Maternal exposure to $PM_{2.5}$ and its major components and the risk of gestational diabetes mellitus: evidence from a case–control study in Southern China

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ABSTRACT

Background Evidence regarding the association between maternal exposure to $PM_{2.5}$ and its major components and the risk of gestational diabetes mellitus (GDM) is still limited. Our study aimed to fill this research gap with a case–control study in Southern China.

Methods 191 cases and 764 controls were enrolled during 2013–2020. Daily mean $PM_{2.5}$ and component concentrations were obtained from the ChinaHighAirPollutants. GDM was diagnosed using the WHO criteria. We used logistic regression integrated with inverse probability weighting and generalised weighted quantile sum regression models to estimate the association between $PM_{2.5}$ components during multiple trimesters and GDM risk.

Results A positive association was observed between $PM_{2.5}$ exposure and GDM risk, with ORs of 1.36 (95% CI 1.11 to 1.66) and 1.34 (95% CI 1.08 to 1.67) per IQR increase in the first (18.8 µg/m³) and second (20.6 µg/m³) trimesters, respectively. Women with low income and education levels were particularly vulnerable to GDM following particulate exposure. Black carbon (weight: 0.33), nitrate (weight: 0.22) and sulfate (weight: 0.20) contributed most of the overall $PM_{2.5}$ mixture effect in the first trimester, while in the second trimester, sulfate (weight: 0.38) made the most significant contribution, followed by black carbon (weight: 0.22) and nitrate (weight: 0.20).

Conclusions The risk of GDM was significantly associated with $PM_{2.5}$ exposure in the first and second trimesters. The mixture impact in the first trimester was mainly attributed to black carbon, nitrate and sulfate, while that in the second trimester was mainly attributed to sulfate, black carbon and nitrate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ $PM_{2.5}$ exposure during different trimesters was positively associated with an increased risk of gestational diabetes mellitus (GDM).
⇒ Experimental evidence suggested the distinct health effects of different $PM_{2.5}$ components and the underlying biological mechanisms.

WHAT THIS STUDY ADDS

⇒ We found that $PM_{2.5}$ exposure during the first and second trimesters was positively associated with GDM risk, particularly among women with low income and education levels.
⇒ Black carbon was the primary contributor to the $PM_{2.5}$ mixture effect in the first trimester, while sulfate made the most significant contribution in the second trimester.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More interventions targeting specific components during different trimesters may be effective in mitigating the risk of GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester without prior overt diabetes before gestation.[1] Due to increased maternal age and the increasing rate of obesity, the incidence of GDM continues to rise. A meta-analysis indicated that the overall prevalence of GDM in mainland China has reached 14.8% in recent years.[2] GDM has been linked to a higher risk of developing metabolic syndrome and cardiovascular disease among the mothers,[3] as well as greater hazards of adverse outcomes among the fetus, including type II diabetes and obesity in later life.

There is growing evidence indicating that environmental factors, particularly air pollution, may contribute to raising the risk of GDM. The association is biologically plausible, with multiple potential pathways such as endothelial dysfunction, inflammation and oxidative stress.[4] A growing number of epidemiological researches have explored the association between fine particulate matter ($PM_{2.5}$) exposure and GDM risk. For instance, a large-scale study in China reported that $PM_{2.5}$ exposure during the second trimester was linked to an 11% greater risk of GDM (95% CI 1 to 22%).[5] Similar findings were also observed elsewhere.[6–8] A recent meta-analysis of 31 cohort studies further confirmed a robust positive relationship between $PM_{2.5}$ exposure and GDM.[8] Building on this evidence, several studies have focused on the contributions of specific constituents. Analyses of US birth cohorts have identified NH_4^+, organic matter (OM), NO_3^-, SO_4^{2-} and black carbon (BC) as key contributors to GDM risk, with mid-pregnancy emerging as the most sensitive window.[9] Similarly, a retrospective cohort study conducted in Guangzhou demonstrated positive associations between GDM and NO_3^-, NH_4^+

and OM.[10] Although these studies provide important insights, evidence remains limited for regions with high $PM_{2.5}$ concentrations, especially regarding which specific $PM_{2.5}$ components are most strongly associated with GDM.

However, there are still several knowledge gaps in understanding the relationship between $PM_{2.5}$ exposure and GDM. first, previous studies generally concentrated on the impact of total $PM_{2.5}$ mass. However, $PM_{2.5}$ particle is a complicated mixture containing components from multiple sources. Different chemical components of $PM_{2.5}$ may generate significantly distinct health effects due to variations in their toxicity and target organs.[9] Existing evidence on how the impact of particles on GDM varies across the constituents is still limited. Furthermore, the synergistic effects of multiple $PM_{2.5}$ components on GDM as well as the most influential components remain unclear. Gaining a more comprehensive insight into the contributions of different components to GDM is crucial.[11] Moreover, the bulk of the available evidence is based on traditional assessment models. The reliability of the estimates largely depends on the correct specification of the function between the covariates and the outcome. When the function is incorrectly specified, the model fit will be affected, and the estimated exposure-outcome relationship may be biased. Over the recent decades, some causal inference approaches have emerged to tackle this challenge in observational data by balancing the covariates using inverse probability weighting (IPW).[12] Specifically, IPW assigns each individual an IPW derived from the covariate-based exposure probability. This creates a pseudo-population where covariates are balanced across exposure groups, thereby simulating a randomised experiment. Furthermore, estimates from the covariate-balanced groups are more prone to reflect the average treatment effect (ATE) at the population level which generally is of more interest to the policymakers.[13] However, solid evidence based on these established approaches is limited.

In this study, we employed a logistic regression with IPW, an established causal inference approach, to evaluate the associations between maternal exposure to $PM_{2.5}$ components and GDM risk. Results were also stratified by a comprehensive set of individual characteristics and lifestyle factors. Additionally, we used generalised weighted quantile sum (gWQS) regression, a solid mixture analysis method, to assess the mixture effects of $PM_{2.5}$ components and their respective weights.

METHODS

Study population

The data for this study were part of the Guangdong Registry of Congenital Heart Disease (GRCHD), covering fetuses and infants diagnosed with congenital heart disease as well as healthy ones in the same hospital and year from 40 collaborating hospitals across Guangdong province, South China.[14] For this specific study, we included a total of 5470 pregnant women with healthy infants during 2013–2020. We excluded 122 pregnant women with missing air pollution data, 233 with multiple pregnancies, 125 with missing GDM information, 20 with pre-pregnancy diabetes and 2 with gestational age less than 22 weeks. In addition, we excluded 331 women with missing maternal age or residence, leaving a total of 4637 women, including 213 GDM cases. For each GDM case, four non-GDM controls were individually matched by the year of conception, age (±2 years), residence (urban or rural areas) and pregnancy season (spring: March–May; summer: June–August; autumn: September–November; or winter: December–February). 22 cases were further excluded due to an insufficient number of matched controls. As a result, 191 cases and 764 controls were finally included in this research (online supplemental figure S.1).

Outcome definition

During the face-to-face interviews, pregnant women self-reported GDM, which was confirmed with the medical records of fasting blood glucose (FBG) and 75 g oral glucose tolerance test (OGTT) during the 24–28 weeks of pregnancy. According to the WHO criteria, a diagnosis of GDM would be confirmed if a pregnant woman met any of the following three criteria: (1) FBG ≥5.1 mmol/L; (2) 1 hour plasma glucose (OGTT) ≥10.0 mmol/L and (3) 2 hour plasma glucose (OGTT) ≥8.5 mmol/L.[15]

Air pollution assessment

Daily average concentrations of $PM_{2.5}$ and its components (ie, BC, OM, ammonium, nitrate and sulfate) at a 1 km spatial resolution were sourced from ChinaHighAirPollutants (CHAP) (https://weijing-rs.github.io/product.html). The data were generated from machine learning and deep learning models, using atmospheric reanalysis products and satellite remote sensing products, well-validated with ground measurements,[16 17] and have been widely employed.

For each pregnant woman, we geocoded the residential address, which generally included the province, city, district or county, and specific street name. After parsing these details and identifying the corresponding administrative divisions, latitude and longitude were obtained using the Gaode Map API. Manual verification was performed when necessary, and participants whose addresses could not be reliably located were excluded. The $PM_{2.5}$ and component concentrations for each woman were assigned according to the value of the nearest 1 km × 1 km CHAP grid cell. Based on the geocoded locations, we estimated the conception date by calculating from the gestational date and birth age, and calculated average $PM_{2.5}$ exposure levels of the predetermined exposure windows, including the first (1–13 weeks) and second trimesters (14–26 weeks). Since GDM screening was conducted before the 28th week of pregnancy, $PM_{2.5}$ exposure during the third trimester was not considered in this study.

Covariates

Obstetricians from the collaborative units of GRCHD conducted a standardised, structured questionnaire to obtain relevant information from pregnant women during early pregnancy. Based on previous studies[5 9 10 18–20] and guided by a directed acyclic graph (online supplemental figure S.2), we selected covariates and potential confounding factors for analysis, including household income, the educational level of pregnant women, ethnicity, fetal sex, gravida and smoking or passive smoking during pregnancy. For confounding variables with a missing rate less than 5%, missing values were imputed using a sequential single imputation approach based on classification tree models.[21]

Statistical analysis

Logistic regression models with IPW were employed to assess the association between air pollution and the risk of GDM. We chose the IPW-based logistic models rather than the conditional logistic models since we focused more on the population-average effects from the covariates-balanced pseudo-population generated following the IPW procedure than the estimates specific to the matched strata from the conditional models. The 1:4 individual matching was employed as a preprocessing step in this cross-sectional dataset to improve covariate balance. First, we

Table 1 Maternal characteristics and air pollution concentrations by GDM groups from 2013 to 2020

Variable	GDM (n=191)	Non-GDM (n=764)	*P* value	Missing, n (%)
Maternal age (years)			0.704	0 (0)
<35	171 (89.5)	674 (88.2)		
≥35	20 (10.5)	90 (11.8)		
Residence			1.000	0 (0)
Urban	161 (84.3)	644 (84.3)		
Countryside	30 (15.7)	120 (15.7)		
Season of conception			1.000	0 (0)
Spring	42 (22.0)	168 (22.0)		
Summer	52 (27.2)	208 (27.2)		
Autumn	38 (19.9)	152 (19.9)		
Winter	59 (30.9)	236 (30.9)		
Ethnicity			0.136	0 (0)
Han	190 (99.5)	744 (97.4)		
Others	1 (0.5)	20 (2.6)		
Household income (yuan per month)			0.922	24 (2.51%)
1–5000	149 (78.0)	601 (78.7)		
5001-	42 (22.0)	163 (21.3)		
Educational level			0.179	15 (1.57%)
Less than secondary school	48 (25.1)	212 (27.7)		
High school	51 (26.7)	240 (31.4)		
College or above	92 (48.2)	312 (40.8)		
Fetal sex			0.289	2 (0.21%)
Male	115 (60.2)	425 (55.6)		
Female	76 (39.8)	339 (44.4)		
Fetal weight			0.246	4 (0.42%)
Low birth weight (<2500 g)	22 (11.5)	61 (8.0)		
Normal (2500–4000 g)	164 (85.9)	688 (90.1)		
High birth weight (>4000 g)	5 (2.6)	15 (2.0)		
Gravida			0.190	5 (0.52%)
Primigravida	83 (43.5)	290 (38.0)		
Multigravida	108 (56.5)	474 (62.0)		
Smoking or passive smoking during pregnancy			0.310	2 (0.21%)
No	164 (85.9)	630 (82.5)		
Yes	27 (14.1)	134 (17.5)		
BMI, mean±SD, kg/m^2	20.97±2.70	20.82±2.84		285 (29.84%)
First trimester, mean±SD, μg/m^3				
$PM_{2.5}$	43.01±18.97	38.75±13.65	<0.001	0 (0)
BC	3.58±1.16	3.33±0.92	0.002	0 (0)
OM	15.22±7.99	13.89±6.36	0.015	0 (0)
Sulfate	9.52±2.79	9.05±2.37	0.017	0 (0)
Ammonium	4.98±2.09	4.65±1.65	0.020	0 (0)
Nitrate	7.18±4.21	6.45±3.41	0.012	0 (0)
Second trimester, mean±SD, μg/m^3				
$PM_{2.5}$	41.51±18.41	37.60±14.07	0.001	0 (0)
BC	3.51±0.99	3.26±0.88	0.001	0 (0)
OM	14.52±6.85	13.44±5.89	0.029	0 (0)
Sulfate	9.26±2.62	8.68±2.37	0.003	0 (0)
Ammonium	4.82±1.87	4.44±1.63	0.006	0 (0)
Nitrate	6.92±3.60	6.17±3.22	0.005	0 (0)

BC, black carbon; BMI, body mass index; GDM, gestational diabetes mellitus; OM, organic matter; $PM_{2.5}$, fine particulate matter, particle with aerodynamic diameter ≤ 2.5 μm.

estimated the generalised propensity score (GPS) by regressing exposure on potential confounders using a linear model (LM), a gradient boosting machine learning approach (ML) and a generalised estimating equation (GEE).[22–24] We then derived stabilised IPWs as the ratio of the marginal exposure density to the conditional density estimated by the GPS. Finally, these calculated weights were applied in logistic regression models to estimate the ORs and 95% CIs for GDM per IQR increase in air pollutant concentrations. We evaluated covariate balance within the weighted pseudo-population using the average absolute correlation (AC), defining good balance as AC<0.1. The balance diagnostics are shown in online supplemental figures S.3 and S.4. Based on the observed covariate balance across different GPS estimation methods, the GEE-based weights achieved the best fit and were therefore selected for the main analysis.

We employed a sequential modelling approach to create three models. Model 1 was a crude model. Model 2 adjusted for household income, educational level, ethnicity, fetal sex, gravida and smoking or passive smoking during pregnancy. Finally, model 3 was based on model 2 refitted using IPWs. In addition, we conducted stratified analyses within predefined subgroups, including household income, educational level, fetal sex, gravida and smoking or passive smoking during pregnancy. We did not include gaseous pollutants such as O_3 and NO_2 in our study, as the spatial variation of the gaseous pollutants is generally subtle compared with particulate matter. As the cases and controls are from the same region, the impact of these gaseous pollutants on our results is limited.

We also applied the gWQS regression to evaluate the effect of $PM_{2.5}$ components on the risk of GDM. The gWQS model is employed in epidemiological studies to address covariance and high-dimensional issues.[25] WQS index based on the particulate mixture estimated the relative contributions of each component, with weights summing to 1. A higher weight indicates a greater contribution of a component to the overall effect of the mixture. Each model obtained WQS indices through 10 000 bootstrap iterations.

To evaluate the stability of the results, we conducted a sensitivity analysis by comparing the main results across the models using three different IPWs. Consistent effect estimates across weighting approaches were interpreted as evidence of stability. Furthermore, the study was also restricted to individuals with available body mass index (BMI) data, with BMI incorporated as a covariate. The analyses were executed in R 4.3.2, and p<0.05 was considered statistically significant.

RESULTS

There were no significant differences in ethnicity, household income, education levels, fetal sex, fetal weight, gravida or smoking or passive smoking during pregnancy. Women with GDM had significantly higher levels of $PM_{2.5}$ and its components compared with those without GDM during the first trimester. For instance, the mean concentrations (μg/m^3) of $PM_{2.5}$, BC, OM, sulfate, ammonium and nitrate in the first trimester between women with and without GDM were 43.01 vs 38.75, 3.58 vs 3.33, 15.22 vs 13.89, 9.52 vs 9.05, 4.98 vs 4.65 and 7.18 vs 6.45, respectively. In the second trimester, similar results were found for the concentrations of $PM_{2.5}$, BC, OM, ammonium, sulfate and nitrate (table 1).

Table 2 shows the relationship between $PM_{2.5}$ exposure and the risk of GDM in the main effect models. After fully adjusting for confounders, an IQR increase in $PM_{2.5}$ concentrations and its compositions was linked to increased odds of GDM, with consistent results across the three IPW methods (online supplemental table S.1). More specifically, the IQR for $PM_{2.5}$, sulfate, ammonium, nitrate, black carbon and organic matter was 18.8, 3.1, 2.5, 5.2, 1.2 and 7.8 μg/m^3 in the first trimester, respectively. For an IQR increase in $PM_{2.5}$, sulfate, ammonium, nitrate, BC and OM in the first trimester, the OR (95% CI) were 1.36 (1.11

Table 2 Association between each IQR increase* in air pollutant concentration during the first and second trimesters and gestational diabetes mellitus in the main effect models†

		Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
First trimester	$PM_{2.5}$	1.39	1.15 to 1.68	1.38	1.14 to 1.67	1.36	1.11 to 1.66
	Sulfate	1.26	1.04 to 1.53	1.26	1.03 to 1.53	1.24	1.01 to 1.52
	Ammonium	1.29	1.04 to 1.59	1.27	1.02 to 1.57	1.26	1.00 to 1.58
	Nitrate	1.32	1.06 to 1.65	1.29	1.04 to 1.62	1.32	1.06 to 1.64
	BC	1.33	1.11 to 1.59	1.30	1.08 to 1.56	1.33	1.11 to 1.59
	OM	1.23	1.04 to 1.47	1.24	1.04 to 1.47	1.23	1.03 to 1.47
Second trimester	$PM_{2.5}$	1.39	1.13 to 1.71	1.40	1.14 to 1.73	1.34	1.08 to 1.67
	Sulfate	1.37	1.11 to 1.69	1.39	1.12 to 1.72	1.39	1.12 to 1.72
	Ammonium	1.39	1.10 to 1.75	1.40	1.11 to 1.77	1.39	1.09 to 1.76
	Nitrate	1.41	1.11 to 1.80	1.40	1.10 to 1.79	1.40	1.09 to 1.78
	BC	1.46	1.17 to 1.81	1.44	1.15 to 1.79	1.43	1.15 to 1.77
	OM	1.24	1.02 to 1.50	1.26	1.03 to 1.53	1.26	1.03 to 1.54

*IQR, per IQR; IQRs for $PM_{2.5}$, sulfate, ammonium, nitrate, BC and OM were 18.8, 3.1, 2.5, 5.2, 1.2 and 7.8 μg/m^3 during the first trimester, and 20.6, 3.3, 2.5, 5.2, 1.3 and 7.8 μg/m^3 during the second trimester.
†(1) Model 1: a crude model. (2) Model 2: adjusted for household income, educational level, ethnicity, fetal sex, gravida and smoking or passive smoking during pregnancy. (3) Model 3: based on model 2 refitted by inverse probability weight.
BC, black carbon; OM, organic matter; $PM_{2.5}$, fine particulate matter.

to 1.66), 1.24 (1.01 to 1.52), 1.26 (1.00 to 1.58), 1.32 (1.06 to 1.64), 1.33 (1.11 to 1.59) and 1.23 (1.03 to 1.47). In the second trimester, the corresponding IQRs were 20.6, 3.3, 2.5, 5.2, 1.3 and 7.8 μg/m^3, and the ORs (95% CIs) for an IQR increase were 1.34 (1.08 to 1.67), 1.39 (1.12 to 1.72), 1.39 (1.09 to 1.76), 1.40 (1.09 to 1.78), 1.43 (1.15 to 1.77) and 1.26 (1.03 to 1.54). Compared with model 2, the estimates from model 3 showed a modest reduction in magnitude, although the direction and statistical significance of the associations remained consistent (table 2).

In subgroup analysis, we observed that the low-income women (1–5000 yuan per month) were particularly vulnerable to the harmful effects, particularly sulfate and OM exposure. Furthermore, the risk of GDM was significant among women with lower educational levels (high school and below), but not among those with higher educational levels (college and above). Those with lower educational levels were particularly sensitive to the impact of $PM_{2.5}$ components. We also observed a stronger association between $PM_{2.5}$ component exposure in the first trimester and GDM risk among non-smokers compared with those with active or passive smoking (figure 1).

We observed that a one-unit increase in the WQS index (ranging from 0 to 1, representing the change from the lowest to the highest quantile group) was associated with a 37% increase in GDM risk (OR=1.37, 95% CI 1.10 to 1.70) during the first trimester and a 25% increase in GDM risk (OR=1.25, 95% CI 1.02 to 1.53) during the second trimester. Figure 2 shows the results of the gWQS regression model. BC had the greatest contribution to the particle mixture effect (weight: 0.33) in the first trimester, followed by nitrate (weight: 0.22) and sulfate (weight: 0.20). In the second trimester, sulfate made the most significant contribution to the overall impact of particles (weight: 0.38), followed by BC (weight: 0.22) and nitrate (weight: 0.20).

The results of the sensitivity analyses are detailed in online supplemental tables. Across all three GPS-based IPW models (LM, ML and GEE), the estimated ORs were comparable in both magnitude and direction (online supplemental table S.1). The BMI-adjusted models (online supplemental table S.2) yielded effect estimates that remained directionally consistent with those from the main analyses.

DISCUSSION

In this study, we found that exposure to $PM_{2.5}$ and its components, especially sulfate, nitrate and BC during the first and second trimesters, was associated with an increased risk of GDM. Moreover, our findings suggested that exposure to $PM_{2.5}$ and its components was associated with an increased risk of GDM among women with lower income or education levels.

Consistent with previous findings, our study revealed a positive association between overall $PM_{2.5}$ exposure during the first and second trimesters and the risk of GDM. A meta-analysis involving 11 studies indicated there was a 4% increased risk of GDM linked to a 10 μg/m^3 rise in $PM_{2.5}$ concentration in the second trimester.[26] Similarly, a retrospective cohort study in Harris County reported that the risk of GDM following an IQR increase in $PM_{2.5}$ concentration was 13% (OR=1.13, 95% CI 1.10 to 1.17) over the first trimester.[7] However, previous studies regarding the impact of $PM_{2.5}$ exposure in the first trimester on GDM showed inconclusive results. Several studies from the USA and China reported no significant association for the exposure in the first trimester.[27 28] In our study, $PM_{2.5}$ effect estimates were stronger than those in previous reports, likely due to differences in population characteristics, regional pollution levels and $PM_{2.5}$ composition. Most studies conducted in Europe and the USA have taken place under relatively low $PM_{2.5}$ concentrations. In contrast, Guangdong has substantially higher pollution levels and broader exposure variability, which may increase the ability to detect associations. In addition, $PM_{2.5}$ in Southern China derives mainly from coal combustion, industrial emissions and secondary inorganic aerosols (sulfate, nitrate, ammonium),[29] while Western studies mainly involve traffic-related $PM_{2.5}$. These pollution sources are known to induce stronger oxidative stress and systemic inflammation, which may help explain the larger effect estimates observed in our results.[30]

Several potential biological mechanisms may explain the adverse effect of $PM_{2.5}$ exposure, inducing oxidative stress, insulin resistance and placental DNA methylation.[4 31] $PM_{2.5}$ stimulates the formation of ROS within the body, leading to oxidative injury to target organs. Simultaneously, it was regarded as an inflammatory stimulus that could enhance the

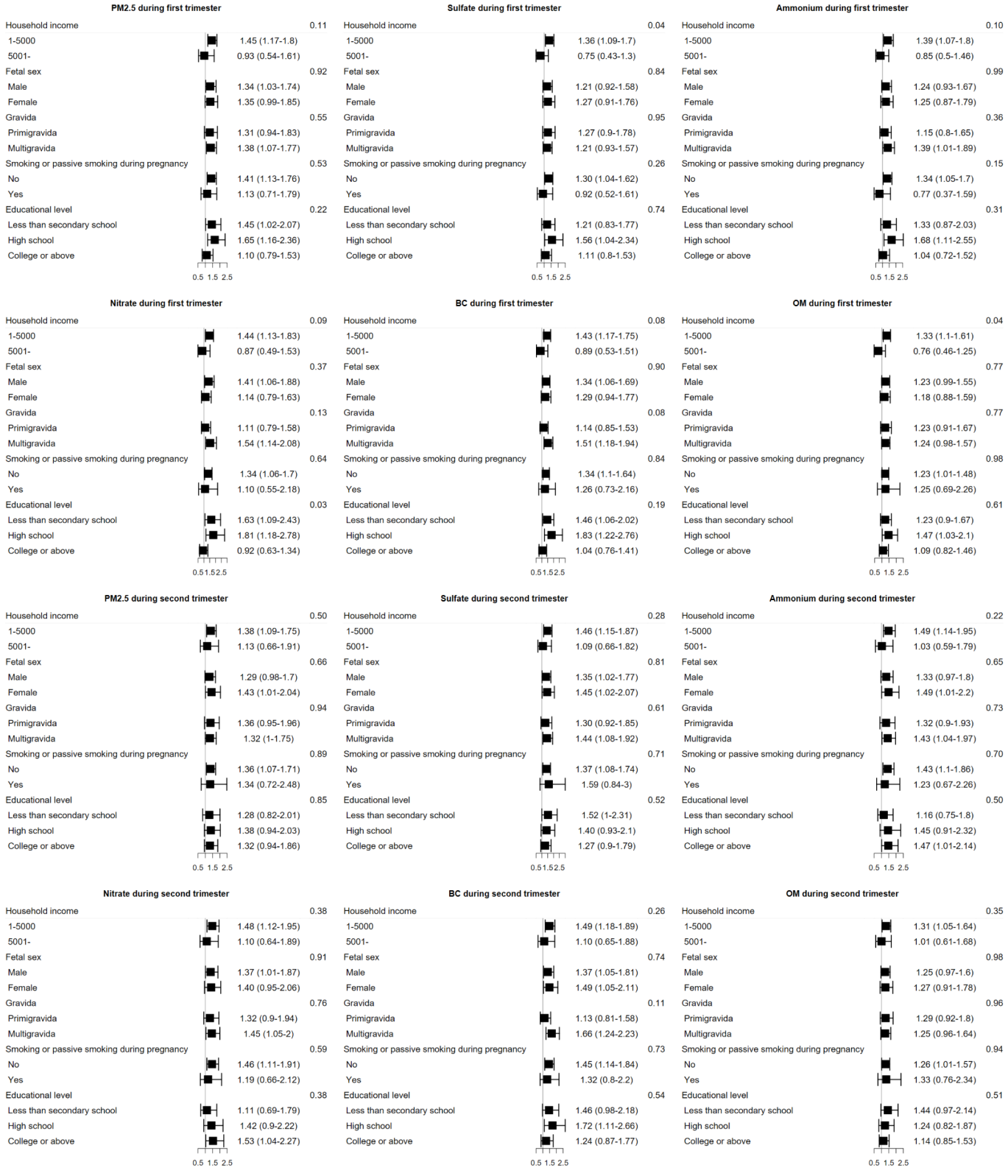

Figure 1 The association between $PM_{2.5}$ components and gestational diabetes mellitus, stratified by maternal sociodemographic characteristics and lifestyle factors.

Note: $PM_{2.5}$, fine particulate matter; BC, black carbon; OM, organic matter

release of inflammatory cytokines. These factors have been observed to impair insulin signal transduction and decrease the activity of insulin receptor tyrosine kinase, resulting in insulin resistance.[32] Placental DNA methylation might act as a mediator in $PM_{2.5}$-induced reproductive and developmental toxicity, consequently increasing GDM risk.[33] The second trimester may be a particularly vulnerable period for these mechanisms. During this stage, rapid placental growth and

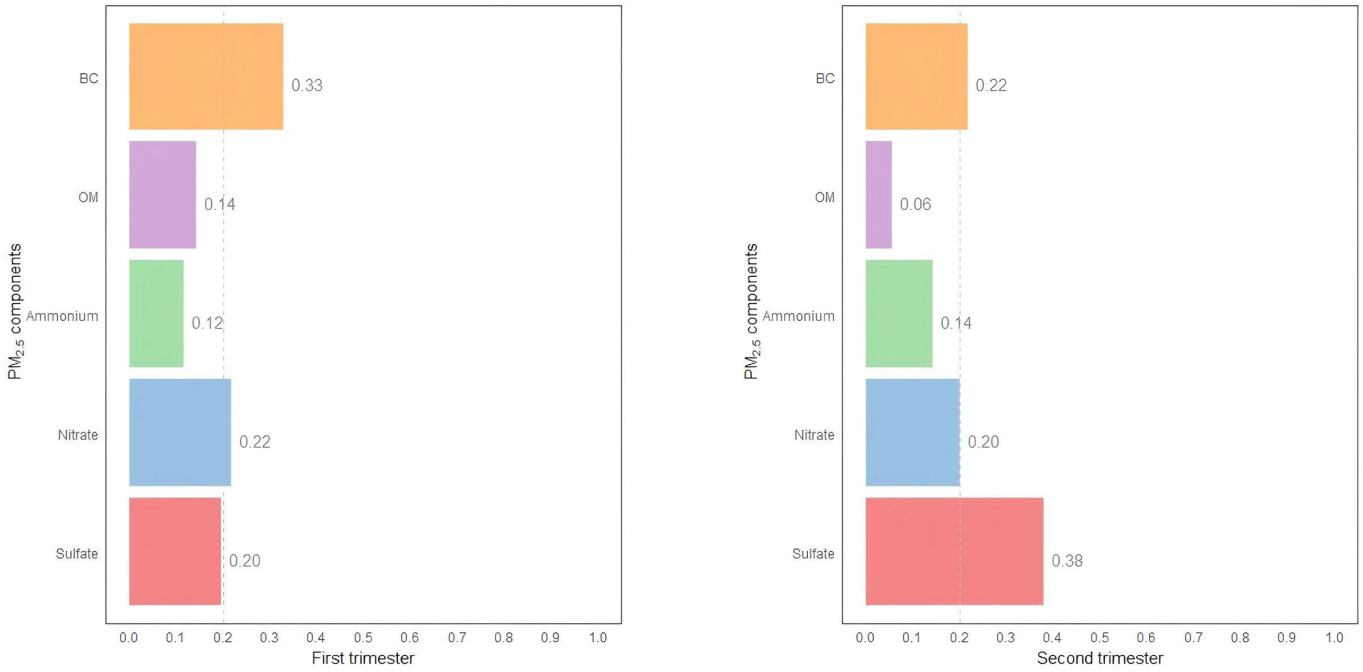

Figure 2 Estimated weights of $PM_{2.5}$ components in the weighted quantile sum index during the first and second trimesters.

Note: $PM_{2.5}$, fine particulate matter; BC, black carbon; OM, organic matter

vascular remodelling occur, while rising placental hormone levels increase maternal insulin demand and physiological insulin resistance.[34] Exposure to $PM_{2.5}$ during this critical stage could further intensify inflammatory and oxidative stress pathways, further impairing insulin function and elevating the risk of GDM.

We observed that exposure to different $PM_{2.5}$ components in the first and second trimesters had a significant effect on the GDM risk. The results from models 2 and 3 were consistent, suggesting the robustness of our findings. The slightly attenuated estimates in the weighted model suggest that IPW reduced residual confounding, a pattern also observed in previous studies.[12] Overall, these findings indicate that the unweighted logistic model may have slightly overestimated the associations due to incomplete adjustment, whereas the weighted results provide a more reliable estimate of the effect of $PM_{2.5}$ components on GDM risk. Most studies have focused on the overall impact of $PM_{2.5}$, while only a few have focused on specific components. Recently, a study in California reported that $PM_{2.5}$ components, including sulfate, OM, BC, nitrate and ammonium, were connected to a greater risk of GDM throughout pregnancy, with IQR-based OR ranging from approximately 1.04 to 1.21.[18] Another study covering 24 provinces in China found that higher risks of GDM were attributable to exposure to $PM_{2.5}$ components in the second trimester, particularly OM (OR=1.14, 95% CI 1.05 to 1.23), BC (OR=1.15, 95% CI 1.07 to 1.25) and nitrate (OR=1.13, 95% CI 1.02 to 1.24).[5] In our study, the estimated effects of $PM_{2.5}$ components were even stronger, which may be attributed to several factors. First, Asian women generally have a higher underlying risk of GDM, as they tend to develop insulin resistance even at relatively lower BMI levels.[35] This metabolic vulnerability may heighten their response to air-pollution exposures. Furthermore, the dominant presence of secondary inorganic aerosols and particles, combined with the warm, humid climate and higher pollution levels, may further amplify toxicity and susceptibility. Moreover, finer trimester-specific exposure assessment may have captured critical windows more accurately, contributing to the stronger observed associations. Our results indicated that the joint toxicity of secondary inorganic aerosols with combustion-related particles may heighten maternal susceptibility through enhanced oxidative stress and inflammatory responses. Future experimental and epidemiological studies focusing on these interacting components could more clearly elucidate their biological pathways.

When considering the mixture effect of these components, our results revealed that black carbon (weight: 0.33) contributed the most to the overall mixture effect in the first trimester, followed by nitrate and sulfate. In the second trimester, the main effect of increased GDM risk was attributed to sulfate (weight: 0.38), followed by black carbon and nitrate. The study conducted in Southern California reported that BC had the highest contribution to the overall combined impact (48%), followed by nitrate and ammonia.[18] The inconsistency in results may be explained by diverse features (eg, chemical composition, particle number and surface area) of $PM_{2.5}$ in various regions. Furthermore, our study distinguished the impact of $PM_{2.5}$ components during different trimesters, while the exposure assessed in the US study was averaged over the entire pregnancy period. Among the three secondary inorganic aerosols, we found that sulfate and nitrate contributed a large proportion to the overall adverse effects of $PM_{2.5}$. However, relevant epidemiological and other human evidence to explain the effect of secondary inorganic aerosol was lacking. A study showed that nitrate was the most harmful pollutant to the respiratory system, followed by sulfate. Oxidative stress and neutrophil infiltration in the lungs were involved in the biological mechanism of nitrate and sulfate toxicity.[36] The toxicity of nitrate and sulfate to metabolism may share similar biological mechanisms. Moreover, the three secondary air pollutants, especially nitrate, induce the formation of ROS by binding to metals or other organic compounds, increasing the bioavailability of metals, or by potential interactions with organic compounds.[37] In addition, we observed that BC exposure

in the first trimester contributed 33% of the related impact on GDM. Due to its small size, compact structure and high capacity for adsorbing hazardous substances, the harmful health effects of BC were slightly stronger than $PM_{2.5}$.[38] BC is extensively documented for its toxicity to stimulate reactive oxygen species, promote inflammation and cause oxidative stress in organs like the liver.[39] This resulted in DNA damage, compromised β-cell function and insulin resistance. Further research is essential to explore the impact and mechanisms of $PM_{2.5}$ components on the risk of GDM.

Stratified analysis indicated that women with lower education levels or income were more vulnerable to the effects of GDM. The low SES women were more likely to engage in unhealthy habits like alcohol consumption and smoking, which tend to result in an increased risk of obesity.[40] Due to heightened inflammatory response and oxidative stress, women with overweight or obesity may be more vulnerable. Moreover, women with low SES may face greater difficulty accessing high-quality healthcare.

As far as we know, this study has been one of the few to investigate the association between $PM_{2.5}$ components and the risk of GDM in highly $PM_{2.5}$-polluted areas. Moreover, we employed logistic regression integrated with IPW to more accurately assess the impact of $PM_{2.5}$ components on GDM. Finally, we applied the gWQS regression to assess the weight of $PM_{2.5}$ mixtures at different gestational periods. This approach could provide more reliable conclusions, which could be used to develop more targeted interventions.

Despite these strengths, there are some limitations to our study. First, the matching of air pollution concentrations was based on residential address, consistent with the majority of previous studies.[9 18] Second, physiological information such as physical activity, height and weight was unavailable. Pre-pregnancy BMI was not taken into account as a covariate in our analysis. However, we restricted our analyses to samples with BMI, and the results of the sensitivity analysis were similar when BMI was included as a covariate. Finally, our study population only included pregnant women corresponding to healthy fetuses and infants in the GRCHD, potentially limiting the generalisability of the results.

CONCLUSIONS

In conclusion, our study indicated a positive association between maternal exposure to $PM_{2.5}$ components and the risk of developing GDM. The increased risk of GDM was mainly attributed to sulfate, nitrate and black carbon exposure in the first and second trimesters, suggesting that future interventions should be targeted at certain components in different trimesters. Women with low income or education levels should be prioritised in policies and interventions aimed at reducing exposure to harmful air pollutants.

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