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Blood cadmium and depressive symptoms: Confounded by cigarette smoking

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ABSTRACT

Our aim was to explore the association between blood cadmium (BCd) and depressive symptoms, adjusting for pack years and blood cotinine, and also stratifying by smoking status. Using data from the US National Health and Nutrition Examination Survey (NHANES) 2005–2012, we categorized depressive symptoms using the PHQ-9 (Patient Health Questionnaire-9) survey and modeled depressive symptoms in relation to BCd adjusted for blood cotinine, pack years of smoking, and other covariates. We also stratified by self-reported smoking status (current, former, never). There were 11,209 subjects from 2005 to 2012, age ≥ 18 with PHQ-9, smoking, and blood cadmium data available. 876 (7.8%) met criteria for depressive symptoms. Depressive symptoms were associated with BCd levels in a crude model and with adjustment for pack years and cotinine. The association disappeared when analyzed among current, former, or never smokers. Consistent with the literature, we found an association between BCd and depressive symptoms; however, that association disappears in analyses stratified by smoking status. This suggests residual confounding may be present. It is important to stratify by smoking status when investigating health outcomes associated with BCd.

1. Introduction

Cadmium, like other heavy metals, is a known neurotoxicant, likely through mechanisms of oxidative stress, alterations in neurotransmitter release, damage to the blood brain barrier, and induction of neuron apoptosis (Mendez-Armenta and Rios, 2007). It has been associated with various psychiatric disorders including schizophrenia, bipolar disorder, and major depressive disorder (Mendez-Armenta and Rios, 2007; Olabanji, 2011; Orisakwe, 2014). In particular, previous studies have shown a positive association between elevated blood cadmium (BCd) levels and depressive symptoms (Berk et al., 2014; Han et al., 2016; Scinicariello and Buser, 2015). The link between urine cadmium (UCd) levels and depressive symptoms is less clear (Shiue, 2015)- possibly due to the fact that BCd is more indicative of short term mixed with long-term exposure and UCd is more representative of lifetime exposure (Jarup et al., 1998).

Cigarette smoking is one of the major sources of cadmium exposure in the US. Tobacco plants absorb cadmium from the soil, and persons who smoke 20 cigarettes per day absorb about 1 μg of cadmium through their lungs from smoking each day (Jarup and Akesson, 2009). In current, never and former smokers, a dose-dependent relationship has been observed in BCd- with highest blood levels in current heavy smokers (Ellingsen et al., 1997). Furthermore, smoking has a known association with depression and other mental health disorders, and smoking cessation is associated with a decreased risk of depression (Bakhshaie et al., 2015). Therefore, it is important to adequately control for cigarette smoking when investigating the association between cadmium and depressive symptoms.

We hypothesize that BCd is associated with depressive symptoms in unadjusted models, and that residual confounding may still be present after controlling for serum cotinine and pack years. Stratifying by cigarette smoking (current, former, never) may be necessary to remove the confounding influence of cigarette smoking.

2. Methods

Data from the US National Health and Nutrition Examination Survey (NHANES) (NCHS, 2016b) was used to examine the cross-sectional relationships between blood cadmium and depressive symptoms. Depressive symptoms were characterized using the PHQ-9, which was administered as part of NHANES starting in 2005 as a screening test. This is a validated Patient Health Questionnaire that has 9 questions pertaining to defining features of depression from the diagnostic statistic manual (DSM) (Kroenke, 2002). The questionnaire is scored to identify patients with depressive symptoms; scores greater than or equal to 10 were accepted as positive results for depressive symptoms

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(Kroenke, 2002; Milette et al., 2010).

Blood cadmium levels were assessed using whole blood specimen collection, which is discussed in further detail in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM) (NCHS, 2016b). The samples are sent to the National Center for Environmental Health, where inductively coupled plasma mass spectrometry is used to determine cadmium concentrations, measured in units of micrograms per liter (NCHS, 2016b). The limit of detection for 2005–2010 was 0.14 μg/L, and 0.11 μg/L for 2011–2012 (NCHS, 2016b). Serum cotinine is also measured via whole blood specimens, following the same protocol as delineated in the LPM. Isotope dilution-high performance liquid chromatography/ atmospheric pressure chemical ionization tandem mass spectrometry is used to determine serum cotinine levels (NCHS, 2016b). The limit of detection for 2005–2012 was 0.11 ng/ml (NCHS, 2016b).

Relevant covariate information, including demographics, smoking and drinking habits, and health history was collected via home interview and available in NHANES. Poverty income ratio (PIR) is a ratio of self-reported income to the local poverty level (NCHS, 2016b). Smoking was assessed from self-report including the current use of cigarettes, past use of cigarettes, cigarettes per day, and years of smoking. Pack-years were calculated from reported cigarettes per day divided by 20 cigarettes per pack, multiplied by years of smoking. Self-reported average number of alcoholic drinks/day in the past 12 months was also downloaded from NHANES.

SAS was used for statistical analysis, by extracting data directly from the NHANES website. Chi-square testing was used to assess for categorical demographic differences (sex, race, smoking status) and *t*-testing was used to assess for continuous variable differences (PIR, age, blood Cd, pack-years, blood cotinine) between depressed and non-depressed subjects. Subjects ≥ 18 were included in the data analysis, and the NHANES weighting system was used to account for sampling and survey design (NCHS, 2016a). Using data from 2005 to 2012, PHQ-9 ≥ 10 was defined as positive for depressive symptoms, and modeled in a crude logistic regression for its association with blood cadmium, adjusted for age, race, alcohol use, and poverty income ratio (PIR), blood cotinine, and pack years smoking. These variables were chosen as they could potentially act as confounders due to associations with both BCd and depressive symptoms. We also modeled the logistic regression without statistical adjustments and present both sets of results. We then stratified by self-reported smoking status (current, former, never) to tease out the role of cadmium independent of variation in smoking. As a sensitivity analysis we repeated all analyses without the NHANES sampling weights and results were similar. We also modeled categorical BCd defined by quartiles, a quadratic regression, and a log transformed logistic regression, and results were similar. We ran *t*-tests for BCd levels between depressed and non-depressed subjects, stratified by smoking status, to aid in interpreting the results.

3. Results

The cohort included 11,209 subjects from 2005 to 2012 with PHQ-9, smoking, and blood cadmium data available, age greater than or equal to 18. Of these subjects, 876 (7.8%) met criteria for depressive symptoms as defined by PHQ-9 ≥ 10. Patients in the depressive symptom group were predominately female ($p < 0.01$), and race distribution showed a greater percentage of Black and non-Mexican Hispanic subjects in the depressed population (Table 1). The mean age was significantly lower in the depressed group but only by two years ($p \leq 0.01$) and mean PIR was lower in the depressed group, ($p < 0.01$). Mean blood cadmium was higher in the depressed group ($p < 0.01$). The depressed group was also more likely to be current smokers. Additionally, both mean pack-years and blood cotinine were higher in the depressed group ($p < 0.01$).

In an unadjusted logistic regression model, depressive symptoms were associated with BCd levels (OR = 1.53, 95% CI: 1.37–1.71). In a model with adjustment for age, sex, race, PIR and alcohol use, depressive symptoms were still associated with BCd levels, although less strongly (OR = 1.37 95% CI: 1.24–1.51). This association was mitigated by further adjustment for pack-years and serum cotinine level but still significant (OR = 1.16 95% CI: 1.04–1.30; interpreted as a 16% increase in risk for depressive symptoms associated with each 1 μg/L increase in BCd) (Table 2). To rule out the possibility of residual confounding by smoking, we stratified by smoking status; however, this resulted in no association between BCd and depressive symptoms in current, former, or never smokers (Table 2), suggesting that residual confounding was present. *T*-tests of BCd levels between depressed and non-depressed subjects stratified by smoking status (Table 3) show a significant difference in the group as a whole and current smokers, but not in former or never smokers.

Table 1
Demographics of cohort (n = 11,209).

	Depressive symptoms +	Depressive symptoms –	*p*-value (Chi-square test or *t*-test)
Total *n* (%)	876 (8)	10,333 (92)	
Female *n* (%)	532 (61)	4621 (45)	< 0.01
Male *n* (%)	344 (39)	5712 (55)	
Race *n* (%)			< 0.01
Caucasian	392 (45)	5307 (51)	
Black	212 (24)	1947 (19)	
Mexican- American	127 (14)	1584 (15)	
Other Hispanic	102 (12)	825 (8)	
Other	43 (5)	670 (7)	
PIR mean ± SD	1.79 ± 1.47	2.84 ± 1.65	< 0.01
Age mean ± SD	44.06 ± 14.44	46.70 ± 17.35	< 0.01
Blood Cd μg/L mean ± SD	0.79 ± 0.84	0.53 ± 0.62	< 0.01
Pack years mean ± SD	12.1 ± 20.3	8.2 ± 17.4	< 0.01
Blood cotinine ng/ml mean ± SD	110.5 ± 156.3	60.9 ± 127.8	< 0.01
Current smokers *n* (%)	406 (46)	2480 (24)	< 0.01
Never smokers *n* (%)	322 (37)	5372 (52)	
Former smokers *n* (%)	148 (17)	2481 (24)	

Depressive symptoms + was defined by a score greater than or equal to 10 on the PHQ-9.
PIR = Poverty Index Ratio.
Cd = Cadmium.

4. Discussion

Consistent with the literature, we found a positive association between BCd and depressive symptoms in this cohort of NHANES subjects, age ≥ 18, from 2005 to 2012. Mean blood cadmium was higher in the 876 subjects who met the criteria for depressive symptoms ($p < 0.01$), and they were more likely to be current smokers, with higher blood cotinine and mean pack-year levels ($p < 0.01$) (Table 1). Since smoking is strongly associated with cadmium (Ellingsen et al., 1997), smoking may confound the association. The association between BCd and depressive symptoms was mitigated by adjusting for pack years and serum cotinine, and disappeared when stratifying by current, former and never smokers, suggesting that residual confounding was present prior to stratification (Table 2). This is supported by the raw BCd data which show a significant difference in BCd between depressed subjects and non-depressed subjects in the group as a whole and in current smokers, but not in former or never smokers (Table 3). The significant difference seen in current smokers in the raw data (Table 3), but not seen in the adjusted regression model (Table 2), may be due to no controls for pack years or blood cotinine levels in the raw analysis (Table 3).

Although recent studies that have shown a link between BCd and depressive symptoms did adjust for smoking (Berk et al., 2014; Han et al., 2016; Scinicariello and Buser, 2015), their models may still have been susceptible to residual confounding. The Berk et al. (2014) study using NHANES 2005–2010- the same population as our study - found an