

REVIEW ARTICLE

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Lead Poisoning

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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.

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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 in-

creased 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

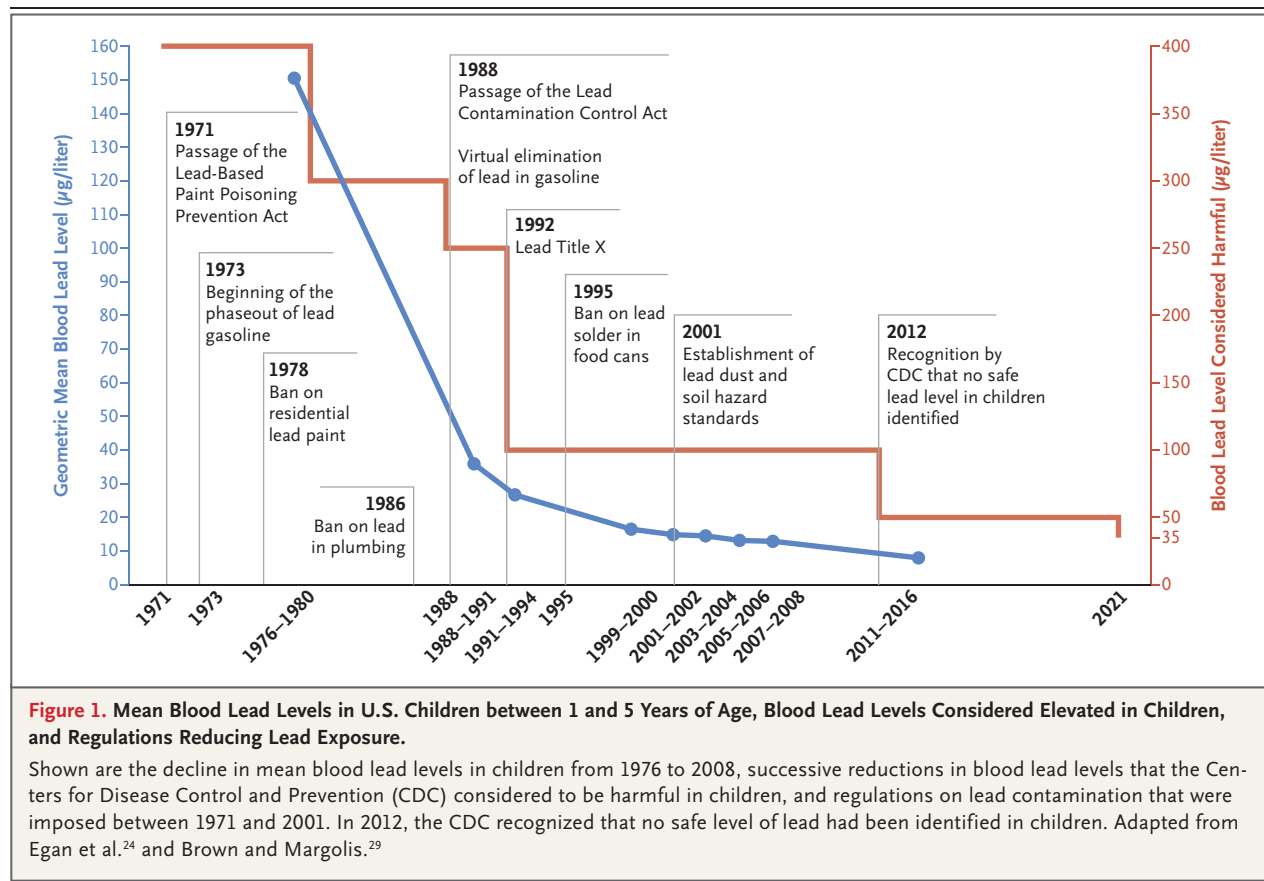
for lead poisoning from ingestion of paint chips and lead-contaminated house dust.^{12,15,24} Persons who drink tap water from lead service lines or live near airports or other sites that emit lead pollution are also at increased risk for low-level lead poisoning.^{12,14} In the United States, airborne 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

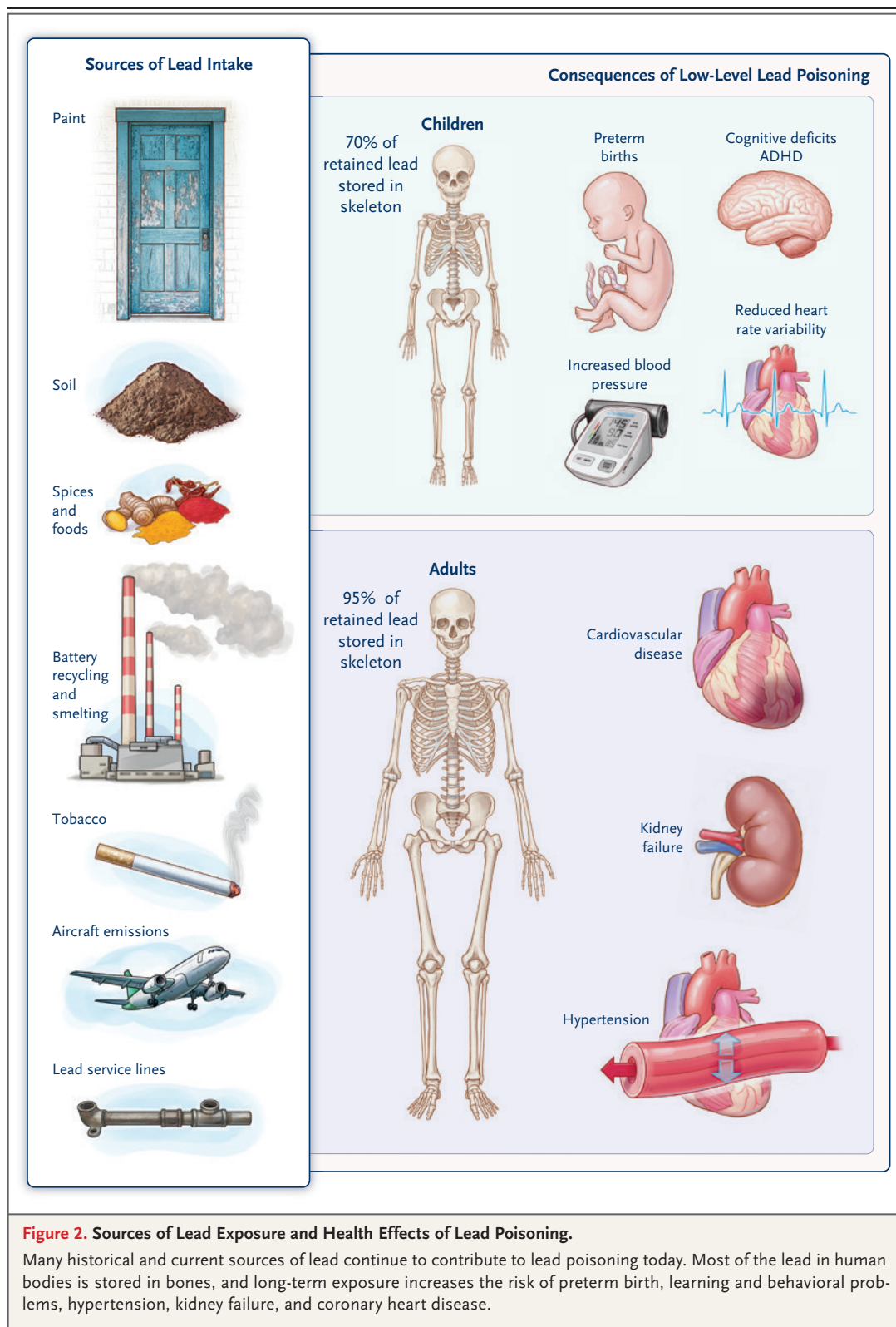
Lead was the first toxic chemical measured in the National Health and Nutrition Examination Survey (NHANES). The figure showing blood lead concentrations plummeting during the initial phaseout of leaded gasoline, from 150 μg per liter in 1976 to 90 μg per liter in 1980, is iconic.^{27,28} The amount 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

DEATH, DISEASE, AND DISABILITY

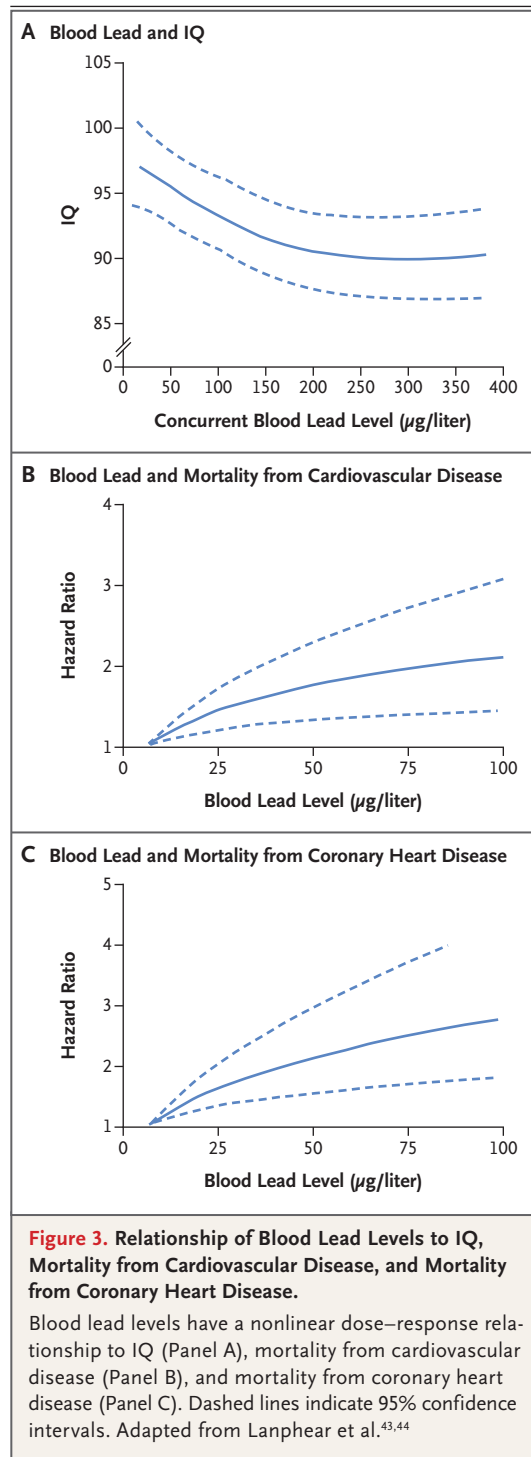
In a 1988 report to Congress, Paul Mushak and Annemarie F. Crocetti wrote, “Lead is potentially toxic wherever it is found, and it is found everywhere.”³¹ The ability to measure lead in blood, teeth, and the skeleton²¹ has revealed an array of medical problems linked with chronic, low-level lead poisoning at lead levels typically





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).



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 m² 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 thrombosis⁶² (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

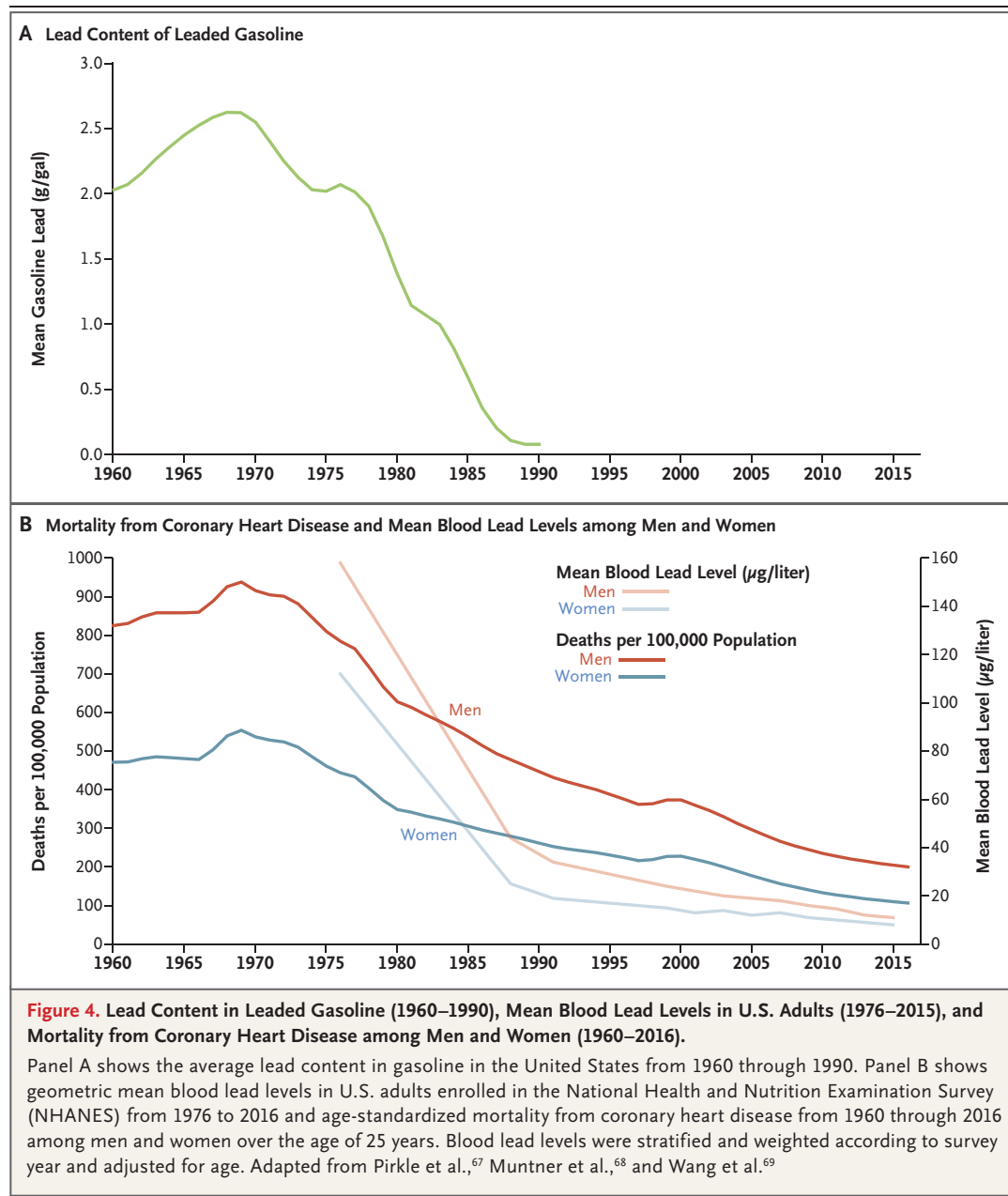
Lead exposure is a leading risk factor for death from cardiovascular disease. Of 14,000 U.S. adults enrolled in the NHANES between 1988 and 1994 and followed for 19 years, 4422 died; 1 in 5 died from coronary heart disease.⁴⁴ After adjustment for other risk factors, an increase from the 10th to the 90th 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



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 non-smokers.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.”⁹⁶

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

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