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Association of Long-term Exposure to PM2.5 with Blood Pressure and Hypertension Prevalence in China

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TITLE PAGE**Association of Long-term Exposure to PM_{2.5} with Blood Pressure and Hypertension
Prevalence in China****Authors:**

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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/m³ 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.

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7 **Keywords:** Air pollution; Blood pressure; Hypertension
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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/m³), 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.

1 INTRODUCTION

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

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

18 China is experiencing a growing epidemic of hypertension and is estimated to have 300
19 million individuals with hypertension by 2025.¹⁸ Meanwhile, outdoor PM_{2.5} has become one of
20 China's most serious environmental problems with provincial population-weighted means of
21 PM_{2.5} ranging from 19.1 µg/m³ to 79.3 µg/m³ in 2015.¹⁵ A deeper understanding of the
22 chronic health effects of PM_{2.5} on hypertension prevalence and blood pressure in moderate

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4 23 to high PM_{2.5} concentrations will help to support policy making of air quality improvement and
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6 24 combat the hypertension epidemic in China.
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9 25 Accordingly, incorporating PM_{2.5} data with a large-scale population-based screening
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11 26 project in China, the China Patient-Centered Evaluative Assessment of Cardiac Events
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14 27 (PEACE) Million Persons Project, we aimed to: (1) explore the association of long-term PM_{2.5}
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17 28 exposure with blood pressure level and the hypertension prevalence, and evaluate
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20 29 subpopulation differences in these associations; (2) assess the concentration-response
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22 30 relationships of long-term PM_{2.5} exposure with hypertension prevalence and blood pressure.
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27 32 **METHODS**

30 33 **Study population**

32 34 Our study population is derived from the China PEACE Million Persons Project, which
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35 35 has been described previously.¹⁹ In brief, we selected sites (rural counties or urban districts)
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38 36 using a convenience sampling strategy in all 31 provinces in mainland China from
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41 37 September 2014 to March 2019. At each site, participants were enrolled if they were aged
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44 38 35 to 75 years, currently registered in the selected region's Hukou (a record officially
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47 39 identifying a person as a resident of an area), or had lived in the region for at least 6 of the
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50 40 previous 12 months. This project was registered on www.clinicaltrials.gov (NCT02536456).
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53 41 In the present study, we included 897,937 participants with more than 330 valid PM_{2.5} values
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56 42 for assessing long-term exposure. After excluding participants with missing data on
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59 43 education level (n=13,714), body mass index (n=321), or blood pressure measurement
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44 (n=2), we further excluded participants with systolic blood pressure (SBP) \geq 250 mmHg or

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4 45 diastolic blood pressure (DBP) ≥ 150 mmHg to minimize the potential bias due to
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6 46 measurement errors in blood pressure values (n=73). Finally, we included 883,827
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9 47 participants in the study sample. The central ethics committee at the China National Center
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11 48 for Cardiovascular Diseases approved this project. All enrolled participants provided written
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14 49 informed consent.

17 50 **Data collection and variable definitions**

19 51 Data collection for each participant was performed by trained personnel with a
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22 52 standardized in-person interview and a physical examination. Information on
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25 53 sociodemographic status (age, gender, and education level), lifestyle (smoking and alcohol
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27 54 use), medical history, and medication use were collected. Medication use was determined by
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30 55 asking participants whether they had taken prescribed medications for antiplatelet or
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33 56 controlling blood pressure, lipid, or glucose in the past 2 weeks. Those who answered "yes"
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35 57 and knew the drug names were asked to report the name, dose, and frequency of each
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38 58 drug. Those who did not remember the exact dose stated the number of pills or tablets
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41 59 taken.

43 60 The blood pressure of each participant was measured twice on the right upper arm after
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45 61 5 minutes of rest in a seated position with a standardized electronic blood pressure monitor
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48 62 (Omron HEM-7430). If the difference between the 2 systolic blood pressure readings was
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51 63 greater than 10 mmHg, a third measurement was obtained, and the average of the last 2
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53 64 readings was used. Hypertension was defined as systolic blood pressure of 140 mmHg or
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56 65 higher, diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive
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59 66 medications, which is consistent with the US Joint National Committee and Chinese

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4 67 definitions²⁰⁻²². Body mass index (BMI) was defined as weight in kilograms divided by height
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6 68 in square meters. Obesity was defined as 28.0 kg/m² or higher, on the basis of
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9 69 recommendations from the Working Group on Obesity in China.²³
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11 70 **Exposure Assessment**

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14 71 Each participant's address (either rural county or urban district) was geocoded into
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17 72 latitude and longitude data. We identified all air monitors located within 10 kilometers from
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20 73 the participants' addresses (**Table S1**). These monitors were mandated to be away from
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23 74 major roads, industrial sources, buildings, or residential sources of emissions from the
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26 75 combustion of coal, waste, or oil so that the measurements from these monitors were more
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29 76 likely to reflect the background air pollution level rather than those from local sources, such
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32 77 as traffic or industrial combustion. The measurements from these monitors strictly followed
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35 78 the methodological standards set by the State Environmental Protection Administration of
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38 79 China. For each participant, daily-specific PM_{2.5} data measured at the nearest monitors to
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41 80 their residence was used to estimate PM_{2.5} exposure. The 1-year average concentration
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44 81 before the medical examination was calculated and treated as an indicator of long-term
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47 82 exposure to PM_{2.5}.

48 83 **Statistical Analysis**

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51 84 Continuous variables were reported as means with standard deviation; categorical
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54 85 variables were presented as percentages. We modeled SBP and DBP using linear
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57 86 regressions with township-specific random intercepts to investigate the independent effect of
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60 87 long-term exposure to PM_{2.5} on these two blood pressure measures. We also developed
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90 88 generalized linear models with a logit link function and township-specific random intercepts

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4 89 to assess the association of long-term exposure to PM_{2.5} with hypertension prevalence. For
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7 90 each of these analyses, we started with a model (Model 1) which only included age and sex.
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9 91 We then incrementally adjusted for additional covariates. The second model (Model 2)
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11 92 included Model 1 and socioeconomic factors (education level and urbanity). The third model
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13 93 (Model 3) included Model 2 and cardiovascular disease risk factors (BMI, smoking status,
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15 94 alcohol consumption, and diabetes). Models of blood pressure were additionally controlled
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17 95 for hypertensive medication use; while models of hypertension were not, as hypertension
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19 96 medication use was a component of the outcome definition.
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24 97 We also used restricted cubic splines to graphically characterize the concentration-
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26 98 response (C-R) relationships of PM_{2.5} exposure with blood pressure and hypertension
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28 99 prevalence.²⁴ Additionally, to examine effect modification by age, gender, smoking status,
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30 100 alcohol consumption, diabetes, and obesity, each potential modifier was tested by adding an
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32 101 interaction term in the regression model separately and testing its statistical significance as
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34 102 well as the association per categories of the tested variable through subgroup analyses.
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40 103 Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc.,
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42 104 Cary, North Carolina). All tests of significance were 2-tailed, with a level of significance set at
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51 107 **RESULT**

52 108 **Study population and baseline characteristics**

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55 109 A total of 883,827 participants were included in the study sample. Summary statistics
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57 110 and baseline characteristics of the study population are shown in **Table S2**. The mean age
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4 111 was 55.5 years, 60.4% were women, 43.1% had hypertension, mean SBP was 143.5 mmHg,
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6 112 mean DBP was 83.1 mmHg, and 19.4% were taking antihypertensive medications. The 1-
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9 113 year PM_{2.5} exposure of total study population ranged from 8.8 to 93.8 µg/m³. There were
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12 114 864,119 (97.8%), 842,356 (95.3%), and 706,415 (79.9%) participants with 1-year PM_{2.5}
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14 115 exposure higher than 15 µg/m³ [World Health Organization (WHO) Interim Target 3 (IT-1)],
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17 116 25 µg/m³ [WHO Interim Target 2 (IT-2)], and 35 µg/m³ [WHO Interim Target 3 (IT-3)],
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20 117 respectively.

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

120 We found a positive association of long-term PM_{2.5} exposure with hypertension
121 prevalence, which was consistent across different model specifications. In the crude model
122 (Model 1), each 10 µg/m³ increase in PM_{2.5} was associated with an 10% increased odds of
123 hypertension prevalence [odds ratio (OR): 1.10; 95% confidence interval (CI): 1.09-1.11].
124 After adjusting for a wide range of potential confounders, the OR of hypertension was 1.09
125 (95% CI: 1.08-1.10) for each 10 µg/m³ increase in PM_{2.5}. (**Table S3**) The C-R relationships
126 between long-term PM_{2.5} exposure and hypertension prevalence were nonlinear with steeper
127 slopes at higher PM_{2.5} exposure levels. Compared to individuals with the lowest level of
128 PM_{2.5} exposure (8.8 µg/m³), the adjusted ORs for hypertension of individuals with 15, 25, and
129 35 µg/m³ of PM_{2.5} exposure were 1.01 (95% CI: 1.01-1.02), 1.03 (95% CI: 1.02-1.04), and
130 1.05 (95% CI: 1.03-1.07), respectively. (**Figure 1**)

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

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4 133 PM_{2.5} exposures were positively associated with SBP and DBP. Adjustment for
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6 134 antihypertensive medications led to small increase in the effect estimate of PM_{2.5} exposure.
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9 135 Among potentially confounding variables, adjustment for cardiovascular disease risk factors
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11 136 (Model 3 vs. Model 2) had the largest impact on effect estimates with a decrease in the
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14 137 positive association with SBP and DBP. In the fully adjusted model (Model 4), each 10 µg/m³
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17 138 increment was associated with increases of 0.50 mmHg (95% CI: 0.41-0.59) in SBP and
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19 139 0.23 mmHg (95% CI: 0.18-0.28) in DBP. (**Table S4**) We found that the shapes of the C-R
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22 140 associations of PM_{2.5} exposure with SBP and DBP were different, as presented in **Figure 2**.
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25 141 For SBP, the fitted C-R functions had upward trends with greater effect estimates of PM_{2.5}
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27 142 at higher concentrations. For DBP, the C-R relationships were generally U-shaped.
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31 32 144 **Stratified analysis and effect modification**

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35 145 The associations of long-term PM_{2.5} exposure with hypertension and blood pressure
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37 146 across different subgroups are provided in **Figure 3** and **Figure 4**. The associations of PM_{2.5}
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40 147 exposure with hypertension were stronger among the elderly (≥65 years of age), men, and
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43 148 non-current smokers compared with younger subjects, women, and current smokers,
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45 149 respectively. Gender significantly modified the effects of PM_{2.5} exposure on all three
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48 150 outcomes (all p for interaction <0.05) with stronger associations among men; while these
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51 151 associations were not modified by alcohol consumption (all p for interaction >0.05). Although
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53 152 age and smoking status were also found to be effect modifiers in the associations of PM_{2.5}
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56 153 exposure with SBP, DBP, and hypertension, the impacts of the two effect modifiers on these
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58 154 associations differed depending on the outcome. We observed greater effect estimates of
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4 155 PM_{2.5} exposure for SBP and hypertension, while smaller estimates for DBP among the
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7 156 elderly (≥65 years of age) and non-current smokers.
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11 158 **DISCUSSION**

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14 159 In this study, we investigated the associations between long-term exposure to PM_{2.5} and
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17 160 hypertension prevalence, SBP, and DBP. We found that PM_{2.5} was associated with
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20 161 increased risk of hypertension prevalence and elevation of blood pressure. Nonlinearity in
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22 162 these associations was also observed. With increasing higher PM_{2.5} concentrations, the C-R
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25 163 curves for PM_{2.5}–hypertension and PM_{2.5}–SBP showed consistent increase with steeper
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27 164 slopes at higher PM_{2.5} concentrations; while the C-R curve for PM_{2.5}–DBP was U-shaped.
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30 165 The elderly, men, and non-current smokers appeared to be more vulnerable to the exposure
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33 166 of PM_{2.5}.

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35 167 Our study contributes to the existing scientific literature in several ways. First, the large
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38 168 size of our study allowed us to comprehensively assess the associations of PM_{2.5} with
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41 169 hypertension prevalence and blood pressure among a wide spectrum of population in China.
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43 170 Our study included 0.8 million participants aged 35–75 years across a large and
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46 171 geographically diverse country, making the results more generalizable. In addition, the large
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49 172 population included in the present study also reflected different PM_{2.5} exposure levels, and
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52 173 thus it adds to our understanding about these associations across a wider range of PM_{2.5}
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54 174 concentrations (8.8–93.8 µg/m³) than reported previously.⁵⁻¹⁴ Furthermore, the large sample
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57 175 size, especially the large number of participants with hypertension and high level of PM_{2.5}
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59 176 exposure (e.g. >35 µg/m³), enabled us to examine these associations with greater precision
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4 177 and sufficient statistical power.
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6 178 Second, we provided new information on the C-R relationship between long-term PM_{2.5}
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9 179 exposure and hypertension prevalence. Previous research reported a U-shaped relationship
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12 180 between long-term exposure to PM_{2.5} and hypertension prevalence with a threshold PM_{2.5} of
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14 181 47.9 µg/m³.⁵ However, in our study, we found no evidence of a discernible threshold — the
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17 182 concentration at which the C-R functions of hypertension prevalence begin to flatten out —
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19 183 at concentrations ranging from as low as 8.8 µg/m³ to as high as 93.8 µg/m³. In fact, PM_{2.5}
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22 184 exposure was associated with consistent high risk of hypertension throughout the entire
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25 185 exposure range and the effects became even more pronounced when PM_{2.5} exposure was
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27 186 extended to higher levels. This result suggests that per unit decrease in the concentration of
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30 187 PM_{2.5} can be translated to a greater reduction in excess hypertension prevalence in highly
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33 188 polluted regions compared with regions with low to moderate levels of PM_{2.5} exposure.
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35 189 Third, we found evidence of nonlinearity relationship of PM_{2.5} exposure with blood
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38 190 pressure, including SBP and DBP. Interestingly, the shapes of nonlinear C-R association
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41 191 were different between PM_{2.5} exposure-SBP and PM_{2.5} exposure-DBP associations.
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43 192 Although we observed a modest-sized change of blood pressure across the full range of
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46 193 PM_{2.5} concentrations, it is still of great public health importance. Since hypertension is the
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49 194 most important risk factor for death, even a small change in blood pressure at population
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52 195 level can potentially lead to an increase in attributable disease burden.²⁵ The mechanism by
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55 196 which the shapes between the associations of PM_{2.5} exposure-SBP vs. PM_{2.5} exposure-DBP
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58 197 are different is unclear. Pathophysiological changes, such as systemic inflammation,
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60 198 atherosclerosis, endothelial dysfunction, and increased arterial stiffness,^{4,26} may have

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4 199 contributed to the observed patterns. The increased arterial stiffness induced by PM_{2.5} would
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7 200 initially lead to elevation in SBP and decline in DBP, creating an increased pulse pressure.²⁷
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9 201 While with further increase of arterial stiffness, the heart rates got higher to maintain the
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11 202 stroke volume, which could result in the rise of DBP afterwards. In addition, prior studies
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14 203 have reported the effects of PM_{2.5} exposure on pulse pressures showing a tendency of rising
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17 204 up first and then declining at higher PM_{2.5} levels, which partially supports this hypothesis.^{11,28}
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19 205 Fourth, we identified the vulnerable subgroups to the exposure of PM_{2.5}. In stratified
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21 206 analyses, we observed the large effect estimates of PM_{2.5} on hypertension among the
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24 207 elderly. Elderly subjects may commonly represent higher prevalence of preexisting
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27 208 cardiovascular and respiratory diseases, which may confer susceptibility to PM_{2.5}. Also, the
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30 209 results showed that PM_{2.5} exposure had larger effects on hypertension in men, which is
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33 210 consistent with a previous study.⁶ Such increased susceptibility may be related to sex-
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36 211 related differences in the deposition localization and rates of air pollutants;²⁹ specifically,
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38 212 men have larger airways and slightly lower airway reactivity.³⁰ Additionally, smoking status
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41 213 was found to be an effect modifier with smaller effects on hypertension among current
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44 214 smokers. This finding is also supported by prior research.^{10,28} One possible explanation is
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47 215 that smoking and PM_{2.5} exposure may share the same pathways in mediating cardiovascular
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50 216 effects and smoking may play a dominant role in smokers. Thus, the exposure to PM_{2.5}
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53 217 might not exert additional harmful effect via the same pathway.²⁸

54 218 Our study should also be interpreted in the context of several limitations. First, given the
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56 219 nature of the cross-sectional study design, the causal relationship could not be established.
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59 220 Additional research is needed to examine these relationships in a prospective manner.
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4 221 Second, a selection bias is possible because our analysis was restricted to participants with
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6 222 available PM_{2.5} data. Third, while we included a number of potential confounders in the
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9 223 analyses, there might be unmeasured confounders that affected the observed associations.
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11 224 In particular, we were unable to control for other confounders such as diet and physical
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14 225 activity, because these data were only available in a subset of the China PEACE Million
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17 226 Persons Project cohort. Fourth, for PM_{2.5} exposure assessment, we used the data from the
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19 227 monitor located nearest to the residence of each subject and did not account for individual
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22 228 time-activity patterns and indoor-related characteristics, which would likely result in
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25 229 nondifferential measurement errors and may cause underestimates in our results³¹.
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27 230 However, this approach is commonly used in prior studies³¹ and previous research have
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30 231 indicated that PM_{2.5} exposure estimated by the nearest monitor was highly correlated with
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33 232 other sophisticated approaches³². Fifth, other gaseous pollutants, such as NO_x and ozone,
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35 233 temperature, and noise were not included in this study. As a result, we were not able to
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38 234 determine whether the observed effects were specifically attributable to PM_{2.5} or to the
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41 235 combined effects of these factors.

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43 236 In conclusion, our study demonstrated that long-term exposure to PM_{2.5} was significantly
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45 237 associated with increased risk of blood pressure elevation and hypertension prevalence. The
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48 238 effect of PM_{2.5} on hypertension prevalence was more pronounced at higher PM_{2.5}
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51 239 concentration. Our findings reinforce the need to develop comprehensive strategies for
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54 240 addressing air pollution problems, especially for areas with severe air pollution.

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244 made by project teams at the National Center for Cardiovascular Diseases in the realms of
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247 **PATIENT AND PUBLIC INVOLVEMENT**

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

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258 **DISCLOSURES**

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

262 **CONTRIBUTORS**

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

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4 264 contributions from XZ, XL, EM, MR, GT, DZ, WZ, JL and MA. JS and SH completed all the
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7 265 statistical analysis. All authors interpreted data, contributed to critical revisions and approved
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9 266 the final version of the article.
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For peer review only

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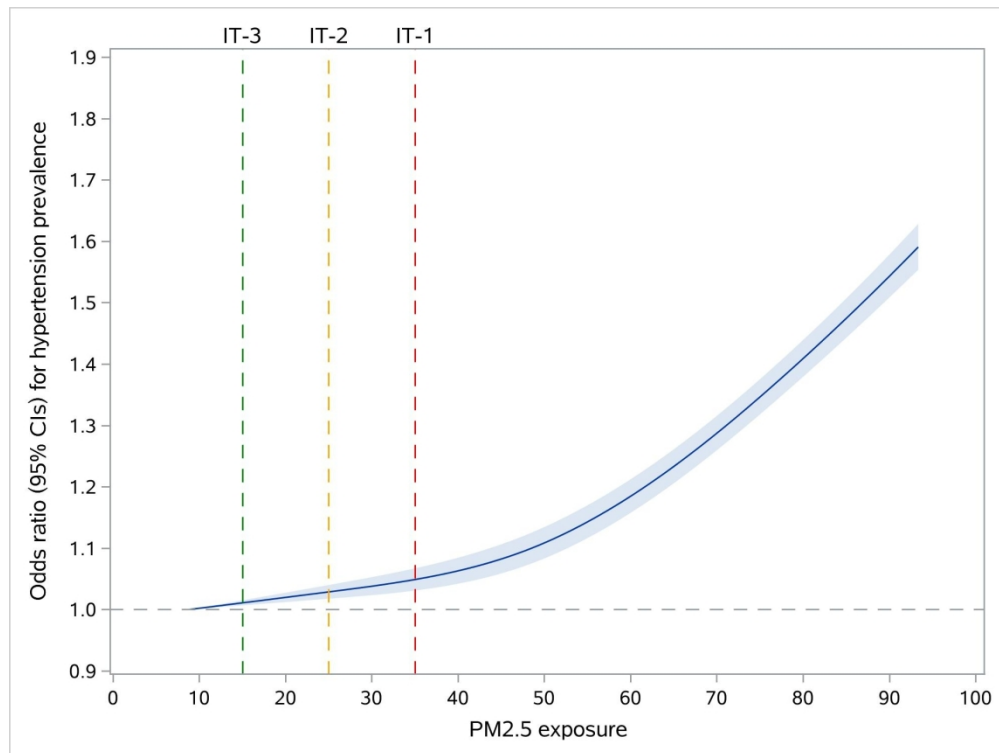


Figure 1. Concentration-response functions of the long-term exposure to PM2.5 with hypertension prevalence.

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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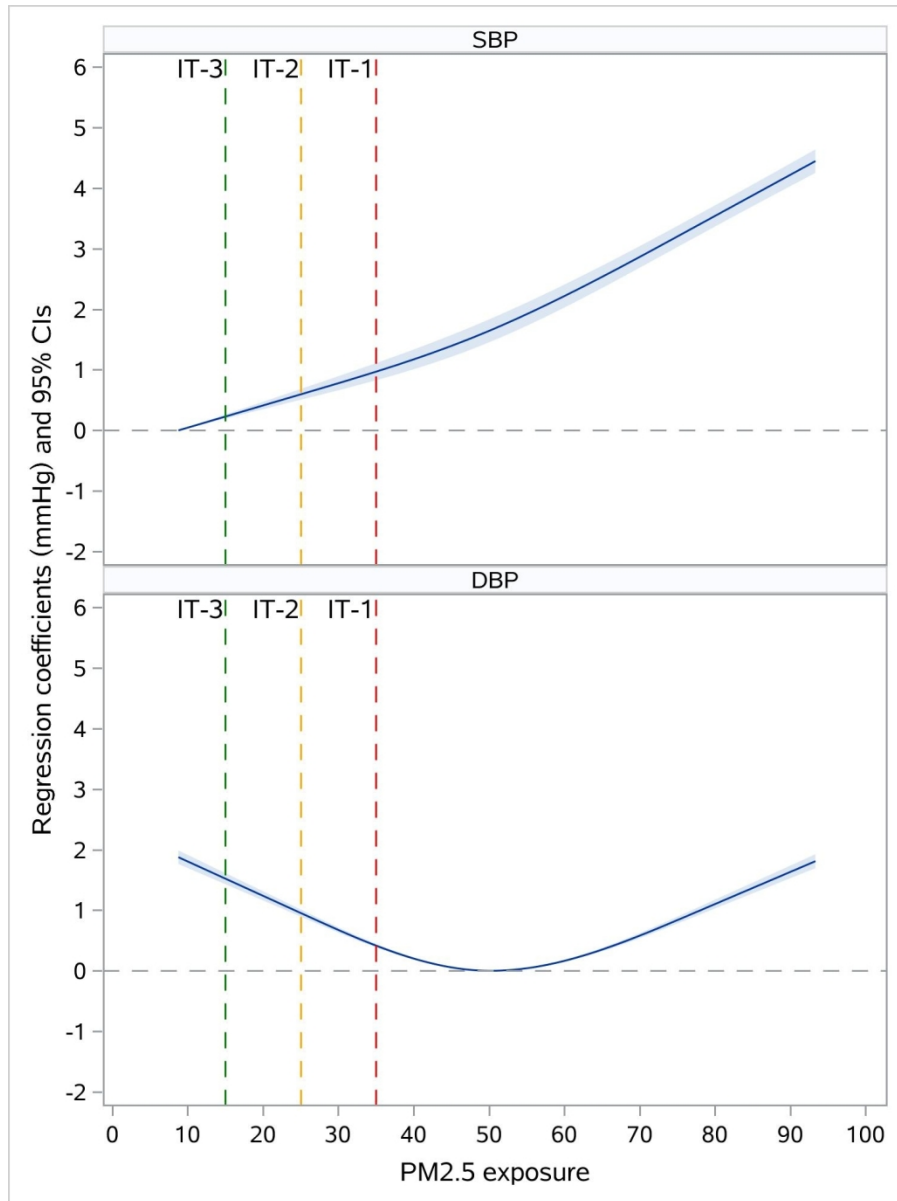


Figure 2. Concentration-response functions of the long-term exposure to PM_{2.5} with systolic blood pressure (SBP) and diastolic blood pressure (DBP). Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with PM_{2.5} exposure 8.8 µg/m³ and changes in DBP compared to individuals with PM_{2.5} exposure 50 µg/m³. 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 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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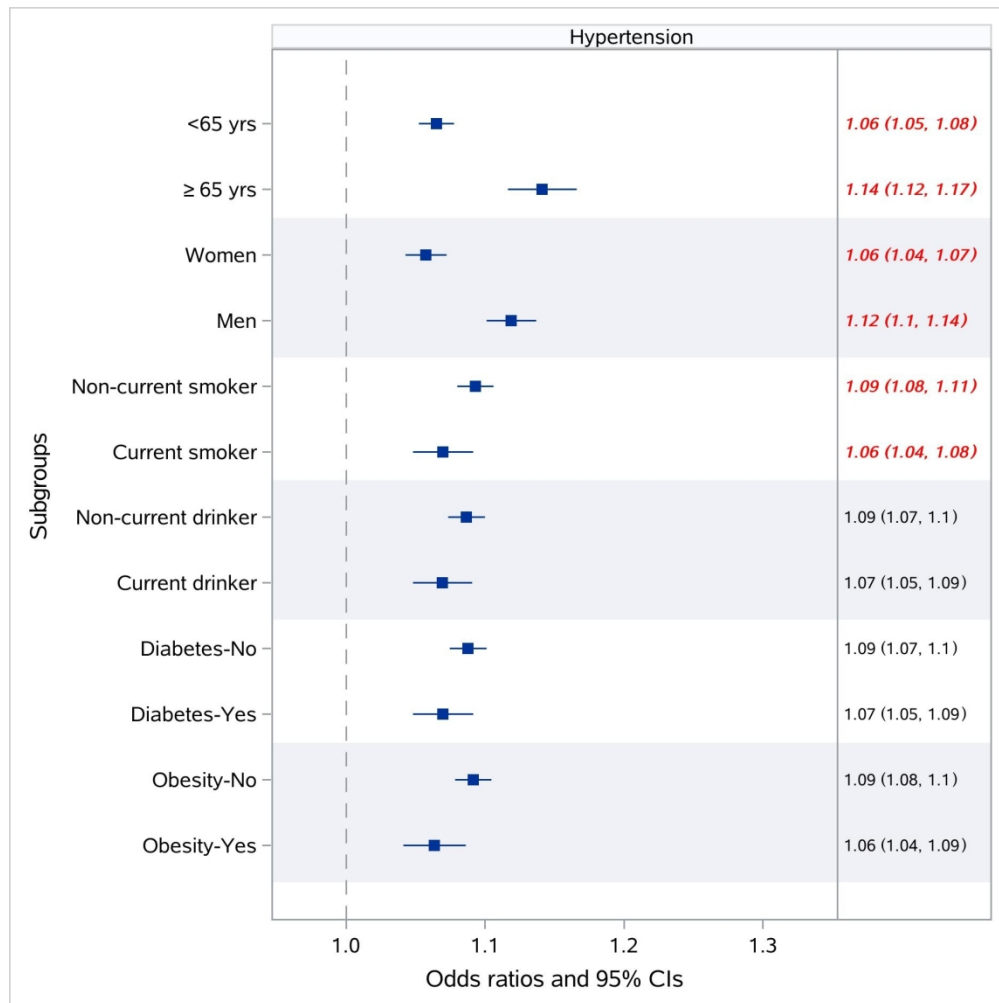


Figure 3. Stratified analysis of the association of long-term exposure to PM2.5 with hypertension prevalence
 Red texts with italics indicated that p-value for interaction terms < 0.05.
 Effect estimates (regression coefficients) were presented as adjusted odds ratios for hypertension prevalence for 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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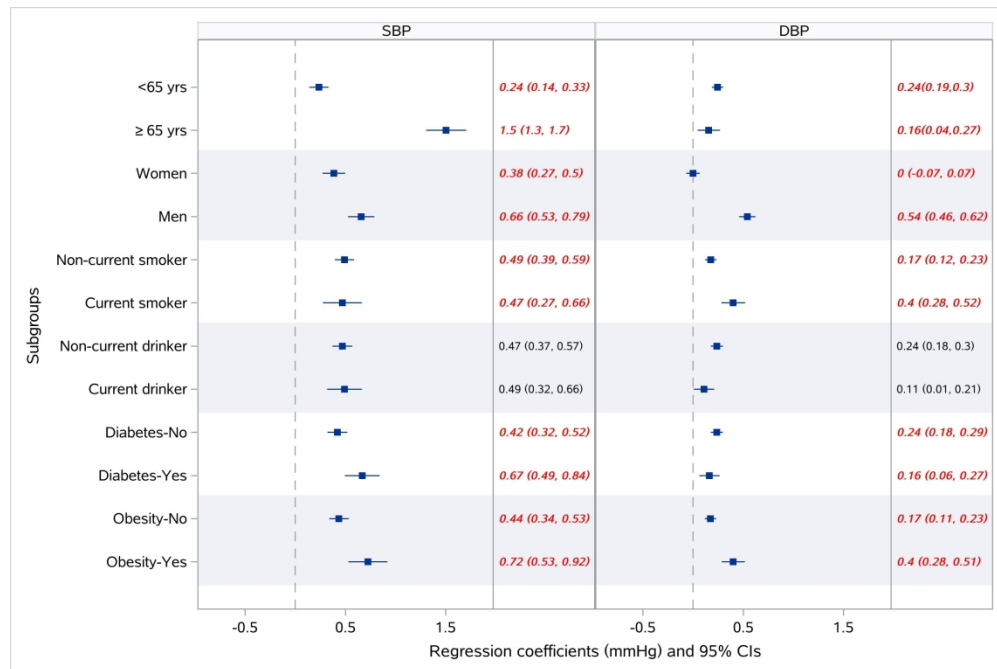


Figure 4. Stratified analysis of the association of long-term exposure to PM_{2.5} with blood pressure

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/m³ increment in the 1-year PM_{2.5} 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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1 APPENDICES

2 Table S1. Summary statistics for daily PM_{2.5} (µg/m³) at 83 monitoring stations in China
3 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

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3	49	39.33	33	23	50	214	6	22.99	12
4	50	32.84	29	20	42	121	5	17.51	22
5	51	32.48	28	18	43	149	5	19.23	35
6	52	27.19	24	14	36	120	3	17.16	31
7	53	38.01	33	21	49	192	5	23.72	16
8	54	35.67	30	19	46	269	3	22.90	13
9	55	50.36	42	27	64	286	6	32.32	23
10	56	44.34	35	23	56	333	5	32.18	6
11	57	35.14	29	16	47	202	3	25.68	22
12	58	22.10	18	14	27	123	3	13.22	31
13	59	15.14	13	9	18	68	2	9.22	12
14	60	37.75	29	18	47	183	5	28.96	708
15	61	49.89	41	30	61	222	8	31.21	27
16	62	60.72	49	32	77	353	5	42.85	8
17	63	42.87	36	24	55	215	5	25.98	16
18	64	49.35	40	24	65	235	3	35.52	13
19	65	32.64	28	18	42	195	4	20.30	23
20	66	30.96	28	21	39	123	7	14.39	10
21	67	29.79	28	20	36	102	7	12.89	23
22	68	13.86	14	12	15	51	3	5.05	109
23	69	25.99	19	13	32	187	5	20.21	33
24	70	24.49	19	13	30	124	2	17.69	156
25	71	11.95	10	7	15	88	2	7.71	87
26	72	51.21	42	30	63	239	10	30.49	238
27	73	10.62	9	7	13	73	4	5.10	46
28	74	53.80	41.5	28	64	328	5	40.55	19
29	75	38.88	32	23	47	169	4	24.72	27
30	76	44.45	36	24	57	581	4	35.96	59
31	77	44.10	36	25	53	287	5	29.00	44
32	78	44.04	38	27	56	139	9	23.42	1000
33	79	55.15	45	30	68	363	5	38.57	14
34	80	44.69	36	24	55	219	5	30.52	50
35	81	65.37	34	20	85	447	5	68.86	97
36	82	57.76	29	19	70	414	3	62.93	58
37	83	51.70	26	14	65	406	3	58.30	42

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

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6 **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)
<i>Above WHO Interim Target 1 (IT-1, 35 µg/m³), n (%)</i>	706415 (79.9)
<i>Above WHO Interim Target 2 (IT-2, 25 µg/m³), n (%)</i>	842356 (95.3)
<i>Above WHO Interim Target 3 (IT-3, 15 µg/m³), n (%)</i>	864119 (97.8)

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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

9 Model 1: Included age and sex;

10 Model 2: Model 1 + education level and urbanity;

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

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

13

14 **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

15 Model 1: Included age and sex;

16 Model 2: Model 1 + education level and urbanity;

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

18 Model 4: Model 3 + use of antihypertensive medications

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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

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2	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
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4			
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6			(b) Report category boundaries when continuous variables were categorized
7			10-11
8			
9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
10			NA
11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
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14	Discussion		
15	Key results	18	Summarise key results with reference to study objectives
16			13
17	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
18			16
19			
20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
21			13-16
22			
23			
24	Generalisability	21	Discuss the generalisability (external validity) of the study results
25			15-16
26			
27	Other information		
28	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
29			17
30			
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*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.

BMJ Open

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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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/m³ (mean 49.2 µg/m³). The adjusted odds ratio of hypertension prevalence related to a 10 µg/m³ increase in one-year PM_{2.5} exposure was 1.09 (95% confidence interval, 1.08–1.10). Each 10 µg/m³ 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 more susceptible to the exposure of PM_{2.5}.

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

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4 increased risk of hypertension prevalence. The effects of PM_{2.5} on hypertension prevalence
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6 become more pronounced at higher PM_{2.5} levels. These findings emphasize the need to
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9 reduce air pollution, especially in areas with severe air pollution.
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14 **Keywords:** Air pollution; Blood pressure; Hypertension
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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/m³), 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.

1 INTRODUCTION

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

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

17
18 China is experiencing a growing epidemic of hypertension and is estimated to have 300
19 million individuals with hypertension by 2025.¹¹ Meanwhile, outdoor PM_{2.5} has become one
20 of China's most serious environmental problems with population-weighted annual means of
21 PM_{2.5} ranging from 19.1 µg/m³ to 79.3 µg/m³ in 2015.¹² A deeper understanding of the
22 chronic health effects of PM_{2.5} on hypertension prevalence and blood pressure in moderate

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4 23 to high PM_{2.5} concentrations will help to develop policies to improve air quality and combat
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6 24 the hypertension epidemic in China.
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11 26 Accordingly, incorporating PM_{2.5} data with a large-scale population-based screening project
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14 27 in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE)
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17 28 Million Persons Project, we aimed to: (1) explore the association of long-term PM_{2.5}
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19 29 exposure with blood pressure level and hypertension prevalence, and evaluate
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22 30 subpopulation differences and effect modification by characteristics of participants in these
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25 31 associations; (2) assess the concentration-response relationships of long-term PM_{2.5}
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27 32 exposure with hypertension prevalence and blood pressure.
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34 **METHODS**

35 **Study population**

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37 36 Our study population is derived from the China PEACE Million Persons Project, which has
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40 37 been described previously.¹³ In brief, we selected county-level regions using a convenience
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43 38 sampling strategy in all 31 provinces in mainland China from September 2014 to March
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46 39 2019. These regions are designated as rural counties or urban districts according to urban-
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49 40 rural division codes of the National Bureau of Statistics of China.¹⁴ Local residents aged 35
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52 41 to 75 years, who were currently registered in the selected region's Hukou (a record officially
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55 42 identifying a person as a resident of an area) or had lived in the region for at least 6 of the
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58 43 previous 12 months, were enrolled in this project. After excluding participants with missing
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60 44 data on education level (n=13,714), body mass index (n=321), or blood pressure

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4 45 measurement (n=2), we further excluded participants with systolic blood pressure (SBP) \geq
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6 46 250 mmHg or diastolic blood pressure (DBP) \geq 150 mmHg to minimize the potential bias due
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9 47 to measurement errors in blood pressure values (n=73). Finally, we included 883,827
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12 48 participants in the study sample. The central ethics committee at the China National Center
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14 49 for Cardiovascular Diseases approved this project. All enrolled participants provided written
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17 50 informed consent.

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22 52 **Data collection and variable definitions**

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24 53 Data collection for each participant was performed by trained personnel with a standardized
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27 54 in-person interview and a medical examination. Information on sociodemographic status
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30 55 (age, gender, and education level), lifestyle (smoking and alcohol use), medical history, and
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33 56 medication use were collected. Medication use was determined by asking participants
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36 57 whether they had taken prescribed medications for controlling blood pressure or glucose in
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39 58 the past 2 weeks. Those who answered "yes" and knew the drug names were asked to
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42 59 report the name, dose, and frequency of each drug. Those who did not remember the exact
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45 60 dose stated the number of pills or tablets taken (**Supplement 1**).

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

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4 67 use of antihypertensive medications, which is consistent with the US Joint National
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6 68 Committee and Chinese definitions^{15, 16}. Body mass index (BMI) was defined as weight in
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9 69 kilograms divided by height in square meters. Obesity was defined as 28.0 kg/m² or higher,
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12 70 based on recommendations from the Working Group on Obesity in China.¹⁷

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17 72 **Exposure Assessment**

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19 73 We geocoded each participant's current address (either rural counties or urban districts) into
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22 74 latitude and longitude data and identified air monitors located within 10 kilometers
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25 75 (**Supplement 2**). The average distance between the address of participants and assigned
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27 76 monitors was 2.7 (interquartile range 1.2, 3.5) kilometers. The measurements from these
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30 77 monitors strictly followed the methodological standards set by the State Environmental
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33 78 Protection Administration of China. For each participant, daily average PM_{2.5} concentrations
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35 79 measured at the nearest monitors to the residence were used to estimate PM_{2.5} exposure.
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38 80 The 1-year average concentration before the medical examination was calculated and
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41 81 treated as an indicator of long-term exposure to PM_{2.5}. In the present study, we included
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43 82 participants with more than 330 valid PM_{2.5} values for assessing long-term exposure, to
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46 83 ensure that, for each participant, the missing rate of PM_{2.5} data in the preceding one year of
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48 84 medical examination is less than 10%.¹⁸

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53 86 **Statistical Analysis**

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56 87 Continuous variables were reported as means with standard deviation; categorical variables
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59 88 were presented as percentages. We developed mixed models with a logit link function to

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4 89 assess the effect of long-term exposure to PM_{2.5} on hypertension prevalence. To assess the
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6 90 association of PM_{2.5} and blood pressure, SBP and DBP were modeled using linear
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9 91 regressions with township-specific random intercepts. For each of these analyses, we
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11 92 started with a model (Model 1) which only included age and sex. We then incrementally
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13 93 adjusted for additional covariates. The second model (Model 2) included Model1 and
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15 94 socioeconomic factors (education level and urbanity). The third model (Model 3) included
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17 95 Model 2 and cardiovascular disease risk factors (BMI, smoking status, alcohol consumption,
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19 96 and diabetes). Models of blood pressure were controlled for hypertensive medication use;
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21 97 while models of hypertension were not, as hypertension medication use was a component of
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23 98 the outcome definition. For sensitivity analysis, we additionally adjusted for the day of week
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25 99 (one indicator variable per day) and season of measurement (summer: June–August; fall:
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27 100 September–November; winter: December–February; spring: March–May) to account for
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29 101 potential time-variant factors. We also used restricted cubic splines to characterize the
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31 102 concentration-response (C-R) relationships of PM_{2.5} with hypertension prevalence and blood
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33 103 pressure.¹⁹ In addition, to examine effect modification by age, gender, smoking status,
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35 104 alcohol consumption, diabetes, and obesity, each potential modifier was tested by adding an
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37 105 interaction term in the regression model separately and testing its statistical significance as
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39 106 well as the association per categories of the tested variable through subgroup analyses.
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53 108 Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc., Cary,
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55 109 North Carolina). All tests of significance were 2-tailed, with a level of significance set at an
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57 110 alpha of 0.05.
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112 **Patient and public involvement**

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

115

116 **RESULT**

117 **Study population and baseline characteristics**

118 We included a total of 883,827 participants distributed in 83 county-level regions of mainland
119 China (**Supplement 3**). The mean age was 55.5 years, 60.4% were women, 43.1% had
120 hypertension, mean SBP was 143.5 mmHg, mean DBP was 83.1 mmHg, and 19.4% were
121 taking antihypertensive medications. The 1-year PM_{2.5} exposure of the total study population
122 ranged from 8.8 to 93.8 µg/m³ (mean 49.2 µg/m³). There were 864,119 (97.8%), 842,356
123 (95.3%), and 706,415 (79.9%) participants with 1-year PM_{2.5} exposure higher than 15 µg/m³
124 [World Health Organization (WHO) Interim Target 3 (IT-1)], 25 µg/m³ [WHO Interim Target 2
125 (IT-2)], and 35 µg/m³ [WHO Interim Target 3 (IT-3)], respectively. (**Supplement 4**)

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

128 After adjusting for sociodemographic characteristics and cardiovascular risk factors, the
129 odds ratio (OR) of hypertension was 1.09 (95% CI: 1.08–1.10) for each 10 µg/m³ increase in
130 PM_{2.5}. The association of PM_{2.5} exposure with hypertension prevalence remained consistent
131 across different model specifications (**Supplement 5**). For the C-R relationship, the curve
132 showed steeper slopes at high PM_{2.5} exposure levels (i.e., higher than ~50 µg/m³), and this

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4 133 trend was also evident in the sensitivity analysis with further adjustment for day of week and
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6 134 season of blood pressure measurements (**Supplement 6**). Compared to individuals with the
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9 135 lowest level of PM_{2.5} exposure (8.8 µg/m³), the adjusted ORs for hypertension of individuals
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12 136 with 15, 25, and 35 µg/m³ of PM_{2.5} exposure were 1.01 (95% CI: 1.01–1.02), 1.03 (95% CI:
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14 137 1.02–1.04), and 1.05 (95% CI: 1.03–1.07), respectively. (**Figure 1**)
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19 139 **Associations of long-term PM_{2.5} exposure with systolic and diastolic blood pressure**

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22 140 In the adjusted Model 4, each 10 µg/m³ increment was associated with increases of 0.50
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24 141 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After
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27 142 adjustment for the day of week and season, these positive associations were also observed
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30 143 [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP].
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32 144 (**Supplement 7**) In addition, we found that the shapes of the C-R curves for SBP and DBP
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35 145 were different. The fitted C-R functions showed upward trends with greater effect estimates
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38 146 of PM_{2.5} at higher concentrations for SBP but were generally U-shaped for DBP. (**Figure 2**)
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40 147 These C-R relationships for blood pressure remained robust after accounting for time-variant
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43 148 factors. (**Supplement 8**)
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48 150 **Subpopulation difference and effect modification**

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51 151 The associations of PM_{2.5} exposure with hypertension were stronger among the elderly (≥
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53 152 65 years), men, and non-current smokers compared with their counterparts (**Figure 3**).
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56 153 Gender significantly modified the effects of PM_{2.5} exposure on all three outcomes (all p for
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58 154 interaction <0.05) with stronger associations among men [e.g., OR for hypertension per 10
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4 155 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ of 1.06 (95% CI: 1.04–1.06) for women, and 1.12 (95% CI: 1.1–1.14)
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6 156 for men]; while these associations were not modified by alcohol consumption (all p for
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9 157 interaction >0.05). Although age and smoking status were also found to be effect modifiers
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11 158 in the associations of $\text{PM}_{2.5}$ exposure with SBP, DBP, and hypertension, the impacts of the
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14 159 two effect modifiers on these associations differed depending on the outcome. We observed
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17 160 greater effect estimates of $\text{PM}_{2.5}$ exposure for SBP and hypertension [e.g., OR for
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19 161 hypertension per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ of 1.14 (95% CI: 1.12–1.17) for the elderly, and
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22 162 1.06 (95% CI: 1.05–1.08) for their younger counterparts], while smaller estimates for DBP
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25 163 among the elderly and non-current smokers [e.g., elevation in DBP per 10 $\mu\text{g}/\text{m}^3$ increase in
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27 164 $\text{PM}_{2.5}$ of 0.16 mmHg (95% CI: 0.04–0.27) for the elderly, and 0.24 mmHg (95% CI: 0.19–0.3)
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30 165 for their younger counterparts]. (**Figure 4**)
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167 **DISCUSSION**

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

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

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4 177 incorporated a large cross-sectional survey with extensive covariates data obtained by
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6 178 personal interviews and standardized blood pressure measurements, which allowed us to
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9 179 comprehensively assess associations among a more diverse spectrum of population with a
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12 180 wider range of PM_{2.5} concentrations. We found long-term exposure to PM_{2.5} was positively
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14 181 associated with hypertension prevalence and blood pressure. This echoed the data showing
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17 182 that there was an absolute increase of 139 million individuals with hypertension in China
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19 183 during a decade from 2002–2013/14²⁰, with the national PM_{2.5} level gradually increasing in
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22 184 the meantime.²¹ Furthermore, the magnitude of the effects for each 10 µg/m³ increment in
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25 185 PM_{2.5} were also similar compared to other studies.^{5, 7, 22-24} For example, one study based on
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27 186 361,560 adults observed that each 10 µg/m³ in PM_{2.5} was associated with increases of 0.45
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30 187 mmHg and 0.07 mmHg in SBP and DBP, respectively.²² For hypertension prevalence, odds
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33 188 ratios related to a 10 µg/m³ increase in PM_{2.5} were ranged from 1.01 to 1.14 in prior
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36 189 studies.^{5, 23, 24} It is also noteworthy that others have reported no or inconsistent
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38 190 associations.^{25, 26} Adar et al. found no associations between exposures to PM_{2.5} and blood
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40 191 pressure based on a longitudinal cohort.²⁵ However, this study only included a small fraction
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43 192 of Chinese populations (10%), and was conducted in the U.S. with a mean annual average
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46 193 PM_{2.5} of 17 µg/m³, which was lower than this study (49.2 µg/m³).

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50 195 Second, we provided new information on the C-R relationship between long-term PM_{2.5}
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53 196 exposure and hypertension prevalence. Previous research reported a U-shaped relationship
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56 197 with a threshold PM_{2.5} of 47.9 µg/m³.⁵ However, in our study, the risk of hypertension
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59 198 associated with PM_{2.5} became even more pronounced when the exposure was extended to
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4 199 higher levels. This finding was in line with a prior study based on prospective cohorts
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6 200 showed that higher PM_{2.5} exposure was significantly associated with increased risk of
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9 201 developing hypertension, with hazard ratios (95% CIs) for hypertension incidence of 1.27
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11 202 (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-
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14 203 73.7 µg/m³), third (73.7-82.2 µg/m³), and fourth quartiles (>82.2 µg/m³) of PM_{2.5}
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16
17 204 concentrations compared with those in the first quartile (<71.9 µg/m³), respectively.²⁷ This
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19 205 result suggests that a per unit decrease in the concentration of PM_{2.5} can be translated to a
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22 206 greater reduction in excess hypertension prevalence in highly polluted regions compared
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25 207 with regions with low to moderate levels of PM_{2.5} exposure.
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27 208
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30 209 Third, we found evidence of nonlinearity in the relationships of PM_{2.5} exposure with SBP and
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32 210 DBP. Interestingly, the shape of curves for SBP and DBP were different. Although the
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35 211 relevant mechanism remains unclear, pathophysiological changes, such as systemic
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38 212 inflammation, atherosclerosis, endothelial dysfunction, and increased arterial stiffness,⁴ may
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41 213 have contributed to the observed patterns. The increased arterial stiffness induced by PM_{2.5}
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43 214 would initially lead to elevation in SBP and decline in DBP, creating an increased pulse
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46 215 pressure.²⁸ While with further increase of arterial stiffness, the heart rates got higher to
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49 216 maintain the stroke volume, which could result in the rise of DBP afterward. In addition, prior
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52 217 studies have reported the effects of PM_{2.5} exposure on pulse pressures showing a tendency
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55 218 of rising first and then declining at higher PM_{2.5} levels, which partially supports this
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58 219 hypothesis.²²
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4 221 Fourth, we assessed the subpopulation differences through stratified analyses and identified
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6 222 the susceptible individuals to the exposure of PM_{2.5}. We observed the large effect estimates
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9 223 of PM_{2.5} on hypertension and SBP among the elderly. Elderly subjects may commonly
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11 224 represent a higher prevalence of preexisting cardiovascular and respiratory diseases, which
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14 225 may confer susceptibility to PM_{2.5}. Also, the results showed that PM_{2.5} exposure had larger
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17 226 effects on hypertension in men, and such increased susceptibility may be related to sex-
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19 227 related differences in the deposition localization and rates of air pollutants; specifically, men
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22 228 have larger airways and slightly lower airway reactivity.²⁹ Additionally, smoking status was
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25 229 found to be an effect modifier with smaller effects on hypertension among current smokers.
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27 230 This finding is also supported by prior research.^{8, 22} One possible explanation is that smoking
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30 231 and PM_{2.5} exposure may share the same pathways in mediating cardiovascular effects and
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33 232 smoking may play a dominant role in smokers. Thus, exposure to PM_{2.5} might not exert
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36 233 additional harmful effects via the same pathway.²² There is also some potential that the
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38 234 greater effect size in non-current smokers could also be connected to some of them being
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41 235 advised to quit smoking because of multiple comorbidities.
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45 237 Our study should also be interpreted in the context of several limitations. First, given the
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48 238 nature of the cross-sectional study design, the causal relationship could not be established.
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51 239 Additional research is needed to examine these relationships in a prospective manner.
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54 240 Second, a selection bias is possible because our analysis was restricted to participants with
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57 241 available PM_{2.5} data. Third, while we included a number of potential confounders in the
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59 242 analyses, there might be unmeasured confounders that affected the observed associations.
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4 243 In particular, we were unable to control for other confounders such as diet and physical
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6 244 activity, because these data were only available in a subset of the China PEACE Million
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9 245 Persons Project cohort. Fourth, we used the data from the fixed monitors to estimate the
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11 246 exposure of PM_{2.5} and did not account for residential proximity to major roads, time-activity
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14 247 patterns, and indoor-related characteristics, which would likely result in nondifferential
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17 248 measurement errors. However, this approach is commonly used and previous research has
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19 249 indicated that PM_{2.5} exposure estimated by the nearest monitor was highly correlated with
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22 250 other sophisticated approaches³⁰. Fifth, other gaseous pollutants, such as NO_x and ozone,
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25 251 temperature, and noise were not included in this study. As a result, we were not able to
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27 252 determine whether the observed effects were specifically attributable to PM_{2.5} or the
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30 253 combined effects of these factors.

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32 254
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35 255 In conclusion, our study demonstrated that long-term exposure to PM_{2.5} was positively
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37 256 associated with blood pressure and hypertension prevalence. The effect of PM_{2.5} on
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40 257 hypertension prevalence was more pronounced at higher PM_{2.5} concentrations. Our findings
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43 258 reinforce the need to develop comprehensive strategies for addressing air pollution
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45
46 259 problems, especially for areas with severe air pollution.

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58
59 264 design, operations, and data collection.

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24
25 273 **DISCLOSURES**

26
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28
29
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31
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33
34
35 277 recipient of research agreements with Amgen, through National Center for Cardiovascular
36
37 278 Diseases (NCCD) and Fuwai Hospital, for a multi-centre trial to assess the efficacy and safety
38
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40 279 of Omecamtiv Mecarbil, and for dyslipidemic patient registration; is a recipient of a research
41
42
43 280 agreement with Sanofi, through Fuwai Hospital, for a multi-centre trial on the effects of
44
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46
47
48 282 Hospital, for a multi-centre trial of empagliflozin; and was a recipient of a research agreement,
49
50
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52
53 284 no other relevant conflicts of interest.
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4 **286 CONTRIBUTORS**

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6 287 JS and XZ conceived of this article. JS and YG wrote the manuscript with further
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8
9 288 contributions from XZ, XL, EM, MR, GT, DZ, WZ, JL, and MA. JS and SH completed all the
10
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12 289 statistical analyses. All authors interpreted data, contributed to critical revisions, and
13
14 290 approved the final version of the article.
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19 **292 DATA AVAILABILITY STATEMENT**

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22 293 No data is available. The China PEACE Million Persons Project is a major national program,
23
24 294 and as the government policy stipulates, it is not permissible for the researchers to
25
26
27 295 make the raw data publicly available at this time. All data generated during
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30 296 this study are included in this manuscript and its supplementary information
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33 297 files.
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4 395 **FIGURE LEGEND**

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6 396 **Figure 1.** Concentration-response functions of the long-term exposure to PM_{2.5} with
7 397 hypertension prevalence

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9 398 **Figure 2.** Concentration-response functions of the long-term exposure to PM_{2.5} with systolic
10 399 blood pressure (SBP) and diastolic blood pressure (DBP)

11
12 400 **Figure 3.** Stratified analysis of the association of long-term exposure to PM_{2.5} with
13 401 hypertension prevalence

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15 402 **Figure 4.** Stratified analysis of the association of long-term exposure to PM_{2.5} with systolic
16 403 blood pressure (SBP) and diastolic blood pressure (DBP)

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For peer review only

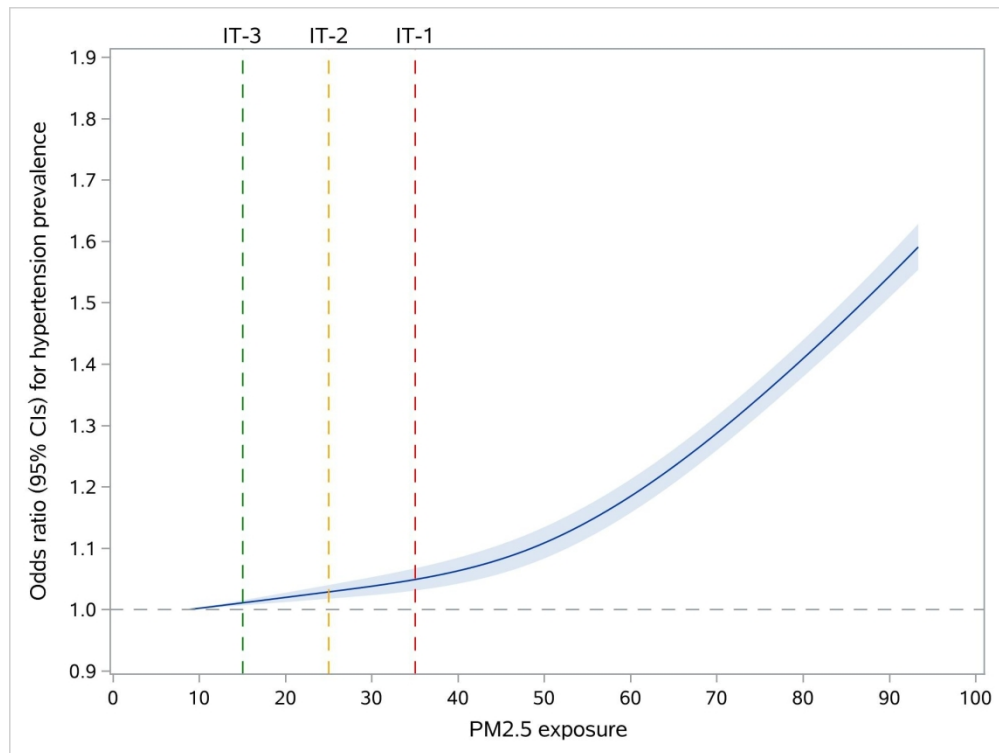


Figure 1. Concentration-response functions of the long-term exposure to PM2.5 with hypertension prevalence.

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

169x127mm (300 x 300 DPI)

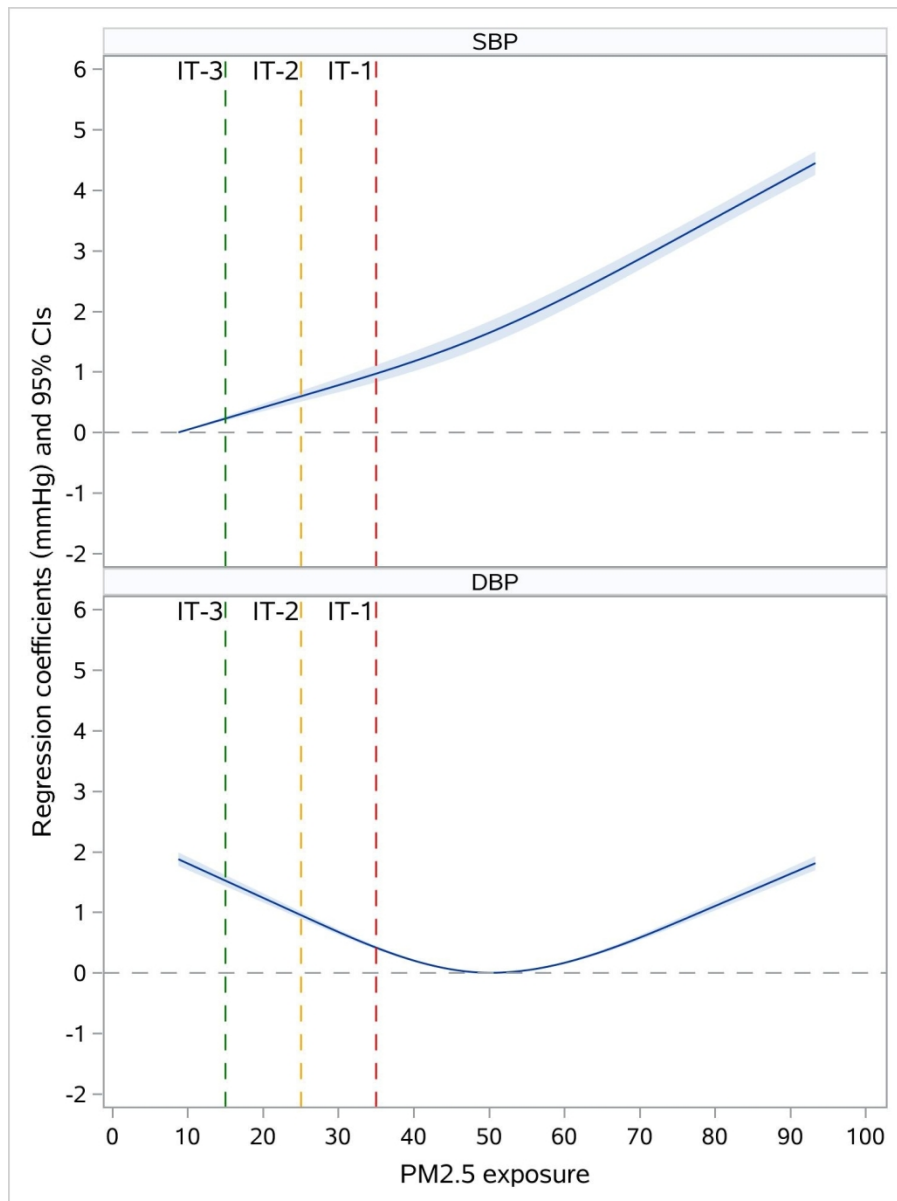
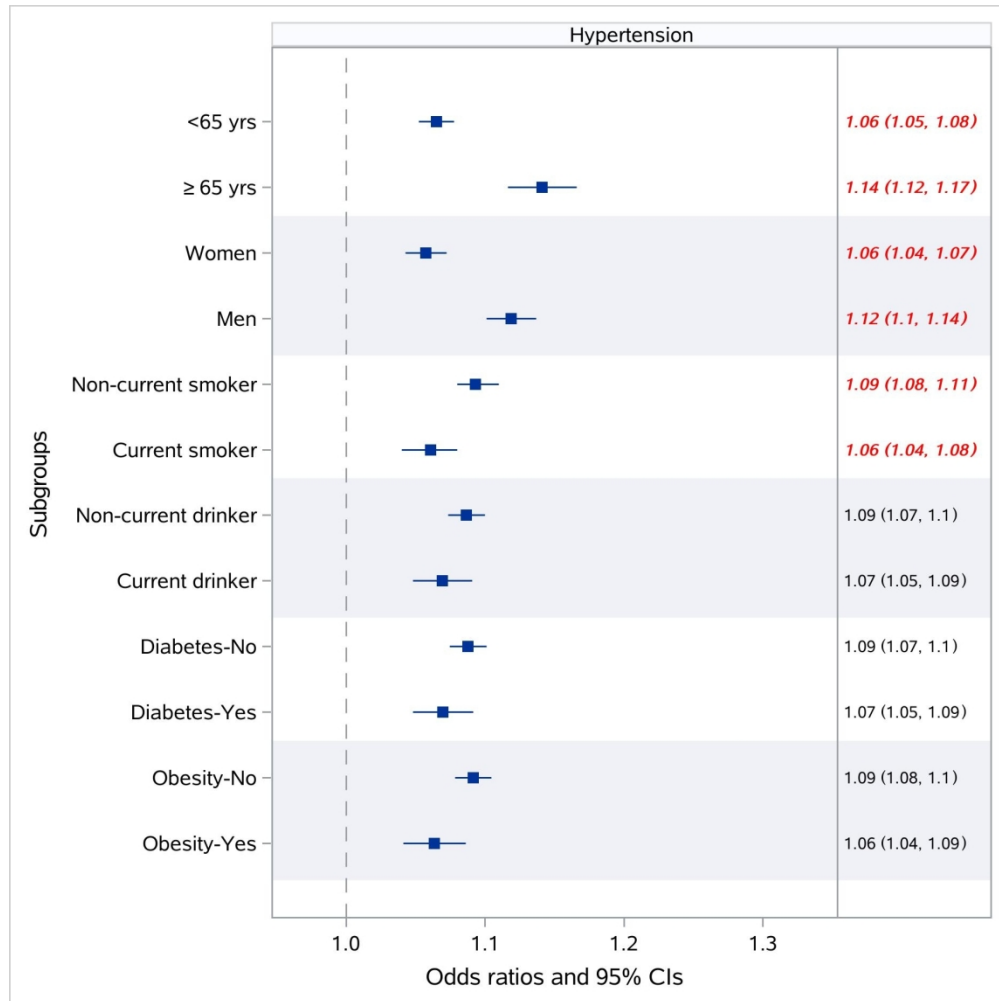


Figure 2. Concentration-response functions of the long-term exposure to PM_{2.5} with systolic blood pressure (SBP) and diastolic blood pressure (DBP). Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with PM_{2.5} exposure 8.8 µg/m³ and changes in DBP compared to individuals with PM_{2.5} exposure 50 µg/m³. 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 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)

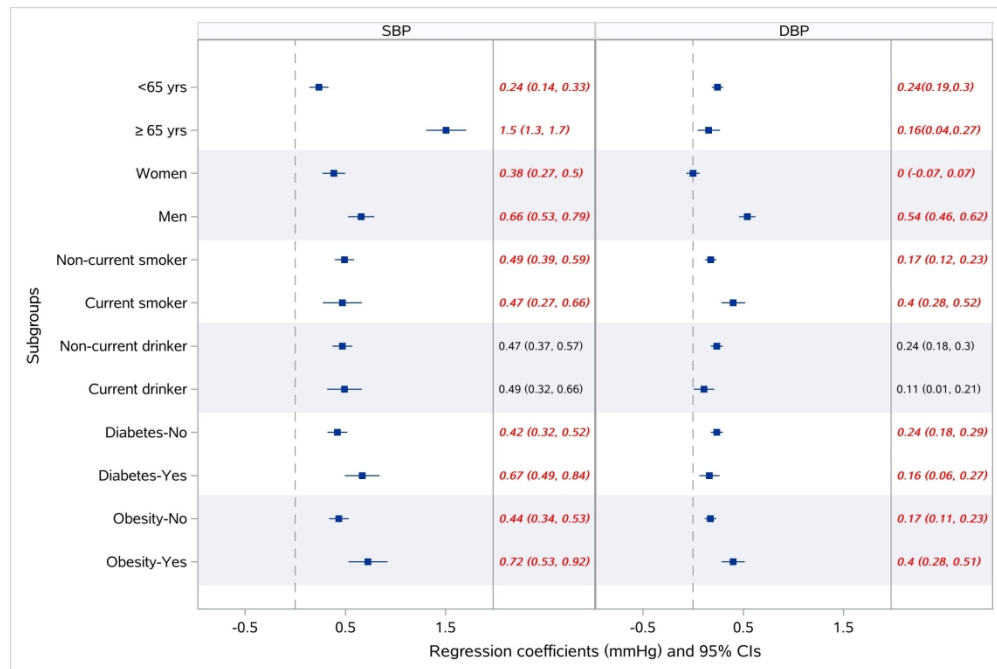


Figure 4. Stratified analysis of the association of long-term exposure to PM_{2.5} with blood pressure

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 $\mu\text{g}/\text{m}^3$ increment in the 1-year PM_{2.5} 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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4 **1 SUPPLEMENTAL MATERIAL**

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6 **2 Supplement 1. Collection of medication data in China PEACE Million Persons Project.**

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8 3 Potential participants who were taking medications were required to bring their drug
9 4 packaging (boxes) to the project sites. During the face-to-face interview, local project staff
10 5 asked participants whether they always took anti-hypertension, lipid-lowering, anti-diabetics,
11 6 or anti-platelet drugs during the past 2 weeks. Those who answered “yes” and knew the
12 7 name of the drug were further asked to report the name, dose, and frequency of each drug.
13 8 For those who did not remember the exact dose of the drug, the number of tablets or pills
14 9 taken was recorded. Interviewers searched and selected drug names or the first letter of the
15 10 Chinese phonetic alphabet participants answered by entering the generic name or trade
16 11 name of each drug in the electronic data collecting system. In this system, a data dictionary
17 12 was used to confirm drug information, including the drug class, generic name, trade name,
18 13 and corresponding unique ID.
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15 **Supplement 2. Summary statistics for daily PM_{2.5} (µg/m³) concentrations of assigned**
 16 **monitors in 83 study regions.**

No.	Mean	Median	25 th percentile	75 th 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

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3	50	32.84	29	20	42	5	121	1461	22
4	51	32.48	28	18	43	5	149	1461	35
5	52	27.19	24	14	36	3	120	1461	31
6	53	38.01	33	21	49	5	192	1461	16
7	54	35.67	30	19	46	3	269	1461	13
8	55	50.36	42	27	64	6	286	1461	23
9	56	44.34	35	23	56	5	333	1461	6
10	57	35.14	29	16	47	3	202	1461	22
11	58	22.1	18	14	27	3	123	1461	31
12	59	15.14	13	9	18	2	68	1461	12
13	60*	37.75	29	18	47	5	183	773	20
14	61	49.89	41	30	61	8	222	1461	27
15	62	60.72	49	32	77	5	353	1461	8
16	63	42.87	36	24	55	5	215	1461	16
17	64	49.35	40	24	65	3	235	1461	13
18	65	32.64	28	18	42	4	195	1461	23
19	66	30.96	28	21	39	7	123	1461	10
20	67	29.79	28	20	36	7	102	1461	23
21	68	13.86	14	12	15	3	51	1461	109
22	69	25.99	19	13	32	5	187	1461	33
23	70	24.49	19	13	30	2	124	1461	156
24	71	11.95	10	7	15	2	88	1461	87
25	72	51.21	42	30	63	10	239	1461	238
26	73	10.62	9	7	13	4	73	1461	46
27	74	53.8	41.5	28	64	5	328	1461	19
28	75	38.88	32	23	47	4	169	1461	27
29	76	44.45	36	24	57	4	581	1461	59
30	77	44.1	36	25	53	5	287	1461	44
31	78*	44.04	38	27	56	9	139	488	27
32	79	55.15	45	30	68	5	363	1461	14
33	80	44.69	36	24	55	5	219	1461	50
34	81	65.37	34	20	85	5	447	1461	97
35	82	57.76	29	19	70	3	414	1461	58
36	83	51.7	26	14	65	3	406	1461	42

17 Note:
 18 * Monitors being available after 2015
 19 Total: Number of days of assigned monitors being available during 2015-2018
 20 Missing: Number of days with missing PM_{2.5} concentration during 2015-2018
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22 **Supplement 3. Distribution of the sites.**



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only

25 **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)

26

27

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

Model	Per 10 µg/m ³ 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

29 ***Sensitivity analysis**

30 Model 1: Included age and sex;

31 Model 2: Model 1 + education level and urbanity;

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

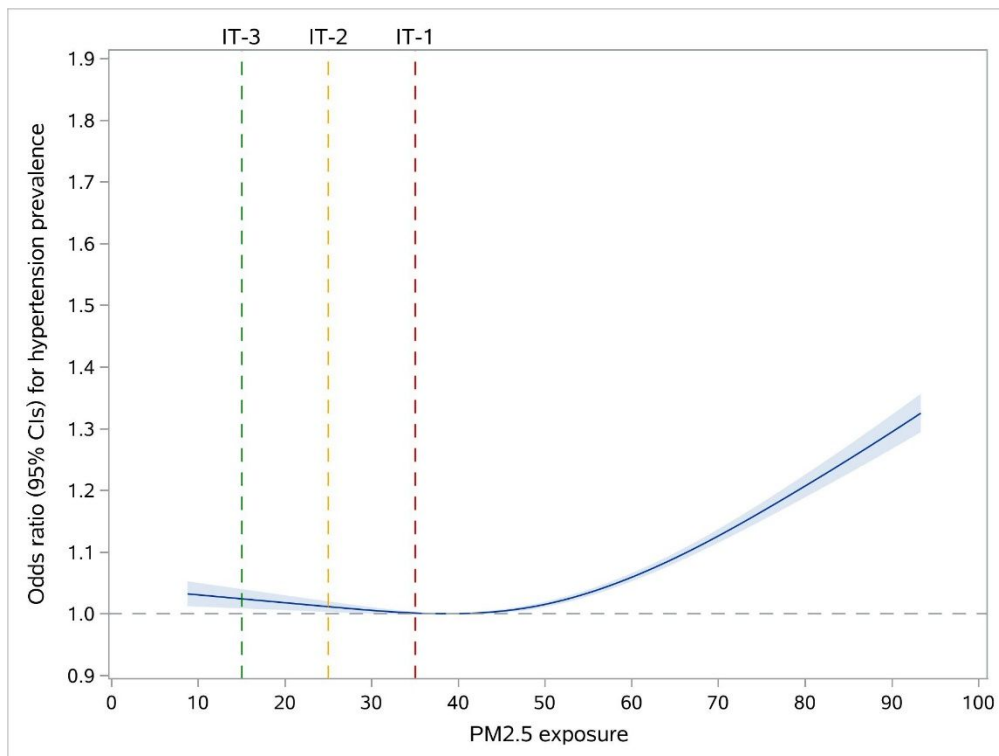
33 Model 4: Model 3 + day of week of the medical examination;

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

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

36

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



39
 40 Effect estimates were presented as adjusted odds ratios for hypertension prevalence
 41 compared to individuals with PM_{2.5} exposure 38.5 µg/m³.

42
 43 The dashed lines represent the air-quality standards for annual average concentrations of
 44 PM_{2.5} according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO
 45 Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).

46
 47 Covariates of the model including age, sex, education level, urbanity, smoking status,
 48 alcohol consumption, obesity, diabetes, as well as the day of week and season of blood
 49 pressure measurement.

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

Model	Per 10 µg/m ³ 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

51 *Sensitivity analysis

52

53 Model 1: Included age and sex;

54 Model 2: Model 1 + education level and urbanity;

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

56 Model 4: Model 3 + use of antihypertensive medication;

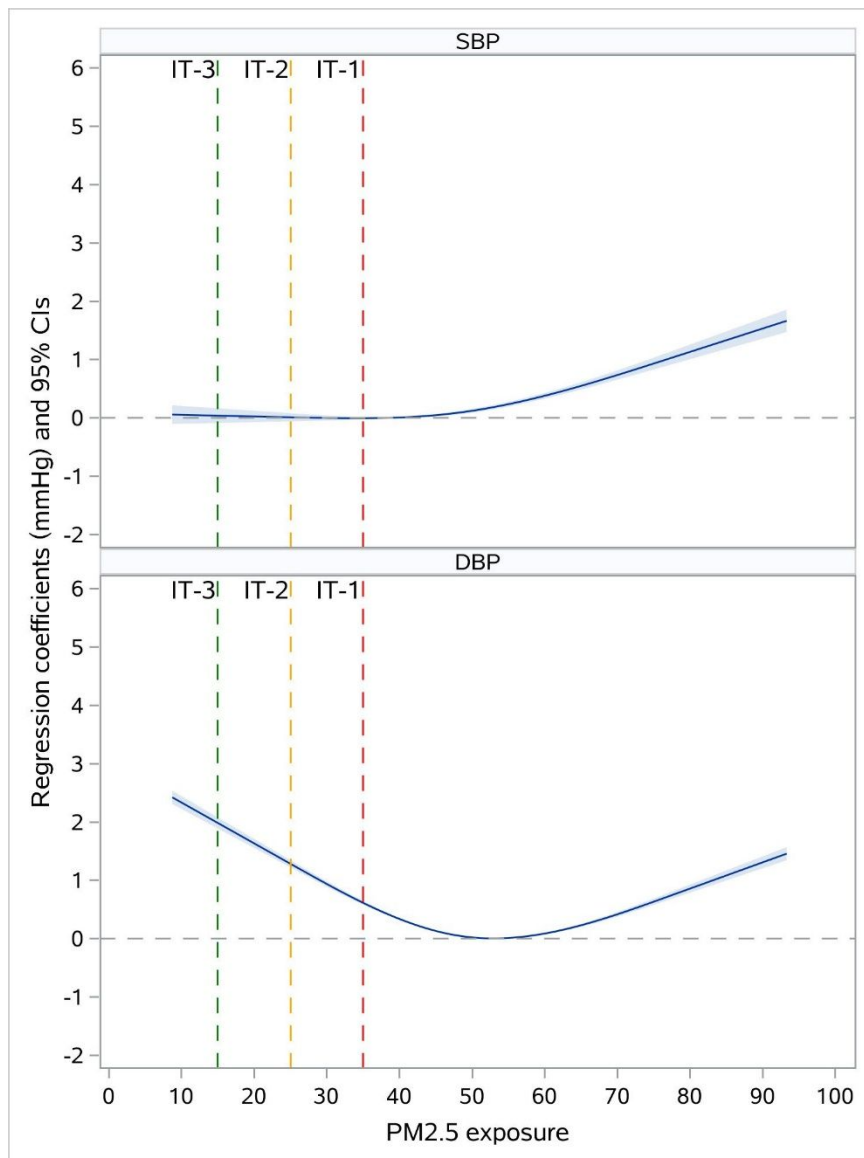
57 Model 5: Model 4 + day of week of the medical examination;

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

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

60

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



64
 65 Effect estimates (regression coefficients) were presented as changes in SBP compared to
 66 individuals with PM_{2.5} exposure 39 µg/m³ and changes in DBP compared to individuals with
 67 PM_{2.5} exposure 53 µg/m³.

68
 69 The dashed lines represent the air-quality standards for annual average concentrations of
 70 PM_{2.5} according to the World Health Organization (WHO) Interim Target 1 (IT-1), WHO
 71 Interim Target 2 (IT-2), WHO Interim Target 3 (IT-3).

72
 73 Covariates of the model including age, sex, education level, urbanity, smoking status,
 74 alcohol consumption, obesity, diabetes, and use of antihypertensive medications, as well as
 75 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

1			
2	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
3			11-12
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6			(b) Report category boundaries when continuous variables were categorized
7			10-11
8			
9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
10			NA
11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
12			12
13			
14	Discussion		
15	Key results	18	Summarise key results with reference to study objectives
16			13
17	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
18			16
19			
20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
21			13-16
22			
23			
24	Generalisability	21	Discuss the generalisability (external validity) of the study results
25			15-16
26			
27	Other information		
28	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
29			17
30			
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*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.

BMJ Open

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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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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Number of figures: 4

For peer review only

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/m³ (mean 49.2 µg/m³). The adjusted odds ratio of hypertension prevalence related to a 10 µg/m³ increase in one-year PM_{2.5} exposure was 1.04 (95% confidence interval, 1.02–1.05). Each 10 µg/m³ 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}.

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4 **Conclusions:** Long-term exposure to PM_{2.5} is associated with higher blood pressure and
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6 increased risk of hypertension prevalence. The effects of PM_{2.5} on hypertension prevalence
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8 become more pronounced at higher PM_{2.5} levels. These findings emphasize the need to
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10 reduce air pollution, especially in areas with severe air pollution.
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17 **Keywords:** Air pollution; Blood pressure; Hypertension
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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/m³), 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.

1 INTRODUCTION

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

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

17
18 China is experiencing a growing epidemic of hypertension and is estimated to have 300
19 million individuals with hypertension by 2025.¹¹ Meanwhile, outdoor PM_{2.5} has become one
20 of China's most serious environmental problems with population-weighted annual means of
21 PM_{2.5} ranging from 19.1 µg/m³ to 79.3 µg/m³ in 2015.¹² A deeper understanding of the
22 chronic health effects of PM_{2.5} on hypertension prevalence and blood pressure in moderate

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4 23 to high PM_{2.5} concentrations will help to develop policies to improve air quality and combat
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6 24 the hypertension epidemic in China.
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11 26 Accordingly, incorporating PM_{2.5} data with a large-scale population-based screening project
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14 27 in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE)
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17 28 Million Persons Project, we aimed to: (1) explore the association of long-term PM_{2.5}
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19 29 exposure with blood pressure level and hypertension prevalence, and evaluate
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22 30 subpopulation differences and effect modification by characteristics of participants in these
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25 31 associations; (2) assess the concentration-response relationships of long-term PM_{2.5}
26
27 32 exposure with hypertension prevalence and blood pressure.
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31 32 34 **METHODS**

33 34 35 **Study population**

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37 36 Our study population is derived from the China PEACE Million Persons Project, which has
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40 37 been described previously.¹³ In brief, we selected county-level regions using a convenience
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43 38 sampling strategy in all 31 provinces in mainland China from September 2014 to March
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46 39 2019. These regions are designated as rural counties or urban districts according to urban-
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49 40 rural division codes of the National Bureau of Statistics of China.¹⁴ Local residents aged 35
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52 41 to 75 years, who were currently registered in the selected region's Hukou (a record officially
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55 42 identifying a person as a resident of an area) or had lived in the region for at least 6 of the
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58 43 previous 12 months, were enrolled in this project. After excluding participants with missing
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60 44 data on education level (n=13,714), body mass index (n=321), or blood pressure

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4 45 measurement (n=2), we further excluded participants with systolic blood pressure (SBP) \geq
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6 46 250 mmHg or diastolic blood pressure (DBP) \geq 150 mmHg to minimize the potential bias due
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8
9 47 to measurement errors in blood pressure values (n=73). Finally, we included 883,827
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12 48 participants in the study sample.

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17 50 **Data collection and variable definitions**

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19 51 Data collection for each participant was performed by trained personnel with a standardized
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21
22 52 in-person interview and a medical examination. Information on sociodemographic status
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24
25 53 (age, gender, and education level), lifestyle (smoking and alcohol use), medical history, and
26
27 54 medication use were collected. Medication use was determined by asking participants
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29
30 55 whether they had taken prescribed medications for controlling blood pressure or glucose in
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32
33 56 the past 2 weeks. Those who answered "yes" and knew the drug names were asked to
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35 57 report the name, dose, and frequency of each drug. Those who did not remember the exact
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38 58 dose stated the number of pills or tablets taken (**Supplement 1**).

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43 60 The blood pressure of each participant was measured twice on the right upper arm after 5
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45 61 minutes of rest in a seated position with a standardized electronic blood pressure monitor
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48 62 (Omron HEM-7430). If the difference between the two SBP readings was greater than 10
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51 63 mmHg, a third measurement was obtained, and the average of the last 2 readings was used.
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53 64 Hypertension was defined as SBP of 140 mmHg or higher, DBP of 90 mmHg or higher, or
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56 65 use of antihypertensive medications, which is consistent with the US Joint National
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59 66 Committee and Chinese definitions^{15, 16}. Body mass index (BMI) was defined as weight in

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4 67 kilograms divided by height in square meters. Obesity was defined as 28.0 kg/m² or higher,
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6 68 based on recommendations from the Working Group on Obesity in China.¹⁷
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10 11 70 **Exposure Assessment**

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14 71 We geocoded each participant's current address (either rural counties or urban districts) into
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17 72 latitude and longitude data and identified air monitors located within 10 kilometers
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19 73 (**Supplement 2**). The average distance between the address of participants and assigned
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22 74 monitors was 2.7 (interquartile range 1.2, 3.5) kilometers. The measurements from these
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25 75 monitors strictly followed the methodological standards set by the State Environmental
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27 76 Protection Administration of China. For each participant, daily average PM_{2.5} concentrations
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30 77 measured at the nearest monitors to the residence were used to estimate PM_{2.5} exposure.
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33 78 The 1-year average concentration before the medical examination was calculated and
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35 79 treated as an indicator of long-term exposure to PM_{2.5}. In the present study, we included
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38 80 participants with more than 330 valid PM_{2.5} values for assessing long-term exposure, to
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41 81 ensure that, for each participant, the missing rate of PM_{2.5} data in the preceding one year of
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43 82 medical examination is less than 10%.¹⁸
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47 48 84 **Statistical Analysis**

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50 85 Continuous variables were reported as means with standard deviation; categorical variables
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53 86 were presented as percentages. We developed mixed models with a logit link function to
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56 87 assess the effect of long-term exposure to PM_{2.5} on hypertension prevalence. To assess the
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59 88 association of PM_{2.5} and blood pressure, SBP and DBP were modeled using linear
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4 89 regressions with township-specific random intercepts. For each of these analyses, we
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6 90 started with a model (Model 1) which only included age and sex. We then incrementally
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9 91 adjusted for additional covariates. The second model (Model 2) included Model1 and
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11 92 socioeconomic factors (education level and urbanity). The third model (Model 3) included
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14 93 Model 2 and cardiovascular disease risk factors (BMI, smoking status, alcohol consumption,
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17 94 and diabetes). Models of blood pressure were controlled for hypertensive medication use;
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19 95 while models of hypertension were not, as hypertension medication use was a component of
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21
22 96 the outcome definition. To account for potential time-variant factors, we additionally adjusted
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25 97 for the day of week (one indicator variable per day) and season of measurement (summer:
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27 98 June–August; fall: September–November; winter: December–February; spring: March–May).
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30 99 We also used restricted cubic splines to characterize the concentration-response (C-R)
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33 100 relationships of PM_{2.5} with hypertension prevalence and blood pressure.¹⁹ In addition, to
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35 101 examine effect modification by age, gender, smoking status, alcohol consumption, diabetes,
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38 102 and obesity, each potential modifier was tested by adding an interaction term in the
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41 103 regression model separately and testing its statistical significance as well as the association
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43 104 per categories of the tested variable through subgroup analyses.
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48 106 Analyses were conducted with SAS version 9.4, 64-bit Windows (SAS Institute Inc., Cary,
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50
51 107 North Carolina). All tests of significance were 2-tailed, with a level of significance set at an
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53 108 alpha of 0.05.
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110 **Patient and public involvement**

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

114 **RESULT**

115 **Study population and baseline characteristics**

116 We included a total of 883,827 participants distributed in 83 county-level regions of mainland
117 China (**Supplement 3**). The mean age was 55.5 years, 60.4% were women, 43.1% had
118 hypertension, mean SBP was 143.5 mmHg, mean DBP was 83.1 mmHg, and 19.4% were
119 taking antihypertensive medications. The 1-year PM_{2.5} exposure of the total study population
120 ranged from 8.8 to 93.8 µg/m³ (mean 49.2 µg/m³). There were 864,119 (97.8%), 842,356
121 (95.3%), and 706,415 (79.9%) participants with 1-year PM_{2.5} exposure higher than 15 µg/m³
122 [World Health Organization (WHO) Interim Target 3 (IT-1)], 25 µg/m³ [WHO Interim Target 2
123 (IT-2)], and 35 µg/m³ [WHO Interim Target 3 (IT-3)], respectively. (**Supplement 4**)

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

126 After adjusting for sociodemographic characteristics and cardiovascular risk factors, the
127 odds ratio (OR) of hypertension was 1.09 (95% CI: 1.08–1.10) for each 10 µg/m³ increase in
128 PM_{2.5}. The adjustment for day of week and season of blood pressure measurements
129 resulted in a slight decrease in the effect estimate of the association of PM_{2.5} exposure with
130 hypertension prevalence (OR: 1.04, 95%CI: 1.02–1.05). (**Supplement 5**) For the C-R
131 relationship, the curve showed steeper slopes at high PM_{2.5} exposure levels (i.e., higher than

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4 132 ~50 $\mu\text{g}/\text{m}^3$). Compared to individuals with $\text{PM}_{2.5}$ exposure of 38.5 $\mu\text{g}/\text{m}^3$, the adjusted ORs
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6 133 for hypertension of individuals with 15, 25, and 35 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ exposure were 1.02 (95%
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9 134 CI: 1.01–1.04), 1.01 (95% CI: 1.00–1.02), and 1.00 (95% CI: 1.00–1.00), respectively.
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12 135 **(Figure 1)**
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17 137 **Associations of long-term $\text{PM}_{2.5}$ exposure with systolic and diastolic blood pressure**

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19 138 In the adjusted Model 4, each 10 $\mu\text{g}/\text{m}^3$ increment was associated with increases of 0.50
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22 139 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After
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24 140 adjustment for the day of week and season, there was some reduction in the effect
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27 141 estimates of the associations between $\text{PM}_{2.5}$ exposure and blood pressure [0.19 mmHg
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29 142 (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP]. **(Supplement 6)** In
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31 143 addition, we found that the shapes of the C-R curves for SBP and DBP were different. The
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34 144 fitted C-R functions showed upward trends with greater effect estimates of $\text{PM}_{2.5}$ at higher
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37 145 concentrations for SBP but were generally U-shaped for DBP. **(Figure 2)**
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43 147 **Subpopulation difference and effect modification**

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45 148 The associations of $\text{PM}_{2.5}$ exposure with hypertension were stronger among men and non-
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48 149 current smokers, compared with their counterparts **(Figure 3)**. Gender significantly modified
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50 150 the effects of $\text{PM}_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger
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53 151 associations among men [e.g., OR for hypertension per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ of 1.01
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55 152 (95% CI: 1.00–1.03) for women, and 1.06 (95% CI: 1.05–1.08) for men]; while these
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58 153 associations were not modified by alcohol consumption and prevalence of diabetes (all p for
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4 154 interaction >0.05). Although smoking status was the effect modifiers in the associations of
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7 155 PM_{2.5} exposure with SBP, DBP, and hypertension, the impacts of smoking on these
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9 156 associations differed depending on the outcome. We observed greater effect estimates of
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12 157 PM_{2.5} exposure for SBP [elevation in SBP per 10 µg/m³ increase in PM_{2.5} of 0.97 mmHg
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14 158 (95% CI: 0.77–1.17) for the elderly, and -0.02 mmHg (95% CI: -0.12–0.08) for their younger
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17 159 counterparts], while smaller estimates for DBP among the elderly [elevation in DBP per 10
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19 160 µg/m³ increase in PM_{2.5} of 0.11 mmHg (95% CI: 0.00–0.22) for the elderly, and 0.14 mmHg
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22 161 (95% CI: 0.08–0.20) for their younger counterparts]. Besides, obesity was also found to be
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25 162 an effect modifier in the associations of PM_{2.5} exposure with SBP and DBP, with greater
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27 163 effect estimates in obese participants. **(Figure 4)**
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31 32 165 **DISCUSSION**

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35 166 In this study, we investigated the associations between long-term exposure to PM_{2.5} and
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38 167 hypertension prevalence, SBP, and DBP. We found that PM_{2.5} was associated with
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41 168 increased risk of hypertension prevalence and elevation of blood pressure. Nonlinearity in
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43 169 these associations was also observed. The C-R curves for hypertension and SBP showed
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45 170 steeper slopes for PM_{2.5} concentration above 50 µg/m³; while the C-R curve for PM_{2.5}–DBP
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48 171 was U-shaped, with the turning point around 50 µg/m³. The elderly, men, non-current
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51 172 smokers, and obese participants appeared to be more susceptible to the exposure of PM_{2.5}.
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56 174 Our study contributes to the existing scientific literature in several ways. First, by including
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59 175 participants in a national cross-sectional survey with long-term exposure to PM_{2.5} ranged
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4 176 from 8.8–93.8 $\mu\text{g}/\text{m}^3$, we are able to comprehensively assess the association of $\text{PM}_{2.5}$
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6 177 exposure with hypertension prevalence and blood pressure among a more diverse spectrum
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9 178 of population with a wider range of $\text{PM}_{2.5}$ concentrations. We found exposure to $\text{PM}_{2.5}$ was
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11 179 positively associated with hypertension prevalence and blood pressure. This echoed the
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14 180 data showing that there was an absolute increase of 139 million individuals with
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17 181 hypertension in China during a decade from 2002 to 2013/14²⁰, with the national annual
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19 182 mean $\text{PM}_{2.5}$ increasing from 39.5 $\mu\text{g}/\text{m}^3$ to 47 $\mu\text{g}/\text{m}^3$ between 2000 and 2013.²¹ Specifically,
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22 183 in some high-polluted areas such as Beijing-Tianjin-Hebei region of 2013, the annual
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24 184 average concentrations of $\text{PM}_{2.5}$ had reached 98.9 $\mu\text{g}/\text{m}^3$, and daily average concentrations
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26 185 had exceeded 300 $\mu\text{g}/\text{m}^3$.^{22, 23} Furthermore, the magnitude of the effects for each 10 $\mu\text{g}/\text{m}^3$
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29 186 increment in $\text{PM}_{2.5}$ was also similar compared to other studies.^{5, 7, 24-26} For example, one
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31 187 study found that each 10 $\mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$ was associated with increases of 0.45 mmHg and
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33 188 0.07 mmHg in SBP and DBP, respectively.²⁴ And odds ratios for hypertension prevalence
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35 189 related to a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ were ranged from 1.01 to 1.14 in prior studies.^{5, 25, 26}
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38 190 It is also noteworthy that others have reported no or inconsistent associations.^{27, 28} Adar et
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40 191 al. found no associations between exposures to $\text{PM}_{2.5}$ and blood pressure based on a
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43 192 longitudinal cohort.²⁷ However, this study only included a small fraction of Chinese
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46 193 populations (10%), and was conducted in the U.S. with a mean annual average $\text{PM}_{2.5}$ of 17
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48 194 $\mu\text{g}/\text{m}^3$, which was lower than the present study (49.2 $\mu\text{g}/\text{m}^3$).

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196 Second, we provided new information on the C-R relationship between long-term $\text{PM}_{2.5}$

197 exposure and hypertension prevalence. Previous research reported a U-shaped relationship

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4 198 with a threshold $PM_{2.5}$ of $47.9 \mu\text{g}/\text{m}^3$.⁵ However, in our study, the risk of hypertension
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6 199 associated with $PM_{2.5}$ became even more pronounced when the exposure was extended to
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9 200 higher levels. This finding was in line with a prior study based on prospective cohorts
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11 201 showed that there was a stepwise increase in the risk of developing hypertension
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14 202 with increasing quartiles of long-term $PM_{2.5}$ exposure.²⁹ This result suggests that, for a given
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17 203 decrease in the concentration of $PM_{2.5}$, a greater reduction in excess hypertension
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19 204 prevalence would be obtained in highly polluted regions compared with regions with low to
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22 205 moderate levels of $PM_{2.5}$ exposure. In this respect, the implication of air quality
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25 206 improvements in highly polluted regions of China in recent years would be more profound. It
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27 207 has shown that from 2013 to 2018, the annual average concentration of $PM_{2.5}$ in Beijing-
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30 208 Tianjin-Hebei region has declined by 49%.³⁰ Considering the population size and baseline
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33 209 $PM_{2.5}$ levels in these areas, the public health impact related to $PM_{2.5}$ reduction would be
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35 210 huge.

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40 212 Third, we found evidence of nonlinearity in the relationships of $PM_{2.5}$ exposure with SBP and
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43 213 DBP. Interestingly, the shape of curves for SBP and DBP were different. Although the
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46 214 relevant mechanism remains unclear, pathophysiological changes, such as systemic
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48 215 inflammation, atherosclerosis, endothelial dysfunction, and increased arterial stiffness,⁴ may
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51 216 have contributed to the observed patterns. The increased arterial stiffness induced by $PM_{2.5}$
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54 217 would initially lead to elevation in SBP and decline in DBP, creating an increased pulse
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56 218 pressure.³¹ While with further increase of arterial stiffness, the heart rates got higher to
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59 219 maintain the stroke volume, which could result in the rise of DBP afterward. In addition, prior
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4 220 studies have reported the effects of PM_{2.5} exposure on pulse pressures showing a tendency
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7 221 of rising first and then declining at higher PM_{2.5} levels, which partially supports this
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9 222 hypothesis.²⁴

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14 224 Fourth, we assessed the subpopulation differences through stratified analyses and identified
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17 225 the susceptible individuals to the exposure of PM_{2.5}. We observed the large effect estimates
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20 226 of PM_{2.5} on SBP among the elderly. Elderly subjects may commonly represent a higher
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22 227 prevalence of preexisting cardiovascular and respiratory diseases, which may confer
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25 228 susceptibility to PM_{2.5}. Also, the results showed that PM_{2.5} exposure had larger effects on
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27 229 hypertension in men, and such increased susceptibility may be related to sex-related
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30 230 differences in the deposition localization and rates of air pollutants; specifically, men have
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33 231 larger airways and slightly lower airway reactivity.³² Further, we found stronger associations
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35 232 of PM_{2.5} and blood pressure in obese participants. The greater response observed in obese
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38 233 individuals may be attributed to the higher deposition rate of PM_{2.5} exposure. This has been
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41 234 demonstrated in overweight children, where there was an increase in tidal volume and
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43 235 resting minute ventilation.³³ Additionally, smoking status was found to be an effect modifier
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46 236 with smaller effects on hypertension among current smokers. This finding is also supported
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48 237 by prior research.^{8, 24} One possible explanation is that smoking and PM_{2.5} exposure may
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51 238 share the same pathways in mediating cardiovascular effects and smoking may play a
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54 239 dominant role in smokers. Thus, exposure to PM_{2.5} might not exert additional harmful effects
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56 240 via the same pathway.²⁴ There is also some potential that the greater effect size in non-
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59 241 current smokers could also be connected to some of them being advised to quit smoking

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4 242 because of multiple comorbidities.
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9 244 Our study should also be interpreted in the context of several limitations. First, given the
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11 245 nature of the cross-sectional study design, the causal relationship could not be established.

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14 246 Additional research is needed to examine these relationships in a prospective manner.

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17 247 Second, a selection bias is possible because our analysis was restricted to participants with
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19 248 available PM_{2.5} data. Third, while we included a number of potential confounders in the
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22 249 analyses, there might be unmeasured confounders that affected the observed associations.

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25 250 In particular, we were unable to control for other confounders such as diet and physical

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27 251 activity, because these data were only available in a subset of the China PEACE Million

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30 252 Persons Project cohort. Fourth, we used the data from the fixed monitors to estimate the

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32 253 exposure of PM_{2.5} and did not account for residential proximity to major roads, time-activity

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35 254 patterns, and indoor-related characteristics, which would likely result in nondifferential

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37 255 measurement errors. However, this approach is commonly used and previous research has

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40 256 indicated that PM_{2.5} exposure estimated by the nearest monitor was highly correlated with

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43 257 other sophisticated approaches³⁴. Fifth, other gaseous pollutants, such as NO_x and ozone,

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45 258 temperature, and noise were not included in this study. As a result, we were not able to

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48 259 determine whether the observed effects were specifically attributable to PM_{2.5} or the

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51 260 combined effects of these factors.

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56 262 In conclusion, our study demonstrated that long-term exposure to PM_{2.5} was positively

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58 263 associated with blood pressure and hypertension prevalence. The effect of PM_{2.5} on
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4 264 hypertension prevalence was more pronounced at higher PM_{2.5} concentrations. Our findings
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6 265 reinforce the need to develop comprehensive strategies for addressing air pollution
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9 266 problems, especially for areas with severe air pollution.
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13 14 268 **ACKNOWLEDGMENTS**

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18
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20
21
22 271 design, operations, and data collection.
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24
25 272

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36
37
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41
42
43 279

44 45 280 **DISCLOSURES**

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47
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49
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51
52
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54
55
56 284 recipient of research agreements with Amgen, through National Center for Cardiovascular
57
58 285 Diseases (NCCD) and Fuwai Hospital, for a multi-centre trial to assess the efficacy and safety
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4 286 of Omecamtiv Mecarbil, and for dyslipidemic patient registration; is a recipient of a research
5
6 287 agreement with Sanofi, through Fuwai Hospital, for a multi-centre trial on the effects of
7
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9 288 sotagliflozin; is a recipient of a research agreement with University of Oxford, through Fuwai
10
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12
13
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15
16
17 291 no other relevant conflicts of interest.
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20 292

21 22 293 **CONTRIBUTORS**

23
24 294 JS and XZ conceived of this article. JS wrote the manuscript with further contributions from
25
26
27 295 XZ, YG, XL, EM, MR, GT, DZ, WZ, JL, and MA. JS and SH completed all the statistical
28
29
30 296 analyses. All authors interpreted data, contributed to critical revisions, and approved the final
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33 297 version of the article.
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36 37 38 299 **ETHICS APPROVAL**

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40 300 The central ethics committee at the China National Center for Cardiovascular Diseases
41
42
43 301 approved this project (Ethical code 2014-574). All enrolled participants provided written
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45
46 302 informed consent.
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49 50 304 **DATA AVAILABILITY STATEMENT**

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53 305 No data is available. The China PEACE Million Persons Project is a major national program,
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56 306 and as the government policy stipulates, it is not permissible for the researchers to make the
57
58
59 307 raw data publicly available at this time. All data generated during this study is included in this
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4 308 manuscript and its supplementary information files.
5

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4 417 **FIGURE LEGEND**

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6 418 **Figure 1.** Concentration-response functions of the long-term exposure to PM_{2.5} with
7 419 hypertension prevalence

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9 420 **Figure 2.** Concentration-response functions of the long-term exposure to PM_{2.5} with systolic
10 421 blood pressure (SBP) and diastolic blood pressure (DBP)

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12 422 **Figure 3.** Stratified analysis of the association of long-term exposure to PM_{2.5} with
13 423 hypertension prevalence

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15 424 **Figure 4.** Stratified analysis of the association of long-term exposure to PM_{2.5} with systolic
16 425 blood pressure (SBP) and diastolic blood pressure (DBP)

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For peer review only

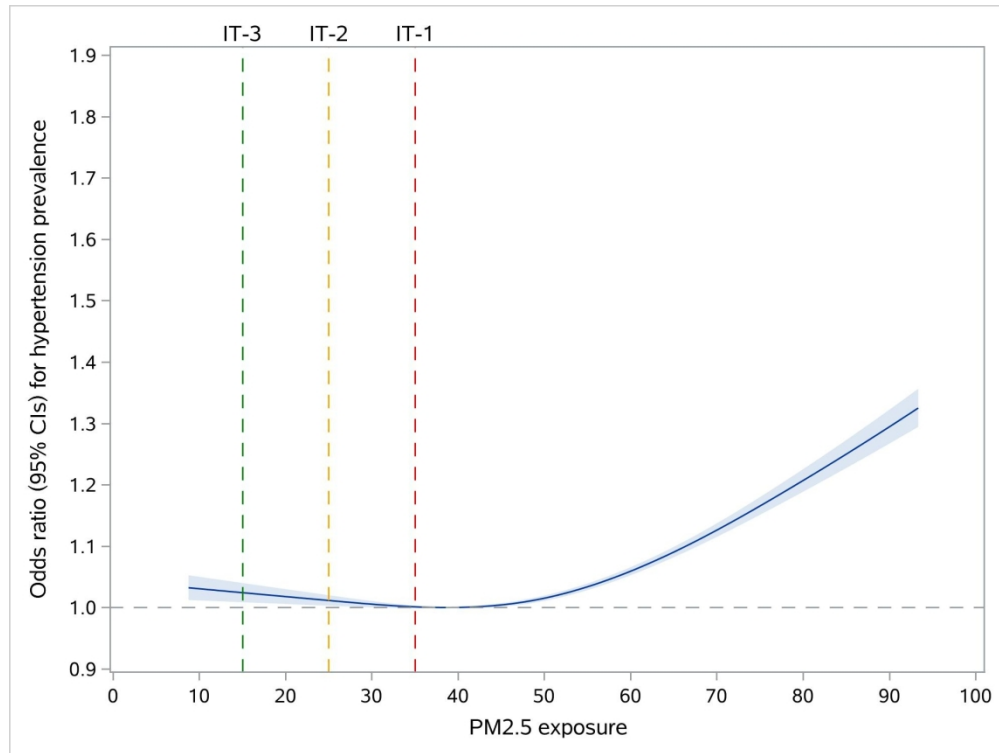


Figure 1. Concentration-response functions of the long-term exposure to PM_{2.5} with hypertension prevalence. Effect estimates were presented as adjusted odds ratios for hypertension prevalence compared to individuals with PM_{2.5} exposure 38.5 µg/m³. The dashed lines represent the air-quality standards 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.

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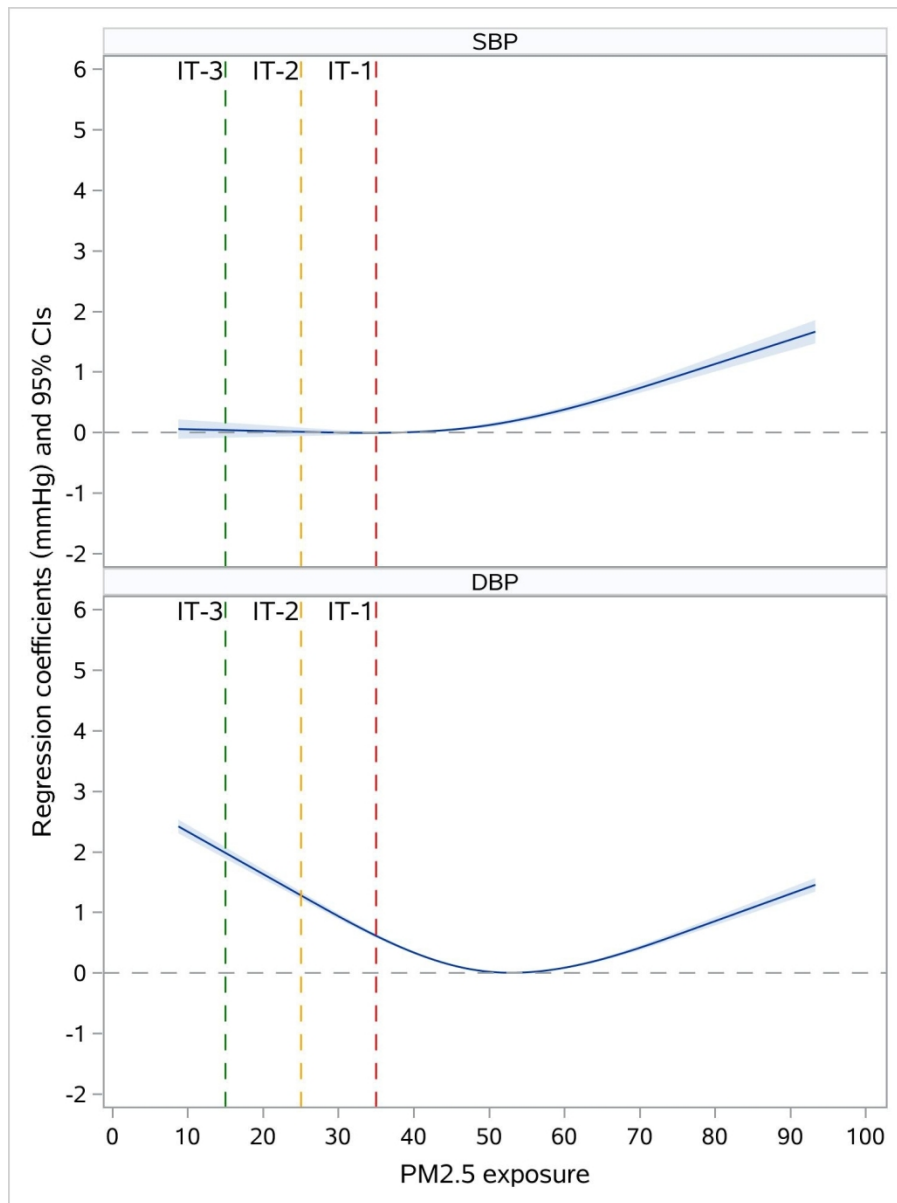


Figure 2. Concentration-response functions of the long-term exposure to $PM_{2.5}$ with systolic blood pressure (SBP) and diastolic blood pressure (DBP). Effect estimates (regression coefficients) were presented as changes in SBP compared to individuals with $PM_{2.5}$ exposure $39 \mu g/m^3$ and changes in DBP compared to individuals with $PM_{2.5}$ exposure $53 \mu g/m^3$. 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.

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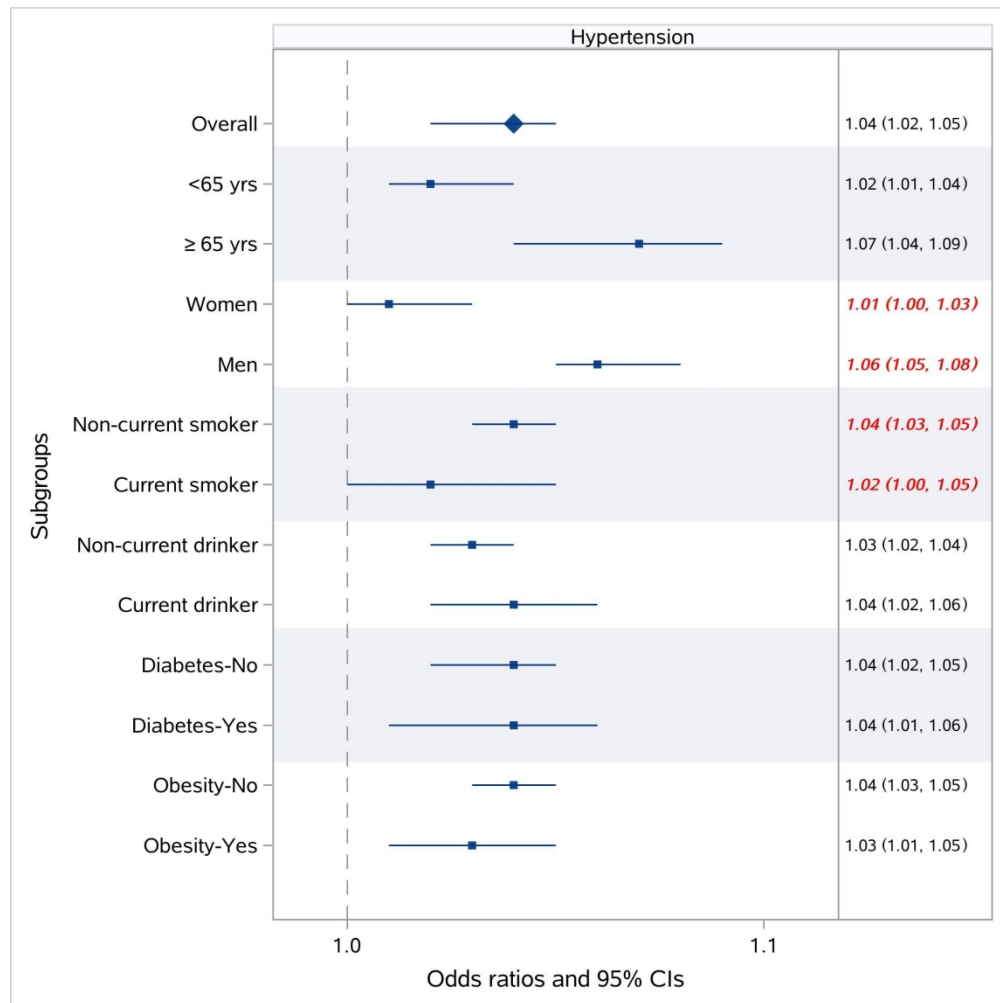


Figure 3. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with hypertension prevalence. Red texts with italics indicated that p-value for interaction terms < 0.05 . Effect estimates (regression coefficients) were presented as adjusted odds ratios for hypertension prevalence 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.

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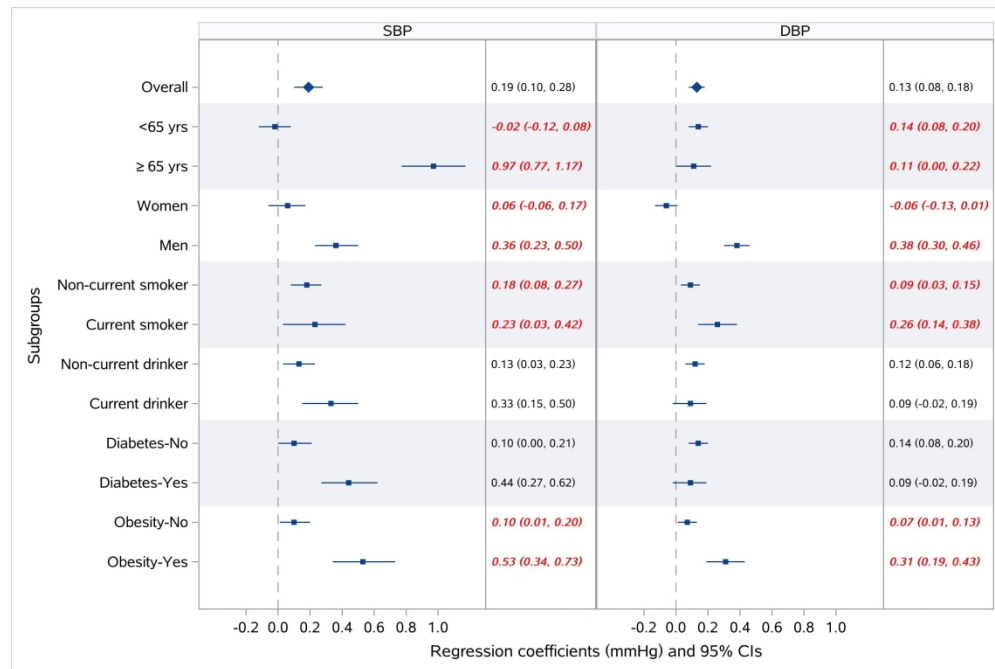


Figure 4. Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with blood pressure. Red texts with italics indicated that p-value for interaction terms < 0.05 . Effect estimates (regression coefficients) were presented as changes in systolic blood pressure (SBP) or diastolic blood pressure (DBP) for each $10 \mu g/m^3$ 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.

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4 **1 SUPPLEMENTAL MATERIAL**

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6 **2 Supplement 1. Collection of medication data in China PEACE Million Persons Project.**

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8 3 Potential participants who were taking medications were required to bring their drug
9 4 packaging (boxes) to the project sites. During the face-to-face interview, local project staff
10 5 asked participants whether they always took anti-hypertension, lipid-lowering, anti-diabetics,
11 6 or anti-platelet drugs during the past 2 weeks. Those who answered “yes” and knew the
12 7 name of the drug were further asked to report the name, dose, and frequency of each drug.
13 8 For those who did not remember the exact dose of the drug, the number of tablets or pills
14 9 taken was recorded. Interviewers searched and selected drug names or the first letter of the
15 10 Chinese phonetic alphabet participants answered by entering the generic name or trade
16 11 name of each drug in the electronic data collecting system. In this system, a data dictionary
17 12 was used to confirm drug information, including the drug class, generic name, trade name,
18 13 and corresponding unique ID.
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15 **Supplement 2. Summary statistics for daily PM_{2.5} (µg/m³) concentrations of assigned**
 16 **monitors in 83 study regions.**

No.	Mean	Median	25 th percentile	75 th 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

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3	51	32.48	28	18	43	5	149	1461	35
4	52	27.19	24	14	36	3	120	1461	31
5	53	38.01	33	21	49	5	192	1461	16
6	54	35.67	30	19	46	3	269	1461	13
7	55	50.36	42	27	64	6	286	1461	23
8	56	44.34	35	23	56	5	333	1461	6
9	57	35.14	29	16	47	3	202	1461	22
10	58	22.1	18	14	27	3	123	1461	31
11	59	15.14	13	9	18	2	68	1461	12
12	60*	37.75	29	18	47	5	183	773	20
13	61	49.89	41	30	61	8	222	1461	27
14	62	60.72	49	32	77	5	353	1461	8
15	63	42.87	36	24	55	5	215	1461	16
16	64	49.35	40	24	65	3	235	1461	13
17	65	32.64	28	18	42	4	195	1461	23
18	66	30.96	28	21	39	7	123	1461	10
19	67	29.79	28	20	36	7	102	1461	23
20	68	13.86	14	12	15	3	51	1461	109
21	69	25.99	19	13	32	5	187	1461	33
22	70	24.49	19	13	30	2	124	1461	156
23	71	11.95	10	7	15	2	88	1461	87
24	72	51.21	42	30	63	10	239	1461	238
25	73	10.62	9	7	13	4	73	1461	46
26	74	53.8	41.5	28	64	5	328	1461	19
27	75	38.88	32	23	47	4	169	1461	27
28	76	44.45	36	24	57	4	581	1461	59
29	77	44.1	36	25	53	5	287	1461	44
30	78*	44.04	38	27	56	9	139	488	27
31	79	55.15	45	30	68	5	363	1461	14
32	80	44.69	36	24	55	5	219	1461	50
33	81	65.37	34	20	85	5	447	1461	97
34	82	57.76	29	19	70	3	414	1461	58
35	83	51.7	26	14	65	3	406	1461	42

17 Note:

18 * Monitors being available after 2015

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

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

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



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26 **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)

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

Model	Per 10 µg/m ³ 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

30 Model 1: Included age and sex;

31 Model 2: Model 1 + education level and urbanity;

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

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

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

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

36

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

Model	Per 10 µg/m ³ 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

38 Model 1: Included age and sex;

39 Model 2: Model 1 + education level and urbanity;

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

41 Model 4: Model 3 + use of antihypertensive medication;

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

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

44 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

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2	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
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6			(b) Report category boundaries when continuous variables were categorized
7			10-11
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9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
10			NA
11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
12			12
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14	Discussion		
15	Key results	18	Summarise key results with reference to study objectives
16			13
17	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
18			16
19			
20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
21			13-16
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24	Generalisability	21	Discuss the generalisability (external validity) of the study results
25			15-16
26			
27	Other information		
28	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
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*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.