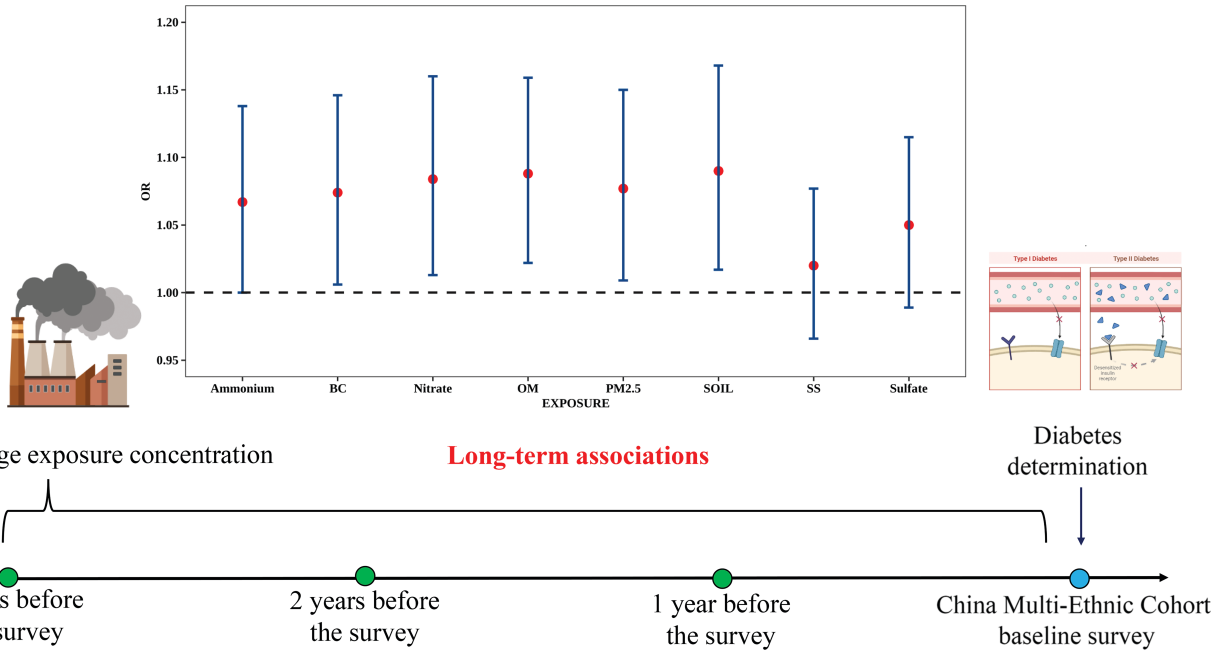
Diabetes Care
American Diabetes Association

Long-term Exposure to Ambient $PM_{2.5}$ and Its Components Associated With Diabetes: Evidence From a Large Population-Based Cohort From China

Sicheng Li, Bing Guo, Ye Jiang, Xing Wang, Lin Chen, Xue Wang, Ting Chen, La Yang, Yangzong Silang, Feng Hong, Jianzhong Yin, Hualiang Lin, and Xing Zhao, on behalf of the China Multi-Ethnic Cohort (CMEC) collaborative group

Diabetes Care 2023;46(1):111–119 | https://doi.org/10.2337/dc22-1585



ARTICLE HIGHLIGHTS

- Long-term exposure to particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$), including black carbon, nitrate, ammonium, organic matter, and soil particles was positively associated with diabetes.
- Age might modify the above associations.
- Organic matter might be most responsible for the $PM_{2.5}$ and diabetes relationship.
- Both single and joint exposure to $PM_{2.5}$ and its components were positively associated with diabetes.

Long-term Exposure to Ambient $PM_{2.5}$ and Its Components Associated With Diabetes: Evidence From a Large Population-Based Cohort From China

Sicheng Li,[1] Bing Guo,[1] Ye Jiang,[1] Xing Wang,[1] Lin Chen,[1] Xue Wang,[2] Ting Chen,[3] La Yang,[4] Yangzong Silang,[5] Feng Hong,[6] Jianzhong Yin,[7,8] Hualiang Lin,[9] and Xing Zhao,[1] on behalf of the China Multi-Ethnic Cohort (CMEC) collaborative group

Diabetes Care 2023;46:111–119 | https://doi.org/10.2337/dc22-1585

OBJECTIVE

Association between particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$) components and diabetes remains unclear. We therefore aimed to investigate the associations of long-term exposure to $PM_{2.5}$ components with diabetes.

RESEARCH DESIGN AND METHODS

This study included 69,210 adults with no history of diabetes from a large-scale epidemiologic survey in Southwest China from 2018 to 2019. The annual average concentrations of $PM_{2.5}$ and its components were estimated using satellite remote sensing and chemical transport modeling. Diabetes was identified as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or hemoglobin A_{1c} ≥48 mmol/mol (6.5%). The logistic regression model and weighted quantile sum method were used to estimate the associations of single and joint exposure to $PM_{2.5}$ and its components with diabetes, respectively.

RESULTS

Per-SD increases in the 3-year average concentrations of $PM_{2.5}$ (odds ratio [OR] 1.08, 95% CI 1.01–1.15), black carbon (BC; 1.07, 1.01–1.15), ammonium (1.07, 1.00–1.14), nitrate (1.08, 1.01–1.16), organic matter (OM; 1.09, 1.02–1.16), and soil particles (SOIL; 1.09, 1.02–1.17) were positively associated with diabetes. The associations were stronger in those ≥65 years. Joint exposure to $PM_{2.5}$ and its components was positively associated with diabetes (OR 1.04, 95% CI 1.01–1.07). The estimated weight of OM was the largest among $PM_{2.5}$ and its components.

CONCLUSIONS

Long-term exposure to BC, nitrate, ammonium, OM, and SOIL is positively associated with diabetes. Moreover, OM might be the most responsible for the relationship between $PM_{2.5}$ and diabetes. This study adds to the evidence of a $PM_{2.5}$-diabetes association and suggests controlling sources of OM to curb the burden of $PM_{2.5}$-related diabetes.

Numerous recent studies have confirmed that long-term exposure to particulate matter (PM) with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$) is a newly identified risk factor for diabetes (1–4). For example, long-term (median 8.5 years) exposure to

[1]West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, Sichuan, China
[2]Chenghua Center for Disease Control and Prevention, Chengdu, Sichuan, China
[3]Chongqing Center for Disease Control and Prevention, Chongqing, China
[4]School of Medicine, Tibet University, Tibet, China
[5]Tibet Center for Disease Control and Prevention, Tibet, China
[6]School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guizhou, China
[7]School of Public Health, Kunming Medical University, Yunnan, China
[8]Baoshan College of Traditional Chinese Medicine, Yunnan, China
[9]Department of Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China

Corresponding authors: Xing Zhao, xingzhao@scu.edu.cn, and Feng Hong, fhong@gmc.edu.cn

Received 15 August 2022 and accepted 19 October 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21363150.

S.L. and B.G. contributed equally.

$PM_{2.5}$ was found to be associated with an increased risk of diabetes in a cohort of 1.7 million U.S. veterans (2). Long-term (5 years) exposure to $PM_{2.5}$ was found to be associated with the risk of diabetes in a cohort of 2.6 million participants living in Denmark (4). According to the Global Burden of Disease Study 2017, 26.1% of disability-adjusted life-years for diabetes were attributable to air pollution (5). Exposure to $PM_{2.5}$, even at concentrations well below World Health Organization air quality guidelines, can increase the risk of diabetes (2). Mechanism hypotheses have been developed regarding the association between $PM_{2.5}$ and diabetes. Inhalation of $PM_{2.5}$ might lead to an increase in reactive oxygen species in the lungs (6), trigger systemic oxidative stress (7), induce subsequent visceral adipose tissue inflammation (8), and further lead to insulin resistance (8). Other possible mechanisms include a disturbed autonomic nervous system (9), endothelial dysfunction (10), alteration of gut microbes (11), and mitochondrial dysfunction (12).

Ambient $PM_{2.5}$ is composed of various components, including black carbon (BC), ammonium, nitrate, organic matter (OM), sulfate, soil particles (SOIL), sea salt (SS), and others. The toxicity of different PM components to humans varies (13). A systematic review of 35 available studies found that only BC and OM were significantly associated with natural, cardiovascular, or respiratory health end points (14). For diabetes, research showed that long-term exposure to $PM_{2.5}$ components was associated with gestational diabetes mellitus (GDM) and emergency hospital admissions for type 2 diabetes (15–17). However, evidence on the relationship between $PM_{2.5}$ components and diabetes is limited. An improved understanding of the relationship between different components of $PM_{2.5}$ and diabetes provides a reasonable explanation for which component is responsible for the $PM_{2.5}$-diabetes relationship and may further offer new opportunities to curb the burden of $PM_{2.5}$-related diabetes.

To address the above research gap, this cross-sectional study assessed the individual and joint associations of $PM_{2.5}$ and its components with diabetes among participants of the China Multi-Ethnic Cohort (CMEC) study. The findings might explain the association between $PM_{2.5}$ and diabetes and provide a basis for targeted prevention and control of $PM_{2.5}$ components.

RESEARCH DESIGN AND METHODS

Study Population

The research data for this study were obtained from the baseline survey of CMEC, a general population-based cohort study in Southwest China in five provinces (Sichuan, Chongqing, Yunnan, Guizhou, and Tibet). Considering the ethnic characteristics and demographic structure of Southwest China, the CMEC collected baseline data from 99,556 participants aged between 30 and 79 years through multistage stratified cluster sampling from May 2018 to September 2019 (18).

Baseline data for the CMEC included questionnaire data (sociodemographic, lifestyle habits, and health-related history), physical examination data (height, weight, blood pressure, bone density, etc.), and biochemical examination data (blood glucose, blood lipids, liver enzymes, etc.). Highly trained investigators collected the questionnaire data through face-to-face interviews using a tablet-administered electronic questionnaire. The local community hospital collected physical examination data after standardized training of personnel and calibration of instruments. Biochemical examination data were collected by a third-party company with corresponding national qualifications. In the Supplementary Methods, more details of CMEC quality control are shown in the Quality Control section. All of the participants signed an informed consent form before data collection. Ethical approval was received from the Sichuan University Medical Ethical Review Board (K2016038, K2020022).

Ultimately, a total of 99,556 participants were enrolled in the baseline survey of the CMEC. The current study excluded *1*) those without a residential address; *2*) Tibetan herders in Aba since they have no fixed place of residence and Tibetans in Lhasa because of concentrated survey sites with low variability in air pollution; *3*) those with a length of residence at the residential address at the time of the survey of <3 years; *4*) those with malignant tumors or ineligible ages (<30 or >80 years); *5*) pregnant women; *6*) those with self-reported diabetes >3 years before the survey; and *7*) those with missing diabetes, exposure, or covariate data. Finally, we included 69,210 participants in this study (Supplementary Fig. 1).

We excluded 2,005 participants with missing covariate or diabetes data. The missing data rate was 2.8%. The variables with the most missing data were diabetes (n = 1,290), metabolic equivalent (MET; n = 352), and Mediterranean diet (MED; n = 199), and no particular pattern of missing data was found, indicating that the data were missing at random in this study.

Outcomes

Fasting venous blood was collected from each participant and tested by a third-party company with corresponding national qualifications. Diabetes was defined as fasting plasma glucose (FPG) $\geq$126 mg/dL (7.0 mmol/L) or hemoglobin A_{1c} (HbA_{1c}) $\geq$48 mmol/mol (6.5%) based on criteria from the American Diabetes Association (19).

Exposure Assessment

The monthly average concentration data of $PM_{2.5}$ and its components from 2001 to 2017 were derived from pollutant data in the Global Burden of Disease (GBD) study and found to be precise (20–22). Briefly, seven different algorithms were used to estimate satellite aerosol optical depth measurements inversely weighted by their errors against the Aerosol Robotic Network based on 10- × 10-km resolution satellite imagery. Concentrations data of $PM_{2.5}$ and its components were estimated based on aerosol optical depth data by using the chemical transport model. Nitrogen dioxide (NO_2) and ozone (O_3) data used in sensitivity analyses were obtained from the ChinaHighAirPollutants data set (https://weijing-rs.github.io/product.html, accessed date: 9 July 2020). More details are shown in the NO_2 and O_3 section in the Supplementary Methods.

According to the geocoded residential address, average concentrations of $PM_{2.5}$ and its components, NO_2 and O_3, were calculated for each participant 3 years before the baseline survey as the estimated surrogate of exposure. The cross-sectional study design is shown in Supplementary Fig. 3.

Statistical Analyses

Single-Exposure Analyses

We used logistic regression to estimate the associations between increases in the 3-year average exposure to $PM_{2.5}$ and its components and diabetes. For $PM_{2.5}$ and each component, we present the odds ratio (OR) and 95% CI corresponding to an

increase in the SD of pollutants. In model 1 (i.e., the crude model), no covariates were included. In model 2, we included the covariates of age, sex, ethnicity, region, income, and education. In model 3, we further included alcohol, BMI level, cigarette smoke, second-hand smoke, indoor air pollution, MET level, MED level, 3-year average temperature, and 3-year average humidity. Specific definitions of each covariate and how they were calculated are shown in the Variables section of the Supplementary Methods.

Joint Exposure Analyses

We used the weighted quantile sum (WQS) method to estimate the effects of the mixtures ($PM_{2.5}$ and its components) adjusted for the same covariates as in the single-exposure analyses. The WQS yields a score for all exposures by assigning weights to all exposures categorized into quartiles or more groups and then incorporates that score into the regression model (23). The results of WQS included weight estimation (importance) for every single exposure and effect estimation for the weighted score, that is, effects of the mixtures. More details of the WQS method are shown in the Weighted Quantile Sum (WQS) section of the Supplementary Methods.

Subgroup Analyses

In addition, subgroup analyses were performed by adding interaction terms of exposure and stratified variables in the regression model. Age ($\geq$65 years or $<$65 years) was considered. We conducted subgroup analyses for the associations between single and joint exposure to $PM_{2.5}$ and its components.

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the results, including *1*) using 1-year, 2-year, 5-year, and 10-year averages of $PM_{2.5}$ and its components as the exposure; *2*) using FPG or HbA_{1c} as the outcome; and *3*) further adjusting for gaseous pollutants (NO_2 or O_3 or both).

In addition, various other statistical methods were used to examine the sensitivity of the results to statistical methods. We used ridge regression and the least absolute shrinkage and selection operator (LASSO) method to estimate single-exposure effects. These two methods achieve coefficient reduction by adding penalty terms to a logistic regression model that incorporates all exposures simultaneously. The difference is that the former estimates coefficients that will be as close to 0 as possible but not equal to 0, while the latter will directly reduce some of the coefficients to 0, serving to select important variables. We used quantile G-computation (QGC) to estimate the mixture effect and weights of a single exposure (24). Based on the WQS, the QGC obtains causal associations and estimates both positive and negative weights by additional statistical assumptions. More details of the statistical methods are shown in the Statistical Methods section of the Supplementary Methods.

We used four methods in this study to estimate the association of joint exposure to $PM_{2.5}$ and its components with diabetes, including the WQS, ridge regression, LASSO, and QGC. The advantages and disadvantages of these methods are discussed in detail in Supplementary Table 5. In brief, compared with ridge regression and LASSO, the WQS could estimate not only the weights of different exposures but also the effects of joint exposure. Compared with QGC, WQS is more widely used and based on fewer prerequisite statistical assumptions. Therefore, the WQS was used in the main text, and the rest of the methods were used for the sensitivity analyses.

Furthermore, we calculated the E-value to evaluate the unmeasured confounding. The E-value is defined as the minimum unmeasured confounding effect required to completely subvert the OR in the study, controlling for the measured confounding factor (25,26). The E-value reflects the sensitivity of the results to unmeasured confounding. Moreover, we restricted the cubic spline transformation of exposure variables to investigate whether the association between exposure and outcome was linear.

We have presented the OR of $PM_{2.5}$ and its components corresponding to an increase in the SDs of concentrations. All analyses were performed by using R 4.0.1 software. Two-sided tests with P values $<$0.05 were considered statistically significant.

RESULTS

General Characteristics

We included 69,210 participants aged 30–79 years in this study. The study population was a mean age of 51.8 years (SD 11.3 years), and 15.2% of the participants were $\geq$65 years old. Men comprised 39.5% of the participants, and 7.4% of the participants had diabetes. More details are provided in Table 1.

The distributions of $PM_{2.5}$ and its components are shown in Fig. 1. The 3-year average concentrations (SD) of $PM_{2.5}$, BC, ammonium, nitrate, OM, sulfate, SOIL, and SS were 40.29 (20.5), 2.07 (1.10), 6.43 (3.28), 8.25 (5.33), 9.02 (4.86), 10.80 (4.76), 3.22 (1.68), and 0.03 (0.03) $\mu g/m^3$, respectively, at the participants' residential addresses. The primary sources and compositions of the seven components are provided in Supplementary Table 2.

Associations of $PM_{2.5}$ and Its Components With Diabetes

In model 3, a per-SD increase in the 3-year average $PM_{2.5}$ concentration was positively associated with diabetes (OR 1.08, 95% CI 1.01–1.15). The per-SD increases in the 3-year average BC (1.07, 1.01–1.15), ammonium (1.07, 1.00–1.14), nitrate (1.08, 1.01–1.16), OM (1.09, 1.02–1.16), and SOIL (1.09, 1.02–1.17) concentrations were positively associated with diabetes. Per-SD increases in the 3-year average sulfate (OR 1.05, 95% CI 0.99–1.12) and SS (1.02, 0.97–1.08) concentrations were not significantly associated with diabetes (Table 2).

In the joint exposure analyses, the estimated weight of OM was the largest among $PM_{2.5}$ and its components (Fig. 2), suggesting that OM was the most important component. Joint exposure to $PM_{2.5}$ and its components was positively associated with diabetes (OR 1.04, 95% CI 1.01–1.07) by the WQS method.

Subgroup Analyses

The effects of $PM_{2.5}$ (P = 0.03), BC (P = 0.03), ammonium (P = 0.02), and sulfate (P = 0.01) were higher in those $\geq$65 years (Supplementary Table 3). For example, a per-SD increase in $PM_{2.5}$ corresponds to an OR of 1.20 (95% CI 1.07–1.33) for people $\geq$65 years old compared with 1.03 (0.95–1.12) for people $<$65 years old. The effect of joint exposure to $PM_{2.5}$ and its components was higher in those $\geq$65 years, but the difference was not significant (P = 0.10).

Sensitivity Analyses

The associations of $PM_{2.5}$, BC, ammonium, nitrate, OM, and SOIL with diabetes were steady in their direction, magnitude, and statistical significance in our sensitivity analyses (Supplementary Tables 6–10 and 12).

Table 1—The general characteristics of the study population

	Total	Diabetes		
		Yes	No	
	N = 69,210	*n* = 5,123 (7.4)	*n* = 64,087 (92.6)	*P* value
Female sex	41,845 (60.5)	2,497 (48.7)	39,348 (61.4)	<0.01
Age <65 years	58,664 (84.8)	3,815 (74.5)	54,849 (85.6)	<0.01
Income, ¥				<0.01
<12,000	12,196 (17.6)	1,038 (20.3)	11,158 (17.4)	
12,000–19,999	11,987 (17.3)	930 (18.2)	11,057 (17.3)	
20,000–59,999	25,063 (36.2)	1,789 (34.9)	23,274 (36.3)	
60,000–99,999	10,454 (15.1)	748 (14.6)	9,706 (15.1)	
≥100,000	9,510 (13.7)	618 (12.1)	8,892 (13.9)	
Education				<0.01
Bachelor degree or above	2,998 (4.3)	140 (2.7)	2,858 (4.5)	
Junior college	4,964 (7.2)	255 (5.0)	4,709 (7.3)	
High school	8,535 (12.3)	629 (12.3)	7,906 (12.3)	
Junior high school	18,928 (27.3)	1,282 (25.0)	17,646 (27.5)	
Primary school	17,747 (25.6)	1,366 (26.7)	16,381 (25.6)	
Illiteracy	16,038 (23.2)	1,451 (28.3)	14,587 (22.8)	
Han ethnicity	43,730 (63.2)	3,213 (62.7)	40,517 (63.2)	0.47
Smoking				
Never smoked	51,326 (74.2)	3,312 (64.6)	48,014 (74.9)	<0.01
Second-hand smoke	35,830 (51.8)	2,522 (49.2)	33,308 (52.0)	<0.01
Indoor air pollution				0.06
Severe	10,969 (15.8)	846 (16.5)	10,123 (15.8)	
Moderate	54,737 (79.1)	3,990 (77.9)	50,747 (79.2)	
Light	3,504 (5.1)	287 (5.6)	3,217 (5.0)	
BMI level				<0.01
Low weight	2,623 (3.8)	101 (2.0)	2,522 (3.9)	
Moderate weight	32,915 (47.6)	1,584 (30.9)	31,331 (48.9)	
Overweight	33,672 (48.7)	3,438 (67.1)	30,234 (47.2)	
MET level				<0.01
1	15,592 (22.5)	1,569 (30.6)	14,023 (21.9)	
2	17,029 (24.6)	1,185 (23.1)	15,844 (24.7)	
3	18,047 (26.1)	1,208 (23.6)	16,839 (26.3)	
4	18,542 (26.8)	1,161 (22.7)	17,381 (27.1)	
Alcohol, never drinker	38,302 (55.3)	2,813 (54.9)	35,489 (55.4)	0.52
MED level				<0.01
1	20,679 (29.9)	1,766 (34.5)	18,913 (29.5)	
2	17,154 (24.8)	1,283 (25.0)	15,871 (24.8)	
3	16,583 (24.0)	1,122 (21.9)	15,461 (24.1)	
4	14,794 (21.4)	952 (18.6)	13,842 (21.6)	
Air pollutants, $\mu g/m^3$, mean (SD)				
$PM_{2.5}$	40.29 (20.56)	40.79 (20.26)	40.25 (20.58)	0.07
BC	2.07 (1.10)	2.10 (1.09)	2.07 (1.10)	0.10
Ammonium	6.43 (3.28)	6.50 (3.22)	6.42 (3.29)	0.16
Nitrate	8.25 (5.33)	8.37 (5.29)	8.24 (5.34)	0.05
OM	9.02 (4.86)	9.15 (4.82)	9.01 (4.86)	0.03
Sulfate	10.80 (4.76)	10.90 (4.64)	10.80 (4.77)	0.41
SOIL	3.22 (1.68)	3.27 (1.66)	3.21 (1.68)	0.03
SS	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.16

Data are presented as *n* (%), unless indicated otherwise.

The effects of sulfate and SS were stable and insignificant (Supplementary Tables 11 and 13).

The selection process of the penalty term λ for ridge regression and LASSO is shown in Supplementary Fig. 2. Finally, λ = 0.070 and λ = 0.008 were chosen. The ORs of $PM_{2.5}$ and its components estimated by the ridge regression were predictably much smaller than the ORs in the manuscript, while the LASSO estimated non-1 ORs for OM (1.06) and SS (1.02) only (Supplementary Table 4), suggesting that OM and SS are important components. The QGC estimated both positive and negative weights (Fig. 2), with the most significant positive weight being OM (0.43) and the largest negative

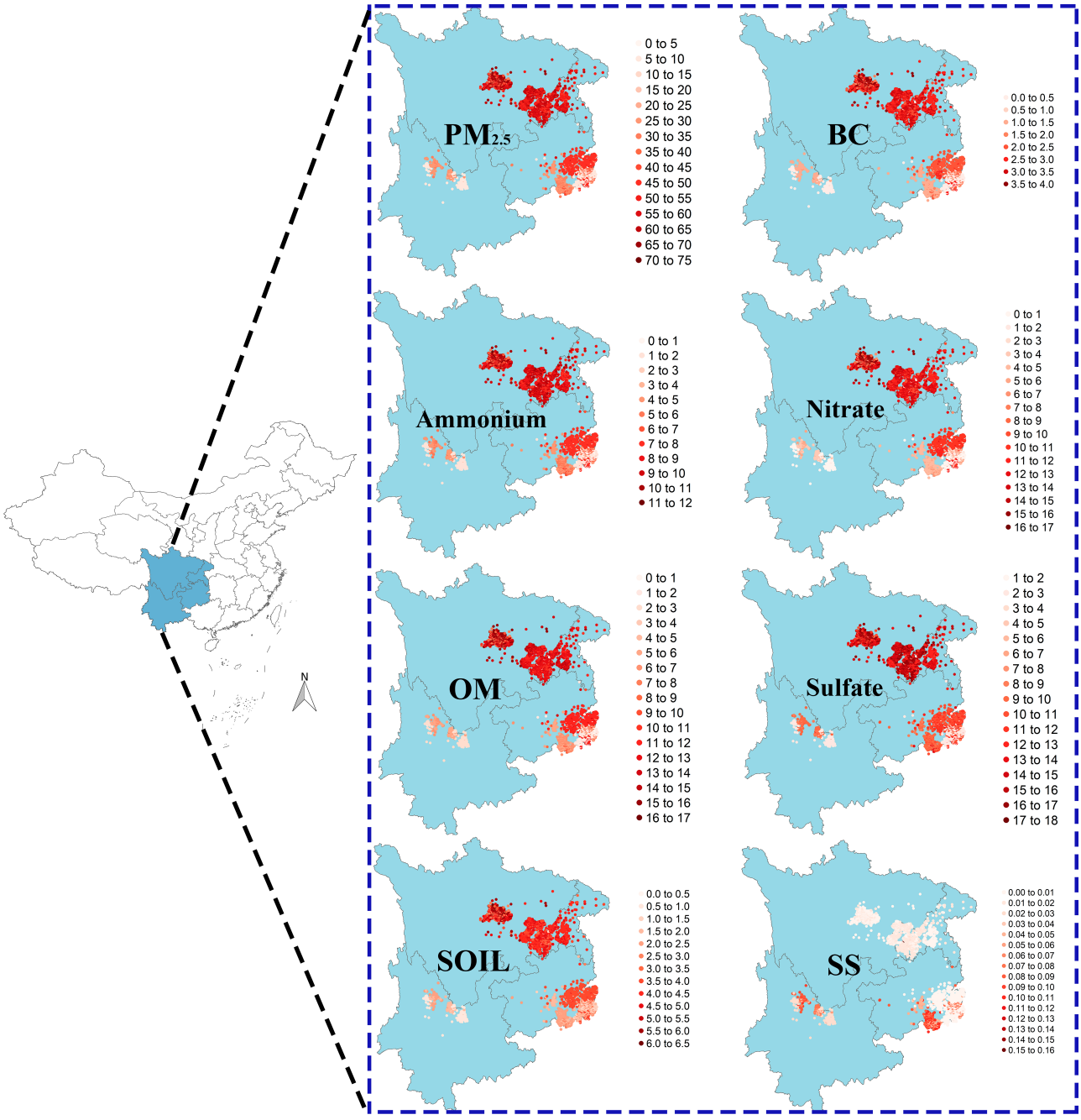


Figure 1—The spatial distributions of the 3-year average $PM_{2.5}$, BC, ammonium, nitrate, OM, sulfate, SOIL, and SS concentrations ($\mu g/m^3$).

weight being sulfate (0.87). Joint exposure to $PM_{2.5}$ and its components was positively associated with diabetes (OR 1.09, 95% CI 1.03–1.16) by using the QGC method. The statistical methods used in the sensitivity analysis drew similar conclusions to those in the main text, which consistently suggested that OM might be most responsible for the $PM_{2.5}$ and diabetes relationship.

The E-values of $PM_{2.5}$, BC, ammonium, nitrate, OM, sulfate, SOIL, and SS were 1.36, 1.36, 1.33, 1.39, 1.40, 1.28, 1.40, and 1.16, respectively. The concentration-response relationships of the 3-year average pollutant exposure and diabetes are presented in Fig. 2. The relationships are approximately linear, except for the relationship with sulfate.

CONCLUSIONS

To the best of our knowledge, this is the first population-based epidemiological study systematically exploring the associations of $PM_{2.5}$ components with diabetes. On the basis of the cross-sectional data of 69,210 participants in Southwest China, ambient $PM_{2.5}$ and its components (BC, ammonium, nitrate, OM, and SOIL) were found to be positively associated with the prevalence of diabetes. The associations are more substantial among those ≥65 years old, and OM might be the most responsible for the relationship between $PM_{2.5}$ and diabetes.

Comparison With Other Studies

Although accumulating studies have thoroughly investigated the relationship

Table 2—Associations of exposure to $PM_{2.5}$ and its components (per SD increase, μg/m^3) with diabetes in Southwest China

	Model 1*		Model 2†		Model 3‡	
Pollutant	OR§ (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
$PM_{2.5}$	1.03 (0.99–1.06)	0.07	1.10 (1.03–1.18)	<0.01	1.08 (1.01–1.15)	0.03
BC	1.02 (0.99–1.05)	0.10	1.10 (1.03–1.17)	0.03	1.07 (1.01–1.15)	0.03
Ammonium	1.02 (0.99–1.05)	0.10	1.09 (1.02–1.16)	0.01	1.07 (1.00–1.14)	0.05
Nitrate	1.03 (0.99–1.06)	0.07	1.11 (1.04–1.19)	<0.01	1.08 (1.01–1.16)	0.02
OM	1.03 (1.00–1.06)	0.04	1.12 (1.05–1.19)	<0.01	1.09 (1.02–1.16)	0.01
Sulfate	1.02 (0.99–1.05)	0.15	1.07 (1.01–1.13)	0.03	1.05 (0.99–1.12)	0.11
SOIL	1.04 (1.01–1.07)	0.01	1.11 (1.04–1.19)	<0.01	1.09 (1.02–1.17)	0.02
SS	1.02 (0.99–1.04)	0.30	1.02 (0.97–1.08)	0.50	1.02 (0.97–1.08)	0.48

*N = 69,210, crude model, adjusted for no covariates. †N = 69,210, adjusted for age, sex, ethnicity, region, income, and education. ‡N = 69,210, adjusted for age, sex, ethnicity, region, income, education, alcohol, BMI, smoke, second-hand smoke, indoor air pollution, MET level, MED level, 3-year average temperature, and 3-year average humidity. §OR of prevalent diabetes.

between $PM_{2.5}$ and diabetes, current literature on $PM_{2.5}$ component exposure and diabetes remains rare. Only three studies have examined the effects of PM components on diabetes-related outcomes (15–17). A study from the U.S., which included data from the electronic health records of nearly 400,000 pregnant women from Kaiser Permanente Southern California, examined the effect of $PM_{2.5}$ components on GDM (16). The results showed that sulfate, nitrate, ammonium, OM, and BC exposure were positively associated with GDM (16). Another study, from Hong Kong, examined the association between short-term exposure of PM with aerodynamic diameters ≤10 μm and emergency hospital admissions for type 2 diabetes (15). The authors found that exposure to BC, OM, and nitrate may lead to exacerbation of acute symptoms or complications in type 2 diabetes (15).

All of the above studies focus on PM components and diabetes-related outcomes.

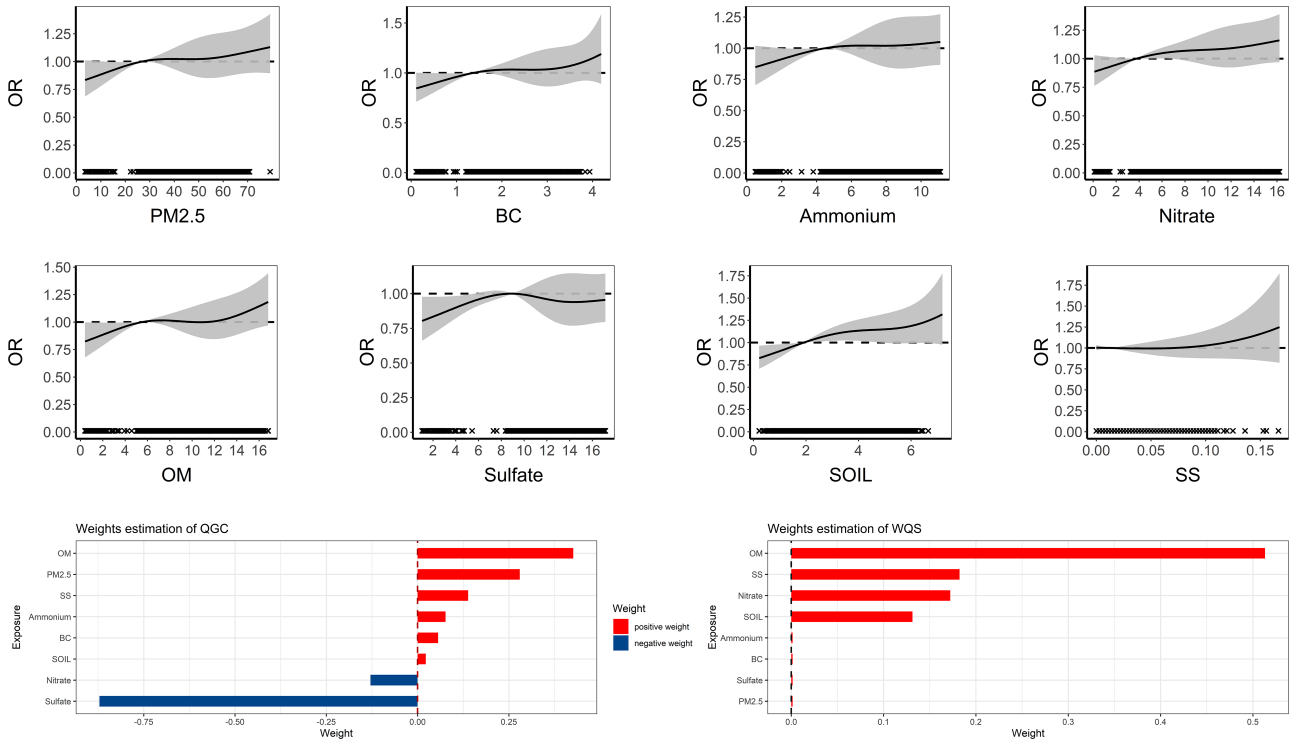


Figure 2—Weight estimations of $PM_{2.5}$ and its components and their exposure-response relationships with diabetes (N = 69,210). All of the results were adjusted for age, sex, ethnicity, region, income, education, alcohol, BMI level, cigarette smoke, second-hand smoke, indoor air pollution, MET level, MED level, 3-year average temperature, and 3-year average humidity. The first two rows show the exposure-response relationship of a single exposure to $PM_{2.5}$ and its components (μg/m^3) with diabetes. The solid black line represents the exposure-response relationship, and the shaded area represents the CI, with the lower quartile used as a reference for each contaminant (i.e., OR = 1, where OR refers to the OR of prevalent diabetes). The last row shows the weight estimation of joint exposure to $PM_{2.5}$ and its components with diabetes by WQS and QGC, respectively.

This study identifies BC, ammonium, nitrate, OM, and SOIL as risk factors for diabetes, which is broadly consistent with the two studies mentioned above. Sulfate was not recognized as a risk factor for diabetes in this study, which may be due to the concentration gradient (10.80 ± 4.76 $\mu g/m^3$) in our research being different from that in the analysis above (1.3 ± 0.3 $\mu g/m^3$) (16). This study adds to the evidence in this area by examining PM components and diabetes for the first time.

We used the WQS, QGC, ridge regression, and LASSO for joint exposure effect estimation, and the advantages and disadvantages of these methods are summarized in detail in the Supplementary Material. The simultaneous use of the above methods showed that the results were robust. However, the above methods were based on the assumption of a linear association of $PM_{2.5}$ and its components with diabetes. As shown in Fig. 2, the association between sulfate and diabetes is not completely linear, and caution should be exercised when viewing the conclusions of the current study. Bayesian kernel machine regression (BKMR) is a newly proposed method that can be used to estimate the multiexposure effect (27). In addition to nonlinear associations, BKMR can also estimate the interaction between exposures. However, the current BKMR runs very slowly when working with large-sample data, and BKMR urgently requires improvement, or new methods need to be proposed to meet the needs of multiexposure analysis of large samples.

Notably, the association of $PM_{2.5}$ and its components with diabetes may vary considerably with exposure concentration and time window. The concentration of $PM_{2.5}$ and its components in this study are high at the global scale (20). In China, the concentrations of $PM_{2.5}$ and its components in the southwestern region are medium to high, but the concentration range is larger, which is one of the advantages of this study (20). Regarding the exposure time window, this study focuses on the effect of long-term exposure, which is defined by the World Health Organization as 1 year to several years of exposure (28). In contrast, short-term exposure is usually a few days to weeks, and medium-term exposure is a few months. Great care must be taken when comparing and extrapolating the study results.

Potential Mechanism

The mechanisms of the associations between the above components (BC, ammonium, nitrate, OM, and SOIL) and diabetes are not fully understood. The potential mechanisms are described separately for the five components.

BC and OM are mainly from combustion-related sources, such as vehicle exhaust and industrial and agricultural combustion (Supplementary Table 2). Exposure to OM and BC may increase the risk of diabetes through the following pathways: oxidative stress, endothelial damage, systemic inflammation, and lipid abnormalities (29). In vitro experiments showed that exposure to high concentrations of BC over 24 h caused reactive oxygen species and inflammation in human umbilical endothelial cells (30). Other cellular experiments also supported the opinion that BC might cause endothelial damage (31). At the population level, a panel study demonstrated that exposure to BC and OM was positively associated with inflammatory and platelet activation biomarkers (C-reactive protein, interleukin 6, and tumor necrosis factor-α soluble receptor II) (32). Another cross-sectional study found that exposure to OM and BC was negatively associated with brachial artery diameter, a predictor of cardiovascular risk (33). From the point of view of pollution prevention and control, BC is considered a tracker of older diesel fuels, and $>$85% of environmental BC can be attributed to vehicle emissions (Supplementary Table 2). In contrast, OM consists of a mixture of hundreds of organic compounds and can be either released directly into the atmosphere (primary organic carbon) or produced from gas-to-particle reactions (secondary organic carbon) (Supplementary Table 2). These results provide a rationale for increased restrictions on transport-related emission sources.

SOIL-containing metal elements and silica are suspended in the air due to mechanical movements (transportation and human activity) (Supplementary Table 2). Animal experiments showed that exposure to particulate samples induced inflammatory activity (tumor necrosis factor-α, interleukin 6, and keratinocyte-derived chemokine) in healthy C57BL/6J mice, which is especially true for transition metals (vanadium and nickel) and SOIL-derived constituents (calcium ions, aluminum, iron, silicon) (34). Previous epidemiological studies have found nickel and potassium ions to be associated with emergency hospital admissions for type 2 diabetes (15), indicating the potential hazards of SOIL, which contains metal elements.

Nitrate was derived mainly from the photochemical transformation of precursor pollutants, for example, NO_2. Nitrate entering the airway may lower the pH value of the airway and thus cause adverse reactions (35). In addition, a population epidemiological study showed that nitrate in $PM_{2.5}$ is positively correlated with extracellular superoxide dismutase and glutathione peroxidase 1 in the blood (36), indicating activation of circulating antioxidant enzymes after exposure to nitrate in $PM_{2.5}$; that is, nitrate in $PM_{2.5}$ might cause oxidative damage.

Ammonium is formed by the neutralization of atmospheric nitric and sulfuric acids by ammonia (Supplementary Table 2). Mechanistic studies of health hazards associated with ammonium are still scarce, and current epidemiological studies seem to yield inconsistent findings. A panel study found that short-term (24-h) exposure to ammonium was positively associated with inflammatory biomarkers (fibrinogen, C-reactive protein, MCP-1, etc.) (37). However, another panel study found that exposure to ammonium was not associated with the arginase-nitric oxide synthase pathway, an indicator for the airway inflammatory response (38). The above research suggests that the effect of ammonium on cardiovascular risk may not be mediated through respiratory inflammation. Animal experiments and epidemiological studies are needed to further investigate the exact mechanism.

Explanation for the Subgroup Analyses Results

Subgroup analyses indicated that age might be a potential effect modifier of the association between diabetes and $PM_{2.5}$ components. The effects are stronger among those $\geq$65 years. One possible explanation is that they are more sensitive to the pollution of $PM_{2.5}$ and its components (39).

Clinical Implications

First, this is the first study exploring the association of single and joint exposure to $PM_{2.5}$ and its components with diabetes. The results showed the potential risk of the components, with OM being the most important. The above results provide new evidence for existing studies and a novel perspective on the disease risk of $PM_{2.5}$ or other environmental risk factors.

Second, these results have important public health implications. Despite the relatively small OR (1.04) of joint exposure to $PM_{2.5}$ and its components, air pollution is ubiquitous and can cause a severe disease burden for the entire population. Furthermore, the risk persists even at lower concentrations, which is consistent with Bowe et al. (2). This finding makes a strong case for redoubling efforts to control harmful pollutants, especially OM.

Third, individuals, especially the elderly and those who already have diabetes (40), should be aware of the air quality in the area where they live and avoid prolonged exposure to harmful exposure. Personal protection should be enhanced to mitigate the hazards of air pollution, especially when automobile exhaust pollution is severe and photochemical smog is frequent (source of OM).

Limitations and Strengths of This Study

Our study has several limitations. First, we matched the study population for exposure to $PM_{2.5}$ and its components by registered residential addresses without considering individual exposure patterns (e.g., time spent outdoors, breathing rate, and range of motion).

Second, statistical analyses were conducted based on cross-sectional data. Even if we used the 3-year average concentrations of pollutants before the survey time as exposure, which roughly ensured the sequence of exposure and outcome, the problem of reversal of cause and effect might also occur. With the collection of follow-up data, we will be able to obtain more accurate effect estimates based on the cohort study design.

Finally, considering the possibility of unmeasured confounding factors, we calculated the E-value, the minimum of which was 1.16. Small risks exist that our conclusions might be overturned.

Despite the above limitations, our study has several strengths. First, the data used are of high quality. The exposure data were collected and used in GBD and were found to have minor errors (21). The development and implementation of well-established standard operating procedures ensure the quality of the questionnaire data, physical examination data, and biochemical examination data in CMEC (see more in the Quality Control section in the Supplementary Methods).

Second, we involved 69,210 participants in the study. We obtained relatively robust associations between diabetes and $PM_{2.5}$ and its components based on the large sample size and further identified age as a potential effect modifier.

Third, the CMEC collected many individual variables, such as indoor air pollution, second-hand smoke, and dietary patterns, which adequately helped adjust the study's covariates.

Fourth, individuals are exposed to both $PM_{2.5}$ and its components, and we used the WQS and QGC methods to estimate the association of simultaneous exposure to $PM_{2.5}$ and its components with diabetes.

Finally, we used methods that are widely accepted in the context of environmental mixture exposure and reached consistent conclusions, which also ensure the robustness of our conclusions.

In conclusion, long-term exposure to $PM_{2.5}$ BC, nitrate, ammonium, OM, and SOIL is positively associated with diabetes, age might modify the above associations, and OM might be the most responsible for the relationship between $PM_{2.5}$ and diabetes. This study explains to which components the $PM_{2.5}$-diabetes association is attributed and suggests controlling the source of OM to curb the burden of $PM_{2.5}$-related diabetes.

Acknowledgments. The authors thank all the team members and participants involved in the China Multi-Ethnic Cohort (CMEC) study. We appreciate Prof. Xiaosong Li, of Sichuan University, for his leadership and fundamental contribution to the establishment of CMEC. Prof. Li died in 2019, and his contribution is worth bearing in our hearts forever.

Funding. This work was supported by the National Key Research and Development Program of China (grant no. 2017YFC0907305), the National Natural Science Foundation of China (grant no. 82103943, 82073667, and 81973151), the China Postdoctoral Science Foundation (grant no. 2020M683335), and Sichuan Science and Technology Program (grant no. 2020JDJQ0014 and 2021YFS0129).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.L. wrote the supplementary material. S.L. and B.G. conducted statistical analyses and wrote the original draft. Y.J., Xi.W., and L.C. revised the manuscript and performed data visualization. T.C., L.Y., and Y.S. acquired the baseline data and searched the literature. F.H., J.Y., and X.Z. designed the study and contributed to the cohort data. H.L. provided the exposure data. X.Z. supervised this work. X.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Liu F, Chen G, Huo W, et al. Associations between long-term exposure to ambient air pollution and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Environ Pollut 2019;252:1235–1245
2. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. The 2016 global and national burden of diabetes mellitus attributable to $PM_{2.5}$ air pollution. Lancet Planet Health 2018;2:e301–e312
3. Yang B-Y, Qian ZM, Li S, et al. Ambient air pollution in relation to diabetes and glucose-homoeostasis markers in China: a cross-sectional study with findings from the 33 Communities Chinese Health Study. Lancet Planet Health 2018;2:e64–e73
4. Sørensen M, Poulsen AH, Hvidtfeldt UA, et al. Exposure to source-specific air pollution and risk for type 2 diabetes: a nationwide study covering Denmark. Int J Epidemiol 2022;51:1219–1229
5. Yin P, Brauer M, Cohen AJ, et al. The effect of air pollution on deaths, disease burden, and life expectancy across China and its provinces, 1990-2017: an analysis for the Global Burden of Disease Study 2017. Lancet Planet Health 2020;4:e386–e398
6. Nathan C, Cunningham-Bussel A. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. Nat Rev Immunol 2013;13:349–361
7. Gangwar RS, Bevan GH, Palanivel R, Das L, Rajagopalan S. Oxidative stress pathways of air pollution mediated toxicity: recent insights. Redox Biol 2020;34:101545
8. Sun Q, Yue P, Deiuliis JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 2009;119:538–546
9. Chen J-C, Stone PH, Verrier RL, et al. Personal coronary risk profiles modify autonomic nervous system responses to air pollution. J Occup Environ Med 2006;48:1133–1142
10. Münzel T, Gori T, Al-Kindi S, et al. Effects of gaseous and solid constituents of air pollution on endothelial function. Eur Heart J 2018;39:3543–3550
11. Zhao L, Fang J, Tang S, et al. $PM_{2.5}$ and serum metabolome and insulin resistance, potential mediation by the gut microbiome: a population-based panel study of older adults in China. Environ Health Perspect 2022;130:27007
12. Xu X, Liu C, Xu Z, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. Toxicol Sci 2011;124:88–98
13. Harrison RM, Yin J. Particulate matter in the atmosphere: which particle properties are important for its effects on health? Sci Total Environ 2000;249:85–101
14. Yang Y, Ruan Z, Wang X, et al. Short-term and long-term exposures to fine particulate matter constituents and health: a systematic review and meta-analysis. Environ Pollut 2019;247:874–882
15. Sun S, Qiu H, Ho KF, Tian L. Chemical components of respirable particulate matter associated with emergency hospital admissions for type 2 diabetes mellitus in Hong Kong. Environ Int 2016;97:93–99
16. Sun Y, Li X, Benmarhnia T, et al. Exposure to air pollutant mixture and gestational diabetes mellitus in Southern California: results from electronic health record data of a large pregnancy cohort. Environ Int 2022;158:106888

17. Yu G, Ao J, Cai J, et al. Fine particular matter and its constituents in air pollution and gestational diabetes mellitus. Environ Int 2020;142:105880
18. Zhao X, Hong F, Yin J, et al.; China Multi-Ethnic Cohort (CMEC) collaborative group. Cohort profile: the China Multi-Ethnic Cohort (CMEC) study. Int J Epidemiol 2021;50:721–721l
19. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S15–S33
20. Li C, Martin RV, van Donkelaar A, et al. Trends in chemical composition of global and regional population-weighted fine particulate matter estimated for 25 years. Environ Sci Technol 2017; 51:11185–11195
21. van Donkelaar A, Martin RV, Li C, Burnett RT. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. Environ Sci Technol 2019;53:2595–2611
22. Brauer M, Freedman G, Frostad J, et al. Ambient air pollution exposure estimation for the Global Burden of Disease 2013. Environ Sci Technol 2016;50:79–88
23. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J Agric Biol Environ Stat 2015;20:100–120
24. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A quantile-based g-computation approach to addressing the effects of exposure mixtures. Environ Health Perspect 2020;128:47004
25. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–274
26. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and R package for computing E-values. Epidemiology 2018;29:e45–e47
27. Bobb JF, Valeri L, Claus Henn B, et al. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 2015;16:493–508
28. WHO global air quality guidelines: Particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva, World Health Organization, 2021
29. Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 2012;61:3037–3045
30. Frikke-Schmidt H, Roursgaard M, Lykkesfeldt J, Loft S, Nøjgaard JK, Møller P. Effect of vitamin C and iron chelation on diesel exhaust particle and carbon black induced oxidative damage and cell adhesion molecule expression in human endothelial cells. Toxicol Lett 2011;203:181–189
31. Yan J, Lai CH, Lung SC, et al. Carbon black aggregates cause endothelial dysfunction by activating ROCK. J Hazard Mater 2017;338:66–75
32. Delfino RJ, Staimer N, Tjoa T, et al. Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health Perspect 2008;116: 898–906
33. Zanobetti A, Luttmann-Gibson H, Horton ES, et al. Brachial artery responses to ambient pollution, temperature, and humidity in people with type 2 diabetes: a repeated-measures study. Environ Health Perspect 2014;122:242–248
34. Happo MS, Hirvonen M-R, Halinen AI, et al. Chemical compositions responsible for inflammation and tissue damage in the mouse lung by coarse and fine particulate samples from contrasting air pollution in Europe. Inhal Toxicol 2008;20:1215–1231
35. Reiss R, Anderson EL, Cross CE, et al. Evidence of health impacts of sulfate- and nitrate-containing particles in ambient air. Inhal Toxicol 2007;19:419–449
36. Wu S, Wang B, Yang D, et al. Ambient particulate air pollution and circulating antioxidant enzymes: a repeated-measure study in healthy adults in Beijing, China. Environ Pollut 2016;208:16–24
37. Liu C, Cai J, Qiao L, et al. The acute effects of fine particulate matter constituents on blood inflammation and coagulation. Environ Sci Technol 2017;51:8128–8137
38. Zhang Q, Wang W, Niu Y, et al. The effects of fine particulate matter constituents on exhaled nitric oxide and DNA methylation in the arginase-nitric oxide synthase pathway. Environ Int 2019; 131:105019
39. Qiu H, Tian L, Ho K-F, Pun VC, Wang X, Yu ITS. Air pollution and mortality: effect modification by personal characteristics and specific cause of death in a case-only study. Environ Pollut 2015; 199:192–197
40. Brook RD, Cakmak S, Turner MC, et al. Long-term fine particulate matter exposure and mortality from diabetes in Canada. Diabetes Care 2013; 36:3313–3320