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Fine particulate matter components associated with exacerbated depressive symptoms among middle-aged and older adults in China

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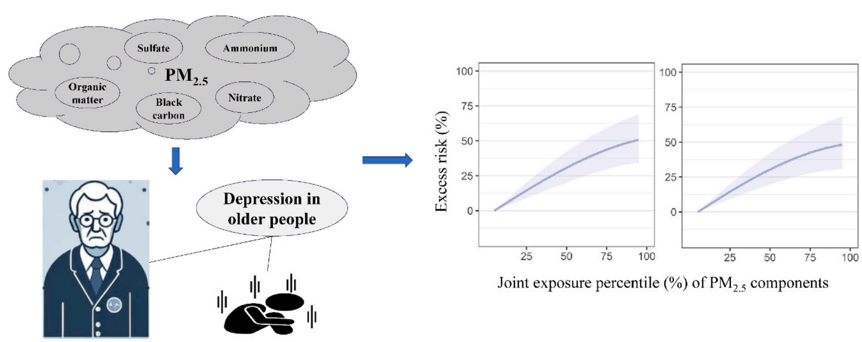
HIGHLIGHTS

- Exposure to the mixture of major $PM_{2.5}$ components was significantly associated with aggravating depressive symptoms.
- Exposure-response curves were linear or supra-linear without a lower threshold.
- Nitrate, sulfate, and black carbon were primary contributors to exacerbated depressive symptoms.

GRAPHICAL ABSTRACT



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ABSTRACT

Growing awareness acknowledges ambient fine particulate matter ($PM_{2.5}$) as an environmental risk factor for mental disorders, especially among older people. However, there remains limited evidence regarding which specific chemical components of $PM_{2.5}$ may be more detrimental. This nationwide prospective cohort study included 22,126 middle-aged and older adult participants of the China Health and Retirement Longitudinal Study (CHARLS, 2011–2016), to explore the individual and joint associations between long-term exposure to various $PM_{2.5}$ components (sulfate, nitrate, ammonium, organic matter, and black carbon) and depressive symptoms. The depressive symptoms were assessed using the 10-item Center for Epidemiological Studies-Depression Scale (CES-D-10). Using the novel quantile-based g-computation for multi-pollutant mixture analysis, we found that exposure to the mixture of major $PM_{2.5}$ components was significantly associated with aggravating depressive symptoms, with the exposure-response curve exhibiting consistent linear or supra-linear shape without a lower threshold. The estimated weight index indicated that, among major $PM_{2.5}$ components, only nitrate, sulfate, and black carbon significantly contributed to the exacerbation of depressive symptoms.

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Given the expanding aging population, stricter regulation on the emissions of particularly toxic $PM_{2.5}$ components may mitigate the escalating disease burden of depression.

1. Introduction

Depression has emerged as a prevalent and escalating mental health disorder that is associated with heightened disability and mortality, particularly in older individuals (WHO, 2017). Current estimates indicate that depression affects around 4.4 % of the world's population (WHO, 2017; Mental Disorders Collaborators, 2022), with projections indicating its rise as the 2nd largest contributor to the global disease burden by 2030 (Mathers and Loncar, 2006). Given the expanding aging population, prevention, and remission of depression by identifying and controlling modifiable risk factors is imperative for public health.

Air pollution, a considerable global health threat (Tong, 2019), has garnered attention for its potential relationship with depression, especially ambient fine particulate matter ($PM_{2.5}$), based on emerging epidemiological evidence (Braithwaite et al., 2019; Borroni et al., 2022; Yang et al., 2023; Qiu et al., 2023). While short-term exposure to $PM_{2.5}$ has been linked to elevated incident depression-related hospitalization or outpatient visits by several reports (Szyszkowicz et al., 2016; F. Wang et al., 2018; Gu et al., 2020), the evidence regarding a long-term association between $PM_{2.5}$ and depression has yielded contradictory results. Some studies have revealed significant detrimental effects of $PM_{2.5}$ (Yang et al., 2023; Qiu et al., 2023; Gao et al., 2023; Pun et al., 2017; Kim et al., 2016; Wei et al., 2022; Park et al., 2023), while others have found no association (Wang et al., 2014, 2021; Kioumourtzoglou et al., 2017; Zhang et al., 2019). This inconsistency in findings may stem from spatiotemporal disparities in the chemical composition of ambient $PM_{2.5}$ (Wu et al., 2021; Li et al., 2023a), a complex mixture of various components (e.g., organic matter, black carbon, mineral dust, etc.), that exhibit diverse toxicities. Previous studies indicate that specific $PM_{2.5}$ components may be more closely related to health effects than aggregated $PM_{2.5}$ (Franklin et al., 2008; Chaudhary et al., 2023).

Limited studies on long-term exposure to $PM_{2.5}$ components and depression (Ju et al., 2023) have primarily focused on individual association via traditional single-exposure parametric regression, neglecting the complex relationship between $PM_{2.5}$ mass and its compositions. Notably, humans are simultaneously exposed to multiple $PM_{2.5}$ components and pollutants, which are spatiotemporally correlated due to shared sources such as traffic and industry (Zhao et al., 2022). Conventional parametric regression may struggle to adequately and accurately assess the health effects on multiple $PM_{2.5}$ components due to severe collinearity. In contrast, the quantile-based g-computation that amalgamates the 'g-method' with the Weighted Quantile Sum (WQS) regression, provides an innovative approach capable of efficiently evaluating joint effects of multiple inter-correlated exposures and pinpointing the main contributors (Keil et al., 2020).

Using a large-scale national cohort, this study aims to prospectively examine the association between long-term exposure to $PM_{2.5}$ components and depression risk among middle-aged and older adults in China, a nation experiencing rapid demographic aging. The advanced quantile-based q-computation was used to assess the joint effect of co-exposure to $PM_{2.5}$ components and to identify toxic components that primarily contribute to the risk of depression.

2. Methods

2.1. Study design and population

This research utilized data from the China Health and Retirement Longitudinal Study (CHARLS) (Zhao et al., 2014), a population-based, longitudinal, and prospective cohort study of Chinese adults aged 45 and above. CHARLS includes participants from 450 communities in 126 cities and counties across 28 provinces in China. China has implemented the Clean Air Policy (CAP) since 2013, and nationally the long-term concentrations of $PM_{2.5}$ decreased rapidly from 67.4 μg/m^3 in 2013 to 45.5 μg/m^3 in 2017 (Xue et al., 2019). Thus, we included 24,958 participants involved in the baseline survey in 2011–12 or two follow-up surveys in 2013–14 and 2015–16, to obtain reliable results from the chance of a natural experimental scenario of CAP with rapid ambient $PM_{2.5}$ changes and with limited variation in unmeasured time-varying confounders during a relatively short period (Xue et al., 2021). After excluding participants aged below 45 years old or with missing age records or missing values for depressive symptoms, our cohort analysis encompassed 22,126 individuals with 49,777 observations. The schematic flow of study sample identification is shown in Fig. S1 of the Supplementary materials. The spatial distribution of study subjects is shown in Supplementary Fig. S2.

All participants enrolled in the CHARLS program were provided with written informed consent. The CHARLS strictly adheres to the ethical principles delineated in the Declaration of Helsinki and has received approval from the Ethics Review Committee of Peking University (IRB00001052–11015). Details concerning the CHARLS cohort have been documented in a prior publication (Zhao et al., 2014). The current study, involving secondary analyses of pre-existing datasets and conforming to data usage protocols, was exempt from further ethical approval.

2.2. Assessment of depression symptoms

The CHARLS survey employs the 10-item Center for Epidemiological Studies-Depression Scale (CES-D-10) to measure depressive symptoms, a tool that has been validated among the middle-aged and older Chinese population (Boey, 1999; Y. Wang et al., 2018). The CES-D-10 comprises ten questions, each specifically addressing different negative moods. Participants scored each question based on frequency over the preceding week: 0 for less than one day, 1 for 1–2 days, 2 for 3–4 days, and 3 for 5–7 days. The aggregate score ranges from 0 to 30 (Cronbach $\alpha = 0.815$) (Lei et al., 2014), with higher scores indicating more severe symptoms of depression.

2.3. Exposure variables

High-quality, high-resolution daily concentrations of $PM_{2.5}$ chemical composition from 2010 to 2016 were sourced from the Tracking Air Pollution (TAP) - $PM_{2.5}$ & species dataset (http://tapdata.org.cn). Concentrations of overall $PM_{2.5}$, sulfate, nitrate, ammonium, organic matter, and black carbon in the dataset were estimated by combining operational Community Multiscale Air Quality (CMAQ) simulations, ground measurements, multisource-fusion $PM_{2.5}$ data, and extreme gradient boosting (XGBoost) algorithms (Liu et al., 2022). $PM_{2.5}$ chemical components in TAP yield a good agreement with in-situ observations on daily (correlation coefficients ranging from 0.67 to 0.80, 2013–2020) and monthly (correlation coefficients ranging from 0.64 to 0.75, 2000–2020) scales, and have been used in other environmental health studies (Han et al., 2023; Cai et al., 2023).

Additionally, the TAP $PM_{2.5}$ & species dataset provides daily concentration data at 10-km spatial resolution throughout China, spanning from the year 2000 to the present. All participants in the CHARLS cohort were geo-coded to the regionalization code of residential address to uphold the participants' privacy. Consequently, the daily gridded $PM_{2.5}$ component concentrations were initially aggregated to city-level averages, which were used for monthly average calculations. The moving average of $PM_{2.5}$ component concentration for 12 months before the survey month was utilized as the proxy for exposure. The annual average of ambient temperature exposure of each participant was similarly calculated using the Global Climate Atmosphere Reanalysis dataset from the European Centre for Medium Range Weather Forecasts (fifth generation, ERA5), which features a spatial resolution of $0.1^\circ \times 0.1^\circ$ and a temporal resolution of 1 h.

2.4. Covariates

A directed acyclic graph was used to discern confounders (Fig. S3). The following covariates were adjusted for in the analyses: age, sex (male vs. female), education level (i.e., illiterate, $\leq$ middle school, and $\geq$ high school), retirement (yes vs. no), residence (urban vs. rural), self-reported health status (i.e., excellent, very good, good, moderate, or bad), engagement in social activities (yes vs. no), frequency of alcohol consumption in the past year (i.e., never, $\leq$ 3 days per week, and $\geq$ 4 days per week), smoking history (ever vs. never), marital status (married vs. otherwise), co-residency with children (yes vs. no), and ambient temperature, with each variable being collected at every survey.

2.5. Statistical analysis

Initially, the change in CES-D-10 scores (log transformation) was assessed utilizing a single-exposure mixed-effects model for $PM_{2.5}$ and each $PM_{2.5}$ component exposure separately. In addition to adjusting for DAG-identified confounders, the regression model incorporated the fixed effects of city and community to control for unmeasured city- and community-specific risk factors (e.g., traditional culture, community economic status, etc.) associated with depression. Additionally, the model accounted for the subject-specific random intercepts to accommodate individual variability. The association was evaluated by excess risk (ER) as $[exp(\beta \bullet \Delta x) - 1] \times 100\%$, with β as a regression coefficient and Δx as the increment of single exposure. Natural cubic splines were also used to evaluate the exposure-response curves for $PM_{2.5}$ and each $PM_{2.5}$ component. Additionally, given the complicated relationship between $PM_{2.5}$ and its components, the component residual model was also constructed to further examine the individual effects of each $PM_{2.5}$ component. The component residual model incorporated the $PM_{2.5}$-adjusted component residual, which was derived from fitting a linear regression model using the given $PM_{2.5}$ component as the dependent variable and $PM_{2.5}$ concentration as the independent variable (Li et al., 2023a; Mostofsky et al., 2012). Generalized variance inflation factors (GVIF) adjusted for the degree of freedom were calculated for the component residual model. The adjusted GVIF exceeding 2 was applied as a sign of multicollinearity (Jakstis and Fischer, 2021).

Next, we applied the quantile-based g-computation to ascertain the joint effects of the overall exposure to five $PM_{2.5}$ components, while controlling for the same covariates as those included in the single-exposure mixed-effects models. Fixed effects of the city and community were also controlled, and the subject index was specified as individual units with multiple observations. Combined with WQS and g-computation, the quantile-based g-computation is capable of (Keil et al., 2020): 1) mitigating potential collinearity among co-varied exposures; 2) estimating overall effects of increasing overall exposures by one quantile; 3) surpassing the constraints of the uni-directional homogeneity assumption inherent to WQS (i.e., the effects of all pollutants are uniformly positive or negative) and generating pollutant-specific index weights quantifying the relative magnitude of the effects of individual exposure on the outcome; 4) incorporating non-linearities of co-exposure. Notably, the index weights of each pollutant might be in the positive or negative direction, indicative of corresponding positive or negative associations; only those weight indexes with the same direction can be compared with each other, which are forced to sum to 1. The joint association was also evaluated by ER as $[exp(\beta \bullet \Delta q) - 1] \times 100\%$, with β as a regression coefficient and Δq as per quintile increment of co-exposure.

We repeated the quantile-based g-computation modeling by additionally adding the overall $PM_{2.5}$ into the exposure mixture, given the complicated relationship between $PM_{2.5}$ mass and its compositions. We conducted a parallel analysis for both the single-exposure and the quantile-based g-computation models by restricting 16,604 subjects with at least two visits, serving as a secondary analysis. The quantile-based g-computation analyses were further extended to explore potential nonlinear effects of exposure mixtures, via incorporating a basic spline function with a degree of 2 (Keil, 2020). Additionally, we also conducted sensitivity analyses of the quantile-based g-computation model to verify the robustness of the joint association of $PM_{2.5}$ components and depressive symptoms: 1) multiple imputation chained equations (MICE) by exposures and covariates was conducted considering the potential bias of missing data; 2) stratification analyses were performed to evaluate how estimated associations varied in sex, education, residence, retirement, self-reported health, and marital status. We employed a two-sample z test for evaluating statistically significant discrepancy in estimate ER between categories within each subgroup (e.g., male vs. female), based on point estimation and corresponding standard error (se): $Z = \frac{ER_1 - ER_2}{\sqrt{se(ER_1)^2 + se(ER_2)^2}}$ (Altman and Bland, 2003; Di et al., 2017).

All statistical analyses were conducted by using R statistical software (version 4.1.3; R Project for Statistical Computing). The single-exposure mixed-effects and quantile-based g-computation models were fitted by the 'lmeTest' and 'qgcomp' packages, respectively. A 2-sided $P < 0.05$ was specified as the statistical significance level.

3. Results

This study identified 22,126 unique middle-aged and older adults with an average visit count of 2.3 times from 450 communities across 126 cities and counties in China. Among them, 48.8 % were males, 25.0 % were illiterate, and 42.6 % lived in urban areas (Table 1). Over the three longitudinal surveys, the average (Standard Deviation, SD) age of participants was 59.1 (9.6), 59.6 (9.5), and 59.9 (9.7) years, the corresponding average (SD) of CES-D-10 scores was 8.4 (6.3), 7.8 (5.8) and 7.9 (6.4), and median (IQR) 12-month $PM_{2.5}$ exposure was 54.1 (39.2–76.8), 53.3 (36.3–75.6) and 44.9 (32.0–60.6) μg/m^3, respectively. Table 2 shows the detailed descriptions of longitudinal variables and $PM_{2.5}$ component exposure of each CHARLS survey. Concentrations of $PM_{2.5}$ component exposure were considerably inter-correlated (Fig. S4).

The single-pollutant mixed-effects model, adjusted for identified covariates but not concomitant pollutant exposure, indicated a significantly positive association of exposure to overall $PM_{2.5}$ and each of the five $PM_{2.5}$ components with increased risk of depressive symptoms (Table 3). In the main analysis of all 22,126 adults in 2011–2016 CHARLS, per 1 μg/m^3 increase in exposure to overall $PM_{2.5}$, sulfate, nitrate, ammonium, organic matter, and black carbon were individually

Table 1
Constant characteristics of the studied subjects.

Characteristics	No. (%)		P-values[a]
	All subjects	Subjects with ≥2 visits	
Total	22,126	16,604	
Gender			0.042
Male	10,807 (48.8)	7936 (47.8)	
Female	11,319 (51.2)	8668 (52.2)	
Education			0.022
Illiterate	5531 (25.0)	4340 (26.1)	
≤Middle school	13,796 (62.4)	10,220 (61.6)	
≥High school	2795 (12.6)	2044 (12.3)	
Unknown	4 (0.0)	0 (0.0)	
Residence			<0.001
Urban	9429 (42.6)	6418 (38.7)	
Rural	12,697 (57.4)	10,186 (61.3)	

[a] P-values for the Chi-square test or Fisher's Exact Test, as appropriate for the data.

Table 2
Longitudinal characteristics of the studied subjects.

Characteristics	1st survey [a]	2nd survey [b]	3rd survey [c]
No. of subjects	15,382	16,048	18,347
Depression score, mean (SD) [d]	8.4 (6.3)	7.8 (5.8)	7.9 (6.4)
Age, mean (SD), y	59.1 (9.6)	59.6 (9.5)	59.9 (9.7)
Retirement, no. (%)			
No	9796 (63.7)	10,750 (67.0)	12,339 (67.3)
Yes	5333 (34.7)	5041 (31.4)	5661 (30.9)
Self-reported health status, no. (%)			
Excellent	913 (5.9)	1446 (9.0)	2194 (12.0)
Very good	2610 (17.0)	2309 (14.4)	2348 (12.8)
Good	7582 (49.3)	8391 (52.3)	9651 (52.6)
Moderate	3560 (23.1)	3084 (19.2)	3254 (17.7)
Bad	709 (4.6)	795 (5.0)	888 (4.8)
Engagement in social activities, no. (%)			
No	8195 (53.3)	7450 (46.4)	9323 (50.8)
Yes	7178 (46.7)	8592 (53.5)	9022 (49.2)
Frequency of alcohol consumption in the past year, no. (%)			
Never	10,376 (67.5)	10,432 (65.0)	11,755 (64.1)
≤3 days per week	2395 (15.6)	2963 (18.5)	3796 (20.7)
≥4 days per week	1825 (11.9)	2603 (16.2)	2732 (14.9)
Smoking history, no. (%)			
Never	9317 (60.6)	9240 (57.6)	10,241 (55.8)
Ever	6063 (39.4)	6806 (42.4)	8104 (44.2)
Marital status, no. (%)			
Married	2653 (17.2)	2757 (17.2)	3382 (18.4)
Otherwise	12,729 (82.8)	13,291 (82.8)	14,965 (81.6)
Co-residency with children, no. (%)			
No	5938 (38.6)	7358 (45.8)	7993 (43.6)
Yes	9059 (58.9)	8355 (52.1)	10,178 (55.5)
Environment variable, median (IQR)			
$PM_{2.5}$, μg/m^3	54.1 (39.2–76.8)	53.3 (36.3–75.6)	44.9 (32.0–60.6)
Sulfate, μg/m^3	10.7 (7.7–14.7)	10.9 (7.5–15.0)	8.6 (6.3–11.7)
Nitrate, μg/m^3	11.2 (7.0–17.1)	11.5 (6.6–17.4)	10.0 (6.1–14.1)
Ammonium, μg/m^3	8.3 (5.7–12.0)	8.3 (5.1–11.8)	7.1 (4.7–9.5)
Organic matter, μg/m^3	13.6 (10.4–18.8)	13.2 (9.5–17.9)	11.1 (8.7–14.4)
Black carbon, μg/m^3	2.9 (2.3–3.8)	2.7 (2.1–3.6)	2.2 (1.8–2.8)
Temperature, °C	15.0 (11.3–16.5)	15.3 (11.5–16.8)	15.0 (12.1–16.8)

Abbreviation: $PM_{2.5}$: fine particulate matter.
Notes: For 1st, 2nd, and 3rd surveys, there were 253, 257, and 347 missing values of retirement; 8, 23, and 12 missing values of self-reported health status; 9, 6, and 2 missing values of engagement in social activities; 786, 50 and 64 missing values of alcohol consumption; 2, 2, and 2 missing values of smoking history; 385, 335 and 176 missing values of co-residency with children, respectively.
[a] The baseline survey conducted during 2011–12.
[b] The follow-up survey conducted during 2013–14.
[c] The follow-up survey conducted during 2015–16.
[d] The depressive symptoms were measured by the 10-item Center for Epidemiological Studies-Depression Scale (CES-D-10).

associated with a 0.30 % (95 % CI: 0.19–0.40 %), 1.35 % (95 % CI: 0.84–1.86 %), 0.95 % (95 % CI: 0.44–1.47 %), 1.56 % (95 % CI: 0.87–2.26 %), 1.35 % (95 % CI: 0.93–1.76 %) and 5.81 % (95 % CI: 4.02–7.63 %) increase in the CES-D-10 score. Similar results were estimated by restricting analysis in subjects with at least two visits (Table 3). The exposure-response curves from the single-pollutant model showed a monotonically increasing association of exposure to $PM_{2.5}$ and its components with depressive symptoms (Figs. S5 and S6). In the component residual model, the results for ammonium and sulfate need to be interpreted cautiously according to adjusted GVIF exceeding 2, while the other three components all showed consistent positive associations with depressive symptoms (Table S1).

Table 3
Estimated associations of $PM_{2.5}$ and its components with depression score by the single-pollutant model.

Exposure variable	All subjects (n = 22,126)	Subjects with ≥2 visits (*n* = 16,604)
	Excess risk, % (95 % CI)[a]	Excess risk, % (95 % CI)[a]
$PM_{2.5}$	0.30 (0.19–0.40)	0.25 (0.14–0.36)
Sulfate	1.35 (0.84–1.86)	1.07 (0.54–1.61)
Nitrate	0.95 (0.44–1.47)	0.74 (0.21–1.28)
Ammonium	1.56 (0.87–2.26)	1.23 (0.51–1.96)
Organic matter	1.35 (0.93–1.76)	1.15 (0.72–1.59)
Black carbon	5.81 (4.02–7.63)	4.89 (3.02–6.79)

Abbreviations: $PM_{2.5}$, fine particulate matter.
[a] Excess risk and 95 % CIs of depression score per 1 μg/m^3 increase in long-term mean exposures (12-month moving average) adjusting for age, gender, education level, retirement, urban/rural residence, self-reported health status, engagement in social activities, frequency of alcohol consumption in the past year, smoking history, marital status, co-residency with children, and ambient temperature.

Based on quantile-based g-computation, the exposure-response relationship between the $PM_{2.5}$ component mixture and depression exhibited consistent linear or supra-linear shapes without a lower threshold (Fig. 1). A significant increase in depression risk was observed with per quintile increase in co-exposure to the overall five $PM_{2.5}$ components (Table 4); the main analysis of 22,126 adults yielded an ER of 6.21 % (95 % CI: 3.89–8.58 %), closely resembling the results when additionally including overall $PM_{2.5}$ in the model. Nitrate (index weight 0.46), sulfate (0.33), and black carbon (0.21) have positive effects on CES-D-10 score and were identified as the main contributors of harmful joint effects, while ammonium (−0.59) and organic matter (−0.41) exhibited negative effects. Given the significant positive ER of the overall effects of the $PM_{2.5}$ component mixture, the negative index weights indicate that the $PM_{2.5}$ components of ammonium and organic matter were not correlated with depressive symptoms. Results from secondary analyses in subjects with multiple visits were similar (Table 4). In addition, in the multi-pollutant analysis adding $PM_{2.5}$, the index weight of $PM_{2.5}$ tended to be non-significantly negative or minimally positive (Table 4), suggesting that focusing on specific components of $PM_{2.5}$ may be more critical than considering overall $PM_{2.5}$.

The results remained robust in sensitivity analysis (Table S3). Subgroup analysis discerned a heterogeneity in the association strengths between exposure to the $PM_{2.5}$ component mixture and depressive symptoms by demographic factors. The joint effect of exposure to the $PM_{2.5}$ component mixture tended to be higher in males than females, higher in not retired population than the retired population, and higher in married individuals than otherwise (Table S4 and Fig. S7).

4. Discussion

The findings of this nationwide cohort study contribute novel insights into the adverse joint effects of long-term co-exposure to a mixture of ambient $PM_{2.5}$ components on heightened depression risk among middle-aged and older adults. To the best of our knowledge, this study is the first to identify such detrimental joint effects among Chinese populations. Nitrate, sulfate, and black carbon emerged as the primary contributors to the toxic effects. The robustness of these results across various model settings strengthens the epidemiological evidence of adverse associations between the $PM_{2.5}$ components exposure and mental health. A non-threshold linear or supra-linear association between the $PM_{2.5}$ mixture and depression was also observed. This study serves as a valuable addition to existing research evidence, highlighting that the potential effects of $PM_{2.5}$ on mental health may be more closely associated with its chemical composition rather than its overall

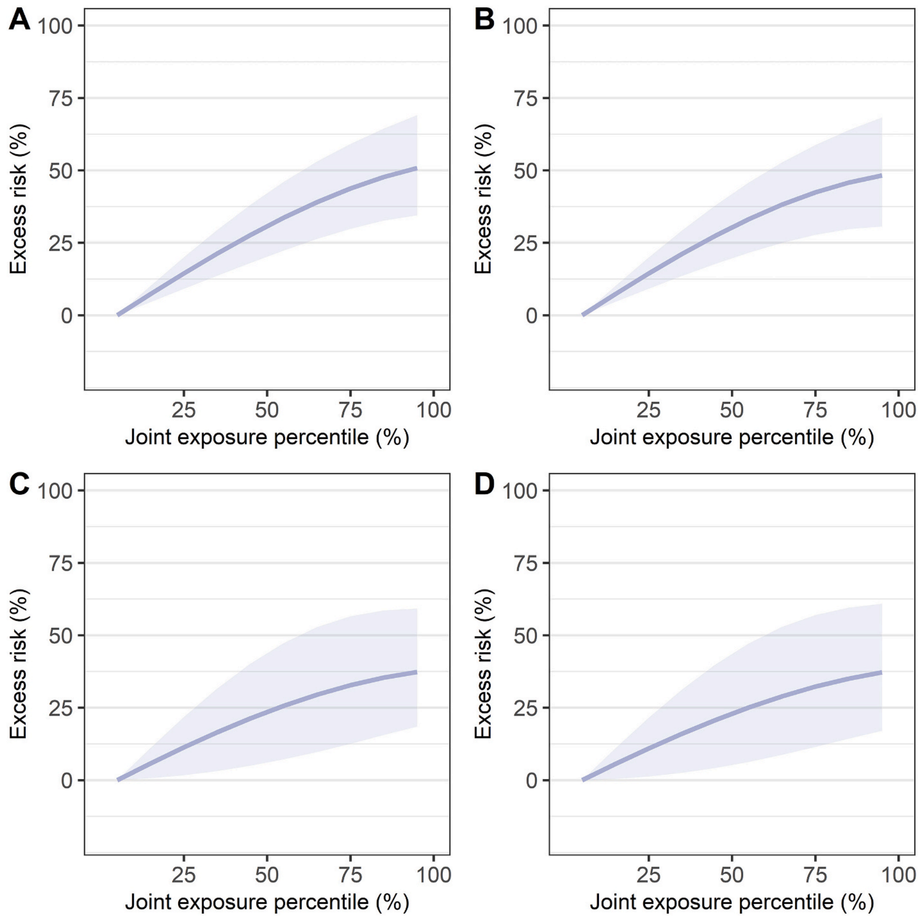

Fig. 1. Association of depression symptoms with percentiles of joint exposure of $PM_{2.5}$ components. A) Exposure-response function for mixture of $PM_{2.5}$ components (sulfate, nitrate, ammonium, organic matter, and black carbon) in relation to depressive score of all 22,126 subjects. B) Exposure-response function for mixture of $PM_{2.5}$ and its five components in relation to depressive score of all 22,126 subjects. C) Exposure-response function for mixture of $PM_{2.5}$ components in relation to depressive score among 16,604 subjects with ≥2 visits. D) Exposure-response function for mixture of $PM_{2.5}$ and its five components in relation to depressive score of all 16,604 subjects with ≥2 visits. The shaded areas are 95 % confidence intervals (CIs). Models were adjusted for age, gender, education level, retirement, urban/rural residence, self-reported health status, engagement in social activities, frequency of alcohol consumption in the past year, smoking history, marital status, co-residency with children, and ambient temperature.

Table 4
Estimated joint association and index weights from the quantile-based g-computation models to depression score with an increase in $PM_{2.5}$ component exposure by one quintile.

Subjects	Overall $PM_{2.5}$	Excess risk, % (95 % CI)[a]	Index weight[b]					
			Nitrate	Sulfate	Black carbon	$PM_{2.5}$	Ammonium	Organic matter
All subjects (n = 22,126)	Excluded	6.21 (3.89, 8.58)	0.46	0.33	0.21		−0.59	−0.41
	Included	6.19 (3.81, 8.61)	0.46	0.33	0.21	−0.03	−0.57	−0.40
Subject with ≥2 visits (n = 16,604)	Excluded	4.30 (1.87, 6.79)	0.37	0.35	0.28		−0.55	−0.45
	Included	4.89 (2.37, 7.47)	0.26	0.25	0.24	0.24	−0.53	−0.47

Abbreviations: $PM_{2.5}$, fine particulate matter.
[a] Excess risk and 95 % CIs of depression score per quintile increase in long-term mixture exposures (12-month moving average) adjusting for age, gender, education level, retirement, urban/rural residence, self-reported health status, engagement in social activities, frequency of alcohol consumption in the past year, smoking history, marital status, co-residency with children, and ambient temperature.
[b] The weights are only compatible with other weights in the same (i.e., positive or negative) direction.

concentration.

Despite that mounting studies have investigated the association between ambient $PM_{2.5}$ exposure and depression risk, the inconsistency in previous findings may underscore the need for further exploration into the ''black box' of $PM_{2.5}$, particularly with a specific focus on its components. Utilizing the quantile-based g-computation approach, our analyses of the pollutant mixture identified nitrate as having the highest weight index, followed by sulfate and black carbon. This finding is biologically plausible, given that nitrate, sulfate, and black carbon are all known triggers of neurotoxicity. An animal study has confirmed that $PM_{2.5}$ and its components can accumulate in the lungs and then be transported to the brain and other organs (Li et al., 2017). Nitrate and sulfate, the main secondary inorganic aerosols in the air, have the potential to penetrate pulmonary barriers and deposit in the brain via systematic circulation. This can result in nitrate-induced oxidative stress (Li et al., 2022; Huang et al., 2012) and sulfate-induced mitochondrial abnormalities (Ku et al., 2016), which may negatively impact mental health. Agriculture is the primary source of nitrate emissions globally, whereas traffic is the predominant source of nitrogen oxide emissions in urban settings. Our findings align with the previous study by Guo et al., 2021, which identified nitrate, among all $PM_{2.5}$ components, as the greatest contributor to increased morbidity from neurological diseases (Guo et al., 2021). Black carbon particles released into the ambient environment during the incomplete combustion of carbonaceous fuels in industry, traffic, and domestic consumption, could also reach the blood-brain barrier (Hopkins et al., 2018), and this process may contribute to neurotoxicity by inducing oxidative stress and inflammatory response (Niranjan and Thakur, 2017). Our findings are consistent with the prior research demonstrating the harmful effects of black carbon on other neurodegenerative disorders, including dementia and cognitive impairment (Li et al., 2022; Power et al., 2011).

In addition, the negative index weights for ammonium and organic matter were estimated in this study. It is important to note that the quantile-based g-computation set a negative direction for the effects of these two exposure variables to ensure model convergence, while it did not imply a significant association of ammonium and organic matter with a depression score (Zhao et al., 2022). The index weights are fixed without confidence intervals in the quantile-based g-computation method (Keil et al., 2020), which is a limitation of this approach because it cannot estimate statistical significance for index weights. Given that we have included six exposures (five $PM_{2.5}$ components and overall $PM_{2.5}$) in the model, adding interaction terms may raise concerns about potential overfitting (Zhao et al., 2022). Further investigation into possible interactions across $PM_{2.5}$ components could be explored using nonparametric Bayesian methods (Bobb et al., 2015).

In our single-pollutant analyses, a significant positive association between overall $PM_{2.5}$ exposure and depression risk were observed with the single-pollutant mixed-effects model, while the multi-pollutant mixture analysis with the quantile-based g-computation method demonstrated its effect was a notably smaller contribution to the joint effect in comparison to some of its specific toxic components. The effect of overall $PM_{2.5}$ in our single-pollutant model was likely to be overestimated, which may be attributed to the strong correlation between $PM_{2.5}$ and its toxic components (Huang et al., 2019; Wu et al., 2021). Similarly, the harmful effects with statistical significance of ammonium and organic matter on depression in our single-exposure models could be an overestimation, although consistent with previous studies (Ju et al., 2023; Shi et al., 2020). In the component residual model, except that the risk effect of ammonium and sulfates may be affected by multicollinearity, the results for black carbon and nitrate were consistent with those from the quantile-based g-computation approach; however, the results for organic matter diverged. The component-specific residual from this model is uncorrelated with total $PM_{2.5}$ levels and represents the variation in the component levels independent of $PM_{2.5}$, which could eliminate confounding by total $PM_{2.5}$ (Mostofsky et al., 2012). Nevertheless, this residual does not address confounding by other $PM_{2.5}$ components, particularly in contexts of significant temporal-spatial variability in $PM_{2.5}$ composition, which may be potential reasons for the inconsistent results of organic matter. Modeling the relationship between specific $PM_{2.5}$ components and health outcomes poses substantial challenges, including the potential confounding effect of other toxic components and the overall concentration of $PM_{2.5}$ (Mostofsky et al., 2012). Given that components constitute the overall $PM_{2.5}$, the traditional single- or multi-pollutant regression model may yield biased results, potentially overlooked in previous studies (Ju et al., 2023, Shi et al., 2020).

Our single-pollutant analyses also examined the cross-sectional association of $PM_{2.5}$ and its components with depression symptoms for each survey wave, and the statistically significant association was only observed in the 2013–2014 survey wave. These cross-sectional analyses for each survey wave mainly focused on the spatial variation of exposure and outcome but ignored temporal variations. Instead, our main analysis, a longitudinal cohort analysis set against the backdrop of a natural experimental scenario involving rapid ambient $PM_{2.5}$ changes coinciding with CAP implementation during the study period, examines how depressive symptoms respond to such temporal variations in $PM_{2.5}$. This is one of the main potential reasons why not all the risk effects from different rounds did not consistently align with the overall results from our longitudinal analysis. The significant association for the 2013–2014 survey wave, which may be the most affected by CAP among the three waves, supported the study design of a natural experiment scenario centered around CAP. Additionally, longitudinal data could provide more statistical power than their cross-sectional counterparts (Lu et al., 2013). The longitudinal mixed models of health effects assessment in populations exposed to ambient pollutants could account for potentially missing and mistimed data, as opposed to a multivariate model that could not accommodate missing data (Harrall et al., 2023). Therefore, integrating data across these three rounds of the CHARLS survey, which have also been validated by several recent CHARLS-based studies on air pollution exposure and health (Wang et al., 2023; Ye et al., 2023; Li et al., 2023b), contributes to obtaining a comprehensive understanding related to our study's design and aim by considering both temporal-spatial changes in $PM_{2.5}$ exposure and depressive symptoms.

Gender emerges as a modifier influencing the relationships between $PM_{2.5}$ components and depressive symptoms. Our subgroup analysis discerned that males exhibit a greater susceptibility to long-term $PM_{2.5}$ components than females. This heightened sensitivity among males to $PM_{2.5}$ aligns with findings from previous research on US older people (Qiu et al., 2023). The non-retired population was observed to be more affected by $PM_{2.5}$ component exposure as compared to the retired population. The non-retired population is more likely to have a higher risk of neuroinflammation triggered by air pollutants in that they are disproportionally exposed to higher exposure levels due to commuting and may possess a heightened susceptible nervous system rooted in various working, social, and environmental stressors. Marital status appears to serve as another modifier for the effects of exposure to $PM_{2.5}$ components. Prior investigation revealed that marriage can play a beneficial role in enhancing individuals' mental well-being, while single people and those who are divorced or widowed showed a substantially increased probability of experiencing depressive symptoms (Qin et al., 2018). Our subgroup estimates suggest that exposure to $PM_{2.5}$ components may not further exacerbate depressive symptoms in unmarried individuals, a group already disproportionately affected by such symptoms, but it potentially diminishes the mental health benefits of marriage.

This study possesses several strengths. First, it explored the synergistic linear and non-linear effects of long-term co-exposure to major ambient $PM_{2.5}$ components on depressive symptoms in middle-aged and older adults, employing a nationwide prospective study design. Second, the advanced quantile-based g-computation model was applied to assess the joint effects of multiple $PM_{2.5}$ components, addressing the potential limitations of single-exposure analysis in capturing the real impact of components of $PM_{2.5}$. Third, using a large population-based dataset provided adequate statistical power and enhanced the generality of findings. Fourth, the availability of detailed information at the individual level contributed to minimizing confounding and identifying vulnerable populations. Several limitations of this study should also be noted. First, the exposure assessments of participants were based on metropolitan division codes due to confidentiality, which might cause misclassification bias of exposure. However, Sheppard et al. (2012) indicated that such measurement errors do not significantly alter the exposure-response relationship in linear models (Sheppard et al., 2012), and Bergen et al. (2013) posited that such measurement errors might lead to an underestimation of the health risks associated with pollutant exposure (Bergen et al., 2013). Additionally, precise residence address-based exposure assessments might be misleading as individuals are usually mobile within their cities when engaging in work and other activities (Yu et al., 2020). Second, some potential residual confounding remained inevitable despite adjusting a set of individual covariates based on DAG. Third, some CHARLS participants withdrew from follow-up surveys, potentially introducing bias to the results. Although some loss of follow-up may be associated with depression, we included all subjects in the main analysis to reduce corresponding bias, and similar effect estimation of the secondary analysis restricting subjects with multiple visits indicated the robustness of results. Fourth, the unavailability of reliable data on ambient concentrations of other important gaseous pollutants (i.e., nitrogen dioxide and sulfur dioxide) potentially restricts the comprehensiveness of our findings.

In conclusion, in this prospective cohort study containing middle-aged and older Chinese adults, we observed robust synergistic detrimental effects of long-term exposure to multiple $PM_{2.5}$ components on depressive symptoms. These findings underscore the necessity of enhanced environmental regulation and improved public health strategies. Tighter controls on nitrate, sulfate, and black carbon emissions may mitigate the rising prevalence of geriatric depression in China's rapidly aging population, given their substantial role in the joint harmful effects. Further research for causal evidence and underlying biological mechanisms is warranted.

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CRediT authorship contribution statement

Haisheng Wu: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Jiaqi Liu:** Visualization, Software, Methodology, Formal analysis. **Erica Conway:** Writing – review & editing, Conceptualization. **Na Zhan:** Writing – review & editing. **Lishuang Zheng:** Writing – review & editing. **Shengzhi Sun:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Jinhui Li:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Data curation, 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.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.174228.

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