Phenotypic aging mediates the association between blood cadmium and depression: A population-based study

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Abstract

Background

Depression is a serious public health problem today, especially in middle-aged and older adults. Although the etiology of the disease has not been fully elucidated, environmental factors are increasingly not negligible. Cadmium is widely used in industrial production. The general population may be chronically exposed to low doses of cadmium. This study aimed to investigate the association between blood cadmium and depression and to explore the mediating role of aging indicators in this process.

Methods

We conducted a cross-sectional study on blood cadmium (N = 7195, age ≥ 20 years) using data from the 2007–2010 National Health and Nutrition Examination Survey (NHANES). Aging indicators (biological and phenotypic age) are calculated by combining multiple biochemical and/ or functional indicators. To determine the relationship between blood cadmium concentrations and depressive symptoms, we used weighted multivariate logistic regression and restricted cubic spline functions and employed mediation analysis to explore the possible mediating effects of aging indicators in the process.

Results

We found a significant positive association between blood cadmium and depression with an OR and 95% CI: 1.22 (1.04,1.43). Restricted cubic spline analysis found a linear positive association between blood cadmium and depression. In the fully covariate-adjusted model, we found a positive association between blood cadmium and biological age and phenotypic age with β and 95% CI: 1.02 (0.65, 1.39) and 2.35 (1.70, 3.01), respectively. In the mediation analysis, we found that phenotypic age mediated 21.32% of the association between blood cadmium and depression.

Conclusion

These results suggest that even exposure to low doses of cadmium can increase the risk of depression and that this process may be mediated by phenotypic aging.

1. Introduction

Depression is one of the most common heavy mental illnesses (WHO depression). According to previous studies, approximately 300 million people worldwide suffer from varying degrees of depression, and the number of depression cases worldwide has increased by as much as nearly 50% in the past three decades (Liu et al. 2020). Depression not only causes serious mental health damage to patients but also brings a huge economic burden to their families and society. As the aging population grows, depression is becoming a more serious public health problem (India State-Level Disease Burden Initiative Mental Disorders 2020; Zhao et al. 2012). Although the etiology of depression has not been fully elucidated, non-negligible environmental factors are increasingly being recognized as potential causes of the disorder.

Cadmium (Cd) is a ubiquitous environmental toxicant, widely present in various environmental media, such as air, soil, drinking water, and food (Olmedo et al. 2017; Satarug et al. 2010; Wang et al. 2015). At the same time, the human body is exposed to cadmium through various pathways (Wang et al. 2021a). Previous studies have shown that the accumulation of cadmium in the body can lead to chronic diseases such as diabetes and cardiovascular disease (Guo et al. 2019; Obeng-Gyasi 2020). Of concern is that metal cadmium is an important neurotoxic agent and has a significant impact on the development of mental illness (Bakulski et al. 2020; Sulaiman et al. 2020; Tsentsevitsky et al. 2020; Zhou et al. 2018). Evidence from animal studies suggests that cadmium is associated with major pathological changes in depression, including impairment of acetylcholinesterase, monoaminergic neurotransmission systems, and mitochondrial dysfunction (Haider et al. 2015; Lanni et al. 2009; Orisakwe 2014; Pillai et al. 2003). For example, the activity of acetylcholinesterase (AChE) was reduced in cadmium-treated rats, along with an increase in depression-like symptoms (Haider et al. 2015), and altered serotonin and norepinephrine levels in the cadmium-exposed group compared to the control group (Pillai et al. 2003). In addition, a study conducted in Iraq among occupational groups involved in battery production found that blood cadmium can increase the risk of depression (Al-Samaraee et al. 2022). And this association was also found in a repeated measures study conducted on the Korean

elderly population (Kim et al. 2016). Nevertheless, evidence from studies on the relationship between low-level cadmium exposure and depression in the general population remains limited. Furthermore, the potential pathways underlying the effects of cadmium on depression are still not fully revealed.

Aging is a process in which the body's ability to balance itself declines, usually accompanied by a decline in body composition, energy metabolism, and brain health (Ferrucci et al. 2018), which can be reflected by multisystem clinical chemistry biomarkers. Many environmental factors can exacerbate the aging process, and the effects of heavy metals are particularly significant (Smith et al. 2021; White et al. 2019). For example, experimental studies have found that cadmium can contribute to cellular senescence and organismal aging through mitochondrial dysfunction, DNA damage, and leukocyte telomere shortening (Ijomone et al. 2020; Luo et al. 2021; Zota et al. 2015). Population studies have also found that cadmium exposure accelerates the phenotypic aging process (Chen et al. 2022b). In addition, aging has been found to be associated with many mental illnesses, such as depression and schizophrenia (Dada et al. 2021; Klopack et al. 2022). A study conducted in Canada found that the level of aging was associated with the severity of schizophrenia and a prospective cohort study found that physiological age, calculated based on multisystem biomarkers, was associated with the risk of depression (Brown et al. 2018). In general, based on the importance of biological aging on cadmium exposure and depression, we hypothesized that cadmium exposure might increase the risk of depression by promoting biological aging.

Therefore, we conducted a cross-sectional study based on the 2007–2010 National Health and Nutrition Examination Survey (NHANES) to investigate the relationship between cadmium exposure and depression in the general population. Based on multiple biochemical parameters to calculate indicators of biological aging, we further explored the mediating role of biological aging between cadmium exposure and depression.

2. Methods

2.1 Study populations

NHANES is a research project using a complex multi-stage sampling methodology designed to comprehensively assess the health and nutritional status of the general U.S. population. Since 1999, the study has published research data every two years. Details of the study sampling procedures, study design, and relevant data were provided by the Centers for Disease Control and Prevention (CDC) (NHANES website: https://www.cdc.gov/nchs/nhanes/index.htm). All study participants were required to complete an informed consent form before enrollment. The study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board.

We chose two study periods from 2007 to 2010, considering the integrity of the data to be studied. A total of 20,686 participants were enrolled, and then we excluded those missing blood cadmium, depression, biochemical indicators, and general demographic information, ultimately 7,195 participants with complete study information were included in this study. The detailed inclusion-exclusion process for study participants is shown in Fig. 1.

2.2 Depression Assessment

The depression status of participants in this study was measured according to the Depression Self-Rating Scale (PHQ-9), which is often used to reflect the depression status of study participants in the past two weeks (Kroenke et al. 2010). The PHQ-9 consists of nine questions related to the frequency of depressive symptoms, with each question scoring from 0 to 3 depending on the frequency of symptoms, for a total score of 27. A previous validation study found that scores of 10 or higher were more than 85% specific and sensitive to major depression (Levis et al. 2019). Therefore, participants who scored 10 or more on the scale were assessed as having depression in this study. Furthermore, to further improve the quality of the PHQ-9 questionnaire, only participants who answered 8 or more questions were included in this study.

2.3 Exposure Assessment

Considering that depression was assessed using the PHQ-9 questionnaire, we chose blood samples to measure cadmium exposure levels because blood cadmium concentrations are often used to reflect recent cadmium exposure levels compared to urinary cadmium (Adams and Newcomb 2014). Blood samples collected from the Mobile Monitoring Center (MEC) are stored in vials at -30 degrees Celsius and sent to the National Center for Environmental Health, Laboratory Sciences, where whole blood cadmium is measured using inductively coupled plasma mass spectrometry. Detailed experimental methods and quality control protocols can be found in the NHANES Laboratory Procedures Manual (https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/PbCd_E_met_lead_cadmium.pdf). Blood cadmium concentrations below the minimum limit of detection (LOD) were replaced with the limit of detection divided by the

square root of 2 according to the NHANES recommendations. The percentage of participants with blood cadmium concentrations higher than LOD in this study was 79.71%.

2.4 Measurement of biological aging markers

In this study, two indicators used to reflect biological aging were quantified based on different biomarkers and computational methods. Phenotypic age (PA) was calculated based on chronological age and nine biomarkers (including chronological age, albumin, creatinine, glucose, CRP, lymphocyte percentage, mean cell volume, erythrocyte distribution width, alkaline phosphatase, and white blood cell count) selected based on a tenfold cross-validated Cox Proportional Hazards Elastic Net mortality model (Levine et al. 2018; Liu et al. 2018; Yang et al. 2022). The phenotypic age was calculated as follows:

Phenotypic age = $141.50 + \frac{\ln\{-0.00553 \times \ln(1 - mortalityrisk)\}}{0.090165}$

where

Mortality risk = $1 - \exp\left(\frac{-1.51714 \times \exp(xb)}{0.0076927}\right)$

and

xb = -19.907–0.0336 * albumin + 0.0095 * creatinine + 0.1953 * glucose + 0.0954 * ln(C-reactive protein) – 0.0120 * lymphocyte percentage + 0.0268 * mean cell volume + 0.3306 * red blood cell distribution width + 0.00188 * alkaline phosphatase + 0.0554 * white blood cell count + 0.0804 * chronological age

Biological age (BA) was proposed by Klemera and Doubal (Levine 2013) and was calculated in this study based on 9 biomarkers (first 1.0 second expiratory effort (fev1.0), Ln-C-reactive protein (CRP), serum creatinine, glycosylated hemoglobin, serum albumin, serum total cholesterol, serum urea nitrogen, serum alkaline phosphatase, systolic blood pressure). The formula for calculating BA is as follows:

$$BA_E = \frac{\sum_{j=1}^{m} \left(x_j - q_j\right)\left(\frac{k_j}{s_j^2}\right)}{\sum_{j=1}^{m} \left(\frac{k_j}{s_j}\right)^2}$$

1

$$r_{char} = \frac{\sum_{j=1}^{m} \frac{r_j^2}{\sqrt{1-r_j^2}}}{\sum_{j=1}^{m} \frac{r_j}{\sqrt{1-r_j^2}}}$$

2

$$s_{BA}^2 = \frac{\sum_{j=1}^{n} \left((BA_{Ei} - CA_i) - \frac{\sum_{i=1}^{n}(BA_{Ei} - CA_i)}{n}\right)^2}{n} - \left(\frac{1 - r_{char}^2}{r_{char}^2}\right) \times \left(\frac{\left(CA_{max} - CA_{min}\right)^2}{12m}\right)$$

3

$$Biologicalage = \frac{\sum_{j=1}^{m} \left(x_j - q_j\right)\left(\frac{k_j}{s_j^2}\right) + \frac{CA}{s_{BA}^2}}{\sum_{j=1}^{m} \left(\frac{k_j}{s_j}\right)^2 + \frac{1}{s_{BA}^2}}$$

4

where, j and i denote the number of biomarkers and samples, respectively. k, q, and s are the regression slope, intercept and root mean square error of the regression of a biomarker with chronological age (CA), respectively. Finally, r_j^2denotes the variance explained by the

regression of the chronological age on the biomarker.

2.5 Covariates

We adjusted a series of covariates in this study based on previous studies (Buser and Scinicariello 2017; Chen et al. 2022b). To fully assess the impact of potential confounders, sequential models were constructed. Model I was adjusted for age and sex and NHANES cycle. Model II was additionally adjusted for basic demographic information such as education level (below high school, high school, and above high school), marital status (married/living with a partner, widowed/divorced/separated, never married), race (Mexican American, Non-Hispanic White, Non-Hispanic Black, other races), family income to poverty ratio(FIR)($\leqq$ 1.3, 1.31–3.5, > 3.5), and Body Mass Index (BMI) (< 25 kg/m^2, 25 to < 30 kg/m^2, $\geq$ 30 kg/m^2). Model III was additionally adjusted for life status factors such as physical activity (vigorous, moderate, or other), alcohol consumption (having at least 12 alcohol drinks per year or not), and smoking levels (Serum cotinine level). Model IV was additionally adjusted for basic disease situations, such as diabetes (yes or no), hypertension (yes or no), and cardiovascular disease (CVD) (yes or no). Diabetes was diagnosed based on the following conditions: self-reported physician diagnosis or glycosylated hemoglobin level (HbA1c) $\geq$ 6.5% or fasting blood glucose (FBG) $\geq$ 7.0 mmol/L or taking hypoglycemic drugs to lower blood sugar. Hypertension was defined as any of the following conditions: self-reported physician diagnosis or systolic blood pressure (SBP) $\geq$ 130 mmHg or diastolic blood pressure (DBP) $\geq$ 80 mmHg or taking medications for hypertension currently. Study participants were diagnosed with CVD if they were told they had the following diseases: congestive heart failure, coronary heart disease, angina, heart attack, or stroke.

2.6 Statistical analysis

Considering that NHANES uses a multi-stage sampling procedure, we calculated sampling weights for four years in this study, and these weights were used to explain the unequal probabilities of selection, oversampling, and non-response of the NHANES project (Xu et al. 2021). To compare the differences in baseline characteristics between the depressed and non-depressed groups, weighted t-tests were used for continuous variables and weighted chi-square tests for categorical variables. The mean ± standard error (SE) and number (weighted percent) were used to express them, respectively. Since blood cadmium shows a strongly skewed distribution, we performed a natural logarithmic transformation in this study. Weighted multivariate logistic regression analysis was used to assess the association between blood cadmium concentrations and depression levels and between biological aging indicators and depression. Weighted multivariate linear regression was used to assess the association between blood cadmium concentrations and biological aging indicators. We also used a restricted cubic spline function with three nodes (5th, 50th, and 95th) to explore the potential nonlinearity in the dose-response relationship between blood cadmium concentration and depression and biochemical indicators and depression (Song et al. 2022). We also quartile-transformed the biological aging indicators and performed trend tests after replacing them with ordered variables (0–3) in the model. Finally, according to the previous studies (Hu et al. 2021; Khosravi 2020), the conditions for the existence of mediating effects were found as follows: "statistically significant association between X and M" and "statistically significant association between M and Y" were satisfied simultaneously. When the conditions for mediation analysis were fulfilled, we performed a mediation analysis to explore the mediating role of biological aging indicators in the association between blood cadmium and depression. Since previous studies have shown that mercury and lead are associated with depressive symptoms, we included log-transformed blood mercury and blood lead in our sensitivity analyzes. In addition, we also included pregnant persons in this study for sensitivity analysis.

The above statistical analyses were performed in R.4.1.1, and the “survey”, “bioAge” and “mediation” packages were used for data weighting analysis and calculation of biological aging indicators, and mediation analysis, respectively. Two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1 Description of the study participants

Table 1 demonstrates the basic characteristics of the study participants. Of the 7295 study participants (male: 3666; female: 3529), their weighted mean age was 45.07 ± 0.36, and 628 (8.73%) were assessed for depression. The weighted mean value of blood cadmium was 0.51 ± 0.01ug/ml, and the weighted mean values of biological age and phenotypic age were 44.47 ± 0.36 and 38.44 ± 0.42 years, respectively. Overall, gender, race, education, FIR, BMI, marital status, physical activity, drinking, diabetes, hypertension, CVD, serum cotinine, cadmium, and phenotypic age were statistically different in the distribution between the depressed and non-depressed groups.

Table 1

Weighted characteristics of the study population (Age≧20 years) with and without depressive symptoms, NHANES, USA.

Characteristics	Total Participants	depression situation		*P* value
		Yes	No	
N	7195	6567 (91.27%)	628 (8.73%)	
Chronological age, years	45.07±0.36	44.12±0.55	45.14±0.38	0.134
20-39 years	2574 (35.78%)	235 (9.13%)	2339 (90.87%)	
40-59 years	2618 (36.39%)	278 (10.62%)	2340 (89.38%)	
60-79 years	2003 (27.83%)	115 (5.74%)	1888 (94.26%)	
Gender				<0.001
Male	3666 (50.95%)	207 (5.65%)	3459 (94.35%)	
Female	3529 (49.05%)	421 (11.93%)	3108 (88.07%)	
Ethnicity				<0.001
Mexican American	1306 (18.15%)	115 (8.81%)	1191 (91.19%)	
Non-Hispanic black	1273 (17.69%)	124 (9.74%)	1149 (90.26%)	
Non-Hispanic white	3590 (49.90%)	287 (7.99%)	3303 (92.01%)	
Other	1026 (14.26%)	102 (9.94%)	90.06%	
Educational level				<0.001
Below high school	1897 (26.37%)	243 (6.65%)	3367 (93.35%)	
High school	1691 (23.50%)	145 (8.58%)	1546 (91.42%)	
Above high school	3607 (50.13%)	243 (12.81%)	1654 (97.19%)	
FIR				<0.001
≦ 1.30	2150 (29.88%)	331 (15.40%)	1819 (84.60%)	
1.31-3.5	2689 (37.37%)	194 (7.22%)	2495 (92.79%)	
> 3.5	2356 (32.75%)	103 (4.37%)	2253 (95.63%)	
BMI (kg/m^2)				0.006
< 25	1992 (27.69%)	156 (7.83%)	1836 (92.17%)	
25 to <30	2454 (34.11%)	181 (7.38%)	2273 (92.62%)	
≧ 30	2749 (38.21%)	291 (10.59%)	2458 (89.41%)	
Marital status				<0.001
Married/Living with partner	4487 (62.36%)	293 (6.53%)	4194 (93.47%)	
Widowed/Divorced/Separated	1451 (20.17%)	198 (13.65%)	1253 (86.35%)	
Never Married	1257 (17.47%)	137 (10.90%)	1120 (89.10%)	
Physical activity				<0.001
Vigorous	2715 (37.74%)	163 (6.00%)	2552 (94.00%)	
Moderate	2313 (32.15%)	195 (8.43%)	2118 (91.57%)	
Other	2167 (30.12%)	270 (12.46%)	1897 (87.54%)	
Drinking				0.017

No	1811 (25.17%)	177 (9.77%)	1634 (90.23%)	
Yes	5358 (74.83%)	451 (8.38%)	4933 (91.62%)	
DM				<0.001
No	6035 (83.88%)	492 (8.15%)	5543 (91.85%)	
Yes	1160 (16.12%)	136 (11.72%)	1024 (88.28%)	
Hypertension				0.021
No	3612 (50.20%)	299 (8.28%)	3313 (91.72%)	
Yes	3583 (49.80%)	329 (9.18%)	3254 (90.82%)	
CVD				<0.001
No	6636 (92.23%)	536 (8.08%)	6100 (91.92%)	
Yes	559 (7.78%)	92 (16.46%)	467 (83.54%)	
Cycle				0.983
1	3492 (48.53%)	297 (8.51%)	3195 (91.49%)	
2	3703 (51.47%)	331 (8.94%)	3372 (91.06%)	
Serum cotinine (ng/ml)	63.97±4.13	105.82±10.35	60.74± 3.81	<0.001
Urinary Cd (ug/L)	0.51±0.01	0.75±0.03	0.49±0.01	<0.001
Biological age (years)	44.47±0.36	44.78±0.59	44.44±0.38	0.605
Phenotypic age (years)	38.44±0.42	40.16±0.69	38.31±0.44	0.012

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as numbers (weighted percentages). FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; Cd: cadmium;

3.2 Associations between blood cadmium concentration and depression risk

Table 2 shows associations between blood cadmium concentrations and depression. We found a significant positive association between blood cadmium concentration and depression in all of the different covariate-adjusted models ($P < 0.05$). In the fully adjusted model (Model IV), we found that the risk of depression was 1.22-fold (95CI: 1.04–1.43) for each unit increase in natural log-transformed blood cadmium concentration. The results of the restricted cubic spline analysis also showed a significant positive association between blood cadmium concentration and depression, which was linear (P-nonlinear > 0.05), as shown in Fig. 2.

Table 2
Weighted regression analyses for the associations of Cd with depression

Cadmium	depression		
	OR	95% CI	*P*
Model I	1.71	(1.52, 1.92)	< 0.001
Model II	1.50	(1.31, 1.71)	< 0.001
Model III	1.21	(1.03, 1.42)	0.033
Model IV	1.22	(1.04, 1.43)	0.031
Model I: Adjusting for age, gender, and NHANES cycle.			
Model II: Model I + adjusting for race, educational level, FIR, BMI, and marital status.			
Model III: Model II + adjusted for physical activity, drinking, and ln-transformed serum cotinine.			
Model IV: Model III + adjusted for DM, hypertension, CVD			
Abbreviations: FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; Cd: cadmium; OR: Odds ratio; CI: Confidence interval;			

3.3 Associations between blood cadmium concentration and biological aging markers

Figure3 shows associations between blood cadmium concentrations and aging markers. In models with different adjusting covariates, blood cadmium concentration as a continuous variable showed a positive association with either biological age or phenotypic age. From Table 3, in the fully covariate-adjusted model, compared to the lowest quartile, we found association effect values of [β = 1.02 (95CI: 0.65, 1.39)] and 2.35 (1.70, 3.01) for blood cadmium at the highest quartile with biological age and phenotypic age, respectively. Furthermore, we also found a significant linear trend between biological age, phenotypic age, and depression (*P* for trend < 0.05).

Table 3
Weighted regression coefficients (95% CI) in blood Cadmium associated with aging markers.

Cadmium	Model I [β (95%CI)]		Model II [β (95%CI)]		Model III [β (95%CI)]		Model IV [β (95%CI)]	
	Phenotypic age	Biological age	Phenotypic age	Biological age	Phenotypic age	Biological age	Phenotypic age	Biological age
Continuous	1.26(1.02, 1.50) *	0.51(0.37, 0.64) *	1.29(1.07, 1.52) *	0.44(0.29, 0.59) *	0.89(0.55, 1.23) *	0.42(0.20, 0.64) *	1.02(0.72, 1.32) *	0.48(0.28, 0.69) *
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	-0.19(-0.67,0.29)	-0.25(-0.55, 0.06)	-0.02(-0.41, 0.37)	-0.24(-0.50, 0.03)	-0.08(-0.47, 0.31)	-0.24(-0.50, 0.03)	-0.03(-0.38, 0.32)	-0.21(-0.42, 0.01)
Q3	0.45(0.02, 0.87) *	0.05(-0.21, 0.32)	0.59(0.23, 0.95) *	-0.06(-0.31, 0.19)	0.40(0.01, 0.78) *	-0.04(-0.31, 0.22)	0.53(0.14, 0.91) *	0.06(-0.19, 0.31)
Q4	2.68(2.13, 3.23) *	1.01(0.74, 1.28) *	2.74(2.23, 3.24) *	0.87(0.59, 1.15) *	2.10(1.33, 2.86) *	0.90(0.52, 1.28) *	2.35(1.70, 3.01) *	1.02(0.65, 1.39) *
P for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.005	< 0.001	0.002
Model I: Adjusting for age, gender, and NHANES cycle.								
Model II: Model I + adjusting for race, educational level, FIR, BMI, and marital status.								
Model III: Model II + adjusted for physical activity, drinking, and ln-transformed serum cotinine.								
Model IV: Model III + adjusted for DM, hypertension, CVD								
Abbreviations: FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; Cd: cadmium; CI: Confidence interval; Q1: First quartile; Q2: Second quartile; Q3: Third quartile; Q4: Fourth quartile.								
*: $P < 0.05$; $P < 0.05$: significant.								

3.4 Associations between biological aging markers and depression risk

Table 4 shows the associations between the aging marker and depression risk based on the weighted logistic regression model. Phenotypic age either as a continuous or categorical variable shows a positive association with depression. Notably, no association was found between biological age as a continuous variable and depression. In models with incomplete adjustment for covariates (except Model IV), we found that biological age was associated with depression at the highest quartile compared with the lowest quartile, and the trend test was statistically significant (*P* for trend < 0.05). To further explore the potential nonlinearity of the dose-response relationship between phenotypic age and depression, the results of restricted cubic spline were presented in Figure S1. We found a non-linear association between phenotypic age and depression (*P*-nonlinear < 0.05).

Table 4
Weight regression associations of aging makers with depression risk

Exposure	Model	Depression [OR (95%CI)]					
		continuous	Q1	Q2	Q3	Q4	*P* for trend
PA	I	1.05(1.04,1.07)	Ref	2.70(1.94, 3.76)	5.85(3.42,10.01)	10.84(6.04,19.47)	< 0.001
	II	1.04(1.03,1.05)		2.34(1.62, 3.40)	4.38(2.43, 7.89)	5.67(2.98,10.81)	< 0.001
	III	1.03(1.02,1.05)		2.09(1.41,3.10)	3.49(1.86,6.53)	4.21(2.12,8.38)	0.001
	IV	1.03(1.01,1.04)		2.07(1.41,3.04)	3.28(1.78,6.05)	3.33(1.69,6.56)	0.005
BA	I	1.07(1.04,1.09)		2.14(1.53, 2.99)	3.06(1.62, 5.78)	4.72(1.75,12.71)	< 0.001
	II	1.02(0.99,1.05)		1.79(1.25,2.57)	2.02(1.05,3.90)	1.98(0.67,5.84)	0.006
	III	1.01(0.98,1.04)		1.68(1.15,2.44)	1.73(0.87,3.41)	1.67(0.56,4.97)	0.021
	IV	0.99(0.96,1.02)		1.57(1.07,2.33)	1.41(0.70,2.84)	1.11(0.37,3.32)	0.052
Model I: Adjusting for age, gender, and NHANES cycle.							
Model II: Model I + adjusting for race, educational level, FIR, BMI, and marital status.							
Model III: Model II + adjusted for physical activity, drinking, and ln-transformed serum cotinine.							
Model IV: Model III + adjusted for DM, hypertension, CVD							
Abbreviations: FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; Cd: cadmium; CI: Confidence interval; PA: phenotypic age; BA: biological age; Ref: reference; p < 0.05: significant; Q1: First quartile; Q2: Second quartile; Q3: Third quartile; Q4: Fourth quartile							

3.5 Mediation analyses

From the above analysis, we found that the association between phenotypic age and blood cadmium and depression satisfied the conditions of the mediation analysis. Therefore, we further explored the mediating effect of phenotypic age in the association between blood cadmium and depression. From Fig. 4, we found that blood cadmium may promote depression by affecting phenotypic age levels. Specifically, phenotypic age effectively mediated 21.32% of the association between blood cadmium and risk of depression (IE = 0.3%, 95% CI: 0.1%-0.4%; DE = 1.00%, 95% CI: 0.4%-3.0%).

Sensitivity analyses showed no substantial changes in the findings of this study after adjustment for blood lead and blood mercury concentrations or inclusion of pregnant individuals, as detailed in TableS1-S6.

4. Discussion

In our study, we investigated the relationship between blood cadmium and depression in adults aged 20 years and older using samples from the United States and explored for the first time the possible mediating effect of aging indicators in this association. There are two main findings in this study. First, we found that blood cadmium can significantly increase the risk of biological aging and depression and that there is a linear dose-response relationship between blood cadmium and depression. Second, phenotypic age mediated 21.32% of the association between blood cadmium and depression risk.

Cadmium is widely distributed in daily life and enters the body through various pathways and accumulates in the central nervous system, thus affecting the levels of dopamine, norepinephrine, mitochondrial dysfunction, and 5-hydroxytryptamine and causing depression-like symptoms (Batool et al. 2019; Blier 2016; Branca et al. 2020; El-Tarras Ael et al. 2016; Nutt 2008; Treviño et al. 2022). Evidence from animal experiments indicated that rats in the cadmium-exposed group showed significant depression-like behavior (Batool et al. 2019; Haider et al. 2015). A repeated-measures study in a Korean elderly population shows that elevated blood cadmium levels may increase the risk of depression (Kim et al. 2016). Similarly, Our study also confirmed this association in the general population. Other studies have also shown that cadmium exposure leads to increased levels of inflammation in the brain, which is one of the possible pathways for the development of depression (Cai et al. 2021; Chen et al. 2022a; Ehsanifar et al. 2022).

A growing number of studies have identified an important role for cadmium in age-related diseases, so we also focused on biological aging as a possible mechanism (Diaz et al. 2021; Min and Min 2016; Wang et al. 2021b). In previous population studies, cadmium was found to shorten the telomere length of body leukocytes, which is often used as an indicator of cellular senescence (Mizuno et al. 2019; Zota et al. 2015). Studies conducted in the U.S. adult population have found that cadmium exposure may slow walking speed and reduce grip strength levels suggesting that cadmium may exacerbate the aging process in humans (García-Esquinas et al. 2020; Kim et al. 2018). Similarly, our study also found that cadmium exposure increased the level of biological aging. In addition, toxicological studies suggest that cadmium exposure may impair metabolic processes and accelerate pathological processes associated with aging (Ali et al. 2021; Ijomone et al. 2020; Sandhu et al. 2014). In short, the above evidence supports our view that cadmium may accelerate organismal aging.

The aging of the body is usually reflected in the accumulation of senescent cells and the production of senescence-associated secretory phenotypes (SASP) (He and Sharpless 2017; Kirkland and Tchkonia 2017). With the increasing aging of the population, organismal aging has received much attention in research, and more and more studies have found an association with chronic diseases, especially mental-related diseases (Diniz 2018; Palmos et al. 2020; Powell et al. 2018). Our study found an association between phenotypic age and the risk of depression. Notably, we did not find that biological age was associated with depression. This may be due to the fact that the biological function indicators used to calculate these two aging indicators are not identical. Specifically, additional indices such as white blood cell count, lymphocyte percentage, and red cell distribution width were applied to calculate phenotypic age, which were also found to be associated with depression in previous studies (Sealock et al. 2021; Shafiee et al. 2017). Animal behavioral experiments also have shown that older mice exhibit less activity and increased anxiety-like behavior compared to younger and middle-aged mice, which may be due to aging that exacerbates the death of hypothalamic glial cells associated with brain dysfunction (Shoji and Miyakawa 2019; Suda et al. 2021). Moreover, toxicological studies also found that the elimination of senescent cells improved brain function in mice (Ogrodnik et al. 2021). Collectively, phenotypic aging may exacerbate the development of depression.

Based on the results mentioned above, we also explored the mediating role of phenotypic age in the association between cadmium and depression. We found a significant mediating role of phenotypic age in the association between cadmium and depression. Importantly, this mediated proportion was above 20%, suggesting that phenotypic aging plays an important role in the association between cadmium exposure and depression.

The present study has some advantages. First, this study explored the association between blood cadmium and indicators of aging and depression using a relatively large sample size of data from NHANES. Second, we explored the mediating effect of phenotypic aging between blood cadmium and depression using mediation analysis. However, some limitations should also be stated. First, the present study is cross-sectional and is limited in its ability to infer a causal association between blood cadmium and depression. Second, the depressive symptoms in this study were the results of the PHQ-9 scale self-reported by the study participants, rather than an accurate clinical diagnosis, and the subjective thoughts of the participants may have biased the results. However, NHANES does not include data for a definitive diagnosis of depression. Finally, single-point measurements of blood cadmium do not provide a good assessment of the true level of cadmium. However, the uncertainty in exposure assessment is likely to be of a non-differential bias and may lead to an underestimation of risk.

5. Conclusion

The present study found that blood cadmium increases the risk of depression and that this process may be mediated by phenotypic aging. Our findings support these ideas that cadmium is toxic even at low exposure levels and that further reductions in current exposure levels are needed to prevent phenotypic aging and depression effectively. Moreover, our findings provide clues for future population and toxicology studies in this field.

Declarations

Availability of data and materials

This study uses publicly available data sets for analysis. All study data are available on NCHS and CDC websites (http://www.cdc.gov/nchs/nhanes.htm).

Ethical approval and consent to participate

The program was approved by the NCHS Research Ethics Review Committee and informed consent was obtained from the participants.

Consent for publication

The authors declare that they agree with the publication of this paper in this journal.

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Competing interest

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design. Data curation, Writing - original draft & editing were performed by **Yudong Wu**, **Qing Wu**, **Weizhuo Yi** and **Rubing Pan**. Conceptualization, Validation were performed by **Yuxuan Li**, **Xiaoyu Jin**, **Yunfeng Liang**, **Lu Mei**, and **Shuangshuang Yan**. Software, Methodology were performed by **Xiaoni Sun**, **Wei Qin**, **Jian Song** and **Jian Cheng**. Supervision, Resources, Project administration, Writing – review & editing were performed by **Hong Su**. All authors read and approved the final manuscript.

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Figures

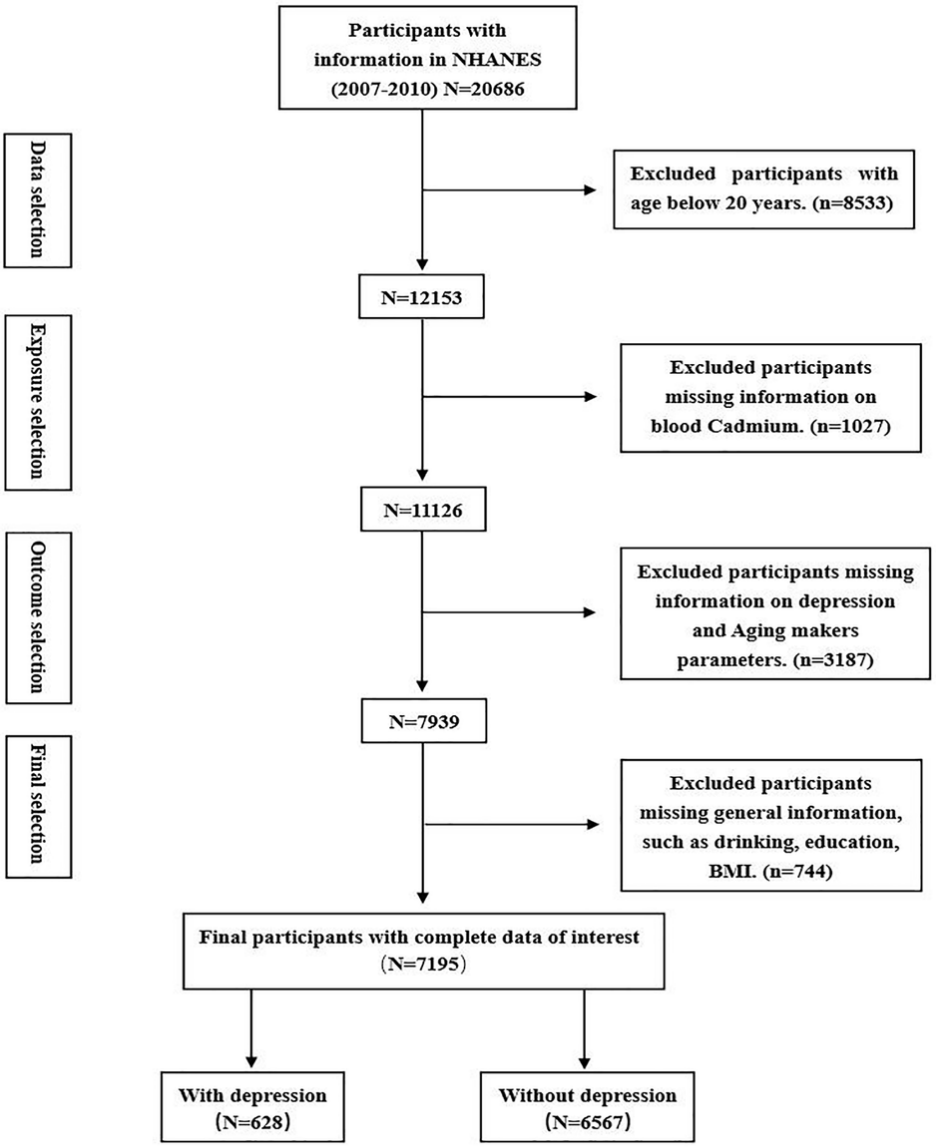

Figure 1

Flow chart of the selection process for the selection of eligible participants.

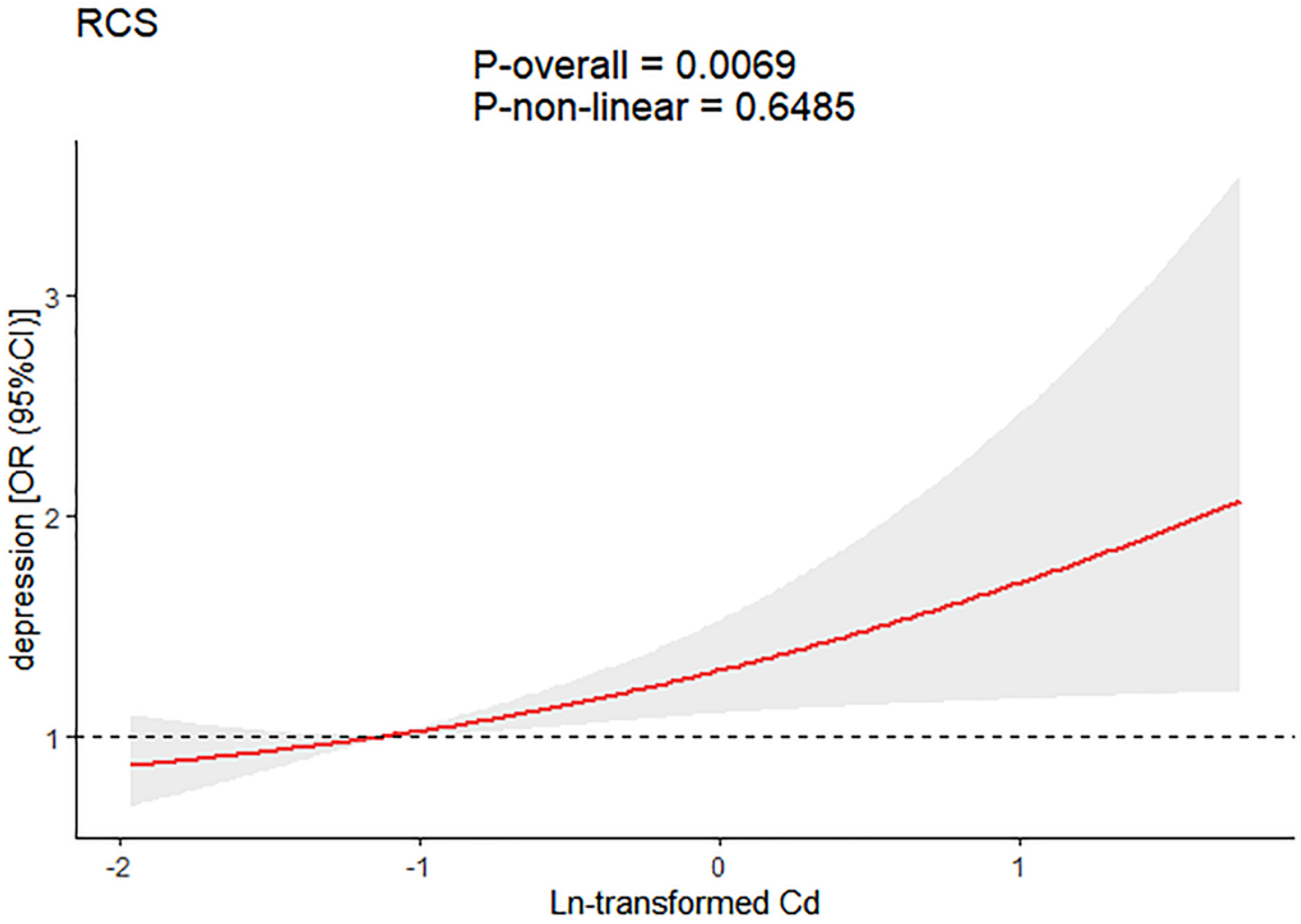

Figure 2

Dose-response relationships between ln-transformed blood cadmium and depressive symptoms. The associations were adjusted for age, gender, NHANES cycle, race, educational level, FIR, BMI, marital status, physical activity, drinking, and ln-transformed serum cotinine, DM, hypertension, and CVD. Abbreviations: OR: Odds ratio; CI: Confidence interval, FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus.

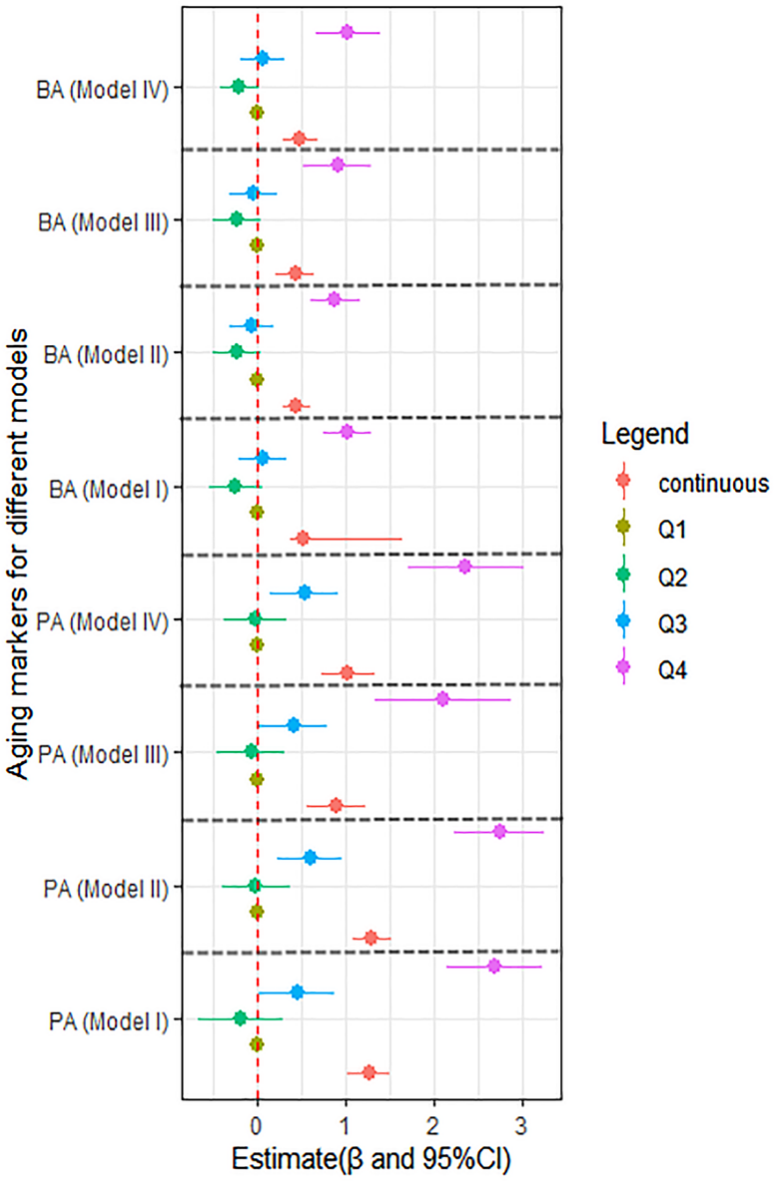

Figure 3

Weighted regression coefficients (95% CI) in ln-transformedblood cadmium concentration associated with aging markers.

Model I: Adjusting for age, gender, and NHANES cycle. Model II: Model I + adjusting for race, educational level, FIR, BMI, and marital status. Model III: Model II + adjusted for physical activity, drinking, and ln-transformed serum cotinine. Model IV: Model III + adjusted for DM, hypertension, and CVD. Abbreviations: FIR: Family income-to-poverty ratio; BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; Cd: cadmium; CI: Confidence interval; PA: phenotypic age; BA: biological age; Ref: reference; $p < 0.05$: significant; Q1: First quartile; Q2: Second quartile; Q3: Third quartile; Q4: Fourth quartile.

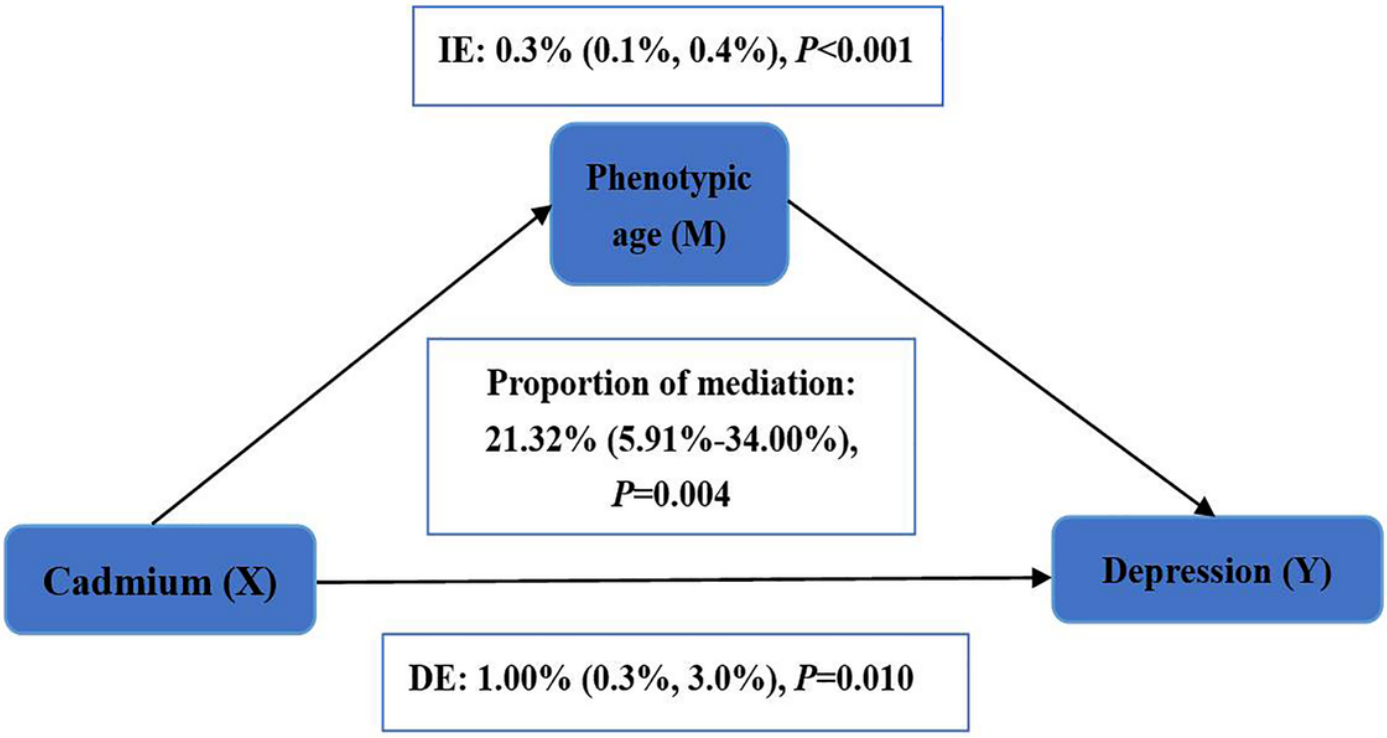

Figure 4

Estimated proportion of the association between blood cadmium and depression mediated by phenotypic age. Abbreviations: DE: direct effect; IE: indirect effect; CI: Confidence interval.

Supplementary Files

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