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Long-term effects of $PM_{2.5}$ constituents on childhood attention deficit hyperactivity disorder: evidence from a large population-based study in the Pearl River Delta Region, China

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ABSTRACT

Background: Evidence linking fine particulate matter ($PM_{2.5}$) constituents to childhood attention deficit hyperactivity disorder (ADHD) was limited.
Objectives: To investigate the individual and joint effects of exposure to $PM_{2.5}$ constituents on ADHD.
Methods: We conducted a large population-based survey involving 110,818 school children aged 6–18 years across six cities in the Pearl River Delta region, China. The three-year average concentrations of $PM_{2.5}$ constituents (black carbon (BC), organic matter (OM), sulfate, nitrate, and ammonium) were estimated using the ChinaHighAirPollutants dataset. Parents completed an ADHD checklist using the Diagnostic and Statistical Manual of Mental Disorders-IV criteria. The individual and joint associations between $PM_{2.5}$ components and ADHD were estimated using generalized linear mixed models and the quantile g-computation regression model, respectively.
Results: The exposure-response relationships between $PM_{2.5}$ constituents and ADHD primarily exhibited a nonlinear pattern. Compared with the lowest tertile, the highest tertiles of $PM_{2.5}$ and its components were linked to greater odds for ADHD (e.g., the adjusted odds ratio (OR) was 1.37 (95 % confidential interval (CI): 1.27, 1.47) for $PM_{2.5}$, 1.51 (95 %CI: 1.40, 1.63) for OM, 1.29 (95 %CI: 1.20, 1.39) for BC, and 1.20 (95 %CI:1.08, 1.34) for sulfate). Similar positive associations were observed between BC and sulfate exposure and ADHD subtypes. Moreover, joint exposure to $PM_{2.5}$ components was associated with ADHD (OR = 1.14, 95 % CI:1.10, 1.18), with OM and BC contributing more to the observed associations.
Conclusions: These findings highlight the varying contributions of $PM_{2.5}$ constituents to ADHD and underscore the importance of reducing specific $PM_{2.5}$ component emissions to mitigate the burden of $PM_{2.5}$-associated neurodevelopmental diseases.

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1. Introduction

With a global prevalence of 5 % in children, attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, inattention, and impulsivity (Cortese et al., 2018). Generally, ADHD frequently co-occurs with other mental health conditions, causing significant burdens for the affected individuals, their families, and the community (Posner et al., 2020). Although short-term medication-based therapies have proven effective and affordable, long-term medical therapies for ADHD remain challenging (Posner et al., 2020). The development of ADHD is influenced by the interaction between genetic and environmental risk factors (Thapar and Cooper, 2016). Therefore, it is critical to identify and mitigate modifiable risk factors, particularly environmental factors, as these factors may play a significant role in the primary prevention of ADHD.

Mounting evidence indicates a positive association between an elevated risk of childhood ADHD and exposure to fine particulate matter ($PM_{2.5}$) (Liu et al., 2022; Siddique et al., 2011; Thygesen et al., 2020; Yuchi et al., 2022). $PM_{2.5}$ is a complex mixture composed of black carbon (BC), elemental carbon (EC), organic matter (OM), ions, metals, and biological components. A recent systematic review suggests that there is more data supporting the negative impacts of different sizes of PM and $PM_{2.5}$ components (e.g., EC and BC) on childhood ADHD than polycyclic aromatic hydrocarbons (PAHs) in PM pollution (Aghaei et al., 2019). Notably, $PM_{2.5}$ constituents, such as BC, OM, sulfate (SO_4^{2-}), nitrate (NO_3^-) and ammonium (NH_4^+), account for approximately 80 % of the total mass of $PM_{2.5}$ in China, with SO_4^{2-}, NO_3^-, and NH_4^+ contributing about 60 % to $PM_{2.5}$ mass (He et al., 2023). However, the relative contributions of other $PM_{2.5}$ components (e.g., OM and ions) to childhood ADHD risks are still unclear. Most existing studies have focused on the effects of individual $PM_{2.5}$ constituents, primarily EC and BC, on ADHD (Aghaei et al., 2019), while the joint association between long-term exposure to multiple $PM_{2.5}$ constituents and ADHD has rarely been explored. Hence, an enhanced comprehension of the associations between various $PM_{2.5}$ constituents and ADHD could offer a rational explanation for the component accountable for the $PM_{2.5}$-ADHD association, potentially providing novel prospects to mitigate the burden of $PM_{2.5}$-associated ADHD.

To address this research gap, we conducted a large population-based survey to explore both the single and joint associations between long-term exposure to $PM_{2.5}$ components and childhood ADHD in the Pearl River Delta (PRD) region, China. We hypothesized that exposure to higher levels of $PM_{2.5}$ components may be related to an increased likelihood of ADHD, and that key-specific $PM_{2.5}$ constituents contributing to ADHD can be identified.

2. Methods

2.1. Study design and participants

We conducted a cross-sectional study between 2016 and 2018 to explore potential associations between environmental exposures and health outcomes in the PRD region, China. The details of participant recruitment were described previously (Wang et al., 2022). In summary, 27 districts across six cities in the PRD region (nine in Guangzhou, six in Zhongshan, five in Foshan, three in Shenzhen, and two each in Zhuhai and Maoming) were initially selected. Subsequently, one or two elementary and middle schools, located within 1.0 km of a municipal air monitoring station, were randomly chosen from each of these 27 study districts. The selection criteria for participants were students who were aged 6–18 years and had lived at their current address for more than two years. All children in the selected schools (n = 105) were invited to participate (n = 131,412), with 122,933 (93.5 %) returning a completed study questionnaire and 8479 returning incomplete questionnaires. Exclusions were made for children who lacked exposure measurements (n = 10,843) or missed data on key variables (n = 1272), resulting in a final study population of n = 110,818 for the present analysis. The details of the flow chart were shown in Fig. S1. Written consent was obtained from the parents or guardians of all participating children before data and sample collection. The study protocol was approved by the Research Ethics Committee of Sun Yat-sen University.

2.2. Exposure data

The concentrations of $PM_{2.5}$ and its constituents, including SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC, were derived from ChinaHighAirPollutants (CHAP) at a spatial resolution of approximately 1 × 1 km across China. The dataset used the four-dimensional spatiotemporal deep forest (4D-STDF) model developed by Jing Wei and colleagues (Wei et al., 2023a, 2023b). The 4D-STDF model employs deep forest techniques to estimate real-time concentrations of $PM_{2.5}$ constituents. The 4D-STDF model integrated ground-based measurements of $PM_{2.5}$ chemical components, satellite-retrieved $PM_{2.5}$ data, CAMS emission inventories, ERA5 meteorological fields, three surface-related and population variables, and space-time terms. Annual average concentrations of $PM_{2.5}$ and its constituents were estimated based on participants residential address for the period from 2016 to 2018. We utilized the three-year average concentrations of $PM_{2.5}$ and its constituents prior to ADHD assessment, as it represented an appropriate period for assessing the adverse health effects of long-term exposure.

2.3. ADHD measurement

We employed the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria to screen participants for ADHD over the last six months (Thapar and Cooper, 2016). This 18-item scale, designed for four to twenty-year-old students, was completed by parents or guardians in this study (Willcutt, 2012). The ADHD DSM-IV criteria categorized the 18 questions into nine symptoms of inattention and nine symptoms of hyperactivity/impulsivity. Each ADHD symptom's frequency was rated on a four-point scale (0 = 'never or rarely', 1 = 'sometimes', 2 = 'often', or 3 = 'very often'). A positive ADHD screening result was assigned if parents reported six or more inattention symptoms rated as 'often' or 'very often' or six or more hyperactive/impulsive symptoms rated as 'often' or 'very often for children up to age 16. For adolescents aged 17 and older, a positive result was assigned with five or more symptoms in either category. ADHD can be further categorized into three subtypes based on DSM-IV criteria: a) the inattentive subtype (ADHD-I) for those with $\geq$ six symptoms of inattention and $<$ six symptoms of hyperactivity/impulsivity; b) the hyperactivity/impulsive subtype (ADHD-HI) for those with $\geq$ six symptoms of hyperactivity/impulsivity and $<$ six symptoms of inattention; c) the combined subtype (ADHD-C) for those with $\geq$ six symptoms of inattention and $\geq$ six symptoms of hyperactivity/impulsivity. Epidemiological investigations across diverse Chinese regions have consistently utilized parent-reported ADHD DSM-IV version for childhood ADHD assessments (Ren et al., 2021; Yang et al., 2019).

2.4. Confounders

We gathered sociodemographic and lifestyle data through our study questionnaire. Sociodemographic details encompassed age (in years), sex (male or female), home address, number of children in the family, annual average household income (<¥10,000, ¥10,000–30,000, ¥30,000–100,000, and > ¥100,000), and parental educational level (high school or lower, and college or higher). Reproductive and medical history encompassed adverse birth outcome (low birth weight (<2500 g) and preterm birth (<37 weeks completed gestation)), cesarean section, and breastfeeding (being breastfed for at least three months). Lifestyle variables included regular outdoor physical exercise, defined as engaging in outdoor physical activities for at least 1 h each day by

National Health Commission of China (Wang et al., 2022) and exposure to second-hand tobacco smoke (living with a parent who smokes cigarettes daily at home). Several studies have identified associations between ADHD and overweight or obesity among children (Khalife et al., 2014). Therefore, we classified body mass index (BMI) into four categories: underweight, normal, overweight, and obesity by the criterion of National Health Commission of China (China, 2018). We also gathered information about the home environment, including any construction or renovation activities within the past three years. Subsequently, we created a directed acyclic graph (DAG) to identify the essential adjustment set (Fig. S2). The final adjusted model retained age, sex, BMI, parental education, annual household income, physical activity time, second-hand smoke exposure, residential distances to major roads, and residence near the factory.

2.5. Statistical analysis

The distributions of demographic factors and lifestyle factors were expressed as mean with standard deviation (SD), number with percentage, or median with interquartile range (IQR), respectively. Contrasts in baseline characteristics across groups screening positive or negative for ADHD were examined using Student's t-test, Mann–Whitney *U* test, or χ^2 test, as appropriate. Air pollutants were treated as continuous variables scaled to μg/m^3.

We employed restricted cubic spline (RCS) functions with three knots according to the lowest Akaike Information Criterion, to reveal the exposure-response association between $PM_{2.5}$ constituents and ADHD in a fully adjusted model. In single-constituent models, we employed generalized linear mixed models to examine the associations between ADHD and $PM_{2.5}$ constituents, treating the city as a random effect and including $PM_{2.5}$ components and adjusted covariates as fixed effects. Since the associations from the RCS plots were nonlinear for most $PM_{2.5}$ constituents (Fig. 1), we categorized the pollutant concentrations into tertiles for the single-exposure analyses. We also estimated the odds ratios (ORs) with corresponding confidence intervals (CIs) per IQR increment for $PM_{2.5}$ and its constituents to advance direct comparisons of the effects of these pollutants on ADHD.

We used the quantile g-computation (QGcomp) regression model to assess the collective impact of exposure to five $PM_{2.5}$ constituents. This model can simultaneously estimate both positive and negative weights while operating at high speed, with the code providing an estimated running time (Keil et al., 2020). Moreover, this method is a powerful tool for addressing nonlinear relationships among multiple pollutants and effectively capturing interactions between exposure factors. We calculated the QGcomp index while adjusting for the same confounding variables as those included in the single-constituent model. This index, representing the overall risk of ADHD associated with five $PM_{2.5}$ constituents, incorporates weights for each constituent to reflect their respective contributions to the QGcomp index.

Stratified analyses were conducted to evaluate how potential modifiers might influence the association between $PM_{2.5}$ components and ADHD. The stratification variables considered were age (≤12 years vs. >12 years), sex (boys vs. girls), weight status (underweight/normal weight vs. overweight/obesity), parental education levels (≤ high school vs. > high school), family income levels (≤30,000 Yuan vs. >30,000 Yuan), outdoor physical activity duration (≤1 h vs. >1 h), and urban-rural areas (urban areas vs. rural areas).

To test the robustness of our regression estimates, we performed sensitivity analyses by randomly excluding specific birth-related factors such as adverse birth outcomes, cesarean births, and breastfed children. In addition, we adjusted the main models for risk factors known to influence indoor air pollutant level (e.g., house renovation). We also estimated associations between $PM_{2.5}$ components and ADHD measured by Conner's Abbreviated Symptom Questionnaire (C-ASQ) scores. The C-ASQ is not specific to ADHD diagnosis but shows high diagnostic accuracy in differentiating children with and without ADHD (Chang et al., 2016). Furthermore, we used weighted quantile sum (WQS) regression to explore the joint effect of $PM_{2.5}$ components on ADHD, as well as the contribution of each individual component.

All analyses were performed using R software (version 4.4.1). Two-

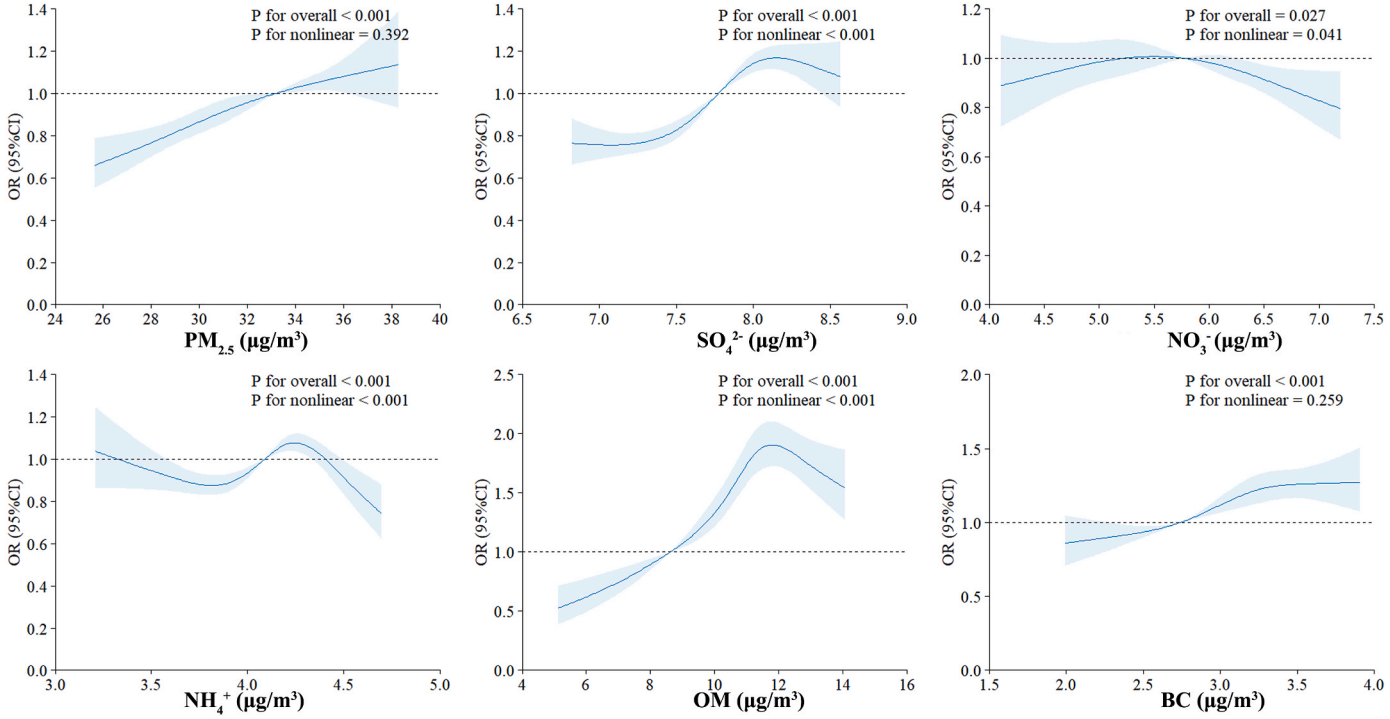

Fig. 1. Restricted cubic spline for the associations between $PM_{2.5}$ and its constituents and ADHD. The model was adjusted for age, sex, BMI, parental education, annual household income, physical activity time, second-hand smoke exposure, residential distances to major roads, and residence near the factory.

sided tests with P values < 0.05 were considered statistically significant.

3. Results

3.1. Descriptive statistics

Table 1 presents the characteristics of the study participants. The study enrolled 58,518 boys and 52,300 girls as participants. Overall, 4.2 % of the children screened positive for ADHD. The mean (SD) age of all participants was 11.8 (2.8) years, with a higher proportion of boys (52.8 %). Children who screened positive for ADHD had several distinct characteristics compared to those who screened negative. Specifically, children who screened positive for ADHD were more likely to be boys (66.8 %), to have parents with a high school education or less (57.9 %), and to have home renovation within the past three years (56.0 %). Similar high proportions were observed in the ADHD-HI group (Table S1).

Table 2 shows the median concentrations of $PM_{2.5}$ and its constituents in the study area, which were 33.15, 7.77, 5.76, 4.09, 10.79, and 3.02 μg/m^3, for $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM and BC, respectively. The most abundant components in $PM_{2.5}$ mass were OM and SO_4^{2-}, comprising approximately 32.94 % and 23.73 % of the total $PM_{2.5}$ mass, respectively. Moreover, $PM_{2.5}$ and its constituents exhibited strong positive correlations (r_s = 0.64–0.99) (Fig. S3). For example, $PM_{2.5}$ was highly correlated with BC, OM, and SO_4^{2-} (r_s = 0.97–0.99).

3.2. Associations between $PM_{2.5}$ constituents and ADHD

We found that $PM_{2.5}$ and BC exhibited linear dose–response relationships with ADHD, while other pollutants showed nonlinear associations (Fig. 1). In the single-exposure analyses, we used both tertile-based and linear methods to examine the association between $PM_{2.5}$ components and ADHD. We observed that long-term exposure to $PM_{2.5}$ and its constituents were associated with an increased likelihood of ADHD, and the adjusted ORs were generally greater in OM, BC, and SO_4^{2-}. For example, compared with the lowest tertile, the adjusted OR for the highest tertile was 1.37 (95 %CI: 1.27, 1.47) for $PM_{2.5}$, 1.51 (95 %CI: 1.40, 1.63) for OM, 1.29 (95 %CI: 1.20, 1.39) for BC, and 1.20 (95 %CI:1.08, 1.34) for SO_4^{2-} (Table 3). We also found that per IQR increase in each pollutant, the adjusted ORs of ADHD were 1.05 (95 % CI: 0.96, 1.15) for $PM_{2.5}$, 1.07 (95 % CI: 1.01, 1.13) for OM, and 1.11 (95 % CI: 1.03, 1.18) for BC (Table S2). Similar results were observed for $PM_{2.5}$ constituents with each 1 μg/m^3 increase (Table S3). Moreover, we observed similar positive associations between $PM_{2.5}$ constituents and ADHD subtypes. For instance, compared to the lowest tertile of SO_4^{2-}, the adjusted OR for the highest tertile was 1.20 (95 % CI: 1.06, 1.35) for the ADHD-I subtype and 1.34 (95 % CI:1.00, 1.79) for the ADHD-C subtype (Table S4).

In the joint exposure analyses, QGcomp regression demonstrated a significant association between the mixture of five $PM_{2.5}$ constituents and ADHD (adjusted OR = 1.14, 95 % CI:1.10, 1.18) (Table S5). Additionally, the estimated weight of each constituent is shown in Fig. 2. We found that OM and BC contributed more significantly to the higher odds of ADHD. Specifically, the contribution weights of OM, BC, SO_4^{2-}, and NH_4^+ to ADHD were determined to be 0.42, 0.35, 0.16, and 0.07, respectively.

3.3. Stratified analyses

To explore the potential effect modification, we conducted stratified analyses by sex, age, BMI, parental education, family income, outdoor physical exercise, and urban-rural areas (Fig. S4 and Table S6). The associations between ADHD and $PM_{2.5}$ mass, BC, and OM were stronger

Table 1
Characteristics of the study participants (n = 110,818).

Characteristic	Study participants	ADHD	Non-ADHD	*P value* [a]
	n = 110,818	n = 4666	n = 106,152	
Age (years), mean (SD)	11.8 (2.8)	11.2 (2.9)	11.8 (2.8)	<0.001
BMI (kg/m^2), mean (SD)	17.8 (3.3)	17.8 (3.5)	17.8 (3.3)	0.707
Sex, n (%)				<0.001
Boys	58,518 (52.8)	3119 (66.8)	55,399 (52.2)	
Girls	52,300 (47.2)	1547 (33.2)	50,753 (47.8)	
Parental educational levels, n (%)				<0.001
≤High school	60,485 (54.6)	2700 (57.9)	57,785 (54.4)	
>High school	50,333 (45.4)	1966 (42.1)	48,367 (45.6)	
Annual household income (Yuan), n (%)				<0.001
<10,000	23,009 (20.8)	1136 (24.3)	21,873 (20.6)	
10,000–30,000	18,664 (16.9)	841 (18.0)	17,823 (16.8)	
30,000–100,000	36,033 (32.7)	1497 (32.1)	34,536 (32.5)	
>100,000	33,112 (29.6)	1192 (25.6)	31,920 (30.1)	
Physical activity time, n (%)				0.249
≤1h/day	76,785 (69.3)	3265 (70.0)	73,520 (69.3)	
>1h/day	34,033 (30.7)	1401 (30.0)	32,632 (30.7)	
Second-hand smoke exposure, n (%)	38,599 (34.8)	2055 (44.0)	36,574 (34.4)	<0.001
House renovation, n (%)	59,274 (53.5)	2615 (56.0)	56,659 (53.4)	<0.001
Residence near the factory, n (%)	17,538 (15.8)	1006 (21.6)	16,532 (15.6)	<0.001
Residence distance to major roads, n (%)				<0.001
≤100m	46,008 (41.5)	2050 (43.9)	43,958 (41.4)	
>100m	64,810 (58.5)	2616 (56.1)	62,194 (58.6)	
Adverse birth outcome, n (%)	9833 (8.9)	652 (14.0)	9181 (8.6)	<0.001
Cesarean section, n (%)	39,618 (35.8)	1711 (36.6)	37,907 (35.7)	0.092
Breastfeeding, n (%)	64,692 (58.4)	2523 (54.1)	62,169 (58.6)	<0.001
City, n (%)				0.017
Foshan	17,039 (15.4)	833 (17.9)	16,206 (15.3)	
Guangzhou	32,928 (29.7)	1480 (31.7)	31,448 (29.6)	
Maoming	17,127 (15.5)	533 (11.4)	16,594 (15.6)	
Shenzhen	13,242 (11.9)	819 (17.6)	12423 (11.7)	
Zhongshan	21,452 (19.4)	863 (18.5)	20,589 (19.4)	
Zhuhai	9030 (8.1)	138 (3.0)	8892 (8.4)	

[a] T-test and chi-square test were used to examine the difference for continuous and categorical variables between different groups. Abbreviations: ADHD, attention deficit hyperactivity disorder; SD, standard deviation; BMI, body mass index.

Table 2
The concentrations of $PM_{2.5}$ and its constituents.

Pollutants (μg/m^3)	Mean (SD)	Median (25th, 75th)	IQR
SO_4^{2-}	7.73 (0.56)	7.77 (7.31, 8.13)	0.82
NO_3^-	5.69 (0.98)	5.76 (4.90, 6.44)	1.53
NH_4^+	4.07 (0.42)	4.09 (3.81, 4.32)	0.50
OM	10.73 (1.33)	10.79 (9.91, 11.73)	1.81
BC	2.97 (0.43)	3.02 (2.63, 3.36)	0.62
$PM_{2.5}$	32.57 (3.33)	33.15 (29.44, 35.25)	5.81

Abbreviations: SD, standard deviation; IQR, interquartile range; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon.

Table 3
The associations between ADHD and exposure to $PM_{2.5}$ and its major constituents.

	OR (95 %CI) [a]		
Pollutants	Tertile 1	Tertile 2	Tertile 3
$PM_{2.5}$	Ref	1.22 (1.13, 1.31)	1.37 (1.27, 1.47)
SO_4^{2-}	Ref	1.13 (1.03, 1.24)	1.20 (1.08, 1.34)
NO_3^-	Ref	0.82 (0.73, 0.91)	0.75 (0.67, 0.85)
NH_4^+	Ref	0.94 (0.87, 1.01)	0.82 (0.74, 0.92)
OM	Ref	1.40 (1.30, 1.51)	1.51 (1.40, 1.63)
BC	Ref	1.12 (1.04, 1.20)	1.29 (1.20, 1.39)

[a] The models were adjusted for age, sex, BMI, parental education, annual household income, physical activity time, second-hand smoke exposure, residential distances to major roads, and residence near the factory. Abbreviations: ADHD, attention deficit hyperactivity disorder; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon. Concentrations for tertile (tertile1, tertile2) (μg/m^3): $PM_{2.5}$ (30.47, 34.69); SO_4^{2-} (744, 8.02); NO_3^- (514, 6.25); NH_4^+ (390, 4.27); OM (10.09, 11.41); BC (2.72, 3.25).

among participants living in rural areas (Table S6). However, no significant effect modification was observed for $PM_{2.5}$ constituents and ADHD in the stratified analyses by sex, age, parental education level, family income, and outdoor physical activity (Fig. S4).

3.4. Sensitivity analyses

In sensitivity analyses, we 1) used C-ASQ scores to measure ADHD (Table S7); 2) explored associations between $PM_{2.5}$ components and ADHD DSM-IV scale scores (Table S8); 3) further excluded participants with adverse birth outcomes (Table S9), cesarean section (Table S10), and breastfeeding (Table S11); 4) additional adjusted models for factors known to affect indoor air pollution (e.g., house renovation) (Table S12); and 5) utilized WQS model to assess the association between the mixture of five $PM_{2.5}$ constituents and ADHD (Table S13 and Fig. S5). Our findings were not substantially altered by these changes, which only slightly altered the estimations.

4. Discussion

4.1. Key findings

Although several research has examined the relationship between single $PM_{2.5}$ constituents and ADHD, the joint effects of long-term exposure to multiple $PM_{2.5}$ constituents on ADHD have been rarely investigated. Here, we conducted a large population-based epidemiological study to systematically explore the single and joint associations between $PM_{2.5}$ constituents and childhood ADHD. We found that long-term exposure to $PM_{2.5}$ and its components (SO_4^{2-}, OM, and BC) was linked to a higher likelihood of ADHD in the PRD region, and that observed associations may be driven by combustion-related OM and BC.

4.2. Comparisons with other studies

Currently, several studies have explored the association between $PM_{2.5}$ components (PAHs, EC, BC) and ADHD, while study on certain $PM_{2.5}$ constituents (e.g., ions and OM) and ADHD is still limited. According to a systematic review, there is greater evidence about the adverse effects of EC and BC on ADHD in comparison to PAHs of PM (three of six studies on EC/BC, and one of seven studies on PAHs) (Aghaei et al., 2019). For example, an epidemiologic study using neuroimaging data from 242 schoolchildren in Barcelona, Spain, explored the effects of PAHs in $PM_{2.5}$ samples on neuropathology and ADHD symptoms (Mortamais et al., 2017). The findings observed that whereas

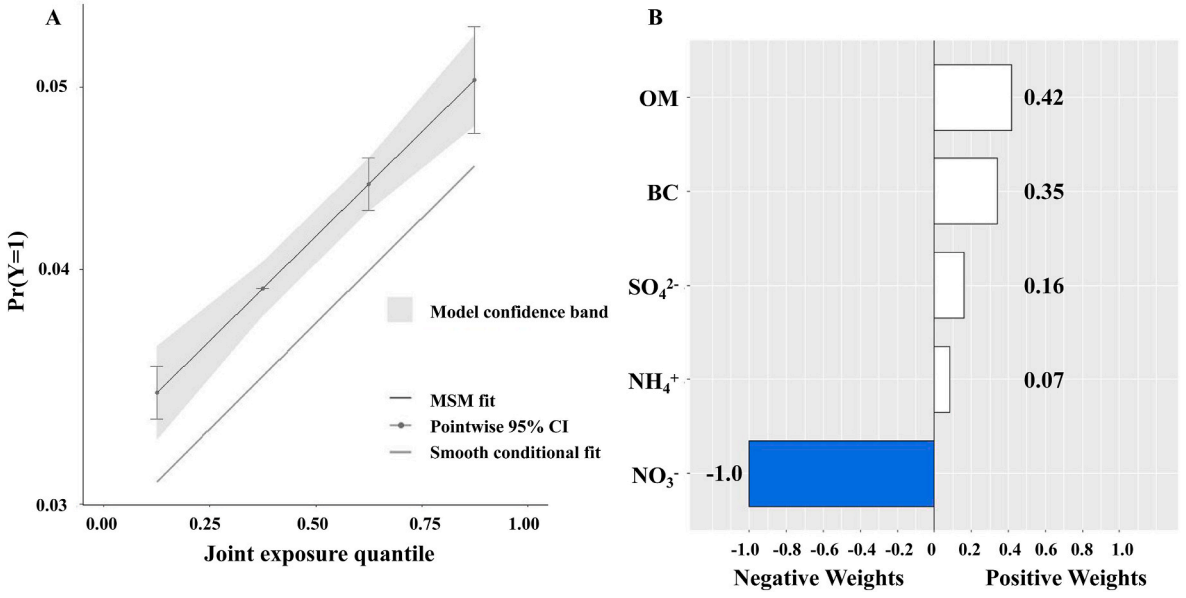

Fig. 2. Association of five major $PM_{2.5}$ constituents and ADHD based on QGcomp regression analysis. (A) The association between the mixture of five $PM_{2.5}$ constituents and ADHD; (B) The weight for each $PM_{2.5}$ constituent in the association between ADHD and the mixture of five $PM_{2.5}$ constituents. The model was adjusted for age, sex, BMI, parental education, annual household income, physical activity time, second-hand smoke exposure, residential distances to major roads, and residence near the factory.

outdoor PAHs were associated with a decrease in caudate nucleus volume, neither indoor nor outdoor PAHs were linked to ADHD symptoms (Mortamais et al., 2017). Another study from Barcelona (n = 2897) found that per IQR increase in indoor and outdoor EC and BC was associated with a rise in ADHD symptoms in schoolchildren (Forns et al., 2016). Our study observed that long-term exposure to three $PM_{2.5}$ components (SO_4^{2-}, OM, and BC) was related to an increased risk of parent-reported ADHD in the PRD region. Notably, in the two studies from Barcelona mentioned above, two separate one-week campaigns were conducted at schools to assess the concentrations of PAHs, EC, and BC, while PAHs and EC concentrations were detected from $PM_{2.5}$ samples. Of note, the relationship between $PM_{2.5}$ components and ADHD can change significantly depending on the exposure window, exposure concentration, and exposure assessment strategies. The concentration of $PM_{2.5}$ constituents in our study is relatively moderate to high at the global scale (Li et al., 2017). Moreover, our large population-based study used accurate residential addresses to estimate $PM_{2.5}$ component concentrations and validated the association between long-term exposure to $PM_{2.5}$ components and ADHD (n = 110,818). Importantly, our study identified OM, which contained PAHs and polychlorinated biphenyls (PCBs), as a risk factor for ADHD. Furthermore, our investigation reported for the first time that exposure to the ionic composition of $PM_{2.5}$ (SO_4^{2-}) was related to a high likelihood of ADHD. However, we observed that the highest tertile of NO_3^- and $NH4^+$ exposure was associated with a decreased risk of ADHD compared to the lowest tertile. This association may be attributed to collinearity among different $PM_{2.5}$ components. The impacts of NO_3^- and NH_4^+ on childhood ADHD still need to be investigated. Overall, our results offer more evidence of the association between $PM_{2.5}$ components and childhood ADHD.

Identifying key specific components of $PM_{2.5}$ is crucial for effectively targeting air pollution management initiatives. An important finding of the present study is that OM, BC, and SO_4^{2-} exhibit higher estimated ORs in ADHD associations compared to the other constituents in the single-exposure models, with OM showing the strongest association, followed by BC and SO_4^{2-}. Significantly, joint exposure to $PM_{2.5}$ components was linked to higher odds of ADHD, with OM and BC together contributing more to the observed associations. Based on these findings, we hypothesize that OM, BC, and SO_4^{2-} could be important contributors to $PM_{2.5}$-ADHD association. In this study, OM and SO_4^{2-} together accounted for more than 50 % of the total $PM_{2.5}$ mass, and three components (OM, BC, and SO_4^{2-}) were highly correlated. These factors may partially explain the observed association between $PM_{2.5}$ components and ADHD. Consistent with our study, other studies have demonstrated similar patterns of $PM_{2.5}$ constituents on various health outcomes (Bachwenkizi et al., 2021; Lu et al., 2023; Shi et al., 2023). For example, a national cohort study conducted in the United States, observed positive associations between long-term exposure to six $PM_{2.5}$ constituents and dementia, with SO_4^{2-}, BC, and OM being the main contributors to the observed associations (Shi et al., 2023). Likewise, a multi-country study conducted in 15 African nations, investigated the relationship between long-term exposure to six $PM_{2.5}$ components and infant mortality, and further observed that SO_4^{2-}, BC, and OM were positively related to infant mortality (Bachwenkizi et al., 2021). Besides, a multicenter longitudinal study in China, reported that long-term exposure to $PM_{2.5}$ constituents was linked to post-stroke disability, with OM and SO_4^{2-} having a greater significance in post-stroke disability (Lu et al., 2023). Overall, our study and others conducted in various regions, with differences in demographic characteristics, $PM_{2.5}$ composition, exposure duration, exposure assessment methods, and health outcomes, consistently indicate a significant role of OM, BC, and SO_4^{2-} in causing adverse health effects. To the best of our knowledge, this is the first large population-based study to systematically investigate the relationship between long-term exposure to $PM_{2.5}$ components and ADHD in China. Therefore, additional well-designed studies on the single and joint associations between $PM_{2.5}$ components with ADHD are required to corroborate our findings.

Our study highlighted that the observed associations were significantly modified by geographical location. Children living in rural areas appeared to be more susceptible to the effects of $PM_{2.5}$ constituents on ADHD compared to their urban counterparts. Two studies examined the national prevalence of ADHD among children and adolescents in China and the United States, both finding that children in rural areas had a significantly higher prevalence of ADHD compared to their urban counterparts (Liu et al., 2018a; Zablotsky and Black, 2020). Children in rural areas may spend more time outdoors or in poorly ventilated environments than those in urban areas, leading to prolonged exposure to airborne pollutants like $PM_{2.5}$, which can pose various health risks (Marcen et al., 2022). In contrast, children in urban areas often spend more time indoors or in controlled environments, potentially reducing direct exposure. Moreover, rural environments may expose children to additional environmental stressors, such as closer proximity to pollution sources like factories or agricultural activities. The cumulative effect of these factors, along with $PM_{2.5}$ exposure, may elevate the risk of ADHD in rural populations.

4.3. Potential mechanisms

The potential biological mechanisms linking $PM_{2.5}$ exposure to ADHD remain an active focus of research. Current experimental studies suggest that $PM_{2.5}$ may contribute to ADHD development through multiple established neurotoxic mechanisms, including neuroinflammation, oxidative stress, white matter damage, DNA methylation, neuronal dysfunction, white matter damage, and neurotransmitter dysfunction (Cory-Slechta et al., 2023; Liu et al., 2023). These findings provide crucial mechanistic insights into the association between $PM_{2.5}$ components and ADHD. Notably, $PM_{2.5}$ exhibits distinct spatiotemporal variability in its chemical composition (Al-Kindi et al., 2020). Therefore, the $PM_{2.5}$-ADHD association may primarily depend on its chemical composition, with key constituents (SO_4^{2-}, BC, and OM) potentially involving distinct biological mechanisms.

As a primary secondary aerosol, SO_4^{2-} is formed via chemical reactions between different precursor gases that derive from combustion processes connected to various human activities (Liang et al., 2016; Liu et al., 2018b). A plausible hypothesis for neurotoxicity-induced by SO_4^{2-} is that it alters the solubility and bioavailability of metals or exerts its own stimulatory effects, which leads to systemic inflammation and oxidative stress (Bates et al., 2019; Maciejczyk et al., 2021; Zhang et al., 2021). For example, SO_4^{2-} can bind to transition metals (e.g., copper, iron, and manganese) to promote the generation of reactive oxygen species (ROS) in human brain cells (Pogue et al., 2012). Once ROS production exceeds cellular antioxidant capacity, oxidative stress occurs. An animal study found that copper sulfate exposure caused oxidative stress (e.g., increased malondialdehyde and nitric oxide) and inflammation (e.g., elevated COX-2 and iNOS level) in rat brains, resulting in brain damage (Arowoogun et al., 2021). Of note, early life exposure to inorganic extract of $PM_{2.5}$ caused microglia and astrocytes activation in various brain regions, and further induced neurobehavioral deficits in male Wistar rats (Rahmatinia et al., 2024). Activated microglia and astrocytes can induce proinflammatory cytokine release and ROS production, thereby triggering inflammation, oxidative stress, and neuronal dysfunction, ultimately impairing neurodevelopment (Vainchtein and Molofsky, 2020). Furthermore, exposure to the inorganic components of $PM_{2.5}$ decreased neurite length and axon branch length in neurons, altered the expression of genes involved in axonal and dendritic morphogenesis, and further impaired neuronal morphogenesis and development (Hou et al., 2023). In addition, a study found that sulfur predominantly existed as SO_4^{2-}, accounting for over 70 % across all particle sizes and even reaching 90 % in $PM_{2.5}$ in China (Long et al., 2014). Collectively, these findings provide clues to neurotoxicity-induced by inorganic components of $PM_{2.5}$ (notably SO_4^{2-}), highlighting the role of SO_4^{2-} in the $PM_{2.5}$-ADHD association.

Ambient BC, generated by combustion processes including fossil fuel

and biomass burning, is principally found in the ultrafine particles (Briggs and Long, 2016; Nie et al., 2022). Moreover, inhaled nano-sized BC particles can penetrate blood-brain barrier to exert adverse effects on the brain (Hopkins et al., 2018). A recent study demonstrated the presence of BC particles in human brain regions associated with memory function, suggesting their potential involvement in the onset and progression of neurological disorders (Vanbrabant et al., 2024). In addition, BC particles may transport extremely hazardous OM species into the brain to cause neurotoxicity, leading inflammation and oxidative stress in the brain (Cornelissen et al., 2005; Shang et al., 2019). For example, a study revealed that exposure to ultrafine BC particles triggered apoptosis, caused mitochondrial oxidative stress, and promoted mitophagy in human neuroblastoma SH-SY5Y cells (Shang et al., 2022). Shang et al. investigated the acute neurotoxic effects of real-world ultrafine BC particles derived from residential solid fuel combustion in SH-SY5Y cells, revealing different combustion sources-related neurotoxicity (Shang et al., 2024). The findings revealed that biomass BC mainly impaired mitochondrial function and disrupted redox homeostasis while coal-BC primarily triggered cytokine/chemokine-mediated inflammatory responses. Overall, these findings provide crucial evidence for understanding the mechanisms underlying BC-induced neurotoxicity, and highlight that emission sources may determine the diversity of BC-induced neurotoxicity.

Ambient OM represents a complex mixture comprising both primary pollutants emitted from combustion processes and secondary pollutants formed through atmospheric oxidation of organic gases (Guo et al., 2012). Some OM species, such as PAHs and PCBs, have been demonstrated to exert neurotoxic effects. Animal models have demonstrated that PAHs and PCB exposure induced aberrant neurological development and neurobehavioral deficits via oxidative stress and inflammation (Peixoto-Rodrigues et al., 2025; Xu et al., 2024). Notably, organic constituents of $PM_{2.5}$ appear to demonstrate greater neurotoxic effects compared to other $PM_{2.5}$ components based on $PM_{2.5}$ extract exposure studies. For example, *in vitro* studies have suggested that exposure to various $PM_{2.5}$ extracts can induce oxidative stress, DNA methylation, and ferroptosis in SH-SY5Y cells, with organic extracts having the greatest effects, followed by water-soluble extracts and carbon core component (Guo et al., 2023; Wei et al., 2016, 2017). Moreover, animal studies revealed that early-life exposure to $PM_{2.5}$ extracts induced neuroinflammation, neuronal dysfunction, and neurobehavioral deficits in mice, with organic extracts exhibiting significantly greater effects than inorganic extracts (Hou et al., 2023; Rahmatinia et al., 2024). OM demonstrates greater capacity to induce oxidative stress and inflammation compared to other $PM_{2.5}$ components likely due to its chemical complexity. Although these findings suggest potential biological mechanisms linking OM to ADHD, further experimental studies employing single and mixed OM species at doses similar to human exposure are required to clarify the possible effects of OM on ADHD.

4.4. Public health implications

Identifying key-specific $PM_{2.5}$ components that contribute to ADHD and implementing region-specific effective exposure reduction measures for these components, may be important for public health system to reduce diseases burden on society. Our study identified that OM, BC, and SO_4^{2-} may mainly drive the relationships between $PM_{2.5}$ constituents and ADHD, providing evidence of the $PM_{2.5}$-ADHD association. Therefore, to reduce the disease burden of $PM_{2.5}$, policymakers should focus on controlling the more hazardous components of $PM_{2.5}$. For example, reducing SO_4^{2-} emission through catalytic sulfur dioxide reduction technologies and decreasing OM emission with advanced diesel technologies both greatly enhance human health (Hernández Paniagua et al., 2023; Ng et al., 2022). In addition, since BC is considered an indicator of older diesel fuel usage, switching to cleaner fuels should be implemented to reduce BC emission and significantly improve public health (Wang et al., 2023). Furthermore, people should be aware of the local air quality and avoid prolonged exposure to hazardous pollutants, especially children and those who already exhibit ADHD-like behavior problems. Overall, our data provides new insights into how to mitigate the burden of $PM_{2.5}$-related neurodevelopmental disorders by supporting the control of transport-related emission sources to reduce combustion-related OM, BC, and SO_4^{2-}.

4.5. Strengths and limitations

Our study has several strengths. First, it provides a comprehensive evaluation of the individual and combined effects of five major $PM_{2.5}$ constituents (OM, BC, SO_4^{2-}, NH_4^+, and NO_3^-) on childhood ADHD, while prior research has never thoroughly examined the relationship between OM and ion compositions with childhood ADHD. Thus, this study may offer new perspectives on the health effects of key-specific $PM_{2.5}$ components to policymakers and researchers. Second, to our knowledge, this study (n = 110,818) is the largest epidemiological investigation of exposure to major components of $PM_{2.5}$ and childhood ADHD in China to date, potentially providing sufficient statistical power to examine the impacts of $PM_{2.5}$ components on childhood ADHD. Third, as this study was conducted in regions with moderate-to-high air pollution levels, the findings may be particularly relevant for similarly polluted areas (e.g., India, Egypt, and Pakistan). These results provide critical evidence to inform region-specific air quality policies and public health interventions targeting $PM_{2.5}$ exposure mitigation. Fourth, we collected numerous covariates, which enabled us to perform stratified and sensitivity analyses to demonstrate the robust findings.

Despite these strengths, several limitations warrant consideration. First, the cross-sectional design of this study precluded the establishment of causal relationships between exposure and outcome, although we employed the three-year average concentrations of $PM_{2.5}$ and its components preceding the survey period as exposure measures. Nevertheless, the possibility of reverse causality, wherein ADHD diagnosis might influence the spatial distribution of air pollution around residential areas, appears unlikely. Second, our estimation of $PM_{2.5}$ constituent concentrations was based on participants' residential addresses without accounting for individual mobility patterns (e.g., outdoor time, breathing rate, and movement range), which may introduce exposure measurement error. Therefore, future studies should incorporate exposure data from additional sources to improve the precision of exposure assessment strategies. Third, despite adjusting for several important confounders, residual confounders due to the lack of data on variables such as prenatal exposure, genetic predisposition, parental ADHD history, and indoor air pollution, cannot be ruled out. Fourth, we used single-pollutant models to examine the health effects of individual $PM_{2.5}$ constituents, but the estimated associations may be confounded by other components or the total $PM_{2.5}$ mass due to high collinearity among different $PM_{2.5}$ components. Although studies have confirmed that parent-reported ADHD based on DSM-criteria is reliable (Cree et al., 2023; Willcutt, 2012), the differences of parent-reported diagnoses and clinical diagnoses cannot be neglected. Parent-reported diagnoses may yield higher prevalence estimates than clinically verified diagnoses due to broader symptom interpretation. Finally, only five $PM_{2.5}$ constituents were examined in this study, and further research should thoroughly explore the health effects of additional $PM_{2.5}$ constituents (e.g., specific organic compounds and heavy metal elements).

5. Conclusion

In conclusion, long-term exposure to $PM_{2.5}$ components was strongly related to an elevated risk of ADHD, and the contributions of individual $PM_{2.5}$ constituents to ADHD may have variation. Notably, the combustion-related SO_4^{2-}, OM, and BC were particularly relevant for the observed associations. Our findings offer policy insights for implementing effective reduction measures of combustion-related $PM_{2.5}$ constituents to mitigate the burden of $PM_{2.5}$-related diseases on society.

CRediT authorship contribution statement

Hui-Xian Zeng: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Wen-Jie Meng:** Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Qing-Guo Zeng:** Writing – original draft, Methodology, Data curation. **Jing Wei:** Writing – review & editing. **Lu-Sheng Liu:** Methodology, Formal analysis, Data curation. **Qi-Zhen Wu:** Methodology, Formal analysis, Data curation. **Bin Zhao:** Writing – review & editing. **Anna Oudin:** Writing – review & editing. **Mo Yang:** Writing – review & editing. **Pasi Jalava:** Writing – review & editing. **Guang-Hui Dong:** Supervision, Conceptualization. **Xiao-Wen Zeng:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121641.

Data availability

Data will be made available on request.

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