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Clinical Research Article

Role of Liver Enzymes in the Relationship Between Particulate Matter Exposure and Diabetes Risk: A Longitudinal Cohort Study

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Abstract

Context: Particulate matter (PM) is an important risk factor for diabetes. However, its underlying mechanisms remain poorly understood. Although liver-derived biological intermediates may play irreplaceable roles in the pathophysiology of diabetes, few studies have explored this in the association between PM and diabetes.

Objective: We investigated the role of liver enzymes in mediating the relationship between PM exposure and diabetes.

Methods: We included a total of 7963 participants from the China Multi-Ethnic Cohort. Residential exposure to PM was assessed using a validated spatial-temporal assessment method. Diabetes was diagnosed according to the criteria from American Diabetes Association. Associations between PM, liver enzyme [including alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase (GGT)], and diabetes were estimated using multivariable regression models. The function of liver enzymes in the relationship between PM and diabetes was assessed using mediation analysis.

Results: PM exposure was positively associated with the odds of diabetes, with odds ratios of 1.32 (95% CI 0.83, 2.09), 1.33 (95% CI 1.07, 1.65), and 1.18 (95% CI 1.02, 1.36) for every 10-μg/m^3 increment in ≤1 μm (PM_1), ≤2.5 μm ($PM_{2.5}$), and ≤10 μm (PM_{10}) PM, respectively. ALT (4.47%) and GGT (4.78%) exhibited statistically significant mediation effects on the association between $PM_{2.5}$ and diabetes, and the ALT (4.30%) also had a mediating role on PM_{10}. However, none of the liver enzymes had a significant mediating effect on PM_1.

Conclusion: The relationship between PM and diabetes is partially mediated by liver enzymes, suggesting that lipid accumulation, oxidative stress, and chronic inflammation in the liver may be involved in its pathogenesis.

Key Words: particulate matter, liver, diabetes, biomarkers, mediation, mechanisms

The ever-expanding pandemic of diabetes has caused a tremendous public health burden around the world. In 2019, there were approximately 463 million diabetic individuals and around 4.2 million diabetes-related deaths worldwide (1). Therefore, it is vital to identify the hazardous factors and causative mechanisms of diabetes to enhance its prevention and delay its progression.

Ambient particulate matter (PM) has been recognized as an important risk factor for diabetes (2-5). Globally, ≤2.5 μm PM ($PM_{2.5}$) has been implicated as the cause of approximately 3.2 million diabetes cases (6). Although several studies have shown that PM exposure increases the risk of diabetes (7), the mechanisms underlying this association have not been fully established. Further investigation of this pathophysiology

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may offer new ideas to inhibit the burden of PM-associated diabetes. Previous studies have hypothesized various plausible mechanisms (8, 9), including the primary initiation response (eg, oxidative stress), transmission pathways (eg, biological intermediates), and end-organ effectors. However, existing epidemiological studies have mainly focused on the primary initiation response (10-12), whereas few studies have explored the importance of biological intermediates in the relationship between PM and diabetes.

As biological intermediates, liver enzymes may play an essential role in the association between PM and diabetes. First, inhaled PM can penetrate the alveoli and gain access into the systemic circulation and then transferring to distal organs (eg, the liver) for metabolism and biotransformation (13). Therefore, PM and its metabolites can directly or indirectly affect liver function, as has been demonstrated in animal studies (14, 15). Epidemiological studies (16, 17) have shown that PM exposure is associated with abnormal liver enzyme levels. Second, as reflected by liver enzymes, steatosis, inflammatory reactions, and oxidative stress are all considered early events in the development of diabetes (18-19), suggesting that liver enzymes may be a link in the metabolic mechanism of diabetes (18). Recently, some relevant literature has verified liver enzymes as risk factors for diabetes in different populations (19-21). Finally, animal studies (22, 23) have established the mechanism of PM exposure → pathological degeneration of the liver → early events in diabetes. Although both animal evidence and epidemiological evidence support the possible role of liver enzymes in the relationship between PM and diabetes, the extent to which this occurs in the population remains unclear.

This study assessed the relationship between PM exposure and diabetes and further analyzed whether liver enzymes mediate this relationship in Chinese adults. We aimed to elucidate the potential role of liver biomarkers and their related physiological changes from air pollution in diabetes and to provide insights into interventions and screening priorities for diabetes.

Materials and Methods

Study Population

Data were obtained from the China Multi-Ethnic Cohort (CMEC), which recruited 99 556 participants aged 30 to 79 years in 5 provinces of southwest China through multistage stratified-cluster sampling, taking into account ethnic features, population distribution, and chronic disease patterns (24). Between May 2018 and September 2019, all participants completed a baseline survey, including an electronic questionnaire (to obtain information on demographic characteristics, behavioral lifestyle, and health-related status), medical examinations (to obtain relevant physical characteristics), and the administration of clinical laboratory tests for biological specimens (to obtain biochemical indicators). From 2020 to 2021, all surviving participants were invited to resurvey based on a telephone follow-up and on-site repeat surveys. The latter was consistent with that of the baseline survey. The data were subjected to rigorous quality control measures, including on-site surveys by local people, audio quality control of the surveys, and a double-entry method for questionnaire verification. All participants signed an informed consent form before the data were collected. Ethical approval was obtained from the Sichuan University Medical Ethical Review Board (approval nos. K2016038 and K2020022).

The current study included participants who received an on-site repeat survey, and it excluded (1) residents of Aba because they lived nomadically and had no fixed residence; (2) residents of Tibet because there was too few air pollution monitoring sites in Tibet to obtain accurate exposure data; (3) individuals with an incomplete residential address; (4) individuals who had lived at their current address for <2 years; (5) individuals with any reported physician-diagnosed liver diseases, including hepatitis, cirrhosis, and liver cancer; (6) individuals with diabetes, including physician-diagnosed and physical examination–diagnosed diabetes, at the time the baseline survey was administered; and (7) individuals without available or accurate information on any exposure, mediator, outcome, or adjusted variable. After implementing these exclusion criteria, 7963 participants were included in the current study (Fig. 1).

Air Pollution Exposure Assessment

Under a spatial resolution of 1 km × 1 km, the daily concentrations of ambient PM [including PM with aerodynamic diameters of ≤1 μm (PM_1), ≤2.5 μm ($PM_{2.5}$), and ≤10 μm (PM_{10})] from 2015 to 2018 were estimated using extremely randomized trees, a tree-based ensemble machine learning approach in which randomness goes 1 step further in way splits. Briefly, ground-based measurements of air pollutants were estimated through an extremely randomized tree model based on ground-based monitoring station data from the National Environmental Monitoring Center of China [see Supplementary Figure 1 (25)], meteorological information, land coverage information, satellite remote-sensing data, topographic information, population distribution data, pollution emission data, and other spatial-temporal predictors. The models have been validated using a 10-fold cross-validation approach, and the results showed that 10-fold cross-validation root mean-square error (R^2) values for the daily prediction of PM_1, $PM_{2.5}$, and PM_{10} were 0.77 (14.6 μg/m^3), 0.90 (10.01 μg/m^3), and 0.86 (24.28 μg/m^3), respectively. Details of the exposure data content and analysis process have been described in previous studies (26-28).

The residential locations acquired at baseline were geocoded, and the annual PM concentrations were subsequently calculated for all participants. The average concentrations of PM_1, $PM_{2.5}$, and PM_{10} at 2 years before the baseline survey were assigned to each participant as surrogate exposure variables.

Outcome and Mediator Ascertainment

Blood samples from all participants, taken after a fasting period of at least 8 hours, were collected on site by professionals and used for clinical laboratory tests according to a standard protocol. The tests included routine blood examinations, blood lipid examinations, fasting blood glucose measurements, and liver function tests, which measured the fasting blood glucose, hemoglobin A1c (HbAlc), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT) levels.

The levels of liver enzymes (ALT, AST, ALP, and GGT) measured in the baseline survey were estimated as mediators for this study. Diabetes status was assessed using criteria from the American Diabetes Association (29), and the diagnoses included self-reported physician-diagnosed diabetes, a fasting blood glucose level of ≥7.0 mmol/L, and an HbAlc of

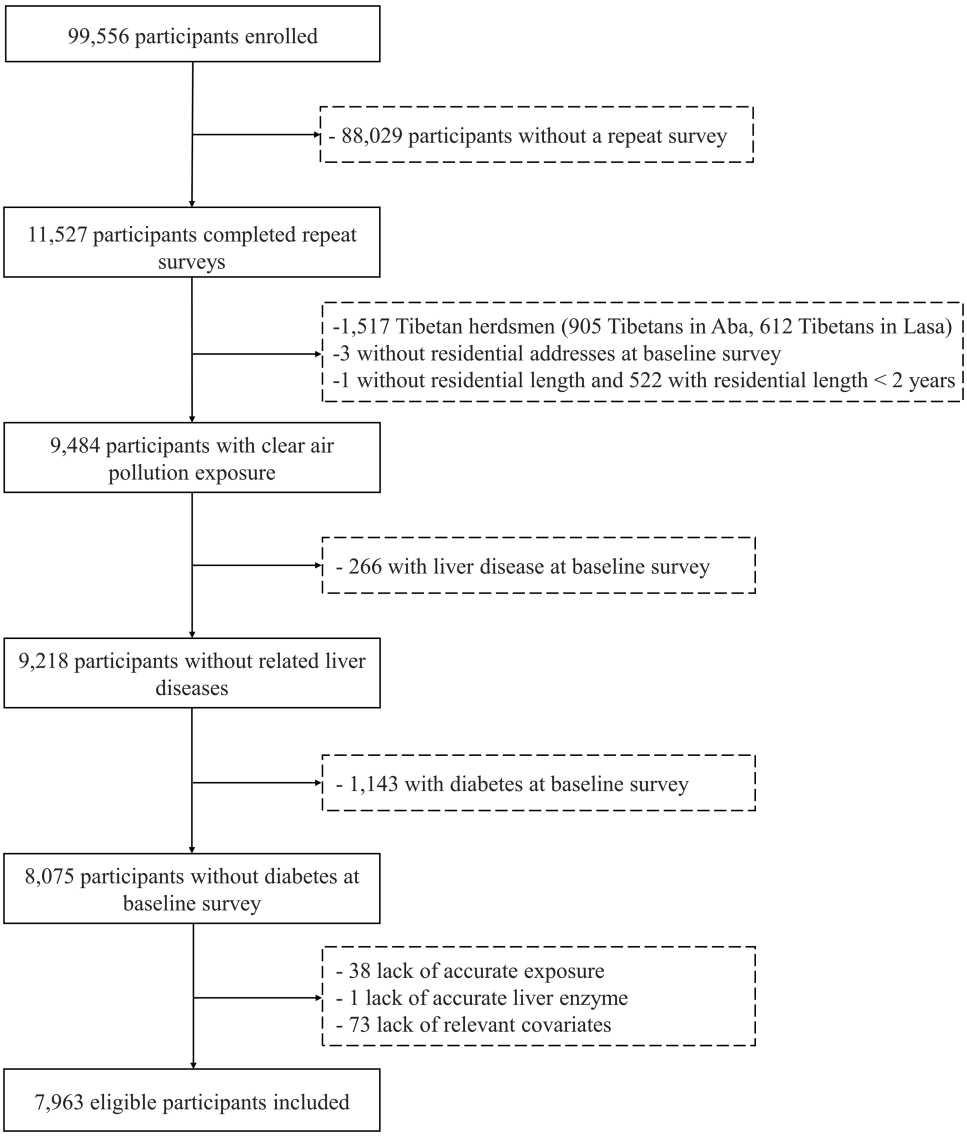

Figure 1. Flow charts for participant enrollment.

≥48 mmol/mol (6.5%), as observed during the repeat survey phase. This diagnostic criteria does not distinguish between diabetes types (type 1 or type 2).

Statistical Analysis

Descriptive Analysis

Descriptive and frequency statistics were generated for continuous and categorical demographic characteristics, lifestyle behaviors, environmental factors, and other information. Exposure maps were created based on the geographical location and exposure concentrations of each study participant, and the overall distribution of the exposure was described for each survey site.

Regression Analysis

Multivariable linear regression models were used to assess the long-term effects of PM exposure and liver enzyme levels as continuous variables. Multivariable logistic regression models were used to estimate the PM exposure and 4 types of liver enzyme levels with diabetes as a dichotomous outcome. To normalize the distribution of the liver enzyme levels, a natural logarithmic transformation was required for analysis, but the results were reported after conversion to the original scale. Odds ratios (ORs) and unstandardized regression coefficients with 95% CIs were reported for dichotomous and continuous outcomes, respectively.

Three models were used to evaluate these associations: a crude model (Model 0) and 2 adjusted models (Models 1 and 2). Model 0 was the initial crude estimated model; Model 1 was adjusted for demographic characteristics (age, sex, annual household income, ethnic group, and residential type), and Model 2 was additionally adjusted for lifestyle behaviors [smoking status, second-hand smoke status, alcohol consumption, indoor pollution, physical activity, and Mediterranean diet (MED) score] and environmental factors (season and nitrogen dioxide (NO_2)].

Mediation Analysis

We defined, identified, and estimated mediating effects within the counterfactual framework of causal inference, a methodological estimation that relies exclusively on counterfactual

outcomes without referencing any specific statistical models (30, 31). On the technical level, for each candidate liver enzyme mediator, we fitted 2 linear regression models: (1) the mediator model, with the liver enzyme level as the outcome and PM exposure as a predictor, adjusting for age, sex, annual household income, ethnic group, residential type, smoking status, secondhand smoke status, alcohol consumption, physical activity, MED score, indoor air pollution, season, and NO_2, and (2) the outcome model, with diabetes as the outcome and PM exposure as a predictor, adjusting for liver enzyme mediators and covariates in the same manner as in the first model. A simulation-based mediation approach was used to estimate and test the mediating effect of liver enzymes on the link between PM and diabetes. We used 2000 simulations to obtain the estimates and 95% CIs. This method was implemented using the *mediation* package in R (32). PM exposure and liver enzymes were included as the continuous variables, whereas diabetes was included as a dichotomous variable.

The previously described model can examine the direct effect of 2-year average PM concentration before the baseline survey on the risk of diabetes at follow-up, as well as the indirect effect of PM on the risk of diabetes via liver enzymes during the baseline investigation (Fig. 2).

Covariate Definitions

Based on previous literature, the adjusted model included the following covariates: age, sex (male or female), annual household income (<20 000 yuan, 20 000-99 999 yuan, or ≥100 000 yuan), ethnic group [Han (basin), Han (highland), Buyi, Dong, Miao, Bai, or Yi), residential type (urban or rural), smoking status (nonsmoker, current smoker, or previous smoker), secondhand smoke status (yes or no), alcohol consumption (never, moderate, or high), physical activity, MED score, indoor air pollution (none, low/moderate, or high), season (spring, summer, autumn, or winter), and NO_2 (μg/m^3). Alcohol consumption was classified according to the amount of alcohol consumed: "never" was defined as no alcohol consumed; "moderate" was classified as ≤25 g/day, and ≤15 g/day of alcohol consumed for men and women, respectively; and "high" was classified as >25 g/day and >15 g/day of alcohol consumed for men and women, respectively. Physical activities were qualified in terms of daily metabolic equivalent tasks, including occupation, transport, exercise, household, and leisure time activities. Indoor air pollution is made up of 2 components, fuel type and fume extraction device settings: "none" if no fuel was used, "low/moderate" if clean energy or a fume extraction device was used, and "high" if nonclean energy (including firewood, charcoal, and coal) and no fume extraction device were used.

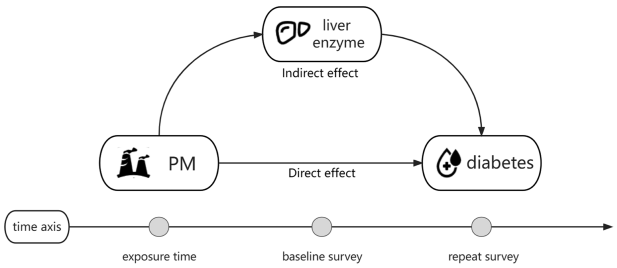

Figure 2. The particulate matter-liver enzyme-diabetes mediation model and temporality relationships.

Sensitivity Analyses

In the sensitivity analysis, we assessed the linearity assumption of the exposure-response relationship using a penalized spline model, including the associations of PM with diabetes and PM with liver enzyme levels. To ensure the stability of the study results, additional analyses were performed: (1) addition of family history of diabetes as a covariate in the fully adjusted model; (2) exclusion of participants with pregnancy, cancer, or tuberculosis (192 participants were excluded, 127 for tuberculosis, 64 for cancer, and 1 for pregnancy); (3) exclusion of participants with suspected type 1 diabetes based on a diagnostic criteria (33) for using age at diagnosis and time to commencing insulin treatment from diagnosis (7 participants were excluded); and (4) use of the concentration of PM for 1-, 3-, and 4-year averages before the baseline survey to determine the long-term effects of PM.

All analytical processes were performed using the R software (version 4.1.1). The significance threshold was set at 0.05, and all significance assessments were 2-sided.

Results

Descriptive Analysis

A total of 7963 participants were included in this study. The average age of the participants was 51.11 years (SD = 10.73 years), and 62.2% (n = 4952) were female. The median (interquartile range) levels of the ALT, AST, ALP, and GGT were 19.00 U/L (12.00 U/L), 24.00 U/L (9.00 U/L), 78.00 U/L (32.00 U/L), and 21.00 U/L (20.80 U/L), respectively. Liver enzymes, demographic characteristics, lifestyle behaviors, environmental factors, and other information classified according to the disease state were shown in Table 1. The mean follow-up time was 1.99 years (SD = 0.29 years), and 345 (4.33%) participants developed diabetes during the follow-up period. A comparison between the 99 556 eligible participants and 7963 included participants was shown in Supplementary Table 1 (25).

The mean PM concentration in the 2 years before the baseline survey varied considerably among the study sites [Fig. 3; Supplementary Table 2 (25)]. The 2-year average concentrations for PM_1, $PM_{2.5}$, and PM_{10} were 27.33 μg/m^3 (SD = 6.29 μg/m^3), 40.74 μg/m^3 (SD = 14.04 μg/m^3), and 70.97 μg/m^3 (SD = 20.72 μg/m^3), respectively.

Regression Analysis

The relationship between PM and liver enzyme levels is shown in Table 2. In the fully adjusted model, increased levels of $PM_{2.5}$ exposure were significantly associated with the increment of 4 liver enzymes. However, there was no statistically significant association between PM_{10} and the GGT level, and only the association between PM_1 and the AST or ALP level was statistically significant. In $PM_{2.5}$, a 10-μg/m^3-increment was related to a 2.84% (95% CI 0.78%, 4.94%), 5.23% (95% CI 3.91%, 6.58%), 11.18% (95% CI 9.91%, 12.47%), and 3.05% (95% CI 0.39%, 5.77%) increase in]ALT, AST, ALP, and GGT levels, respectively. PM_{10} had a weaker relationship with the liver enzymes than did $PM_{2.5}$. Each 10-μg/m^3 increment in PM_1 led to a 4.39% (95% CI 1.56%, 7.31%) and 7.57% (95% CI 4.87%, 10.34%) increase in the AST level and ALP level, respectively.

Table 1. Characteristics of the participants according to the presence of diabetes

Characteristics	Overall (n = 7963)	Diabetes (n = 345)	Nondiabetes (n = 7618)	*P*-value[a]
Liver enzyme				
ALT, U/L	19.00 (12.00)	21.00 (15.00)	18.50 (12.00)	0.001
AST, U/L	24.00 (9.00)	25.00 (9.00)	24.00 (9.00)	0.002
ALP, U/L	78.00 (32.00)	83.00 (35.00)	78.00 (32.00)	<0.001
GGT, U/L	21.00 (20.80)	28.00 (29.00)	21.00 (20.00)	<0.001
Demographic characteristics				
Age at baseline, years	51.11 (10.73)	56.57 (9.97)	50.86 (10.70)	<0.001
Sex, female	4952 (62.2)	199 (57.7)	4753 (62.4)	0.088
Annual household income, ¥				0.037
<20 000	2354 (29.6)	123 (35.7)	2231 (29.3)	
20 000-99 999	4281 (53.8)	172 (49.9)	4109 (53.9)	
≥100 000	1328 (16.7)	50 (14.5)	1278 (16.8)	
Ethnic group				<0.001
Han (basin) ethnicity	4480 (56.3)	159 (46.1)	4321 (56.7)	
Han (highland) ethnicity	823 (10.3)	49 (14.2)	774 (10.2)	
Buyi ethnicity	511 (6.4)	7 (2.0)	504 (6.6)	
Dong ethnicity	541 (6.8)	31 (9.0)	510 (6.7)	
Miao ethnicity	470 (5.9)	47 (13.6)	423 (5.6)	
Bai ethnicity	739 (9.3)	28 (8.1)	711 (9.3)	
Yi ethnicity	399 (5.0)	24 (7.0)	375 (4.9)	
Rural	3724 (46.8)	169 (49.0)	3555 (46.7)	0.430
Lifestyle behaviors				
Smoking status				0.035
Nonsmoker	6133 (77.0)	252 (73.0)	5881 (77.2)	
Current smoker	1444 (18.1)	80 (23.2)	1364 (17.9)	
Previous smoker	386 (4.8)	13 (3.8)	373 (4.9)	
Secondhand smoke status	4069 (51.1)	168 (48.7)	3901 (51.2)	0.391
Alcohol consumption				0.001
Never	4343 (54.5)	177 (51.3)	4166 (54.7)	
Moderate	3238 (40.7)	137 (39.7)	3101 (40.7)	
High	382 (4.8)	31 (9.0)	351 (4.6)	
Physical activity (METs/day)	26.59 (17.88)	24.75 (17.44)	26.67 (17.90)	0.051
MED score	8.57 (2.44)	8.65 (2.51)	8.57 (2.44)	0.527
Indoor pollution				0.230
None	1330 (16.7)	56 (16.2)	1274 (16.7)	
Low/moderate	6369 (80.0)	283 (82.0)	6086 (79.9)	
High	264 (3.3)	6 (1.7)	258 (3.4)	
Environmental factors				
Season				0.001
Spring	246 (3.1)	8 (2.3)	238 (3.1)	
Summer	1001 (12.6)	67 (19.4)	934 (12.3)	
Autumn	3025 (38.0)	123 (35.7)	2902 (38.1)	
Winter	3691 (46.4)	147 (42.6)	3544 (46.5)	
NO_2, μg/m^3	30.04 (11.96)	27.02 (10.42)	30.18 (12.00)	<0.001
Other information				
Follow time, years	1.99 (0.29)	2.06 (0.31)	1.99 (0.29)	<0.001
Length of residence, years	17.49 (15.50)	21.65 (18.69)	17.30 (15.31)	<0.001

Data are mean (SD) for continuous variables and number (percentage) for categorical variables. Liver enzymes do not follow a normal distribution, so the expression is the median (interquartile range).
Abbreviations: MET, metabolic equivalent task; MED, Mediterranean diet; NO_2, nitrogen dioxide.
[a]*P*-values were based on the Wilcoxon rank-sum test for the liver enzyme, Pearson's Chi-squared test for sex, annual household income, ethnic group, residential type, smoking status, secondhand smoke status, alcohol consumption, indoor pollution, and season; *t*-test for age, physical activity, MED score, NO_2, follow time, and length of residence. All statistical tests were 2-sided.

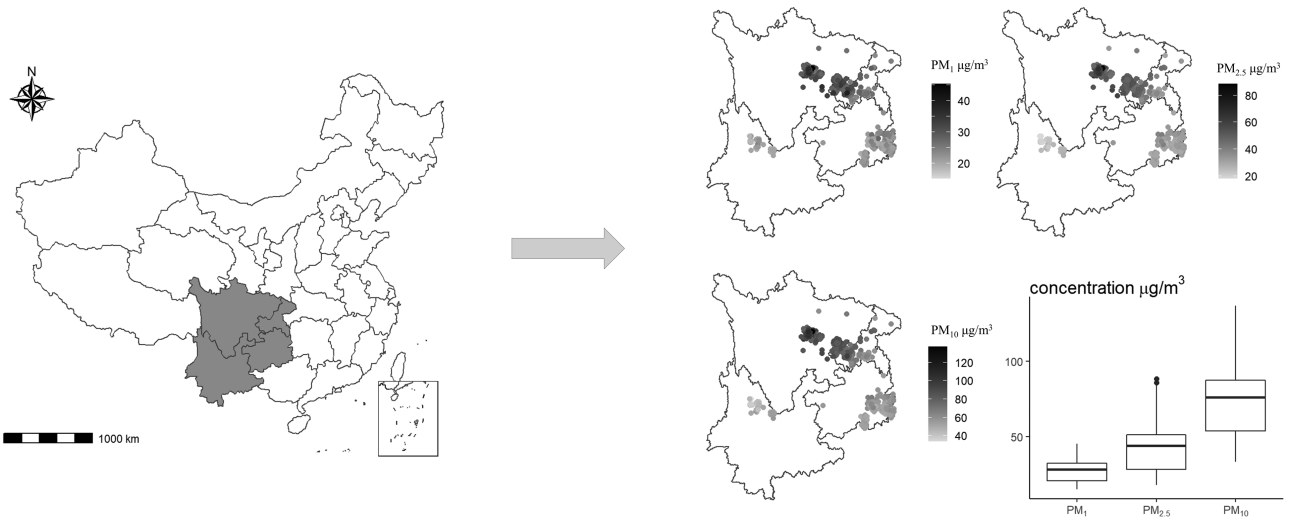

Figure 3. Two-year average ≤1, ≤2.5, and ≤10 μm particulate matter concentrations before the baseline survey in this study.

Table 2. Association between long-term particulate matter exposure and serum liver enzyme levels

Particulate matter, 10 μg/m³	% Change (95% CI) in liver enzyme[a]		
	Model 0[b]	Model 1[c]	Model 2[d]
PM_1			
ALT, U/L	−2.27 (−4.02, −0.49)	2.63 (−1.39, 6.82)	2.22 (−2.16, 6.80)
AST, U/L	−5.35 (−6.42, −4.27)	4.92 (2.30, 7.60)	4.39 (1.56, 7.31)
ALP, U/L	−2.86 (−3.90, −1.81)	9.31 (6.76, 11.92)	7.57 (4.87, 10.34)
GGT, U/L	−12.72 (−14.82, −10.56)	1.01 (−4.14, 6.42)	1.31 (−4.26, 7.20)
$PM_{2.5}$			
ALT, U/L	−0.50 (−1.30, 0.31)	3.36 (1.43, 5.31)	2.84 (0.78, 4.94)
AST, U/L	−1.78 (−2.28, −1.28)	6.08 (4.83, 7.34)	5.23 (3.91, 6.58)
ALP, U/L	0.00 (−0.48, 0.48)	12.75 (11.54, 13.98)	11.18 (9.91, 12.47)
GGT, U/L	−5.45 (−6.47, −4.41)	3.67 (1.15, 6.24)	3.05 (0.39, 5.77)
PM_{10}			
ALT, U/L	−0.50 (−1.04, 0.05)	2.02 (0.78, 3.28)	1.61 (0.26, 2.99)
AST, U/L	−1.29 (−1.63, −0.95)	3.77 (2.97, 4.57)	3.15 (2.29, 4.02)
ALP, U/L	0.00 (−0.33, 0.33)	7.57 (6.81, 8.34)	6.61 (5.79, 7.43)
GGT, U/L	−3.73 (−4.44, −3.01)	2.02 (0.40, 3.67)	1.72 (−0.03, 3.49)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase.
[a]Liver enzymes were natural log-transformed to normalize the data for analysis, and then the original scale was transformed back to present the effects as the percentage difference in liver enzymes with 95% CI.
[b]Model 0, not adjusted for any covariates.
[c]Model 1, adjust for demographic characteristics, including age, sex, annual household income, ethnic group, and residential type.
[d]Model 2, additionally adjusted for lifestyle behaviors (smoking status, secondhand smoke status, alcohol consumption, indoor pollution, physical activity, and Mediterranean diet score), and environmental factors (season and nitrogen dioxide).

Table 3 showed the relationship between PM and diabetes. In the fully adjusted model, each 10-μg/m³ increment in $PM_{2.5}$ and PM_{10} was related to an increased likelihood of developing diabetes during the follow-up, with increases in the odds by approximately 33% (OR 1.33, 95% CI 1.07, 1.65) and 18% (OR 1.18, 95% CI 1.02, 1.36), respectively. The link between PM_1 and diabetes risk was not statistically significant, although it was in the direction of a risk indication (OR 1.32, 95% CI 0.83, 2.09).

Increased levels of ALT or GGT were related to an increased odd of diabetes, with each 1-U/L increase leading to approximately 1.18-fold (OR 1.18, 95% CI 1.09, 1.28) and 1.18-fold (OR 1.18, 95% CI 1.12, 1.25) increases, respectively. However, increases in the AST and ALP levels were not statistically associated with the development of diabetes, although they were indicative of a risk of diabetes (AST: OR 1.07, 95% CI 0.95, 1.22; ALP: OR 1.12, 95% CI 0.97, 1.29).

Mediation Analysis

The results of the mediation analysis using each of the 4 liver enzymes as the only potential mediator in the model demonstrated that the AST and ALP levels did not mediate the relationship between PM and diabetes risk and that the ALT and GGT levels partially mediated the association between $PM_{2.5}$ or PM_{10} and diabetes risk (Fig. 4). The indirect effect of $PM_{2.5}$ or PM_{10} on increasing diabetes risk through ALT

Table 3. Odds ratios (95% CIs) of diabetes are associated with particulate matter exposure and liver enzyme

	OR (95% CI)		
	Model 0 [a]	Model 1 [b]	Model 2 [c]
Exposure, 10 μg/m^3			
PM_1	0.71(0.59, 0.84)	1.07 (0.70, 1.63)	1.32 (0.83, 2.09)
$PM_{2.5}$	0.90 (0.83, 0.97)	1.19(0.97, 1.45)	1.33 (1.07, 1.65)
PM_{10}	0.93 (0.88, 0.98)	1.08 (0.95, 1.24)	1.18 (1.02, 1.36)
Liver enzyme, 1 U/L			
ALT	1.14 (1.06, 1.23)	1.18 (1.09, 1.27)	1.18 (1.09, 1.28)
AST	1.20(1.07, 1.33)	1.08 (0.95, 1.22)	1.07 (0.95, 1.22)
ALP	1.33 (1.17, 1.51)	1.11 (0.97, 1.28)	1.12 (0.97, 1.29)
GGT	1.22 (1.16, 1.28)	1.20 (1.14, 1.27)	1.18 (1.12, 1.25)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; OR, odds ratio; PM1, particulate matter with aerodynamic diameters ≤ 1 μm; PM2.5, particulate matter with aerodynamic diameters ≤ 2.5 μm; PM10, particulate matter with aerodynamic diameters ≤ 10 μm.
[a]Model 0, not adjusted for any covariates.
[b]Model 1, adjust for demographic characteristics, including age, sex, annual household income, ethnic group, and residential type.
[c]Model 2, additionally adjusted for lifestyle behaviors (smoking status, secondhand smoke status, alcohol consumption, indoor pollution, physical activity, and Mediterranean diet score) and environmental factors (season and nitrogen dioxide).

was 2.21 × 10 and 1.24 × 10, with proportions mediated by 4.47% and 4.30%, respectively. The indirect effects of $PM_{2.5}$ increasing the risk of diabetes through GGT was 2.35 × 10, with a proportion mediated by 4.78%.

Sensitivity Analysis

The results of the penalized spline models regarding the associations of PM with diabetes and liver enzymes were shown in Supplementary Figure 2 (25). The results showed that the linearity assumption of the exposure-response relationship was appropriate, except for the association between PM and diabetes, which was mildly nonlinear. Given the presence of mild nonlinearity, we further assessed this association using the PM quartile as an exposure variable. Results were shown in Supplementary Table 3 (25). The findings indicated that the association of $PM_{2.5}$ and PM_{10} with diabetes was consistent with continuous exposure, but PM_1 changed from not statistically significant to statistically significant. The results of other sensitivity analyses are presented in Table 4. We observed that the results of the proportion-mediated value remained robust after adjusting for a family history of diabetes and restricting the sample for the analysis. When excluding patients with suspected type 1 diabetes, the mediating role of liver enzymes in PM-associated diabetes remained stable. When using the average concentrations of PM from a series of exposure windows, the mediated results for PM_1 were more variable but still not statistically significant, while the mediated results for $PM_{2.5}$ and PM_{10} exhibited a U-shaped relationship with the time of accumulation.

Discussion

Principal Findings

This longitudinal study demonstrated that long-term PM exposure was associated with elevated serum liver enzyme levels and positively associated with subsequent diabetes risk. To our knowledge, this is the first epidemiological study to provide evidence of the mediating role of altered liver enzymes in the association between PM and diabetes. Mediation analysis revealed that the serum ALT and GGT levels had a statistically significant mediating effect on diabetes risk associated with $PM_{2.5}$ or PM_{10}. Our findings highlight the significance of the potential application of tools or drugs associated with liver biomarkers for the prevention and treatment of air pollution-induced diabetes.

Comparison With Other Studies

The statistically significant association of diabetes with long-term exposure to $PM_{2.5}$ and PM_{10} was in line with the previous studies (5, 34, 35). Meta-analysis indicated that a 10-μg/m^3 increase in $PM_{2.5}$ concentration led to an increase in the risk of type 2 diabetes by 39% (95% CI 14%, 68%) (34). Another cohort study found that the risk of diabetes increased by 17% (hazard ratio 1.17, 95% CI 1.08, 1.26) for each 10-μg/m^3 increment in ambient PM_{10} (35). However, few studies have investigated the association between PM_1 and diabetes. A study conducted in rural China observed that a 1-μg/m^3 increase in PM_1 was positively associated with a 4.0% (95% CI 2.6%, 5.4%) increase in the odds of type 2 diabetes (36). However, our study only showed a positive, but not statistically significant, association between PM_1 exposure and diabetes risk. This contradiction is found at present owing to the diversity in research objects, research areas, pollutant composition, or sources. In this study, we observed a stronger association of diabetes with $PM_{2.5}$ than with PM_1 or PM_{10}. Studies have confirmed that the diameter of the PM directly determines where it can enter the body, and particles with smaller diameters are more likely to enter the deep layer (37). However, the virulence of PM depends not only on its diameter but also on the various substances it carries (38). Moreover, some sources of $PM_{2.5}$ may be enriched with factors that can lead to adverse health effects compared to PM_1 (38).

Our study found that long-term exposure to PM was associated with elevated liver enzyme levels, which is consistent with most published studies. A study (16) revealed that AST, ALT, and GGT levels increased by 0.02% (95% CI −0.04%, 0.08%), 0.61% (95% CI 0.51%, 0.70%), and 1.60% (95% CI 1.50%, 1.70%), respectively, for every 10-μg/m^3 increase in $PM_{2.5}$ annual average concentration (2 years). However, Markevych et al (39) demonstrated that only $PM_{2.5}$ was related to GGT, and there was no significant correlation

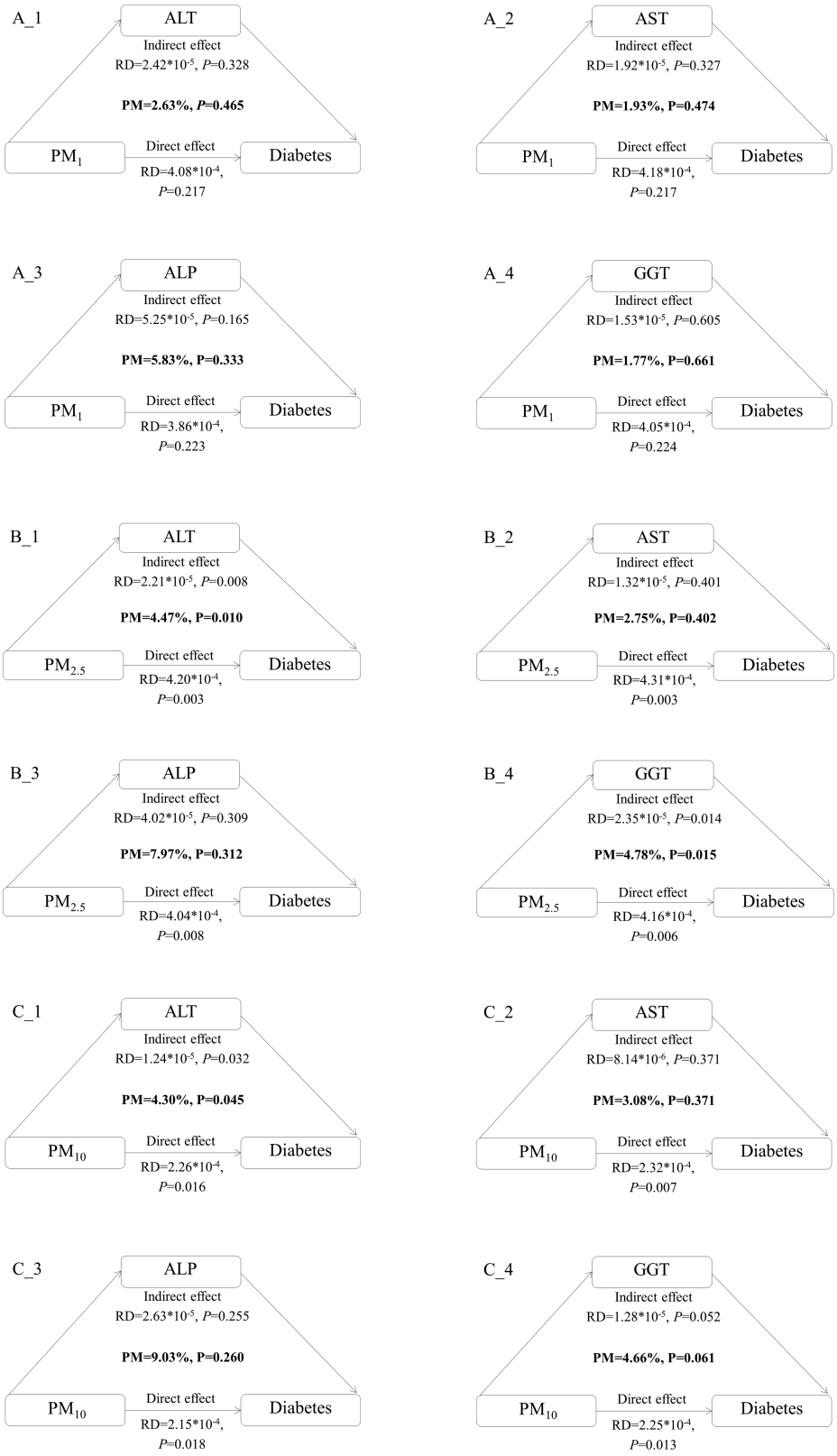

Figure 4. Mediating effect of liver enzymes on the particulate matter–associated diabetes. PM_1, particulate matter with aerodynamic diameters ≤ 1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameters ≤ 10 μm. Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; PM, proportion mediated; RD, risk difference.

between other types of liver enzymes or pollutants. However, the results are not comparable, as the study was conducted in Germany, where the mean PM concentrations are significantly lower than those in the current study area. In conclusion, existing studies have indicated that PM showed a stable positive correlation with elevated liver enzymes in different

Table 4. Sensitivity analyses for mediation effect (%, proportion mediated) of serum liver enzyme levels on particulate matter exposure with risks of diabetes

	Liver enzyme			
	ALT	AST	ALP	GGT
PM_1				
Main analyses[a]	2.63	1.93	5.83	1.77
Additional adjustments for:				
Family histories of diabetes	2.28	2.04	6.04	1.42
Restricted to:				
Those without pregnancy, cancer, or tuberculosis	2.92	2.03	7.61	2.35
Those without suspected type 1 diabetes	2.48	1.81	5.94	1.50
Exposure windows				
1 year before the baseline survey	1.34	1.34	7.71	0.80
3 years before the baseline survey	2.89	1.35	2.53	1.52
4 years before the baseline survey	2.09	0.94	0.19	1.06
$PM_{2.5}$				
Main analyses [a]	4.47[b]	2.75	7.97	4.78[b]
Additional adjustments for:				
Family histories of diabetes	4.22[c]	2.58	8.13	4.73[b]
Restricted to:				
Those without pregnancy, cancer, or tuberculosis	4.63[b]	2.80	9.79	5.02[b]
Those without suspected type 1 diabetes	4.10[b]	2.52	8.66	4.52[b]
Exposure windows				
1 year before the baseline survey	3.70[b]	2.88	8.31	3.96
3 years before the baseline survey	3.81[c]	2.24	6.42	4.79[b]
4 years before the baseline survey	4.58[b]	2.80	8.55	5.46[b]
PM_{10}				
Main analyses [a]	4.30[b]	3.08	9.03	4.66
Additional adjustments for:				
Family histories of diabetes	4.44[b]	3.12	9.78	4.63
Restricted to:				
Those without pregnancy, cancer, or tuberculosis	4.83[b]	3.54	11.57	5.05
Those without suspected type 1 diabetes	4.03[b]	2.90	9.55	4.24
Exposure windows				
1 year before the baseline survey	5.22	5.42	15.31	5.11
3 years before the baseline survey	5.43[b]	3.69	10.50	5.95[b]
4 years before the baseline survey	6.92[b]	4.52	12.80	7.27

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; PM1, particulate matter with aerodynamic diameters ≤ 1 μm; PM2.5, particulate matter with aerodynamic diameters ≤ 2.5 μm; PM10, particulate matter with aerodynamic diameters ≤ 10 μm.
[a]Model was adjusted for demographic characteristics (age, sex, annual household income, ethnic group, and residential type), lifestyle behaviors (smoking status, second-hand smoke status, alcohol consumption, indoor pollution, physical activity, and Mediterranean diet score), and environmental factors (season and nitrogen dioxide).
[b]*P*-value < 0.05.
[c]*P*-value < 0.01.

populations, including the elderly (40), newborns (41), and the general population (16).

This study also found that alterations in liver enzymes were related to the development of diabetes; however, only 2 enzymes, ALT and GGT, had statistically significant associations. To date, a strong link between diabetes risk and liver enzymes has been established in a large number of studies (42, 43). Most of the existing studies have concentrated on the relationship between ALT or GGT and diabetes, and studies have found ALT and GGT to be independent risk predictors for diabetes, which is consistent with the findings of this study. Few studies have elucidated the function of ALP in diabetes risk, with 1 cohort study conducted in China showing a positive association between baseline serum ALP levels and new-onset diabetes in patients with hypertension (20). As the participants in the study were patients, the distribution of health status and relevant characteristics of the population were not consistent with our study, causing results that are not comparable. In addition, our diagnostic criteria for diabetes were different from those of the study (excluding HbA1c), which may have led to the underdiagnosis of diabetic patients.

Potential Mechanism

The exact biological mechanisms by which PM induces diabetes remain unclear. Published studies have proposed a variety of potential pathways, such as oxidative stress response, proinflammatory mechanisms, and endothelial dysfunction. Recent findings, including animal experiments and epidemiological investigations, have indicated that changes in the physiological response within the liver may be another important mechanism. Reactive oxygen species (ROS) affect the liver. Excessive ROS levels disrupt liver homeostasis and increase oxidative stress in the liver. Some studies have hypothesized that exposure to ambient PM could activate ROS production (44) and enhance systemic stress (45), which can directly affect the normal metabolic process of the liver. Another reasonable assumption is that PM may also play a role in the pathology of liver diseases by altering lipid metabolism and inducing a proinflammatory environment, thereby indirectly affecting liver function (13). Impairment of liver function, which is responsible for detoxification, metabolism, bile secretion, and immune defense, can directly increase the risk of developing metabolic diseases such as diabetes. As a biomarker of liver injury, fluctuations in liver enzymes directly reflect physiological changes within the liver. Elevated liver enzyme levels may be the first response to air pollution in the liver.

This study focused on the role of 4 different liver enzymes, and the results suggest that ALT and GGT may partially mediate the association between PM and diabetes, which is consistent with the findings of several studies (43, 46, 47). ALT, a specific marker of hepatic fat accumulation, is related to hepatic insulin sensitivity, and fat changes are a specific response of the liver to proinflammatory cytokines (48). Furthermore, as a gluconeogenic enzyme, elevated ALT levels may indicate an insulin signal block. Therefore, fat changes and concomitant ALT elevation may reflect liver inflammation, which may damage local and systemic insulin-related signal transduction. Elevated GGT levels are a response to oxidative stress (21). Pancreatic β cells, which play an important role in the regulation of insulin secretion, are specifically susceptible to oxidative reactions because they contain fewer antioxidant enzymes (49). Oxidative stress is known to reduce insulin secretion by damaging the pancreatic β cells. In addition to this, GGT may also affect insulin secretion by regulating the activity of fat metabolism-related factors such as leptin and lipocalin, disrupting the normal feedback axis and leading to insulin resistance and diabetes (50). Taken together, our study suggests that liver enzymes have a significant and logical mediating role in the association between PM and diabetes, but the proportion of mediation suggests that liver enzymes have a limited mediating role, which may be related to the fact that the 4 liver enzymes in our study did not fully respond to all physiological changes within the liver.

Strengths and Weaknesses

This study has some limitations. First, we calculated the PM exposure concentration based on the participant's residential address rather than individual exposure (without consideration of travel and activity patterns). However, evidence suggests that this type of misclassification usually biases the effect estimates to null (51), indicating that our results were probably conservative. Second, liver enzyme levels were measured at only 1 time point, and this single measurement may bias the assessment of liver abnormalities owing to the presence of other nonpathological elevations. However, rigorous measurement procedures and quality control may reduce potential bias to some extent. Third, this study did not adjust for other environmental factors associated with diabetes such as traffic noise and green spaces. Furthermore, we made partial adjustments to the area-level socioeconomic status via adjusting for ethnic group (province and ethnic agglomerations) and residential type (rural and urban) but not for neighborhood socioeconomic status, which might bias the study results somewhat. Finally, not differentiating between type 1 and type 2 diabetes based on the gold standard may cause biases in interpreting the mechanism between PM and diabetes, even though the prevalence of type 1 diabetes was very low. Despite these limitations, this is the first and currently the largest epidemiological study to clarify the mediating role of liver enzymes in the association between ambient PM exposure and diabetes. A considerable sample size, strict investigation process, high-quality data, and the definition of the same outcome enabled us to acquire reliable and stable effect estimates. Furthermore, this study was longitudinal with a clear temporal relationship between exposure, mediators, and outcomes, which can address the problem of causal inversion in cross-sectional studies. This chronological relationship can further ensure the plausibility of this result. Finally, the sufficient diversity of the population and heterogeneity of environmental exposure from multiple sites increased the repeatability of our findings.

Future Research

Current studies have focused on the mediating role of liver enzymes in PM-related diabetes; however, the liver enzymes included in this study were primarily markers of liver injury. In addition, markers of liver function such as albumin, bilirubin, and prothrombin time may also reflect physiological changes in the liver. Therefore, the role of other liver biomarkers in the association between PM and diabetes should be investigated in the future.

Conclusion

This longitudinal study demonstrated that liver enzymes can partially mediate the relationship between long-term exposure to ambient PM and diabetes. These findings extend the knowledge of the current mechanisms of air pollution-induced diabetes and provide new insights into preventing diabetes and screening those at risk of diabetes.

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Conflict of Interest

All authors report no competing interests.

Data Availability

Data used in this study are available from the corresponding author upon reasonable request.

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