

# Blood Lead Levels and Major Depressive Disorder, Panic Disorder, and Generalized Anxiety Disorder in US Young Adults

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**Context:** Lead is a ubiquitous neurotoxicant, and adverse cognitive and behavioral effects are well-documented in children and occupationally exposed adults but not in adults with low environmental exposure.

**Objective:** To investigate the association of current blood lead levels with 3 common psychiatric disorders—major depression, panic, and generalized anxiety—in young adults.

**Design:** Cross-sectional epidemiologic survey.

**Setting:** Nationally representative sample of US adults.

**Participants:** A total of 1987 adults aged 20 to 39 years who responded to the National Health and Nutrition Examination Survey (1999-2004).

**Main Outcome Measures:** Twelve-month DSM-IV criteria-based diagnoses of major depressive disorder, panic disorder, and generalized anxiety disorder assessed using the Composite International Diagnostic Interview.

**Results:** The mean (SD) blood lead level was 1.61 (1.72)

μg/dL (range, 0.3-37.3 μg/dL) (to convert to micromoles per liter, multiply by 0.0483). Increasing blood lead levels were associated with higher odds of major depression ( $P = .05$  for trend) and panic disorder ( $P = .02$  for trend) but not generalized anxiety disorder ( $P = .78$  for trend) after adjustment for sex, age, race/ethnicity, education status, and poverty to income ratio. Persons with blood lead levels in the highest quintile had 2.3 times the odds of major depressive disorder (95% confidence interval [CI], 1.13-4.75) and 4.9 times the odds of panic disorder (1.32-18.48) as those in the lowest quintile. Cigarette smoking was associated with higher blood lead levels and outcome, but models that excluded current smokers also resulted in significantly increased odds of major depression ( $P = .03$  for trend) and panic disorder ( $P = .01$  for trend) with higher blood lead quintiles.

**Conclusions:** In these young adults with low levels of lead exposure, higher blood lead levels were associated with increased odds of major depression and panic disorders. Exposure to lead at levels generally considered safe could result in adverse mental health outcomes.

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**L**EAD IS A WELL-KNOWN NEUROTOXICANT that is ubiquitous in the environment, found in air, soil, dust, and water. Blood lead levels measured in the National Health and Nutrition Examination Survey (NHANES) have been a cornerstone of lead exposure surveillance in the United States since the early 1970s.<sup>1</sup> Data show a dramatic decline in average blood lead levels since 1980<sup>2</sup> due, in large part, to the removal of lead from gasoline. However, several sources of exposure remain, such as paint, industrial processes, water contaminated by corroding pipes or solder, mining, pottery, and folk medicine. Adverse effects of lead exposure have been reported for different organ systems, most notably the nervous system<sup>3</sup> but also the cardiovascular<sup>4,5</sup> and renal<sup>6</sup> systems.

Research on the neurotoxic effects of low-level lead exposure has focused on the in utero and early childhood periods.<sup>7</sup> In adult populations, the neurotoxic effects of lead have been studied mainly in the context of occupational exposures, with levels of exposure orders of magnitude greater than that experienced by the general population. Lead-exposed workers in foundries, battery plants, and lead smelters were reported to experience cognitive and neuromotor deficits as well as mood disorders such as anxiety, hostility, and depressive states.<sup>8-13</sup> Almost all of the participants in these investigations were men, with mean blood lead levels as high as 40 μg/dL (to convert to micromoles per liter, multiply by 0.0483).

Few studies have addressed the nervous system effects of lead exposure at the

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low levels commonly encountered in the general adult population. Between 1999 and 2002, the geometric mean blood lead level in 20- to 59-year-old adults living in the United States was 1.5  $\mu\text{g}/\text{dL}$ .<sup>14</sup> The results of one study<sup>15</sup> in the general adult population suggest that lead exposure might adversely affect emotional regulation. Higher blood and bone lead levels in 526 men living in or near Boston were associated with a higher degree of anxiety, phobic anxiety, and depression on a symptom questionnaire after adjusting for covariates.<sup>15</sup> The association between lead exposure and adverse neuropsychiatric symptoms was greater in  $\delta$ -aminolevulinic acid dehydratase (ALAD) 1-1 carriers than in 1-2/2-2 carriers, suggesting possible effect modification by genotype.<sup>16</sup> The mean blood lead level in this sample of older men (mean age, 63 years) was 6.3  $\mu\text{g}/\text{dL}$ , and the assessment of psychiatric symptoms relied on self-reported symptoms rather than on psychiatric disorders defined by standard diagnostic criteria.

Depression and anxiety disorders are common forms of psychiatric disorder in the general adult population, causing substantial morbidity. Most research on environmental risk factors has focused on the social environment. Exposures to environmental contaminants with neurotoxic properties, however, could also be important risk factors. The objective of the present study is to assess the possible role of exposure to lead in adverse mental health outcomes in a more broadly distributed and younger population. We used data from the NHANES for 1999 to 2004 to investigate the relation between blood lead levels and the odds of major depressive disorder (MDD), panic disorder (PD), and generalized anxiety disorder (GAD) in a sample representative of the US population aged 20 to 39 years.

## METHODS

### STUDY DESIGN AND POPULATION

The NHANES is a population-based health survey of noninstitutionalized US residents conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The NHANES uses a complex, multistage probability sampling design, with oversampling of adolescents 12 to 19 years of age, adults 60 years and older, low-income persons, Mexican American individuals, and non-Hispanic black individuals. All the participants completed household surveys conducted by trained study staff that included questions about demographics and health history. The study protocol also included standardized medical examinations at mobile centers that included a private interview and collection of a blood sample. The study protocol is described in detail elsewhere.<sup>1</sup>

The World Health Organization Composite International Diagnostic Interview (CIDI)<sup>17</sup> was administered to a random subsample of the participants composed of 50% of those aged 20 to 39 years. The CIDI was administered in English or Spanish. All the interviews were conducted directly with the respondents during a private session; persons who required proxies were ineligible (ie, non-English and non-Spanish speakers). This study includes the 1987 individuals who had available data on CIDI diagnoses of MDD, PD, or GAD; blood lead levels; and all of the covariates.

## MEASURES

### Psychiatric Outcomes

The CIDI is a fully structured diagnostic interview used to assess psychiatric disorders following criteria defined in *DSM-IV*.<sup>18</sup> Three diagnostic modules were administered: MDD, PD, and GAD. The CIDI questions address *DSM-IV* criteria for each of the 3 disorders, and a diagnosis is established based on the answers. Only disorders present during the previous 12 months were identified in this survey.

Major depressive disorder is defined as 1 or more major depressive episodes characterized by at least 2 weeks of depressed mood or loss of interest, accompanied by at least 4 of the following additional symptoms of depression: significant appetite or weight change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate or indecisiveness, and recurrent thoughts of death or planning, or attempts. The symptoms must cause significant distress or impairment and are not the result of bereavement. Panic disorder is defined by intense periods of fear or discomfort, that is, panic attacks that are recurrent and occur unexpectedly. A panic attack is identified when at least 4 of the following symptoms are present: heart racing, sweating, shaking, shortness of breath, feeling choked, chest pain, nausea, dizziness, feeling unreal/situation is unreal, afraid to lose control, hot flashes, and numbness. A positive diagnosis is established if 4 or more panic attacks occurred and if at least 1 attack caused concern, worry, or behavior change during 1 month or more. Generalized anxiety disorder is defined by excessive anxiety and worry that is difficult to control, with at least 3 of the following symptoms of anxiety present: unusual fatigue, trouble sleeping, trouble concentrating, irritability, and feeling tense, sore, or muscles aching. The anxiety must cause clinically significant distress or impairment. For all 3 disorders, symptoms must not be caused by the direct physiologic effects of a substance or another medical condition.

Participants completed the CIDI during a private interview with trained interviewers. An automated version of the CIDI (version 2.1) was used to facilitate the interview process and data management.<sup>17</sup> The CIDI addresses the symptoms listed in the previous paragraph, the context in which they occurred and the exterior factors possibly explaining them, and the distress associated with them to establish the diagnoses based on *DSM-IV* criteria. The CIDI responses are evaluated using a computer algorithm that assesses each criterion, and criteria are combined into diagnoses. The diagnoses are designated as part of NHANES data processing, and the dichotomous diagnosis variables—that is, yes or no for a diagnosis in the previous 12 months—were in the NHANES downloaded data sets. These variables are the outcomes in the present study.

The CIDI has been widely used in research and population surveys.<sup>19-21</sup> It can be administered by lay interviewers with excellent reliability, it does not require outside informants or medical records, and it does not assume the presence of a current disorder.<sup>17</sup> In a validity study,<sup>22</sup> CIDI diagnoses were compared with diagnoses from the Structured Clinical Interview (SCID) for *DSM-IV*, and a high level of concordance was observed. Specifically, 84% of cases of anxiety disorder and 70% of cases of mood disorder identified in the clinical interview were also identified using the CIDI. The CIDI lifetime prevalence estimates were generally lower than the SCID estimates. The concordance between the SCID and the CIDI is likely to be constrained because the SCID itself has only moderate reliability. Also, the difference in the mode of administration, that is, telephone interview for the SCID and in-person interview for the CIDI, could contribute to discordant diagnoses.

## Blood Lead Levels

Whole blood specimens were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and to the Centers for Disease Control and Prevention for analysis. Vials were stored at  $-20^{\circ}\text{C}$  until they were shipped. For samples collected in 1999 to 2002, the blood lead concentration was determined by means of graphite furnace atomic absorption spectrophotometry, and the limit of detection was  $0.3\text{ }\mu\text{g/dL}$ .<sup>23,24</sup> For samples collected in 2003 and 2004, the whole blood lead concentration was determined by means of inductively coupled plasma mass spectrometry, and the limit of detection was  $0.2\text{ }\mu\text{g/L}$ . The NHANES quality assurance and quality control protocols meet the 1988 Clinical Laboratory Improvement Act mandates.<sup>25</sup>

## Other Variables

We included the following variables in the analyses because of their known associations with lead exposure, mental health status, or both: sex, age, race/ethnicity, education status, and poverty to income ratio (PIR). Non-Hispanic black persons have higher rates of depression than do non-Hispanic white persons.<sup>26</sup> Women have higher rates of depressive and anxiety disorders,<sup>21</sup> as do individuals with less education.<sup>27</sup> The prevalence of several disorders is higher in those with lower socioeconomic status,<sup>21</sup> which herein was assessed using the PIR, a parameter that compares self-reported family income with the US Census-based poverty threshold value for each calendar year adjusted for inflation and the age of the family reference person. The PIR was coded into 4 categories to reflect the current standards used in government-financed welfare programs (the lowest category,  $\leq 1.0$ , corresponds to the poorest group). Finally, smoking is strongly associated with depression and anxiety disorders.<sup>28</sup> Past and current use of tobacco products was assessed by means of questionnaire, and serum cotinine levels were measured to further identify active smokers (based on the  $10\text{-ng/mL}$  cutoff value commonly used).<sup>29</sup> Six hundred twenty-eight persons were considered current smokers: 526 based on questionnaire responses and an additional 102 based on serum cotinine levels. Lead exposure also differs with respect to sex (higher in men), race/ethnicity (higher in black persons), education status (higher with lower educational attainment), socioeconomic status (higher in lower socioeconomic strata), and smoking (higher in smokers).<sup>30,31</sup>

## STATISTICAL ANALYSES

We used the Complex Samples module of SPSS 17.0 (SPSS Inc, Chicago, Illinois) to obtain effect estimates and their confidence intervals (CIs), accounting for the multistage probability sampling design of the NHANES. The NHANES provides sample weights to generate population prevalence estimates, adjusting for the oversampling of certain population subgroups and accounting for nonresponse and noncoverage.<sup>32</sup> For estimates of outcome prevalences and odds ratios (ORs), we used the special examination sample weights for the subsample eligible to be administered the CIDI, computing 6-year weights (1999-2004) using the method recommended by the Centers for Disease Control and Prevention.<sup>32</sup>

To reduce the effect of extreme values on these analyses, we analyzed blood lead levels in quintiles (first [lowest]:  $\leq 0.7\text{ }\mu\text{g/dL}$ ; second:  $0.71\text{--}1.0\text{ }\mu\text{g/dL}$ ; third:  $1.01\text{--}1.4\text{ }\mu\text{g/dL}$ ; fourth:  $1.41\text{--}2.1\text{ }\mu\text{g/dL}$ ; and fifth [highest]:  $\geq 2.11\text{ }\mu\text{g/dL}$ ). Thirty-three participants (1.7%) had blood lead levels lower than the limits of detection. We fit multivariable-adjusted logistic regression models to estimate the prevalence ORs and 95% CIs

of MDD, PD, and GAD across increasing blood lead level quintiles relative to the lowest quintile (ie, the referent). To assess the linear trend in these associations, we fit models using a term created by assigning to each individual the median value of his or her blood lead quintile. All models were adjusted for sex, age (20-24, 25-29, 30-34, and 35-39 years), race/ethnicity (non-Hispanic white, Mexican American, non-Hispanic black, and other race or multiracial), education status (less than high school, high school diploma, and more than high school), and PIR ( $<1.0$ ,  $1.0\text{--}1.84$ ,  $1.85\text{--}3.0$ , and  $>3.0$ ). As an alternative modeling strategy, we also fit logistic regression models using  $\log_{10}$ -transformed blood lead values. The presence of a possible time trend was assessed by adding a dummy variable for the wave of data collection years (1=1999-2000, 2=2001-2002, and 3=2003-2004) in the models. Finally, we also used subpopulation analyses to obtain results stratified by sex. We used  $P < .05$  as the level of statistical significance.

## RESULTS

Descriptive statistics are given in **Table 1**. The study population included more women than men, but, once weighted, the observations accounted for an equal representation of men and women. The age distribution was fairly uniform and ranged from 20 to 39 years. The numbers of persons meeting the 12-month DSM-IV criteria were 134 (6.7%) for MDD, 44 for PD (2.2%), and 47 (2.4%) for GAD (**Table 2**). The corresponding population prevalence estimates, determined after applying the sample weights, were 7.8%, 2.6%, and 3.0%. There were no significant differences in blood lead levels, age, sex, race/ethnicity, education, PIR, or smoking between those to whom the CIDI was administered and those to whom it was not ( $P > .1$ ).

The geometric mean (SD) blood lead level was  $1.24$  ( $1.96$ )  $\mu\text{g/dL}$ . The arithmetic mean (SD) blood lead level was  $1.61$  ( $1.72$ )  $\mu\text{g/dL}$ , and values ranged from  $0.3$  to  $37.3\text{ }\mu\text{g/dL}$ ; 13 values (0.7%) exceeded  $10\text{ }\mu\text{g/dL}$ , and 4 values (0.2%) exceeded  $15\text{ }\mu\text{g/dL}$ . In multivariable-adjusted analyses, significantly higher blood lead levels were observed with the following characteristics: being a man, older age, being Mexican American, lower education status, and current smoking. Blood lead levels were also higher in the poorest group ( $\text{PIR} < 1.0$ ), although differences by PIR groups were not significant ( $P = .80$ ).

Logistic regression analyses adjusting for age, sex, race/ethnicity, education status, and PIR showed that higher blood lead quintile was significantly associated with higher odds of meeting DSM-IV criteria for MDD ( $P = .05$  for trend) and PD ( $P = .02$  for trend) but not for GAD ( $P = .78$ ) (**Table 3** [model A]). Persons with blood lead levels in the highest quintile had 2.3 times the odds of MDD (95% CI,  $1.13\text{--}4.75$ ) and nearly 5 times the odds of PD ( $1.32\text{--}18.48$ ) as those in the lowest quintile. Sex and race/ethnicity were significantly associated with the risk of disorders (both at  $P < .01$ ), but age, education status, and PIR ( $P > .3$  for each) were not. Mexican American persons had the lowest rates of MDD and PD but the highest blood lead levels. Men had lower rates of disorders but higher blood lead levels than did women.

We saw little difference by sex in the associations of blood lead levels with MDD, and an interaction term added to the logistic regression model was not significant

**Table 1. Characteristics and Blood Lead Levels of the Sample**

|                                  | Persons, No. (N=1987) | Unweighted, % | Weighted, % | Blood Lead, Geometric Mean (SD), µg/dL <sup>a</sup> |
|----------------------------------|-----------------------|---------------|-------------|-----------------------------------------------------|
| Sex                              |                       |               |             |                                                     |
| Female                           | 1100                  | 55.4          | 50.0        | 0.96 (1.79)                                         |
| Male                             | 877                   | 44.1          | 50.0        | 1.71 (1.90)                                         |
| Age, y                           |                       |               |             |                                                     |
| 20-24                            | 521                   | 26.2          | 24.5        | 1.14 (1.89)                                         |
| 25-29                            | 490                   | 24.7          | 22.2        | 1.15 (2.03)                                         |
| 30-34                            | 505                   | 25.4          | 26.8        | 1.27 (2.02)                                         |
| 35-39                            | 471                   | 23.7          | 26.5        | 1.24 (1.87)                                         |
| Race/ethnicity                   |                       |               |             |                                                     |
| Non-Hispanic white               | 924                   | 46.5          | 66.0        | 1.07 (1.87)                                         |
| Mexican American                 | 498                   | 25.1          | 10.9        | 1.57 (2.13)                                         |
| Non-Hispanic black               | 382                   | 19.2          | 12.1        | 1.28 (1.83)                                         |
| Other ethnic groups, multiracial | 183                   | 9.2           | 11.0        | 1.23 (1.84)                                         |
| Educational status               |                       |               |             |                                                     |
| <High school                     | 492                   | 24.8          | 17.7        | 1.65 (1.98)                                         |
| High school diploma              | 494                   | 24.9          | 25.6        | 1.28 (1.97)                                         |
| >High school                     | 1001                  | 50.4          | 56.7        | 1.06 (1.85)                                         |
| Poverty to income ratio          |                       |               |             |                                                     |
| <1.0                             | 424                   | 21.3          | 16.8        | 1.38 (1.97)                                         |
| 1.0-1.84                         | 462                   | 23.3          | 20.5        | 1.33 (2.07)                                         |
| 1.85-3.0                         | 352                   | 17.7          | 18.8        | 1.24 (1.90)                                         |
| >3.0                             | 749                   | 37.7          | 43.8        | 1.11 (1.88)                                         |
| Smoking                          |                       |               |             |                                                     |
| Never                            | 1113                  | 56.0          | 52.9        | 1.09 (1.91)                                         |
| Former                           | 246                   | 12.4          | 11.8        | 1.47 (1.97)                                         |
| Current                          | 628                   | 31.6          | 35.3        | 1.61 (1.90)                                         |
| <b>Total</b>                     | <b>1987</b>           | <b>100</b>    | <b>100</b>  | <b>1.24 (1.96)</b>                                  |

SI conversion factor: To convert lead to micromoles per liter, multiply by 0.0483.

<sup>a</sup>Unweighted.

**Table 2. Individuals With Major Depressive Disorder, Panic Disorder, and Generalized Anxiety Disorder by Blood Lead Level Quintile**

| Quintile <sup>a</sup> | Blood Lead Level Quintile, µg/dL |        | Individuals, No. (%) |                           |                 |                              |
|-----------------------|----------------------------------|--------|----------------------|---------------------------|-----------------|------------------------------|
|                       | Range                            | Median | Total                | Major Depressive Disorder | Panic Disorder  | Generalized Anxiety Disorder |
| 1 [Lowest]            | <0.7                             | 0.6    | 449                  | 30 (6.7)                  | 5 (1.1)         | 6 (1.3)                      |
| 2                     | 0.71-1.0                         | 0.9    | 386                  | 26 (6.7)                  | 9 (2.3)         | 6 (1.6)                      |
| 3                     | 1.01-1.4                         | 1.2    | 408                  | 26 (6.4)                  | 8 (2.0)         | 13 (3.2)                     |
| 4                     | 1.41-2.1                         | 1.7    | 375                  | 22 (5.9)                  | 9 (2.4)         | 13 (3.5)                     |
| 5 [Highest]           | ≥2.11                            | 3.0    | 369                  | 30 (8.1)                  | 13 (3.5)        | 9 (2.4)                      |
| <b>Total</b>          | NA                               | NA     | <b>1987</b>          | <b>134 (6.7)</b>          | <b>44 (2.2)</b> | <b>47 (2.4)</b>              |

Abbreviation: NA, not applicable.

SI conversion factor: To convert lead to micromoles per liter, multiply by 0.0483.

<sup>a</sup>Blood lead level quintiles were defined as follows: 1 [lowest]: <0.7 µg/dL; 2: 0.71-1.0 µg/dL; 3: 1.01-1.4 µg/dL; 4: 1.41-2.1 µg/dL; and 5 [highest]: ≥2.11 µg/dL.

( $P=.76$ ). There were too few cases of PD among men to analyze them separately, but the association among women only was similar to the combined results.

To evaluate possible cohort effects, we added a term for years of data collection to the models, but this term was not significant ( $P=.99$  for MDD,  $P=.53$  for PD, and  $P=.54$  for GAD) and did not appreciably change the associations with blood lead. We also evaluated the odds of each of the 3 disorders with respect to blood lead levels on a continuous scale ( $\log_{10}$  transformed), and this resulted in findings similar to the previous trend analyses, with higher blood lead levels being associated with increased odds of MDD (for each doubling of blood lead: OR, 1.19; 95% CI, 0.93-1.53;  $P=.16$ ) and PD (1.44; 1.02-2.03;  $P=.04$ ) but not GAD (1.11; 0.76-1.63;  $P=.56$ ).

Because current smoking is related to blood lead level and psychiatric disorder status, we conducted sensitivity analyses excluding the 628 current smokers (Table 3 [model B]). For MDD, this resulted in ORs slightly higher than those obtained when including these individuals and a significant trend for increasing odds across increasing blood lead quintiles ( $P=.03$ ). Increasing quintiles of blood lead levels were also significantly associated with higher odds of PD ( $P=.01$  for trend). The OR for the highest blood lead quintile was substantially higher than that in model A; however, its wide 95% CI was owing to the few cases in this analysis ( $n=14$ ).

Exclusion of individuals with blood lead levels of 10 µg/dL or higher ( $n=13$ ) did not affect the results, with changes only to the second decimal of the estimates. The



**Table 3. Logistic Regression Analyses for Major Depressive Disorder, Panic Disorder, and Generalized Anxiety Disorder by Blood Lead Level Quintile**

|                                   | Model A <sup>a</sup>     |                   | Model B <sup>b</sup>     |                   |
|-----------------------------------|--------------------------|-------------------|--------------------------|-------------------|
|                                   | Persons, No.<br>(n=1987) | OR (95% CI)       | Persons, No.<br>(n=1359) | OR (95% CI)       |
| Major depressive disorder         |                          |                   |                          |                   |
| Lowest quintile (1) <sup>c</sup>  | 30                       | 1 [Reference]     | 23                       | 1 [Reference]     |
| Quintile 2 <sup>c</sup>           | 26                       | 1.39 (0.71-2.72)  | 16                       | 1.26 (0.55-2.88)  |
| Quintile 3 <sup>c</sup>           | 26                       | 1.28 (0.69-2.38)  | 12                       | 1.50 (0.75-3.01)  |
| Quintile 4 <sup>c</sup>           | 22                       | 1.41 (0.76-2.60)  | 11                       | 1.47 (0.68-3.17)  |
| Highest quintile (5) <sup>c</sup> | 30                       | 2.32 (1.13-4.75)  | 11                       | 2.93 (1.24-6.92)  |
| <b>Subtotal</b>                   | <b>134</b>               |                   | <b>73</b>                |                   |
| <i>P</i> value for trend          |                          | .05               |                          | .03               |
| Panic disorder                    |                          |                   |                          |                   |
| Lowest quintile (1)               | 5                        | 1 [Reference]     | 2                        | 1 [Reference]     |
| Quintile 2                        | 9                        | 2.88 (0.72-11.49) | 2                        | 1.02 (0.14-7.41)  |
| Quintile 3                        | 8                        | 1.80 (0.44-7.44)  | 3                        | 2.22 (0.24-20.56) |
| Quintile 4                        | 9                        | 3.13 (0.78-12.57) | 1                        | 0.79 (0.07-9.09)  |
| Highest quintile (5)              | 13                       | 4.94 (1.32-18.48) | 6                        | 9.57 (1.28-71.43) |
| <b>Subtotal</b>                   | <b>44</b>                |                   | <b>14</b>                |                   |
| <i>P</i> value for trend          |                          | .02               |                          | .01               |
| Generalized anxiety disorder      |                          |                   |                          |                   |
| Lowest quintile (1)               | 6                        | 1 [Reference]     | 5                        | 1 [Reference]     |
| Quintile 2                        | 6                        | 1.26 (0.47-3.36)  | 4                        | 1.17 (0.28-4.88)  |
| Quintile 3                        | 13                       | 2.25 (0.75-6.70)  | 4                        | 1.29 (0.33-5.09)  |
| Quintile 4                        | 13                       | 2.16 (0.76-6.09)  | 10                       | 3.18 (0.96-10.49) |
| Highest quintile (5)              | 9                        | 1.53 (0.39-5.96)  | 3                        | 1.59 (0.19-13.31) |
| <b>Subtotal</b>                   | <b>47</b>                |                   | <b>26</b>                |                   |
| <i>P</i> value for trend          |                          | .78               |                          | .44               |

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Adjusted for age, sex, race/ethnicity, education, and poverty to income ratio.

<sup>b</sup>Same as model A but excludes current smokers.

<sup>c</sup>Blood lead level quintiles were defined as follows: 1 [lowest]: <0.7 µg/dL; 2: 0.71-1.0 µg/dL; 3: 1.01-1.4 µg/dL; 4: 1.41-2.1 µg/dL; and 5 [highest]: ≥2.11 µg/dL (To convert lead to micromoles per liter, multiply by 0.0483.).

results were only minimally affected by the exclusion of pregnant women and women whose pregnancy status could not be ascertained (n=299), with estimates within 10% of those for model A and similar *P* values for trend (MDD: *P* = .05; PD: *P* = .02; and GAD: *P* = .50).

Many individuals met the criteria for more than 1 disorder, thus, we wanted to explore the specificity of the blood lead association for a single diagnosis. Of individuals with MDD, 6% also met the criteria for PD, 10% for GAD, and 7% for both. In an analysis of the 104 cases of MDD with no comorbid disorders, the findings were similar to those for all cases. The numbers of persons with PD (n=24) and GAD (n=22) with no comorbidity were too small to restrict the analytic sample to these individuals only.

## COMMENT

In the present study, we observed that increasing blood lead levels were associated with a significantly higher risk of MDD and PD in young adults in the United States. Compared with persons with a blood lead level of less than 0.7 µg/dL (the lowest quintile of blood lead in the study population), those with a level greater than 2.1 µg/dL (the highest quintile) had a 2.3-fold increased risk of meeting DSM-IV criteria for MDD and a 4.9-fold increased risk of PD. After excluding current smokers, the elevation in risk was increased to 2.5-fold for MDD and to 8.2-fold

for PD. Although estimates of risk for specific quintiles were imprecise because of the few cases, particularly for PD, the trend analyses support the presence of a significant increase in risk across blood lead levels. Likewise, models that use a continuous parameter for blood lead levels also support this conclusion.

These results support previously reported associations of mood and anxiety disorders with high occupational lead exposure<sup>8-12</sup> and less well-documented association with lower environmental levels of exposure in older men.<sup>15,16</sup> The present findings extend these observations to the general US population of younger adults. Women are at significantly increased risk of meeting the diagnostic criteria for MDD and anxiety disorders, an observation that is well documented.<sup>19</sup> In exploratory analyses, we saw no evidence of differential association by sex for blood lead levels and odds for these disorders, but a larger sample is necessary to carefully verify this hypothesis.

If lead exposure contributes to the etiology of these disorders, the mechanism of action could involve perturbation of neurochemical processes, such as brain monoamine neurotransmission. Lead exposure is known to disrupt catecholaminergic systems,<sup>33-35</sup> and depression and anxiety disorders are strongly associated with disturbances in these systems.<sup>36</sup> Studies in animals<sup>35</sup> show that long-term lead exposure can decrease serotonergic activity in several brain regions, including the nucleus ac-

cumbens, frontal cortex, and brainstem. In a study<sup>37</sup> of patients with PD with or without depression, positron emission tomography revealed that serotonin receptor type 1A levels were reduced by almost one third in the anterior and posterior cingulates and the raphe nuclei.<sup>37</sup> Exposure to lead in predisposed individuals could trigger the development of depression and PD, increase their severity, or modify the response to treatments. Investigations on how low lead exposure disrupts neurochemical processes could provide insights into the mechanisms of depressive and anxious states.

Comorbidity was observed in the present study, particularly for the 2 anxiety disorders with depression. When we conducted an analysis of MDD in which we excluded persons with MDD and another disorder, the findings were similar to those in which we included all persons, suggesting that the increased odds of MDD with higher blood lead levels was not explained by the anxiety disorders.

One of the strengths of the present study is the use of structured diagnostic assessments of psychiatric disorders.<sup>17</sup> The CIDI has been widely used in psychiatric research and has a high degree of correspondence with clinical interviews.<sup>22</sup> Also, the prevalences observed in the present study for the 3 conditions studied were comparable with those of other national estimates<sup>19</sup> (MDD: 7.8% vs 6.7%, PD: 2.6% vs 2.7%, and GAD: 3.0% vs 3.1%). This suggests that the results of the present study can be generalized to the broader US population.

The present study has several limitations, the most important being its cross-sectional design. Thus, we cannot rule out the possibility that MDD or PD leads to behavioral changes that increase exposure to lead, except in the case of smoking, for which the sensitivity analysis in current nonsmokers argues strongly against. In addition, the mental health outcomes under study herein are chronic conditions often associated with genetic predisposition in conjunction with long-term stressors.<sup>38</sup> Therefore, in assessing the role of lead as a risk factor for mental health outcomes, it would have been desirable to have an indicator of long-term lead exposure, such as bone lead level, assessed before the onset of psychiatric symptoms. Bone lead level has a clearance half-life of years to decades, depending on the bone type.<sup>39</sup> In a previous study,<sup>15</sup> blood and patella bone lead levels were associated with a combined measure of anxiety, phobia, and depression symptoms. In the present study, lead was measured in blood only. The half-life of lead in blood after acute exposure is short, but blood lead concentration integrates lead released from bones and current external exposures. In settings in which external exposures are low, lead released from bones can be the major contributor to blood lead levels. Thus, blood lead level may be a reasonable marker of long-term exposure when the system is in equilibrium, with little variation in intake, clearance, or bone-blood partitioning. Situations in which this would not apply are occupational exposures, which might vary greatly in time, and osteoporosis, during which lead is released from the bone matrix to the blood at an increased rate after demineralization.<sup>40</sup> In the present study, however, few individuals were likely to have osteoporosis because of their young age (maximum age, 40 years). We could not exclude occupationally exposed individu-

als because of limited information on job exposures, but the exclusion of those with elevated blood lead levels would likely capture any current work-related lead exposure and did not alter the results.

As in any observational study, the associations in this study could be biased by uncontrolled confounders. We did, however, adjust for several important likely confounding factors (sex, age, race/ethnicity, education status, and annual income). Furthermore, the sensitivity analyses that excluded current smokers indicate that residual confounding by smoking does not explain the associations of blood lead levels and risk of psychiatric disease but, in fact, may partly mask it.

Current blood lead levels in the US population are lower than they were in the mid-20th century,<sup>2</sup> but they remain elevated from an evolutionary perspective, that is, in relation to the natural lead levels before industrialization.<sup>41</sup> Widespread lead pollution has occurred only in relatively modern history as a result of anthropogenic activity.<sup>42</sup> The finding of an association between blood lead level and MDD and PD, despite the low levels and narrow range of observed lead levels, supports the contention that current lead exposures at low levels may have important effects on mental health. Because the current measurements of blood lead level reflect, in part, lead sequestered in bone, the observed relations with increased odds of depression and PD could also reflect latent effects of past exposures during critical developmental periods, which would be consistent with neurodevelopmental hypotheses of mood and anxiety disorders.<sup>43</sup> If lead exposure contributes to the etiology of MDD and PD, continued efforts at reducing population exposures even beyond currently acceptable levels may decrease their incidence.

In conclusion, risks of MDD and PD in young adults increased with higher blood lead levels. These findings suggest that lead neurotoxicity may contribute to adverse mental health outcomes, even at levels generally considered to pose low or no risk. These findings, combined with recent reports<sup>44,45</sup> of adverse behavioral outcomes in children with similarly low blood lead levels, should underscore the need for considering ways to further reduce environmental lead exposures.

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## REFERENCES

- Centers for Disease Control and Prevention; National Center for Health Statistics. National Health and Nutrition Examination Survey data. <http://www.cdc.gov/nchs/nhanes.htm>. Accessed October 1, 2008.
- Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, Matte TD; The National Health and Nutrition Examination Surveys (NHANES). The decline in blood lead levels in the United States. *JAMA*. 1994;272(4):284-291.
- Schwartz BS, Stewart WF, Bolla KI, Simon PD, Bandeen-Roche K, Gordon PB, Links JM, Todd AC. Past adult lead exposure is associated with longitudinal decline in cognitive function [published correction appears in *Neurology*. 2001;56(2):283]. *Neurology*. 2000;55(8):1144-1150.
- Glenn BS, Bandeen-Roche K, Lee BK, Weaver VM, Todd AC, Schwartz BS. Changes in systolic blood pressure associated with lead in blood and bone. *Epidemiology*. 2006;17(5):538-544.
- Lee BK, Lee GS, Stewart WF, Ahn KD, Simon D, Kelsey KT, Todd AC, Schwartz BS. Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and  $\delta$ -aminolevulinic acid dehydratase genes. *Environ Health Perspect*. 2001;109(4):383-389.
- Weaver VM, Jaar BG, Schwartz BS, Todd AC, Ahn KD, Lee SS, Wen J, Parsons PJ, Lee BK. Associations among lead dose biomarkers, uric acid, and renal function in Korean lead workers. *Environ Health Perspect*. 2005;113(1):36-42.
- Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect*. 2005;113(7):894-899.
- Lilis R, Fischbein A, Eisinger J, Blumberg WE, Diamond S, Anderson HA, Rom W, Rice C, Sarkozi L, Kon S, Selikoff IJ. Prevalence of lead disease among secondary lead smelter workers and biological indicators of lead exposure. *Environ Res*. 1977;14(2):255-285.
- Baker EL, Feldman RG, White RA, Harley JP, Niles CA, Dinse GE, Berkey CS. Occupational lead neurotoxicity: a behavioural and electrophysiological evaluation: study design and year one results. *Br J Ind Med*. 1984;41(3):352-361.
- Baker EL, White RF, Pothier LJ, Berkey CS, Dinse GE, Travers PH, Harley JP, Feldman RG. Occupational lead neurotoxicity: improvement in behavioural effects after reduction of exposure. *Br J Ind Med*. 1985;42(8):507-516.
- Parkinson DK, Ryan C, Bromet EJ, Connell MM. A psychiatric epidemiologic study of occupational lead exposure. *Am J Epidemiol*. 1986;123(2):261-269.
- Maizlish NA, Parra G, Feo O. Neurobehavioural evaluation of Venezuelan workers exposed to inorganic lead. *Occup Environ Med*. 1995;52(6):408-414.
- Schwartz BS, Lee BK, Bandeen-Roche K, Stewart W, Bolla K, Links J, Weaver V, Todd A. Occupational lead exposure and longitudinal decline in neurobehavioral test scores. *Epidemiology*. 2005;16(1):106-113.
- Agency for Toxic Substances and Disease Registry. Toxicological profile for lead. August 2007. <http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf>. Accessed January 11, 2009.
- Rhodes D, Spiro A III, Aro A, Hu H. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. *J Occup Environ Med*. 2003;45(11):1144-1151.
- Rajan P, Kelsey KT, Schwartz JD, Bellinger DC, Weuve J, Sparrow D, Spiro A III, Smith TJ, Nie H, Hu H, Wright RO. Lead burden and psychiatric symptoms and the modifying influence of the  $\delta$ -aminolevulinic acid dehydratase (ALAD) polymorphism: the VA Normative Aging Study. *Am J Epidemiol*. 2007;166(12):1400-1408.
- Kessler RC, Üstün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res*. 2004;13(2):93-121.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):709]. *Arch Gen Psychiatry*. 2005;62(6):617-627.
- Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1997;54(4):313-321.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8-19.
- Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *Int J Methods Psychiatr Res*. 2006;15(4):167-180.
- Miller DT, Paschal DC, Gunter EW, Stroud PE, D'Angelo J. Determination of lead in blood using electrothermal atomisation atomic absorption spectrometry with a L'vov platform and matrix modifier. *Analyst*. 1987;112(12):1701-1704.
- Parsons PJ, Slavin W. A rapid Zeeman graphite furnace atomic absorption spectrometric method for the determination of lead in blood. *Spectrochimica Acta*. 1993;48B(6/7):925-939.
- Centers for Disease Control and Prevention. NHANES laboratory/medical technologists procedures manual. April 2001. <http://www.cdc.gov/nchs/data/nhanes/lab1-6.pdf>. Accessed February 6, 2009.
- Pratt LA, Brody DJ. *Depression in the United States Household Population, 2005-2006: NCHS Data Brief*. Baltimore, MD: US Dept of Health and Human Services; 2008.
- Bjelland I, Krokstad S, Mykletun A, Dahl AA, Tell GS, Tambs K. Does a higher educational level protect against anxiety and depression? the HUNT study. *Soc Sci Med*. 2008;66(6):1334-1345.
- Wiesbeck GA, Kuhl HC, Yaldizli O, Wurst FM; WHO/ISBRA Study Group on Biological State and Trait Markers of Alcohol Use and Dependence. Tobacco smoking and depression: results from the WHO/ISBRA study. *Neuropsychobiology*. 2008;57(1-2):26-31.
- Aigne CA, Moss ME, Auinger P, Weitzman M. Association of pediatric dental caries with passive smoking. *JAMA*. 2003;289(10):1258-1264.
- Hu H, Payton M, Korrick S, Aro A, Sparrow D, Weiss ST, Rotnitzky A. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men: the normative aging study. *Am J Epidemiol*. 1996;144(8):749-759.
- Theppang K, Glass TA, Bandeen-Roche K, Todd AC, Rohde CA, Schwartz BS. Gender and race/ethnicity differences in lead dose biomarkers. *Am J Public Health*. 2008;98(7):1248-1255.
- National Center for Health Statistics. National Health and Nutrition Examination Survey analytic guidelines. [http://www.cdc.gov/nchs/data/nhanes\\_03\\_04/nhanes\\_analytic\\_guidelines\\_dec\\_2005.pdf](http://www.cdc.gov/nchs/data/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf). Accessed July 1, 2008.
- Lasley SM, Greenland RD, Minnema DJ, Michaelson IA. Influence of chronic inorganic lead exposure on regional dopamine and 5-hydroxytryptamine turnover in rat brain. *Neurochem Res*. 1984;9(12):1675-1688.
- Minnema DJ, Greenland RD, Michaelson IA. Effect of in vitro inorganic lead on dopamine release from superfused rat striatal synaptosomes. *Toxicol Appl Pharmacol*. 1986;84(2):400-411.
- Kala SV, Jadhav AL. Region-specific alterations in dopamine and serotonin metabolism in brains of rats exposed to low levels of lead. *Neurotoxicology*. 1995;16(2):297-308.
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007;64(3):327-337.
- Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, Eckelman W, Herscovitch P, Charney DS, Drevets WC. Reduced serotonin type 1A receptor binding in panic disorder. *J Neurosci*. 2004;24(3):589-591.
- Kendler KS, Prescott CA. *Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders*. New York, NY: Guilford Press; 2006.
- Rabinowitz MB. Toxicokinetics of bone lead. *Environ Health Perspect*. 1991;91:33-37.
- Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. *Environ Res*. 1988;47(1):79-94.
- Flegal AR, Smith DR. Lead levels in preindustrial humans. *N Engl J Med*. 1992;326(19):1293-1294.
- Bellinger DC, Bellinger AM. Childhood lead poisoning: the tortuous path from science to policy. *J Clin Invest*. 2006;116(4):853-857.
- van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. *Arch Gen Psychiatry*. 1997;54(7):625-631.
- Braun JM, Froehlich TE, Daniels JL, Dietrich KN, Hornung R, Auinger P, Lanphear BP. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. *Environ Health Perspect*. 2008;116(7):956-962.
- Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect*. 2006;114(12):1904-1909.