Association Between Essential Tremor and Blood Lead Concentration

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Association Between Essential Tremor and Blood Lead Concentration

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Abbreviations: ET (essential tremor), BPb (blood lead), OR (odds ratio), CI (confidence interval), CPMC (Columbia-Presbyterian Medical Center).
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Abstract

Lead is a ubiquitous toxicant that causes tremor and cerebellar damage. Essential tremor (ET) is a highly prevalent neurological disease associated with cerebellar involvement. While environmental toxicants may play a role in ET etiology and their identification is a critical step in disease prevention, these toxicants have received little attention. Our objective was to test the hypothesis that ET is associated with lead exposure. Therefore, blood lead (BPb) concentrations were measured and a lifetime occupational history was assessed in ET patients and in controls. One hundred ET patients and 143 controls were frequency matched on age, gender, and ethnicity. BPb concentrations were analyzed using graphite furnace atomic absorption spectrophotometry. A lifetime occupational history was reviewed by an industrial hygienist. BPb concentration was higher in ET patients than in controls (means = 3.3 ± 2.4 and 2.6 ± 1.6 µg/dl; medians = 2.7 vs. 2.3 µg/dl, p = 0.038). In a logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient, OR per unit increase = 1.21, 95% CI = 1.05 - 1.39, p = 0.007). BPb concentration was associated with diagnosis (OR per unit increase = 1.19, 95% CI = 1.03 - 1.37, p = 0.02) after adjusting for potential confounders. Prevalence of lifetime occupational lead exposure was similar in ET patients and controls. We report an association between BPb concentration and ET. Whether this association is due to increased exposure to lead or a difference in lead kinetics in ET patients requires further investigation.
Introduction

Essential tremor (ET) is a neurological disease that is characterized by an action tremor of the hands and/or head. Patients also may have signs of more widespread cerebellar involvement (e.g., intention tremor, ataxia), (Stolze et al. 2000, Deuschl et al. 2000, Singer et al. 1994) abnormalities referable to the basal ganglia (e.g., rest tremor, subclinical signs of bradykinesia), (Rajput et al. 1993, Cohen et al. 2003) and cognitive deficits (Gasparini et al. 2001, Lombardi et al. 2001). ET is considered to be distinct from age-related enhanced physiological tremor, which has different clinical and electrophysiological features (Louis et al. 1997; Louis and Pullman 2001). The disease is highly prevalent in the general population (1% - 6%) (Louis et al. 1998b; Rautakorpi et al. 1982) and occurs in all populations studied to date (Louis et al. 1998b; Hornabrook and Nagurney 1976). The prevalence increases with age. Estimates of the prevalence in individuals who are in their sixties and seventies have been as high as 20.5% (Khattar et al. 1996). As such, ET is one of the most common neurological diseases. The pathogenesis of this progressive (Louis et al. 2003) and often disabling (Louis et al. 2001a) disease is poorly understood, although there is evidence of cerebellar involvement (Wills et al. 1994; Louis et al. 2002a; Bucher et al. 1997). There is no cure for ET, and there has been no attempt to favorably modulate or halt its progression with neuroprotective therapy. Medical treatment merely aims to lessen the severity of the tremor, which is the major symptom, and the first-line medications are ineffective in up to 50% of patients (Louis and Greene 2000; Sasso et al. 1990; Gironell et al. 1999).

While genetic susceptibility is an important determinant of disease etiology (Tanner et al. 2001; Louis et al. 2001b), it has been hypothesized that non-genetic factors (i.e.,
environmental factors such as toxicants) could contribute to disease etiology in many cases (Tanner et al. 2001; Louis 2001; Louis et al. 2002b). The identification of these factors is a critical step in disease prevention, yet they have received little attention (Louis 2001).

Lead is a ubiquitous toxicant (Schroeder and Tipton 1968; Konat and Clausen 1974), and laboratory animals and humans who are exposed to high levels of either inorganic or organic forms of lead develop neurological disorders in which action tremor is prominent (Konat and Clausen 1974; Coulehan et al. 1983; Goldings and Stewart 1982; Seshia et al. 1978; Valpey et al. 1978; Young et al. 1977; Booze et al. 1983). Destruction of cerebellar Purkinje cells is a major feature of the pathology of lead toxicity (Valpey et al. 1978). The effect of chronic, low level exposure to lead has been linked with developmental problems, deficits in intellectual performance and decreased stature in children (Brody et al. 1994), and poorer performance on cognitive tests (Payton et al. 1998; Muldoon et al. 1993) in adults.

To test the hypothesis that ET is associated with lead exposure (Louis 2001), (1) blood lead (BPb) concentrations were measured and (2) lifetime occupational history was assessed in ET patients and in control subjects who were enrolled in a study of the environmental epidemiology of ET.

### Methods

**Participants**

ET patients were cared for by neurologists at the Neurological Institute of New York, Columbia-Presbyterian Medical Center (CPMC)(Louis et al. 2002b). They were
Louis et al. identified from a computerized database listing patients billed within the last three years supplemented by a computerized database at the Center for Parkinson’s Disease and Other Movement Disorders, CPMC, which listed patients seen within the last ten years. All patients had received a diagnosis of ET from their treating neurologist at the Institute. ET patients were selected for enrollment in a study of the environmental epidemiology of ET. Office records were reviewed and patients with physical signs or diagnoses of dystonia, Parkinsonism (rigidity, bradykinesia) or spinocerebellar ataxia were excluded. The CMPC Internal Review Board approved of all study procedures and written informed consent was obtained at the time of enrollment.

Controls were identified from the New York Metropolitan area using random digit dialing. These controls were frequency matched to CPMC patients based on five-year age strata, gender and ethnicity.

Patients and controls were contacted; 77.2% of patients and 57.0% of controls agreed to participate. Enrollees were similar to refusers in terms of age (68.0 ± 10.0 vs. 66.8 ± 16.7 years), gender (54.7% vs. 54.2% female), race (90.1% vs. 86.1% white) and education (14.7 ± 4.0 vs. 14.6 ± 3.6 years)(all p > 0.05).

Prior to enrollment, ET patients and controls were screened for cognitive impairment using the 10-minute Telephone Interview for Cognitive Status (Brandt et al. 1988). This was done to minimize the enrollment of individuals with invalid occupational, dietary and smoking histories. Three individuals (one patient and two controls) with cognitive impairment (score < 30 of 41) were excluded. Patients and controls were also screened by telephone using a brief neurological disease questionnaire. This included one question about each of the following conditions: Parkinson’s disease, Alzheimer’s
disease, dystonia, epilepsy, and multiple sclerosis. They were not enrolled if one of these conditions was reported to be present.

As described below, each patient and control had a videotaped tremor examination. Each videotape was reviewed by Dr. Louis who assigned a diagnosis of ET or normal. The diagnosis of ET was based on published diagnostic criteria (moderate or greater amplitude tremor [tremor rating greater or equal to 2] during three or more activities or a head tremor)(Louis et al. 2001b). These criteria are unique in three regards. First, their reliability has been demonstrated (Louis et al. 1998a). Second, they have been validated against quantitative computerized tremor analysis-derived diagnoses (Louis and Pullman 2001). Most important, these criteria were specifically designed to minimize the inclusion of individuals with enhanced physiological tremor, which is highly prevalent (Louis et al. 1997). They do so by specifying the number and types of activities during which kinetic tremor must be present in order to qualify for a diagnosis of ET. In this regard, the criteria are particularly useful for population-based, familial aggregation, and epidemiological studies.

Demographic and Medical History

Once enrolled, all participants were evaluated in person by a trained tester. The tester was trained for one month by a neurologist (E.D.L.) to administer clinical questionnaires and to perform a videotaped examination. Data were collected on age, gender, self-reported ethnicity, socioeconomic variables (e.g., years of education, number of rooms in home), and smoking history (including current and past use of cigarettes and pack-years). ET patients were asked whether they had a first-degree
relative with ET or with tremor. Patients who responded affirmatively to this question were considered to have a family history of tremor.

**Lifetime Occupational History**

The tester also administered an in-person lifetime occupational history designed for the study by an industrial hygienist (L.A.) The tester was trained by the hygienist to administer this history. To minimize reporting bias, study participants were informed that this was a study of living and working habits of people in the New York Metropolitan area rather than a study of lead as a risk factor for ET. Information was collected on all jobs held for six or more months, including the name, location, and type of employer(s), job titles and description of work duties and tasks performed, and the time period and duration of employment. For each job for which a reasonable probability existed for exposure to lead, there were detailed follow-up questions about the work environment, including the amount of time spent at that job, type of ventilation, housekeeping and sanitation practices, personal and protective equipment used and material handling procedures.

The industrial hygienist, blinded to patient-control status, reviewed these data to assess the possibility of lifetime occupational exposure to lead. Final lifetime occupational exposure status was coded as none, possible, or probable. Possible lifetime occupational exposure was defined as one of the following: (1) there was one or more employment with a possible association with lead, or (2) the participant identified lead exposure, or (3) the participant described work site factors that the industrial hygienist judged to be indicative of possible, but not conclusive exposure, or (4) the
participant described work site factors that the industrial hygienist judged to be indicative of probable occupational exposure only at minimal levels. Probable lifetime occupational exposure was the classification used when one or more of the participant’s employments were clearly associated with lead or if the participant described work site factors that the industrial hygienist judged to be indicative of probable and significant exposure. In addition to lifetime exposure, the industrial hygienist assessed whether the exposure to lead was current.

**Dietary Assessment**

Data on current diet were collected using a semi-quantitative food-frequency questionnaire (Willett et al. 1985), which included questions on frequency of consumption of 61 foods and on the use of vitamins and mineral supplements. Food frequency data may be used to compute mean daily intake of vitamins and minerals including vitamin C, calcium, and iron in mg, each of which has been associated with blood or bone lead concentrations (Cheng et al. 1998; Hernandez-Avila et al. 1996; Dawson et al. 1999; Willett 1990). The questionnaire has shown good reliability and validity related to recent nutrient intake (Willett et al. 1985; Wilet 1990). As in a previous study of lead exposure (Hu et al. 1996), ethanol intake was stratified into two groups: “heavy use” was defined as > 2 drinks either of wine, beer, or spirits per day; “light use” was defined as < 2 drinks per day.

**Videotaped Examination**

For all participants, the tester videotaped a tremor examination that included one test
to elicit postural tremor (sustained arm extension) and five tests to elicit kinetic tremor (pouring, drinking, using a spoon, touching finger to nose, and drawing spirals) (Louis et al. 2001b). Each of the six tests was performed with the dominant arm and then the nondominant arm (12 tests total) (Louis et al. 2001b). Each videotape was reviewed by Dr. Louis who rated the tremor during each of the 12 tests on a scale of 0 to 3, which resulted in a total tremor score (0 – 36 [maximum]). The diagnosis of ET also was confirmed by Dr. Louis using published diagnostic criteria (moderate or greater amplitude tremor [tremor rating > 2] during three or more activities or a head tremor) (Louis et al. 2001b).

**BPb Assessment**

Venous blood samples were collected in lead-free tubes and analyzed using graphite furnace atomic absorption spectrophotometry (Perkin-Elmer Analyst 600; Perkin Elmer, Chelmsford, MA) (Fernandez and Hilligoss 1982) in the NIEHS Trace Metal Laboratory at Columbia University. These analyses were performed blinded to clinical information. The detection limit for BPb measurements using these instruments was 0.1 ug/dl. Day-to-day variability was 3.7%. The laboratory participates in the BPb quality control program of the Centers for Disease Control. The intraclass correlation coefficient, which quantifies the association between the measured and the quality control values for BPb, was 0.99 during the course of this study.

**Bone Lead Assessment**

To assess whether BPb concentrations were correlated with bone lead
concentrations, which reflect accumulated exposure to lead (Todd and Chettle 1994), bone lead concentrations were assessed at the Mount Sinai School of Medicine (A.C.T./S.C.) in a sub-sample of 5% - 10% of participants without current occupational lead exposure. These participants were selected based on their proximity to the medical center. Tibia lead was assessed via a 30-minute measurement at the left mid-tibial shaft using $^{109}$Cd-induced K-shell x ray fluorescence (Todd et al. 2001a; Todd et al. 2001b; Todd et al. 2002), which yields a concentration in units of µg lead per gram of bone mineral. Bone lead concentrations were not assessed on the same day as BPb concentrations, but were performed within two months of one another.

Statistical Analyses

Statistical analyses were performed in SPSS (Version 11.0). BPb concentrations were not normally distributed. Each analysis was first performed using $\log_{10}$ BPb and then repeated using BPb. The results were similar. Results were presented using BPb because non-transformed data can be expressed in units of µg/dl, which is a more easily understandable unit of measure. When examining group differences in BPb concentration, medians were compared using a nonparametric approach (Mann Whitney test). To assess associations between BPb concentration and other continuous variables (e.g., total tremor score) we used Spearman’s correlation coefficients ($r$). To evaluate differences between categorical variables (e.g., gender by diagnosis [ET patient vs. control]), chi-square ($\chi^2$) tests were used. To assess group differences in normally-distributed continuous variables (e.g., age), Student’s $t$ test was used.

Logistic regression analyses were performed to test the association of BPb
concentration with diagnostic status (ET patient vs. control). We began with an unadjusted model and then considered variables that were suspected to confound the lead-diagnosis association or were known to be associated with BPb (Cheng et al. 1998; Hernandez-Avila et al. 1996; Dawson et al. 1999). These were: age in years, gender, race (white vs. non-white), number of rooms in home, years of education, current cigarette smoker (yes vs. no), pack-years of smoking, reported daily consumptions of vitamin C, calcium, and iron, and ethanol use (heavy vs. light use). In the final model, we included a variable if in a univariate model it was either (1) associated with the diagnosis (at p < 0.10) or (2) it was associated with the BPb concentration (at p < 0.10). This value (p < 0.10) was chosen because we did not want to miss a potential association and so used a more liberal criteria than in typically used in hypothesis testing.

Diagnosis by family history groups (control, ET patients with a family history of tremor, ET patients without a family history of tremor) were used to test the hypothesis that ET patients without a family history of tremor might have higher BPb concentrations than controls. Multivariate logistic regression analyses were performed to test the association of BPb lead concentration with diagnosis by family history group, using the same confounding variables that were used to model the association of BPb concentration with ET diagnostic status (ET patient vs. control).

We based sample size calculations on pilot data collected from 20 controls. To detect a 25% increase in mean BPb concentrations in patients, and assuming an alpha = 0.05, the power with 100 participants in each group was 84.7% and with 150 participants in each group was 95.5%. Control recruitment was faster than that of ET
patients, so that we reached 143 controls at a point when we had 100 ET patients. The power to detect a 25% difference with our sample (100 ET patients and 143 controls) was 90.5%.

Results

There were 100 ET patients and 143 controls. Patients were, on average, four to five years older than controls, but were otherwise similar (Table 1). BPb concentrations and bone lead concentrations in the 17 participants (10 patients and 7 controls) were correlated with one another (Spearman’s r = 0.52, p = 0.03), suggesting that individuals with higher current blood lead levels may have had higher lifetime exposures.

In controls, we assessed the associations between BPb concentrations and possible confounding variables, including age, years of education, number of rooms in home, number of cigarette pack years, and current reported consumption (in mg/day) of vitamin C, calcium and iron, but there were no associations. In controls, BPb concentration was higher in current cigarette smokers vs. nonsmokers (medians = 3.5 µg/dl vs. 2.3 µg/dl, Mann Whitney z = 2.08, p = 0.038) but similar in males and females (medians = 2.4 µg/dl vs. 2.2 µg/dl, Mann Whitney z = 1.60, p = 0.11) and whites compared to nonwhites (medians = 2.3 µg/dl vs. 2.6 µg/dl, Mann Whitney z = 0.78, p = 0.43). In the eight controls who were heavy ethanol users, the median BPb concentration was 3.1 µg/dl compared to 2.3 µg/dl in the 135 controls who were light users (Mann Whitney z = 0.97, p = 0.33).

The median BPb concentration was 2.7 µg/dl in ET patients vs. 2.3 µg/dl in controls (Mann Whitney z = 2.08, p = 0.038). The respective mean BPb concentrations were 3.3
± 2.4 and 2.6 ± 1.6 µg/dl (Figure 1). A BPb concentration > 10 µg/dl was present in two (2%) ET patients and no (0%) controls.

There was a correlation between the total tremor score and BPb concentration (Spearman’s r = 0.14, p = 0.03) in the 243 study subjects. In the ET patients, this correlation was not significant (Spearman’s r = 0.07, p = 0.48, Figure 2). The 44 ET patients who were taking a medication for their tremor had BPb concentrations that did not differ significantly from those of the 56 ET patients who were not taking a medication (medians = 2.5 vs. 2.7 µg/dl, respectively, t = 1.26, p = 0.21).

In the unadjusted logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient, OR per unit increase = 1.21, 95% CI = 1.05 - 1.39, p = 0.007). The final model included BPb concentration as well as age and current cigarette smoker (yes vs. no). In this model, the association between BPb concentration and diagnosis (OR per unit increase = 1.19, 95% CI = 1.03 - 1.37, p = 0.02) was similar to that obtained in the unadjusted model (OR per unit increase = 1.21).

BPb concentration was higher in the 39 ET patients without a family history of tremor compared to the 61 ET patients who had a family history (medians = 3.0 µg/dl vs. 2.4 µg/dl, Mann Whitney z = 2.30, p = 0.02). When ET patients without a family history of tremor were compared to controls, BPb concentrations differed (medians = 3.0 µg/dl vs. 2.3 µg/dl, Mann Whitney z = 2.94, p = 0.003). In the unadjusted logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient without a family history of tremor, OR per unit increase = 1.40, 95% CI = 1.18 - 1.66, p = 0.001). In the adjusted logistic regression model, the association between BPb concentration and diagnosis remained significant (control vs. ET patient without a family history of tremor, OR per unit increase = 1.40, 95% CI = 1.18 - 1.66, p = 0.001).
Two percent of patients and 2% of controls had current (possible or probable) occupational lead exposure. Prevalence of lifetime occupational lead exposure was similar in ET patients and controls as well. Possible lifetime occupational lead exposure occurred in 13 (13%) ET patients and 19 (13.3%) controls and probable lifetime occupational lead exposure occurred in 15 (15%) ET patients and 15 (10.5%) controls ($\chi^2 = 1.11, p = 0.57$). The prevalence of lifetime occupational exposure to lead did not differ between ET patients without a family history of tremor and controls. There were 62 participants with possible or probable lifetime occupational lead exposure. Their BPb concentration was higher than that of the 181 participants without this exposure (medians = 3.1 µg/dl vs. 2.4 µg/dl, Mann Whitney $z = 2.91, p = 0.004$). In a logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient, OR per unit increase = 1.18, 95% CI = 1.03 - 1.37, $p = 0.02$) after adjusting for age, current cigarette smoker (yes vs. no), and possible or probable lifetime occupational lead exposure.

**Discussion**

In this case-control study, we found that the BPb concentration was higher in ET patients than in controls. This association between higher BPb concentration and the diagnosis of ET persisted after adjusting for confounding variables. The association was strongest in patients with sporadic ET, i.e., those with no family history of tremor, suggesting that lead as a toxicant might be of more relevance in ET patients without a genetic susceptibility for ET. The prevalence of lifetime occupational exposure to lead
was similar in ET patients and controls, suggesting that the higher BPb concentration in ET patients was not due to increased risk of occupational exposure. However, the prevalence of occupational lead exposure was very low in our study population; thus, we cannot definitively exclude occupational lead exposure as a risk factor for ET.

Although the BPb concentration differed between ET patients and controls, the concentration in our study participants was low, reflecting the national decline in BPb concentrations since the removal of lead from gasoline and paint (Brody et al. 1994). BPb concentrations in our population may have been higher in the past. BPb concentrations <10 µg/dl were previously thought to be safe; however, they have been associated with neurological problems in children and adults (Brody et al. 1994), suggesting that there are neurological sequelae of low levels of lead exposure. In a report of 141 men taking part in a normative aging study (Payton et al. 1998), mean BPb concentrations were 5.5 µg/dl, and higher concentrations of blood and bone lead were associated with poorer performance on cognitive tests. In 530 women aged 65-87 years who were participants in a study of osteoporotic fractures, BPb concentrations > 8 µg/dl were associated with poorer performance on tests of memory, visual perception, psychomotor speed, manual dexterity, attention, and mental flexibility (Muldoon et al. 1993).

While our data demonstrate an association between ET and higher BPb concentrations, one must be cautious about the interpretation of these data. It is unlikely that a BPb concentration of 3.3 ug/dL alone is sufficient to cause ET. If this were so, the prevalence of ET might be higher than 1 - 6%. An incidence study is needed to directly address the issue of whether higher BPb concentrations precede or follow the diagnosis.
of ET. Second, a study of bone lead concentration is required, as this is a better measure of cumulative exposure to lead than are BPb concentrations. These types of studies are needed before a chelation trial, to try to modify the subsequent progression of the disease (i.e., worsening of tremor) among ET cases, should be considered.

Humans may be exposed to both inorganic and organic forms of lead from occupational and non-occupational sources (Coulehan et al. 1983; Winegar et al. 1997). In humans and rats, lead exposure may lead to acute and chronic progressive disorders in which action tremor is a prominent feature (Coulehan et al. 1983; Goldings and Stewart 1982; Seshia et al. 1978; Valpey et al. 1978; Young et al. 1977; Booze et al. 1983). There is also evidence that lead toxicity causes cerebellar pathology. Rat pups fed a diet containing 4% lead acetate demonstrated changes in the topology of Purkinje cell dendritic trees due to a change in Purkinje cell metabolism (McConnell and Berry 1979). Perinatal exposure to inorganic lead results in degenerative changes in Purkinje cells in the rabbit cerebellum (Walsh and Tilson 1984). Inorganic lead exposure causes a reduction in the total number of cerebellar cells in developing rat brains (Michaelson 1973). Moreover, an autopsy study of humans with chronic organic lead exposure revealed severe destruction of cerebellar Purkinje cells (Valpey et al. 1978). Multiple lines of evidence suggest that the cerebellum is involved in ET, including imaging studies (positron emission tomography (Wills et al. 1994), functional magnetic resonance imaging (Bucher et al. 1997), and magnetic resonance spectroscopic imaging (Louis et al. 2002a)), clinical studies and electrophysiological studies (Deuschl et al. 2000; Stolze et al. 2000; Gironell et al. 2000), and case reports (Dupuis et al. 1989). Unfortunately, there have been few postmortem studies of ET; several studies
revealed loss of cerebellar Purkinje cells, but without control brains for comparison, these results are difficult to interpret (Louis 2001).

One limitation of the current study is its cross-sectional rather than longitudinal design. We did not study incident patients with ET. The data do not directly address the issue of whether higher BPb concentrations preceded or followed the diagnosis of ET. Prospective studies of are needed to further assess the associations we reported in this study. Second, we assessed BPb concentrations. Bone lead concentrations are a better measure of cumulative exposure to lead, although there is a correlation between the two in “steady-state” exposure (Cheng et al. 1998). We performed bone lead assessments on a sub-sample of ET patients and controls and demonstrated a correlation between the two measures, as has been reported in several other studies of non-occupationally exposed (Cheng et al. 1998; Farias et al. 1998; Kosnett et al. 1994) and occupationally exposed cohorts in steady-state exposure (Borjesson et al. 1997). Sole use of BPb as a measure of lead exposure might not have optimized our ability to detect an association between lead exposure and ET, thereby resulting in conservative estimates of this association. In addition, in this study, ET patients were asked whether they had a first-degree relative with tremor. Patients who responded affirmatively to this question were considered to have a family history of tremor. It is possible that this approach resulted in an over-estimation of the genetic component of ET and that individuals without a genetic pre-disposition for tremor were included as individuals with a family history of tremor. This would have resulted in our having derived lower (i.e., conservative) estimates of the association between BPb concentration and familial ET. Despite these limitations, this is the first study to test the hypothesis that lead exposure
may be associated with ET. We therefore deem this positive association to be potentially very important.

In summary, we report an association between BPb concentration and ET. Whether this association is due to increased exposure to lead or a difference in lead kinetics in ET patients requires further investigation.

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Table 1: ET Patients vs. Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>ET Patients (N = 100)</th>
<th>Controls (N = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.7 (9.9)**</td>
<td>66.2 (9.7)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>54 (54%)</td>
<td>79 (55.2%)</td>
</tr>
<tr>
<td>Race (white)</td>
<td>91 (91%)</td>
<td>129 (89.5%)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.2 (4.7)</td>
<td>15.1 (3.3)</td>
</tr>
<tr>
<td>Rooms in home</td>
<td>5.4 (2.3)</td>
<td>6.0 (2.4)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>8 (8%)</td>
<td>14 (9.8%)</td>
</tr>
<tr>
<td>Cigarette pack-years</td>
<td>7.4 (18.8)</td>
<td>9.8 (21.3)</td>
</tr>
<tr>
<td>Vitamin C (mg/day)(^a)</td>
<td>444.1 (386.2)</td>
<td>432.8 (398.9)</td>
</tr>
<tr>
<td>Calcium (mg/day)(^a)</td>
<td>973.4 (590.7)</td>
<td>935.5 (563.8)</td>
</tr>
<tr>
<td>Iron (mg/day)(^a)</td>
<td>14.7 (8.4)</td>
<td>16.4 (13.1)</td>
</tr>
<tr>
<td>&gt; 2 alcoholic drinks/day (^a)</td>
<td>10 (10.0%)</td>
<td>8 (5.6%)</td>
</tr>
</tbody>
</table>

All values are either means with standard deviations or numbers with percentages.

*\(p < 0.05\), **\(p < 0.01\), ***\(p < 0.001\).

\(^a\) Reported current daily intake based on the semi-quantitative food frequency questionnaire.
Table 2: Association Between BPb Concentration and Other Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation with BPb Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$r = 0.009$, $p = 0.91$</td>
</tr>
<tr>
<td>Education (years)</td>
<td>$r = -0.005$, $p = 0.95$</td>
</tr>
<tr>
<td>Number of rooms in home</td>
<td>$r = -0.003$, $p = 0.98$</td>
</tr>
<tr>
<td>Number of cigarette pack-years</td>
<td>$r = -0.04$, $p = 0.64$</td>
</tr>
<tr>
<td>Current reported consumption of vitamin C (mg/day)$^a$</td>
<td>$r = -0.11$, $p = 0.21$</td>
</tr>
<tr>
<td>Current reported consumption of calcium (mg/day)$^a$</td>
<td>$r = -0.10$, $p = 0.25$</td>
</tr>
<tr>
<td>Current reported consumption of iron (mg/day)$^a$</td>
<td>$r = -0.13$, $p = 0.12$</td>
</tr>
</tbody>
</table>

All $r$ values are Spearman's $r$.

$^a$ Reported current daily intake based on the semi-quantitative food frequency questionnaire.
Figure Legend:

Figure 1: Blood lead (BPb) concentration in µg/dl in ET patients and controls. The central box represents the mean and the bars, 2 x the standard error.

Figure 2: Blood lead (BPb) concentration vs. total tremor score in ET patients. The regression line is shown.
Figure 1: BPb Concentration in Cases and Controls
Figure 2: BPb Concentration vs. Total Tremor Score

The scatter plot shows the relationship between BPb concentration and total tremor score. There is a weak positive correlation, with points scattered across the graph, indicating some individuals have higher BPb concentrations associated with higher tremor scores.