

## Low-Level Environmental Exposure to Lead Unmasked as Silent Killer

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Since the dawn of human civilization, lead has been a ubiquitous environmental pollutant.<sup>1</sup> In 370 BC, Hippocrates described colic in a lead worker.<sup>2</sup> The industrial application of lead continues to the present day. Lead is a toxic metal that, during a lifetime, accumulates in the human body.<sup>1</sup> Recent evidence<sup>3–6</sup> suggests that lead affects human health at levels of exposure that, until now, were considered safe. The underlying premise is that a dose-related continuum of toxicity exists. Asymptomatic health effects may occur at even a very low dose and may evolve into clinically overt adverse effects if the exposure persists during a person's lifetime or becomes more intense. The report published by Menke et al<sup>7</sup> in this issue of *Circulation* breaks new ground by extending the dose–effect relation to considerably lower blood lead concentrations than reported in previous studies.<sup>3–6</sup>

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Menke et al<sup>7</sup> analyzed the database of the Third National Health and Nutrition Examination Survey (NHANES III) to investigate the relation between total and cause-specific mortality and blood lead in a representative sample of the US population. All 13 946 participants ( $\geq 17$  years of age) included in the analysis had a blood lead concentration  $< 0.48$   $\mu\text{mol/L}$  (10  $\mu\text{g/dL}$ ). (To convert micromoles per liter of lead into micrograms per deciliter, multiply by 20.712.) Follow-up lasted until December 31, 2000. With adjustments applied for confounders, subjects in the highest third of the blood lead distribution ( $\geq 0.17$   $\mu\text{mol/L}$ ), as compared with those in the lowest third ( $< 0.09$   $\mu\text{mol/L}$ ), experienced a significantly higher risk of death. Estimates of the excess risk amounted to 25% and 55% for total and cardiovascular mortality, respectively, and 89% and 151% for myocardial infarction and stroke.<sup>7</sup> The blood lead concentration did not predict mortality from cancer. These risk estimates withstood adjustment for confounders, including race-ethnicity, sex, age, body

mass index, current or former smoking, alcohol intake, diabetes, C-reactive protein, total cholesterol, physical activity, low income, high education, urban residence, and postmenopausal status. Sensitivity analyses of total mortality stratified for race, sex, age, body mass index, smoking, hypertension, diabetes, calculated glomerular filtration rate, and urban versus rural residence also produced consistent results. Spline regression models additionally demonstrated that the all-cause and cardiovascular mortality started to rise at blood lead levels as low as 0.10  $\mu\text{mol/L}$ .<sup>7</sup>

Two previous population studies<sup>8,9</sup> documented an association between total mortality and blood lead, albeit at higher blood lead concentrations than in the Menke et al<sup>7</sup> report. Among 1052 inhabitants recruited in 1976 at 40 years of age in Copenhagen County (Denmark), the blood lead concentration was 0.46  $\mu\text{mol/L}$  in women and 0.66  $\mu\text{mol/L}$  in men.<sup>8</sup> Blood lead fell by  $\approx 30\%$  over the first 5 years of follow-up. Over 14 years, 46 deaths occurred, and the incidence of fatal and nonfatal events totaled 54 for cardiovascular disorders and 40 for coronary heart disease. With adjustments applied for sex, serum cholesterol, smoking, and alcohol intake, the risk associated with blood lead at baseline was of borderline significance ( $P=0.03$ ) for total mortality but it was not significant for fatal and nonfatal cardiovascular disease or coronary complications. Further adjustment for alcohol intake weakened the hazard ratio for total mortality to a nonsignificant level ( $P=0.12$ ).<sup>8</sup> The NHANES II investigators recruited participants (age, 30 to 74 years) from 1976 until 1980. Of the 4292 subjects who had their blood lead measured at baseline, 102 were excluded from analysis because their lead concentration exceeded the contemporary standard of the Occupational Safety and Health Administration (1.45  $\mu\text{mol/L}$ ). Of the remaining 4190 subjects, 929 had died by December 31, 1992.<sup>9</sup> Compared with the reference group with a blood lead concentration  $< 0.48$   $\mu\text{mol/L}$ , the multivariate-adjusted hazard ratios were significant for total (1.46), cardiovascular (1.39), and cancer (1.68) mortality in the subgroup with a blood lead concentration of  $\geq 0.97$   $\mu\text{mol/L}$  but not in the subgroup with intermediate levels (hazard ratios, 1.17, 1.10, and 1.46, respectively).<sup>9</sup> The report from Lustberg and Silbergeld<sup>9</sup> did not provide any rationale for the cutoff thresholds to categorize the NHANES II participants or information on the number of subjects or deaths per category. In 2004, the same group reported a cross-sectional analysis of 2125 participants who were 40 years of age in the 1999 to 2000 NHANES survey.<sup>5</sup> The mean blood lead concentration was 0.10  $\mu\text{mol/L}$ . Peripheral arterial disease was defined as an ankle brachial index  $< 0.9$  in at least one leg. With cumulative adjustment for demographics and cardiovascular risk factors, the odds ratios in quartiles 2 to 4 of the blood

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(*Circulation*. 2006;114:1347-1349.)

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*Circulation* is available at <http://www.circulationaha.org>  
DOI: 10.1161/CIRCULATIONAHA.106.650440

lead distribution compared with the lowest quartile were 1.63 (95% CI, 0.51 to 5.15), 1.92 (95% CI, 0.62 to 9.47), and 2.88 (95% CI, 0.87 to 9.47), respectively.<sup>5</sup> Although the CIs of the odds ratios encompassed unity, the probability value for trend was 0.02. Navas-Acien et al<sup>5</sup> concluded that peripheral arterial disease was associated with blood lead levels well below current safety standards. In 428 participants in the Flemish Study on Environment, Genes, and Health Outcomes,<sup>10</sup> we replicated the observations of Navas-Acien et al, albeit it at a mean lead concentration of 0.43  $\mu\text{mol/L}$ .

In the Menke et al<sup>7</sup> study, the association of total and cardiovascular mortality with blood lead persisted after adjustment for hypertension, an estimated glomerular filtration rate  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , and C-reactive protein. These observations suggest, but by no means prove, that mechanisms other than hypertension, impaired renal function, and inflammation might underlie the observed associations. Indeed, with the exception of cases of frank lead intoxication,<sup>1</sup> the relation between hypertension and exposure to lead, remains controversial.

The suspicion that environmental lead exposure might play a role in the pathogenesis of hypertension arose mainly after publication of NHANES II reports<sup>11,12</sup> describing a direct relation between blood pressure and blood lead, which was particularly strong in white middle-aged men. However, other researchers found later that the positive correlation in 40- to 59-year-old men did not characterize the other sex and age strata and questioned the quality of the blood pressure measurements.<sup>13,14</sup> In a meta-analysis of 31 studies,<sup>15</sup> we found that a doubling of the blood lead concentration entailed increases in blood pressure averaging 1.0 mm Hg (0.5 to 1.4 mm Hg) systolic and 0.6 mm Hg (0.4 to 0.8 mm Hg) diastolic. Furthermore, in 1985 to 1989, we randomly selected 728 subjects ( $\geq 20$  years of age) from a Belgian population.<sup>16</sup> Over 5.2 years of follow-up (median), the mean blood lead concentration, initially 0.42  $\mu\text{mol/L}$ , dropped by 32%. In this prospective study,<sup>16</sup> we did not notice any consistent relation between the changes over time in blood pressure on conventional sphygmomanometric measurement and those in blood lead. Moreover, the blood lead concentration at baseline did not predict the 24-hour ambulatory blood pressure at follow-up. Ambulatory blood pressure recordings have high reproducibility, are not subject to digit preference or observer bias, and avoid the transient rise in a patient's blood pressure in response to a medical environment, the so-called white-coat effect. Cheng et al<sup>17</sup> reported on 519 men enrolled in the Normative Aging Study who were free of hypertension at baseline. With adjustments applied for the linear and squared terms of age, body mass index, family history of hypertension, alcohol use, and calcium intake, the standardized hazard ratios for the risk of hypertension over the 5.5-year follow-up were 1.37 (95% CI, 0.02 to 2.73) for tibia lead, a biomarker for long-term exposure, but only  $-0.13$  (95% CI,  $-1.35$  to 1.09) for blood lead. Unfortunately, the Cheng et al<sup>17</sup> analysis was not adjusted for baseline blood pressure or for the percentage change in body weight, both of which are important determinants of the incidence of hypertension.<sup>18</sup> Finally, our own analysis of the NHANES III database<sup>19</sup> demonstrated only a weak multivar-

iate-adjusted association between blood pressure and blood lead in blacks but not in whites.

The evidence that changes in renal function might represent an intermediate mechanism possibly explaining the association between mortality and environmental lead exposure might be more plausible than that of hypertension. In 1992, in a cross-sectional population study of 1016 women and 965 men ( $\geq 20$  years of age) with mean blood concentrations of 0.36 and 0.55  $\mu\text{mol/L}$ , respectively, we observed that a 10-fold increase in blood lead was associated with a 10- to 12-mL/min reduction in the measured creatinine clearance.<sup>4</sup> More recently, in adolescents with a mean blood lead concentration of 0.09  $\mu\text{mol/L}$ , we noticed an independent and positive association of the serum concentration of cystatin-c and the urinary excretion of  $\beta_2$ -microglobulin with blood lead.<sup>3</sup> Serum cystatin-c is a measure of glomerular filtration that, unlike serum creatinine, is independent of sex, age, height, and body composition.  $\beta_2$ -Microglobulin passes through the glomerular filter but is subsequently completely absorbed by the renal tubules. Our observations,<sup>3,4</sup> in agreement with other reports,<sup>20</sup> suggested that in adolescents environmental lead exposure can affect both glomerular and tubular renal function. Reverse causality is always an issue in observational studies. However, the alternative hypothesis—that slight renal dysfunction, resulting from innate or acquired causes, might reduce the renal excretion of lead and explain the positive association between renal dysfunction and the blood lead concentration—is unlikely. Indeed, Lin et al<sup>21</sup> reported that high-normal levels of chelatable lead predicted the decline of renal function in patients with chronic renal insufficiency. Moreover, chelation therapy in these patients improved renal function and slowed the progression of renal impairment.<sup>21</sup> These findings implied that, in line with the findings in intoxicated workers<sup>1</sup> and in environmentally exposed subjects,<sup>3,4</sup> increased blood lead must be the cause rather than the consequence of renal impairment. In addition to renal dysfunction, several other mechanisms might underlie the toxic effects of lead on the cardiovascular system such as enhanced vascular reactivity to sympathetic stimulation, enhanced oxidative stress, and diminished DNA repair, which might be relevant for rapidly dividing cells in the inflamed arterial wall.

Menke et al<sup>7</sup> carefully discussed the results of their study within the context of its possible limitations such as residual confounding. Two major limitations and one strong point deserve to be highlighted. First, blood lead has a half-life of  $\approx 30$  days. Its concentration in the blood primarily reflects recent exposure and can revert to normal when exposure ceases.<sup>1</sup> However, within days to weeks, lead is stored in tissues, particularly bones, which hold  $\approx 90\%$  of the body burden. Bone lead has a biological half-life ranging from 7 years to several decades.<sup>1</sup> Bone remodeling, like that which occurs in postmenopausal women, releases lead into the blood, a process described as endogenous contamination. Thus, in the Menke et al report,<sup>7</sup> the blood lead concentrations might reflect exposure levels before 1988 to 1994, which were considerably higher than at present. Second, the introduction of intensive care units, invasive coronary procedures, and thrombolysis reduced the case-fatality rate of cardiovas-

cular complications. Not accounting for nonfatal events, as in the Menke et al report,<sup>7</sup> limits the generalizability of the results. On the other hand, in contrast to some previous reports based on an the arbitrary classification of subjects according to blood lead,<sup>9</sup> Menke et al confirmed their categorical results by a continuous analysis relating mortality to blood lead.

In view of the Menke et al<sup>7</sup> report and our observations in adolescents,<sup>3</sup> blood lead concentrations as low as 0.10  $\mu\text{mol/L}$  likely represent a public health hazard. In NHANES 1999 to 2000,<sup>5</sup> 38% of US adults had a blood lead level above this threshold. This proportion is likely to be higher among the less privileged in industrialized countries and among citizens of developing countries, where environmental regulations are either less stringent, nonexistent, or not applied. In areas with historical contamination of the soil by heavy metals, house dust remains a persistent source of exposure even decades after the cessation of the industrial activity.<sup>22</sup> People living on polluted soils remain exposed to lead via fine particulate (PM10) suspended in the air at a level 17 times the normal background value (measuring station OBE01, 576 versus 17  $\text{ng/m}^3$ ; <http://www.vmm.be>, accessed on August 2, 2006). Belgium is no exception, and similar levels of environmental exposure likely persist in the United States and other European countries. Almost 5 years ago, we reported to our government that such exposure levels are intolerable.<sup>3</sup> Worldwide, regulators and the industry should no longer remain indifferent but accept their responsibility.

### Disclosures

None.

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KEY WORDS: epidemiology ■ mortality ■ hypertension ■ risk factors ■ lead