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Original Research

Synergistic air pollution exposure elevates depression risk: A cohort study

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ABSTRACT

Depression is a leading mental health disorder worldwide, contributing substantially to the global disease burden. While emerging evidence suggests links between specific air pollutants and depression, the potential interactions among multiple pollutants remain underexplored. Here we show the influence of six common air pollutants on depressive symptoms among middle-aged and older Chinese adults. In single-pollutant models, a 10 μg m^{-3} increase in SO_2, CO, PM_{10}, and $PM_{2.5}$ is associated with increased risks of depressive symptoms, with odds ratios (95% confidence intervals) of 1.276 (1.238–1.315), 1.007 (1.006–1.008), 1.066 (1.055–1.078), and 1.130 (1.108–1.153), respectively. In two-pollutant models, SO_2 remains significantly associated with depressive symptoms after adjusting for other pollutants. Multi-pollutant models uncover synergistic effects, with SO_2, CO, NO_2, PM_{10}, and $PM_{2.5}$ exhibiting significant interactions, identifying SO_2 as the primary driver of these associations. Mediation analyses further indicate that cognitive and physical impairments partially mediate the relationship between air pollution and depressive symptoms. These findings underscore the critical mental health impacts of air pollution and highlight the need for integrated air quality management strategies. Targeted mitigation of specific pollutants, particularly SO_2, is expected to significantly enhance public mental health outcomes.

1. Introduction

Air pollution significantly contributes to the worldwide disease burden as a major environmental factor, causing the premature demise of more than 4.2 million individuals annually across the globe, of whom approximately 89% are from economically underdeveloped countries [1]. Previous studies have confirmed connections between exposure to air pollutants and various health issues, including cardiovascular, respiratory, and kidney diseases [2–4]. However, research into the possible associations between air pollution and psychiatric disorders remains nascent. Depression, a prevalent mental health disorder, has been estimated by the World Health Organization to affect approximately 5% of the global population. In addition, it is a major cause of suicide, which accounts for more than 700,000 deaths annually, highlighting its impact on public health [5]. Moreover, from 2010 to 2018, the financial impact of major depressive disorder (MDD) on adults from the United States increased by 37.9%, that is, $236.6–326.2 billion in 2020 dollars [6]. Considering the significant economic burden of depression, a deeper understanding of environmental factors, particularly those that can be modified, is crucial for effective disease control and prevention.

Epidemiologic research increasingly points to a correlation between air pollution and psychological health issues [7–9]. Short-term exposure to air pollutants has been linked to increased rates of depression-related hospitalization or outpatient visits [10–12]. However, evidence regarding its long-term effects is less conclusive, with conflicting results reported. A prospective cohort investigation in the United States revealed that exposures to $PM_{2.5}$ and O_3 might increase the likelihood of depression among middle-aged and older women [13]. A similar correlation was observed in another longitudinal study conducted among the insured elderly population in the United States [14]. However, a meta-analysis

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revealed that exposures to SO_2, $PM_{2.5}$, and PM_{10} showed no association with depression [15]. A scarcity of research has investigated the prolonged impacts of air contaminants on the prevalence of depressive disorder in the broader populace [16–18]. Furthermore, the bulk of previous investigations have focused on single air pollutants. Therefore, a comprehensive assessment that considers both particulate matter and gaseous pollutants is essential owing to the complex composition of ambient air pollution.

Although the exact mechanism that links air pollutants to depressive disorders remains largely unclear, experimental studies have suggested a possible connection between oxidative stress and inflammatory responses within the nervous system [19–22]. Several epidemiological investigations have examined the potential mediating roles of fecal short-chain fatty acids, gut microbiota, metabolic risk factors, prefrontal cortex, and insula in the relationship between chronic exposure to air pollutants and depression [23–25]. However, the mediating effects of sleep duration, cognitive function, activities of daily living (ADL), and instrumental activities of daily living (IADL) on the development of depression caused by air pollution have been largely overlooked. Cognitive impairment is a common symptom in patients with depression, and research has indicated that it may be exacerbated by air pollution [26,27]. Exposure to air pollutants, both in the short and long term, may disrupt sleep patterns and cognitive functions via increased oxidative stress and neurotransmitter imbalances, which are mechanisms that parallel those implicated in the development of depressive disorders [28–30]. Furthermore, the capacity to perform daily living tasks is linked to mental health and can be affected by environmental factors such as air quality [31–33]. In light of the potential causal chain between the aforementioned factors and depressive mood caused by air pollution, further research, especially focusing on cognitive and physical performance, is necessary to identify potential mediators.

Given these literature gaps, our aims in this study were (1) to evaluate the associations between exposure to single, dual, and multiple air pollutants and depressive symptoms using a large representative national prospective cohort dataset; (2) to identify the primary pollutants that contribute to depressive symptoms; and (3) to investigate the underlying processes through mediation analysis. The insights gained from this study could provide valuable information on the relationship between exposure to air contaminants and the prevalence of depressive symptoms in China.

2. Methods

2.1. Study population

This study was based on data from the China Health and Retirement Longitudinal Study (CHARLS), a comprehensive and ongoing longitudinal survey that targets the Chinese population aged 45 years and older. CHARLS employs a multistage stratified probability-proportional-to-size sampling method to select participants from 150 districts or counties and 450 urban settlements or villages across 28 provinces, ensuring a representative sample. The sampling procedures and comprehensive study design are explained in detail in previous documentation [34]. The initial investigation, which involved 17,708 respondents, was performed between June 2011 and March 2012. Follow-ups were conducted every 2–3 years, and a limited number of new participants were recruited from each subsequent survey. Since the baseline, four follow-up surveys have been conducted in the years 2013, 2015, 2018, and 2020. The data used in this study is accessible at https://charls.pku.edu.cn/.

For the current analysis, we examined a seven-year dynamic cohort of CHARLS data ranging from the second wave in 2013 to the fifth wave in 2020. Participants were excluded from the study if they (1) attended fewer than two follow-up visits, (2) were younger than 45 years, (3) had a diagnosis of depressive symptoms at baseline, or (4) had missing data for the primary variables. Following these exclusion criteria, the final dataset for analysis encompassed 12,389 participants (for further details, see Supplementary Material Fig. S1).

2.2. Assessment of depressive symptoms

A 10-item questionnaire from the Center for Epidemiologic Studies-Depression (CESD) was used to evaluate symptoms of depression. The participants were requested to report the frequency with which they experienced each item during the week preceding the survey. Responses to the questionnaire were based on a 4-point Likert scale defined as follows: 0 (never or seldom, less than 1 day), 1 (some or a little of the time, 1–2 days), 2 (occasionally or a moderate amount of the time, 3–4 days), or 3 (most or all of the time, 5–7 days). The scale ranged from 0 to 30, with lower ratings corresponding to milder symptoms. For the purposes of this study, participants with scores of 10 or higher were classified as exhibiting depressed symptoms. Previous research has demonstrated that this threshold exhibits reasonable sensitivity and specificity in the Chinese elderly population [35,36].

2.3. Exposure assessment

Ground-level concentrations of CO, O_3, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ were sourced from the ChinaHighAirPollutants (CHAP) datasets, publicly available at https://weijing-rs.github.io/product.html. CHAP data are produced using the space-time extremely randomized trees model, which integrates large database sources such as satellite retrievers, model simulations such as emission inventory, land-use data, topographical information, meteorological data, and aerosol optical depth (AOD). Atmospheric correction techniques were used at multiple angles to extract AOD data from a moderate-resolution image spectroradiometer. In this study, the yearly mean PM_{10} [37] and $PM_{2.5}$ levels [38,39] at a spatial resolution of 0.01° (approximately 1 km) and the yearly mean concentrations of SO_2 [40], NO_2 [41], CO [40], and O_3 [42] at 0.1° (roughly 10 km) were used in the analysis. These datasets underwent rigorous cross-validation procedures, demonstrating high accuracy, with tenfold cross-validation reliability coefficients ranging from 0.80 to 0.92. Owing to privacy considerations, the participants' residential addresses were not made publicly available. Therefore, in our analysis, we estimated air pollution exposure at the city level by linking participants to 126 prefectural cities. For each participant, the exposure to air pollution was measured as the annual mean ambient air pollution level from the year the participant entered the cohort until the onset of depressive symptoms or the end of the follow-up period, whichever came first.

2.4. Mediator assessment

This study considered sleep hours (as a continuous variable), cognitive function (score range, 0–31), ADL (yes or no), and IADL (yes or no) as possible mediators in the mediation analyses. Cognitive function was evaluated using the following measures: immediate word recall (0–10 point), delayed word recall (0–10 point), identification of current date (month, day, year, and season) and day of the week (0–5 point), figure redrawing (0–1 point), and serial subtraction tasks (0–5 point). Higher scores reflect better cognitive function, with the total score ranging from 0 to 31. ADL encompassed basic self-care activities, including difficulty eating, bathing, dressing, toileting, walking, and transferring in and out of

bed. IADL included more complex daily tasks such as performing domestic chores, cooking, shopping, making phone calls, managing finances, and administering medication. Responses to the questions on ADL and IADL were rated on a 4-point scale from 1 (no difficulty) to 4 (unable to perform), with the aggregate score ranging from 6 to 24. Participants who registered higher scores were deemed to have functional impairments.

2.5. Covariates

Drawing from previous research [43,44], the following covariates were selected for analysis. The demographic covariates encompassed sex (female and male) and age. The socioeconomic factors consisted of urbanicity (urban and rural), marital status (never married, divorced/separated/widowed, and married/partnered), educational level (primary school or lower, or middle school or higher), employment status (employed or unemployed), and income (income positive or income zero). The health behavior variables included drinking status (drinker or non-drinker) and smoking status (smoker or non-smoker). In addition, social activity participation (yes or no) was also included in the analysis.

2.6. Statistical analyses

Means and standard deviations (SDs) were used to describe continuous variables, while percentages and frequencies were applied to categorical variables. The chi-square test was used to compare the categorical variables, and the *t*-test was applied for the continuous variables to evaluate differences in the distributions of the variables between individuals with and without depressive symptoms. A Pearson correlation analysis was performed to investigate the associations between all exposure variables.

In the primary analysis, logistic regression was applied to examine the correlation between individual air contaminants and depressive symptoms. Odds ratios (ORs) were presented with their corresponding 95% CIs. Air pollutant concentrations were introduced into the logistic regression model as both continuous and categorical variables, categorized into quartiles as follows: Q1 (reference), Q2, Q3, and Q4. Three models were constructed: (1) Model 1, an unadjusted model; (2) Model 2, adjusted for age and sex; and (3) Model 3, a fully adjusted model, which included additional adjustments for educational level, marital status, alcohol consumption, urbanicity, smoking status, social activity, and employment status. To identify potential effect modifiers, stratified analyses were performed based on sex (males or females) and age group (45–59 years and 60 years or older). In addition, potential nonlinear correlations between exposure to each air pollutant and depressive symptoms were simulated using a restricted cubic spline. We then examined two pollutant models, each time adjusting for one additional air pollutant in the regression models. The variance inflation factor (VIF) was used to detect multicollinearity, revealing significant collinearity between $PM_{2.5}$ and PM_{10}, while the multicollinearity between the other pairs of pollutants was weak or nonexistent (Supplementary Material Table S1). The quantile-based *g*-computation (qgcomp) model [45], a multi-pollutant analysis approach, was used to evaluate the combined effect of air pollutants on depressive symptoms and determine each pollutant's individual contribution. The qgcomp model estimates the combined impact of raising all exposures by one quantile simultaneously, capturing a "mixture effect" that is particularly relevant for air pollution mixture exposure. This method overcomes the limitations of the traditional weighted quantile sum regression model by not assuming a unidirectional relationship and accommodating the nonlinear characteristics of joint exposures. CO, O_3, SO_2, NO_2, PM_{10}, and $PM_{2.5}$ were incorporated into the multi-pollutant analysis, with adjustments made for all covariates, as in the primary analysis. Binomial distributions were specified as a link function. The quantile indicator was set to 4, and the 95% CIs were calculated using 500 bootstrap resamples. Similarly, the VIF was used again to test the collinearity in the multi-pollutant model, and the VIF results showed that $PM_{2.5}$ and PM_{10} had considerable multicollinearity problems (Supplementary Material Table S2). To address this, we conducted mixture analyses, both with $PM_{2.5}$ and PM_{10} included simultaneously and with each included individually. Finally, mediation analyses were performed using functions developed within the "mediation" R package, employing quasi-Bayesian Monte Carlo simulation techniques with 1000 iterations.

Four sensitivity analyses were performed to affirm the robustness of the main outcomes. First, using repeated measurements of depressive symptom scores as the dependent variable, the linear mixed-effects model was used to examine the impact of air pollutants on depression scores, with all covariates adjusted. Second, the same data were substituted into the qgcomp model for repeating the main analysis. Third, further adjustments were performed for medical history, including self-reported conditions at baseline, such as diabetes, hypertension, asthma, arthritis, heart problems, digestive disease, liver disease, kidney disease, lung disease, and stroke, to control potential confounders. The total number of conditions was calculated and grouped into categories of 0 condition, 1 condition, and $\geq$2 conditions. Finally, to mitigate the impact of reverse causation, cases of depressive symptoms occurring within the initial two years of follow-up were excluded from the analysis. All statistical analyses were conducted in R v4.2.1 (R Development Core Team), and a two-tailed P value < 0.05 was considered to indicate statistical significance.

3. Results

This study involved 12,389 participants from the second to the fifth wave of CHARLS, encompassing 28 provinces across China. The participants' geographic distribution is illustrated in Fig. S2 (Supplementary Material). Over a median follow-up period of five years, 5830 new cases of depressive symptoms were identified. The basic characteristics of the participants are presented in Table 1, with a mean (±SD) age of 57.77 ± 9.42 years. Among all participants, 46.96% were female, and 48.76% and 44.61% were current alcohol drinkers and smokers at baseline, respectively. During the follow-up period, individuals who developed depressive symptoms were more inclined to be female, reside in rural areas, be single or separated/divorced, be nonsmokers, be nondrinkers, show less engagement in social activities, and have lower educational levels.

Fig. S3 (Supplementary Material) depicts the mean annual exposure concentrations of six pollutants for the study participants from 2013 to 2020. Overall, a general decreasing trend was observed in the mean exposure concentrations of all contaminants except for O_3. Table S3 and Fig. S4 (Supplementary Materials) display the statistical descriptions of the assumed exposure concentrations of air pollutants for all participants and the results of the Pearson correlation analysis, respectively. The mean (±SD) exposure concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 were 53.55 ± 18.89, 92.66 ± 34.42, 24.12 ± 12.26, 33.83 ± 10.60, 1.07 ± 0.33, and 89.92 ± 11.35 μg m^{-3}, respectively. The annual means for $PM_{2.5}$ and PM_{10} exceeded the guidelines established by the World Health Organization (Air Quality Guidelines 2021, $PM_{2.5}$: 5 μg m^{-3}, PM_{10}: 10 μg m^{-3}) and the secondary standard of the Chinese ambient air quality guideline (GB 3095–2012, $PM_{2.5}$: 35 μg m^{-3}, PM_{10}: 70 μg m^{-3}). The correlation between PM_{10} and $PM_{2.5}$ was particularly strong, with a high coefficient of 0.94. By contrast, the correlations between O_3 and the other five air

Table 1
Basic characteristics of participants according to depressive symptoms.

Characteristics	Total (n = 12,389)	CES-D < 10 (n = 6559)	CES-D ≥ 10 (n = 5830)	Statistic	P value
Age, Mean ± SD	57.77 ± 9.42	57.93 ± 9.70	57.59 ± 9.09	t = 2.03	0.043
Sex, n (%)	-	-	-	χ^2 = 214.59	<0.001
Male	6571 (53.04)	3885 (59.23)	2686 (46.07)	-	-
Female	5818 (46.96)	2674 (40.77)	3144 (53.93)	-	-
Urbanicity, n (%)	-	-	-	χ^2 = 140.75	<0.001
Urban	5259 (42.45)	3110 (47.42)	2149 (36.86)	-	-
Rural	7130 (57.55)	3449 (52.58)	3681 (63.14)	-	-
Education level, n (%)	-	-	-	χ^2 = 36.00	<0.001
Primary school or below	8015 (64.69)	4084 (62.27)	3931 (67.43)	-	-
Middle school or above	4374 (35.31)	2475 (37.73)	1899 (32.57)	-	-
Marital status, n (%)	-	-	-	χ^2 = 9.34	0.009
Married/partnered	11,264 (90.92)	5981 (91.19)	5283 (90.62)	-	-
Divorced/separated/widowed	1056 (8.52)	554 (8.45)	502 (8.61)	-	-
Never married	69 (0.56)	24 (0.37)	45 (0.77)	-	-
Employment status, n (%)	-	-	-	χ^2 = 12.14	<0.001
Unemployed	3578 (28.88)	1982 (30.22)	1596 (27.38)	-	-
Employed	8811 (71.12)	4577 (69.78)	4234 (72.62)	-	-
Income, n (%)	-	-	-	χ^2 = 39.20	<0.001
No	8750 (70.63)	4474 (68.21)	4276 (73.34)	-	-
Yes	3639 (29.37)	2085 (31.79)	1554 (26.66)	-	-
Smoking status, n (%)	-	-	-	χ^2 = 79.92	<0.001
Non-smoker	6862 (55.39)	3386 (51.62)	3476 (59.62)	-	-
Smoker	5527 (44.61)	3173 (48.38)	2354 (40.38)	-	-
Drinking status, n (%)	-	-	-	χ^2 = 62.06	<0.001
Non-drinker	6348 (51.24)	3142 (47.90)	3206 (54.99)	-	-
Drinker	6041 (48.76)	3417 (52.10)	2624 (45.01)	-	-
Social activity, n (%)	-	-	-	χ^2 = 8.93	0.003
No	5399 (43.58)	2776 (42.32)	2623 (44.99)	-	-
Yes	6990 (56.42)	3783 (57.68)	3207 (55.01)	-	-

Note: CES-D, Center for Epidemiologic Studies Depression.

pollutants were relatively weak. Moreover, the correlation coefficients between the other pollutants ranged from 0.09 to 0.74.

Table 2 presents the estimates of the single-pollutant models when air pollutant concentrations were treated as continuous variables. Statistically significant correlations were observed between $PM_{2.5}$, PM_{10}, SO_2, and CO and the depressive symptoms. Although the relationship between NO_2 and depressive symptoms was consistently positive across all models, it was not consistently statistically significant. However, O_3 demonstrated a negative relationship with the occurrence of depressive symptoms. In the primary model, the ORs (95% CIs) for depressive symptoms associated with a 10 μg m^{-3} increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 were 1.130 (1.108–1.153), 1.066 (1.055–1.078), 1.276 (1.238–1.315), 1.019 (0.985–1.054), 1.007 (1.006–1.008), and 0.732 (0.708–0.757), respectively. The risk of depressive symptoms corresponding to the air pollutant quartiles is illustrated in Fig. 1. Consistently, compared with the first quartile, the risk of depressive symptoms increased in the highest quartile of $PM_{2.5}$ (OR: 1.838, 95% CI: 1.657–2.038), the third quartile of PM_{10} (OR: 1.746, 95% CI: 1.575–1.935), the highest quartile of SO_2 (OR: 1.986, 95% CI: 1.789–2.204), and the highest quartile of CO (OR: 1.606, 95% CI: 1.657–2.038) in the completely adjusted model, with all P values being <0.05.

Fig. 2 depicts the exposure-response (E-R) relationships for all pollutants related to depressive symptoms. The data indicated that the relationships between PM_{10} and SO_2 with depressive symptoms were nearly linear, with no evident thresholds (Fig. 2b, e). By contrast, for $PM_{2.5}$ and CO, the curves remained relatively flat at lower concentrations but dramatically increased beyond 52 μg m^{-3} for $PM_{2.5}$ and 1 mg m^{-3} for CO, displaying J-shaped patterns (Fig. 2a, d). The curve for NO_2 presented an inflection point, with a gradual decline in risk below 33 μg m^{-3}, followed by an inverted curve as the concentration continued to increase (Fig. 2c). Regarding O_3, the curve demonstrated a reversed J-shape, showing a sharper incline below 90 μg m^{-3} but tended to plateau at higher concentrations (Fig. 2f).

Table 2
Associations between per 10 μg m^{-3} increase in CO, O_3, NO_2, SO_2, $PM_{2.5}$, and PM_{10} and depressive symptoms risk in single-pollutant models.

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
$PM_{2.5}$	1.131 (1.110, 1.153)	<0.001	1.132 (1.110, 1.154)	<0.001	1.130 (1.108, 1.153)	<0.001
PM_{10}	1.067 (1.056, 1.078)	<0.001	1.067 (1.056, 1.078)	<0.001	1.066 (1.055, 1.078)	<0.001
NO_2	1.004 (0.971, 1.038)	0.812	1.000 (0.967, 1.034)	0.983	1.019 (0.985, 1.054)	0.281
SO_2	1.292 (1.255, 1.330)	<0.001	1.293 (1.256, 1.332)	<0.001	1.276 (1.238, 1.315)	<0.001
CO	1.007 (1.006, 1.008)	<0.001	1.007 (1.006, 1.008)	<0.001	1.007 (1.006, 1.008)	<0.001
O_3	0.730 (0.707, 0.754)	<0.001	0.725 (0.701, 0.749)	<0.001	0.732 (0.708, 0.757)	<0.001

Note.
1. Model 1: The crude model.
2. Model 2: The base model, adjusted for age at baseline and sex.
3. Model 3: The main model, further adjusted for educational level, marital status, employment status, urbanicity, cigarette smoking, alcohol drinking, and social activity.
4. OR, odds ratio. CI, confidence interval.

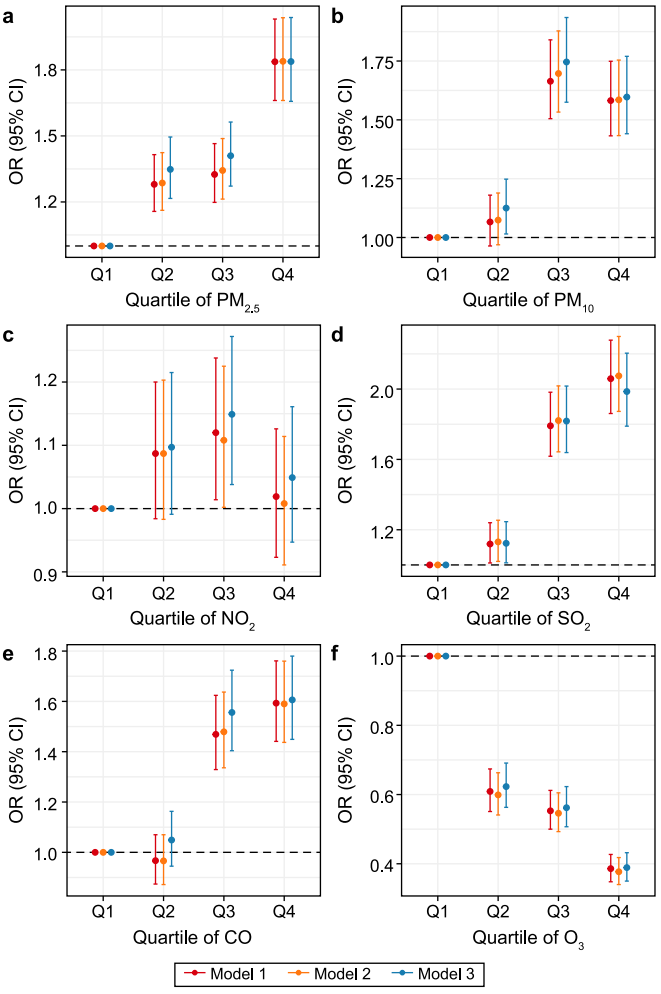

Fig. 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between long-term air pollution exposure and incidence of depressive symptoms. **a**, $PM_{2.5}$. **b**, PM_{10}. **c**, NO_2. **d**, SO_2. **e**, CO. **f**, O_3.

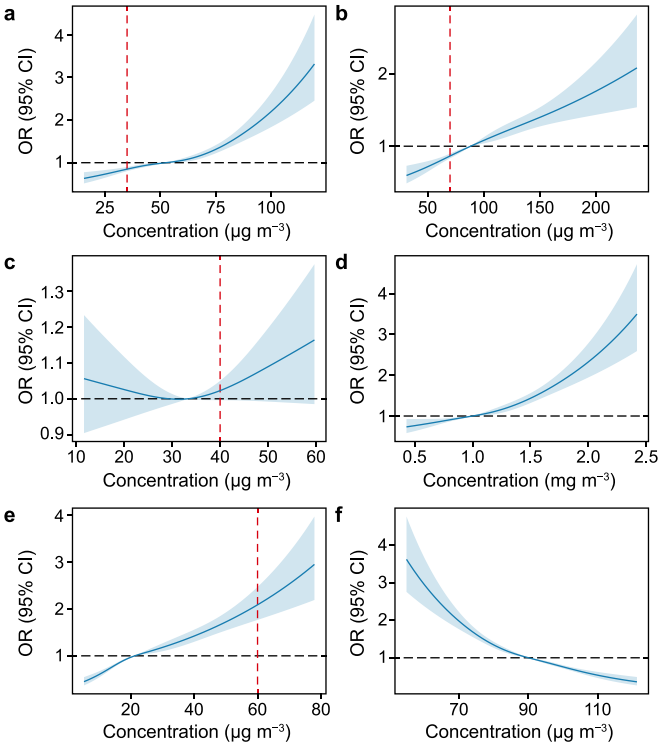

Fig. 2. The exposure-response relationships between air pollutants and depressive symptoms. **a**, $PM_{2.5}$. **b**, PM_{10}. **c**, NO_2. **d**, CO. **e**, SO_2. **f**, O_3. The red vertical dotted line reflects the air quality thresholds set by Chinese national standards, with matching amounts set at 60 μg m^{-3} for SO_2, 40 μg m^{-3} for NO_2, 70 μg m^{-3} for PM_{10}, and 35 μg m^{-3} for $PM_{2.5}$. OR, odds ratio; CI, confidence interval.

Furthermore, the findings from the subgroup analyses based on age and sex are presented in Fig. 3. In the analysis stratified by age, more pronounced associations between NO_2, SO_2, and CO with depressive symptoms were observed among individuals aged 45–59 years compared with those aged 60 years and older (Fig. 3a). For PM_{10} and $PM_{2.5}$, no discernible disparities in the effects were found between the age groups (Fig. 3a). In terms of sex as a potential effect modifier, the females appeared to be more susceptible than the males to the effects of air pollutant exposure to SO_2, CO, PM_{10}, and $PM_{2.5}$ (Fig. 3b). However, the distinctions in susceptibility within the sex groups did not prove statistically significant.

The results of the two-pollutant models indicated that the correlation of SO_2 remained robust after controlling for other air pollutants in the model, while the correlations of CO, PM_{10}, and $PM_{2.5}$ became insignificant after controlling for SO_2. For NO_2, its correlation turned notable upon adjustment for other pollutants but exhibited a significant negative correlation when considering CO, SO_2, PM_{10}, and $PM_{2.5}$. With O_3 as the controlling factor, NO_2 reversed to a significant positive correlation. In addition, the effect of PM_{10} was no longer statistically significant when $PM_{2.5}$ was factored into the model (Table 3).

The coefficients in the multi-pollutant model indicated the combined impact on depressive symptoms when the levels of mixed ambient air pollutants increased by a quarter simultaneously (Table 4). In the initial analysis, when all six air pollutants were examined, the results indicated a nonsignificant correlation between air pollution and depressive symptoms (OR: 0.954, 95% CI: 0.908–1.003, $P > 0.05$). This nonsignificance could indicate that certain pollutants may counteract the effects of others when considered in combination. After controlling for O_3 in the analysis, a significant relationship with depressive symptoms was observed for CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$, and the OR for each quantile increase in the combined air pollutant concentrations was 1.382 (95% CI: 1.324–1.442, $P < 0.05$). The combined exposure effect was substantially greater than the individual effects. In the qgcomp model, the results from simultaneously including both $PM_{2.5}$ and PM_{10} were essentially in line with those obtained when $PM_{2.5}$ or PM_{10} were included in the model. As depicted in Fig. 4, SO_2 contributed most significantly to the positive effect on depressive symptoms, with a weight of 40.0%, followed by CO, $PM_{2.5}$, and PM_{10}. NO_2 was the only contaminant that was assigned a negative weight.

Mediation analyses examined potential mediators for the four air contaminants that correlated positively with depressive symptoms (Table 5). Among the mediating variables, ADL exhibited a mediating effect that ranged from 5.70% for SO_2 to 9.22% for PM_{10}. The IADL had a more pronounced mediating impact, explaining 9.46% for SO_2 to 11.63% for PM_{10}. Sleep duration failed to demonstrate a statistically significant mediating effect in this situation. By contrast, cognitive function played a strong mediating role in the process through which air pollution led to depressive symptoms; the proportion of mediation effect ranged from 23.52% for PM_{10} to 28.59% for $PM_{2.5}$.

The sensitivity analyses conducted using a linear mix-effects model revealed that the effects of CO, SO_2, PM_{10}, and $PM_{2.5}$ on the depressive symptoms scores persisted, but the effect of PM_{10}

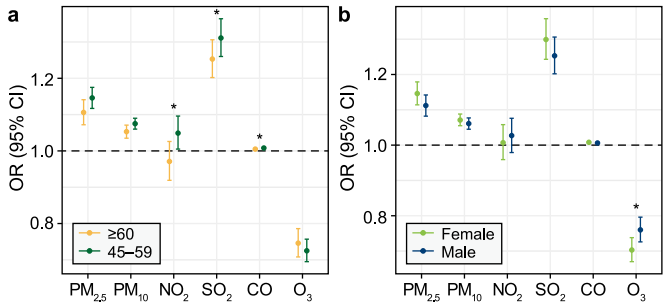

Fig. 3. Associations of per 10 μg m^{-3} increase in CO, O_3, NO_2, SO_2, $PM_{2.5}$, and PM_{10} with depressive symptoms, stratified by subgroups: **a**, age; **b**, sex. *$P < 0.05$. OR, odds ratio; CI, confidence interval.

was not significant (Supplementary Material Table S4). When repeated measures of the depressive symptoms scores were analyzed, the results of the qgcomp model were almost identical to those in the main analysis, with no significant negative correlation when all six air pollutants were monitored but with a significant positive correlation after adjusting for O_3 (Supplementary Material Table S5). Recognizing that physical health conditions might exacerbate mental health issues and potentially lead to depressive symptoms; additional analyses were performed. The correlations between air pollutants and depressive symptoms were not substantially altered, even after adjusting for medical history (Supplementary Material Table S6). When cases of depressive symptoms occurring within the first two years of follow-up were excluded to mitigate the impact of reverse causation, the patterns of associations remained similar, although the strength of the associations was somewhat weaker than those in the main models (Supplementary Material Table S7).

4. Discussion

This study comprehensively evaluates the associations between air pollutants and depressive symptoms in China. It established independent relationships of exposures to CO, SO_2, PM_{10}, and $PM_{2.5}$ with the incidence of depressive symptoms. When linked to depressive symptoms, the E-R curves for the individual air pollutants were either linear or J-shaped, suggesting the absence of safe threshold levels. SO_2 demonstrated a persistently strong correlation even when other pollutants were considered, whereas when $PM_{2.5}$ concentrations were factored into the model, the effect of PM_{10} was no longer statistically discernible. The analysis using the qgcomp model demonstrated that co-exposure to CO, SO_2, NO_2, PM_{10}, and $PM_{2.5}$ was positively correlated with the occurrence of depressive symptoms. SO_2 emerged as the primary contributor to the positive effect, while NO_2 was the sole contributor to the negative correlation. In addition, cognitive function, ADL, and IADL partially mediated the depressive symptoms caused by air pollutants.

This study supports the positive link between depressive symptoms and all examined contaminants except for O_3. The positive correlation with NO_2 was not significant, which aligns with the

Table 4
ORs (95% CI) of incidence risk of depressive symptoms associated with air pollutants in multi-pollutant models.

Mixture variables	OR (95% CI)	*P*
$PM_{2.5} + PM_{10} + CO + SO_2 + NO_2 + O_3$	0.954 (0.908, 1.003)	0.066
$PM_{10} + CO + SO_2 + NO_2 + O_3$	0.955 (0.909, 1.003)	0.063
$PM_{2.5} + CO + SO_2 + NO_2 + O_3$	0.979 (0.933, 1.026)	0.371
$PM_{2.5} + PM_{10} + CO + SO_2 + NO_2$	1.382 (1.324, 1.442)	<0.001
$PM_{10} + CO + SO_2 + NO_2$	1.383 (1.325, 1.443)	<0.001
$PM_{2.5} + CO + SO_2 + NO_2$	1.378 (1.320, 1.439)	<0.001

Note.
1. OR, odds ratio. CI, confidence interval.
2. The Model 3 covariates were included.

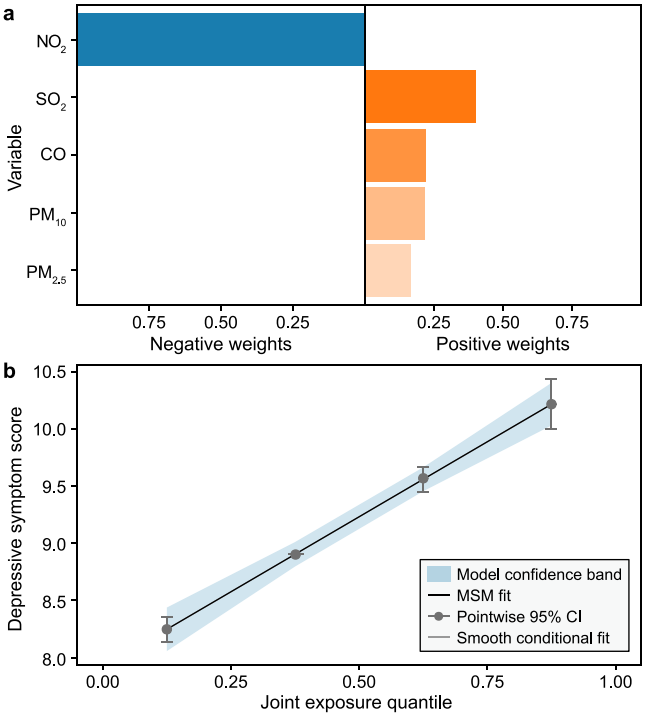

Fig. 4. Qgcomp model regression index weights (**a**) and joint effects with 95% CI (**b**) of air pollutants (CO, SO_2, NO_2, PM_{10}, and $PM_{2.5}$) on depressive symptoms. The Model 3 covariates were included. MSM, marginal structural model; CI, confidence interval. The MSM fit line (black line) completely overlaps with the smooth conditional fit line (grey line), thus covering the latter.

Table 3
Associations (OR and 95% CI) between air pollutants (per 10 μg m^{-3} increase) and depressive symptoms risk in two-pollutant models.

Variables	Adjusted for $PM_{2.5}$	Adjusted for PM_{10}	Adjusted for NO_2	Adjusted for SO_2	Adjusted for CO	Adjusted for O_3
$PM_{2.5}$	-	1.118 (1.055, 1.186)*	1.265 (1.230, 1.302)*	1.025 (0.998, 1.053)	1.079 (1.049, 1.110)*	1.212 (1.187, 1.238)*
PM_{10}	1.007 (0.975, 1.040)	-	1.121 (1.104, 1.139)*	1.009 (0.994, 1.023)	1.037 (1.021, 1.052)*	1.114 (1.101, 1.128)*
NO_2	0.758 (0.721, 0.797)*	0.793 (0.756, 0.832)*	-	0.869 (0.835, 0.903)*	0.872 (0.836, 0.908)*	1.147 (1.106, 1.190)*
SO_2	1.247 (1.197, 1.299)*	1.259 (1.209, 1.311)*	1.352 (1.306, 1.398)*	-	1.274 (1.219, 1.331)*	1.350 (1.308, 1.394)*
CO	1.004 (1.002, 1.005)*	1.004 (1.003, 1.006)*	1.010 (1.008, 1.011)*	1.000 (0.999, 1.002)	-	1.009 (1.007, 1.010)*
O_3	0.667 (0.644, 0.691)*	0.659 (0.635, 0.683)*	0.701 (0.677, 0.726)*	0.695 (0.671, 0.719)*	0.708 (0.684, 0.732)*	-

Note.
1. The Model 3 covariates were included.
2. *$P < 0.05$.

Table 5
Potential mediators of the association between air pollutants and depressive symptoms.

Mediators	Direct effect		Indirect effect		Total effect		Proportion Mediated	
	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*	% (95% CI)	*P*
Cognitive function								
$PM_{2.5}$	0.1758 (0.1210, 0.2306)	<0.001	0.0704 (0.0576, 0.0832)	<0.001	0.2462 (0.1908, 0.3016)	<0.001	28.59 (21.99, 38.00)	<0.001
PM_{10}	0.0988 (0.0689, 0.1287)	<0.001	0.0304 (0.0236, 0.0372)	<0.001	0.1292 (0.0983, 0.1601)	<0.001	23.52 (17.27, 32.00)	<0.001
CO	0.0110 (0.0077, 0.0145)	<0.001	0.0035 (0.0028, 0.0042)	<0.001	0.0145 (0.0111, 0.0179)	<0.001	23.95 (17.55, 33.00)	<0.001
SO_2	0.3380 (0.2510, 0.4250)	<0.001	0.1340 (0.1140, 0.1540)	<0.001	0.4710 (0.3900, 0.5520)	<0.001	28.40 (22.70, 36.00)	<0.001
Sleep								
$PM_{2.5}$	0.2439 (0.1948, 0.2931)	<0.001	0.0022 (−0.0058, 0.0102)	0.58	0.2461 (0.1969, 0.2953)	<0.001	0.89 (−2.33, 4.11)	0.58
PM_{10}	0.1324 (0.1048, 0.1599)	<0.001	−0.0022 (−0.0064, 0.0001)	0.34	0.1302 (0.1018, 0.1587)	<0.001	−1.65 (−5.36, 1.00)	0.34
CO	0.0156 (0.0127, 0.0186)	<0.001	−0.0004 (−0.0008, 0.0001)	0.1	0.0153 (0.0123, 0.1819)	<0.001	−2.55 (−5.67, 0.58)	0.1
SO_2	0.5100 (0.4362, 0.5838)	<0.001	−0.0102 (−0.0223, 0.0019)	0.1	0.4998 (0.4285, 0.5711)	<0.001	−2.05 (−4.60, 0.50)	0.1
ADL								
$PM_{2.5}$	0.0328 (0.0260, 0.0396)	<0.001	0.0026 (0.0016, 0.0036)	<0.001	0.0354 (0.0287, 0.0421)	<0.001	7.39 (4.43, 12.00)	<0.001
PM_{10}	0.0161 (0.0126, 0.0196)	<0.001	0.0016 (0.0011, 0.0022)	<0.001	0.0177 (0.0143, 0.0211)	<0.001	9.22 (5.96, 12.48)	<0.001
CO	0.0017 (0.0013, 0.0021	<0.001	0.0001 (0.0000, 0.0002)	<0.001	0.0018 (0.0014, 0.0022)	<0.001	6.01 (2.60, 9.42)	<0.001
SO_2	0.0619 (0.0516, 0.0715)	<0.001	0.0037 (0.0022, 0.0052)	<0.001	0.0656 (0.0560, 0.7523)	<0.001	5.70 (3.41, 7.99)	<0.001
IADL								
$PM_{2.5}$	0.0277 (0.0226, 0.0328)	<0.001	0.0033 (0.0024, 0.0043)	<0.001	0.0310 (0.0258, 0.0362)	<0.001	10.64 (7.43, 13.85)	<0.001
PM_{10}	0.0141 (0.0112, 0.0169)	<0.001	0.0019 (0.0014, 0.0023)	<0.001	0.0159 (0.0130, 0.0188)	<0.001	11.63 (8.43, 14.82)	<0.001
CO	0.0016 (0.0013, 0.0019)	<0.001	0.0002 (0.0001, 0.0003)	<0.001	0.0018 (0.0015, 0.0021)	<0.001	11.25 (8.19, 14.32)	<0.001
SO_2	0.0571 (0.0496, 0.0646)	<0.001	0.0060 (0.0045, 0.0742)	<0.001	0.0631 (0.0553, 0.0708)	<0.001	9.46 (7.12, 11.80)	<0.001

Note.
1. ADL, activities of daily living. IADL, instrumental activities of daily living.
2. $PM_{2.5}$, PM_{10}, CO, and SO_2 were included as continuous data in the mediation analyses.
3. The Model 3 covariates were included.

findings of previous research. Numerous studies have confirmed the positive correlation of $PM_{2.5}$ with depression [17,46,47]. For instance, a study encompassing 75 cities in China revealed that short-term exposures to ambient $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO substantially increased the risk of hospitalization for depressive disorder [10]. Similarly, time-series research conducted in Canada demonstrated substantial connections between depression and exposure to CO, SO_2, NO_2, and PM_{10} [48]. In addition, a Korean cross-sectional study indicated that chronic exposures to CO, NO_2, and PM_{10} (excluding SO_2) were linked to depressive disorder [49]. In concordance with our results, a nested case-control study in Korea showed no link between NO_2 and depression throughout the follow-up periods [50]. Conversely, a meta-analysis of 39 articles revealed a direct correlation between NO_2 and $PM_{2.5}$ exposures and increased risk of depressive disorder, with relative risks (RR) of 1.037 (95% CI: 1.011−1.064) and 1.074 (95% CI: 1.021−1.120) per 10 μg m^{-3} increase, respectively [8]. Furthermore, a significant negative correlation with O_3 exposure was observed in this study. This result was also detected in an investigation in Ningbo, China [18], which reported a significant negative link with O_3 on the sixth lag day. These results were not entirely consistent, which might be due to variations in the study populations, design, weather conditions, and air pollution levels.

Analyzing E-R curves is essential for health impact evaluation and the development of improved strategies. This study revealed a continuous increase in the E-R curves for CO, PM_{10}, SO_2, and $PM_{2.5}$ concentrations in relation to depressive symptoms. A study in Shijiazhuang, China, observed a linear correlation between air pollution levels and hospitalization rates due to mental health issues [51]. Another study that covered 26 Chinese cities reached a similar conclusion [12]. When compared with the Chinese national standards of air pollutants (as indicated by the red vertical dotted line in Fig. 2), our findings indicate that exposure levels below the air quality standards, particularly 60 μg m^{-3} for SO_2 and 4 mg m^{-3} for CO, can still present a risk for the development of depressive symptoms. This underscored the necessity of continued efforts to reduce these pollutants. Although particulate matter may not be considered harmful to mental health at the standard concentrations in China, the mean exposure concentrations (63.55 μg m^{-3} for $PM_{2.5}$ and 92.66 μg m^{-3} for PM_{10}) among the population exceeded these standards (35 μg m^{-3} for $PM_{2.5}$ and 70 μg m^{-3} for PM_{10}), suggesting a potential danger. Therefore, the implementation of stricter standards and a reduction in exposure to various contaminants are necessary to help mitigate the burden of depression.

Despite the unclear biological mechanism that links air pollution to depression, several possible pathways have been proposed. Previous studies have indicated that SO_2 could potentially cause brain injury by interacting with lipids, nucleic acids, along with proteins through free radical activity [52]. Exposure to SO_2 has also been linked to alterations in the plasticity of synapses in the hippocampus [53]. In addition, particulate matters such as $PM_{2.5}$ are hypothesized to activate the hypothalamic-pituitary-adrenal axis, compromise the integrity of the blood-brain barrier, and boost the generation of reactive oxygen species, thereby stimulating the release of proinflammatory mediators [54,55]. Essentially, air pollutants could affect the central nervous system through oxidative stress and inflammatory responses, potentially via systemic circulation, the trigeminal nerve, or olfactory receptor neurons [56]. Further investigation is necessary to elucidate the precise processes that link air pollution exposure to mental health outcomes.

Identifying a sensitive subpopulation is crucial for the development of effective public health strategies. Previous research findings have indicated that females may exhibit higher susceptibility to air pollutant exposure than males [12,57], which is similar to our results for PM_{10}, CO, SO_2, and $PM_{2.5}$. However, the sex disparities observed between the groups did not reach statistical significance. Factors such as work-related co-exposures and hormonal status could contribute to this sex disparity [58]. In terms of age, the participants aged 45−59 years appeared to be more vulnerable, which aligned with the finding of a previous study that anxiety outpatients typically fall within the age range of 37−59 years [59]. The age-specific discrepancy may be attributed to greater social pressure. Conversely, two studies on hospitalization for depression have reported stronger associations in the group aged 65 years or older [10,12], and studies of other diseases have

suggested that older individuals are consistently more vulnerable to the effects of air pollution [60,61]. In brief, the reasons for these discrepancies are likely to be multifaceted. Further exploration of factors such as genetic susceptibility, socioeconomic status, and previous health records in future studies may shed further light on this complex issue.

In the multiple pollutant analysis, SO_2 was identified as a stable and primary contributor to the adverse effects of multiple air pollutants on depressive symptoms. Following SO_2, $PM_{2.5}$, PM_{10}, and CO also showed significant contributions, whereas the adverse impacts associated with NO_2 were mostly mitigated and overshadowed by those of the other contaminants. The two-exposure model confirmed that the effect of SO_2 on depressive symptoms was not affected by other pollutants and might have affected the effects of other pollutants. Comparable findings were found in studies in Hefei, China [62,63], where SO_2 retained a strong effect even after adjustment for other air pollutants, which suggests its pivotal role in the mixture of air pollutants. In addition, Zhou et al. noted that the impacts of PM_{10} and NO_2 were diminished after adjustment for SO_2, rendering the association with NO_2 statistically insignificant [59]. The dual-pollutant model also found that PM_{10} had a limited independent contribution to depressive symptoms when $PM_{2.5}$ exposure levels were considered. Similarly, previous research indicated that finer particulate matter ($PM_{2.5}$) is more detrimental to human health, and even the health risks associated with PM_{10} may primarily stem from its $PM_{2.5}$ component [64,65]. Moreover, a case-crossover study found that $PM_{2.5}$ had a more pronounced negative effect on hospital admissions linked to anxiety than PM_{10}, which suggests a greater influence on anxiety [66]. Nevertheless, the published evidence regarding the relative contributions of each air pollutant and its combined effects on depression is limited. A cohort study in the United Kingdom that involved 389,185 participants examined the joint impacts of air pollutants and depressive disorders using air pollution scores derived from a principal component analysis [67]. The results revealed that prolonged exposure to various air pollutants was associated with an increased risk of mental disorders. Overall, the specific contribution of each air contaminant to long-term health impacts remains uncertain owing to limited evidence. This study suggests that SO_2 may exhibit the most substantial long-term association with depressive symptoms among the various air pollutants, emphasizing the importance of reducing SO_2 concentrations to a relatively low threshold in China's future air quality management strategies.

The mediation analyses in this study revealed that cognitive function, ADL, and IADL may underlie the relationship between air pollution and depressive symptoms, with cognitive function exerting a particularly robust mediating effect. Although epidemiological studies that investigated the mediating role of cognitive capacity in the impact of air pollution on mental health are limited, our findings confirm this view. A cross-sectional study showed that a composite cognitive score was a partial mediating factor in the relationship between exposure to $PM_{2.5}$ and depressive symptoms [68]. Another longitudinal study that focused on older women arrived at a similar conclusion [69]. There is a paucity of evidence regarding the potential mediating roles of ADL and IADL in the link between air pollution and depression. However, an American study suggested that time spent on physical activity might partly explain the link between $PM_{2.5}$ levels and depression [70]. In addition, a Chinese study identified both cognitive impairment and ADL limitation as risk factors of depression [71], which may lend some support to the notion that ADL and IADL are mediating functions, although further research is necessary to confirm this. Therefore, further investigation is required to fully understand the mediation effects of these factors on the relationship between air pollution and depression. Such insights are pivotal for clarifying the pathways through which air pollution may influence mental health and for crafting more precise and effective intervention strategies.

Compared with previous studies, this study represents a large-scale investigation into the combined impacts of multiple air pollutants on depressive symptoms among middle-aged and elderly individuals in China. It provides a comprehensive analysis by incorporating all six major air pollutants (CO, O_3, SO_2, NO_2, PM_{10}, and $PM_{2.5}$) in relation to depressive symptoms while also considering various individual-level factors that could influence these associations. Furthermore, a multi-pollutant model was used to address the potential synergistic or additive effects and collinearity among air pollutants, thus characterizing the combined impacts of air pollution on depressive symptoms and discerning the specific contribution of each pollutant. Moreover, the potential mediating factors were assessed to provide evidence for the mechanism research.

This study has several limitations that should be mentioned. First, the reliance on self-reported information from the participant questionnaires might have potentially introduced information bias. For example, the CESD-10 scale, used as a screening tool, was based on subjective participant reports rather than clinical diagnoses, which could misrepresent the actual conditions. Second, the exposure levels to the air pollutants were assessed solely based on the participants' residential cities. Given the vast scale of Chinese cities, this approach may not account for regional variations within a single city and could potentially result in exposure misclassification. This limitation could affect the accuracy of our findings. Therefore, future studies should consider using exposure data with higher spatial resolution to more accurately assess the health effects of air pollution and capture spatial heterogeneity within cities. Third, the study did not consider other sources of indoor air pollutants, such as solid fuel used in households and smoking, which could lead to underestimating household air pollution levels. Finally, the findings might have limited generalizability, as the study population was restricted to middle-aged and elderly individuals, who are known to have a higher prevalence of depression.

5. Conclusion

In conclusion, this study identified a positive connection between long-term exposures to $PM_{2.5}$, PM_{10}, CO, and SO_2 and the incidence of depressive symptoms. The findings suggest that cognitive function, ADL, and IADL may partially mediate this association. Among the air pollutants examined, SO_2 was the primary and stable contributor to the increased risk of depressive symptoms, both in individual and combined exposures. The research presents increasing proof regarding the detrimental effects of airborne contaminants on mental health and thus advocates for specific interventions such as stricter regulations, along with improved air quality management, to bolster public mental health.

CRediT authorship contribution statement

Yuqing Hao: Writing - Original Draft, Methodology, Data Curation, Formal Analysis, Investigation. **Longzhu Xu:** Validation, Writing - Review & Editing. **Meiyu Peng:** Validation, Writing - Review & Editing. **Zhugen Yang:** Writing - Review & Editing. **Weiqi Wang:** Supervision, Methodology. **Fanyu Meng:** Writing - Review & Editing, Supervision.

Ethical approval

Approval for the original CHARLS was obtained from the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants signed informed consent at the time of participation.

Data availability statement

The datasets that support this article are publicly available from the project of the China Health and Retirement Longitudinal Study (CHARLS) and China High Air Pollutants (CHAP) datasets.

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.ese.2024.100515.

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