Supplementary Information

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

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Supplementary Methods

Exposure assessment of $PM_{2.5}$ and its constituents

Daily concentrations of fine particulate matter ($PM_{2.5}$) and its constituents, including organic matter, black carbon, nitrate, sulfate, and ammonium during the study period were extracted from Tracking Air Pollution in China (TAP) dataset (http://tapdata.org.cn). TAP estimates daily concentrations using a model-based approach, which 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. 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[1-2].

Weighted quantile sum regression

Weighted quantile sum (WQS) regression is a modeling technique which can identify the association between mixtures and the outcome of interest while reducing the impact of high collinearity[5]. The main principle of WQS regression is to combine multiple correlated predictors into a single index that represents the overall mixture. The basic weighted index model is as follows[5]:

$$g(\mu) = \beta_0 + \beta_1(\sum_{i=1}^{c} w_i q_i) + z'\phi \quad (1)$$

where w_i is the unknown weight for the ith component; β_0 is the intercept; β_1 is the regression coefficient for the weighted quantile sum (constraining its association with the mean to be either non-positive or non-negative); z' is a vector of covariates (risk factors and confounders) determined prior to estimating the weights; ϕ is a vector of regression coefficients for the covariates; and g represents any monotonic, differentiable link function as in a generalized linear model, which links the mean μ, to the predictor variables. The term $\sum_{i=1}^{c} w_i q_i$ represents the weighted index for the set of c chemicals of interest. The weights are constrained to sum to 1 and are constrained by the limit $0 \le w_i \le 1$.

The process begins with randomly splitting the original data into a training dataset (40%) and a validation dataset (60%). 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. The model first estimates the empirical weight index (i.e., w_i) of individual component among each bootstrapping sample using maximum likelihood estimation. The final weights are defined as average weights across the bootstrap samples. The WQS index is then constructed by using these final weights and subsequently incorporated into the regression model given in equation (1) using the validation dataset to estimate the joint effects of components mixture on the health outcome. Interpretation of the estimated WQS regression model follows in two steps. First, a test for significance of β_1 determines whether there is an association between the index and the outcome variable. The significance of the regression coefficient permits the further interpretation of the weights. Second, the important components in the index are identified by comparing the “average” (across the bootstrap samples) weight for each component to a selection threshold parameter, usually defined as 1/number of chemicals. In the present analysis, 40% of the dataset was used for training and 60% for validation, with the bootstrap set at 100 times. The direction of association was assumed positive for all the constituents according to existing evidence[6-7].

Supplementary Table 1. Descriptive information of study population.

Baseline characteristics	N or N (%)
Case days	2,113,728
Control days	7,196,661
Age at onset, years	
< 65	1,057,510 (50.0)
≥ 65	1,055,834 (50.0)
Missing	384 (0.0)
Sex	
Male	1,431,036 (67.7)
Female	682,564 (32.3)
Missing	128 (0.0)
Disease type	
AMI	1,207,625 (57.1)
STEMI	758,464 (35.9)
NSTEMI	449,161 (21.2)
UA	906,103 (42.9)
Season	
Warm	1,038,028 (49.1)
Cold	1,075,700 (50.9)
Region	
South	890,849 (42.1)
North	1,222,879 (57.9)

Abbreviations: AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

Supplementary Table 2. Spearman correlation coefficients across $PM_{2.5}$ total mass and its chemical constituents during lag 0 day.

	$PM_{2.5}$	Organic matter	Black carbon	Nitrate	Sulfate
Organic matter	0.93				
Black carbon	0.88	0.95			
Nitrate	0.90	0.77	0.70		
Sulfate	0.90	0.83	0.81	0.86	
Ammonium	0.90	0.77	0.72	0.98	0.89

Abbreviations: $PM_{2.5}$, fine particulate matter.

Supplementary Table 3. Percent changes in the risk of onset of ACS and its subtypes per 10 μg/m^3 increase in $PM_{2.5}$ total mass and per 1 μg/m^3 increase in chemical constituents during different lag periods.

Pollutants	Lag	ACS	AMI	STEMI	NSTEMI	UA
$PM_{2.5}$	0 d	0.66 (0.57, 0.75)	0.82 (0.71, 0.94)	0.76 (0.61, 0.90)	0.94 (0.74, 1.13)	0.45 (0.32, 0.58)
	1 d	0.18 (0.10, 0.27)	0.26 (0.14, 0.38)	0.23 (0.08, 0.38)	0.32 (0.13, 0.52)	0.08 (-0.06, 0.21)
	2 d	-0.02 (-0.11, 0.07)	0.07 (-0.05, 0.19)	0.09 (-0.06, 0.24)	0.03 (-0.16, 0.23)	-0.05 (-0.19, 0.09)
	3 d	-0.08 (-0.16, 0.01)	0.00 (-0.12, 0.12)	-0.00 (-0.15, 0.14)	0.00 (-0.19, 0.20)	-0.00 (-0.14, 0.14)
Organic matter	0 d	0.30 (0.27, 0.34)	0.37 (0.32, 0.42)	0.34 (0.28, 0.40)	0.43 (0.35, 0.51)	0.21 (0.16, 0.26)
	1 d	0.10 (0.06, 0.13)	0.13 (0.08, 0.18)	0.12 (0.06, 0.18)	0.16 (0.08, 0.24)	0.05 (-0.01, 0.10)
	2 d	-0.01 (-0.04, 0.03)	0.03 (-0.01, 0.08)	0.04 (-0.02, 0.10)	0.02 (-0.06, 0.10)	-0.02 (-0.08, 0.03)
	3 d	-0.03 (-0.06, 0.01)	-0.01 (-0.06, 0.04)	-0.00 (-0.06, 0.06)	-0.02 (-0.10, 0.05)	0.01 (-0.04, 0.07)
Black carbon	0 d	1.57 (1.38, 1.77)	1.91 (1.65, 2.17)	1.71 (1.39, 2.03)	2.26 (1.83, 2.69)	1.13 (0.84, 1.42)
	1 d	0.49 (0.29, 0.68)	0.67 (0.41, 0.92)	0.55 (0.23, 0.87)	0.87 (0.45, 1.30)	0.25 (-0.04, 0.54)
	2 d	-0.04 (-0.24, 0.15)	0.20 (-0.05, 0.46)	0.27 (-0.06, 0.59)	0.09 (-0.33, 0.52)	-0.15 (-0.46, 0.15)
	3 d	0.03 (-0.17, 0.22)	-0.02 (-0.27, 0.24)	-0.01 (-0.33, 0.31)	-0.03 (-0.45, 0.39)	-0.03 (-0.33, 0.27)
Nitrate	0 d	0.19 (0.16, 0.22)	0.24 (0.20, 0.28)	0.21 (0.16, 0.27)	0.28 (0.21, 0.35)	0.12 (0.07, 0.17)
	1 d	0.06 (0.03, 0.09)	0.08 (0.03, 0.12)	0.07 (0.02, 0.13)	0.08 (0.01, 0.16)	0.03 (-0.01, 0.08)
	2 d	-0.02 (-0.05, 0.02)	0.02 (-0.02, 0.06)	0.02 (-0.04, 0.07)	0.03 (-0.05, 0.10)	-0.04 (-0.09, 0.01)
	3 d	-0.02 (-0.05, 0.01)	0.02 (-0.02, 0.06)	0.03 (-0.02, 0.09)	-0.00 (-0.07, 0.07)	-0.02 (-0.07, 0.03)
Sulfate	0 d	0.30 (0.25, 0.35)	0.37 (0.30, 0.43)	0.33 (0.25, 0.41)	0.43 (0.33, 0.54)	0.21 (0.14, 0.29)

	1 d	0.13 (0.08, 0.18)	0.16 (0.10, 0.23)	0.13 (0.05, 0.21)	0.22 (0.12, 0.33)	0.09 (0.02, 0.16)
	2 d	0.01 (-0.04, 0.05)	0.05 (-0.01, 0.12)	0.05 (-0.03, 0.14)	0.05 (-0.06, 0.15)	-0.06 (-0.13, 0.02)
	3 d	-0.02 (-0.06, 0.03)	0.00 (-0.06, 0.06)	-0.01 (-0.09, 0.07)	0.01 (-0.09, 0.12)	-0.04 (-0.11, 0.04)
Ammonium	0 d	0.30 (0.25, 0.35)	0.37 (0.30, 0.43)	0.33 (0.25, 0.41)	0.44 (0.32, 0.55)	0.20 (0.13, 0.28)
	1 d	0.08 (0.03, 0.13)	0.11 (0.04, 0.18)	0.10 (0.02, 0.19)	0.12 (0.01, 0.24)	0.04 (-0.04, 0.12)
	2 d	0.00 (-0.05, 0.05)	0.02 (-0.05, 0.09)	0.02 (-0.06, 0.11)	0.02 (-0.09, 0.14)	-0.07 (-0.14, 0.00)
	3 d	-0.04 (-0.09, 0.02)	0.01 (-0.06, 0.08)	0.02 (-0.06, 0.11)	-0.01 (-0.12, 0.11)	-0.01 (-0.09, 0.07)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina; $PM_{2.5}$, fine particulate matter.

Supplementary Table 4. The p values for the interaction terms in the associations between $PM_{2.5}$ chemical constituents and ACS onset during lag 0 day [a].

Grouping factor	$PM_{2.5}$	Organic matter	Black carbon	Nitrate	Sulfate	Ammonium
Age	0.51	0.36	0.34	0.76	0.76	0.21
Sex	0.17	0.07	0.07	0.92	0.19	0.74
Season	0.85	0.05	0.06	0.91	0.02	0.51
Region	2.39×10^{-3}	0.04	2.69×10^{-3}	0.06	1.23×10^{-5}	0.06

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

[a] P values for the interaction terms were obtained by including interaction terms between the grouping factor (i.e., age, sex, season, and region) and $PM_{2.5}$ constituents in the conditional logistic regression models. Tests were two sided, and a p value <0.05 was considered statistically significant.

Supplementary Table 5. The fraction and number of ACS cases that could be prevented in the present database if the level of $PM_{2.5}$ total mass and each constituent is reduced by an interquartile range.

Pollutants	Fraction of cases (%)	Number of cases
$PM_{2.5}$	1.96 (1.70, 2.21)	41,348 (35,976, 46,705)
Organic matter	2.11 (1.86, 2.35)	44,566 (39,402, 49,716)
Black carbon	1.99 (1.75, 2.23)	42,147 (37,066, 47,216)
Nitrate	1.52 (1.27, 1.77)	32,107 (26,764, 37,436)
Sulfate	1.55 (1.31, 1.78)	32,664 (27,640, 37,676)
Ammonium	1.49 (1.24, 1.74)	31,436 (26,157, 36,701)

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

Supplementary Table 6. Percent changes in the risk of onset of ACS and its subtypes per interquartile range increase in concentrations of $PM_{2.5}$ chemical constituents during lag 0 day with adjustment of $PM_{2.5}$ total mass.

Pollutants	ACS	AMI	STEMI	NSTEMI	UA
Organic matter	2.04 (1.46, 2.63)	2.48 (1.71, 3.27)	2.51 (1.53, 3.51)	2.40 (1.14, 3.69)	1.42 (0.53, 2.32)
Black carbon	1.90 (1.36, 2.44)	2.42 (1.71, 3.13)	2.24 (1.35, 3.15)	2.75 (1.59, 3.92)	1.19 (0.37, 2.02)
Nitrate	-0.61 (-1.27, 0.06)	-0.35 (-1.22, 0.54)	-0.44 (-1.55, 0.67)	-0.19 (-1.61, 1.26)	-1.01 (-2.03, 0.01)
Sulfate	-0.41 (-1.02, 0.20)	-0.75 (-1.53, 0.03)	-0.35 (-1.37, 0.68)	-0.14 (-1.41, 1.15)	-0.52 (-1.41, 0.38)
Ammonium	1.02 (0.59, 1.46)	1.17 (0.60, 1.74)	1.06 (0.34, 1.78)	1.37 (0.44, 2.31)	0.83 (0.17, 1.50)

Abbreviations: $PM_{2.5}$, fine particulate matter; ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

Supplementary Table 7. Percent changes in the risk of onset of ACS and its subtypes per interquartile range increase in concentrations of $PM_{2.5}$ chemical constituents during lag 0 day among cases with complete address of ACS onset (n= 1,025,744).

Models	Pollutants	ACS	AMI	STEMI	NSTEMI	UA
Hospital-address analysis [a]	$PM_{2.5}$	1.82 (1.44, 2.21)	2.41 (1.91, 2.91)	2.45 (1.80, 3.11)	2.48 (1.68, 3.29)	0.95 (0.37, 1.53)
	Organic matter	1.96 (1.59, 2.33)	2.54 (2.06, 3.03)	2.48 (1.86, 3.10)	2.63 (1.86, 3.41)	1.17 (0.61, 1.73)
	Black carbon	1.87 (1.51, 2.23)	2.43 (1.96, 2.90)	2.37 (1.76, 2.97)	2.57 (1.81, 3.34)	1.10 (0.56, 1.66)
	Nitrate	1.46 (1.08, 1.84)	1.99 (1.49, 2.49)	1.86 (1.22, 2.50)	2.18 (1.39, 2.98)	0.75 (0.17, 1.34)
	Sulfate	1.41 (1.06, 1.76)	1.82 (1.36, 2.29)	1.79 (1.20, 2.39)	1.86 (1.13, 2.61)	0.85 (0.32, 1.39)
	Ammonium	1.48 (1.11, 1.86)	1.97 (1.48, 2.46)	1.91 (1.28, 2.54)	2.08 (1.29, 2.86)	0.82 (0.24, 1.39)
Onset-address analysis [b]	$PM_{2.5}$	1.72 (1.35, 2.10)	2.25 (1.75, 2.75)	2.27 (1.64, 2.91)	2.14 (1.37, 2.92)	1.02 (0.46, 1.59)
	Organic matter	1.93 (1.56, 2.29)	2.41 (1.93, 2.89)	2.51 (1.90, 3.13)	2.26 (1.49, 3.03)	1.27 (0.71, 1.83)
	Black carbon	1.81 (1.45, 2.17)	2.33 (1.86, 2.81)	2.28 (1.68, 2.89)	2.39 (1.64, 3.16)	1.12 (0.58, 1.67)
	Nitrate	1.41 (1.03, 1.79)	1.89 (1.40, 2.39)	1.83 (1.19, 2.47)	1.99 (1.20, 2.79)	0.75 (0.17, 1.34)
	Sulfate	1.42 (1.07, 1.77)	1.76 (1.29, 2.22)	1.77 (1.17, 2.36)	1.74 (1.00, 2.48)	0.97 (0.43, 1.51)
	Ammonium	1.46 (1.09, 1.84)	1.96 (1.47, 2.46)	1.90 (1.27, 2.53)	2.07 (1.29, 2.86)	0.78 (0.21, 1.36)

Abbreviations: $PM_{2.5}$, fine particulate matter; ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

[a] In the hospital-address analysis (n= 1,025,744), the pollutants data were matched by the addresses of the reporting hospitals.

[b] In the onset-address analysis (n= 1,025,744), the pollutants data were matched by the addresses of the event onset.

Supplementary Table 8. Percent changes in the risk of onset of ACS and its subtypes per interquartile range increase in concentrations of $PM_{2.5}$ chemical constituents during lag 0 day by matching controls by temperature.

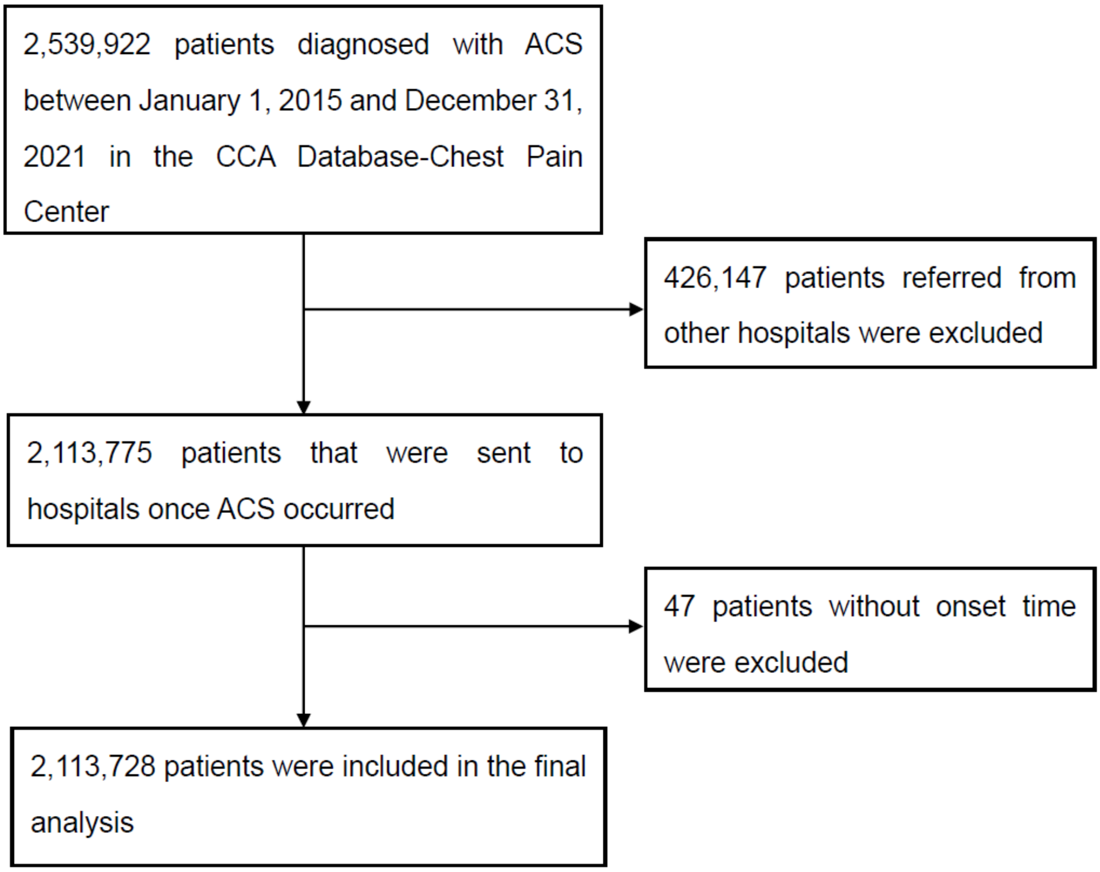
Pollutants	ACS	AMI	STEMI	NSTEMI	UA
$PM_{2.5}$	1.66 (1.40, 1.92)	2.18 (1.84, 2.52)	2.10 (1.66, 2.54)	2.45 (1.88, 3.01)	0.92 (0.53, 1.31)
Organic matter	2.05 (1.80, 2.29)	2.55 (2.22, 2.88)	2.44 (2.02, 2.86)	2.74 (2.20, 3.27)	1.41 (1.03, 1.79)
Black carbon	1.94 (1.69, 2.18)	2.40 (2.07, 2.72)	2.25 (1.83, 2.66)	2.65 (2.12, 3.19)	1.33 (0.96, 1.70)
Nitrate	1.04 (0.79, 1.30)	1.52 (1.19, 1.86)	1.43 (1.01, 1.86)	1.67 (1.13, 2.22)	0.42 (0.03, 0.81)
Sulfate	1.15 (0.91, 1.40)	1.51 (1.19, 1.83)	1.47 (1.06, 1.87)	1.60 (1.08, 2.12)	0.71 (0.34, 1.08)
Ammonium	1.06 (0.81, 1.32)	1.50 (1.17, 1.84)	1.45 (1.03, 1.88)	1.58 (1.04, 2.13)	0.50 (0.11, 0.89)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina; $PM_{2.5}$, fine particulate matter.

Supplementary Table 9. Percent changes in the risk of onset of ACS and its subtypes per interquartile range increase in concentrations of the remaining components during different lag periods.

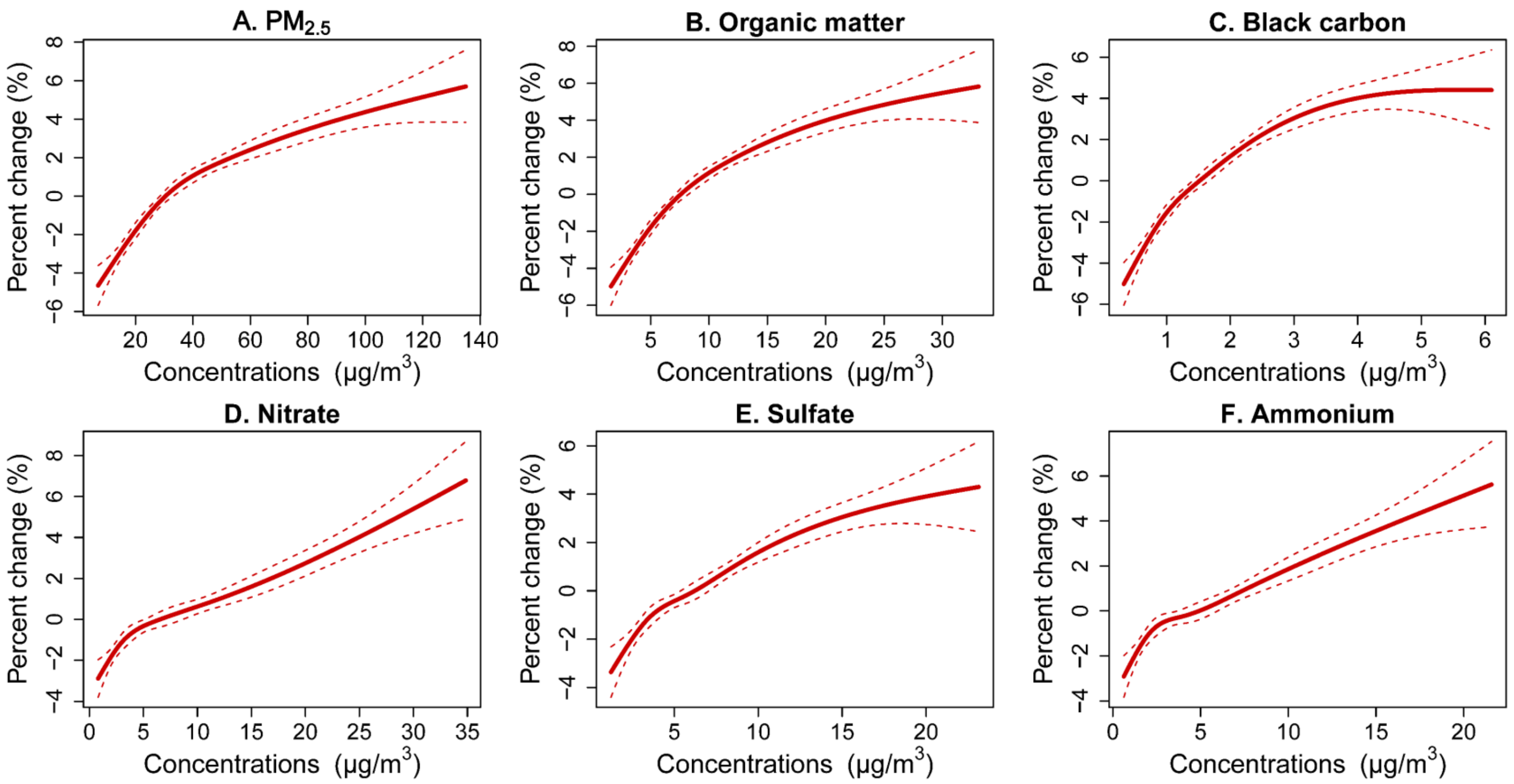
Lag	ACS	AMI	STEMI	NSTEMI	UA
0 d	1.59 (1.33, 1.85)	1.84 (1.50, 2.18)	1.73 (1.30, 2.16)	2.03 (1.48, 2.59)	1.27 (0.88, 1.66)
1 d	0.44 (0.19, 0.70)	0.43 (0.10, 0.77)	0.40 (-0.03, 0.83)	0.51 (-0.05, 1.06)	0.46 (0.07, 0.85)
2 d	-0.07 (-0.33, 0.18)	0.00 (-0.33, 0.34)	0.15 (-0.28, 0.58)	-0.25 (-0.80, 0.30)	-0.16 (-0.55, 0.23)
3 d	-0.09 (-0.34, 0.16)	0.04 (-0.29, 0.38)	-0.07 (-0.49, 0.36)	0.25 (-0.30, 0.79)	-0.25 (-0.64, 0.13)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

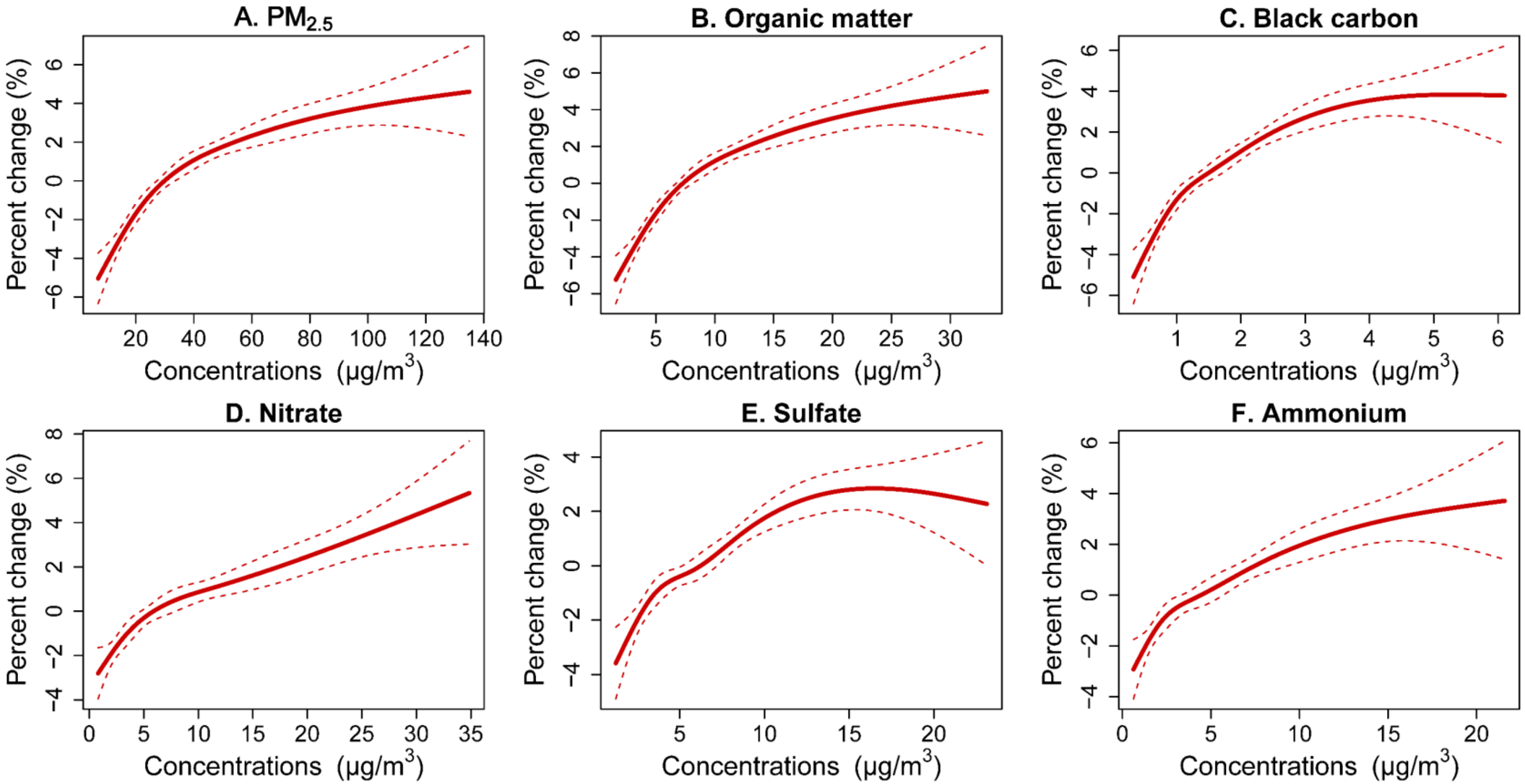


Supplementary Fig. 1. Flow chart of the study inclusion.

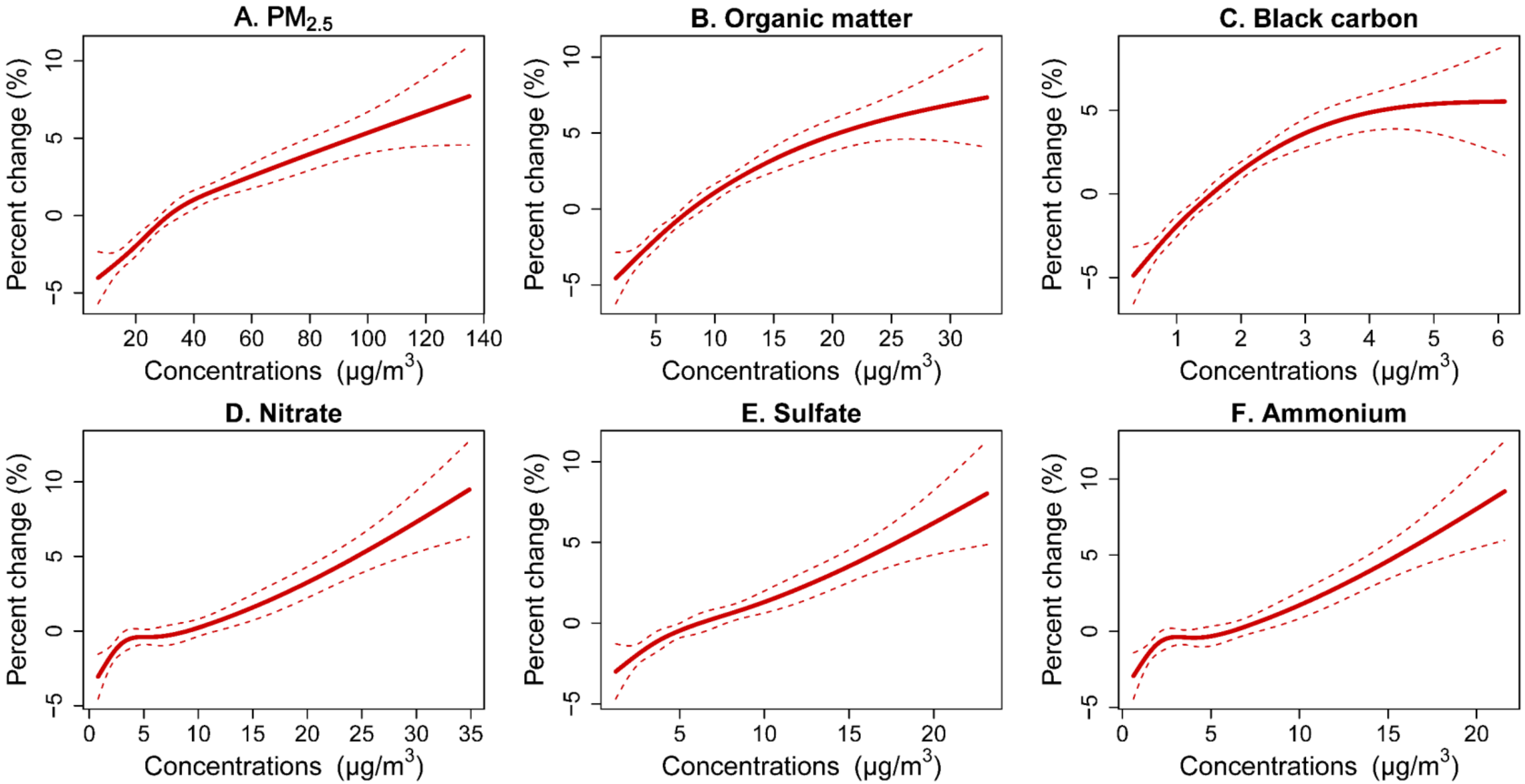
Abbreviation: ACS, acute coronary syndrome; CCA, the Chinese Cardiovascular Association.



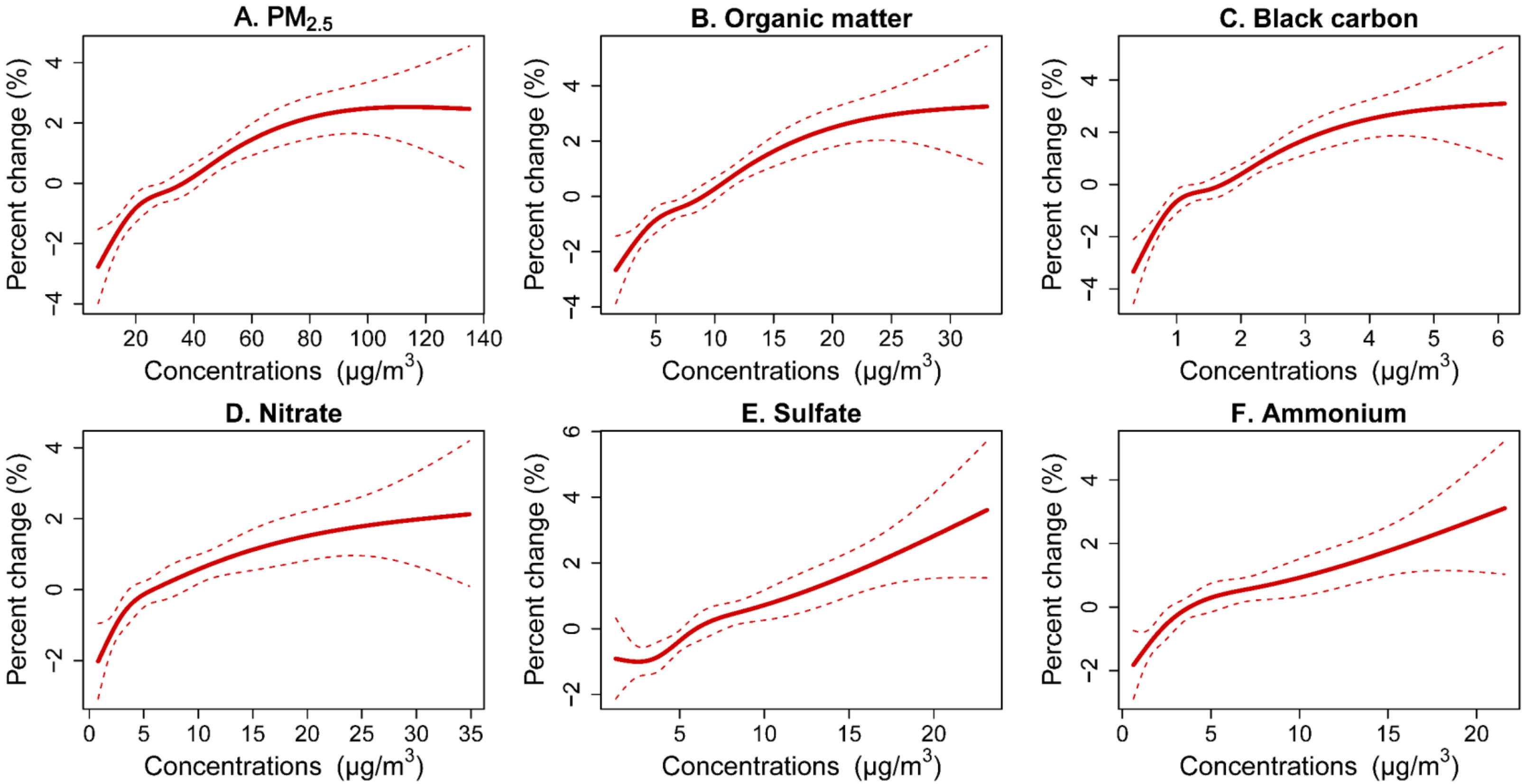
Supplementary Fig. 2. Exposure–response curves for the associations of $PM_{2.5}$ total mass and its chemical constituents with AMI onset during lag 0 day. The solid lines represent the point estimates of percent change in the risk of AMI onset, and the dashed lines indicate the corresponding 95% confidence intervals. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; AMI, acute myocardial infarction.



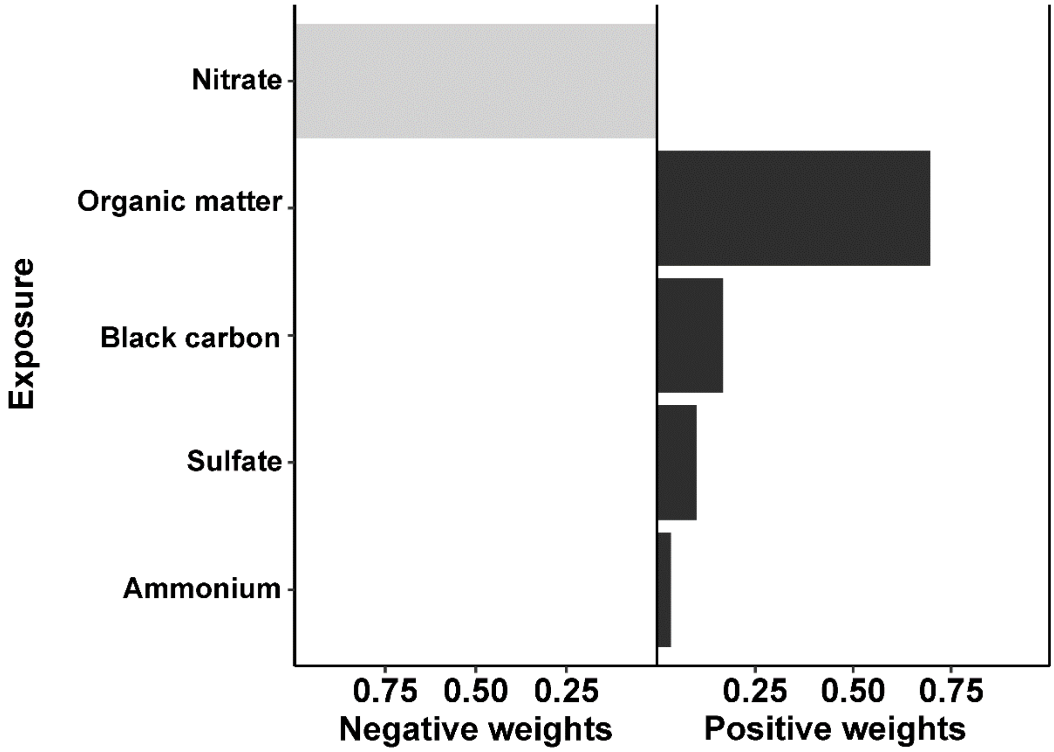
Supplementary Fig. 3. Exposure–response curves for the associations of $PM_{2.5}$ total mass and its chemical constituents with STEMI onset during lag 0 day. The solid lines represent the point estimates of percent change in the risk of STEMI onset, and the dashed lines indicate the corresponding 95% confidence intervals. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; STEMI, ST-segment-elevation myocardial infarction.



Supplementary Fig. 4. Exposure–response curves for the associations of $PM_{2.5}$ total mass and its chemical constituents with NSTEMI onset during lag 0 day. The solid lines represent the point estimates of percent change in the risk of NSTEMI onset, and the dashed lines indicate the corresponding 95% confidence intervals. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; NSTEMI, non-ST-segment-elevation myocardial infarction.

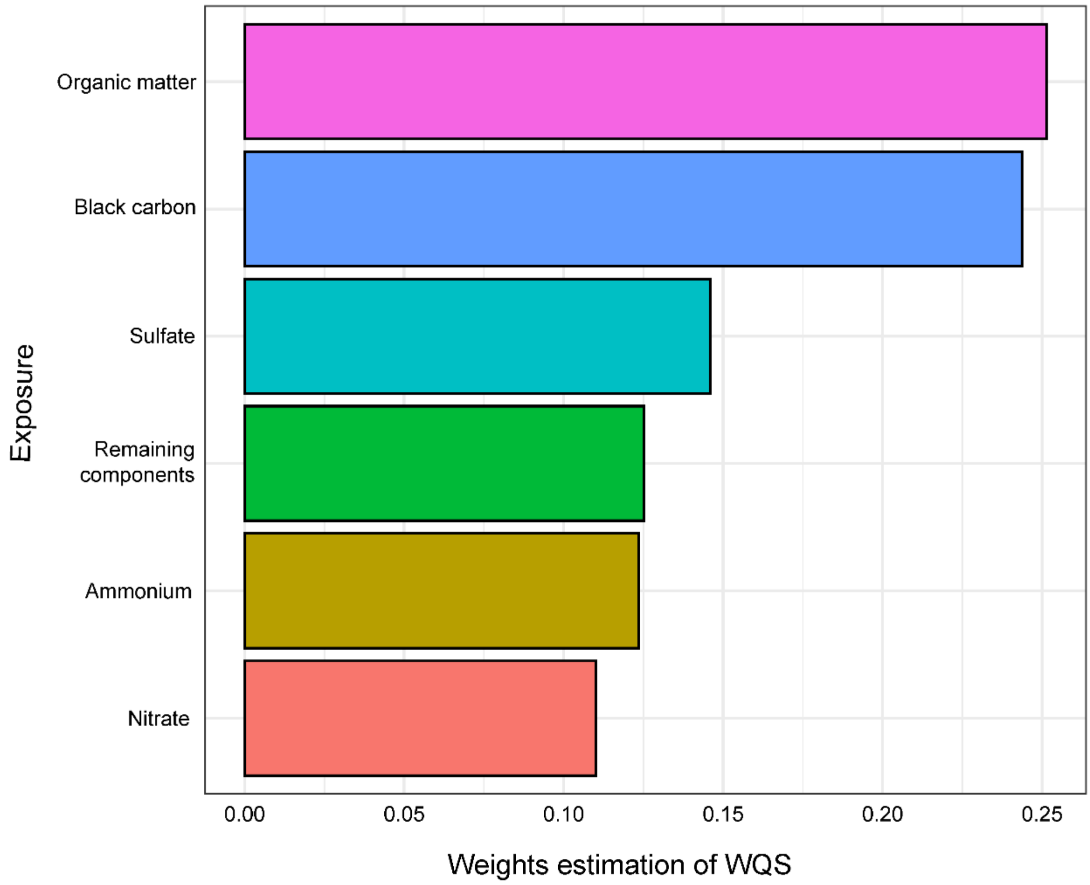


Supplementary Fig. 5. Exposure–response curves for the associations of $PM_{2.5}$ total mass and its chemical constituents with UA onset during lag 0 day. The solid lines represent the point estimates of percent change in the risk of UA onset, and the dashed lines indicate the corresponding 95% confidence intervals. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; UA, unstable angina.



Supplementary Fig. 6. The importance of $PM_{2.5}$ chemical constituents in the associations with ACS onset by using quantile-based g computation [a]. Each bar represents a specific component, with the bar length indicating its relative weight. The weight values are shown along the x-axis, while the components are listed on the y-axis. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; ACS, acute coronary syndrome.

[a] The positive and negative weights should not be compared with each other; the weights are only compatible with other weights in the same (i.e. positive or negative) direction.



Supplementary Fig. 7. The importance of $PM_{2.5}$ chemical constituents in the associations with ACS onset by including the remaining components. Each bar represents a specific component, with the bar length indicating its relative weight derived from the WQS regression. The weight values are shown along the x-axis, while the components are listed on the y-axis. Source data are provided as a Source Data file. Abbreviations: $PM_{2.5}$, fine particulate matter; ACS, acute coronary syndrome; WQS: weighted quantile sum.

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