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Mediating effect of diabetes in the association between long-term $PM_{2.5}$ exposure and cancer risk in CHARLS

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Long-term exposure to air pollutants and diabetes are both linked to cancer development. However, their combined effect remains unclear. This study examined the relationship between air pollutants and cancer incidence, with diabetes as a potential mediator. Data from 10,590 participants in the 2015 China Health and Retirement Longitudinal Study (CHARLS) were analyzed. Participants were grouped based on cancer diagnosis, and air pollutant exposure levels were estimated using satellite-based spatiotemporal models. Generalized linear regression and restricted cubic spline (RCS) analysis were used to assess the impact of air pollutants and diabetes in covariates-adjusted models. Further analyses, including conditional independence test, mediation effect and sensitivity analysis based on Bayesian networks, were performed to further analyze specific air pollutants. After adjusting for covariates, particulate matter (PM) (PM ≤ 1 μm in aerodynamic diameter [PM_1], $PM_{2.5}$, ammonium (NH_4), nitrate (NO_3) and diabetes showed significant associations with cancer incidence. RCS analysis confirmed significant direct effects of $PM_{2.5}$ and PM_{10} on cancer and the mediated effects of diabetes. The interaction between diabetes and both $PM_{2.5}$ and PM_{10} was further supported by conditional independence tests, highlighting diabetes as a significant mediator in the $PM_{2.5}$-cancer relationship. This study offers a novel perspective by identifying diabetes as a key intermediary in the association between $PM_{2.5}$ exposure and cancer risk, providing evidence that diabetes plays a significant mediating role in air pollutant-related cancer development.

Keywords Cancer, Air Pollutant, Diabetes, CHARLS

Abbreviations

CHARLS	China health and retirement longitudinal study
RCS	Restricted cubic spline
CHAP	China high air pollutants
STET	Space-time extremely randomized trees
PM	Particulate matter
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_3	Ozone
Cl	Chlorine
NH_4	Ammonium
NO_3	Nitrate
SO_4	Sulfate
SD	Standard deviation
GLM	Generalized linear models
95% CI	95% confidence intervals

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OR	Odds ratios
BMI	Body mass index
IARC	Agency for research on cancer
ROS	Reactive oxygen species
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-α
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
NF-κB	Nuclear factor kappa-B
CRP	C-reactive protein

Cancer represents a major global health issue, with an estimated 19.3 million new cases and 10 million deaths reported in 2020[1]. As cancer incidence rises annually, it imposes substantial economic and social burdens worldwide, especially in developing countries. In China, epidemiological data indicate that cancer predominantly affects the elderly[2]; however, a gradual trend toward younger demographics has been observed in recent years[3]. Consequently, cancer prevention and the identification of potential risk factors have become pressing public health concerns. Among these, diabetes, as a widespread condition characterized by hyperglycemia and chronic inflammation, is notably associated with an increased risk of various cancers[4]. This association is particularly pronounced among middle-aged and elderly populations, exacerbating disease burdens and mortality rates. These observations underscore the importance of diabetes management in cancer prevention.

Air pollution, resulting from the contamination of indoor and outdoor air by chemical, physical, or biological agents, poses significant risks to human health[5]. As air pollution issues have intensified in recent years[6], there has been growing research interest in understanding how environmental pollutants might contribute to cancer incidence. Studies have demonstrated that numerous substances in air pollutants such as particulate Matter (PM) ($PM \leq 2.5$ μm in aerodynamic diameter [$PM_{2.5}$], nitrogen dioxide (NO_2) and nitrogen oxides (NO_x), increase cancer risks, particularly among individuals over the age of 50 [7]. Similarly, air pollution is also recognized as a major risk factor for diabetes[8]. Approximately 3.2 million people worldwide with type 2 diabetes are affected by $PM_{2.5}$ exposure, particularly in developing countries, contributing to over 200,000 deaths annually[9]. Recently, interest has grown in examining the combined effects of air pollution and other risk factors, such as genetic predispositions. For instance, a retrospective study utilizing the UK Biobank database revealed that individuals with both high genetic risk and elevated air pollution exposure (PM and NO_x) had significantly higher probabilities of developing lung cancer, with approximate increases of 50% and 63%, respectively[10]. Further understanding of the interactions between these environmental pollutants, diabetes, and cancer could provide crucial evidence for preventing diabetes and cancer associated with environmental exposures.

This cross-sectional study evaluates the relationships among $PM_{2.5}$, other air pollutants, diabetes, and cancer. Although both air pollutants and diabetes are independently associated with cancer risk, the mechanisms through which they interact in cancer development are not fully understood. Investigating the mediating role of diabetes could provide deeper insights into the carcinogenic mechanisms of air pollutants, thereby enhancing the effectiveness of cancer prevention and intervention strategies. Therefore, this study utilizes data from the China Health and Retirement Longitudinal Study (CHARLS) to analyze the mediating effect of diabetes on the association between air pollutants and cancer risk, aiming to provide evidence for more effective preventive measures.

Methods

Study population and design

This study utilized publicly available data from the CHARLS (http://charls.pku.edu.cn). The CHARLS project was approval by the Biomedical Ethics Committee of Peking University (IRB00001052-11015, Beijing, China), and informed consent was obtained from all participants. For our analysis, we used data from the 2015 CHARLS survey data. After excluding participants with missing data on cancer status and other key variables, the final study population comprised 10,590 individuals. The large sample size and high quality of the CHARLS data provide a robust foundation for the analyses conducted in this study.

Assessment of air pollutants

Ground-level concentrations of air pollutants [($PM_{2.5}$, PM_{10}, PM_1, ozone (O_3), chlorine (Cl), Ammonium (NH_4), Nitrate (NO_3), and Sulfate (SO_4)] were estimated for each individual at a spatial resolution of 0.1° (~ 10 km) using artificial intelligence models and the China High Air Pollution (CHAP) dataset (https://weijing-rs.github.io/product.html). Data sources included ground-based measurements, remote sensing data, atmospheric reanalysis, and model simulations, with the space-time extremely randomized trees (STET) model used to estimate daily pollutant concentrations. Each participant's annual exposure to air pollution was calculated based on their county-level residential address. For the 28 provinces included in CHARLS, mean, standard deviation, minimum, and maximum values of each pollutant were calculated, with average values presented in Table 1. Due to missing data on NH_4, SO_4, NO_3, and Cl in Qinghai and Xinjiang, these provinces were excluded from specific analyses. For subsequent analyses, the mean concentration of each pollutant was used.

Data collection

We collected data on various covariates, including demographic, socioeconomic, and chronic disease-related factors. Demographic variables comprised age (in years) body mass index (BMI) and sex (male or female). Socioeconomic factors included residence (urban or rural), education level (elementary school or below, secondary school, or high school and above), marital status (married or unmarried), and region (east, midland, or west). Lifestyle factors such as smoking and drinking were recorded as binary variables (yes or no). Chronic

Characteristics	Total ($n=10,590$)	Non-cancer ($n=10,418$)	Cancer ($n=172$)	*P*-value
Age, years, mean (SD)	61.4(9.4)	61.4 (9.5)	60.9 (9.0)	0.518
BMI, kg/m^2, mean (SD)	23.8 (3.7)	23.8 (3.7)	24.3 (4.3)	0.900
Gender (%)				
Male	4663 (44.0)	4560 (43.8)	103 (59.9)	< 0.001
Female	4322 (40.8)	4276 (41.0)	46 (26.7)	
Marital status (%)				
Married	9122 (86.1)	8973 (86.1)	149 (86.6)	0.939
Unmarried	1468 (13.9)	1445 (13.9)	23 (13.4)	
Education (%)				
Elementary school or below	7979 (75.3)	7853 (75.4)	126 (73.3)	0.193
Secondary school	868 (8.2)	849 (8.1)	19 (11.0)	
High school or above	133 (1.3)	129 (1.2)	4 (2.3)	
Residence (%)				0.040
Urban	3738 (35.3)	3664 (35.2)	74 (43.0)	
Rural	6852 (64.7)	6754 (64.8)	98 (57.0)	
Smoking status (%)				
Yes	4630 (43.7)	4585 (44.0)	45 (26.2)	< 0.001
No	5958 (56.3)	5831 (56.0)	127 (73.8)	
Drink (%)				
Yes	4822 (45.6)	4756 (45.7)	66 (38.4)	0.066
No	5755 (54.4)	5649 (54.3)	106 (61.6)	
Hypertension (%)				
Yes	3683 (35.3)	3611 (35.2)	72 (41.9)	0.040
No	6753 (64.7)	6658 (64.8)	95 (55.2)	
Region (%)				
West	4080 (38.5)	4005 (38.4)	75 (43.6)	0.031
Midland	3123 (29.5)	3065 (29.4)	58 (33.7)	
East	3387 (32.0)	3348 (32.1)	39 (22.7)	

Table 1. Basic characteristics of participants ($n=10,590$). *BMI* body mass index, *SD* standard deviation.

disease-related variables included the presence of hypertension (yes or no). Diabetes, the mediating factor in this study, was identified by combining self-reported diabetes diagnosis and blood glucose measurements. Diabetes was defined as a self-reported physician diagnosis, use of hypoglycemic drugs, fasting blood glucose ≥ 126 mg/dL, and/or glycated hemoglobin ≥ 6.5% at baseline, following established diagnostic criteria[11]. A Directed Acyclic Graph (DAG) was employed to illustrate the potential causal relationships between air pollutants, diabetes, and cancer, incorporating a minimally sufficient set of confounding variables. In the DAG, air pollutants were modeled as the primary exposure, which may influence cancer both directly and indirectly through diabetes and other covariates, including demographic factors, chronic disease-related factors, and socioeconomic factors. These confounders affected both the exposure to air pollutants and the risk of diabetes and cancer. Additionally, diabetes was hypothesized as both an outcome of air pollution and a mediator in the pathway leading to cancer (Fig. S1).

Statistical analysis

Descriptive statistics were used to summarize the data: continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as counts (percentages). Differences between participants with and without cancer were analyzed using t-tests for continuous variables and chi-squared tests for categorical variables. Generalized linear models (GLM) were employed to investigate the relationship between air pollution, diabetes, and cancer. Results were reported as odds ratios (OR) and 95% confidence intervals (95% CI). An initial model was unadjusted, while Model 2 included adjustments for geographic factors (region and residence). Model 3 further adjusted for additional covariates, including gender, smoking, and hypertension. To explore potential non-linear associations between pollutants, diabetes, and cancer risk, restricted cubic splines (RCS) were applied, allowing for a more nuanced analysis of exposure effects.

A Bayesian network model was then constructed to examine conditional dependencies and explore the indirect effects of PM_1 and $PM_{2.5}$ on cancer risk, with diabetes as a mediator. Conditional independence tests were first conducted to assess associations between PM_1, $PM_{2.5}$, and cancer, and to explore the mediating role of diabetes. To assess the mediating role of diabetes in the relationship between air pollution and cancer risk, we conducted a mediation analysis using the causal steps method by Baron and Kenny[12]. First, GLM established the association between air pollution (independent variable) and cancer incidence (dependent variable). Next, logistic regression examined the association between air pollution and diabetes (mediate). Finally, both air pollution and diabetes were included in a GLM to predict cancer incidence. Mediation was supported if

the association between diabetes and cancer remained significant, while the direct effect of air pollution was attenuated or non-significant. The product-of-coefficients approach was used to estimate the indirect effect (Path a: air pollution on diabetes; Path b: diabetes on cancer), and the Sobel test evaluated its statistical significance. In sensitivity analysis, we performed a two-way interaction analysis to evaluate whether diabetes modifies the association between air pollution and cancer risk (effect modification). All statistical analyses were performed using R software (Version 4.4.1), with the "mice" package used for imputing missing covariate data. A two-tailed P-value < 0.05 was considered statistically significant.

Results

Population characteristics

Among the 19,675 participants initially enrolled, 10,590 individuals were included in the analysis after excluding those with missing data. The detailed population distribution of the 28 provinces included in the baseline data is presented in Figure S2. The province with the largest population is Shandong ($n = 1126$), followed closely by Henan ($n = 928$) and Sichuan ($n = 864$). The mean age of participants was 61.4 ± 9.4 years; 4663 (51.9%) were male, and 4322 (48.1%) were female. Participants were categorized based on cancer status, with a total of 172 middle-aged and older adults diagnosed with cancer (Table 2). In terms of the residence distribution, the majority of participants were from rural areas (64.7%), while the remainder were from urban areas (35.3%). The regional distribution was relatively balanced, with 4080 participants (38.5%) from the western region, 3123 (29.5%) from the central region, and 3387 (32.0%) from the eastern region. According to t-tests, gender ($P < 0.001$), residence ($P = 0.040$), smoking status ($P < 0.001$), hypertension ($P = 0.040$), and region ($P = 0.031$) showed statistically significant differences between participants with and without cancer (Table 2).

Air Pollutant exposure

The average annual concentrations of the eight pollutants shown in Figure S3 were as follows: PM_1 (24.46 ± 4.26 μg/m^3), $PM_{2.5}$ (45.10 ± 7.44 μg/m^3), PM_{10} (81.66 ± 14.90 μg/m^3), O_3 (82.67 ± 5.80 μg/m^3), Cl (1.83 ± 0.33 μg/m^3), NH_4 (6.08 ± 0.92 μg/m^3), NO_3 (8.00 ± 1.52 μg/m^3), and SO_4 (9.83 ± 1.30 μg/m^3). Notably, the concentrations of $PM_{2.5}$ and PM_{10} exceeded both the WHO air quality guidelines ($PM_{2.5}$: 10 μg/m^3, PM_{10}: 20 μg/m^3) and the secondary Chinese ambient air quality standards (GB 3095–2012, $PM_{2.5}$: 35 μg/m^3, PM_{10}: 70 μg/m^3).

Generalized linear analysis of air pollutants, diabetes and cancer

Using t-test analysis, significant covariates such as gender, residence, smoking status, hypertension, and region were identified and were subsequently included in the model construction. Figure 1 illustrates the results of the generalized linear model examining associations among air pollutants, diabetes, and cancer. In the unadjusted model (Model 1), diabetes (OR: 1.10, 95% CI: 1.05–1.16, $P < 0.001$), PM_1 (OR: 1.01, 95% CI: 1.01–1.02, $P = 0.043$), $PM_{2.5}$ (OR: 1.00, 95% CI: 1.00–1.00, $P = 0.041$) and NO_3 (OR: 1.00, 95% CI: 1.00–1.00, $P = 0.035$) showed significantly associated with cancer prevalence. Model 2, adjusted for geographic factors, PM_1 (OR: 1.01, 95% CI: 1.00-1.01, $P = 0.011$), $PM_{2.5}$ (OR: 1.01, 95% CI: 1.00-1.01, $P = 0.016$), NH_4 (OR: 1.01, 95% CI: 1.00-1.01, $P = 0.038$), NO_3 (OR: 1.01, 95% CI: 1.00-1.01, $P = 0.025$), and diabetes (OR: 1.01, 95% CI: 1.01–1.02, $P = 0.001$) confirmed significant associations between long-term exposure to with odds of cancer. After further adjustment for additional covariates in Model 3, including gender, smoking status, and hypertension, the associations between diabetes (OR: 1.01, 95% CI: 1.01–1.02, $P = 0.002$) and $PM_{2.5}$ (OR: 1.01, 95% CI: 1.00-1.01, $P = 0.016$) with odds of cancer remained significant, reinforcing the robustness of the findings in Model 2. Detailed results are available in Table S1.

Restricted cubic splines analysis

RCS analysis demonstrated a significant association between diabetes and odds of cancer, suggesting that diabetes (for nonlinearity, $P < 0.001$) may increase cancer susceptibility (Fig. 2). Additionally, a significant dose-response relationship was observed between exposure of $PM_{2.5}$ (for nonlinearity, $P = 0.036$) and PM_1 (for nonlinearity, $P = 0.042$) and cancer, indicating that higher levels of $PM_{2.5}$ and PM_1 may be linked to elevated cancer risk. In contrast, NH_4 (for nonlinearity, $P = 0.105$) and NO_3 (for nonlinearity, $P = 0.088$) did not show significant associations with cancer, suggesting a limited or negligible impact on cancer risk.

Air pollution (μg/m^3)	Mean	SD	Min	Max
PM_1	24.46	4.26	13.95	40.20
$PM_{2.5}$	45.10	7.44	27.14	72.40
PM_{10}	81.66	14.90	49.22	131.67
O_3	82.67	5.80	50.90	109.94
SO_4	9.83	1.30	5.75	14.12
Cl	1.83	0.33	0.93	4.17
NH_4	6.08	0.92	3.26	9.30
NO_3	8.00	1.52	4.02	13.60

Table 2. Descriptive statistics of the average levels of air pollution in 2015. PM_1, particle with aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particle with aerodynamic diameter ≤ 10 μm; O_3, ozone; SO_4, sulfate; Cl, chlorine; NH_4, ammonium; NO_3, nitrate; SD, standard deviation.

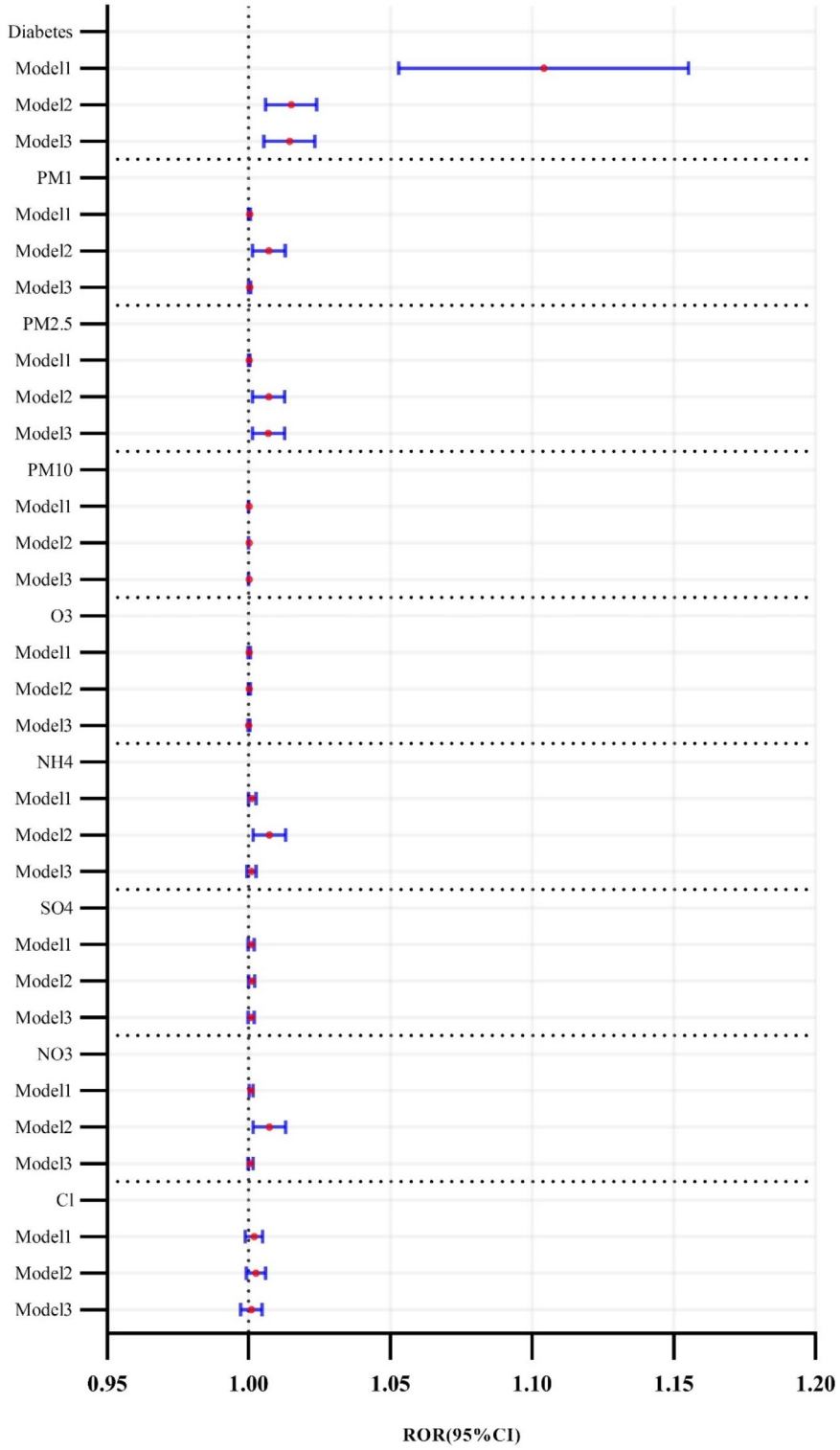

Fig. 1. Generalized linear analysis of the association air pollutants, diabetes and cancer. Model 1, crude model, without adjustment; Model 2, adjusted for residence and region; Model 3, adjusted for gender, smoking status, hypertension, region and residence.

Interaction and mediation analysis in the PM1 and PM2.5-cancer pathway

To further assess the association between diabetes and cancer while accounting for PM_1 and $PM_{2.5}$ exposure, we conducted conditional independence testing based on Bayesian network framework. The mutual information values for PM_1 (14.845, $P=0.002$) and $PM_{2.5}$ (14.379, $P=0.002$) indicated statistically significant associations

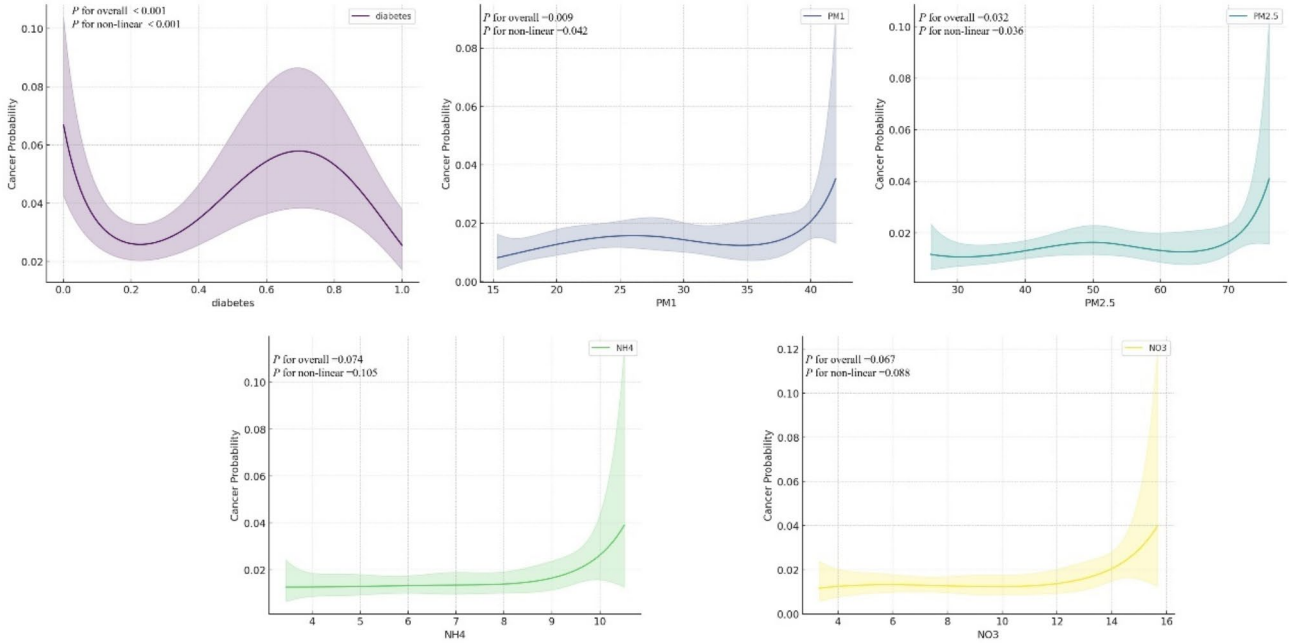

Fig. 2. Restricted cubic splines analysis of the association between air pollutants (PM_1, $PM_{2.5}$, NH_4 and NO_3), diabetes and cancer probability.

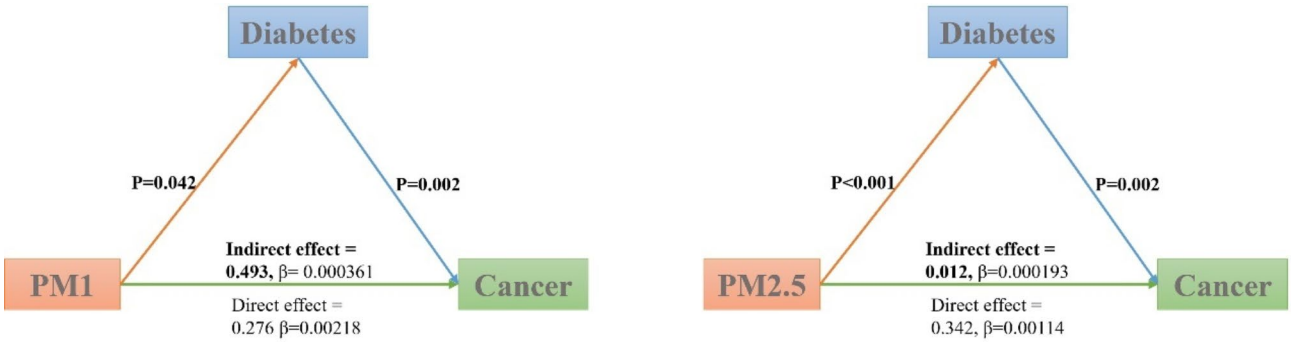

Fig. 3. Mediation and interaction effect of diabetes in the PM_1 and $PM_{2.5}$ pathways to cancer risk.

between diabetes and cancer, supporting the hypothesis that diabetes may serve as a direct risk factor for cancer (Table S2).

Interaction and mediation analyses indicated that the indirect effect of $PM_{2.5}$ on odds of cancer via diabetes was statistically significant ($\beta = 0.000193$, $P < 0.001$), while the indirect effect of PM_1 was not significant ($\beta = 0.000361$, $P = 0.493$), suggesting a potential pathway in which $PM_{2.5}$ exposure mediates the impact of diabetes on cancer risk (Fig. 3). The specific distribution of $PM_{2.5}$ in each province is shown in Fig. 4 and Table S3. The sensitivity analysis revealed significant differences in cancer risk across various $PM_{2.5}$ exposure levels (Fig. 5). Diabetic individuals exhibited a substantially higher cancer risk compared to non-diabetics at high $PM_{2.5}$ exposure levels. Similarly, cancer risk remained elevated for diabetics at low and medium $PM_{2.5}$ levels compared to non-diabetics. This pattern suggests that diabetes may exacerbate the effect of $PM_{2.5}$ on cancer risk, highlighting the need for further research into the biological mechanisms underlying this pathway. These findings also provide a basis for targeted interventions to mitigate cancer risk in diabetic populations, especially in areas with high $PM_{2.5}$ exposure. Future studies are needed to quantify this indirect effect more precisely and to validate these findings in larger, more diverse populations.

Discussion

To our knowledge, this is the first nationwide study in China to reveal diabetes as a mediating factor in the association between ambient $PM_{2.5}$ exposure and cancer incidence, based on cross-sectional data. Our findings indicate a significant association between $PM_{2.5}$ levels and cancer prevalence, with diabetes playing a critical mediating role. People with diabetes face a higher odds of developing cancer when exposed to elevated levels of

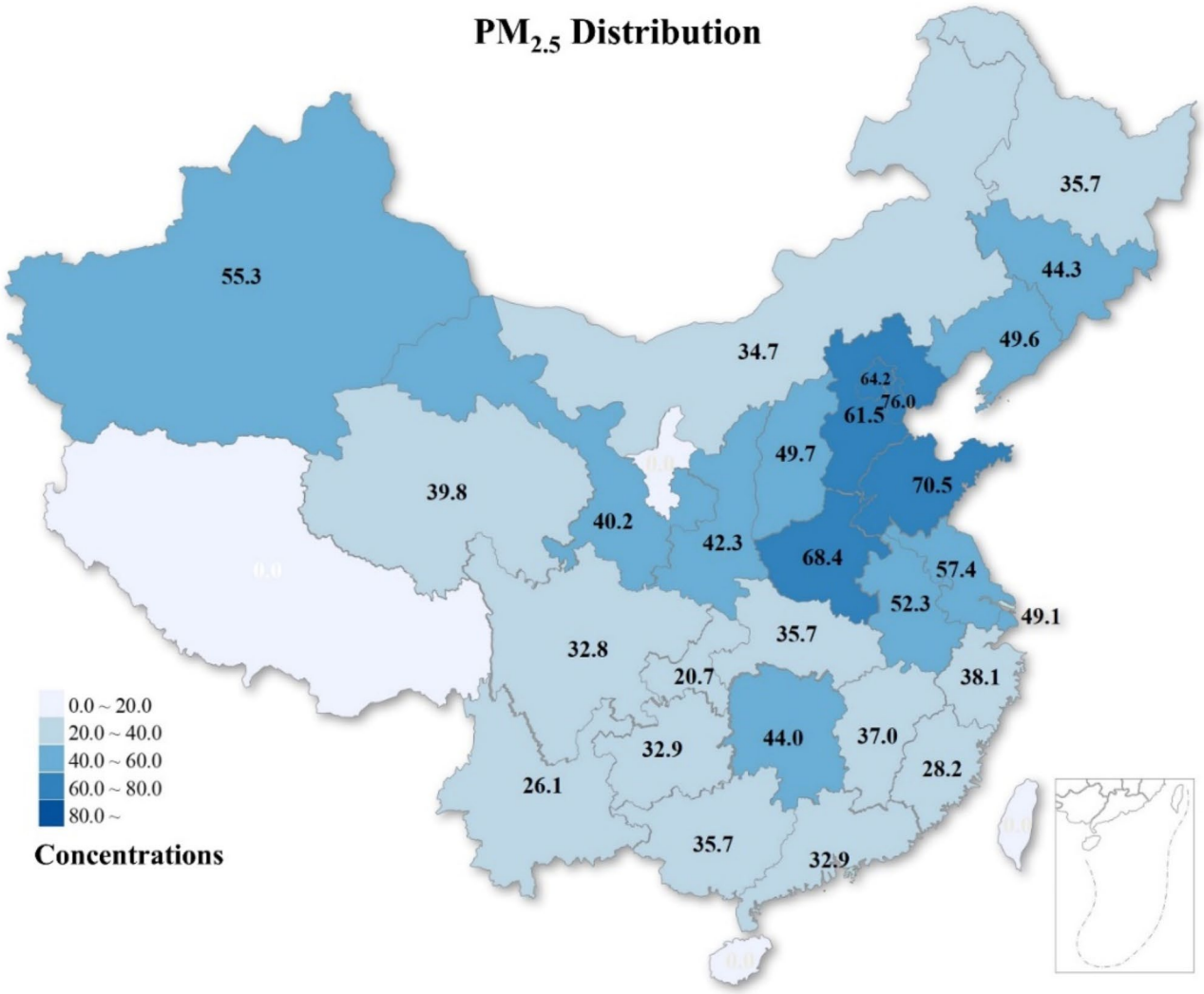

Fig. 4. The geographical distribution of $PM_{2.5}$ concentrations in China. The map is cited by https://www.rdocumentation.org/packages/rnaturalearth/versions/1.0.1 and created in R software (Version 4.4.1).

$PM_{2.5}$ compared to others. This finding suggests that reducing $PM_{2.5}$ exposure could help lower odds of cancer, with diabetes acting as a mediating factor, providing a novel angle for integrating environmental health measures with clinical practices.

Our study employed generalized linear analysis and RCS to confirm the link between $PM_{2.5}$ and odds of cancer (for nonlinearity, $P = 0.036$), highlighting the potential hazards of air pollution for individuals with cancer. To investigate long-term exposure, we estimated annual mean $PM_{2.5}$ concentration for each province using the STET model. Our results showed that $PM_{2.5}$ level are particularly high in China, with the highest concentrations in Tianjin, Shandong and Henan, likely due to high industrialization in these regions (Table S3). Such regional variation is consistent with evidence that PM, from both natural and anthropogenic sources, exhibits substantial geographic heterogeneity in concentration and chemical composition in China[13]. In light of the health risks associated with PM exposure, the International Agency for Research on Cancer (IARC) classified PM as a Group 1 carcinogen for lung cancer in 2013, drawing on evidence from both clinical and preclinical studies[14]. Further studies have demonstrated that $PM_{2.5}$ exposure, particularly from wildfire events, is linked to higher incidence and mortality rates of various cancers[15]. The carcinogenic mechanisms of $PM_{2.5}$ include oxidative stress, chronic inflammation, and genotoxicity[16,17]. Specifically, $PM_{2.5}$ exposure induces oxidative stress and inflammation, leading to cellular damage, DNA mutations, and impaired repair mechanisms[18,19], which in turn promote cancer progression. Reactive oxygen species (ROS) generated by $PM_{2.5}$ exposure damages cellular structures and activates immune cells to release pro-inflammatory factors [e.g., Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α)], creating a pro-carcinogenic environment[20,21].

The association between air pollution and diabetes is also well established. A 12-year follow-up study demonstrated a significant positive correlation between air pollution and diabetes progression[22]. Our findings support evidence that $PM_{2.5}$ exposure is linked to cancer as a complication of diabetes. $PM_{2.5}$-generated ROS can damage pancreatic islet cells, impairing insulin secretion[23], while systemic inflammatory triggered by $PM_{2.5}$

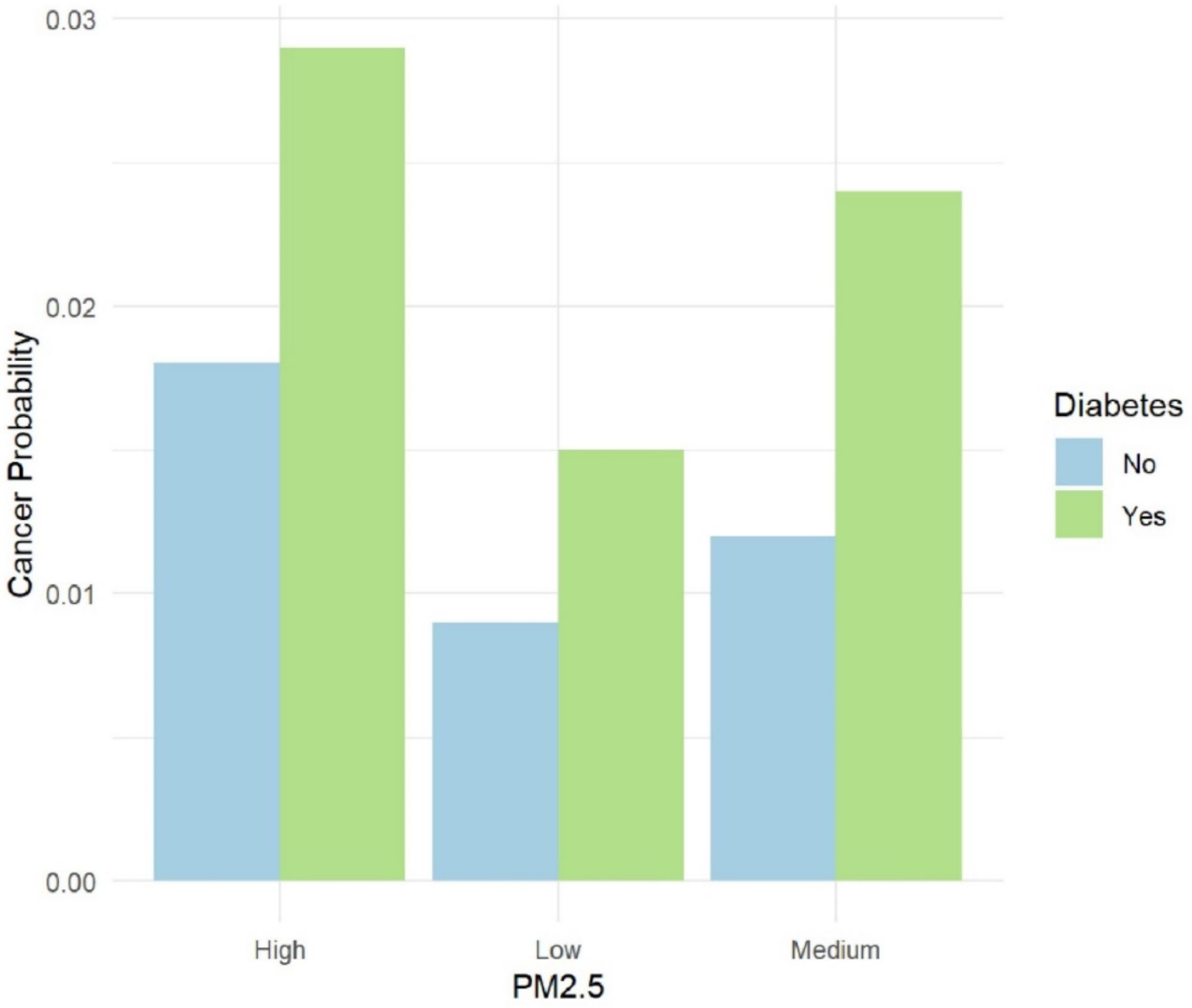

Fig. 5. Sensitivity analysis of cancer risk across different $PM_{2.5}$ exposure levels in individuals with and without diabetes.

affects metabolic tissues, such as adipose and liver tissue, leading to insulin resistance[24]. Together, these effects reduce insulin sensitivity and may advance to diabetes if left unaddressed[25]. Mechanistically, the same pathways of oxidative stress and inflammation that underlie $PM_{2.5}$'s carcinogenic effects may also contribute to diabetes onset and its subsequent impact on cancer risk (Zhang et al., 2020). By investigating diabetes as a mediating factor in the $PM_{2.5}$-cancer relationship, this study sheds light on the intricate interactions between air pollution, diabetes, and cancer.

Previous studies have shown that diabetes is associated with various cancer, including lung[26], liver[17], and kidney cancers[27], and that diabetic patients are more susceptible to environmental factors like $PM_{2.5}$, which further increases their cancer risk. This study investigates diabetes as a mediating factor in the $PM_{2.5}$-cancer association, focusing on two key pathways: chronic inflammation and oxidative stress. First, $PM_{2.5}$ exposure activates alveolar macrophages and neutrophils, leading to the release of pro-inflammatory factors that trigger the JAnus Kinase- Signal Transducer and Activator of Transcription (JAK/STAT) and Nuclear Factor kappa-B (NF-κB) signaling pathways. In vitro studies have shown that inhibiting the JAK2/STAT1/NF-κB pathway can reduce $PM_{2.5}$-induced inflammatory[28]. Since pancreatic β-cell dysfunction and JAK/STAT signaling plays a role in diabetes[29], $PM_{2.5}$ exposure may exacerbate inflammation in diabetic patients through this pathway. Second, individuals with diabetic, due to weakened antioxidant defenses, are particularly susceptible to $PM_{2.5}$-induced oxidative stress, which leads to DNA damage, inflammation, and cancer progression[30,31]. The NF-κB pathway, activated by this oxidative stress, promotes cell proliferation and invasiveness, ultimately increasing cancer risk[32]. Research on mouse alveolar macrophages indicated that high-glucose conditions enhance NF-κB activation and inflammatory factor secretion under $PM_{2.5}$ exposure[33]. Moreover, diabetic patients exhibit higher baseline levels of oxidative stress and inflammation markers than non-diabetic individuals, potentially due to impaired antioxidant defenses and chronic inflammation[34]. Under $PM_{2.5}$ exposure, they often show amplified responses,

with increased ROS production and decreased cellular antioxidant activity. This heightened oxidative stress may aggravate DNA damage and impair repair capacity, contributing to elevated cancer risk. Additionally, elevated levels of inflammatory markers, such as IL-6, TNF-α, and C-reactive protein (CRP) in diabetic individuals, create a pro-inflammatory environment conducive to cancer development[35]. Future research could explore diabetes's role as a mediator in the $PM_{2.5}$-cancer pathway, deepening our understanding of these mechanisms.

This is the first nationwide study in China to analyze diabetes as a mediating factor in the association between air pollution and cancer. Through a stepwise approach, we applied linear analysis, RCS analysis, Bayesian network-based conditional independence testing, and mediation analysis to validate our findings, followed by sensitivity analysis to enhance the reliability of the results. By examining commonly encountered air pollutants, this study provides valuable insights into cancer risk factors and highlights how varying concentrations of $PM_{2.5}$ exposure influence cancer risk, especially in the context of diabetes. These findings support clinicians and public health professionals in developing targeted prevention strategies tailored to regional conditions.

However, there are several limitations to consider. First, the cross-sectional nature of this study restricts causal inference; future longitudinal studies are needed to confirm these associations. Second, although we controlled for confounders previously identified, genetic factors were not included, potentially impacting the generalizability of the results. Third, while we aimed to explore the mediating role of diabetes in the relationship between air pollution and cancer, the limited sample size for specific cancer types in the CHARLS database prevented stratified analyses by cancer type. For instance, the number of cases for certain cancers, such as lung cancer ($n = 14$) and liver cancer ($n = 18$), was too small to produce statistically reliable results. As a result, we aggregated all cancer cases to analyze overall cancer risk, which may have obscured potential heterogeneity across different cancer types. Fourth, this study focused on a Chinese population, necessitating multi-country research to verify these findings across diverse geographic and ethnic contexts. Lastly, while PM levels were estimated with a satellite-based spatiotemporal model, intra-provincial variations in exposure were not accounted for, which may affect the accuracy of our exposure assessments.

Conclusion

In summary, our study reveals a dual role of $PM_{2.5}$ in elevating cancer risk, both directly and indirectly through diabetes as a mediating factor. This underscores the importance of addressing air pollution and managing diabetes to reduce cancer incidence, offering valuable insights for public health strategies.

Data availability

The CHARLS data used in this work are publicly available; they are unrestricted use data that any researcher can obtain from the CHARLS website. The URL is https://charls.charlsdata.com/.

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Author contributions

Z. L.: Conceptualization; Formal analysis; Software; Writing-original draft; Writing-review & editing. Y. S.: Writing-original draft; Software; Visualization; Data curation. H.T.: Writing-review & editing; Formal analysis; Methodology. B.Z.: Methodology. X. L.: Writing-review & editing, Data curation, Methodology. J. G.: Resources; Writing-review & editing. Y. S.: Funding acquisition; Supervision; Writing-review & editing, Project administration, Conceptualization.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The Medical Ethics Board Committee of Peking University granted the study an exemption from review.

Additional information

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