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Long-term exposure to fine particulate matter and site-specific cancer mortality: A difference-in-differences analysis in Jiangsu province, China

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ABSTRACT

Background: Accumulating studies have reported that chronic exposure to ambient fine particulate matter ($PM_{2.5}$) can lead to adverse effects on lung cancer mortality; however, such chronic effects are less clear for mortality from other site-specific cancers.
Objective: To explore the causal effect of long-term $PM_{2.5}$ exposure on mortality from all-site and a variety of site-specific cancers in Jiangsu province, China during 2015–2020 using a difference-in-differences analysis.
Methods: For each of 53 county-based spatial units in Jiangsu province, we calculated annual death counts for all-site cancer and 23 site-specific cancers. Using a validated high-resolution $PM_{2.5}$ grid dataset, long-term $PM_{2.5}$ exposure of a spatial unit within a given year was evaluated as the average of population-weighted annual concentrations during recent 10 years. Conditional Poisson regression models were employed to evaluate exposure-response associations adjusting for spatial and temporal variables, seasonal temperatures, relative humidity, and gross domestic product (GDP).
Results: During the study period, we identified 947,337 adult cancer deaths in Jiangsu province. Each 1 μg/m^3 increment in $PM_{2.5}$ exposure was significantly associated with a 2.7% increase in the risk of all-site cancer mortality. $PM_{2.5}$-mortality associations were also observed in cancer of lip, oral cavity and pharynx, stomach, colorectum, pancreas, lung, bone and joints, ovary, prostate, and lymphoma (all adjusted $P < 0.05$), with the relative risks ranging from 1.028 (95% confidence interval [CI]: 1.011, 1.046) for stomach cancer to 1.201 (95% CI: 1.120, 1.308) for bone and joints cancers. Exposure-response curves showed that these associations were close to linearity, though most of them had increasing slopes at high exposure levels. Overall, women and subjects in low GDP regions were more vulnerable to $PM_{2.5}$ exposures.
Conclusions: Long-term exposure to ambient $PM_{2.5}$ contributes to a higher risk of mortality from multiple site-specific cancers.

1. Introduction

Ambient fine particulate matter ($PM_{2.5}$) continues to be a major environmental issue, which has raised critical public health concerns worldwide (GBD, 2020). It is estimated that 99% of the entire global population breathes unhealthy air exceeding the concentration limits of the updated World Health Organization (WHO) Air Quality Guidelines (annual average $PM_{2.5}$: 5 μg/m^3) in 2022 (WHO, 2022; WHO, 2021).

Abbreviations: $PM_{2.5}$, fine particulate matter; RR, relative risk; CI, confidence interval; GDP, gross domestic product.

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Extensive evidence suggests that ambient $PM_{2.5}$ exposure is detrimental to human health by increasing morbidity and mortality from a number of diseases including cancer (Lelieveld et al., 2015; Turner et al., 2020). In 2020, cancer caused 9.96 million deaths and was ranked as the second primary cause of death globally (Sung et al., 2021). Considering that most cancers are attributable to genetic and environmental interactions (Mbemi et al., 2020), it is of great necessity to estimate the cancer mortality associated with $PM_{2.5}$ exposure. Accumulating epidemiological studies have found chronic detrimental effects of $PM_{2.5}$ exposure on mortality from all-site cancer and lung cancer (Chen and Hoek, 2020; Chen et al., 2021; Ciabattini et al., 2021; Coleman et al., 2020b; Pope et al., 2020; Turner et al., 2020; Wang et al., 2020a; Wong et al., 2016). The Global Burden of Disease (GBD) Study 2019 estimated that 308,000 lung cancer deaths were attributable to $PM_{2.5}$ exposure worldwide, including 171,300 deaths in China (GBD, 2020).

While most studies explored the association of long-term exposure to $PM_{2.5}$ with mortality from all-site cancer or lung cancer, the chronic effects of $PM_{2.5}$ exposure on mortality from other site-specific cancers remain less clear. Only a small number of studies provided epidemiological evidence on the associations of long-term $PM_{2.5}$ exposure with mortality from cancer of stomach, colorectum, liver, pancreas, breast, ovary, bladder, kidney, and leukemia (Coleman et al., 2020b; Guo et al., 2020; Guo et al., 2021; Hung et al., 2012; Turner et al., 2017; Wang et al., 2019; Wang et al., 2018; Wong et al., 2016; Yeh et al., 2017; Yu et al., 2022a–c), and the results are mixed. Note that some of these studies are limited by a small sample size, less accurate exposure assessment, and/or narrow range of exposure level, which can introduce great heterogeneity and make it difficult in comparing the results across studies or across different cancers. Given the high disease burden of a series of site-specific cancers, it is of great importance to systematically quantify the association of long-term $PM_{2.5}$ exposure with the risk of mortality from site-specific cancers in a single study.

Here, we performed a validated difference-in-differences (DID) analysis to assess the causal effect of long-term $PM_{2.5}$ exposure on multiple cancer mortality, utilizing large-scale and population-based mortality surveillance data in Jiangsu province, China during 2015–2020. We aimed to quantitatively evaluate the association of long-term ambient $PM_{2.5}$ exposure with mortality from all-site and a variety of site-specific cancers. Population vulnerability was further investigated by demographic characteristic and socioeconomic status (SES).

2. Materials and methods

2.1. Study area and population

Our study was conducted in Jiangsu province, which is a coastal province in East China with a total area of 107,200 square kilometers. Jiangsu is one of the leading provinces in finance, education, technology, and tourism in China. As a densely populated province, Jiangsu had a population of 84.7 million in 2020, contributing 6.0% of the national population in China. In this analysis, we divided Jiangsu province into 53 spatial units according to China's county-level administrative divisions (Table S1).

We identified 947,337 cancer deaths aged over 20 years who lived in Jiangsu province and died from cancer between 2015 and 2020 from the mortality surveillance system of Jiangsu province. This system was managed by the Jiangsu Provincial Center for Disease Control and Prevention and was implemented to routinely monitor causes of death among the general population of Jiangsu province. We collected information for each death on sex, date of birth, date of death, residential address, and underlying cause of death coded by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Based on the residential address, we aggregated annual death counts for all-site and site-specific cancers by spatial unit and calendar year during our study period.

2.2. Exposure assessment

Based on the ChinaHigh$PM_{2.5}$ data from the ChinaHighAirPollutants (CHAP; available at https://weijing-rs.github.io/product.html) datasets, we extracted annual average $PM_{2.5}$ grid data with the spatial resolution of 0.01° in Jiangsu province between 2006 and 2020. The CHAP datasets were generated by hybrid machine-learning prediction models integrating ground measurement data, satellite remote sensing products, and atmospheric reanalysis data (Wei et al., 2020; Wei et al., 2021). The cross-validation coefficient of determination (CV-R^2) value of the annual average $PM_{2.5}$ grid data was 0.94, which has been validated and used in our published studies (Li et al., 2022; Liu et al., 2021; Wang et al., 2021). Annual grid data (spatial resolution: 30 arc seconds, equates to about 1 km at 0° latitude) on population distribution in Jiangsu province during 2006–2020 were obtained from Landscan Global grid datasets (available at https://landscan.ornl.gov/). We used a 2-stage approach to evaluate long-term $PM_{2.5}$ exposure. First, we calculated the population-weighted annual average $PM_{2.5}$ concentrations for each spatial unit using the sum of the product between the grid population weight and the grid $PM_{2.5}$ concentration within each spatial unit's geographical boundary. The population weight was defined as the percentage of the population in each grid accounting for the total population of all grids within each spatial unit's geographical boundary. Second, considering the potential lag impacts of $PM_{2.5}$ exposure on cancer death, which generally referred to the elapsed duration between exposure to cancer-causing substances (e.g., $PM_{2.5}$) and the occurrence of cancer death, we set the exposure lag period to 10 years based on the lowest Bayesian Information Criterion (BIC). We extracted the population-weighted $PM_{2.5}$ exposures of each spatial unit in the past 9 years before 2015–2020 and assessed the long-term exposure to $PM_{2.5}$ in a given year during the study period by averaging the annual concentrations in the current year and the preceding 9 years. For example, long-term exposure to $PM_{2.5}$ in the year 2015 was estimated by averaging population-weighted exposures from 2006 to 2015.

2.3. Outcomes

The study outcomes were mortality from all-site cancer (ICD-10 codes: C00–C97) and 23 site-specific cancers, including cancer of lip, oral cavity and pharynx (C00–C14), nasopharynx (C11), digestive system (C15–C26), esophagus (C15), stomach (C16), colorectum (C18–C21), liver (C22), pancreas (C25), respiratory system (C30–C39), lung (C33–C34), bone and joints (C40–C41), breast (C50), female genital system (C51–C58), cervix (C53), ovary (C56), male genital system (C60–C63), prostate (C61), urinary system (C64–C68), kidney (C64–C65), bladder (C67), brain (C71), lymphoma (C81–C85), and leukemia (C91–C95).

2.4. Covariates

To control potential confounding biases induced by meteorological factors (Gasparrini et al., 2015; Renzi et al., 2019; Wang et al., 2016; Yu et al., 2022a), we adopted 24-h average grid data (temporal resolution: daily; spatial resolution: 0.0625° × 0.0625°) on air temperature (°C) and relative humidity (%) in Jiangsu province during 2015–2020 from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0), which was generated and routinely updated by the China National Meteorological Information Center (Liu et al., 2020). After converting the meteorological grid data to those with the spatial resolution of 0.01°, annual average temperatures in summer (June, July, and August) and winter (January, February, and December) and annual mean relative humidity were calculated by averaging values of all grids within each spatial unit's geographical boundary during 2015–2020. Information on population size and gross domestic product (GDP) in each spatial unit by year was extracted from the Jiangsu Statistical Yearbook 2016–2021.

2.5. Statistical analysis

We applied a DID design with multiple periods and spatial units to examine the causal effect of long-term $PM_{2.5}$ exposure on mortality from all-site and site-specific cancers (Wang et al., 2016). As a causal modeling approach, the DID analysis examined the effects of $PM_{2.5}$ exposure on health outcomes by evaluating the relevance of differences in $PM_{2.5}$ exposure with differences in the study outcome in each spatial unit over time, and has been widely applied to explore the causal effects of long-term ambient pollutant exposures on various health outcomes (Leogrande et al., 2019; Renzi et al., 2019; Wang et al., 2016; Yitshak-Sade et al., 2019; Yu et al., 2020). Because the population in a given spatial unit was compared to itself over different periods, unmeasured confounders that rarely changed over time or kept constant during the study period were naturally controlled; however, factors that were correlated with the temporal exposures and varied differently across spatial units over time still needed to be adjusted. As proposed in previous studies (Renzi et al., 2019; Wang et al., 2016; Yu et al., 2022a,c; Yu et al., 2020), we considered seasonal temperatures, relative humidity, and GDP as potential spatiotemporal confounders and fitted a conditional Poisson regression model to qualify the causal and long-term association between $PM_{2.5}$ exposure and cancer mortality:

$$\ln\left[E\left(Y_{c,t}\right)\right]=\beta_0+\beta_1 PM_{2.5\,c,t}+\beta_2 I_c+\beta_3 I_t+ns(\beta_4 Temp_{sum\,c,t})+ns(\beta_5 Temp_{win\,c,t}) +ns\left(\beta_6 RH_{c,t}\right)+\beta_7 GDP_{c,t}+offset\left(\log\left(Pop_{c,t}\right)\right) \quad (1)$$

where $Y_{c,t}$ means the expected amount of cancer deaths in spatial unit c and year t; $PM_{2.5c,t}$ denotes the population-weighted $PM_{2.5}$ exposure in spatial unit c and year t; I_c refers to a dummy variable for each of the 53 spaces in Jiangsu province, which was adjusted by the *eliminate* argument of the model; I_t defines a dummy variable for each calendar year during 2015–2020; $ct\ Temp_{sum\,c,t}$, $Temp_{win\,c,t}$ and $RH_{c,t}$ represent the average temperatures in summer and winter and the average relative humidity in spatial unit c and year t, respectively, all of which are modeled as natural cubic spline function (function *ns*) with 3 degrees of freedom (*df*) to consider the possible nonlinear associations of temperature and relative humidity with mortality; $GDP_{c,t}$ indicates the value of GDP in spatial unit c and year t; $\log(Pop_{c,t})$ represents the natural logarithm of annual population size in spatial unit c and year t, which was adjusted as the offset term in the model; β_0 is the intercept term; $\beta_1$represents the regression coefficient for the chronic effect of $PM_{2.5}$ exposure on a variety of site-specific cancer mortality; β_2 and β_3 are regression coefficients adjusting for spatial and temporal variables of I_c and I_t, respectively; β_4 to β_7 are regression coefficients for mean summer temperature, mean winter temperature, mean relative humidity, and GDP, respectively.

As proposed previously (Wang et al., 2016; Yitshak-Sade et al., 2019), the DID approach had two presupposed assumptions. The first assumption was the parallel trend assumption, which means that all spatial units should have common trends of cancer mortality. If $PM_{2.5}$ levels do not fluctuate over time under the counterfactual framework, the differences in cancer mortality across spatial units should remain stable over time as well. While, in the actual $PM_{2.5}$ exposure settings, it is allowed that the trends of cancer deaths across spatial units vary over time because other factors influencing mortality may exist. Therefore, as long as the differences in cancer deaths over time by spatial units were not correlated with these in $PM_{2.5}$, the parallel trend assumption would hold. Since we were unable to observe the counterfactual hypothesis and no statistical method was available to examine this assumption, we used the relative change rate ($RC_{c,t}$) to assess and visualize the corresponding fluctuations of differences in $PM_{2.5}$ and the number of cancer deaths across each spatial unit between 2015 and 2020 (Fig. S1) (Hu et al., 2022; Yu et al., 2020).

$$E_c=\frac{\sum_{t=2015}^{t=2020}R_{c,t}}{6} \quad (2)$$

$$RC_{c,t}=\frac{R_{c,t}-E_c}{E_c}\times 100\% \quad (3)$$

where $R_{c,t}$ represents population-weighted $PM_{2.5}$ exposures or cancer deaths in spatial unit c and year t; E_c is the mean of $PM_{2.5}$ or cancer deaths in spatial unit c during 2015–2020; $RC_{c,t}$ is the relative change of $PM_{2.5}$ or cancer deaths in spatial unit c and year t. Second, we assumed that no spatiotemporal factors other than seasonal temperatures and GDP have confounded the association between $PM_{2.5}$ exposure and cancer mortality.

Using the conditional Poisson regression model established in the previous section, we estimated relative risks (RRs) and corresponding 95% confidence intervals (95% CIs) of mortality from all-site and site-specific cancers associated with per 1 μg/m^3 increment in $PM_{2.5}$ exposure. To plot exposure-response curves of $PM_{2.5}$ with cancer mortality, we fitted $PM_{2.5}$ exposure using natural cubic spline function with 3 degrees of freedom in our model and further checked the nonlinearity using likelihood ratio tests. All P values from multiple testing were adjusted using the false discovery rete (FDR) method (Benjamini and Hochberg, 1995; Coleman et al., 2020a).

We performed stratified analyses by sex and GDP (categorized by the median of GDP values across 53 spatial units in 2015). The two-sample z test was applied to detect the effect modification by stratification variables (Altman and Bland, 2003):

$$z=\frac{\beta_1-\beta_2}{\sqrt{(SE_1)^2+(SE_2)^2}} \quad (4)$$

where β_1 and β_2 represent the regression coefficients of $PM_{2.5}$ extracted from the conditional Poisson regression models in each stratum; SE_1 and SE_2 are the corresponding standard errors.

Several sensitivity analyses were performed to check the robustness of the results, including: (1) using natural cubic spline function with 4 and 5 *df* in the adjustment for seasonal temperatures and annual relative humidity; (2) adjusting for annual average temperature instead of seasonal temperatures; (3) adjusting for ozone (O_3) and coarse particulate matter ($PM_{2.5\text{-}10}$) exposures in the model, respectively; (4) modifying the lag periods of long-term $PM_{2.5}$ exposure from 10 years to 7–9 years which were also commonly used in previous studies in estimating the chronic effect of $PM_{2.5}$ (Crouse et al., 2020; Wang et al., 2020b); (5) excluding the current year's exposure when estimating the long-term $PM_{2.5}$ exposure during the study period. We utilized R software (version 4.1.2) to perform all data analyses and data visualizations (R Core Team, 2021). The conditional Poisson regression models were fitted with the *gnm* package (Armstrong et al., 2014). The statistically significant level of the two-tailed P value was set to 0.05.

3. Results

During 2015–2020, we collected 947,337 cancer deaths from 53 spatial units in Jiangsu province, including 239,087 cancers of lung (25.2%), 146,401 of stomach (15.5%), 127,286 of esophagus (13.4%), 116,236 of liver (12.3%), 64,736 of colorectum (6.8%), 47,206 of pancreas (5.0%), 19,492 of breast (2.1%), and 19,273 of leukemia (2.0%). Among these deaths, 63.9% were men and 71.0% were over 65 years. Stomach and lung cancers were the two primary causes of cancer death among men, women, and older adults (≥65 years), while liver and lung cancers were the two primary causes of cancer death in adults aged 20–65 years (Table S2). Annual average population-weighted $PM_{2.5}$ exposure was 60.3 μg/m^3 (standard deviation [SD]: 7.0 μg/m^3), with a range of 40.2–81.6 μg/m^3. Annual average temperatures in summer and winter and annual relative humidity were 27.0 °C (SD: 0.9 °C), 4.6 °C

Table 1
Characteristics of cancer deaths and summary statistics of demographic, socioeconomic, and environmental data for 53 spatial units in Jiangsu province, China during 2015–2020.

Characteristic	Total	Mean (SD)	Min	P_{25}	Median	P_{75}	Max	IQR
Death data								
Cancer deaths	947,337	2,979 (2,158)	744	1,643	2,338	3,256	12,877	1,613
Sex								
Male	605,452 (63.9)	1,904 (1,375)	454	1,064	1,468	2,071	8,248	1,007
Female	341,885 (36.1)	1,075 (785)	261	580	871	1,176	4,712	596
Age								
<65 years	274,619 (29.0)	864 (597)	178	497	678	966	3,766	470
≥ 65 years	672,718 (71.0)	2,115 (1,582)	511	1,146	1,666	2,282	9,705	1,137
Demographic data								
Population size, 10^6	84.7	1.5 (1.4)	0.3	0.8	1.0	1.6	9.3	0.8
Sex								
Male	43.0	0.8 (0.7)	0.1	0.4	0.5	0.8	4.8	0.4
Female	41.7	0.8 (0.7)	0.1	0.4	0.5	0.8	4.6	0.4
Socioeconomic data								
GDP, 10^8, CNY	NA	1,700 (2,200)	217	505	859	1,960	14,800	1,460
Environmental data								
$PM_{2.5}$, lag 0-year, μg/m^3	NA	47.6 (8.7)	25.9	41.6	47.3	52.9	74.8	11.3
$PM_{2.5}$, lag 09-year, μg/m^3	NA	60.3 (7.0)	40.2	55.7	60.2	64.3	81.6	8.6
Summer temperature, °C	NA	27.0 (0.9)	24.9	26.4	27.0	27.6	28.9	1.2
Winter temperature, °C	NA	4.6 (1.3)	1.6	3.5	4.6	5.8	7.5	2.2
Relative humidity, %	NA	74.7 (2.5)	65.2	73.2	74.9	76.4	80.6	3.2

Abbreviations: SD, standard deviation; IQR, interquartile range; GDP, gross domestic product; CNY, Chinese Yuan; $PM_{2.5}$, fine particulate matter; NA, not available. Column percentages are expressed as n (%) and the averages of continuous variables are given as mean (SD).

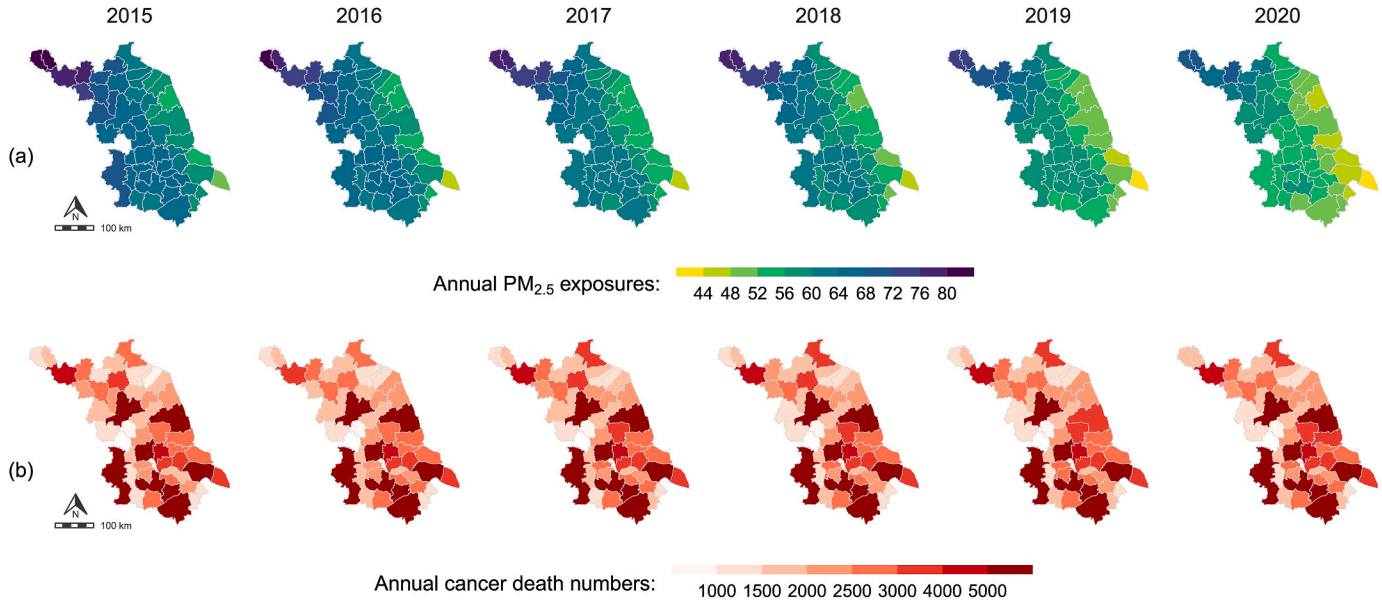

Fig. 1. Spatial distribution of the annual $PM_{2.5}$ exposures and cancer deaths in 53 spatial units in Jiangsu province, China during 2015–2020.

(SD: 1.3 °C), and 74.7% (SD: 2.5%), respectively (Table 1).

Fig. 1 displays the distribution of long-term $PM_{2.5}$ exposure levels and all-site cancer deaths in 53 spatial units in Jiangsu province, China from 2015 to 2020. The $PM_{2.5}$ exposure showed an overall decreasing trend in Jiangsu province over time. The high-polluted areas were mainly located in the northwest of Jiangsu province. Fig. S1 presents the relative change rates on both $PM_{2.5}$ and all-site cancer deaths in each spatial unit during 2015–2020. Over the study period, the trend of relative change in cancer mortality was generally stable and it was slightly opposite to the fluctuation in $PM_{2.5}$ exposure, which can provide evidence to support the parallel trend assumption.

Table 2 presents the estimated relative risks of mortality from all-site and site-specific cancer deaths associated with each 1 μg/m^3 increase of long-term exposure to ambient $PM_{2.5}$. With each 1 μg/m^3 increment in $PM_{2.5}$ exposure, the estimated RR of all-site cancer mortality was 1.027 (95% CI: 1.020, 1.034). After the multiple testing adjustment using the FDR method, long-term $PM_{2.5}$ exposure was significantly associated with elevated risks of cancer mortality from lip, oral cavity and pharynx (RR: 1.069; 95% CI: 1.011, 1.130), digestive system (1.020; 1.011, 1.030), stomach (1.028; 1.011, 1.046), colorectum (1.029; 1.004, 1.055), pancreas (1.065; 1.035, 1.096), respiratory system (1.035; 1.022, 1.049), lung (1.035; 1.021, 1.049), bone and joints (1.201; 1.120, 1.308), ovary (1.108; 1.031, 1.190), male genital system (1.088; 1.034, 1.145), prostate (1.089; 1.034, 1.148), urinary system (1.061; 1.012, 1.112), and lymphoma (1.106; 1.049, 1.168). As shown in Fig. 2, we plotted nonlinear exposure-response curves of long-term $PM_{2.5}$ exposure with cancer mortality. The risk of all-site cancer mortality showed a monotonically increasing trend with incremental $PM_{2.5}$ exposure across the entire exposure range, with increasing slopes at high exposure levels (P for nonlinear trend <0.001; Table 2). Similar nonlinear trends significantly associated with $PM_{2.5}$ exposure were also found for mortality from cancer of digestive system, stomach, colorectum, pancreas,

Table 2
Estimated RR (95% CI) of cancer mortality associated with each 1 μg/m^3 increase of long-term exposure to ambient $PM_{2.5}$ in Jiangsu province, China during 2015–2020.

Site-specific cancer (ICD-10 codes)	Per 1 μg/m^3 increase	FDR-adjusted *P* for linear trend	FDR-adjusted *P* for nonlinear trend
All sites (C00–C97)	1.027 (1.020, 1.034)	<0.001	<0.001
Lip, oral cavity and pharynx (C00–C14)	1.069 (1.011, 1.130)	0.03	0.25
Nasopharynx (C11)	1.080 (1.001, 1.165)	0.07	0.11
Digestive system (C15–C26)	1.020 (1.011, 1.030)	<0.001	0.004
Esophagus (C15)	1.015 (0.992, 1.037)	0.24	0.56
Stomach (C16)	1.028 (1.011, 1.046)	0.002	0.03
Colorectum (C18–C21)	1.029 (1.004, 1.055)	0.03	0.01
Liver (C22)	1.000 (0.980, 1.020)	0.98	<0.001
Pancreas (C25)	1.065 (1.035, 1.096)	<0.001	<0.001
Respiratory system (C30–C39)	1.035 (1.022, 1.049)	<0.001	<0.001
Lung (C33–C34)	1.035 (1.021, 1.049)	<0.001	<0.001
Bone and joints (C40–C41)	1.201 (1.120, 1.308)	<0.001	0.16
Breast (C50)	0.976 (0.933, 1.022)	0.34	0.09
Female genital system (C51–C58)	1.028 (0.986, 1.072)	0.24	0.05
Cervix (C53)	0.942 (0.885, 1.003)	0.08	0.41
Ovary (C56)	1.108 (1.031, 1.190)	0.01	0.03
Male genital system (C60–C63)	1.088 (1.034, 1.145)	0.002	0.39
Prostate (C61)	1.089 (1.034, 1.148)	0.002	0.41
Urinary system (C64–C68)	1.061 (1.012, 1.112)	0.03	0.65
Kidney (C64–C65)	1.092 (1.006, 1.185)	0.06	0.39
Bladder (C67)	1.054 (0.994, 1.119)	0.11	0.58
Brain (C71)	1.024 (0.976, 1.075)	0.36	0.38
Lymphoma (C81–C85)	1.106 (1.049, 1.168)	<0.001	0.04
Leukemia (C91–C95)	0.998 (0.952, 1.046)	0.98	0.39

Abbreviations: RR, relative risk; CI, confidence interval; $PM_{2.5}$, fine particulate matter; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; FDR, false discovery rate.
The *P* values for linear trend and nonlinear trend were adjusted by the FDR method.
A FDR-adjusted *P* value < 0.05 was considered significant.

respiratory system, lung, ovary, and lymphoma (all *P* for nonlinear trend <0.05; Table 2).

Fig. 3 demonstrates the associations of $PM_{2.5}$ exposure with mortality from all-site and site-specific cancers stratified by sex and GDP (Data are displayed in Table S3 and Table S4 in Supplementary Materials). No significant effect modification by sex was identified, except that the association of pancreas cancer mortality was significantly greater in women (*P* for effect modification = 0.045). Subjects in low GDP regions had significantly stronger associations for all-site and stomach cancer (all *P* for effect modification <0.05), while the risk of ovary cancer mortality was higher in subjects living in high GDP areas (*P* for effect modification = 0.03).

In sensitivity analyses, no substantial change was observed when adjusting for seasonal temperatures and relative humidity with different *df*s or adjusting for annual average temperature (Table S5). The analyses with the adjustment for O_3 and coarse particulate matter exposures yielded similar results (Table S6). The analyses adopting 7- to 9-year average exposure to $PM_{2.5}$ also yielded similar results to those of the main analyses using 10-year average exposure (Table S7). When applying the long-term exposure with excluding the current year's exposure, similar $PM_{2.5}$-mortality associations were observed (Table S6).

4. Discussion

This is the first DID analysis to investigate the causal effect of long-term ambient $PM_{2.5}$ exposure on site-specific cancer mortality in China. We identified that long-term exposure to $PM_{2.5}$ was positively associated with mortality from all-site cancer and cancer of lip, oral cavity and pharynx, stomach, colorectum, pancreas, lung, bone and joints, ovary, prostate, and lymphoma. Stratified analyses revealed that women and people living in low GDP regions had higher risks of mortality from certain site-specific cancer.

The positive $PM_{2.5}$-mortality association for all-site cancer was generally in line with those in prior studies. A national DID analysis in Brazil during 2010–2018 reported that with per 10 μg/m^3 increment in 3-year average $PM_{2.5}$ exposure, the risk of all-site cancer mortality significantly increased by 16% (Yu et al., 2022a), which was lower than that in our results (27%). Results from the Hong Kong, China and the US cohorts showed that with per 10 μg/m^3 increment in long-term $PM_{2.5}$ exposure, the estimated risk of all-site cancer mortality increased by 22.0%, 15.0%, and 2.5%, respectively (Coleman et al., 2020b; Wang et al., 2020a; Wong et al., 2016), which were also lower than our estimates. The difference in the magnitude of the effect estimates can be due to: (1) Diverse $PM_{2.5}$ exposure ranges. The $PM_{2.5}$ exposures of studies in Brazil and the US covered a range of less than 30 μg/m^3, whereas our results were derived from a much higher and wider $PM_{2.5}$ exposure range (40.2–81.6 μg/m^3); (2) Different populations. The cohorts from Hong Kong and the US only included people over 65 years, while our analysis was conducted among adults 20 years or older.

Similar with some previous studies conducted in China (Guo et al., 2017; He et al., 2018; Li et al., 2020; Yin et al., 2017), we found a negative effect of $PM_{2.5}$ exposure on lung cancer mortality (per 10 μg/m^3 increase in $PM_{2.5}$, RR: 1.35), though our estimated value was higher than that in a national men cohort (per 10 μg/m^3 increase in $PM_{2.5}$, hazard ratio: 1.12) and a study using lung cancer death data from 75 Chinese communities (per 10 μg/m^3 increase in $PM_{2.5}$, RR: 1.08) (Guo et al., 2017; Yin et al., 2017). In addition, in line with the cohort study of the China-PAR project (Li et al., 2020), our findings showed that

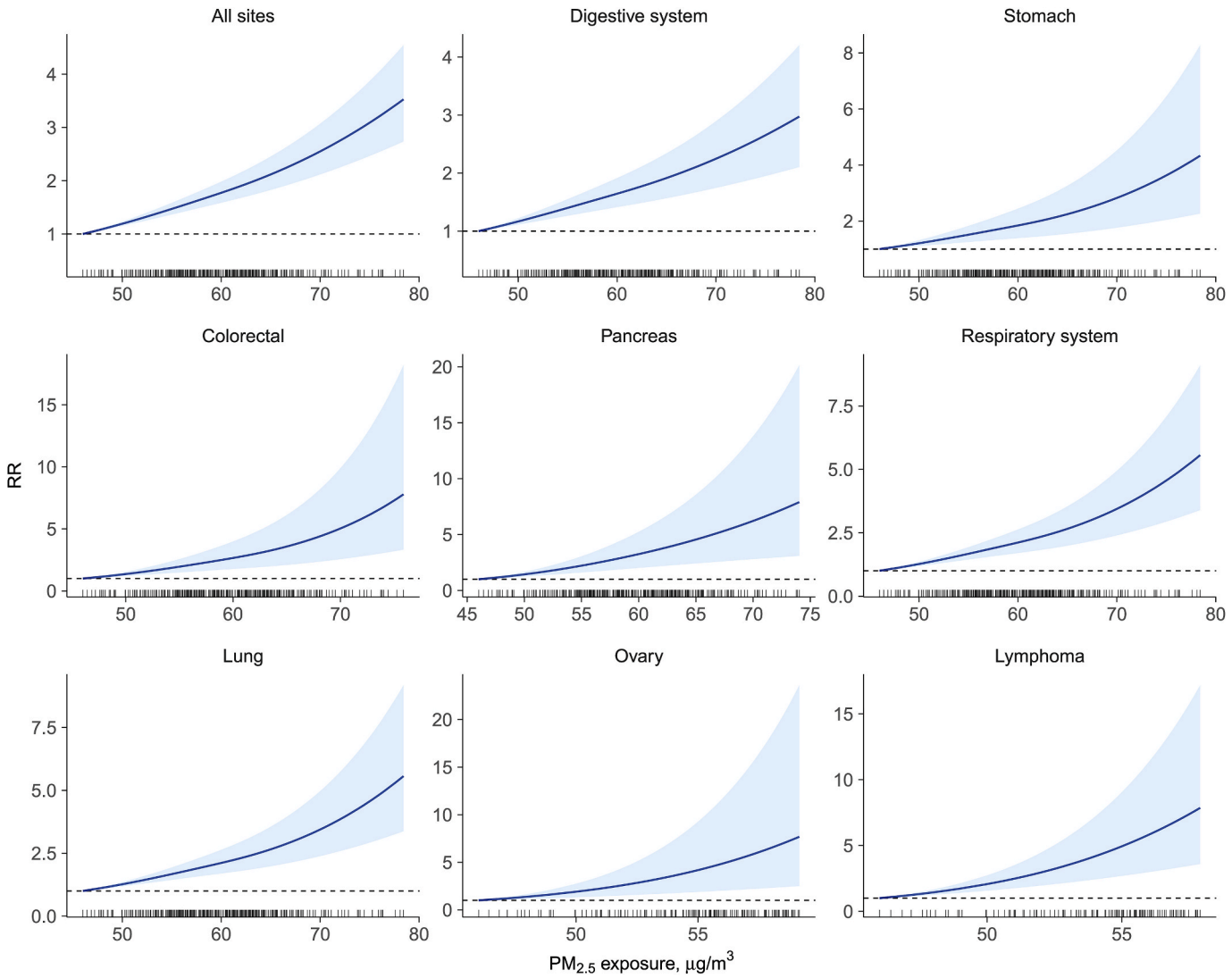

Fig. 2. Exposure-response curve of long-term exposure to ambient $PM_{2.5}$ with cancer mortality with a significant nonlinear association. The solid blue lines with shaded regions indicate RRs of cancer mortality and their 95% CIs, respectively. Abbreviations: $PM_{2.5}$, fine particulate matter; RR, relative risk; CI, confidence interval.

the $PM_{2.5}$-mortality association for lung cancer exhibited a similar nonlinear exposure-response shape, with a monotonically increasing trend at low $PM_{2.5}$ exposure levels and steeper slopes at the high $PM_{2.5}$ exposure levels. This exposure-response pattern can be useful in developing effective strategies to minimize the burden of lung cancer death. Moreover, we observed that long-term exposure to $PM_{2.5}$ showed significant adverse effects on the risks of mortality from a variety of site-specific cancers including lip, oral cavity and pharynx, stomach, colorectum, pancreas, lung, bone and joints, ovary, prostate, and lymphoma, which have rarely been investigated and the results remain inconclusive. For digestive system cancer, existing studies reported $PM_{2.5}$ exposure was associated with cancer mortality from stomach, colorectum, and digestive accessory organs (e.g., liver and pancreas) (Coleman et al., 2020b; Guo et al., 2020; Turner et al., 2017; Wang et al., 2018; Wong et al., 2016). For urinary system cancer, two cohort studies in the US and one spatial analysis in Taiwan, China consistently reported a positive association with the risk of bladder cancer mortality (Coleman et al., 2020b; Turner et al., 2017; Yeh et al., 2017); however, we did not observe significant $PM_{2.5}$-mortality associations either from kidney cancer or bladder cancer. Studies have also observed negative associations of exposure to $PM_{2.5}$ with cancer mortality from breast, ovary, prostate, lymphoma, and leukemia (Coleman et al., 2020b; Guo et al., 2021; Hung et al., 2012; Turner et al., 2017; Wang et al., 2019). Overall, our findings and previous studies provide evidence on the harmful effect of $PM_{2.5}$ exposure on mortality from cancer of many organs. Further studies focusing on site-specific cancers are warranted to facilitate the assessment of cancer burden concerning long-term exposure to ambient $PM_{2.5}$.

The risk of mortality from certain site-specific cancers in our study was higher than several previous studies (Chen et al., 2021; Coleman et al., 2020b; Turner et al., 2017; Wang et al., 2020a; Wong et al., 2016; Yu et al., 2022a–c) with possible reasons including: (1) Different study design. Most previous studies used a cohort design to control only a limited number of measured confounding factors (Chen et al., 2021; Coleman et al., 2020b; Turner et al., 2017; Wang et al., 2020a; Wong et al., 2016), and were usually subject to residual confounding that can induce biased estimates. In this DID analysis, we considered temporal variables, spatial variables, and measured confounders (i.e. temperature, relative humidity, and socioeconomic status), which can indirectly control a number of common factors that changed across areas over time. Since the population of a spatial unit was compared with itself at different periods, unmeasured confounders that rarely changed over time or kept constant during the study period were also controlled through the study design. (2) Different exposure level. Most previous

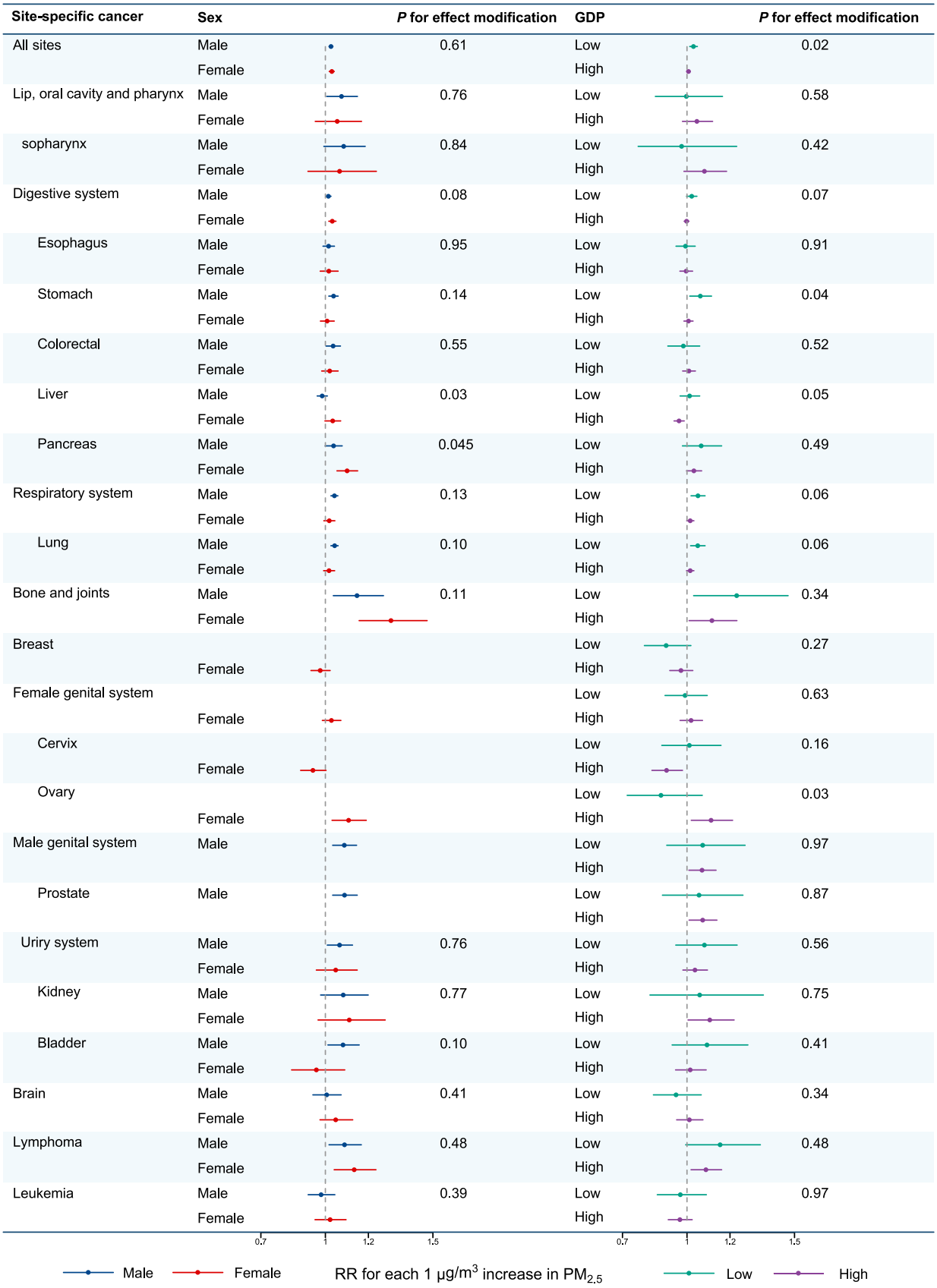

Fig. 3. Estimated RR (95% CI) of cancer mortality associated with each 1 μg/m^3 increase of long-term exposure to ambient $PM_{2.5}$ stratified by sex and GDP. Abbreviations: RR, relative risk; CI, confidence interval; $PM_{2.5}$, fine particulate matter; GDP, gross domestic product.

studies on $PM_{2.5}$ exposure and site-specific cancer mortality were mainly conducted in the US and Brazil (Coleman et al., 2020b; Turner et al., 2017; Wang et al., 2020a; Yu et al., 2022a–c). The exposure level of $PM_{2.5}$ and its constituents in China were different from that in these regions, which can lead to various susceptibility to $PM_{2.5}$ exposure across site-specific cancers. (3) Limited sample size. Consistent with published literature, the sample size of site-specific cancers with higher effect estimates was typically smaller (Turner et al., 2017), which can add more uncertainties and warrants large-scale investigations in future.

We assessed exposure-response curves of $PM_{2.5}$ with mortality from a variety of site-specific cancers in China. Our results suggest that the associations of long-term exposure to $PM_{2.5}$ with cancer mortality were approximately linear across the exposure range of 40.2–81.6 $\mu g/m^3$, though there was a steeper increase of mortality risk in higher exposure levels. One possible explanation is that $PM_{2.5}$ exposure interacts with other factors (e.g., socioeconomic status and medical accessibility) to synergistically increase the mortality risk at higher exposure levels (Han et al., 2021; Zhao et al., 2021). Note that these curves did not indicate a potential exposure threshold for risk of cancer mortality, suggesting that reducing $PM_{2.5}$ exposures in any level within our exposure range (especially at high exposure levels) can yield significant health benefits. It should also be noted that more uncertainties were observed for the risk of cancer mortality associated with high level of $PM_{2.5}$ exposures, which needs to be confirmed in further studies.

In stratified analysis, we found that the association of pancreas cancer mortality was significantly stronger in women than that in men. This finding can be explained by the difference in individual habits on cooking oil fumes exposure and the sexual discrepancy in metabolism. For the GDP level, subjects living in low GDP regions showed stronger $PM_{2.5}$-mortality associations of all-site cancer and stomach cancer. Perhaps these differences are related to the inhabitants in these areas spending more time on outdoor activities, which further leads to higher exposure to ambient air pollution (Han et al., 2021). Moreover, low socioeconomic status regions may have the insufficient budget to control air pollution, which can aggravate the vulnerability of populations to air pollution (Zhao et al., 2021).

Several possible pathways could explain the potential biological mechanisms between $PM_{2.5}$ exposure and cancer mortality. First, $PM_{2.5}$ contains various mutagens and carcinogenic substances including polycyclic aromatic hydrocarbons, volatile organic compounds, and heavy metals, which can transport and metabolize in the body and trigger the progression of cancer (Castano-Vinyals et al., 2004; Manisalidis et al., 2020; Moorthy et al., 2015). Second, previous studies have connected air pollution exposure with epigenetic modifications including DNA hypermethylation and hypomethylation, both of which are considered as cancer-related and early-effect biomarkers (Demetriou and Vineis, 2015; Sanchez-Guerra et al., 2015; Zhang et al., 2020). Third, $PM_{2.5}$ may cause oxidative stress and inflammation, which are proven to be connected with several cancers such as breast, colorectum, and stomach cancer (Baulig et al., 2007; Kruk and Aboul-Enein, 2017). Finally, $PM_{2.5}$ can penetrate the alveolar-blood barrier and blood-brain barrier (Cristaldi et al., 2022). $PM_{2.5}$-bound toxic substances are then able to enter the bloodstream, transport throughout the body, and cause adverse effects on different organs (Anderson et al., 2012; Choi et al., 2018).

Our study has the following advantages. First, we enrolled over 80 million general population with 0.95 million cancer deaths across 53 spatial units during 6 consecutive years. Our sample size is large enough to provide sufficient statistical power and allow u to make a novel contribution to the causal effect of long-term $PM_{2.5}$ exposure on mortality from multiple site-specific cancers using the DID analysis in China. Second, the $PM_{2.5}$ exposure was assessed using a high-quality and high-resolution ($0.01^\circ \times 0.01^\circ$) dataset, which can reduce the uncertainty in exposure measurement (Wei et al., 2022). Third, the use of historical estimates on long-term ambient concentrations over a 10-year exposure window can give better evaluations of the cumulative chronic impacts of $PM_{2.5}$ exposure on the progression of cancer death.

There are also some limitations. First, we only adjusted for seasonal temperatures, relative humidity, and GDP in the model. Other spatio-temporal variables, including employment rates and behavior trends in smoking and alcohol consumption, may confound the associations between $PM_{2.5}$ exposure and cancer mortality (Wang et al., 2016; Yitshak-Sade et al., 2019). Although these unmeasured confounders were unable to be adjusted in the model, the dummy variables for years and spatial units in the model can in part control the corresponding change trends of these confounders and reduce potential bias. Second, we were unable to consider the individuals' residential mobility and used exposure estimates at the county of death as a proxy of long-term exposure indicators. Nonetheless, it is suggested that the exposure misclassification due to the lack of residential history is probably non-differential and may lead the bias of estimated associations to null effects (Cheng et al., 2020; Crouse et al., 2015). Finally, since the lack of historical ambient pollutants data, we were unable to conduct analyses by further adjusting for other gaseous pollutants (e.g., nitrogen dioxide, sulfur dioxide, carbon monoxide) in the models. Given that published literature also linked other pollutant exposures to cancer mortality (Turner et al., 2020; W. Wei et al., 2021), future studies can account for co-pollutants exposure when estimating $PM_{2.5}$-mortality associations.

5. Conclusion

In summary, our results established causal associations between long-term exposure to $PM_{2.5}$ and the increased risk of mortality from all-site cancer and site-specific cancers including the digestive system, the respiratory system, the reproductive system, the urinary system, and the hematopoietic system. Our findings suggest that women and people living in low SES regions are more vulnerable to $PM_{2.5}$ exposures. Our study provides further evidence that ambient $PM_{2.5}$ can be a contributor to mortality from a number of site-specific cancers and highlights the needs to take effective measures for both policymakers and individuals to reduce exposures to $PM_{2.5}$ pollution.

Credit authorship and contribution statement

Zhaoyu Fan, Yingxin Li: Methodology, Formal analysis, Writing – original draft, Visualization. Jing Wei: Data collection. Gongbo Chen, Rui Wang, Ruijun Xu, Tingting Liu, Ziquan Lv, Suli Huang: Writing – review & editing. Hong Sun: Data collection, Writing – review & editing. Yuewei Liu: Conceptualization, Methodology, Writing – review & editing, Supervision.

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

Data on air pollution and grid population density are available at https://weijing-rs.github.io/and https://landscan.ornl.gov/, respectively. Data on weather and mortality are 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.2023.115405.

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