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Long-term exposure to ambient fine particulate matter and fasting blood glucose level in a Chinese elderly cohort

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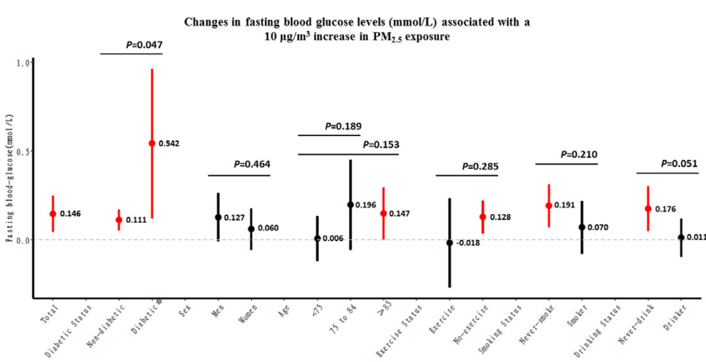
HIGHLIGHTS

- A longitudinal study was conducted in eight Chinese counties.
- Long-term $PM_{2.5}$ exposure was associated with an increase in fasting blood glucose.
- Elderly individuals with diabetes were more vulnerable to high exposure of $PM_{2.5}$.

GRAPHICAL ABSTRACT



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ABSTRACT

Fasting blood glucose level is the primary indicator for the diagnosis of diabetes. We aim to conduct a longitudinal study on the association between long-term fine particulate matter ($PM_{2.5}$) exposure and fasting blood glucose concentrations. We recruited and followed up 1449 participants older than 65 years of age in 2009, 2012, 2014, and 2017 in eight counties in China. Fasting blood glucose was repeatedly measured 3697 times in total among these participants. Data on annual ground-level $PM_{2.5}$ concentrations with a 0.01° spatial resolution from 2005 to 2016 were used to assess exposures. An increase of 10 μg/m^3 in 3-year average exposure to $PM_{2.5}$ was associated with an increase of 0.146 mmol/L (95% confidence interval [CI]: 0.045, 0.248) in fasting blood glucose in all participants. The association was more pronounced among the subgroup with diabetes compared to the subgroup without diabetes ($P < .05$). In conclusion, Long-term $PM_{2.5}$ exposure was associated with an increase in fasting blood glucose levels among elderly people. Elderly individuals with diabetes are particularly vulnerable to high level exposures of $PM_{2.5}$.

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Summary: Long-term $PM_{2.5}$ exposure was associated with an increase in fasting blood glucose levels among elderly people. Elderly individuals with diabetes are particularly vulnerable to high level exposures of $PM_{2.5}$.

1. Introduction

A total of 383 million people were diagnosed with diabetes in 2016, making it one of the leading causes of years lived with disability in 2016 (GBD-2016-Disease-and-Injury-Incidence-and-Prevalence-Collaborators, 2017). Based on data from the International Diabetes Federation, the global prevalence of diabetes is expected to increase to 592 million by 2035(Guariguata et al., 2014). The elderly population is a vulnerable group that is more susceptible to diabetes and diabetic complications (Mordarska and Godziejewska-Zawada, 2017). According to the sixth population census in China in 2010, there are 176 million people that are over 60 years of age, and that number will continue to grow (Gerland et al., 2014). The prevalence of diabetes in China was 11.6%, and higher in older age groups (Xu et al., 2013). Fasting blood glucose levels are traditionally used to diagnose and manage diabetes (American-Diabetes-Association, 2012; Internal-Clinical-Guidelines-Team, 2015) and is associated with altered risk of other major chronic conditions such as cardiovascular disease and cancer (Coutinho et al., 1999; Liao et al., 2015).

In addition to a number of established causes or risk factors for diabetes such as unhealthy behavior (drinking alcohol, or smoking, etc.), genetic factors, and chronic diseases (Bellou et al., 2018; Kong et al., 2016), ambient air pollution has been also associated with increased diabetes prevalence (Liu et al., 2016; Liu et al., 2019; Yang et al., 2020), and especially particular matter (PM) exposure (Liang et al., 2019; Meo et al., 2015; Park and Wang, 2014; Rao et al., 2015; Yang et al., 2018). Diabetes progresses over time, and even before formal diagnosis of diabetes, impaired fasting blood glucose levels alone may be hazardous to human health (Kong et al., 2016). There are many studies that have showed significant associations between fine particular matter ($PM_{2.5}$) and fasting blood glucose. However, most of these studies only explored the short-term effects of $PM_{2.5}$ on fasting blood glucose (Brook et al., 2013; Chen et al., 2016; Li et al., 2018b; Lucht et al., 2018; Ma et al., 2019; Meo et al., 2015; Peng et al., 2016). Studies focusing on long-term exposure of $PM_{2.5}$ and fasting blood glucose, on the other hand, are still lacking. Most existing long-term studies are cross-sectional studies, which has limited power in verifying causality (Chuang et al., 2011; Liu et al., 2016; Lu et al., 2017; Wolf et al., 2017; Yang et al., 2018; Zhang et al., 2019). Therefore, we conducted this repeated measurement longitudinal study in an elderly cohort to examine the association between long-term exposure to ambient $PM_{2.5}$ and fasting blood glucose concentrations.

2. Methods

2.1. Study population

We investigated 1449 participants older than 65 years of age in eight Chinese counties (Chengmai, Hainan Province; Sanshui, Guangzhou Province; Yongfu, Guangxi Province; Mayang, Hunan Province; Rudong, Jiangsu Province; Zhongxiang, Hubei Province; Xiayi, Henan Province; Laizhou, Shandong Province) (Fig. 1). Some participants (542) were recruited in 2009, and were followed up three times, in 2012, 2014 and 2017. In 2012, new participants (907) were also recruited and followed up two times, in 2014 and 2017. All individuals older than 100 were included; their neighbors younger than 100 were invited to participate in the study. Additional details regarding the participants are described in the previously published articles(Ma et al., 2017; Yin et al., 2012). Written consent forms were provided by each participant, and the ethics committee of Peking University approved this study.

2.2. FBG assessment

Participants were asked not to eat for at least 8 h prior to the morning of blood collection day to accurately determine fasting glucose. Among the 1449 participants, two, three and four serial fasting blood glucose measurements were available for 769, 561 and 119 participants, respectively. We defined diabetes using the data from the baseline survey. Self-reported physician-diagnosed diabetes or fasting glucose levels >7.0 mmol/L were defined as diabetes. In total, we analyzed 3697 fasting blood glucose measurements and questionnaire data acquired over an 8-year timespan.

2.3. Assignment of exposure data

Ambient annual $PM_{2.5}$ data from 2005 to 2016 were obtained from the Atmospheric Composition Analysis Group, Dalhousie University (Nova Scotia, Canada). Ground-level $PM_{2.5}$ concentrations with a 0.01° spatial resolution were estimated by applying geographically weighted regression using information from satellite-, simulation- and monitor-based sources. The R^2 of the satellite-based estimation and $PM_{2.5}$ concentrations from monitors is 0.81 (van Donkelaar et al., 2016). $PM_{2.5}$ concentrations were assigned to each participant by home address. Because the cohort was followed up in 3 years averages, $PM_{2.5}$ concentrations were assigned to the previous year (lag1), and we then calculated the previous year to 2-year (lag1–2) and the previous year to 3-year (lag1–3) moving averages, based on the year of survey.

Meteorological data were obtained from the European Centre for Medium-Range Weather Forecasts (https://cds.climate.copernicus.eu/cdsapp#!/search?type= dataset). Annual temperature and humidity data were matched by the home address of the participant and the investigation year.

2.4. Assessment of potential confounders

Potential confounders related to $PM_{2.5}$ exposure and fasting blood glucose were collected by questionnaire from face to face interviews, including sociodemographic characteristics (such as sex, age, education years, marital status, and home address), smoking and drinking status, exercise habits, and dietary intake. We defined former and current smokers as ever smokers, and similarly defined former and current drinkers as ever drinkers.

2.5. Statistical analysis

Linear mixed models in the package "lme4" were used for the analysis between $PM_{2.5}$ and fasting blood glucose concentrations using the statistical software R, version 3.4.2. First, we conducted a nonlinear analysis. We introduced a basis matrix generated by "dlnm" package for $PM_{2.5}$ concentration (lag1–3), modeled using a natural spline with 2 degrees of freedom. The model adjusted for age, years of education, body mass index (BMI), family income, staple food intake linearly; sex, marital status, residence, smoking and drinking status as indicator/categorical variables; exercise status as fixed effects; and participant and county as random effects. We found that the shape of the curve was

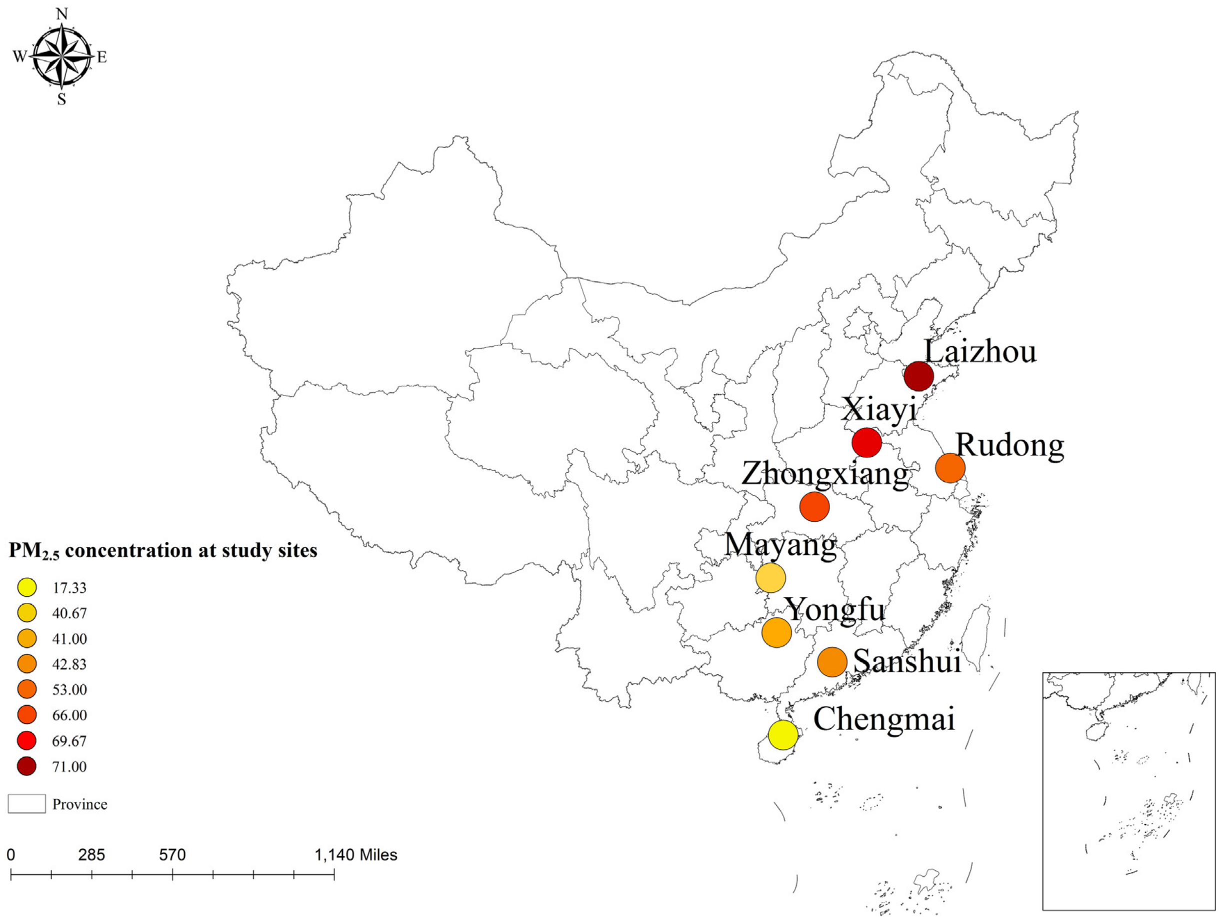

Fig. 1. Map of the median of $PM_{2.5}$ annual average concentration in eight counties.

almost linear (Fig. 2.). We then remodeled $PM_{2.5}$ concentration as a linear variable, and adjusted for the same covariates mentioned above as with our non-linear model. We also tested various lag effects of $PM_{2.5}$ concentrations. The correlations of independent variables are shown in Table S1.

We then conducted stratified analyses by sex, age groups, smoking status, and drinking status. We used the following formula (Di et al., 2017) to determine whether the risk estimates of $PM_{2.5}$ in subgroup *a* versus subgroup *b* were statistically different (H0: $\beta a = \beta b$):

$$Z = \frac{\beta_a - \beta_b}{\sqrt{se(\beta_a)^2 + se(\beta_b)^2}}$$

As sensitivity analyses, we removed the covariates one-by-one from the main analysis model to determine the stability of our model. Furthermore, we replaced smoking and drinking status (ever vs never) in the main analysis model with current smoking and drinking status. To determine whether fruit intake is a potential confounder, we added the intake of fruit to the main analysis model (Du et al., 2017). In addition, we introduced temperature and humidity into the main analysis model. Finally, we used a linear regression model instead of a linear mixed model to determine the change in the effect estimate without adjusting for the random effects. In the linear regression model, we removed the random effect of participants from the main analysis model, and changed the random effect of the county to a fixed effect, keeping all other covariates identical to that of the main analysis model.

3. Results

The ages of the participants ranged from 65 to 112 years. Almost half of the participants were women (52.6%), and more than half had not

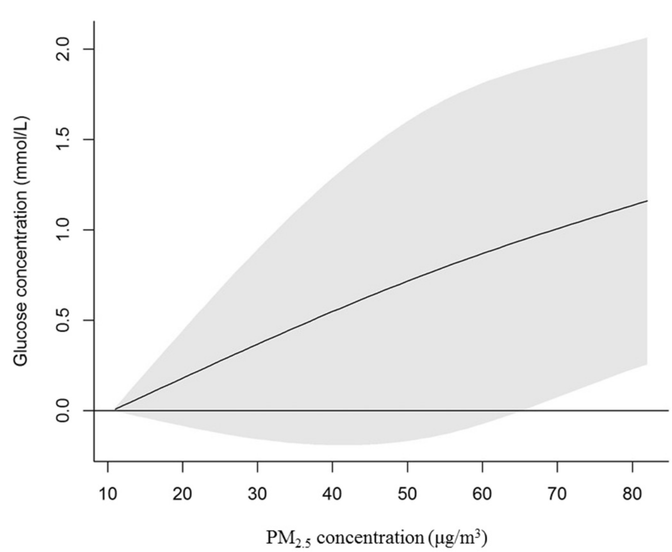

Fig. 2. Increase of glucose concentration (mmol/L) associated with increase of previous 3 years average $PM_{2.5}$ exposure (compared with the minimum concentration of $PM_{2.5}$ exposure).

received education in school (53.1%). Most of the participants lived in rural areas (82.9%) (Table 1). The 3-year average $PM_{2.5}$ concentration ranged from 11 to 82 μg/m^3 with a median concentration of 56 μg/m^3; the interquartile range of $PM_{2.5}$ exposure was 27 μg/m^3. The $PM_{2.5}$ exposure of participants in the baseline survey in each county is shown in Fig. 1. The participants with the highest exposure resided in Laizhou County, Shandong Province, and the lowest exposure was in Chengmai, Hainan Province.

Table 2 shows the variation in estimated fasting blood glucose levels with each 10 μg/m^3 increase in annual $PM_{2.5}$ exposure. An increase of 10 μg/m^3 in previous 3 years average exposure to $PM_{2.5}$ was associated with a blood glucose increase of 0.146 mmol/L (95% confidence interval [CI]: 0.045, 0.248) in the main analysis for all participants. For participants with an increase in annual exposure of $PM_{2.5,}$ subgroups analyses showed significant differences among those with and without diabetes, age ≥ 85, without regular exercise, never smoking or never drinking. The subgroup with diabetes had a higher estimated increase in fasting blood glucose levels than the subgroup without diabetes ($Z = 1.99$, $P = .047$). Details comparing estimated value between subgroups are shown in Table S3. After conducting relevant sensitivity analyses (changing the covariates and estimation approach), the estimated effects were stable (Table 3), suggesting that our models were robust.

4. Discussion

To the best of our knowledge, this is the first multi-center longitudinal study focused on the association between fasting blood glucose levels and long-term $PM_{2.5}$ exposure. We observed an increase in fasting blood glucose level in the elderly population exposed long-term to $PM_{2.5}$. Furthermore, elderly participants with diabetes were more likely to have increased fasting blood glucose levels under high exposure to $PM_{2.5}$.

A few studies have explored the relationship between long-term $PM_{2.5}$ exposure and fasting blood glucose concentrations, and most of the studies have been cross-sectional. In a survey conducted in southern Germany with 2944 participants, Wolf et al. (2017) found no statistically significant association of $PM_{2.5}$ exposure and fasting blood glucose concentrations in the entire population ($\beta = 0.308$ mmol/L; 95%CI: 0, 0.634). Studies have also been conducted in China. For example, Lu et al. (2017) observed a significant association ($\beta = 0.305$ mmol/L; 95%CI: 0.22, 0.39) between blood glucose level and $PM_{2.5}$ exposure in 3288 pregnant women with an increment of 10 μg/m^3. Chuang et al.(Chuang et al., 2011) found positive results in 1023 elderly individuals, and estimated an increase of 0.994 mmol/L (95%CI: 0.522, 1.466) in glucose per 10 μg/m^3 $PM_{2.5}$. In mainland China, Liu et al. (2016) performed a nation-wide baseline survey with 11,847 participants, revealing an increase of 0.063 mmol/L (95%CI: 0.049, 0.078) in glucose in type 2 diabetes patients exposed to $PM_{2.5}$. A cross-sectional study with 15,477 participants in 33 communities in Liaoning province in Northeastern China by Yang et al. (2018) revealed an increase of 0.031 mmol/L (95%CI: 0.015, 0.046) in glucose per 10 μg/m^3 $PM_{2.5}$ exposure in participants aged 18–74 (Yang et al., 2018). Our results differed from those of cross-sectional studies. In addition to different study designs, the differences may have been due to the different study populations; Wolf et al. (2017) focused on the entire population, Lu et al. (2017) focused on women at midterm pregnancy, and Yang et al. (2018) studied adults 50 years or older. In addition, because with the eight study counties spread in China our study evaluated a wider range of annual $PM_{2.5}$ exposure than previous studies, the dose-response relationship derived from our study has wider applicability, and yielded results related to high concentration exposure levels not seen in previous studies (Lu et al., 2017; Wolf et al., 2017).

Fasting blood glucose of the elderly with diabetes were increased more than that of the elderly without diabetes. It may be caused by the weaker glycemic regulation of diabetics, and it is potentially more difficult to resist the harmful effects of $PM_{2.5}$ pollution. The increase in fasting glucose level in the oldest population may be caused by oxidative stress, systemic inflammation, alterations in insulin signaling and β-cell function deficiency (Liu et al., 2019), and oxidative stress was suggested as the key factor among the mechanisms (Lim and Thurston, 2019).

The covariate selection methods used in air pollution and health not only include traditional criteria such as Akaike's Information Criteria (AIC), Bayesian information criterion (BIC) (Jones, 2011) and least absolute shrinkage and selection operator (LASSO) (Zhang et al., 2017), but also references existing literature (Li et al., 2018a). Covariate selection is often done by the reviewing of relevant published studies, such as a study of long-term $PM_{2.5}$ exposure and diabetes (Liang et al., 2019), and a study using mixed effects models in exploring the association between $PM_{2.5}$ exposure and fasting blood glucose (Lucht et al., 2018).

This study had several strengths. First, our longitudinal design provides stronger causal validation than cross-sectional studies. Second, we conducted subgroup analyses to assess vulnerable populations such as participants with diabetes. These analyses facilitate development of more targeted preventative measures. However, this study had several limitations. First, information on medication intake was not collected in the cohort. Since only 32 participants reported suffering from diabetes, the awareness of diabetes was extremely low (about one fifth) in our study; it is reasonable to assume that most diabetic participants did not take prescribed drugs to regulate blood glucose, possibly because the study area was remote and almost all of the participants were illiterate. Furthermore, we have conducted subgroup analysis about participants with or without diabetes, and the results showed both significant association between $PM_{2.5}$ and fasting blood glucose in the two subgroups. Second, we used the estimated ambient $PM_{2.5}$ concentration instead of individual exposure to $PM_{2.5}$; thus, actual $PM_{2.5}$ exposure may have differed from the ambient concentration (Zhou et al., 2018). Third, due to the low education status of our old age participants and most of them living in the rural areas, the generalization of our study participants is limited. Fourth, without controlling for district-level social economic status (SES), it may result the potential residual confounding. Nonetheless, we have controlled for county as a random effect in our main model, which controls for a portion of potential spatial confounding.

Table 1
Characteristics of the study population and $PM_{2.5}$ concentration.

Variables	Value
Total	1449
Age (mean ± SD)	83 ± 12
Sex	
Men (n)	687
Women (n)	762
Education in Years (n, median(Q1-Q3))	0(0–4)
BMI(kg/m^2, mean ± SD)	21.4 ± 13.2
County	
Chengmai, Hainan Province (n)	84
Sanshui, Guangdong Province (n)	123
Yongfu, Guangxi Province (n)	98
Mayang, Hunan Province (n)	97
Rudong, Jiangsu Province (n)	177
Zhongxiang, Hubei Province (n)	214
Xiayi, Henan Province (n)	417
Laizhou, Shandong Province (n)	239
Smoking status	
Current smoker (n)	296
Former smoker (n)	413
Drinking status	
Current drinker(n)	285
Former drinker (n)	350
Residence	
Rural (n)	1201
Exercise status	
Exercises regularly (n)	279
Diabetes	
Prevalence (%)	10.1
Fasting glucose (mmol/L, mean ± SD)	5.11 ± 1.82
$PM_{2.5}$ (μg/L, median (Q1-Q3))	56 (43–70)

Table 2
Changes in fasting blood glucose levels (mmol/L) associated with a 10 μg/m^3 increase of $PM_{2.5}$ exposure.

Groups		Lag1[a]	Lag1–2[a]	Lag1–3[a]
Total		0.096(0.027,0.164) *	0.109(0.023,0.195) *	0.146(0.045,0.248) *
Diabetes	Non-diabetic	0.064(0.022,0.107) *	0.079(0.028,0.130) *	0.111(0.052,0.170) *
Status	Diabetic	0.437(0.121,0.753) *	0.494(0.123,0.865) *	0.542(0.121,0.962) *
Sex	Men	0.073(−0.022,0.167)	0.095(−0.022,0.212)	0.127(−0.009,0.262)
	Women	0.074(−0.013,0.161)	0.046(−0.055,0.148)	0.060(−0.057,0.177)
Age	<75	0.010(−0.084,0.103)	0.010(−0.102,0.122)	0.006(−0.120,0.132)
	75 to 84	0.033(−0.130,0.196)	0.085(−0.122,0.292)	0.196(−0.057,0.448)
	≥85	0.041(−0.052,0.134)	0.082(−0.038,0.203)	0.147(0.000,0.294) *
Exercise status	Exercise	−0.018(−0.208,0.173)	−0.039(−0.259,0.182)	−0.018(−0.269,0.234)
	No-exercise	0.086(0.022,0.149) *	0.096(0.017,0.174) *	0.128(0.036,0.220) *
Smoking status	Never-smoke	0.127(0.045,0.209) *	0.156(0.055,0.258) *	0.191(0.073,0.310) *
	Smoker	0.064(−0.043,0.171)	0.049(−0.081,0.18)	0.070(−0.079,0.218)
Drinking status	Never-drink	0.109(0.025,0.193) *	0.134(0.029,0.240) *	0.176(0.050,0.301) *
	Drinker	0.024(−0.062,0.109)	0.005(−0.092,0.103)	0.011(−0.096,0.119)

[a] Lag 1 is previous year average of $PM_{2.5}$ exposure; Lag 1–2 is previous year to 2-year average of $PM_{2.5}$ exposure; Lag 1–3 is previous year to 3-year average of $PM_{2.5}$ exposure.
* $P < .05$.

5. Conclusions

This study adds significant evidence on the increase of fasting blood glucose level with long-term $PM_{2.5}$ exposure within the elderly population. Elderly individuals with diabetes are more likely to experience an increase in fasting blood glucose levels with high $PM_{2.5}$ exposure. The results suggested that elderly individuals, especially those with diabetes, should take protection measures during high $PM_{2.5}$ polluted periods.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.137191.

Author contributions

XS, TL and YZhang conceived of the design of the study. ZY and YL collected the data. JW, RM, YZhong and DX prepared and cleaned the data. YZhang and TL performed the statistical analysis and drafted the article. MZH, PLK, VBK and XG reviewed the draft, assisted with data interpretation and helped improve the quality of the manuscript. All authors contributed to manuscript revision and approved the final version for submission.

Table 3
Results of the sensitivity analyses for a 10 μg/m^3 increase in previous 3 years average of $PM_{2.5}$ exposure (lag1–3).

No.	Model[a]	B (95%CI)[mmol/L]
Model 1	Main analysis	0.146 (0.045,0.248)
Model 2	Main analysis excluding age variable	0.148 (0.047,0.250)
Model 3	Main analysis excluding sex variable	0.151 (0.049,0.253)
Model 4	Main analysis excluding smoking status	0.148 (0.047,0.250)
Model 5	Main analysis excluding drinking status	0.146 (0.044,0.248)
Model 6	Main analysis excluding marital status	0.148 (0.047,0.249)
Model 7	Main analysis excluding income	0.141 (0.040,0.242)
Model 8	Main analysis excluding education years	−0.053 (−0.136,0.030)
Model 9	Main analysis excluding exercise status	0.149 (0.046,0.252)
Model 10	Main analysis excluding staple food intake	0.151 (0.050,0.252)
Model 11	Main analysis excluding residence	0.135 (0.037,0.233)
Model 12	Main analysis excluding BMI	0.146 (0.045,0.247)
Model 13	Current smoking and drinking status	0.144 (0.042,0.246)
Model 14	Adding the intake of fruit	0.144 (0.043,0.246)
Model 15	Adding temperature and humidity	0.260(0.144,0.375)
Model 16	Linear regression model	0.216 (0.112,0.319)

[a] In the main analysis we controlled for age, sex, marital status, education years, family income, residence, smoking and drinking status, exercise status, staple food intake, and BMI as the fixed effect. In the linear regression model, we excluded the random effects of individual from the main analysis, and changed the county as the fixed effect; other covariates were as the same as the main analysis.

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.

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