

Blood cadmium, smoking-related factors, and depressive symptoms among U.S. adults: a cross-sectional analysis of NHANES 2005–2020

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Research Article

Keywords: blood cadmium, depressive symptoms, tobacco exposure, NHANES, environmental epidemiology, cross-sectional study

Posted Date: August 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10466396/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Blood cadmium has been associated with depressive symptoms, but tobacco exposure is a major source of cadmium and is itself strongly related to depression. We examined the associations of blood cadmium and lead with depressive symptoms and assessed how estimates changed after accounting for smoking-related and lifestyle factors.

Methods

This cross-sectional study used data from 30,358 adults aged 20 years or older in the 2005–2020 pre-pandemic National Health and Nutrition Examination Survey. Depressive symptoms were defined as a Patient Health Questionnaire-9 score of at least 10. Blood cadmium and lead concentrations were natural-log transformed and standardized. Survey-weighted logistic regression was used to estimate associations across sequential covariate models. Quartile, restricted cubic spline, sensitivity, subgroup, and exploratory indirect-pathway analyses were also performed.

Results

The weighted prevalence of depressive symptoms was 7.81%. In the demographic- and socioeconomic-adjusted model, each 1-standard-deviation increase in log-transformed blood cadmium was associated with higher odds of depressive symptoms (odds ratio 1.258, 95% confidence interval 1.193–1.326), whereas blood lead was not (odds ratio 1.006, 95% confidence interval 0.930–1.087). Cadmium remained positively associated in the mutually adjusted lead–cadmium model (odds ratio 1.296, 95% confidence interval 1.228–1.367), and dose–response analyses were consistent with an approximately linear association. After additional adjustment for smoking and alcohol use, however, the cadmium estimate was attenuated to the null (odds ratio 1.020, 95% confidence interval 0.942–1.104); estimates also remained non-significant in models accounting for body mass index, serum cotinine, or chronic conditions. Exploratory analyses identified indirect-pathway signals involving inflammation, sleep disturbance, and nutritional factors, but these cross-sectional estimates cannot establish mediation.

Conclusions

Blood cadmium was associated with depressive symptoms before, but not after, adjustment for smoking-related and lifestyle factors. The findings do not support a strong association independent of tobacco-related factors and underscore the need for longitudinal studies with detailed measures of smoking and cumulative cadmium exposure.

Background

Depressive disorders are a major public health concern and a leading contributor to disability worldwide [1, 2]. Recent national estimates show that depressive symptoms remain common among both adolescents and adults in the United States [3, 4]. Because depression arises from interacting biological, social, behavioral, and environmental determinants, identifying potentially modifiable environmental contributors is an important public health objective [5, 6].

Lead and cadmium are persistent environmental toxicants to which exposure remains widespread through food, tobacco smoke, environmental contamination, and occupational sources [7–10]. Both metals can affect the nervous system through oxidative stress, mitochondrial dysfunction, inflammatory signaling, and other neurotoxic processes [11–14]. These mechanisms overlap with biological pathways implicated in depression, providing a plausible basis for epidemiologic associations.

Epidemiologic findings have nevertheless been inconsistent [15–19]. Studies in the United States, Korea, and China have reported positive associations between blood cadmium and depressive symptoms, but estimates have differed across populations and covariate specifications [16–18]. Smoking is particularly important because it is a major source of cadmium exposure and is also associated with depressive symptoms, socioeconomic disadvantage, alcohol use, sleep disturbance, and chronic disease [10, 20, 21]. Consequently, an apparent cadmium–depression association may reflect an independent toxic effect, residual confounding by tobacco exposure, or both.

Potential explanatory pathways also remain uncertain. Inflammation, oxidative stress, sleep disturbance, and nutritional status have each been linked to environmental exposures and depressive symptoms [6, 23–27]. Recent NHANES analyses have evaluated sleep duration, dietary fiber, and physical activity as potential mediators or modifiers of metal-related associations [22, 28, 29]. However, cross-sectional pathway analyses are vulnerable to temporal ambiguity and should be interpreted as hypothesis-generating rather than causal.

We therefore used nationally representative NHANES 2005–2020 pre-pandemic data to examine the associations of blood cadmium and lead with depressive symptoms among U.S. adults. Lead was evaluated as a comparator metal to determine whether any association was specific to cadmium rather than common to measured blood metals. We assessed the stability of estimates across sequential covariate models, with particular attention to smoking status and serum cotinine, and examined dose–response patterns, alternative outcome definitions, population subgroups, and exploratory indirect pathways.

Methods

Study design and population

We conducted a cross-sectional analysis of seven NHANES public-use data periods: 2005–2006 (n = 10,348), 2007–2008 (n = 10,149), 2009–2010 (n = 10,537), 2011–2012 (n = 9,756), 2013–2014 (n = 10,175), 2015–2016 (n = 9,971), and the combined 2017–March 2020 pre-pandemic period (n = 15,560). Together, the original public-use demographic files contained 76,496 participants of all ages before application of the study-specific eligibility criteria. The final data period was treated as a single nationally representative release in accordance with National Center for Health Statistics guidance.

NHANES uses a complex, multistage probability design to represent the civilian, non-institutionalized U.S. population [30, 31]. The National Center for Health Statistics Research Ethics Review Board approved all survey protocols, and all participants provided written informed consent. The present study used publicly available, de-identified data and required no additional ethics approval.

Adults aged 20 years or older were eligible. We excluded pregnant participants and those without valid survey-design variables or positive metal-specific sampling weights. Of 42,672 age-eligible, non-pregnant adults, 40,502 had valid design variables and positive metal weights, 36,310 had complete PHQ-9 data, and 33,466 had blood lead and cadmium measurements. The main analytic sample comprised 30,358 participants with complete PHQ-9 and blood lead/cadmium data. Complete cases were used for each model according to the availability of its covariates, mediators, and outcome.

Metal-specific examination weights, strata, and primary sampling units were incorporated in all analyses. Weights were rescaled for the combined survey period in accordance with NHANES guidance, including the special weighting procedures for the 2017–March 2020 pre-pandemic file [31, 32].

Depressive symptoms

Depressive symptoms during the preceding 2 weeks were assessed with the nine-item Patient Health Questionnaire (PHQ-9). Items are scored from 0 to 3 and summed to a total score of 0–27. The primary outcome was a PHQ-9 score of at least 10, a widely used threshold for clinically relevant depressive symptoms [33]. Sensitivity analyses treated the PHQ-9 score as continuous and used a threshold of at least 15 to identify more severe symptoms.

Blood lead and cadmium

Whole-blood lead and cadmium concentrations were measured using standardized mass spectrometry-based NHANES laboratory methods [34]. Lead was reported in $\mu\text{g}/\text{dL}$ and cadmium in $\mu\text{g}/\text{L}$. Because both distributions were right-skewed, concentrations were natural-log transformed and then standardized. Effect estimates therefore represent the change in the outcome per 1-standard-deviation increase in the log-transformed metal concentration.

Covariates and model specification

Covariates were selected a priori from previous NHANES analyses, epidemiologic evidence, and biological plausibility. Demographic variables were age, sex, race/ethnicity, and survey cycle. Socioeconomic variables were family poverty-income ratio, educational attainment, and marital status. Lifestyle and tobacco-related variables were smoking status, alcohol use, body mass index (BMI), and serum cotinine. Chronic conditions were hypertension, diabetes, and chronic kidney disease.

Six covariate specifications were used to show how estimates changed as smoking-related and other factors were introduced. Model 1 included age, sex, race/ethnicity, and survey cycle. Model 2 additionally included family poverty-income ratio, education, and marital status. Model 3 added smoking status and alcohol use to Model 2, and Model 4 further added BMI. Model 5 comprised Model 4 plus serum cotinine. Model 6 comprised Model 4 plus hypertension, diabetes, and chronic kidney disease; it did not additionally include serum cotinine.

Because smoking is both a major source of cadmium and an established correlate of depressive symptoms, results from the models with and without tobacco-related adjustment address different conditional associations. Model 2 was used as the common covariate set for dose–response, subgroup, and exploratory pathway analyses, while interpretation emphasized the pattern across all six models rather than any single specification. Inflammatory, sleep-related, and nutritional variables were not entered as ordinary covariates because they were evaluated as potential pathway factors.

Exploratory indirect-pathway analysis

We screened potential indirect pathways for both metals. Cadmium-related results were emphasized because cadmium showed the more consistent association under Model 2; lead-related results are provided in Additional file 1.

Candidate variables included white blood cell count, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, sleep duration, self-reported sleep problems, serum vitamin C, dietary fiber, dietary polyunsaturated fatty acids, dietary protein, dietary selenium, and dietary total fat. For each candidate, we estimated the exposure–mediator association and the mediator–outcome association conditional on exposure and Model 2 covariates. The indirect effect was calculated using the product-of-coefficients method, with Monte Carlo 95% confidence intervals [35]. False discovery rate correction accounted for multiple testing [36]. Each analysis used participants with complete data for the exposure, candidate variable, outcome, and covariates.

The ordering required for causal mediation cannot be established in cross-sectional NHANES data [37–39]. We therefore describe these estimates as exploratory indirect-pathway signals and do not interpret them as evidence that a mediator causally transmits the association.

Statistical analysis

Analyses incorporated sampling weights, strata, and primary sampling units using standard complex-survey methods [40]. Continuous characteristics are reported as weighted means with standard errors, and categorical characteristics as weighted percentages. Survey-weighted regression or chi-square tests were used for comparisons by depressive symptom status, as appropriate.

Survey-weighted logistic regression estimated odds ratios (ORs) and 95% confidence intervals (CIs) for depressive symptoms. A mutually adjusted model included both blood lead and cadmium under the Model 2 covariate set. Dose–response patterns were examined using weighted quartiles and restricted cubic splines [41]. Quartile trends were assessed by modeling quartile rank as an ordinal term. Spline models tested both the overall association and departure from linearity.

Sensitivity analyses used continuous PHQ-9 scores and the PHQ-9 threshold of at least 15. Subgroup analyses were conducted by sex, age group, smoking status, BMI category, and sleep-duration category; interaction terms were tested in survey-weighted models. All tests were two-sided. $P < 0.05$ was considered statistically significant, and false discovery rate-adjusted q values were used for exploratory pathway screening. Except for the pathway screen, analyses were not adjusted for multiple comparisons; subgroup findings were therefore considered exploratory.

Results

Study population and prevalence

The participant-selection process is shown in Fig. 1. Among 36,310 adults with complete PHQ-9 data, 3,245 met the depressive-symptom threshold. The main analytic sample included 30,358 participants with complete PHQ-9 and blood lead/cadmium data. The weighted prevalence of depressive symptoms was 7.81% (95% CI 7.36–8.25%).

Participant characteristics

Table 1 presents selected weighted characteristics; the complete set is provided in Additional file 1: Table S1. Compared with participants without depressive symptoms, those with depressive symptoms had a higher mean BMI, lower family poverty-income ratio, higher blood cadmium concentration, and higher serum cotinine concentration. Mean age and blood lead concentration did not differ materially between groups.

Participants with depressive symptoms were more often women, current smokers, less highly educated, and widowed, divorced, or separated. They also reported sleep problems more frequently and had higher prevalences of hypertension, diabetes, and chronic kidney disease. In the expanded table, the depressive-symptom group had lower mean energy, selenium, fiber, and polyunsaturated fatty acid intake and lower serum vitamin C and alpha-tocopherol concentrations, together with higher C-reactive protein, white blood cell count, and neutrophil-to-lymphocyte ratio.

Table 1
Weighted characteristics according to depressive symptom status

Variable	No depressive symptoms	Depressive symptoms	<i>P</i> value
Continuous variables, mean (SE)			
Age, years	47.914 (0.241)	47.139 (0.476)	0.133
BMI, kg/m ²	29.049 (0.088)	30.907 (0.237)	< 0.001
Family poverty-income ratio	3.115 (0.034)	2.135 (0.059)	< 0.001
PHQ-9 total score	2.118 (0.023)	14.077 (0.075)	< 0.001
Blood lead, µg/dL	1.387 (0.019)	1.329 (0.036)	0.085
Blood cadmium, µg/L	0.459 (0.006)	0.682 (0.022)	< 0.001
Serum cotinine, ng/mL	53.623 (1.610)	100.897 (5.030)	< 0.001
Sleep duration, h	7.218 (0.015)	7.030 (0.084)	0.028
Categorical variables, weighted %			
Sex			< 0.001
Male	50.2%	36.0%	
Female	49.8%	64.0%	
Race/ethnicity			< 0.001
Mexican American	8.3%	7.7%	
Other Hispanic	5.5%	8.0%	
Non-Hispanic White	68.0%	63.6%	
Non-Hispanic Black	10.8%	13.4%	
Non-Hispanic Asian	3.6%	1.4%	
Other race/multiracial	3.9%	5.8%	
Education level			< 0.001
<High school	14.0%	24.5%	
High school/GED	23.1%	27.9%	
Some college/AA	31.5%	33.3%	
Note. Values are weighted mean (standard error) or weighted percentage. <i>P</i> values were obtained from survey-weighted regression or chi-square tests, as appropriate. BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.			

Variable	No depressive symptoms	Depressive symptoms	<i>P</i> value
College or above	31.3%	14.3%	
Marital status			< 0.001
Married/partnered	64.6%	47.8%	
Widowed/divorced/separated	17.7%	30.3%	
Never married	17.8%	21.9%	
Smoking status			< 0.001
Never	56.3%	38.7%	
Former	25.8%	22.4%	
Current	17.9%	38.9%	
Alcohol status			< 0.001
Never	15.1%	14.1%	
Former/not current	17.4%	24.5%	
Current	67.4%	61.4%	
Sleep problem			< 0.001
No	73.7%	35.0%	
Yes	26.3%	65.0%	
Hypertension			< 0.001
No	68.3%	55.4%	
Yes	31.7%	44.6%	
Diabetes			< 0.001
No/borderline	90.5%	84.0%	
Yes	9.5%	16.0%	
Chronic kidney disease			< 0.001
No	97.6%	93.1%	
Yes	2.4%	6.9%	
Note. Values are weighted mean (standard error) or weighted percentage. <i>P</i> values were obtained from survey-weighted regression or chi-square tests, as appropriate. BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.			

Associations of blood lead and cadmium with depressive symptoms

Table 2 summarizes the sequential regression models. In Model 1, both lead (OR 1.099, 95% CI 1.021–1.183; $P = 0.014$) and cadmium (OR 1.457, 95% CI 1.381–1.538; $P < 0.001$) were associated with higher odds of depressive symptoms. After socioeconomic adjustment in Model 2, the lead estimate was null (OR 1.006, 95% CI 0.930–1.087), whereas cadmium remained positively associated (OR 1.258, 95% CI 1.193–1.326).

Adding smoking status and alcohol use attenuated the cadmium estimate to the null (Model 3: OR 1.020, 95% CI 0.942–1.104). Cadmium was also not statistically significant after further adjustment for BMI (Model 4), after adding serum cotinine to Model 4 (Model 5), or after adding chronic conditions to Model 4 (Model 6). These models provide no evidence of a strong cadmium association independent of the included tobacco-related and lifestyle factors.

Table 2
Sequential associations of blood metals with depressive symptoms

Covariate specification	Blood lead OR (95% CI)	<i>P</i> value	Blood cadmium OR (95% CI)	<i>P</i> value
Model 1: demographic factors	1.099 (1.021–1.183)	0.014	1.457 (1.381–1.538)	< 0.001
Model 2: Model 1 + socioeconomic factors	1.006 (0.930–1.087)	0.886	1.258 (1.193–1.326)	< 0.001
Model 3: Model 2 + smoking and alcohol use	0.915 (0.839–0.997)	0.046	1.020 (0.942–1.104)	0.634
Model 4: Model 3 + BMI	0.970 (0.885–1.063)	0.519	1.064 (0.989–1.145)	0.097
Model 5: Model 4 + serum cotinine	0.950 (0.868–1.040)	0.272	1.033 (0.959–1.113)	0.396
Model 6: Model 4 + chronic conditions	0.978 (0.889–1.075)	0.643	1.064 (0.987–1.147)	0.112
Note. Blood lead and cadmium were natural-log transformed and standardized. Demographic factors were age, sex, race/ethnicity, and survey cycle. Socioeconomic factors were family poverty-income ratio, education, and marital status. Chronic conditions were hypertension, diabetes, and chronic kidney disease. Models 5 and 6 were separate extensions of Model 4; Model 6 did not additionally include serum cotinine. BMI, body mass index; CI, confidence interval; OR, odds ratio.				

When both metals were included simultaneously under the Model 2 covariate set, cadmium remained positively associated with depressive symptoms (OR 1.296, 95% CI 1.228–1.367), whereas lead was inversely associated (OR 0.896, 95% CI 0.823–0.975) (Table 3). Because the lead estimate changed direction after mutual adjustment and no corresponding dose–response pattern was observed, it was not interpreted as evidence of a protective association.

Table 3
Mutually adjusted associations of blood metals with depressive symptoms

Exposure	OR (95% CI)	P value
Blood lead	0.896 (0.823–0.975)	0.012
Blood cadmium	1.296 (1.228–1.367)	< 0.001
Note. Both metals were included simultaneously and were natural-log transformed and standardized. The model adjusted for age, sex, race/ethnicity, survey cycle, family poverty-income ratio, education, and marital status. CI, confidence interval; OR, odds ratio.		

Dose–response analyses

Blood lead quartiles were not associated with progressively higher odds of depressive symptoms, and the trend test was null (P for trend = 0.824). By contrast, participants in the highest cadmium quartile had higher odds than those in the lowest quartile (OR 1.796, 95% CI 1.492–2.162), with evidence of a positive trend across quartiles (P for trend < 0.001) (Table 4).

Table 4
Quartile associations of blood metals with depressive symptoms

Metal	Exposure category	OR (95% CI)	P value
Blood lead	Q2 versus Q1	1.199 (0.968–1.485)	0.100
Blood lead	Q3 versus Q1	1.086 (0.876–1.346)	0.455
Blood lead	Q4 versus Q1	1.061 (0.843–1.335)	0.614
Blood lead	Per-quartile increase	1.008 (0.941–1.080)	0.824
Blood cadmium	Q2 versus Q1	1.172 (0.942–1.458)	0.158
Blood cadmium	Q3 versus Q1	1.195 (0.930–1.534)	0.167
Blood cadmium	Q4 versus Q1	1.796 (1.492–2.162)	< 0.001
Blood cadmium	Per-quartile increase	1.211 (1.141–1.285)	< 0.001
Note. Models adjusted for age, sex, race/ethnicity, survey cycle, family poverty-income ratio, education, and marital status. Q1 was the reference. The P value for the per-quartile estimate is the trend test. CI, confidence interval; OR, odds ratio.			

Restricted cubic splines were consistent with the quartile results (Fig. 2; Additional file 1: Table S2). For lead, neither the overall association nor the nonlinear component was significant (P overall = 0.609; P nonlinearity = 0.462). For cadmium, the overall association was significant (P overall < 0.001), with no evidence of departure from linearity (P nonlinearity = 0.357).

Legend. Panel A shows blood lead and panel B blood cadmium. Solid lines are adjusted odds ratios and shaded areas are 95% confidence intervals. Vertical dashed lines indicate reference concentrations;

horizontal dashed lines indicate an odds ratio of 1. Models adjusted for age, sex, race/ethnicity, survey cycle, family poverty-income ratio, education, and marital status.

Sensitivity analyses

Alternative outcome definitions yielded results similar to Model 2 (Additional file 1: Table S3). Blood cadmium was associated with a higher continuous PHQ-9 score (β 0.337, 95% CI 0.265–0.409) and with PHQ-9 ≥ 15 (OR 1.195, 95% CI 1.096–1.303), whereas blood lead was not associated with either outcome.

Exploratory indirect-pathway analyses

Table 5 presents cadmium-related pathways that remained statistically significant after false discovery rate correction; lead-related results are provided in Additional file 1: Table S4. White blood cell count showed an indirect-effect OR of 1.020 (95% CI 1.011–1.029; false discovery rate-adjusted $q < 0.001$), corresponding to 8.6% of the total association under the decomposition used. Self-reported sleep problems showed an indirect-effect OR of 1.028 (95% CI 1.013–1.044; $q < 0.001$) and a proportion of 12.0%. The sleep result warrants particular caution because sleep disturbance overlaps conceptually and empirically with depressive symptom measurement.

Dietary fiber, polyunsaturated fatty acids, protein, selenium, and total fat also showed small positive indirect-effect estimates. The systemic immune-inflammation index, systemic inflammation response index, and neutrophil-to-lymphocyte ratio had statistically significant but small estimates. Serum vitamin C had the largest estimated proportion, but its analysis was based on a substantially smaller sample and is not directly comparable with the other pathways. Collectively, these analyses identify candidate inflammatory, sleep-related, and nutritional pathways but do not establish temporal or causal mediation.

Table 5
Exploratory indirect pathways for blood cadmium and depressive symptoms

Mediator	n	Events	Indirect-effect OR (95% CI)	FDR-adjusted <i>q</i>	Proportion mediated
White blood cell count	27,607	2,421	1.020 (1.011, 1.029)	< 0.001	8.6%
Serum vitamin C	3,627	228	1.073 (1.032, 1.120)	< 0.001	37.8%
Dietary fiber	23,741	2,136	1.008 (1.004, 1.012)	< 0.001	3.3%
Dietary PUFA	23,741	2,136	1.006 (1.002, 1.009)	< 0.001	2.3%
Dietary protein	23,741	2,136	1.006 (1.003, 1.011)	< 0.001	2.7%
Sleep problem	27,650	2,425	1.028 (1.013, 1.044)	< 0.001	12.0%
Dietary selenium	23,741	2,136	1.006 (1.002, 1.010)	< 0.001	2.3%
Systemic immune-inflammation index	27,569	2,415	1.003 (1.001, 1.006)	0.017	1.2%
Systemic inflammation response index	27,569	2,415	1.006 (1.002, 1.011)	0.017	2.7%
Dietary total fat	23,741	2,136	1.002 (1.000, 1.004)	0.024	0.9%
Neutrophil-to-lymphocyte ratio	27,569	2,415	1.002 (1.000, 1.005)	0.041	1.0%
Note. Models were adjusted for age, sex, race/ethnicity, survey cycle, family poverty-income ratio, education, and marital status. Indirect effects were estimated using the product-of-coefficients method with Monte Carlo 95% confidence intervals. These cross-sectional estimates are descriptive and should not be interpreted as causal mediation.					

Legend. Panels show pathways through white blood cell count, sleep problems, inflammatory indices, and nutritional factors. Blue arrows represent exposure–candidate and candidate–outcome paths; red arrows represent the exposure–outcome association conditional on the candidate. Indirect effects used the product-of-coefficients method with Monte Carlo 95% confidence intervals and false discovery rate correction. Because NHANES is cross-sectional, the paths should not be interpreted as causal mediation.

Subgroup and interaction analyses

Subgroup estimates are provided in Additional file 1: Table S5 and interaction tests in Table S6. Cadmium was positively associated with depressive symptoms in both sexes and across BMI and sleep-duration categories under the Model 2 covariate set. The association was stronger among adults aged 20–59 years than among those aged at least 60 years (P for interaction = 0.003), and evidence of interaction was also observed for BMI category (P = 0.035). Interaction by smoking status was not statistically significant (P = 0.080), although the positive within-stratum estimate was confined to current smokers. Given the number of comparisons, these findings should be considered exploratory.

Discussion

In this nationally representative cross-sectional study, blood cadmium was associated with depressive symptoms after adjustment for demographic and socioeconomic factors, whereas blood lead was not. The cadmium association followed an approximately linear dose–response pattern under this covariate set and persisted when lead was included in the same model. However, the estimate was attenuated to the null after smoking status and alcohol use were added and remained non-significant in models that additionally accounted for BMI, serum cotinine, or chronic conditions. Thus, the principal finding is the sensitivity of the cadmium estimate to tobacco-related and lifestyle adjustment, rather than evidence of a robust association independent of those factors.

This pattern helps reconcile previously inconsistent findings [15–19]. Positive associations between blood cadmium and depressive symptoms have been reported in U.S., Korean, and Chinese populations [16–18]. Scinicariello and Buser observed an association in NHANES young adults [18], whereas Kostrubiak and colleagues showed substantial attenuation when smoking history and cotinine were more fully considered [19]. Our results reproduce both features: a clear association under demographic and socioeconomic adjustment and little evidence of an association conditional on measured smoking-related factors. Differences in exposure distributions, smoking patterns, outcome definitions, and covariate strategies may therefore explain part of the heterogeneity across studies.

An association remains biologically plausible. Cadmium may affect the nervous system through mitochondrial dysfunction, altered neurotransmitter signaling, oxidative stress, and inflammatory responses [9, 12, 13]. Oxidative and inflammatory processes have also been implicated in serotonergic dysfunction, impaired neurogenesis, altered synaptic plasticity, and stress-related changes in depression [6, 24, 25, 27]. These mechanisms justify continued investigation, but biological plausibility alone cannot distinguish a direct cadmium effect from confounding in observational data.

The attenuation after tobacco-related adjustment is therefore central. Smoking is a major source of cadmium and is also associated with depressive symptoms and a cluster of socioeconomic, behavioral, and health characteristics [5, 10, 20, 21]. Models containing smoking status and cotinine estimate the cadmium association conditional on measured tobacco exposure; the resulting null estimates argue against a large independent association in these data. At the same time, the strong correlation between tobacco exposure and blood cadmium can reduce the independent exposure contrast and increase

uncertainty. The sequential models should consequently be read together: they demonstrate how strongly the estimate depends on the treatment of tobacco-related factors, but they do not by themselves identify the causal structure [10, 19].

Blood lead showed no consistent pattern. Its positive estimate in Model 1 disappeared after socioeconomic adjustment, quartile and spline analyses did not indicate a dose–response association, and the estimate became inverse when cadmium was included simultaneously. That reversal may reflect statistical suppression, shared exposure sources, collinearity, or residual confounding. It should not be interpreted as a protective effect. Lead therefore served primarily as a comparator, supporting the specificity of the cadmium signal observed before tobacco-related adjustment rather than a general association across measured blood metals [11, 14, 15].

The exploratory pathway analyses provide hypotheses rather than mechanistic proof. White blood cell count and composite inflammatory indices showed small indirect-effect estimates, consistent with evidence linking cadmium to systemic inflammation and inflammation to depression [6, 24, 25, 42]. Sleep problems also showed an indirect-pathway signal, but sleep disturbance is both a contributor to and a symptom of depression [23, 43, 44]. Cross-sectional measurement further precludes establishing whether sleep disturbance preceded depressive symptoms. The sleep finding should therefore be treated as descriptive.

Several dietary and nutritional variables also had small indirect-effect estimates [26, 45–48]. The vitamin C estimate was larger but came from a much smaller subsample, making comparison with the other pathways inappropriate. Antioxidant status and diet may influence cadmium absorption, oxidative balance, inflammation, and mental health [5, 26, 49]. A recent NHANES study also reported modification of the cadmium–depression association by dietary fiber [28]. These observations support further prospective work with repeated exposure, diet, and biomarker measurements.

Age and BMI showed statistical evidence of interaction, and the smoking-stratified association was apparent only among current smokers. These patterns are compatible with differences in exposure source, toxicokinetics, adiposity, or residual tobacco exposure, but the subgroup analyses involved multiple comparisons and were not multiplicity-adjusted. They should not be viewed as confirmatory evidence of effect modification.

This study has several strengths. It used a large, nationally representative sample across multiple NHANES cycles; incorporated the complex survey design; and relied on standardized laboratory measurements and a validated depressive-symptom instrument. The sequential covariate framework made the dependence of the cadmium estimate on smoking-related adjustment explicit. The analysis also examined dose–response form, alternative outcomes, subgroups, and candidate indirect pathways.

Several limitations warrant emphasis. First, the cross-sectional design precludes determining whether cadmium exposure preceded depressive symptoms or whether depression-related behaviors contributed to exposure [37–39]. Second, PHQ-9 is a screening instrument rather than a clinical diagnosis, and the $\geq$

10 threshold does not directly estimate the prevalence of major depressive disorder [33, 50]. Third, residual confounding may remain from smoking intensity and duration, secondhand smoke, occupational exposures, diet, co-exposures, and psychosocial stressors. Fourth, a single blood measurement may not capture cumulative body burden or etiologically relevant exposure windows. Fifth, the exploratory pathway analyses cannot establish temporal ordering or causal mediation [37, 38]. Finally, mediator availability varied by survey cycle, and the vitamin C analysis in particular had a substantially smaller sample. Recent prospective mixture research has also shown that individual metals can act in opposing directions [51], reinforcing the need for longitudinal, mixture-aware analyses with repeated measurements.

Conclusions

Blood cadmium was associated with depressive symptoms among U.S. adults after demographic and socioeconomic adjustment, but the association was not evident after smoking-related and lifestyle factors were included. Blood lead showed no consistent association. These results suggest that tobacco exposure and correlated behavioral or social factors account for much of the observed cadmium signal and do not support a strong association independent of those factors. Longitudinal studies with repeated measures of cadmium, detailed tobacco exposure, and temporally ordered pathway variables are needed.

Abbreviations

BMI	
body mass index	
CI	
confidence interval	
CRP	
C-reactive protein	
FDR	
false discovery rate	
NHANES	
National Health and Nutrition Examination Survey	
NLR	
neutrophil-to-lymphocyte ratio	
OR	
odds ratio	
PHQ-9	
Patient Health Questionnaire-9	
PUFA	
polyunsaturated fatty acid	
SII	

systemic immune-inflammation index
SIRI
systemic inflammation response index
WBC
white blood cell.

Declarations

Ethics approval and consent to participate

All NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board, and written informed consent was obtained from all participants. This secondary analysis used publicly available, de-identified data and required no additional ethics approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Supplementary information

Additional file 1 (.docx). Supplementary tables S1–S6, including complete weighted participant characteristics, restricted cubic spline tests, sensitivity analyses, exploratory lead-related indirect pathways, subgroup estimates, and interaction tests.

Funding

The authors received no funding for this study.

Author Contribution

KL conceptualized the study, developed the methodology, performed the formal analysis and visualization, and drafted the manuscript. MH interpreted the findings and critically reviewed and revised the manuscript. RYP supervised the study, contributed to its conceptualization, and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the participants and staff of the National Health and Nutrition Examination Survey.

Data Availability

The datasets analysed during the current study are publicly available from the National Center for Health Statistics NHANES repository: <https://www.cdc.gov/nchs/nhanes/> . This study used the 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–March 2020 pre-pandemic public-use datasets. The datasets and accompanying documentation can be downloaded directly from the NHANES website without special permission. No new datasets were generated during this study.

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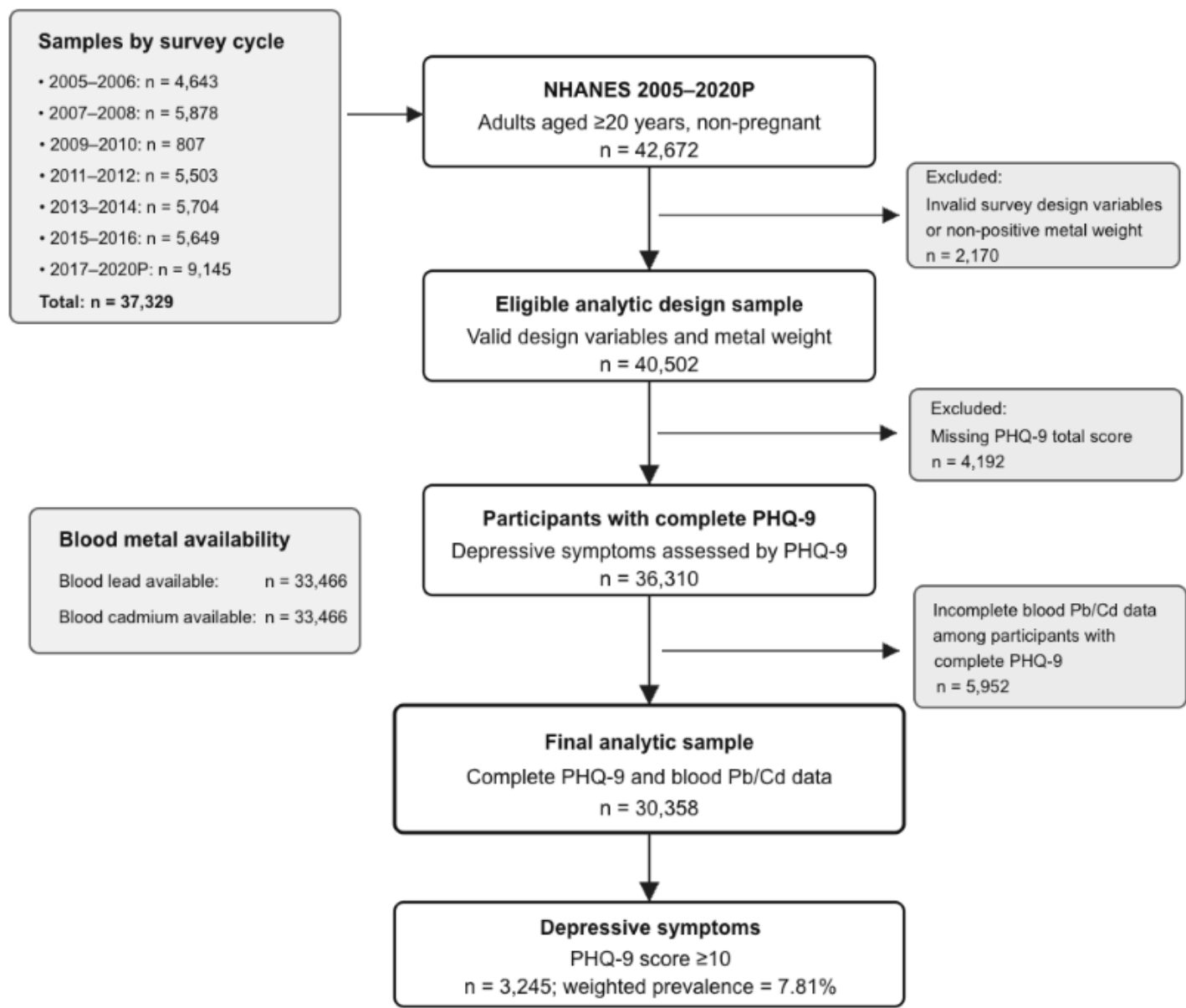
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Figures



Note: Pb, lead; Cd, cadmium; PHQ-9, Patient Health Questionnaire-9.

Figure 1

Flow chart of participant inclusion and exclusion.

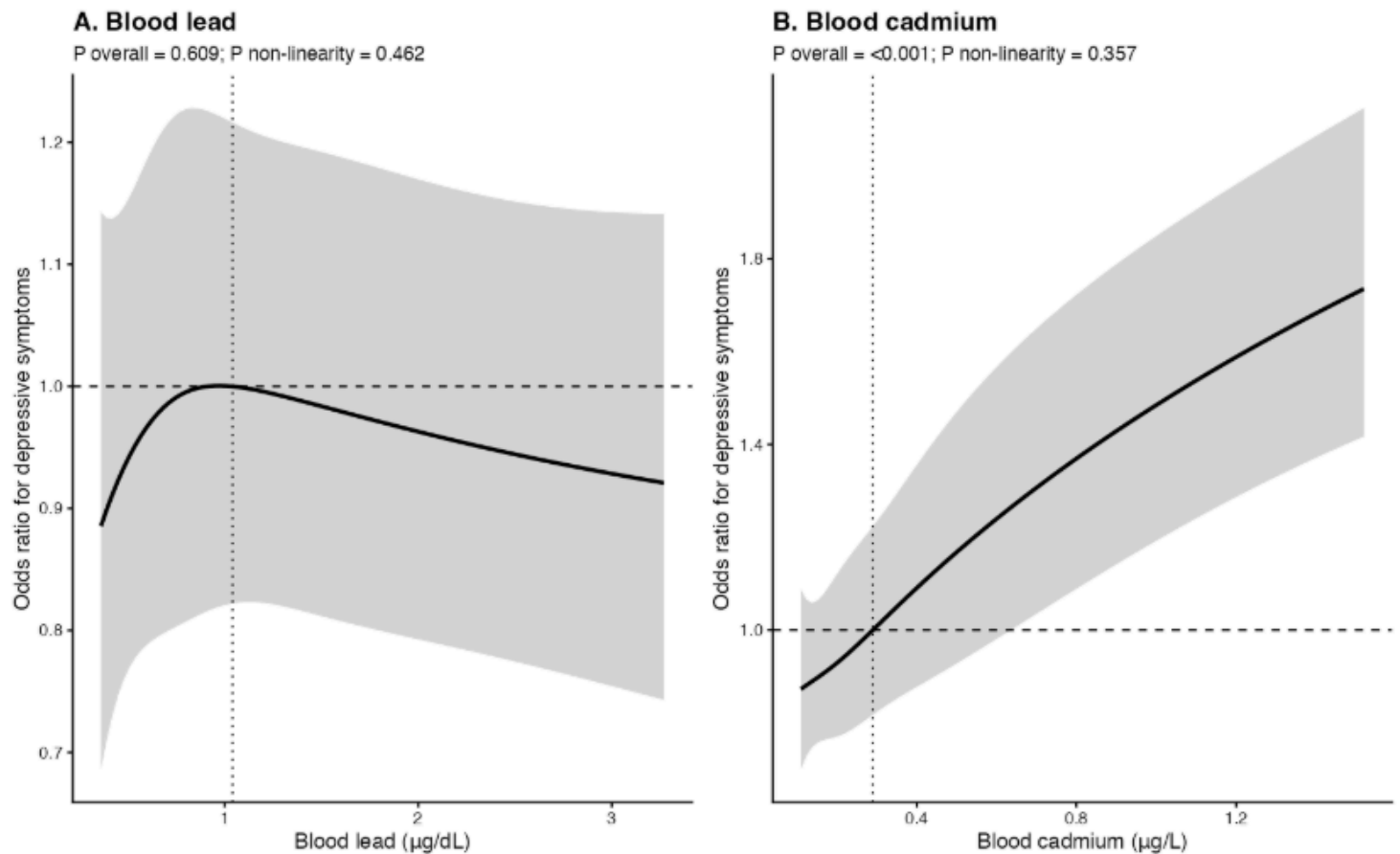


Figure 2

Restricted cubic spline associations of blood metals with depressive symptoms.

Legend. Panel A shows blood lead and panel B blood cadmium. Solid lines are adjusted odds ratios and shaded areas are 95% confidence intervals. Vertical dashed lines indicate reference concentrations; horizontal dashed lines indicate an odds ratio of 1. Models adjusted for age, sex, race/ethnicity, survey cycle, family poverty-income ratio, education, and marital status.

Exploratory mediation pathways between blood cadmium and depressive symptoms

Main mediation model adjusted for age, sex, race/ethnicity, survey cycle, poverty-income ratio, education, and marital status

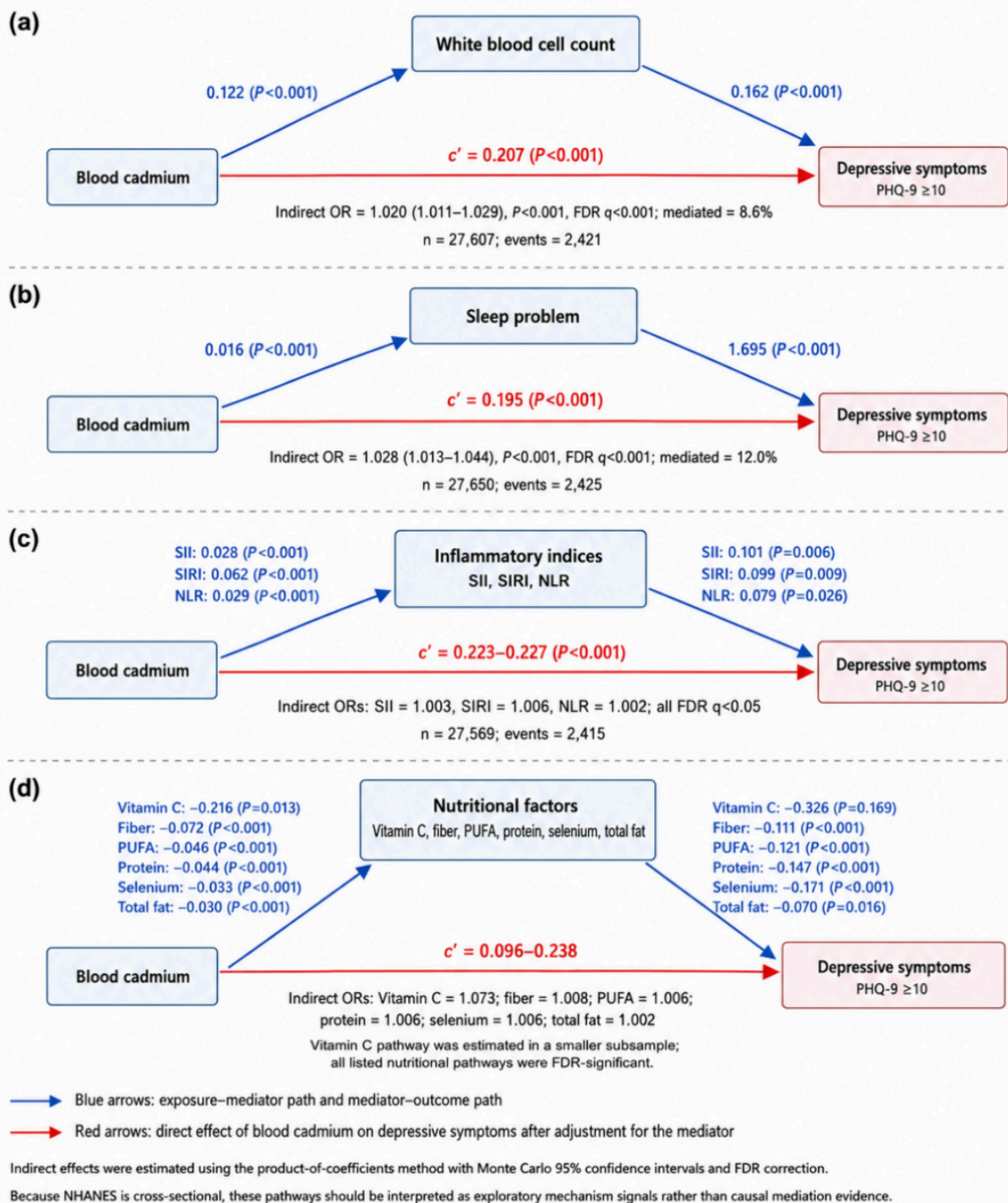


Figure 3

Exploratory indirect pathways linking blood cadmium to depressive symptoms.

Legend. Panels show pathways through white blood cell count, sleep problems, inflammatory indices, and nutritional factors. Blue arrows represent exposure–candidate and candidate–outcome paths; red arrows represent the exposure–outcome association conditional on the candidate. Indirect effects used

the product-of-coefficients method with Monte Carlo 95% confidence intervals and false discovery rate correction. Because NHANES is cross-sectional, the paths should not be interpreted as causal mediation.

Supplementary Files

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