ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of long-term exposure to PM2.5 with hypertension prevalence and blood pressure in China: a cross-sectional study
AUTHORS	Song, Jiali; Gao, Yan; Hu, Shuang; Medda, Emanuela; Tang, Guigang; Zhang, Di; Zhang, Wenbo; Li, Xi; Li, Jing; Renzi, Matteo; Stazi, Maria Antonietta; Zheng, Xin

VERSION 1 – REVIEW

REVIEWER	Wyatt, Lauren United States Environmental Protection Agency
REVIEW RETURNED	06-May-2021

GENERAL COMMENTS	The manuscript entitled “Association of Long-term Exposure to PM2.5 with Blood Pressure and Hypertension Prevalence in China” describes the association between long-term PM2.5 and hypertension. The study advances knowledge about this association in regions with higher ambient PM2.5 levels. The topic is interesting and statistical analyses are well powered. However, I have a few concerns: Major comments: 1. Methods related to the exposure assessment need to be described in more detail. - The authors indicate that monitors used in the study were within 10km of participant addresses. How far were participants on average from their address assigned monitor? It's mentioned in lines 73-77 that the monitors could be more likely to be located away from PM sources. Are there instances where participants could live closer to PM emitters (major roads and industry) than monitors? Would this lead to a bias for lower PM exposure estimates? - Why was 330 days used as a cut off for the number of days (line 41)? For participants with 330+ days of PM data available, was this data missing at random (with respect to time) or more likely in certain months? - Also how were monitors with frequent missing data handled? From Table S1, a few monitors are missing more than 500 days (34% of days) with one missing 1000 days (68%). Considering this, was a sensitivity analysis performed excluding stations with a high percentage of missing data? 2. The authors indicated that one of the aims was to evaluate subpopulation differences (line 29), but this was not evident in the results or discussion. Was this part of the original research objectives but not examined due to extenuating circumstances?

	3. In the results for the stratified models, the means and CIs should be added to significant results for context. Also, the authors note effect modification by smoking group (non-current smokers, current smokers) for hypertension. However, the results presented in Fig 3 are conflicting. In the figure the error bars for the CIs overlap for these two groups, but the CI's noted on the right side indicate there could be separation. If there isn't a significant difference perhaps these should be noted as trends. 4. Since this is a cross-sectional study, some additional discussion on how results from this study could be interpreted with trends in disease. Is PM increasing in these areas? Since hypertension could be chronic some discussion on cumulative prevalence over time could frame this with the knowledge that hypertension prevalence in China is growing. 5. The authors have made a convincing argument of a positive association similar to other studies. Some additional discussion to compare effect sizes observed in other studies would be helpful. For example, one study for the C-R relationship is sited in lines 179-181 but are there other studies that agree? Minor comments: Introduction - Line 2: In the intro sentence hypertension is more likely an intermediate condition brought upon by modifiable factors like diet, physical inactivity, and smoking - Lines 10,11: "contries" and "coutries" may be typos for "countries" - Line 21: What is the time reference for the PM concentrations, is this daily or average mean PM? Methods - Line 35: The reference (#19) doesn't point to a description for the China PEACE Million Persons Project - Line 35: Need details regarding how sites were designated as rural counties or urban districts. Was this based on population density? Results - Adding a map of the study region would be helpful. - Line 128: The current wording "adjusted ORS for hypertension of individuals with 15, 25, and 35.." suggests that comparison models were run for individuals with these PM levels. Are these estimates from separate models or were they evaluated at the three concentrations? Discussion - Line 162: Knowing that there was a range of PM concentrations in this study, I would suggest the authors add a PM concentration reference for where non-linearity was observed (above ## ug/m3 non-linearity…) - Lines 165, 205: Should "vulnerable" be "susceptible"? Also, from the data presented, differences in smoking categories may be overstated for hypertension as there appeared to be a 3% difference between groups. - Could the greater effect size in non-smokers also be connected to individuals with multiple comorbidities being advised to quit smoking?

REVIEWER	Xi, Yuzhi US Environmental Protection Agency (ORISE)
REVIEW RETURNED	08-May-2021

GENERAL COMMENTS	Abstract • It would be helpful if the abstract can clearly state the study design is cross-sectional. The current abstract can be confusing and misleading for readers to interpret the study design and results. Methods • It would be helpful if the authors can provide additional information on the proportion of study population whose exposure were linked based on “Hukou” region vs. “6-month in prior year” region. • Furthermore, to the reviewer’s understanding, Hukou’s registered address is likely to be different from the participant’s current address. Hukou’s address information is collected at the time of registration which could occur years before (for some people, this could be the time at birth). Can the author justify on why/whether they consider the exposure linkage based on Hukou’s registry is reliable and accurate? • Have the authors validated the self-reported use of antihypertensive medication with any medical and/or prescription records? Have the authors performed any sensitivity analysis to assess the PM effects by different hypertension definitions (e.g. blood pressure measurements vs. self-reported hypertension medication usage)? • It is unclear when the medical examination occurred for all the participants. Were all of the medical examinations toke place in the same day, week, or month? If the medical examinations were done across a period of time, should potential time-variant factors (e.g. holiday, day of the week, season, etc.) be considered and adjusted in the model? Discussion • Adar et al. conducted a longitudinal study on the association between long-term PM2.5 exposure and blood pressure. Could the authors discuss the similarity and difference of this study in relevant to Adar et al.’s ? Adar SD, Chen YH, D'Souza JC, et al. Longitudinal Analysis of Long-Term Air Pollution Levels and Blood Pressure: A Cautionary Tale from the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect. 2018;126(10):107003. doi:10.1289/EHP2966 • Could the author elaborate on the possibility of exposure misclassification due to inaccurate residential addresses information in relevant to the source (Hukou etc.) of information?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Dr. Lauren Wyatt, United States Environmental Protection Agency

Comments to the Author:
The manuscript entitled “Association of Long-term Exposure to PM2.5 with Blood Pressure and Hypertension Prevalence in China” describes the association between long-term PM2.5 and hypertension. The study advances knowledge about this association in regions with higher ambient PM2.5 levels. The topic is interesting and statistical analyses are well powered. However, I have a few concerns:

Major comments:
Comment 1: Methods related to the exposure assessment need to be described in more detail. The authors indicate that monitors used in the study were within 10km of participant addresses. How far were participants on average from their address assigned monitor? It's mentioned in lines 73-77 that the monitors could be more likely to be located away from PM sources. Are there instances where participants could live closer to PM emitters (major roads and industry) than monitors? Would this lead to a bias for lower PM exposure estimates?

Response: We appreciate this comment. We supplement the averaged distance between the address of participants and assigned monitors. Additionally, we acknowledge that using data from fixed monitors to estimate the exposure levels would inevitably lead to measurement errors, and include this as a limitation.

> Methods (Lines 75–76): “The average distance between the address of participants and assigned monitors was 2.7 (interquartile range 1.2, 3.5) kilometers.”
>
> Discussion (Lines 245–250): “Fourth, we used the data from the fixed monitors to estimate the exposure of $PM_{2.5}$ and did not account for residential proximity to major roads, time-activity patterns, and indoor-related characteristics, which would likely result in nondifferential measurement errors. However, this approach is commonly used and previous research has indicated that $PM_{2.5}$ exposure estimated by the nearest monitor was highly correlated with other sophisticated approaches[30].”

Comment 2: Why was 330 days used as a cut off for the number of days (line 41)? For participants with 330+ days of PM data available, was this data missing at random (with respect to time) or more likely in certain months?

Response: We appreciate this comment. As indicated by Dr. Bennett, statistical analysis is likely to be biased when more than 10% of data is missing. Thus, we used 330 days as the cutoff. We also have revised the manuscript to clarify this accordingly. We have viewed data and found that, in our study sample, the median of the longest time interval with consecutive daily $PM_{2.5}$ concentration missing was 1 day (inter-quartile: 1-2; 95^{th} percentile: 5). Thus, this data is missing at random with respect to time, instead of in certain months.

Methods (Lines 81–84): “In the present study, we included participants with more than 330 valid $PM_{2.5}$ values for assessing long-term exposure, to ensure that, for each participant, the missing rate of $PM_{2.5}$ data in the preceding one year of medical examination is less than 10%.[18.]”
Reference 18: Bennett DA. How can I deal with missing data in my study? Australian and New Zealand journal of public health. 2001;25(5):464-469

Comment 3: Also how were monitors with frequent missing data handled? From Table S1, a few monitors are missing more than 500 days (34% of days) with one missing 1000 days (68%). Considering this, was a sensitivity analysis performed excluding stations with a high percentage of missing data?

Response: Thank you for this comment. We included monitors with frequent missing data as long as it could provide 330 valid $PM_{2.5}$ concentrations in the preceding one year of medical examination for one participant in the study sample. Moreover, the reason why frequent data were missing in these monitors during 2015–2018 is that they were started to use in 2017 or 2016. We have also updated the number of days with missing data in this table, accounting for the time of these monitors being available as below. In this updated table, only about 2%–7% of data were missing among the five monitors, so we did not perform such sensitivity analysis.

Supplement 2: Summary statistics for daily $PM_{2.5}$ ($\mu g/m^3$) concentrations of assigned monitors in 83 study regions between 2015 and 2018. (Only presented monitors being available after 2015 below)

No.	Mean	Median	25^{th} percentile	75^{th} percentile	Minimum	Maximum	Total (days)	Missing (days)
30*	49.23	40	28	62	10	271	797	1
37*	32.18	25	14	45	4	155	650	15
42*	70.49	57	40	82	6	514	797	56
43*	56.69	46	34	65	14	257	606	15
60*	37.75	29	18	47	5	183	773	20
78*	44.04	38	27	56	9	139	488	27

Note:

* Monitors being available after 2015

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

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

Comment 4: The authors indicated that one of the aims was to evaluate subpopulation differences

(line 29), but this was not evident in the results or discussion. Was this part of the original research objectives but not examined due to extenuating circumstances?

Response: Thanks for this comment. The subpopulation difference and effect modification by the characteristics of participants were the research objectives. We have revised the manuscript to make it more evident as below. In the revised manuscript, Line 150–165 and Line 221–235 were the corresponding results and discussion sections, respectively.

> Introduction (Lines 26–32): "Accordingly, incorporating $PM_{2.5}$ data with a large-scale population-based screening project in China, the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project, we aimed to: (1) explore the association of long-term $PM_{2.5}$ exposure with blood pressure level and hypertension prevalence, and evaluate subpopulation differences and effect modification by characteristics of participants in these associations; (2) assess the concentration-response relationships of long-term $PM_{2.5}$ exposure with hypertension prevalence and blood pressure."
>
> Results (Lines 150–165): "Subpopulation difference and effect modification:
> The associations of $PM_{2.5}$ exposure with hypertension were stronger among the elderly (≥65 years of age), men, and non-current smokers compared with their counterparts…"
>
> Discussion (Lines 221–235): "Fourth, we assessed the subpopulation differences through stratified analyses and identified the susceptible individuals to the exposure of $PM_{2.5}$. We observed the large effect estimates of $PM_{2.5}$ on hypertension and SBP among the elderly…"

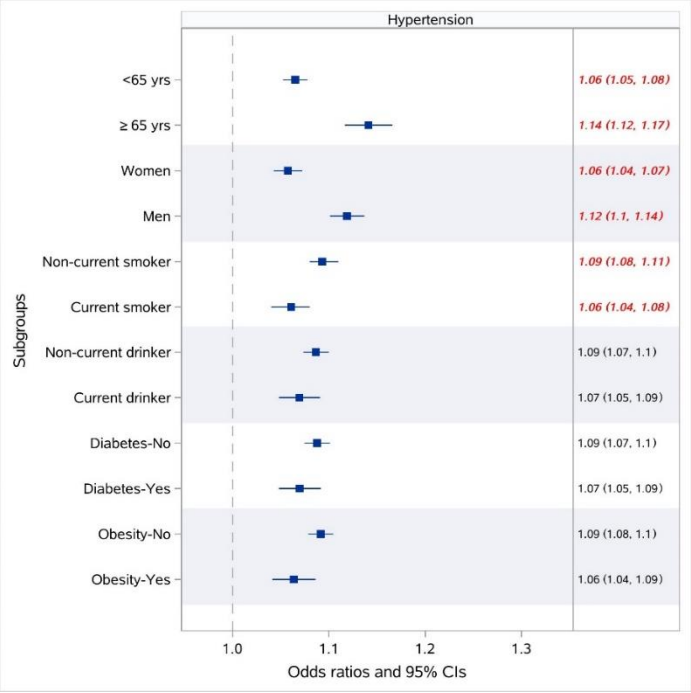
Comment 5: In the results for the stratified models, the means and CIs should be added to significant results for context. Also, the authors note effect modification by smoking group (non-current smokers, current smokers) for hypertension. However, the results presented in Fig 3 are conflicting. In the figure the error bars for the CIs overlap for these two groups, but the CI's noted on the right side indicate there could be separation. If there isn't a significant difference perhaps these should be noted as trends.

Response: We appreciate this comment. We have revised the results section and added means and CIs to significant results. For Figure 3, we found a bug in the code of drawing this figure led to the unmatching of the error bars and CIs on the right side of the non-current smokers and current smokers. We are sorry for the confusion and have updated the figure as below. We also have checked the statistical significance of the interaction term between smoking status and $PM_{2.5}$ exposure in the regression model. In line with the data presented currently, there were significant differences in the association of $PM_{2.5}$ and hypertension between the two groups (P for interaction<0.05).

> Results (Lines 159–165): "We observed greater effect estimates of $PM_{2.5}$ exposure for SBP and hypertension [e.g., OR for hypertension per 10 μg/m^3 increase in $PM_{2.5}$ of 1.14 (95% CI 1.12-1.17) for the elderly, and 1.06 (95% CI 1.05-1.08) for their younger counterparts], while smaller estimates for DBP among the elderly (≥65 years) and non-current smokers [e.g., elevation in DBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.16 mmHg (95% CI 0.04-0.27) for the elderly, and 0.24 mmHg (95% CI 0.19-0.3) for their younger counterparts]"

Results (Lines 153–157): “Gender significantly modified the effects of $PM_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger associations among men [e.g., OR for hypertension per 10 μg/m^3 increase in $PM_{2.5}$ of 1.06 (95% CI 1.04-1.06) for women, and 1.12 (95% CI 1.1-1.14) for men]; while these associations were not modified by alcohol consumption (all p for interaction >0.05).”

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



Note: 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/m^3 increment in the 1-year $PM_{2.5}$ exposure.

Covariates used within the multivariate-adjusted models included age, sex, education level, urbanity, smoking status, alcohol consumption, obesity, and diabetes.

Comment 6: Since this is a cross-sectional study, some additional discussion on how results from this study could be interpreted with trends in disease. Is PM increasing in these areas? Since hypertension could be chronic some discussion on cumulative prevalence over time could frame this with the knowledge that hypertension prevalence in China is growing.

Response: Thanks for this comment. As indicated by one prior study (Reference 21), the annual mean $PM_{2.5}$ concentrations increased from 2000 to 2013 in China. We also have added some discussion on the trends of hypertension prevalence and $PM_{2.5}$ over time as suggested by the Reviewer.

Reference 21: Liang F, Xiao Q, Huang K, et al. The 17-y spatiotemporal trend of $PM_{2.5}$ and its mortality burden in China. Proceedings of the National Academy of Sciences. 2020;117(41):25601-25608. doi:10.1073/pnas.1919641117

> Discussion (Lines 180–184): "We found long-term exposure to $PM_{2.5}$ was positively associated with hypertension prevalence and blood pressure. This echoed the data showing that there was an absolute increase of 139 million individuals with hypertension in China during a decade from 2002–2013/14[20], with the national $PM_{2.5}$ level gradually increasing in the meantime.[21]"

Comment 7: The authors have made a convincing argument of a positive association similar to other studies. Some additional discussion to compare effect sizes observed in other studies would be helpful. For example, one study for the C-R relationship is sited in lines 179-181 but are there other studies that agree?

Response: We appreciate this comment. There were a number of studies assessing the effect estimates of $PM_{2.5}$ reported as odds ratios of hypertension prevalence or blood pressure changes for each 10 μg/m^3 increment. However, for the C-R relationship, relevant studies are relatively limited. We found one study based on the prospective cohort (Reference 27) showed similar results to the present study that higher $PM_{2.5}$ exposure was significantly associated with increased risk of developing hypertension. We have added some discussion as suggested by the Reviewer.

> Discussion (Lines 184–189): "Furthermore, the magnitude of the effects for each 10 μg/m^3 increment in $PM_{2.5}$ were also similar compared to other studies.[5, 7, 22-24] For example, one study based on 361,560 adults observed that each 10 μg/m^3 in $PM_{2.5}$ was associated with increases of 0.45 mmHg and 0.07 mmHg in SBP and DBP, respectively.[22] For hypertension prevalence, odds ratios related to a 10 μg/m^3 increase in $PM_{2.5}$ were ranged from 1.01 to 1.14 in prior studies.[5, 23, 24]"

> Discussion (Lines 197–204): "However, in our study, the risk of hypertension associated with $PM_{2.5}$ became even more pronounced when the exposure was extended to higher levels. This finding was in line with a prior study based on prospective cohorts showed that higher $PM_{2.5}$ exposure was significantly associated with increased risk of developing hypertension, with hazard ratios (95% CIs) for hypertension incidence of 1.27 (1.17–1.39), 1.44 (1.30–1.58), and 1.77 (1.56–2.00) for the participants in the second (71.9-73.7 μg/m^3), third (73.7-82.2 μg/m^3), and fourth quartiles (>82.2 μg/m^3) of $PM_{2.5}$ concentrations compared with those in the first quartile (<71.9 μg/m^3), respectively.[27]"

Minor comments:

Comment 1: Line 2: In the intro sentence hypertension is more likely an intermediate condition brought upon by modifiable factors like diet, physical inactivity, and smoking

Response: Thanks for this comment. We have revised this sentence as below.

> Introduction (Lines 2): "Hypertension is the leading risk factor for death globally."

Comment 2: Lines 10,11: "contries" and "coutries" may be typos for "countries".

Response: Sorry for the typos. We have revised them accordingly, and proofread the text of the whole manuscript.

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Comment 3: Line 21: What is the time reference for the PM concentrations, is this daily or average mean PM?

Response: It is the annual mean of $PM_{2.5}$, which was estimated was at 0.1×0.1° (~11 km×11 km at the equator) resolution using estimates from satellites combined with a chemical transport model, surface measurements, and geographical data. We revise the manuscript to clarify this as below.

> Methods (Lines 19–21): "Meanwhile, outdoor $PM_{2.5}$ has become one of China's most serious environmental problems with population-weighted annual means of $PM_{2.5}$ ranging from 19.1 μg/m³ to 79.3 μg/m³ in 2015.[12]"

Comment 4: Line 35: The reference (#19) doesn't point to a description for the China PEACE Million Persons Project

Response: Sorry for the confusion. We have updated the Reference as below.

> Reference (Lines 36–37): "Our study population is derived from the China PEACE Million Persons Project, which has been described previously.[13]"
> Reference (Lines 340–342): "Lu J, Xuan S, Downing NS, et al. Protocol for the China PEACE (Patient-centered Evaluative Assessment of Cardiac Events) Million Persons Project pilot. BMJ Open. Jan 4 2016;6(1):e010200. doi:10.1136/bmjopen-2015-010200"

Comment 5: Line 35: Need details regarding how sites were designated as rural counties or urban districts. Was this based on population density?

Response: Thanks for this suggestion and we have revised the manuscript as below. We used a convenience sampling strategy to select sites (counties or districts) from all 31 provinces in mainland China. Sites are designated as rural counties or urban districts according to urban-rural division codes of the National Bureau of Statistics of China. Population density is one of the factors considered during the compilation of the urban-rural division code.

> Methods (Lines 39–40): "These regions are designated as rural counties or urban districts according to urban-rural division codes of the National Bureau of Statistics of China.[14]"

Comment 6: Adding a map of the study region would be helpful.

Response: Done. We have added a map to this manuscript as Supplement 3.

> Supplement 3: Distribution of the sites.

Comment 7: Line 128: The current wording “adjusted ORS for hypertension of individuals with 15, 25, and 35..” suggests that comparison models were run for individuals with these PM levels. Are these estimates from separate models or were they evaluated at the three concentrations?

Response: Thanks for this comment. These adjusted ORs for hypertension are evaluated at three concentrations based on the same model. The estimates of these associations were provided in the output of SAS macro by Desquilbet et al after we specified the reference value and the values to be compared with the reference. (Reference 19).

Reference 19: Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Statistics in medicine. 2010;29(9):1037-1057

Comment 8: Line 162: Knowing that there was a range of PM concentrations in this study, I would suggest the authors add a PM concentration reference for where non-linearity was observed (above ## ug/m3 non-linearity…)

Response: We appreciate this comment. We have revised the manuscript as below.

> Discussion (Lines 171–174): “The C-R curves for hypertension and SBP showed steeper slopes as $PM_{2.5}$ concentration exceeding 50 μg/m^3; while the C-R curve for $PM_{2.5}$–DBP was U-shaped, with the turning point around 50 μg/m^3.”

Comment 9: Lines 165, 205: Should “vulnerable” be “susceptible”? Also, from the data presented, differences in smoking categories may be overstated for hypertension as there appeared to be a 3% difference between groups. Could the greater effect size in non-smokers also be connected to individuals with multiple comorbidities being advised to quit smoking?

Response: Thank you for this comment. We have revised “vulnerable” to “susceptible” as suggested. We also agree with the Reviewer that the greater effect size in non-smokers also could be connected to individuals with multiple comorbidities being advised to quit smoking. We have revised the discussion as below.

> Discussion (Lines 173–174): “The elderly, men, and non-current smokers appeared to be more susceptible to the exposure of $PM_{2.5}$.”
>
> Discussion (Lines 221–223): “Fourth, we assessed the subpopulation differences through stratified analyses and identified the susceptible individuals to the exposure of $PM_{2.5}$.”
>
> Discussion (Lines 233–235): “There is also some potential that the greater effect size in non-current smokers could also be connected to some of them being advised to quit smoking because of multiple comorbidities.”

Reviewer 2:

Ms. Yuzhi Xi, US Environmental Protection Agency (ORISE), UNC CH

Comments to the Author:

Comment 1: It would be helpful if the abstract can clearly state the study design is cross-sectional. The current abstract can be confusing and misleading for readers to interpret the study design and results.

Response: Thanks for this comment. We agree with the Reviewer and have revised the abstract as below.

> Abstract (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 $PM_{2.5}$…”

Comment 2: It would be helpful if the authors can provide additional information on the proportion of study population whose exposure were linked based on “Hukou” region vs. “6-month in prior year” region. Furthermore, to the reviewer’s understanding, Hukou’s registered address is likely to be different from the participant’s current address. Hukou’s address information is collected at the time of registration which could occur years before (for some people, this could be the time at birth). Can the author justify on why/whether they consider the exposure linkage based on Hukou’s registry is reliable and accurate?

Response: We appreciate this comment. The exposure of all participants in our study was based on the region where they had lived for at least 6 of the previous 12 months, except that of one participant enrolled in the China PEACE MPP pilot (2014-2015) was based on Hukou. As noted by the Reviewer, for some people, the address of Hukou is different from the current address. However, only local residents in the selected regions could meet the inclusion criteria of the China PEACE MPP (i.e., for participants whose exposure linked based on Hukou, their current address was consistent with their address of Hukou). To better clarify this, we have revised the manuscript as below.

Methods (Lines 37–43): “In brief, we selected county-level regions using a convenience sampling strategy… Local residents aged 35 to 75 years, who were currently registered in the selected region's Hukou (a record officially identifying a person as a resident of an area) or had lived in the region for at least 6 of the previous 12 months, were enrolled in this project.”

Methods (Lines 73–74): “We geocoded each participant’s current address (either rural county or urban district) into latitude and longitude data and identified air monitors located within 10 kilometers...”

Comment 4: Have the authors validated the self-reported use of antihypertensive medication with any medical and/or prescription records? Have the authors performed any sensitivity analysis to assess the PM effects by different hypertension definitions (e.g. blood pressure measurements vs. self-reported hypertension medication usage)?

Response: Thank you for this comment. We did not validate the self-reported use of antihypertensive medications with medical and/or prescription records, because such data was not available at the project sites. To improve the accuracy of the documentation of medication use, some approaches have been used during the data collection. For example, potential participants who were taking medications were required to bring their drug packaging (boxes) to the project sites, and the name, dose, and frequency of each medication were also collected. We have added this detailed information about the data collection of medication use in Supplement 1 as below.

Among patients having hypertension in our study sample, 171045 (44.9%) took antihypertensive medications, and 232511 (70.0%) had measured high blood pressure. Using measured high blood pressure or self-reported antihypertension medication usage as outcomes would lead to an underestimate of the prevalence of hypertension. In addition, the definition of hypertension is consistent with past guidelines. Thus, we did not conduct such sensitivity analysis.

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

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

Comment 5: It is unclear when the medical examination occurred for all the participants. Were all of the medical examinations take place in the same day, week, or month? If the medical examinations were done across a period of time, should potential time-variant factors (e.g. holiday, day of the week, season, etc.) be considered and adjusted in the model?

Response: We appreciate this comment. The medical examinations of all participants were not taken place on the same day, week, or month. Considering the medical examinations were done across a period of time, we have added a sensitivity analysis additionally adjusting for the day of week and season of medical examination. Since the day of week was included in the model as one indicator variable per day which had accounted for the impact of holiday (Saturday and Sunday), we did not adjust for holiday in this sensitivity analysis. Although there were some changes in the magnitude of the effect of $PM_{2.5}$ in this analysis, it did not affect the conclusion of the study because the direction of the associations and the shape of C-R curves remained robust. We have revised the manuscript as below, and the results of this sensitivity analysis were added in Supplement 5–8.

Methods (Lines 98–101): “For sensitivity analysis, we additionally adjusted for the day of week (one indicator variable per day) and season of measurement (summer: June–August; fall: September–November; winter: December–February; spring: March–May) to account for potential time-variant factors.”

Results (Lines 128–134): “After adjusting for sociodemographic characteristics and cardiovascular risk factors, the odds ratio (OR) of hypertension was 1.09 (95% CI: 1.08–1.10) for each 10 μg/m^3 increase in $PM_{2.5}$. The association of $PM_{2.5}$ exposure with hypertension prevalence remained consistent across different model specifications (Supplement 5). For the C-R relationship, the curve showed steeper slopes at high $PM_{2.5}$ exposure levels (i.e., higher than ~50 μg/m^3), and this trend was also evident in the sensitivity analysis with further adjustment for day of week and season of blood pressure measurements (Supplement 6).”

Results (Lines 140–148): “In the adjusted Model 4, each 10 μg/m^3 increment was associated with increases of 0.50 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After adjustment for the day of week and season, these positive associations were also observed [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP]. (Supplement 7) In addition, we found that the shapes of the C-R curves for SBP and DBP were different. The fitted C-R functions showed upward trends with greater effect estimates of $PM_{2.5}$ at higher concentrations for SBP but were generally U-shaped for DBP. (Figure 2) These C-R relationships for blood pressure remained robust after accounting for time-variant factors. (Supplement 8)”

Comment 6: Adar et al. conducted a longitudinal study on the association between long-term PM2.5 exposure and blood pressure. Could the authors discuss the similarity and difference of this study in relevant to Adar et al.’s ?
Adar SD, Chen YH, D'Souza JC, et al. Longitudinal Analysis of Long-Term Air Pollution Levels and Blood Pressure: A Cautionary Tale from the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect. 2018;126(10):107003. doi:10.1289/EHP2966

Response: We appreciate this comment. Although this longitudinal study by Adar et al. also assessed the association between long-term $PM_{2.5}$ exposure and blood pressure, they found no associations. The differences in the study population and the exposure ranges between the two studies may explain the inconsistency of the study results. We have also added some discussion accordingly as below.

Discussion (Lines 189–193): “It is also noteworthy that others have reported no or inconsistent associations.[25, 26] Adar et al. found no associations between exposures to $PM_{2.5}$ and blood pressure based on a longitudinal cohort.[25] However, this study only included a small fraction of Chinese populations (10%), and was conducted in the U.S. with a mean annual average $PM_{2.5}$ of 17 μg/m^3, which was lower than this study (49.2 μg/m^3).”

Comment 7: Could the author elaborate on the possibility of exposure misclassification due to inaccurate residential addresses information in relevant to the source (Hukou etc.) of information?

Response: We appreciate this thoughtful comment. As mentioned in the response to Comment 2, the exposure estimates of all participants were linked based on their current addresses, where either their Hukou were registered or they had lived for at least 6 months of the previous 12 months. Thus, the issue of Hukou is unlikely to be the source of exposure misclassification. Even so, we cannot exclude the possible exposure misclassification in this study, since the air pollution exposure was estimated based on fixed monitors. We have included this as a limitation as below. Additionally, the wide geographic coverage and the large sample size in our study may have minimized the bias because of the exposure misclassification.

Discussion (Lines 245–250): “Fourth, we used the data from the fixed monitors to estimate the exposure of $PM_{2.5}$ and did not account for residential proximity to major roads, time-activity patterns, and indoor-related characteristics, which would likely result in nondifferential measurement errors. However, this approach is commonly used and previous research has indicated that $PM_{2.5}$ exposure estimated by the nearest monitor was highly correlated with other sophisticated approaches[30].”

VERSION 2 – REVIEW

REVIEWER	Wyatt, Lauren United States Environmental Protection Agency
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	The authors have revised the manuscript adequately and largely addressed my previous concerns. Minor comments - Abstract (last sentence of the Results section): There appears to be a word missing in this sentence. - Results (lines 130-131 and 147-148): I agree with the authors that the main observations hold between their different models, but they may want to mention the slight reduction in effect estimates when controlling for season and day of week.

REVIEWER	Xi, Yuzhi US Environmental Protection Agency (ORISE)
REVIEW RETURNED	05-Aug-2021

GENERAL COMMENTS	I appreciate that the authors addressed most of the previous comments. There are several additional comments. Major Comments: • Thank you for performing additional analysis that showing adjusting for seasonality changes the effect estimates. However, based on the results reported, it appears that adjusting for seasonality, the effect estimates changes were significant with non-overlapping CIs (e.g., Supplemental 5, Model 3 HR: 1.09, 1.08-1.10, Model 5 HR: 1.04, 1.02-1.05). Please justify why the authors still report Model 3 result as the primary result with apparently un-controlled time-variant confounder of seasonality. This comment applies to results on blood pressure analyses as well. • Line 181-184, the author cited that the overall PM2.5 in China were rising, could the author provide more discussion on how much the PM2.5 is rising in China currently? Also, based on the reviewers understanding, for parts of the highly-populated area of China, the annual PM2.5 were decreasing in the past 5 years (e.g., Beijing). Could the authors also interpret the results of this study in relevant to decreasing in long-term PM2.5?

	Minor Comments: • Additional dot representing the effect estimate of the overall population in Figure 3 and Figure 4 could be helpful. • Please apply unified rounding rule for Figure 3 and Figure 4, and keep the number of decimal places reported consistent. (e.g., 0.3 vs. 0.30) • Figure 3. Missing “Figure 3.” in the plot legend. • Page 3/25, line 56 (Abstract). There is a typo “o be”. • Supplement 3. Please specify what the dots represent in the map. Are those monitoring sites or locations of study participants?

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Dr. Lauren Wyatt, United States Environmental Protection Agency

Comments to the Author:
The authors have revised the manuscript adequately and largely addressed my previous concerns.

Response: We thank the reviewer for your kind comment.

Minor comments:
Comment 1: Abstract (last sentence of the Results section): There appears to be a word missing in this sentence.

Response: Thanks for this comment. We have corrected the typo as below.

> Abstract (Results): “The elderly, men, non-current smokers, and obese participants were more susceptible to the exposure of $PM_{2.5}$.”

Comment 2: Results (lines 130-131 and 147-148): I agree with the authors that the main observations hold between their different models, but they may want to mention the slight reduction in effect estimates when controlling for season and day of week.

Response: Thanks for this comment. We have added some description about the reduction in effect estimates when controlling for season and day of week as suggested by the reviewer.

> Results (Lines 132–134): “The adjustment for day of week and season of blood pressure measurements resulted in a slight decrease in the effect estimate of the association of $PM_{2.5}$ exposure with hypertension prevalence.”
>
> Results (Lines 142–146): “In the adjusted Model 4, each 10 μg/m^3 increment was associated with increases of 0.50 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After adjustment for the day of week and season, there was some reduction in the effect estimates of the associations between $PM_{2.5}$ exposure and blood pressure [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP].”

Reviewer 2:
Dr. Yuzhi Xi, US Environmental Protection Agency (ORISE), UNC CH

Comments to the Author:
I appreciate that the authors addressed most of the previous comments.
There are several additional comments.
Major Comments:
Comment 1: Thank you for performing additional analysis that showing adjusting for seasonality changes the effect estimates. However, based on the results reported, it appears that adjusting for seasonality, the effect estimates changes were significant with non-overlapping CIs (e.g., Supplemental 5, Model 3 HR: 1.09, 1.08-1.10, Model 5 HR: 1.04, 1.02-1.05). Please justify why the authors still report Model 3 result as the primary result with apparently un-controlled time-variant confounder of seasonality. This comment applies to results on blood pressure analyses as well.

Response: We appreciate this comment. We agree with the reviewer that results with further adjustment for time-variant confounders of seasonality and week of day should be reported as the primary in this study. We have updated all analyses (including associations related to each 10 μg/m^3 increase in $PM_{2.5}$ exposure, C-R curves, and stratified analysis) using seasonality and week of day adjusted models. The manuscript has been revised as below.

> Abstract (Results): "The adjusted odds ratio of hypertension prevalence related to a 10 μg/m^3 increase in one-year $PM_{2.5}$ exposure was 1.04 (95% confidence interval, 1.02–1.05). Each 10 μg/m^3 increment in $PM_{2.5}$ exposure was associated with increases of 0.19 mmHg (95% confidence interval, 0.10–0.28) and 0.13 mmHg (95% confidence interval, 0.08–0.18) in systolic blood pressure and diastolic blood pressure, respectively."
>
> Results (Lines 132–134): "The adjustment for day of week and season of blood pressure measurements resulted in a slight decrease in the effect estimate of the association of $PM_{2.5}$ exposure with hypertension prevalence.
> "
> Results (Lines 142–146): "In the adjusted Model 4, each 10 μg/m^3 increment was associated with increases of 0.50 mmHg (95% CI: 0.41–0.59) in SBP and 0.23 mmHg (95% CI: 0.18–0.28) in DBP. After adjustment for the day of week and season, there was some reduction in the effect estimates of the associations between $PM_{2.5}$ exposure and blood pressure [0.19 mmHg (95% CI: 0.10–0.28) in SBP; 0.13 mmHg (95% CI: 0.08–0.18) in DBP]."
>
> Results (Lines 153–156): "Gender significantly modified the effects of $PM_{2.5}$ exposure on all three outcomes (all p for interaction <0.05) with stronger associations among men [e.g., OR for hypertension per 10 μg/m^3 increase in $PM_{2.5}$ of 1.01 (95% CI: 1.00–1.03) for women, and 1.06 (95% CI: 1.05–1.08) for men]…"
>
> Results (Lines 160–165): "We observed greater effect estimates of $PM_{2.5}$ exposure for SBP [elevation in SBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.97 mmHg (95% CI: 0.77–1.17) for the elderly, and -0.02 mmHg (95% CI: -0.12–0.08) for their younger counterparts], while smaller estimates for DBP among the elderly [elevation in DBP per 10 μg/m^3 increase in $PM_{2.5}$ of 0.11 mmHg (95% CI: 0.00–0.22) for the elderly, and 0.14 mmHg (95% CI: 0.08–0.20) for their younger counterparts]."

Comment 2: Line 181-184, the author cited that the overall PM2.5 in China were rising, could the author provide more discussion on how much the PM2.5 is rising in China currently? Also, based on

the reviewers understanding, for parts of the highly-populated area of China, the annual PM2.5 were decreasing in the past 5 years (e.g., Beijing). Could the authors also interpret the results of this study in relevant to decreasing in long-term PM2.5?

Response: Thanks for this comment. One prior study (Reference 21) has demonstrated that annual mean $PM_{2.5}$ concentrations across China fluctuated between 39.5 and 47.0 μg/m^3 from 2000 to 2016, with the lowest level observed in 2000. The national $PM_{2.5}$ level peaked in 2013, followed by a gradual decline from 2013 (47.0 μg/m^3) to 2016 (41.5 μg/m^3). Combined with the context, we have added how much the $PM_{2.5}$ is rising in China in the revised manuscript. Moreover, we also have provided additional discussion about the interpretation of the results relevant to decreasing in long-term $PM_{2.5}$ as suggested by the reviewer.

> Discussion (Lines 184–190): "This echoed the data showing that there was an absolute increase of 139 million individuals with hypertension in China during a decade from 2002 to 2013/14[20], with the national annual mean $PM_{2.5}$ increasing from 39.5 μg/m^3 to 47 μg/m^3 between 2000 and 2013. [21] Specifically, in some high-polluted areas such as Beijing-Tianjin-Hebei region of 2013, the annual average concentrations of $PM_{2.5}$ had reached 98.9 μg/m^3, and daily average concentrations had exceeded 300 μg/m^3.[22, 23]"

> Discussion (Lines 204–216): "…in our study, the risk of hypertension associated with $PM_{2.5}$ became even more pronounced when the exposure was extended to higher levels. This finding was in line with a prior study based on prospective cohorts showed that there was a stepwise increase in the risk of developing hypertension with increasing quartiles of long-term $PM_{2.5}$ exposure.[29] This result suggests that, for a given decrease in the concentration of $PM_{2.5}$, a greater reduction in excess hypertension prevalence would be obtained in highly polluted regions compared with regions with low to moderate levels of $PM_{2.5}$ exposure. In this respect, the implication of air quality improvements in highly polluted regions of China in recent years would be more profound. It has shown that from 2013 to 2018, the annual average concentration of $PM_{2.5}$ in Beijing-Tianjin-Hebei region has declined by 49%.[30] Considering the population size and baseline $PM_{2.5}$ levels in these areas, the public health impact related to $PM_{2.5}$ reduction would be huge."

Minor Comments:

Comment 1: Additional dot representing the effect estimate of the overall population in Figure 3 and Figure 4 could be helpful.

Response: Thanks for this comment. We have added the effect estimate of the overall population in the first row of Figure 3 and Figure 4 as below.

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

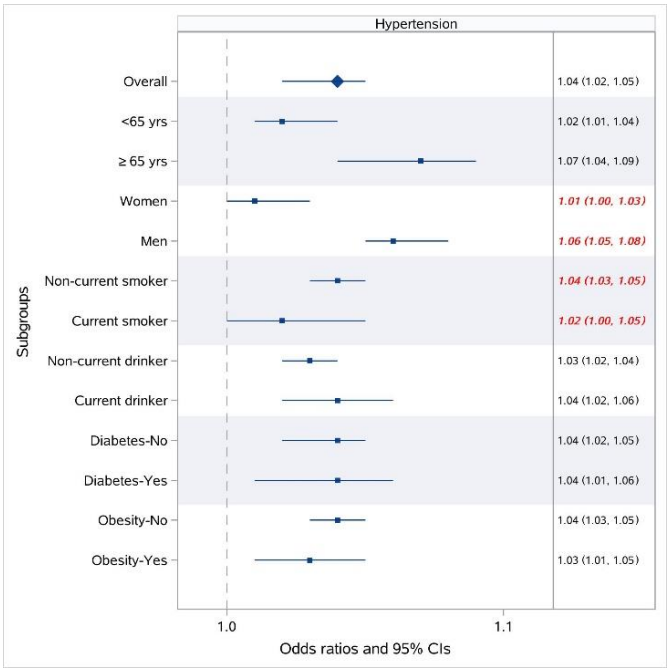
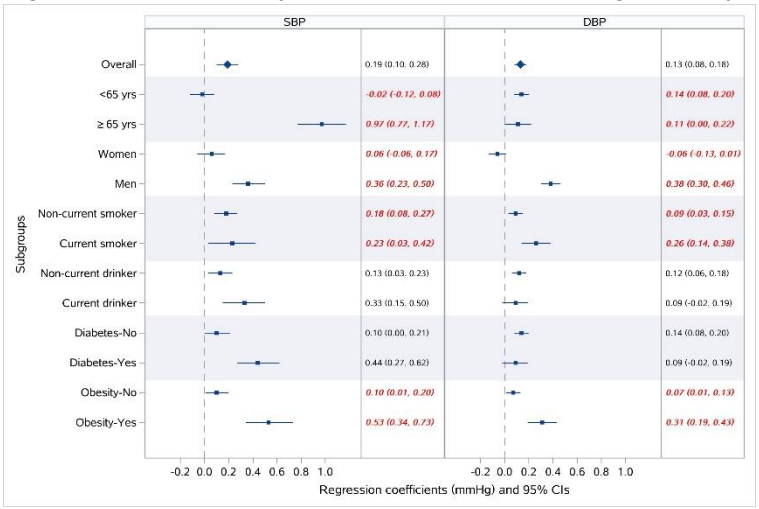


Figure 4: Stratified analysis of the association of long-term exposure to $PM_{2.5}$ with blood pressure



Comment 2: Please apply unified rounding rule for Figure 3 and Figure 4, and keep the number of decimal places reported consistent. (e.g., 0.3 vs. 0.30)

Response: We appreciate this comment. The effect estimates and their 95% CIs in Figure 3 and Figure 4 have uniformly kept to two decimals places.

Comment 3: Figure 3. Missing “Figure 3.” in the plot legend.

Response: Thanks. We have added ‘Figure 3’ in the plot legend.

Comment 4: Page 3/25, line 56 (Abstract). There is a typo “o be”.

Response: Thanks for this comment. We have corrected the typo as below.

Abstract (Results): “The elderly, men, non-current smokers, and obese participants were more susceptible to the exposure of $PM_{2.5}$.”

Comment 5: Supplement 3. Please specify what the dots represent in the map. Are those monitoring sites or locations of study participants?

Response: Thanks. The dots in the map represent the study sites of the China Patient-Centered Evaluative Assessment of Cardiac Events Million Persons Project, where participants’ Hukou are registered or participants have lived for at least 6 of the previous 12 months. We have revised the title of the figure to clarify this.

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

VERSION 3 – REVIEW

REVIEWER	Xi, Yuzhi US Environmental Protection Agency (ORISE)
REVIEW RETURNED	04-Oct-2021

GENERAL COMMENTS	The authors have satisfactorily addressed my concerns. Thank you!