Long-term exposure to $PM_{2.5}$ chemical constituents and diabesity: evidence from a multi-center cohort study in China

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Summary

Background Long-term exposure to $PM_{2.5}$ is known to increase the risks for diabetes and obesity, but its effects on their coexistence, termed diabesity, remain uncertain. This study aimed to investigate the associations of long-term exposure to $PM_{2.5}$ and its chemical constituents with the risks for diabesity, diabetes, and obesity.

Methods This cross-sectional study used the baseline data of a multi-center cohort, consisting of three provincially representative cohorts comprising a total of 134,403 participants from the eastern (Fujian Province), central (Hubei Province), and western (Yunnan Province) regions of China. Obesity and diabetes, and diabesity were identified by a body mass index (BMI) ≥28 kg/m^2 and fasting plasma glucose (FPG) ≥126 mg/dL. The average concentrations of $PM_{2.5}$ and five chemical constituents (NO_3^-, SO_4^{2-}, NH_4^+, organic matter, and black carbon) over participants' residence during the past three years were estimated using machine learning models. Logistic regression models with double robust estimators, Bayesian kernel machine regression, and weighted quantile sum regression were employed to estimate independent and joint effects of $PM_{2.5}$ chemical constituents on the risks for diabesity, diabetes, and obesity, as well as the differences from the effects on obesity. Stratified analyses were performed to examine effect modification of sociodemographic and lifestyle factors.

Findings There were 129,244 participants with a mean age of 54.1 ± 13.8 years included in the study. Each inter-quartile range increase in $PM_{2.5}$ concentration (8.53 μg/m^3) was associated with an increased risk for diabesity (OR = 1.23 [1.17, 1.30]), diabetes only (OR = 1.16 [1.13, 1.19]), and obesity only (OR = 1.03 [1.00, 1.05]). Long-term exposure to each $PM_{2.5}$ chemical constituent was associated with an increased risk for diabesity, where organic matter exposure, with maximum weight (48%), was associated with a higher risk for diabesity (OR = 1.21 [1.16, 1.27]). Among those with obesity, black carbon contributed most (68%) to the joint effect of $PM_{2.5}$ chemical constituents on diabesity (OR = 1.16 [1.11, 1.22]). Physical activity reduced adverse effects of $PM_{2.5}$ on diabesity. Also, additive rather than multiplicative effects of obesity on the $PM_{2.5}$-diabetes association were observed.

Interpretation Long-term exposure to $PM_{2.5}$ and its chemical constituents was associated with an increased risk for diabesity, stronger than associations for diabetes and obesity alone. The main constituents associated with diabesity and obesity were black carbon and organic matter.

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Keywords: Diabesity; Obesity; Diabetes; Air pollution; $PM_{2.5}$ chemical constituents

Research in context

Evidence before this study

The coexistence of diabetes and obesity, also referred to as *diabesity*, could synergistically exacerbate cardiometabolic diseases and has become an emerging global public health burden due to the widespread obesity epidemic. Exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) has been associated with an increased risk for obesity and diabetes, separately. A recent study has shown a stronger association between $PM_{2.5}$ exposure and diabetes in individuals with obesity, compared to those without. $PM_{2.5}$ is a complex mixture of chemical constituents, which may have varying health effects. No studies have investigated the effects of $PM_{2.5}$ and its chemical constituents on diabesity.

Added value of this study

Each interquartile range (IQR) increase in all $PM_{2.5}$ chemical constituents was associated with an increased risk for diabesity and diabetes only. Each IQR increase in the concentration of individual $PM_{2.5}$ chemical constituents was associated with an increased risk for diabesity, including SO_4^{2-}, NO_3^-, organic matter, and black carbon. The largest contribution to joint effects of $PM_{2.5}$ chemical constituents on diabesity was from organic matter (36%), followed by black carbon (28%) and NO_3^- (22%). Compared to those with obesity, an increased risk for diabesity was associated with SO_4^{2-}, NO_3^-, NH_4^+, organic matter, and black carbon, and their joint effect on diabesity was mainly contributed by black carbon (34%), NH_4^+ (33%), and NO_3^- (25%). Physical activity reduced adverse effects of $PM_{2.5}$ chemical constituents on diabesity.

Implications of all the available evidence

This study used the data of three cohorts from the eastern, central and western China to examine independent and joint effects of $PM_{2.5}$ chemical constituents on the risks for diabesity. Our findings would serve as evidence for developing strategies to prevent diabesity from an environmental health perspective, and point out future research directions for revealing mechanisms between $PM_{2.5}$ chemical constituents and diabesity.

Introduction

Diabetes is a chronic health condition that affects how the body converts food into energy and is frequently developed in people with obesity, which can disrupt glycemic control and promote insulin resistance, thus increasing the risk for diabetes.[1] About 90% of type 2 diabetes is attributable to overweight or obesity, and the number of people who have obesity-related impaired glucose tolerance is expected to increase to 420 million worldwide by 2025.[2] The coexistence of diabetes and obesity, also referred to as *diabesity*, could synergistically exacerbate cardiometabolic diseases and has become an emerging global public health burden due to the widespread obesity epidemic.[3] To effectively control and prevent diabesity on a large scale, it is crucial to understand its modifiable risk factors.

Air pollutants, particularly particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), are among the most pervasive environmental hazards worldwide. Studies have shown that exposure to $PM_{2.5}$ is associated with an increased risk for obesity[4,5] and diabetes,[6,7] separately. Nevertheless, no studies have investigated the effects of $PM_{2.5}$ exposure on diabesity. It has been found in animal experiments that exposure to $PM_{2.5}$ could lead to insulin resistance and systemic inflammatory responses,[8,9] ultimately resulting in obesity,[10] also to impaired glucose tolerance, reduced circulating concentrations of adipokines (such as adiponectin and leptin), and mitochondrial alteration, ultimately resulting in diabetes.[11] Recent population-based epidemiological research from the UK Biobank has also highlighted a stronger association between $PM_{2.5}$ exposure and diabetes in individuals with obesity, compared to those without. Despite these findings, the potential additive or synergistic effects of obesity on the $PM_{2.5}$-diabetes association have yet to be fully elucidated. This knowledge gap has hindered our ability to accurately estimate the disease burden of diabesity attributable to $PM_{2.5}$ exposure.[7]

Additionally, $PM_{2.5}$ is a complex mixture of chemical constituents, mainly including secondary inorganic

aerosols such as sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), organic matter, and black carbon,[12] which may have varying health effects.[13] To accurately predict the effects of $PM_{2.5}$ on diabesity, it is necessary to investigate the contribution of each chemical constituent to their joint effects on diabesity. However, this may be difficult to achieve by the commonly used parametric regression, due to high correlations among those chemical constituents.[14]

To address the aforementioned gaps, we established a population-based multi-center cohort study covering three provinces in the east, central, and west of China. Using the baseline data, we examined independent and joint effects of $PM_{2.5}$ chemical constituents on the risks for diabesity, diabetes, and obesity. To identify the relative importance of independent $PM_{2.5}$ chemical constituents in their joint effect on diabesity, we employed a weighted quantile sum (WQS) regression, which overcomes the limitations of the commonly used regression methods. Our findings would serve as evidence for developing strategies to prevent diabesity from an environmental perspective, and point out future research directions for revealing mechanisms between $PM_{2.5}$ constituents and diabesity.

Methods

Study design and population

This cross-sectional study utilized the baseline data of a multi-center cohort established in the eastern (Fujian Province), central (Hubei Province) and western (Yunnan Province) regions of China, which was designed to examine chronic diseases and their risk factors among adults (Fig. 1).[15] A multi-stage cluster random sampling method, adopted by the Chinese Center for Disease Prevention and Control to carry out the national Chronic Disease and Risk Factor Surveillance,[16,17] was used to recruit participants from the general population in selected communities, which were chosen from each of the selected districts/counties

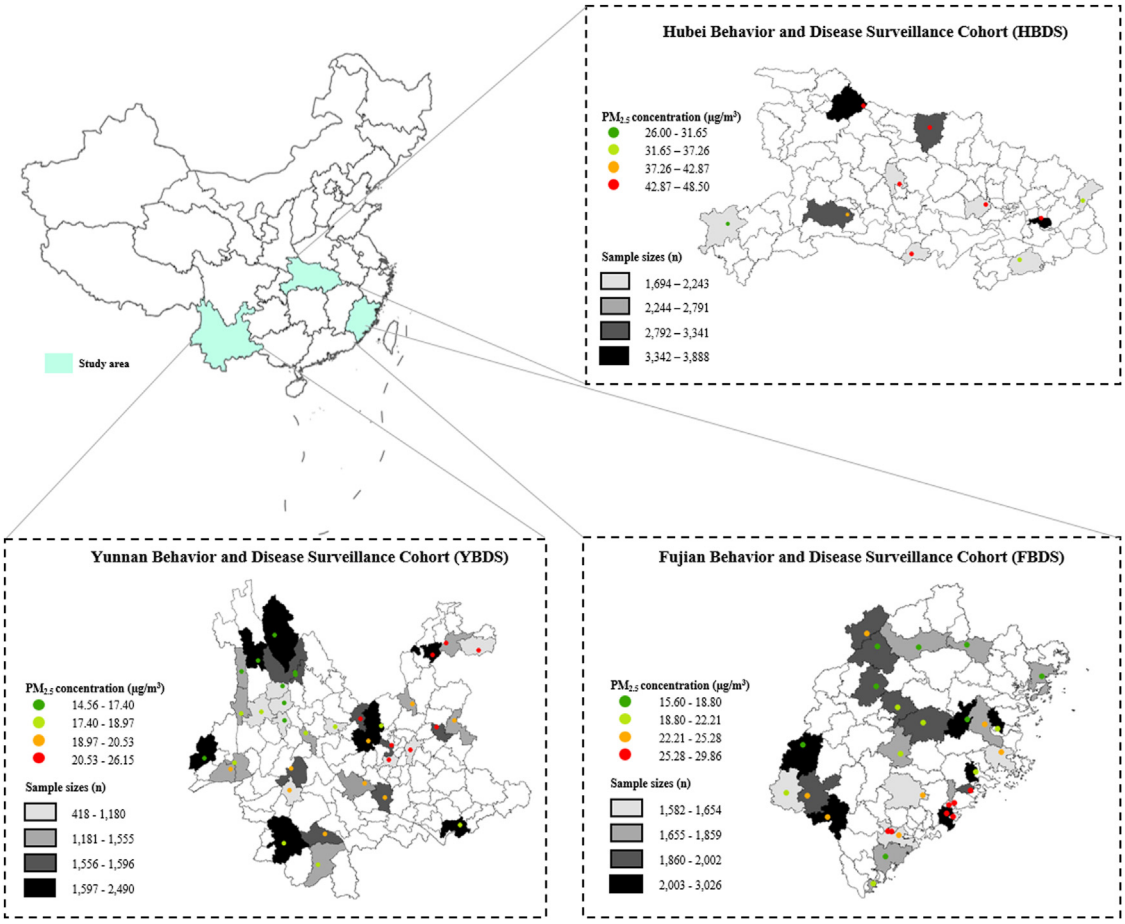

Fig. 1: Distributions of the study participants and the 3-year average $PM_{2.5}$ concentrations in three provinces. Polygons represent the cities/counties in which the study participants were recruited, colored by sample size; dots correspond to polygons, colored by the 3-year average concentration of $PM_{2.5}$ over the cities/counties.

in three provinces. Participants were invited to participate in the surveys if meeting all following inclusion criteria: 1) being aged 18 or older on the day of the survey; 2) living in the selected communities for more than three years; and 3) not having severe mental illnesses, such as paraplegia, schizophrenia, and terminal illnesses. A standardized questionnaire was used to collect sociodemographic and lifestyle characteristics through face-to-face interviews. As a result, the Fujian Behavior and Disease Surveillance Cohort (FBDS) was established during 2018–2020, recruiting 54,961 adults aged >18 years from 29 districts/counties of the province, with a participation rate of 85%–92%; the Hubei Behavior and Disease Surveillance Cohort (HBDS) was established during 2018–2020, recruiting 27,962 adults aged >18 years from 10 districts/counties of the province, with a participation rate of 91%; and the Yunnan Behavior and Disease Surveillance Cohort (YBDS) was established from January to August 2021, recruiting 51,480 adults aged >18 years from 35 districts/counties of the province, with a participation rate of 99.7%.[15]

In this study, participants were excluded if having missing information on body mass index (BMI), fasting plasma glucose (FPG), or home addresses. The 682 (1.2%) in FBDS, 3200 (11.4%) in HBDS and 1277 (2.3%) participants in YBDS were excluded, resulting in a final sample of 129,244 participants. The study received ethical approval from the ethical review board of the National Center for Chronic and Noncommunicable Disease Control and Prevention, the Fujian Center for Disease Prevention and Control (2,018,001), and the Yunnan Center for Disease Prevention and Control (202,017). Written informed consent was obtained from all participants prior to data collection, and the study was conducted in accordance with the principles of the Helsinki Declaration.

Outcome variables

Diabesity was defined as the co-existence of diabetes and obesity.[3] One was diagnosed as having diabetes if having an FPG level of ≥126 mg/dL (7.0 mmol/L) or taking medication (oral glucose-lowering agents or insulin) for diabetes.[18,19] Fast venous blood was collected after an overnight fast of at least 8 h, using vacuum blood collection tubes and blood lancets. According to the criteria from the Expert Consensus on Obesity Prevention and Treatment in China, obesity was defined as an BMI of ≥28 kg/m^2, with measurements of body weight and height taken in light clothing and without shoes.[20] Weight and height were measured to a precision of 0.1 kg and 0.1 cm, respectively, with the mean of three measurements calculated and used for analysis. Anthropometric and laboratory tests were performed by qualified medical practitioners following standard protocols.

Exposure variables

The daily concentrations of $PM_{2.5}$ and its chemical constituents, including SO_4^{2-}, NO_3^-, NH_4^+, organic matter, and black carbon, were obtained as separate variables at a spatial resolution of 10 km from the "Tracking Air Pollution in China" database. They were estimated by a two-stage machine learning model, coupled with a synthetic minority oversampling technique and a tree-based gap-filling method, on the basis of multiple data sources including ground observations, satellite aerosol optical depth, operational chemical transport model simulations, and other ancillary data such as meteorological fields, land use data, population, and elevation. The out-of-bag cross validation for $PM_{2.5}$ led to the R^2 of 0.80–0.88 and root-mean-square error (RMSE) of 13.9–22.1 μg/m^3.[21] The estimated daily concentrations of $PM_{2.5}$ chemical constituents were in good agreement with the available ground-based measurements, with correlation coefficients ranging from 0.67 to 0.80 and most normalized mean biases within ±20%.[22] The 3-year average concentrations of $PM_{2.5}$ and its chemical constituents over the residence of the participants preceding the survey were calculated as surrogates of the individuals' exposures to $PM_{2.5}$ and its chemical constituents.[23]

Covariates

A directed acyclic graph (DAG) was made to identify the covariates to be adjusted in the models (Figure S1).[24] Sociodemographic covariates included age (<60 years, ≥60 years), sex (male, female), ethnicity (Han, minorities), marital status (married, unmarried/divorced), educational level (below elementary school, elementary and middle school, high school and above), and gross domestic product (GDP) per capita (*yuan*). Lifestyle covariates included smoking (yes, no), alcohol drinking (yes, no), vegetable intake, fruit intake, meat intake, and physical activity. Physical activity was based on individual metabolic equivalent minutes per week (MET-min/w) and was categorized as low (<600 MET-min/w), moderate (600–3000 MET-min/w), and high (≥3000 MET-min/w). The MET intensity was calculated using personal physical activity, including occupational, transport, leisure, and household physical activity.[25] Additionally, the outcomes of interest may intrinsically vary across cohorts, so cohort was also adjusted in the pooled analysis of the three cohorts.

Statistical analyses

Categorical variables were presented as numbers and percentages, and continuous variables as median (25th percentile, 75th percentile) for the four groups of participants: diabesity, diabetes only, obesity only, and normal. The normality assumption of variables was evaluated by an Anderson-Darling test. Wilcoxon rank-sum tests were used for continuous variables and chi-square tests for categorical variables. A multiple

imputation by chained equations (MICE) method, with the number of imputations set to 5, was used to address missing data of the covariates, where the univariate estimates of the complete data model and the total variance across the repeated analyses were calculated using the rule of thumb.[26]

To assess independent and joint effects of $PM_{2.5}$ chemical constituents on the risk for diabesity, diabetes, and obesity, as well as the differences from the effects on obesity, we conducted a three-step analysis. First, we used one-pollutant regression models with double-robust estimators to estimate the associations of each IQR increase in the concentration of $PM_{2.5}$ constituents with the risks for diabesity, diabetes, and obesity, and presented as odds ratio (OR) with 95% confidence interval (CI); ORs for the risk of diabesity were also estimated with participants with obesity. Logistic regression with double-robust estimator was used because it can provide more accurate estimates than conventional likelihood-based or inverse probability-weighted estimators, if a propensity score or outcome regression model is properly specified.[4] This method is divided into two phases: at the design phase, a pseudo population was constructed using the generalized linear model to balance the covariates across levels of exposure; then, logistic regression was used to examine the links between exposure to $PM_{2.5}$ chemical constituents and the risks for diabesity, diabetes, and obesity in the pseudo-population after controlling for covariates.

Second, weighted quantile sum (WQS) regression was used to determine the joint effects of all $PM_{2.5}$ chemical constituents on the risks for diabesity, diabetes only, and obesity only, as all $PM_{2.5}$ chemical constituents were assumed to affect the outcome in a consistent (positive) direction.[27] The relative importance (i.e., weight) of each $PM_{2.5}$ chemical constituent to their joint effect was also calculated in WQS, presented as percentages. To check the interactions between $PM_{2.5}$ chemical constituents which is not allowed for conducting WQS, 1000 participants were randomly selected from each province based on computational constraints and the complexity of the model. A Bayesian kernel machine regression (BKMR) model, with an assumption of slab prior distribution and Gaussian kernel function, was fit using a Markov chains Monte Carlo algorithm for 50,000 iterations with different seeds.[28] Further, we used restricted cubic spline (RCS) regression to examine potential nonlinear associations between $PM_{2.5}$ chemical constituents and the outcomes.

Third, an interactive term of $PM_{2.5}$ and obesity and a relative excess risk due to interaction (RERI) with the attributable proportion due to interaction (AP) and the synergy index (S) were used to assess multiplicative and additive effects of obesity on the $PM_{2.5}$-diabetes association, respectively.[29] The additive interaction was considered significant if the 95% CIs of RERI and AP were completely on one side of 0, or the 95% CI of S was completely on one side of 1, where CIs were estimated using a bootstrap simulation method.[30]

Additionally, several stratified analyses were performed to explore potential effect modification of age, sex, educational level, smoking, alcohol drinking, vegetable intake, fruit intake, meat intake, and physical activity. The significance of effect modification was tested by an interaction term of the exposure variable and stratifier, and raw CIs without multiplicity correction were provided. To ensure the robustness of our findings, we also conducted several sensitivity analyses. First, we examined the associations between the 1- and 5-year average concentrations of $PM_{2.5}$ chemical constituents and the risks for diabesity, diabetes only, and obesity only to evaluate potential influences of exposure duration. Second, we excluded participants with a family history of diseases, such as coronary heart disease, stroke, and diabetes, to reduce inherent influences. Third, we excluded participants with self-reported diabetes to mitigate reporting bias. Fourth, we employed a multi-level logistic regression model to examine influences of provincial-level factors on our results. Finally, as the normal participants were consistently used as the reference group for easy comparison of ORs in the main analysis, those without each disease were also used as the reference group, i.e., (diabesity vs. non-diabesity, obesity vs. non-obesity, and diabetes vs. non-diabetes).

All statistical analyses were conducted using R version 4.2.0, with *gWQS* package (version 3.0.4) used for WQS, *bkmr* (version 0.2.2) for BKMR model, *mice* (version 3.14.0) for multiple imputation, and *lme4* for multi-level logistic regression model. The significance threshold was 0.05, and all tests were 2-sided.

Role of the funding source

The funding source has no role in the study design, in the collection, analysis and interpretation of data, in the writing of manuscript and in the decision to submit the paper for publication.

Results

Characteristics of study participants

The 129,244 included participants had a mean age of 54.1 ± 13.8 years, with about 35.4% being ≥60 years, 43.1% being males, and 80.9% being Hans (Table 1). Differences existed in the proportions of age, sex, ethnicity, educational level, marital status, smoking, alcohol drinking, physical activity level, and intakes of fruit, vegetable, and meat among normal, obesity, diabetes, and diabesity. The overall prevalences of diabesity, diabetes, and obesity were 2.2%, 10.4%, and 12.5%, respectively. The participants in three provinces were exposed to different levels of $PM_{2.5}$, highest in Hubei and followed by Fujian and Yunnan. In general, those with diabesity, diabetes, and obesity were exposed

Variables	Number (%) or median (25th percentile, 75th percentile)					*P* value
	Overall (n = 129,244)	Normal (n = 102,466)	Obesity (n = 13,301)	Diabetes (n = 10,654)	Diabesity (n = 2823)	
Age						<0.0001
<60 years	83,550 (64.6)	67,480 (65.9)	9636 (72.4)	4879 (45.8)	1555 (55.1)	
≥60 years	45,694 (35.4)	34,986 (34.1)	3665 (27.6)	5775 (54.2)	1268 (44.9)	
Sex						<0.0001
Male	55,646 (43.1)	44,411 (43.3)	5204 (39.1)	4879 (45.8)	1152 (40.8)	
Female	73,598 (56.9)	58,055 (56.7)	8097 (60.9)	5775 (54.2)	1671 (59.2)	
Ethnicity						<0.0001
Han	104,518 (80.9)	82,680 (80.7)	10,120 (76.1)	9346 (87.7)	2372 (84.0)	
Minorities	247,26 (19.1)	19,786 (19.3)	3181 (23.9)	1308 (12.3)	451 (16.0)	
Educational level						<0.0001
Below elementary school	47,869 (37.0)	37,268 (36.4)	4970 (37.4)	4493 (42.2)	1138 (40.3)	
Elementary and middle school	61,541 (47.6)	48,817 (47.6)	6503 (48.9)	4849 (45.5)	1372 (48.6)	
High school and above	19,834 (15.3)	16,381 (16.0)	1828 (13.7)	1312 (12.3)	313 (11.1)	
Marital status						<0.0001
Married	114,824 (88.8)	90,958 (88.8)	12,023 (90.4)	9349 (87.8)	2494 (88.3)	
Unmarried/divorced	14,420 (11.2)	11,508 (11.2)	1278 (9.6)	1305 (12.2)	329 (11.7)	
GDP per capita (*yuan*)	64,466.0 (45,469.3, 91,078.3)	64,466.0 (45,469.3, 91,078.3)	59,413.0 (44,944.3, 88,898.7)	68,395.3 (47,340.7, 94,639.0)	66,845.7 (46,231.3, 93,956.3)	<0.0001
Smoking						<0.0001
No	91,694 (70.9)	72,138 (70.4)	10,001 (75.2)	7438 (69.8)	2117 (75.0)	
Yes	37,550 (29.1)	30,328 (29.6)	3300 (24.8)	3216 (30.2)	706 (25.0)	
Alcohol drinking						<0.0001
No	88,607 (68.6)	69,650 (68.0)	9221 (69.3)	7702 (72.3)	2034 (72.1)	
Yes	40,637 (31.4)	32,816 (32.0)	4080 (30.7)	2952 (27.7)	789 (27.9)	
Fruit intake (g/day)	48.6 (14.3, 102.9)	50.0 (14.3, 107.1)	50.0 (14.3, 114.3)	29.5 (6.6, 100.0)	35.7 (6.6, 100.0)	<0.0001
Vegetable intake (g/day)	300.0 (200.0, 450.0)	300.0 (200.0, 450.0)	300.0 (200.0, 450.0)	300.0 (200.0, 450.0)	300.0 (200.0, 450.0)	0.073
Meat intake (g/day)	64.3 (28.6, 150.0)	64.3 (28.6, 150.0)	71.4 (28.6, 150.0)	50.0 (21.4, 120.0)	57.1 (20.7, 142.9)	<0.0001
Physical activity						<0.0001
Low	49,795 (38.5)	39,143 (38.2)	4471 (33.6)	5020 (47.1)	1161 (41.1)	
Moderate	32,209 (24.9)	25,436 (24.8)	3309 (24.9)	2706 (25.4)	758 (26.9)	
High	47,240 (36.6)	37,887 (37.0)	5521 (41.5)	2928 (27.5)	904 (32.0)	
$PM_{2.5}$ ($\mu g/m^3$)	21.3 (18.8, 27.4)	21.2 (18.8, 27.2)	21.2 (18.7, 27.2)	22.2 (19.3, 28.3)	22.9 (19.4, 29.4)	<0.0001
$PM_{2.5}$ constituents ($\mu g/m^3$)						
SO_4^{2-}	4.6 (4.1, 5.4)	4.6 (4.1, 5.4)	4.6 (4.1, 5.4)	4.7 (4.2, 5.5)	4.8 (4.3, 5.9)	<0.0001
NO_3^-	3.5 (3.0, 4.8)	3.5 (3.0, 4.8)	3.5 (3.0, 4.8)	3.8 (3.2, 4.8)	3.9 (3.2, 5.7)	<0.0001
NH_4^+	3.0 (2.7, 3.4)	3.0 (2.7, 3.4)	3.0 (2.7, 3.5)	3.0 (2.7, 3.4)	3.1 (2.8, 4.7)	<0.0001
OM	6.4 (5.7, 8.4)	6.3 (5.7, 8.1)	6.4 (5.7, 8.2)	6.6 (5.8, 9.1)	6.7 (5.8, 9.4)	<0.0001
BC	1.4 (1.2, 1.6)	1.4 (1.2, 1.6)	1.4 (1.2, 1.6)	1.4 (1.2, 1.8)	1.4 (1.3, 1.8)	<0.0001

BC, black carbon; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO_4^{2-}, sulfate.

Table 1: **Characteristics of the study population.**

to higher concentrations of $PM_{2.5}$ and its chemical constituents than their counterparts without diabetes and obesity (Table S1). The concentrations of $PM_{2.5}$ chemical constituents also varied among three provinces, with organic matter having a higher concentration on average than the other constituents in all three provinces. Similar to the trends of $PM_{2.5}$ concentrations in three provinces, all $PM_{2.5}$ chemical constituents had higher concentrations in Hubei than in Fujian and Yunnan (Fig. 1).

Associations between $PM_{2.5}$ and diabesity

Compared to the normal group, each IQR increase in $PM_{2.5}$ concentration was associated with the risk for diabesity (OR [95% CI] = 1.23 [1.17, 1.30]), which was stronger than the risks for diabetes only (OR = 1.16 [1.13, 1.19]) and obesity only (OR = 1.03 [1.00, 1.05]) (Fig. 2). The five $PM_{2.5}$ chemical constituents, account for a large part (>90%) of $PM_{2.5}$, had a similar joint effect on diabesity (OR = 1.24 [1.18, 1.30]), diabetes only (OR = 1.13 [1.10, 1.15]), and obesity only (OR = 1.05 [1.03, 1.08]). Compared to those with obesity only, each IQR increase in $PM_{2.5}$ concentration was also associated with an increased risk for diabesity (OR = 1.20 [1.13, 1.26]).

Each IQR increase in the concentration of individual $PM_{2.5}$ chemical constituents was also associated with an increased risk for diabesity, including SO_4^{2-} (OR = 1.20 [1.14, 1.25]), NO_3^- (OR = 1.15 [1.09, 1.21]), NH_4^+ (OR = 1.07 [1.02, 1.13]), organic matter (OR = 1.21 [1.16, 1.27]), and black carbon (OR = 1.19 [1.15, 1.25]) (Fig. 2). These chemical constituents were also positively associated with the risks for diabetes only. The largest contribution to joint effects of $PM_{2.5}$ on diabesity was from organic matter (48%), followed by black carbon (30%) and SO_4^{2-} (19%), while the largest contributions to joint effects on diabetes only (80%) and obesity only (60%) were from black carbon (OR = 1.12 [1.10, 1.15]) and organic matter (OR = 1.04 [1.02, 1.07]), respectively (Fig. 3, Table S2). Compared to those with obesity only, an increased risk for diabesity was associated with SO_4^{2-} (OR = 1.15 [1.10, 1.21]), NO_3^- (OR = 1.10 [1.04, 1.17]), NH_4^+ (OR = 1.08 [1.02, 1.14]), organic matter (OR = 1.15 [1.09, 1.21]), and black carbon (OR = 1.16 [1.11, 1.22]), with main contributions to their joint effect on diabesity from black carbon (68%), SO_4^{2-} (12%), and NH_4^+ (11%). No interactions between $PM_{2.5}$ chemical constituents were detected (Figures S2 and S3). Nonlinear associations were only observed between NO_3^- and black carbon and obesity only (Figures S4–S7).

The aforementioned associations were also to different extents observed in each of the three provinces. For example, the stronger association between $PM_{2.5}$

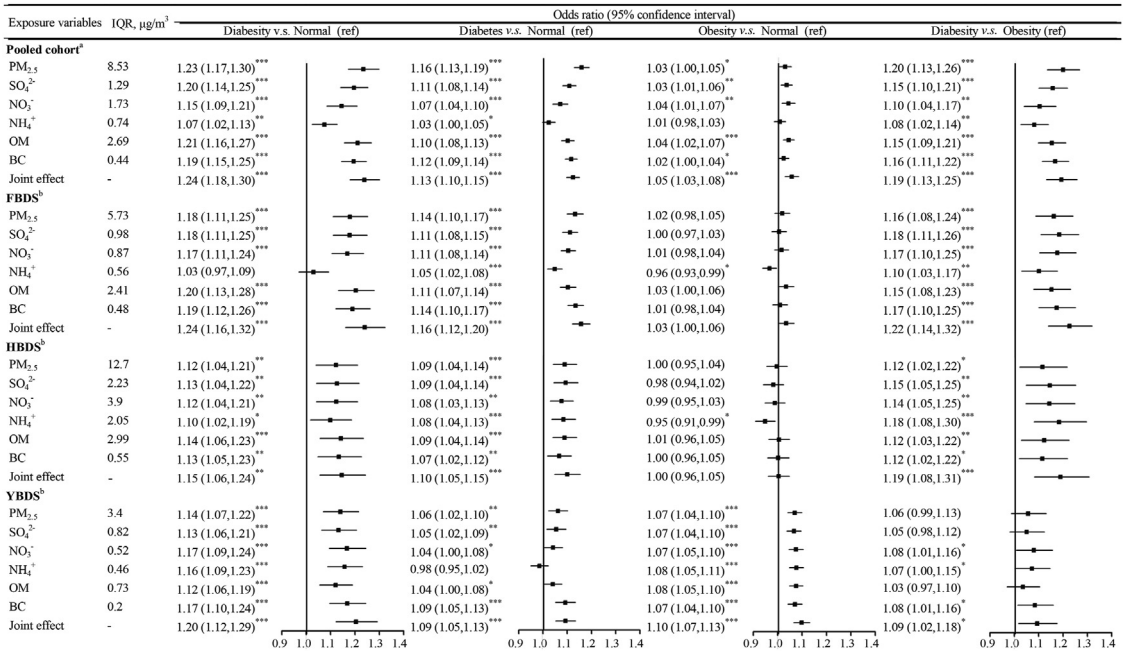

Fig. 2: Associations of $PM_{2.5}$ and its chemical constituents with the risks for diabesity, diabetes, and obesity [a]Covariates adjusted included age, sex, ethnicity, marital status, educational level, GDP per capita, smoking, alcohol drinking, diet intake, physical activity, and province. [b]Covariates adjusted included age, sex, ethnicity, marital status, educational level, and GDP per capita, smoking, alcohol drinking, diet intake, and physical activity. BC, black carbon; FBDS, Fujian Behavior and Disease Surveillance cohort; HBDS, Hubei Behavior and Disease Surveillance cohort; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO_4^{2-}, sulfate; YBDS, Yunnan Behavior and Disease Surveillance cohort. *P < 0.05; **P < 0.01; ***P < 0.001.

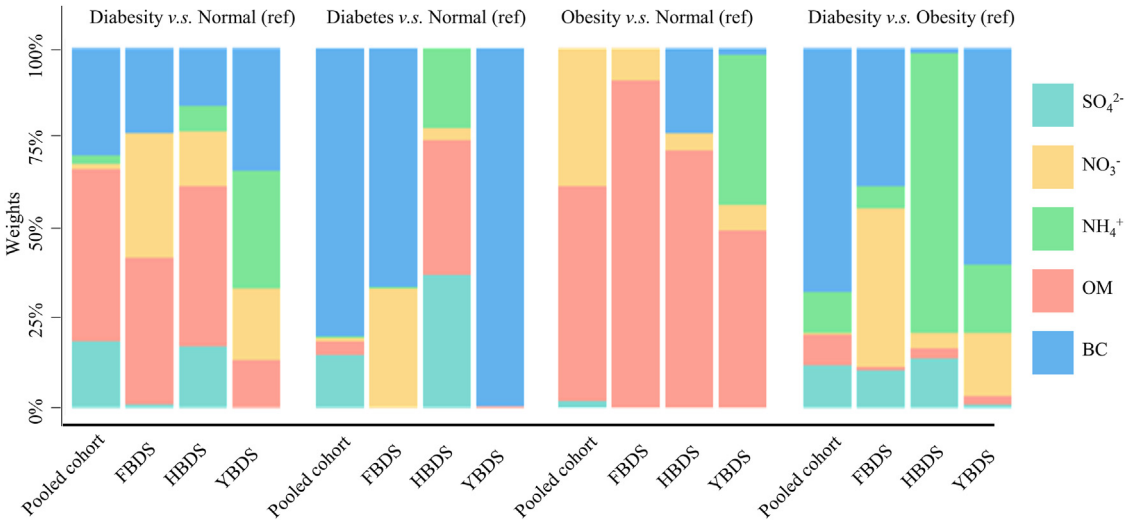

Fig. 3: Relative importance of $PM_{2.5}$ chemical constituents to their joint effects on the risks for diabesity, diabetes, and obesity BC, black carbon; FBDS, Fujian Behavior and Disease Surveillance cohort; HBDS, Hubei Behavior and Disease Surveillance cohort; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate; YBDS, Yunnan Behavior and Disease Surveillance cohort.

and diabesity was observed in Fujian Province (OR = 1.19 [1.12, 1.26]) than in Yunnan (OR = 1.16 [1.09, 1.23]) and Hubei (OR = 1.12 [1.04, 1.21]). Each IQR increase in $PM_{2.5}$ chemical constituents were also associated with an elevated risk for diabesity in all three provinces, except for NH_4^+ in Fujian Province (Fig. 2). Organic matter contributed most to the joint effect on diabesity risk in Fujian (41%, OR = 1.20 [1.13, 1.28]) and Hubei (45%, OR = 1.14 [1.06, 1.23]), while black carbon contributed most in Yunnan (34%, OR = 1.17 [1.10, 1.24]). Compared to those with obesity only, NO_3^- contributed most to the joint effect on diabesity risk in Fujian province (44%, OR = 1.17 [1.10, 1.25]), while NH_4^+ contributed most in Hubei (77%, OR = 1.18 [1.08, 1.30]) and black carbon contributed most in Yunnan (60%, OR = 1.08 [1.02, 1.16]).

Additionally, we observed additive interaction with synergistic effects (RERI [95% CI] = 0.26 [0.17, 0.33], AP [95% CI] = 0.10 [0.07, 0.13)], S [95% CI] = 1.20 [1.12, 1.28]) of obesity with $PM_{2.5}$ on diabetes risk, while the multiplicative interaction was no significant (P value > 0.05) (Table S3). Notably, we observed an interaction between each $PM_{2.5}$ chemical constituent and obesity on an additive scale. Additionally, we noted significant multiplicative interactions specifically between SO_4^{2-} and NH_4^+, black carbon, and obesity.

Stratified analysis of the $PM_{2.5}$-diabesity association

The association between $PM_{2.5}$ and diabesity risk varied only by physical activity, with the lower risk observed in those with a high level of physical activity (OR = 1.20 [1.11, 1.29]) (Table S4). No variations in the $PM_{2.5}$-diabesity association were observed by age, sex, educational level, smoking, alcohol drinking, and intakes of vegetable, fruit, and meat. Moreover, the risks for diabetes only and obesity only were higher among those aged ≥60 years than those aged <60 years. Also, the risk for diabetes only was higher in those with higher fruit intake (OR = 1.21 [1.16, 1.25]) than those with lower fruit intake.

Sensitivity analysis of the $PM_{2.5}$-diabesity association

The associations of $PM_{2.5}$ and its chemical constituents with the risks for diabesity, diabetes only and obesity only were all stable across different periods of exposure (Fig. 4 and Figures S8–S10), and after excluding the participants with family history of coronary heart disease, stroke, and diabetes, and self-reported diabetes (Tables S5–S8). The results were also stable after controlling for random effects of provinces in this multi-center cohort and when comparing the group with a certain disease to the group without that disease (Tables S9 and S10).

Discussion

To our knowledge, this study is the first to investigate the associations between exposure to $PM_{2.5}$ and its chemical constituents and the risks for diabesity in a large, multi-center cohort study in China, with a particular focus on the effects of obesity on the $PM_{2.5}$-diabetes association. Our results revealed that increased concentrations of $PM_{2.5}$ and its chemical constituents were associated with the elevated risk for diabesity. Specifically, we found that exposure to organic matter played a pivotal role in the risk for diabesity when

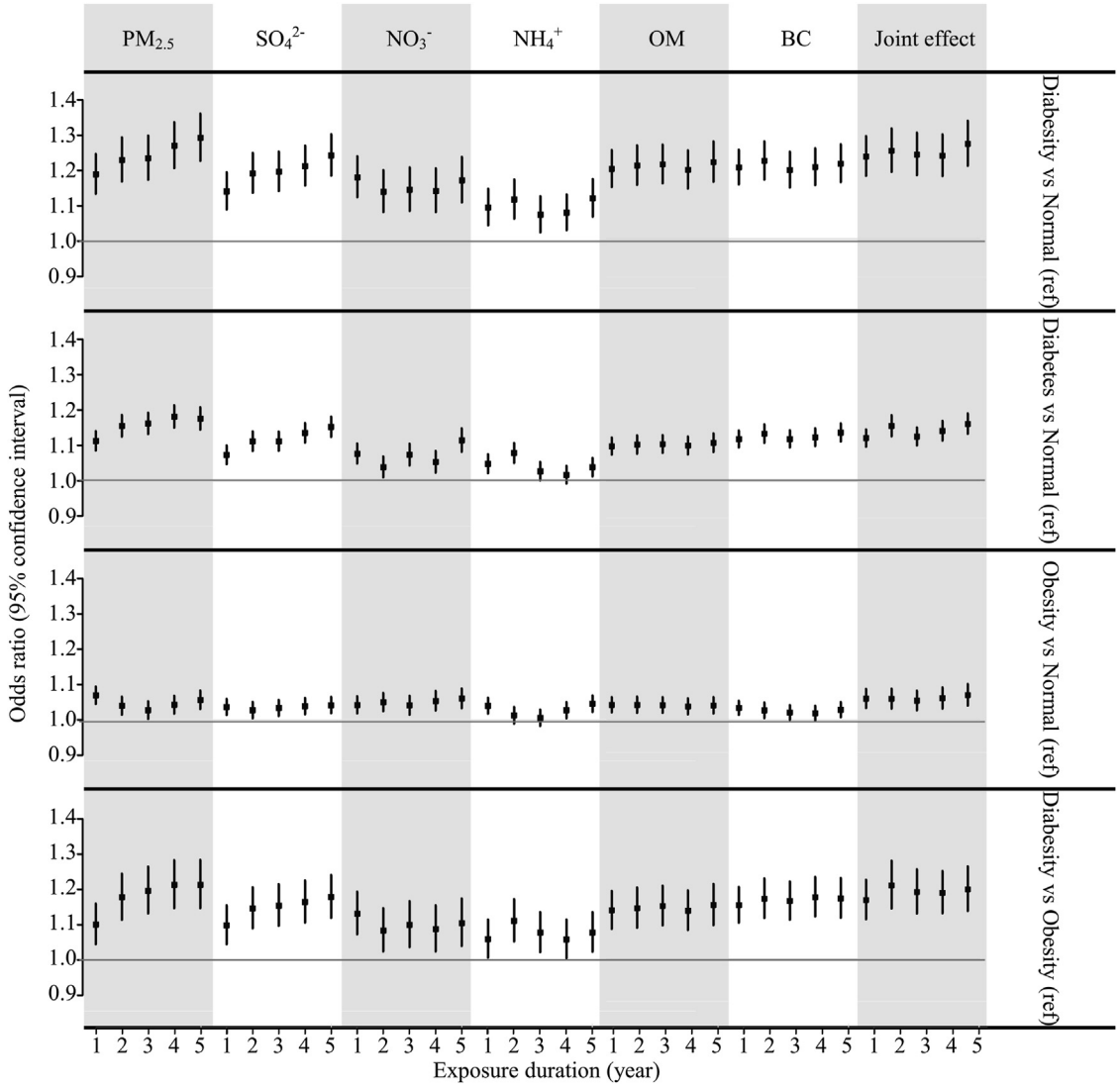

Fig. 4: Associations between exposure to $PM_{2.5}$ chemical constituents and the risks for diabesity, diabetes, and obesity across different periods of exposure. Covariates adjusted included age, sex, ethnicity, marital status, educational level, GDP per capita, smoking, alcohol drinking, diet intake, physical activity, and province. BC, black carbon; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO_4^{2-}, sulfate.

compared with participants without obesity and diabetes, while exposure to black carbon was a key factor in the risk for diabesity in comparison to those with obesity. Also, organic matter and black carbon were found to be the largest contributors to joint effects of $PM_{2.5}$ chemical constituents on obesity and diabetes, respectively. Furthermore, physical activity was found to modify the association between exposure to $PM_{2.5}$ chemical constituents and diabesity risk.

We observed a strong positive association of exposure to $PM_{2.5}$ and its chemical constituents with the risk for diabesity, which was more pronounced than the risk for obesity and diabetes alone. The underlying mechanisms may be the amplification of the $PM_{2.5}$-diabetes association by overweight/obesity, since obesity is a pro-inflammatory state that can lead to increased inflammatory response and oxidative stress. In the presence of air pollution and obesity, there may be a multiplicative effect.[31,32] Previous studies have shown a positive association between tidal volume and obesity, with greater tidal volume leading to increased doses of inhaled particulate matter in people with obesity.[33,34] One study of 449,006 participants from the UK biobank reported a similar finding that the association between exposure to $PM_{2.5}$ and diabetes was more pronounced in participants with obesity than with

normal weight.[7] Therefore, obesity may have an additive or synergistic effect on the $PM_{2.5}$-diabetes association and accelerate the progression of diabesity, which could explain the greater diabesity risk attributed to $PM_{2.5}$ and its chemical constituents than the risks for diabetes and obesity alone.

Notably, our study suggests that organic matter may be the primary obesogenic constituent, and black carbon may interact with obesity and contribute more to the $PM_{2.5}$-diabetes association in the participants with obesity. Although underlying mechanisms linking $PM_{2.5}$ chemical constituents and the increased risk for diabesity remain unclear, some possible mechanisms have been proposed. For example, organic matter and black carbon are mainly from liquid fuel sources (e.g., vehicle emissions), coal combustion, and biomass burning.[35] Organic matter 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).[36] It may reach all internal organs, but due to their lipophilicity, levels are particularly high in adipose tissue.[37] Thus, organic matter is involved in the regulation of inflammatory and metabolic responses in adipocytes, which may explain why it may be the primary obesogenic constituent.[38,39] Black carbon is considered a tracer of older diesel fuels, and environmental black carbon can be the largest contributor to road diesel emissions.[40] Due to its higher porosity, black carbon may operate as a carrier of various constituents with different chemical toxicities affecting people's health, especially organic matter.[41] Furthermore, black carbon exposure may increase serum leptin levels, which is an inflammatory cytokine secreted primarily by adipose tissue, and elevated levels of serum leptin may increase the risk for coronary events and the incidence of diabetes.[42,43] Regarding population-based evidence, only a recent study in 69,210 adults in Western China showed that exposures to organic matter, black carbon, NO_3^- and NH_4^+ were positively associated with diabetes, and organic matter may be most responsible for the relationship between $PM_{2.5}$ and diabetes.[44] However, failing to consider the effects of obesity when estimating the $PM_{2.5}$-diabetes association may lead to mixed results to an uncertain extent, i.e., overestimation among those with obesity and underestimation among those without obesity.

Our study found that secondary inorganic aerosols, such as NH_4^+, NO_3^- and SO_4^{2-}, were also contributors to diabesity risk. NH_4^+ and NO_3^- are primarily secondary compounds produced through the acidification and oxidation of nitrogen oxides. These compounds have been linked to oxidative stress and diabetic endothelial dysfunction,[45,46] according to previous research. Long-term exposure to NH_4^+ may result in abnormal uric acid cycles, which have been associated with type 2 diabetes risk.[47] Additionally, NO_3^- has been linked to the activation of reactive oxygen species (ROS), which may induce the obesity and insulin resistance.[48–52] Furthermore, NH_4^+ and NO_3^- are mainly present in the atmosphere as ammonium nitrate ($NH_4\ NO_3$).[53] This may explain why both compounds had a relatively similar weight in the association between $PM_{2.5}$ and diabesity risk in our study. We also found that SO_4^{2-} increased diabesity risk, which may be attributed to mechanisms of inflammation, endothelial dysfunction, and oxidative stress.[54]

We found that adverse effects of $PM_{2.5}$ chemical constituents on diabesity risk were less pronounced in those with a high level of physical activity. This suggests that physical activity may modify the association between $PM_{2.5}$ chemical constituents and diabesity risk. Despite harmful effects of air pollutants on diabesity, regular physical activity may reduce the risk of developing diabesity by improving various metabolic functions. First, aerobic physical activity can increase mitochondrial density, insulin sensitivity, oxidative enzymes, vascular compliance and reactivity, and cardiac output, and accelerate lipid hydrolysis involving oxidative metabolism for energy supply.[55] These benefits may contribute to reducing adiposity, triglycerides, and insulin resistance.[56] Second, regular physical activity may promote insulin activity, such as glucose uptake in skeletal muscle, adipose tissue, and liver.[57] Third, resistance training could improve body composition, muscle strength, and insulin resistance, leading to even greater metabolic improvement when combined with aerobic exercise.[58] Thus, our findings suggest that more physical activity may help mitigate deleterious effects of $PM_{2.5}$ exposure on diabesity risk. Moreover, we found that participants aged ≥60 years were more vulnerable to diabetes and obesity under long-term exposure to $PM_{2.5}$ chemical constituents, similar to previous studies.[44] One reason may be that they are more sensitive to $PM_{2.5}$.[59] The elderly is a group with poorer immune function and health status than the younger, whose underlying comorbidities may trigger adverse diabetes and obesity when being exposed to $PM_{2.5}$ chemical constituents.[60] Individuals, especially the elderly, should be aware of air quality in their neighborhood and avoid long exposure to harmful substances.

The robustness of the results was demonstrated by employing multiple methods (logistic regression, WQS, and BKMR) for estimation of exposure effects. However, due to correlations among $PM_{2.5}$ chemical constituents, logistic regression was unsuitable for estimating their joint effect. The WQS could overcome this limitation by addressing issues of overfitting and collinearity effectively. Notably, WQS exhibited a lower mean-squared error and higher specificity compared to shrinkage methods.[27] The BKMR, known for its ability to address multicollinearity and high dimensionality, was used to estimate interactions among $PM_{2.5}$ chemical constituents.[61] However, it is worth mentioning the

slow computational speed of BKMR. Consequently, there is a pressing need for enhancements in BKMR or the development of new methods to effectively analyze multi-pollutant exposures in large samples. Our study highlights the necessity of integrating multiple statistical approaches when estimating health effects of multi-pollutant exposures.

Several limitations should be mentioned in this study. First, the cross-sectional design may be limited in drawing causal inferences, so follow-up data are expected to improve the strength of evidence.[62] Second, although 10 km is the highest spatial resolution of concentrations of $PM_{2.5}$ chemical constituents available in China, these data were statically matched to the participants by their residential addresses and may not accurately represent the actual exposure level.[63] Previous studies showed that the lower spatial resolution of $PM_{2.5}$ constituents may lead to measurement errors by decreasing between-person variance in exposure, and thus underestimate adverse effects of $PM_{2.5}$.[64] Further studies involving wearable devices are warranted to collect more precise data of exposure to $PM_{2.5}$ constituents. Also, the five chemical constituents generally accounted for more than 90% of total $PM_{2.5}$ with about 10% of $PM_{2.5}$ constituents unidentified, so the relative importance of the five chemical constituents might be slightly distorted. To be consistent with $PM_{2.5}$ chemical constituent products, the $PM_{2.5}$ concentrations used in this study were from the same source, which could be replaced by other $PM_{2.5}$ products with a higher spatio-temporal resolution.[65] Third, our results may be affected by some unmeasured or unknown potential confounders, such as indoor exposure to air pollution (e.g., solid fuel used for cooking), which should be better measured and considered in follow-ups or other future studies. Finally, the study areas are all in the southern part of China without northern regions of China and have limited generalizability to other provinces or other developing countries. Further investigation is necessary to delve into the potential regional disparities and incorporate a broader range of regions, particularly those located in the northern region of China, within future research endeavors.

However, despite the limitations, two strengths deserve special attention. First, to our knowledge, this is the first study to investigate the association between exposure to $PM_{2.5}$ chemical constituents and diabesity risk, which would fill the knowledge gap regarding effects of $PM_{2.5}$ chemical constituents on diabesity and potentially additional effects of obesity on the $PM_{2.5}$-diabetes association. Second, the three cohorts from different regions of China provided with large variations in natural and social environmental exposures, which has made our findings more representative and generalizable to the general population in China.

Conclusions

In this large-scale, multi-center cohort study conducted among community-based populations, we observed that long-term exposure to $PM_{2.5}$ and its chemical constituents, particularly organic matter, was associated with a higher risk for diabesity in comparison to participants without obesity or diabetes. In contrast, the association with diabesity showed the highest importance of black carbon exposure when compared with participants with obesity. Furthermore, our findings suggest that a high level of physical activity weakened adverse effects of $PM_{2.5}$ and its chemical constituents on diabesity risk. Our findings provide evidence for the mechanism of the effects of $PM_{2.5}$ and its constituents on diabesity risk. These results provide evidence for the mechanism of the effects of $PM_{2.5}$ constituents on diabesity risk, and suggest that emission reductions of certain toxic constituents, such as organic matter and black carbon, could potentially reduce the burden of diabesity.

Contributors

Shujuan Yang and Peng Jia conceived and designed the study. Changwei Cai, Shuzhen Zhu, Mingfang Qin, Xiaoqing Li, Chuanteng Feng, Bin Yu, Shujuan Yang and Peng Jia were responsible for data collection and data cleaning. Changwei Cai, Chuanteng Feng, Shaoqing Dai, Ge Qiu, Shujuan Yang and Peng Jia performed data analysis. Changwei Cai, Chuanteng Feng, Shujuan Yang and Peng Jia wrote the original draft. All authors critically revised the manuscript. Shujuan Yang and Peng Jia supervised the study. All authors read and approved the final manuscript.

Data sharing statement

The datasets from this study are held in coded form, and legal data sharing agreements prohibit the authors from making the dataset publicly available. Access to individual de-identified participant data (including data dictionaries) may be granted to those who send a request with specific data needs, analysis plans, and dissemination plans to the corresponding authors.

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101100.

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