CME Article #2

# Relationship of Bone and Blood Lead Levels to Psychiatric Symptoms: The Normative Aging Study

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## Learning Objectives

- Explain the merits of estimating lead levels in bone as well as in blood when examining relationships between body lead stores and psychiatric symptoms.
- Recall the relationships, if any, between bone and blood lead levels and scores on a range of psychiatric symptom scales.
- Discuss possible mechanisms by which high lead levels may induce or magnify psychiatric symptoms.

## Abstract

*Blood and bone lead levels were used to investigate lead's potential effect on psychiatric symptoms among middle-aged to elderly men from the Normative Aging Study. Symptoms were assessed using the Brief Symptom Inventory (BSI) and analyzed as individual outcomes as well as a measure that combined anxiety, depression, and phobic anxiety. Blood and bone lead averaged 6.3 μg/dL (standard deviation [SD] = 4.16), 21.9 μg/g (SD = 13.5), and 32.1 μg/g (SD = 19.8) for blood, tibia, and patella lead, respectively. In logistic regression models that adjusted for age, alcohol intake, employment status, and education status, we found that patella bone lead was significantly associated with an increased risk of phobic anxiety and the combined outcome measure at the* $P \leq 0.05$ *level. Tibia and blood lead had similar associations. We conclude that cumulative lead exposure, which bone lead levels reflect, could be a risk factor for psychiatric symptoms even at modest levels of exposure.* (J Occup Environ Med. *2003;45:1144–1151*)

Lead has various acute and chronic effects. Moderately high exposure of an acute nature, as could be seen in occupationally exposed individuals, can result in abdominal colic, encephalopathy, hemolysis, and acute renal failure. High-level exposure of a chronic nature, as could be seen in community-exposed individuals, can result in fatigue, myalgias, anemia, peripheral motor neuropathy, neurobehavioral disturbances/chronic encephalopathy, and chronic renal failure. Many studies have demonstrated that lead exposure has a negative effect on the central nervous system with regard to cognitive function, eg, reaction time, pattern comparison, vocabulary, memory, and intelligence.[1–6]

There have been relatively few studies that have investigated the effect of lead on psychiatric aspects of the central nervous system such as anxiety, depression, anger, and irritability. An early study of lead smelter workers showed that long-term occupational lead exposure was associated with symptoms of depression and irritability as well as symptoms and laboratory evidence of other medical problems involving the gastrointestinal and renal systems.[7] Another occupational study showed that elevated blood lead levels were associated with increased rates of depression, irritability, and emotional lability.[8] This study was performed on lead-exposed foundry workers with mean blood lead levels of 33.9 μg/dL who were compared to unexposed referents with a mean

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blood lead of 18.6 μg/dL. Mood testing was done using the Profile of Mood States (POMS) questionnaire. A more recent study of inorganic lead-exposed Venezuelan workers also used the POMS questionnaire to assess mood.[9] Mean blood lead levels among exposed workers and control subjects were 42 μg/dL and 15 μg/dL, respectively. Measures of lead exposure used in the analysis included current, peak, and cumulative blood lead measures (based on time-weighted average). The current and cumulative measures of lead exposure were significantly associated with the POMS subscales of tension, anxiety, hostility, and depression. Finally, POMS was used by Lindgren et al. to investigate mood and its relation to occupational lead exposed smelter workers.[10] Both blood lead and a cumulative/long-term lead measure (integrated blood lead) were used. A calculated measure of cumulative blood lead was estimated as an integral using measured blood leads over each employee's working lifetime. Mean blood lead was 28 μg/dL and mean integrated blood lead was 711 μg/year per deciliter. Results showed that a general distress factor that included POMS subscales of anger, confusion, depression, fatigue, and tension was significantly related to integrated blood lead, but not to blood lead.

Although these studies all suggest a relationship between lead exposure and psychiatric symptoms, none of these studies have used a directly measured parameter of cumulative, long-term exposure. Only blood lead or measures of long-term exposure calculated from serial blood lead levels have been used. Autopsy studies indicate that 95% human body lead is stored in the skeleton.[11,12] Toxicokinetic studies show that the half-life of bone lead is years to decades.[13] Once environmental exposure sources have lessened, accumulated lead in bone can become a major contributor with bone supplying constant low levels of lead to circulating plasma. The development of in vivo K-x-ray fluorescence (KXRF) has made it possible to directly measure levels of lead in bone, allowing bone lead to be used as a cumulative lead measure.[14] This study used blood lead as well as directly measured tibia and patella bone lead to investigate the relationship of lead exposure to aspects of psychiatric symptoms using the Brief Symptom Inventory (BSI) in community-exposed males.

## Methods

This study was a cross-sectional study of aspects of psychiatric symptoms in middle-aged and elderly men from the Normative Aging Study. The Institutional Review Boards of the Brigham and Women's Hospital, the Harvard School of Public Health, and the Boston VA Medical Center approved this research.

### Study Subjects

Study subjects were participants of the Normative Aging Study (NAS). The NAS is a longitudinal study of aging established in 1961 by the Veterans Administration.[15] The cohort consists of 2280 community-dwelling men from the Greater Boston area who were aged 21–80 years on enrollment in the study. Men with past or present chronic medical conditions at the time of enrollment were not eligible to participate. These conditions included heart disease, cancer, recurrent asthma, sinusitis, bronchitis, diabetes, gout, peptic ulcer, and systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. Participants were evaluated by detailed medical history, physical examination, laboratory tests, and questionnaires. Starting in 1988, a fresh whole blood sample for lead was obtained from study participants. Permission to obtain bone lead measurements was begun in 1991. Those granting consent had bone lead measurements at the outpatient Clinical Research Center of Brigham and Women's Hospital in Boston.

Participants were seen approximately every 3 years for follow up, at which time self-administered questionnaires were used to obtain demographic characteristics, including age, alcohol intake, education level, income level, and to update work history, medical history, and psychiatric history. Psychiatric symptoms assessed using the standardized psychiatric self-report scale, the BSI. Blood samples were obtained on the same day and analyzed for blood lead. Patella and tibia bone leads were generally measured within 1 month of the blood lead samples and questionnaire data. For the purpose of this analysis, subjects with first bone lead visits between January 1, 1991, and December 31, 1995, were considered for participation. Among these, subjects missing any variable of interest or having bone lead measurements greater than 3 months after BSI data and blood lead collection were considered as nonparticipants and compared with the remaining participants.

### Brief Symptom Inventory

The BSI is a 53-item self-report questionnaire, which was included in the Health and Social Behavior Survey given to NAS subjects. The original version validated by Derogatis was used.[16] The inventory is scaled on a 5-point scale of distress ranging from "not at all" to "extremely," or 0 to 4. Scores assess 9 primary symptom dimensions and 3 global indices of distress. The symptom dimensions and descriptions are: 1) somatization (S)—distress arising from perceptions of bodily dysfunction; 2) obsessive–compulsive (O-C)—ego-dystonic, unwanted thoughts, impulses, and actions which are unremitting; 3) interpersonal sensitivity (I-S)—feelings of personal inadequacy and inferiority; 4) depression (D)—indications of clinical depression; 5) anxiety (ANX)—nervousness and tension; 6) hostility (HOS)—thoughts, feelings, or actions of anger; 7) phobic anxiety (PHO)—persistent fear, irrational and

disproportionate to a stimulus; 8) paranoid ideation (PaI)—disordered mode of thinking; and 9) psychoticism (PSY)—withdrawn, isolated schizoid behaviors and lifestyle. The BSI solicits symptoms experienced in the last 30 days.

The 3 global indices of distress, reflecting overall psychopathologic status, are the Global Severity Index (GSI), the Positive Symptom Distress Index (PSD), and the Positive Symptom Total (PST). BSI scale scores are calculated by adding the responses of the items comprising each scale, eg, 6 questions each for depression and anxiety scales. GSI is calculated based on all 53 items. This total is then divided by the number of valid items. PST counts all items. The BSI scores are also expressed in T scores (mean, 50; standard deviation [SD], 10). For the purposes of this study, only anxiety, depression, phobic anxiety, GSI, and PST scales, as well as a combined measure using anxiety, depression, and phobic anxiety scales, were used in the analysis. As was detailed in the introduction, depression and irritability have been shown in previous studies to be associated with lead exposure. GSI and PST were chosen as general global scales for analysis. The combined measure was chosen to represent those with higher scores on multiple scales used. A combined measure has previously been shown to be significantly related to lead levels.[10] For each BSI scale, we determined the score for each that was 1 SD above the mean for a normal population, 0.5 for anxiety and depression, 0.2 for phobic anxiety, 0.44 for GSI, and 18 for PST. The combined measure required a subject to be above the cutoff for anxiety, depression, and phobic anxiety.

## Blood Lead Measurement

Whole blood samples for lead measurement were obtained in special lead-free tubes containing edentate calcium disodium (EDTA) and analyzed at ESA Laboratories, Inc., Chelmsford, Massachusetts. After room temperature digestion with nitric acid, the samples were centrifuged and the supernatant analyzed by Zeeman background-corrected flameless atomic absorption. The instrument was calibrated before use with national Bureau of Standards blood lead standards materials, rechecked every 21 samples, and again after the last sample. Ten percent of samples were run in duplicate, 10% were blanks, and ≥10% were control subjects. To prevent lead contamination, all glassware used was soaked overnight in 20% nitric acid and rinsed with distilled water. Supernatant and reagents were transferred with disposable polyethylene-tipped micropipettes. Reference samples from the Centers for Disease Control (CDC) yielded a coefficient of variation ranging from 8% for concentration below 30 μg/dL to 1% for higher concentrations. Twenty-four measurements by this method yielded a mean of 5.3 μg/dL with a SD of 1.23, compared with a National Bureau of Standards target of 5.7 μg/dL.

## KXRF Bone Lead Measurements

Midtibia shaft and patella bone lead measurements were taken using an ABIOMED KXRF instrument (Abiomed, Inc., Danvers, MA). The physical principles, technical specifications, validation, and quality control procedures for this instrument have been described in detail elsewhere,[17–19] as have those of other KXRF instruments.[20,21] A 109-Cd gamma-ray source is used to provoke the emission of fluorescent photons from target tissue that are then detected, counted, and arrayed on a spectrum.[22] A linear least-squares algorithm is used to subtract Compton background counts to yield the net lead signal. The lead fluorescence signal is then normalized to the elastic or coherently scattered gamma-ray signal arising primarily from the calcium and phosphorus present in bone mineral. The unit of measurement is micrograms of lead per gram of bone mineral (μg/g). The instrument provides a continuous unbiased point estimate that oscillates around the true bone lead value. Because of this, a negative point estimate can be produced when the true bone lead level is close to zero. An estimate of the uncertainly associated with each measurement is also provided. This estimate is derived from a goodness-of-fit calculation of the spectrum curves and is equivalent to a single SD. Although a minimum detectable limit calculation of twice this value has been proposed for interpreting an individual's bone lead estimate,[23] retention of all point estimates makes better use of the data in epidemiologic studies.[24]

Thirty-minute measurements at midshaft of the left tibia (cortical bone) and left patella (trabecular bone) were taken after each area had been washed with 50% isopropyl alcohol solution. The KXRF beam collimator was sited perpendicular to the tibia bone surface and at 30° lateral for the patella.

## Statistical Analysis

All analyses were performed with Statistical Analysis System, version 8 (SAS Inc.). All variables were initially categorized for comparison of participants with nonparticipants. Participants were then dichotomized by BSI scale into those above the determined cutoff (yes) and those below (no). For participants, means and SDs were calculated for all variables by BSI yes/no status, except for education and employment, which were categorized. *T* tests and Chi-squared tests were used to compare continuous data and categorical data, respectively. Fisher's exact test was used to compare categorical data for the combined BSI measure. Four logistic regression models were run for each BSI outcome, one without a lead measure and one with each lead measure, blood, patella, and tibia. All models included age, age$^2$, alcohol, education, and employment variables. The age$^2$ term was used to adjust for the likely nonlinear relationship of psychiatric symptoms and age. *P* values were used to determine significance of the models, with

**TABLE 1**
Demographic Characteristics, Lead Levels, and BSI Indices Among NAS Subjects Who Were Participants and Non-Participants in the Current Study

| Variable | Participants ($n$ = 526) No. (%) | Nonparticipants ($n$ varies) N | Nonparticipants ($n$ varies) No. (%) |
|---|---|---|---|
| Age (years) | | 178 | |
| 48–59 | 93 (18) | | 32 (18) |
| 60–69 | 260 (49) | | 95 (53) |
| 70 | 173 (33) | | 51 (29) |
| Education | | 96 | |
| Never finished high school | 56 (11) | | 12 (13) |
| High school graduate | 189 (36) | | 29 (30) |
| Some college/technical school | 124 (23) | | 23 (24) |
| College graduate or more | 157 (30) | | 32 (33) |
| Employment status | | 115 | |
| Retired/unemployed | 306 (58) | | 57 (50) |
| Retired and working part time | 105 (20) | | 22 (19) |
| Retired and working full time | 115 (22) | | 36 (31) |
| Current alcohol consumption | | 141 | |
| <10 g/day | 305 (58) | | 91 (65) |
| 11–50 g/day | 192 (36) | | 44 (31) |
| >50 g/day | 29 (6) | | 6 (4) |
| Blood lead (μg/dL) | | 178 | |
| <5 | 210 (40) | | 65 (36) |
| 5–10 | 254 (48) | | 92 (52) |
| 11–20 | 55 (11) | | 20 (11) |
| 20 | 7 (1) | | 1 (1) |
| Tibia lead (μg/g) | | 178 | |
| <1–15 | 173 (33) | | 56 (31) |
| 16–24 | 186 (35) | | 62 (35) |
| 25–126 | 167 (32) | | 60 (34) |
| Patella lead (μg/g) | | 178 | |
| <1–22 | 189 (36) | | 67 (38) |
| 23–35 | 165 (31) | | 50 (28) |
| 36–165 | 172 (33) | | 61 (34) |
| Anxiety (≥0.5) | | 178 | |
| No | 449 (85) | | 156 (88) |
| Yes | 77 (15) | | 22 (12) |
| Depression (≥0.5) | | 178 | |
| No | 441 (84) | | 151 (85) |
| Yes | 85 (16) | | 27 (15) |
| Phobic anxiety (≥0.2) | | 178 | |
| No | 486 (92) | | 164 (92) |
| Yes | 40 (8) | | 14 (8) |
| General severity index (> 0.44) | | 178 | |
| No | 455 (86) | | 150 (84) |
| Yes | 71 (14) | | 28 (16) |
| Positive symptom total (>18) | | 178 | |
| No | 443 (84) | | 151 (85) |
| Yes | 83 (16) | | 27 (15) |
| Combined BSI measure (≥0.5 anxiety, ≥0.5 depression, and ≥0.2 phobic anxiety) | | 178 | |
| No | 506 (96) | | 173 (97) |
| Yes | 20 (4) | | 5 (3) |

* = $P < 0.05$

calculation of odd ratios for those significant at the $P \leq 0.05$ level.

## Results

Of 2775 subjects having any data (including multiple visits) and seen for their NAS visit between January 1, 1991, and December 31, 1995, 704 had their first bone lead visit during this time period and had bone lead measurements within 3 months of blood lead level/BSI data collection. Of these, 526 had all variables of interest and were considered participants, whereas 178 were missing at least one variable and considered nonparticipants.

Descriptive statistics, including number and percentage in each category for participants and nonparticipants, are shown in Table 1. Participants used in the analysis for this study were not significantly different from nonparticipants with respect to the distributions of the characteristics of interest.

The mean age for participants was 67.1 years (SD = 7.20) and the means for the lead levels were 6.3 μg/dL (SD = 4.16), 21.9 μg/g (SD = 13.51), and 32.1 μg/g (SD = 19.84) for blood, tibia, and patella lead, respectively. The percentage of participants who exceeded cutoff levels for our psychiatric symptom outcomes were 15% for anxiety, 16% for depression, 8% for phobic anxiety, 13% for the general severity index, 16% for the positive symptom total, and 4% for the combined measure.

### Comparisons of Participant Data by BSI Scale Status

For each respective BSI scale, the number of subjects above and below the cutoff as well as the mean and SD for age, alcohol consumption, and lead levels are presented in Table 2. The number and percent for each education and employment category are also presented. Crude comparisons using $t$ tests and Chi-squared from these data tables indicate a possible relationship between patella bone lead levels, as well as employment and education, and several BSI scales. Patella bone lead levels were associated with higher risks with $P$ values of 0.05 and 0.10 for anxiety, depression, phobic anxiety, and GSI scales. All lead measures were significantly higher at $P$ values of 0.05 for the combined measure. More people with depression were unemployed or working part-time than without depression, and more without depres-

**TABLE 2**
Characteristics by BSI Scale Status, the Normative Aging Study

| Characteristic | Anxiety | | Depression | | Phobic Anxiety | |
|---|---|---|---|---|---|---|
| | ≥0.5 (*n* = 77) Mean (SD) | <0.5 (*n* = 449) Mean (SD) | ≥0.5 (*n* = 85) Mean (SD) | <0.5 (*n* = 441) Mean (SD) | ≥0.2 (*n* = 40) Mean (SD) | <0.2 (*n* = 486) Mean (SD) |
| Age (years) | 67.2 (8.8) | 67.1 (6.9) | 67.7 (8.7) | 66.9 (6.9) | 68.5 (8.0) | 67.0 (7.1) |
| Alcohol consumption (g/day) | 10.5 (14.8)* | 13.6 (17.9)* | 11.0 (15.6) | 13.6 (17.8) | 14.0 (19.2) | 13.1 (17.4) |
| Blood Pb levels (μg/dL) | 6.5 (4.3) | 6.2 (4.1) | 6.6 (4.6) | 6.2 (4.1) | 7.3 (4.5) | 6.2 (4.1) |
| Tibia bone Pb levels (μg/g) | 22.4 (14.2) | 21.8 (13.4) | 23.4 (14.8) | 21.6 (13.2) | 26.3 (17.1)‡ | 21.5 (13.1)‡ |
| Patella bone Pb levels (μg/g) | 35.6 (23.6)† | 31.5 (19.1)† | 36.5 (24.0)‡ | 31.3 (18.9)‡ | 40.3 (29.0)‡ | 31.5 (18.8)† |
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| Education Status | | | | | | |
| Never finished high school | 7 (9) | 49 (11) | 10 (12) | 46 (10) | 5 (13) | 51 (11) |
| High school graduate | 33 (43) | 156 (35) | 36 (42) | 153 (35) | 17 (43) | 172 (35) |
| Some college/tech. school | 18 (23) | 106 (23) | 20 (24) | 104 (24) | 9 (22) | 115 (24) |
| College graduate or more | 19 (25) | 138 (31) | 19 (22) | 138 (31) | 9 (22) | 148 (30) |
| Employment Status | | | | | | |
| Retired/unemployed | 49 (64) | 257 (57) | 55 (65)† | 251 (57)† | 26 (65) | 280 (58) |
| Retired/working part time | 15 (19) | 90 (20) | 19 (22) | 86 (19) | 8 (20) | 97 (20) |
| Retired/working full time | 13 (17) | 102 (23) | 11 (13) | 104 (24) | 6 (15) | 109 (22) |

| Characteristic | GSI | | PST | | Combined Measure | |
|---|---|---|---|---|---|---|
| | >0.44 (*n* = 71) Mean (SD) | 0.44 (*n* = 455) Mean (SD) | >18 (*n* = 83) Mean (SD) | 18 (*n* = 443) Mean (SD) | (*n* = 20) Mean (SD) | (*n* = 506) Mean (SD) |
| Age (years) | 68.6 (9.0)† | 66.8 (6.9)† | 68.2 (8.6)[a] | 66.8 (6.9)* | 69.7 (9.1) | 66.9 (7.1) |
| Alcohol consumption (g/day) | 10.2 (16.3)* | 13.7 (17.6)* | 11.5 (16.4) | 13.5 (17.7) | 11.1 (20.1) | 13.3 (17.4) |
| Blood Pb levels (μg/dL) | 6.8 (4.4) | 6.2 (4.1) | 6.4 (4.1) | 6.3 (4.2) | 8.8 (5.4)‡ | 6.2 (4.1)‡ |
| Tibia bone Pb levels (μg/g) | 23.5 (14.4) | 21.6 (13.4) | 23.4 (14.2) | 21.6 (13.4) | 31.8 (21.2)‡ | 21.5 (13.0)‡ |
| Patella bone Pb levels (μg/g) | 36.3 (23.5)† | 31.5 (19.2)† | 35.3 (23.3)* | 31.5 (19.1)* | 51.8 (35.9)‡ | 31.4 (18.6)‡ |
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| Education Status | | | | | | |
| Never finished high school | 5 (7)† | 51(11)† | 6 (7) | 50 (11) | 1 (5)† | 55 (11)† |
| High school graduate | 35 (49) | 154 (34) | 38 (46) | 151 (34) | 12 (60) | 177 (35) |
| Some college/tech. school | 15 (21) | 109 (24) | 19 (23) | 105 (24) | 5 (25) | 119 (23) |
| College graduate or more | 16 (23) | 141 (31) | 20 (24) | 137 (31) | 2 (10) | 155 (31) |
| Employment Status | | | | | | |
| Retired/unemployed | 45 (63) | 261 (57) | 48 (58) | 258 (58) | 14 (70) | 292(58) |
| Retired/working part time | 14 (20) | 91 (20) | 20 (24) | 85 (19) | 3 (15) | 102 (20) |
| Retired/working full time | 12 (17) | 103 (23) | 15 (18) | 100 (23) | 3 (15) | 112 (22) |

* = $P < 0.15$ † = $P < 0.10$ ‡ = $P < 0.05$

sion were working full-time. Finally, a higher percentage of subjects below GSI and combined measure cutoff had completed college or more schooling, whereas a higher percentage of subjects above GSI and combined measure had only completed high school.

## Logistic Regression Modeling

Table 3 presents the logistic regression model results for prediction of BSI status. In general, there was a consistent trend for each of our lead biomarkers of an increased risk for mood symptoms with all beta coefficients being positive. The lead biomarker that was most closely associated with psychiatric symptoms was clearly patella bone lead, which had beta coefficients with $P$ values $<0.10$ for 4 of the 6 outcomes (anxiety, depression, phobic anxiety, and the combined measure) and $<0.05$ for 2 of the 6 outcomes (phobic anxiety and the combined measure). Tibia bone lead and blood lead also had beta coefficients with a $P$ value $<0.05$ for the combined measure. Table 4 presents the odds ratios and 95% confidence intervals for those results with $P$ values $<0.05$ by taking the beta coefficients for the lead measures from each model and estimating the odds of an increase in lead measure from the midpoints of the lowest quintile to the highest quintile.

Conversely, none of our covariates (age, age 2, alcohol ingestion, education, or employment status) had consistent associations with mood symptoms in any of our models (results not shown). Being retired or unemployed had a significant association in the multivariate logistic regression of depression (with a beta coefficient of 1.0132 and a $P$ value

**TABLE 3**
Results of Logistic Regression Models for Mood Symptoms for 619 Participants from NAS*

| | Anxiety Status | | | Depression Status | | | Phobic Anxiety Status | | |
|---|---|---|---|---|---|---|---|---|---|
| **Lead Measure** | **â** | **SE** | ***P*** | **â** | **SE** | ***P*** | **â** | **SE** | ***P*** |
| Blood Pb | 0.0241 | 0.0293 | 0.41 | 0.0275 | 0.0285 | 0.33 | 0.0541 | 0.0349 | 0.12 |
| Tibia Pb | 0.0046 | 0.0097 | 0.64 | 0.0067 | 0.0090 | 0.45 | 0.0151 | 0.0107 | 0.16 |
| Patella Pb | 0.0112 | 0.0062 | 0.07 | 0.0109 | 0.0059 | 0.07 | 0.0144 | 0.0072 | 0.05 |
| | **GSI > 0.44** | | | **PST > 18** | | | **Combined Measure** | | |
| **Lead Measure** | **â** | **SE** | ***P*** | **â** | **SE** | ***P*** | **â** | **SE** | ***P*** |
| Blood Pb | 0.0436 | 0.0291 | 0.13 | 0.0161 | 0.0293 | 0.58 | 0.1201 | 0.0423 | 0.005 |
| Tibia Pb | 0.0036 | 0.0098 | 0.72 | 0.0058 | 0.0092 | 0.53 | 0.0271 | 0.0127 | 0.03 |
| Patella Pb | 0.0082 | 0.0064 | 0.20 | 0.0071 | 0.0061 | 0.25 | 0.0286 | 0.0091 | 0.002 |

* Each column represents the results of three separate multivariate regression models that control for age (years), age$t^2$, alcohol ingestion (g/day), education (4 levels), employment status (3 levels) and that include either blood lead (μg/dL), tibia bone lead (μg/g), or patella bone lead (μg/g).

**TABLE 4**
Odds Ratios and Confidence Intervals based on Quintile Increase in Lead Measure

| BSI Scale | Lead Measure | Quintile Range (midpoints lowest to highest) | Odds Ratio | Confidence Interval |
|---|---|---|---|---|
| Phobic anxiety | Patella Bone | 45 μg/dL | 1.91 | 1.01–3.61 |
| Combined measure | Blood | 8.9 μg/dL | 2.91 | 1.39–6.09 |
| Combined measure | Tibia Bone | 27 μg/dL | 2.08 | 1.06–4.07 |
| Combined measure | Patella Bone | 45 μg/dL | 3.62 | 1.62–8.08 |

of 0.01). Also, high school graduate had a significant association in the multivariate logistic regression of GSI (with a beta coefficient of 0.7435 and a *P* value of 0.03).

## Discussion

These results suggest a potential association between bone lead levels and increased risk of psychiatric symptoms of anxiety and depression. Blood lead is immediately available and relatively short-lived over a period of months. Once an individual is removed from current lead exposures, stored bone lead supplies to lead into circulation, years for patella bone, and decades for tibia bone. Because of the different types of bone making up the tibia and patella, namely cortical and trabecular, respectively, there are differences in their contribution to chronic elevations in blood lead levels. Patella lead (as a reflection of trabecular bone lead concentrations) contributes to the majority of blood lead levels (for those individuals not currently exposed), accounting in a previous study of these same subjects for over 80% of the explainable variance.[25] This could lead to chronically elevated levels in the elderly when bone demineralization is increased, and therefore blood lead levels could be chronically elevated as well. Bone lead has been shown to be a more accurate measure of plasma lead levels, which is the most biologically active fraction of lead in blood. Because patella lead has been shown to contribute to the majority of blood lead levels, it probably also contributes the majority of lead to the plasma portion. This could be the reason patella lead was significant or approached significance for several of the BSI subscales in this analysis and blood lead on one scale. Studies have shown, as discussed in the introduction, that chronic low levels of lead can lead to poor cognitive performance. These low levels of lead could also contribute to increases in mood symptoms, including depression, anxiety, and irritability. Tibia bone lead could be more closely related to depression levels over the long term, and this could be more easily detected in a longitudinal-type analysis.

We also found that employment status (being retired/unemployed or retired/working part-time) was significantly associated with depressive symptoms. This could be because individuals working or those with more social interactions have less depression.[26,27] The effect appears to be independent of lead exposure used in the model, because the *P* value does not change with the addition of each measure.

For most models of the GSI and PST scales, high school graduates had significantly higher odds of having GSI or PST symptoms. This could be related to general stress regarding one's socioeconomic status. Stress levels have been shown to increase with decreasing socioeconomic status.[26] Additionally, studies have shown a relationship between education status and bone lead levels, possibly as a result of unmeasured lead exposures related to socioeconomic status (housing, traffic, water source).[27] This further sup-

ports education status as a confounder and justifies its inclusion in the model. Education status becomes nonsignificant with the addition of lead measures, patella bone lead in particular. This could be because education status represents unmeasured lead exposure.

This study has several limitations. We looked at a number of different outcomes, raising the issue of chance findings in a setting of multiple comparisons. On the other hand, we identified 4 statistically significant relationships among the 18 total relationships investigated (ie, 6 psychologic outcomes by 3 different biologic markers of lead dose), perhaps 3 more than what would have been expected by chance. Moreover, an a priori reason exists for believing that bone lead, not blood lead, would be most predictive of chronic psychologic outcomes and patella bone lead was consistently associated with an increased risk for all 6 outcomes of interest.

Another potential limitation is that specific work history was not obtained. Certain jobs impose more of an exposure to lead, as alluded to earlier, and could at the same time effect mood. Work history could have also shed light on exposures not considered. Regarding education, it is possible that those with lower education levels had difficulty completing or fully understanding the questionnaires. This could have biased the BSI scores, but would have done so toward the null.

The mechanism of action of lead's effect on the central nervous system regarding cognition or psychiatric symptoms is unknown. Are current blood lead levels more important to aspects of mood or are stored, long-term, cumulative bone lead levels? Blood lead could directly interfere with neurotransmitter release by interaction with neuron/gap junctions. Cumulative bone lead could decrease neurotransmitter concentration by decreasing actual neurons through neuronal damage from cumulative oxidative effects. Studies have shown that lead's effect could be diverse, affecting several aspects of the neurologic system. Lead has been shown to increase basal release of neurotransmitters (dopamine and others), but to inhibit release evoked by potassium by mimicking or inhibiting calcium mediated processes.[28,29] Studies have shown that lead has effects on calcium homeostasis and calcium-dependent systems. Tyrosine hydroxylase, involved in the synthesis of catecholamines, has been shown to be regulated by cAMP and calcium calmoduline protein kinases.[30–32] Also, brain mitochondrion respiration and ADP phosphorylation has been shown to be affected by lead.[33] Lead can exert its effect directly on tyrosine hydroxylase through a calcium-dependent process or through effects on phosphorylation of adenosine monophosphate. Studies have shown that lead affects neurotransmitter system function in specific areas of rat brains. One study investigated low level effects of lead on the dopaminergic and serotonergic neurotransmitter systems in various parts of rat brains.[34] Both these systems have been shown to be involved with mood (depression and anxiety) as well as other systems, including blood pressure regulation. The results showed, after chronic lead exposures of 25–50 parts per million (10–19 μg/dL), decreased activities of dopamine and serotonin in certain areas of the brain, especially the nucleus accumbens. This information seems to indicate that longer-term exposure to lead could be more important to aspects of mood.

The studies discussed in the introduction showed a significant relationship between cumulative lead exposure, through a calculated time-weighted average or integrated blood lead, and mood symptoms. This study's results appear to agree with these earlier studies and are the first to derive from a study that uses directly measured bone leads as a marker for cumulative lead exposure. Future studies could be improved by using less subjective outcome measures, including actual psychiatric interviewer's rating of mood or direct measures of neuronal/neurotransmitter activity by single photon emission computed tomography scanning.

## Conclusions

This study showed that low exposure to lead can contribute to depression, anxiety, or other psychiatric issues. Future studies can be improved by using less subjective outcome measures. The results from this analysis further support the idea that lead exposure can play a role in psychiatric problems, including depression, anxiety, and general stress on the central nervous system.

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