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A Population-Based Study of Blood Lead Levels in Relation to Depression in the United States

Natalia I. Golub[1], **Paul C. Winters**[2], and **Edwin van Wijngaarden**[1,3]

[1]Department of Community and Preventive Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642

[2]Department of Family Medicine, University of Rochester, 1381 South Avenue, Rochester, New York, 14620

[3]Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, 575 Elmwood Avenue, Rochester, NY 14642

Abstract

Purpose—Lead is a known neurotoxicant. Several studies have suggested that occupational exposure to lead may lead to depression, anxiety and other psychiatric illness, but few studies have examined environmental lead exposure and depression. We evaluated the relationship between blood lead levels (BLL) and depression in a sample representative of the United States population.

Methods—We analyzed data from 4,159 adults ages ≥20 who participated in the 2005-2006 cycle of the National Health and Nutrition Examination Survey (NHANES). Depression was assessed by the Patient Health Questionnaire-9 (PHQ-9). Relative risks were calculated using Poisson regression and odds ratios were calculated with ordinal logistic regression using SUDAAN, controlling for pertinent covariates.

Results—The risk of depression was only slightly elevated with increasing blood lead levels when lead was modeled as a categorical variable, with adjusted relative risks of 1.16 (95% confidence interval (CI) = 0.99-1.36), 1.20 (CI=1.07-1.36) and 1.16 (CI=0.87-1.54) for 0.89-1.40 μg/dL, 1.41-2.17 μg /dL, and >2.17 μg/dL, respectively, as compared to 0-0.88 μg/dL using Poisson regression. Similar results were obtained with ordinal logistic regression. Analyses using BLL as a continuous variable did not show a significant relationship with depression.

Conclusions—This cross-sectional study did not provide consistent evidence for an association between environmental lead exposure and depression within the investigated blood lead levels.

Keywords

blood lead levels; depression; NHANES; PHQ-9

Introduction

Depression is a prevalent psychiatric condition in the United States with an estimated 16.2% lifetime prevalence of major depressive disorder (Kessler et al. 2003). Approximately half of all Americans will meet DSM-IV criteria sometime during their lives (Kessler et al. 2005).

Please address correspondence to: Edwin van Wijngaarden, Ph.D., Department of Community and Preventive Medicine, 601 Elmwood Avenue, Box 644, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, Tel: 585-275-1985, Fax: 585-461-4532, edwin_van_wijngaarden@urmc.rochester.edu.

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Family history of mood disorders (Sullivan et al. 2000), age (Kessler et al. 2005), sex, ethnicity, and chronic illness (Clarke and Currie 2009) are known to increase the risk of depression. Furthermore, it has been postulated that exposure to environmental contaminants may play a role in the development of psychiatric disorders (Shih et al. 2007). Lead, a known neurotoxicant with well-documented cognitive and neurobehavioral effects, is one such contaminant that is suspected to be associated with psychiatric disorders (Cory-Slechta et al. 2008).

The mechanisms of how exposure to lead may lead to such disorders are just beginning to be elucidated. Animal studies have demonstrated that lead exposure affects the hypothalamic-pituitary-adrenal (HPA) axis and can lead to permanent HPA axis dysfunction (Cory-Slechta et al. 2004; Rossi-George et al. 2009; Virgolini et al. 2005). Cory-Slechta and colleagues proposed that alterations in the HPA axis due to lead exposure result in changes in glucocorticoid and catecholamine levels, with neuropsychiatric disorders such as depression as potential consequences (Cory-Slechta et al. 2008). Human studies have shown that HPA axis dysregulation may lead to elevated CRH and cortisol levels in depression (Holsboer 2000; Vreeburg et al. 2009). In addition, normalization of HPA axis function in previously depressed patients portends a good prognosis, while persistent elevated cortisol and CRH make depression remission less likely and increase the chance of relapse (Holsboer 2000). HPA axis dysregulation involves altered glucocorticoid receptor function that leads to impaired negative feedback and HPA axis overdrive, resulting in increased CRH and cortisol. The increased levels of cortisol lead to a decrease in the ratio of activated mineralocorticoid/glucocorticoid receptors (resulting in memory impairment), attenuated monoaminergic systems in the brain, and hippocampal volume reduction; changes similar to those seen in depression (de Kloet et al. 2005; Holsboer 2000). In addition to the role of elevated cortisol in depression, increased CRH levels and CRH receptors are involved in depression, and CRH receptor antagonists have anti-depressant effects. Furthermore, lead affects levels and metabolism of serotonin (Cory-Slechta et al. 2004; Kala and Jadhav 1995; Pillai et al. 2003; Virgolini et al. 2005), and abnormalities in the serotonergic system are present in depression (Moore and Jefferson 2004). Finally, lead affects the mesocorticolimbic system (Cory-Slechta et al. 2004), aberrances in which have also been linked to depression (Martin-Soelch 2009; Naranjo et al. 2001).

Epidemiological studies addressing the neuropsychiatric effects of lead in general, and depression specifically, have been sparse. Nevertheless, several studies have found that increased blood (Baker et al. 1984; Baker et al. 1983; Hanninen et al. 1998; Hogstedt et al. 1983; Lilis et al. 1977; Lindgren et al. 1999; Maizlish et al. 1995; Rhodes et al. 2003; Sciarillo et al. 1992; Stanley and Wakwe 2002) and bone (Rhodes et al. 2003; Schwartz et al. 2005) lead levels are significantly associated with depression. A cross-sectional study of 99 occupationally exposed individuals and 61 controls found a dose-dependent association between lead exposure (10-80 μg/dl) and increased reports of depression, confusion, anger, tension, and fatigue as measured by Profile of Mood States (POMS) questionnaire, especially in individuals with lead levels above 40 μg/dL (Baker et al. 1984). Maizlish and coworkers (1995) found that current and cumulative measures of blood lead levels in 43 occupationally exposed individuals (mean blood lead 42 μg/dL) and 45 controls (mean blood lead 15 μg/dL) were associated with significantly increased symptoms of anger, depression, and fatigue. Multiple linear regression adjusting for covariates such as age, education, alcohol intake, and medical conditions showed a significant association between blood lead and tension-anxiety, hostility, and depression, as measured by POMS, in a dose-related manner (current, peak, time weighted average for lead). In a longitudinal study of 576 occupationally exposed individuals, there was a significant association between tibia lead levels (mean tibia lead = 8.4 μg/g) and depressive symptoms as measured by the Center for Epidemiologic Studies Depression (CES-D) scale. The study did not find a significant association between blood lead levels (mean blood lead 31.4 μg/dL) and depressive symptoms (Schwartz et al. 2005)

The majority of these studies included small samples consisting of workers occupationally exposed to high lead levels. It is not known whether environmental exposure to lead, which leads to lower blood lead levels than in occupationally exposed individuals, may lead to psychiatric illness in adults. We examined the association between depression and current background levels of environmental lead exposure in a cross-sectional study of individuals participating in the 2005-2006 cycle of the continuous National Health and Nutrition Examination Survey (NHANES).

Methods

Study Population

NHANES is a complex, multi-stage survey of non-institutionalized civilians of the US population that collects information about health, nutrition, demographic, and socioeconomic factors (Centers for Disease Control and Prevention (CDC) 2009). The survey is conducted by trained physicians, medical and health technicians, and dietary and health interviewers. Data is collected in the form of standardized home interviews and an examination component consisting of a medical, dental, and laboratory test evaluation conducted in Mobile Examination Centers. Approximately 5,000 individuals from 15 counties across the country are surveyed each year. The sample selected for data collection is representative of the US population. Persons over 60, African-Americans, and Hispanic individuals are over-sampled. For this study, adults ages 20 and over (Harris et al. 2009) from NHANES 2005-2006 were selected.

A total of 10,348 individuals participated in the 2005-2006 NHANES cycle, including 4,979 individuals ages 20 and over. Of those, 4,321 individuals answered the questionnaire addressing depression and 4,159 of those had reported blood lead levels. Thus, 4,159 individuals remained for our analyses.

Blood Lead Measurements

Blood lead levels (BLL) were obtained from individuals 1 year and older (Centers for Disease Control and Prevention (CDC) 2009). Non-fasting blood samples (minimum of .25 mL/vial) were collected by venipuncture in pre-screened polyethylene vials and pre-screened vacutainers. Blood samples were transported and stored at $\leq 4°C$. Samples were sent to Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention. Once received, they were frozen at $\leq -20°C$ until analysis. For analysis, blood samples were diluted with 18 mega-ohm water and with diluent, containing 1% v/v tetramethylammonium hydroxide (TMAH), 0.5% disodium ethylenediamine tetraacetate (EDTA), 10% ethyl alcohol, 0.05% Triton X-100, and bismuth was added for standardization. Whole blood lead concentrations were determined using inductively coupled plasma mass spectrometry (PerkinElmer ELAN 6100 ICP-DRC-MS Plus System). Two lower detection limits of 0.25 μg/dL and 0.30 μg/dL were reported. When the value was below the detection limit, the original NHANES investigators divided the detection limit by square root of two as an estimate of the BLL.

Depression Assessment

The Patient Health Questionnaire (PHQ-9) was included as part of the computer assisted personal interview (CAPI) in the mobile exam center (MEC) (Centers for Disease Control and Prevention (CDC) 2009). PHQ-9 is a version of the Prime-MD diagnostic instrument for common mental disorders. It consists of nine questions based on DSM-IV symptoms of depression. Each question is scored ranging from 0-3, with 0 as having a symptom “not at all”, and 3 being “nearly every day”. A score out of 27 is tabulated based on the answers to the nine questions, with 0-4 representing no depression, 5-9 mild depression, 10-14 moderate

depression, 15-19 moderately severe depression, 20-27 severe depression. PHQ-9 is commonly used as a screening method for depression in primary care settings and it is validated as an effective tool in diagnosis of depression, with a PHQ-9 score ≥ 10 having an 88% sensitivity and specificity for depression (Kroenke et al. 2001).

Potential Confounders

Data on all covariates was collected by an interviewer during the home interview portion of NHANES 2005-2006 using the Sample Person and Family Demographics questionnaires (Centers for Disease Control and Prevention (CDC) 2009). The following covariates were evaluated: age (continuous), sex (male as reference), education level (<high school, high school, >high school (reference)), ethnicity (Mexican American, Other Hispanic, Non-Hispanic White (reference), Non-Hispanic Black, Other Race - Including Multi-Racial), and poverty income ratio (PIR; ratio of family income to poverty threshold, with a PIR value less than 1 indicating an income below the poverty threshold and a PIR greater than 1 indicating an income above the poverty threshold). No subjects had missing data for age, gender, and ethnicity, but 3,991 individuals (96% of our eligible sample) remained in the analysis after considering PIR and education.

Statistical Analyses

We used SAS 9.1 and SAS-callable SUDAAN 10, applying NHANES medical examination weights for all analyses. Initially we computed descriptive statistics for our study population, including proportions and means. Estimates of average BLLs and depression prevalence (as defined by PHQ-9 score of >4) were obtained. Subsequently we estimated prevalence ratios using Poisson regression analyses with the LOGLINK function in SUDAAN. In these analyses, depression was a dichotomous variable (PHQ-9 score 0-4: not depressed; score 5+: depressed) and BLL was examined as a continuous variable as well as a categorical variable based on quartiles of the distribution of BLL in the population (Q1: 0-0.88 μg/dL, Q2: 0.89-1.40 μg / dL, Q3: 1.41-2.17 μg /dL, Q4: >2.17 μg/dL). Additionally, odds ratios were estimated using ordinal logistic regression with the MULTILOG function in SUDAAN, with depression defined as an ordinal variable (PHQ-9 score 0-4: not depressed; score 5-9: mildly depressed; and score 10-27: moderately/severely depressed) and BLL again defined as a continuous and categorical variable (see above). The proportionality assumption of the ordinal logistic regression model was assessed via graphical methods (Scott et al. 1997). Analyses were performed with and without covariates to assess the extent of confounding.

Results

Table 1 displays characteristics of the study population by covariates. The sample population was majority non-Hispanic White at 73.27%, 58.11% received an education beyond high school, 51.59% were female, average age was 46.50, and the average PIR was 3.13. Mean blood lead in this population was 1.75 μg/dL. Individuals with depression (defined as PHQ-9 score >4, anyone with mild to severe depression) had a mean blood lead of 1.73 μg/dL while individuals who were not depressed had a mean lead of 1.75 μg/dL. The prevalence of depression was 20.09%.

Table 2 shows the results of Poisson regression analyses for BLL as a categorical and continuous variable and PHQ-9 score as a dichotomous variable (PHQ-9 score 0-4: not depressed; 5+: depressed). The percent weighted positive for depression ranged from 19.43%-20.19% across the BLL categories. Results of unadjusted analyses showed no increased risk of depression with increasing BLL. There was no significant effect of lead on depression when lead was modeled as continuous variable after controlling for age, gender and ethnicity. However, BLL modeled as a categorical variable showed significantly increased risk

of depression with increasing quartile of lead, from 1.00 to 1.29 (p=.0148). Similarly, after additional adjustment for PIR, and education, BLL as a continuous variable did not increase risk of depression. BLL as a categorical variable continued to show a significantly increased risk of depression (p=.0185), but there was no clear trend in risk of depression with increasing BLLs.

Table 3 displays the results of ordinal logistic regression analyses for blood lead as a categorical and continuous variable and PHQ-9 score as an ordinal variable (PHQ-9 score 0-4: not depressed; 5-9: mildly depressed; and 10-27: moderately/severely depressed). The percentage of individuals with no depression was approximately 80%, mild depression 14% and moderate/severe depression 6%. Results were very similar to those attained with Poisson regression, with lead as a continuous variable showing no effect on depression (odds ratios ranging from . 99-1.05) with and without covariates, and BLL as a categorical variable showing significantly increased risk for depression when age, sex, and gender were considered (p=.0210), with odds ratios of 1.00-1.36. However, after additional adjustment for PIR and education, BLL as a categorical variable showed no clear trend of increased risk of depression with increasing BLLs.

Discussion

Lead levels have decreased drastically in the US over the past few decades and continue to decline (Muntner et al. 2005; Pirkle et al. 1994). However, lead accumulates in bone over time, and is then released into blood (Rabinowitz 1991). Thus, individuals that were previously exposed to higher lead levels have higher bone lead levels and have lead chronically released into the blood stream. This effect worsens with age as osteoporotic changes occur and more lead is released into the blood stream. In addition, while lead levels in the general US population have declined drastically, there are continuing problems with high lead exposure and lead poisoning in children living in old housing, especially minority children in urban settings (Pirkle et al. 1998). Furthermore, studies in humans have demonstrated that lead levels below 10 μg/dL, CDC's action level for children (Centers for Disease Control and Prevention (CDC) 1991), have detrimental effects on cognitive and behavioral functioning (Canfield et al. 2003; Lanphear et al. 2005; Surkan et al. 2007). Similarly, there appears to be no known safe level of lead in environmentally exposed adults with demonstrated effects on oxidative stress, inflammation, hypertension and cardiovascular disease even at current low BLLs (Iavicoli et al. 2006; Lee et al. 2006; Menke et al. 2006; Navas-Acien et al. 2007; Vaziri 2008; Vaziri and Gonick 2008).

A recent study addressed environmental lead exposure and neuropsychiatric symptoms by assessing for anxiety, phobic anxiety, and depression in men enrolled in the Normative Aging Study using the Brief Symptom inventory and a combined outcome measure (anxiety, phobic anxiety, depression) (Rhodes et al. 2003). Tibia (mean = 21.9 μg/g), patella (mean = 32.1 μg/g), and blood lead (mean = 6.3 μg/dL) were measured. Logistic regression models showed that all measures of lead were significantly associated with increased risk of the combined outcome measure, and patella lead was significantly associated with increased risk of phobic anxiety. These results appear to corroborate studies demonstrating an association between lead exposure and psychiatric disorders.

In contrast, while our study found a statistically significant association between BLL and depression when exposure was modeled as a categorical variable and only age, gender and sex were considered, the effect was small with a relative risk around 1.3. In addition, when education level and PIR were added to the model, there were no clear trends of increasing risk of depression with increasing BLLs. These findings underline the importance of considering the effects of socio-economic measures such as education and PIR in the investigation of lead

effects on health. It is possible that PIR and education are confounders in the effect of lead on depression, whereby individuals who have higher lead levels also have lower education levels and lower PIR, leading to depression. Alternatively, the effects of lead on depression may be mediated by socioeconomic factors because early lead exposure has been shown to result in behavioral/developmental problems which may in turn lead to lower educational achievement and lower PIR, potential risk factors for depression (Bjelland et al. 2008; Mezuk et al. 2008; Samaan 2000; Yen and Kaplan 1999). Finally, there is a possibility of a combination of confounding and mediation effect of socioeconomic factors on the relationship between lead exposure and depression.

The limitations of this study must be considered when interpreting our findings. In this cross-sectional study BLL and depression were measured at the same point in time. Therefore, there is no consideration of past lead exposure and past BLLs on the risk of depression. Blood lead levels reflect primarily recent environmental exposures and the mobilization of lead from the skeleton back into the circulation (Hu et al. 2007). Bone lead levels have been shown to accurately reflect accumulated exposure (Gerhardsson et al. 1993; Hu et al. 1998; Hu et al. 2007), which may be more relevant to the etiology of depression. Longitudinal studies are needed to fully assess the relationship between lead exposure and depression, including the potentially permanent changes in HPA axis due to early life lead exposure and consequent development of depression later in life.

In addition, the average BLL of individuals in the study was 1.75 μg/dL, which may be too low to detect an existing effect of current BLLs on depression, considering that the occupational exposure limit for blood lead is 40 μg/dL (Occupational Safety and Health Administration (OSHA) 2008). We were not able to account for other potentially important covariates, for example, genetic factors affecting the risk of depression such as polymorphisms in the 5-HT transporter and the glucocorticoid receptor (de Kloet et al. 2005). Also, although the PHQ-9 is an established, validated tool to assess for presence and severity of depression, its sensitivity and specificity of 88% will result in some people receiving a different diagnosis as compared to examination by a mental health professional (Kroenke et al. 2001).

It is clear that HPA axis dysregulation is associated with depression (de Kloet et al. 2005; Holsboer 2000; Vreeburg et al. 2009), and animal studies have demonstrated that lead can cause HPA axis dysregulation (Cory-Slechta et al. 2008; Cory-Slechta et al. 2004; Rossi-George et al. 2009; Virgolini et al. 2005). This study could not assess the relationship between BLLs and HPA axis dysfunction in humans as cortisol levels were not available. Despite these limitations, the study is a nationally representative sample of the US population, and NHANES employs rigorous standardized methods for data collection, generating high quality data.

Conclusion

This study did not demonstrate a consistent association between environmental lead exposure and depression within the investigated blood lead levels. Longitudinal studies will be necessary to more fully examine the effect of environmental lead exposure on depression and other neuropsychiatric outcomes, including measures of HPA axis function to help elucidate potential biological mechanisms.

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Table 1

Characteristics of Study Population: Individuals 20 years and older in NHANES 2005-2006

Characteristic	Overall	Depressed	Not depressed
		Percentage[†]	
Total	100.00	20.09	79.91
Gender			
Male	48.41	16.30	83.70
Female	51.59	23.65	76.35
Ethnicity			
Non-Hispanic White	73.27	19.02	80.98
Non-Hispanic Black	10.85	22.71	77.29
Mexican American	7.76	20.14	79.86
Other Hispanic	3.24	28.60	71.40
Other Race	4.88	24.56	75.44
Education Level			
Less than high school	16.98	27.03	72.97
High school	24.90	22.89	77.11
More than high school	58.11	16.87	83.13
		Mean (SE)	
Lead (μg/dL)	1.75 (0.05)	1.73 (0.04)	1.75 (0.05)
Poverty Income Ratio (PIR)	3.13 (0.07)	2.64 (0.07)	3.26 (0.07)
Age	46.50 (0.73)	45.79 (0.90)	46.48 (0.77)

[†]for depressed and non-depressed: % of participants in subgroup

Table 2

Blood lead levels in relation to depression prevalence, Poisson regression: NHANES 2005-2006

	% depressed	Crude RR	Adjusted RR I[†]	Adjusted RR II[‡]
Continuous lead	20.02	0.99(.94-1.04)	1.04 (0.98-1.10)	1.01 (0.96-1.07)
Categorical lead				
0-0.88 μg/dL	20.19	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.89-1.40 μg/dL	20.53	1.02 (0.85-1.22)	1.17 (0.98-1.40)	1.16 (.99-1.36)
1.41-2.17 μg/dL	19.93	1.00(0.90-1.11)	1.24 (1.09-1.41)	1.20 (1.07-1.36)
2.18-26.4 μg/dL	19.43	0.97 (0.76-1.24)	1.29 (0.94-.77)	1.16 (.87-1.54)

[†] adjusted for age, gender, and ethnicity (n=4,159)

[‡] adjusted for age, gender, ethnicity, education, and PIR (n=3,991)

Table 3

Blood lead levels in relation to depression prevalence, Ordinal logistic regression: NHANES 2005-2006

	% no; mild; and severe depression	Crude OR	Adjusted OR I†	Adjusted OR II‡
Continuous lead	79.98; 14.36; 5.66	0.99 (0.92-1.06)	1.05 (0.97-1.14)	1.01 (0.94-1.09)
Categorical lead				
0-0.88 μg/dL	79.81; 14.39; 5.80	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.89-1.40 μg/dL	79.47; 14.66; 5.86	1.03 (0.82-1.28)	1.22 (0.97-1.53)	1.22 (0.98-1.51)
1.41-2.17 μg/dL	80.07; 14.80; 5.13	0.99 (0.87-1.12)	1.29 (1.10-1.52)	1.25 (1.07-1.47)
2.18-26.4 μg/dL	80.57; 13.58; 5.85	0.97 (0.72-1.30)	1.36 (0.92-2.02)	1.18 (0.83-1.68)

† adjusted for age, gender, and ethnicity (n=4,159)

‡ adjusted for age, gender, ethnicity, education, and PIR (n=3,991)