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Long-term exposure to ambient fine particulate matter constituents and mortality from total and site-specific gastrointestinal cancer

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ABSTRACT

Background: Ambient fine particulate matter ($PM_{2.5}$) exposure has been associated with an increased risk of gastrointestinal cancer mortality, but the attributable constituents remain unclear.
Objectives: To investigate the association of long-term exposure to $PM_{2.5}$ constituents with total and site-specific gastrointestinal cancer mortality using a difference-in-differences approach in Jiangsu province, China during 2015–2020.
Methods: We split Jiangsu into 53 spatial units and computed their yearly death number of total gastrointestinal, esophagus, stomach, colorectum, liver, and pancreas cancer. Utilizing a high-quality grid dataset on $PM_{2.5}$ constituents, we estimated 10-year population-weighted exposure to black carbon (BC), organic carbon (OC), sulfate, nitrate, ammonium, and chloride in each spatial unit. The effect of constituents on gastrointestinal cancer mortality was assessed by controlling time trends, spatial differences, gross domestic product (GDP), and seasonal temperatures.
Results: Overall, 524,019 gastrointestinal cancer deaths were ascertained in 84.77 million population. Each interquartile range increment of BC (0.46 μg/m^3), OC (4.56 μg/m^3), and nitrate (1.41 μg/m^3) was significantly associated with a 27%, 26%, and 34% increased risk of total gastrointestinal cancer mortality, respectively, and these associations remained significant in $PM_{2.5}$-adjusted models and constituent-residual models. We also identified robust associations of BC, OC, and nitrate exposures with site-specific gastrointestinal cancer mortality. The mortality risk generally displayed increased trends across the total exposure range and rose steeper at higher levels. We did not identify robust associations for sulfate, ammonium, or chlorine exposure. Higher mortality risk ascribed to constituent exposures was identified in total gastrointestinal and liver cancer among women, stomach cancer among men, and total gastrointestinal and stomach cancer among low-GDP regions.
Conclusions: This study offers consistent evidence that long-term exposure to $PM_{2.5}$-bound BC, OC, and nitrate is associated with total and site-specific gastrointestinal cancer mortality, indicating that these constituents need to be controlled to mitigate the adverse effect of $PM_{2.5}$ on gastrointestinal cancer mortality.

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1. Introduction

Gastrointestinal (GI) cancer continues to be a major cause of mortality, which contributed to an estimated 3.6 million death cases and over one-third (36.5%) of total cancer-related deaths worldwide in 2020 (Chen et al., 2023). According to the Global Cancer Observatory (GLOBOCAN) 2020 estimates of cancer mortality, site-specific GI cancer accounted for five of the ten top cancer mortality causes, including cancer at colorectum, liver, stomach, esophagus, and pancreas, which resulted in 9.4%, 8.3%, 7.7%, 5.5%, and 4.7% of entire cancer death cases, respectively (Sung et al., 2021). As particulate matter (PM) has been identified as a widely influential environmental issue globally and classified as Group 1 carcinogen to human health, its effect on GI cancer has drawn much concern, especially fine particulate matter ($PM_{2.5}$) (Pritchett et al., 2022). Accumulating epidemiological studies have explored the association between $PM_{2.5}$ exposure and GI cancer and reported that long-term exposure to $PM_{2.5}$ can increase the mortality risk from total GI cancer and cancer in the GI tract and accessory organs, but the findings remain inconsistent (Guo et al., 2020; Pritchett et al., 2022). One underlying explanation is the discrepancy in the chemical composition of $PM_{2.5}$ among different study regions. Because the source, property, and toxicity of $PM_{2.5}$ constituents are various (Yang et al., 2019), their effects on GI cancer mortality are unlikely to be identical, which makes it difficult to yield consistent results on the health effect of $PM_{2.5}$ with different compositions. Therefore, it is of great importance to elucidate the effect of particular $PM_{2.5}$ constituent exposure on GI cancer mortality.

To date, the association of long-term exposure to $PM_{2.5}$ constituents with total and site-specific GI cancer mortality remains largely unknown (Pritchett et al., 2022), especially carbonaceous compounds and water-soluble inorganic ions (WSIIs), which form the majority of $PM_{2.5}$ mass and are suspected to be mainly responsible for the cancer-promoting effect of $PM_{2.5}$ (Lequy et al., 2021; So et al., 2021). Clarifying which constituents in $PM_{2.5}$ can detrimentally affect GI cancer mortality and to what extent can benefit in understanding the potential mechanism and offering evidence to build targeted guides on the management of $PM_{2.5}$-induced GI cancer mortality risk.

Here, we conducted a study among 84.77 million population with over 0.5 million GI cancer deaths in Jiangsu province, China during 2015–2020 to investigate the association of long-term exposure to $PM_{2.5}$ constituents with total and site-specific GI cancer mortality using a variant of the difference-in-differences approach. Stratified analyses on sex and socioeconomic status were performed to explore underlying susceptible populations.

2. Methods

2.1. Study region and population

Located in the eastern-central coastal district of China, Jiangsu province covers an area of 107,200 km^2. In 2020, it had a population of 84.77 million, which contributed to 6.0% of the gross population of China. In this study, Jiangsu was split into 53 spatial units based on the Chinese county-level administrative divisions. The spatial distribution of the average population number across the 53 spatial units during the study period is shown in Fig. S1.

A total of 524,183 individuals who died from GI cancer were identified in Jiangsu province during 2015–2020 from the Jiangsu provincial mortality surveillance system. We excluded cancer deaths aged below 20 because of the disparity in type, treatment, prognosis, and survival between adult cancers and cancers in children and adolescents (n = 164, 0.03%) (Yu et al., 2022a). Finally, 524,019 GI cancer deaths were included in our analysis. We collected the personal information of each decedent, including sex, date of birth and death, cause of death, and residential address. This study has obtained approval for research ethics from the Ethics Committee of the School of Public Health, Sun Yat-sen University with an exemption from informed consent.

2.2. Exposure assessment

We derived monthly grid data (spatial resolution: 0.01° × 0.01°, approximately 1 km × 1 km) on $PM_{2.5}$-bound black carbon (BC), organic carbon (OC), sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), and chlorine (Cl^-) from the ChinaHighAirPollutantes (CHAP, available at https://weijing-rs.github.io/product.html) database in Jiangsu province during 2006–2020. This $PM_{2.5}$ constituent dataset was generated by a deep-learning model, which integrated measurements from a high-density observation network, satellite $PM_{2.5}$ retrievals, atmospheric reanalyzes, and model simulations. Estimates of $PM_{2.5}$ constituents in this dataset agree well with ground-based measurements. The cross-validation coefficient of determination for daily BC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- concentrations were 0.82, 0.74, 0.75, 0.71, and 0.66, respectively. The root-mean-square error (RMSE) for BC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- were 1.6 μg/m^3, 6.0 μg/m^3, 6.6 μg/m^3, 4.3 μg/m^3, and 2.3 μg/m^3 (Wei et al., 2023a, 2023b). The grid data for OC was calculated by subtracting the concentration for BC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- from the $PM_{2.5}$ mass concentration in each grid cell. To offer a more precise exposure assessment, we considered the spatiotemporal distribution of population in the estimations of $PM_{2.5}$ constituent exposures. Yearly grid data for population distribution in Jiangsu during 2006–2020 was derived from the LandScan™ annual global population distribution datasets (https://landscan.ornl.gov/; spatial resolution: 30 arc-seconds, approximately 1 km near the equator) and was transformed to a spatial resolution of 0.01° × 0.01°. Utilizing $PM_{2.5}$ constituent and population distribution grid data, we computed the yearly mean population-weighted exposure to $PM_{2.5}$ constituent in each spatial unit based on the following formula.

$$PWE_{s,t} = \sum_{g=1}^{n}\left(P_{g,s,t} \times C_{g,s,t}\right) \Big/ \sum_{g=1}^{n} P_{g,s,t}$$

where:

- $PWE_{s,t}$ is the population-weighted exposure to each $PM_{2.5}$ constituent in spatial unit *s*, year *t*;
- $P_{g,s,t}$ refers to the population size in grid cell *g*, spatial unit *s*, year *t*;
- $C_{g,s,t}$ indicates the level of each $PM_{2.5}$ constituent in grid cell *g*, spatial unit *s*, year *t*;
- *n* denotes the overall number of grid cells in spatial unit *s*, year *t*.

To account for the accumulated effects of $PM_{2.5}$ constituent exposure on GI cancer mortality, we assessed constituent exposures for up to 10 years by averaging the population-weighted exposure in a year and its prior 9 years (Fan et al., 2023; Lequy et al., 2021). For example, long-term exposure to $PM_{2.5}$ constituents for a specific spatial unit in 2020 was estimated by the mean of population-weighted exposure during 2011–2020.

2.3. Outcomes

The underlying death cause of each decedent was coded by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). The outcomes of interest were mortality from GI cancer (ICD-10 codes: C15–C26) and its 5 main types, including esophagus cancer (C15), stomach cancer (C16), colorectum cancer (C18–C21), liver cancer (C22), and pancreas cancer (C25; more information on the outcomes is provided in Method S1). We summarized the yearly death number for total and site-specific GI cancer in each spatial unit.

2.4. Covariables

The yearly population size and gross domestic product (GDP) in each spatial unit were retrieved from the Jiangsu Statistical Yearbook 2016–2021. From the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0), we obtained daily grid data on 24-h average air temperature (unit: °C; spatial resolution: 0.0625° × 0.0625°) in Jiangsu during 2015–2020. Summer and winter mean temperatures for each year and each spatial unit were computed by averaging the daily temperature in summer (June, July, and August) and winter (December, January, and February) over total grid cells within each spatial unit, respectively. Standard deviations (SDs) of summer and winter temperatures were calculated to account for the underlying impact of temperature variation (Renzi et al., 2019; Yu et al., 2022a).

2.5. Statistical analyses

We evaluated the association of long-term exposure to $PM_{2.5}$ constituents with total and site-specific GI cancer mortality by a variant of the difference-in-differences approach. In brief, this causal methodology can assess the relationship between long-term air pollutant exposure and mortality by evaluating the associations of yearly changes in pollutant exposure with the contemporaneous changes in mortality rates in each spatial unit (more information on this approach is shown in Method S2) (Renzi et al., 2019; Wang et al., 2016). As previous studies suggested that socioeconomic status and temperatures would confound the associations (Han et al., 2021; Yu et al., 2022a, 2022b), we included GDP and seasonal temperatures as confounders and assumed that only these factors can confound the associations of $PM_{2.5}$ constituent exposures with total and site-specific GI cancer mortality. In addition, the difference-in-differences approach is subject to the parallel trend assumption (the introduction and examination of this assumption are present in Method S3 and Fig. S2). We used conditional Poisson regression models to evaluate the associations and fitted the following model.

$$\ln\left[\mathrm{E}\left(Y_{s,t}\right)\right] = \beta_0 + \beta_1 I_s + \beta_2 I_t + \beta_3 \mathrm{PWE}_{s,t} + \ln\left(\mathrm{P}_{s,t}\right) + \beta_4 \mathrm{GDP}_{s,t} + \beta_5 \mathrm{Ts}_{s,t} + \beta_6 \mathrm{Tw}_{s,t} + \beta_7 \mathrm{SD}\left(\mathrm{Ts}_{s,t}\right) + \beta_8 \mathrm{SD}\left(\mathrm{Tw}_{s,t}\right)$$

where:

- $Y_{s,t}$ refers to the number of cancer deaths in spatial unit *s,* year *t*;
- I_s and I_t are dummy variables for spatial unit *s* and year *t*, respectively;
- $\mathrm{PWE}_{s,t}$ represents the population-weighted exposure of a specific $PM_{2.5}$ constituent in spatial unit *s,* year *t*;
- $\ln(\mathrm{P}_{s,t})$ is an offset term indicating the natural log of the population in spatial unit *s,* year *t*;
- $\mathrm{GDP}_{s,t}$ denotes the GDP for spatial unit *s* and year *t*, which was categorized by its quintiles;
- $\mathrm{Ts}_{s,t}$, $\mathrm{Tw}_{s,t}$, SD ($\mathrm{Ts}_{s,t}$), and SD ($\mathrm{Tw}_{s,t}$) are the mean values of summer and winter temperatures and their SDs in spatial unit *s,* year *t*, respectively;
- β_0 is the intercept term;
- β_1 and β_2 indicate regression coefficients controlling spatial and temporal confounders, respectively;
- β_3 refers to the regression coefficient for the effect of $PM_{2.5}$ constituent exposure;
- β_4, β_5, β_6, β_7, and β_8 refer to regression coefficients for the effects of GDP, the summer and winter mean temperatures and their SDs, respectively.

Relative risk (RR) in total and site-specific GI cancer mortality and its 95% confidence interval (CI) associated with each interquartile range (IQR) increase of exposure to $PM_{2.5}$ constituent was estimated. We included each constituent exposure as a natural cubic spline function (degrees of freedom [*df*] = 3) in the model to draw the exposure-response curve, and further used a likelihood ratio test (LRT) to examine the possible nonlinearity by comparing with a model that treated the $PM_{2.5}$ constituent exposure as a continuous variable (Li et al., 2023; Xu et al., 2023).

To investigate possibly susceptible populations, we implemented stratified analyses by sex and GDP (classified by the median values of GDP among 53 spatial units in 2015) and examined their effect modification by 2-sample z-tests using the point estimate and standard error. The robustness of results was tested by several sensitivity analyses. First, we implemented the $PM_{2.5}$-adjusted model by further adding $PM_{2.5}$ mass exposures as a natural cubic spline function (*df* = 3) to the single-pollutant model, which can evaluate the effect of a particular constituent keeping other constituent constant (Huang et al., 2019; Mostofsky et al., 2012). Second, we performed the constituent-residual model by introducing a residual into the single-pollutant model to replace the constituent exposure, which can evaluate the effect of a particular constituent keeping $PM_{2.5}$ mass constant. The residual of each constituent was obtained from a linear regression model with a particular constituent as the dependent variable and $PM_{2.5}$ as the independent variable (Mostofsky et al., 2012). Third, we applied 9-year, 8-year, and 7-year exposure to $PM_{2.5}$ constituents in the models to verify the stability of the results. Fourth, we adjusted for annual mean temperature rather than summer and winter mean temperatures in the models. Fifth, we used a natural cubic spline function with 4 or 5 *df* to control $PM_{2.5}$ in the $PM_{2.5}$-adjusted models. All statistical analyses were accomplished by R (version 4.1.2). A two-tailed test with $P < 0.05$ was considered statistically significant.

3. Results

A total of 524,019 GI cancer deaths were identified from 84.77 million population in Jiangsu during 2015–2020 (Table 1). Of these death cases, 65.7% (n = 344,466) were men and 68.9% (n = 361,125) resided in high-GDP regions. The majority of deaths died from stomach cancer (27.9%), esophagus cancer (24.3%), and liver cancer (22.2%), while the number of colorectum cancer (12.4%) and pancreas cancer (9.0%) deaths was relatively small. The number of death cases of site-specific GI cancer was larger in men and in high-GDP regions (Table S1). Mean population-weighted exposure to BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- were 3.23 μg/m^3, 21.18 μg/m^3, 11.29 μg/m^3, 13.91 μg/m^3, 8.35 μg/m^3, and 2.31 μg/m^3, respectively. The range of $PM_{2.5}$ mass exposure was 40.21–81.61 μg/m^3, with a mean exposure of 60.27 μg/m^3. Fig. 1 shows the spatial distribution of average population-weighted exposure to $PM_{2.5}$ constituents and the average number of total and site-specific GI cancer deaths among 53 spatial units during 2015–2020. The temporal distribution and average annual change of $PM_{2.5}$ constituent exposures and cancer death numbers are presented in Figs. S3–S4. Yearly exposure to BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- presented declining trends from 2015 to 2020. Moderately to strongly positive correlations were identified between $PM_{2.5}$ mass exposure and each of BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- exposure, with pairwise Spearman's correlation coefficients of 0.86, 0.93, 0.97, 0.79, 0.75, and 0.64, respectively (all $P < 0.05$; Table S2).

Long-term exposure to BC and OC was significantly associated with an increased mortality risk of total GI, esophagus, stomach, colorectum, liver, and pancreas cancer in single-pollutant models (Table 2). The risk of total GI cancer mortality displayed a monotonically increasing trend with incremental exposure, and the slopes became larger at relatively high concentrations (*P* for nonlinear trend <0.05; Fig. 2); similar trends were found in associations of exposure to BC and OC with esophagus, stomach, colorectum, liver, and pancreas cancer mortality, while the exposure-response association of OC with colorectum and liver cancer mortality was linear (*P* for nonlinear trend = 0.107 and 0.338; Fig. S5). Results in $PM_{2.5}$-adjusted models and constituent-residual models were similar to those in single-pollutant models, but the estimates on the

Table 1
Characteristic of 53 spatial units in Jiangsu province, China, 2015–2020.

	Total	Mean	SD	Percentiles				
				P_5	P_{25}	P_{50}	P_{75}	P_{95}
Health data								
GI cancer death, n	524,019	1648	1182	554	876	1284	1754	3954
Esophagus cancer death, n	127,286	400	288	99	192	336	510	942
Stomach cancer death, n	146,401	460	380	131	220	358	516	1144
Colorectum cancer death, n	64,736	204	212	52	84	128	226	692
Liver cancer death, n	116,236	366	240	120	213	280	458	781
Pancreas cancer death, n	47,206	148	132	37	66	106	172	450
Demographic data								
Population size, million	84.77	1.53	1.43	0.50	0.80	0.98	1.62	3.96
Socioeconomic data								
GDP, 10^9, CNY	–	170.03	219.10	34.87	50.51	85.92	196.05	609.66
Environmental data								
BC, μg/m^3	–	3.23	0.41	2.64	2.97	3.20	3.43	3.97
OC, μg/m^3	–	21.18	3.61	15.86	18.68	20.95	23.24	28.38
SO_4^{2-}, μg/m^3	–	11.29	1.20	9.52	10.50	11.21	11.88	13.61
NO_3^-, μg/m^3	–	13.91	1.14	11.91	13.30	14.05	14.71	15.47
NH_4^+, μg/m^3	–	8.35	1.15	6.34	7.54	8.35	9.29	10.10
Cl^-, μg/m^3	–	2.31	0.37	1.75	2.08	2.28	2.48	3.07
$PM_{2.5}$ mass, μg/m^3	–	60.27	6.96	49.05	55.69	60.20	64.26	73.00
Mean of T_{summer}, °C	–	26.96	0.86	25.43	26.36	27.01	27.56	28.29
Mean of T_{winter}, °C	–	4.65	1.32	2.51	3.60	4.66	5.76	6.67
SD of T_{summer}, °C	–	0.20	0.11	0.07	0.12	0.18	0.25	0.41
SD of T_{winter}, °C	–	0.22	0.11	0.09	0.14	0.21	0.27	0.40

BC, black carbon; Cl^-, chloride; GDP, gross domestic product; GI, gastrointestinal; NH_4^+, ammonium; NO_3^-, nitrate; OC, organic carbon; $PM_{2.5}$, fine particulate matter; SD, standardized deviation; SO_4^{2-}, sulfate; T_{summer}, summer temperature; T_{winter}, winter temperature.

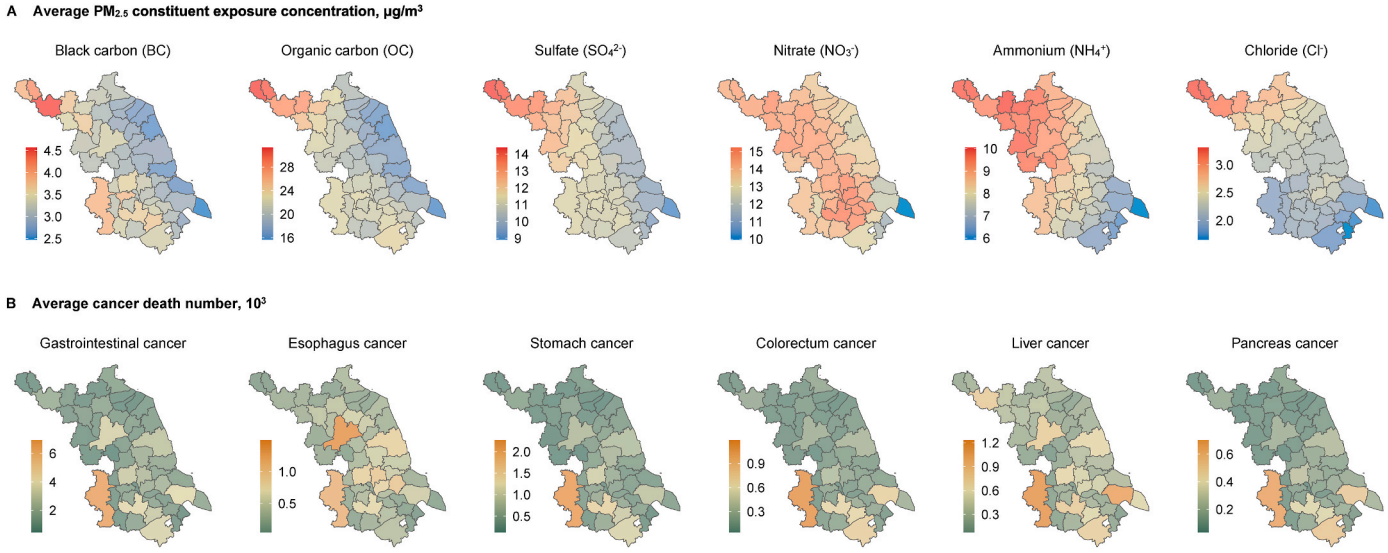

Fig. 1. Spatial distribution of average $PM_{2.5}$ constituent exposure concentrations (A) and average death number for total and site-specific GI cancer (B) across 53 spatial units in Jiangsu province, China, 2015–2020. Abbreviations as in Table 1.

association of BC with total GI and pancreas cancer mortality were significantly lower in constituent-residual models (P for difference <0.05; Table 2). Each IQR increase of BC exposure (0.46 μg/m^3) was significantly associated with a 27%, 31%, 37%, 56%, 13%, and 74% increased risk of total GI, esophagus, stomach, colorectum, liver, and pancreas cancer mortality, respectively. An IQR increment in OC exposure (4.56 μg/m^3) was significantly associated with a 26%, 33%, 33%, 40%, 10% and 76% increased risk of total GI, esophagus, stomach, colorectum, liver, and pancreas cancer mortality, respectively.

SO_4^{2-} exposure was significantly associated with an increased risk of total GI, stomach, colorectum, and pancreas cancer mortality in single-pollutant models (Table 2). The exposure-response association between SO_4^{2-} and total GI cancer showed a growing trend with a larger slope at higher exposures (P for nonlinear trend <0.05; Fig. 2) and similar curves were identified in stomach, colorectum, and pancreas cancer mortality (Fig. S6). However, the associations for total GI, stomach, colorectum, and pancreas cancer mortality turned to null or reversed in $PM_{2.5}$-adjusted models and constituent-residual models (all P for difference <0.05). As for NO_3^-, in single-pollutant models, significant associations were found in total GI, esophagus, stomach, colorectum, liver, and pancreas cancer mortality (Table 2); these associations displayed a growing risk and the risk rose steeper at higher levels (P for nonlinear trend <0.05) except that the association for pancreas cancer mortality was linear (P for nonlinear trend = 0.182; Fig. 2 and Fig. S6). We identified robust results for NO_3^- exposure in $PM_{2.5}$-adjusted models and constituent-residual models (all P for difference >0.05) except that the association for pancreas cancer mortality turned to null in the $PM_{2.5}$-adjusted model (P for difference <0.05). Each IQR increment of NO_3^-

Table 2
Estimated relative risk (95% CI) in total and site-specific GI cancer mortality associated with $PM_{2.5}$ constituent exposures.

	Single-pollutant model	$PM_{2.5}$-adjusted model		Constituent-residual model	
	Relative risk (95% CI)[a]	Relative risk (95% CI)[a]	P[b]	Relative risk (95% CI)[c]	P[b]
BC					
GI cancer	1.27 (1.22, 1.33)	1.15 (1.02, 1.31)	0.141	1.17 (1.10, 1.25)	0.034
Esophagus cancer	1.31 (1.18, 1.46)	1.21 (0.92, 1.60)	0.595	1.22 (1.06, 1.41)	0.408
Stomach cancer	1.37 (1.26, 1.49)	1.12 (0.88, 1.42)	0.115	1.24 (1.10, 1.41)	0.210
Colorectum cancer	1.56 (1.38, 1.77)	1.90 (1.33, 2.71)	0.310	1.63 (1.36, 1.96)	0.693
Liver cancer	1.13 (1.03, 1.25)	1.16 (0.92, 1.47)	0.864	1.13 (1.0002, 1.28)	0.976
Pancreas cancer	1.74 (1.49, 2.02)	1.32 (0.87, 2.02)	0.233	1.33 (1.07, 1.65)	0.047
OC					
GI cancer	1.26 (1.21, 1.32)	1.22 (0.98, 1.53)	0.789	1.22 (1.16, 1.28)	0.274
Esophagus cancer	1.33 (1.20, 1.48)	1.58 (0.97, 2.57)	0.505	1.33 (1.19, 1.48)	0.955
Stomach cancer	1.33 (1.23, 1.45)	1.11 (0.73, 1.70)	0.403	1.23 (1.12, 1.35)	0.202
Colorectum cancer	1.40 (1.25, 1.58)	0.86 (0.46, 1.61)	0.133	1.23 (1.07, 1.41)	0.150
Liver cancer	1.10 (1.004, 1.21)	1.26 (0.79, 2.00)	0.587	1.09 (0.98, 1.20)	0.839
Pancreas cancer	1.76 (1.52, 2.03)	1.75 (0.83, 3.71)	0.996	1.69 (1.43, 1.99)	0.729
SO_4^{2-}					
GI cancer	1.23 (1.15, 1.31)	0.73 (0.60, 0.87)	<0.001	0.90 (0.88, 0.92)	<0.001
Esophagus cancer	1.13 (0.97, 1.31)	0.39 (0.25, 0.60)	<0.001	0.84 (0.80, 0.88)	<0.001
Stomach cancer	1.49 (1.31, 1.69)	0.80 (0.57, 1.13)	0.001	0.91 (0.87, 0.95)	<0.001
Colorectum cancer	1.50 (1.26, 1.80)	0.81 (0.49, 1.34)	0.023	0.86 (0.81, 0.92)	<0.001
Liver cancer	1.01 (0.88, 1.15)	0.76 (0.52, 1.12)	0.183	0.94 (0.90, 0.98)	0.306
Pancreas cancer	1.65 (1.34, 2.04)	0.99 (0.54, 1.80)	0.114	0.76 (0.71, 0.82)	<0.001
NO_3^-					
GI cancer	1.34 (1.28, 1.40)	1.48 (1.27, 1.73)	0.219	1.44 (1.34, 1.55)	0.086
Esophagus cancer	1.43 (1.27, 1.61)	1.47 (1.06, 2.03)	0.882	1.54 (1.30, 1.83)	0.468
Stomach cancer	1.39 (1.27, 1.52)	1.59 (1.18, 2.15)	0.398	1.41 (1.23, 1.61)	0.887
Colorectum cancer	1.53 (1.34, 1.73)	1.31 (0.83, 2.06)	0.527	1.65 (1.37, 2.00)	0.500
Liver cancer	1.21 (1.09, 1.34)	1.49 (1.08, 2.05)	0.222	1.40 (1.21, 1.62)	0.102
Pancreas cancer	1.83 (1.57, 2.14)	0.76 (0.45, 1.29)	0.002	1.90 (1.52, 2.38)	0.798
NH_4^+					
GI cancer	1.58 (1.34, 1.86)	0.46 (0.34, 0.63)	<0.001	0.59 (0.54, 0.64)	<0.001
Esophagus cancer	1.60 (1.10, 2.34)	0.52 (0.28, 0.96)	0.002	0.56 (0.46, 0.68)	<0.001
Stomach cancer	2.24 (1.65, 3.06)	0.60 (0.34, 1.06)	<0.001	0.54 (0.46, 0.65)	<0.001
Colorectum cancer	2.88 (1.85, 4.50)	0.78 (0.32, 1.90)	0.010	0.48 (0.37, 0.61)	<0.001
Liver cancer	0.77 (0.54, 1.09)	0.23 (0.12, 0.43)	0.001	0.67 (0.55, 0.81)	0.475
Pancreas cancer	3.03 (1.76, 5.21)	0.16 (0.06, 0.45)	<0.001	0.28 (0.21, 0.37)	<0.001
Cl^-					
GI cancer	0.98 (0.92, 1.04)	0.76 (0.71, 0.82)	<0.001	0.73 (0.69, 0.78)	<0.001
Esophagus cancer	0.88 (0.75, 1.02)	0.63 (0.52, 0.77)	0.009	0.61 (0.53, 0.70)	0.001
Stomach cancer	1.08 (0.97, 1.22)	0.75 (0.65, 0.86)	<0.001	0.72 (0.65, 0.81)	<0.001
Colorectum cancer	1.24 (1.05, 1.45)	0.92 (0.76, 1.13)	0.027	0.78 (0.67, 0.90)	<0.001
Liver cancer	0.97 (0.86, 1.09)	0.86 (0.74, 1.01)	0.237	0.88 (0.79, 0.99)	0.250
Pancreas cancer	1.19 (0.98, 1.45)	0.87 (0.68, 1.12)	0.055	0.59 (0.49, 0.71)	<0.001

CI, confidence interval; IQR, interquartile range; other abbreviations as in Table 1.

[a] Relative risk (95% CI) is for per IQR increase in $PM_{2.5}$ constituent exposures. The IQR for exposure to BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- was 0.46 μg/m^3, 4.56 μg/m^3, 1.38 μg/m^3, 1.41 μg/m^3, 1.75 μg/m^3, and 0.40 μg/m^3, respectively.

[b] P value was used to test the difference between the $PM_{2.5}$-adjusted model or the constituent-residual model and the single-pollutant model, which was computed by 2-sample z-tests using the point estimate and standard error.

[c] Relative risk (95% CI) is for per IQR increase in $PM_{2.5}$ constituent residual. The IQR for the residual to BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- was 0.26 μg/m^3, 1.44 μg/m^3, 0.36 μg/m^3, 0.98 μg/m^3, 1.22 μg/m^3, and 0.39 μg/m^3, respectively.

exposure (1.41 μg/m^3) was significantly associated with a 34%, 43%, 39%, 53%, and 21% increased risk of total GI, esophagus, stomach, colorectum, and liver cancer mortality, respectively.

NH_4^+ exposure was significantly associated with total GI, esophagus, stomach, colorectum, and pancreas cancer mortality in single-pollutant models (Table 2). The total GI cancer mortality risk associated with NH_4^+ presented an increasing trend and rose steeper at higher levels (P for nonlinear trend <0.05; Fig. 2); the associations for esophagus, stomach, colorectum, and pancreas cancer mortality yielded similar trends (Fig. S7). However, these associations became null or reversed in $PM_{2.5}$-adjusted models and constituent-residual models (all P for difference <0.05). As for Cl^-, we found a significant association for colorectum cancer mortality in the single-pollutant model, but this association changed significantly in $PM_{2.5}$-adjusted models and constituent-residual models (both P for difference <0.05).

In stratified analyses, a significantly higher risk was observed for SO_4^{2-}, NO_3^-, and NH_4^+ exposure with total GI cancer mortality and SO_4^{2-} exposure with liver cancer mortality among women, while the association of OC exposure with stomach cancer mortality was significantly stronger in men (all P for effect modification <0.05;Table 3 and S3). Stronger associations were identified in low-GDP regions in OC exposure with GI cancer mortality and OC, SO_4^{2-}, and NH_4^+ exposure with stomach cancer mortality (all P for effect modification <0.05). Utilizing 9-year, 8-year, and 7-year exposure to $PM_{2.5}$ constituents in the models yielded generally similar results to the main analyses (Table S4). We found similar results when adjusting for the annual mean temperature, but the associations of BC and OC with liver cancer mortality turned insignificant (Table S5). Generally similar results were observed when using a natural cubic spline function with 4 or 5 *df* in the adjustment for $PM_{2.5}$ mass (Table S6).

4. Discussion

In this study in Jiangsu province, China during 2015–2020, we applied a variant of the difference-in-differences approach to assess the causal association of long-term exposure to $PM_{2.5}$ constituents with mortality from total and site-specific GI cancer. Overall, we found robust

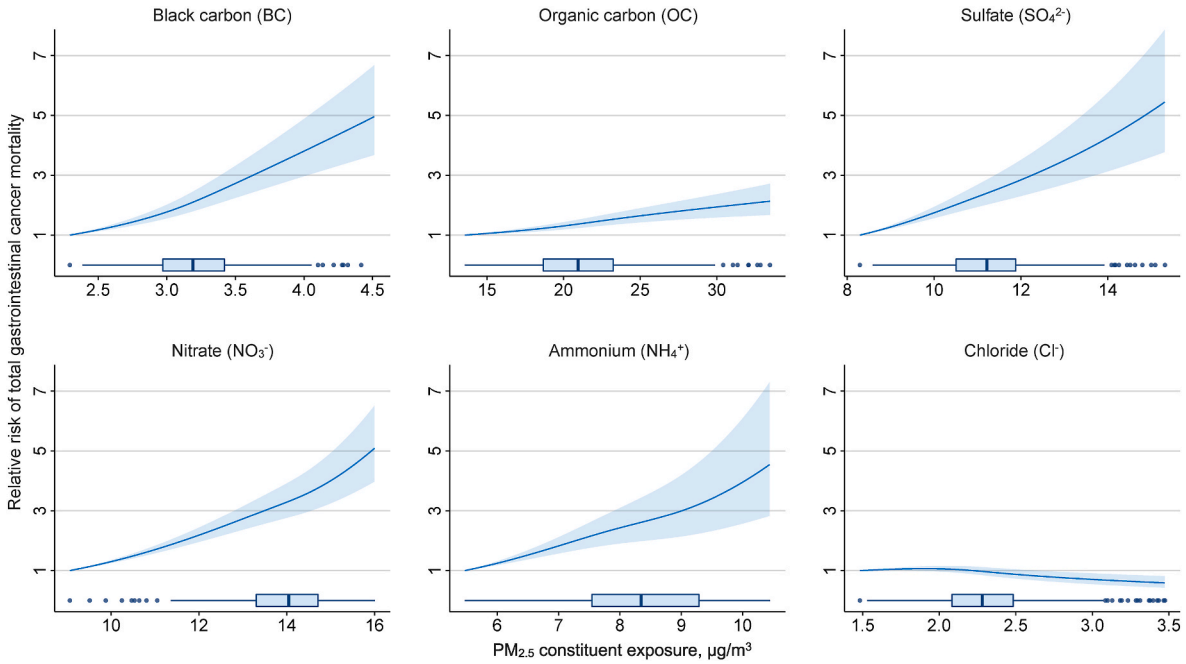

Fig. 2. Exposure-response associations of $PM_{2.5}$ constituent exposures with total GI cancer mortality. Abbreviations as in Table 1. All *P* values for the nonlinear trend were less than 0.05. The boxplot shows the distribution of $PM_{2.5}$ constituent exposures across 53 spatial units during 2015–2020.

associations of exposure to BC, OC, and NO_3^- with total and site-specific GI cancer mortality. Each IQR increase of BC, OC, and NO_3^- was significantly associated with a 27%, 26%, and 34% increased risk of total GI cancer mortality. These associations generally displayed an increased mortality risk across the total constituent exposures range and the risk rose steeper at higher exposure. Higher mortality risk ascribed to constituent exposures was identified in total GI and liver cancer among women, stomach cancer among men, and total GI and stomach cancer among low-GDP regions.

We identified the significant associations of long-term exposure to $PM_{2.5}$-bound BC, OC, and NO_3^- with mortality from total and site-specific GI cancer. These carbonaceous compounds and WSIIs constitute the bulk of $PM_{2.5}$, which mainly originates from combustion. BC is generally present in submicron particles emitted by incomplete burning of fossil fuel, biofuels, and biomass (Kirrane et al., 2019; Liu et al., 2021), while OC is largely produced from transportation, industrial emission, and biomass burning (Kirrane et al., 2019; Yang et al., 2019). NO_3^- is a secondary inorganic ion sourced from both anthropogenic combustion and nature (Yang et al., 2019). Given that BC, OC, and NO_3^- can exert an adverse effect on GI cancer mortality, abatement on exposure to these combustion-related constituents can be a targeted and feasible solution to reduce $PM_{2.5}$-induced GI cancer mortality and contribute to great health benefits to society. Nevertheless, to date, air quality standards on the content of toxic constituents bounding to PM are quite scarce, while most guidelines solely focus on the concentration of the whole PM. Our study adds evidence to the necessity to establish guidelines on the long-term level of specific constituents in PM. The quantitative data on the effect of long-term exposure to $PM_{2.5}$ constituents on total and site-specific GI cancer mortality in our study would be informative to the formulation of air quality standards on $PM_{2.5}$ constituents. Moreover, our study highlights the significance for policymakers and implementers to take effective measures to reduce the emission of combustion-related constituents, such as improving burning efficiency or encouraging the application of clean energy.

This is the first study to investigate the causal effect of long-term exposure to $PM_{2.5}$ constituents on total and site-specific GI cancer mortality. Previous studies regarding $PM_{2.5}$ constituents and cancer primarily focused on all sites of the body and respiratory system but were rarely specifically concerned about the digestive system (Kim et al., 2015; Lequy et al., 2021; Nilsson Sommar et al., 2021). In 2018, a cohort study in 6 European countries investigated the effect of elemental components in $PM_{2.5}$ on stomach cancer incidence and found a significant association for sulphur (Weinmayr et al., 2018). Another cohort study in Europe in 2021 reported a significant association between annual mean BC exposure and liver cancer incidence (So et al., 2021). In this study, we offered new evidence that long-term exposure to BC, OC, and NO_3^- can increase the risk of total and site-specific GI cancer mortality. Although evidence regarding the association of these constituent exposures with GI cancer mortality is limited, they are of great interest from a public health perspective as substantial studies suggest a deleterious effect of combustion-related air pollution on various health outcomes (Hwa Jung et al., 2022; Wang et al., 2022; Zhou et al., 2022). The null associations of SO_4^{2-}, NH_4^+ and Cl^- exposure with total and site-specific GI cancer mortality in our study was in line with many experimental and epidemiological studies that reported little or null adverse health impact of exposure to these constituents at atmospheric levels (Cai et al., 2023; Fang et al., 2022; Krall et al., 2013; Lin et al., 2016; Pang et al., 2020; Tang et al., 2021). Our findings on the exposure-response relationship generally displayed an increasing trend with the risk rising steeper at a relatively high level, which was similar to the nonlinear curves of $PM_{2.5}$ mass exposure with GI, stomach, colorectum, and pancreas cancer mortality in our previous publication (Fan et al., 2023). An explanation is that the potentially synergistic interaction between $PM_{2.5}$ constituent exposure and some factors (e.g., socioeconomic disparity) may magnify the GI cancer mortality risk at relatively high exposures (Fan et al., 2023; Han et al., 2021).

The biological mechanisms of the association between $PM_{2.5}$ constituents and GI cancer mortality remain less clear. Inhale $PM_{2.5}$ can be swallowed or cleared from the lung by mucociliary transport to directly gain access to the GI tract. $PM_{2.5}$ that entered into the lower airways can be sequestered and engulfed by macrophagocytes and adsorbed in the mucus layer, which would be returned to the oropharynx and further swallowed into the GI tract (Mutlu et al., 2018; Salim et al., 2014). Moreover, $PM_{2.5}$ constituents that pass through the alveolar-capillary barrier can arrive at the digestive system by circulation. The constituents in $PM_{2.5}$ may boost the generation of reactive oxygen species and

Table 3
Estimated relative risk (95% CI) of total and site-specific GI cancer mortality associated with each IQR increase in $PM_{2.5}$ constituent exposure stratified by sex and GDP.

	Sex			GDP		
	Male	Female	P^a	Low	High	P^a
BC						
GI cancer	1.24 (1.17, 1.31)	1.35 (1.25, 1.46)	0.064	1.08 (0.92, 1.26)	0.95 (0.87, 1.04)	0.157
Stomach cancer	1.44 (1.30, 1.60)	1.22 (1.04, 1.42)	0.077	1.32 (0.99, 1.75)	1.00 (0.84, 1.18)	0.090
Liver cancer	1.08 (0.96, 1.21)	1.30 (1.09, 1.56)	0.078	0.87 (0.62, 1.24)	0.94 (0.79, 1.12)	0.718
OC						
GI cancer	1.23 (1.17, 1.30)	1.32 (1.23, 1.43)	0.134	1.26 (1.07, 1.47)	0.94 (0.87, 1.02)	0.001
Stomach cancer	1.44 (1.31, 1.59)	1.12 (0.96, 1.30)	0.006	1.82 (1.37, 2.41)	0.88 (0.75, 1.03)	<0.001
Liver cancer	1.05 (0.94, 1.18)	1.26 (1.06, 1.50)	0.081	0.93 (0.66, 1.31)	0.89 (0.75, 1.05)	0.824
SO_4^{2-}						
GI cancer	1.16 (1.07, 1.26)	1.36 (1.22, 1.53)	0.021	1.07 (0.94, 1.22)	0.92 (0.84, 1.01)	0.068
Stomach cancer	1.54 (1.32, 1.79)	1.39 (1.10, 1.74)	0.456	1.80 (1.39, 2.33)	0.98 (0.82, 1.17)	<0.001
Liver cancer	0.90 (0.77, 1.06)	1.33 (1.04, 1.70)	0.010	0.92 (0.72, 1.17)	0.86 (0.71, 1.03)	0.643
NO_3^-						
GI cancer	1.29 (1.22, 1.37)	1.43 (1.32, 1.55)	0.049	1.17 (0.97, 1.42)	1.12 (1.05, 1.20)	0.697
Stomach cancer	1.46 (1.31, 1.63)	1.26 (1.07, 1.48)	0.137	1.33 (0.92, 1.94)	1.11 (0.98, 1.27)	0.372
Liver cancer	1.15 (1.01, 1.30)	1.39 (1.16, 1.67)	0.091	0.97 (0.66, 1.44)	1.09 (0.94, 1.26)	0.593
NH_4^+						
GI cancer	1.36 (1.11, 1.66)	2.11 (1.59, 2.81)	0.013	0.63 (0.39, 1.004)	0.96 (0.76, 1.22)	0.110
Stomach cancer	2.30 (1.58, 3.34)	2.19 (1.25, 3.84)	0.887	3.25 (1.30, 8.08)	1.03 (0.66, 1.61)	0.027
Liver cancer	0.63 (0.42, 0.96)	1.30 (0.68, 2.47)	0.067	0.19 (0.08, 0.47)	0.62 (0.38, 1.02)	0.025
Cl^-						
GI cancer	0.95 (0.89, 1.03)	1.02 (0.92, 1.14)	0.284	0.44 (0.35, 0.55)	0.94 (0.88, 1.01)	<0.001
Stomach cancer	1.06 (0.93, 1.22)	1.15 (0.93, 1.42)	0.559	0.65 (0.41, 1.01)	1.03 (0.91, 1.17)	0.048
Liver cancer	0.94 (0.82, 1.08)	1.04 (0.83, 1.31)	0.441	0.52 (0.34, 0.79)	0.97 (0.85, 1.10)	0.005

CI, confidence interval; IQR, interquartile range; other abbreviations as in Table 1.

The IQR for exposure to BC, OC, SO_4^{2-}, NO_3^-, NH_4^+, and Cl^- was 0.46 μg/m^3, 4.56 μg/m^3, 1.38 μg/m^3, 1.41 μg/m^3, 1.75 μg/m^3, and 0.40 μg/m^3, respectively. Results for stratified analyses on the esophagus, colorectum, and pancreas cancer mortality are displayed in Table S3.

[a] *P* value for effect modification.

pro-inflammatory oxidative lipids and affect the composition of the GI microbiome, which may accelerate the progression in GI cancer patients (Aslam and Roeffaers, 2022; Feng et al., 2020; Mutlu et al., 2018; Zhang et al., 2019, 2022). More evidence is needed to clarify the biological mechanisms.

Modeling constituent exposure alone is a common method to explore the association between constituent exposure and outcome of interest, but it may produce bias because $PM_{2.5}$ may confound the associations. The strong associations of specific constituents with health outcomes were probably ascribed to its strong correlation with $PM_{2.5}$ but were less likely to hinge on its intrinsic toxicity (Huang et al., 2019; Mostofsky et al., 2012). Given this, we introduced the $PM_{2.5}$-adjusted models and constituent-residual models to evaluate the associations between $PM_{2.5}$ constituent exposure and GI cancer mortality (Mostofsky et al., 2012). The $PM_{2.5}$-adjusted models evaluated the effect of higher levels of a particular constituent when holding the other constituent constant. However, because $PM_{2.5}$ often strongly correlates with its constituent, simultaneously including them in a regression model may lead to unstable estimates with big variances. To separate the effect of a constituent from that of $PM_{2.5}$, we employed constituent-residual models, which can provide an estimation of the risk associated with higher levels of a particular constituent when keeping the constancy on $PM_{2.5}$. For example, when including residuals from regressing NH_4^+ on $PM_{2.5}$ in the models, higher levels of NH_4^+ and its correlates and lower levels of other constituents that did not correlate with NH_4^+ composed the overall $PM_{2.5}$, and thus $PM_{2.5}$ and constituents that coexist with NH_4^+ were controlled (Lequy et al., 2021). In our analysis, we observed that some significant associations reversed in constituent-residual models, especially SO_4^{2-} and NH_4^+, which suggested that these associations may be confounded by $PM_{2.5}$ or by co-occurring constituents. For SO_4^{2-}, its high correlation with $PM_{2.5}$ exposure (the correlation coefficient: 0.97) may account for its significant associations in single-pollutant models. For NH_4^+, as it often coexists with NO_3^- in the form of NH_4NO_3 (Yang et al., 2020), its significant associations in single-pollutant models may primarily ascribe to its strong correlation with NO_3^-. Since the results from single-pollutant models, $PM_{2.5}$-adjusted models, and constituent-residual models have different interpretations, robust associations among these models should be more reliable and convincing.

This study has several strengths. First, we utilized death registration data covering approximately 84.77 million population with over 0.5 million GI cancer deaths in 6 continuous years, which had a great representativeness to the entire population and offered us a unique opportunity to explore the effect of $PM_{2.5}$ constituent exposures on mortality from various site-specific GI cancers with sufficient power. Second, taking advantage of the validated grid $PM_{2.5}$ constituent dataset with a high spatial resolution, we assessed exposure to carbonaceous compounds and 4 main WSIIs in $PM_{2.5}$, which are major constituents of $PM_{2.5}$ and form the bulk of the entire $PM_{2.5}$ mass. Moreover, evaluating exposure to $PM_{2.5}$ constituents for up to a 10-year period enabled us to provide novel evidence on the lag effect of $PM_{2.5}$ constituent exposures on GI cancer mortality. Third, the difference-in-differences approach can eliminate most confounding by design and allowed us to investigate the causal relationship between $PM_{2.5}$ constituent exposures and GI cancer mortality, which was relatively difficult to accomplish in most cohort studies because of the residual confounding caused by unmeasured or mismeasured confounders.

Despite these strengths, our study should be interpreted considering some limitations. First, as we only adjusted for GDP and seasonal temperatures as confounders, other factors that linked to $PM_{2.5}$ constituent exposures and changed by both time and spatial units were not ruled out, such as unemployment rates and alcohol and cigarette consumption rates. Second, although the application of dummy variables can provide strong control for time trends and spatial confounding, it drastically reduced the distinction of $PM_{2.5}$ constituent exposures across spatial units over time and further weakened statistical power. Third, exposure misclassification may exist as we allotted the same $PM_{2.5}$ constituent

exposures to all people within a spatial unit. Nevertheless, its bias would be migrated as we evaluated population-weighted exposure to $PM_{2.5}$ constituents by assigning proportionately larger weight to constituent concentrations in areas that more people resided in, which offered a relatively refined assessment of constituent exposures in contrast with studies without accounting for population distribution.

5. Conclusions

In summary, we found a causal association of long-term exposure to $PM_{2.5}$-bound BC, OC, and NO_3^- with mortality from total and site-specific GI cancer, which suggests that these constituents may bear responsibility for the carcinogenic and cancer-promoting effects of $PM_{2.5}$ on total and site-specific GI cancer and expedite GI cancer mortality. Our study highlights the necessity to formulate guidelines on specific $PM_{2.5}$ constituents and adopt valid methods to curb the emission of toxic constituents.

CRediT authorship contribution statement

Yingxin Li: Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft. **Zhimin He:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Jing Wei:** Data curation, Methodology, Writing – review & editing. **Ruijun Xu:** Writing – review & editing. **Tingting Liu:** Writing – review & editing. **Zihua Zhong:** Writing – review & editing. **Likun Liu:** Writing – review & editing. **Sihan Liang:** Writing – review & editing. **Yi Zheng:** Writing – review & editing. **Gongbo Chen:** Writing – review & editing. **Ziquan Lv:** Writing – review & editing. **Suli Huang:** Writing – review & editing. **Xi Chen:** Writing – review & editing. **Hong Sun:** Conceptualization, Data curation, Methodology, Resources, Validation, Writing – review & editing. **Yuewei Liu:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117927.

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