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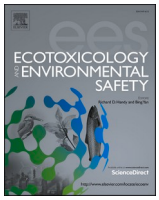

Role of metabolic risk factors in the relationship between ambient fine particulate matter and depressive symptoms: Evidence from a longitudinal population study

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ABSTRACT

Background: There is growing evidence indicating a connection between fine particulate matter ($PM_{2.5}$) and depressive symptoms. Metabolic risk factors are critical determinants of depressive symptoms. However, the mediating role of these factors on the association between $PM_{2.5}$ and depressive symptoms remains elusive. We aimed to investigate whether and to what extent metabolic risk factors mediated the link between long-term $PM_{2.5}$ exposure and depressive symptoms.

Methods: This study comprised 7794 individuals aged between 30 and 79 years who participated in two waves of the on-site surveys in the China Multi-Ethnic Cohort. Ambient $PM_{2.5}$ concentrations were assessed utilizing a random forest method based on satellite data. We employed the Patient Health Questionnaire-9 to assess depressive symptoms at wave 2, and the overall as well as three sub-domain symptom scores (emotional, neurovegetative, and neurocognitive symptoms) were calculated. Three metabolic risk factors, including hypertension, diabetes, and dyslipidemia, were considered. Mediation analyses were conducted to assess the indirect effects of $PM_{2.5}$ on depressive symptoms through metabolic risk factors.

Results: We found a positive association between chronic exposure to ambient $PM_{2.5}$ and overall depressive symptoms as well as the three sub-domains. In mediation analyses, metabolic risk factors partially mediated the associations of $PM_{2.5}$ on depressive symptoms. The natural indirect effects (RR, 95% CI) of $PM_{2.5}$ on overall, emotional, neurovegetative, and neurocognitive symptoms mediated through metabolic risk factors were 1.004 (1.001, 1.007), 1.004 (1.001, 1.008), 1.004 (1.001, 1.007), and 1.003(0.999, 1.007), respectively. Larger

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indirect effects were found in elderly participants (mediated proportion, 29.3%), females (13.3%), and people who did not consume alcohol (19.6%).
Conclusions: Metabolic risk factors may act as mediators in the relationship between chronic $PM_{2.5}$ exposure and depression. Treatment of metabolic risk factors may be an opportunity to reduce the burden of depression caused by long-term exposure to $PM_{2.5}$.

1. Introduction

Depression is a highly prevalent but poorly recognized illness (Herrman et al., 2022), with about 6% of the worldwide population encountering major depressive disorder annually (Kessler and Bromet, 2013; Malhi and Mann, 2018). Insights into the etiology of depression and its prevention remain a clinical and public health priority, in particular with increasing population exposure to adverse environmental conditions and the current absence of curative treatment (Herrman et al., 2022; Malhi and Mann, 2018).

Recently, the environmental determinants of depression have received increased attention, with air pollution (especially fine particulate matter [$PM_{2.5}$]) having the largest evidence. Short-term effects of air pollution on negative emotions are well understood (Benedetti et al., 2001; Kent et al., 2009; Xu et al., 2020) and intuitively perceived (e.g., effects of decreased visibility or strong odor or smog on people's mood (Li et al., 2019; Zhang et al., 2017; Zheng et al., 2019)). With regard to long-term effects of air pollution, recent epidemiological investigations have linked chronic exposure to $PM_{2.5}$ to a higher depression risk (Borroni et al., 2022; Braithwaite et al., 2019; Kioumourtzoglou et al., 2017; Shi et al., 2020; Wei et al., 2022; Yang et al., 2023; Zhang et al., 2019; Zijlema et al., 2016). However, the specific mechanism by which prolonged exposure to $PM_{2.5}$ causes depression remains elusive.

It has been well demonstrated that long-term exposure to $PM_{2.5}$ increases metabolic risks such as hypertension(Yang et al., 2018), dyslipidemia (Gaio et al., 2019), and diabetes (Liu et al., 2019). Additionally, a large body of research has established that metabolic risk factors are associated with the increased risk of depression (Akbaraly et al., 2011; Arango et al., 2021; Jeon et al., 2019; Pan et al., 2012). A recent umbrella review detected that metabolic factors were class I (convincing)-III (suggestive) risk factors for depressive disorders(Arango et al., 2021). From a mechanistic perspective, $PM_{2.5}$ leads to metabolic disturbances in the body through inflammatory processes, oxidative stress, and disruption of the autonomic nervous system (Al-Kindi et al., 2020; Brook et al., 2010). Further, metabolic disorders upregulate cytokine expression and contribute to cerebrovascular injury, which may induce depressive symptoms (Alexopoulos et al., 1997; Pan et al., 2012; Schiepers et al., 2005; Vykoukal and Davies, 2011). Therefore, it is plausible to hypothesize that metabolic risk factors are the potential pathway between long-term exposure to $PM_{2.5}$ and depression. To date, no epidemiological study has examined whether and to what extent metabolic risk factors play a mediating role in the relationship between chronic exposure to $PM_{2.5}$ and depression.

The current study aims to examine the mediating role of metabolic risk factors in the association of long-term exposure to $PM_{2.5}$ with depressive symptoms, as well as the changes in the strength of the mediating effect among different characteristics of individuals. We constructed a causal mediation analysis in a well-characterized prospective cohort in China. In addition, the measure of depressive symptoms relies on multidimensional symptoms that constitute a syndrome, including emotional, neurovegetative, and neurocognitive symptoms (Malhi and Mann, 2018). Considering that the three sub-domain symptoms may differ in terms of their underlying etiologies, comorbidities, and response to treatment (Majd et al., 2021; Vares et al., 2015), we further conducted mediation analyses on the three sub-domain symptoms of depression. With this study, we hope to provide not only important insight into the causal mechanism of $PM_{2.5}$-depression, but also to contribute to the development of public policy recommendations that can reduce the burden of depression.

2. Methods

2.1. Study participants

The current study utilized data collected during two waves of on-site surveys conducted in the China Multi-Ethnic Cohort (CMEC). Overall, CMEC aims to represent the general adult population in Southwest China. Comprehensive details regarding the CMEC are available elsewhere (Zhao et al., 2021). At wave 1, CMEC enrolled 99,556 participants aged 30–79 residing in Southwest China (five provinces). This recruitment was carried out utilizing a multi-stage, stratified cluster sampling approach, with data collection between May 2018 and September 2019. The estimated population response rate was approximately 60% (60–90% in rural areas and 40–60% in urban areas). All participants of wave 1 completed face-to-face interviews with the aid of tablets, comprehensive physical examinations, and clinical laboratory tests. Wave 2 was conducted between August 2020 and July 2021, approximately two years after wave 1. Multi-stage random sampling was applied to recruit 10% of the participants from wave 1, and these participants (n = 11,527) were invited to complete the same questionnaires, physical examinations, and clinical laboratory tests that had been used in wave 1. Prior to both surveys, informed consent was collected from every individual, and the Sichuan University Medical Ethics Review Committee gave its approval to the study (K2016038, K2020022).

The present study drew on participants who took part in both wave 1 and wave 2 on-site surveys. We excluded Tibetan residents because they lived in a particular environment with extremely high altitude (>3500 m above sea level), hypoxia, and deep cold. This extreme environment may impact the underlying mechanism pathway of "PM → metabolic risk factors → depression" (Beall, 2007; Bigham and Lee, 2014; Penaloza and Arias-Stella, 2007) and weaken the comparability between Tibetan residents and lowlanders. For example, Individuals living at high altitudes may exhibit specific circulatory, metabolic, and hematological adaptations (Beall, 2007; Bigham and Lee, 2014; Penaloza and Arias-Stella, 2007). We further excluded participants who 1) lived in Aba area due to their herding life without a permanent residence, 2) had incomplete address information or had been living at their current address for less than three years at the time of wave 1, 3) self-reported depression symptoms at wave 1, 4) had any physician-diagnosed mental illness, neurasthenia, traumatic brain injury or cancer, or 5) were pregnant, 6) had missing information on the outcome or covariates. After these exclusions, 7794 participants were examined in the following analyses (Supplementary Fig. S1).

To explore the mediating role of metabolic risk factors, we estimated the average of resident PM2.5 concentrations in the three years prior to the wave 1 survey, and then assessed metabolic risk factors at wave 1. Finally, the measurement of depressive symptoms was conducted at wave 2. Fig. 1 displays the timeline of study assessments and a directed acyclic graph visualizing associations between $PM_{2.5}$, metabolic risk factors, and depressive symptoms.

2.2. Fine particulate matter

The outdoor $PM_{2.5}$ data were sourced from the ChinaHighAirPollutants (CHAP) dataset (https://weijingrs.github.io/product.html, accessed July 9, 2020). As previously mentioned (Wei et al., 2020; Wei

et al., 2021), daily average PM2.5 concentrations, spatially resolved at a 1 km × 1 km scale, were produced using artificial intelligence techniques and satellite remote sensing. A Space-Time Extra-Trees (STET) model was proposed to estimate $PM_{2.5}$ concentrations. This model utilizes various data inputs, including the Moderate Resolution Imaging Spectroradiometer Multiangle Implementation of Atmospheric Correction AOD product, pollutant emissions, land use data, and meteorology variables. The 10-fold cross-validation (CV) displayed a good and steady prediction capacity of the STET model (R^2 = 0.90, root-mean-square error = 10.01 μg/m^3). To assess the influence of long-term exposure, we assigned 3-year average $PM_{2.5}$ concentrations before wave 1 to each participant, based on the geocoding of their home addresses.

2.3. Mediator assessment

Three main metabolic risk factors, including hypertension, diabetes, and dyslipidemia, were assessed at wave 1. Hypertension was identified as having systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or a self-reported diagnosis of hypertension at wave 1 (Liu, 2011). Dyslipidemia status of the participants was defined as total cholesterol ≥ 6.22 mmol/L, triglyceride ≥ 2.26 mmol/L, high-density lipoprotein cholesterol < 1.04 mmol/L, low-density lipoprotein cholesterol ≥ 4.14 mmol/L, or self-report of diagnosed hyperlipidemia at wave 1 (Joint committee for guideline revision, 2018). Diabetes was defined by the presence of any of the following: fasting plasma glucose ≥ 7.0 mmol/L, glycated hemoglobin ≥ 6.5%, or self-report of physician-diagnosed diabetes at wave 1 (American Diabetes Association, 2014). Detailed information on measuring these three metabolic risk factors is provided in Supplementary Section 1. Finally, we calculated the number of metabolic risk factors (0, 1, and ≥2 [as there were few participants with 3 risk factors]) identified at wave 1, which served as the mediating variable in the analysis.

2.4. Depressive symptoms

Depression symptoms were measured at wave 2 using the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001; Spitzer et al., 1999; Zimmerman, 2019), a tool designed for screening depression in primary healthcare settings(Negeri et al., 2021; Wang et al., 2014). The PHQ-9 consists of nine items, representing the emotional, neurovegetative, and neurocognitive domains of depression (Malhi and Mann, 2018; Spitzer et al., 1999; Zimmerman, 2019). Each item underwent assessment on a 4-point scale, spanning from 0 (indicating not at all) to 3 (representing nearly every day). In this study, the overall degree of depressive symptoms was quantified with the sum score for all nine items. Elevated scores on this scale denoted more pronounced and severe depressive symptoms. In addition to overall depressive symptoms, we also analyzed emotional symptoms (sum-score for the items of depressed mood, anhedonia, feelings of guilt/worthlessness, and tendency to commit suicide), neurovegetative symptoms (sum-score for the items of fatigue, sleep disturbance, and weight/appetite change), and neurocognitive symptoms (sum-score for the items of psychomotor retardation/agitation, and concentration problem).

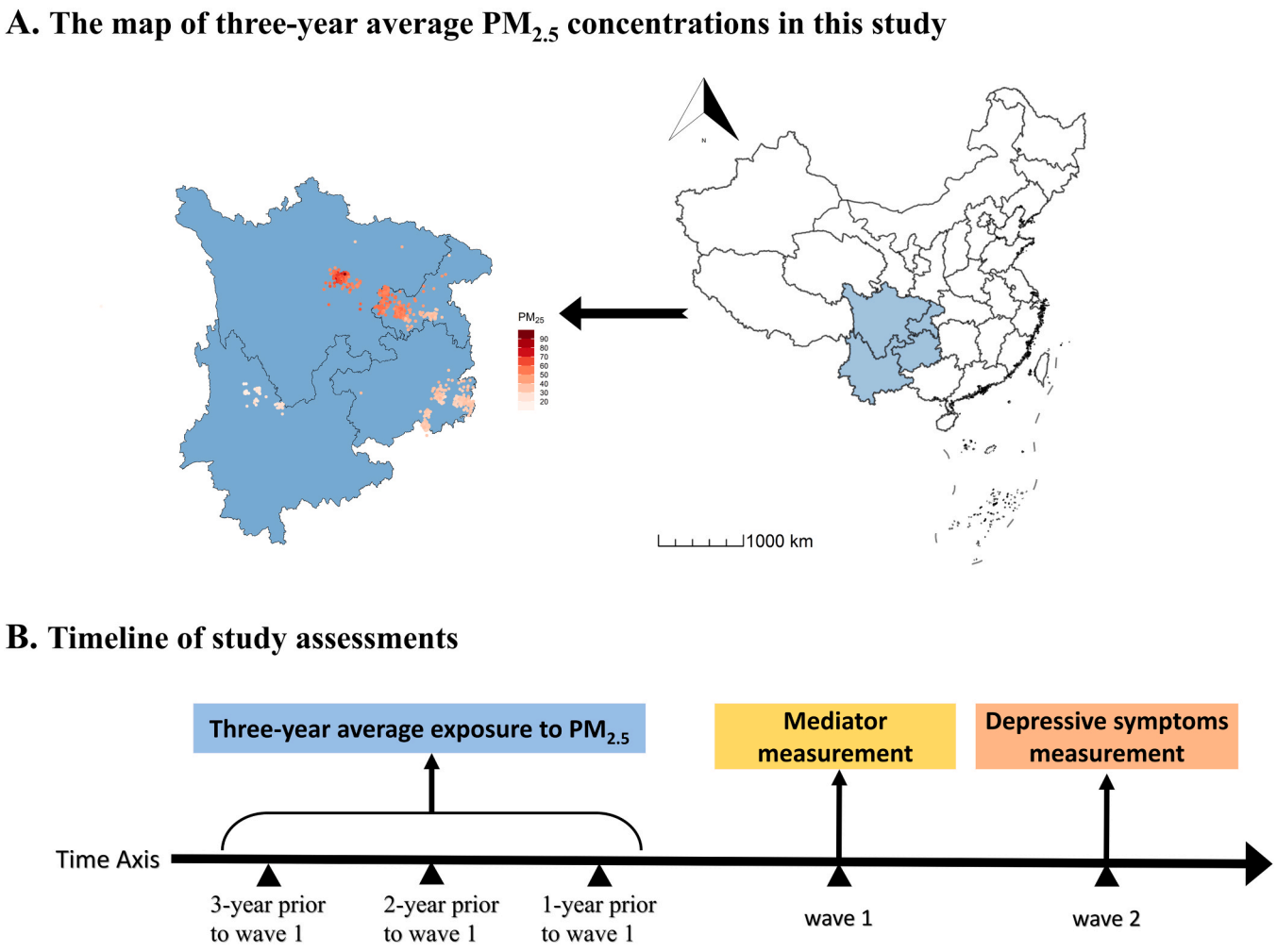

Fig. 1. The map of three-year average $PM_{2.5}$ concentrations and the timeline of study assessments.

2.5. Covariates

Drawing from earlier relevant research on the link between air pollution, cardiometabolic factors, and depression (Borroni et al., 2022; Braithwaite et al., 2019; Kioumourtzoglou et al., 2017; Lin et al., 2021; Shi et al., 2020; van Sloten et al., 2023; Wei et al., 2022; Yang et al., 2019; Yang et al., 2023; Zhang et al., 2019; Zijlema et al., 2016), we incorporated potential confounders into our analysis using directed acyclic graphs. Specifically, we considered age, gender, ethnicity, marriage status, education level, annual family income, smoking status, secondhand smoke status, alcohol consumption, dietary status, physical activity, indoor air pollution, body mass index (BMI), negative life events, region, and rural/urban areas. Details of all the confounders can be found in Supplementary Table S1.

2.6. Statistical analysis

Preliminary analyses explored the relationships between exposure ($PM_{2.5}$), mediators (hypertension, dyslipidemia, and diabetes), and outcomes (overall depressive symptoms, emotional symptoms, neurovegetative symptoms, and neurocognitive symptoms). Associations between exposures and the mediator were assessed with multinomial logistic regression models. Negative binomial regression models were used to analyze the relationships between exposure-outcome and mediator-outcome since PHQ-9 total and subscale scores were right-skewed (Fig. S2). Additionally, we investigated the exposure-outcome relationships using a restricted cubic spline with 4 knots (3 df) to assess the linearity trend.

This study performed causal mediation analyses to identify potential mechanisms in a hypothesized causal pathway between $PM_{2.5}$ and depressive symptoms. Based on a causal counterfactual framework, mediation analyses decomposed the total effect (TE) of chronic exposure to $PM_{2.5}$ on depression risk into natural direct effect (NDE) and natural indirect effect (NIE) (VanderWeele and Vansteelandt, 2009; Vansteelandt et al., 2012). The TE denotes the relative risk (RR_{TE}) of depressive symptoms associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations as compared with the pre-increase concentrations. The NDE can be interpreted as the relative risk (RR_{NDE}) of depressive symptoms associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations compared with pre-increase concentrations, with the mediator fixes at the potential value they would have been in the absence of $PM_{2.5}$ concentration increases. The NIE can be interpreted as the relative risk (RR_{NIE}) of depressive symptoms if the mediator changes from the value they would get under the 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration to the value they would get prior to $PM_{2.5}$ concentration increases, with the exposure concentration fixes. The proportion mediated (Hafeman, 2009) is calculated by $\frac{RR_{TE}-RR_{NDE}}{RR_{TE}-1}$. Mediation analysis was completed using natural effect models (Vansteelandt et al., 2012). In addition, effect modification by individual characteristics, education, and lifestyles was also investigated in the mediation approach. This moderation analysis aimed to determine whether the magnitude of the direct or indirect effects changed across sub-populations of people with different characteristics. To evaluate the significance of each modification effect, we conducted a likelihood ratio test to compare the model fit with and without the corresponding interaction terms. A Benjamini-Hochberg false discovery rate (FDR) was calculated to correct for multiple hypothesis testing. The detailed implementation of the mediation approach is given in Supplementary Section S2. All mediation analyses were completed by natural effect models using the *medflex* package (Steen et al., 2017) in R version 4.1.0. Confidence intervals of TE, NDE, and NIE estimations were estimated with a sandwich method. All causal mediation analysis relies on the following assumptions (VanderWeele and Vansteelandt, 2009; Vansteelandt et al., 2012): no unmeasured confounder of exposure-outcome, exposure-mediator, and mediator-outcome, and no mediator-outcome confounder affected by the exposure. As a sensitivity analysis, we calculated Evidence-for-causality values (E-values) to check the assumption of no unmeasured confounding in the mediation analysis (Ding and VanderWeele, 2016; VanderWeele and Ding, 2017). The E-value is defined as the least intensity of an unobserved confounder that needs to be associated with both the exposure and the outcome to nullify the study's findings, given the presence of all measured covariates.

2.7. Sensitivity analysis

We also performed the following sensitivity analyses. (a)We additionally allow for potential exposure–mediator interactions. (b)To assess the influence of the exposure windows, concentrations of $PM_{2.5}$ for 2- and 4-year averages before wave 1 were used. (c) Missing data rates for the study variables ranged from 0% to 2.8%. We also performed analysis on 100 datasets that had been multiply imputed via chained equations. (d) According to established guidelines (Kroenke et al., 2001; Wang et al., 2014), depressive symptoms were also categorized as a binary indicator, that probably depression (PHQ-9 score >=5) vs. no such indication (PHQ-9 score <5).

3. Results

3.1. Descriptive characteristics

Characteristics of study participants are displayed in Table 1. A total of 7794 eligible individuals were included in this study, with a mean age at wave 1 of 51.85 (standard deviation [SD]=10.74) years. Approximately 4666 (59.9%) participants were female, and 7039 (90.3%) were married or cohabiting. Participants in high $PM_{2.5}$ exposure areas had higher education and income, lower physical activity, and were more likely to consume alcohol or smoke. At wave 1, approximately 35.5% of the participants had one metabolic risk factor, and 18.6% had two or more metabolic risk factors. A map of three-year average $PM_{2.5}$ concentrations in this study is provided in Fig. 1.

3.2. Exploratory analyses

Exploratory analysis results of bivariate associations are shown in Supplementary Table S2. For the 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations, the relative risks (RR, *95%CI*) of the overall depressive symptoms, emotional symptoms, neurovegetative symptoms, and neurocognitive symptoms were 1.064 (1.014, 1.116), 1.099 (1.032, 1.170), 1.053 (1.005, 1.103), and 1.020 (0.939, 1.109), respectively. For mediator-outcome relationships, in comparison with participants without metabolic risk factors, the RR (*95%CI*) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was 1.091 (1.002, 1.188) for participants with 1 metabolic risk factor, and 1181 (1.056, 1.318) for those with 2 or more metabolic risk factors. Concerning mediator-outcome relationships, we found significant positive associations between metabolic risk factors and depressive symptoms, except for neurocognitive symptoms. As the number of metabolic risk factors increased, the relative risks of depressive symptoms increased gradually. Concentration-response curves show a roughly linear increased trend in depressive symptom scores (as well as emotional, neurovegetative, and neurocognitive symptom scores) with the increase in outdoor $PM_{2.5}$ exposure concentrations (Fig. 2).

3.3. Mediation analyses

The results of mediation analyses are displayed in Table 2. We observed that metabolic risk factors partially mediated the associations of $PM_{2.5}$ with depressive symptoms (overall and three symptom subdomain scores). The natural indirect effects of $PM_{2.5}$ on overall depressive symptoms and the three sub-domains were almost identical (RR, 1.003–1.004). Metabolic risk factors mediated approximately

Table 1
Characteristics of study participants, overall and stratified by $PM_{2.5}$ concentrations.

Variables	Participant group		
	overall	Individuals with low $PM_{2.5}$ exposure[a]	Individuals with High $PM_{2.5}$ exposure
Population	7794	3926	3868
Age at wave 1, mean (SD)	51.85 (10.74)	52.71 (9.75)	50.98 (11.60)
Sex, n (%)			
Male	3128 (40.1)	1317 (33.5)	1811 (46.8)
Female	4666 (59.9)	2609 (66.5)	2057 (53.2)
Marital status, n (%)			
Married/Cohabiting	7036 (90.3)	3542 (90.2)	3494 (90.3)
Never married/ Separated/Divorced/ Widowed	758 (9.7)	384 (9.8)	374 (9.7)
Education level, n (%)			
Illiteracy	1563 (20.1)	1244 (31.7)	319 (8.2)
Primary school	1789 (23.0)	1078 (27.5)	711 (18.4)
Junior high school	2244 (28.8)	1010 (25.7)	1234 (31.9)
High school	1132 (14.5)	342 (8.7)	790 (20.4)
Junior college and above	1066 (13.7)	252 (6.4)	814 (21.0)
Annual family income, yuan, n (%)			
< 12 000	1081 (13.9)	737 (18.8)	344 (8.9)
12 000–19 999	1190 (15.3)	763 (19.4)	427 (11.0)
20 000–59 999	2880 (37.0)	1555 (39.6)	1325 (34.3)
60 000–99 999	1347 (17.3)	469 (11.9)	878 (22.7)
≥ 100 000	1296 (16.6)	402 (10.2)	894 (23.1)
Smoking status, n (%)			
Never smoking	5900 (75.7)	3060 (77.9)	2840 (73.4)
Quit smoking	404 (5.2)	177 (4.5)	227 (5.9)
Smoking	1490 (19.1)	689 (17.5)	801 (20.7)
Secondary smoking, n (%)			
No	3836 (49.2)	1805 (46.0)	2031 (52.5)
Yes	3958 (50.8)	2121 (54.0)	1837 (47.5)
Indoor air pollution, n (%)			
Low	1324 (17.0)	633 (16.1)	691 (17.9)
Moderate	6211 (79.7)	3101 (79.0)	3110 (80.4)
High	259 (3.3)	192 (4.9)	67 (1.7)
Alcohol drinking status, n (%)			
Never	4287 (55.0)	2470 (62.9)	1817 (47.0)
Occasionally	2471 (31.7)	1026 (26.1)	1445 (37.4)
Regularly	1036 (13.3)	430 (11.0)	606 (15.7)
Negative life events, n (%)			
0	3924 (50.3)	2006 (51.1)	1918 (49.6)
1	2913 (37.4)	1467 (37.4)	1446 (37.4)
> =2	957 (12.3)	453 (11.5)	504 (13.0)
DASH diet index, mean (SD)	21.31 (4.38)	20.50 (4.02)	22.13 (4.57)
Physical activity, METs/d, mean (SD)	26.17 (17.73)	30.04 (19.15)	22.24 (15.18)
BMI, mean (SD)	24.33 (3.35)	24.30 (3.59)	24.36 (3.10)
Number of metabolic risk factors, n (%)			
0	3583 (46.0)	1712 (43.6)	1871 (48.4)
1	2764 (35.5)	1452 (37.0)	1312 (33.9)
> = 2	1447 (18.6)	762 (19.4)	685 (17.7)

Abbreviations: SD, standard deviation; METs, metabolic equivalent tasks; BMI, body mass index
[a] Less than or equal to the median (<= 49.16 μg/m^3) is defined as low $PM_{2.5}$ exposure and vice versa as high $PM_{2.5}$ exposure.

6.4%, 4.7%, 7.5%, and 14.0% of the associations of $PM_{2.5}$ with overall depressive, emotional, neurovegetative, and neurocognitive symptoms, respectively.

Fig. 3 (and Supplementary Table S3- S6) displays the moderation effects of the mediation associations for depression symptoms by individual characteristics, education, and lifestyle. Age, gender, education level, and alcohol and smoking status significantly moderated natural indirect effects and direct effects of $PM_{2.5}$ on overall depressive symptoms (likelihood ratio test for interaction, P int-values<0.02). We observed that natural indirect effects mediated by metabolic risk factors increased among subjects who were older, female, had lower education, and were non-drinking and non-smoking. Meanwhile, natural direct effects were attenuated in the respective sub-groups. After correction for multiple hypothesis testing using FDR, a significant natural indirect effect (P_FDR < 0.05) was detected in older age (RR 1.028 [95% CI 1.01,1.045]), females (1.013[1.005,1.022]) and non-drinking persons (1.018[1.007,1.029]). Among those, the mediated proportion reached up to 30%. Effect modifications for the three sub-domain symptoms were similar to those for overall depression symptoms.

3.4. Sensitivity analyses

In this study, the E-values of the associations of the exposure-outcome, the exposure-mediator, and the mediator-outcome ranged from 1.16 to 1.86. The results implied that the possibility of unmeasured confounding among the exposure, mediator, and outcome to distort the associations was slight (Supplementary Table S2). To test the statistical significance of exposure-mediator interactions, we used *P* values of the likelihood ratio statistic to compare model fit with and without exposure-mediator interaction term. The *P* values of the likelihood ratio statistic for the overall and three sub-domain depressive symptoms were 0.77, 0.81, 0.60, and 0.57, respectively, indicating the absence of exposure-mediator interaction. The total, natural direct and indirect effects of ambient $PM_{2.5}$ on depressive risk were similar when using different exposure windows (Table S7). The results of multiply imputed data were also consistent with the presented results (Table S8). In addition, when using a binary indicator (no depression, depression) as the outcome variable, we still observed that metabolic risk factors mediated approximately 6.7% of the association between ambient $PM_{2.5}$ and depression (Table S9).

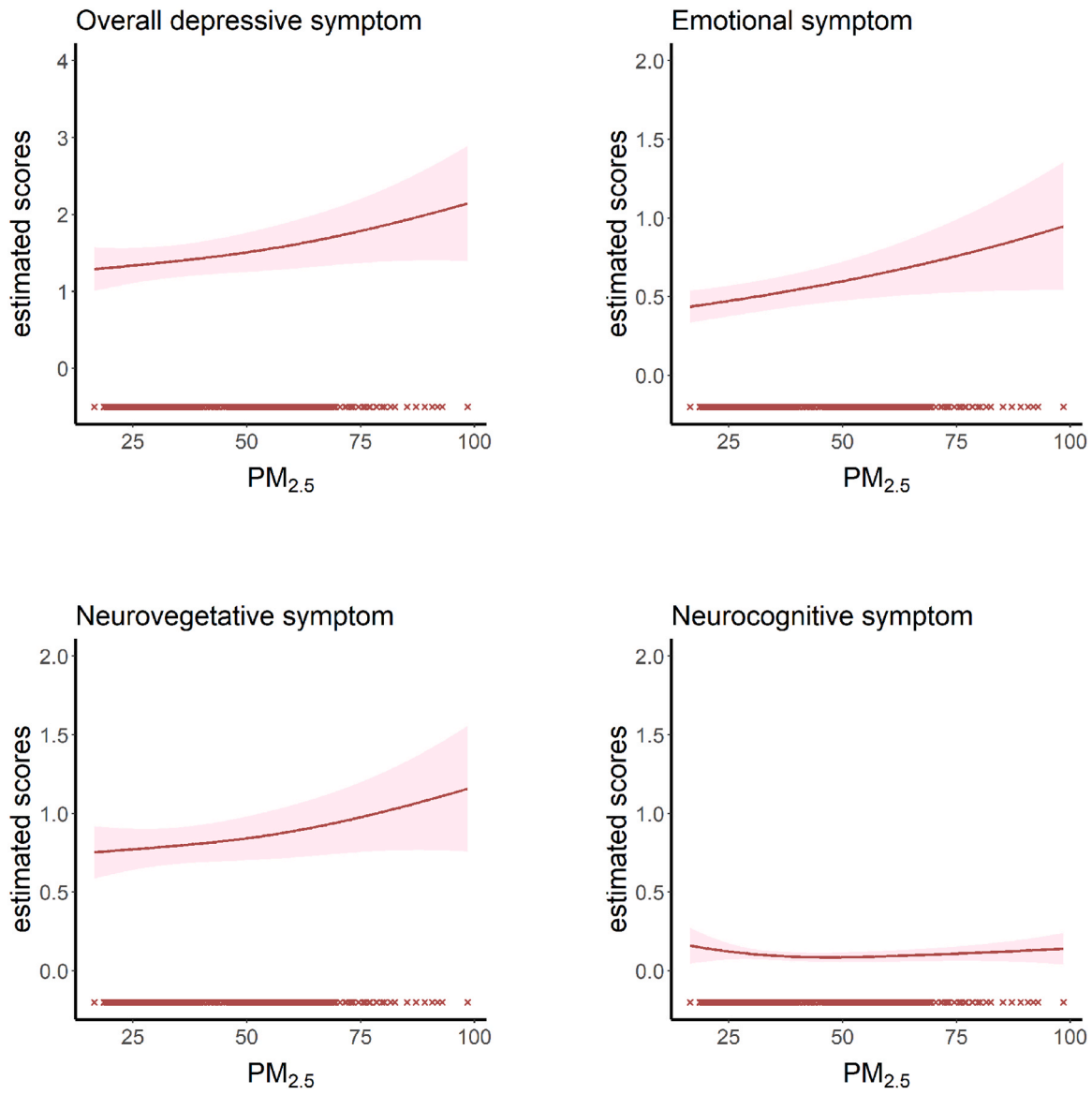

Fig. 2. Concentration-response curves regarding the association between long-term exposure to $PM_{2.5}$ and various types of depression symptom scores. The x-axis represents three-year average concentrations of ambient $PM_{2.5}$. The y-axis indicates estimated depression symptom scores after fixing all covariates at same levels.

4. Discussion

In this large, population-based cohort study, chronic exposure to $PM_{2.5}$ was positively associated with an increased risk of depressive symptoms. Among the three sub-types of depressive symptoms, $PM_{2.5}$ exposure exerted the most harmful effect in the emotional domain. We demonstrated that the positive effect of $PM_{2.5}$ on depressive symptoms was partially attributable to the mediating role of metabolic risk factors. Furthermore, metabolic risk factors had a stronger mediating effect in the elderly, females, and people abstaining from alcohol consumption.

This study found a positive association between long-term $PM_{2.5}$ exposure and the risk of overall depressive symptoms as well as the three sub-domain scores. To our knowledge, this is the first epidemiological study to examine the effects of PM2.5 on sub-domains of depression. Depression is a prevalent mental condition, characterized by symptoms in three domains (emotional, neurovegetative, and neurocognitive), forming a syndrome and causing functional impairment (Malhi and Mann, 2018). Symptoms in the emotional domain are more specific to depression, such as depressed mood, anhedonia, and feelings of worthlessness or guilt. In contrast, other symptoms, such as the neurovegetative domain (e.g., fatigue, weight loss, or insomnia), are broadly found in other psychiatric and medical disorders (Malhi et al., 2014). Interestingly, we observed the strongest harmful effects of long-term exposure to $PM_{2.5}$ on emotional symptoms. Since the consequences of emotional symptoms are more serious and may lead to self-harm or suicide, the higher risk of emotional disturbances induced by $PM_{2.5}$ exposure deserves to be taken seriously. This finding also strengthens previous evidence on the association between air pollution and depression by further specifying the direction of harmful effects.

Our study focused on the potential role of metabolic risk factors and implied that metabolic risk factors partially mediate the relationship between $PM_{2.5}$ and depression. There is some biological evidence of metabolic risk factors as an intermediate in the PM-depression pathway. Inhaled particulate matter can induce pro-inflammatory mediators, oxidative stress, and disruption of the autonomic nervous system, leading to metabolic disorders such as hypertension, hyperglycemia, and hyperlipidemia (Al-Kindi et al., 2020; Brook et al., 2010). Patients with metabolic disorders are often characterized by elevated inflammatory cytokines (Eckel et al., 2005). The "cytokine hypothesis of depression" proposes that these inflammatory cytokines play a crucial

Table 2
Total, natural direct and indirect effects of ambient $PM_{2.5}$ on depressive symptoms in mediation analysis.

Effect[a]	RR	95% CI	Proportion Explained (%)
Overall depressive symptoms			
NDE	1.059	(1.013, 1.109)	6.4
NIE	1.004	(1.001, 1.007)	
TE	1.064	(1.016, 1.113)	
Emotional symptoms			
NDE	1.094	(1.029, 1.164)	4.7
NIE	1.004	(1.001, 1.008)	
TE	1.099	(1.034, 1.168)	
Neurovegetative symptoms			
NDE	1.049	(1.002, 1.098)	7.5
NIE	1.004	(1.001, 1.007)	
TE	1.053	(1.005, 1.102)	
Neurocognitive symptoms			
NDE	1.017	(0.938, 1.104)	14.0
NIE	1.003	(0.999, 1.007)	
TE	1.020	(0.940, 1.107)	

Abbreviations: NDE, Natural Direct Effect; NIE, Natural Indirect Effect; TE, Total effect; CI Confidence Intervals.

[a] The effects were measured as the relative risk (RR) of depression associated with a 10 $\mu g/m^3$ increase in ambient PM2.5 concentrations.

role in regulating the behavioral, neuroendocrine, and neurochemical features of depression (Schiepers et al., 2005). Furthermore, metabolic risk factors could result in subclinical vascular impairment (Vykoukal and Davies, 2011). The vascular depression hypothesis suggests that vascular impairment in the brain may induce depressive symptoms (Alexopoulos et al., 1997). Other metabolic disturbances, including insulin-glucose homeostasis and adipokine synthesis and secretion, have also been associated with the pathophysiological mechanisms of depression (McIntyre et al., 2007).

Considering that the three sub-domain symptoms may be different in terms of their underlying etiologies, comorbidities, and response to treatment (Majd et al., 2021; Vares et al., 2015), we also conducted mediation analyses on the three sub-domain symptoms of depression. We found that metabolic risk factors explained approximately 5% of the association between $PM_{2.5}$ exposure and emotional symptoms. Previous studies have demonstrated that high levels of cholesterol could reduce the fluidity of cell membranes in the central nervous system, which may reduce or inhibit the release of 5-hydroxytryptamine (5-HT)(Papakostas et al., 2004). Individuals with lower levels of 5-HT are more likely to experience depressed emotions and anhedonia(Jenkins et al., 2016). In addition, this study found that metabolic risk factors have a higher mediating proportion (about 7.5%) concerning neurovegetative symptoms. Accumulating evidence shows that some metabolic biomarkers, such as leptin (a product of adipocytes), insulin, and vascular endothelial growth factors, could influence vegetative symptoms of depression (Caroleo et al., 2019).

The effect modification in the mediation analysis may help identify subgroups with a high magnitude of the mediation effect, thus aiding in developing targeted interventions. We observed that the mediation effect of metabolic risk factors between ambient $PM_{2.5}$ and depression risk was modulated by age, gender, education level, smoking status, and alcohol consumption. In this study, a significant natural indirect effect was found in female participants only. Prior evidence had suggested that biological factors (e.g., lung size, rate of air absorption, sex hormones), lifestyle, and activity patterns may contribute to this gender-based difference (Clougherty, 2010). Our study also showed a larger mediating effect in the elderly, which is in line with a previous study that reported stronger associations between $PM_{2.5}$ and metabolic risk factors in older adults (Eze et al., 2015; Yang et al., 2022). Interestingly, our study found that among those with healthy lifestyles, the $PM_{2.5}$-induced depressive risk was mediated to a greater extent by metabolic risk factors. One reason could be that people with healthy lifestyles may be more concerned about their disease status and more likely to be depressed by their illness. Another possible explanation is that the effects of air pollution on metabolism are greater in this subgroup due to the absence of other lifestyle-induced risk factors.

Causal mediation analysis helps to understand the causal pathways from exposure to disease outcome, thereby offering critical insights into disease etiology and pathophysiology. At the public health level, mediation analysis informs the development of targeted medical and public health interventions by identifying critical mediators in the causal pathway. The current study underscores the mediating role of metabolic risk factors in the causal pathway between $PM_{2.5}$ and depressive symptoms. The proportion of the association between PM2.5 and the depressive risk mediated by metabolic risk factors can be up to 30% in some specific populations. These findings could provide valuable insights for the development of prevention strategies for depression. As metabolic risk factors have effective preventive and management measures, efforts to reduce metabolic risk factors may have a valuable gain in preventing the occurrence and development of depression. On the other hand, the disease burden caused by air pollution is not negligible. Air pollution is ranked as the fourth leading risk factor for mortality worldwide, responsible for approximately 6.67 million deaths in 2019 (GBD, 2019 Risk Factors Collaborators, 2020). Given the pervasiveness of the air pollution effect, reducing the disease burden of air pollution is a daunting challenge. There is an urgent need for governments around the world to develop effective prevention and intervention policies to reduce air pollution exposure levels. People, especially vulnerable populations, should prioritize personal protective measures.

This study has several strengths. It features a prospective design including exposure data collection three years prior to wave 1, mediators' collection in wave 1, and outcomes' collection in wave 2. Moreover, this study also divided symptoms assessed with the PHQ-9 scale into three sub-dimensions: emotional, neurovegetative, and neurocognitive. As there are differences in the underlying etiology, course, and treatment response of different dimensions, investigating different dimensions can provide a more targeted reference for the development of interventions (Vares et al., 2015).

Our study also has several limitations that warrant mentioning. First, we assessed residential pollutant concentrations as a proxy for participants' air pollution exposure levels without considering individual behavior patterns, which may result in exposure measurement bias. Second, outcome measures were based on self-report (PHQ-9) rather than clinical diagnoses. However, PHQ-9 is a valid and reliable screening tool in primary care or large-scale population surveys with low costs and good acceptability (Herrman et al., 2022). Finally, although this study adequately adjusted for confounders based on the literature review, unmeasured confounders, including antidepressant medication use and family history of depression, may still play a role. To deal with this problem, this study also assessed the effect of potential unmeasured confounding, with the result indicating that the probability of unmeasured confounder distorting the study's association appeared to be relatively low.

5. Conclusion

Our study found a positive relationship between chronic exposure to ambient $PM_{2.5}$ and depressive symptoms. The association between $PM_{2.5}$ and depressive symptoms appears to be partially mediated through the presence of metabolic risk factors. Our study provided novel insights into the mechanisms underlying the association between $PM_{2.5}$ and depressive symptoms. Optimizing treatment of metabolic risk factors may, to some extent, contribute to the reduction of the depressive burden induced by long-term exposure to $PM_{2.5}$, especially among the elderly, women, and people with healthy lifestyles.

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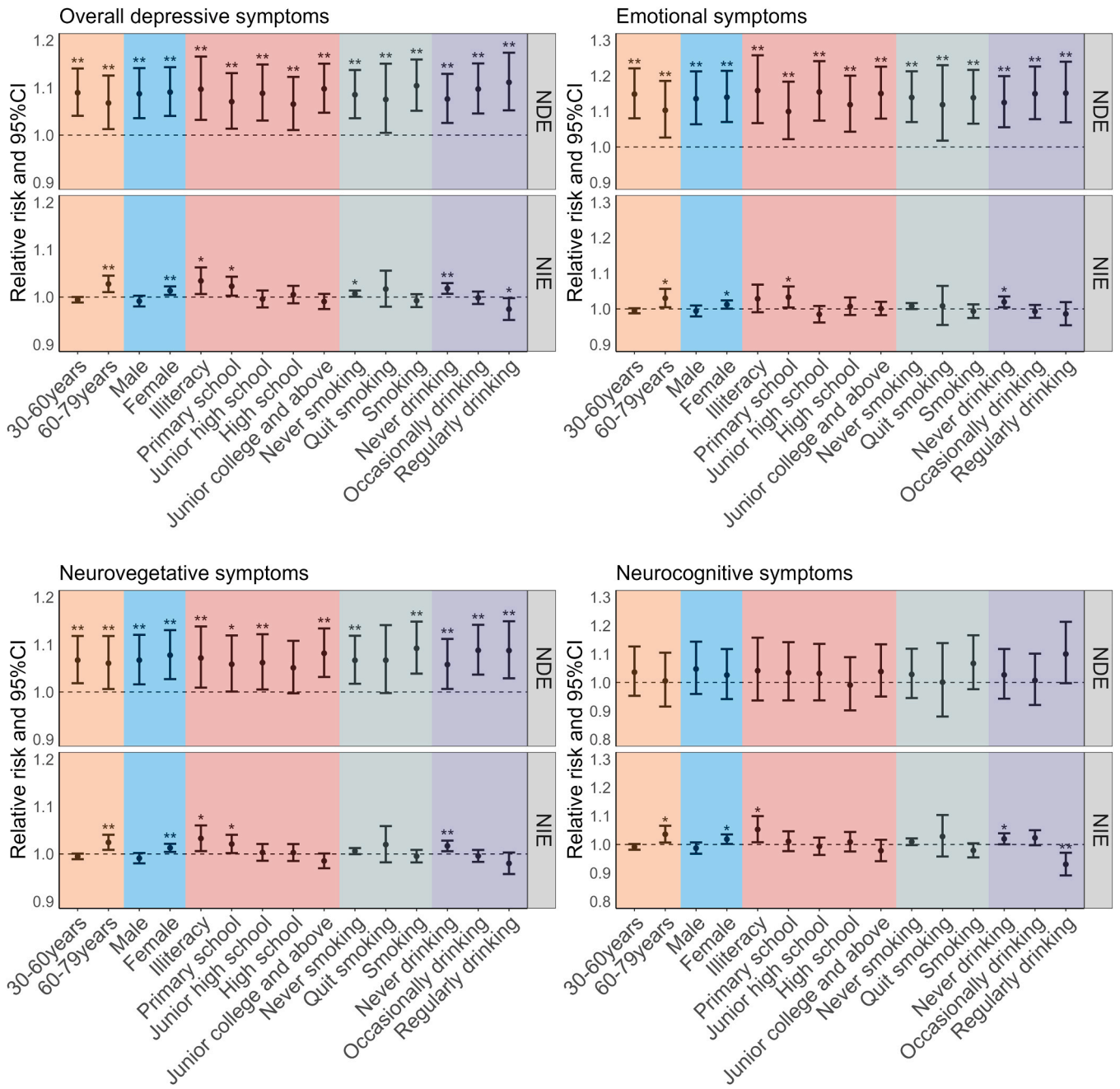

Fig. 3. Effect modification by individual characteristics, education, and lifestyle in mediation analysis of various types of depression symptom scores. The effects were measured as relative risk (RR) of depression associated with a 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ concentrations. Abbreviations: NDE, Natural Direct Effect; NIE, Natural Indirect Effect. "* " indicated the P value < 0.05. "* " indicated the P_FDR value < 0.05.

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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

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.115839.

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