nature portfolio

# Peer Review File

# Differential effects of fine particulate matter constituents on acute coronary syndrome onset

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**This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.**

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The goal of this paper (to identify the most toxic components of PM2.5 mass) is laudable. However, there is a major problem in treating highly correlated variables, as shown in table S2 (which should be in the main document) as if they are independent, and then applying a statistical approach to parse the effects of such highly correlated components as if they act independent of one another (which they clearly are not). So just tossing them all in a weighted least squares and seeing where the cards fall is inappropriate.
In addition, past PM2.5 research has shown that the constituents do not act independent of one another (as assumed in this analysis, as it seeks to parse the PM2.5 among the constituents considered), but instead interact with each other, depending on the source mixture. For example, Weichenthal et al have found that sulfates were not related with CVD events unless transition metals were also present at high levels, such as found in fossil fuel combustion particle mixtures (Association of Sulfur, Transition Metals, and the Oxidative Potential of Outdoor with Acute Cardiovascular Events: A Case-Crossover Study of Canadian Adults. EHP, 2021.). Clearly, there is a need to look at the interactive influences of transition metals not at all considered here. Best would be to do source apportionment PM2.5, and compare the source specific mixture effects. Are these data not available from the models employed? If not, the analysis is ignoring the source specific mixture effects, and this must be well acknowledged.
As to what could be done to improve the analysis, given the lack of a full characterization of the pollutant mixtures. At minimum, there is a need to try other approaches and compare, such as looking at each constituent individually, as others have done, and see which serves as the best single index of the highly intercorrelated mixture. That is not to say that that would be the causal constituent, but instead it must be realized by the authors that their metrics are just indices, not necessarily the causal agent. Measurement and estimation error by the model may drive the results. (The relative errors of their respective estimations should also be incorporated into the Confidence Intervals). One example where misleading results can come from the approach used here is ammonium, which is correlated with nitrate and sulfate because ammonia has neutralized ambient sulfuric and nitric acid to form ammonium sulfate and ammonium nitrate. But while ammonium may be a good index of these two toxic ions, it itself has no known toxicity of its own, perse. These biological plausibility arguments must be considered and addressed.
The weighted least squares approach used here is highly unstable, statistically, given the very high intercorrelations among the variables it attempts to parse. The authors do trim the data, which may help, but they should, at minimum, also apply a 10 fold cross-validation approach to assess the uncertainty of the results to choice of observations (in addition to ther relative accuracy of estimation: have these estimates been compared with ambient data in the locale considered?). I expect adding those uncertainties will indicate much wider confidence intervals in the estimates than those presented in Table 2 or 3. In other words, it seems unlikely that a fuller consideration of the uncertainties in this approach will actually yield estimates that differ across the various constituent indices.

Reviewer #2

(Remarks to the Author)
Using a nationwide health database with more than 2 million acute coronary syndrome (ACS) patients and a case-crossover design, this manuscript reported the results of a data analysis examining the differential effects of fine particulate constituents on ACS onset. The strengths of this study include a large and representative sample of ACS patients in China, the high spatial and temporal resolution model for the constituent data of fine particulate matter exposure, and the use of a

novel statistical model to assess the joint effects of correlated co-exposures.

The findings of differential effects of fine particulate constituents on ACS onset are interesting and have some potential to significantly advance the current literature in relevant research fields. However, my enthusiasm for this manuscript is reduced by a few major concerns:

1. As reported in this study, each of the constituents was only associated with 2% or less increased odds in ACS onset. Given the low magnitude of the associations, the significance of the study findings are not very convincing. At the population level, however, the authors may want to report the total number of ACS cases that could be prevented if the level of each constituent is reduced by 1 standard deviation or interquartile range. Reporting the number of ACS cases that can be prevented by reducing air pollution level will give this study a lot higher public health relevance.

2. Some of the comments in the Introduction do not seem to be correct or appropriate. For example, “The majority of studies utilized time-series design based on daily counts of CVD hospitalization or death, rather than disease onset. This inevitably leads to ecological fallacy and temporal misclassification of exposure.”. This statement sounds too absolute and strong, as not all of the studies with those types of design would have ecological fallacy or temporal misclassification. Pls revise this statement and clearly specify under what circumstances that ecological fallacy and temporal misclassification would happen.

3. It is not appropriate to examine the differences between groups using a Z-test as specified on page 10. Instead, it is better to use interaction terms to test potential effect modifications.

4. Page 17, 2nd paragraph: The discussions regarding potential mechanisms for the observed differential associations between PM2.5 constituents and ACS subtypes are unclear and hard to following. It’ll be helpful to add a more thoughtful discussion here that may explain some of the study findings related to ACS subtypes.

Reviewer #3

(Remarks to the Author)
The authors analyzed the joint and individual effect of five PM2.5 chemical compounds (organic matter, black carbon, ammonium, nitrate and sulfate) on the occurrence of ACS. An impressive number of more than 2,100,000 patients from 2,096 Chinese hospitals were included in a seven-year time period, and a case-crossover design was applied. The total PM2.5 mass and the mass of all five chemical compounds were significantly associated with an increased risk of acute coronary syndrome. The effects were higher in lag 0, for chemical compounds organic matter and black carbon, in older patients, in cold season and in the southern part of China. A sensitivity analysis with adjustment for total PM2.5 mass showed significant results for organic matter, black carbon and ammonium, but not for nitrate or sulfate.

The topic of this article is highly relevant, novel and interesting. Indeed, acute effects of ambient PM2.5 mass on ACS are widely described and recognized. However, only the size of the particles is taken into consideration to classify the exposure to this air pollutant and only very few studies have focused on the qualitative aspects of the particle composition. Indeed, toxicity of particles depends of their chemical composition and, in 2024, we have very few evidences on the chemical compounds triggering the cardiovascular consequences of air pollutantion exposure. Even if this study is highly relevant, there are some mains points needing some revision.

Major comments:
1) The methodology of how the PM2.5 constituents were measured needs is not explained in the method section. This is not acceptable for a study aiming to describe the effects of PM chemical constituents on the triggering of ACS. Only after reading the dedicated TAP website it appears that the chemical nature of the PM2.5 were not directly evaluated at it was done by other investigators from China, Canada or US but comes from a modelization method based on daily measured values of fixed stations, completed by a machine learning algorithm. This method merits a better description and explanation on how it was validated against field measurement.

2) Line 83 and 374: Exposure misclassification is indeed an important limitation in the modelization of PM2.5 effects on health. This study used again a combination of weather forecasting, ground observations, machine learning and multisource PM2.5 data to estimate the PM2.5 constituent mass at the hospital address on a 10x10km resolution. Although this reduces the exposure misclassification compared to using aggregated regional pollution data or the values of fixed monitoring stations, the modelization was not done at the patient living address and authors assume that the patient exposure was related to the exposure at the admission hospital. Consequently, there is still a major possible exposure misclassification bias left.

3) Air temperature changes are a main trigger of AMI. All pollutants are negatively (PM, NO2) or positively (O2) associated with temperature. Control of temperature bias is one of the most important interest in the use of case crossover design with stratification of control periods in the case crossover are frequently done in the same temperature range (+/- 1 or 2°C for ex.). Could you explain why you chose to add temperature as a confounder in the model, instead of matching the cases and controls according to ambient temperature?

4) Line 145: “To avoid the potential influence of outliers in air pollutants concentrations, the highest and lowest 2.5% of daily

concentrations during the study period were removed before formal analyses". China is known as one of the hot spot of air pollutant exposure worldwide. Are these outliers related to some errors in modelization or related to real major air pollution peaks only observable in highly industrialized country like China ? Do you mean that ACS during these outlier days were not included into the study ? Were the values investigated before the decision to remove them from the analysis ? If the outliers are no errors, than they should leave into the analysis as they reflect the variability of the study area ?

5) Line 269 and Figure 3: a WQS is used and a bar chart illustrates the weight of the five constituents in the effect of PM2.5 on ACS. However, a limitation of the study is the non-measurement of transition metals. Figure 3 gives a clear overview but the reader may falsely conclude that all five compounds together explain 100% of the effect of the PM2.5 on ACS. Is the WQS model able to estimate the effect of non-measured compounds?

6) While literature is not always able to show significant results regarding the effect of PM2.5 on ACS (only a positive trend is very common), this study has significant results, not only for the effect of total PM2.5 mass on ACS in the total study population, but as well in all subgroups and for all measured chemical constituents. This can be explained by the very high power because of the very large database, but also because of the choise to estimate the risk for ACS per IQR increase in PM2.5. Indeed most studies investigate the effect of an increase of 10µg/m3, while in this study the IQR equals an increase of 30µg/m3. To generalize the findings and be able to compare them with other literature, I suggest performing an additional analysis on the effect of a 10µg/m3 PM2.5 increase.

7) Line 220: In contrast with literature, the proportion of STEMI (35.9%) is higher than NSTEMI (21.2%). Can you explain this please?

Minor comments:

- Line 45. "All five constituents" is mentioned, but the different constituents are not yet listed. This creates confusion for the readers.

- Line 80: For me, it is not clear why the term ecologic fallacy is used here. Can you explain this please?

- Line 265: the sensitivity analysis shows that the effect nitrate and sulfate is completely dependent on the total PM2.5 mass, correct? This should be mentioned clearer.

- Line 235 and Figure 1: "Generally, the onset risk increased immediately on the concurrent day of exposure, attenuated thereafter, and became null at lag 2 day." On figure 1 the effect decreases even more at lag3, nearly showing a significant negative association. Have you explored the log4, log5 or other lag effects? This negative effect could be explained by the harvesting effect, a period of excess mortality followed by a period with a mortality deficit because of the deaths of vulnerable patients at the pollution peak.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The model applied is a weighted linear model, and the problem of very high intercorrelations remains. The model has the limitation that it assumes linearity (see Renzetti et al, Front Public Health.2023), which the Supplementary Figures indicate not to be satisfied. As seen in Supplementary Figure 5, for example, sulfates is the index that tends to satisfy linearity for that NSTEMI outcome, as well as for UA. The very bent over shape of the carbon metrics is contrary to biological plausibility for it to be causal, itself: Why would there be diminished (or no) added health effects as concentrations rise (e.g., for Black Carbon above 4 µg/m3 )? This needs acknowledgement and addressing in the paper. The likely reason for the bending of the carbon metrics is that the dominant source of carbon must change as the concentration rises, perhaps from fossil fuel combustion at low levels, to biomass burning at the highest levels? This is a situation similar to that confronted by Rahman et al, Int J Epidemiol, 2021), and applying their approach to these data would be informative.
Looking at the sulfate effect coefficients, for example, it is apparent that its associated PM2.5 mass is more toxic than the average overall PM2.5 mass. Using Supplemental Table 3, the % NSTEM1 (lag 0) increase is 0.43% per 1 µg/m3 SO4. So, since it is likely as ammonium sulfate, that is 0.43% per 1 x 132/96 (based on molecular wts) = 1.375 µg/m3 sulfate PM2.5 mass for the .43% effect, yielding an effect of (10/1.375) x .43% = 3.1% per sulfate associated PM2.5 , or (3.1/.94 =) 3.3 times the STEM1 effect per 10 µg/m3 of the overall PM2.5 . This also needs consideration and discussion.

Reviewer #2

(Remarks to the Author)
This revision has adequately addressed all of my previous concerns. I have no further comments.

Reviewer #3

(Remarks to the Author)
All my comments are properly answered. No further comments. Congrats for your work.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This revision has adequately addressed my previous concerns.

**Response to Comments from Reviewers:**

We sincerely appreciate your valuable time in reviewing our manuscript and the excellent suggestions and comments you provided. We have performed additional analyses and made changes to our manuscript in response to the comments. Point-by-point responses were made for each comment. The line numbers in this response letter refer to those in the revised manuscript. According to the journal's formatting requirements, we have placed the Methods section at the end, after the Discussion.

**REVIEWER COMMENTS**

**Reviewer #1 (Remarks to the Author):**

1. The goal of this paper (to identify the most toxic components of PM2.5 mass) is laudable. However, there is a major problem in treating highly correlated variables, as shown in table S2 (which should be in the main document) as if they are independent, and then applying a statistical approach to parse the effects of such highly correlated components as if they act independent of one another (which they clearly are not). So just tossing them all in a weighted least squares and seeing where the cards fall is inappropriate.

**Response:** Thanks for your comment. We believe the reviewer's negative comments mainly stem from a misunderstanding of our methodology. **Our study applied the WQS (i.e., weighted quantile sum) regression, not the weighted least squares (WLS) regression.**

First, WQS regression is a common and classic modeling technique which can identify the association between mixtures and the outcome of interest while reducing the impact of high collinearity [1]. It has been widely used in environmental epidemiological studies to explore the health effects of multiple environmental factors such as $PM_{2.5}$ chemical constituents [2-7]. **The main principle of WQS regression is to combine multiple correlated predictors into a single index that represents the overall mixture. Different from WLS which applies weights to observations to address heteroscedasticity, WQS gives weights to predictive variables of interest to build a composite index**. Specifically, the process begins with randomly splitting the original data

into a training set and a validation set. Each constituent exposure is converted into a categorical variable representing the quantiles (quartiles in our case). A fixed number of bootstrap samples of the same size as the training dataset are first generated from the training dataset, and are used to estimate the weights through maximum likelihood estimation. The weights are constrained to sum to 1. The final weights are defined using average weights across the bootstrap samples. Then a weighted index is constructed by using the final weights and subsequently incorporated into the regression model using the validation set to estimate the joint effects of components mixture on the health outcome. In the present analysis, 40% of the dataset was used for training and 60% for validation, with the bootstrap set at 100 times. We have also added more details on the WQS regression in the revised manuscript (see **lines 456-485** and **Supplementary Methods**).

Second, we acknowledge that our results reflect statistical associations rather than causal relationships. **Future research, such as randomized controlled trials, is warranted to validate the true effects of the components and better understand their individual contributions.** We have also included this limitation in the **Discussion** section of the revised manuscript (see **lines 344-348**).

Third, following your suggestion, we have placed **Supplementary Table 2** into the main document. Please refer to **Table 2** in the revised manuscript.

**If you suppose that there are other appropriate methods that could be applied in the present analyses, we are very willing to add the corresponding analyses.**

**References:**


1. Carrico, C., Gennings, C., Wheeler, D.C. & Factor-Litvak, P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J Agric Biol Environ Stat* **20**, 100-120 (2015).
2. Li, S., et al. Long-term Exposure to Ambient PM2.5 and Its Components Associated With Diabetes: Evidence From a Large Population-Based Cohort From China. *Diabetes Care* **46**, 111-119 (2023).
3. Huang, Q., et al. Association between manganese exposure in heavy metals mixtures and the prevalence of sarcopenia in US adults from NHANES 2011-2018. *J Hazard Mater* **464**, 133005 (2024).
4. Cai, C., et al. Long-term exposure to PM(2.5) chemical constituents and diabesity: evidence from a multi-center cohort study in China. *Lancet Reg Health West Pac* **47**, 101100 (2024).
5. Guo, B., et al. Long-term exposure to ambient PM2.5 and its constituents is associated with MAFLD. *JHEP Rep* **5**, 100912 (2023).
6. Li, J., et al. Ambient PM2.5 and its components associated with 10-year

atherosclerotic cardiovascular disease risk in Chinese adults. *Ecotoxicol Environ Saf* **263**, 115371 (2023).
7. Pu, F., et al. Heterogeneous associations of multiplexed environmental factors and multidimensional aging metrics. *Nat Commun* **15**, 4921 (2024).

2. In addition, past PM2.5 research has shown that the constituents do not act independent of one another (as assumed in this analysis, as it seeks to parse the PM2.5 among the constituents considered), but instead interact with each other, depending on the source mixture. For example, Weichenthal et al have found that sulfates were not related with CVD events unless transition metals were also present at high levels, such as found in fossil fuel combustion particle mixtures (Association of Sulfur, Transition Metals, and the Oxidative Potential of Outdoor with Acute Cardiovascular Events: A Case-Crossover Study of Canadian Adults. EHP, 2021.). Clearly, there is a need to look at the interactive influences of transition metals not at all considered here. Best would be to do source apportionment PM2.5, and compare the source specific mixture effects. Are these data not available from the models employed? If not, the analysis is ignoring the source specific mixture effects, and this must be well acknowledged.

**Response:** Thanks for your insightful comment.

First, we acknowledge the importance of considering the interactions between different $PM_{2.5}$ constituents, especially transition metals. **Unfortunately, our study did not include metallic elements due to the lack of publicly available nationwide exposure data of high spatiotemporal resolution for these constituents in China.** On the one hand, we added this issue as a limitation and the study of Weichenthal et al as a reference, and emphasized the need for future research to fully investigate the health impacts of metallic elements (**see lines 351-353**). On the other hand, to explore the potential presence of unmeasured constituents with health effects, **we subtracted the concentrations of the five measured constituents from the total $PM_{2.5}$ mass to obtain the remaining unmeasured components, and reran the main models based on these remaining components**. As shown in **Supplementary Table 9** and **Supplementary Fig. 8**, their effects were weaker than organic matter and black carbon, and comparable to nitrate, sulfate, and ammonium. These results suggest that there may be important

unmeasured constituents of $PM_{2.5}$ that warrant further investigation. **We added this as a supplementary analysis (see lines 186-192, 251-253**, and **505-509), and did not explore the interactions between $PM_{2.5}$ constituents and the remaining components for the following reasons**: 1) since both $PM_{2.5}$ and the five constituents were model-predicted, directly subtracting the concentrations of the five constituents from total $PM_{2.5}$ mass is a rather crude approach and could introduce double exposure measurement errors; 2) there may be various unknown chemicals other than metallic elements in the remaining components, making it difficult to identify the nature of unmeasured constituents.

Second, **analyzing the health effects of $PM_{2.5}$ components and $PM_{2.5}$ sources are distinct topics**. There is a lack of nationwide $PM_{2.5}$ source data of high spatiotemporal resolution in China, which limits our ability to explore the source-specific mixture effects. **We have acknowledged this limitation in the revised manuscript (see lines 351-353)**. Additionally, we believe our analysis on the health effects of $PM_{2.5}$ components could provide valuable clues and support for future research on source-specific effects.

3. As to what could be done to improve the analysis, given the lack of a full characterization of the pollutant mixtures. At minimum, there is a need to try other approaches and compare, such as looking at each constituent individually, as others have done, and see which serves as the best single index of the highly intercorrelated mixture. That is not to say that that would be the causal constituent, but instead it must be realized by the authors that their metrics are just indices, not necessarily the causal agent. Measurement and estimation error by the model may drive the results. (The relative errors of their respective estimations should also be incorporated into the Confidence Intervals). One example where misleading results can come from the approach used here is ammonium, which is correlated with nitrate and sulfate because ammonia has neutralized ambient sulfuric and nitric acid to form ammonium sulfate and ammonium nitrate. But while ammonium may be a good index of these two toxic ions, it itself has no known toxicity of its own, perse. These biological plausibility arguments must be considered and addressed.

**Response:** This is a thought-provoking question! **In this study, we did**

**examine the effects of individual constituents and reported the corresponding effect estimates with 95% confidence intervals, as previous studies have done [1-3]. Then we utilized weighted quantile sum (WQS) regression to investigate the joint effects and each constituent's relative contribution.**

Currently, **the mainstream approaches for evaluating health effects of highly-correlated pollutant mixtures include WQS regression [4], quantile-based g computation (QGC) [5], and Bayesian kernel machine regression (BKMR) [6]**. We provide a brief comparison among the three approaches in **Table R1**.

**Table R1**. A brief comparison among WQS, QGC, and BKMR.

| Methods | Advantages | Limitations |
|---|---|---|
| WQS | • Examines the joint effects of chemical mixture exposures<br>• Provides interpretable weights for each component of the mixture, aiding in identifying key components | • Limited in assessing joint effects of chemicals with diverse effect directions<br>• Limited in chemical interactions identification |
| QGC | • Combines WQS regression and g-computation without assuming directional homogeneity | • Results can be harder to interpret compared to WQS |
| BMKR | • Facilitates the visualization of the effect of a single and combined exposure<br>• Extrapolating nonlinear exposure-response functions | • Very computationally intensive, particularly for large datasets or many exposures<br>• Fixing other chemicals at certain levels to extrapolate the exposure–response function limits the ability to estimate the effects of co-exposure patterns with both high and low levels of chemicals |

Abbreviations: WQS, weighted quantile sum; QGC, quantile-based g

computation; BKMR, Bayesian kernel machine regression.

This reviewer rightly highlighted the importance of incorporating the relative errors of each component into the confidence intervals. **However, none of the three methods mentioned above (WQS, QGC, and BKMR) provide confidence intervals for individual components when estimating their relative importance** (i.e., weights in WQS and QGC, and posterior inclusion probabilities in BKMR). Despite this limitation, WQS, QGC, and BKMR remain widely utilized in thousands of previous studies. A newly proposed method, named repeated holdout validation for WQS, can help characterize the uncertainty of weights by randomly partitioning the dataset for 100 times and repeating WQS regression on each set to simulate a distribution of validated results [7]. However, it is computationally intensive and up to 100 times more time-consuming than standard WQS. This method is considered suitable for smaller sample sizes (hundreds to thousands). For large datasets like ours, this approach is not feasible, and our sample size is stable enough that such extensive random partitioning is generally unnecessary. In summary, **addressing the technical limitation proposed by the reviewer is still a promising area for future methodological development by statisticians**. We have included these issues in the limitation section of the revised manuscript (**see below or refer to lines 348-351**).

*"Fourth, both WQS and QGC provide fixed index weights without confidence intervals, which is a shortcoming in this area as it prevents estimating the statistical significance of the weights."*

**In response to your suggestion of trying other approaches, we added an analysis by using QGC** (see **lines 182-186, 240-251, 498-504,** and **Supplementary Fig. 7**). This method maintains the simple inferential framework of WQS without assuming directional homogeneity, and the weights may go in either direction. The sum of positive and negative weights is both equal to 1. The weights are only compatible with other weights in the same (i.e., positive or negative) direction, whereas positive and negative weights should not be compared with each other. Results showed that a quartile increase in mixture of the five constituents was significantly associated with an increase of

0.92% (95%CI: 0.75%–1.09%) in the risk of ACS onset. **Organic matter and black carbon had higher weights, which was consistent with our initial results.** An interesting finding is that the estimated weight for nitrate became negative. However, it does not necessarily indicate a significant negative association between nitrate and ACS onset. This may be explained by high correlations among these constituents, which can lead to some constituents being non-significant in QGC and ultimately result in the overall negative effect being close to zero and negative weights being substantive [8]. Similar patterns have also been observed in previous studies [8-10]. **We did not implement BKMR due to its substantial computational demands.** Current applications of BKMR are typically limited to sample sizes less than 10,000. The computational resources and time would become prohibitive for our dataset of over 2,000,000 cases and 7,000,000 controls. **Besides, we are open to other specific methodological suggestions you may have and are willing to incorporate further modifications to improve our analyses.**

We agree that biological plausibility is crucial in interpreting our results. In the revised manuscript, we emphasized that results on ammonium should be interpreted with caution, and future studies are warranted to clarify this issue. Please see below or refer to **lines 262-266**.

*"Furthermore, ammonium is often correlated with nitrate and sulfate [17], which complicates the interpretation of the results, as the observed health effects may be attributed to nitrate and sulfate rather than ammonium itself. Therefore, results on ammonium should be interpreted with caution and warrant future elucidation."*

**References:**


1. Peng, R.D., et al. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect* **117**, 957-963 (2009).
2. Mo, S., et al. Short-term effects of fine particulate matter constituents on myocardial infarction death. *J Environ Sci (China)* **133**, 60-69 (2023).
3. Liu, L., Zhang, Y., Yang, Z., Luo, S. & Zhang, Y. Long-term exposure to fine particulate constituents and cardiovascular diseases in Chinese adults. *J Hazard Mater* **416**, 126051 (2021).
4. Carrico, C., Gennings, C., Wheeler, D.C. & Factor-Litvak, P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J Agric Biol Environ Stat* **20**, 100-120 (2015).
5. Keil, A.P., et al. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. *Environ Health Perspect* **128**, 47004 (2020).
6. Bobb, J.F., et al. Bayesian kernel machine regression for estimating the health effects

of multi-pollutant mixtures. *Biostatistics* **16**, 493-508 (2015).
7. Tanner, E.M., Bornehag, C.G. & Gennings, C. Repeated holdout validation for weighted quantile sum regression. *MethodsX* **6**, 2855-2860 (2019).
8. Zhou, H., et al. Associations of Long-Term Exposure to Fine Particulate Constituents With Cardiovascular Diseases and Underlying Metabolic Mediations: A Prospective Population-Based Cohort in Southwest China. *J Am Heart Assoc* **13**, e033455 (2024).
9. Zhao, N., Smargiassi, A., Chen, H., Widdifield, J. & Bernatsky, S. Systemic autoimmune rheumatic diseases and multiple industrial air pollutant emissions: A large general population Canadian cohort analysis. *Environ Int* **174**, 107920 (2023).
10. Zhao, N., et al. Fine particulate matter components and interstitial lung disease in rheumatoid arthritis. *Eur Respir J* **60**(2022).

4. The weighted least squares approach used here is highly unstable, statistically, given the very high intercorrelations among the variables it attempts to parse. The authors do trim the data, which may help, but they should, at minimum, also apply a 10 fold cross-validation approach to assess the uncertainty of the results to choice of observations (in addition to ther relative accuracy of estimation: have these estimates been compared with ambient data in the locale considered?). I expect adding those uncertainties will indicate much wider confidence intervals in the estimates than those presented in Table 2 or 3. In other words, it seems unlikely that a fuller consideration of the uncertainties in this approach will actually yield estimates that differ across the various constituent indices.

**Response:** Thanks for the comment.

Firstly, **it is important to clarify that our study utilized weighted quantile sum (WQS) regression, not weighted least squares (WLS) regression. Details on WQS regression and its difference from WLS have been provided in our response to the first comment of Reviewer #1**. The standard practice for WQS involves the use of bootstrap resampling (100 times in our analysis) among the training dataset when estimating the empirical weight index. For each bootstrap sample, a dataset of the same size as the training dataset is created by sampling with replacement from the training dataset. The weights of each exposure component are first estimated through maximum likelihood estimation for each bootstrap sample. After the bootstrap ensemble is completed, the final weights are averaged across the bootstrap samples. Then a weighted index is constructed by using the final weights and incorporated into the regression model using the validation dataset to estimate the joint effects of components mixture. **Bootstrap resampling in WQS**

**regression significantly enhances model sensitivity, provides robust parameter uncertainty estimates, and ensures model robustness, which substantially improves the reliability of model results** [1].

Secondly, **we did not apply a 10-fold cross-validation approach for the following reasons**: 1) the 10-fold validation is more appropriate when the goal is predictive accuracy, whereas the primary focus of WQS regression is on the sensitivity and specificity of chemical weights [2]; 2) we attempted to set the proportion of training and validation datasets as 90% and 10%, respectively, but the computational load was exceedingly high and impractical to complete. Repeating this process 10 times would far exceed our computational capacity. **To enhance the stability of WQS estimates, an alternative method called repeated holdout validation has been proposed [2].** This method involves **randomly partitioning the dataset for 100 times and repeating WQS regression on each set** to simulate a distribution of validated results. However, this approach is computationally intensive and up to 100 times more time-consuming than standard WQS, making it suitable primarily for smaller sample sizes (hundreds to thousands). **For large datasets like ours, such extensive random partitioning is both generally unnecessary due to the inherent stability of our data and impractical due to the extreme computational demands.** Therefore, the standard WQS approach that we are currently using is relatively suitable.

Thirdly, **$PM_{2.5}$ and its chemical components in the Tracking Air Pollution in China (TAP) dataset are in good agreement with the available ground observations**, and have been widely used in previous epidemiological studies [3-5]. For daily $PM_{2.5}$ total mass, the out-of-bag cross-validation $R^2$ ranges from 0.80 to 0.88, and the root-mean-square error (RMSE) is between 13.9 and 22.1 μg/$m^3$ when compared with ground observations for different years during 2013–2020. For daily $PM_{2.5}$ chemical constituents, the correlation coefficients range from 0.67 to 0.80 and most normalized mean biases were within ± 20% when compared with ground observations during 2013–2020. The spatiotemporal variations in $PM_{2.5}$ chemical components are also well captured, including the long-term trend and day-to-day variability across China. More details on the model performance have been described in recently published papers [6-7]. We have also added a detailed description of this methodology and

its validation against ground observations in the revised manuscript (**see line 407** and **Supplementary Methods**).

Finally, we did conduct several sensitivity analyses to test the robustness of our results, such as constituent-$PM_{2.5}$ models and quantile-based g computation (**see lines 173-175, 182-186, 240-251, 254-266, 487-490, 498-504, Supplementary Table 6,** and **Supplementary Fig. 7**). Results generally remained robust, indicating organic matter and black carbon might play more important roles.

We hope these explanations and additional analyses could address your concerns. **If there are any further analyses or modifications you feel are necessary, please let us know, and we are very willing to further improve our manuscript**.

**References:**
1. Carrico, C., Gennings, C., Wheeler, D.C. & Factor-Litvak, P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J Agric Biol Environ Stat* **20**, 100-120 (2015).
2. Tanner, E.M., Bornehag, C.G. & Gennings, C. Repeated holdout validation for weighted quantile sum regression. *MethodsX* **6**, 2855-2860 (2019).
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4. Ma, H., et al. Short-Term Exposure to PM(2.5) and O(3) Impairs Liver Function in HIV/AIDS Patients: Evidence from a Repeated Measurements Study. *Toxics* **11**(2023).
5. Qiu, T., et al. Short-term exposures to PM(2.5), PM(2.5) chemical components, and antenatal depression: Exploring the mediating roles of gut microbiota and fecal short-chain fatty acids. *Ecotoxicol Environ Saf* **277**, 116398 (2024).
6. Liu, S., et al. Tracking Daily Concentrations of PM(2.5) Chemical Composition in China since 2000. *Environ Sci Technol* **56**, 16517-16527 (2022).
7. Geng, G., et al. Tracking Air Pollution in China: Near Real-Time PM(2.5) Retrievals from Multisource Data Fusion. *Environ Sci Technol* **55**, 12106-12115 (2021).

**Reviewer #2 (Remarks to the Author):**

Using a nationwide health database with more than 2 million acute coronary syndrome (ACS) patients and a case-crossover design, this manuscript reported the results of a data analysis examining the differential effects of fine particulate constituents on ACS onset. The strengths of this study include a large and representative sample of ACS patients in China, the high spatial and temporal resolution model for the constituent data of fine particulate matter exposure, and the use of a novel statistical model to assess the joint effects of correlated co-exposures.

The findings of differential effects of fine particulate constituents on ACS onset are interesting and have some potential to significantly advance the current literature in relevant research fields. However, my enthusiasm for this manuscript is reduced by a few major concerns:

**Response:** We appreciate your positive and generous comments. We have revised the manuscript accordingly and provided point-to-point responses to your comments.

1. As reported in this study, each of the constituents was only associated with 2% or less increased odds in ACS onset. Given the low magnitude of the associations, the significance of the study findings are not very convincing. At the population level, however, the authors may want to report the total number of ACS cases that could be prevented if the level of each constituent is reduced by 1 standard deviation or interquartile range. Reporting the number of ACS cases that can be prevented by reducing air pollution level will give this study a lot higher public health relevance.

**Response:** Thanks for this brilliant suggestion! Although the magnitudes of the associations are relatively low, their cumulative effect at the population level could have a significant public health impact. In the revised version, we calculated the fraction and number of ACS cases that could be prevented if the level of each constituent is reduced by an interquartile range to convey the public health significance more clearly. As shown in **Supplementary Table 5**, reducing total $PM_{2.5}$ concentrations by an interquartile range could have prevented 1.96% of ACS cases, equivalent to 41,348 cases in the present database. If reducing different constituents of $PM_{2.5}$ by an interquartile range, the preventable fractions of ACS cases range from 1.49% for ammonium to 2.11% for organic matter, corresponding to a reduction of 31,436 to 44,566 cases. We hope these revisions could address your concerns. Please refer to **lines 160-165, 447-455,** and **Supplementary Table 5** for more details.

2. Some of the comments in the Introduction do not seem to be correct or appropriate. For example, “The majority of studies utilized time-series design based on daily counts of CVD hospitalization or death, rather than disease onset. This inevitably leads to ecological fallacy and temporal misclassification

of exposure.". This statement sounds too absolute and strong, as not all of the studies with those types of design would have ecological fallacy or temporal misclassification. Pls revise this statement and clearly specify under what circumstances that ecological fallacy and temporal misclassification would happen.

**Response:** We apologize for the inappropriate statements. Ecological fallacy occurs when inferences about the nature of specific individuals are based solely upon aggregate statistics collected for the group to which those individuals belong [1]. Thus, the conclusions do not reflect the reality of individuals within that group. **For time-series studies and aggregate-level case-crossover studies, ecological fallacy can occur because**: 1) the exposure is assumed to be the same for all events in a city on a given day; 2) the analysis is based on daily aggregated counts of events rather than individual cases. The use of individual-level time-stratified case-crossover study design could significantly mitigate this concern. Regarding temporal misclassification, we acknowledge that this term may not be the most suitable here. **The major advantage of using disease onset as the health outcome lies in that it is more sensitive and immediate than hospital admissions or deaths, and can offer earlier opportunities for public health interventions.** We have included more detailed explanations in the revised manuscript. Please see below or refer to **lines 79-86**.

*"Previous time-series studies and aggregate-level case-crossover studies often used daily pollutant concentrations and daily counts of CVD hospitalization or death in specific cities [14,15,17], rather than individual-level data, which can lead to apparent ecological fallacy [18]. Accordingly, utilizing the individual-level time-stratified case-crossover study design could significantly reduce this concern. Additionally, disease onset is more sensitive and immediate than hospital admissions or deaths, which provides earlier opportunities for public health interventions."*

**References:**
1. Duque, J.C., Artís, M. & Ramos, R. The ecological fallacy in a time series context: evidence from Spanish regional unemployment rates. J *Geograph Syst* **8**, 391-410 (2006).

3. It is not appropriate to examine the differences between groups using a Z-test as specified on page 10. Instead, it is better to use interaction terms to test

potential effect modifications.

**Response:** Thanks for the kind reminder! In the revised version, we removed the *z*-test analysis and conducted interaction analyses by including interaction terms between the grouping factor (i.e., age, sex, season, and region) and $PM_{2.5}$ constituents in the models. Results showed significant effect modifications by season for the associations of organic matter and sulfate, and by region for the associations of $PM_{2.5}$ total mass, organic matter, black carbon, and sulfate. Please refer to **lines 151-159, 444-446** and **Supplementary Table 4** for more details.

4. Page 17, 2nd paragraph: The discussions regarding potential mechanisms for the observed differential associations between PM2.5 constituents and ACS subtypes are unclear and hard to following. It'll be helpful to add a more thoughtful discussion here that may explain some of the study findings related to ACS subtypes.

**Response:** Thanks! Our results showed that stronger associations were observed for NSTEMI, followed by STEMI, and UA, which was consistent across different $PM_{2.5}$ constituents. Evidence on the associations between $PM_{2.5}$ constituents and ACS subtypes is extremely limited, making direct comparisons with existing studies difficult. However, previous findings on the associations between $PM_{2.5}$ total mass or other air pollutants and AMI provide some support for our results. **We have compared our results with these studies and added some more thoughtful and detailed discussion on findings related to ACS subtypes**. Please see the revised text below or refer to **lines 267-289**.

*"Our results show that stronger associations were observed for NSTEMI, followed by STEMI, and UA, which was consistent across different $PM_{2.5}$ constituents. Evidence on the associations between specific constituents of $PM_{2.5}$ and ACS subtypes is extremely limited, making direct comparisons with previous studies difficult. However, previous findings on the associations between total $PM_{2.5}$ mass or other air pollutants and AMI provide some support for our results. For example, a few studies reported stronger associations of air pollution with NSTEMI than STEMI [37-39]. Nevertheless, another study in the U.S. found statistically significant associations between $PM_{2.5}$ and STEMI, rather*

*than NSTEMI [40]. Mechanistically, STEMI mainly results from coronary artery occlusion following plaque rupture, and can lead to complete blood flow cessation and ischemic necrosis of the myocardial region. In contrast, NSTEMI usually involves plaque erosion and less severe coronary artery obstruction [40,41]. The observed stronger association with NSTEMI than STEMI suggests that acute exposure to $PM_{2.5}$ and its constituents is more likely to trigger plaque erosion and less severe obstructions, compared to complete coronary artery occlusion [39]. UA results from various causes, including coronary artery spasm, transient increases in myocardial oxygen demand, and partial blockages of coronary artery [42]. The diverse causes may make UA influenced by multiple factors beyond acute $PM_{2.5}$ exposure, which helps explain its weaker association with $PM_{2.5}$ and constituents. Nevertheless, given the mixed findings and scarce existing evidence, further research is urgently warranted to corroborate our results and fully elucidate the underlying mechanisms."*

**Reviewer #3 (Remarks to the Author):**

The authors analyzed the joint and individual effect of five PM2.5 chemical compounds (organic matter, black carbon, ammonium, nitrate and sulfate) on the occurrence of ACS. An impressive number of more than 2,100,000 patients from 2,096 Chinese hospitals were included in a seven-year time period, and a case-crossover design was applied. The total PM2.5 mass and the mass of all five chemical compounds were significantly associated with an increased risk of acute coronary syndrome. The effects were higher in lag 0, for chemical compounds organic matter and black carbon, in older patients, in cold season and in the southern part of China. A sensitivity analysis with adjustment for total PM2.5 mass showed significant results for organic matter, black carbon and ammonium, but not for nitrate or sulfate.

The topic of this article is highly relevant, novel and interesting. Indeed, acute effects of ambient PM2.5 mass on ACS are widely described and recognized. However, only the size of the particles is taken into consideration to classify the exposure to this air pollutant and only very few studies have focused on the qualitative aspects of the particle composition. Indeed, toxicity of particles

depends of their chemical composition and, in 2024, we have very few evidences on the chemical compounds triggering the cardiovascular consequences of air pollutantion exposure. Even if this study is highly relevant, there are some mains points needing some revision.

**Response**: Thanks for your constructive and encouraging comments. We have revised the manuscript accordingly and provided point-to-point responses to your comments.

Major comments:

1) The methodology of how the PM2.5 constituents were measured needs is not explained in the method section. This is not acceptable for a study aiming to describe the effects of PM chemical constituents on the triggering of ACS. Only after reading the dedicated TAP website it appears that the chemical nature of the PM2.5 were not directly evaluated at it was done by other investigators from China, Canada or US but comes from a modelization method based on daily measured values of fixed stations, completed by a machine learning algorithm. This method merits a better description and explanation on how it was validated against field measurement.

**Response:** Thanks for pointing out this important issue. In our study, the concentrations of $PM_{2.5}$ and its chemical constituents were not directly evaluated through field measurements but estimated using a model-based approach. **This approach relies on ground observations, satellite-retrieved aerosol optical depth (AOD), chemical transport models (CTM) simulations, ancillary data (e.g., meteorological, land use, population, and elevation data), and advanced machine learning algorithms [1-4]**. Firstly, ground observations were collected from several operational monitoring networks (e.g., China National Environmental Monitoring Centre, China's National Aerosol Composition Monitoring Network, the China Atmosphere Watch Network, and the Surface Particulate Matter Network) and literature studies. A total of 1640 stations for $PM_{2.5}$ and 571 stations for $PM_{2.5}$ chemical composition covering all provinces were used for model training and validation. Secondly, the $PM_{2.5}$ estimation relied on a two-stage machine learning model, incorporating multisource data fusion from ground observations, satellite-retrieved AOD, CTM simulations, and ancillary data (e.g., meteorological, land

use, population, and elevation data) [2]. Thirdly, the $PM_{2.5}$ chemical composition information (i.e., $PM_{2.5}$ component proportions as conversion factors [CFs]) is obtained from the operational Weather Research and Forecasting–Community Multiscale Air Quality (WRF–CMAQ) modeling system. These factors were then revised by using the extreme gradient boosting (XGBoost) models trained on collected ground observations. Finally, the revised conversion factors were used to partition the total $PM_{2.5}$ concentrations into specific components including organic matter, black carbon, nitrite, sulfate, and ammonium.

**$PM_{2.5}$ and its chemical components in the TAP dataset are in good agreement with the available ground observations**, and have been widely used in previous epidemiological studies [5-7]. For daily $PM_{2.5}$ total mass, the out-of-bag cross-validation $R^2$ ranges from 0.80 to 0.88, and the root-mean-square error (RMSE) is between 13.9 and 22.1 $\mu g/m^3$ when compared with ground observations for different years during 2013–2020. For daily $PM_{2.5}$ chemical constituents, the correlation coefficients range from 0.67 to 0.80 and most normalized mean biases were within ± 20% when compared with ground observations during 2013–2020. The spatiotemporal variations in $PM_{2.5}$ chemical components are also well captured, including the long-term trend and day-to-day variability across China. More details on the model performance have been described in recently published papers [1-2].

We have also added a detailed description of this methodology and its validation against field measurements in the revised manuscript (**see line 407 and Supplementary Methods**). We hope this detailed explanation addresses your concerns.

**References:**


1. Liu, S., et al. Tracking Daily Concentrations of PM(2.5) Chemical Composition in China since 2000. *Environ Sci Technol* **56**, 16517-16527 (2022).
2. Geng, G., et al. Tracking Air Pollution in China: Near Real-Time PM(2.5) Retrievals from Multisource Data Fusion. *Environ Sci Technol* **55**, 12106-12115 (2021).
3. Xiao, Q., et al. Separating emission and meteorological contributions to long-term PM2.5 trends over eastern China during 2000–2018. *Atmos Chem Phys* **21**, 9475-9496 (2021).
4. Xiao, Q., et al. Evaluation of gap-filling approaches in satellite-based daily PM2.5 prediction models. *Atmos Environ* **244**, 117921 (2021).
5. Xiao, Q., et al. Tracking PM2.5 and O3 Pollution and the Related Health Burden in China 2013–2020. *Environ Sci Technol* **56**, 6922-6932 (2022).
6. Ma, H., et al. Short-Term Exposure to PM(2.5) and O(3) Impairs Liver Function in HIV/AIDS Patients: Evidence from a Repeated Measurements Study. *Toxics* **11**(2023).
7. Qiu, T., et al. Short-term exposures to PM(2.5), PM(2.5) chemical components, and antenatal depression: Exploring the mediating roles of gut microbiota and fecal short-chain

2) Line 83 and 374: Exposure misclassification is indeed an important limitation in the modelization of PM2.5 effects on health. This study used again a combination of weather forecasting, ground observations, machine learning and multisource PM2.5 data to estimate the PM2.5 constituent mass at the hospital address on a 10x10km resolution. Although this reduces the exposure misclassification compared to using aggregated regional pollution data or the values of fixed monitoring stations, the modelization was not done at the patient living address and authors assume that the patient exposure was related to the exposure at the admission hospital. Consequently, there is still a major possible exposure misclassification bias left.

**Response:** This is a thought-provoking question! In the previous manuscript, we matched exposure data for each patient based on hospital addresses rather than the specific addresses of symptom onset, as more than 50% of patients did not provide complete onset addresses. **However, this would not be a major concern because:** 1) ACS patients in China are always sent to the nearest hospital for timely care, and we had further excluded those transferred from other hospitals; and 2) the median distance between hospitals and the onset address was 6.2 kilometers among participants who provided complete onset addresses; and this distance is generally acceptable in epidemiological studies on short-term exposures, in which the temporal variations of exposures are more important than spatial variations.

In the revised version, **we restricted the analysis to participants who provided complete addresses of their location at the time of ACS onset (N= 1,025,744), and reran the main model using air pollution data matched according to the address of disease onset and reporting hospital, respectively.** According to **Supplementary Table 7**, the results were little affected by using air pollutant concentrations matched by the addresses of the event onset versus hospitals. We included this as a sensitivity analysis (see **lines 176-178, 490-493,** and **Supplementary Table 7**), and additionally discussed this limitation (**see below** or refer to **lines 332-344**) in the revised manuscript.

*"Second, in the main analysis, we matched exposure data for each patient*

*based on hospital addresses rather than the specific addresses of symptom onset, as more than 50% of patients did not provide complete onset addresses. However, this would not be a major concern because: 1) ACS patients in China are always sent to the nearest hospital for timely care, and we had further excluded those transferred from other hospitals; 2) the median distance between hospitals and the onset address was 6.2 kilometers among participants who provided complete onset addresses; and this distance is generally acceptable in epidemiological studies on short-term exposures, in which the temporal variations of exposures are more important than spatial variations; and 3) our sensitivity analysis based on addresses of disease onset yielded comparable results to those estimated using hospital addresses."*

3) Air temperature changes are a main trigger of AMI. All pollutants are negatively (PM, NO2) or positively (O2) associated with temperature. Control of temperature bias is one of the most important interest in the use of case crossover design with stratification of control periods in the case crossover are frequently done in the same temperature range (+/- 1 or 2°C for ex.).
Could you explain why you chose to add temperature as a confounder in the model, instead of matching the cases and controls according to ambient temperature?

**Response:** Great points! This study currently utilizes a time-stratified case-crossover design. By matching cases and controls within the same year, month, and day of the week, this design effectively controls for seasonal trends, long- and mid-term trends, and day-of-week effects [1]. However, **time-varying factors such as ambient temperature are not controlled by design, which is why we adjust for temperature as a confounder in the model.** This methodology has been widely applied in recent environmental epidemiological studies on air pollution and health [2-7].

Following the reviewer's suggestion on matching controls by temperature, **we re-performed the analysis by selecting control days based on three criteria** [8]: (1) control days were taken from the same month and year as the case days; (2) control days and case days had to be at least 3 days apart from each other to avoid short-term autocorrelation; (3) only control days with a daily average temperature within 2°C from that on the case day were selected. **The**

**results showed slightly weaker but significant effects, and the overall pattern for the differential effects of constituents remained consistent.** Nevertheless, it is noteworthy that based on this strategy, the number of control days per case ranged from 0 to a maximum of 28, with an average of 10. **This variability in the number of control days per case can introduce some imbalance, which is a major limitation**. Besides, **matching the cases and controls according to ambient temperature was relatively less used**, and it was not a mainstream approach. **Recent studies have increasingly adopted the method of matching by day of the week and adjusting for temperature as a confounder** [2-7]. Therefore, we kept our main analyses and added this temperature-matching approach as a sensitivity analysis. Please refer to **lines 179-182, 493-498**, and **Supplementary Table 8** for more details.

**References:**


1. Janes, H., Sheppard, L. & Lumley, T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology* **16**, 717-726 (2005).
2. Di, Q., et al. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. *JAMA* **318**, 2446-2456 (2017).
3. Wei, Y., et al. Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. *BMJ* **367**, l6258 (2019).
4. Liu, Y., et al. Short-Term Exposure to Ambient Air Pollution and Mortality From Myocardial Infarction. *J Am Coll Cardiol* **77**, 271-281 (2021).
5. Zhang, Y., et al. Risk of Cardiovascular Hospital Admission After Exposure to Fine Particulate Pollution. *J Am Coll Cardiol* **78**, 1015-1024 (2021).
6. Pollution on Mortality in California: Implications for Climate Change. *Am J Respir Crit Care Med* **206**, 1117-1127 (2022).
7. Liu, Y., et al. Short-Term Exposure to Ambient Air Pollution and Asthma Mortality. *Am J Respir Crit Care Med* **200**, 24-32 (2019).
8. Scheers, H., et al. Does air pollution trigger infant mortality in Western Europe? A case-crossover study. *Environ Health Perspect* **119**, 1017-1022 (2011).


4) Line 145: “To avoid the potential influence of outliers in air pollutants concentrations, the highest and lowest 2.5% of daily concentrations during the study period were removed before formal analyses”. China is known as one of the hot spot of air pollutant exposure worldwide. Are these outliers related to some errors in modelization or related to real major air pollution peaks only observable in highly industrialized country like China? Do you mean that ACS during these outlier days were not included into the study? Were the values investigated before the decision to remove them from the analysis? If the outliers are no errors, than they should leave into the analysis as they reflect

the variability of the study area?

**Response:** Thank you for your important questions. Our exposure data were derived from a predictive model rather than direct measurements. Here, the "outliers" actually means the "extremes". **The extreme values are not necessarily errors but may represent the greater uncertainty of model predictions in air pollution extremes. Including such extremes can potentially skew results and reduce the reliability of the analysis.** Therefore, we omitted the highest and lowest 2.5% of daily concentrations in the dataset to reduce this uncertainty. **Besides, excluding the extreme values in exposure data has been a common practice in environmental epidemiology researches on air pollution [1-6], as it helps in achieving more robust effect estimations.** In the revised version, we added several references accordingly (see **lines 414-417**).

We hope these explanations could address your concerns. **If you still believe that we should include the extremes in our analysis, we are very willing to make the necessary revisions.**

**References:**


1. Xue, X., et al. Hourly air pollution exposure and the onset of symptomatic arrhythmia: an individual-level case-crossover study in 322 Chinese cities. *CMAJ* **195**, E601-e611 (2023).
2. Hu, J., et al. The acute effects of particulate matter air pollution on ambulatory blood pressure: A multicenter analysis at the hourly level. *Environ Int* **157**, 106859 (2021).
3. Liu, C., et al. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. *N Engl J Med* **381**, 705-715 (2019).
4. Samet, J.M., Dominici, F., Curriero, F.C., Coursac, I. & Zeger, S.L. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. *N Engl J Med* **343**, 1742-1749 (2000).
5. Zhang, Q., et al. Air pollution may increase the sleep apnea severity: A nationwide analysis of smart device-based monitoring. *The Innovation* **4**, 100528 (2023).
6. Lei, J., et al. Fine and coarse particulate air pollution and hospital admissions for a wide range of respiratory diseases: a nationwide case-crossover study. *Int J Epidemiol* **52**, 715-726 (2023).


5) Line 269 and Figure 3: a WQS is used and a bar chart illustrates the weight of the five constituents in the effect of PM2.5 on ACS. However, a limitation of the study is the non-measurement of transition metals. Figure 3 gives a clear overview but the reader may falsely conclude that all five compounds together explain 100% of the effect of the PM2.5 on ACS. Is the WQS model able to estimate the effect of non-measured compounds?

**Response:** This is a thought-provoking question! We agree that transition metals are also critical components to consider. Unfortunately, our study did not

include metallic elements **due to the lack of publicly available nationwide exposure data of high spatiotemporal resolution for these constituents in China**. To address this concern, **we subtracted the concentrations of the five measured constituents from the total $PM_{2.5}$ mass to obtain the remaining unmeasured components**, and reran the main models based on these remaining components. As shown in **Supplementary Table 9** and **Supplementary Fig. 8**, their effects were weaker than organic matter and black carbon, and comparable to nitrate, sulfate, and ammonium. **These results suggest that there may be important unmeasured constituents in $PM_{2.5}$ that warrant further investigation. We kept our main analyses and only added this as a supplementary analysis for the following reasons**: 1) since both $PM_{2.5}$ and the five constituents were model-predicted, directly subtracting the concentrations of the five constituents from total $PM_{2.5}$ is a rather crude approach and could introduce double exposure measurement errors; 2) there may be various unknown chemicals other than metallic elements in the remaining components, making it difficult to identify the nature of unmeasured constituents. We further acknowledged the lack of data on metallic elements as a limitation in the revised manuscript. Please see **lines 186-192, 251-253**, **351-353, 505-509, Supplementary Table 9,** and **Supplementary Fig. 8.**

**Figure 3** aims to provide a clear overview of the relative contributions of the five measured constituents. We have added an explanation that these weights represent each component's contribution to the health effects of the mixture of the five measured constituents, rather than all of $PM_{2.5}$ total mass. Please see below or refer to **lines 248-253**.

*"Still, it should be noted that these five constituents do not account for all of $PM_{2.5}$ total mass, and the weights derived from WQS and QGC only represent each component's contribution to the health effects of the mixture of the five measured constituents. The supplementary analysis based on the remaining components also reveals that there may be important unmeasured constituents in $PM_{2.5}$ that warrant further investigation."*

6) While literature is not always able to show significant results regarding the effect of PM2.5 on ACS (only a positive trend is very common), this study has significant results, not only for the effect of total PM2.5 mass on ACS in the total

study population, but as well in all subgroups and for all measured chemical constituents. This can be explained by the very high power because of the very large database, but also because of the choise to estimate the risk for ACS per IQR increase in PM2.5. Indeed most studies investigate the effect of an increase of 10µg/m3, while in this study the IQR equals an increase of 30µg/m3. To generalize the findings and be able to compare them with other literature, I suggest performing an additional analysis on the effect of a 10µg/m3 PM2.5 increase.

**Response:** Thanks. We agree that the large sample size increases statistical power, contributing to the significance of the results. However, using the IQR affects only the magnitude of the effect estimates, not their significance. In the original submission, we presented effect estimates per IQR increase to facilitate direct comparisons among various constituents, given their different ranges of variations in concentrations. Following your suggestions, **we have further reported the effect estimates per 10 µg/m$^3$ increase for PM$_{2.5}$ and per 1 µg/m$^3$ increase for chemical constituents in the supplementary file** (**lines 135-137, 519-521**, and **Supplementary Table 3**).

7) Line 220: In contrast with literature, the proportion of STEMI (35.9%) is higher than NSTEMI (21.2%). Can you explain this please?

**Response:** Thanks for your important comment. We double-checked the data and confirmed that STEMI and NSTEMI patients accounted for 35.9% and 21.2% of the total ACS cases, respectively. **The higher proportion of STEMI in our study is consistent with previous studies conducted in China** [1-5]. For example, China Acute Myocardial Infarction Registry (CAMI), a prospective, nationwide, multicenter observational study for AMI care covering 108 hospitals from 31 provinces and municipalities across Chinese mainland since 2013, also reported a higher number of STEMI than NSTEMI [2-4].

Although this differs from western developed countries such as the US and Germany, where the presentation of AMI was more frequently NSTEMI than STEMI [6,7], **there has been a notable trend in China over the past few years that the proportion of STEMI was decreasing while NSTEMI was increasing**. **Table R2** presents the annual proportion of STEMI and NSTEMI in our database, which clearly shows the trend.

**There were two possible reasons for the changing proportions in STEMI and NSTEMI in China.** First, population aging contributed to the rise in NSTEMI incidence. Multiple studies have confirmed that an aging population can lead to a higher incidence of NSTEMI [7,8]. Second, the sensitivity of diagnostic tests for cardiac biomarkers (e.g., high-sensitive troponin) has increased, which significantly enhanced the diagnosis rate of AMI, particularly NSTEMI [6,9]. Since this is beyond the primary scope of our study, we only explained this issue in the reply letter and did not include additional discussion in the manuscript.

**Table R2**. Annual proportions of STEMI and NSTEMI in the study population, 2015-2021.

| | STEMI (%) | NSTEMI (%) |
|---|---|---|
| 2015 | 46.4 | 15.8 |
| 2016 | 42.7 | 16.2 |
| 2017 | 39.0 | 19.0 |
| 2018 | 35.7 | 19.2 |
| 2019 | 34.9 | 20.3 |
| 2020 | 36.1 | 22.5 |
| 2021 | 34.3 | 24.1 |

Abbreviations: STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction.

**References:**


1. Li, J., *et al*. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. *Lancet* **385**, 441-451 (2015).
2. Wei, Z.Y., Yang, J.G., Qian, H.Y. & Yang, Y.J. Impact of Marital Status on Management and Outcomes of Patients With Acute Myocardial Infarction: Insights From the China Acute Myocardial Infarction Registry. *J Am Heart Assoc* **11**, e025671 (2022).
3. Xu, H., *et al*. Association of Hospital-Level Differences in Care With Outcomes Among Patients With Acute ST-Segment Elevation Myocardial Infarction in China. *JAMA Netw Open* **3**, e2021677 (2020).
4. Zhao, Q., *et al*. Current Status and Hospital-Level Differences in Care and Outcomes of Patients With Acute Non-ST-Segment Elevation Myocardial Infarction in China: Insights From China Acute Myocardial Infarction Registry. *Front Cardiovasc Med* **8**, 800222 (2021).
5. Gao, X.J., *et al*. [Age-related coronary risk factors in Chinese patients with acute myocardial infarction]. *Zhonghua Yi Xue Za Zhi* **96**, 3251-3256 (2016).
6. Mefford, M.T., *et al*. Sex-Specific Trends in Acute Myocardial Infarction Within an Integrated Healthcare Network, 2000 Through 2014. *Circulation* **141**, 509-519 (2020).
7. Freisinger, E., *et al*. German nationwide data on current trends and management of acute myocardial infarction: discrepancies between trials and real-life. *Eur Heart J* **35**, 979-

988 (2014).
8. Rosengren, A., *et al*. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *Eur Heart J* **27**, 789-795 (2006).
9. Reynolds, K., *et al*. Trends in Incidence of Hospitalized Acute Myocardial Infarction in the Cardiovascular Research Network (CVRN). *Am J Med* **130**, 317-327 (2017).

Minor comments:

- Line 45. “All five constituents” is mentioned, but the different constituents are not yet listed. This creates confusion for the readers.

**Response:** Thanks. In the revised manuscript, we listed the specific names of the five constituents (i.e., organic matter, black carbon, nitrate, sulfate, and ammonium) when they were first introduced in **Abstract**. Please see **line 35**.

- Line 80: For me, it is not clear why the term ecologic fallacy is used here. Can you explain this please?

**Response:** We apologize for the ambiguous statements. Ecological fallacy occurs when inferences about the nature of specific individuals are based solely upon aggregate statistics collected for the group to which those individuals belong [1]. Thus, the conclusions do not reflect the reality of individuals within that group. For time-series studies and aggregate-level case-crossover studies, ecological fallacy can occur because: 1) the exposure is assumed to be the same for all events in a city on a given day; 2) the analysis is based on daily aggregated counts of events rather than individual cases. We have included more detailed explanations in the revised manuscript. Please see below or refer to **lines 79-84**.

*“Previous time-series studies and aggregate-level case-crossover studies often used daily pollutant concentrations and daily counts of CVD hospitalization or death in specific cities [14,15,17], rather than individual-level data, which can lead to apparent ecological fallacy [18]. Accordingly, utilizing the individual-level time-stratified case-crossover study design could significantly reduce this concern.”*

**References:**

1. Duque, J.C., Artís, M. & Ramos, R. The ecological fallacy in a time series context: evidence from Spanish regional unemployment rates. J *Geograph Syst* **8**, 391-410 (2006).

- Line 265: the sensitivity analysis shows that the effect nitrate and sulfate is completely dependent on the total PM2.5 mass, correct? This should be mentioned clearer.

**Response:** Thanks for your insightful comment. After adjusting for $PM_{2.5}$ in the models, the effects of nitrate and sulfate became non-significant. **However, this finding does not necessarily imply that their effects are completely dependent on the total $PM_{2.5}$ mass**. This may represent a statistical dependency rather than a true mechanistic one. Several factors might contribute to this observation. First, constituent-$PM_{2.5}$ models may mask the effects of specific components due to overadjustment related to the high collinearity with $PM_{2.5}$, leading to an underestimation of associations [1]. Second, the impacts of exposure measurement errors usually become more complicated in multi-pollutant models, adding to the statistical uncertainty of results. Therefore, future studies are warranted to clarify this issue. We have mentioned this point clearer in the **Discussion**. Please see **lines 254-262**.

**Reference:**
1. Cai, J., *et al*. Prenatal Exposure to Specific PM(2.5) Chemical Constituents and Preterm Birth in China: A Nationwide Cohort Study. *Environ Sci Technol* **54**, 14494-14501 (2020).

- Line 235 and Figure 1: “Generally, the onset risk increased immediately on the concurrent day of exposure, attenuated thereafter, and became null at lag 2 day.” On figure 1 the effect decreases even more at lag3, nearly showing a significant negative association. Have you explored the log4, log5 or other lag effects? This negative effect could be explained by the harvesting effect, a period of excess mortality followed by a period with a mortality deficit because of the deaths of vulnerable patients at the pollution peak.

**Response:** Thanks for the insightful suggestion! As suggested, we have extended our analysis to explore lagged effects for up to 5 days. The results indicate that the effects at lag 4 and lag 5 gradually approach null, and no obvious harvesting effect is observed (**Table R3**). We have provided the supplementary results for your reference.

**Table R3**. Percent changes in the risk of onset of ACS per interquartile range increase in concentrations of $PM_{2.5}$ total mass and its chemical constituents during different lag days.

| Lag | $PM_{2.5}$ | Organic matter | Black carbon | Nitrate | Sulfate | Ammonium |
|---|---|---|---|---|---|---|
| 0 d | 2.00 (1.73, 2.26) | 2.15 (1.90, 2.41) | 2.03 (1.78, 2.28) | 1.54 (1.28, 1.80) | 1.57 (1.32, 1.81) | 1.51 (1.25, 1.77) |
| 1 d | 0.55 (0.29, 0.82) | 0.69 (0.43, 0.94) | 0.63 (0.38, 0.88) | 0.49 (0.22, 0.75) | 0.68 (0.43, 0.93) | 0.41 (0.15, 0.67) |
| 2 d | -0.06 (-0.33, 0.21) | -0.06 (-0.31, 0.20) | -0.05 (-0.30, 0.20) | -0.13 (-0.39, 0.14) | 0.03 (-0.23, 0.28) | 0.00 (-0.28, 0.28) |
| 3 d | -0.23 (-0.49, 0.04) | -0.21 (-0.46, 0.04) | 0.03 (-0.22, 0.28) | -0.16 (-0.42, 0.10) | -0.08 (-0.33, 0.16) | -0.18 (-0.44, 0.08) |
| 4 d | -0.14 (-0.41, 0.14) | -0.12 (-0.37, 0.14) | -0.15 (-0.41, 0.10) | -0.16 (-0.44, 0.11) | 0.08 (-0.18, 0.34) | -0.09 (-0.34, 0.16) |
| 5 d | -0.08 (-0.33, 0.18) | -0.03 (-0.27, 0.21) | -0.11 (-0.34, 0.13) | -0.12 (-0.37, 0.13) | -0.05 (-0.31, 0.21) | -0.05 (-0.29, 0.18) |

Abbreviations: ACS, acute coronary syndrome; $PM_{2.5}$, fine particulate matter.

**Reviewer #4 (Remarks to the Author):**

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

**Response:** Thanks for your valuable time in reviewing our manuscript and the constructive suggestions you provided. Our detailed responses to the comments are provided above. Because of the valuable comments, we believe that our manuscript has been improved.

Finally, we would like to thank the editors and reviewers once again for your thoughtful and detailed comments, which substantially improved our manuscript.

**Response to Comments from Reviewers:**

We sincerely appreciate your valuable time in reviewing our manuscript and the excellent suggestions and comments you provided. We have made changes to our manuscript in response to the comments. Point-by-point responses were made for each comment.

**REVIEWER COMMENTS**

Reviewer #1 (Remarks to the Author):

The model applied is a weighted linear model, and the problem of very high intercorrelations remains. The model has the limitation that it assumes linearity (see Renzetti et al, Front Public Health.2023), which the Supplementary Figures indicate not to be satisfied. As seen in Supplementary Figure 5, for example, sulfates is the index that tends to satisfy linearity for that NSTEMI outcome, as well as for UA. The very bent over shape of the carbon metrics is contrary to biological plausibility for it to be causal, itself: Why would there be diminished (or no) added health effects as concentrations rise (e.g., for Black Carbon above 4 μg/m3 )? This needs acknowledgement and addressing in the paper. The likely reason for the bending of the carbon metrics is that the dominant source of carbon must change as the concentration rises, perhaps from fossil fuel combustion at low levels, to biomass burning at the highest levels? This is a situation similar to that confronted by Rahman et al, Int J Epidemiol, 2021), and applying their approach to these data would be informative.

**Response**: Thank you for raising this important issue. We acknowledge that the weighted quantile sum (WQS) regression used in our study has limitations, particularly regarding the assumption of linearity (**see below or refer to lines 371-374**). Although most components exhibited a linear relationship with ACS onset, some of the exposure-response curves flattened slightly at higher concentrations. However, our results suggest that these associations are approximately linear overall. Additionally, previous studies have also demonstrated approximately linear relationships between $PM_{2.5}$ components and health outcomes, and many of them have applied WQS regression to

explore these associations [1-4]. Importantly, the WQS regression is specifically designed to evaluate health effects of highly-correlated pollutant mixtures while reducing the impact of high collinearity [5].

*"Fourth, WQS assumes linearity for these relationships. Although most components exhibited a linear relationship with ACS onset, some of the exposure-response curves flattened slightly at higher concentrations, which could affect the stability of our estimates."*

Regarding the non-linear shape observed for some components (e.g., black carbon), there are two main explanations. One reason is the limited number of data points at higher concentrations, which leads to less stable estimates. The other explanation, as the reviewer pointed out, is that the sources of these components may vary with concentration levels. **At lower concentrations, they are likely to originate from fossil fuel combustion, whereas at higher concentrations, biomass burning which has lower cardiovascular toxicity may dominate [6].** However, there still lacks nationwide $PM_{2.5}$ source data of high spatiotemporal resolution in China. Besides, in our study, we did not have data on specific tracers such as potassium and sulfur, which limits our ability to calculate source-specific concentrations in the way described by Rahman et al, and differentiate between $PM_{2.5}$ sources such as fossil fuel combustion and biomass burning. As a result, we cannot directly validate this hypothesis within our study. Nonetheless, we believe our analysis on the health effects of $PM_{2.5}$ components could provide valuable clues and support for future research on source-specific effects. We have added further discussion to the revised manuscript, and emphasized the need for future research on source-specific effects. **Please see below or refer to lines 259-273**.

*"In our analysis, most $PM_{2.5}$ components exhibited linear exposure-response relationships with ACS onset. However, the exposure-response curves of some components, such as black carbon, flattened slightly at higher concentrations, indicating a lower health impact per unit increase of the components on highly polluted days. One possible explanation for this flattening is the limited number of data points at higher concentrations, which may lead to less stable estimates. Another possible explanation is that the sources of these components may vary with concentration levels. For instance, a time-series*

*study conducted in Dhaka, Bangladesh, observed a similar plateau in the exposure-response curve at higher $PM_{2.5}$ levels. Their findings suggested that at lower concentrations, $PM_{2.5}$ is primarily from fossil fuel combustion, while at higher concentrations, biomass burning which has lower cardiovascular toxicity may become more dominant. However, due to the lack of nationwide $PM_{2.5}$ source data with high spatiotemporal resolution in China, further research on source-specific effects is warranted to fully elucidate this issue."*

**References:**


1. Guo, B., et al. Long-term exposure to ambient PM2.5 and its constituents is associated with MAFLD. *JHEP Rep* **5**, 100912 (2023).
2. Pan, X., et al. Long-term exposure to ambient PM(2.5) constituents is associated with dyslipidemia in Chinese adults. *Ecotoxicol Environ Saf* **263**, 115384 (2023).
3. Li, S., et al. Long-term Exposure to Ambient PM2.5 and Its Components Associated With Diabetes: Evidence From a Large Population-Based Cohort From China. *Diabetes Care* **46**, 111-119 (2023).
4. Li, J., et al. Ambient PM2.5 and its components associated with 10-year atherosclerotic cardiovascular disease risk in Chinese adults. *Ecotoxicol Environ Saf* **263**, 115371 (2023).
5. Carrico, C., Gennings, C., Wheeler, D.C. & Factor-Litvak, P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J Agric Biol Environ Stat* **20**, 100-120 (2015).
6. Rahman, M.M., et al. Cardiovascular morbidity and mortality associations with biomass- and fossil-fuel-combustion fine-particulate-matter exposures in Dhaka, Bangladesh. *Int J Epidemiol* **50**, 1172-1183 (2021).


Looking at the sulfate effect coefficients, for example, it is apparent that its associated PM2.5 mass is more toxic than the average overall PM2.5 mass. Using Supplemental Table 3, the % NSTEM1 (lag 0) increase is 0.43% per 1 µg/m3 SO4. So, since it is likely as ammonium sulfate, that is 0.43% per 1 x 132/96 (based on molecular wts) = 1.375 µg/m3 sulfate PM2.5 mass for the .43% effect, yielding an effect of (10/1.375) x .43% = 3.1% per sulfate associated PM2.5 , or (3.1/.94 =) 3.3 times the STEM1 effect per 10 µg/m3 of the overall PM2.5 . This also needs consideration and discussion.

**Response**: This is a thought-provoking comment. We appreciate your detailed analysis, and indeed, based on your calculation, it suggests that the sulfate component could exert a stronger effect than the average $PM_{2.5}$ mass. In response to your suggestion, we have added further discussion in the revised manuscript emphasizing the possibility of a stronger effect associated with sulfate, and this warrants further investigation. **Please see below or refer to lines 248-252.**

*"Although carbonaceous components showed relatively stronger effects, other components (e.g., sulfate, nitrate, and ammonium) should not be overlooked. Specifically, we observed that sulfate, which is mainly in the form of ammonium sulfate, exhibited a stronger health effect per unit increase in concentration compared to that of total $PM_{2.5}$ mass in the single-pollutant models."*

However, we would also like to clarify that while the assumption that sulfate exists predominantly as ammonium sulfate is reasonable, sulfate in ambient air can also exist in other forms, depending on environmental conditions and the availability of other ions. Therefore, the application of this molecular weight ratio (132/96 for ammonium sulfate) may not fully capture the variability in the sulfate species present in $PM_{2.5}$. Furthermore, in the present study, we assess the strength of the health effects of $PM_{2.5}$ components primarily based on statistical results. The findings provide important insights into the varying toxicities of these components, but at the same time should be interpreted with caution. **We acknowledge that further toxicological studies and randomized controlled trials are needed to explore the specific effects of individual components, such as sulfate, in more detail.** We added this issue as a limitation in the revised manuscript. **Please see below or refer to lines 364-371**.

*"Third, given the high correlation between different constituents, our results only reflect statistical associations rather than causal relationships, and the strength of their health effects was evaluated primarily based on statistical findings. Therefore, the findings should be interpreted with caution, and future researches, such as toxicological studies and randomized controlled trials, are warranted to validate the true effects of the components and better understand their individual contributions."*

**Reviewer #2 (Remarks to the Author):**

This revision has adequately addressed all of my previous concerns. I have no further comments.

**Response**: Thank you for your positive comments and for taking the time to review our manuscript. We are pleased that the revisions have significantly

improved our work.

**Reviewer #3 (Remarks to the Author):**

All my comments are properly answered. No further comments. Congrats for your work.

**Response**: Thank you for your kind words and thorough review of our manuscript. We are grateful for your comments, which have helped strengthen our work.

**Reviewer #4 (Remarks to the Author):**

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

**Response:** Thanks for your constructive reviews and thoughtful suggestions. Our detailed responses to the comments are provided above.

Finally, we would like to thank the editors and reviewers once again for your thoughtful and detailed comments, which have substantially improved our manuscript.

**Response to Comments from Reviewers:**

We sincerely appreciate your valuable time in reviewing our manuscript and the excellent suggestions and comments you provided. We have made changes to our manuscript in response to the comments. Point-by-point responses were made for each comment.

**REVIEWERS' COMMENTS**

**Reviewer #1 (Remarks to the Author):**

This revision has adequately addressed my previous concerns.

**Response**: Thank you for your kind words and thorough review of our manuscript. We are pleased that the revisions have significantly improved our work.