 0.04	<0.001

* Data are presented as number (percentage) of study participants unless otherwise indicated.
Abbreviations: SD, stand deviation; BMI, body mass index; NDVI, normalized difference vegetation index;

3.2. All-cause mortality and PM exposure

Fig. 1 shows that, after fully adjusting for confounders, for each 1 μg/m^3 increase in PM_1, $PM_{2.5}$, and PM_{10} concentrations, the HRs of all-cause mortality were 1.042 (95 % CI: 1.037–1.046), 1.031 (95 % CI: 1.028–1.033), and 1.029 (95 % CI: 1.027–1.031) in the casual inference model (i.e., model 3), respectively. Based on the traditional model (i.e., model 2), the effect estimates were slightly higher, with 1.059 (95 % CI: 1.055–1.064), and 1.030 (95 % CI: 1.028–1.032) per 1-ug/m^3 increase in PM_1 and PM_{10} concentrations, respectively.

3.3. Subgroup analyses

Results of the modification analysis showed that participants over 65 years old tended to be more vulnerable to the impact of PM_1 on mortality (HR: 1.071, 95 % CI: 1.066–1.076), compared to the younger ones (HR: 1.044, 95 % CI: 1.035–1.052) (Table 3). Similar trends were observed for $PM_{2.5}$ and PM_{10}, although the modification effects were not statistically significant. The association was greater among participants

Table 2
Estimated exposure concentrations of PM_1, $PM_{2.5}$, and PM_{10} (μg/m^3) from 2009 to 2020.

	PM_1	$PM_{2.5}$	PM_{10}
	Mean ± SD	Mean ± SD	Mean ± SD
2009	25.33 ± 1.11	50.09 ± 0.27	77.75 ± 0.68
2010	24.26 ± 1.16	47.26 ± 0.31	74.02 ± 0.75
2011	24.73 ± 1.29	49.55 ± 0.24	77.05 ± 0.66
2012	24.27 ± 1.18	47.75 ± 0.29	73.17 ± 0.66
2013	26.97 ± 1.25	53.36 ± 1.04	78.27 ± 1.36
2014	24.93 ± 1.42	49.48 ± 1.18	71.11 ± 1.11
2015	20.31 ± 1.21	40.45 ± 0.78	63.34 ± 1.39
2016	18.65 ± 1.11	36.24 ± 0.46	58.43 ± 1.60
2017	18.43 ± 1.39	36.17 ± 1.07	60.44 ± 2.65
2018	16.84 ± 1.07	35.26 ± 0.71	56.66 ± 1.96
2019	15.89 ± 1.18	30.97 ± 0.65	54.49 ± 1.11
2020	12.41 ± 1.03	23.97 ± 0.76	43.30 ± 0.92

Abbreviations: PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; SD, stand deviation.

with primary or lower education level [PM_1 (HR: 1.045, 95 % CI: 1.038–1.053); $PM_{2.5}$ (HR: 1.038, 95 % CI: 1.034–1.042); PM_{10} (HR: 1.037, 95 % CI: 1.034–1.041), respectively] than those with second and high education level [PM_1 (HR:1.010, 95 % CI: 1.005–1.055); $PM_{2.5}$ (HR:1.022, 95 % CI: 1.019–1.025); PM_{10} (HR:1.018, 95 % CI: 1.016–1.021), respectively]. Similar disparity was observed among participants with college or above education level, although the modifications were not statistically significant.

In addition, we found that the risk of mortality with PM_1 was greater among participants who never married (HR: 1.054, 95 % CI: 1.036–1.073) compared to the married (HR: 1.044, 95 % CI: 1.039–1.049) and widowed and divorce (HR: 1.053, 95 % CI: 1.042–1.064) groups. Similar trends were observed in the associations of $PM_{2.5}$ and PM_{10} exposure with mortality. There were also significant modification effects observed for the smoking status, with higher effect estimates for never smokers than ever or current smokers. We also observed significant differences in PM–mortality associations among participants with different exercise frequency. The effect of PM on mortality tended to be lower in participants with low exercise frequency than those with moderate or high exercise frequency.

We further examined mortality following PM exposure among individuals who always exposed to low pollutant concentration throughout the follow-up period (Fig.S3). The effect estimates for the low-exposure group generally were larger than their counterparts based on the entire cohort.

3.4. Sensitivity analyses

Table S3 shows that the estimated HRs of morality for PM exposures were similar when the analytical sample was restricted to the complete dataset. The results were also consistent across three different marginal structural Cox models using IPWs with a LM, ML and GEE, respectively (Table S3). The effect of PM also remained unchanged across different definitions of NDVI exposures (i.e., using 250 m and or 1 km buffers) (Table S4). The E value suggested that our estimates would be robust if no unmeasured confounders have a relative risk association greater than 1.2 with both the exposure and outcome (Table S5).

4. Discussion

In this large cohort study of 580,757 participants in South China, we found that long-term PM exposure were associated with an increased risk of all-cause mortality, implicating PM exposure as an important

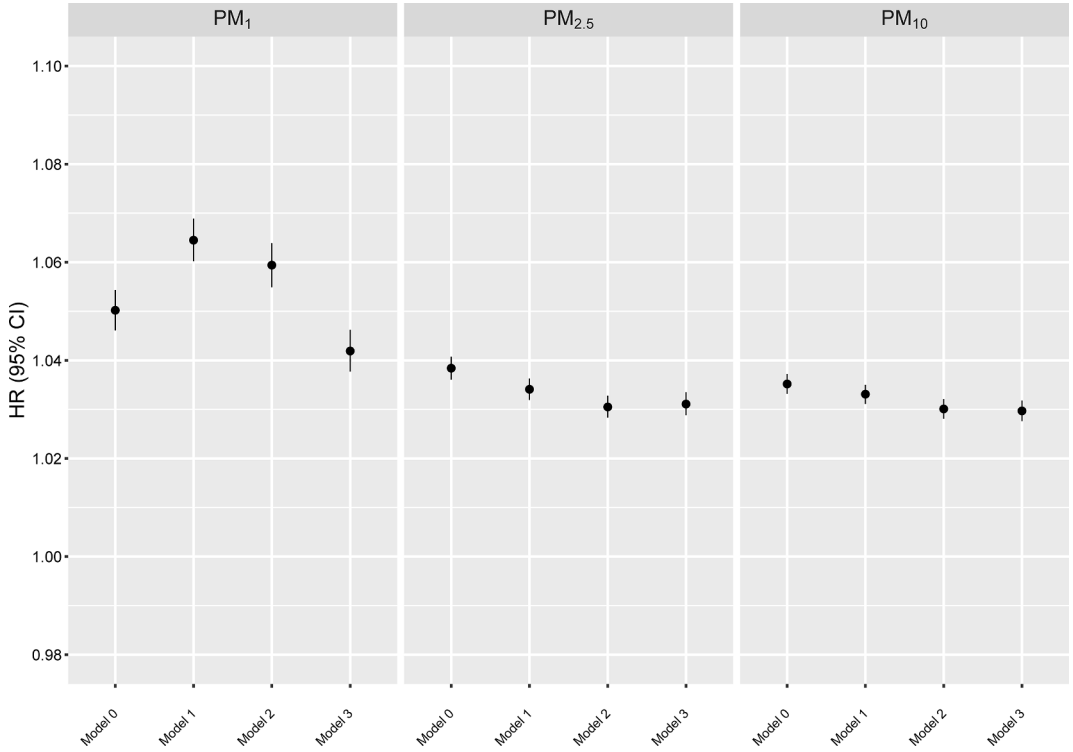

Fig. 1. Hazard ratios and 95 % confidence interval of mortality associated with 1 μg/m^3 increase in particulate matter concentrations, under two different statistical approaches (traditional approach and causal inference approach). Note: 1) Model 0 was a crude model under conventional Cox proportional 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_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm;

Table 3
Hazard ratios and 95 % confidence interval of mortality associated with 1 μg/m^3 increase in particulate matter concentrations, stratified by demographic and lifestyle factors.

	PM_1		$PM_{2.5}$		PM_{10}	
Effect modifiers	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age						
<65 years	1.044 (1.035–1.052)	Ref.	1.033 (1.028–1.038)	Ref.	1.031 (1.027–1.035)	Ref.
≥65 years	1.071 (1.066–1.076)	<0.001	1.039 (1.036–1.041)	0.14	1.038 (1.036–1.040)	0.10
Sex						
Men	1.030 (1.024–1.035)	Ref.	1.025 (1.022–1.028)	Ref.	1.024 (1.022–1.027)	Ref.
Women	1.054 (1.048–1.061)	0.10	1.038 (1.034–1.041)	0.62	1.035 (1.032–1.038)	0.34
Education						
Primary school and below	1.045 (1.038–1.053)	Ref.	1.038 (1.034–1.042)	Ref.	1.037 (1.034–1.041)	Ref.
Second and high school	1.010 (1.005–1.015)	0.002	1.022 (1.019–1.025)	<0.001	1.018 (1.016–1.021)	<0.001
College degree or above	1.032 (1.015–1.050)	0.62	1.025 (1.015–1.034)	0.60	1.020 (1.012–1.028)	0.75
Marital status						
Never married	1.054 (1.036–1.073)	Ref.	1.039 (1.029–1.050)	Ref.	1.036 (1.027–1.046)	Ref.
Married	1.044 (1.039–1.049)	0.008	1.031 (1.028–1.033)	0.02	1.029 (1.027–1.031)	0.02
Widowed/ Divorce	1.053 (1.042–1.064)	<0.001	1.033 (1.028–1.039)	<0.001	1.033 (1.028–1.038)	<0.001
Smoking status						
Never	1.046 (1.041–1.050)	Ref.	1.035 (1.033–1.038)	Ref.	1.033 (1.030–1.035)	Ref.
Ever	1.038 (1.015–1.061)	0.11	1.015 (1.004–1.026)	0.02	1.017 (1.007–1.027)	0.03
Current	1.011(1.000–1.023)	<0.001	1.007 (1.002–1.013)	<0.001	1.010 (1.006–1.015)	<0.001
Exercise frequency						
Very low	1.039 (1.030–1.047)	Ref.	1.021 (1.017–1.026)	Ref.	1.023 (1.020–1.027)	Ref.
Moderate*	1.040 (1.031–1.049)	<0.001	1.036 (1.031–1.040)	<0.001	1.033 (1.028–1.037)	<0.001
High	1.047 (1.041–1.053)	<0.001	1.037 (1.034–1.041)	<0.001	1.034 (1.031–1.037)	<0.001

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.
* The group of low exercise frequency was combined into the group of moderate exercise frequency due to sample size limit in the stratified analysis.
Abbreviations: HR, hazard ratio; CI, confidence interval; PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm.

environmental hazard which may be targeted to effectively reduce the mortality burden. Furthermore, our results showed that the elderly and those with low education attainment were more vulnerable to PM-mortality risk. Moreover, we observed higher risks related to PM in participants exposed to long-term low PM concentrations compared with the entire cohort. Our study provides most robust and interpretable evidence to date on the causal links between long term PM exposure and mortality in China with multiple sensitivity analyses.

Our study provided evidence for the potential causal links between long-term PM (PM_1, $PM_{2.5}$, and PM_{10}) exposure and mortality. The results showed positive association of $PM_{2.5}$ and PM_{10} on mortality, consistent with previous findings (Chen and Hoek, 2020). Nevertheless, limited studies focused on the effect of PM_1. Although limited evidence on the association between long-term PM_1 exposure and all-cause mortality was available for comparison, our estimates were within the range of those reported for other outcomes in previous cross-sectional studies. For example, a study in rural Chinese population found that the odds ratio for hypertension was 1.043 (95 % CI: 1.033, 1.053) per each 1 μg/m^3 increase in long-term PM_1 exposure (Li et al., 2019). Another cross-sectional study in China showed that the risk of suicidal ideation was also associated with the long-term PM_1 exposure, with an excess risk of 8 % (95 % CI: 1 %-15 %) per 1 μg/m^3 increase in PM_1 (Luo et al., 2020). Our study is among the first to add potential casual evidence to the current knowledge on the PM_1-mortality association in highly polluted cities, which should be fully considered in policy making to protect public health from air pollution.

Our estimates of the mortality risk following $PM_{2.5}$ and PM_{10} exposure tended to be greater than those reported in previous studies. The disparity in the results could be partly due to the different characteristics of the air pollutants. Our study area is located in the center of the Pearl River Delta region, where a large number of manufacturing and chemical industries and heavy traffics were producing pollutants with higher toxicity. For example, a nationwide study in China showed that the mortality risk associated with PM exposures in Guangzhou approximately 2–3 times greater than the estimates in other cities, suggesting a greater toxicity of the particles in this area (Chen et al., 2012). In addition, Guangzhou has a suitable climate throughout the year and people generally have more outdoor activities, and subsequently, more exposure to ambient air pollution.

The potential biological mechanisms underlying the adverse impact of PM generally include increased inflammation and oxidative stress and disruption of the coagulation cascade (Anderson et al., 2012). More importantly, we found a greater impact of PM_1 in comparison with those large particles, which was also consistent with the existing evidence (Chen et al., 2017a,b). PM_1 particles are mainly from automobile exhaust and direct emissions during the combustion process (Meng et al., 2013; Jaiprakash et al., 2017). PM_1 was considered to be even more toxic than large particles due to its smaller diameter, which allows them to quickly enter the circulation system, and its larger active surface area, which enable them to adsorb more toxic substances (e.g., heavy metals) and produce stronger biological effects (Izhar et al., 2016). Previous studies also suggested that the smaller size of the inhaled particles was associated with more gene alterations, resulting in a higher risk of airway inflammation (Frydas et al., 2020). These findings may have implications for policy makers to evaluate the long-term adverse impact of air pollution, develop intervention policies, and can be the basis for future studies evaluating the cost-efficiency of PM-reducing policies.

Moreover, our findings showed that the elderly and participants with low education attainment may suffer from greater effects of PM than their counterparts. The increased susceptibility among the elderly may be due to the fact that these people usually are suffering from preexisting diseases and longer exposure to air pollution compared to younger people (Gouveia and Fletcher, 2000). The greater risk of mortality among participants with low education attainment was also observed previously, a time series study in China showed a higher risk of mortality attributable to PM_{10} exposure among the less-educated participants (Chen et al., 2012). The higher vulnerability among the participants with low education attainment may be resulted from the disparity in factors related to their social disadvantages, such as environmental

health inequalities, less affordable health care resources, etc. (Yusuf et al., 2017). Taken together, evidence from previous studies as well as ours suggested that the elderly and less-educated participants, should take more protective measures against ambient PM.

Furthermore, participants who were unmarried, never smoking, or those with moderate or high exercise frequency had a greater risk of mortality from PM exposure than their counterparts. Previous studies reported the complex role of marital status on the health effects of PM. A case-crossover study in Korean showed a larger association between nitrogen dioxide and suicide mortality among the married participants, whereas a higher association between ozone and suicide mortality among unmarried participants (Lee et al., 2018). Previous studies on the modification effects of smoking and physical activity on the PM-health association did not come to consistent conclusions. Consistent with our study, a cohort study of American Cancer Society showed that never smokers had a higher risk of mortality from lung cancer from $PM_{2.5}$ exposure than ever or current smokers (Pope et al., 2002). There is some evidence that long-term air pollution exposure may reduce health benefits from physical activity, which supports our results (Tainio et al., 2021). Further studies are needed to illustrate the underlying mechanisms.

The current study highlighted that the effects of PM exposure on mortality were more pronounced among the low-exposure group than the entire cohort. Consistent with our findings, a cohort study from the Southeast USA reported a higher risk of hospital admissions with respiratory disease among the Medicare recipients with lower $PM_{2.5}$ exposure levels ($PM_{2.5} \leq 12$ μg/m^3) than the entire group (Danesh et al., 2019). Another cohort study among the elderly in the U.S. showed that the risk of death associated with an increase of 10-μg/m^3 in $PM_{2.5}$ was 1.37 (95 %CI: 1.34–1.40) among the low-exposure group ($PM_{2.5} \leq 12$ μg/m^3), which was larger than the entire population (1.23, 95 %CI: 1.18–1.28) (Wu et al., 2020). The higher vulnerability among the low-exposure group may be due to decreased adaptation. The findings showed that the health-benefit-*per*-unit decrease in the concentration of PM is larger for participants with low PM_{10} exposure levels than those with high PM exposure.

This study furthers the use of causal inference models in examining associations between long-term PM exposure and mortality in highly polluted areas. Our results showed that the HRs estimated by the casual inference models were smaller than those from the traditional Cox models, though the difference was not statistically significant, which is in line with some previous studies (Higbee et al., 2020; Wu et al., 2020). For example, a cohort study using data from the National Health Interview Survey, found that the estimated HR from the IPW model was lower than that from the Cox model by approximately 5 % for all-cause mortality (Higbee et al., 2020). A unique advantage of causal inference models is that they provide a "marginal effect" of moving the entire population from high exposed conditions to low exposed conditions, i.e., the average effect at the population level. In contrast, traditional Cox models usually estimate a "conditional effect", i.e., the effect on the outcome following a certain change in exposure with the values of all the other covariates kept constant (Dominici and Zigler, 2017; Janes et al., 2010). Since individuals generally have different confounders, the conditional effect is more likely to represent the average effect at the individual level. In comparison, "marginal effect" is of a greater interest in population studies (Mansournia and Greenland, 2015). In this study, the use of the casual inference models provides a reasonable estimate for the effects of PM on mortality.

Our results contribute to the potential causal evidence between the long-term ambient PM exposure and all-cause mortality. This is the first study that investigated the long-term adverse effect of PM_1 exposure on mortality in high polluted cities. The study took the advantages of a large sample size providing sufficient statistical power to detect the casual effects of PM exposure on mortality (partly reflected in the narrow CI) and ensuring the generalizability of our results. Furthermore, the previous studies may suffer from bias inherent with traditional association assessments, this study minimized these issues by using a casual inference approach that simulates the randomized controlled trial, making exposure independent of other predictors of health outcomes and yielding more reliable effect estimates.

Some limitations should also be noted. First, the causal inference models were relied on the assumption of no unmeasured confounders which is actually hard to be ruled out. Some potential confounders such as socioeconomic measures, and neighborhood measures other than NDVI were not included due to data limit. However, we have included a set of important confounders as suggested by previous studies (Chen et al., 2017a,b; Katanoda et al., 2011), which may minimize this issue. For example, the education level and the type of medical insurance in our model may be the proxy of the personal socioeconomic status such as income and access to health care. Our study followed a standard framework of causal inference based on the observational data, and the E-value (i.e., E = 1.2) was within the range (e.g., 1.02 to 1.30) of those reported in previous studies (Danesh et al., 2021; Wu et al., 2020; Zheng et al., 2021). Second, since PM exposure was modeled, exposure misclassification may occur when assigning the annual averaged PM to individuals due to unavailability of accurate personal exposure measurements. However, the simulation model showed satisfactory performance, thus, our main conclusions were unlikely to be changed. Third, the missing data might affect the estimated effect. However, we conducted several sensitivity analyses and found that the HRs were similar between the complete and the entire dataset.

5. Conclusion

In conclusion, our study provided comprehensive evidence for the potential causal links between long-term PM exposure and all-cause mortality, and suggested stronger links for PM_1 compared to large particles and among certain vulnerable subgroups.

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Data availability statement

Data are available upon reasonable request. The CHAP data set is available at https://weijing-rs.github.io/product.html.

CRediT authorship contribution statement

Ying Wang: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Wei Jing:** Conceptualization, Methodology, Software, Validation. **Yuqin Zhang:** Conceptualization, Methodology, Software, Writing – original draft. **Tong Guo:** Formal analysis, Investigation, Data curation. **Shirui Chen:** Methodology, Software, Data curation. **Wenjing Wu:** Formal analysis, Investigation, Data curation. **Shimin Chen:** Formal analysis, Investigation, Data curation. **Ziqiang Li:** Conceptualization, Writing – review & editing. **Yanji Qu:** Conceptualization, Methodology, Software, Validation. **Jianpeng Xiao:** Conceptualization, Writing – review & editing. **Xinlei Deng:** Conceptualization, Methodology, Software, Validation. **Yu Liu:** Conceptualization, Validation, Investigation, Data curation. **Zhicheng Du:** Conceptualization, Methodology, Software, Writing – review & editing. **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.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107726.

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