Cadmium, Lead, and Depressive Symptoms: Analysis of National Health and Nutrition Examination Survey 2011–2012

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ABSTRACT

Background: Several studies have noted an association between tobacco smoke and depression. Cadmium and lead are neurotoxicant components of tobacco smoke. The objective of the present study is to investigate the potential association between blood cadmium (BCd) and blood lead (BPb) with current depressive symptoms in the US adult population.

Methods: We conducted cross-sectional analyses of adult participants (≥ 20 years) from the National Health and Nutrition Examination Survey 2011–2012 (N = 3,905). Multivariate logistic regressions were used to analyze the association between BCd and BPb with depressive symptoms; analyses were also stratified on sex and age groups (20–47 years and ≥ 48 years). Presence or absence of depressive symptoms was determined using the Patient Health Questionnaire module.

Results: Individuals in the highest quartile of BCd had higher odds of having depressive symptoms (odds ratio = 1.68; 95% confidence limits: 1.12, 2.51). This association was found only in male participants and, more specifically, in younger adult male participants (20–47 years). We found that BPb, cigarette smoking, and obesity were associated with depressive symptoms in younger female adults.

Conclusions: In this study, we report associations between BCd and BPb with current depressive symptoms that were modified by age and sex. Reverse causation cannot be ruled out as a possible explanation since depression may lead to behavioral changes that increase exposure to cadmium and lead (ie, tobacco smoke). The continued efforts at reducing cadmium through tobacco smoking cessation programs may decrease the prevalence of current depressive symptoms.

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Depression is a common mental disorder with an estimated prevalence of 9.1% among US adults (18 years and older).[1] Moreover, depression has become an important cause of disability worldwide, which is also reflected in decreased work productivity.[2] Genetic and environmental factors contribute to the risk of depression.[3] Additionally, it has been suggested that sex differences play a role in the development of depression, with women having higher rates.[4]

Cigarette smoking is strongly associated with depression, and this association may be bidirectional: smoking increases the risk of depression,[5,6] and, on the other hand, depression increases the use of cigarette smoking as a self-medicating behavior.[7,8] Although smoking is more common in males,[9] depression is more commonly associated with smoking in women than men.[10,11]

More than 8,400 chemical constituents are present in tobacco and tobacco smoke.[12] Among them are the heavy metals cadmium and lead. Cadmium is a widespread industrial and environmental pollutant, with inhalation being the primary route of exposure.[13] Moreover, cadmium from cigarette smoking is a significant source of environmental exposure.[13] Cadmium is also present in low amounts in food, but dietary intake and gastrointestinal absorption are minimal.[13] Cadmium toxicity affects several organs including kidney, lung, liver, and brain[13]; an association between blood cadmium and depressive symptoms was recently reported in young adults.[14] Lead is a neurotoxicant,[15] and the association between blood lead and depression has shown inconsistent results, with one study reporting a positive association[16] while several others found no statistically significant association.[14,17]

The objective of the present study was to investigate the potential association between blood cadmium and blood lead with current depressive symptoms in the National Health and Nutrition Examination Survey (NHANES) 2011–2012. Additionally, we conducted stratified analyses to identify differences in risk factors associated with current depression symptoms by sex and age.

METHODS

Study Population

NHANES is a cross-sectional, nationally representative survey of the non-institutionalized civilian population of the United States conducted annually by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC).[18] For our study, we used the publicly available files for NHANES 2011–2012. The survey employs a multistage stratified probability sample based on selected counties, blocks, households, and persons within households.

NCHS-trained professionals conducted interviews and extensive physical examinations in participants' homes and collected blood and urine samples at mobile examination centers. All procedures were approved by the NCHS Research Ethics Review Board (Continuation of Protocol #2011-17 http://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants provided written informed consent. CDC/ATSDR determined that our present research did not meet the criteria for human research as per federal regulation and therefore did not require review. For our analyses, we included adult participants (≥ 20 years of age) who answered the Patient Health Questionnaire (PHQ)-9 module

Clinical Points

- Cadmium and lead are neurotoxic substances, and few epidemiologic studies have addressed the possible association of these metals with depression.
- Given that cadmium and lead are associated with several chronic diseases, the benefits of smoking cessation are multifold by decreasing the incidence of smoking-related diseases as well as cadmium- and lead-associated diseases.

(N = 3,905). Pregnant women and women breastfeeding were excluded; however, inclusion of these persons did not change the statistical significance of our analyses (data not shown). Additionally, participants with missing covariables included in the multivariable-adjusted models were excluded for a final sample size of 3,903 participants.

Outcome Measure

The outcome was the presence or absence of depressive symptoms as determined by a participant's score on the PHQ-9, a self-administered version of the depression module of the Primary Care Evaluation of Mental Disorders Questionnaire.[19] PHQ-9 contains 9 questions about the frequency of symptoms of depression over the past 2 weeks that are used as a depression screener in NHANES 2011–2012. These are based on the 9 signs and symptoms for depression listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*). Responses to these 9 questions were on a 4-point Likert scale of 0 to 3, indicating that the participant experienced the symptom "not at all," "on several days," "on more than half the days," or "nearly every day" during the past 2 weeks for a total score ranging from 0 to 27. A prior validation study found that a score 10 or higher achieved 88% sensitivity and 88% specificity for major depression.[19] Therefore, a participant who scored of 10 or more was defined as having depressive symptoms.

Exposure Measures

Whole blood cadmium (BCd) and blood lead (BPb) concentrations were measured using inductively coupled plasma mass spectrometry by CDC's National Center for Environmental Health, Division of Laboratory Sciences. Detailed methodology and quality assurance/quality control instructions are discussed in the NHANES Laboratory Procedures Manual (http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/PbCd_E_met_lead_cadmium.pdf; http://www.cdc.gov/NCHS/data/nhanes/nhanes_09_10/PbCd_F_met.pdf).

BCd and BPb were categorized as weighted quartiles based on the distribution of the metals levels among the study population. Participants who had BCd or BPb values below the limit of detection (LOD 2011–2012: 0.16 µg/L for BCd and 0.25 µg/dL for BPb) were assigned the LOD divided by the square root of 2, as recommended by NHANES. The percentages of participants in the study with measurement below LOD were 14.17% for BCd and 0.66% for BPb.

Table 1. Sample Size and Weighted Characteristics of Adult Participants in NHANES 2011–2012

Characteristic	All (N = 3,905)	Men (n = 1,998)	Women (n = 1,907)
Men, % (SE)	50.08 (0.90)		
Women, % (SE)	49.92 (0.90)		
Blood cadmium, µg/L, GM (SE)	0.33 (0.01)	0.30 (0.01)	0.37 (0.01)
Blood lead, µg/dL, GM (SE)	1.09 (0.03)	1.29 (0.04)	0.93 (0.03)
Age, y, GM (SE)	44.33 (0.98)	43.41 (0.96)	45.27 (1.05)
BMI, kg/m^2, GM (SE)	28.16 (0.22)	28.05 (0.23)	28.28 (0.23)
Serum cotinine, ng/mL, GM (SE)	0.23 (0.03)	0.40 (0.07)	0.14 (0.02)
Depression, % (SE)			
Yes	9.38 (1.02)	7.30 (0.99)	11.46 (1.24)
No	90.62 (1.02)	92.70 (0.99)	88.54 (1.24)
Body weight status, % (SE)			
Underweight/normal weight	30.29 (1.76)	28.10 (1.62)	32.49 (2.05)
Overweight	33.60 (1.44)	37.47 (1.58)	29.73 (2.01)
Obese	36.11 (1.53)	34.43 (1.51)	37.79 (2.04)
Poverty income ratio, % (SE)			
Below or equal poverty line	16.25 (1.63)	15.61 (1.72)	16.90 (1.66)
Above poverty line	83.75 (1.63)	84.39 (1.72)	83.10 (1.66)
Smoking status, % (SE)			
Current smoker	19.78 (1.11)	23.17 (1.66)	16.39 (1.37)
Former smoker	25.05 (1.48)	27.22 (1.76)	22.87 (2.13)
Never smoked	55.17 (1.50)	49.61 (1.99)	60.74 (1.92)
Alcohol consumption, % (SE)			
No alcohol	18.64 (0.98)	10.11 (0.91)	27.19 (1.64)
1–4 drinks per week	73.16 (1.26)	76.61 (1.90)	69.71 (1.48)
> 4 drinks per week	8.20 (1.05)	13.29 (1.63)	3.10 (0.57)
Education level, % (SE)			
Less than high school	14.53 (1.79)	15.52 (1.86)	13.53 (1.84)
Completed high school	20.26 (1.58)	21.90 (1.99)	18.63 (1.52)
More than high school	65.21 (2.76)	62.58 (3.09)	67.84 (2.66)
Race/ethnicity, % (SE)			
Non-Hispanic White	69.64 (3.74)	69.91 (3.78)	69.37 (3.81)
Non-Hispanic Black	10.26 (2.09)	8.93 (1.93)	11.59 (2.28)
Hispanic	13.12 (2.45)	13.89 (2.63)	12.34 (2.33)
Other	6.98 (1.01)	7.27 (1.05)	6.70 (1.05)

Abbreviations: BMI = body mass index, GM = geometric mean, NHANES = National Health and Nutrition Examination Survey.

Covariates

Models were adjusted for a priori factors based on previous literature demonstrating an association with depression.[20–22] These include age (categorized in weighted quartiles), sex, race/ethnicity, education, poverty income ratio, obesity, alcohol consumption, cigarette smoking, and serum cotinine as a biomarker of tobacco smoke exposure. We obtained information about age (years), sex, race/ethnicity, and education from the household interview. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. Poverty income ratio is a measure of socioeconomic status and represents the calculated ratio of household income to the poverty threshold after accounting for inflation and family size. Body mass index (BMI) was obtained from the physical examination and was calculated by dividing measured weight in kilograms by measured height in meters squared. The adult population was classified as normal/underweight, overweight, and obese with BMI measures of < 25, 25–29.9, and ≥ 30 kg/m^2, respectively. Alcohol consumption (amount consumed per week) and smoking information were obtained from the associated questionnaire. Smoking status was defined as nonsmoker (smoke < 100 cigarettes ever), former smoker (not currently smoking, but has

smoked ≥ 100 cigarettes ever), and current smoker. Serum cotinine was categorized as weighted tertiles; because more than a third of the participants had serum cotinine levels below the limit of detection (LOD: 0.015 ng/mL), the lowest, referent tertile contained those participants with levels below the LOD. Furthermore, adding to our analyses chronic conditions such as self-reported diabetes, hypertension, self-reported cardiovascular disease (defined as an answer of yes to any of coronary artery disease, angina pectoris, heart attack, stroke, or congestive heart failure on the medical questionnaire) did not change the statistically significant association that we reported (data not shown).

Statistical Methods

The Mobile Examination Center exam sample weights were used for analyses to account for the complex sampling design and nonresponse of NHANES (http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/mecinterviewers.pdf). We used logistic regression to calculate adjusted odds to have depressive symptoms; odds ratios and 95% confidence intervals are reported in the tables. Furthermore, we stratified our analyses on sex and age group (20–47 years of age and > 47 years of age); age-group stratification was based on the weighted median of the study population. SAS 9.3 (SAS Institute, Cary, North Carolina) was used for all statistical analyses, and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, North Carolina) was used to account for the NHANES complex sample design. *P* values from Satterthwaite statistics were presented at the significance level ≤ .05.

RESULTS

Table 1 presents the characteristics of the study population. The geometric mean age of all participants was approximately 44 years, and women (average age of 45 years) were slightly older than men (average age of 43 years). Roughly 70% of the participants were either overweight or obese; the prevalence of obesity was higher in women (about 38%) than in men (34%). The geometric mean BCd levels for all, male, and female adult participants were 0.33 µg/L, 0.30 µg/L, and 0.37 µg/L, respectively; the geometric mean BPb levels for all, male, and female adult participants were 1.09 µg/dL, 1.29 µg/dL, and 0.93 µg/dL, respectively. Nearly 10% of all adult participants were categorized as having depressive symptoms, with a higher prevalence in women (11.5%) than in men (7.3%) (Table 1).

Multivariate logistic regression analyses found that among all adult participants, those in the highest quartile of BCd were statistically significantly associated with higher odds to have depressive symptoms (OR = 1.68, 95% confidence limits [CL]: 1.12, 2.51) compared to those in the lowest referent quartile (Table 2). After stratification by sex, this statistically significant association was found in adult male participants (OR = 2.59,

Table 2. Multivariate Logistic Regression[a] OR (95% CL) of Having Depression in NHANES 2011–2012 Adult Participants

	All (N = 3,903)	Men (n = 1,997)	Women (n = 1,906)
Depressed yes, n	429	170	259
Depressed no, n	3,474	1,827	1,647
Sex			
Men	1.00		
Women	1.78 (1.33, 2.37)***		
Race/ethnicity			
Non-Hispanic White	1.00	1.00	1.00
Non-Hispanic Black	0.98 (0.64, 1.49)	0.66 (0.40, 1.09)	1.16 (0.59, 2.28)
Hispanic	1.10 (0.66, 1.83)	0.98 (0.56, 1.72)	1.31 (0.68, 2.52)
Other	1.05 (0.70, 1.57)	0.71 (0.36, 1.38)	1.54 (0.84, 2.82)
Age quartile			
1 (20–32 years)	1.00	1.00	1.00
2 (33–47 years)	1.19 (0.74, 1.90)	0.85 (0.37, 1.96)	1.45 (0.77, 2.70)
3 (48–60 years)	1.55 (0.98, 2.46)	1.85 (0.94, 3.64)	1.41 (0.73, 2.70)
4 (> 60 years)	0.78 (0.42, 1.43)	0.57 (0.15, 2.12)	0.91 (0.43, 1.92)
Education level			
Less than high school	1.00	1.00	1.00
Completed high school	0.87 (0.52, 1.46)	0.97 (0.47, 2.00)	0.79 (0.47, 1.30)
More than high school	0.68 (0.37, 1.27)	0.64 (0.31, 1.32)	0.69 (0.37, 1.30)
Poverty income ratio			
≤ 1	1.00	1.00	1.00
> 1	0.41 (0.27, 0.63)***	0.40 (0.20, 0.82)*	0.46 (0.30, 0.73)**
Body weight status			
Underweight/normal	1.00	1.00	1.00
Overweight	1.11 (0.61, 2.01)	0.97 (0.42, 2.21)	1.16 (0.66, 2.05)
Obese	1.73 (1.06, 2.82)*	1.01 (0.47, 2.18)	2.48 (1.39, 4.45)**
Alcohol consumption			
No alcohol	1.00	1.00	1.00
1–4 drinks per week	1.02 (0.71, 1.46)	0.68 (0.37, 1.27)	1.10 (0.70, 1.75)
> 4 drinks per week	1.06 (0.54, 2.06)	0.52 (0.22, 1.20)	2.07 (0.70, 6.15)
Smoking status			
Current smoker	1.79 (1.19, 2.69)**	0.85 (0.43, 1.67)	3.50 (1.67, 7.31)**
Former smoker	1.46 (0.94, 2.28)	1.28 (0.68, 2.44)	1.76 (0.97, 3.20)
Never smoked	1.00	1.00	1.00
Serum cotinine tertile[b]			
Serum cotinine T1	1.00	1.00	1.00
Serum cotinine T2	0.76 (0.48, 1.22)	0.52 (0.25, 1.08)	0.93 (0.59, 1.45)
Serum cotinine T3	1.01 (0.71, 1.45)	1.23 (0.55, 2.74)	0.79 (0.43, 1.45)
Blood lead quartile[c]			
1	1.00	1.00	1.00
2	1.19 (1.00, 1.42)	0.89 (0.50, 1.58)	1.28 (0.96, 1.69)
3	1.26 (0.93, 1.71)	0.70 (0.33, 1.50)	1.72 (1.09, 2.71)*
4	0.94 (0.65, 1.35)	0.54 (0.24, 1.20)	1.20 (0.68, 2.11)
Blood cadmium quartile[d]			
1	1.00	1.00	1.00
2	1.12 (0.70, 1.77)	0.83 (0.46, 1.52)	1.66 (0.72, 3.85)
3	1.12 (0.67, 1.87)	1.08 (0.65, 1.79)	1.47 (0.64, 3.39)
4	1.68 (1.12, 2.51)*	2.59 (1.11, 6.00)*	1.58 (0.77, 3.24)

[a]Adjusted for sex, age, race/ethnicity, blood lead levels, obesity, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level.
[b]Cotinine tertiles: T1: < 0.016 ng/mL; T2: 0.016–0.13 ng/mL; T3: > 0.13 ng/mL.
[c]Lead quartiles: Q1: < 0.70 µg/dL; Q2: 0.70–1.06 µg/dL; Q3: 1.07–1.67 µg/dL; Q4: > 1.67 µg/dL.
[d]Cadmium quartiles: Q1: < 0.18 µg/L; Q2: 0.18–0.29 µg/L; Q3: 0.30–0.54 µg/L; Q4: > 0.54 µg/L.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviation: NHANES = National Health and Nutrition Examination Survey.

Table 3. Multivariate Logistic Regression[a] OR (95% CL) of Having Depression in NHANES 2011–2012 for Adult Participants Aged 20–47 Years

	All (N = 1,887)	Men (n = 1,007)	Women (n = 880)
Depressed yes, n	190	75	115
Depressed no, n	1,697	932	765
Sex			
Men	1.00		
Women	2.28 (1.63, 3.19)***		
Age	1.01 (0.98, 1.03)	1.00 (0.95, 1.05)	1.01 (0.97, 1.05)
Race/ethnicity			
Non-Hispanic White	1.00	1.00	1.00
Non-Hispanic Black	1.10 (0.62, 1.95)	0.65 (0.22, 1.91)	1.52 (0.69, 3.35)
Hispanic (Mexican-American and other)	1.20 (0.69, 2.10)	1.44 (0.66, 3.12)	1.35 (0.66, 2.78)
Other	1.48 (0.89, 2.46)	0.87 (0.28, 2.74)	2.43 (1.00, 5.92)
Education level			
Less than high school	1.00	1.00	1.00
Completed high school	1.10 (0.65, 1.87)	2.00 (1.17, 3.42)*	0.79 (0.29, 2.13)
More than high school	0.76 (0.55, 1.03)	1.25 (0.63, 2.49)	0.61 (0.39, 0.94)*
Poverty income ratio			
≤ 1	1.00	1.00	1.00
> 1	0.50 (0.30, 0.85)*	0.40 (0.17, 0.94)*	0.65 (0.34, 1.24)
Body weight status			
Underweight/normal	1.00	1.00	1.00
Overweight	1.47 (0.65, 3.34)	1.18 (0.42, 3.36)	1.52 (0.68, 3.42)
Obese	2.30 (1.25, 4.26)*	1.23 (0.43, 3.54)	3.36 (1.83, 6.15)***
Alcohol consumption			
No alcohol	1.00	1.00	1.00
1–4 drinks per week	0.98 (0.55, 1.75)	0.49 (0.29, 1.07)	1.19 (0.52, 2.72)
> 4 drinks per week	1.34 (0.60, 2.97)	0.49 (0.20, 1.23)	2.76 (0.81, 9.37)
Smoking status			
Current smoker	1.80 (0.92, 3.53)	0.76 (0.48, 1.22)	4.14 (1.17, 14.68)*
Former smoker	1.54 (0.87, 2.71)	0.81 (0.37, 1.79)	2.56 (1.16, 5.67)*
Never smoked	1.00	1.00	1.00
Serum cotinine tertile[b]			
1	1.00	1.00	1.00
2	0.57 (0.31, 1.05)	0.34 (0.14, 0.82)*	0.66 (0.30, 1.45)
3	1.14 (0.63, 2.04)	1.58 (0.70, 3.60)	0.82 (0.28, 2.39)
Blood lead quartile[c]			
1	1.00	1.00	1.00
2	1.19 (0.77, 1.82)	1.04 (0.44, 2.50)	1.23 (0.71, 2.13)
3	1.75 (1.12, 2.72)**	1.51 (0.50, 4.60)	1.86 (1.01, 3.41)*
4	1.13 (0.61, 2.07)	0.49 (0.17, 1.42)	2.97 (1.01, 8.74)*
Blood cadmium quartile[d]			
1	1.00	1.00	1.00
2	0.97 (0.49, 1.91)	0.62 (0.28, 1.37)	1.16 (0.49, 2.74)
3	1.00 (0.36, 2.74)	1.21 (0.48, 3.05)	1.05 (0.29, 3.75)
4	1.62 (0.79, 3.32)	3.16 (1.26, 7.91)*	1.04 (0.41, 2.62)

[a]Adjusted for sex, age, race/ethnicity, blood lead levels, obesity, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level.
[b]Cotinine tertiles: T1: < 0.016 ng/mL; T2: 0.016–0.13 ng/mL; T3: > 0.13 ng/mL.
[c]Lead quartiles: Q1: < 0.70 μg/dL; Q2: 0.70–1.06 μg/dL; Q3: 1.07–1.67 μg/dL; Q4: > 1.67 μg/dL.
[d]Cadmium quartiles: Q1: < 0.18 μg/L; Q2: 0.18–0.29 μg/L; Q3: 0.30–0.54 μg/L; Q4: > 0.54 μg/L.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviation: NHANES = National Health and Nutrition Examination Survey.

95% CL: 1.11, 6.00), but not in females (OR = 1.58, 95% CL: 0.77, 3.24) (Table 2). Further stratification by age groups found that younger male adults (ages 20–47 years) in the highest quartile of BCd were statistically significantly associated with higher odds for having depressive symptoms (OR = 3.16, 95% CL: 1.26, 7.91) compared to the lowest, referent quartile (Table 3); however, in older adult male participants (≥ 48 years) BCd was not significantly associated with higher odds for having depressive symptoms (Table 4). Interestingly, older adult female participants in the highest BCd quartile were statistically significantly associated with higher odds for having depressive symptoms (OR = 3.30, 95% CL: 1.02, 10.69) compared to the referent quartile (Table 4).

Blood lead and serum cotinine were not associated with depressive symptoms in all participants (Table 2). After stratification by sex, we observed a non-monotonic association between BPb in women; women in the third quartile of BPb have statistically significantly higher odds to have depressive symptoms (OR = 1.72; 95% CL: 1.09, 2.71) compared to the referent quartile (Table 2). Interestingly, after further stratification by age group, the highest third and fourth BPb quartiles were statistically significantly associated with higher odds for having depressive symptoms in younger adult women (20–47 years) compared to the referent BPb quartile (Table 3). Although BPb was not statistically significantly associated with depression in men, with further stratification by age, we found an inverse association among male individuals older than 47 years between the third quartile of BPb (OR = 0.15; 95% CL: 0.03, 0.76) and current depressive symptoms (Table 4). Current smoking status was a predictive risk factor for depressive symptoms in all participants; however, this association remained statistically significant only in female participants (Table 2). After further stratification by age, current smoking status remained a predictive risk factor for having depressive symptoms in both age groups of women (Tables 3 and 4). Moreover, in the younger group (20–47 years of age), former smoking was also a predictive risk factor for depressive symptoms (Table 3). Other than the BCd and smoking status differences observed after sex and age stratification, it is interesting to note that obesity was associated with depressive symptoms only in women (Table 2), and specifically only those women in the younger age group (Table 3).

DISCUSSION

We previously reported an association of blood cadmium with depressive symptoms in young adults (20–39 years) using the NHANES 2007–2010 cross-sectional study. In that study, we found that participants in the highest BCd quartile had increased odds of having depressive symptoms compared to those participants in the lowest BCd quartile.[14] In the present study, we confirmed the association of BCd with depressive symptoms in all adults (≥ 20 years) using NHANES 2011–2012. Furthermore, we confirmed that the observed association of BCd with depressive symptoms was independent of cotinine and smoking status. Moreover, in this study, we assessed the role of sex as a potential

Table 4. Multivariate Logistic Regression[a] OR (95% CL) of Having Depression in NHANES 2011–2012 for Adult Participants Aged > 47 Years

	All (N = 2,016)	Men (n = 990)	Women (n = 1,026)
Depressed yes, n	239	95	144
Depressed no, n	1,777	895	882
Sex			
Men	1.00		
Women	1.44 (0.94, 2.20)		
Age	0.96 (0.93, 0.98)***	0.94 (0.89, 0.99)*	0.97 (0.94, 0.99)**
Race/ethnicity			
Non-Hispanic White	1.00	1.00	1.00
Non-Hispanic Black	0.87 (0.49, 1.55)	0.69 (0.27, 1.72)	0.93 (0.48, 1.80)
Hispanic (Mexican-American and other)	0.93 (0.44, 2.00)	0.54 (0.16, 1.79)	1.35 (0.56, 3.24)
Other	0.58 (0.24, 1.41)	0.54 (0.26, 1.12)	0.66 (0.18, 2.42)
Education level			
Less than high school	1.00	1.00	1.00
Completed high school	0.69 (0.30, 1.61)	0.58 (0.14, 2.37)	0.90 (0.41, 1.95)
More than high school	0.62 (0.20, 1.92)	0.42 (0.14, 1.21)	0.96 (0.27, 3.48)
Poverty income ratio			
≤ 1	1.00	1.00	1.00
> 1	0.31 (0.16, 0.59)**	0.37 (0.19, 0.72)**	0.28 (0.12, 0.66)**
Body weight status			
Underweight/normal	1.00	1.00	1.00
Overweight	0.78 (0.39, 1.56)	0.72 (0.27, 1.89)	0.74 (0.31, 1.77)
Obese	1.13 (0.65, 1.97)	0.66 (0.25, 1.74)	1.64 (0.75, 3.55)
Alcohol consumption			
No alcohol	1.00	1.00	1.00
1–4 drinks per week	1.05 (0.52, 2.15)	0.62 (0.20, 1.94)	1.02 (0.43, 2.40)
> 4 drinks per week	0.65 (0.15, 2.77)	0.37 (0.06, 2.41)	1.04 (0.11, 9.55)
Smoking status			
Current smoker	1.44 (0.65, 3.20)	0.73 (0.15, 3.55)	3.26 (1.43, 7.42)**
Former smoker	1.39 (0.76, 2.55)	1.57 (0.47, 5.25)	1.55 (0.77, 3.14)
Never smoked	1.00	1.00	1.00
Serum cotinine tertile[b]			
1	1.00	1.00	1.00
2	0.93 (0.46, 1.88)	0.63 (0.21, 1.89)	1.12 (0.51, 2.45)
3	0.85 (0.47, 1.52)	1.07 (0.32, 3.58)	0.60 (0.24, 1.48)
Blood lead quartile[c]			
1	1.00	1.00	1.00
2	1.05 (0.45, 2.49)	0.38 (0.07, 2.21)	1.49 (0.81, 2.75)
3	0.88 (0.32, 2.38)	0.15 (0.03, 0.76)*	1.71 (0.62, 4.73)
4	0.75 (0.28, 1.99)	0.27 (0.04, 1.72)	0.94 (0.39, 2.25)
Blood cadmium quartile[d]			
1	1.00	1.00	1.00
2	1.19 (0.49, 2.87)	0.83 (0.22, 3.19)	2.89 (0.75, 11.05)
3	1.19 (0.58, 2.44)	0.79 (0.40, 1.59)	2.68 (0.87, 8.24)
4	1.81 (0.73, 4.46)	1.81 (0.41, 7.99)	3.30 (1.02, 10.69)*

[a]Adjusted for sex, age, race/ethnicity, blood lead levels, obesity, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level.
[b]Cotinine tertiles: T1: < 0.016 ng/mL; T2: 0.016–0.13 ng/mL; T3: > 0.13 ng/mL.
[c]Lead quartiles: Q1: < 0.70 μg/dL; Q2: 0.70–1.06 μg/dL; Q3: 1.07–1.67 μg/dL; Q4: > 1.67 μg/dL.
[d]Cadmium quartiles: Q1: < 0.18 μg/L; Q2: 0.18–0.29 μg/L; Q3: 0.30–0.54 μg/L; Q4: > 0.54 μg/L.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviation: NHANES = National Health and Nutrition Examination Survey.

moderator for the association of cadmium and depressive symptoms. Stratification analyses by sex found that BCd was associated with depressive symptoms in all adult men and, more specifically, in men who were 20–47 years of age. There was also in association of BCd with depressive symptoms in women, but it was limited only to those women in the third and fourth highest age quartiles (> 48–60 years and > 60 years). It is possible that this association is due to reverse causation since the increase in blood cadmium in the older woman may reflect mobilization of cadmium from bone as result of underlying conditions, such as osteoporosis, which generally affect older, postmenopausal women.[13]

In this study, we also found that younger adult women (20–47 years) in the third and fourth BPb quartiles had statistically significantly higher odds for having depressive symptoms compared to the referent BPb quartile. This finding is similar to that reported previously by Bouchard and colleagues[16] of an association between BPb and major depression among young adult (20–39 years of age) participants in NHANES 1999–2004. However, that study did not look at whether the association was restricted to 1 sex. Analyses of adult (≥ 20 years) participants of NHANES 2005–2006[17] and analyses of young adult (20–39 years of age) participants in NHANES 2007–2010[14] did not find any association between BPb and depressive symptoms. These inconsistencies may be due to the lack of sex stratification in the previous studies and/or to residual confounding. Furthermore, we found an inverse association among individuals in the third quartile of BPb and current depressive symptoms in men older than 47 years. We do not know how lead exposure may have a beneficial role, and this might represent a spurious finding.

In the present study, the associations of depressive symptoms with smoking status and obesity are seen in women but not in men. These associations are consistent with previous findings. Women have higher rates of depression,[4] and although smoking is less common in women than in men,[9] several studies have reported that depression in women is more commonly associated with smoking than in men.[10,11]

The link of depression and obesity has been thought to be bidirectional, and several studies found that the association between obesity and depression is limited to women, rather than men.[23] A possible explanation of these findings in women may lie in maladaptive coping behaviors, where depressed individuals engage in unhealthy eating (eg, binge eating, higher caloric intake) and smoking behavior to cope with their depression.[24,25] The cultural stigma of obesity may be a further reinforcing factor with a tendency for obese women to eat in response to negative emotions[24]; this could explain the association we observed between obesity and depressive symptoms being confined only to women of reproductive age (20–47 years). Moreover, the association between cigarette smoking and depression is seen to be bidirectional: depression increases the risks of smoking,[7,8] and smoking increases the risks of depression.[5,6]

The underlying biological mechanism of how cadmium and lead may play a role in depression could potentially involve dysregulation of the hypothalamic-pituitary-adrenal axis. Cadmium can increase the permeability of the blood-brain barrier, leading to intracellular cadmium accumulation in the brain in adult rats.[26,27] Furthermore, cadmium may contribute to the development of depression by perturbing the catecholamine/serotonin system; decreased levels of serotonin, dopamine, and norepinephrine in the brain have been found in adult male rats exposed to cadmium.[28,29] Lead exposure disrupts catecholaminergic systems; studies in animals show that long-term lead exposure may result in decreased serotonergic activity in the brain.[30] Impairment of the monoaminergic neurotransmission system is associated with depression and anxiety disorder.[3]

The use of the structured diagnostic assessments of psychiatric disorders is a strength of the present analysis. The PHQ-9 is widely used in psychiatric research and has a high degree of correspondence with clinical interviews.[31] However, the present study also has several limitations, the most important being its cross-sectional design, which limits the inferences that can be made based on the findings. Medical conditions such as osteoporosis, during which cadmium and lead are released from the bone matrix to the blood, may have affected our findings. However, we stratified our analyses by age group (20–47 and > 47 years of age) in order to minimize the effect that such underlying conditions may have had on our results. As we mentioned previously, the finding in the older female age groups (> 47 years of age) of an association between BCd and depressive symptoms may easily be attributable to reverse causation, since mobilization of cadmium from the bone may increase BCd levels. The depressive symptoms status in our study is limited to answers in the PHQ-9 about the experience of the participants during the past 2 weeks, so the depressive symptoms status may reflect a short-term health condition, and not necessarily a chronic condition. The half-life of cadmium in blood has been estimated to be 3–4 months,[32] whereas the half-life of lead in adult human blood has been estimated to be from 28–36 days.[15] Therefore, BCd and BPb, which reflect recent, short-term exposure, may be appropriate to use in this case. The association reported in this study could be biased by uncontrolled factors such as genetic predisposition.[3] However, the models were adjusted for several likely important confounding factors. Reverse causation cannot be ruled out as a possible reason for the results since depression may lead to behavioral changes that increase exposure to cadmium or lead (ie, tobacco smoke). However, the lack of association between cotinine and current smoking status with depression in younger adult men (ages 20–47 years) where we observed the association between cadmium and depression suggests that the association we observed may be more than just coincidence. By contrast, the association that we found between BPb and depressive symptoms in young women (aged 20–47 years) may be a result of reverse causation, since in this group we found that tobacco smoking (both current and former users) was also associated with depression, and tobacco smoke is a source of environmental lead exposure.[15]

CONCLUSION

If cadmium exposure is associated with depressive symptoms and depression, continued efforts at reducing cadmium exposure in the general population may help decrease the population incidence of depression. This could be achieved through continued efforts to curb tobacco smoking, since a main source of non-occupational cadmium exposure is smoking.[13] Additionally, this would have the added benefit of decreasing cadmium exposure from secondhand and thirdhand smoke as well. The finding of an association between BPb and depressive symptoms in young women (20–47 years of age) is intriguing, particularly because we found tobacco smoking (both current and former) as well as obesity to be predictive risk factors to have depressive symptoms in this age group. A recent meta-analysis reported that smoking cessation is associated with reduced depression,[33] findings that may help to overcome professional reluctance to intervene with smokers who have mental health problems.[34,35] Given that cadmium[13] and lead[15] are associated with several chronic diseases, the benefits of smoking cessation are multifold by decreasing both the incidence of smoking-related diseases as well as cadmium-associated and lead-associated diseases. However, further studies, such as well-designed prospective studies to evaluate the effect of cadmium and lead exposure on the risk of developing depression, are needed to more fully understand the implications of the findings of this study.

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