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TITLE PAGE

Association of Long-term Exposure to $PM_{2.5}$ with Blood Pressure and Hypertension Prevalence in China

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ABSTRACT

Objective: We aim to assess associations of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure, especially in populations exposed to high $PM_{2.5}$ concentrations in China.

Methods: We studied 883,827 participants aged 35–75 years in the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project. The 1-year average concentration of daily-specific $PM_{2.5}$ from monitoring stations was calculated to estimate the $PM_{2.5}$ exposure. The associations of $PM_{2.5}$ exposure with hypertension prevalence and blood pressure were investigated by generalized linear models. $PM_{2.5}$ was included through either linear or spline functions to assess evidence of nonlinearity.

Results: On average, each 10 μg/m^3 increase in the $PM_{2.5}$ exposure was associated with increased odds of hypertension prevalence (adjusted OR: 1.09, 95% CI: 1.08–1.10), systolic blood pressure (0.50 mmHg, 95% CI: 0.41–0.59), and diastolic blood pressure (0.23 mmHg, 95% CI: 0.18–0.28). The concentration-response curves for hypertension prevalence and systolic blood pressure showed a consistent increase with increasing $PM_{2.5}$ concentration, with steeper slopes at high $PM_{2.5}$ levels; while the curve for diastolic blood pressure was U-shaped. The elderly, men, and non-current smokers were more prone to adverse effects of $PM_{2.5}$.

Conclusions: Long-term exposure to $PM_{2.5}$ is associated with higher blood pressure and an increased risk of hypertension prevalence. The effects of $PM_{2.5}$ become more pronounced at higher $PM_{2.5}$ levels. These findings emphasize the need to reduce air pollution, especially in areas with severe air pollution.

Keywords: Air pollution; Blood pressure; Hypertension

Strengths and limitations of this study

- The large size of our study allowed us to comprehensively assess these associations among a diverse spectrum of population across a wider range of $PM_{2.5}$ concentrations in China.
- The large number of participants with hypertension and high level of $PM_{2.5}$ exposure (e.g. >35 μg/m^3), enabled us to examine these assocations with greater precision and sufficient statistical power.
- Given the nature of the cross-sectional study design, the causal relationship could not be established.
- A selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data.

INTRODUCTION

Hypertension is the leading modifiable risk factor for death globally.[1] Although hypertension is a worldwide public health concern, three quarters of the world's population with the condition are living in low- and middle-income countries (LMICs).[2] The causes of hypertension are complex. Apart from genetic predisposition, social determinants, and lifestyle factors, air pollution, especially fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), may also contribute to increased risk for hypertension.[3,4]

Over the past few years, a growing body of epidemiological evidence indicated the association of long-term exposure to $PM_{2.5}$ with blood pressure and hypertension.[5-14] However, such studies were mostly undertaken in high-income contries.[9-14] Compared with high-income coutries, exposure to $PM_{2.5}$ is substantially higher in LMICs; and genetic characteristics as well as lifestyle also differ,[15,16] limiting direct extrapolation of risk estimates from high-income countries to LMICs. Several studies have been performed in LMICs, but they were largely confined to specific populations (such as reproductive-aged adults) or regions.[5-8,17] Therefore, further studies are needed to assess the associations of $PM_{2.5}$ with blood pressure and prevalence of hypertension among a wider spectrum of populations with high $PM_{2.5}$ concentrations, especially in LMICs.

China is experiencing a growing epidemic of hypertension and is estimated to have 300 million individuals with hypertension by 2025.[18] Meanwhile, outdoor $PM_{2.5}$ has become one of China's most serious environmental problems with provincial population-weighted means of $PM_{2.5}$ ranging from 19·1 μg/m³ to 79·3 μg/m³ in 2015.[15] A deeper understanding of the chronic health effects of $PM_{2.5}$ on hypertension prevalence and blood pressure in moderate

to high $PM_{2.5}$ concentrations will help to support policy making of air quality improvement and combat the hypertension epidemic in China.

Accordingly, incorporating $PM_{2.5}$ data with a large-scale population-based screening project in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project, we aimed to: (1) explore the association of long-term $PM_{2.5}$ exposure with blood pressure level and the hypertension prevalence, and evaluate subpopulation differences in these associations; (2) assess the concentration-response relationships of long-term $PM_{2.5}$ exposure with hypertension prevalence and blood pressure.

METHODS

Study population

Our study population is derived from the China PEACE Million Persons Project, which has been described previously.[19] In brief, we selected sites (rural counties or urban districts) using a convenience sampling strategy in all 31 provinces in mainland China from September 2014 to March 2019. At each site, participants were enrolled if they were aged 35 to 75 years, currently registered in the selected region's Hukou (a record officially identifying a person as a resident of an area), or had lived in the region for at least 6 of the previous 12 months. This project was registered on www.clinicaltrials.gov (NCT02536456). In the present study, we included 897,937 participants with more than 330 valid $PM_{2.5}$ values for assessing long-term exposure. After excluding participants with missing data on education level (n=13,714), body mass index (n=321), or blood pressure measurement (n=2), we further excluded participants with systolic blood pressure (SBP) ≥250 mmHg or

diastolic blood pressure (DBP) ≥150 mmHg to minimize the potential bias due to measurement errors in blood pressure values (n=73). Finally, we included 883,827 participants in the study sample. The central ethics committee at the China National Center for Cardiovascular Diseases approved this project. All enrolled participants provided written informed consent.

Data collection and variable definitions

Data collection for each participant was performed by trained personnel with a standardized in-person interview and a physical examination. Information on sociodemographic status (age, gender, and education level), lifestyle (smoking and alcohol use), medical history, and medication use were collected. Medication use was determined by asking participants whether they had taken prescribed medications for antiplatelet or controlling blood pressure, lipid, or glucose in the past 2 weeks. Those who answered "yes" and knew the drug names were asked to report the name, dose, and frequency of each drug. Those who did not remember the exact dose stated the number of pills or tablets taken.

The blood pressure of each participant was measured twice on the right upper arm after 5 minutes of rest in a seated position with a standardized electronic blood pressure monitor (Omron HEM-7430). If the difference between the 2 systolic blood pressure readings was greater than 10 mmHg, a third measurement was obtained, and the average of the last 2 readings was used. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medications, which is consistent with the US Joint National Committee and Chinese

definitions[20-22]. Body mass index (BMI) was defined as weight in kilograms divided by height in square meters. Obesity was defined as 28.0 kg/m^2 or higher, on the basis of recommendations from the Working Group on Obesity in China.[23]

Exposure Assessment

Each participant's address (either rural county or urban district) was geocoded into latitude and longitude data. We identified all air monitors located within 10 kilometers from the participants' addresses (**Table S1**). These monitors were mandated to be away from major roads, industrial sources, buildings, or residential sources of emissions from the combustion of coal, waste, or oil so that the measurements from these monitors were more likely to reflect the background air pollution level rather than those from local sources, such as traffic or industrial combustion. The measurements from these monitors strictly followed the methodological standards set by the State Environmental Protection Administration of China. For each partcipant, daily-specific $PM_{2.5}$ data measured at the nearest monitors to their residence was used to estimate $PM_{2.5}$ exposure. The 1-year average concentration before the medical examination was calculated and treated as an indicator of long-term exposure to $PM_{2.5}$.

Statistical Analysis

Continuous variables were reported as means with standard deviation; categorical variables were presented as percentages. We modeled SBP and DBP using linear regressions with township-specific random intercepts to investigate the independent effect of long-term exposure to $PM_{2.5}$ on these two blood pressure measures. We also developed generalized linear models with a logit link function and township-specific random intercepts

to assess the association of long-term exposure to $PM_{2.5}$ with hypertension prevalence. For each of these analyses, we started with a model (Model 1) which only included age and sex. We then incrementally adjusted for additional covariates. The second model (Model 2) included Model1 and socioeconomic factors (education level and urbanity). The third model (Model 3) included Model 2 and cardiovascular disease risk factors (BMI, smoking status, alcohol consumption, and diabetes). Models of blood pressure were additionally controlled for hypertensive medication use; while models of hypertension were not, as hypertension medication use was a component of the outcome definition.

We also used restricted cubic splines to graphically characterize the concentration-response (C-R) relationships of $PM_{2.5}$ exposure with blood pressure and hypertension prevalence.[24] Additionally, to examine effect modification by age, gender, smoking status, alcohol consumption, diabetes, and obesity, each potential modifier was tested by adding an interaction term in the regression model separately and testing its statistical significance as well as the association per categories of the tested variable through subgroup analyses.

Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc., Cary, North Carolina). All tests of significance were 2-tailed, with a level of significance set at an alpha of 0.05.

RESULT

Study population and baseline characteristics

A total of 883,827 participants were included in the study sample. Summary statistics and baseline characteristics of the study population are shown in **Table S2**. The mean age

was 55.5 years, 60.4% were wowen, 43.1% had hypertension, mean SBP was 143.5 mmHg, mean DBP was 83.1 mmHg, and 19.4% were taking antihypertensive medications. The 1-year $PM_{2.5}$ exposure of total study population ranged from 8.8 to 93.8 μg/m^3. There were 864,119 (97.8%), 842,356 (95.3%), and 706,415 (79.9%) participants with 1-year $PM_{2.5}$ exposure higher than 15 μg/m^3 [World Health Organization (WHO) Interim Target 3 (IT-1)], 25 μg/m^3 [WHO Interim Target 2 (IT-2)], and 35 μg/m^3 [WHO Interim Target 3 (IT-3)], respectively.

Associations of long-term $PM_{2.5}$ exposure with hypertension prevalence

We found a positive association of long-term $PM_{2.5}$ exposure with hypertension prevalence, which was consistent across different model specifications. In the crude model (Model 1), each 10 μg/m^3 increase in $PM_{2.5}$ was associated with an 10% increased odds of hypertension prevalence [odds ratio (OR): 1.10; 95% confidence interval (CI): 1.09-1.11)]. After adjusting for a wide range of potential confounders, the OR of hypertension was 1.09 (95% CI: 1.08-1.10) for each 10 μg/m^3 increase in $PM_{2.5}$. (**Table S3**) The C-R relationships between long-term $PM_{2.5}$ exposure and hypertension prevalence were nonlinear with steeper slopes at higher $PM_{2.5}$ exposure levels. Compared to individuals with the lowest level of $PM_{2.5}$ exposure (8.8 μg/m^3), the adjusted ORs for hypertension of individuals with 15, 25, and 35 μg/m^3 of $PM_{2.5}$ exposure were 1.01 (95% CI: 1.01-1.02), 1.03 (95% CI: 1.02-1.04), and 1.05 (95% CI: 1.03-1.07), respectively. (**Figure 1**)

Associations of long-term $PM_{2.5}$ exposure with systolic and diastolic blood pressure

$PM_{2.5}$ exposures were positively associated with SBP and DBP. Adjustment for antihypertensive medications led to small increase in the effect estimate of $PM_{2.5}$ exposure. Among potentially confounding variables, adjustment for cardiovascular disease risk factors (Model 3 vs. Model 2) had the largest impact on effect estimates with a decrease in the positive association with SBP and DBP. In the fully adjusted model (Model 4), each 10 $\mu g/m^3$ increment was associated with increases of 0.50 mmHg (95% CI: 0.41-0.59) in SBP and 0.23 mmHg (95% CI: 0.18-0.28) in DBP. (**Table S4**) We found that the shapes of the C-R associations of $PM_{2.5}$ exposure with SBP and DBP were different, as presented in **Figure 2**. For SBP, the fitted C-R functions had upward trends with greater effect estimates of $PM_{2.5}$ at higher concentrations. For DBP, the C-R relationships were generally U-shaped.

Stratified analysis and effect modification

The associations of long-term $PM_{2.5}$ exposure with hypertension and blood pressure across different subgroups are provided in **Figure 3** and **Figure 4**. The associations of $PM_{2.5}$ exposure with hypertension were stronger among the elderly (≥65 years of age), men, and non-current smokers compared with younger subjects, women, and current smokers, respectively. Gender siginificantly modified the effects of $PM_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger associations among men; while these associations were not modified by alcohol consumption (all p for interaction >0.05). Although age and smoking status were also found to be effect modifiers in the associations of $PM_{2.5}$ exposure with SBP, DBP, and hypertension, the impacts of the two effect modifiers on these associations differed depending on the outcome. We observed greater effect estimates of

$PM_{2.5}$ exposure for SBP and hypertension, while smaller estimates for DBP among the elderly (≥65 years of age) and non-current smokers.

DISCUSSION

In this study, we investigated the associations between long-term exposure to $PM_{2.5}$ and hypertension prevalence, SBP, and DBP. We found that $PM_{2.5}$ was associated with increased risk of hypertension prevalence and elevation of blood pressure. Nonlinearity in these associations was also observed. With increasing higher $PM_{2.5}$ concentrations, the C-R curves for $PM_{2.5}$–hypertension and $PM_{2.5}$–SBP showed consistent increase with steeper slopes at higher $PM_{2.5}$ concentrations; while the C-R curve for $PM_{2.5}$–DBP was U-shaped. The elderly, men, and non-current smokers appeared to be more vulnerable to the exposure of $PM_{2.5}$.

Our study contributes to the existing scientific literature in several ways. First, the large size of our study allowed us to comprehensively assess the associations of $PM_{2.5}$ with hypertension prevalence and blood pressure among a wide spectrum of population in China. Our study included 0.8 million participants aged 35–75 years across a large and geographically diverse country, making the results more generalizable. In addition, the large population included in the present study also reflected different $PM_{2.5}$ exposure levels, and thus it adds to our understanding about these associations across a wider range of $PM_{2.5}$ concentrations (8.8–93.8 μg/m^3) than reported previously.[5-14] Furthermore, the large sample size, especially the large number of participants with hypertension and high level of $PM_{2.5}$ exposure (e.g. >35 μg/m^3), enabled us to examine these assocations with greater precision

and sufficient statistical power.

Second, we provided new information on the C-R relationship between long-term $PM_{2.5}$ exposure and hypertension prevalence. Previous research reported a U-shaped relationship between long-term exposure to $PM_{2.5}$ and hypertension prevalence with a threshold $PM_{2.5}$ of 47.9 μg/m^3.[5] However, in our study, we found no evidence of a discernible threshold — the concentration at which the C-R functions of hypertension prevalence begin to flatten out — at concentrations ranging from as low as 8.8 μg/m^3 to as high as 93.8 μg/m^3. In fact, $PM_{2.5}$ exposure was associated with consistent high risk of hypertension throughout the entire exposure range and the effects became even more pronounced when $PM_{2.5}$ exposure was extended to higher levels. This result suggests that per unit decrease in the concentration of $PM_{2.5}$ can be translated to a greater reduction in excess hypertension prevalence in highly polluted regions compared with regions with low to moderate levels of $PM_{2.5}$ exposure.

Third, we found evidence of nonlinearity relationship of $PM_{2.5}$ exposure with blood pressure, including SBP and DBP. Interestingly, the shapes of nonlinear C-R association were different between $PM_{2.5}$ exposure-SBP and $PM_{2.5}$ exposure-SBP associations. Although we observed a modest-sized change of blood pressure across the full range of $PM_{2.5}$ concentrations, it is still of great public health importance. Since hypertension is the most important risk factor for death, even a small change in blood pressure at population level can potentially lead to an increase in attributable disease burden.[25] The mechanism by which the shapes between the associations of $PM_{2.5}$ exposure-SBP vs. $PM_{2.5}$ exposure-DBP are different is unclear. Pathophysiological changes, such as systemic inflammation, atherosclerosis, endothelial dysfunction, and increased arterial stiffness,[4,26] may have

contributed to the observed patterns. The increased arterial stiffness induced by $PM_{2.5}$ would initially lead to elevation in SBP and decline in DBP, creating an increased pulse pressure.[27] While with further increase of arterial stiffness, the heart rates got higher to maintain the stroke volume, which could result in the rise of DBP afterwards. In addition, prior studies have reported the effects of $PM_{2:5}$ exposure on pulse pressures showing a tendency of rising up first and then declining at higher $PM_{2.5}$ levels, which partially supports this hypothesis.[11,28]

Fourth, we identified the vulnerable subgroups to the exposure of $PM_{2.5}$. In stratified analyses, we observed the large effect estimates of $PM_{2.5}$ on hypertension among the elderly. Elderly subjects may commonly represent higher prevalence of preexisting cardiovascular and respiratory diseases, which may confer susceptibility to $PM_{2.5}$. Also, the results showed that $PM_{2.5}$ exposure had larger effects on hypertension in men, which is consistent with a previous study.[6] Such increased susceptibility may be related to sex-related differences in the deposition localization and rates of air pollutants;[29] specifically, men have larger airways and slightly lower airway reactivity.[30] Additionally, smoking status was found to be an effect modifier with smaller effects on hypertension among current smokers. This finding is also supported by prior research.[10,28] One possible explanation is that smoking and $PM_{2.5}$ exposure may share the same pathways in mediating cardiovascular effects and smoking may play a dominant role in smokers. Thus, the exposure to $PM_{2.5}$ might not exert additional harmful effect via the same pathway.[28]

Our study should also be interpreted in the context of several limitations. First, given the nature of the cross-sectional study design, the causal relationship could not be established. Additional research is needed to examine these relationships in a prospective manner.

Second, a selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data. Third, while we included a number of potential confounders in the analyses, there might be unmeasured confounders that affected the observed associations. In particular, we were unable to control for other confounders such as diet and physical activity, because these data were only available in a subset of the China PEACE Million Persons Project cohort. Fourth, for $PM_{2.5}$ exposure assessment, we used the data from the monitor located nearest to the residence of each subject and did not account for individual time-activity patterns and indoor-related characteristics, which would likely result in nondifferential measurement errors and may cause underestimates in our results[31]. However, this approach is commonly used in prior studies[31] and previous research have indicated that $PM_{2.5}$ exposure estimated by the nearest monitor was highly correlated with other sophisticated approaches[32]. Fifth, other gaseous pollutants, such as NOx and ozone, temperature, and noise were not included in this study. As a result, we were not able to determine whether the observed effects were specifically attributable to $PM_{2.5}$ or to the combined effects of these factors.

In conclusion, our study demonstrated that long-term exposure to $PM_{2.5}$ was significantly associated with increased risk of blood pressure elevation and hypertension prevalence. The effect of $PM_{2.5}$ on hypertension prevalence was more pronounced at higher $PM_{2.5}$ concentration. Our findings reinforce the need to develop comprehensive strategies for addressing air pollution problems, especially for areas with severe air pollution.

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PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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DISCLOSURES

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and declared no competing interests.

CONTRIBUTORS

JS and XZ conceived of this article. JS and YG wrote the manuscript with further

contributions from XZ, XL, EM, MR, GT, DZ, WZ, JL and MA. JS and SH completed all the statistical analysis. All authors interpreted data, contributed to critical revisions and approved the final version of the article.

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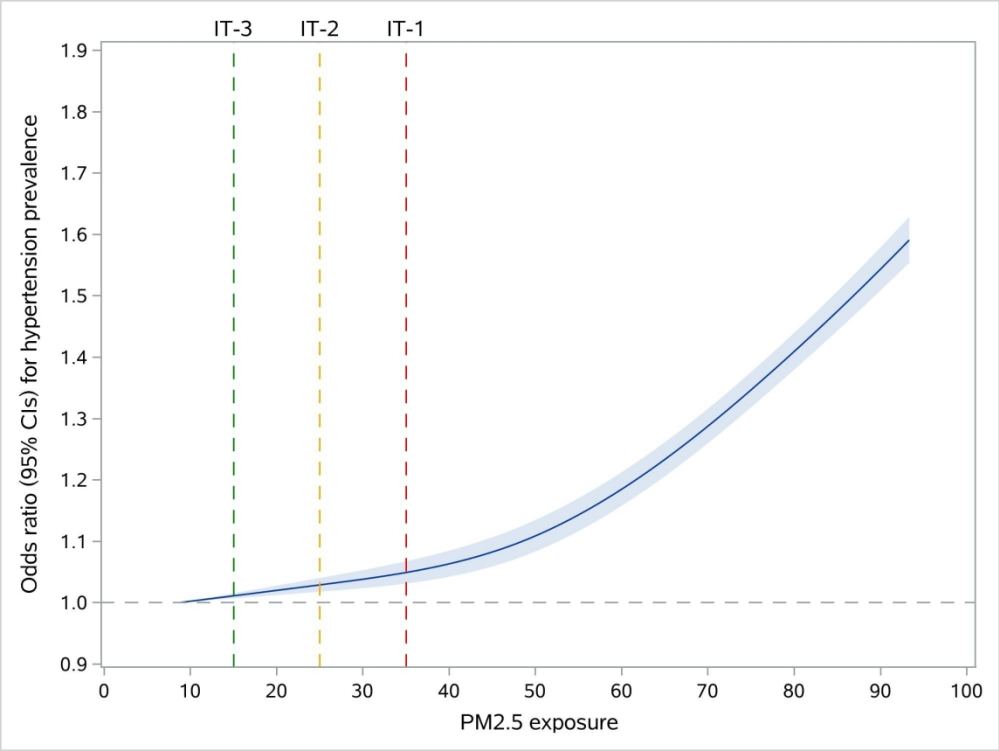

Figure 1. Concentration-response functions of the long-term exposure to PM2.5 with hypertension prevalence.
Effect estimates were presented as adjusted odds ratios for hypertension prevalence compared to individuals with PM2.5 exposure 8.8 μg/m3.
The dashed lines represent the air-quality standards for annual average concentrations of PM2.5 according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, and diabetes

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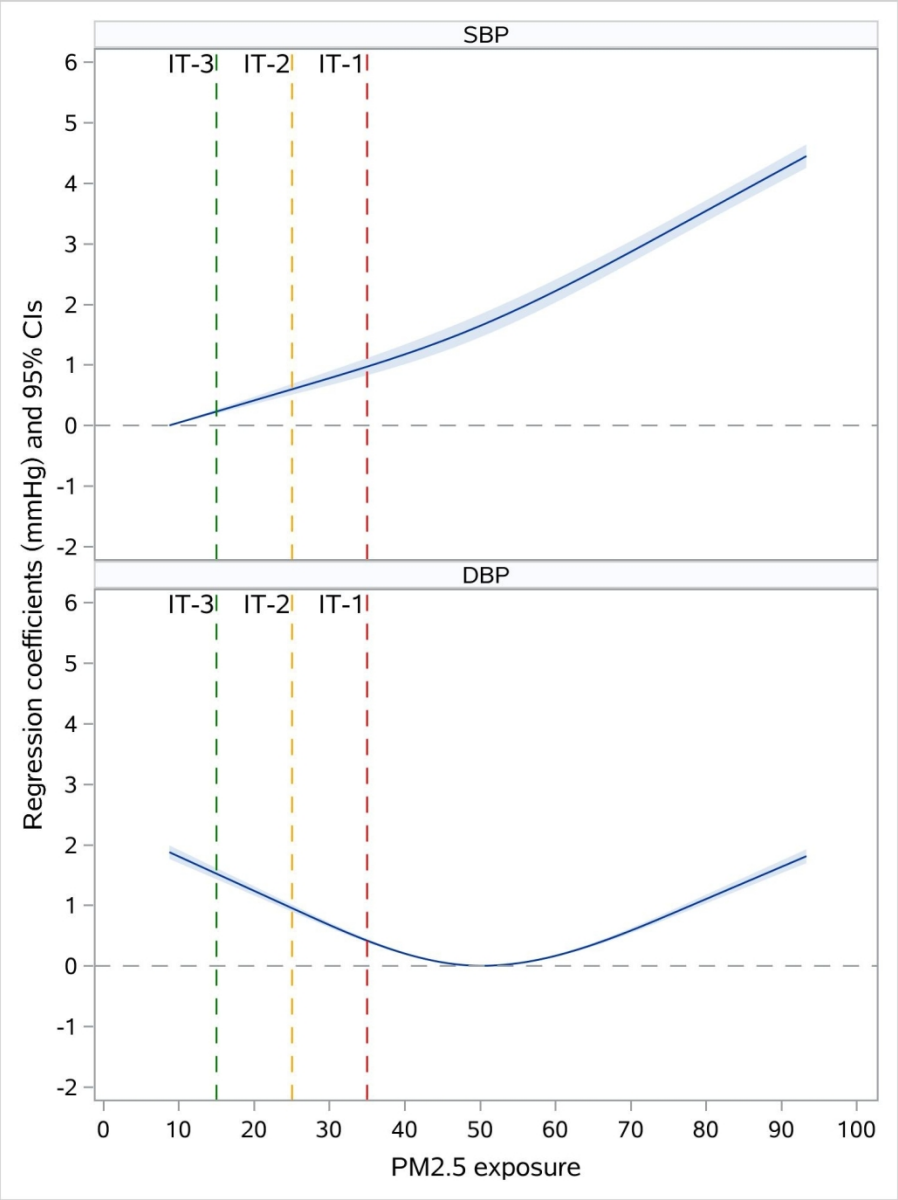

Figure 2. Concentration-response functions of the long-term exposure to PM2.5 with systolic blood pressure (SBP) and diastolic blood pressure (DBP)
Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with PM2.5 exposure 8.8 μg/m3 and changes in DBP compared to individuals with PM2.5 exposure 50 μg/m3. The dashed lines represent the air-quality standards for annual average concentrations of PM2.5 according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications.

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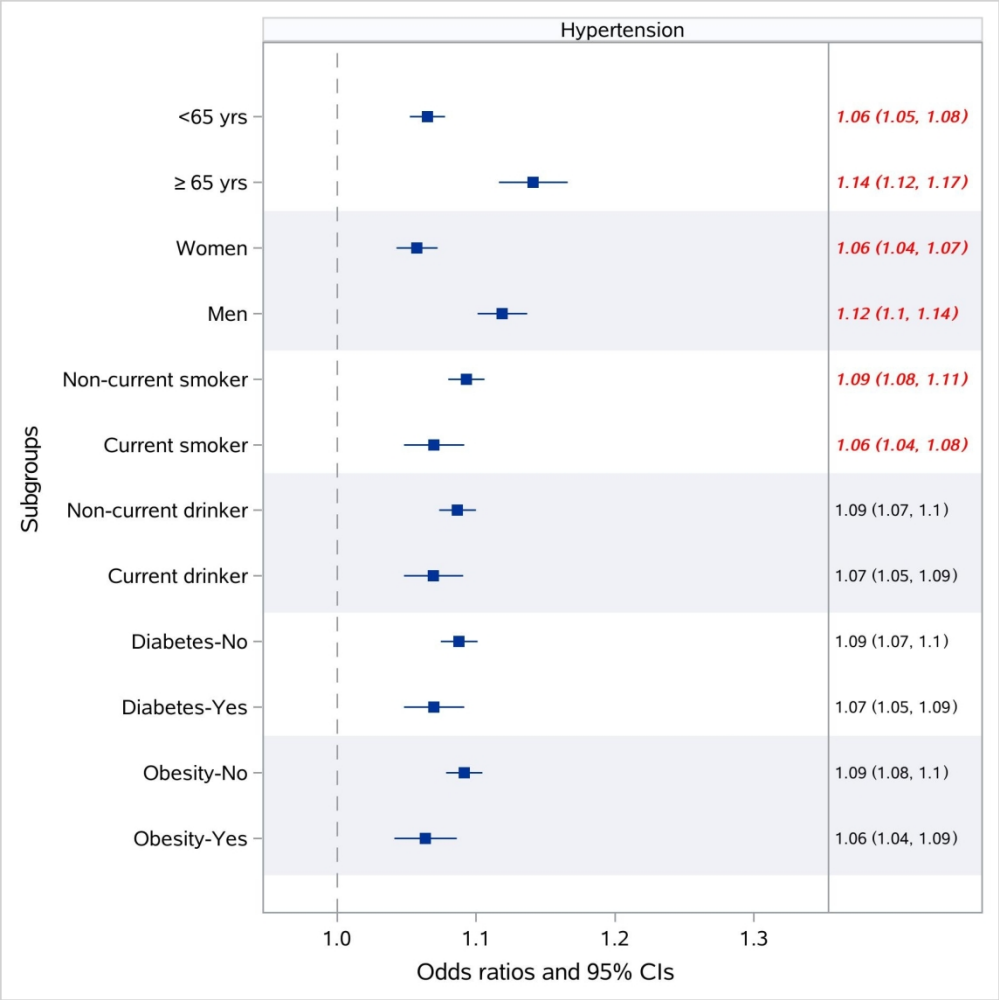

Figure 3. Stratified analysis of the association of long-term exposure to PM2.5 with hypertension prevalence
Red texts with italics indicated that p-value for interaction terms<0.05.
Effect estimates (regression coefficients) were presented as adjusted odds ratios for hypertension prevalence for each 10 μg/m3 increment in the 1-year PM2.5 exposure.
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity and diabetes.

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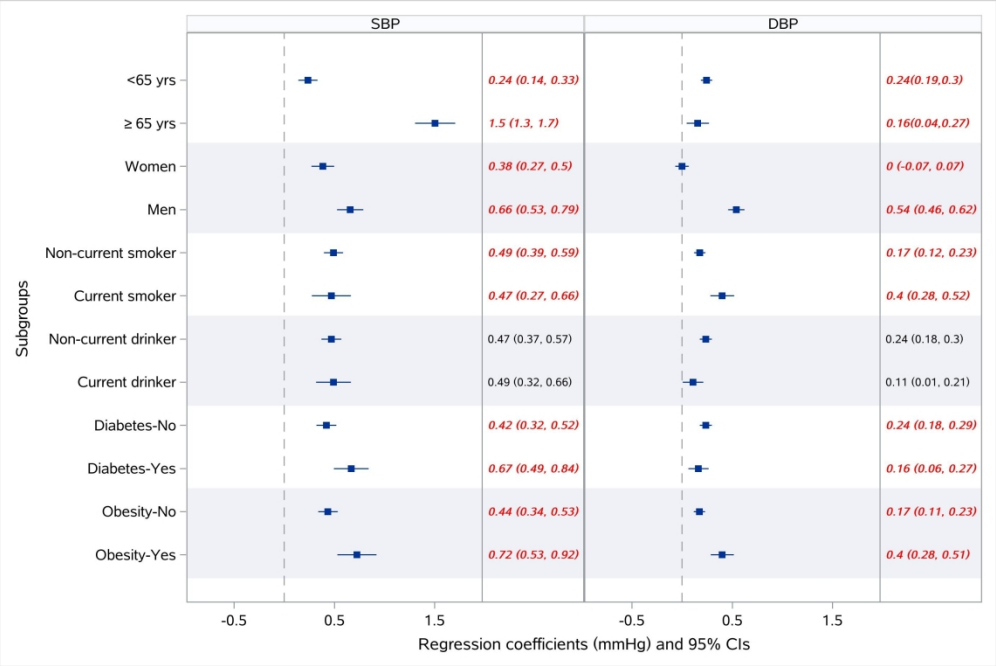

Figure 4. Stratified analysis of the association of long-term exposure to PM2.5 with blood pressure
Red texts with italics indicated that p-value for interaction terms<0.05.
Effect estimates (regression coefficients) were presented as changes in systolic blood pressure (SBP) or diatolic blood pressure (DBP) for each 10 μg/m3 increment in the 1-year PM2.5 exposure deriving from multivariable linear regression. Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications.

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APPENDICES

Table S1. Summary statistics for daily $PM_{2.5}$ (μg/m^3) at 83 monitoring stations in China between 2015 and 2018.

Station	Mean	Median	P25	P75	Maximum	Minimum	SD	Missing (days)
1	67.90	50	26	88	540	5	62.47	22
2	65.48	48	23	85	515	3	61.39	25
3	56.39	40	19	76	448	2	53.72	18
4	69.26	50	27	88	529	4	65.93	10
5	57.73	41	20	77	446	4	54.56	9
6	64.46	51	32	79.5	350	6	49.30	13
7	62.85	50	30	78	409	4	50.02	38
8	68.35	54	34	83.5	408	7	54.03	37
9	64.46	51	32	79.5	350	6	49.30	13
10	65.52	51	32	81	410	7	52.07	34
11	86.31	61	38	107	708	5	77.17	37
12	63.99	52	37	76	421	6	43.18	18
13	61.01	50	30	79	290	2	44.39	24
14	60.51	49	32	76	390	7	42.41	70
15	46.19	40	29	55	276	7	26.03	44
16	22.90	18	12	29	187	3	17.44	59
17	54.55	41	26	68	932	3	48.40	14
18	40.93	32	20	50	450	5	32.88	16
19	44.97	35	22	56	353	6	35.16	39
20	48.80	37	24	59	508	6	42.08	15
21	45.30	31	19	55	612	3	45.58	27
22	30.54	22	14	39	308	2	26.22	17
23	45.36	34	21	58	378	3	36.92	24
24	54.24	33	21	66	730	5	59.99	24
25	39.52	29	18	49	502	3	35.05	78
26	42.91	36	22	55	235	4	29.42	24
27	44.22	36	22	58	225	5	30.20	60
28	44.97	38	24	58	218	5	29.10	22
29	44.32	37	23	57	224	6	29.52	12
30	49.23	40	28	62	271	10	32.35	665
31	52.70	42	27	67	284	7	37.07	9
32	51.19	43	28	64	250	3	33.85	40
33	49.98	44	31	61	259	6	28.45	26
34	47.59	40	27	59	233	3	30.88	30
35	27.35	25	17	35	114	2	14.53	46
36	26.16	22	14	34	233	2	16.88	5
37	32.18	25	14	45	155	4	24.63	826
38	45.33	40	29	57	209	9	22.66	32
39	49.12	44	31	62	356	3	26.44	27
40	74.08	60	40	92	431	7	50.63	22
41	56.81	46	31	70	327	7	38.51	44
42	70.49	57	40	82	514	6	51.28	720
43	56.69	46	34	65	257	14	35.08	870
44	69.96	53	35	88	548	5	54.64	57
45	62.00	50	31	81	275	3	44.29	20
46	44.01	38	26	56	195	5	26.01	31
47	48.13	43	29	61	478	6	27.90	43
48	51.57	43	29	65	289	5	33.64	10

49	39.33	33	23	50	214	6	22.99	12
50	32.84	29	20	42	121	5	17.51	22
51	32.48	28	18	43	149	5	19.23	35
52	27.19	24	14	36	120	3	17.16	31
53	38.01	33	21	49	192	5	23.72	16
54	35.67	30	19	46	269	3	22.90	13
55	50.36	42	27	64	286	6	32.32	23
56	44.34	35	23	56	333	5	32.18	6
57	35.14	29	16	47	202	3	25.68	22
58	22.10	18	14	27	123	3	13.22	31
59	15.14	13	9	18	68	2	9.22	12
60	37.75	29	18	47	183	5	28.96	708
61	49.89	41	30	61	222	8	31.21	27
62	60.72	49	32	77	353	5	42.85	8
63	42.87	36	24	55	215	5	25.98	16
64	49.35	40	24	65	235	3	35.52	13
65	32.64	28	18	42	195	4	20.30	23
66	30.96	28	21	39	123	7	14.39	10
67	29.79	28	20	36	102	7	12.89	23
68	13.86	14	12	15	51	3	5.05	109
69	25.99	19	13	32	187	5	20.21	33
70	24.49	19	13	30	124	2	17.69	156
71	11.95	10	7	15	88	2	7.71	87
72	51.21	42	30	63	239	10	30.49	238
73	10.62	9	7	13	73	4	5.10	46
74	53.80	41.5	28	64	328	5	40.55	19
75	38.88	32	23	47	169	4	24.72	27
76	44.45	36	24	57	581	4	35.96	59
77	44.10	36	25	53	287	5	29.00	44
78	44.04	38	27	56	139	9	23.42	1000
79	55.15	45	30	68	363	5	38.57	14
80	44.69	36	24	55	219	5	30.52	50
81	65.37	34	20	85	447	5	68.86	97
82	57.76	29	19	70	414	3	62.93	58
83	51.70	26	14	65	406	3	58.30	42

Note: Missing: Number of days with missing $PM_{2.5}$ value during 2015-2018

Table S2. Characteristics of the study population.

Variable	Total (n=883,827)
Socio-demographics	
Age, mean (SD), years	55.5 (10.1)
Female, n (%)	533897 (60.4)
Urban residence, n (%)	657608 (74.4)
Han ethnic group, n (%)	805479 (91.1)
College or above	102764 (11.6)
Regions, n (%)	
Eastern	325253 (36.8)
Central	178435 (20.2)
Western	311599 (35.3)
NorthEastern	68540 (7.8)
Cardiovascular risk factors, n (%)	
Obesity	142150 (16.1)
Current drinker	194967 (22.1)
Diabetes	173950 (19.7)
Current smoker	161006 (18.2)
Hypertension	381223 (43.1)
Blood pressures	
Systolic blood pressure, mean (SD)	143.5 (22.2)
Diastolic blood pressure, mean (SD)	83.1 (12.3)
$PM_{2.5}$ exposures	
1-y average $PM_{2.5}$ exposure, mean (SD)	49.2 (16.4)
Above WHO Interim Target 1 (IT-1, 35 μg/m^3), n (%)	706415 (79.9)
Above WHO Interim Target 2 (IT-2, 25 μg/m^3), n (%)	842356 (95.3)
Above WHO Interim Target 3 (IT-3, 15 μg/m^3), n (%)	864119 (97.8)

Table S3. The effect of $PM_{2.5}$ exposure on hypertension prevalence.

Model	Per 10 μg/m^3 $PM_{2.5}$ increment	
	OR (95% CI)	p-Value
Hypertension prevalence		
Model 1	1.10 (1.09-1.11）	<0.001
Model 2	1.10 (1.09-1.11）	<0.001
Model 3	1.09 (1.08-1.10）	<0.001

Model 1: Included age and sex;

Model 2: Model 1 + education level and urbanity;

Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes

OR: odds ratio; 95% CI: 95% confidence intervals.

Table S4. The effect of $PM_{2.5}$ exposure on blood pressure.

Model	Per 10 μg/m^3 $PM_{2.5}$ increment	
	mmHg (95% CI)	p-value
Systolic blood pressure		
Model 1	0.58 (0.49-0.67)	<0.001
Model 2	0.57 (0.48-0.66)	<0.001
Model 3	0.45 (0.36-0.54)	<0.001
Model 4	0.50 (0.41-0.59)	<0.001
Diastolic blood pressure		
Model 1	0.29 (0.23-0.34)	<0.001
Model 2	0.28 (0.23-0.34)	<0.001
Model 3	0.21 (0.15-0.26)	<0.001
Model 4	0.23 (0.18-0.28)	<0.001

Model 1: Included age and sex;

Model 2: Model 1 + education level and urbanity;

Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes

Model 4: Model 3 + use of antihypertensive medications

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure in China: a cross-sectional study

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TITLE PAGE

Association of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure in China: a cross-sectional study

Authors

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Word count: 2,931 words (main text)

Number of figures: 4

ABSTRACT

Objective: Evidence of the effects of long-term fine particulate matter ($PM_{2.5}$) exposure on hypertension and blood pressure is limited for populations exposed to high levels of $PM_{2.5}$. We aim to assess associations of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure, and further explore the subpopulation differences and effect modification by participant characteristics in these associations in China.

Methods: We analyzed cross-sectional data from 883,827 participants aged 35–75 years in the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project. Data from the monitoring station was used to estimate the one-year average concentration of $PM_{2.5}$. The associations of $PM_{2.5}$ exposure with hypertension prevalence and blood pressure were investigated by generalized linear models, with $PM_{2.5}$ included as either linear or spline functions.

Results: The 1-year $PM_{2.5}$ exposure of the study population ranged from 8.8 to 93.8 μg/m^3 (mean 49.2 μg/m^3). The adjusted odds ratio of hypertension prevalence related to a 10 μg/m^3 increase in one-year $PM_{2.5}$ exposure was 1.09 (95% confidence interval, 1.08–1.10). Each 10 μg/m^3 increment in $PM_{2.5}$ exposure was associated with increases of 0.50 mmHg (95% confidence interval, 0.41–0.59) and 0.23 mmHg (95% confidence interval, 0.18–0.28) in systolic blood pressure and diastolic blood pressure, respectively. The concentration-response curves for hypertension prevalence and systolic blood pressure showed steeper slopes at higher $PM_{2.5}$ levels; while the curve for diastolic blood pressure was U-shaped. The elderly, men, and non-current smokers were o be more susceptible to the exposure of $PM_{2.5}$.

Conclusions: Long-term exposure to $PM_{2.5}$ is associated with higher blood pressure and

increased risk of hypertension prevalence. The effects of $PM_{2.5}$ on hypertension prevalence become more pronounced at higher $PM_{2.5}$ levels. These findings emphasize the need to reduce air pollution, especially in areas with severe air pollution.

Keywords: Air pollution; Blood pressure; Hypertension

Strengths and limitations of this study

- The large size of our study allowed us to comprehensively assess these associations among a diverse spectrum of population across a wider range of $PM_{2.5}$ concentrations in China.
- The large number of participants with hypertension and high level of $PM_{2.5}$ exposure (e.g. >35 μg/m^3), enabled us to examine these associations with greater precision and sufficient statistical power.
- Given the nature of the cross-sectional study design, the causal relationship could not be established.
- A selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data.

INTRODUCTION

Hypertension is the leading risk factor for death globally.[1] Although hypertension is a worldwide public health concern, three-quarters of the world's population with the condition are living in low- and middle-income countries (LMICs).[2] The causes of hypertension are complex. Apart from genetic predisposition, social determinants, and lifestyle factors, air pollution, especially fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), may also contribute to increased risk for hypertension.[3, 4]

Over the past few years, a growing body of epidemiological evidence indicated the association of long-term exposure to $PM_{2.5}$ with blood pressure and hypertension.[5-10] However, most of the studies were undertaken in high-income countries.[8, 10] Compared with high-income countries, exposure to $PM_{2.5}$ is substantially higher in LMICs. Although several studies have been performed in LMICs, they were largely confined to specific populations (such as reproductive-aged adults) or regions.[5-7] Therefore, further studies are needed to assess the associations of $PM_{2.5}$ with blood pressure and prevalence of hypertension among a wider spectrum of populations with high $PM_{2.5}$ concentrations, especially in LMICs.

China is experiencing a growing epidemic of hypertension and is estimated to have 300 million individuals with hypertension by 2025.[11] Meanwhile, outdoor $PM_{2.5}$ has become one of China's most serious environmental problems with population-weighted annual means of $PM_{2.5}$ ranging from 19.1 μg/m³ to 79.3 μg/m³ in 2015.[12] A deeper understanding of the chronic health effects of $PM_{2.5}$ on hypertension prevalence and blood pressure in moderate

to high $PM_{2.5}$ concentrations will help to develop policies to improve air quality and combat the hypertension epidemic in China.

Accordingly, incorporating $PM_{2.5}$ data with a large-scale population-based screening project in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project, we aimed to: (1) explore the association of long-term $PM_{2.5}$ exposure with blood pressure level and hypertension prevalence, and evaluate subpopulation differences and effect modification by characteristics of participants in these associations; (2) assess the concentration-response relationships of long-term $PM_{2.5}$ exposure with hypertension prevalence and blood pressure.

METHODS

Study population

Our study population is derived from the China PEACE Million Persons Project, which has been described previously.[13] In brief, we selected county-level regions using a convenience sampling strategy in all 31 provinces in mainland China from September 2014 to March 2019. These regions are designated as rural counties or urban districts according to urban-rural division codes of the National Bureau of Statistics of China.[14] Local residents aged 35 to 75 years, who were currently registered in the selected region's Hukou (a record officially identifying a person as a resident of an area) or had lived in the region for at least 6 of the previous 12 months, were enrolled in this project. After excluding participants with missing data on education level (n=13,714), body mass index (n=321), or blood pressure

measurement (n=2), we further excluded participants with systolic blood pressure (SBP) ≥ 250 mmHg or diastolic blood pressure (DBP) ≥150 mmHg to minimize the potential bias due to measurement errors in blood pressure values (n=73). Finally, we included 883,827 participants in the study sample. The central ethics committee at the China National Center for Cardiovascular Diseases approved this project. All enrolled participants provided written informed consent.

Data collection and variable definitions

Data collection for each participant was performed by trained personnel with a standardized in-person interview and a medical examination. Information on sociodemographic status (age, gender, and education level), lifestyle (smoking and alcohol use), medical history, and medication use were collected. Medication use was determined by asking participants whether they had taken prescribed medications for controlling blood pressure or glucose in the past 2 weeks. Those who answered "yes" and knew the drug names were asked to report the name, dose, and frequency of each drug. Those who did not remember the exact dose stated the number of pills or tablets taken (**Supplement 1**).

The blood pressure of each participant was measured twice on the right upper arm after 5 minutes of rest in a seated position with a standardized electronic blood pressure monitor (Omron HEM-7430). If the difference between the two SBP readings was greater than 10 mmHg, a third measurement was obtained, and the average of the last 2 readings was used. Hypertension was defined as SBP of 140 mmHg or higher, DBP of 90 mmHg or higher, or

use of antihypertensive medications, which is consistent with the US Joint National Committee and Chinese definitions[15, 16]. Body mass index (BMI) was defined as weight in kilograms divided by height in square meters. Obesity was defined as 28.0 kg/m^2 or higher, based on recommendations from the Working Group on Obesity in China.[17]

Exposure Assessment

We geocoded each participant's current address (either rural counties or urban districts) into latitude and longitude data and identified air monitors located within 10 kilometers (**Supplement 2**). The average distance between the address of participants and assigned monitors was 2.7 (interquartile range 1.2, 3.5) kilometers. The measurements from these monitors strictly followed the methodological standards set by the State Environmental Protection Administration of China. For each participant, daily average $PM_{2.5}$ concentrations measured at the nearest monitors to the residence were used to estimate $PM_{2.5}$ exposure. The 1-year average concentration before the medical examination was calculated and treated as an indicator of long-term exposure to $PM_{2.5}$. In the present study, we included participants with more than 330 valid $PM_{2.5}$ values for assessing long-term exposure, to ensure that, for each participant, the missing rate of $PM_{2.5}$ data in the preceding one year of medical examination is less than 10%.[18]

Statistical Analysis

Continuous variables were reported as means with standard deviation; categorical variables were presented as percentages. We developed mixed models with a logit link function to

assess the effect of long-term exposure to $PM_{2.5}$ on hypertension prevalence. To assess the association of $PM_{2.5}$ and blood pressure, SBP and DBP were modeled using linear regressions with township-specific random intercepts. For each of these analyses, we started with a model (Model 1) which only included age and sex. We then incrementally adjusted for additional covariates. The second model (Model 2) included Model1 and socioeconomic factors (education level and urbanity). The third model (Model 3) included Model 2 and cardiovascular disease risk factors (BMI, smoking status, alcohol consumption, and diabetes). Models of blood pressure were controlled for hypertensive medication use; while models of hypertension were not, as hypertension medication use was a component of the outcome definition. For sensitivity analysis, we additionally adjusted for the day of week (one indicator variable per day) and season of measurement (summer: June–August; fall: September–November; winter: December–February; spring: March–May) to account for potential time-variant factors. We also used restricted cubic splines to characterize the concentration-response (C-R) relationships of $PM_{2.5}$ with hypertension prevalence and blood pressure.[19] In addition, to examine effect modification by age, gender, smoking status, alcohol consumption, diabetes, and obesity, each potential modifier was tested by adding an interaction term in the regression model separately and testing its statistical significance as well as the association per categories of the tested variable through subgroup analyses.

Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc., Cary, North Carolina). All tests of significance were 2-tailed, with a level of significance set at an alpha of 0.05.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULT

Study population and baseline characteristics

We included a total of 883,827 participants distributed in 83 county-level regions of mainland China (**Supplement 3**). The mean age was 55.5 years, 60.4% were women, 43.1% had hypertension, mean SBP was 143.5 mmHg, mean DBP was 83.1 mmHg, and 19.4% were taking antihypertensive medications. The 1-year $PM_{2.5}$ exposure of the total study population ranged from 8.8 to 93.8 μg/m^3 (mean 49.2 μg/m^3). There were 864,119 (97.8%), 842,356 (95.3%), and 706,415 (79.9%) participants with 1-year $PM_{2.5}$ exposure higher than 15 μg/m^3 [World Health Organization (WHO) Interim Target 3 (IT-1)], 25 μg/m^3 [WHO Interim Target 2 (IT-2)], and 35 μg/m^3 [WHO Interim Target 3 (IT-3)], respectively. (**Supplement 4**)

Associations of long-term $PM_{2.5}$ exposure with hypertension prevalence

After adjusting for sociodemographic characteristics and cardiovascular risk factors, the odds ratio (OR) of hypertension was 1.09 (95% CI: 1.08–1.10) for each 10 μg/m^3 increase in $PM_{2.5}$. The association of $PM_{2.5}$ exposure with hypertension prevalence remained consistent across different model specifications (**Supplement 5**). For the C-R relationship, the curve showed steeper slopes at high $PM_{2.5}$ exposure levels (i.e., higher than ~50 μg/m^3), and this

trend was also evident in the sensitivity analysis with further adjustment for day of week and season of blood pressure measurements (**Supplement 6**). Compared to individuals with the lowest level of $PM_{2.5}$ exposure (8.8 μg/m^3), the adjusted ORs for hypertension of individuals with 15, 25, and 35 μg/m^3 of $PM_{2.5}$ exposure were 1.01 (95% CI: 1.01–1.02), 1.03 (95% CI: 1.02–1.04), and 1.05 (95% CI: 1.03–1.07), respectively. (**Figure 1**)

Associations of long-term $PM_{2.5}$ exposure with systolic and diastolic blood pressure

In the adjusted Model 4, each 10 μg/m^3 increment was associated with increases of 0.50 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After adjustment for the day of week and season, these positive associations were also observed [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP]. (**Supplement 7**) In addition, we found that the shapes of the C-R curves for SBP and DBP were different. The fitted C-R functions showed upward trends with greater effect estimates of $PM_{2.5}$ at higher concentrations for SBP but were generally U-shaped for DBP. (**Figure 2**) These C-R relationships for blood pressure remained robust after accounting for time-variant factors. (**Supplement 8**)

Subpopulation difference and effect modification

The associations of $PM_{2.5}$ exposure with hypertension were stronger among the elderly (≥ 65 years), men, and non-current smokers compared with their counterparts (**Figure 3**). Gender significantly modified the effects of $PM_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger associations among men [e.g., OR for hypertension per 10

μg/m^3 increase in $PM_{2.5}$ of 1.06 (95% CI: 1.04–1.06) for women, and 1.12 (95% CI: 1.1–1.14) for men]; while these associations were not modified by alcohol consumption (all p for interaction >0.05). Although age and smoking status were also found to be effect modifiers in the associations of $PM_{2.5}$ exposure with SBP, DBP, and hypertension, the impacts of the two effect modifiers on these associations differed depending on the outcome. We observed greater effect estimates of $PM_{2.5}$ exposure for SBP and hypertension [e.g., OR for hypertension per 10 μg/m^3 increase in $PM_{2.5}$ of 1.14 (95% CI: 1.12–1.17) for the elderly, and 1.06 (95% CI: 1.05–1.08) for their younger counterparts], while smaller estimates for DBP among the elderly and non-current smokers [e.g., elevation in DBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.16 mmHg (95% CI: 0.04–0.27) for the elderly, and 0.24 mmHg (95% CI: 0.19–0.3) for their younger counterparts]. (**Figure 4**)

DISCUSSION

In this study, we investigated the associations between long-term exposure to $PM_{2.5}$ and hypertension prevalence, SBP, and DBP. We found that $PM_{2.5}$ was associated with increased risk of hypertension prevalence and elevation of blood pressure. Nonlinearity in these associations was also observed. The C-R curves for hypertension and SBP showed steeper slopes for $PM_{2.5}$ concentration above 50 μg/m^3; while the C-R curve for $PM_{2.5}$–DBP was U-shaped, with the turning point around 50 μg/m^3. The elderly, men, and non-current smokers appeared to be more susceptible to the exposure of $PM_{2.5}$.

Our study contributes to the existing scientific literature in several ways. First, we

incorporated a large cross-sectional survey with extensive covariates data obtained by personal interviews and standardized blood pressure measurements, which allowed us to comprehensively assess associations among a more diverse spectrum of population with a wider range of $PM_{2.5}$ concentrations. We found long-term exposure to $PM_{2.5}$ was positively associated with hypertension prevalence and blood pressure. This echoed the data showing that there was an absolute increase of 139 million individuals with hypertension in China during a decade from 2002–2013/14[20], with the national $PM_{2.5}$ level gradually increasing in the meantime.[21] Furthermore, the magnitude of the effects for each 10 μg/m^3 increment in $PM_{2.5}$ were also similar compared to other studies.[5, 7, 22-24] For example, one study based on 361,560 adults observed that each 10 μg/m^3 in $PM_{2.5}$ was associated with increases of 0.45 mmHg and 0.07 mmHg in SBP and DBP, respectively.[22] For hypertension prevalence, odds ratios related to a 10 μg/m^3 increase in $PM_{2.5}$ were ranged from 1.01 to 1.14 in prior studies.[5, 23, 24] It is also noteworthy that others have reported no or inconsistent associations.[25, 26] Adar et al. found no associations between exposures to $PM_{2.5}$ and blood pressure based on a longitudinal cohort.[25] However, this study only included a small fraction of Chinese populations (10%), and was conducted in the U.S. with a mean annual average $PM_{2.5}$ of 17 μg/m^3, which was lower than this study (49.2 μg/m^3).

Second, we provided new information on the C-R relationship between long-term $PM_{2.5}$ exposure and hypertension prevalence. Previous research reported a U-shaped relationship with a threshold $PM_{2.5}$ of 47.9 μg/m^3.[5] However, in our study, the risk of hypertension associated with $PM_{2.5}$ became even more pronounced when the exposure was extended to

higher levels. This finding was in line with a prior study based on prospective cohorts showed that higher $PM_{2.5}$ exposure was significantly associated with increased risk of developing hypertension, with hazard ratios (95% CIs) for hypertension incidence of 1.27 (1.17–1.39), 1.44 (1.30–1.58), and 1.77 (1.56–2.00) for the participants in the second (71.9-73.7 μg/m^3), third (73.7-82.2 μg/m^3), and fourth quartiles (>82.2 μg/m^3) of $PM_{2.5}$ concentrations compared with those in the first quartile (<71.9 μg/m^3), respectively.[27] This result suggests that a per unit decrease in the concentration of $PM_{2.5}$ can be translated to a greater reduction in excess hypertension prevalence in highly polluted regions compared with regions with low to moderate levels of $PM_{2.5}$ exposure.

Third, we found evidence of nonlinearity in the relationships of $PM_{2.5}$ exposure with SBP and DBP. Interestingly, the shape of curves for SBP and DBP were different. Although the relevant mechanism remains unclear, pathophysiological changes, such as systemic inflammation, atherosclerosis, endothelial dysfunction, and increased arterial stiffness,[4] may have contributed to the observed patterns. The increased arterial stiffness induced by $PM_{2.5}$ would initially lead to elevation in SBP and decline in DBP, creating an increased pulse pressure.[28] While with further increase of arterial stiffness, the heart rates got higher to maintain the stroke volume, which could result in the rise of DBP afterward. In addition, prior studies have reported the effects of $PM_{2:5}$ exposure on pulse pressures showing a tendency of rising first and then declining at higher $PM_{2.5}$ levels, which partially supports this hypothesis.[22]

Fourth, we assessed the subpopulation differences through stratified analyses and identified the susceptible individuals to the exposure of $PM_{2.5}$. We observed the large effect estimates of $PM_{2.5}$ on hypertension and SBP among the elderly. Elderly subjects may commonly represent a higher prevalence of preexisting cardiovascular and respiratory diseases, which may confer susceptibility to $PM_{2.5}$. Also, the results showed that $PM_{2.5}$ exposure had larger effects on hypertension in men, and such increased susceptibility may be related to sex-related differences in the deposition localization and rates of air pollutants; specifically, men have larger airways and slightly lower airway reactivity.[29] Additionally, smoking status was found to be an effect modifier with smaller effects on hypertension among current smokers. This finding is also supported by prior research.[8, 22] One possible explanation is that smoking and $PM_{2.5}$ exposure may share the same pathways in mediating cardiovascular effects and smoking may play a dominant role in smokers. Thus, exposure to $PM_{2.5}$ might not exert additional harmful effects via the same pathway.[22] There is also some potential that the greater effect size in non-current smokers could also be connected to some of them being advised to quit smoking because of multiple comorbidities.

Our study should also be interpreted in the context of several limitations. First, given the nature of the cross-sectional study design, the causal relationship could not be established. Additional research is needed to examine these relationships in a prospective manner. Second, a selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data. Third, while we included a number of potential confounders in the analyses, there might be unmeasured confounders that affected the observed associations.

In particular, we were unable to control for other confounders such as diet and physical activity, because these data were only available in a subset of the China PEACE Million Persons Project cohort. Fourth, we used the data from the fixed monitors to estimate the exposure of $PM_{2.5}$ and did not account for residential proximity to major roads, time-activity patterns, and indoor-related characteristics, which would likely result in nondifferential measurement errors. However, this approach is commonly used and previous research has indicated that $PM_{2.5}$ exposure estimated by the nearest monitor was highly correlated with other sophisticated approaches[30]. Fifth, other gaseous pollutants, such as NOx and ozone, temperature, and noise were not included in this study. As a result, we were not able to determine whether the observed effects were specifically attributable to $PM_{2.5}$ or the combined effects of these factors.

In conclusion, our study demonstrated that long-term exposure to $PM_{2.5}$ was positively associated with blood pressure and hypertension prevalence. The effect of $PM_{2.5}$ on hypertension prevalence was more pronounced at higher $PM_{2.5}$ concentrations. Our findings reinforce the need to develop comprehensive strategies for addressing air pollution problems, especially for areas with severe air pollution.

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DISCLOSURES

Dr. Jing Li discloses that she is a recipient of research grants from the government of China, through Fuwai Hospital, for research to improve the management of hypertension and blood lipids, and to improve care quality and patient outcomes of cardiovascular disease; is a recipient of research agreements with Amgen, through National Center for Cardiovascular Diseases (NCCD) and Fuwai Hospital, for a multi-centre trial to assess the efficacy and safety of Omecamtiv Mecarbil, and for dyslipidemic patient registration; is a recipient of a research agreement with Sanofi, through Fuwai Hospital, for a multi-centre trial on the effects of sotagliflozin; is a recipient of a research agreement with University of Oxford, through Fuwai Hospital, for a multi-centre trial of empagliflozin; and was a recipient of a research agreement, through NCCD, from AstraZeneca for clinical research methods training. The authors declare no other relevant conflicts of interest.

CONTRIBUTORS

JS and XZ conceived of this article. JS and YG wrote the manuscript with further contributions from XZ, XL, EM, MR, GT, DZ, WZ, JL, and MA. JS and SH completed all the statistical analyses. All authors interpreted data, contributed to critical revisions, and approved the final version of the article.

DATA AVAILABILITY STATEMENT

No data is available. The China PEACE Million Persons Project is a major national program, and as the government policy stipulates, it is not permissible for the researchers to make the raw data publicly available at this time. All data generated during this study are included in this manuscript and its supplementary information files.

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FIGURE LEGEND

Figure 1. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with hypertension prevalence

Figure 2. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Figure 3. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with hypertension prevalence

Figure 4. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP)

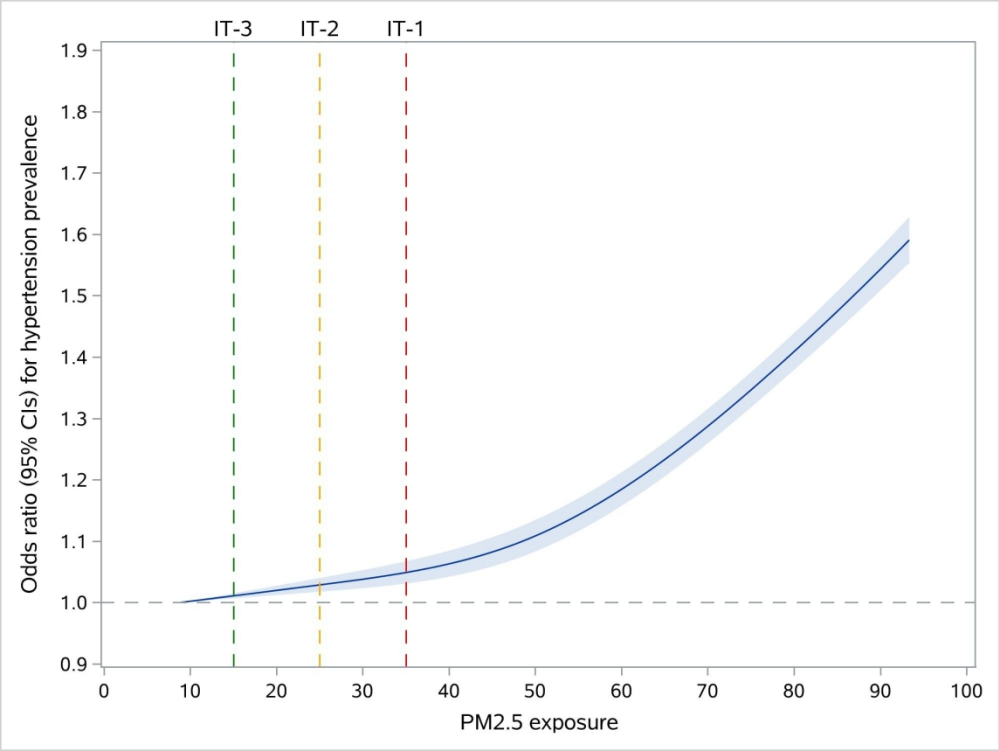

Figure 1. Concentration-response functions of the long-term exposure to PM2.5 with hypertension prevalence.
Effect estimates were presented as adjusted odds ratios for hypertension prevalence compared to individuals with PM2.5 exposure 8.8 μg/m3.
The dashed lines represent the air-quality standards for annual average concentrations of PM2.5 according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, and diabetes

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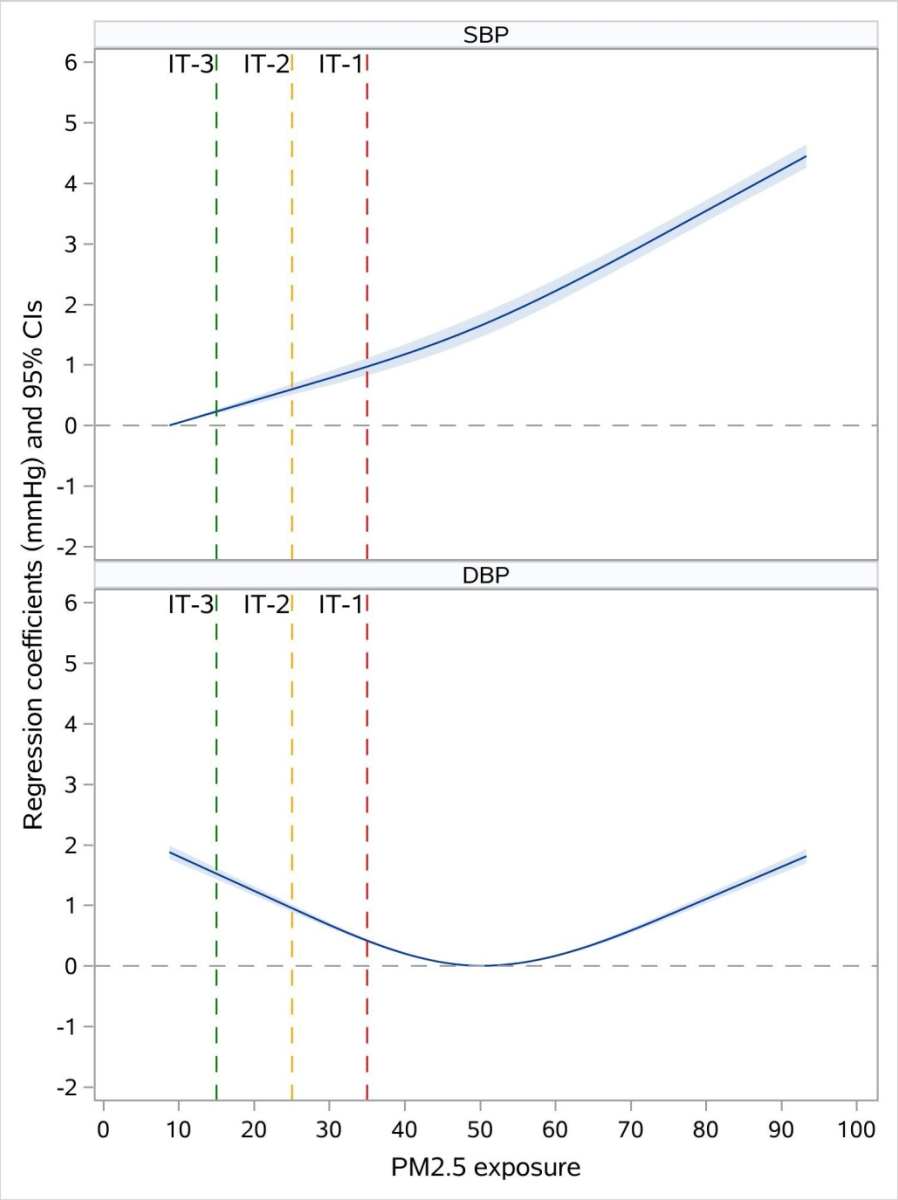
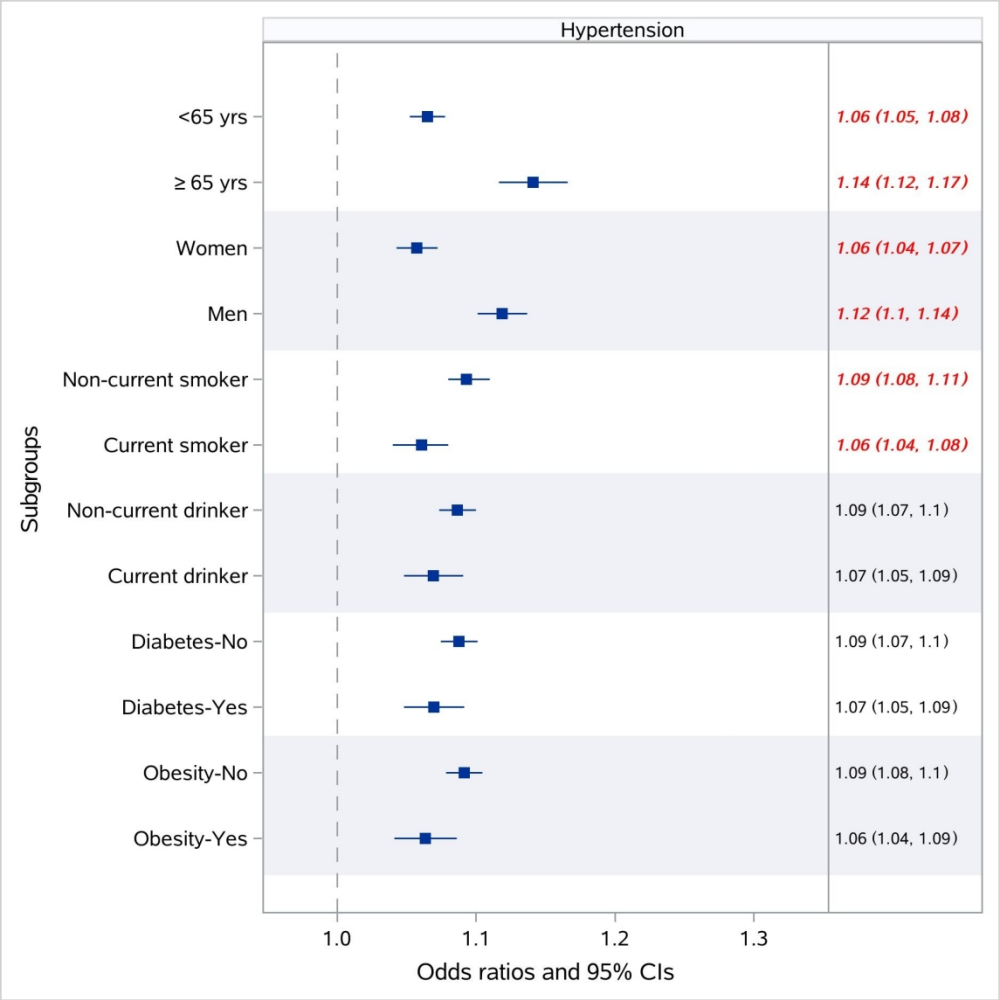


Figure 2. Concentration-response functions of the long-term exposure to PM2.5 with systolic blood pressure (SBP) and diastolic blood pressure (DBP)
Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with PM2.5 exposure 8.8 μg/m3 and changes in DBP compared to individuals with PM2.5 exposure 50 μg/m3. The dashed lines represent the air-quality standards for annual average concentrations of PM2.5 according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications.

127x169mm (300 x 300 DPI)



Stratified analysis of the association of long-term exposure to PM2.5 with hypertension prevalence.
Red texts with italics indicated that p-value for interaction terms<0.05.
Effect estimates (regression coefficients) were presented as adjusted odds ratios for hypertension prevalence for each 10 μg/m3 increment in the 1-year PM2.5 exposure.
Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity and diabetes.

158x158mm (300 x 300 DPI)

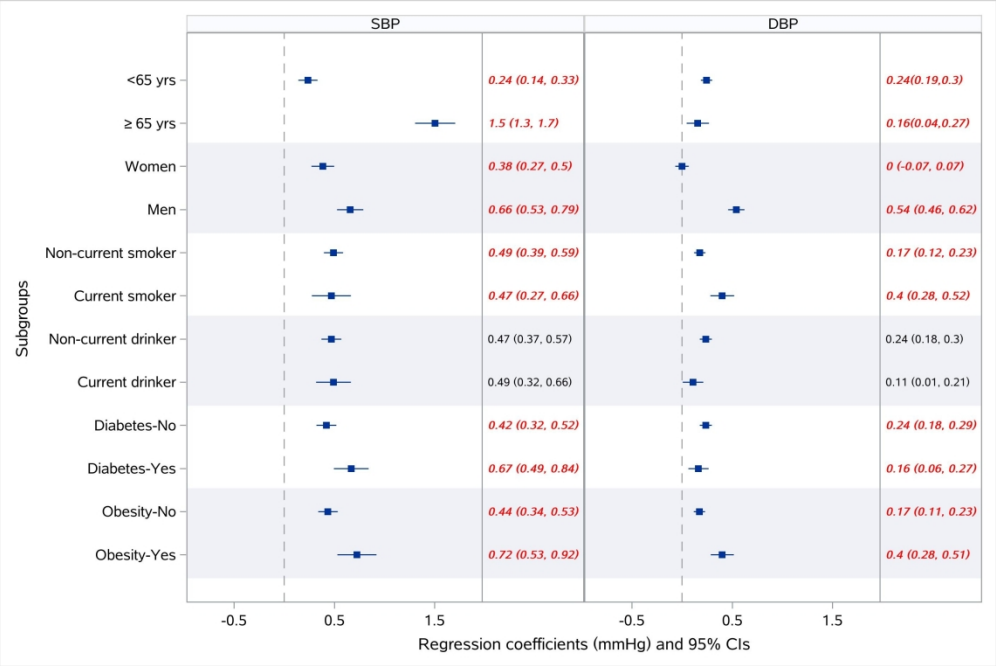


Figure 4. Stratified analysis of the association of long-term exposure to PM2.5 with blood pressure
Red texts with italics indicated that p-value for interaction terms<0.05.
Effect estimates (regression coefficients) were presented as changes in systolic blood pressure (SBP) or diatolic blood pressure (DBP) for each 10 μg/m3 increment in the 1-year PM2.5 exposure deriving from multivariable linear regression. Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications.

238x158mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

Supplement 1. Collection of medication data in China PEACE Million Persons Project.

Potential participants who were taking medications were required to bring their drug packaging (boxes) to the project sites. During the face-to-face interview, local project staff asked participants whether they always took anti-hypertension, lipid-lowering, anti-diabetics, or anti-platelet drugs during the past 2 weeks. Those who answered “yes” and knew the name of the drug were further asked to report the name, dose, and frequency of each drug. For those who did not remember the exact dose of the drug, the number of tablets or pills taken was recorded. Interviewers searched and selected drug names or the first letter of the Chinese phonetic alphabet participants answered by entering the generic name or trade name of each drug in the electronic data collecting system. In this system, a data dictionary was used to confirm drug information, including the drug class, generic name, trade name, and corresponding unique ID.

Supplement 2. Summary statistics for daily $PM_{2.5}$ ($\mu g/m^3$) concentrations of assigned monitors in 83 study regions.

No.	Mean	Median	25th percentile	75th percentile	Minimum	Maximum	Total (days)	Missing (days)
1	67.9	50	26	88	5	540	1461	22
2	65.48	48	23	85	3	515	1461	25
3	56.39	40	19	76	2	448	1461	18
4	69.26	50	27	88	4	529	1461	10
5	57.73	41	20	77	4	446	1461	9
6	64.46	51	32	79.5	6	350	1461	13
7	62.85	50	30	78	4	409	1461	38
8	68.35	54	34	83.5	7	408	1461	37
9	64.46	51	32	79.5	6	350	1461	13
10	65.52	51	32	81	7	410	1461	34
11	86.31	61	38	107	5	708	1461	37
12	63.99	52	37	76	6	421	1461	18
13	61.01	50	30	79	2	290	1461	24
14	60.51	49	32	76	7	390	1461	70
15	46.19	40	29	55	7	276	1461	44
16	22.9	18	12	29	3	187	1461	59
17	54.55	41	26	68	3	932	1461	14
18	40.93	32	20	50	5	450	1461	16
19	44.97	35	22	56	6	353	1461	39
20	48.8	37	24	59	6	508	1461	15
21	45.3	31	19	55	3	612	1461	27
22	30.54	22	14	39	2	308	1461	17
23	45.36	34	21	58	3	378	1461	24
24	54.24	33	21	66	5	730	1461	24
25	39.52	29	18	49	3	502	1461	78
26	42.91	36	22	55	4	235	1461	24
27	44.22	36	22	58	5	225	1461	60
28	44.97	38	24	58	5	218	1461	22
29	44.32	37	23	57	6	224	1461	12
30*	49.23	40	28	62	10	271	797	1
31	52.7	42	27	67	7	284	1461	9
32	51.19	43	28	64	3	250	1461	40
33	49.98	44	31	61	6	259	1461	26
34	47.59	40	27	59	3	233	1461	30
35	27.35	25	17	35	2	114	1461	46
36	26.16	22	14	34	2	233	1461	5
37*	32.18	25	14	45	4	155	650	15
38	45.33	40	29	57	9	209	1461	32
39	49.12	44	31	62	3	356	1461	27
40	74.08	60	40	92	7	431	1461	22
41	56.81	46	31	70	7	327	1461	44
42*	70.49	57	40	82	6	514	797	56
43*	56.69	46	34	65	14	257	606	15
44	69.96	53	35	88	5	548	1461	57
45	62	50	31	81	3	275	1461	20
46	44.01	38	26	56	5	195	1461	31
47	48.13	43	29	61	6	478	1461	43
48	51.57	43	29	65	5	289	1461	10
49	39.33	33	23	50	6	214	1461	12

50	32.84	29	20	42	5	121	1461	22
51	32.48	28	18	43	5	149	1461	35
52	27.19	24	14	36	3	120	1461	31
53	38.01	33	21	49	5	192	1461	16
54	35.67	30	19	46	3	269	1461	13
55	50.36	42	27	64	6	286	1461	23
56	44.34	35	23	56	5	333	1461	6
57	35.14	29	16	47	3	202	1461	22
58	22.1	18	14	27	3	123	1461	31
59	15.14	13	9	18	2	68	1461	12
60*	37.75	29	18	47	5	183	773	20
61	49.89	41	30	61	8	222	1461	27
62	60.72	49	32	77	5	353	1461	8
63	42.87	36	24	55	5	215	1461	16
64	49.35	40	24	65	3	235	1461	13
65	32.64	28	18	42	4	195	1461	23
66	30.96	28	21	39	7	123	1461	10
67	29.79	28	20	36	7	102	1461	23
68	13.86	14	12	15	3	51	1461	109
69	25.99	19	13	32	5	187	1461	33
70	24.49	19	13	30	2	124	1461	156
71	11.95	10	7	15	2	88	1461	87
72	51.21	42	30	63	10	239	1461	238
73	10.62	9	7	13	4	73	1461	46
74	53.8	41.5	28	64	5	328	1461	19
75	38.88	32	23	47	4	169	1461	27
76	44.45	36	24	57	4	581	1461	59
77	44.1	36	25	53	5	287	1461	44
78*	44.04	38	27	56	9	139	488	27
79	55.15	45	30	68	5	363	1461	14
80	44.69	36	24	55	5	219	1461	50
81	65.37	34	20	85	5	447	1461	97
82	57.76	29	19	70	3	414	1461	58
83	51.7	26	14	65	3	406	1461	42

Note:

* Monitors being available after 2015

Total: Number of days of assigned monitors being available during 2015-2018

Missing: Number of days with missing $PM_{2.5}$ concentration during 2015-2018

Supplement 3. Distribution of the sites.

Supplement 4. Characteristics of the study population.

Variable	Total (n=883,827)
Socio-demographics	
Age, mean (SD), years	55.5 (10.1)
Female, n (%)	533897 (60.4)
Urban residence, n (%)	657608 (74.4)
Han ethnic group, n (%)	805479 (91.1)
College or above	102764 (11.6)
Regions, n (%)	
Eastern	325253 (36.8)
Central	178435 (20.2)
Western	311599 (35.3)
NorthEastern	68540 (7.8)
Cardiovascular risk factors, n (%)	
Obesity	142150 (16.1)
Current drinker	194967 (22.1)
Diabetes	173950 (19.7)
Current smoker	161006 (18.2)
Hypertension	381223 (43.1)
Blood pressures	
Systolic blood pressure, mean (SD)	143.5 (22.2)
Diastolic blood pressure, mean (SD)	83.1 (12.3)
$PM_{2.5}$ exposures	
1-y average $PM_{2.5}$ exposure, mean (SD)	49.2 (16.4)
Above WHO Interim Target 1 (IT-1, 35 μg/m^3), n (%)	706415 (79.9)
Above WHO Interim Target 2 (IT-2, 25 μg/m^3), n (%)	842356 (95.3)
Above WHO Interim Target 3 (IT-3, 15 μg/m^3), n (%)	864119 (97.8)

Supplement 5. The effect of $PM_{2.5}$ exposure on hypertension prevalence.

Model	Per 10 μg/m³ $PM_{2.5}$ increment	
	Odds ratios (95% confidence intervals)	p-Value
Hypertension prevalence		
Model 1	1.10 (1.09-1.11)	<0.001
Model 2	1.10 (1.09-1.11)	<0.001
Model 3	1.09 (1.08-1.10)	<0.001
Model 4*	1.09 (1.08-1.10)	<0.001
Model 5*	1.04 (1.02-1.05)	<0.001
Model 6*	1.04 (1.02-1.05)	<0.001

*Sensitivity analysis

Model 1: Included age and sex;

Model 2: Model 1 + education level and urbanity;

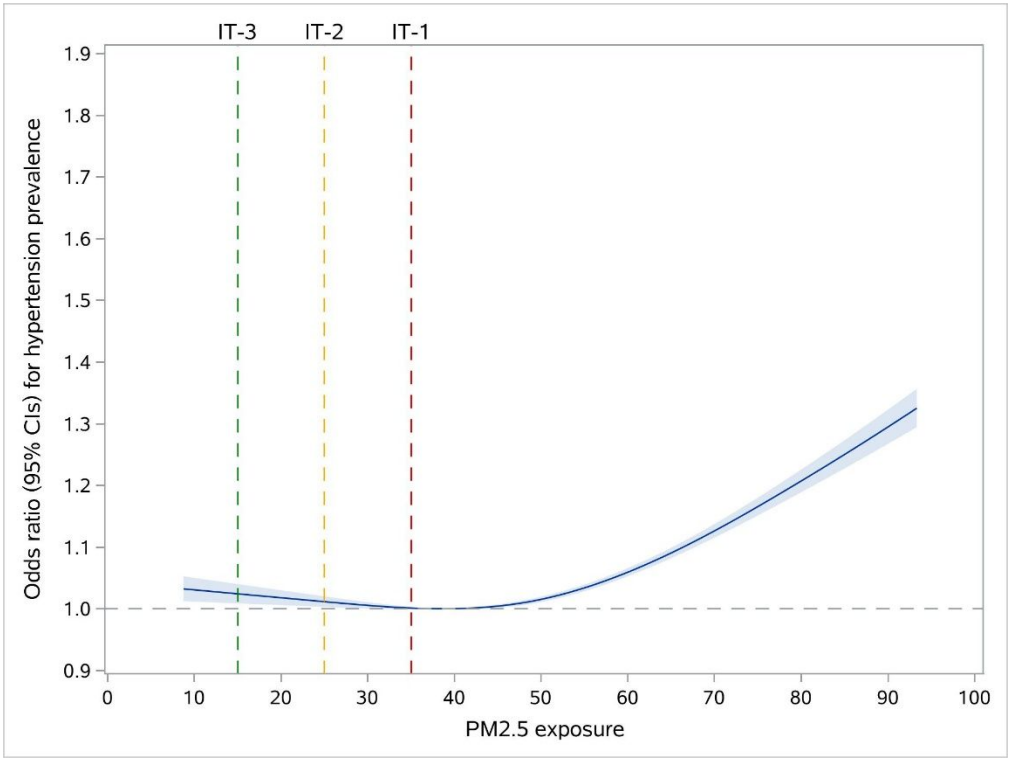
Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes;

Model 4: Model 3 + day of week of the medical examination;

Model 5: Model 3 + season of the medical examination;

Model 6: Model 3 + day of week + season.

Supplement 6. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with hypertension prevalence in the sensitivity analysis.



Effect estimates were presented as adjusted odds ratios for hypertension prevalence compared to individuals with $PM_{2.5}$ exposure 38.5 μg/m^3.

The dashed lines represent the air-quality standards for annual average concentrations of $PM_{2.5}$ according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).

Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, as well as the day of week and season of blood pressure measurement.

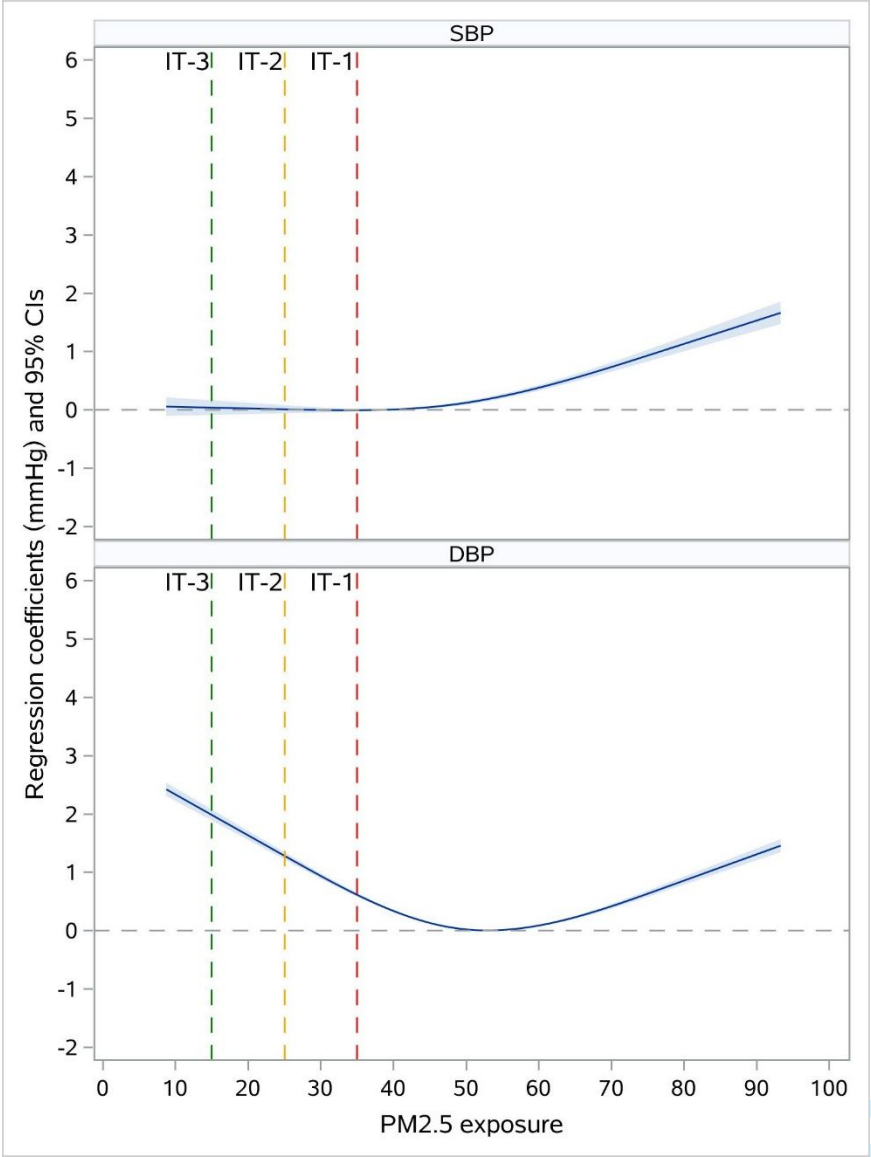
Supplement 7. The effect of $PM_{2.5}$ exposure on blood pressure.

Model	Per 10 μg/m³ $PM_{2.5}$ increment	
	mmHg (95% confidence intervals)	p-value
Systolic blood pressure		
Model 1	0.58 (0.49-0.67)	<0.001
Model 2	0.57 (0.48-0.66)	<0.001
Model 3	0.45 (0.36-0.54)	<0.001
Model 4	0.50 (0.41-0.59)	<0.001
Model 5*	0.50 (0.41-0.59)	<0.001
Model 6*	0.19 (0.10-0.28)	<0.001
Model 7*	0.19 (0.10-0.28)	<0.001
Diastolic blood pressure		
Model 1	0.29 (0.23-0.34)	<0.001
Model 2	0.28 (0.23-0.34)	<0.001
Model 3	0.21 (0.15-0.26)	<0.001
Model 4	0.23 (0.18-0.28)	<0.001
Model 5*	0.23 (0.18-0.28)	<0.001
Model 6*	0.13 (0.08-0.18)	<0.001
Model 7*	0.13 (0.08-0.18)	<0.001

*Sensitivity analysis

Model 1: Included age and sex;
Model 2: Model 1 + education level and urbanity;
Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes;
Model 4: Model 3 + use of antihypertensive medication;
Model 5: Model 4 + day of week of the medical examination;
Model 6: Model 3 + season of the medical examination;
Model 7: Model 3 + day of week + season.

Supplement 8. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the sensitivity analysis.



Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with $PM_{2.5}$ exposure 39 μg/m^3 and changes in DBP compared to individuals with $PM_{2.5}$ exposure 53 μg/m^3.

The dashed lines represent the air-quality standards for annual average concentrations of $PM_{2.5}$ according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).

Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications, as well as the day of week and season of blood pressure measurement.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure in China: a cross-sectional study

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES, Hypertension < CARDIOLOGY

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TITLE PAGE

Association of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure in China: a cross-sectional study

Authors

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ABSTRACT

Objective: Evidence of the effects of long-term fine particulate matter ($PM_{2.5}$) exposure on hypertension and blood pressure is limited for populations exposed to high levels of $PM_{2.5}$. We aim to assess associations of long-term exposure to $PM_{2.5}$ with hypertension prevalence and blood pressure, and further explore the subpopulation differences and effect modification by participant characteristics in these associations in China.

Methods: We analyzed cross-sectional data from 883,827 participants aged 35–75 years in the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project. Data from the monitoring station was used to estimate the one-year average concentration of $PM_{2.5}$. The associations of $PM_{2.5}$ exposure with hypertension prevalence and blood pressure were investigated by generalized linear models, with $PM_{2.5}$ included as either linear or spline functions.

Results: The 1-year $PM_{2.5}$ exposure of the study population ranged from 8.8 to 93.8 μg/m^3 (mean 49.2 μg/m^3). The adjusted odds ratio of hypertension prevalence related to a 10 μg/m^3 increase in one-year $PM_{2.5}$ exposure was 1.04 (95% confidence interval, 1.02–1.05). Each 10 μg/m^3 increment in $PM_{2.5}$ exposure was associated with increases of 0.19 mmHg (95% confidence interval, 0.10–0.28) and 0.13 mmHg (95% confidence interval, 0.08–0.18) in systolic blood pressure and diastolic blood pressure, respectively. The concentration-response curves for hypertension prevalence and systolic blood pressure showed steeper slopes at higher $PM_{2.5}$ levels; while the curve for diastolic blood pressure was U-shaped. The elderly, men, non-current smokers, and obese participants were more susceptible to the exposure of $PM_{2.5}$.

Conclusions: Long-term exposure to $PM_{2.5}$ is associated with higher blood pressure and increased risk of hypertension prevalence. The effects of $PM_{2.5}$ on hypertension prevalence become more pronounced at higher $PM_{2.5}$ levels. These findings emphasize the need to reduce air pollution, especially in areas with severe air pollution.

Keywords: Air pollution; Blood pressure; Hypertension

Strengths and limitations of this study

- The large size of our study allowed us to comprehensively assess these associations among a diverse spectrum of population across a wider range of $PM_{2.5}$ concentrations in China.
- The large number of participants with hypertension and high level of $PM_{2.5}$ exposure (e.g. >35 μg/m^3), enabled us to examine these associations with greater precision and sufficient statistical power.
- Given the nature of the cross-sectional study design, the causal relationship could not be established.
- A selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data.

INTRODUCTION

Hypertension is the leading risk factor for death globally.[1] Although hypertension is a worldwide public health concern, three-quarters of the world's population with the condition are living in low- and middle-income countries (LMICs).[2] The causes of hypertension are complex. Apart from genetic predisposition, social determinants, and lifestyle factors, air pollution, especially fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), may also contribute to increased risk for hypertension.[3, 4]

Over the past few years, a growing body of epidemiological evidence indicated the association of long-term exposure to $PM_{2.5}$ with blood pressure and hypertension.[5-10] However, most of the studies were undertaken in high-income countries.[8, 10] Compared with high-income countries, exposure to $PM_{2.5}$ is substantially higher in LMICs. Furthermore, prior studies have largely focused on specific populations or regions.[5-7] Therefore, further studies are needed to assess the associations of $PM_{2.5}$ with blood pressure and prevalence of hypertension among a wider spectrum of populations with high $PM_{2.5}$ concentrations, especially in LMICs.

China is experiencing a growing epidemic of hypertension and is estimated to have 300 million individuals with hypertension by 2025.[11] Meanwhile, outdoor $PM_{2.5}$ has become one of China's most serious environmental problems with population-weighted annual means of $PM_{2.5}$ ranging from 19.1 μg/m³ to 79.3 μg/m³ in 2015.[12] A deeper understanding of the chronic health effects of $PM_{2.5}$ on hypertension prevalence and blood pressure in moderate

to high $PM_{2.5}$ concentrations will help to develop policies to improve air quality and combat the hypertension epidemic in China.

Accordingly, incorporating $PM_{2.5}$ data with a large-scale population-based screening project in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project, we aimed to: (1) explore the association of long-term $PM_{2.5}$ exposure with blood pressure level and hypertension prevalence, and evaluate subpopulation differences and effect modification by characteristics of participants in these associations; (2) assess the concentration-response relationships of long-term $PM_{2.5}$ exposure with hypertension prevalence and blood pressure.

METHODS

Study population

Our study population is derived from the China PEACE Million Persons Project, which has been described previously.[13] In brief, we selected county-level regions using a convenience sampling strategy in all 31 provinces in mainland China from September 2014 to March 2019. These regions are designated as rural counties or urban districts according to urban-rural division codes of the National Bureau of Statistics of China.[14] Local residents aged 35 to 75 years, who were currently registered in the selected region's Hukou (a record officially identifying a person as a resident of an area) or had lived in the region for at least 6 of the previous 12 months, were enrolled in this project. After excluding participants with missing data on education level (n=13,714), body mass index (n=321), or blood pressure

measurement (n=2), we further excluded participants with systolic blood pressure (SBP) ≥ 250 mmHg or diastolic blood pressure (DBP) ≥150 mmHg to minimize the potential bias due to measurement errors in blood pressure values (n=73). Finally, we included 883,827 participants in the study sample.

Data collection and variable definitions

Data collection for each participant was performed by trained personnel with a standardized in-person interview and a medical examination. Information on sociodemographic status (age, gender, and education level), lifestyle (smoking and alcohol use), medical history, and medication use were collected. Medication use was determined by asking participants whether they had taken prescribed medications for controlling blood pressure or glucose in the past 2 weeks. Those who answered "yes" and knew the drug names were asked to report the name, dose, and frequency of each drug. Those who did not remember the exact dose stated the number of pills or tablets taken (**Supplement 1**).

The blood pressure of each participant was measured twice on the right upper arm after 5 minutes of rest in a seated position with a standardized electronic blood pressure monitor (Omron HEM-7430). If the difference between the two SBP readings was greater than 10 mmHg, a third measurement was obtained, and the average of the last 2 readings was used. Hypertension was defined as SBP of 140 mmHg or higher, DBP of 90 mmHg or higher, or use of antihypertensive medications, which is consistent with the US Joint National Committee and Chinese definitions[15, 16]. Body mass index (BMI) was defined as weight in

kilograms divided by height in square meters. Obesity was defined as 28.0 kg/m^2 or higher, based on recommendations from the Working Group on Obesity in China.[17]

Exposure Assessment

We geocoded each participant's current address (either rural counties or urban districts) into latitude and longitude data and identified air monitors located within 10 kilometers (**Supplement 2**). The average distance between the address of participants and assigned monitors was 2.7 (interquartile range 1.2, 3.5) kilometers. The measurements from these monitors strictly followed the methodological standards set by the State Environmental Protection Administration of China. For each participant, daily average $PM_{2.5}$ concentrations measured at the nearest monitors to the residence were used to estimate $PM_{2.5}$ exposure. The 1-year average concentration before the medical examination was calculated and treated as an indicator of long-term exposure to $PM_{2.5}$. In the present study, we included participants with more than 330 valid $PM_{2.5}$ values for assessing long-term exposure, to ensure that, for each participant, the missing rate of $PM_{2.5}$ data in the preceding one year of medical examination is less than 10%.[18]

Statistical Analysis

Continuous variables were reported as means with standard deviation; categorical variables were presented as percentages. We developed mixed models with a logit link function to assess the effect of long-term exposure to $PM_{2.5}$ on hypertension prevalence. To assess the association of $PM_{2.5}$ and blood pressure, SBP and DBP were modeled using linear

regressions with township-specific random intercepts. For each of these analyses, we started with a model (Model 1) which only included age and sex. We then incrementally adjusted for additional covariates. The second model (Model 2) included Model1 and socioeconomic factors (education level and urbanity). The third model (Model 3) included Model 2 and cardiovascular disease risk factors (BMI, smoking status, alcohol consumption, and diabetes). Models of blood pressure were controlled for hypertensive medication use; while models of hypertension were not, as hypertension medication use was a component of the outcome definition. To account for potential time-variant factors, we additionally adjusted for the day of week (one indicator variable per day) and season of measurement (summer: June–August; fall: September–November; winter: December–February; spring: March–May). We also used restricted cubic splines to characterize the concentration-response (C-R) relationships of $PM_{2.5}$ with hypertension prevalence and blood pressure.[19] In addition, to examine effect modification by age, gender, smoking status, alcohol consumption, diabetes, and obesity, each potential modifier was tested by adding an interaction term in the regression model separately and testing its statistical significance as well as the association per categories of the tested variable through subgroup analyses.

Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc., Cary, North Carolina). All tests of significance were 2-tailed, with a level of significance set at an alpha of 0.05.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULT

Study population and baseline characteristics

We included a total of 883,827 participants distributed in 83 county-level regions of mainland China (**Supplement 3**). The mean age was 55.5 years, 60.4% were women, 43.1% had hypertension, mean SBP was 143.5 mmHg, mean DBP was 83.1 mmHg, and 19.4% were taking antihypertensive medications. The 1-year $PM_{2.5}$ exposure of the total study population ranged from 8.8 to 93.8 μg/m^3 (mean 49.2 μg/m^3). There were 864,119 (97.8%), 842,356 (95.3%), and 706,415 (79.9%) participants with 1-year $PM_{2.5}$ exposure higher than 15 μg/m^3 [World Health Organization (WHO) Interim Target 3 (IT-1)], 25 μg/m^3 [WHO Interim Target 2 (IT-2)], and 35 μg/m^3 [WHO Interim Target 3 (IT-3)], respectively. (**Supplement 4**)

Associations of long-term $PM_{2.5}$ exposure with hypertension prevalence

After adjusting for sociodemographic characteristics and cardiovascular risk factors, the odds ratio (OR) of hypertension was 1.09 (95% CI: 1.08–1.10) for each 10 μg/m^3 increase in $PM_{2.5}$. The adjustment for day of week and season of blood pressure measurements resulted in a slight decrease in the effect estimate of the association of $PM_{2.5}$ exposure with hypertension prevalence (OR: 1.04, 95%CI: 1.02–1.05). (**Supplement 5**) For the C-R relationship, the curve showed steeper slopes at high $PM_{2.5}$ exposure levels (i.e., higher than

~50 μg/m^3). Compared to individuals with $PM_{2.5}$ exposure of 38.5 μg/m^3, the adjusted ORs for hypertension of individuals with 15, 25, and 35 μg/m^3 of $PM_{2.5}$ exposure were 1.02 (95% CI: 1.01–1.04), 1.01 (95% CI: 1.00–1.02), and 1.00 (95% CI: 1.00–1.00), respectively. (**Figure 1**)

Associations of long-term $PM_{2.5}$ exposure with systolic and diastolic blood pressure

In the adjusted Model 4, each 10 μg/m^3 increment was associated with increases of 0.50 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After adjustment for the day of week and season, there was some reduction in the effect estimates of the associations between $PM_{2.5}$ exposure and blood pressure [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP]. (**Supplement 6**) In addition, we found that the shapes of the C-R curves for SBP and DBP were different. The fitted C-R functions showed upward trends with greater effect estimates of $PM_{2.5}$ at higher concentrations for SBP but were generally U-shaped for DBP. (**Figure 2**)

Subpopulation difference and effect modification

The associations of $PM_{2.5}$ exposure with hypertension were stronger among men and non-current smokers, compared with their counterparts (**Figure 3**). Gender significantly modified the effects of $PM_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger associations among men [e.g., OR for hypertension per 10 μg/m^3 increase in $PM_{2.5}$ of 1.01 (95% CI: 1.00–1.03) for women, and 1.06 (95% CI: 1.05–1.08) for men]; while these associations were not modified by alcohol consumption and prevalence of diabetes (all p for

interaction >0.05). Although smoking status was the effect modifiers in the associations of $PM_{2.5}$ exposure with SBP, DBP, and hypertension, the impacts of smoking on these associations differed depending on the outcome. We observed greater effect estimates of $PM_{2.5}$ exposure for SBP [elevation in SBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.97 mmHg (95% CI: 0.77–1.17) for the elderly, and -0.02 mmHg (95% CI: -0.12–0.08) for their younger counterparts], while smaller estimates for DBP among the elderly [elevation in DBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.11 mmHg (95% CI: 0.00–0.22) for the elderly, and 0.14 mmHg (95% CI: 0.08–0.20) for their younger counterparts]. Besides, obesity was also found to be an effect modifier in the associations of $PM_{2.5}$ exposure with SBP and DBP, with greater effect estimates in obese participants. (**Figure 4**)

DISCUSSION

In this study, we investigated the associations between long-term exposure to $PM_{2.5}$ and hypertension prevalence, SBP, and DBP. We found that $PM_{2.5}$ was associated with increased risk of hypertension prevalence and elevation of blood pressure. Nonlinearity in these associations was also observed. The C-R curves for hypertension and SBP showed steeper slopes for $PM_{2.5}$ concentration above 50 μg/m^3; while the C-R curve for $PM_{2.5}$–DBP was U-shaped, with the turning point around 50 μg/m^3. The elderly, men, non-current smokers, and obese participants appeared to be more susceptible to the exposure of $PM_{2.5}$.

Our study contributes to the existing scientific literature in several ways. First, by including participants in a national cross-sectional survey with long-term exposure to $PM_{2.5}$ ranged

from 8.8–93.8 μg/m^3, we are able to comprehensively assess the association of $PM_{2.5}$ exposure with hypertension prevalence and blood pressure among a more diverse spectrum of population with a wider range of $PM_{2.5}$ concentrations. We found exposure to $PM_{2.5}$ was positively associated with hypertension prevalence and blood pressure. This echoed the data showing that there was an absolute increase of 139 million individuals with hypertension in China during a decade from 2002 to 2013/14[20], with the national annual mean $PM_{2.5}$ increasing from 39.5 μg/m^3 to 47 μg/m^3 between 2000 and 2013.[21] Specifically, in some high-polluted areas such as Beijing-Tianjin-Hebei region of 2013, the annual average concentrations of $PM_{2.5}$ had reached 98.9 μg/m^3, and daily average concentrations had exceeded 300 μg/m^3.[22, 23] Furthermore, the magnitude of the effects for each 10 μg/m^3 increment in $PM_{2.5}$ was also similar compared to other studies.[5, 7, 24-26] For example, one study found that each 10 μg/m^3 in $PM_{2.5}$ was associated with increases of 0.45 mmHg and 0.07 mmHg in SBP and DBP, respectively.[24] And odds ratios for hypertension prevalence related to a 10 μg/m^3 increase in $PM_{2.5}$ were ranged from 1.01 to 1.14 in prior studies.[5, 25, 26] It is also noteworthy that others have reported no or inconsistent associations.[27, 28] Adar et al. found no associations between exposures to $PM_{2.5}$ and blood pressure based on a longitudinal cohort.[27] However, this study only included a small fraction of Chinese populations (10%), and was conducted in the U.S. with a mean annual average $PM_{2.5}$ of 17 μg/m^3, which was lower than the present study (49.2 μg/m^3).

Second, we provided new information on the C-R relationship between long-term $PM_{2.5}$ exposure and hypertension prevalence. Previous research reported a U-shaped relationship

with a threshold $PM_{2.5}$ of 47.9 μg/m^3.[5] However, in our study, the risk of hypertension associated with $PM_{2.5}$ became even more pronounced when the exposure was extended to higher levels. This finding was in line with a prior study based on prospective cohorts showed that there was a stepwise increase in the risk of developing hypertension with increasing quartiles of long-term $PM_{2.5}$ exposure.[29] This result suggests that, for a given decrease in the concentration of $PM_{2.5}$, a greater reduction in excess hypertension prevalence would be obtained in highly polluted regions compared with regions with low to moderate levels of $PM_{2.5}$ exposure. In this respect, the implication of air quality improvements in highly polluted regions of China in recent years would be more profound. It has shown that from 2013 to 2018, the annual average concentration of $PM_{2.5}$ in Beijing-Tianjin-Hebei region has declined by 49%.[30] Considering the population size and baseline $PM_{2.5}$ levels in these areas, the public health impact related to $PM_{2.5}$ reduction would be huge.

Third, we found evidence of nonlinearity in the relationships of $PM_{2.5}$ exposure with SBP and DBP. Interestingly, the shape of curves for SBP and DBP were different. Although the relevant mechanism remains unclear, pathophysiological changes, such as systemic inflammation, atherosclerosis, endothelial dysfunction, and increased arterial stiffness,[4] may have contributed to the observed patterns. The increased arterial stiffness induced by $PM_{2.5}$ would initially lead to elevation in SBP and decline in DBP, creating an increased pulse pressure.[31] While with further increase of arterial stiffness, the heart rates got higher to maintain the stroke volume, which could result in the rise of DBP afterward. In addition, prior

studies have reported the effects of $PM_{2:5}$ exposure on pulse pressures showing a tendency of rising first and then declining at higher $PM_{2.5}$ levels, which partially supports this hypothesis.[24]

Fourth, we assessed the subpopulation differences through stratified analyses and identified the susceptible individuals to the exposure of $PM_{2.5}$. We observed the large effect estimates of $PM_{2.5}$ on SBP among the elderly. Elderly subjects may commonly represent a higher prevalence of preexisting cardiovascular and respiratory diseases, which may confer susceptibility to $PM_{2.5}$. Also, the results showed that $PM_{2.5}$ exposure had larger effects on hypertension in men, and such increased susceptibility may be related to sex-related differences in the deposition localization and rates of air pollutants; specifically, men have larger airways and slightly lower airway reactivity.[32] Further, we found stronger associations of $PM_{2.5}$ and blood pressure in obese participants. The greater response observed in obese individuals may be attributed to the higher deposition rate of $PM_{2.5}$ exposure. This has been demonstrated in overweight children, where there was an increase in tidal volume and resting minute ventilation.[33] Additionally, smoking status was found to be an effect modifier with smaller effects on hypertension among current smokers. This finding is also supported by prior research.[8, 24] One possible explanation is that smoking and $PM_{2.5}$ exposure may share the same pathways in mediating cardiovascular effects and smoking may play a dominant role in smokers. Thus, exposure to $PM_{2.5}$ might not exert additional harmful effects via the same pathway.[24] There is also some potential that the greater effect size in non-current smokers could also be connected to some of them being advised to quit smoking

because of multiple comorbidities.

Our study should also be interpreted in the context of several limitations. First, given the nature of the cross-sectional study design, the causal relationship could not be established. Additional research is needed to examine these relationships in a prospective manner. Second, a selection bias is possible because our analysis was restricted to participants with available $PM_{2.5}$ data. Third, while we included a number of potential confounders in the analyses, there might be unmeasured confounders that affected the observed associations. In particular, we were unable to control for other confounders such as diet and physical activity, because these data were only available in a subset of the China PEACE Million Persons Project cohort. Fourth, we used the data from the fixed monitors to estimate the exposure of $PM_{2.5}$ and did not account for residential proximity to major roads, time-activity patterns, and indoor-related characteristics, which would likely result in nondifferential measurement errors. However, this approach is commonly used and previous research has indicated that $PM_{2.5}$ exposure estimated by the nearest monitor was highly correlated with other sophisticated approaches[34]. Fifth, other gaseous pollutants, such as NOx and ozone, temperature, and noise were not included in this study. As a result, we were not able to determine whether the observed effects were specifically attributable to $PM_{2.5}$ or the combined effects of these factors.

In conclusion, our study demonstrated that long-term exposure to $PM_{2.5}$ was positively associated with blood pressure and hypertension prevalence. The effect of $PM_{2.5}$ on

hypertension prevalence was more pronounced at higher $PM_{2.5}$ concentrations. Our findings reinforce the need to develop comprehensive strategies for addressing air pollution problems, especially for areas with severe air pollution.

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DISCLOSURES

Dr. Jing Li discloses that she is a recipient of research grants from the government of China, through Fuwai Hospital, for research to improve the management of hypertension and blood lipids, and to improve care quality and patient outcomes of cardiovascular disease; is a recipient of research agreements with Amgen, through National Center for Cardiovascular Diseases (NCCD) and Fuwai Hospital, for a multi-centre trial to assess the efficacy and safety

of Omecamtiv Mecarbil, and for dyslipidemic patient registration; is a recipient of a research agreement with Sanofi, through Fuwai Hospital, for a multi-centre trial on the effects of sotagliflozin; is a recipient of a research agreement with University of Oxford, through Fuwai Hospital, for a multi-centre trial of empagliflozin; and was a recipient of a research agreement, through NCCD, from AstraZeneca for clinical research methods training. The authors declare no other relevant conflicts of interest.

CONTRIBUTORS

JS and XZ conceived of this article. JS wrote the manuscript with further contributions from XZ, YG, XL, EM, MR, GT, DZ, WZ, JL, and MA. JS and SH completed all the statistical analyses. All authors interpreted data, contributed to critical revisions, and approved the final version of the article.

ETHICS APPROVAL

The central ethics committee at the China National Center for Cardiovascular Diseases approved this project (Ethical code 2014-574). All enrolled participants provided written informed consent.

DATA AVAILABILITY STATEMENT

No data is available. The China PEACE Million Persons Project is a major national program, and as the government policy stipulates, it is not permissible for the researchers to make the raw data publicly available at this time. All data generated during this study is included in this

manuscript and its supplementary information files.

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FIGURE LEGEND

Figure 1. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with hypertension prevalence

Figure 2. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Figure 3. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with hypertension prevalence

Figure 4. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP)

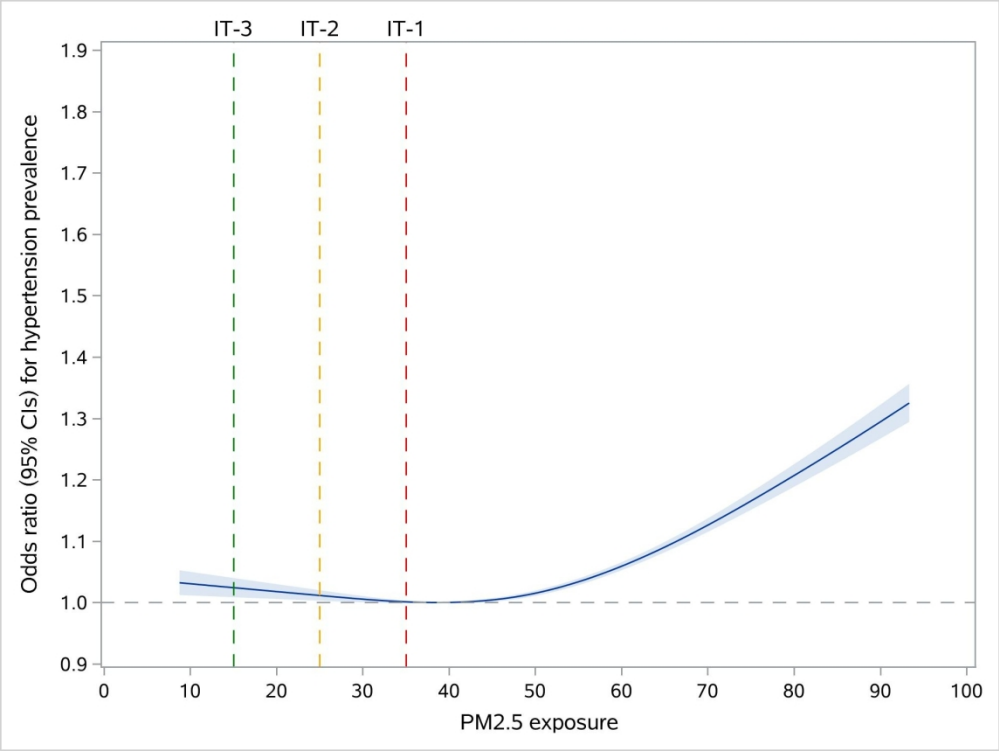

Figure 1. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with hypertension prevalence. Effect estimates were presented as adjusted odds ratios for hypertension prevalence compared to individuals with $PM_{2.5}$ exposure 38.5 μg/m^3. The dashed lines represent the air-quality standards for annual average concentrations of PM2.5 according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3). Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, as well as the day of week and season of blood pressure measurement.

169x127mm (300 x 300 DPI)

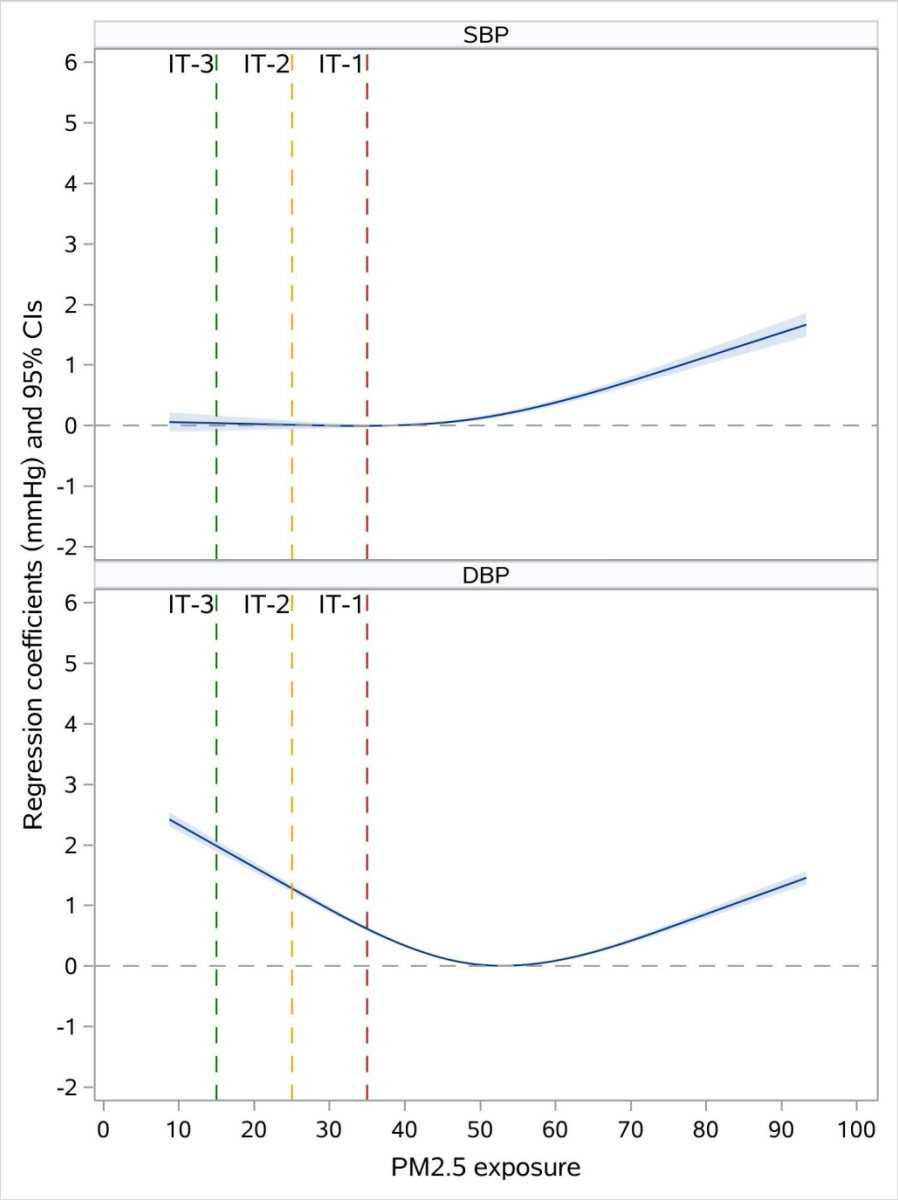

Figure 2. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP). Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with $PM_{2.5}$ exposure 39 μg/m^3 and changes in DBP compared to individuals with $PM_{2.5}$ exposure 53 μg/m^3. The dashed lines represent the air-quality standards for annual average concentrations of $PM_{2.5}$ according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3). Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications, as well as the day of week and season of blood pressure measurement.

127x169mm (300 x 300 DPI)

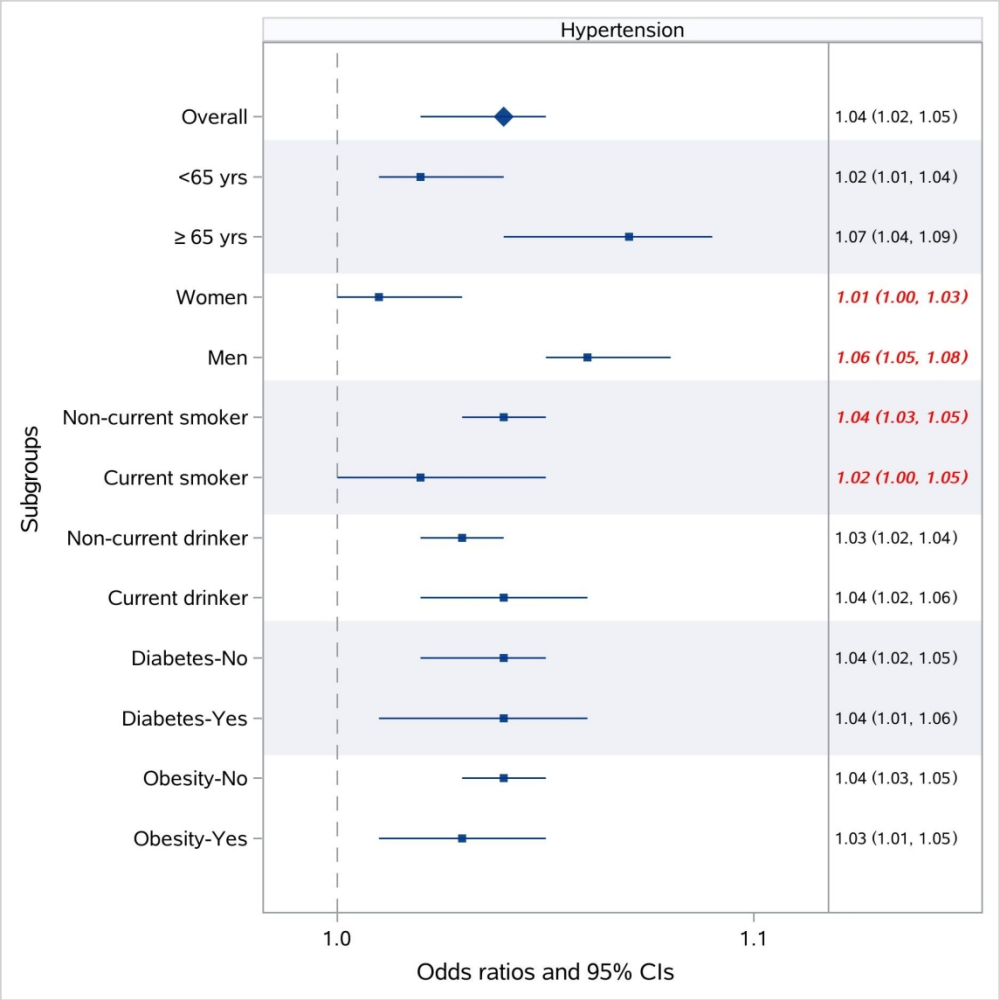

Figure 3. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with hypertension prevalence. Red texts with italics indicated that p-value for interaction terms<0.05. Effect estimates (regression coefficients) were presented as adjusted odds ratios for hypertension prevalence for each 10 $\mu g/m^3$ increment in the 1-year $PM_{2.5}$ exposure. Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, as well as the day of week and season of blood pressure measurement.

158x158mm (300 x 300 DPI)

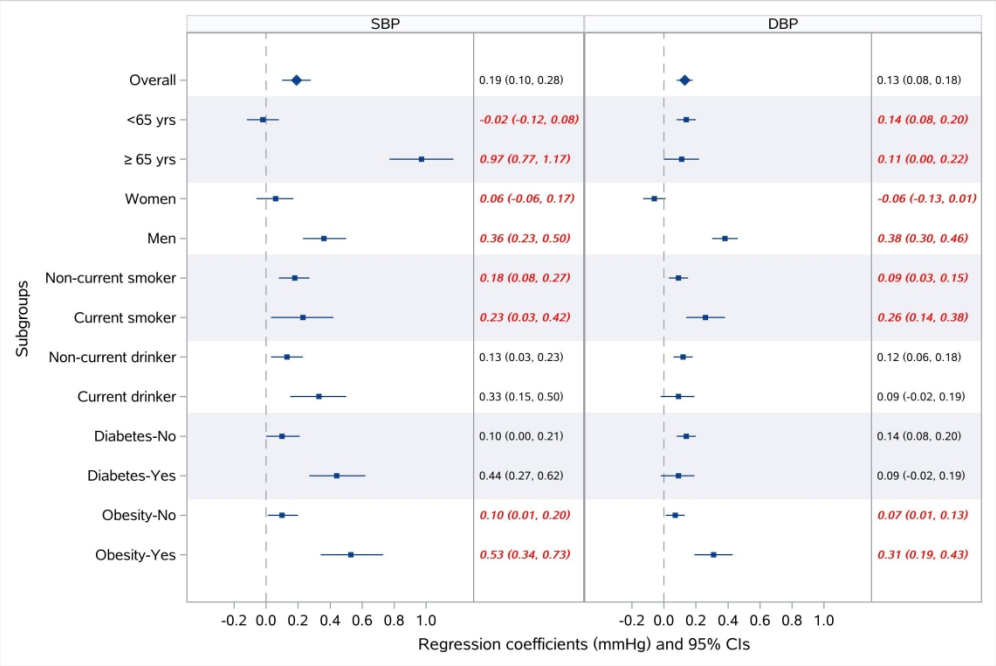

Figure 4. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with blood pressure. Red texts with italics indicated that p-value for interaction terms<0.05. Effect estimates (regression coefficients) were presented as changes in systolic blood pressure (SBP) or diastolic blood pressure (DBP) for each 10 μg/m^3 increment in the 1-year $PM_{2.5}$ exposure deriving from multivariable linear regression. Covariates of the model including age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, diabetes, and use of antihypertensive medications, as well as the day of week and season of blood pressure measurement.

238x158mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

Supplement 1. Collection of medication data in China PEACE Million Persons Project.

Potential participants who were taking medications were required to bring their drug packaging (boxes) to the project sites. During the face-to-face interview, local project staff asked participants whether they always took anti-hypertension, lipid-lowering, anti-diabetics, or anti-platelet drugs during the past 2 weeks. Those who answered “yes” and knew the name of the drug were further asked to report the name, dose, and frequency of each drug. For those who did not remember the exact dose of the drug, the number of tablets or pills taken was recorded. Interviewers searched and selected drug names or the first letter of the Chinese phonetic alphabet participants answered by entering the generic name or trade name of each drug in the electronic data collecting system. In this system, a data dictionary was used to confirm drug information, including the drug class, generic name, trade name, and corresponding unique ID.

Supplement 2. Summary statistics for daily $PM_{2.5}$ ($\mu g/m^3$) concentrations of assigned monitors in 83 study regions.

No.	Mean	Median	25th percentile	75th percentile	Minimum	Maximum	Total (days)	Missing (days)
1	67.9	50	26	88	5	540	1461	22
2	65.48	48	23	85	3	515	1461	25
3	56.39	40	19	76	2	448	1461	18
4	69.26	50	27	88	4	529	1461	10
5	57.73	41	20	77	4	446	1461	9
6	64.46	51	32	79.5	6	350	1461	13
7	62.85	50	30	78	4	409	1461	38
8	68.35	54	34	83.5	7	408	1461	37
9	64.46	51	32	79.5	6	350	1461	13
10	65.52	51	32	81	7	410	1461	34
11	86.31	61	38	107	5	708	1461	37
12	63.99	52	37	76	6	421	1461	18
13	61.01	50	30	79	2	290	1461	24
14	60.51	49	32	76	7	390	1461	70
15	46.19	40	29	55	7	276	1461	44
16	22.9	18	12	29	3	187	1461	59
17	54.55	41	26	68	3	932	1461	14
18	40.93	32	20	50	5	450	1461	16
19	44.97	35	22	56	6	353	1461	39
20	48.8	37	24	59	6	508	1461	15
21	45.3	31	19	55	3	612	1461	27
22	30.54	22	14	39	2	308	1461	17
23	45.36	34	21	58	3	378	1461	24
24	54.24	33	21	66	5	730	1461	24
25	39.52	29	18	49	3	502	1461	78
26	42.91	36	22	55	4	235	1461	24
27	44.22	36	22	58	5	225	1461	60
28	44.97	38	24	58	5	218	1461	22
29	44.32	37	23	57	6	224	1461	12
30*	49.23	40	28	62	10	271	797	1
31	52.7	42	27	67	7	284	1461	9
32	51.19	43	28	64	3	250	1461	40
33	49.98	44	31	61	6	259	1461	26
34	47.59	40	27	59	3	233	1461	30
35	27.35	25	17	35	2	114	1461	46
36	26.16	22	14	34	2	233	1461	5
37*	32.18	25	14	45	4	155	650	15
38	45.33	40	29	57	9	209	1461	32
39	49.12	44	31	62	3	356	1461	27
40	74.08	60	40	92	7	431	1461	22
41	56.81	46	31	70	7	327	1461	44
42*	70.49	57	40	82	6	514	797	56
43*	56.69	46	34	65	14	257	606	15
44	69.96	53	35	88	5	548	1461	57
45	62	50	31	81	3	275	1461	20
46	44.01	38	26	56	5	195	1461	31
47	48.13	43	29	61	6	478	1461	43
48	51.57	43	29	65	5	289	1461	10
49	39.33	33	23	50	6	214	1461	12
50	32.84	29	20	42	5	121	1461	22

51	32.48	28	18	43	5	149	1461	35
52	27.19	24	14	36	3	120	1461	31
53	38.01	33	21	49	5	192	1461	16
54	35.67	30	19	46	3	269	1461	13
55	50.36	42	27	64	6	286	1461	23
56	44.34	35	23	56	5	333	1461	6
57	35.14	29	16	47	3	202	1461	22
58	22.1	18	14	27	3	123	1461	31
59	15.14	13	9	18	2	68	1461	12
60*	37.75	29	18	47	5	183	773	20
61	49.89	41	30	61	8	222	1461	27
62	60.72	49	32	77	5	353	1461	8
63	42.87	36	24	55	5	215	1461	16
64	49.35	40	24	65	3	235	1461	13
65	32.64	28	18	42	4	195	1461	23
66	30.96	28	21	39	7	123	1461	10
67	29.79	28	20	36	7	102	1461	23
68	13.86	14	12	15	3	51	1461	109
69	25.99	19	13	32	5	187	1461	33
70	24.49	19	13	30	2	124	1461	156
71	11.95	10	7	15	2	88	1461	87
72	51.21	42	30	63	10	239	1461	238
73	10.62	9	7	13	4	73	1461	46
74	53.8	41.5	28	64	5	328	1461	19
75	38.88	32	23	47	4	169	1461	27
76	44.45	36	24	57	4	581	1461	59
77	44.1	36	25	53	5	287	1461	44
78*	44.04	38	27	56	9	139	488	27
79	55.15	45	30	68	5	363	1461	14
80	44.69	36	24	55	5	219	1461	50
81	65.37	34	20	85	5	447	1461	97
82	57.76	29	19	70	3	414	1461	58
83	51.7	26	14	65	3	406	1461	42

Note:

* Monitors being available after 2015

Total: Number of days of assigned monitors being available during 2015-2018

Missing: Number of days with missing $PM_{2.5}$ concentration during 2015-2018

Supplement 3. Distribution of study sites in China Patient-Centered Evaluative Assessment of Cardiac Events Million Persons Project.

Supplement 4. Characteristics of the study population.

Variable	Total (n=883,827)
Socio-demographics	
Age, mean (SD), years	55.5 (10.1)
Female, n (%)	533897 (60.4)
Urban residence, n (%)	657608 (74.4)
Han ethnic group, n (%)	805479 (91.1)
College or above	102764 (11.6)
Regions, n (%)	
Eastern	325253 (36.8)
Central	178435 (20.2)
Western	311599 (35.3)
Northeastern	68540 (7.8)
Cardiovascular risk factors, n (%)	
Obesity	142150 (16.1)
Current drinker	194967 (22.1)
Diabetes	173950 (19.7)
Current smoker	161006 (18.2)
Hypertension	381223 (43.1)
Blood pressures	
Systolic blood pressure, mean (SD)	143.5 (22.2)
Diastolic blood pressure, mean (SD)	83.1 (12.3)
$PM_{2.5}$ exposures	
1-y average $PM_{2.5}$ exposure, mean (SD)	49.2 (16.4)
Above WHO Interim Target 1 (IT-1, 35 μg/m^3), n (%)	706415 (79.9)
Above WHO Interim Target 2 (IT-2, 25 μg/m^3), n (%)	842356 (95.3)
Above WHO Interim Target 3 (IT-3, 15 μg/m^3), n (%)	864119 (97.8)

Supplement 5. The effect of $PM_{2.5}$ exposure on hypertension prevalence.

Model	Per 10 μg/m³ $PM_{2.5}$ increment	
	Odds ratios (95% confidence intervals)	p-Value
Hypertension prevalence		
Model 1	1.10 (1.09–1.11)	<0.001
Model 2	1.10 (1.09–1.11)	<0.001
Model 3	1.09 (1.08–1.10)	<0.001
Model 4	1.09 (1.08–1.10)	<0.001
Model 5	1.04 (1.02–1.05)	<0.001
Model 6	1.04 (1.02–1.05)	<0.001

Model 1: Included age and sex;
Model 2: Model 1 + education level and urbanity;
Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes;
Model 4: Model 3 + day of week of the medical examination;
Model 5: Model 3 + season of the medical examination;
Model 6: Model 3 + day of week + season.

Supplement 6. The effect of $PM_{2.5}$ exposure on blood pressure.

Model	Per 10 μg/m³ $PM_{2.5}$ increment	
	mmHg (95% confidence intervals)	p-value
Systolic blood pressure		
Model 1	0.58 (0.49–0.67)	<0.001
Model 2	0.57 (0.48–0.66)	<0.001
Model 3	0.45 (0.36–0.54)	<0.001
Model 4	0.50 (0.41–0.59)	<0.001
Model 5	0.50 (0.41–0.59)	<0.001
Model 6	0.19 (0.10–0.28)	<0.001
Model 7	0.19 (0.10–0.28)	<0.001
Diastolic blood pressure		
Model 1	0.29 (0.23–0.34)	<0.001
Model 2	0.28 (0.23–0.34)	<0.001
Model 3	0.21 (0.15–0.26)	<0.001
Model 4	0.23 (0.18–0.28)	<0.001
Model 5	0.23 (0.18–0.28)	<0.001
Model 6	0.13 (0.08–0.18)	<0.001
Model 7	0.13 (0.08–0.18)	<0.001

Model 1: Included age and sex;

Model 2: Model 1 + education level and urbanity;

Model 3: Model 2 + smoking status, alcohol consumption, obesity, and diabetes;

Model 4: Model 3 + use of antihypertensive medication;

Model 5: Model 4 + day of week of the medical examination;

Model 6: Model 3 + season of the medical examination;

Model 7: Model 3 + day of week + season.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.