Blood Lead Is a Predictor of Homocysteine Levels in a Population-Based Study of Older Adults

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Lead and homocysteine are both associated with cardiovascular disease and cognitive dysfunction. We evaluated the relations among blood lead, tibia lead, and homocysteine levels by cross-sectional analysis of data among subjects in the Baltimore Memory Study, a longitudinal study of 1,140 randomly selected residents in Baltimore, Maryland, who were 50–70 years of age. Tilia lead was measured by 109Cd K-shell X-ray fluorescence. The subject population had a mean ± SD age of 59.3 ± 5.9 years and was 66.0% female, 53.9% white, and 41.4% black or African American. Mean ± SD blood lead, tibia lead, and homocysteine levels were 3.5 ± 2.4 µg/dL, 18.9 ± 12.5 µg/g, and 10.0 ± 4.1 µmol/L, respectively. In unadjusted analysis, blood lead and homocysteine were moderately correlated (Pearson’s r = 0.27, p < 0.01). After adjustment for age, sex, race/ethnicity, educational level, tobacco and alcohol consumption, and body mass index using multiple linear regression, results revealed that homocysteine levels increased 0.35 µmol/L per 1.0 µg/dL increase in blood lead (p < 0.01). The relations of blood lead with homocysteine levels did not differ in subgroups distinguished by age, sex, or race/ethnicity. Tilia lead was modestly correlated with blood lead (Pearson’s r = 0.12, p < 0.01) but was not associated with homocysteine levels. To our knowledge, these are the first data to reveal an association between blood lead and homocysteine. These results suggest that homocysteine could be a mechanism that underlies the effects of lead on the cardiovascular and central nervous systems, possibly offering new targets for intervention to prevent the long-term consequences of lead exposure. Key words: blood lead, cross-sectional study, homocysteine, tibia lead. Environ Health Perspect 113:31–35 (2005). doi:10.1289/ehp.7369 available via http://dx.doi.org/ [Online 7 September 2004]

As a result of centuries of human use, lead is omnipresent in the environment. Commercial use of this substance continues even though its toxic effects have been recognized since ancient times (Nriagu 1983), and more recent studies report health effects associated with lower and lower lead doses (Canfield et al. 2003; Glenn et al. 2003; Nash et al. 2003; Schwartz et al. 2000). Lead is not rapidly cleared from the body; the biologic residence time of lead in bone is on the order of years to decades (Hu et al. 1998). In occupational and general population samples, low blood lead levels have been associated with increased blood pressure and elevated risk of hypertension, effects that may be progressive (Cheng et al. 2001; Glenn et al. 2003; Nash et al. 2003); increased circulatory and cardiovascular mortality (Lustberg and Silbergeld 2002); and progressive declines in cognitive function over time, even years after cessation of occupational exposure (Schwartz et al. 2000, 2002, in press). One of the key remaining problems in the research of lead toxicity is that the mechanisms for these effects are not well understood.

Interestingly, homocysteine is also associated with cardiovascular disease and cognitive dysfunction (Dufouil et al. 2003; Homocysteine Collaboration 2002). Homocysteine is an independent risk factor for vaso-occlusive disease; elevated levels of homocysteine increase the risk of heart disease, stroke, and peripheral vascular disease and, perhaps through vascular mechanisms, cognitive dysfunction (Bautista et al. 2002; Dufouil et al. 2003; Homocysteine Collaboration 2002; Prins et al. 2002; Ravaglia et al. 2003; Wald et al. 2002). Vascular damage by homocysteine may occur through impaired vascular endothelial and smooth muscle cell function (Rodrigo et al. 2003). The mechanisms of this impairment may involve inhibition of nitric oxide synthesis, increased oxidative stress, proliferation of vascular smooth muscle cells, and altered elasticity of the vascular wall (Rodrigo et al. 2003).

Despite the similarities in these health effects, the relation of homocysteine and lead dose has not been previously examined. Herein, we report associations of blood lead, tibia lead, and homocysteine in a population-based study of persons 50–70 years of age in Baltimore, Maryland. Participants were selected from the general population, and most are without occupational lead exposure.

Materials and Methods

Study design. The Baltimore Memory Study, one of the National Institutes of Health’s disparities initiative grants, is a multilevel cohort study of risk factors for cognitive decline in Baltimore city residents of targeted neighborhoods. The methods are described elsewhere (Schwartz et al. 2004). The selected neighborhoods were chosen to provide areas with a broad range of socioeconomic status and large numbers of both whites and African Americans. A cross-sectional analysis of first visit data was performed.

Subject selection and recruitment. Sampling and recruitment have been previously described (Schwartz et al. 2004). In brief, individual dwellings in the study area were linked to telephone numbers, and households with telephones were randomly selected for recruitment. Eligibility was then determined on 2,351 subjects (50–70 years of age, living at selected household, lived in Baltimore at least 5 years), and of these subjects, 60.8% were scheduled for an enrollment visit. Of the 1,403 scheduled for an appointment, 1,140 (81.3%) were enrolled and subsequently tested. The study was approved by the Committee for Human Research of the Johns Hopkins Bloomberg School of Public Health. All participants provided written, informed consent before testing and were paid $50 for their participation.

Data collection. All data were collected at the study clinic by trained research assistants. A structured interview included the following information: demographics, socioeconomic status (household income, household assets, occupational status, and educational attainment), medical history, smoking and alcohol history, and lead history. First and second visits were conducted between May 2001 and September 2002, and October 2002 and February 2004, respectively. A trained phlebotomist drew a 10-mL blood specimen into a red-top (no anticoagulant) tube, which was clotted, centrifuged, and stored at −20°C within 1 hr.

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This work was supported by R01 AG19604 (B.S.S.). The authors declare they have no competing financial interests.

Received 30 June 2004; accepted September 7 2004.
Samples were transported to the Johns Hopkins Bloomberg School of Public Health and stored at –70°C. Serum homocysteine was measured by a commercial laboratory using fluorescence polarization immunoassay (Abbott AxSYM, Abbott Park, IL). The coefficients of variation for the quality control samples for three concentration levels were 3.64% (low range), 2.24% (mid range), and 2.32% (high range). Fasting was not requested of the subjects because study visits were scheduled at all times of the day for logistical reasons. The variability between fasting and nonfasting samples is not likely to exaggerate the association but instead would dampen it. Conditions that cause short-term fluctuations in homocysteine levels, such as protein intake, are not likely to be related to whole-blood lead levels. Homocysteine was measured from a sample obtained at the first visit in most subjects; however, 254 subjects provided plasma only at the first visit so had serum obtained at the second visit for homocysteine measurement. Lead was measured in the metals laboratory of the Kennedy Krieger Institute (Baltimore, MD) from the first study visit whole-blood specimen using anodic stripping voltammetry (Schwartz et al. 2004). Tibia lead concentration was measured at the second study visit by 109Cd-induced K-shell X-ray fluorescence using previously reported methods (Todd 2000; Todd and McNeill 1993; Todd et al. 1992, 2000). In this population of older adults without occupational lead exposure, tibia lead, which has a biologic residence time of 25–30 years, should not have changed appreciably between the first and second study visits.

**Statistical methods.** The main objectives of this analysis were a) to evaluate relations of blood lead and tibia lead levels with homocysteine, controlling for age, race/ethnicity, sex, and other potential confounding variables; and b) to evaluate whether these relations were modified by age, sex, or race/ethnicity. Of the 1,140 persons enrolled at the first visit, 78 subjects were missing homocysteine values; 10 were missing blood lead values; 7 missing information on alcohol consumption; 6 missing body mass index (BMI); and 1 each was missing information on education and tobacco use. A total of 1,022 (89.6%) subjects completed the second study visit, so 82 participants were missing tibia lead data. Thus, in analyses with blood lead and tibia lead, 1,037 and 955 subjects were included, respectively. Subjects with missing homocysteine data were not statistically different regarding blood lead, age, or race/ethnicity. To minimize the influence of large tibia lead values, tibia lead was log transformed before use in models. Negative values for tibia lead were converted to 0.1 before log transformation. Associations with tibia lead were also examined nonparametrically, using a percentile transformation for tibia lead; results did not differ from those using the log-transformed tibia lead and are not reported.

We used multiple linear regression to examine the relations of blood lead with homocysteine levels, controlling for covariates. Models were first constructed including known homocysteine covariates (e.g., age, sex, and race/ethnicity); then, other potential confounding variables were included in a forward stepwise fashion. Variables were retained in the final models if they were associated with homocysteine levels or significantly influenced the relation of blood or tibia lead with homocysteine (changed the lead coefficient by more than 10%). The final model included age, race/ethnicity, sex, educational level (four categories based on reported years of education and information on graduate equivalency diploma, training for trades, and additional educational certificates), alcohol (four categories based on the number of alcoholic drinks per month, with a drink being defined as one beer, one glass of wine, one wine cooler, one cocktail, or one shot of liquor), smoking (four categories based on the number of cigarettes smoked per day), and BMI (kilograms per square meter).

We evaluated effect modification by including cross-product terms in the model (e.g., to evaluate effect modification by race/ethnicity, a cross-product of race/ethnicity and blood lead was included in the model). All statistical analyses were performed using Stata version 8.0 (Stata Corporation, College Station, TX). We checked final models for the assumptions of linear regression and model fit using influence diagnostic procedures, examination of residuals, and residual–residual plots.

**Results**

Study subjects were 66.0% female, 41.4% non-Hispanic black/African American, and 53.9% non-Hispanic white or white/Native

### Table 1. Demographic characteristics for the inclusive study population and lead quartile subgroups, Baltimore Memory Study, 2001–2002.

| Characteristic | Total (n = 1,037) | Quartile 1 (n = 241) | Quartile 2 (n = 271) | Quartile 3 (n = 262) | Quartile 4 (n = 263) | p-Valuea |
|---------------|-----------------|---------------------|---------------------|---------------------|---------------------|----------|
| Blood lead level (mean [range], µg/dL) | 3.5 (0.1–27.3) | 1.1 (0.1–1.9) | 2.5 (2.0–3.0) | 3.8 (3.1–4.4) | 6.5 (4.5–27.3) | < 0.001 |
| Homocysteine (mean ± SD, µmol/L) | 10.4 ± 4.1 | 9.2 ± 3.4 | 9.3 ± 3.5 | 9.7 ± 3.6 | 11.7 ± 5.1 | < 0.001 |
| Age (mean ± SD, years) | 59.3 ± 5.9 | 59.3 ± 5.9 | 59.3 ± 5.8 | 59.0 ± 5.9 | 59.8 ± 6.2 | 0.52 |
| Sex (% female) | 66.0 | 83.0 | 72.3 | 63.7 | 46.0 | < 0.001 |
| Race/ethnicity (%) | | | | | | 0.73 |
| Non-Hispanic black/African American | 41.4 | 44.4 | 39.9 | 38.9 | 42.6 | |
| Non-Hispanic white or white/Native American | 53.9 | 49.4 | 55.7 | 56.1 | 54.0 | |
| African American mixed race/ethnicity | 2.7 | 2.9 | 3.0 | 3.1 | 1.9 | |
| Asian, Hawaiian, Native American, or other | 2.0 | 3.3 | 1.4 | 1.9 | 1.5 | |
| BMI (mean ± SD, kg/m²) | 29.8 ± 6.9 | 31.5 ± 7.8 | 30.7 ± 7.2 | 28.8 ± 6.4 | 28.3 ± 5.4 | < 0.001 |
| Current cigarette use (%) | | | | | | 0.008 |
| None | 79.8 | 85.9 | 80.8 | 82.4 | 70.7 | |
| < Half pack per day | 5.6 | 3.7 | 7.8 | 3.5 | 7.2 | |
| Half pack to < 1 pack per day | 7.6 | 4.2 | 5.9 | 8.0 | 12.2 | |
| ≥ 1 pack per day | 7.0 | 6.2 | 5.5 | 6.1 | 9.9 | |
| Alcoholic beverage use (%) | | | | | | < 0.001 |
| None | 40.6 | 49.9 | 43.9 | 38.5 | 30.8 | |
| < 4 per month | 15.1 | 17.4 | 15.9 | 13.4 | 13.7 | |
| 4–8 per month | 12.8 | 11.2 | 15.1 | 14.5 | 10.3 | |
| ≥ 8 per month | 31.5 | 21.6 | 25.1 | 33.6 | 45.2 | |
| Education level (%) | | | | | | 0.9 |
| < High school or trade school | 10.2 | 10.4 | 9.2 | 8.4 | 12.9 | |
| Completed high school or trade school | 41.7 | 41.5 | 43.2 | 41.2 | 40.7 | |
| Some college or associate degree | 5.9 | 6.2 | 6.3 | 6.1 | 4.9 | |
| ≥ College degree | 42.2 | 41.9 | 41.3 | 44.3 | 41.5 | |

*p-Value from chi-square test for categorical variables or for continuous variables analysis of variance F-test for linear trend across quartiles.
American and had a mean (range) age of 59.3 (49–71) years. The mean ± SD blood lead and homocysteine levels were 3.5 ± 2.4 µg/dL and 10.0 (4.1) µmol/L, respectively (Table 1). Subjects had a wide range of educational levels, smoking habits, and alcohol habits; in unadjusted analysis, these were differentially associated with blood lead and homocysteine levels, evaluated in quartiles (Tables 1 and 2). Using blood lead and homocysteine as continuous measures, in unadjusted analysis, these were moderately correlated, with Pearson’s $r = 0.27$ ($p < 0.01$). Blood lead and tibia lead levels were only modestly correlated (Pearson’s $r = 0.11$, for the log transformed data (Figure 1), and $r = 0.12$ for the untransformed data; both $p$-values < 0.01).

We next used multiple linear regression to evaluate predictors of homocysteine levels, controlling for covariates (Table 3, Figure 2). Controlling for age, sex, race/ethnicity, smoking habits, alcohol habits, and educational level, the results revealed that an increase of 0.35 µmol/L in homocysteine levels was associated with an increase of 1.0 µg/dL in blood lead and 1.0 µg/dL in blood lead was associated with an increase of 0.35 µmol/L in homocysteine levels. Additionally, because the first 254 subjects provided plasma, these subjects had blood redrawn at the second study visit to obtain serum. There was no difference in the mean homocysteine levels based on the sample was obtained, and associations of blood lead with homocysteine did not vary by visit number.

**Discussion**

To our knowledge, this is the first study to examine relations of blood lead and tibia lead with homocysteine levels. We observed a significant association between blood lead and homocysteine in an older, community-dwelling, adult, population-based sample in a major U.S. urban area after controlling for age, sex, race/ethnicity, alcohol intake, cigarette smoking, educational level, and BMI. As previously observed, sex, age, and smoking a pack or more per day were predictors of homocysteine levels (Jacques et al. 2001). Blood lead may influence homocysteine levels at very low dose levels (Figure 2). Among study subjects, blood lead levels were generally < 15 µg/dL, as expected in the general population. The study thus provides evidence of an association at low blood lead levels, but we were unable to characterize the association at higher blood lead levels. Although tibia lead was modestly associated with blood lead levels, it was neither a predictor of homocysteine levels nor a confounder of its relation with blood lead. Tibia lead levels were obtained at the second study visit. Subjects who did not complete the second study visit were more likely to be African American (52.4 vs. 40.4%) and were slightly younger (58.5 vs. 59.4 years of age) compared with subjects who completed the visit, but there was no difference in blood lead levels. We do not believe these small differences account for the differences in homocysteine levels.

![Figure 1. Crude relation of log₁₀-transformed blood lead levels and log₁₀-transformed tibia lead levels for 955 participants in the Baltimore Memory Study. Dashed line represents a locally weighted smoothing fit (lowess bandwidth, 0.10) (Cleveland 1979).](image-url)
the contrasting associations of blood and tibia lead levels with homocysteine. Tibia lead, a measure of cortical bone lead, is generally a less important source of blood lead levels than is lead in trabecular bone, but is a good estimate of cumulative lead dose (Hu et al. 1998). The data suggest that bioavailable lead (i.e., blood lead) was a more important predictor of homocysteine levels than was cumulative lead dose (i.e., tibia lead).

Lead and homocysteine are both associated with an increased risk of cardiovascular disease and, possibly through vascular system mechanisms, central nervous system disease. In epidemiologic studies of central nervous system disease and cardiovascular outcomes, it is interesting to note that study results for lead parallel those for homocysteine. For example, in an occupational cohort of men with previous lead exposure (on average 18 years prior), the systolic blood pressure increased on average 0.64 mm Hg (SE = 0.25) for every SD increase in blood lead at baseline (Glenn et al. 2003). In a recent meta-analysis using data from 30 prospective or retrospective studies, a 25% lower homocysteine level (~3 µmol/L) was associated with an approximately 11% lower homocysteine increase in blood lead at baseline (Glenn et al. 2003). A recent meta-analysis of 20 prospective studies found that for an increase in serum homocysteine of 5 µmol/L, the OR for ischemic heart disease was increased (OR = 1.32; 95% CI, 1.19–1.45), as was the OR for stroke (OR = 1.59; 95% CI, 1.29–1.96) (Wald et al. 2002). Other studies support the similarities between the cardiovascular effects of lead and homocysteine (Baustista et al. 2002; Cheng et al. 2001; Kopp et al. 1988; Moller and Kristensen 1992; Nash et al. 2003; Pocock et al. 1988).

Table 3. Predictors of homocysteine levels in subjects with complete data (n = 1037), Baltimore Memory Study, 2001–2002.

Table: | Predictor | Total (n = 1037) | Female (n = 684) | Male (n = 353) |
|-----------|----------------|----------------|----------------|
| Blood lead (µg/dL) | 0.35 (0.05) | 0.24 (0.07) | 0.43 (0.08) |
| Age (years) | 0.09 (0.02) | 0.14 (0.02) | -0.02 (0.04) |
| Female | -1.46 (0.27) | 0.05 (0.02) | 0.05 (0.02) |
| BMI (kg/m²) | 0.05 (0.02) | 0.05 (0.02) | 0.03 |
| Current cigarette use | 0.04 | 0.02 | 0.04 |
| < Half pack per day | 1.01 (0.53) | 0.78 (0.62) | 1.30 (0.96) |
| Half pack to < 1 pack per day | 1.53 (0.47) | 2.05 (0.56) | 0.80 (0.84) |
| ≥ 1 packs per day | 2.29 (0.49) | 2.12 (0.90) | 2.11 (0.83) |

*Adjusted for age, sex, race/ethnicity, educational level, alcohol consumption (none, < 4 per month, 4–8 per month, > 8 per month), and alcohol use. Values were adjusted for age, sex, race/ethnicity, BMI, educational level, and tobacco and alcohol use. The three data points with blood lead concentrations > 15 µg/dL have been excluded from the plot (but not from the regression model) so that the portion of the plot with the most data could be more clearly visualized. The solid line is the predicted linear fit, and the dashed line is from a locally weighted smoothing fit (lowess bandwidth, 0.05) (Cleveland 1979).

Several targets that lead could be acting upon could explain this association. Lead can interact with proteins, particularly those with a sulfhydryl group (Goering 1993). An example of this occurrence is the inhibition of the ß-aminolevulinic acid dehydratase (ALAD) enzyme in the heme-synthesis pathway. ALAD is an octameric metalloenzyme that contains zinc in the activated state (Simons 1995). The active site for zinc binding contains two cysteine residues. There is competitive inhibition between lead and zinc, with the ratio of the affinity of lead to zinc at the metal-binding site being about 25:1 for the 1-1 ALAD phenotype (Simons 1995). Such sulfhydryl binding by lead could be one mechanism that could account for the observed lead–homocysteine relation. In the metabolism of methionine, homocysteine can be remethylated by two different pathways or undergo transulfuration to cysteine (Ueland and Refsum 1989). In the transulfuration pathway there is a unique heme-containing enzyme, cystathionine ß-synthase, that catalyzes a pyridoxal 5’-phosphate–dependent condensation of serine and homocysteine to give cystathionine (Banerjee et al. 2003). Work in the elucidation of the structure of cystathionine ß-synthase has revealed several sulfhydryl groups contained within the heme-binding site (Meier et al. 2001). Furthermore, homocysteine itself contains a sulfhydryl group, so if lead has an affinity for this sulfhydryl group, the metabolism of homocysteine could be directly inhibited, leading to an accumulation of homocysteine.

It has been unclear whether homocysteine is a causative agent or only a marker of disease. In 1962, homocystinuria in mentally retarded children was discovered as an inborn error of homocysteine metabolism. The presence of elevated homocysteine levels in plasma was interpreted as a marker of disease. However, recent epidemiologic studies have suggested that homocysteine levels are increased in a variety of conditions, including coronary artery disease, stroke, and diabetes. These studies have led to the hypothesis that elevated homocysteine levels may be a marker of increased cardiovascular risk. However, the association between elevated homocysteine levels and cardiovascular disease remains controversial.

The association between lead and homocysteine levels is consistent with the hypothesis that lead may inhibit the methylation of homocysteine. The methylation of homocysteine is an important process for the maintenance of normal methionine levels. Lead has been shown to inhibit the activity of the enzyme methionine synthase, which catalyzes the methylation of homocysteine to methionine. This inhibition may be responsible for the increased homocysteine levels observed in lead-exposed populations.

This study was supported by the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Neurological Disorders and Stroke (NINDS). The authors would like to thank the Baltimore Memory Study participants and personnel for their contributions to this research.
of metabolism (Carson and Neill 1962; Gerritsen et al. 1962). In 1964, cystathionine β-synthetase deficiency was demonstrated as a cause of this disorder (Mudd et al. 1964). The natural history of cystathionine β-synthetase deficiency includes a 50% chance of a vascular event (stroke, myocardial infarction, peripheral arterial or venous thrombosis) by 30 years of age (Yap 2003). Recent experimental evidence suggests homocysteine to be a causal agent. Experimentation has shown isolated hyperhomocysteinemia to be atherogenic in cystathionine β-synthetase and apolipoprotein-E double knock-out mice (Wang et al. 2003). Additionally, homocysteine has been shown to stimulate the expression and secretion of biologically active monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) in human monocytes (Zeng et al. 2003), two chemokines that are thought to be important to the development of atherosclerotic plaques.

In conclusion, blood lead was found to be associated with homocysteine levels in a large, general population sample. Although causality cannot be determined from cross-sectional data, it is interesting to consider the possibility that this relation of lead and homocysteine could explain one of the mechanisms of the influence of lead on the central nervous and cardiovascular systems. Whether lead elevates homocysteine through enzyme inhibition, as earlier suggested, or conversely, whether homocysteine elevates lead because of intravascular binding (homocysteine has a structure similar to dimeric polyacrycic acid (DMSA) and penicillin, compounds that are known to bind lead), it is evident that the association exists at very low blood lead levels, and if the former mechanism is operative, supports a biologic effect of lead at low levels. This knowledge may offer new targets for prevention of the progressive health effects of lead.

REFERENCES

ATSDR. 1999. Toxicologic Profile for Lead (Update). Atlanta, GA:Agency for Toxic Substances and Disease Registry. Balbius-Kornfeld JM, Stewart W, Bolla KI, Schwartz BS. 1995. Cumulative exposure to inorganic lead and neurobehavioral test performance in adults: an epidemiological review. Occup Environ Med 52:2–12.

Banerjee R, Evande R, Kabil O, Ojha S, Taoka S. 2003. Reaction mechanism and regulation of cystathionine beta-synthase. Biochim Biophys Acta 1587:30–35.

Bautista LE, Arenas IA, Peneuca A, Martinez LX. 2002. Total plasma homocysteine level and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. J Clin Epidemiol 55:882–887.

Cainfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Langheer BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med 348:1917–1926.

Carson N, Neill D. 1962. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. Arch Dis Child 37:509–513.

Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. 2001. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. Am J Epidemiol 152:164–171.

Cleveland WS. 1979. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836.

Dufouil C, Alperovitch A, Ducros V, Tourou C. 2003. Homocysteine, white matter hyperintensities, and cognition in elderly people. Ann Neurol 53:214–221.

Gerritsen T, Vaughn JS, Waisman HA. 1962. The identification of homocysteine in the urine. Biochem Biophys Res Commun 9:403–406.

Glenn BS, Stewart WF, Links JM, Todd AC, Schwartz BS. 2003. The longitudinal association of lead with blood pressure. Epidemiology 14:30–36.

Goering PL. 1983. Lead-protein interactions as a basis for lead toxicity. Neurotoxicology 14:45–60.

Homocysteine Collaboration. 2002. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 288:2015–2022.

Hu H, Rabinowitz M, Smith D. 1998. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ Health Perspect 106:1–8.

Jacobson MD, Bostrom AG, Wilson PW, Rich S, Rosenbarg IH, Selhub J. 2001. Determinants of plasma total homocysteine concentration in the Framingham offspring cohort. Am J Clin Nutr 73:613–621.

Kopp SJ, Barron JT, Tow JP. 1988. Cardiovascular actions of lead and relationship to hypertension: a review. Environ Health Perspect 78:91–99.

Lustberg M, Silbergeld E. 2002. Blood lead levels and mortality. Arch Intern Med 162:2443–2449.

Meier M, Janosik M, Kery V, Kraus JP, Burkhard P. 2001. Structure of human cystathionine beta-synthase: a unique pyridoxal 5´-phosphate-dependent heme protein. EMBO J 20:3910–3916.

Moller L, Kristensen T. 1992. Blood lead as a cardiovascular risk factor. Am J Epidemiol 136:1091–1100.

Mudd S, Finklestein J, Irreverre F, Laster L. 1964. Homocystinuria: an enzymatic defect. Science 143:1443–1445.

Nash D, Lustberg M, Shewin RW, Rubin RJ, Kaufmann R, Silbergeld E. 2003. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA 289:1523–1528.

Nriagu JO. 1983. Lead and Lead Poisoning in Antiquity. New York: Plenum.

Prins ND, Den Hiejer T, Holfman A, Koudstaal PJ, Jolles J, Clarke R, et al. 2002. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology 59:1375–1380.

Ravaglia G, Forti P, Maioli F, Muscarri A, Sacchetti L, Arronne G, et al. 2003. Homocysteine and cognitive function in healthy elderly community dwellers in Italy. Am J Clin Nutr 77:668–673.

Rodrigo R, Passalacqua W, Araya J, Drellina M, Rivera G. 2003. Implications of oxidative stress and homocysteine in the pathophysiology of essential hypertension. J Cardiovasc Pharmacol 42:453–461.

Schwartz BS, Glass T, Bolla K, Glass G, Stewart W, Todd A, et al. 2004. Disparities in cognitive functioning by race/ethnicity in the Baltimore Memory Study. Environ Health Perspect 112:314–320.

Schwartz BS, Lee B, Bandeen-Roche K, Stewart W, Bolla K, Links J, et al. In press. Lead dose is associated with longitudinal decline in neurobehavioral test scores in South Korean lead workers. Epidemiology.

Schwartz BS, Lee BK, Lee GS, Stewart WF, Lee SS, Hwang KY, et al. 2001. Associations of blood lead, dimercaptoacetic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. Am J Epidemiol 153:453–464.

Schwartz BS, Stewart WF, Bolla KI, Simon PD, Bandeen-Roche K, Gordon PB, et al. 2000. Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology 55:1144–1150.

Schwartz BS, Stewart W, Hu H. 2002. Neurobehavioral testing in workers occupationally exposed to lead. Occup Environ Med 59:684–689.

Simons TJ. 1995. The affinity of human erythrocyte porphobilinogen synthase for Zn2+ and Fe2+. Eur J Biochem 234:175–183.

Todd AC. 2000. Contamination of in vivo bone-lead measuremets. Phys Med Biol 45:229–240.

Todd AC, Carroll S, Godbold JH, Mosher EL, Khan FA. 2000. Variability in XRF-measured tibia lead levels. Phys Med Biol 45:3737–3748.

Todd AC, McNeill FE. 1993. In vivo measurements of lead in bone using a 203Hg spot source. Basic Life Sci 60:299–302.

Todd AC, McNeill FE, Palethorpe JE, Peach DE, Chettle DR, Tobin MJ, et al. 1992. In vivo X-ray fluorescence of lead in bone using X-ray excitation with 203Hg sources: radiation dosimetry studies. Environ Res 57:117–132.

Ueland PM, Refsum H. 1989. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease, and drug therapy. J Lab Clin Med 114:472–501.

Wald DS, Law M, Morris JK. 2002. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. Br Med J 325:1202–1206.

Wang H, Jiang X, Yang F, Gaubatz JW, Ma L, Magera MJ, et al. 2003. Hyperhomocysteinemia accelerates atherosclerosis in cystathionine beta-synthase and apolipoprotein E double knock-out mice with and without dietary perturbation. Blood 101:3901–3907.

Yap S. 2003. Classical homocystinuria: vascular risk and its prevention. J Inherit Metab Dis 26:259–265.

Zeng X, Dai J, Remick DG, Wang X. 2003. Homocysteine mediated expression and secretion of monocyte chemoattractant protein-1 and interleukin-8 in human monocytes. Circ Res 93:311–320.