Lead and the heart: an ancient metal's contribution to modern disease

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Lead is an ancient poison; its toxicity has been recognised since at least the second century BCE, when the Greek physician Discorides observed that "lead makes the mind give way".[1] In the early 1700s, Ramazzini presented detailed descriptions of lead poisoning in painters and potters.[2] Until the modern era, lead poisoning was a rare disease confined largely to populations exposed occupationally. This rarity changed in the late 19th and early 20th centuries when lead mines opened in Australia, the western USA, and Zambia, and global production of lead rose to unprecedented levels. Lead was incorporated into a growing range of consumer products and spread far beyond the workplace. The first cases of paediatric lead poisoning were reported in 1904 among children in Australia exposed to lead in paint.[3] In 1922, lead began to be added to gasoline to enhance engine performance. This use increased sharply after 1950, spread globally, and at its peak in the early 1970s was greater than 100 000 tons per year in the USA alone.[4] Widescale environmental contamination and population exposure resulted.[5] Global lead production continues to increase today, driven principally by rising global demand for batteries.[6] Population exposure has, however, declined after the removal of lead from gasoline and paint in more than 175 countries since the 1970s.

Research into lead poisoning has shown that toxic effects arise in multiple organ systems at relatively low levels of exposure that were previously considered safe. Needleman[7] showed that lead could reduce children's cognitive function and disrupt behaviour at levels too low to produce symptoms—so-called subclinical lead poisoning. Subsequent investigation of the toxic effects of lead, using ever stronger study designs and sharper analytical methods, has shown that lead has toxic effects down to the lowest measurable levels. An especially striking and unexpected finding in these studies is that the association between lead and disease is proportionately greater at lower levels of exposure—a so-called supralinear dose-response relation.[8]

Lead has long been recognised to be a cause of hypertension and a risk factor for heart disease, stroke, and chronic kidney disease.[9] In the 2015 Global Burden of Disease study,[10] an estimated 558 000 deaths (range 293 000–883 000) were attributed to lead, all of them adult deaths, half in people older than age 70 years. In *The Lancet Public Health*, Bruce Lanphear and colleagues report findings that make an important addition to understanding lead's cardiovascular toxic effects,[11] and their work has important implications for future iterations of the Global Burden of Disease study. Their study is based on a nationally representative sample of 14 289 adults in the USA who were enrolled and examined through the Third National Health and Nutrition Examination Survey (NHANES-III) between 1988 and 1994, then followed up to Dec 31, 2011 (median 19·3 years [IQR 17·6–21·0]). The geometric mean amount of lead in blood of the population at the start of the study was 2·71 µg/dL (SE 1·31).

Lanphear and colleagues noted strong correlations between initial amounts of lead in blood and subsequent mortality in this population. Comparing mortality in the tenth percentile (level of lead in blood 1·0 µg/dL) with that in the 90th percentile (6·7 µg/dL), they found a 37% increase in all-cause mortality (hazard ratio [HR] 1·37, 95% CI 1·17–1·60), a 70% increase in cardiovascular disease mortality (1·70, 1·30–2·22), and a more than doubling of mortality from ischaemic heart disease (2·08, 1·52–2·85). A similar pattern of increased risk was seen when the analysis was restricted to people with blood lead levels below 5 µg/dL. Furthermore, the authors estimated that the fraction of all-cause mortality in the USA attributable to lead is 18%, accounting for 412 000 deaths per year.

Lanphear and colleagues examined potential confounders and effect modifiers, including age, sex, ethnic origin, urban residence, smoking status, diabetes, hypertension, serum cholesterol, alcohol intake, and household income. They noted no appreciable attenuation of their estimates by any of these factors. The effect of lead on all-cause mortality and on cardiovascular disease mortality was greater in people younger than 50 years than in older adults, and it was significantly larger for non-smokers than for smokers.

A key conclusion to be drawn from this analysis is that lead has a much greater effect on cardiovascular mortality than previously recognised. Lanphear and colleagues' calculation that lead accounts for more than 400 000 deaths annually in the USA represents a tenfold increase over the number of deaths currently ascribed to lead. The authors argue that previous estimates have produced lower numbers because those analyses assumed that lead has no effect on mortality at amounts of lead in blood below 5 µg/dL and, thus, did not consider the effects of lower exposures.

These findings have substantial implications for global assessments of cardiovascular disease mortality. Deaths from cardiovascular disease increased 12·5% worldwide from 2005 to 2015, with the sharpest increases seen in rapidly developing low-income and middle-income countries.[10] Analyses of this trend have ascribed it to population growth and ageing coupled with the global spread of behavioural and metabolic risk factors—eg, tobacco, hypertension, diet, physical inactivity, obesity, and the harmful use of alcohol. Until now, little attention has been directed to lead's possible contribution. Inattention to lead's contribution to cardiovascular mortality is part of a broader disregard of the contribution of all forms of pollution, including lead, to mortality from non-communicable diseases. This neglect persists even though pollution accounts for an estimated 16% of deaths from non-communicable diseases globally, including 22% of all cardiovascular disease deaths, 26% of deaths from ischaemic heart disease, and 25% of stroke deaths.[12] Pollution's effect on non-communicable disease mortality is especially strong in low-income and middle-income countries, where it exceeds that of any of the recognised behavioural and metabolic risk factors.[13]

The data from Lanphear and colleagues' report take on added meaning in view of these findings. The time has come to end inattention to the contribution of pollution to mortality from non-communicable diseases and to thoroughly re-examine lead's role in changing global patterns of cardiovascular disease. The information that emerges from this reassessment will increase understanding of lead's contribution to mortality from non-communicable diseases, could foster collaboration between the environmental and chronic disease research communities, guide realignment of cardiovascular disease prevention strategies, and ultimately save lives.

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I declare no competing interests.

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