REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*

Lead Poisoning

Bruce Lanphear, M.D., M.P.H., Ana Navas-Acien, M.D., Ph.D., M.P.H., and David C. Bellinger, Ph.D.

Lead poisoning, or plumbism, is an ancient disease. Dioscorides, who wrote *De Materia Medica*, the leading pharmacologic text for centuries, described the symptoms of overt lead poisoning nearly 2000 years ago.[1] Persons with overt lead poisoning report fatigue, headache, irritability, and bouts of intense colic with constipation.[1] At blood lead concentrations exceeding 800 μg per liter, acute lead poisoning can cause seizures, encephalopathy, and death.[1]

Chronic lead poisoning was recognized as a cause of atherosclerosis and "saturnine" gout more than a century ago. On autopsy, 69 of 107 patients with lead-induced gout had "sclerosis of the arterial coats, along with atheromatous changes."[2] In 1912, Dr. William Osler wrote, "Alcohol, lead, and gout play an important role in the causation of arteriosclerosis, although the precise mode of their action is not yet very clear."[3] Burton's line — a thin, blue deposit of lead sulfide along the gingival margin — is characteristic of chronic lead poisoning in adults.[4]

In 1924, after 80% of workers manufacturing tetraethyl lead at Standard Oil in New Jersey were found to have lead poisoning, some of whom died, sales of leaded gasoline were banned in New Jersey, Philadelphia, and New York City.[5,6] On May 20, 1925, Hugh Cumming, the U.S. surgeon general, convened scientists and industry representatives to determine whether it was safe to add tetraethyl lead to gasoline.[5] Yandell Henderson, a physiologist and chemical warfare expert, warned, "The use of tetraethyl lead will cause vast numbers of the population to suffer from slow lead poisoning with hardening of the arteries."[6,7] Robert Kehoe, chief medical officer of the Ethyl Corporation, argued that until tetraethyl lead from automobile emissions was shown to be toxic, government agencies should not prohibit it. Kehoe said, "The question is not whether lead is dangerous, but whether a certain concentration of lead is dangerous."[6]

Although lead has been mined for 6000 years, lead processing skyrocketed in the 20th century.[1,8] A malleable and durable metal, lead was used to prevent fuel from burning too quickly and to reduce "engine knock" in automobiles, transport drinking water, solder food cans, make paints durable and bright, and kill insects. Unfortunately, much of the lead used for these purposes ended up in people's bodies. At the peak of the U.S. lead-poisoning epidemic, hundreds of children were hospitalized with lead encephalopathy every summer, and one in four died.[9]

Humans are currently exposed to levels of lead that are much higher than natural background levels. In the 1960s, Clair Patterson, a geochemist who used lead isotopes to estimate the age of the earth at 4.5 billion years, found that atmospheric deposition of lead in glacial core samples from mining, smelting, and automobile emissions was 1000 times as high as natural background levels.[10] Patterson also found that bone lead concentrations in people in industrialized countries were 1000 times as high as those in humans who lived in preindustrial times.

From the Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada (B.L.); the Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York (A.N.-A.); and the Department of Neurology, Harvard Medical School, and Boston Children's Hospital — both in Boston (D.C.B.). Dr. Lanphear can be contacted at blanphear@sfu.ca or at the Faculty of Health Sciences, Simon Fraser University, 8888 University Dr., Burnaby, BC V5A 1S6, Canada.

N Engl J Med 2024;391:1621-31.
DOI: 10.1056/NEJMra2402527

CME

KEY POINTS

LEAD POISONING

- Lead exposure among people in the United States has declined by more than 95% since the 1970s, but the body lead burden is still 10 to 100 times as high as the lead burden in humans who lived in preindustrial times.
- Studies conducted over the past 40 years have established that chronic, low-level lead poisoning is a major risk factor for cardiovascular disease in adults and cognitive deficits in children, even at levels previously thought to be safe or innocuous.
- Lead exposure is a risk factor for chronic kidney disease and preterm births at concentrations commonly found in people today.
- In 2019, lead exposure accounted for 5.5 million deaths from cardiovascular disease and an annual loss of 765 million IQ points in children globally.
- The steep decrease in IQ and the sharp increase in the risk of death from cardiovascular disease, even at the lowest measurable blood lead concentrations, coupled with ubiquitous exposure, indicate that population strategies are critical for eliminating lead poisoning.

Lead exposure has declined by more than 95% since the 1970s, but contemporary humans still have body lead burdens that are 10 to 100 times as high as those in humans who lived in preindustrial times.[11]

With few exceptions — such as lead in aviation fuel and ammunition and lead acid batteries for motor vehicles — lead is no longer used in the United States and Europe.[12-14] Many physicians assume that lead poisoning is a problem of the past. Yet exposures linger from lead paint in older houses, deposition of leaded gasoline in soil, leaching of lead from water lines, and emissions from industrial plants and incinerators.[8,12,15] In many countries, lead is emitted by smelting, battery production, and electronic waste, and it is often found in paints, ceramics, cosmetics, and spices.[12,16] Studies have established that chronic, low-level lead poisoning is a risk factor for cardiovascular disease in adults and cognitive deficits in children, even at levels previously thought to be safe or innocuous. Our purpose in this article is to review the effects of chronic, low-level lead poisoning.

EXPOSURE, ABSORPTION, AND BODY BURDEN

Ingestion and inhalation are the primary routes of lead exposure.[1] Lead is readily absorbed by rapidly growing infants, and absorption can be enhanced in the context of iron or calcium deficiency.[15] Lead, which mimics calcium, iron, and zinc, can enter cells through calcium channels and metal transporters, such as divalent metal transporter 1 (DMT1).[17] Lead absorption is increased in persons with genetic polymorphisms that enhance iron or calcium absorption, such as those that cause hemochromatosis.[18,19]

Once absorbed, 95% of retained lead in adults is stored in the skeleton; in children, 70% is stored in the skeleton.[20] Approximately 1% of the total body lead burden is circulating in blood; 99% of lead in blood is found in red cells. The concentration of lead in whole blood — a mixture of newly absorbed lead and remobilized lead from skeletal stores — is the most widely used biomarker of exposure.[21] Factors altering bone metabolism, such as menopause and hyperthyroidism, release lead sequestered in the skeleton, which causes a spike in blood lead concentrations.[22,23]

In 1975, when lead was still being added to gasoline, Pat Barry quantified the total body burden of lead in a postmortem study of 129 Britons.[20] The average total body burden among the men was 165 mg, the weight of a paper clip. The body burden among men with lead poisoning was 566 mg, only three times as high as the average burden in the entire sample of men. By contrast, the average total body burden among the women was 104 mg. In men and women, the lead concentrations in soft tissues were highest in the aorta, but atheromas in men had even higher concentrations.[20]

Some persons are at increased risk for lead poisoning as compared with the general population. The mouthing behaviors of infants and toddlers put them at greater risk for lead ingestion, and they absorb lead more readily than older children and adults.[15] Toddlers who live in poorly maintained housing built before 1960 are at risk

for lead poisoning from ingestion of paint chips and lead-contaminated house dust.[12,15,24] Persons who drink tap water from lead service lines or live near airports or other sites that emit lead pollution are also at increased risk for low-level lead poisoning.[12,14] In the United States, airborne lead concentrations are markedly higher in racially segregated communities than in integrated communities.[25] Workers in smelting, battery recycling, and construction, as well as persons who use firearms or have retained bullet fragments in their bodies, are at increased risk for lead poisoning.[26]

Lead was the first toxic chemical measured in the National Health and Nutrition Examination Survey (NHANES). The figure showing blood lead concentrations plummeting during the initial phaseout of leaded gasoline, from 150 μg per liter in 1976 to 90 μg per liter in 1980, is iconic.[27,28] The amount of lead in blood that is considered to signify potential harm has been revised downward several times (Fig. 1). In 2012, the Centers for Disease Control and Prevention (CDC) declared that no safe level of lead in children's blood had been identified. The CDC lowered the blood lead level considered elevated in children — which is often used to indicate when action should be taken to mitigate lead exposure — from 100 μg per liter to 50 μg per liter in 2012 and to 35 μg per liter in 2021.[30] These reductions, which influenced our decision to use micrograms per liter as the units of measurement for blood lead levels in this article instead of the more common micrograms per deciliter, reflect extensive evidence of lead toxicity at ever lower levels.[15]

ppb, or parts per billion

DEATH, DISEASE, AND DISABILITY

In a 1988 report to Congress, Paul Mushak and Annemarie F. Crocetti wrote, "Lead is potentially toxic wherever it is found, and it is found everywhere."[31] The ability to measure lead in blood, teeth, and the skeleton[21] has revealed an array of medical problems linked with chronic, low-level lead poisoning at lead levels typically

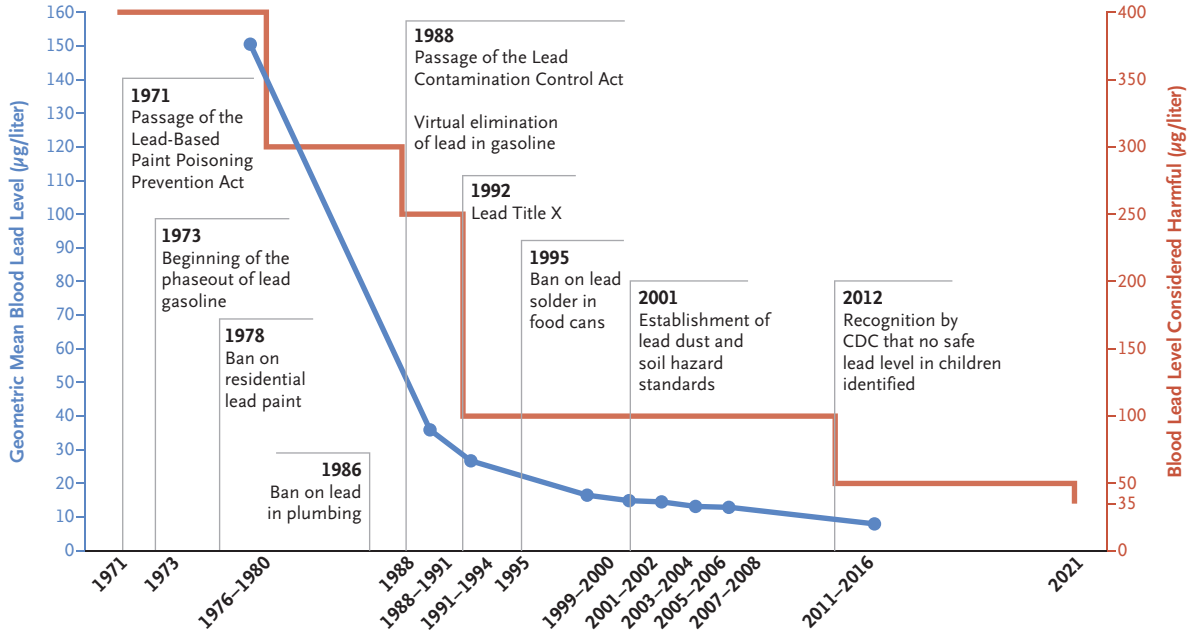

Figure 1. Mean Blood Lead Levels in U.S. Children between 1 and 5 Years of Age, Blood Lead Levels Considered Elevated in Children, and Regulations Reducing Lead Exposure.

Shown are the decline in mean blood lead levels in children from 1976 to 2008, successive reductions in blood lead levels that the Centers for Disease Control and Prevention (CDC) considered to be harmful in children, and regulations on lead contamination that were imposed between 1971 and 2001. In 2012, the CDC recognized that no safe level of lead had been identified in children. Adapted from Egan et al.[24] and Brown and Margolis.[29]

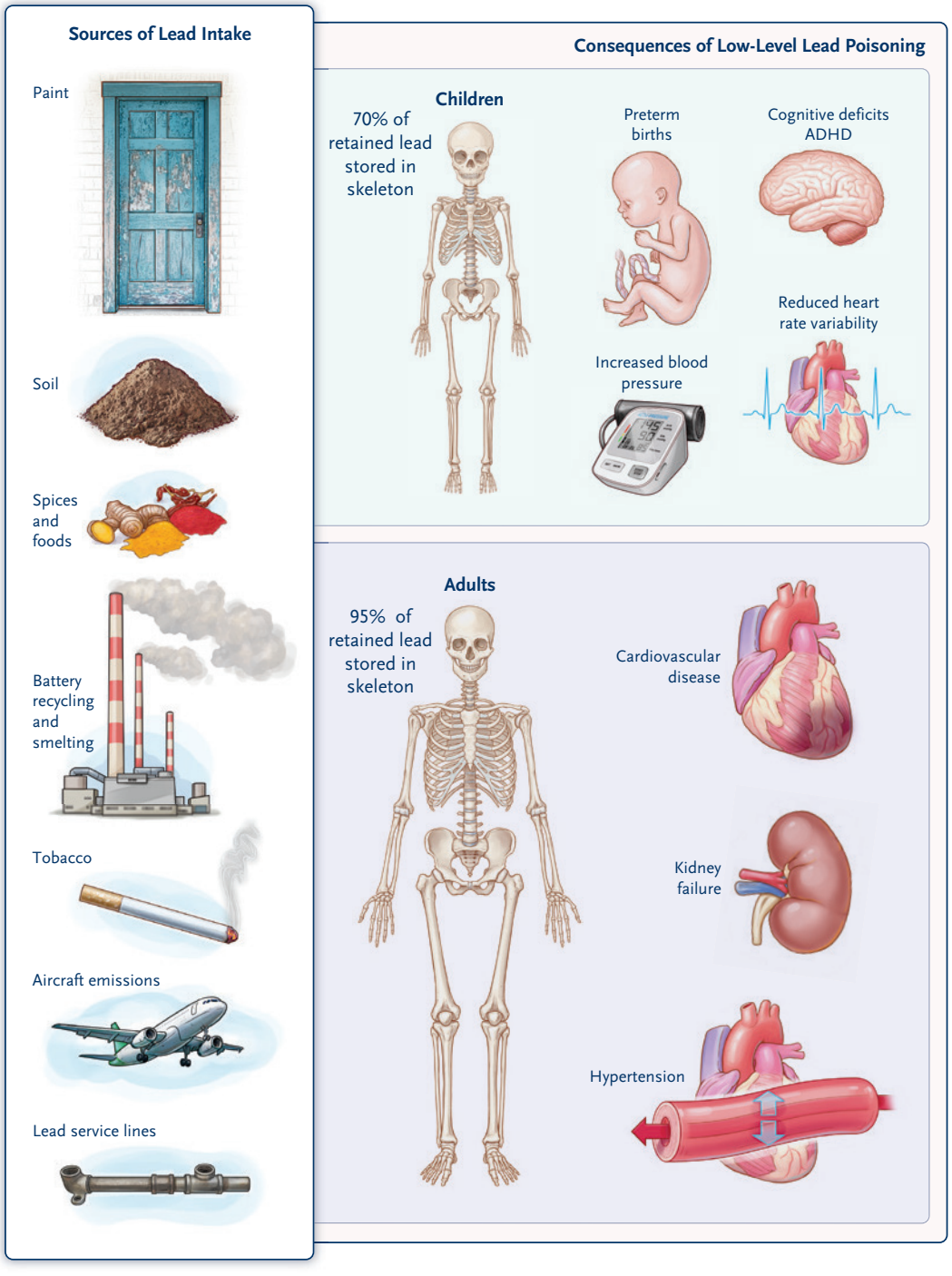

Figure 2. Sources of Lead Exposure and Health Effects of Lead Poisoning.

Many historical and current sources of lead continue to contribute to lead poisoning today. Most of the lead in human bodies is stored in bones, and long-term exposure increases the risk of preterm birth, learning and behavioral problems, hypertension, kidney failure, and coronary heart disease.

found in humans. Low-level lead poisoning is a risk factor for preterm birth and for cognitive deficits and attention deficit–hyperactivity disorder (ADHD), as well as increased blood pressure and reduced heart rate variability, in children.[32-34] In adults, low-level lead poisoning is a risk factor for chronic kidney failure, hypertension, and cardiovascular disease[35-37] (Fig. 2).

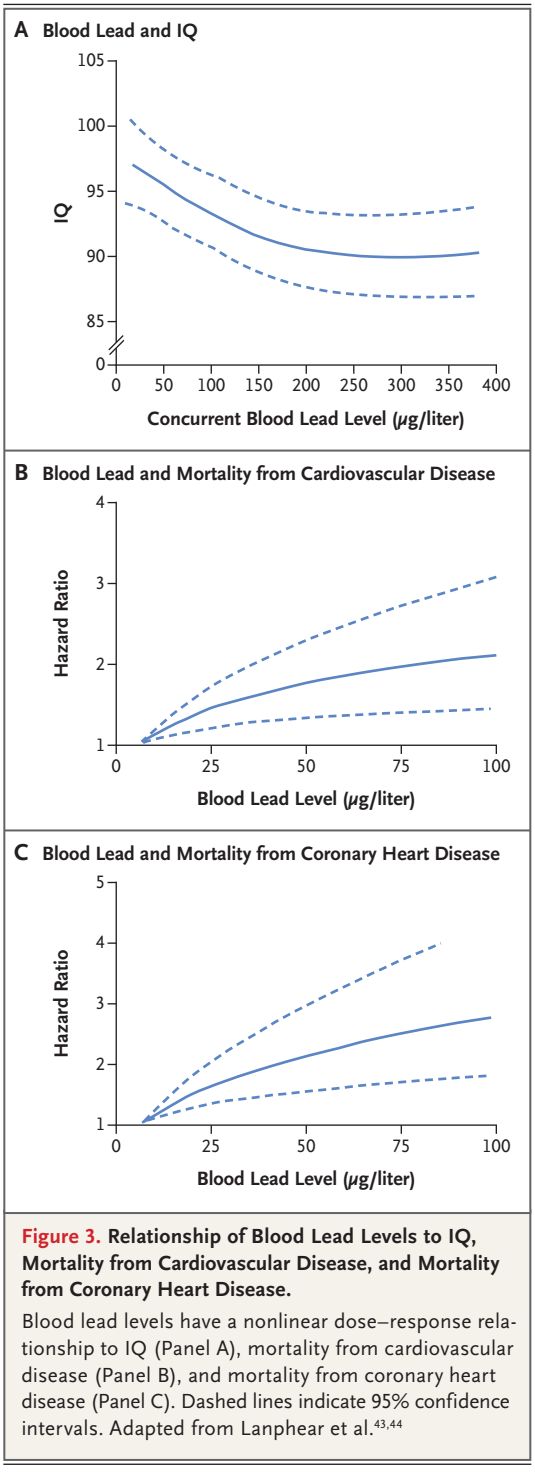

Figure 3. Relationship of Blood Lead Levels to IQ, Mortality from Cardiovascular Disease, and Mortality from Coronary Heart Disease.

Blood lead levels have a nonlinear dose–response relationship to IQ (Panel A), mortality from cardiovascular disease (Panel B), and mortality from coronary heart disease (Panel C). Dashed lines indicate 95% confidence intervals. Adapted from Lanphear et al.[43,44]

GROWTH AND NEURODEVELOPMENT

Lead exposure is a risk factor for preterm birth at concentrations commonly found in pregnant women.[38-40] In a prospective Canadian birth cohort, an increase of 10 μg per liter in the maternal blood lead level was associated with a 70% increase in the risk of spontaneous preterm birth. For women with a serum vitamin D level of less than 50 nmol per liter and an increase of 10 μg per liter in the blood lead level, the risk of spontaneous preterm birth was increased by a factor of 3.[40]

In an early, landmark study involving children without clinical signs of lead poisoning, Needleman et al. found that children with higher dentin lead levels were more likely to have neuropsychological deficits and to be rated unfavorably by their teachers with respect to distractibility, organizational ability, impulsivity, and other behavioral characteristics than children with lower dentin lead levels.[32] Ten years later, children in the group with higher dentin lead levels were 5.8 times as likely to have a reading disability and 7.4 times as likely to drop out of school as children in the group with lower levels.[41]

Lead-associated cognitive deficits in children are proportionately larger at lower lead levels.[42] In a pooled analysis of seven prospective cohorts, an increase in blood lead levels from 10 μg per liter to 300 μg per liter was associated with a nine-point IQ deficit in children, but the largest incremental deficit (six IQ points) occurred with the first increase of 100 μg per liter (Fig. 3A).[43] The dose–response curve was similar for the cognitive deficits associated with lead measured in bone and plasma.[45,46]

Lead exposure is a risk factor for behavioral conditions, such as ADHD.[34,47] In a nationally representative study of 8- to 15-year-old children, those with blood lead levels exceeding 13 μg per liter were twice as likely to have ADHD as children in the lowest tertile of blood lead levels.[34] Approximately 1 in 5 cases of ADHD

among these children was attributed to lead exposure.

Childhood lead exposure is a risk factor for antisocial behaviors, including those associated with conduct disorder, delinquent behavior, and criminal behavior.[48-50] In a meta-analysis of 16 studies, increased blood lead concentrations were consistently associated with conduct disorder in children.[50] In two prospective cohort studies, higher childhood blood lead or dentin lead levels were associated with higher rates of delinquent behavior and arrests among young adults.[48,49]

Higher childhood lead exposure is associated with reductions in brain volume, which may result from reduced neuronal size or dendritic arborization, and the reduced volume persists into adulthood.[51,52] In a study involving older adults, higher blood or bone lead levels were prospectively associated with accelerated cognitive decline, particularly in persons with *APOE4* alleles.[53,54] Lead exposure early in life may be a risk factor for late-onset Alzheimer's disease, but the evidence is inconclusive.[55-57]

KIDNEY DISEASE

Lead exposure is a risk factor for chronic kidney disease.[35,58,59] Nephrotoxic effects of lead are characterized by intranuclear inclusion bodies in proximal tubule cells, tubulointerstitial fibrosis, and chronic kidney failure.[60] Among participants in the NHANES between 1999 and 2006, adults with a blood lead level exceeding 24 μg per liter were 56% more likely to have a reduced glomerular filtration rate (<60 ml per minute per 1.73 m^2 of body-surface area) than persons with a blood lead level below 11 μg per liter.[61] In a prospective cohort study, the risk of chronic kidney disease was 49% higher among persons with blood lead levels exceeding 33 μg per liter than among those with lower blood lead levels.[59]

CARDIOVASCULAR DISEASE

Lead induces cellular alterations that are characteristic of hypertension and atherosclerosis. In laboratory studies, chronic, low-level lead exposure causes sustained hypertension by increasing oxidative stress, reducing levels of biologically active nitric oxide, and inducing vasoconstriction through activation of protein kinase C.[62] Lead exposure causes atherosclerosis by inactivating nitric oxide, increasing hydrogen peroxide formation, inhibiting endothelial repair, impairing angiogenesis, and promoting thrombosis[62] (Fig. 2).

An in vitro study showed that incubating endothelial cells for 72 hours in lead — at concentrations ranging from 0.14 to 8.2 μg per liter — caused membrane damage (small tears or perforations observed on scanning electron microscopy).[63] This study provided ultrastructural evidence that newly absorbed lead or recirculating lead that has been sequestered in the skeleton may cause endothelial dysfunction, the earliest detectable change in the natural history of an atherosclerotic lesion.[64] In a cross-sectional analysis involving a representative sample of adults with a mean blood lead level of 27 μg per liter and no history of cardiovascular disease, an increase of 10 μg per liter in the blood lead level was associated with an odds ratio of 1.24 (95% confidence interval, 1.01 to 1.53) for severe coronary-artery calcification (i.e., an Agatston score of >400, on a scale starting at zero, indicating no calcification, with higher numbers indicating more extensive calcification).[65]

Lead exposure is a leading risk factor for death from cardiovascular disease. Of 14,000 U.S. adults enrolled in the NHANES between 1988 and 1994 and followed for 19 years, 4422 died; 1 in 5 died from coronary heart disease.[44] After adjustment for other risk factors, an increase from the 10th to the 90th percentile of blood lead levels was associated with twice the risk of death from coronary heart disease. The risk of death from cardiovascular disease and coronary heart disease increased sharply at levels below 50 μg per liter, with no apparent threshold (Figs. 3B and 3C). The study investigators attributed 250,000 premature deaths from cardiovascular disease each year to chronic, low-level lead poisoning; 185,000 of those deaths were from coronary heart disease.[44]

Lead exposure probably contributed to the increase and subsequent decline in coronary heart disease mortality over the past century. In the United States, mortality from coronary heart disease increased sharply during the first half of the 20th century, peaked in 1968, and then steadily decreased; today, it is 70% below the peak in 1968.[66] Lead exposure from leaded gasoline declined in parallel with the decline in coronary heart disease[8,66] (Fig. 4). Of the total decrease in the rate of coronary heart disease

among participants in the NHANES during the 1988–1994 and 1999–2004 periods, who were followed for up to 8 years, 25% was explained by lower blood lead levels.[70]

The incidence of hypertension decreased precipitously in the United States during the initial phaseout of leaded gasoline. From 1976 to 1980, 32% of American adults had hypertension; by 1988 to 1992, the percentage was only 20%.[71] The usual factors — smoking, antihypertensive medicines, obesity, or even the larger size of the cuff used to measure blood pressure in persons with obesity — did not explain the decline.[72] However, the median blood lead level among Americans decreased from 130 μg per liter in 1976 to 30 μg per liter in 1994, which suggests that decreases in lead exposure contributed to the decline.[71] In the Strong Heart Family Study, involving a cohort of American Indians, a decline in the blood lead level of 9 μg per liter or more was associated with an adjusted mean decline of 7.1 mm Hg in systolic blood pressure.[73]

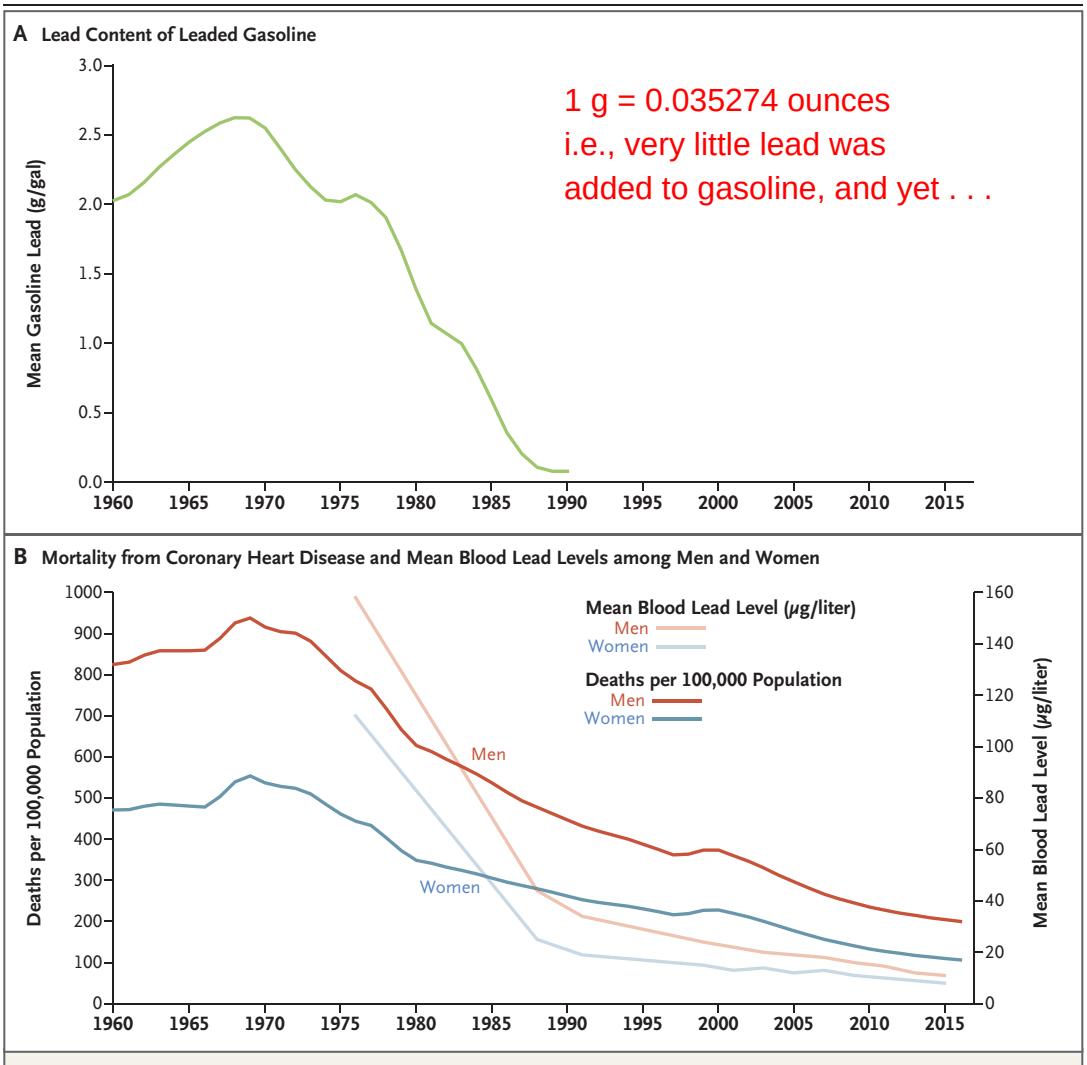

Figure 4. Lead Content in Leaded Gasoline (1960–1990), Mean Blood Lead Levels in U.S. Adults (1976–2015), and Mortality from Coronary Heart Disease among Men and Women (1960–2016).

Panel A shows the average lead content in gasoline in the United States from 1960 through 1990. Panel B shows geometric mean blood lead levels in U.S. adults enrolled in the National Health and Nutrition Examination Survey (NHANES) from 1976 to 2016 and age-standardized mortality from coronary heart disease from 1960 through 2016 among men and women over the age of 25 years. Blood lead levels were stratified and weighted according to survey year and adjusted for age. Adapted from Pirkle et al.,[67] Muntner et al.,[68] and Wang et al.[69]

Many questions about the contribution of lead exposure to cardiovascular disease remain unanswered. The duration of exposure that is necessary to cause hypertension or cardiovascular disease is not well understood, but long-term, cumulative lead exposure measured in bone appears to be a stronger predictor than short-term exposure measured in blood.[74] Still, reducing lead exposure appears to result in reductions in blood pressure and the risk of death from cardiovascular causes within 1 to 2 years.[73,75] One year after a ban on leaded fuel in NASCAR races, mortality from coronary heart disease declined significantly in communities near racetracks as compared with those in bordering communities.[75] Finally, studies in which long-term cardiovascular effects in populations with chronic exposure to lead levels below 10 μg per liter are needed.

Reductions in exposure to other toxic chemicals have contributed to the decline in coronary heart disease. From 1980 to 2000, reductions of airborne particles in 51 metropolitan areas during the phaseout of leaded gasoline led to a 15% increase in life expectancy.[76] Smoking also became less common. In 1970, approximately 37% of American adults smoked cigarettes; by 1990, only 25% of Americans smoked.[77] Smokers have markedly higher blood lead levels than nonsmokers.[78] Disentangling the historical and current contributions of air pollution, tobacco smoke, and lead to coronary heart disease will be challenging.

Coronary heart disease is the primary cause of death worldwide.[79] More than a dozen studies have indicated that lead exposure is a leading, if overlooked, risk factor for death from coronary heart disease.[37] In a meta-analysis, Chowdhury et al. found that increased blood lead levels were a significant risk factor for coronary heart disease.[80] In eight prospective studies (involving a total of 91,779 participants), the risk of nonfatal myocardial infarction, bypass surgery, or death from coronary heart disease was 85% higher among persons with blood lead concentrations in the highest tertile than among those in the lowest tertile.[80] In 2013, the Environmental Protection Agency concluded that lead exposure is a causal risk factor for coronary heart disease; 10 years later, the American Heart Association concurred.[81,82]

ESTIMATED GLOBAL BURDEN OF DISEASE

The global burden of disease from lead exposure is staggering. In contrast to the decline in the rate of coronary heart disease in industrialized countries, the rate has increased over the past 30 years in industrializing countries.[79] One in three children worldwide — more than 600 million children — have lead poisoning, defined as a blood lead level exceeding 50 μg per liter; 90% of children with lead poisoning live in industrializing countries.[83]

In 2019, a total of 5.5 million deaths from cardiovascular disease were attributed to lead exposure.[84] Every year, lead exposure accounts for a loss of 765 million IQ points in children and 30% of the global burden of idiopathic intellectual disability, defined as an IQ of less than 70.[84,85] In 2019, the economic cost of reductions in intellectual ability and increases in mortality from cardiovascular causes associated with lead poisoning was $6 trillion, equivalent to 7% of the global gross domestic product.[84] The costs were based on the value of a statistical life (i.e., the economic benefit of avoiding a fatal outcome) with regard to mortality from cardiovascular causes and on future income loss with regard to reduced cognitive ability. Industrialized countries account for more than 90% of deaths from cardiovascular causes and intellectual disability attributed to lead exposure.[84]

SCREENING, SURVEILLANCE, AND TREATMENT

Screening high-risk children and adults for lead poisoning is recommended.[15,26] Screening is indicated for persons with suspected exposure (e.g., toddlers living in housing built before 1960, persons exposed to lead-glazed pottery, or persons who have ingested Ayurvedic medicines or other herbal supplements), those with unexplained symptoms that are consistent with lead poisoning (e.g., abdominal pain, memory impairment, and high blood pressure), and workers in certain industries (e.g., smelters, construction workers, and military personnel).[26] Biomonitoring surveys, such as the NHANES, are critical for identifying risk factors and monitoring trends in lead exposure.

Lead chelation is effective in reducing the body lead burden, but findings regarding the effects on health outcomes are inconsistent.[86-88] In a randomized, controlled trial involving 1708 participants, a weekly infusion of EDTA, a chelating agent that binds to lead in blood and enhances excretion of lead, resulted in an 18% lower risk of cardiovascular events than placebo.[87] In a more recent replication trial (involving 956 participants), the corresponding, nonsignificant reduction in risk was 7%.[86] In another randomized, controlled trial, involving 202 patients with chronic renal insufficiency, a weekly infusion of EDTA led to a significant 12% increase from baseline in the glomerular filtration rate in the EDTA group, as compared with a 3.6% decrease from baseline in the placebo group.[88] In a randomized, controlled trial involving 780 children with blood lead levels between 200 and 440 μg per liter, treatment with succimer (2,3-dimercaptosuccinic acid), an oral chelating agent, did not improve cognitive scores or behavioral profiles.[89] The inconsistent findings regarding the efficacy of chelation indicate that primary prevention is critical.

PREVENTION OF LEAD POISONING

The steep decrease in IQ and the sharp increase in the risk of death from cardiovascular disease even at the lowest measurable blood lead levels, coupled with ubiquitous exposure, indicate that government-funded population strategies are critical for eliminating lead poisoning. Surveillance to identify highly exposed populations and targeted screening for persons with high levels of exposure are important, but the solution to protecting people from lead poisoning is to identify and eliminate environmental sources of lead, wherever they are found (Fig. 1). In the United States, that means eliminating lead acid batteries and secondary lead smelters, replacing lead service lines, banning leaded aviation fuel, reducing lead in foods, abating lead paint in older housing, and further reducing lead-contaminated soil and other legacy sources. Geoffrey Rose, a cardiovascular epidemiologist who died before lead was recognized as a risk factor for coronary heart disease, anticipated the cure: "Where exposure is collective and unavoidable, only collectively enforced control can be effective."[90]

The lead pandemic — the largest mass poisoning in history — is a humbling reminder that widespread exposure to an ancient metal, rarely found in high concentrations on the surface of the earth before human activity, has resulted in a staggering number of deaths and disabilities. The failure to prevent this century-long pandemic, despite early warnings, exposes an anemic regulatory system ill-suited to protect the public from industry-orchestrated campaigns and regulatory delays.[5,6] In 1925, Yandell Henderson warned, "This is probably the greatest single question in the field of public health that has ever faced the American public. It is the question whether scientific experts are to be consulted, and the action of Government guided by their advice; or whether, on the contrary, commercial interests are to be allowed to subordinate every other consideration to that of profit."[6]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Christopher Keys of Mountain Data Group for compiling the data on the production of leaded gasoline and mortality from coronary heart disease; and Filippo Ravalli, M.P.H., at Columbia University for providing data from the National Health and Nutrition Examination Survey (1976 to 2016) to plot geometric mean blood lead levels in the U.S. population.

REFERENCES

1. Hernberg S. Lead poisoning in a historical perspective. Am J Ind Med 2000;38:244-54.
2. Lorimer G. Saturnine gout, and its distinguishing marks. Br Med J 1886;2:163.
3. Osler W. Principles and practice of medicine. 8th ed. New York: D. Appleton, 1912:843.
4. Helmich F, Lock G. Burton's line from chronic lead intoxication. N Engl J Med 2018;379(19):e35.
5. Rosner D, Markowitz G. A 'gift of God'? The public health controversy over leaded gasoline during the 1920s. Am J Public Health 1985;75:344-52.
6. Kovarik W. Ethyl-leaded gasoline: how a classic occupational disease became an international public health disaster. Int J Occup Environ Health 2005;11:384-97.
7. Sees deadly gas a peril in streets. New York Times. April 22, 1925:25.
8. Mielke HW, Gonzales CR, Powell ET, Egendorf SP. Lead in air, soil, and blood: Pb poisoning in a changing world. Int J Environ Res Public Health 2022;19:9500.
9. Christian JR, Celewycz BS, Andelman SL. A three-year study of lead poisoning in Chicago. I. Epidemiology. Am J Public Health Nations Health 1964;54:1241-5.
10. Patterson C, Ericson J, Manea-Krichten M, Shirahata H. Natural skeletal levels of lead in Homo sapiens sapiens uncontaminated by technological lead. Sci Total Environ 1991;107:205-36.

11. Flegal AR, Smith DR. Lead levels in preindustrial humans. N Engl J Med 1992; 326:1293-4.

12. Levin R, Brown MJ, Kashtock ME, et al. Lead exposures in U.S. Children, 2008: implications for prevention. Environ Health Perspect 2008;116:1285-93.

13. Bellinger DC, Burger J, Cade TJ, et al. Health risks from lead-based ammunition in the environment. Environ Health Perspect 2013;121:A178-A179.

14. Zahran S, Keyes C, Lanphear B. Leaded aviation gasoline exposure risk and child blood lead levels. PNAS Nexus 2023; 2:pgac285.

15. Council on Environmental Health. Prevention of childhood lead toxicity. Pediatrics 2016;138(1):e20161493.

16. Ericson B, Hu H, Nash E, Ferraro G, Sinitsky J, Taylor MP. Blood lead levels in low-income and middle-income countries: a systematic review. Lancet Planet Health 2021;5(3):e145-e153.

17. Kayaaltı Z, Akyüzlü DK, Söylemezoğlu T. Evaluation of the effect of divalent metal transporter 1 gene polymorphism on blood iron, lead and cadmium levels. Environ Res 2015;137:8-13.

18. Schwartz BS, Lee BK, Lee GS, et al. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the vitamin D receptor and [delta]-aminolevulinic acid dehydratase genes. Environ Health Perspect 2000;108:949-54.

19. Wright RO, Silverman EK, Schwartz J, et al. Association between hemochromatosis genotype and lead exposure among elderly men: the Normative Aging Study. Environ Health Perspect 2004;112:746-50.

20. Barry PSI. A comparison of concentrations of lead in human tissues. Br J Ind Med 1975;32:119-39.

21. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect 2005;113:1669-74.

22. Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ Res 1988;47:79-94.

23. Cagin CR, Diloy-Puray M, Westerman MP. Bullets, lead poisoning and thyrotoxicosis. Ann Intern Med 1978;89:509-11.

24. Egan KB, Cornwell CR, Courtney JG, Ettinger AS. Blood lead levels in U.S. children ages 1-11 years, 1976-2016. Environ Health Perspect 2021;129:37003.

25. Kodros JK, Bell ML, Dominici F, et al. Unequal airborne exposure to toxic metals associated with race, ethnicity, and segregation in the USA. Nat Commun 2022;13:6329.

26. Shaffer RM, Gilbert SG. Reducing occupational lead exposures: strengthened standards for a healthy workforce. Neurotoxicology 2018;69:181-6.

27. Air quality criteria for lead (final report). Washington, DC: Environmental Protection Agency, 1986. (Publication no. EPA-600/8-83/028AF.)

28. Bridbord K, Hanson D. A personal perspective on the initial federal health-based regulation to remove lead from gasoline. Environ Health Perspect 2009; 117:1195-201.

29. Brown MJ, Margolis S. Lead in drinking water and human blood lead levels in the United States. MMWR Suppl 2012;61: 1-9.

30. Ruckart PZ, Jones RL, Courtney JG, et al. Update of the blood lead reference value — United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1509-12.

31. Agency for Toxic Substances and Disease Registry. The nature and extent of lead poisoning in children in the United States: a report to Congress. Atlanta: Centers for Disease Control and Prevention, July 1988.

32. Needleman HL, Gunnoe C, Leviton A, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 1979;300:689-95.

33. Clay K, Hollingsworth A, Severnini ER. The impact of lead exposure on fertility, infant mortality, and infant birth outcomes. Cambridge, MA: National Bureau of Economic Research, June 2023 (http://www.nber.org/papers/w31379).

34. Froehlich TE, Lanphear BP, Auinger P, et al. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 2009;124(6): e1054-e1063.

35. Batuman V, Landy E, Maesaka JK, Wedeen RP. Contribution of lead to hypertension with renal impairment. N Engl J Med 1983;309:17-21.

36. Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epidemiol 1985;121:246-58.

37. Navas-Acien A. Lead and cardiovascular mortality: evidence supports lead as an independent cardiovascular risk factor. NCEE working paper 21-03. Washington, DC: National Center for Environmental Economics, May 2021 (https://www.epa.gov/environmental-economics/lead-and-cardiovascular-mortality-evidence-supports-lead-independent).

38. Taylor CM, Golding J, Emond AM. Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: a prospective birth cohort study. BJOG 2015;122:322-8.

39. Bui LTM, Shadbegian R, Marquez A, Klemick H, Guignet D. Does short-term, airborne lead exposure during pregnancy affect birth outcomes? Quasi-experimental evidence from NASCAR's deleading policy. Environ Int 2022;166:107354.

40. Fisher M, Marro L, Arbuckle TE, et al. Association between toxic metals, vitamin D and preterm birth in the Maternal-Infant Research on Environmental Chemicals study. Paediatr Perinat Epidemiol 2023;37:447-57.

41. Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood: an 11-year follow-up report. N Engl J Med 1990;322:83-8.

42. Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med 2003; 348:1517-26.

43. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 2005;113:894-9.

44. Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health 2018;3(4):e177-e184.

45. Wasserman GA, Factor-Litvak P, Liu X, et al. The relationship between blood lead, bone lead and child intelligence. Child Neuropsychol 2003;9:22-34.

46. Hu H, Téllez-Rojo MM, Bellinger D, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect 2006;114:1730-5.

47. Nigg JT, Knottnerus GM, Martel MM, et al. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. Biol Psychiatry 2008;63:325-31.

48. Wright JP, Dietrich KN, Ris MD, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. PLoS Med 2008;5(5):e101.

49. Fergusson DM, Boden JM, Horwood LJ. Dentine lead levels in childhood and criminal behaviour in late adolescence and early adulthood. J Epidemiol Community Health 2008;62:1045-50.

50. Marcus DK, Fulton JJ, Clarke EJ. Lead and conduct problems: a meta-analysis. J Clin Child Adolesc Psychol 2010;39:234-41.

51. Cecil KM, Brubaker CJ, Adler CM, et al. Decreased brain volume in adults with childhood lead exposure. PLoS Med 2008; 5(5):e112.

52. Reuben A, Caspi A, Belsky DW, et al. Association of childhood blood lead levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood. JAMA 2017;317:1244-51.

53. Schwartz BS, Stewart WF, Bolla KI, et al. Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology 2000;55:1144-50.

54. Prada D, Colicino E, Power MC, et al. APOE ε4 allele modifies the association of lead exposure with age-related cognitive decline in older individuals. Environ Res 2016;151:101-5.
55. Basha MR, Wei W, Bakheet SA, et al. The fetal basis of amyloidogenesis: exposure to lead and latent overexpression of amyloid precursor protein and β-amyloid in the aging brain. J Neurosci 2005;25:823-9.
56. Lee M, Lee H, Warren JR, Herd P. Effect of childhood proximity to lead mining on late life cognition. SSM Popul Health 2022;17:101037.
57. Wu J, Basha MR, Brock B, et al. Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. J Neurosci 2008;28:3-9.
58. Muntner P, He J, Vupputuri S, Coresh J, Batuman V. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. Kidney Int 2003;63:1044-50.
59. Harari F, Sallsten G, Christensson A, et al. Blood lead levels and decreased kidney function in a population-based cohort. Am J Kidney Dis 2018;72:381-9.
60. Bennett WM. Lead nephropathy. Kidney Int 1985;28:212-20.
61. Navas-Acien A, Tellez-Plaza M, Guallar E, et al. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. Am J Epidemiol 2009;170:1156-64.
62. Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. Am J Physiol Heart Circ Physiol 2008;295:H5454-H465.
63. van Strijp L, Van Rooy M, Serem J, Basson C, Oberholzer H. Investigating the effect of the heavy metals cadmium, chromium and lead, alone and in combination on an endothelial cell line. Ultrastruct Pathol 2023;47:205-18.
64. Gimbrone MA Jr, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118:620-36.
65. Park E, Kim S, Cho S, et al. The association between blood lead levels and coronary artery calcium score determined by using coronary computed tomography angiography. J Korean Med Sci 2023;38(26):e203.
66. Ritchey MD, Wall HK, George MG, Wright JS. US trends in premature heart disease mortality over the past 50 years: where do we go from here? Trends Cardiovasc Med 2020;30:364-74.
67. Pirkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). JAMA 1994;272:284-91.
68. Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. Arch Intern Med 2005;165:2155-61.
69. Wang T, Zhou YP, Sun Y, Zheng YX. Trends in Blood Lead Levels in the U.S. From 1999 to 2016. Am J Prev Med 2021;60(4):e179-e187.
70. Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, et al. Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004. Int J Epidemiol 2017;46:1903-12.
71. Lanphear BP, Hornung RW, Auinger P, Allen R. Environmental exposure to lead: old myths never die. Lancet Public Health 2018;3(8):e363.
72. Wright JD, Stevens J, Poole C, Flegal KM, Suchindran C. The impact of differences in methodology and population characteristics on the prevalence of hypertension in US adults in 1976-1980 and 1999-2002. Am J Hypertens 2010;23:620-6.
73. Lieberman-Cribbin W, Li Z, Lewin M, et al. The contribution of declines in blood lead levels to reductions in blood pressure levels: longitudinal evidence in the Strong Heart Family Study. J Am Heart Assoc 2024;13(2):e031256.
74. Weisskopf MG, Jain N, Nie H, et al. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. Circulation 2009;120:1056-64.
75. Hollingsworth A, Rudik I. The effect of leaded gasoline on elderly mortality: evidence from regulatory exemptions. Am Econ J 2021;13:345-73 (https://www.aeaweb.org/articles?id=10.1257/pol.20190654).
76. Pope CA III, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 2009;360:376-86.
77. Giovino GA, Schooley MW, Zhu BP, et al. Surveillance for selected tobacco-use behaviors — United States, 1900–1994. MMWR CDC Surveill Summ 1994;43:1-43.
78. Mannino DM, Homa DM, Matte T, Hernandez-Avila M. Active and passive smoking and blood lead levels in U.S. adults: data from the Third National Health and Nutrition Examination Survey. Nicotine Tob Res 2005;7:557-64.
79. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76:2982-3021.
80. Chowdhury R, Ramond A, O'Keeffe LM, et al. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2018;362:k3310.
81. Integrated science assessment for lead. Final report. Washington, DC: Environmental Protection Agency, June 2013 (http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=518908).
82. Lamas GA, Bhatnagar A, Jones MR, et al. Contaminant metals as cardiovascular risk factors: a scientific statement from the American Heart Association. J Am Heart Assoc 2023;12(13):e029852.
83. Rees N, Fuller R. The toxic truth: children's exposure to lead pollution undermines a generation of future potential. New York: United Nations Children's Fund, July 2020 (https://www.unicef.org/reports/toxic-truth-childrens-exposure-to-lead-pollution-2020).
84. Larsen B, Sánchez-Triana E. Global health burden and cost of lead exposure in children and adults: a health impact and economic modelling analysis. Lancet Planet Health 2023;7(10):e831-e840.
85. World Health Organization. The public health impact of chemicals: knowns and unknowns. May 23, 2016 (https://www.who.int/publications/i/item/WHO-FWC-PHE-EPE-16-01).
86. Lamas GA, Anstrom KJ, Navas-Acien A, et al. Edetate disodium-based chelation for patients with a previous myocardial infarction and diabetes: TACT2 randomized clinical trial. JAMA 2024;332:794-803.
87. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. JAMA 2013;309:1241-50.
88. Lin J-L, Lin-Tan D-T, Hsu K-H, Yu CC. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. N Engl J Med 2003;348:277-86.
89. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med 2001;344:1421-6.
90. Rose G. Khaw K-T. Marmot M. Rose's strategy of preventive medicine. New York: Oxford University Press, 2008.