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Original Article

High Cadmium Levels in Individuals with Depressive Mood: Results from the 2008–2013 Korean National Health and Nutrition Survey

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Abstract

Background: The relationship between cadmium (Cd) exposure and depression remains unclear. This nationwide study aimed to compare the levels of blood Cd with the presence of depressive mood in Korean adults.

Methods: From the 2008–2013 Korea National Health and Nutrition Examination Survey, 10,968 individuals over 20 yr old were identified. Data on demographics, health behaviors, depressive mood, and blood Cd (B-Cd) levels were used in the analysis. Estimated levels of B-Cd were drawn from multivariate regression models.

Results: Higher age-adjusted B-Cd levels were noted among women, rural residents, people who have a low economic or educational status, smoke currently, drink frequently, or have depressive mood than the counterpart groups. In fully adjusted models, men with depressive mood exhibited significantly higher B-Cd levels than those without depressive mood, and these levels were strongly mediated by smoking status.

Conclusion: Our results suggest a need for Cd accumulation screening among individuals with depressive mood.

Keywords: Cadmium; Depression; Causality; Smoking; South Korea

Introduction

Chronic exposure to cadmium (Cd), a widespread environmental pollutant, leads to various adverse effects in the renal, skeletal, endocrine, and neurological systems (1). For the general population, a major source of Cd exposure is the consumption of food grown in Cd-contaminated soil, where it biologically accumulates and affects all levels of the food chain (1). Because no effective treatment for Cd toxicity exists, minimizing its exposure is crucial.

Depression is a growing public health issue linked to medical illness and disability worldwide (2). Although the pathobiology of depression is not fully understood, epidemiologists have identified a number of sociodemographic and behavioral correlates as risk factors (3-6). Simultaneously, it can reversely affect health-related habits or socioeconomic status (7).

The causality between Cd exposure and depression has yet to be elucidated. Following a preliminary study identifying higher blood Cd (B-Cd) levels in 21 patients with depression (8), several cross-sectional studies have reported a higher likelihood of having depressive symptoms in individuals with high B-Cd levels, using the same source of database (9-11). Smoking status strongly affected this association (12). To our knowledge, only one prospective study has explored the contribution of Cd exposure to depressive symptoms in older adults; however, they conclusively failed to find a positive relationship (13). Results from animal studies have also been contradictory. Rat studies have shown that applying Cd reduces the release of excitatory neurotransmitters and increases inhibitory ones (14, 15), this is a salient feature of major depression (16). However, earlier studies in rats found the opposite association (17, 18).

The association between tobacco smoking and depression is known to be bidirectional (5, 19). Low socioeconomic status and/or unhealthy habits including smoking -potential mediators- are causes of Cd burden, but not vice versa. Thus, we hypothesized that depression leads to behavioral changes that increase exposure to Cd.

We aimed to determine whether a causal relationship exists between depression and cadmium exposure by analyzing B-Cd levels in adults with or without depressive mood who participated in a nationally representative Korean survey.

Methods

Design and participants

We used data from the 2008-2013 Korea National Health and Nutrition Examination Survey (KNHANES), a nationally representative survey conducted periodically by the Korea Centers for Disease Control and Prevention. All ethical aspects had observed already. The sampling units were households randomly selected through a stratified, multistage, probability-sampling design. Detailed information on the survey has been provided elsewhere (20).

We identified 11,928 participants who were 20 yr of age or older and had available data on the blood levels of heavy metals. Of these cases, participants who were diagnosed with overt cardiovascular disease (myocardial infarction or stroke, n=355), cancer (n=46), current depression (n=314), and those who had no available data on two main variables (heavy metals and depressive mood; n=245) were excluded. Thus, a dataset of 10,968 participants was used in the final analysis.

Data collection

All participants of the KNHANES underwent three components: health interview, health examination, and nutrition survey. All interviews and examinations were performed in specially designed and equipped mobile centers that traveled to locations throughout the country. During health interviews, information on demographics (age, sex, residential location, household income, educational level, and employment), health behaviors (smoking history and alcohol consumption), and physician-diagnosed disease history (cancer, myocardial infarction, stroke, and depression) was collected by self-reported questionnaires. Health behaviors were assessed by questioning participants about their habits during the month prior to the interview. Height and weight were measured by trained medical staff. Body mass index (BMI) was calculated as the proportion of weight (kg) to height^2 (m^2).

Obesity was defined as BMI ≥ 25 kg/m^2 based on data from the Korean Society for the Study of Obesity (21). Residential location was classified as "urban" or "rural." Economic status was classified into "low" or "high" according to mean monthly family size–adjusted household income, which was calculated by dividing household income by the square root of the number of persons in the household. Educational level was categorized as "middle school or lower" and "high school or beyond". Employment was reorganized into two groups: "unemployed" or "employed." Participants were considered a "current smoker" if they currently smoked cigarettes. For alcohol consumption, participants were considered "frequent drinkers" if they consumed more than seven drinks (men) or five drinks (women) in one sitting more than 2 d per week (22).

B-Cd levels and depressive mood

Information on heavy metals (i.e., Cd, mercury, lead, manganese, and nickel) added from 2005, but the measured metals and covered ages were different across the years (20). To measure Cd concentrations in whole blood, 3-mL blood samples were drawn into standard commercial evacuated tubes coated with sodium heparin during the health examination. B-Cd levels were measured via graphite furnace atomic absorption spectrometry (Perkin Elmer AAnalyst 600, Turku, Finland). The detection limit was 0.087 µg/L blood cadmium. All blood sample analyses were carried out by the Soul Medical Science Institute certified by the Korean Ministry of Health and Welfare. For internal quality assurance, standard reference material was obtained from Bio-Rad (Lymphochek Whole Blood Metals Quality Control, Hercules, CA, USA). External quality control was achieved via participation in an international program set by the German External Quality Assessment Scheme. To enhance the readability, based on its distribution in the current sample, we arbitrarily classified B-Cd levels into four groups: 0–0.5 µg/L, 0.51–1.0 µg/L, 1.0–1.49 µg/L, and ≥1.5 µg/L.

Depressive mood was assessed using participants' yes/no answer reported for the question, "Have you ever felt sadness or despair continuously for more than 2 wk during the past year?"

Statistical analysis

Data are expressed as percentages, and differences in characteristics across B-Cd levels were calculated using the chi-square test. Estimated levels of blood cadmium were drawn from univariate or multivariate regression analyses. All analyses were performed using STATA SE 9.2 (Stata Corp., College Station, TX). All statistical tests were two-sided, and statistical significance was defined as a *P*-value less than 0.05.

Results

Participant characteristics by B-Cd levels are shown in Table 1. High B-Cd levels were associated with female sex, old age, rural residency, low educational and economic status, obesity, current smoking, frequent alcohol drinking, and depressive mood (all *P*<0.01).

Table 1: Participant characteristics by blood cadmium levels

Variable	***Blood cadmium levels (µg/L)***				
%	0–0.5 (n = 1,523)	0.51–1.0 (n = 4,107)	1.0–1.49 (n = 2,932)	≥1.5 (n = 2,406)	*P* for trend
Demographics					
Age group (yr)					
20–39	78.9	50.6	27.6	18.7	<0.001
40–59	16.6	35.1	48.5	54.1	
≥60	4.5	14.4	23.9	27.3	
Female sex	40.4	45.2	53.6	60.6	<0.001
Rural residency	14.4	17.9	19.8	23.2	<0.001
Low economic state[a]	31.9	37.2	42.3	49.2	<0.001
Low education level (≤middle school)	6.8	18.7	33.8	46.8	<0.001
Unemployed	36.6	31.8	35.4	37.6	0.101
Health-related habits					
Obese	28.4	30.4	33.3	33.2	0.005
Currently smoking	9.6	20.4	27.8	34.9	<0.001
Frequent drinking	2.9	4.3	6.3	7.7	<0.001
Having depressive mood	9.1	9.7	12.9	14.6	0.002

P-values from logistic regression analysis.

[a] Based on the mean monthly family size–adjusted household income

Because age was the strongest prognostic factor for B-Cd levels, B-Cd levels were adjusted for age (Table 2). B-Cd levels were significantly higher among women, rural residents, people who have a low economic or educational status, those who frequently drink alcohol, and those with depressive mood than among their corresponding counterpart groups. The association of smoking was in a dose-response manner. Gender difference in B-Cd levels was remarkable from 40 yr old.

Multivariate regression analysis revealed that men with depressive mood had significantly higher B-Cd levels than men without depressive mood. No significant difference in B-Cd levels was found between women with depressive mood and women without depressive mood (Table 3). However, the significance was mitigated after adjusting for smoking status (Table 3) and was not found in smoking-stratified analysis.

Table 2: Age-adjusted blood cadmium levels by characteristics

Variable	***Blood cadmium levels (µg/L)*** *Mean (95% confidence interval)*	*P-value*
Sex		<0.001
Male	1.03 (1.01–1.04)	
Female	1.20 (1.19–1.22)	
Residency		0.001
Urban	1.11 (1.09–1.12)	
Rural	1.15 (1.13–1.18)	
Economic status[a]		<0.001
High	1.09 (1.08–1.11)	
Low	1.15 (1.13–1.16)	
Education level		<0.001
High (≥ high school)	1.07 (1.06–1.09)	
Low (≤middle school)	1.22 (1.20–1.25)	
Employment		0.983
Employed	1.11 (1.10–1.13)	
Unemployed	1.11 (1.09–1.13)	
Obese		0.788
No	1.12 (1.10–1.13)	
Yes	1.11 (1.09–1.13)	
Smoking status		<0.001
Never	1.04 (1.02–1.05)	
Past	1.18 (1.16–1.19)	
Current	1.32 (1.29–1.34)	
Frequent drinking		<0.001
No	1.10 (1.09–1.12)	
Yes	1.32 (1.27–1.37)	
Depressive symptom		<0.001
No	1.10 (1.09–1.12)	
Yes	1.20 (1.16–1.23)	

[a] Based on the mean monthly family size–adjusted household income

Table 3: Blood cadmium levels (µg/L) according to depressive mood stratified by sex

Variable	Male			Female		
	With depression	Without depression	P-value	With depression	Without depression	P-value
Age-adjusted	1.14 (1.09–1.20)	1.02 (1.00–1.03)	<0.001	1.22 (1.18–1.26)	1.20 (1.18–1.22)	0.460
Model I[a]	1.10 (1.04–1.15)	1.00 (0.98–1.02)	0.001	1.23 (1.18–1.27)	1.22 (1.20–1.24)	0.748
Model II[b]	0.96 (0.91–1.01)	0.89 (0.88–0.91)	0.014	1.29 (1.24–1.33)	1.29 (1.26–1.31)	0.978

P-values from multivariate regression analysis.
[a] Adjusted for all variables in Table 1 except smoking status.
[b] Adjusted for all variables in Table 1

Discussion

The direction of association determines the implications. If Cd exposure is a cause of depressive symptoms, reducing Cd exposure (i.e., smoking cessation) may be helpful for decreasing the incidence of depression. However, our results indicated that people with depression were more likely to have high B-Cd levels than people without depression were, suggesting a need to screen for Cd accumulation among individuals with depressive symptoms.

Consistent with findings of a previous study (12), our study reported that cigarette smoking is a strong confounding factor in the association between depressive mood and B-Cd levels. A dose-dependent relationship with smoking status was also observed in age-adjusted B-Cd levels. Cigarette smoking is one of the major sources of cadmium exposure (23), and thus smoking status can be an overall proxy for Cd exposure. The association between smoking and depression is bidirectional. If smoking cessation can reduce depression compared with continuing to smoke (5, 24), the reverse may be true (19). The same can be true of socioeconomic status, which is traditionally measured via factors such as wealth and level of education or occupation. Generally, socioeconomic status is known to be associated with depressive problems (25, 26), and furthermore, socioeconomic deprivation is associated with poorer treatment outcomes (27). Besides, potential mechanisms have been suggested to account for the association between Cd exposure and psychiatric problems (e.g., oxidative stress, mitochondrial dysfunction, and Hypothalamic-Pituitary-Adrenal axis dysregulation) (28). Future experimental studies are warranted to disentangle the linkage.

The most remarkable finding of our study was the opposite direction of association, considering B-Cd levels as a dependent variable. We estimated the R^2 of the regression model in both directions. R^2 is a statistical measure that indicates how much variation of a dependent variable is explained by the independent variables in a regression model (29). R^2 was 0.035 in a model with depressive mood as a dependent variable, while it was 0.243 for B-Cd levels. Many hidden factors exist that influence the likelihood an individual has depressive mood. For example, individuals with a low socioeconomic status may be at a higher risk for depression, possibly mediated by exposures to a wide range of stressors (30).

High B-Cd levels in women who are less likely to smoke indicate that Cd causes depressive mood. However, although smoking is more common in men, depression is more commonly associated with smoking in women than in men (31). Our further analysis also suggested a marked sex difference in B-Cd levels after the mid-life, which could be explained by mobilization of Cd from bone (i.e., osteoporosis).

In this nationally representative sample, the overall Cd burden was substantially high in Korea. Based on the data from the KNHANES, the NHANES, and the Canadian Health Measures Survey, B-Cd levels in Koreans are approximately two times higher than those of Americans and Canadians (32). For the general population, considerable exposure to Cd occurs by consuming food grown from cadmium-contaminated soil (33). Our further analysis revealed that Koreans who reside in rural areas had significantly higher B-Cd levels than those in urban areas, after adjusting for age, sex, and smoking status (1.15 (1.13–1.18) vs. 1.11 (1.09–1.12); *P*=0.001; data not shown). This finding may be due to high levels of Cd in the soil of rural areas. Therefore, a focused assessment is needed that targets cadmium exposure and its adverse outcomes in the high-risk population.

Besides its cross-sectional design, the present study has a critical flaw. The association reported in this study could be biased by uncontrolled factors, such as genetic predisposition (34) and occupational exposure to Cd, as well as the lack of detailed information on smoking exposure (e.g., pack-years or duration of cessation) and depression (e.g., Patient Health Questionnaire scores or in-depth psychiatric interviewing).

Conclusion

However, despite the limitations, this is the first study to suggest another direction for the relationship between depression and B-Cd levels. Notably, B-Cd levels increase continuously with age in everyone, as no effective Cd excretion from the body exists. To understand more fully the causality on this issue, we recommend tracking both B-Cd levels and depressive mood with well-designed sequential studies, which would be easily conducted in a highly exposed population such as Korean adults.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interests.

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