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Article

Long-term PM_1 exposure and hypertension hospitalization: A causal inference study on a large community-based cohort in South China

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ABSTRACT

Limited evidence exists on the effect of submicronic particulate matter (PM_1) on hypertension hospitalization. Evidence based on causal inference and large cohorts is even more scarce. In 2015, 36,271 participants were enrolled in South China and followed up through 2020. Each participant was assigned single-year, lag0–1, and lag0–2 moving average concentration of PM_1 and fine inhalable particulate matter ($PM_{2.5}$) simulated based on satellite data at a 1-km resolution. We used an inverse probability weighting approach to balance confounders and utilized a marginal structural Cox model to evaluate the underlying causal links between PM_1 exposure and hypertension hospitalization, with $PM_{2.5}$-hypertension association for comparison. Several sensitivity studies and the analyses of effect modification were also conducted. We found that a higher hospitalization risk from both overall (*HR*: 1.13, 95% *CI*: 1.05–1.22) and essential hypertension (*HR*: 1.15, 95% *CI*: 1.06–1.25) was linked to each 1 μg/m^3 increase in the yearly average PM_1 concentration. At lag0–1 and lag0–2, we observed a 17%–21% higher risk of hypertension associated with PM_1. The effect of PM_1 was 6%–11% higher compared with $PM_{2.5}$. Linear concentration-exposure associations between PM_1 exposure and hypertension were identified, without safety thresholds. Women and participants that engaged in physical exercise exhibited higher susceptibility, with 4%–22% greater risk than their counterparts. This large cohort study identified a detrimental relationship between chronic PM_1 exposure and hypertension hospitalization, which was more pronounced compared with $PM_{2.5}$ and among certain groups.

1. Introduction

A leading environmental concern to human health globally is airborne particulate matter (PM) pollution, among which $PM_{2.5}$ was estimated to have contributed to 118 million disability-adjusted life-years in 2019, with cardiovascular disease accounting for approximately 51.5% [1]. Hypertension is among the leading cardiovascular diseases, meanwhile, is one of the most significant risk factors for other cardiovascular endpoints, such as stroke. In 2019, there were estimated 1.3 billion hypertension patients worldwide, and the number is projected to exceed 1.6 billion by 2025 [2,3]. In China, the estimated prevalence of hypertension was 23.2% between 2012 and 2015 [4].

The relationship between chronic ambient PM exposure and hypertension has been investigated extensively [5]. However, most studies focused on routinely monitored PM species such as $PM_{2.5}$, leaving a significant gap in our understanding of the hypertensive impact of PM_1. Although PM_1 was the major component of the $PM_{2.5}$ particles, the smaller size fraction of PM_1 particles makes them easier to adhere to cell surfaces and penetrate more deeply into the respiratory tracts. Only part of these particles could be cleaned by the alveolar macrophages [6], while the rest are likely to enter and damage the epithelial cells, then spread throughout the circulatory system [7]. Studies also suggested a cumulative health impact of PM_1 exposure [8], further highlighting the public

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health significance of evidence on the long-term cumulative detrimental effects of PM_1 on hypertension.

A large proportion of studies on the effect of long-term air pollution exposure on hypertension risk were largely cross-sectional studies or based on areal observations, and incorporated traditional statistical models. Evidence from cross-sectional studies are not as informative as cohort studies. The traditional approaches may bias the estimates due to inherent methodology limitations. In observational studies, environmental exposure such as PM generally is not allocated randomly to participants. The traditional statistical models try to estimate effects by directly adjusting for confounders in the model, which often yields conditional estimates. While a conditional estimate represents the effect of exposure to the specific populations (e.g., exposed population) and is widely used in existing studies, a marginal estimate represents the average treatment effect in the entire population and may mimic the effect determined in the context of a randomized trial, thus, is considered of more interest [9]. In addition, a time-dependent covariate is a common issue where the covariate on a certain day could be affected by the exposure of previous periods, thus, over time the covariate plays both the role of confounder and mediator of the effect of exposure on outcome. Traditional statistical models usually fail to accommodate this issue [10]. Another approach, the marginal structural model, attempts to mimic randomized trials by re-weighting the observations using inverse probability weights (IPWs), to estimate marginal effects [9,11]. IPWs theoretically aim to adjust for confounders by balancing the confounders across levels of exposure using exposure weight and producing a pseudo-population. Then the data can be regarded as coming from a randomized controlled trial and thus estimates of effect are considered to have causal explanations [11]. However, evidence on the long-term PM-hypertension hospitalization relationship under cohort design and incorporating causal methods is even more scarce.

To fill these gaps, a set of causal approaches for observational data were employed to examine the relationship between average annual PM_1 exposure with both overall and essential hypertension hospitalizations, based on a sizable community-based cohort in South China. We also investigated the long-term detrimental cumulative effects of PM_1 over different time windows. Potential effect modifications by demographic characteristics and lifestyle factors were examined to identify particularly susceptible populations.

2. Materials and methods

2.1. Study cohort

The Major Projects of Scientific Research for the 11th (2006–2010) and 12th (2012–2017) Five-year Plans of China served as the prospective research foundation for the early development of our cohort. Initially concentrating on the prevalence of hepatitis B virus and carriers within the general population of southern China, these projects laid the groundwork for the establishment of our cohort [12]. The sub-cohort in Guangzhou, one of the biggest cities in China, comprised 36,271 individuals who were recruited from January 2015 to December 2015. The study included all the permanent residents who willingly signed a health service contract for a physical examination at their local healthcare centres. Participants were excluded if they were incapable of long-term follow-up, those under 18 years of age, individuals with reported hospitalization date being later than the reported date of death, or those with unclear residential addresses (Fig. 1). Physical examinations were performed according to protocol, and trained nurses conducted face-to-face interviews to collect baseline information on personality traits and lifestyle factors using a computer-based questionnaire. Before taking part in the study, each participant gave their written informed consent, which was approved by the Human Ethics Council at Sun Yat-sen University (ethical approval No. L201703). Details on the cohort's exact design and operations are published elsewhere [12].

The demographic and lifestyle factors in the current study included age, sex, ethnicity, educational attainment, marital status, health insurance, body mass index (BMI), family history of cardiovascular disease and metabolic disorders, smoking status, alcohol use, and frequency of exercise. In *Supplementary Methods*, the categories for each variable were thoroughly explained.

2.2. Outcome definition

Data on the causes of hospitalization between January 1st, 2016 and December 31st, 2020, were gathered via record linkage to 418 healthcare institutions in Guangzhou (71 tertiary, 100 secondary, 71 primary, and 176 other facilities, covering the entire area). The causes for hospitalization were coded using the International Classification of Diseases 10th edition (ICD-10) system. Both first hospital admissions due to overall (ICD-10: I10-I16) and essential (primary, ICD-10: I10) hypertension were considered as outcomes of interest in the current investigation.

2.3. Environmental exposures and covariates

In this study, the primary exposure variable was PM_1, with $PM_{2.5}$ being included as a secondary exposure for comparison. The ChinaHighAirPollutants (CHAP) datasets spanning 2013 to 2020 were utilized to derive annual PM concentrations at a high spatial resolution of 1 km^2. The procedures for gathering data and modelling have been previously described [13–15]. Briefly, daily PM_1 *in situ* measurements were obtained from the China Atmosphere Watch Network of the China Meteorological Administration. The measurements were collected using the GRIMM Model 1.180 Aerosol Spectrometer, an optical particle counter that recorded particle mass and size distribution every five minutes. These measurements covered wavelengths from 1.0 to 10 μm and were converted into mass concentrations according to the GRIMM protocols. Hourly $PM_{2.5}$ *in situ* observations were obtained from the China National Environmental Monitoring Center using the tapered element oscillating microbalance or β-attenuation method, with precision levels of ±1.5 or 0.1 μg/m^3, respectively. Calculations of daily PM_1 and $PM_{2.5}$ concentrations were estimated by space-time extremely randomized tree models [13–15] and cross-verified effectively against the ground observations, with R^2 values of 0.83 and 0.92, and *RMSE*s of 9.50 and 10.80 μg/m^3. Each residential address was standardized into geodetic longitude and latitude coordinates. Subsequently, annual PM exposure values were assigned to participants based on their residential addresses using a nearest-neighbor matching approach. Cumulative PM exposure over years for each participant was calculated using moving averages for the current year and the previous years, aiming to explore the cumulative lag effect. Specifically, the 2-year (lag0–1) cumulative exposure was the moving average of the current year and preceding the exposure, and the 3-year (lag0–2) cumulation was referred to moving average over the current and the two preceding years.

We considered greenness as a potential confounder [16]. A renowned indicator of greenness, the Normalized Difference Vegetation Index (NDVI), was retrieved from 2015 to 2020 (https://lpdaac.usgs.gov). Specifically, it was derived from Moderate Resolution Imaging Spectroradiometer—MOD13Q1 (Collection 6) Terra composite NDVI data at a spatial resolution of

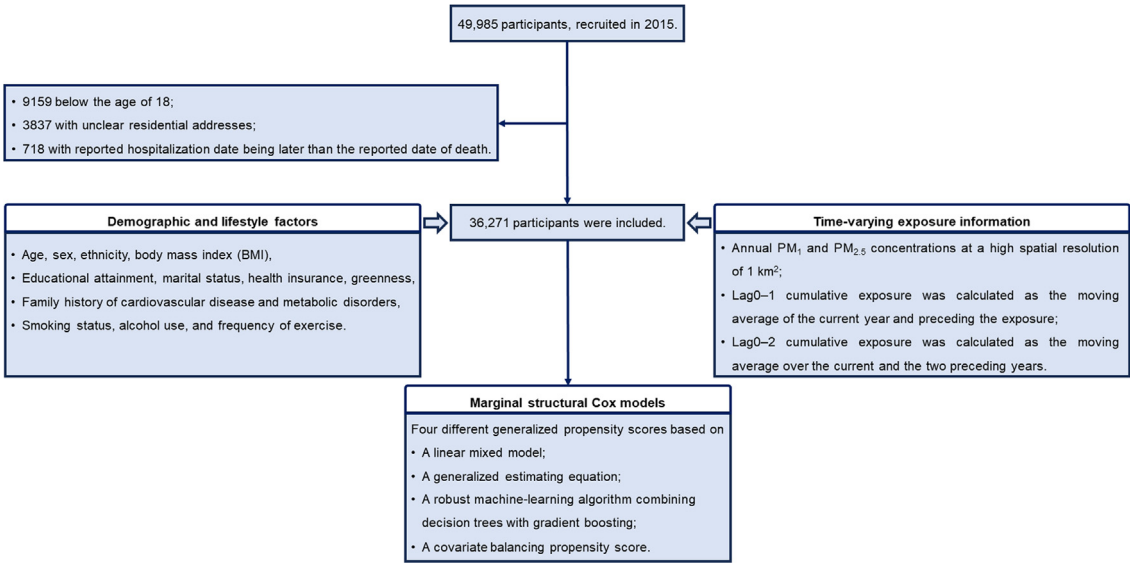

Fig 1. Flow chart of the study design.

250 meters (m) [17,18]. Yearly average NDVI was calculated within a 500 m radius surrounding the residence for each participant.

2.4. Statistical analyses

In the current analysis, the marginal structural Cox model with time-dependent covariates was used to assess possible causative relationships between long-term PM_1 exposure and hospitalization for both overall hypertension and essential hypertension. We first calculated four different generalized propensity scores (GPS) based on a linear mixed model (LMM) [19], a generalized estimating equation (GEE) [20], a robust machine-learning algorithm combining decision trees with gradient boosting (XGBoost) [21], and a covariate balancing propensity score (CBPS) [22], respectively. Then stabilized IPWs were developed based on the inverse of GPSs for each time point of every participant. To construct a weighted pseudo-population, cumulative weights were determined for each participant by multiplying the weights up to that observation period [23]. Lastly, the PM_1-outcome association was evaluated based on the re-weighted population. The covariate balance among the re-weighted pseudo-population was examined using the average absolute correlation, with values of 0.1 reflecting a reasonable level of resemblance to randomized studies [24]. Due to the optimum confounder balance in our final model (Fig. 2), hazard ratios (HRs) and 95% confidence intervals (CIs) for both overall and essential hypertension hospitalization per 1 $\mu g/m^3$ increase in annual PM_1 concentration were assessed using the GEE-IPWs method.

The time-dependent variables, such as yearly PM_1 concentrations and NDVI, were particularly taken into account while constructing marginal structural Cox models. Age, sex, ethnicity, educational attainment, marital status, health insurance, smoking status, frequency of exercise, family history of cardiovascular disease and metabolic disorders, and NDVI were identified as confounders based on a directed acyclic graph (DAG) (Fig. S1 online) and previous research [8,25,26]. For comparison, we additionally developed the conventional Cox proportional hazard models with time-varying variables [27].

In general, we created the four models below: Model 1: The basic model which has been modified for PM_1 exposure using the conventional method. Model 2: Model 1 further modified to account for age and gender. Model 3: Model 2 with additional adjustments for NDVI, educational attainment, health insurance, marital status, smoking status, family history of cardiovascular disease and metabolic disorders, and exercise frequency. Model 4: Updated Model 3 using the marginal structural Cox proportional hazard model. In the current investigation, model 4 served as the primary model. In addition to assessing the annual effect, the cumulative effects of PM_1 exposure over two and three years were evaluated (Fig. S2 online presented the average absolute correlation for the cumulative exposure). PM_1 exposure in different time windows was refitted as a smoothing term using penalized splines to estimate the concentration-response (C-R) relationships of PM_1 exposure and outcomes. The degrees of freedom were determined by comparing Bayesian information criterion values. The annual and cumulative exposure effects of $PM_{2.5}$ concentrations were examined for comparison. Conventional Cox proportional hazard models were used for $PM_{2.5}$ analysis, as the original data demonstrated good covariate balance.

Results from the final model were further stratified by age (<65 years and ≥65 years), sex (men and women), marital status (three categories: never married, married, and widowed/divorced), educational attainment (three categories: primary school or below, second and high school, and college degree or above), exercise frequency (three categories: very low, moderate, and high), smoking status (never and ever), and family history of cardiovascular disease and metabolic disorders. The modification effect of these factors was statistically tested using a 2-sample *z*-test [28]. Multiple imputations by chained equations were used to address missing data for confounding factors [29].

2.5. Sensitivity analyses

We performed several sensitivity studies in order to evaluate the robustness of our conclusions. Initially, we employed marginal structural Cox models with different weighting techniques to evaluate the relationships between chronic PM_1 exposure and outcomes (i.e., LMM, GEE, XGBoost, and CBPS). To assess how resistant our results were to conceivable unmeasured confounding, we further estimated E-values for four alternative models. Greater E-values show that unmeasured confounding is less likely to overturn our results [30]. Additionally, we explored PM_1-hypertension correlation under several sizes of NDVI buffers (i.e., 250 m, 500 m, and 1000 m) to evaluate the impact of different NDVI definitions. Further sensitivity analyses were conducted to investigate the

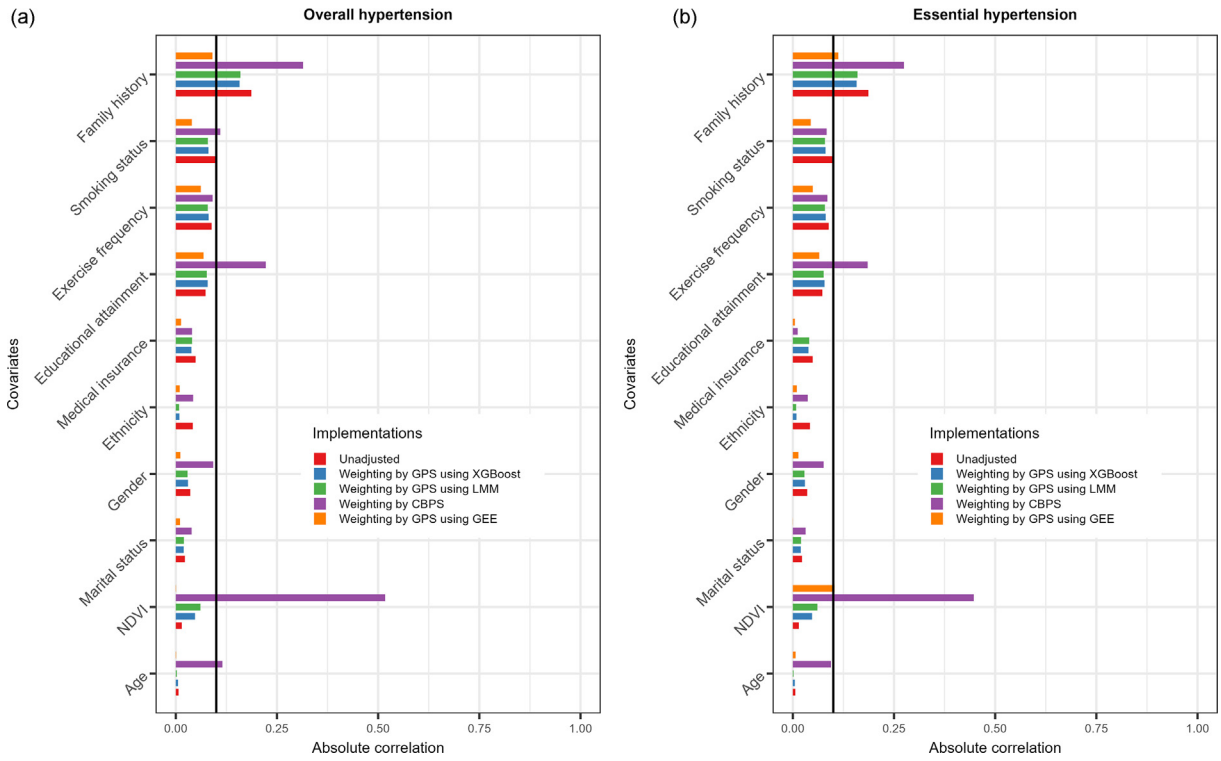

Fig. 2. Average absolute correlation of original and re-weighted participants for annual PM_1 exposure. Note: Average AC was smaller than 0.1 using causal inference based on GEE-IPWs, indicating good covariate balance. CBPS: covariate balancing propensity score; GPS: generalized propensity scores; GEE: generalized estimating equation; IPW: inverse probability weight; LMM: linear mixed model; NDVI: normalized difference vegetation index; XGBoost: a robust machine-learning algorithm combining decision trees with gradient boosting.

potential impact of gaseous pollutants, namely carbonic oxide (CO), nitrogen dioxide (NO_2), and ozone (O_3). Adjustments were made for these pollutants in multi-pollutant models, utilizing data at a 10 km^2 resolution from the CHAP datasets [31,32]. The impact of missing data imputation was evaluated by comparing the results from the datasets before and after imputation. Finally, we compared the statistical differences in *HR*s between various sensitivity models and the main model using a meta-regression model that generates *P*-values, testing the inter-group difference in effect estimates through a likelihood test [33]. R (version 4.1.3, available at https://www.r-project.org/) was used for all statistical analyses. Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Basic characteristics of the study participants

The cohort consisted of 36,271 participants (mean (*SD*) age = 50.9 (17.8) years; 14,727 (40.6%) men at baseline]), with an average of 6.0 years (*SD* = 0.5) and 209,834 person-years of follow-up. We observed 617 hypertension hospitalizations occurred, among which 509 were due to essential hypertension. Fig. S3 (online) displayed the typical PM concentrations between 2015 and 2020. The annual average values of PM_1 and $PM_{2.5}$ were 17.4 $\mu g/m^3$ (*SD* = 2.8) and 33.7 $\mu g/m^3$ (5.2), respectively. The characteristics of the entire participants and the complete case dataset were displayed in Table 1; Table S1 (online).

3.2. Annual and cumulative effects of PM exposure

The relationship between long-term PM_1 pollutants and hypertension hospitalization from crude and adjusted models are presented in Table 2. In crude models (model 1), the *HR* (and 95% *CI*) of hospitalization from overall hypertension was 1.11 (1.04–1.18) per 1 $\mu g/m^3$ increase in annual PM_1 concentration. With additional adjustment for age and sex (model 2) and other covariates (model 3), we observed also a significant association (*HR*, 1.12, 95% *CI*: 1.04–1.20 in model 2; *HR*, 1.11, 95% *CI*: 1.03–1.20 in model 3). In the marginal structural model (model 4), the *HR* (95% *CI*) was 1.13 (1.05–1.22). Similar results were observed for essential hypertension.

When considering multi-year cumulative exposure, the adjusted 2-year cumulative *HR*s (and 95% *CI*) of PM_1 concentrations were found to be 1.21 (1.04–1.40) for overall hypertension hospitalization, and 1.19 (1.08–1.32) for essential hypertension hospitalization respectively. Cumulative *HR*s of both overall and essential hypertension were not statistically significant for a 3-year PM_1 exposure duration. Additionally, in comparison to PM_1, the annual and cumulative effects of $PM_{2.5}$ on hospitalization for overall hypertension were relatively smaller, showing risks 6.0%, 11.0% and 8.1% lower than those associated with PM_1, respectively. Similar trends, indicating relatively smaller effects of $PM_{2.5}$ compared with PM_1, were observed across various exposure durations for hospitalization due to essential hypertension (Table S2 online).

Linear relationships between PM_1 exposure and hospitalization from the overall and essential hypertension were observed throughout the entire exposure range. We did not identify a safe threshold below which PM_1 concentration had no harmful effects (Fig. 3). The shapes of the C-R relationships were visualized by using penalized spline function with 3 degrees of freedom (*P* values of the likelihood ratio test of the non-linearity ranged between 0.518 and 0.883). The optimal degree of freedom was determined to minimize the Bayesian information criterion values, as outlined in Table S3 (online).

Table 1
Study population demographic characteristics by hypertension hospitalization outcomes.

Variable	Total (n = 36,271)	Overall hypertension (n = 617)	Essential hypertension (n = 509)
Demographics			
Age (mean (SD))	50.93 (17.76)	66.74 (11.64)	66.69 (11.66)
Gender (%)			
Female	21,544 (59.40)	402 (65.15)	338 (66.40)
Male	14,727 (40.60)	215 (34.85)	171 (33.60)
Ethnicity (%)			
Han ethnicity	35,991 (99.23)	615 (99.68)	507 (99.61)
Ethnic minorities	280 (0.77)	2 (0.32)	2 (0.39)
Educational attainment (%)			
Illiterate or semiliterate	741 (2.04)	30 (4.86)	24 (4.72)
Elementary school	5052 (13.93)	155 (25.12)	128 (25.15)
Middle school	7545 (20.80)	139 (22.53)	115 (22.59)
High school	16,310 (44.97)	258 (41.82)	215 (42.24)
College or above	6623 (18.26)	35 (5.67)	27 (5.30)
Marital status (%)			
Spinsterhood	5455 (15.04)	30 (4.86)	24 (4.72)
Married	29,264 (80.68)	516 (83.63)	424 (83.30)
Widowed/Divorced	1552 (4.28)	71 (11.51)	61 (11.98)
Medical insurance (%)			
For urban workers	24,922 (68.71)	446 (72.29)	366 (71.91)
For urban residents	7308 (20.15)	134 (21.72)	110 (21.61)
The new rural cooperative medical insurance	677 (1.87)	6 (0.97)	6 (1.18)
Others	3364 (9.27)	31 (5.02)	27 (5.30)
Family history (%)			
Negative	21,241 (58.56)	320 (51.86)	258 (50.69)
Positive	15,030 (41.44)	297 (48.14)	251 (49.31)
BMI (mean (SD))	22.60 (2.95)	23.76 (3.21)	23.79 (3.12)
Lifestyle factors			
Exercise frequency (%)			
Very low	13,954 (38.47)	226 (36.63)	187 (36.74)
Low	3403 (9.38)	50 (8.10)	44 (8.64)
Moderate	2574 (7.10)	38 (6.16)	34 (6.68)
Everyday	16,340 (45.05)	303 (49.11)	244 (47.94)
Smoking status (%)			
Current smoker	10,550 (29.09)	141 (22.85)	112 (22.00)
Previous smoker	529 (1.46)	16 (2.59)	13 (2.55)
Non-smoker	25,192 (69.45)	460 (74.55)	384 (75.44)
Alcohol use (%)			
Never	25,551 (70.44)	473 (76.66)	393 (77.21)
Ever	10,720 (29.56)	144 (23.34)	116 (22.79)
Air pollution			
PM_1 (mean (SD), $\mu g/m^3$)	17.4 (2.75)	19.0 (2.01)	19.1 (1.96)
$PM_{2.5}$ (mean (SD), $\mu g/m^3$)	33.7 (5.24)	36.7 (3.30)	36.8 (3.17)
Land-use variable			
NDVI (mean (SD))	0.22 (0.04)	0.22 (0.05)	0.22 (0.04)

Abbreviations: SD, stand deviation; BMI, body mass index; NDVI, normalized difference vegetation index.

3.3. Effect modifications

When these estimates of annual averaged PM_1 were stratified based on demographic variables, we determined that women were generally more susceptible to the effects of PM_1 exposure on both overall and essential hypertension hospitalization than men (*HR*: 1.16 vs. 1.01 for overall hypertension; 1.18 vs. 1.04 for essential hypertension). The impact of annual PM_1 exposure on hospitalization from both overall and essential hypertension generally was not significant among men, as displayed in Table 3.

Additionally, there was a marginally significant difference between the estimates for the high exercise group (*HR*, 1.20, 95% *CI:* 1.09–1.32) and the estimates for the low and moderate exercise group (1.14, 0.98–1.33) or the group with very low frequency of exercise (1.03, 0.92–1.14), in terms of the association between annual PM_1 and overall hypertension hospitalization (*P* for interaction was 0.033). Similar patterns were seen with the essential hypertension hospitalization (*P* for interaction was 0.019). We did not observe the modification effect of other factors on the annual PM_1-hypertension association.

3.4. Sensitivity analyses

Using four alternative marginal structural Cox models utilizing LMM-, GEE-, XGBoost-, and CBPS-IPWs, respectively, we observed comparable effect estimates (Table S4 online). The results were suggested to stand up well in the presence of unmeasured confounding bias, as evidenced by the E-values in Table S5 (online). After taking into account the complete case dataset, various NDVI buffer sizes (i.e., 250 m, 500 m, and 1000 m), and gaseous pollutants (i.e., NO_2, CO, and O_3), the PM_1-hypertension links did not alter appreciably (Table S6 online).

4. Discussion and conclusion

4.1. Long-term PM_1 exposure and hypertension hospitalization

We observed that each 1 $\mu g/m^3$ increment in the annual average PM_1 exposure was significantly associated with an elevated risk of 13.1% and 15.3% for overall and essential hypertension hospitalization, respectively. Although no cohort studies are available

Table 2
Estimated independent associations of PM_1 with overall and essential hypertension hospitalization risk in the 1-, 2-, and 3-year exposure durations.

	Overall hypertension (n = 617)		Essential hypertension (n = 509)	
	HR (95% *CI*)	*P* value	*HR* (95% *CI*)	*P* value
1-year exposure duration				
Model 1	1.105 (1.037–1.178)	0.002	1.126 (1.048–1.210)	0.001
Model 2	1.115 (1.041–1.195)	0.002	1.139 (1.054–1.231)	0.001
Model 3	1.113 (1.034–1.197)	0.004	1.128 (1.039–1.224)	0.004
Model 4	1.131 (1.051–1.218)	0.001	1.153 (1.061–1.254)	<0.001
2-year exposure duration				
Model 1	1.105 (1.031–1.184)	0.005	1.139 (1.053–1.232)	0.001
Model 2	1.117 (1.037–1.204)	0.004	1.155 (1.061–1.256)	0.001
Model 3	1.117 (1.030–1.210)	0.007	1.146 (1.048–1.253)	0.003
Model 4	1.207 (1.038–1.404)	0.015	1.190 (1.077–1.315)	<0.001
3-year exposure duration				
Model 1	1.119 (1.046–1.197)	0.001	1.150 (1.066–1.241)	<0.001
Model 2	1.128 (1.049–1.213)	0.001	1.162 (1.070–1.262)	<0.001
Model 3	1.130 (1.045–1.222)	0.002	1.156 (1.060–1.261)	0.001
Model 4	1.191 (0.979–1.450)	0.081	1.173 (0.948–1.450)	0.142

Note: Model 1 was crude cox model; Model 2 was Cox model adjusted for age and sex; Model 3 was Cox model adjusted for age, sex, ethnicity, educational attainment, marital status, medical insurance, smoking status, exercise frequency, family history of cardiovascular disease and metabolic disorders, and NDVI; Model 4 was marginal structural Cox models.

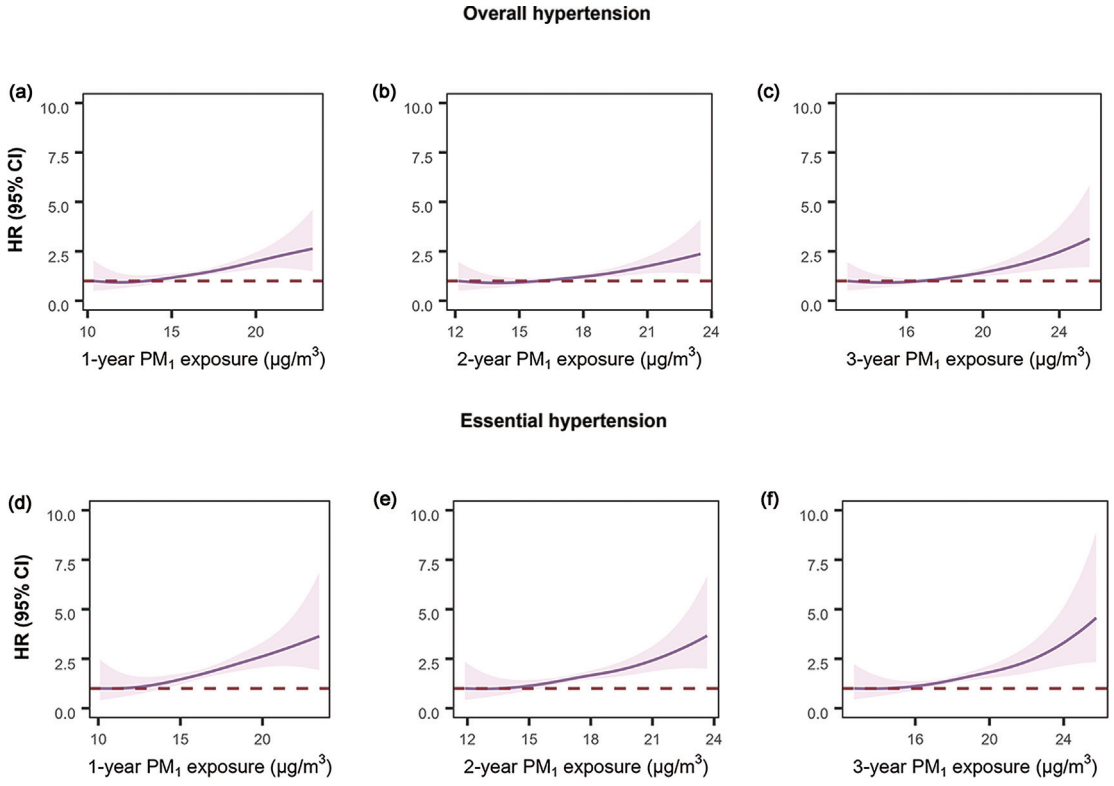

Fig. 3. Concentration-response curves (and 95% *CI*) for hypertension hospitalization from long-term PM_1 in different exposure durations under the marginal structural Cox models.

for comparison, some cross-sectional studies did support our findings. For example, a study among the rural Chinese population in Henan reported a significant association between 3-year average PM_1 exposure and an increased risk of hypertension, with the corresponding *OR* (95% *CIs*) per 1 μg/m^3 increase being 1.04 (1.03–1.05) [34]. Other two studies from northeastern China indicated that each 10 μg/m^3 increase in long-term PM_1 exposure was associated with a 5%–12% increase in the risk of prevalent hypertension [26,35]. Our study, based on a large population cohort and the established causal inference approaches, provided the most comprehensive and reliable evidence to date on the hypertensive impact of long-term PM_1 exposure.

A noteworthy observation is that the cumulative effects of PM_1 on hypertension hospitalization over 2- and 3-year periods were 4%–8% and 2%–6% higher than the annual effect, respectively, despite the non-statistically significant effects estimated for a 3-year PM_1 exposure. Additionally, linear C-R relationships were consistently observed between PM_1 and hospitalization due to hypertension, regardless of different cumulative lags. While C-R relationships regarding $PM_{2.5}$ have been reported in earlier studies, our findings contribute evidence concerning PM_1, which is considered more toxic than $PM_{2.5}$. Recently, several studies conducted in developed countries such as the USA, Spain, South Korea, and Lithuania, showed hypertensive risks ranging from 2.5%–6.8% per

Table 3
HRs (95% *CIs*) for overall and essential hypertension hospitalization associated with each 1 μg/m^3 increase in annual concentrations of PM_1, stratified by potential modifiers.

Effect modifiers	Overall hypertension (n = 617)		Essential hypertension (n = 509)	
	HR (95% *CI*)	*P* value [a]	*HR* (95% *CI*)	*P* value [a]
Main analyses [b]	1.131 (1.051–1.218)	0.001	1.153 (1.061–1.254)	<0.001
Age				
<65 years	1.186 (1.076–1.306)	Ref.	1.176 (1.054–1.312)	Ref.
≥65 years	1.073 (0.979–1.175)	0.140	1.124 (1.013–1.247)	0.559
Sex				
Men	1.011 (0.899–1.137)	Ref.	1.039 (0.904–1.194)	Ref.
Women	1.164 (1.080–1.254)	0.048	1.183 (1.089–1.286)	0.116
Marital status				
Never married	1.096 (0.860–1.397)	Ref.	1.068 (0.804–1.417)	Ref.
Married	1.127 (1.050–1.210)	0.830	1.158 (1.068–1.255)	0.589
Widowed/Divorced	1.046 (0.856–1.277)	0.769	1.045 (0.840–1.300)	0.908
Educational attainment				
Primary school or below	1.105 (0.985–1.241)	Ref.	1.143 (1.001–1.304)	Ref.
Second and high school	1.028 (0.946–1.116)	0.314	1.044 (0.952–1.144)	0.269
College degree or above	1.225 (0.958–1.567)	0.458	1.235 (0.919–1.659)	0.640
Exercise frequency				
Very low	1.026 (0.924–1.139)	Ref.	1.019 (0.907–1.146)	Ref.
Moderate [c]	1.139 (0.976–1.331)	0.270	1.196 (1.009–1.417)	0.130
High	1.197 (1.087–1.319)	0.033	1.235 (1.107–1.377)	0.019
Smoking status				
Never	1.078 (1.005–1.156)	Ref.	1.092 (1.009–1.181)	Ref.
Ever	1.159 (1.003–1.339)	0.375	1.199 (1.016–1.414)	0.318
Family history				
No	1.035 (0.954–1.124)	Ref.	1.038 (0.946–1.139)	Ref.
Yes	1.143 (1.027–1.271)	0.151	1.179 (1.046–1.329)	0.100

Note:
[a] *P* values from each stratum represent the interaction effects between air pollutants and possible modifiers.
[b] The main effects were estimated under marginal structural Cox models using IPWs based on a GEE with adjustment for sex, age, ethnicity, educational attainment, marital status, medical insurance, smoking status, exercise frequency, family history of cardiovascular disease and metabolic disorders, and NDVI (500 m).
[c] The group of low exercise frequency was combined into the group of moderate exercise frequency due to sample size limit in the stratified analysis.

1 μg/m^3 increase in $PM_{2.5}$ [36–40]. Our study, alongside other relevant research in China, identified higher hypertensive risks associated with PM compared with studies in developed countries [36–41]. This may be attributed to unique environmental factors in China, especially in certain regions like Guangzhou city, where higher concentrations of particle pollution are influenced by local factors such as industrialization, traffic pollution, and energy consumption. Also, the distinctive population characteristics and social lifestyle factors in China may contribute to an augmented susceptibility to hypertension. These findings underscore the continued importance of monitoring and controlling particles. More importantly, considering the substantial population in China, implementing effective policy measures to regulate particle pollution levels may yield more significant health benefits in reducing hypertension compared with other developed countries. Furthermore, although many countries, including China, have established air quality standards for inhalable particulate matter (PM_{10}) and $PM_{2.5}$, there are currently no such standards for PM_1. Our study provides valuable insights that could inform the development of PM_1-related standards and public health policies. Additionally, it has practical implications for implementing effective measures to reduce the risk of hospitalizations due to hypertension resulting from exposure to PM_1. Rapid improvements in air quality may significantly lower the risk of hypertension hospitalizations within 1–2 years and lead to prompt improvements in health.

4.2. Potential mechanism

Long-term exposure to ultrafine and fine PM causes a systemic inflammatory response with oxidative stress [42,43]. After directly activating alveolar macrophages and upregulating the expression of inflammatory cytokine, PM could lead to pulmonary inflammation; these activated inflammatory cytokines such as tumor necrosis factors and interleukins can in turn lead to a hepatic acute phase response, with resultant increases in C-reactive protein, which is associated with blood pressure [44,45]. Additionally, both ultrafine and fine PM exposure contribute to the dysfunction of high-density lipoprotein with anti-inflammatory and antioxidant capacities [46]. Thus, as a consequence of low levels of high-density lipoprotein, its vascular protective effect may decrease while the risk of hypertension may increase [47].

Our findings also suggest that higher *HRs* of hypertension hospitalization are associated with PM_1 than $PM_{2.5}$, consistent with other studies [26,35]. A toxicologic study has demonstrated that smaller PM particles could penetrate cells and lodge in the mitochondria of macrophages and epithelial cells, thereby damage the mitochondria [48]. A range of animal studies have observed translocation of inhaled nanoparticles across the alveolar-blood barrier, indicating that inhaled ultrafine PM may induce adverse effects on blood systemic circulation even in the absence of lung inflammation [7,49]. Furthermore, PM_1 particles typically have a disproportionally large surface area, enabling them to adsorb more organic chemical components and transition metals compared with $PM_{2.5}$ or PM_{10}. This leads to a potent cytotoxic effect on the cardiovascular system [49]. However, such demonstration of translocation in humans needs to be further warranted.

4.3. Susceptible populations

In this study, our findings indicated that each 1 μg/m^3 increment in the annual PM_1 exposure may lead to a 15.3% higher risk of hypertension hospitalization for women compared with men. The susceptibility difference between men and women can be attributed to several physiological factors. First, adult women have airways that are nearly 20% smaller in diameter than those of males, resulting in increased mechanical labor and flow resistance during breathing [50]. As a result, women may experience greater deposition in the tracheobronchial regions of their respiratory system when exposed to ambient PM. Second, women have lower arterial compliance and a coronary artery diameter that is 0.30

mm smaller compared with men. Additionally, their physiology is influenced by hormonal fluctuations during various stages, such as menstrual cycles, pregnancy, and menopause [51,52]. Sex differences in gene expression may also contribute to susceptibility. A recent animal study indicated that female mice with an XX sex chromosome complement may be more susceptible to atherosclerosis than male mice with an XY complement. This suggests that women may have a higher genetic vulnerability to cardiovascular risks after the protective effects of female sex hormones have diminished [53].

Our results indicated that physical exercise may modify the PM_1-hypertension hospitalization association. Chronic PM exposure is a risk factor for cardiovascular events, while physical activity is a preventive factor, although the equilibrium points are unknown [54]. While no direct evidence was reported, our findings were biologically plausible and aligned with existing research on the cardiovascular effects of PM_1 exposure. A clinical study involving 16 male intercollegiate athletes in the U.S. may support our results. After 30-minute exercise, while inhaling high PM_1 (near a major highway, 143,501 ± 58,565 particles/cm^3), the basal brachial artery showed that a 4% vasoconstriction and flow-mediated brachial artery dilation was impaired [42]. In spite of a decrease in pro-inflammatory indicators and an increase in markers of the anti-inflammatory pathway, a recent animal study indicated that cardiovascular events could not be prevented when male mice were exposed to 24 μg/m^3 $PM_{2.5}$ or filtered air following a 10-week exercise regimen [55]. In brief, exposure to high amounts of air pollution might cause vascular damage and make hypertension worse while exercising. Therefore, improving the quality of air particles, with a particular focus on ultrafine particles (e.g., PM_1), may represent an effective strategy for promoting better cardiovascular health.

4.4. Strengths and limitations

This work was based on a sizable cohort, providing sufficient statistical power to identify moderate annual as well as cumulative impact of long-term PM_1 exposure on hypertension hospitalizations. Our utilization of multiple cutting-edge causal techniques, decreasing covariate imbalance across exposure groups and providing potential causal clues, is another strength of the study. Additionally, comprehensive sensitivity analyses were conducted to confirm the robustness of the results. Despite its novelty and strengths, some limitations should be acknowledged. First, personal PM_1 exposure data was simulated rather than individually collected. The modeled high-resolution PM_1 exposure was allocated to individuals, which probably leads to Classical and Berkson errors and may underestimate the hospitalization risk of hypertension associated with PM_1 [56]. Second, due to the unavailability of data, indoor PM exposure resulting from the combustion of biomass and coal is not assessable. Third, we utilized hospitalization as the outcome. Existing studies focusing on the hospitalization of chronic outcomes [25,57–59], including our present study, generally are challenged by the issue that some patients may not be hospitalized. Although existing evidence on the association between PM_1 and hypertension is limited, based on the existing findings of the cardiovascular impact of $PM_{2.5}$, we found the effect estimates for outpatient visits are even greater than those for hospitalization [25,57,60], suggesting that our study may have underestimated the effects of PM_1, while the actual impact could be even more pronounced. However, this point could not be validated due to data limitations. More data are needed in the future to confirm or refute this hypothesis. Finally, it is acknowledged that unmeasured confounding variables, such as medical history, occupation, stress levels, and dietary habits, may taint the observed correlations. While we have incorporated a set of crucial confounders, as recommended by previous studies [8,25,26], our subsequent sensitivity analyses, employing E-values, indicate the resilience of our results against the potential residual confounding issues.

4.5. Conclusions

In this study, we revealed a deleterious effect of 1–3-year exposure to PM_1 on both overall and essential hypertension hospitalization in South China. Additionally, our results suggest that PM_1 may pose a higher hypertension risk compared with $PM_{2.5}$. The effect of PM_1 on hospitalization for hypertension was more significant among females and those who exercised regularly. Overall, this study expands the current knowledge on causal links between PM_1 and hypertension hospitalization based on a sizable general population cohort. A reduction in ambient PM_1 may improve effectively cardiovascular health.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Yuqin Zhang and Shirui Chen conceived the concept, conducted the statistical analysis, and cleaned the data. Yuqin Zhang drafted the manuscript. Jing Wei performed the exposure estimation and validation. Yuqin Zhang, Jie Jiang and Xiao Lin interpreted the results; Ying Wang and Chun Hao participated in data collection and assembly. Yuqin Zhang, Wenjing Wu, Zhupei Yuan, Jie Sun, and Han Wang revised the manuscript. Zhicheng Du, Wangjian Zhang, and Yuantao Hao designed the study and participated in data collection and assembly. Wangjian Zhang and Yuantao Hao provided the funding. All authors reviewed the manuscript, and approved its final submission.

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2024.03.028.

Data availability

Air pollution datasets are obtained from the CHAP dataset (https://weijing-rs.github.io/product.html). The NDVI dataset is publicly available from the Land Processing Distributed Active Archive Center (https://lpdaac.usgs.gov). The cohort datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

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