EPA/600/R-23/375
January 2024
www.epa.gov/isa

Integrated Science Assessment for Lead

Appendix 4: Cardiovascular Effects

January 2024

Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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DOCUMENT GUIDE

This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 12 appendices, which can all be found at https://assessments.epa.gov/isa/document/&deid=359536.

Front Matter

Executive Summary

Integrated Synthesis

Appendix 1. Lead Source to Concentration

Appendix 2. Exposure, Toxicokinetics, and Biomarkers

Appendix 3. Nervous System Effects

Appendix 4. Cardiovascular Effects

Appendix 5. Renal Effects

Appendix 6. Immune System Effects

Appendix 7. Hematological Effects

Appendix 8. Reproductive and Developmental Effects

Appendix 9. Effects on Other Organ Systems and Mortality

Appendix 10. Cancer

Appendix 11. Effects of Lead in Terrestrial and Aquatic Ecosystems

Appendix 12. Process for Developing the Pb Integrated Science Assessment

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS AND ABBREVIATION

A	peak late diastolic velocity
AAC	abdominal aortic calcification
AAS	atomic absorption spectrometry
ABLES	Adult Blood Lead Epidemiology and Surveillance
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ADMA	asymmetric dimethylarginine
AF	atrial fibrillation
AGT	angiotensinogen
AHA	American Heart Association
AL	allostatic load
ALAD	δ-aminolevulinic acid dehydratase
ANS	autonomic nervous system
APOE	apolipoprotein E
AQCD	Air Quality Criteria Document
ARCA	Automobile Racing Club of America
ASCVD	atherosclerotic cardiovascular disease
ASV	anodic stripping voltammetry
BEST	Bangladesh Vitamin E and Selenium Trial
BLL	blood lead level
BMI	body mass index
BP	blood pressure
BRHS	British Regional Heart Study
BW	body weight
Ca^{2+}	calcium ion(s)
C282Y HFE	mutant of the HFE wildtype
CAD	coronary artery disease
CAS	coronary artery stenosis
CCA	common carotid artery
Cd	cadmium
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIF	cumulative incidence function
CRP	C-reactive protein
CT	computerized tomography
CVD	cardiovascular disease
d	day(s)
DBP	diastolic blood pressure
E	peak early diastolic velocity
e’	peak early diastolic mitral annular velocity
EAF	electric arc furnace
ECG	electrocardiography
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EMM	effect measure modification
ETAAS	Electrothermal Atomic Absorption Spectrometry
Eyr	erythrocyte
FABP4	adipocyte fatty acid-binding protein
FBG	fasting blood glucose
Fe	iron
FRS	Framingham risk score
GFAAS	graphite furnace atomic absorption spectrometry
GFR	glomerular filtration rate
GLS	global longitudinal strain
GM	geometric mean
GRS	genetic risk score
GSD	geometric standard deviation
GSE	geometric standard error
GuLF	Gulf Long-Term Follow-up
GW	gestational week
HbA1c	hemoglobin A1c
H63D HFE	mutant of the HFE
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	high frequency
HFE	hemochromatosis gene
HMOX1	heme oxygenase-1
HOME	Health Outcomes and Measures of the Environment
hr	hour(s)
HR	hazard ratio
HRV	heart rate variability
HTN	hypertension
ICD	International Classification of Diseases
ICP-MS	inductively coupled plasma mass spectrometry
IHD	ischemic heart disease
IMT	intimal medial thickening
IQR	interquartile range
ISA	Integrated Science Assessment
IVS	interventricular septum
KNHANES	Korea National Health and Nutrition Examination Survey
K-XRF	K-shell X-ray fluorescence
LCL	lower confidence limit

LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LF	low frequency
LV	left ventricular
LVDP	left ventricular diastolic pressure
LVMI	left ventricular mass index
LVPW	left ventricular posterior wall
LVSP	left ventricular systolic pressure
MAP	mean arterial pressure
MDCS-CC	cardiovascular cohort of the Malmö Cancer and Diet Study
METAL	Environmental Pollutant Exposure and Metabolic Diseases in Shanghai
METS	Modeling the Epidemiologic Transition Study
MI	myocardial infarction
mo	month(s)
NA	not available
NAS	Normative Aging Study
NASCAR	National Association for Stock Car Auto Racing
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NN	normal-to-normal
NO	nitric oxygen
NR	not reported
nu	normalized units
OR	odds ratio
PAD	peripheral artery disease
Pb	lead
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PHQ	Patient Health Questionnaire
PIR	poverty-income ratio
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
PND	postnatal day
PP	pulse pressure
PR	prevalence ratio
PROGRESS	Programming Research in Obesity, Growth Environment and Social Stressors
PVD	peripheral vascular disease
PWV	pulse wave velocity
Q	quartile
QRS	QRS complex in ECG
QRSc	corrected QRS duration
QT	QT interval in ECG
QTc	corrected QT interval
RAAS	renin-angiotensin-aldosterone system
RCT	randomized control trial
RLS	regional longitudinal strain
rMSSD	root-mean-square of successive differences
ROS	reactive oxygen species
RR	relative risk
RRS	regional radial strain
RV	right ventricular
RVDP	right ventricular diastolic pressure
RVSP	right ventricular systolic pressure
RWT	relative wall thickness
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SNP	single nucleotide polymorphism
SOD	superoxide dismutase
SOF	Study of Osteoporotic Fractures
ST	segment measured from the J point to the end of the T-wave in an ECG
T#	tertile #
TACT	Trial to Assess Chelation Therapy
TC	total cholesterol
TPR	total peripheral resistance
TRI	Toxic Release Inventory
UCL	upper confidence limit
VA-NAS	Veterans Affairs Normative Aging Study
VDR	vitamin D receptor
yr	year(s)

APPENDIX 4 CARDIOVASCULAR EFFECTS

Causality Determination for Lead (Pb) Exposure and Cardiovascular Effects and Cardiovascular-Related Mortality

This appendix characterizes the scientific evidence that supports causality determinations for lead (Pb) exposure and cardiovascular effects. The types of studies evaluated within this appendix are consistent with the overall scope of the ISA as detailed in the Process Appendix (see Section 12.4). In assessing the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in Table 12–5 of the Process Appendix (see Section 12.6.1). More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this appendix supports the following causality conclusion:

Outcome	Causality Determination
Cardiovascular Effects and Cardiovascular-Related Mortality	Causal

The Executive Summary, Integrated Synthesis, and all other appendices of this Pb ISA can be found at https://assessments.epa.gov/isa/document/&deid=359536.

4.1 Introduction and Summary of the 2013 Integrated Science Assessment

The 2013 Integrated Science Assessment for Lead (hereinafter referred to as the 2013 Pb ISA) (U.S. EPA, 2013) made four causality determinations with respect to cardiovascular disease, using the U.S. Surgeon General's Report on Smoking as a guideline to group evidence into health outcome categories (CDC, 2004). The categories included hypertension, subclinical atherosclerosis, coronary heart disease (CHD), and cerebrovascular disease. Evidence was sufficient to conclude causal relationships between Pb exposure and hypertension and CHD. The causal determination for hypertension was not only informed by evidence of hypertension and increases in blood pressure (BP), but also cardiovascular-related mortality. The 2013 Pb ISA indicated a coherence between epidemiologic and toxicological studies, and animal toxicological studies provided strong evidence to support biologic plausibility. Specifically, oxidative stress from Pb exposure can result in an inactivation of nitrous oxide, which can lead to increased vasoconstriction and therefore increased BP. The causal determination for CHD was informed by epidemiologic evidence for heart rate variability (HRV); myocardial infarction (MI); ischemic heart disease (IHD); mortality from MI, IHD, and CHD; and increased thrombosis, coagulation, and arrhythmia in animals. The biological plausibility and mode of action for these cardiovascular effects was provided by evidence for oxidative stress, inflammation, and vascular cell activation or dysfunction. Specifically, coherence between epidemiologic and toxicologic evidence demonstrated that Pb exposure

may promote a procoagulant state that can potentially contribute to thrombus formulation and therefore reduced blood supply to the heart. Causality determinations for each of the four categories are summarized in Table 4-1 and some of the evidence supporting these determinations is discussed in Sections 4.1.1 to 4.1.4.

Table 4-1 Summary of causality determinations from the 2013 Pb Integrated Science Assessment

Outcome Group	Causality Determination
Hypertension and Increased Blood Pressure	Causal
Subclinical Atherosclerosis	Suggestive
Coronary Heart Disease	Causal
Cerebrovascular Disease	Inadequate

The current ISA is consistent with more recent ISAs (e.g., 2019 Particulate Matter and 2020 Ozone ISAs) (U.S. EPA, 2020, 2019) in that it makes a single causality determination for cardiovascular effects. This approach recognizes that many cardiovascular endpoints are inter-related (e.g., both atherosclerosis and endothelial dysfunction can contribute to increases in BP), and therefore not easily discussed in isolation. The remainder of this section summarizes the evidence for Pb exposures and cardiovascular effects assessed in the 2013 Pb ISA, including the evidence for hypertension and increased BP (Section 4.1.1), atherosclerosis (Section 4.1.2), CHD (Section 4.1.3), and cerebrovascular disease (Section 4.1.4). Subsequent sections of this appendix provide an overview of study inclusion criteria for the cardiovascular effects evidence in the current ISA (Section 4.2), summaries and evaluations of recent health effects evidence (Sections 4.3 to 4.10), a discussion of biological plausibility (Section 4.1.1), and a discussion of how all the individual lines of cardiovascular evidence were considered and integrated to inform the causality determination for Pb exposure and cardiovascular effects (Section 4.1.2). Study-specific details, including information on study design; exposure metrics, concentrations, and durations; and select results are presented in summary tables in Section 4.1.3.

4.1.1 Hypertension and Increased Blood Pressure

The 2013 Pb ISA (U.S. EPA, 2013) indicated that the combined evidence from epidemiologic and animal toxicological studies was sufficient to conclude that there is a causal relationship between Pb exposure and hypertension. This conclusion was informed by the coherence of effects observed between epidemiologic and toxicological studies with respect to hypertension and its related endpoints. A number of prospective epidemiologic studies clearly supported the relationship between biomarkers of Pb exposure and hypertension incidence and changes in BP (U.S. EPA, 2013). The prospective evidence

was supported by meta-analyses that underscored the consistency and reproducibility of Pb-associated increases in BP and hypertension across diverse populations and different study designs. Importantly, many epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) adjusted for a wide range of potential confounders to reduce uncertainty due to potential unmeasured confounding. Although the adjustment for specific factors varied by study, the collective body of evidence included adjustments for multiple potential key confounding factors, including age, diet, sex, body mass index (BMI), BP-lowering medication use, socioeconomic status (SES), race/ethnicity, alcohol consumption, cholesterol, smoking, preexisting disease (e.g., diabetes), measures of renal function, and copollutant exposures (e.g., cadmium [Cd]), while still maintaining positive associations between biomarkers of Pb exposure and changes in BP/hypertension.

Results from animal toxicological studies examining BP-related endpoints were consistent with the epidemiologic findings. In the previous review, all the animal toxicological studies providing blood Pb level (BLL) and BP measurements reported increases in BP with increasing BLLs. Most of these studies examined Pb exposures that resulted in mean BLLs >10 µg/dL; however, a single animal toxicological study conducted in rats after drinking water exposure found a continuous increase in BP in animals with mean BLLs ranging from 0.05 to 29 µg/dL with no evidence of a threshold (U.S. EPA, 2013).

Animal toxicological studies also provided strong support for the biological plausibility of the Pb-associated increases in BP and hypertension observed in epidemiologic studies. Studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) demonstrated that oxidative stress following Pb exposure inactivates vasodilator nitric oxide, which may lead to increased vasoconstriction and increased BP. If increases in BP persist, the result is hypertension (i.e., chronically elevated BP). Oxidative stress can also damage the endothelium, further disrupting endothelium-dependent vascular relaxation and increasing the contractile response. Studies also suggested Pb exposure disrupts normal contractile processes by altering the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the balance between production of vasodilators and vasoconstrictors (U.S. EPA, 2013).

Although the relationship between exposure to Pb and increases in BP in adults was well established at the time of the last review, some uncertainties were identified in the evidence for BP changes, specifically among children. The 2013 Pb ISA noted that some of the BP results (and other cardiovascular effects) observed in children may be antecedent to later-in-life effects. Therefore, there is at least some uncertainty in the level, timing, frequency, and duration of Pb exposure contributing to the reported cardiovascular effects in adults. That is, although there is a clear relationship between exposure to Pb and changes in BP in adults, it is possible that childhood Pb exposures could contribute to adult BLLs through processes such as bone remodeling that occurs during aging and/or pregnancy. Thus, Pb-associated changes in BP reported in adults may be appreciably influenced by past Pb exposures, perhaps as early as childhood.

Overall, epidemiologic and toxicological evidence from the previous review consistently demonstrated that Pb exposures are associated with increased BP and hypertension in adults. The epidemiologic studies have been replicated by different researchers in different cohorts and associations reported in these studies have largely remained positive after adjusting for numerous potential confounding factors. These studies are also coherent with numerous animal toxicological studies demonstrating increases in BP following Pb exposure. In addition, toxicological studies provided biological plausibility and a potential mode of action for the results observed in epidemiologic studies. Thus, in the 2013 Pb ISA, the combined evidence from epidemiologic and animal toxicological studies was sufficient to conclude that there is a causal relationship between Pb exposure and hypertension.

Since the last review, the evidence relating Pb exposure to increases in BP and hypertension have expanded greatly (see Section 4.3), further reinforcing an already strong evidence base established in the last ISA. As a result, evidence from epidemiologic and animal toxicological studies related to BP and hypertension are a key driver for the current ISA's conclusion of a causal relationship between Pb exposure and cardiovascular effects. A discussion of how the epidemiologic and animal toxicological evidence of hypertension and increased BP contributes to the determination of a causal relationship between exposure to Pb and cardiovascular effects in this ISA can be found in Section 4.1.2.

4.1.2 Subclinical Atherosclerosis

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the evidence was suggestive of, but not sufficient to infer, a causal relationship between exposure to Pb and subclinical atherosclerosis. Studies considered in the last review included an analysis from the 2006 Pb Air Quality Criteria Document (AQCD) indicating that exposure to Pb was associated with peripheral artery disease (PAD) in the National Health and Nutrition Examination Survey (NHANES) population, and that co-exposure with Cd did not confound the association (U.S. EPA, 2006). Additional epidemiologic findings presented in the 2013 Pb ISA were limited to cross-sectional analyses. One such analysis reported an increasing trend in the odds of PAD across concurrent BLL groups in adult NHANES participants. Furthermore, in an epidemiologic study conducted in a Pb-exposed population, positive associations were reported between BLLs and increases in intima-media thickness and atherosclerotic plaque presentation (U.S. EPA, 2013). However, the 2013 Pb ISA noted that most of the available epidemiologic analyses were cross-sectional in nature, contributing to uncertainty in the level, timing, frequency, and duration of the Pb exposures that contributed to the observed associations.

In addition to the epidemiologic evidence, toxicological studies provided limited evidence to suggest Pb exposure may initiate atherosclerotic vessel disease. The 2013 Pb ISA (U.S. EPA, 2013) noted that in vitro Pb exposure resulted in a concentration-dependent increase in arterial intimal thickness in human radial and internal mammary arteries. Moreover, exposure to Pb in rats increased aortic medial thickness. Following Pb exposure, toxicological studies also demonstrated evidence of oxidative stress

and systemic inflammation, processes which are important to the development of atherosclerosis. Finally, toxicological studies indicated a relationship between Pb exposure and elevation of cholesterol (U.S. EPA, 2013). Taken together with the epidemiologic evidence and its associated uncertainties, the 2013 Pb ISA concluded that the evidence was suggestive of a causal relationship between Pb exposure and subclinical atherosclerosis.

Since the last review, there is additional evidence supporting the potential contribution of Pb exposures to atherosclerosis. This evidence includes recent epidemiologic studies reporting positive associations with markers of atherosclerosis and a recent toxicological study in rats demonstrating morphological changes in the aorta consistent with the potential for atherosclerosis (see Section 4.3). A discussion of how the epidemiologic and animal toxicological evidence of atherosclerosis contributes to the determination of a causal relationship between exposure to Pb and cardiovascular effects in this ISA can be found in Section 4.1.2.

4.1.3 Coronary Heart Disease

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the evidence supports a causal relationship between exposure to Pb and CHD. This conclusion was primarily based on the results of epidemiologic studies examining the incidence of MI, IHD, and HRV, and on studies examining mortality from CHD, MI, or IHD. The rationale for this determination is summarized below.

The 2013 Pb ISA (U.S. EPA, 2013) described longitudinal studies in cohorts in different locations with follow-up periods of up to 12 years. These studies consistently reported that biomarkers of Pb exposure are associated with risk of mortality from MI, IHD, or CHD. The strongest associations were observed with MI mortality. Despite the differences in design and methods used across epidemiologic studies, associations between higher levels of tissue Pb (blood, bone) and higher risk of CHD-related mortality were generally observed 2013 Pb ISA (U.S. EPA, 2013). The body of evidence demonstrating associations with mortality from CHD was substantiated by several studies indicating associations between biomarkers of Pb exposure and incidence of CHD-related outcomes. For example, a prospective analysis examined the incidence of IHD (physician-confirmed MI, angina pectoris) and reported that blood and bone Pb levels contributed independently to IHD incidence. The 2013 Pb ISA further noted that coherence for the associations in humans was provided by an animal toxicological study suggesting that Pb exposure promoted a procoagulant state that could contribute to thrombus formation, and thus, potentially reduce the blood supply to the heart (U.S. EPA, 2013).

Previous research has indicated that decreased HRV is associated with higher mortality from MI and can be used as a predictor of the physiological processes underlying CHD. The 2013 Pb ISA described several cohort studies demonstrating associations between Pb exposure and decreases in HRV (U.S. EPA, 2013). Additionally, a prospective analysis reported that higher tibia Pb levels were associated with increases in certain ECG measurements, including the corrected QT interval (QTc) and

corrected QRS duration (QRSc), which can be indicative of impaired cardiac electrophysiology. As CHD is the result of vascular blockage, the previous Pb ISA also noted that these epidemiologic associations were supported, at least in part, by the limited evidence for subclinical atherosclerosis (Section 4.1.2). The 2013 Pb ISA (U.S. EPA, 2013) additionally noted that the strong and consistent evidence for Pb-induced hypertension supported the biological plausibility of the Pb-induced increase in CHD risk.

In summary, in the 2013 Pb ISA (U.S. EPA, 2013), several studies examining CHD morbidity and mortality and contributing cardiovascular effects reported consistent associations between Pb exposure and CHD. In addition, both animal toxicological and epidemiologic studies describe a biologically plausible potential mode of action (e.g., hypertension, atherosclerosis, potentially adverse changes in cardiac electrophysiology). Taken together, the 2013 Pb ISA (U.S. EPA, 2013) concluded that epidemiologic evidence, supported by toxicological evidence, was sufficient to conclude a causal relationship exists between Pb exposure and CHD.

Since the last review, the epidemiologic evidence describing the relationship between Pb exposure and endpoints related to CHD has expanded (see Section 4.4) and further strengthens the evidence base established in the last ISA. In particular, there are new epidemiologic studies reporting associations with IHD and MI mortality. Results of animal toxicological studies of HRV and cardiac electrophysiology published since the last review have been largely mixed. A discussion of how this epidemiologic and animal toxicological evidence contributed to the determination of a causal relationship between exposure to Pb and cardiovascular effects in this current review can be found in Section 4.1.2.

4.1.4 Cerebrovascular Disease

The 2013 Pb ISA (U.S. EPA, 2013) concluded there was insufficient evidence to inform the relationship between cerebrovascular disease and Pb exposure. Despite strong evidence indicating effects of Pb exposure on hypertension and CHD, very few studies evaluated in the 2013 Pb ISA examined the effects of Pb exposure on cerebrovascular disease. Furthermore, the studies that were available reported relatively imprecise associations between BLLs and stroke-related mortality. With respect to animal toxicological studies, there was some evidence for processes that could lead to cerebrovascular disease, such as an increase in markers of oxidative stress, inflammation, and coagulation that could potentially aid in clot formation. When considered as a whole, however, this limited evidence was insufficient to inform the relationship between Pb exposure and cerebrovascular disease. In the current review, studies examining the potential relationship between Pb exposure and cerebrovascular disease remain quite limited (see Section 4.9). Consideration of this evidence in the causality determination for Pb exposures and cardiovascular effects is presented in Section 4.1.2.

4.2 Scope

The scope of this appendix is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria and thereby facilitates identification of the most relevant literature to inform the Pb ISA.[1] To identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and many of the studies referenced therein do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Many of those studies are discussed in this appendix to establish the state of the evidence prior to this assessment. With the exception of supporting evidence used to demonstrate the biological plausibility of Pb-associated cardiovascular effects, recent studies were only included if they satisfied all of components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect;

Exposure: Exposure to Pb[2] as indicated by biological measurements of Pb in the body—with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure,[3] or intervention groups in randomized trials and quasi-experimental studies;

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles);

Outcome: Cardiovascular effects including but not limited to CHD, hypertension and increased BP, and cardiovascular-related mortality; and

[1]The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

[2]Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area that was of particular relevance to the National Ambient Air Quality Standards review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[3]Studies that estimate Pb exposure by measuring Pb concentrations in PM_{10} and $PM_{2.5}$ ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

Study design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages);

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below;[4,5]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control

Outcome: Cardiovascular effects; and

Study design: Controlled exposure studies of animals in vivo.

4.3 Blood Pressure and Hypertension

High BP typically is defined as a systolic BP (SBP) above 130 mmHg or a diastolic blood pressure (DBP) above 80 mmHg. SBP represents the pressure in the arteries as the heart contracts, while DBP represents the pressure in the arteries as the heart is relaxed and is filling with blood. Prolonged high BP is known as hypertension and can lead to a thickening of the ventricular wall resulting in diminished filling during diastole. Hypertension can contribute ultimately to the development of arrythmia and heart failure. Pulse pressure (PP), or the difference between SBP and DBP, as well as mean arterial pressure (MAP)—which is a function of cardiac output, systemic vascular resistance, and central venous pressure—are additional metrics used in studies of air pollution's effects on BP. Moreover, hypertension is one of several conditions, including high blood sugar, excess body fat around the waist, and abnormal triglyceride levels, that comprise metabolic syndrome (see Appendix 9), which is a risk factor for heart disease, stroke, and diabetes.

4.3.1 Epidemiologic Studies of Blood Pressure and Hypertension

Several epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) and previous AQCD documents (U.S. EPA, 2006, 1990) indicate an association between biomarkers of Pb exposure

[4]Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[5]This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

and changes in BP and hypertension risk. Although previous studies evaluated in the 2006 Pb AQCD (U.S. EPA, 2006) and a supplement to the 1986 Pb AQCD (U.S. EPA, 1990) most likely represented populations historically exposed to higher levels of air Pb (measured during the 1970s and 1980s) compared with populations today, they indicated there was no apparent threshold below which blood Pb was not significantly associated with changes in BP, for mean BLLs ranging from 7 μg/dL to 34 μg/dL. The 2013 Pb ISA (U.S. EPA, 2013) further demonstrated an association between Pb biomarkers and increased BP and hypertension risk at BLLs <2 μg/dL. The majority of the evidence for this association was derived from the Normative Aging Study (NAS) cohort of mostly older white men (Zhang et al., 2010; Perlstein et al., 2007; Elmarsafawy et al., 2006) and a Korean study composed of workers with high BLLs (mean BLLs ~20–35 μg/dL), due to occupational Pb exposure (Weaver et al., 2008; Glenn et al., 2006). The 2013 Pb ISA (U.S. EPA, 2013) also highlighted specific groups that may be at higher risk of an adverse BP outcome with increased Pb biomarkers, including those with high stress, certain genetic variants, and minority populations.

Recent studies continue to provide consistent evidence that exposure to Pb is associated with increased BP and hypertension risk. The majority of recent studies evaluating Pb biomarkers and changes in BP or hypertension are cross-sectional, which can be useful for assessing concurrent associations between blood Pb and increased BP or hypertension risk. A smaller number of studies implemented a longitudinal study design, useful for evaluating long-term effects of elevated Pb biomarkers. Generally, the evidence continues to indicate that changes in BP are most strongly associated with concurrent BLLs, whereas increased risk of hypertension is more likely to be associated with cumulative Pb measures (such as bone Pb levels).

4.3.1.1 Blood Pressure

Several recent studies specifically evaluated SBP and DBP, while other studies examined changes in PP and MAP. Study-specific details, including blood/bone Pb levels, study population characteristics, confounders, and selected results from these studies, are highlighted in Table 4-3. Studies in Figure 4-1 are standardized to be interpreted as changes in BP associated with a 1 μg/dL increase in BLL or a 10 μg/g increase in bone Pb level. Study details in Table 4-3 include standardized results as well as results that could not be standardized on the basis of information provided in each paper. Many of these studies evaluated this association cross-sectionally. Specifically, most used population-level cross-sectional study designs using NHANES (Huang, 2022; Everson et al., 2021; Teye et al., 2020; Obeng-Gyasi, 2019; Obeng-Gyasi et al., 2018; Hara et al., 2015; Hicken et al., 2013; Zota et al., 2013a; Hicken et al., 2012; Scinicariello et al., 2011), Korea National Health and Nutrition Examination Survey (KNHANES) (Lee et al., 2016a), a Canadian population-level survey (Canadian Health Measures Survey) (Bushnik et al., 2014), or a Chinese longitudinal survey (China National Human Biomonitoring) (Qu et al., 2022). These types of population-level cross-sectional studies have the advantage of assessing relatively low average blood Pb (<5 μg/dL) levels with concurrent BP measurements among a large sample size of participants.

A single study (Scinicariello et al., 2010) used this type of data in the 2013 Pb ISA to evaluate BLLs and changes in BP measurements. Additionally, two recent studies longitudinally evaluated the association between biomarkers of Pb exposure and BP changes (Yu et al., 2020; Bulka et al., 2019).

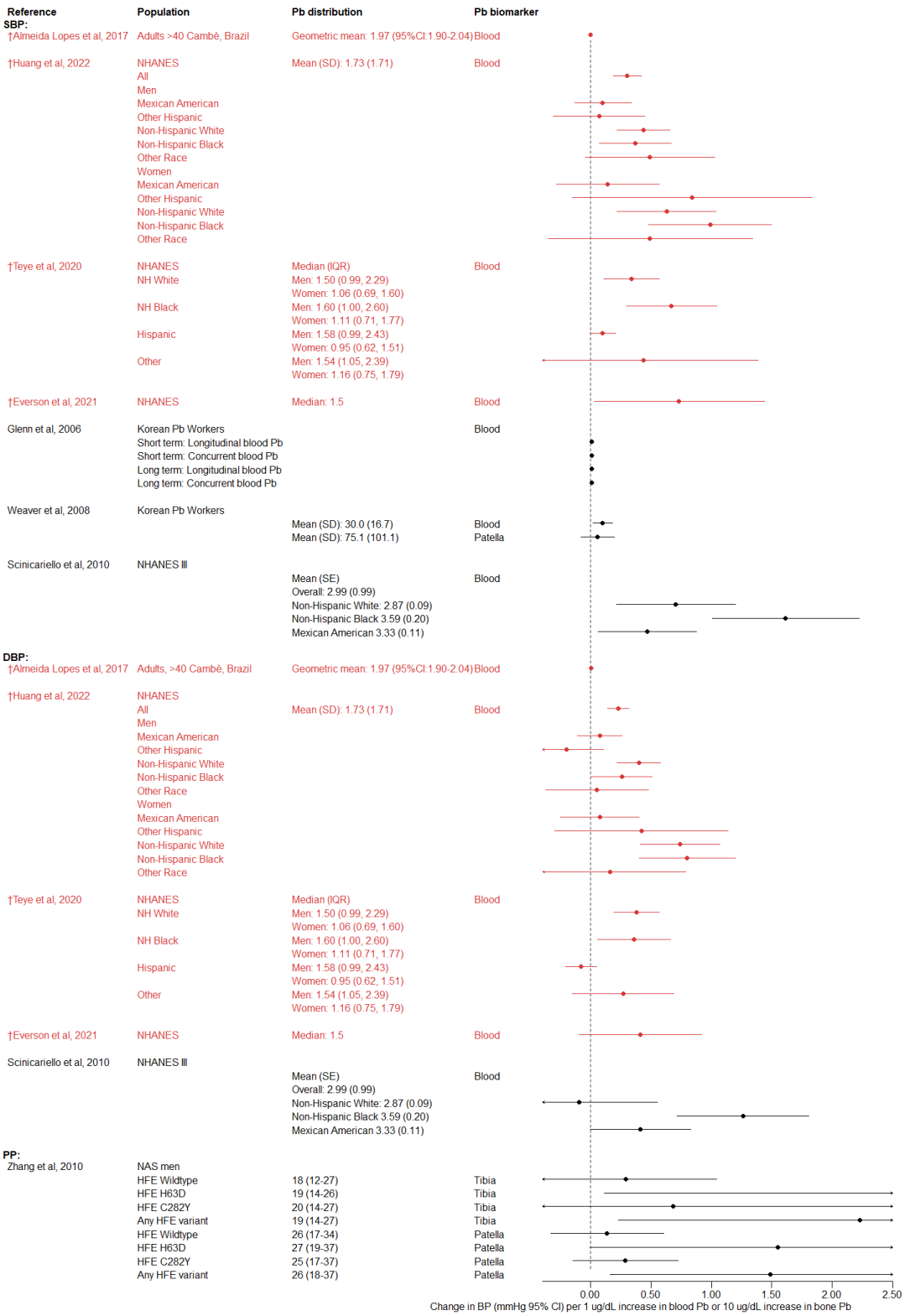

Reference
Population
Pb distribution
Pb biomarker
SBP:
†Almeida Lopes et al, 2017
Adults >40 Cambè, Brazil
Geometric mean: 1.97 (95%CI:1.90-2.04)
Blood
†Huang et al, 2022
NHANES
Mean (SD): 1.73 (1.71)
Blood
All
Men
Mexican American
Other Hispanic
Non-Hispanic White
Non-Hispanic Black
Other Race
Women
Mexican American
Other Hispanic
Non-Hispanic White
Non-Hispanic Black
Other Race
†Teye et al, 2020
NHANES
Median (IQR)
Blood
NH White
Men: 1.50 (0.99, 2.29)
Women: 1.06 (0.69, 1.60)
NH Black
Men: 1.60 (1.00, 2.60)
Women: 1.11 (0.71, 1.77)
Hispanic
Men: 1.58 (0.99, 2.43)
Women: 0.95 (0.62, 1.51)
Other
Men: 1.54 (1.05, 2.39)
Women: 1.16 (0.75, 1.79)
†Everson et al, 2021
NHANES
Median: 1.5
Blood
Glenn et al, 2006
Korean Pb Workers
Blood
Short term: Longitudinal blood Pb
Short term: Concurrent blood Pb
Long term: Longitudinal blood Pb
Long term: Concurrent blood Pb
Weaver et al, 2008
Korean Pb Workers
Mean (SD): 30.0 (16.7)
Blood
Mean (SD): 75.1 (101.1)
Patella
Scinicariello et al, 2010
NHANES III
Mean (SE)
Blood
Overall: 2.99 (0.99)
Non-Hispanic White: 2.87 (0.09)
Non-Hispanic Black 3.59 (0.20)
Mexican American 3.33 (0.11)
DBP:
†Almeida Lopes et al, 2017
Adults, >40 Cambè, Brazil
Geometric mean: 1.97 (95%CI:1.90-2.04)
Blood
†Huang et al, 2022
NHANES
All
Mean (SD): 1.73 (1.71)
Blood
Men
Mexican American
Other Hispanic
Non-Hispanic White
Non-Hispanic Black
Other Race
Women
Mexican American
Other Hispanic
Non-Hispanic White
Non-Hispanic Black
Other Race
†Teye et al, 2020
NHANES
Median (IQR)
Blood
NH White
Men: 1.50 (0.99, 2.29)
Women: 1.06 (0.69, 1.60)
NH Black
Men: 1.60 (1.00, 2.60)
Women: 1.11 (0.71, 1.77)
Hispanic
Men: 1.58 (0.99, 2.43)
Women: 0.95 (0.62, 1.51)
Other
Men: 1.54 (1.05, 2.39)
Women: 1.16 (0.75, 1.79)
†Everson et al, 2021
NHANES
Median: 1.5
Blood
Scinicariello et al, 2010
NHANES III
Mean (SE)
Blood
Overall: 2.99 (0.99)
Non-Hispanic White: 2.87 (0.09)
Non-Hispanic Black 3.59 (0.20)
Mexican American 3.33 (0.11)
PP:
Zhang et al, 2010
NAS men
HFE Wildtype
18 (12-27)
Tibia
HFE H63D
19 (14-26)
Tibia
HFE C282Y
20 (14-27)
Tibia
Any HFE variant
19 (14-27)
Tibia
HFE Wildtype
26 (17-34)
Patella
HFE H63D
27 (19-37)
Patella
HFE C282Y
25 (17-37)
Patella
Any HFE variant
26 (18-37)
Patella
0.00
0.50
1.00
1.50
2.00
2.50
Change in BP (mmHg 95% CI) per 1 ug/dL increase in blood Pb or 10 ug/dL increase in bone Pb

Figure 4-1 (Continued) Association between biomarkers of Pb exposure and blood pressure.

AL = allostatic load; BP = blood pressure; HFE C282Y = mutant of the HFE wildtype; CI = confidence interval; DBP = diastolic blood pressure; GSE = geometric standard error; HFE H63D = mutant of the HFE wildtype; HFE = hemochromatosis gene; IQR = interquartile range; NAS = Normative Aging Study; NH = non-Hispanic; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; Q# = quartile number; RR = relative risk; SBP = systolic blood pressure; SD = standard error; SE = standard error.
Note: †Red text: Studies published since the 2013 Pb ISA, Black text: Studies included in the 2013 Pb ISA.
Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

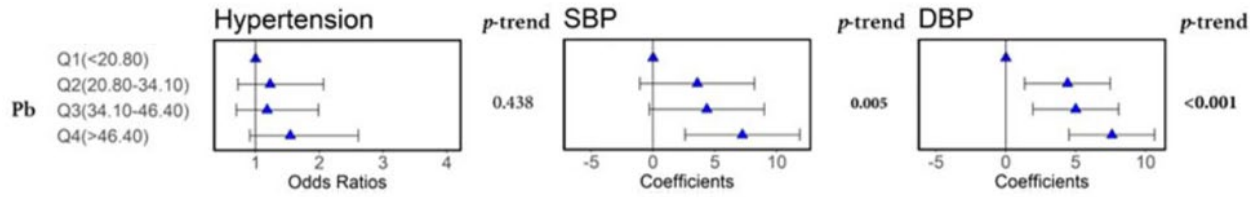
Figure 4-1 Association between biomarkers of Pb exposure and blood pressure.

Many nationally representative cross-sectional studies evaluated the association between increases in BLLs and changes in either SBP or DBP using continuous Pb biomarkers. Generally, increases in BLLs were concurrently associated with higher SBP and DBP (Huang, 2022; Qu et al., 2022; Teye et al., 2020; Lee et al., 2016a; Hara et al., 2015; Hicken et al., 2013; Scinicariello et al., 2011). However, some nationally representative studies noted null associations for SBP, but positive associations for DBP (Obeng-Gyasi et al., 2018; Bushnik et al., 2014; Zota et al., 2013a), while others noted positive associations for SBP and null associations for DBP (Everson et al., 2021). Studies containing the necessary information to standardize effect estimates to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone represent similar trends (Figure 4-1) and conclusions as studies that did not contain the necessary information needed for standardization (Figure 4-1 and Table 4-3). Specifically, in a KNHANES (2008–2013) analysis, Lee et al. (2016a) reported 0.71 mmHg higher DBP with each doubling of blood Pb (95% CI: 0.29, 1.13 mmHg) and a similar association with SBP (0.73 mmHg [95% CI: 0.09, 1.36 mmHg]). In an NHANES (1999–2006) analysis Scinicariello et al. (2011) indicated higher SBP (1.07 mmHg [95% CI: 0.384, 1.76 mmHg]) and higher DBP (0.71 mmHg [95% CI: 0.18, 1.24 mmHg]) for a twofold higher BLL. In contrast, in an analysis of more recent NHANES cycles (2007–2010), Obeng-Gyasi et al. (2018) noted a 0.268 mmHg higher DBP (95% CI: 0.079, 0.458 mmHg), but reported a null association between ln-Pb and SBP (0.052 mmHg [95% CI: −0.233, 0.458 mmHg]) (Table 4-3).

Several smaller cross-sectional studies have also examined the relationship between Pb biomarkers and BP (Yan et al., 2022; Xu et al., 2021; Chung et al., 2020; Wang et al., 2020; Guo et al., 2019; Lopes et al., 2017b; Gambelunghe et al., 2016; Ettinger et al., 2014). These studies tended to support the larger nationally representative studies. Several studies indicated positive associations both SBP and DBP (Yan et al., 2022; Chung et al., 2020; Wang et al., 2020; Gambelunghe et al., 2016). For example, a moderately sized study (n = 770) in Taiwan noted higher SBP (1.34 mmHg [95% CI: 0.34, 2.52 mmHg]) and DBP (0.69 mmHg [95% CI: 0.01, 1.37 mmHg]) per 1 µg/dL higher blood Pb (Chung et al., 2020). Additionally, a large cohort (with a cross-sectional component) in Malmö, Sweden (n = 4,452) assessed BP and BLLs in the early nineties (1991–1994). This population was likely exposed to historically high levels of Pb in the environment. The fully adjusted model indicated higher SBP (1.8 mmHg [95% CI: 0.52, 3.08 mmHg]) and DBP (1.4 mmHg [95% CI 0.57, 2.54 mmHg]) when

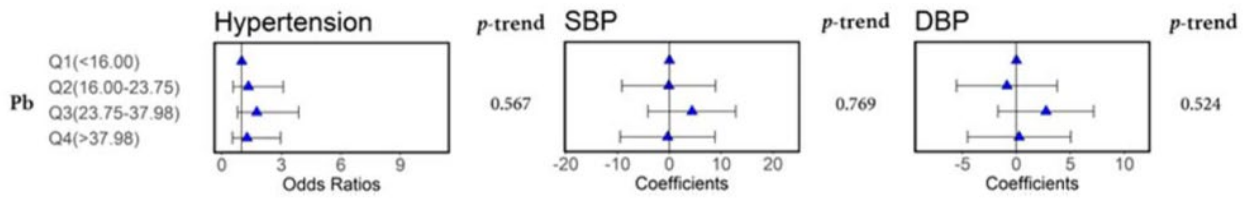
comparing the highest quartile of BLLs (mean 4.7 µg/dL) with the lower three quartiles (mean 1.5–2.8 µg/dL) (Gambelunghe et al., 2016). Yan et al. (2022) (n = 2,504) cross-sectionally evaluated a Haitian population with relatively higher BLLs (geometric mean [GM]: 4.73 µg/dL). This study had a high limit of detection (3.3 µg/dL), however, and ~30% of the study population had BLLs below the limit of detection. Yet, this study indicated positive associations between blood Pb and SBP (2.42 mmHg [95% CI: 0.36, 4.49]) and DBP (1.96 mmHg [95% CI: 0.56, 3.37]) when comparing the highest quartile (6.5–58.2 µg/dL) with the lowest (<3.3 µg/dL).

In addition, a moderately sized study (n = 816) among older adults (aged 40–75) living in rural southwest China compared the associations between BLL quartiles and BP measurements among those subsisting off rice and vegetables grown in a polluted region (Cd) concentration >0.2 mg/kg) with the associations among those in an unpolluted region (Cd <0.05 mg/kg) (Wang et al., 2020). In the polluted region, this study reported positive associations with both SBP and DBP when the highest BLL quartile (>4.6 µg/dL) was compared with the lowest BLL quartile (<2.1 µg/dL) (Figure 4-2). In contrast, there was no relationship observed in the unpolluted region (Figure 4-3). The authors of this study hypothesize that this discrepancy in association between polluted and unpolluted regions may be due in part to differences in mean BLLs in the polluted (3.5 µg/dL) and unpolluted (2.6 µg/dL) areas, or that more pollution may modify the association between blood Pb and BP, in addition to the small sample size in the unpolluted area (n = 214) compared with the polluted area (n = 602).



DBP = diastolic blood pressure; Pb = lead; Q = quartile; SBP = systolic blood pressure.
Source: Adapted from Wang et al. (2020).

Figure 4-2 Association between blood Pb level quartiles and systolic blood pressure, diastolic blood pressure, and hypertension, polluted region of rural southwest China.



DBP = diastolic blood pressure; Pb = lead; Q = quartile; SBP = systolic blood pressure.
Source: Adapted from Wang et al. (2020).

Figure 4-3 Association between blood Pb level quartiles and systolic blood pressure, diastolic blood pressure, and hypertension, unpolluted region of rural southwest China.

In contrast, a study in Cambè, Brazil (n = 948) indicated a null association between BLLs and SBP. However, when comparing the 90th percentile (6.03 µg/dL) with the 10th percentile (0.74 µg/dL), DBP was 0.005 mmHg higher (95% CI: 0.002, 0.008 mmHg) per 1 µg/dL increase in blood Pb concentration (Lopes et al., 2017b). Additionally, a recent study cross-sectionally evaluated the association between blood Pb and BP among participants in the Gulf Long-Term Follow-up (GuLF) study (Xu et al., 2021). The GuLF study is a longitudinal cohort of individuals involved in the 2010 *Deepwater Horizon* oil spill. Baseline blood Pb and BP measurements were obtained between 2011 and 2013. BLLs within this study were low overall (quartile 1: 0.06 µg/dL, quartile 4: 0.27 µg/dL). This study indicated null associations between the highest quartile and the lowest quartile for SBP (−0.96 [95% CI: −4.13, 2.22]) and DBP (−0.01 mmHg [95% CI: −2.21, 2.10]).

Additionally, a smaller number of cross-sectional studies evaluated either SBP or DBP categorically. Typically, these studies dichotomized either SBP or DBP at a particular clinically relevant threshold prior to conducting categorical statistical analyses. The results of these studies were more mixed compared with the results presented using continuous BLLs, presented above. For example, in a small study (n = 150) Ettinger et al. (2014) evaluated the association between BLLs and high SBP (>130 mmHg) and high DBP (≥85 mmHg) among young adults (aged 25–45) of African descent. This study yielded null results for both high SBP (>130 mmHg) (OR: 1.69 [95% CI: 0.55, 5.15]) and high DBP (≥85 mmHg) (OR: 2.20 [95% CI: 0.59, 8.16]) when comparing blood Pb values above and below the median (1.66 µg/dL). In contrast, a different larger study among young adults (aged 18–44) (n = 7,730) indicated higher odds of SBP >120 mmHg (OR: 1.21 [95% CI: 1.07, 1.38]) and DBP >80 mmHg (OR: 1.32 [95% CI: 1.10, 1.58]) when comparing BLLs above and below 5 µg/dL (Obeng-Gyasi, 2019). These cross-sectional results were similar to the results generated from studies evaluating concurrent BLLs and hypertension (see Section 4.3.1.2).

While most cross-sectional studies evaluated the association between concurrent BLLs and SBP and DBP, some studies assessed in the 2013 Pb ISA also considered concurrent bone Pb measurements and BP. Bone Pb tends to represent cumulative or long-term exposure to Pb, whereas BLLs are representative of recent exposure. Several analyses previously presented in the 2013 Pb ISA indicated

mixed results for the association between bone Pb levels and SBP and DBP, although associations were generally positive. For example, (Elmarsafawy et al., 2006) evaluated whether calcium intake affects the relationship between SBP and bone Pb levels in a cross-sectional analysis of the NAS cohort. (Elmarsafawy et al., 2006) reported higher SBP for each 10 μg/g increase in bone Pb level in both high (>800 mg/day) and low calcium (<800 mg/day) groups. However, the association with bone Pb was substantially larger in the low calcium group (4.00 mmHg [95% CI: 1.05, 6.95]) than in the high calcium group (1.90 mmHg [95% CI: 0.10, 3.70]). Although these results are not presented in Figure 4-1, they are comparatively larger than results presented for SBP and BLLs. No recent studies evaluated the association between bone Pb levels and BP.

In addition to the numerous cross-sectional studies previously mentioned, several recent studies longitudinally evaluated the relationship between biomarkers of Pb exposure and BP measurements. Bulka et al. (2019) evaluated a small Bangladeshi cohort (n = 255) with baseline BLLs (median: 8.5 μg/dL) measurements between April 2006 and August 2009, from an arsenic-endemic area. Residents in this area are chronically exposed to high levels of Pb in the air, water, and other industrial sources. BP was assessed biennially for a total of 6 years. This study indicated that SBP was increased in the highest quartile of baseline blood Pb compared with the lowest quartile, corresponding to a 1.16 mmHg annual increase (95% CI: 0.21, 2.11 mmHg). Results for DBP (0.53 mmHg [95% CI: −0.10, 1.16 mmHg]) and PP (0.63 mmHg [95% CI: −0.08, 1.34]) were smaller in magnitude, compared with SBP when comparing the highest quartile of BLLs to the lowest quartiles. All analyses considered several appropriate confounders, in addition to urinary arsenic (creatinine standardized). While there was an annual increase in the association between blood Pb and SBP, BP measurements remained stable across visits, but antihypertensive medication use increased from 7.5% at baseline to 15.3% at the last visit, which was controlled for as a confounder in all statistical models. A longitudinal study in Belgium(Yu et al., 2020) (n = 267) evaluated the association between baseline BLLs (collected between 1985 and 2005) and BP measured an average of 9.4 years following blood Pb measurement (Yu et al., 2020). For each doubling of BLLs there were null associations between peripheral SBP (2.41 mmHg [95% CI: −0.38, 5.20 mmHg]), DBP (0.50 mmHg [95% CI: −1.07, 2.07 mmHg]), and PP (1.91 mmHg [95% CI: −0.32, 4.14 mmHg]). Similarly, the association between a doubling of BLLs and central SBP, DBP, and PP were also null. Overall, associations from these studies remained stable even after controlling for Cd at baseline and considering the high endemic levels of arsenic in the Bangladeshi cohort.

Several studies also assessed PP in addition to SBP and DBP. To reiterate, PP is the force the heart requires to contract and is calculated by subtracting DBP from SBP. Overall, there was a null relationship between BLLs and PP in both cross-sectional (Hara et al., 2015; Scinicariello et al., 2010 Perlstein, 2007, 194019) and cohort analyses (Yu et al., 2020; Bulka et al., 2019). However, the relationship between bone Pb levels and PP was positive in cross-sectional analyses (Zhang et al., 2010; Perlstein et al., 2007). Hara et al. (2015) additionally evaluated MAP, which is the average BP during a single cardiac cycle. This study indicated an increase in MAP associated with BLLs.

The 2013 Pb ISA included two different meta-analyses focused on the relationship between Pb exposure biomarkers and BP changes or hypertension status. Nawrot et al. (2002) included over 30 cross-sectional and prospective studies on BLLs and BP, including >58,000 adults. This meta-analysis concluded that each doubling of concurrent BLLs was associated with a 1 mmHg increase in systolic BP and a 0.6 mmHg increase in diastolic BP. Furthermore, Navas-Acien et al. (2008) conducted a similar meta-analysis based on bone Pb measurements (three prospective, five cross-sectional). The pooled estimate from the cross-sectional studies indicated an increase in SBP of 0.26 mmHg (95% CI: 0.02, 0.50) per 10 μg/g tibia Pb. When considering hypertension, pooled results indicated increased odds of hypertension (OR: 1.04 [95% CI: 1.01, 1.07]) per 10 μg/g increase in tibia Pb and 1.04 (95% CI: 0.96, 1.12) per 10 μg/g increase in patella Pb.

4.3.1.1.1 Effect Measure Modification

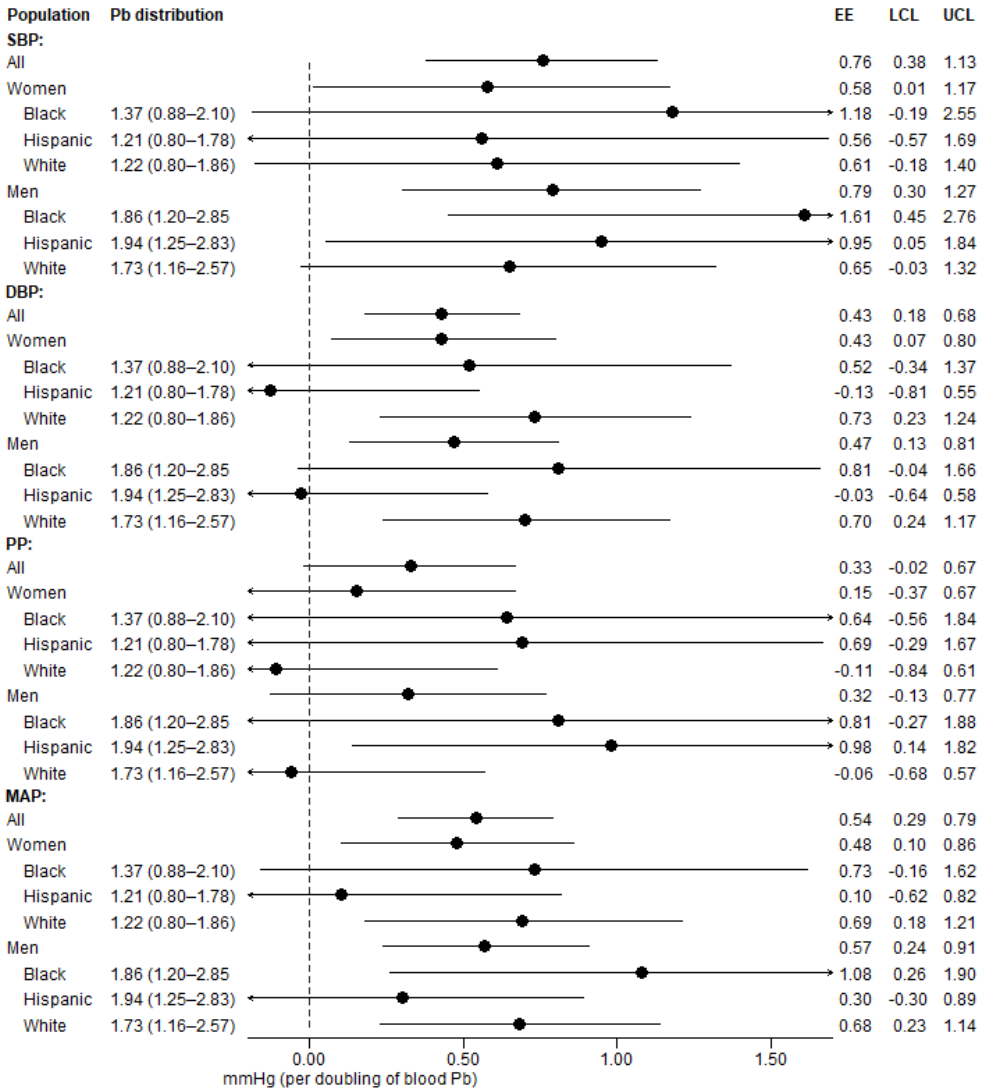
Several recent studies went beyond only evaluating the direct association between BLL and BP, but also evaluated effect measure modification (EMM) by several different variables, including race (Huang, 2022; Teye et al., 2020; Hara et al., 2015; Hicken et al., 2013; Hicken et al., 2012; Scinicariello et al., 2011), sex (Gambelunghe et al., 2016; Hara et al., 2015; Bushnik et al., 2014; Hicken et al., 2013; Hicken et al., 2012; Scinicariello et al., 2011), age (Huang, 2022; Obeng-Gyasi, 2019; Gambelunghe et al., 2016; Bushnik et al., 2014), stress/depression (Hicken et al., 2013; Zota et al., 2013a), genetic variations (Jhun et al., 2015), and smoking (Gambelunghe et al., 2016). These analyses can help to further highlight specific subgroups of the population that may have an increased risk of elevated BP associated with Pb biomarkers of exposure.

Race was a common measure to evaluate differential effects of biomarkers of Pb exposure and BP. An NHANES (1999–2016) study indicated that both SBP and DBP were statistically significantly higher among non-Hispanic white individuals (SBP: 0.34 mmHg [95% CI: 0.11, 0.57 mmHg], DBP: 0.38 mmHg [95% CI: 0.19, 0.57 mmHg]) and non-Hispanic Black individuals (SBP: 0.67 mmHg [95% CI: 0.29, 1.05 mmHg], DBP: 0.36 mmHg [95% CI: 0.06, 0.66 mmHg]), with each 1 μg/dL increase in BLLs compared to other races evaluated in the study(Teye et al., 2020). As described in the 2013 Pb ISA, Scinicariello et al. (2010) used NHANES III (1988–1994) to evaluate BP and BLLs by race/ethnicity. This study indicated a higher SBP (1.615 mmHg [95% CI: 1.007, 2.223 mmHg]) and DBP (1.261 mmHg [95% CI: 0.716, 1.805 mmHg]) among non-Hispanic Black individuals per 1 μg/dL higher blood Pb, compared with non-Hispanic white and Mexican-American individuals (Figure 4-1, Table 4-3).

Evaluation of effect modification by sex was less common, and the results were less consistent than for race. The Malmö Diet and Cancer Study evaluated the relationship between BLLs and changes in BP stratified by sex (Gambelunghe et al., 2016). In this study, sex did not modify the positive association between BLLs and SBP or DBP increases. Additionally, an NHANES (2003–2010) analysis reported

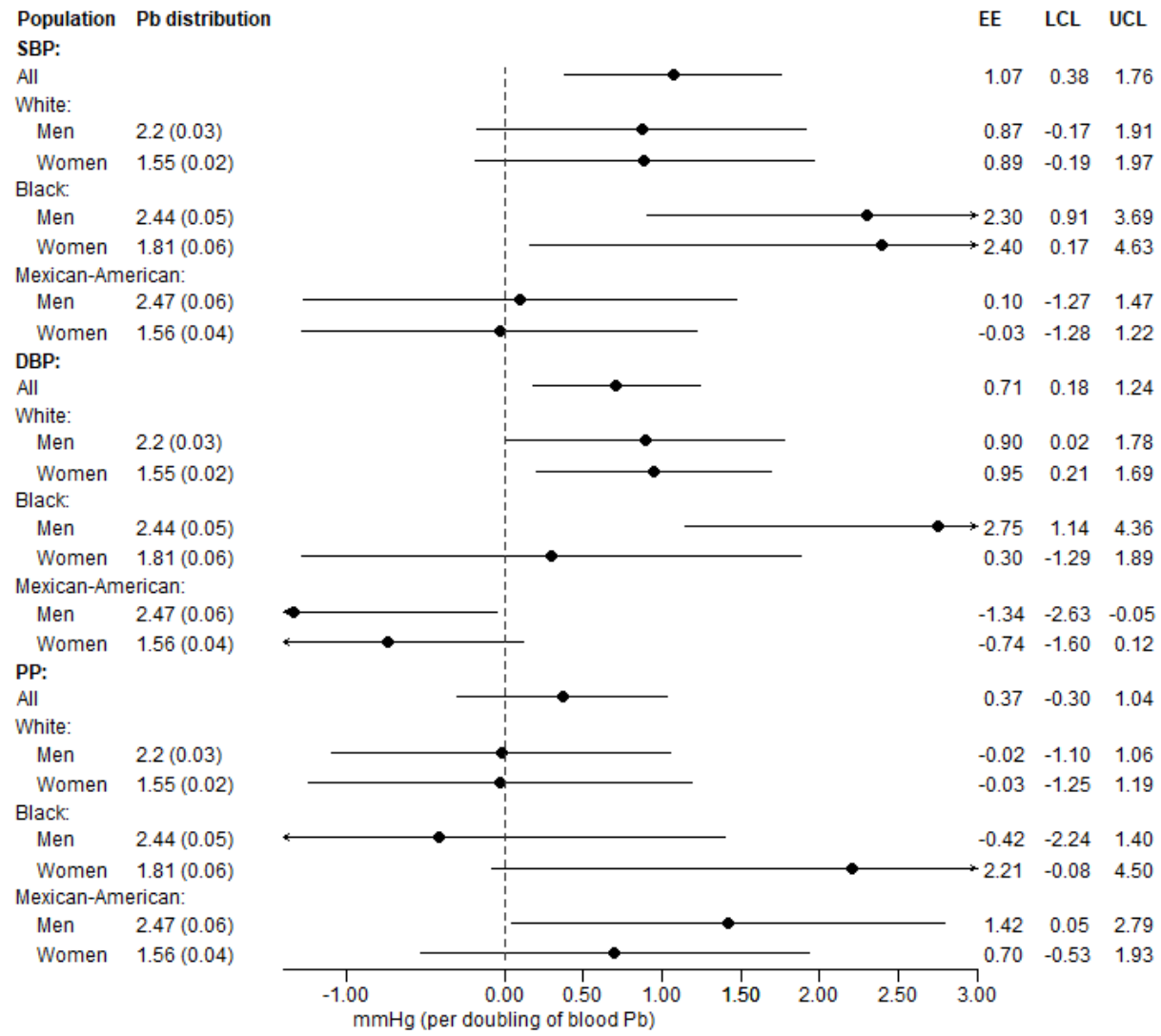
higher SBP and DBP for each doubling of BLLs among both sexes (Hara et al., 2015) (Figure 4-4, Table 4-3).

Several studies evaluated the intersectionality of sex and race as potential modifiers of the association between BLLs and changes in BP. In a cross-sectional study using NHANES (2003–2010), Hara et al. (2015) evaluated SBP and DBP stratified by both sex and race (Figure 4-4). This study indicated that qualitatively, compared with white females, Black females experienced higher SBP with each doubling of BLLs. White females had higher DBP, compared with Black females, however. Compared with white males, Black and Hispanic males had higher SBP with each doubling of BLLs. White and Black men had similar associations between higher DBP and higher BLLs (Figure 4-4, Table 4-3). Scinicariello et al. (2011) used NHANES (1999–2006) to evaluate sex and racial disparities for changes in BP and BLLs (Figure 4-5). This study reported the highest SBP among Black males (2.40 mmHg [95% CI: 0.91, 3.69 mmHg]) and Black females (2.40 mmHg [95% CI: 0.17, 4.63 mmHg]) associated with a doubling of BLLs, compared with other races. Conversely, Mexican-American males had lower DBP associated with a doubling of BLLs (−1.34 mmHg [95% CI: −2.63, −0.05 mmHg]). Huang (2022) also conducted an analysis using NHANES (1999–2006). This study generally noted similar positive associations with higher SBP and DBP among non-Hispanic white males and females and non-Hispanic Black males and females; however, there were null associations for Mexican-American and other Hispanic males and females for both SBP and DBP.



DBP = diastolic blood pressure; EE = effect estimate; MAP = mean arterial pressure; Pb = lead; PP = pulse pressure; SBP = systolic blood pressure; LCL = lower confidence limit; UCL = upper confidence limit.
Note: Pb distribution presented as geometric mean (IQR).
Source: Hara et al. (2015).

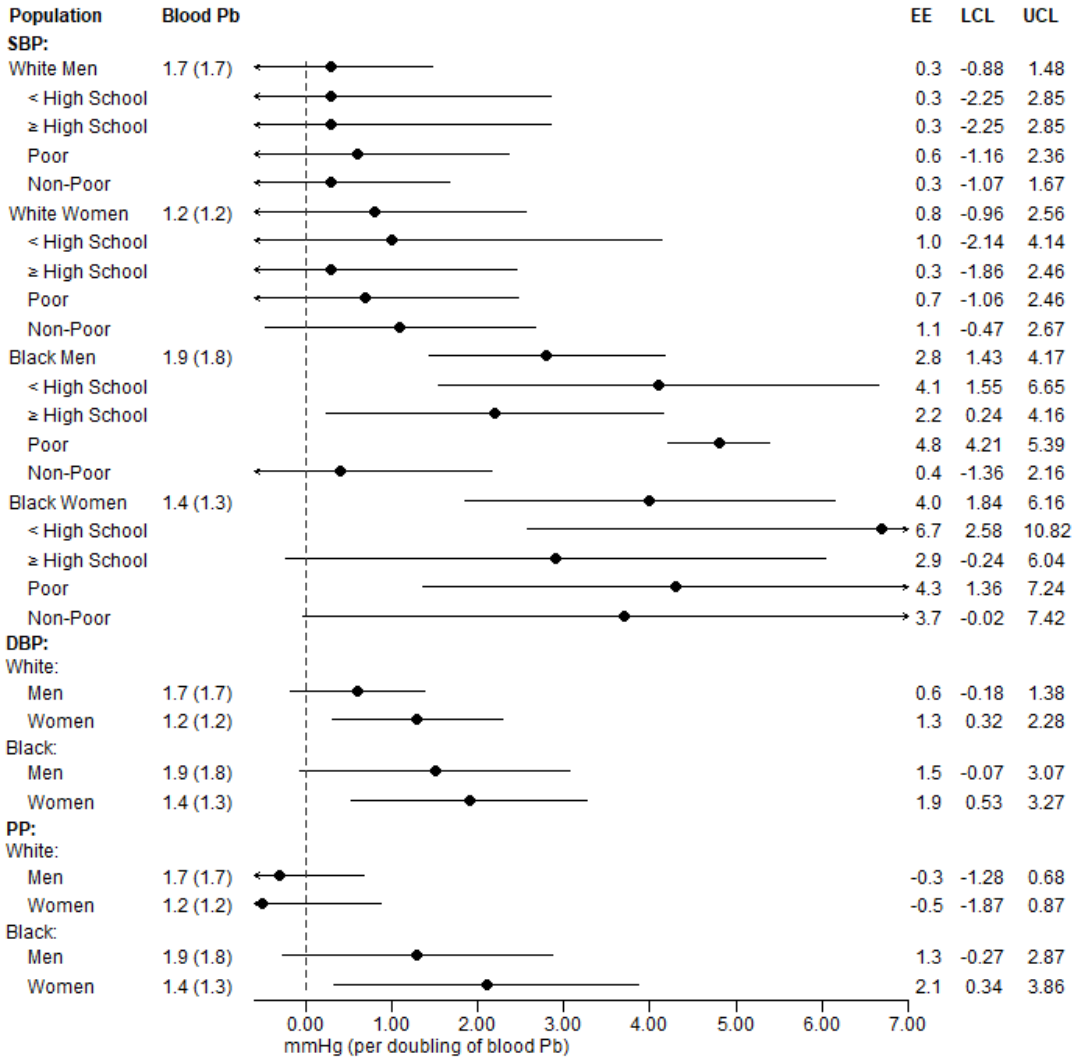
Figure 4-4 Effect measure modification by sex and race for blood pressure (systolic and diastolic) and a doubling of blood Pb levels, National Health and Nutrition Examination Survey (2003–2010).



DBP = diastolic blood pressure; EE = effect estimate; LCL = lower confidence limit; PP = pulse pressure; SBP = systolic blood pressure; UCL = upper confidence limit.
Note: Pb distribution presented as mean (SE).
Source: Scinicariello et al. (2011).

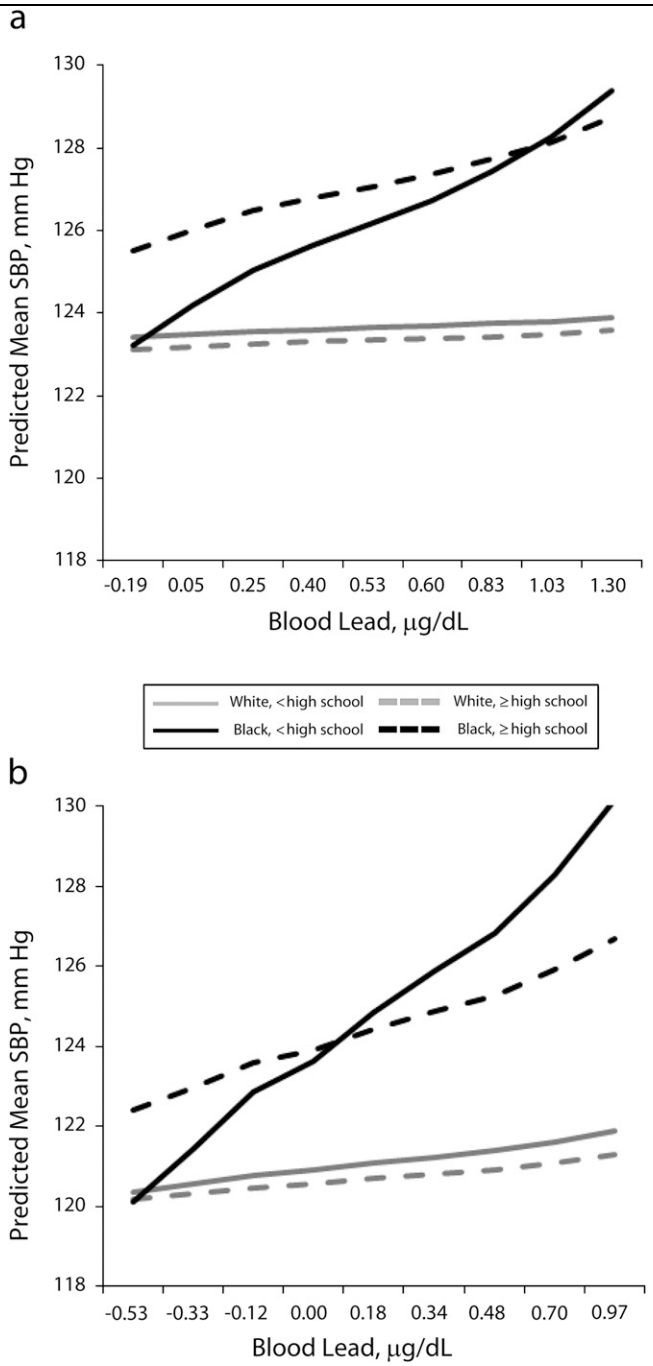
Figure 4-5 Effect measure modification by sex and race for blood pressure (systolic, diastolic, and pulse pressure) and a doubling of blood Pb level, National Health and Nutrition Examination Survey (1999–2006).

Additionally, using NHANES (2001–2008) Hicken et al. (2012) indicated differences in SBP, DBP, and PP when comparing white and Black males and females (Figure 4-6). The associations between BLLs and SBP, DBP, and PP were consistently higher among Black females compared with white females. Furthermore, this discrepancy by race and sex was also altered by educational attainment (Figure 4-7) and family poverty (Figure 4-8).



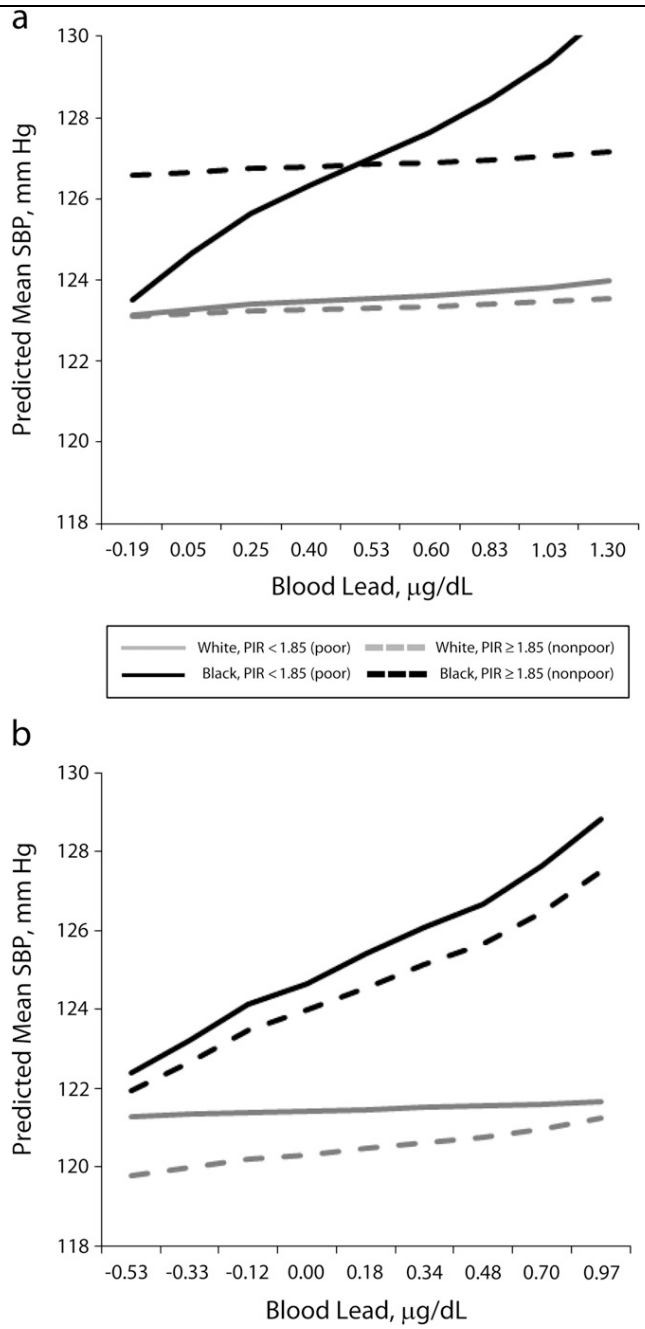
DBP = diastolic blood pressure; EE = effect estimate; LCL = lower confidence limit; Pb = lead; PP = pulse pressure; SBP = systolic blood pressure; UCL = upper confidence limit.
Note: Pb distribution presented as mean (median).
Source: Hicken et al. (2012).

Figure 4-6 Effect measure modification by sex and race for blood pressure (systolic, diastolic, and pulse pressure) and a doubling of blood Pb levels, National Health and Nutrition Examination Survey (2001–2008).



SBP = systolic blood pressure.
Note: Association between SBP and log-transformed BLL by educational attainment for men (a) and women (b).
Source: Hicken et al. (2012).

Figure 4-7 Effect measure modification between blood Pb levels, race, and education level, National Health and Nutrition Examination Survey (2001–2008).

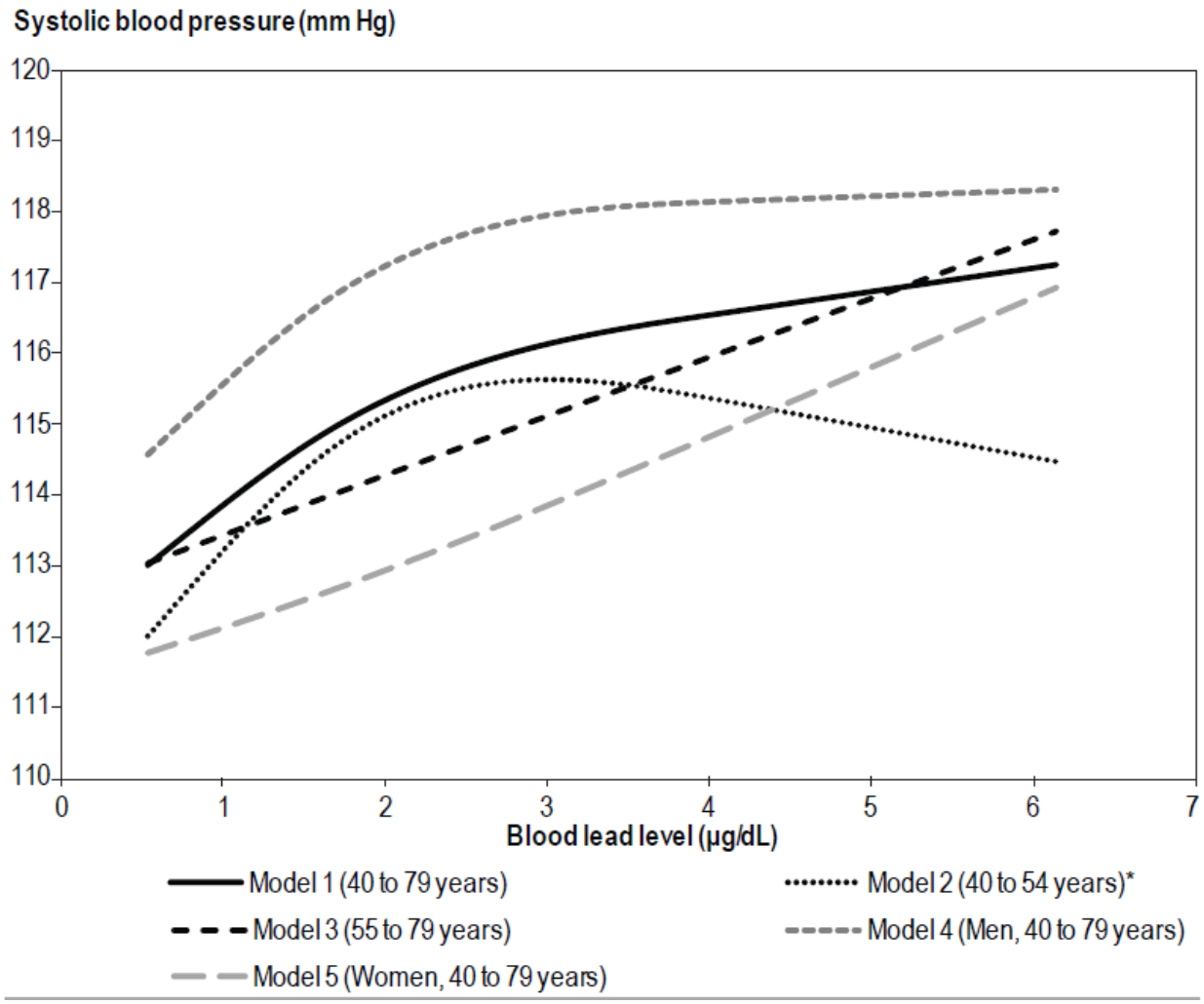


SBP = systolic blood pressure, PIR = poverty-income ratio.
Note: Association between SBP and log-transformed BLL by poverty level for men (a) and women (b).
Source: Hicken et al. (2012).

Figure 4-8 Effect measure modification between blood Pb levels, race, and poverty level, National Health and Nutrition Examination Survey (2001–2008).

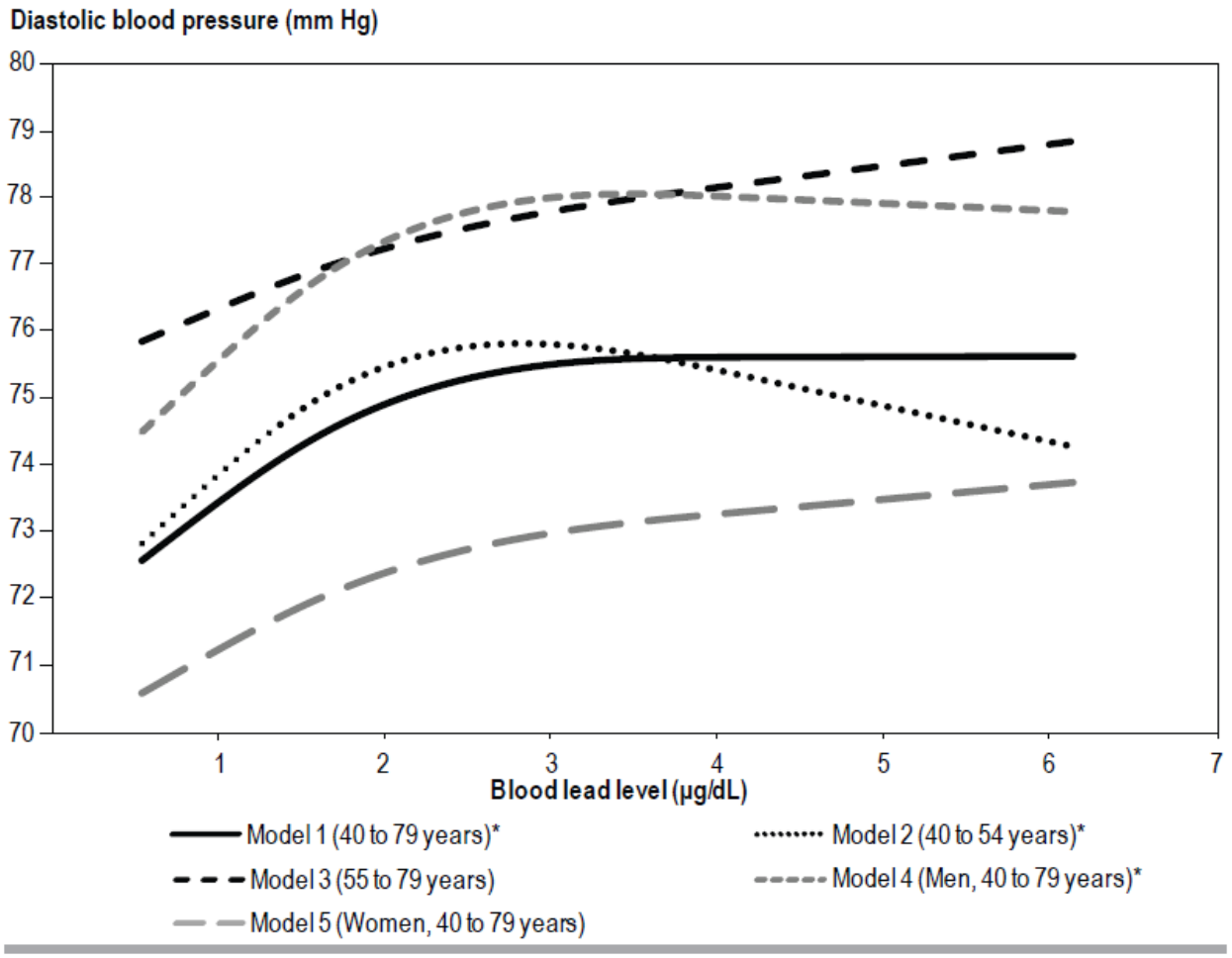
Another NHANES (2005–2008) analysis further evaluated EMM by racial differences and depressive symptoms on the effects of a doubling of BLLs on BP (Hicken et al., 2013). First, the association between higher SBP and a doubling of BLLs was larger among Black participants (3.2 mmHg [95% CI: 1.5, 5.0 mmHg]) than white participants (1.0 mmHg [95% CI: −0.3, 2.4 mmHg]). However, higher DBP was similar when comparing Black and white participants. This study further evaluated potential EMM by considering depressive symptoms, defined using the Patient Health Questionnaire (PHQ-9), which may indicate psychosocial stress. The PHQ-9 score was parsed into low (score <3) and high (score ≥3). The association between BLLs and BP (both SBP and DBP) was greater among those with high PHQ-9 scores. High psychosocial stress (PHQ-9 score ≥3) particularly modified the association between blood Pb and BP among Black individuals, compared with white individuals (Table 4-3). Specifically, a doubling of BLLs was associated with 5.6 mmHg (95% CI: 2.0, 9.2 mmHg) higher SBP among Black individuals with high levels of depression (PHQ-9 score ≥3), compared with only 1.2 mmHg (95% CI: −0.5, 2.9 mmHg) higher SBP among white individuals with high levels of depression (PHQ-9 score ≥3).(Zota et al., 2013a)

Several studies also evaluated if age was an effect modifier of the relationship between biomarkers of Pb exposure and changes in BP. Specifically, an NHANES (2009–2016) analysis evaluated the odds of the associations between BLLs and higher SBP (>120 mmHg) or DBP (>80 mmHg) for middle-aged (46–65 years) and young (aged 18–44 years) adults (Obeng-Gyasi, 2019). This study demonstrated similar odds of higher SBP for middle-aged adults (OR: 1.32 [95% CI: 1.14, 1.52]) as with young adults (OR: 1.21 [95% CI: 1.07, 1.38]) when comparing BLLs above and below 5 µg/dL. The association between BLLs and higher DBP was also similar in middle-aged (OR: 1.16 [95% CI: 0.98, 1.38]) and young (OR: 1.32 [95% CI: 1.10, 1.58]) adults. The young adults included in this analysis were likely not exposed to air emissions associated with leaded gasoline in the past, and therefore can help disentangle the effects of past high Pb exposures on CVD health endpoints. Additionally, the Malmö Diet and Cancer Study also considered both sex and age as potential effect modifiers when evaluating associations between BLLs and changes in BP (Gambelunghe et al., 2016). This study noted marginally increased associations between BLLs and higher SBP among adults aged ≥57 years (2.4 mmHg [95% CI: 1.20, 3.60 mmHg]) compared with adults <57 years (1.3 mmHg [95% CI: −0.55, 3.15]), when comparing the highest blood Pb quartile (4.7 µg/dL) with the lowest three quartiles (range 1.5–2.8 µg/dL). There were no differences, however, in the association between BLLs and higher DBP by age. However, this cohort was likely exposed to air emissions associated with leaded gasoline in the past. In addition, a cross-sectional study, using the Canadian Health Measures Survey (2007–2011), (Bushnik et al., 2014) demonstrated a steep increase in SBP and DBP associated with BLLs, up to 3 µg/dL, especially among middle-aged adults (40–54 years) and men. Specifically, this study indicated for each 1 µg/dL of BLL would correspond with a 1–2 mmHg higher SBP and a 2–3 mmHg higher DBP (Figure 4-9, Figure 4-10).



*significant association between blood Pb level and systolic blood pressure ($p < 0.05$).
BMI = body mass index; HDL = high-density lipoprotein.
Source: Bushnik et al. (2014).

Figure 4-9 Effect measure modification by sex and age of the relationship between blood Pb levels and systolic blood pressure, Canadian Health Measures Survey.

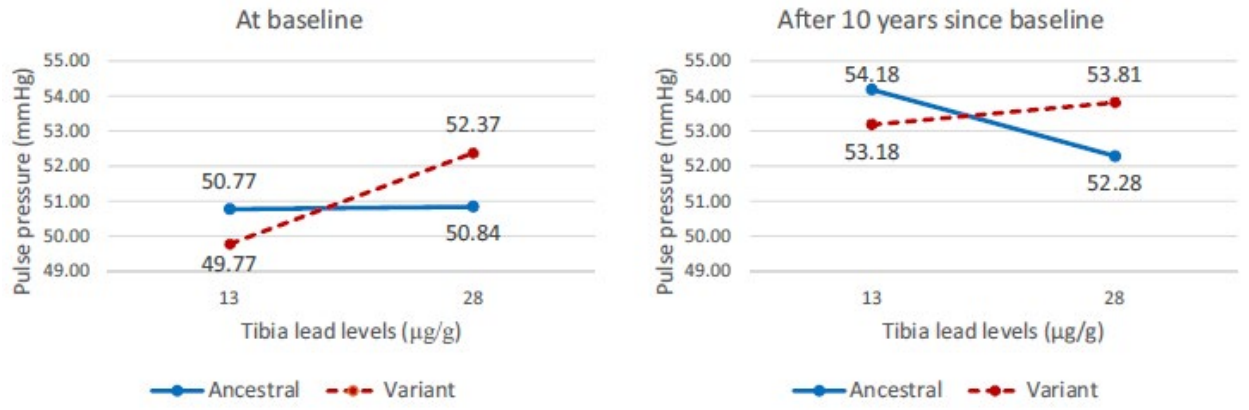


*significant association between blood Pb level and diastolic blood pressure ($p < 0.05$)
BMI = body mass index; HDL = high-density lipoprotein.
Source: Bushnik et al. (2014).

Figure 4-10 Effect measure modification by sex and age of the relationship between blood Pb levels and diastolic blood pressure, Canadian Health Measures Survey.

Certain genetic polymorphisms can be important in assessing the risk of increased BP as a result of elevated levels of biomarkers of Pb exposure, and therefore can be an important effect modifier to evaluate. In a longitudinal analysis of the NAS cohort, Jhun et al. (2015) evaluated potential EMM by vitamin D receptors (VDR) between PP and bone level and BLL. Genetic variations in VDR genes can potentially influence the accumulation, absorption, and retention of Pb in the body. After the initial baseline bone Pb, blood Pb, and BP measurements, PP was reassessed every 3–5 years. At the initial visit, an IQR increase in either tibia or patella Pb level was associated with an increased PP among those with the variant (opposed to ancestral) genotype (single nucleotide polymorphisms [SNPs] in *Bsm1*, *Taq1*, *Apa1*, or *Fok1*). Although there was an association with PP and tibia Pb levels by VDR genotype at baseline, this relationship appeared to diminish with time (Figure 4-11). However, the three-way

interaction terms between bone Pb levels, VDR receptor type, and time since baseline, used to further assess EMM, was almost zero, indicating that VDR consistently modifies the association between bone Pb levels and PP. In addition to genetic polymorphisms in VDR, the 2013 Pb ISA also evaluated studies that assessed other genetic factors that may increase susceptibility to Pb. Specifically, Scinicariello et al. (2010) used NHANES III (1988–1994), to stratify by δ-aminolevulinic acid dehydratase (ALAD) status. A critical mechanism of Pb toxicity is its ability to interact and inhibit key enzymes, such as ALAD, in the heme biosynthetic pathway. This study indicated that non-Hispanic white carriers of the *ALAD2* polymorphism had higher measures of SBP and DBP associated with BLLs. However, in a South Korean occupational study, BLLs were associated with higher SBP only, and there was no evidence of EMM by either VDR or ALAD (Weaver et al., 2008). In another evaluation of the NAS, Zhang et al. (2010) examined changes in the hemochromatosis gene (HFE), which can promote excessive iron absorption and is thought to also alter Pb biomarker concentrations. Two mutations to HFE (*C282Y* and *H63D*) were examined within this older population. This study suggested that those with the *H63D* mutation were more likely to have an increase in PP with a 10 µg/g increase in tibia (2.54 mmHg [95% CI: 0.12, 4.96 mmHg]) and patella (2.23 mmHg [95% CI: 0.23, 4.23 mmHg]) Pb levels. Taken together, certain genetic polymorphisms appear capable of predisposing some groups to greater effects on BP related to biomarkers of Pb exposure.



BMI = body mass index; VDR = vitamin D receptor.
Source: Jhun et al. (2015).

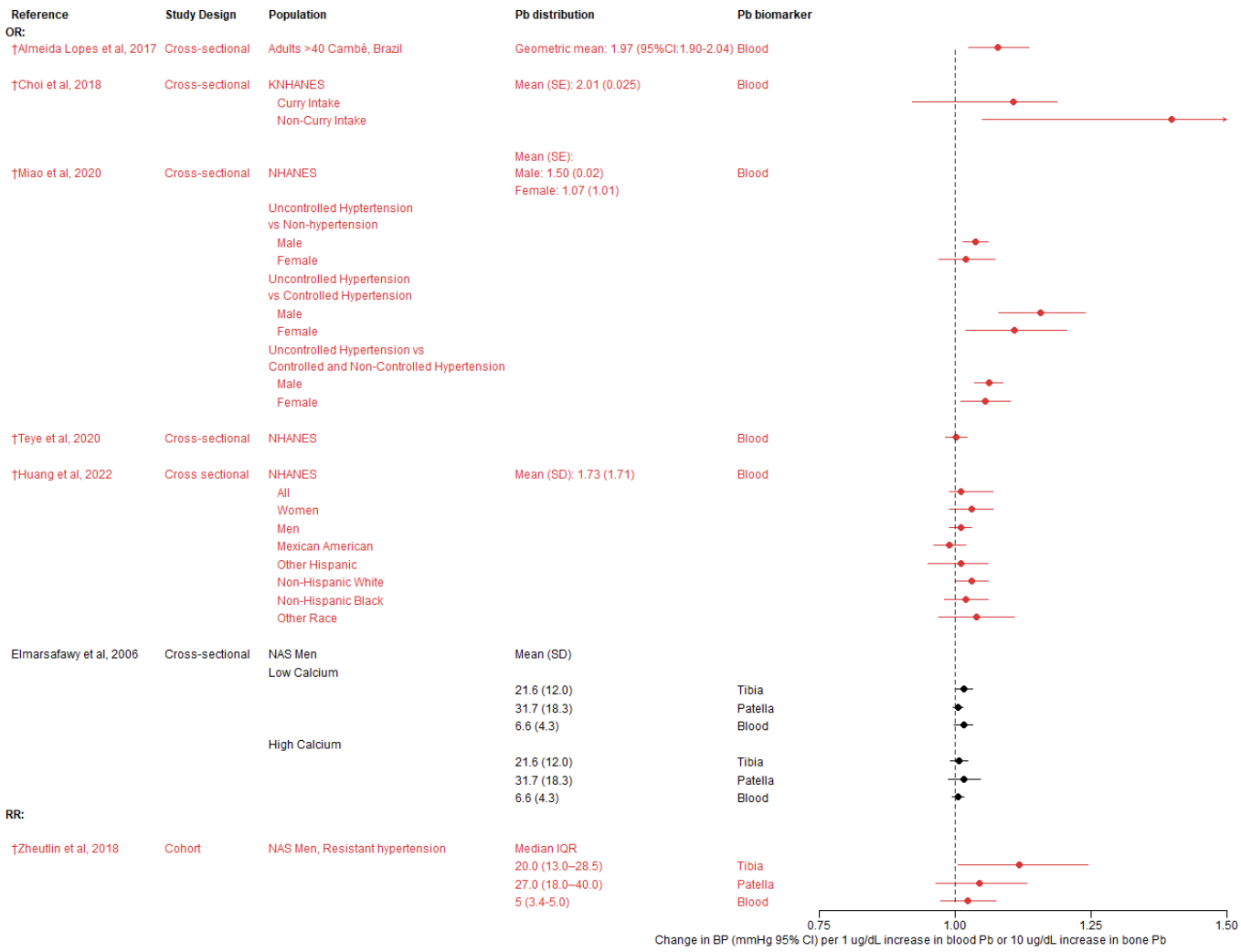
Figure 4-11 Effect measure modification by vitamin D receptor variant for the association between pulse pressure and tibial Pb levels, Normative Aging Study cohort.

The Malmö Diet and Cancer Study further evaluated EMM by smoking status for the association between BLLs and BP (Gambelunghe et al., 2016). The cross-sectional component of the study indicated that smokers (ever-smokers) had 3.9 mmHg (95% CI: 1.59, 6.21 mmHg) higher SBP, compared with only 0.6 mmHg (−1.46, 2.66 mmHg) among never-smokers when comparing the highest quartile of BLLs

(mean 4.7 µg/dL) with the lower three quartiles (mean 1.5–2.8 µg/dL). Similarly, smokers had a 1.6 mmHg (95% CI: 0.65, 2.54 mmHg) higher DBP, compared with 1.1 mmHg (95% CI: −0.05, 2.25 mmHg) higher DBP among never-smokers.

4.3.1.2 Hypertension

Fewer recent studies evaluated the relationship between biomarkers of Pb exposure and hypertension. Study-specific details, including blood and bone Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 4-4 and Figure 4-12. Studies in Figure 4-4 are standardized to represent the risk of prevalent or incident hypertension associated with a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level. Study details shown in Table 4-4 include standardized results as well as results that could not be standardized based on the information provided in each paper. Generally, hypertension refers to chronic BP readings of >140 mmHg for SBP and >90 mmHg for DBP, while prehypertension, typically thought of as a precursor to chronic hypertension, is usually defined as SBP 120–139 mmHg or DBP 80–89 mmHg. However, some studies may choose to define hypertension, or prehypertension, differently. Some cross-sectional studies evaluated associations between biomarkers of Pb exposure and prevalent or preexisting hypertension (Huang, 2022; Qu et al., 2022; Xu et al., 2021; Teye et al., 2020; Wang et al., 2020; Choi et al., 2018; Lopes et al., 2017a; Hara et al., 2015; Bushnik et al., 2014). However, other studies specifically evaluated prehypertension, or SBP or DBP values that approach a predefined clinical definition of hypertension (Qu et al., 2022; Lee et al., 2016b; Lee et al., 2016a). Additionally, longitudinal studies examined associations between baseline Pb biomarkers and incident, or newly developed hypertension (Gambelunghe et al., 2016) whereas other studies evaluated associations with hypertension that may not respond to medication (resistant) or completely untreated (uncontrolled) hypertension using NHANES (Miao et al., 2020) or the NAS cohort (Zheutlin et al., 2018).



BP = blood pressure; CI = confidence interval; IQR = interquartile range; KNHANES = Korea National Health and Nutrition Examination Survey; NAS = Normative Aging Study; NH = non-Hispanic; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; RR = relative risk; SD = standard error; SE = standard error.
Note: †Red text: Studies published since the 2013 Pb ISA, Black text: Studies included in the 2013 Pb ISA.
Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

Figure 4-12 Associations between biomarkers of Pb exposure and hypertension.

Cross-sectional studies identified positive associations between BLLs and prevalent hypertension but were not statistically significant. Wang et al. (2020) (n = 816) indicated no association between BLLs and hypertension prevalence among an older adult Chinese population (Figure 4-2 and Figure 4-3). Similarly, Bushnik et al. (2014), (n = 4,550) also indicated no association between BLLs and hypertension prevalence among participants of the Canadian Health Measures Survey. Studies evaluating

NHANES (1999–2016) (Teye et al., 2020), NHANES (1999–2018) (Huang, 2022), and NHANES (2003–2010) (Hara et al., 2015) did not identify associations between BLLs and prevalent hypertension. Additionally, the GuLF study, (n = 957) which cross-sectionally evaluated concurrent BLLs and prevalent hypertension among those involved in the 2010 *Deepwater Horizon* oil spill, indicated no associations (Xu et al., 2021). However, this study had low (quartile 1: 0.06 µg/dL, quartile 4: 0.27 µg/dL) mean BLLs. These results are consistent with the 2013 Pb ISA, which generally summarized studies reporting null associations between concurrent BLLs and prevalent hypertension. For example, a study of South Korean Pb workers indicated no association between BLLs and prevalent hypertension, despite this population having relatively high BLLs (mean: 31.9 µg/dL) (Weaver et al., 2008).

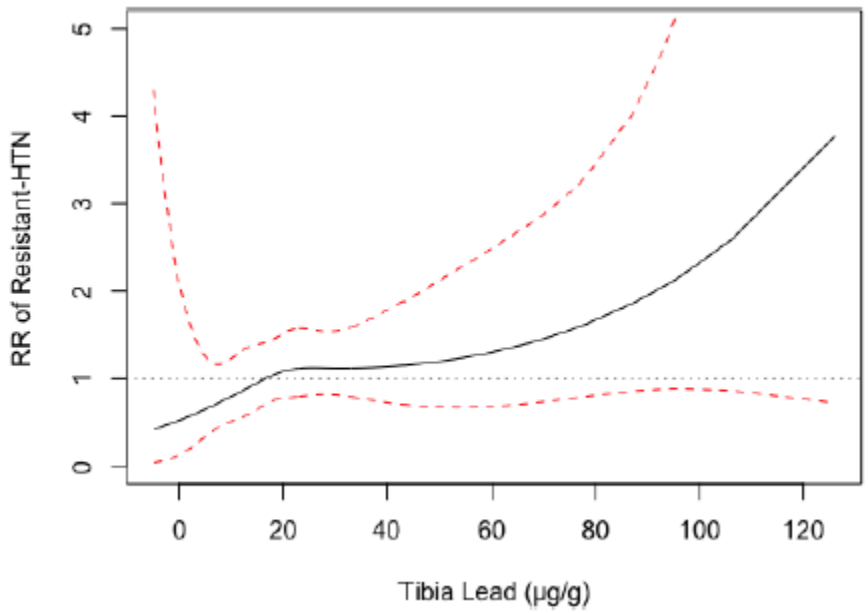
Although most cross-sectional studies did not observe associations between BLLs and prevalent hypertension, some of these studies did report positive associations. A cross-sectional Brazilian study evaluated BLLs among adults ≥40 years and indicated an association between BLLs and prevalent hypertension (Lopes et al., 2017a). There were higher odds of hypertension prevalence noted (OR: 1.08 [95% CI: 1.03, 1.14]), for each 1 µg/dL higher BLLs. Additionally, a KNHANES (2008–2013) study also indicated a marginal association for each doubling of BLLs for prevalent hypertension (OR: 1.09 [95% CI: 0.98, 1.22]) (Lee et al., 2016a). Another more recent analysis using the China National Human Biomonitoring longitudinal survey evaluated the relationship between concurrent BLLs and several different definitions of hypertensive status (Qu et al., 2022). When hypertension was defined according to the 2010 Chinese Hypertension Guidelines (SBP ≥140 mmHg, DBP ≥90 mmHg), there were higher odds of hypertension associated with BLLs (OR: 2.33 [95% CI: 1.67, 3.24]), when comparing the largest quartile (≥3.2 µg/dL) with the lowest (<1.5 µg/dL). Another recent NHANES (1999–2016) analysis (Tsoi et al., 2021) indicated higher odds of prevalent hypertension for each doubling of BLLs (OR: 1.09 [95% CI: 1.04, 1.14]) and when comparing the highest quartile (>2.10 µg/dL) with the lowest quartile (<0.89 µg/dL) (OR: 1.21 [95% CI 1.07, 1.36]).

Several studies also evaluated the association between BLLs and prehypertension, a common precursor to chronic hypertension. Qu et al. (2022) (n = 11,037) considered several prehypertension definitions. Using the 2010 Chinese Hypertension Guidelines for prehypertension (SBP 120–139 mmHg, DBP 80–89 mmHg), there were increased odds of prehypertension comparing the highest with the lowest quartile (OR: 1.56 [95% CI: 1.22, 1.99]). This study also considered the 2017 American College of Cardiologists (ACC)/American Heart Association (AHA) guidelines for elevated BP (SBP 120–129 mmHg, DBP <80) and stage 1 hypertension (SBP 130–139 mmHg, DBP 80–89). Using these definitions, there was a null association between BLLs and elevated BP (OR: 1.18 [95% CI: 0.88, 1.57]), but a positive association with stage 1 hypertension (OR: 1.75 [95% CI: 1.31, 2.33]). Lee et al. (2016a) also evaluated prehypertension, which was defined as DBP ≥80 mmHg or SBP ≥120 mmHg in a KNHANES (2008–2013) analysis. This study indicated that for each doubling of BLLs there was an increased association with prehypertension (OR: 1.09 [95% CI: 0.99, 1.21]). In another KNHANES (2007–2013) analysis, Lee et al. (2016b) also specifically evaluated prehypertension, which was defined as DBP between 80–89 mmHg or SBP between 120–139 mmHg and the absence of any current treatment

or diagnosis of hypertension. When comparing the highest quartile (2.717 to 24.532 µg/dL) to the lowest quartile (0.206 to 1.539 µg/dL) there was an association between BLLs and prehypertension (OR: 1.30 [95% CI: 1.07, 1.60]).

A recent longitudinal study (Malmö Diet and Cancer Study), within a cohort with high historical Pb exposure, explored BLLs as they relate to incident hypertension (Gambelunghe et al., 2016). This study defined hypertension status as SBP ≥140 mmHg or DBP ≥90 mmHg or the use of antihypertensive medication. At baseline (time = 0) there was a cross-sectional relationship between hypertension and the highest quartile of BLLs, compared with the lowest three quartiles (OR: 1.3 [95% CI: 1.1, 1.5]). Participants in this study were followed for approximately 16 years. When analyzed at the follow-up, there was no association between baseline BLLs and the use of antihypertensive medication (OR: 1.0 [95% CI: 0.8, 1.2]) or high BP at follow-up (OR: 1.0 [0.7, 1.3]).

Another longitudinal analysis evaluated resistant hypertension and both blood and bone Pb levels among participants of the NAS cohort (Zheutlin et al., 2018). Resistant hypertension was defined as having either uncontrolled hypertension (SBP ≥140 or DBP ≥90 while taking ≥3 antihypertensive medications), or controlled hypertension (SBP <140 and DBP <90 while taking ≥4 antihypertensive medications). Overall, a 10 µg/g increase in tibia Pb level was associated with resistant hypertension (RR: 1.12 [95% CI: 1.01, 1.25]) but the association with same increase in patella Pb levels was smaller in magnitude (RR: 1.04 [95% CI: 0.96, 1.13]). The dose-response relationship between tibia Pb levels and resistant hypertension risk is relatively linear, with the steepest slope noted in the lower part of the distribution of tibia Pb concentrations (0 to 20 µg/g) (Figure 4-13); a flattening of the slope between 20 and 80 µg/g; and a steepening of the slope for the highest bone Pb concentrations (>80 µg/g). This dose-response relationship supports previous findings of a supralinear association between Pb exposures and Pb-related health outcomes (U.S. EPA, 2013). However, among the same study participants. (Zheutlin et al., 2018) for a 1 µg/dL increase in BLLs, the association between BLL and resistant hypertension was smaller in magnitude (RR: 1.02 [95% CI: 0.97, 1.08]).



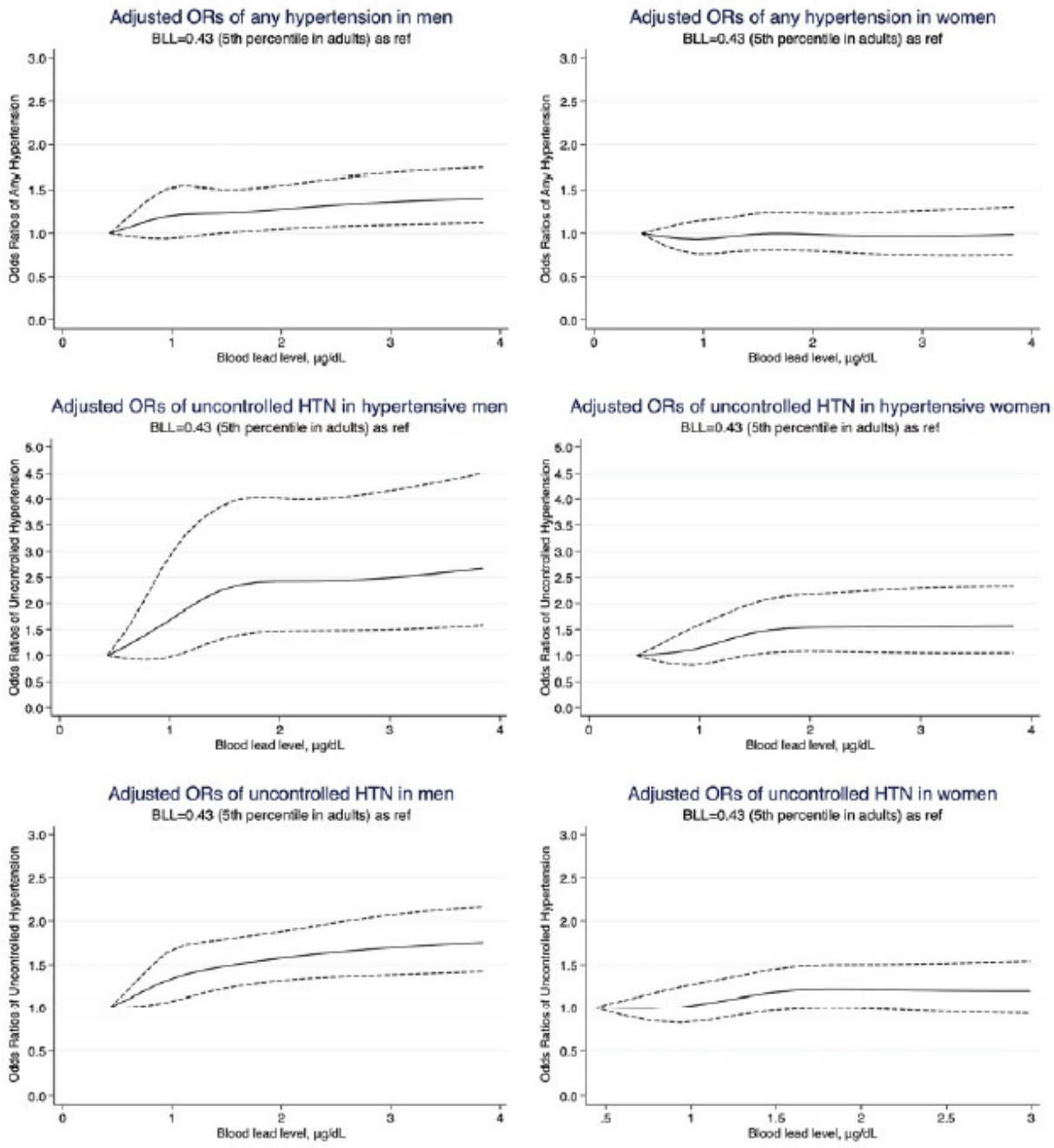
HTN = hypertension; RR = relative risk.
Source: Zheutlin et al. (2018).

Figure 4-13 Dose-response curve between tibia Pb levels and resistant hypertension, Normative Aging Study cohort.

4.3.1.2.1 Effect Measure Modification

Several recent studies also evaluated EMM by a variety of factors when assessing the relationship between biomarkers of Pb exposure and hypertension outcomes. In a recent NHANES (1999–2006) analysis, Miao et al. (2020) evaluated EMM by sex for the relationship between BLL and any hypertension status and uncontrolled hypertension (Figure 4-14, Figure 4-16, Table 4-4). Any hypertension was defined as SBP ≥130 mmHg or DBP ≥80 mmHg or the use of antihypertension medication, while uncontrolled hypertension was defined as an average SBP ≥130 mmHg or DBP ≥80 mmHg, regardless of antihypertension medication use. When considering continuous BLLs, for each 1 µg/dL increase in blood Pb there were higher odds of any hypertension among males (OR: 1.037 [95% CI: 1.015, 1.060]), but less so among females (OR: 1.020 [95% CI: 0.970, 1.074]). However, for each 1 µg/dL increase in BLLs, there were higher odds of uncontrolled hypertension for both hypertensive males (OR: 1.157 [95% CI: 1.080, 1.239]) and females (OR: 1.109 [95% CI: 1.020, 1.205]) and a smaller elevation in the odds of uncontrolled hypertension among all males (OR: 1.062 [95% CI: 1.036, 1.088]) and females (OR: 1.056 [95% CI: 1.011, 1.102]). The dose-response relationship, when considering a restricted cubic spline for BLLs, indicated a steeper slope up to around 2 µg/dL, like has been observed for other Pb exposure and hypertension outcomes (Figure 4-14, See Section 4.3.1.2). This relationship appears to be more pronounced in males than in females, especially when comparing uncontrolled

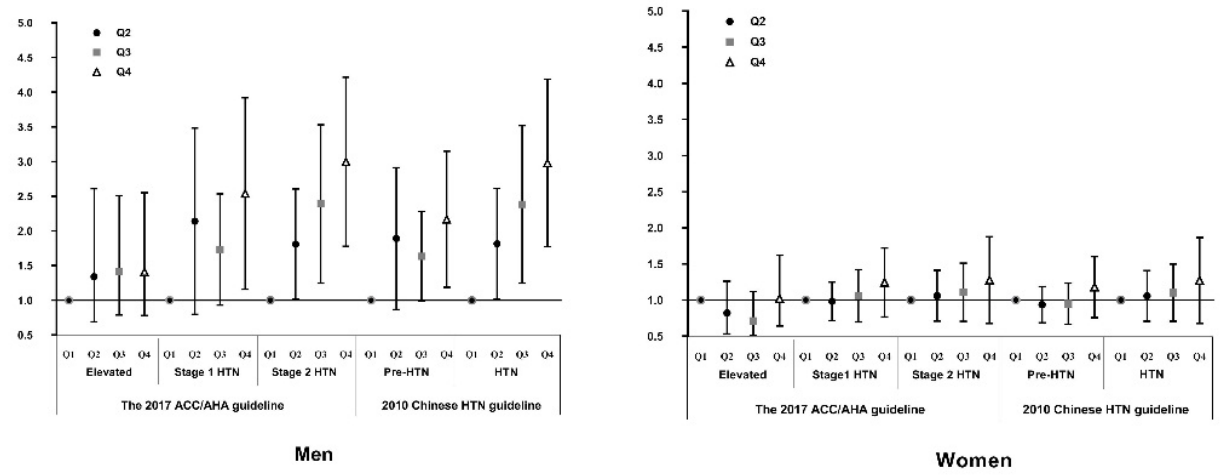
hypertension to those with controlled hypertension.



BMI = body mass index; BLL = blood lead level; HTN = hypertension; OR = odds ratio.
Source: Miao et al. (2020).

Figure 4-14 Dose-response curve between blood Pb and any hypertension or uncontrolled hypertension, restricted cubic splines, National Health and Nutrition Examination Survey (1999–2006).

Several other studies also evaluated EMM by sex for the association between biomarkers of Pb exposure and hypertension. Lee et al. (2016a) evaluated both hypertension and prehypertension using KNHANES (2008–2013) and observed positive associations between BLLs and hypertension (OR: 1.29 [95% CI: 1.10, 1.51]) and prehypertension (OR: 1.21 [95% CI: 1.06, 1.38]) in females only for each doubling of BLLs. Similarly, in the cross-sectional analysis of the Malmö Diet and Cancer Study, Gambelunghe et al. (2016) indicated an elevated effect of prevalent hypertension among females (OR: 1.4 [95% CI: 1.1, 1.7]), compared with males (OR: 1.2 [(0.6, 1.5]). However, Qu et al. (2022) indicated associations larger in magnitude, but with less precision, among males compared with females (Figure 4-15) in the China National Human Biomonitoring cohort.



ACC = American College of Cardiologists; AHA = American Heart Association; HTN = hypertension; Q = quartile.
Source: Adapted from Qu et al. (2022).

Figure 4-15 Effect measure modification by sex for the association between quartiles of blood Pb and prevalent hypertension.

Evaluation of EMM by race/ethnicity and other socioeconomic factors was less common in studies of hypertension, compared with studies examining BP alone. Scinicariello et al. (2011) examined EMM by both race/ethnicity and sex for the relationship between blood Pb and prevalent hypertension, using NHANES (1999–2006). Although the overall relationship between hypertension and blood Pb was null, an association was reported among Black males (OR: 2.69 [95% CI: 1.08, 6.72]) when comparing those with BLLs at the 10th percentile (<0.6 µg/dL) to those at the 90th percentile (3.5–10 µg/dL). Hara et al. (2015) indicated an overall null association between blood Pb and hypertension, however, an outcome that persisted even when stratifying by race/ethnicity in NHANES (2003–2010). In addition, the GuLF study (Xu et al., 2021) indicated a null association between concurrent blood Pb and hypertension in the full sample and in analyses stratified by race (Table 4-4).

Diet has also been considered as an EMM of this association. A recent KNHANES (2013) analysis evaluated the association between BLLs and hypertension by curry intake (Choi et al., 2018). Curcumin, a major component of curry, is known to have anti-inflammatory properties and can act as a chelating agent for heavy metals, such as Pb. This study defined hypertension as SBP >140 mmHg, DBP >90 mmHg, or current use of antihypertensive medication. This study indicated a null association between prevalent hypertension and blood Pb among those who regularly consumed curry (consumed at least one curry dish/month in the past year) (OR: 1.108 [95% CI: 0.827, 1.485]), for a 1 μg/dL increase in BLLs; however, an association was reported in those who did not regularly consume curry (OR: 1.399 [95% CI: 1.054, 1.857]). A previous analysis of the NAS cohort (Elmarsafawy et al., 2006) evaluated whether calcium intake affects the relationship between hypertensive status and bone Pb levels. High calcium intake has been associated with lower BP measurements and it has been hypothesized that calcium and Pb may interact with one another biologically. Using detailed dietary information to estimate calcium intake indicated there were moderate associations between either concurrent blood or bone Pb measurements and prevalent hypertension, but this association did not differ among those with low calcium intake (≤800 mg/d) compared with those with high calcium intake (>800 mg/d).

4.3.1.3 Blood Pressure and Hypertension in Children

The 2013 Pb ISA (U.S. EPA, 2013) indicated that the small body of evidence presented suggested a relationship between biomarkers of Pb exposure and BP and hypertensive effects in children, adding to the few studies presented in the 2006 Pb AQCD (U.S. EPA, 2006). Although BP effects are often more prevalent in adult populations compared with child populations, evidence from earlier studies suggested BP increases related to Pb biomarkers levels in children and adolescents. In the 2013 Pb ISA (U.S. EPA, 2013), the strongest evidence of a relationship between Pb biomarkers and increased childhood BP came from longitudinal studies (Zhang et al., 2012; Gump et al., 2005) and cross-sectional studies (Gump et al., 2011; Factor-Litvak et al., 1999). More recent data supports the previous findings. Study-specific details, including Pb biomarker levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 4-5. These details include standardized results as well as those that could not be standardized based on the information provided in each paper.

Several recent longitudinal studies highlight associations between increased BP associated with increased levels of biomarkers of Pb exposure in children. A longitudinal study in Mexico City (n = 457 mother-child pairs) evaluated cord BLLs (GM 4.67 μg/dL) and maternal bone Pb levels (patella [median: 11.6 μg/g] and tibia [median 9.3 μg/g]) 1-month postpartum and subsequently assessed BP in their offspring (aged 9–15) (Zhang et al., 2012). The associations between any Pb biomarker and changes in BP were null, but when evaluating sex as an effect modifier, a 10 μg/g increase in maternal tibia Pb levels was associated with increased SBP (1.62 mmHg [95% CI: 0.53, 2.71 mmHg]) and DBP (1.24 mmHg [95% CI: 0.23, 2.25]) in female children, but not in male children. There was no such association for

patella Pb or cord BLLs. Cortical (tibia) bone is reflective of cumulative exposure, whereas trabecular (patella) bone has a shorter half-life and a higher turnover rate of Pb. Additionally, cord blood is mostly representative of the BLLs in late-pregnancy and at birth, and not necessarily the BLLs the fetus was exposed to throughout pregnancy. In addition, a small prospective study (n = 122) among 9.5-year-old children, described in the 2013 Pb ISA, observed an increase in SBP (12.16 mmHg [95% CI: 2.44, 21.88 mmHg]), but only suggested an increase in DBP (8.54 mmHg [−0.45, 17.35 mmHg]) corresponding with a 1 μg/dL increase in cord BLLs (GM: 2.56 μg/dL) (Gump et al., 2005); even so, null associations were observed between concurrent blood levels and BP measurements.

In contrast, several recent longitudinal studies including mother-child pairs have been implemented and generally have yielded null results. Kupsco et al. (2019) assessed blood levels for several metals, including Pb (mean: 3.7 μg/dL), during the second trimester of pregnancy and specific cardiac and metabolic endpoints were evaluated among children, in a small prospective study (n = 548 mother-child pairs). The associations between the natural log of maternal BLLs and children's SBP or DBP were null. Another larger study (n = 1,511 mother-child pairs) using maternal BLLs evaluated the association between the erythrocyte fraction (Ery-Pb) in maternal blood and BP among children (~4.5 years) (Skröder et al., 2016). The Ery-Pb was assessed at both 14 weeks (median: 73 μg/kg) and 30 weeks (median: 86 μg/kg) gestation. Linear regression analyses identified no associations with SBP or DBP among young children. In addition, another recent study Zhang et al. (2021) of mother-child pairs (n = 1,194), evaluated BLLs in mothers 24–72 hours after delivery, BP was then subsequently assessed in children (aged 3–15). Among this cohort, there were null associations between mother's BLL and children's BP measurements.

Several recent cross-sectional studies that evaluated the association between concurrent BLLs and BP indicated positive associations. Gump et al. (2011) evaluated BP change as a response to acute stress. Children aged 9–11 (n = 140) were subjected to a variety of experimental tasks to stimulate the stress response. Children with higher quartiles of concurrent blood Pb (1.21 to 3.76 μg/dL) exhibited a greater change in SBP (7.23 mmHg; 95% CI not reported) compared with children with lower blood Pb (0.14 to 0.68 μg/dL; 5.3 mmHg) (Table 4-5). An earlier study, included in the 2013 Pb ISA, evaluated children (n = 281) with higher Pb blood levels (4.1 to 76.4 μg/dL) from two different towns in Kosovo, when it was part of Yugoslavia, with high (mean: 37.3 μg/dL) and low (mean: 8.7 μg/dL) BLLs. This study identified a modest association between a 1 μg/dL increase in concurrent BLLs and SBP (0.05 mmHg [−0.02, 0.13]) (Factor-Litvak et al., 1996). Additionally, a recent study from China, evaluated childhood BP and concurrent child blood Pb (Lu et al., 2018). Children in this study (n = 590) were recruited from two regions of similar SES in China, corresponding to an e-waste (high environmental Pb, mean: 7.14 μg/dL) exposed area (Guiyu) and a reference (low environmental Pb, mean: 3.91 μg/dL) area (Haojiang); no association was noted between log-transformed BLLs and either SBP or DBP among these children.

Several recent studies assessing BP and BLLs in children have relied on cross-sectional nationally representative data sets (NHANES, KNHANES). A large study evaluated seven 2-year NHANES cycles (1999–2012) among adolescents aged 12–19, with an average BLL of 1.17 µg/dL (Xu et al., 2017). In this cohort, there was no association between BLLs and BP. Another NHANES (2009–2016) analysis also indicated a null association between BP changes and blood Pb among children aged 8–17 (Desai et al., 2021). Similarly, a smaller study included three KNHANES cycles (2010–2016) among adolescents 10–18 years of age with a GM BLL of 1.19 µg/dL (Ahn et al., 2018). In this study, there was no association reported between a doubling of BLLs (log-transformed) and BP or prehypertension (SBP 120–140 mmHg, DBP 80–90 mmHg). Another NHANES analysis, used five 2-year NHANES cycles (2007–2016) among children and adolescents aged 8–17. This cohort had a GM of BLLs ranging between 0.98 µg/dL and 0.60 µg/dL from the first (2007–2008) to last (2015–2016) NHANES cycle evaluated. Similarly, there were no associations between BLLs and BP. However, when race/ethnicity was considered as an effect modifier, twofold higher BLLs were associated with lower DBP among Black children (−1.59 mmHg [95% CI: −3.04, −0.16 mmHg]), and higher DBP among white children (1.38 mmHg [95% CI: 0.40, 2.36 mmHg]) (Yao et al., 2020).

Several studies also evaluated total peripheral resistance (TPR) and its relationship with biomarkers of Pb in children. In general, TPR measures the total amount of force circulating blood imposes on the vasculature in the body and is represented by the ratio between MAP and cardiac output. Gump et al. (2011) evaluated cardiovascular responses, including sympathetic and parasympathetic activation, in response to acute stress in children. Children aged 9–11 were subjected to a variety of experimental tasks to stimulate the stress response. Overall, increased BLL quartiles corresponded to an increase in TPR. These results support a previous study by Gump et al. (2005), which reported higher Pb exposures during early childhood. In this study, Gump et al. (2005) indicated that an increase in early childhood (average age 2.6 years) BLLs was associated with a greater TPR response to acute stress years later (at 9.5 years of age). Overall, in this cohort, TPR increased with increasing quartiles of BLLs. Furthermore, BLL was identified as a mediator within this cohort between the relationship between SES and TPR reactivity. Specifically, Gump et al. (2007) indicated that BLLs may also mediate the association between SES and the cortical responses to acute stress. Furthermore, when controlling for childhood BLLs, family income (a measure of SES) was no longer predictive of cortisol levels.

4.3.2 Toxicological Studies of Blood Pressure and Hypertension

In the 2013 Pb ISA for Pb and previous Pb AQCDs, animal toxicological studies have consistently demonstrated a relationship between exposure to Pb and increases in BP. Nearly all animal toxicological studies provided evidence that long-term Pb exposure (>4 weeks), resulting in BLLs less than 10 µg/dL, could result in the onset of hypertension (after a latency period) in experimental animals that persists long after the cessation of Pb exposure (U.S. EPA, 2006). For example, Tsao et al. (2000) presented evidence for increased systolic and diastolic BP in rats with BLLs somewhat similar to the

current U.S. adult population (mean 2.15 µg/dL blood Pb), compared with untreated controls. In addition, there was a statistically significant, positive trend for increasing BP with increasing BLLs up to 56 µg/dL, with the effect leveling off at higher BLLs. There were a number of other studies from previous reviews demonstrating increases in measures of BP following exposure to Pb (Mohammad et al., 2010; Zhang et al., 2009; Badavi et al., 2008); Grizzo and Cordellini (2008); (Reza et al., 2008; Bravo et al., 2007; Robles et al., 2007); Heydari et al. (2006); (Bagchi and Preuss, 2005; Nakhoul et al., 1992). More information on these studies can be found in Section 4.4.2.2 of the 2013 Pb ISA (U.S. EPA, 2013).

Since the publication of the 2013 Pb ISA, animal toxicological studies with mean blood Pb values of ≤30 µg/dl have further demonstrated a relationship between exposure to Pb and increases in measures of BP. More specifically, rats with a mean BLL of 13.6 µg/dl following a 30-day drinking water exposure had statistically significantly higher SBP ($p < 0.05$) at 1, 2, 3, and 4 weeks of exposure when compared with control animals (Fioresi et al., 2014). At the end of the 30-day exposure, these authors also reported statistically significant increases in SBP, DBP, and MAP (Fioresi et al., 2014). Similarly, Nunes et al. (2015) reported that rats with an 8.4 µg/dl mean BLL had statistically significantly higher SBP from 7 to 28 days following a 30-day exposure, relative to control animals. In another multi-day measurement study, Xu et al. (2015) reported a statistically significant increase ($p < 0.05$) in SBP and DBP between the 6th and 17th day of a 40-day Pb exposure, but no difference from days 19 to 40. Pb levels in this study were 19.3 µg/dl at day 12 and 24.6 µg/dl on day 40 Xu et al. (2015).

In agreement with the studies that measured BP on multiple occasions throughout exposure, Silva et al. (2015) reported that rats with a 12.3 µg/dl BLL had statistically significantly ($p < 0.05$) higher SBP following a 30-day exposure relative to control animals. In an additional study, Shvachiy et al. (2018) exposed rats first through lactation. After weaning, rats were then exposed by drinking water either continuously until 28 weeks or were given 8 weeks of Pb abstinence and then exposed until 28 weeks. This study reported a statistically significant increase in DBP and MAP in rats continuously or intermittently exposed to Pb, as well as a significant increase in SBP in rats continuously exposed to Pb relative controls. In addition, for both exposure groups, the authors reported a statistically significant ($p < 0.05$) decrease in BP regulation as measured by differences in baroflex gain. Notably, a decreased baroflex response can impair BP recovery (i.e., lowering of BP) following stimulation of chemoreceptors that increase BP. BLLs in this study were ~24 µg/dl for the constant exposure group and ~19 µg/dl for the intermittent exposed group (Shvachiy et al., 2018). Similarly, in a study of rats exposed to Pb through lactation and weaning, statistically significant increases ($p < 0.05$) in SBP at timepoints ranging from PND 22 to PND 100 were reported relative to control animals. Mean BLLs ranged from ~11 µg/dl to 20 µg/dl in this study (Gaspar and Cordellini, 2014). In agreement with these studies, a pair of analyses demonstrated a statistically significant increase ($p < 0.05$) in SBP (but not DBP) relative to control animals following maternal exposure and then an additional a 1-year drinking water exposure that resulted in a BLL of <30 µg/dl (Zhu et al., 2019; Zhu et al., 2018).

While the above studies all reported some statistically significant increases in BP at one or multiple timepoints, Wildemann et al. (2015) reported no change relative to control animals for SBP, DBP, or PP for rats with a 1.7 µg/dl or 8.6 µg/dl BLL after 4 weeks of exposure. Moreover, combined exposure of Pb, mercury, and methylmercury resulted in no change in any of these BP measures relative to control (Wildemann et al., 2015).

When considered as a whole, the animal toxicological evidence presented above continues to demonstrate a clear relationship between Pb exposure and increases in measures of BP. All but one animal toxicological study evaluated above reported at least some measure of increased BP following Pb exposure. Additional details on these studies and their designs can be found in Table 4-6.

4.3.2.1 Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of BP. For example, angiotensin II (Ang II) stimulates arteriolar vasoconstriction leading to increases in BP. Angiotensin-converting enzyme (ACE) is involved in the activation of Ang II. In the 2013 Pb ISA, most studies demonstrated an effect of Pb on RAAS consistent with increases in BP. For example, following Pb exposure, vascular reactivity to Ang II was found to increase (Robles et al., 2007). Moreover, exposure to Pb also resulted in increases in kidney and/or serum ACE activity and renal angiotensin II positive cells (Rodríguez-Iturbe et al., 2005; Sharifi et al., 2004; Carmignani et al., 1999). In addition, Pb exposure increased activity and levels of the α-1 subunit protein of Na+/K+ATPase, which plays a major role in Na+ reabsorption and is regulated by the RAAS (Fiorim et al., 2011; Simões et al., 2011). Other studies demonstrating effects on RAAS can be found in Section 4.4.2.3 of the 2013 Pb ISA (U.S. EPA, 2013).

Since the 2013 Pb ISA, Fioresi et al. (2014) reported a statistically significant increase in NA^+ K^+ ATPase ($p < 0.05$) but no change in ACE activity in plasma and cardiac tissue. Thus, there is limited additional evidence for changes in RAAS following Pb exposure resulting in BLLs ≤30 µg/dl. Additional details for this toxicological study can be found in Table 4-6 of this ISA.

4.3.3 Integrated Summary of Blood Pressure and Hypertension

Several studies presented in the 2013 Pb ISA demonstrated positive associations between BP measurements and biomarkers of Pb exposure. The current literature continues to support these findings. Since the 2013 Pb ISA, several nationally representative cross-sectional studies (e.g., NHANES, KNHANES) have evaluated the association between concurrent blood Pb values and BP measurements or hypertension status. These studies can contribute substantially to the current evidence base, especially since there were fewer of nationally representative studies available at the time of the 2013 Pb ISA. Typically, cross-sectional studies can provide information on the association between concurrent blood

Pb values and BP measurements or on hypertension status taken at the time of the interview. While cross-sectional study designs have several limitations, it is important to emphasize the exposure window reflected in the different Pb biomarkers being considered. Specifically, blood Pb is a better reflection of more recent exposures and bone Pb is more closely linked with cumulative exposure. However, longitudinal studies can typically provide information on the relationship between historic Pb biomarker information and the change in BP since baseline or the development of hypertension. However, longitudinal studies may be biased if there is a large loss of follow-up. Both study types are valuable in discerning the associations between biomarkers of Pb exposure, BP, and hypertension. Overall, recent cross-sectional studies provided consistent evidence that higher concurrent BLLs are associated with higher SBP and DBP within adult populations. Evidence for higher PP and MAP were less consistent but these endpoints were examined in fewer studies. Associations between concurrent BLLs and BP among children were inconsistent, and mostly suggested a null association. Yet, a series of studies evaluating TPR among children indicated an association with increasing blood Pb values. In addition, studies evaluating a concurrent BLL and BP at a particular threshold (i.e., SBP >130 mmHg), mostly indicated null results.

Longitudinal studies less commonly evaluated changes in BP measurements (in mmHg) but were more likely to evaluate the development of clinical hypertension or prehypertension over a prolonged period of time. Most longitudinal studies evaluating incident hypertension or prehypertension and a marker of cumulative Pb exposure (measured in bone) indicated positive associations. In contrast, associations with incident hypertension or prehypertension were mostly null when using blood Pb measurements. Of the few longitudinal studies that evaluated BP changes, the results were mostly null, with a few indicating associations between baseline blood Pb measurements and changes in BP measurements over time.

Animal toxicological studies continue to support the epidemiologic evidence. Recent animal toxicological studies reaffirm the clear association between Pb exposure in animals and increases in BP, presented in the 2013 Pb ISA. Current studies specifically were restricted to only include lower BLLs (<30 μg/dL), and the majority of relevant studies indicated a persistent relationship between BLLs, whether it be related to continuous or intermittent exposures, and increases in BP. The evidence supporting changes in RAAS following Pb exposure is less consistent.

Several recent epidemiologic studies also evaluated EMM by race/ethnicity, sex, age genetic polymorphisms, among others. Taken together the evidence suggests that in addition to having higher blood Pb measurements, associations between blood Pb and BP are larger among non-Hispanic Black populations when compared with Hispanic or non-Hispanic white populations. When considered alone, there were mixed conclusions as to whether there were any differences in the association between Pb biomarkers and BP or hypertension by sex. However, when combined with race, Black males clearly demonstrated increased risk of Pb-associated BP changes, when compared with other sex/race groups. These results were consistent across several analyses. Taken together, the most recent evidence supports

the conclusions of the previous ISA, indicating an association between biomarkers of Pb exposure and changes in either BP or hypertension status, with evidence that certain populations may be at increased risk.

4.4 Ischemic Heart Disease and Associated Cardiovascular Effects

IHD, also known as CHD or CAD, is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart. The majority of IHD is caused by atherosclerosis (Section 4.8), which can lead to the blockage of the coronary arteries and restriction of blood flow to the heart muscle. An MI or heart attack is an acute event that occurs when heart tissue death occurs secondary to prolonged ischemia. Several studies within this section evaluate IHD as a composite measure mostly defined as the presence of MI, angina pectoris, or CHD death, whereas other studies evaluate composite IHD- risk scores using cross-sectional data. There were no animal toxicological studies examining indicators of IHD at BLLs ≤30 μg/dL published since the 2013 Pb ISA.

4.4.1 Epidemiologic Studies of Ischemic Heart Disease

The 2006 Pb AQCD (U.S. EPA, 2006) indicated an association between Pb biomarker levels and MI (Gustavsson et al., 2001). The 2013 Pb ISA (U.S. EPA, 2013) further contributed to this small amount of evidence with the inclusion of a study among the NAS cohort. This longitudinal study among (mostly white) men indicated an increased incidence of IHD associated with bone (both tibia and patella) Pb levels (Jain et al., 2007).

Several recent studies have been published since the 2013 Pb ISA that specifically evaluate the association between biomarkers of Pb exposure and measures of IHD, CHD, or CAD. Study-specific details, including biomarker Pb levels, study population characteristics, confounders, and select results from these studies are highlighted in Table 4-7. These details include standardized results as well as those that could not be standardized based on the information provided in each paper.

A recent study evaluated whether the relationship between CHD and bone Pb levels is modified by certain genetic polymorphisms (Ding et al., 2016). It is thought that certain genetic factors may predispose an individual to increased Pb toxicity. Using the NAS cohort, several genes and encoding proteins including ALAD, HFE, heme oxygenase-1 (HMOX1), VDR, apolipoprotein E (APOE), glutathione S-transferases, and the RAAS, were evaluated as effect measure modifiers of the relationship between bone Pb measurements and incident CHD. All these different genes and encoding proteins appear to play a role in influencing Pb uptake and or retention or may alter Pb toxicity. Overall, 22 different SNPs corresponding to these Pb-related genes were studied separately and in combination in a genetic risk score (GRS). Two GRSs were constructed; the first (GRS 1) summed all 22 SNPs, whereas

the second (GRS 2) only included the nine SNPs found to significantly modify the association between patella Pb levels and incident CHD within this study. Overall, without considering any genetic polymorphisms, the association between a twofold increase in patella Pb levels and CHD incidence was positive (HR: 1.36 [95% CI: 1.15, 1.61]). Several genetic polymorphisms appeared to further modify this relationship. Specifically, positive associations were observed for individuals with at least one minor allele in VDR (rs1544410 (*Bsm1*) HR: 1.65 [95% CI: 1.31, 2.08]); rs731236 (*Taq1*) HR: 1.61 [95% CI: 1.29, 2.02]); rs1073581 (*Fok1*) HR: 1.47 [95% CI: 1.17, 1.83]); rs757343 (*Tru91*) HR: 1.48 [95% CI: 1.18, 1.85]) and HMOX1 (rs2071749) HR: 1.51 [95% CI: 1.22, 1.86]), whereas individuals without any minor alleles had null associations. However, positive associations were observed among individuals without any minor alleles in HMOX1 (rs2071746 HR: 1.51 [95% CI: 1.07, 2.13]; rs5995098 HR: 1.62 [95% CI: 1.23, 2.14]), APOE (rs429358 HR: 1.43 (95% CI: 1.17, 1.75]) and angiotensinogen (AGT; rs699 HR: 2.17 [95% CI: 1.51, 3.12]; rs5046 HR: 1.57 [95% CI: 1.27, 1.94]). When considered in combination, both GRS values identified significant EMM for the association between a twofold increase in patella Pb and risk of incident CHD (GRS 1 HR: 2.27 [95% CI: 1.50, 3.42] and GRS 2 HR: 2.77 [(95% CI: 1.78, 4.31]).

Another study of the NAS cohort measured if incident CAD and bone Pb measurements were modified by diet (Ding et al., 2019). Evidence suggests that a diet deficient in essential metals (zinc, calcium, selenium, iron) can augment Pb absorption and retention in the body, while certain vitamins (C, E, and B_6) may function as antioxidants against Pb toxicity. Specifically, vitamins E and C can act by inhibiting lipid peroxidation by neutralizing Pb-related reactive oxygen species (ROS) by rapid electron transfer, while vitamin B_6 can act by reducing Pb-related increases in homocysteine. Additionally, vitamins B_1 and B_6 are composed of ring structures containing nitrogen, which may mediate interactions with Pb. This study collected detailed dietary information from each NAS member and classified diets high in fruit, legumes, whole grains, tomatoes, seafood, poultry, cruciferous vegetables, dark-yellow vegetables, leafy vegetables, and other vegetables as "prudent" diets. Alternatively, diets with a high intake of processed meat, red meat, refined grains, butter, high-fat dairy products, eggs, and fries, was considered a "Western" diet. The diet types were considered separately and were not mutually exclusive. For example, a low prudent diet was not equivalent to a high Western diet, and there could be some overlap in diet type between participants. Overall, results indicated that for each doubling of bone Pb levels there was a higher risk of CAD associated with both tibia (HR: 1.25 [95% CI: 1.06, 1.48]) and patella (HR: 1.30 [95% CI: 1.09, 1.56]). However, low prudent diet modified this association with patella Pb levels. Those with a low prudent diet (HR: 1.64 [95% CI: 1.27, 2.11]) had a higher association between patella Pb levels and CAD risk compared with those with a high prudent diet (HR: 1.07 [95% CI: 0.86, 1.34]). A Western diet did not appear to modify the results.

In a Canadian prospective cohort of patients on hemodialysis, incident cardiovascular events during the 2-year follow-up period were evaluated (Tonelli et al., 2018). Cardiovascular events were defined as acute MI, percutaneous coronary angioplasty, coronary artery bypass grafting, heart failure, and stroke or transient ischemic attack. Patients in this cohort (n = 1,278) had relatively low BLLs (1st

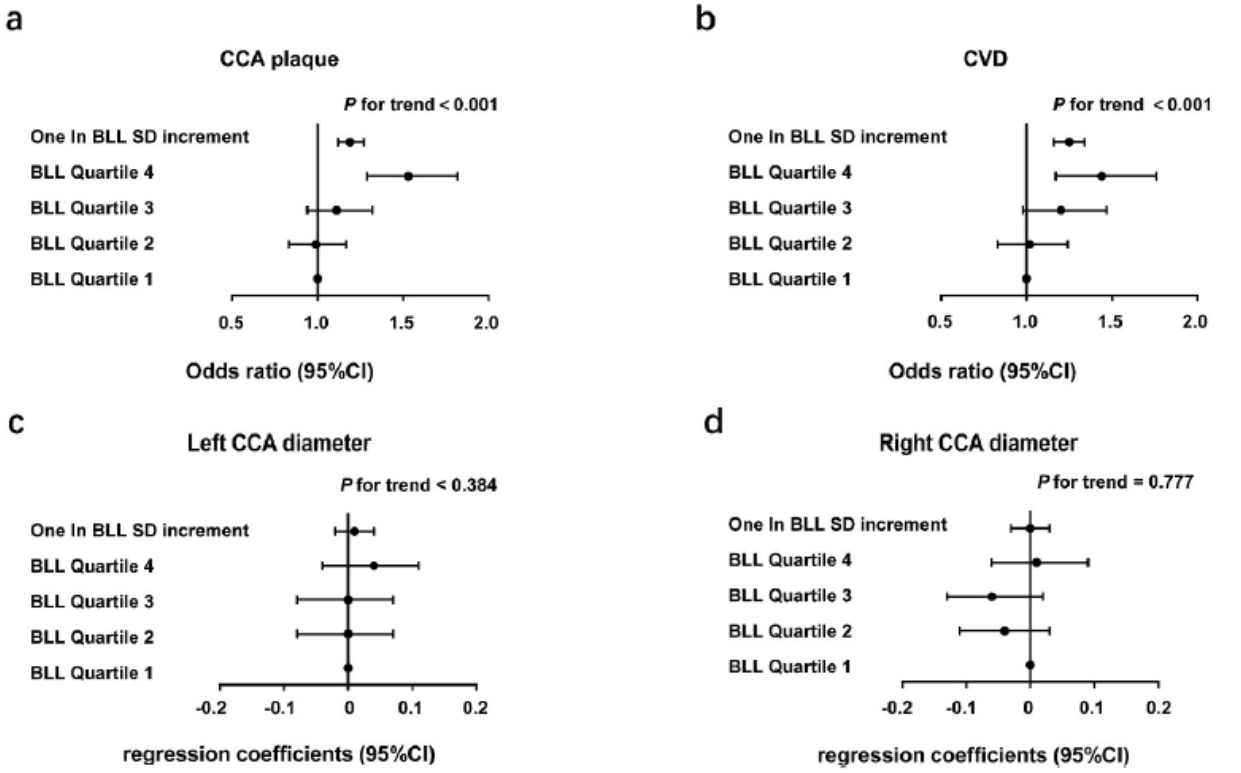
decile: 0.06 µg/dL, 10th decile 1.74 µg/dL), and there was no observed relationship between BLLs and cardiovascular events when comparing the highest with the lowest decile (results not shown).

Several recent cross-sectional analyses have assessed 10-year CHD risks in association with biomarkers of Pb exposure (Nguyen et al., 2021; Park and Han, 2021; Choi et al., 2020; Cho et al., 2016). Cho et al. (2016) calculated the Framingham risk score (FRS) to predict the 10-year risk of CHD in asymptomatic patients associated with BLLs among Korean men and women taking part in KNHANES IV and V (2008–2010). The FRS incorporates various CHD risk factors including age, gender, SBP, total cholesterol, and high-density lipoprotein cholesterol (HDL-C). This study indicated that for each increasing BLL quartile, there were statistically significant increased odds of an elevated FRS, compared with the lowest quartile among men. Specifically, there was a positive effect (OR: 3.13 [95% CI: 2.09, 4.69]) for the highest quartile of BLLs (3.519–26.507 µg/dL) compared with the lowest quartile of BLLs (0.711–2.129 µg/dL) among males. This effect was not observed among females (OR: 0.88 [95% CI: 0.26, 2.97]). Park and Han (2021) also calculated a CVD risk score based of the FRS from 2008. Again, using data obtained from KNHANES, this study calculated the effect of a log increase in BLLs associated with a 10%–20% increase in FRS. Park and Han (2021) indicated that a one-unit increase in log-transformed blood Pb was associated with an odds ratio of 2.4 (95% CI: 1.89, 3.18) of having an FRS increase between 10%–20% in men. However, this association was not observed among females (OR: 1.05 [95% CI: 0.68, 1.63]). Similarly, a >20% increase in the FRS score was associated with an odds ratio of 2.85 (95% CI: 2.02, 4.01) among males, but not among females (OR: 0.71 [0.19, 2.66]). Another assessment of KNHANES indicated that a doubling of BLLs was associated with an 0.10% (0.02, 0.21%]) increase in 10-year CVD risk (Nguyen et al., 2021) (Table 4-7)

(Choi et al., 2020) used KNHANES to evaluate associations between BLLs and the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score. The ASCVD risk score was calculated first based of the ACC and AHA guideline on the assessment of CVD risk. This formula incorporates factors such as age, total cholesterol, HDL-C, hypertension treatment, smoking status, and diabetes. For this analysis, the risk score was scaled to be more relevant to the Korean population, as the risk score was created based on mostly non-Hispanic white and non-Hispanic Black populations in the United States. This study also noted a higher ASCVD risk of 0.117 (95% CI: 0.005, 0.229) among men when comparing the highest with the lowest quartiles (distribution information not reported), but not among women (0.072, [95% CI: −0.004, 0.148]). When EMM was considered for urban versus rural locations, there was a higher ASCVD risk score effect estimate among men living in urban areas (0.133 [95% CI: 0.011, 0.254]) and among women living in rural communities (0.212 [95% CI: 0.045, 0.379]).

A recent cross-sectional study evaluated older, diabetic patients in China (Wan et al., 2021). This study (n = 4,324) evaluated BLLs and prevalent CVD. In this context, CVD was defined as a composite measure including a history of CHD, MI, or stroke. When comparing the highest quartile of BLLs (≥3.7 µg/dL) with the lowest quartile of BLLs (≤1.8 µg/dL), there were higher odds (OR: 1.44 [95% CI: 1.17, 1.76]) of CVD within this population at elevated BLLs (Figure 4-16). Additionally, another recent

study (n = 175) evaluated a collection of emerging predictive CVD biomarkers including asymmetric dimethylarginine (ADMA), adipocyte fatty acid-binding protein (FABP4, also known as aP2 and AFABP), adiponectin, and chemerin (Ochoa-Martínez et al., 2018). When comparing the highest tertile (T3: >9.1 µg/dL) with the lowest tertile (T1: <3.5 µg/dL), there was a positive association with ADMA (0.75 µmol/L [95% CI: 0.15, 1.85 µmol/L]) and FABP4 (27.5 ng/mL [95% CI: 10.0, 34.5 ng/mL]). Other biomarkers evaluated had null associations with BLLs.

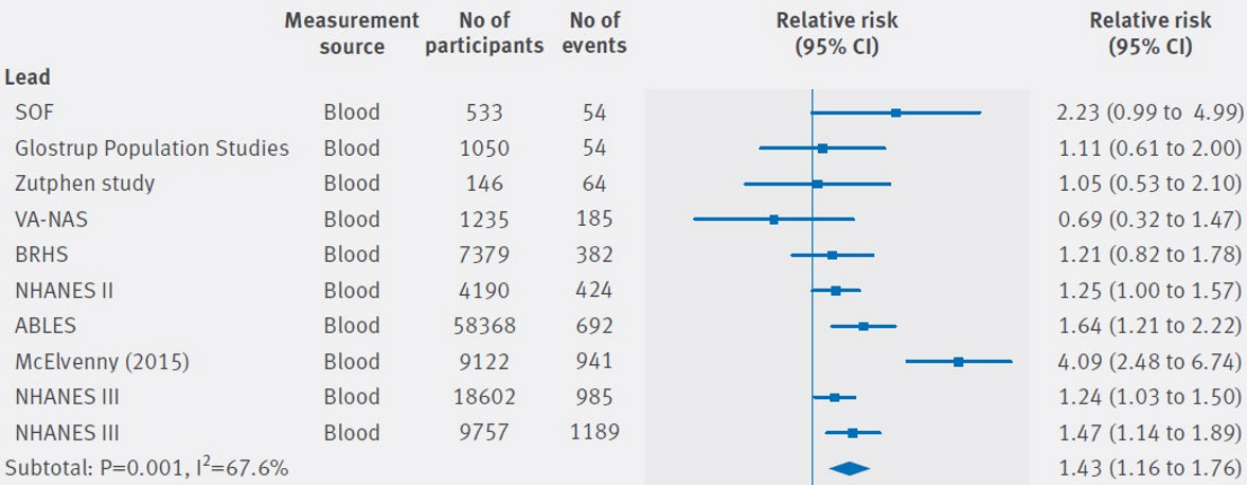


BLL = blood lead level; CCA = common carotid artery; CI = confidence interval; CVD = cardiovascular disease; SD standard deviation.
Source: Wan et al. (2021).

Figure 4-16 Relationship between blood Pb levels and common carotid artery plaques, common carotid artery diameter, and cardiovascular disease among diabetic patients.

A recent meta-analysis evaluating blood metals (including blood Pb) evaluated the aggregate association between BLLs and CHD risk (Chowdhury et al., 2018). For this study, CHD was defined as non-fatal MI, angina, coronary revascularization (i.e., percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or CHD mortality. It included studies with cohort, case-control, or nested-case-control study designs. In this analysis, a total of eight studies were identified including those that evaluated CHD mortality, those that were previously included in the 2006 Pb AQCD (U.S. EPA,

2006), and occupational studies. Even though none of the studies presented in this meta-analysis of CHD and BLLs were included in this section (cardiovascular mortality discussed in Section 4.10), the overall results further support an association between biomarkers of Pb exposure and IHD (Figure 4-17).



ABLES = Adult Blood Lead Epidemiology and Surveillance; BRHS = British Regional Heart Study; CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; SOF = Study of Osteoporotic Fractures; VA-NAS = Veterans Affairs Normative Aging Study.
Source: Adapted from Chowdhury et al. (2018).

Figure 4-17 Meta-analysis of the association between biomarkers of Pb exposure and coronary heart disease.

4.4.2 Summary of Ischemic Heart Disease

Limited evidence was presented in the 2013 Pb ISA (U.S. EPA, 2013) indicating an association between biomarkers of Pb exposure and incident IHD. Although this effect was strong across both blood and bone (patella) Pb measurements, there were not enough published studies at the time to fully evaluate the association.

Several recent epidemiologic studies have been published further supporting this association. Studies using the NAS cohort of elderly (mostly white) men indicated a positive association between patella Pb levels and incident IHD (Ding et al., 2019; Ding et al., 2016). These studies had extensive follow-up periods (~20 years), with patella Pb levels ranging between 29.2 and 32.2 µg/g. Additionally, a series of 10-year CVD risk evaluations (Nguyen et al., 2021; Park and Han, 2021; Choi et al., 2020; Cho et al., 2016) were conducted using KNHANES data. These studies used cross-sectional data to create a score that could be predictive of future CVD risk, and all indicated higher 10-year CVD risk with increasing BLLs. BLLs in these studies generally averaged <3 µg/dL.

While many of these studies evaluated the overall associations between biomarkers of Pb exposure and IHD or other similar outcomes, many evaluated EMM by sex, diet, and other distinguishing characteristics such as genetic polymorphisms. Overall, males (Park and Han, 2021; Choi et al., 2020;

Cho et al., 2016) tended to have larger Pb-associated IHD risks than females and certain genetic polymorphisms (Ding et al., 2016) modified the relationship between bone Pb levels and incident IHD. Furthermore, associations between bone Pb levels and incident IHD were larger for people with diets low in fruit, whole grains, and vegetables (Ding et al., 2019).

4.5 Heart Failure and Impaired Cardiac Function

Heart failure refers to a set of conditions in which the heart's pumping action is weakened. With congestive heart failure (CHF), the flow of blood from the heart slows and fails to meet the oxygen demands of the body, and the returning blood can back up and cause swelling or edema in the lungs or other tissues (typically in the legs and ankles). Right-sided heart failure is typically a consequence of left-sided heart failure but can also result from damage to the pulmonary vasculature, which can result in increased right ventricular (RV) mass, reduced flow to the left ventricle, and reduced left ventricular (LV) mass. In chronic heart failure, the heart typically enlarges and develops more muscle mass. The 2006 Pb AQCD (U.S. EPA, 2006) presented limited epidemiologic evidence on the association between biomarkers of Pb exposure and cardiac function. Little evidence was added in the 2013 Pb ISA. Since then, the evidence has expanded modestly, with recent epidemiologic and toxicological studies providing support for an effect between biomarkers of Pb exposure and cardiac function.

4.5.1 Epidemiologic Studies of Impaired Cardiac Function

The 2006 Pb AQCD presented a cross-sectional study indicating an association between Pb biomarker levels and LV hypertrophy (Schwartz, 1991). More recent studies indicate an association between Pb biomarkers and cardiac function. Study-specific details, including biomarker Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 4-8. These details include standardized results as well as those that could not be standardized based on the information provided in each paper.

A recent small (n = 179) prospective study (Yang et al., 2017) of a Flemish population evaluated potential toxic effects of Pb on the myocardium by assessing the association between blood Pb and LV function. Doppler imaging of transmitral blood flow was used to assess systolic and diastolic LV function. In this study, there was evidence of decreased LV systolic function for each doubling of blood Pb. Specifically, there were decreases in global longitudinal strain (GLS) by 0.497% (95% CI: −0.957, −0.038%), regional longitudinal strain (RLS) by 0.784% (−1.482, −0.087%), regional radial strain (RRS) by 2.316% (−4.748, −0.115%), and regional longitudinal strain rate by 0.071s^{-1} (95% CI: −0.124, −0.019s^{-1}). There was no association between BLLs and diastolic LV function. A cross-sectional study (n = 993) among a Swedish population evaluated LV measurements using two-dimensional echocardiography measuring septal thickness, posterior wall thickness, LV diameter in end diastole, and

LV diameter in end systole (Lind et al., 2012). For natural log increases in serum Pb, there was lower LV mass index (LVMI) (β: −0.73 [95% CI: −2.20, 0.74]) and higher relative wall thickness (RWT) (β: 0.011 [95% CI: −0.001, 0.022]), but neither were statistically significant.

4.5.1.1 Impaired Cardiac Function in Children

The 2013 Pb ISA (U.S. EPA, 2013)indicated that the small body of available evidence suggested a relationship between biomarkers of Pb exposure and cardiac function in children, adding to the few studies presented in the 2006 Pb AQCD (U.S. EPA, 2006). Specifically, Gump et al. (2011) evaluated cardiovascular responses, including sympathetic and parasympathetic activation, to acute stress in children. Children aged 9–11 were subjected to a variety of experimental tasks to stimulate the stress response. Cardiovascular measurements, including cardiac output and stroke volume were assessed at baseline and following each task. In general, increasing quartiles (Q1: 0.14–0.68 μg/dL, Q4: 1.21–3.76 μg/dL) of BLLs corresponded to decreases in stroke volume and cardiac output, compared with baseline. These results support a previous study by Gump et al. (2005), which had higher Pb exposures during early childhood.

A recent cross-sectional study provided further evidence of an association between more sensitive cardiac outcomes (Chen et al., 2021). This study evaluated Pb's potential effect on structural function and inflammation related to LV function in children. Children were recruited from two different primary areas, including an e-waste exposed area (Guiyu) and a reference area (Haojiang). Several different LV measurements were obtained. A 1-unit increase in BLL was associated with smaller (natural log) interventricular septum (IVS) measurements (β: −0.004 (95% CI: −0.007, −0.001). Other natural log echocardiogram measurements indicated null associations (LV posterior wall β: −0.001 [95% CI: −0.003, 0.001]); ejection fraction β: −0.001 (95% CI: −0.002, 0.001) with a unit increase in BLL.

4.5.2 Toxicological Studies of Impaired Cardiac Function

The previous ISA did not include any animal toxicological studies examining impaired cardiac function. However, animal toxicological studies published since the last review have looked at the potential for Pb exposure to alter cardiac function. Wildemann et al. (2015) reported no evidence for an effect of Pb exposure on stroke volume or cardiac output in rats. Moreover, combined exposure to Pb, mercury, and methylmercury resulted in no change in these measures relative to controls. In contrast, Fioresi et al. (2014) reported a statistically significant increase in some measures of cardiac contractility in rats. More specifically, they found a statistically significant increase in left ventricular systolic pressure (LVSP) and LV dP/dt, (change in pressure/change in time; $p < 0.05$), but not right ventricular systolic pressure (RVSP) or RV dP/dt following a 30-day exposure to Pb (13.6 μg/dl mean BLL). There were also no changes reported in left or right ventricular diastolic pressure (LVDP, RVDP) (Fioresi et al., 2014).

Additional studies examining the potential for impaired cardiac function were done in isolated LV papillary muscle. Silva et al. (2015) reported no significant difference in force generation between muscle isolated from control or Pb-treated (15-day exposure, 12.3 μg/dl BLL) rats following pulse stimulation. However, the time to peak tension and 90% relaxation was statistically significantly ($p < 0.05$) shorter in LV papillary muscle derived from Pb-treated animals relative to muscle from control animals. Moreover, inotropic contractile force was statistically significantly decreased in muscle from Pb-treated animals following treatment with calcium chloride, but not isoproterenol (Silva et al., 2015) and Pb exposure significantly lowered tetanic (sustained) peak and plateau force. In a similar analysis in LV papillary muscle, Fioresi et al. (2014) reported that following a 30-day exposure to Pb resulting in a mean 13.6 μg/dl BLL, there were not significant differences in isometric contraction force, time to peak contraction or relaxation rates. However, in contrast to Silva et al. (2015), following rest and calcium treatment, there was a statistically significant increase in contractile force in muscle from Pb-treated animals (Fioresi et al., 2014). When considered as a whole, the animal toxicological evidence for changes in cardiac function is limited and, in some cases, results across studies are conflicting. Additional details for the toxicological studies discussed in this section can be found in Table 4-9 of this ISA.

4.5.3 Integrated Summary of Impaired Cardiac Function

Limited evidence was presented in the 2013 Pb ISA (U.S. EPA, 2013) indicating an association between biomarkers of Pb exposure and indicators of cardiac function. The recent epidemiologic evidence suggests that the potential effect of Pb exposure on cardiac function may be more likely among children and the elderly. An analysis of participants >70 years of age indicated positive associations between markers of LV function and blood Pb, with relatively low mean BLLs (<2 μg/dL) (Lind et al., 2012). Associations with these same outcomes were null in a cohort of middle-aged participants (mean age ~39 years), although there was evidence of an association with markers of LV structure within this cohort (Yang et al., 2017). A study among children indicated a relationship between smaller IVS measurements with increased BLLs (Chen et al., 2021). Results of available animal studies examining cardiac function have been inconsistent, and conflicting results were reported in studies examining contractile force in isolated papillary muscle following calcium treatment (Silva et al., 2015; Fioresi et al., 2014).

A small number of studies presented associations between decreased stroke volume with increasing BLLs (Gump et al., 2011; Gump et al., 2005), but results were less consistent when considering cardiac output. In animal toxicological studies there was no evidence of an effect of Pb exposure on stroke volume or cardiac output, but limited evidence for an effect on measures of cardiac contractility. Taken together, there is limited evidence to support a relationship between biomarkers of Pb exposure and cardiac function.

4.6 Endothelial Dysfunction

Endothelial dysfunction is the physiological impairment of the inner lining of blood vessels that is characterized by an imbalance between vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1 (ET-1). High BP is often the result of an imbalance of these factors that leads to greater vasoconstriction.

4.6.1 Toxicological Studies of Endothelial Dysfunction

In the 2013 Pb ISA, animal toxicological studies provided mixed evidence for Pb exposure having an effect on vascular relaxation and constriction. For example, although Pb exposure decreased acetylcholine (ACh)-induced vasodilation in isolated rat tail arteries (Silveira et al., 2010; Zhang et al., 2007), Skoczynska and Stojek (2005) reported that Pb exposure enhanced vasodilation by ACh in rat mesenteric arteries. Moreover, in aortic rings of perinatally exposed rats, there was no change observed in the relaxation response to ACh (Fiorim et al., 2011; Rizzi et al., 2009; Grizzo and Cordellini, 2008). More information on these and other studies examining vascular reactivity from previous reviews can be found in Section 4.4.2.3 of the 2013 Pb ISA (U.S. EPA, 2013).

Since the publication of the 2013 Pb ISA, additional toxicological studies of vascular function have been published in animals with BLLs <30 µg/dl. In a study of young rats exposed to Pb through lactation, Pb exposure (BLL of ~11 µg/dl to 20 µg/dl) resulted in a statistically significant ($p < 0.05$) increase in the maximum contractile response to the vasoconstrictor noradrenaline in intact rat aortas at days 52, 70, and 100 (but not at day 23) relative to control animals (Gaspar and Cordellini, 2014). In denuded aortas (i.e., aortas with no endothelium), the contractile response to noradrenaline increased comparably from both control and Pb-treated animals, thereby suggesting that the difference in the contractile response in intact aortas was the result of Pb's effect on the endothelium (Gaspar and Cordellini, 2014). However, in an additional study using adult rats, there was no difference in intact rat aortic segments from control or Pb-exposed rats when treated with the vasodilators ACh or sodium nitroprusside, and a statistically significant ($p < 0.05$) *decrease* in the contractile response following exposure to the vasoconstrictor phenylephrine, but not potassium chloride (Nunes et al., 2015). The BLL in this study was 8.4 µg/dl and when the endothelium was mechanically removed, phenylephrine-induced contractility increased in both groups but to a greater extent in aortic segments from Pb-treated rats. Using a number of chemical inhibitors, the authors suggest that the decrease in contractility in response to phenylephrine (in intact aortic segments) was not due to a Pb effect on the vasodilator NO, but rather to increasing levels of hydrogen peroxide, which can also have vasodilatory effects. That is, incubation with catalase increased the constriction response to phenylephrine in aortic segments from Pb-treated rats but not control rats. The authors go on to show that differences in hydrogen peroxide activity between aortic segments from Pb-treated and control rats is potentially due to Pb increasing the levels of the hydrogen peroxide generating enzyme superoxide dismutase (SOD) (Nunes et al., 2015).

4.6.2 Summary of Endothelial Dysfunction

Taken together, the limited toxicological evidence presented above suggests that Pb exposure may result in changes in endothelial function. However, the direction of this response varies in that Pb exposure can either increase or decrease the response to vasodilators/vasoconstrictors. These studies also suggest that Pb's effects on the endothelium are complicated and differ depending on age, treatment (e.g., vasodilators testing endothelium-dependent versus endothelium-independent mechanisms), and/or type of endothelial cells tested. Additional details for the toxicological studies discussed in this section can be found in Table 4-10 of this ISA.

4.7 Cardiac Electrophysiology and Arrythmia

Electrical activity in the heart is crucial for regulating the heartbeat and is typically measured using surface electrocardiography (ECG). ECGs measure electrical activity in the heart that is due to depolarization and repolarization of the atria and ventricles. Changes in electrical activity can lead to changes in cardiac depolarization, repolarization, and development of arrythmia (Section 4.7.1) and changes in heart rate and HRV (Section 4.7.2)

4.7.1 Cardiac Depolarization, Repolarization, and Arrythmia

Experimental and epidemiologic studies typically use surface ECGs to measure electrical activity in the heart resulting from depolarization and repolarization of the atria and ventricles. The P-wave of the ECG corresponds to atrial depolarization, the QRS complex represents ventricular depolarization, and the T-wave represents ventricular repolarization. The ventricles account for the largest proportion of heart mass overall and thus are the primary determinants of the electrical activity recorded in the ECG. Therefore, ECG changes indicating abnormal electrical activity in the ventricles are of greatest concern. Endpoints denoting ventricular electrical activity include QTc interval, transmural dispersion duration, and T-wave shape. Changes in QT and ST, as well as changes in T-wave shape, duration, or amplitude, may indicate abnormal impulse propagation in the ventricles.

Cardiac arrhythmias can vary in severity from the benign to the potentially lethal, such as in cardiac arrest when an electrical disturbance disrupts the heart's pumping action causing loss of heart function. Atrial fibrillation (AF) is the most common type of arrhythmia. Clinical and subclinical forms of AF are associated with reduced functional status and quality of life, as well as downstream consequences such as ischemic stroke (Prystowsky et al., 1996; Anonymous, 1994) and CHF (Roy et al., 2009), contributing to both cardiovascular disease and all-cause mortality (Kannel et al., 1983). Ventricular fibrillation is a well-known cause of sudden cardiac death and is commonly associated with MI, heart failure, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease. Pathophysiologic

mechanisms underlying arrhythmia include electrolyte abnormalities, modulation of the autonomic nervous system (ANS), membrane channels, gap junctions, oxidant stress, myocardial stretch, and ischemia. Ventricular conduction and repolarization abnormalities such as QRS complex and QT interval prolongation, as well as LV hypertrophy and clinical antecedents including hypertension, are also associated with cardiac arrest (Rautaharju et al., 1994).

4.7.1.1 Epidemiologic Studies of Cardiac Depolarization, Repolarization, and Arrythmia

Numerous epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) strengthened the evidence presented in the 2006 Pb AQCD (U.S. EPA, 2006) that described an association between biomarkers of Pb exposure and changes in ECG measures. Current studies continue to support prior analyses. Study-specific details, including blood and bone Pb levels, study population characteristics, potential confounders, and select results from these studies, are highlighted in Table 4-11. These study details include standardized results as well as results that could not be standardized based on the information provided in each paper.

Previous ISAs described analyses evaluating the association between Pb biomarkers and electrophysiologic outcomes using the NAS cohort, of mostly white men. For example, Cheng et al. (1998) described an association between bone Pb and corrected QT interval (QTc) among men >65 years, and Eum et al. (2011) prospectively evaluated ECG findings and bone Pb levels within the NAS cohort. Eum et al. (2011) reported an association between tibia Pb levels and increases in QTc interval (7.94 msec [95% CI: 1.42, 14.45]) and QRSc duration (5.94 msec [95% CI: 1.66, 10.22]) when comparing the highest tertile of bone Pb levels with the lowest. Additionally, a cross-sectional analysis of elderly NAS men provided evidence of EMM of certain genetic polymorphisms in genes affecting iron (Fe) metabolism (HFE *C282Y* and HMOX1 L variants) on the relationship between biomarkers of Pb exposure and prolonged QT interval (Park et al., 2009).

A recent study supports these previous findings in a more diverse population (NHANES), compared with the NAS cohort of mostly white men. Jing et al. (2019) used NHANES III (1988–1994) to evaluate the relationship between log-transformed BLLs and the QRS-T angle. The QRS-T angle can quantify the relationship between ventricular depolarization (QRS-axis) and repolarization (T-axis) and is a predictor of ventricular arrythmia. The QRS-T angle was measured using a standard 12-lead ECG, and sex-specific tertiles of QRS-T angle were created. This study indicated that higher BLLs were associated with a greater QRS-T angle (third tertile versus first tertile) among men (OR: 1.35 [95% CI: 1.05, 1.74]), but not among women (OR: 1.05 [95% CI: 0.82, 1.36]).

4.7.1.2 Toxicological Studies of Cardiac Depolarization, Repolarization, and Arrythmia

The 2013 Pb ISA evaluated an animal toxicological study demonstrating that exposure to Pb resulted in increased incidence of arrhythmia and atrioventricular conduction block (i.e., disruption of electrical signals from the atria to the ventricles) after 12 weeks of Pb exposure (Reza et al., 2008). This study also reported a prolonged ST interval, without alteration in QRS duration. Since the last review, Wildemann et al. (2015) reported no change relative to control animals for PR, QRS, or QT for rats with a 1.7 μg/dl or 8.6 μg/dl BLL. A combined exposure of Pb, mercury, and methylmercury resulted, however, in significant increases in the QRS and QT intervals. Taken together, there is little animal evidence for an effect of Pb exposure alone on cardiac depolarization and/or repolarization.

4.7.2 Heart Rate and Heart Rate Variability

Heart rate is a key indicator of autonomic function. It is modulated at the sinoatrial node of the heart by both parasympathetic and sympathetic branches of the ANS and represents the number of times the heart beats in a given time frame (e.g., per minute). In general, increased sympathetic activation increases heart rate, while enhanced activation of parasympathetic, vagal tone decreases heart rate (Lahiri et al., 2008). HRV represents the degree of difference in the inter-beat intervals of successive heartbeats. Given that both arms of the ANS contribute, changes in HRV are an indicator of the relative balance of sympathetic and parasympathetic tone to the heart and their interaction (Rowan et al., 2007). Low HRV is associated with an increased risk of cardiac arrhythmia and an increased risk of mortality in patients with CHF awaiting a heart or lung transplant (Fauchier et al., 2004; Bigger et al., 1992). Low HRV has also been shown to be predictive of CAD (Kotecha et al., 2012). Notably, increases in HRV have also been associated with increases in mortality (Carll et al., 2018). In general, the two most common ways to measure HRV are time-domain measures of variability and frequency-domain analysis of the power spectrum. With respect to time-domain measures, the standard deviation of normal-to-normal (NN) intervals (i.e., the interval between consecutive normal beats) reflects overall HRV, and root-mean-square of successive differences (rMSSD) in NN intervals reflects parasympathetic influence on the heart. In terms of frequency domain, high-frequency (HF) domain is widely thought to reflect cardiac parasympathetic activity while the low-frequency (LF) domain has been posited as an indicator of the interaction of the sympathetic and parasympathetic nervous systems (Billman, 2013), although its linkage with sympathetic tone is controversial and uncertain (Notarius et al., 1999).

4.7.2.1 Epidemiologic Studies of Heart Rate and Heart Rate Variability

A small number of studies examining the relationship between Pb biomarkers and heart rate or HRV were evaluated in the 2013 Pb ISA(U.S. EPA, 2013). However, the studies characterized in the

2013 Pb ISA related to heart rate and HRV were all within the NAS cohort. Specifically, Park et al. (2006) presented evidence of a relationship between patella Pb levels and decreased HRV among those with three or more metabolic abnormalities (waist circumference >102 cm, hypertriglyceridemia ≥150 mg/dL, HDL-C <40 mg/dL, BP ≥130/85 mmHg, fasting glucose ≥110 mg/dL). The results of this study supported previous research presented in the 2006 Pb AQCD. Study-specific details, including blood and bone Pb levels, study population characteristics, potential confounders, and select results from these studies are presented in Table 4-11. These study details include standardized results as well as results that could not be standardized based on the information provided in each paper.

In a more recent study (n = 203), Gump et al. (2017) evaluated the association between BLLs and HRV among children (aged 9–11) as part of the Environmental Exposures and Child Health Outcomes study. However, associations between BLLs (range: 0.19–3.25 μg/dL) and HRV were null within this group. Another recent analysis (n = 408) evaluated the effect of BLLs and HRV among children (age 12) (Halabicky et al., 2022).This study obtained blood Pb measurements at two time points (aged 3–5 and 12), while HRV was measured only at age 12. Children in this study were given a standardized stressful stimulus known as the Public Speaking Stress task. In this task, children were asked to first plan a speech to deliver (planning phase) and then present that speech to the research assistant (speaking phase) while being continuously monitored for HRV. For the planning phase, there was a null association between a HRV frequency measure (LF/HF) and BLLs at ages 3–5 (0.03 [−0.02, 0.09]) and at age 12 (−0.04 [−0.16, 0.07]). For the speaking phase, there was a positive association between HRV frequency and BLLs at ages 3–5 (0.06 [0.01, 0.12]), but not with BLLs at age 12 (0.05 [−0.18, 0.08]). An increase in the LF/HF ratio is associated with a shift to sympathetic dominance and an overall decrease in HRV, which is suggestive of a dysregulated stress response.

4.7.2.2 Toxicological Studies of Heart Rate and Heart Rate Variability

The 2013 Pb ISA discussed a limited number of animal toxicological studies demonstrating that exposure to Pb increased heart rate (Simões et al., 2011; Badavi et al., 2008; Lai et al., 2002). There were no studies that examined changes in HRV in response to Pb exposure.

Since the publication of the 2013 Pb ISA, there have been additional toxicological studies published with respect to exposure to Pb and HR. Fioresi et al. (2014) reported statistically significantly higher heart rate ($p < 0.05$) in rats with a BLL of 13.6 μg/dl, relative to control animals. However, Wildemann et al. (2015) reported no change relative to control animals for heart rate in rats with a 1.7 μg/dl or 8.6 μg/dl BLL or following combined exposure with mercury or methylmercury. Other studies were similarly mixed, with some reporting statistically significant increases in heart rate following Pb exposure (Zhu et al., 2019; Zhu et al., 2018), while another study using two different exposure scenarios did not (Shvachiy et al., 2018). Thus, overall, there is mixed evidence from animal toxicological

studies for an increase in heart rate following Pb exposure. Additional details for the toxicological studies discussed above can be found in Table 4-12 of this ISA.

Since the 2013 Pb ISA, there have also been animal toxicological studies published with BLLs ≤30 μg/dl examining the relationship between Pb exposure and changes in HRV. Shvachiy et al. (2018) reported a statistically significant increase in LF in rats continuously, but not intermittently exposed to Pb relative to control animals. However, no changes in HF, or the LF/HF ratio were reported in either group relative to controls. BLLs in this study were approximately 24 μg/dl for the constant exposure group and approximately 19 μg/dl for the intermittent exposed group (Shvachiy et al., 2018). Additionally, in a pair of analyses by the same laboratory, there was a statistically significant increase ($p < 0.05$) in the LF/HF ratio and a statistically significant decrease in LF and HF. BLLs in this study were <30 μg/dl (Zhu et al., 2019; Zhu et al., 2018). Thus, there is only limited evidence from animal toxicological studies for an effect of Pb exposure on measures of HRV at BLLs ≤30 μg/dl. Additional details for the toxicological studies discussed above can be found in Table 4-12 of this ISA.

4.7.3 Integrated Summary of Cardiac Electrophysiology and Arrythmia

Exposure to Pb has been shown to affect contractility in animals and to be associated with cardiac contractility in epidemiologic studies. The epidemiologic evidence supports an association between altered ECG measures and biomarkers of Pb exposure. Specifically, a series of studies using the NAS cohort presented in the 2013 Pb ISA indicated an association between bone Pb levels and a prolonged QT interval (Eum et al., 2011; Park et al., 2009; Cheng et al., 1998). There is evidence suggesting that a lengthening of the QT interval increases risk of future abnormal heart rhythm or sudden cardiac arrest. However, these NAS studies were small and evaluated mostly white, elderly men. A recent study evaluated an earlier cohort of NHANES participants (NHANES III 1988–1994) (Jing et al., 2019). This study included a much larger sample size and a more diverse group of subjects. In this cross-sectional analysis, there was evidence of an increased QRS-T angle associated with BLLs. The effect was most prominent in males compared with females. Despite the relatively consistent evidence observed within the epidemiologic literature, the toxicological literature is sparce and more mixed. There was a single study in the last review demonstrating increased incidence of arrhythmia, atrioventricular block, and a prolonged ST segment interval (Reza et al., 2008). Since the last review, an additional study reported no change in the PR, QRS, or QT segments in rats (Wildemann et al., 2015)

The epidemiologic evidence for an association between biomarkers of Pb exposure and either heart rate or HRV are less compelling. Few studies evaluate this outcome. An earlier analysis of the NAS cohort indicated an association between bone Pb measurements and a decrease in HRV among elderly white men (Park et al., 2006). This supported evidence from occupational studies presented in the 2013 Pb ISA (U.S. EPA, 2013). Results from recent studies in children are not consistent. An analysis among a small group of children yielded no association between BLLs and HRV Gump et al. (2017), whereas a

separate analysis indicated a slight decrease in HRV among 12-year-old children with their BLLs when they were between the ages of 3–5 (Halabicky et al., 2022). The toxicological evidence for exposure to Pb and changes in heart rate was largely mixed. Some animal toxicological studies reported increases in heart rate following Pb exposures (Zhu et al., 2019; Zhu et al., 2018; Fioresi et al., 2014), whereas other animal studies reported no change (Shvachiy et al., 2018; Wildemann et al., 2015). With respect to HRV, there was a limited number of animal toxicological studies, but they reported changes in some measures of HRV following Pb exposure (Zhu et al., 2019; Shvachiy et al., 2018; Zhu et al., 2018). That said, there were differences among these studies with respect to which measures of HRV changed, or the direction of change for a given measure. Taken together, the relatively small body of evidence from epidemiologic and toxicological studies examining Pb exposure and changes in cardiac electrophysiology and arrythmia have reported mixed results.

4.8 Atherosclerosis and Peripheral Artery Disease

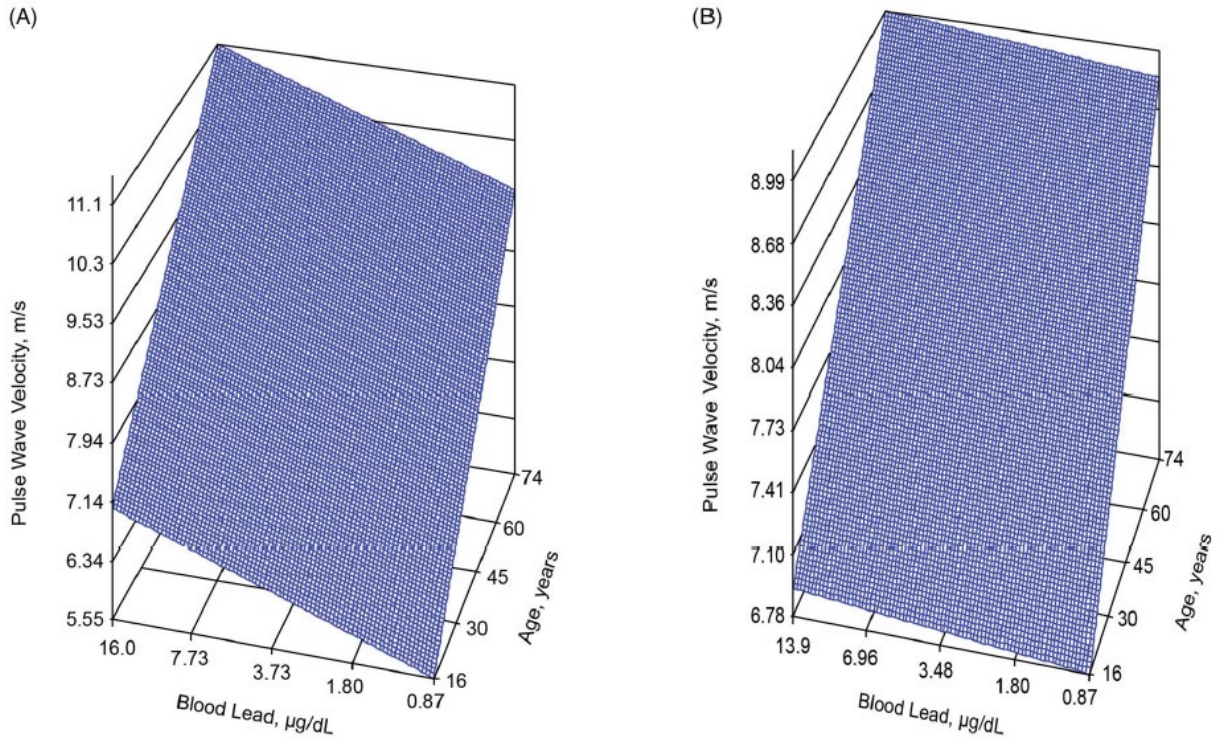
Atherosclerosis is the process of plaque buildup into lesions on the walls of the coronary arteries that can lead to vessel narrowing, reduced blood flow to the heart, and IHD. The development of atherosclerosis is dependent on the interplay between plasma lipoproteins, inflammation, endothelial activation, and neutrophil attraction to the endothelium, extravasation, and lipid uptake. Risk factors for atherosclerosis include high low-density lipoprotein (LDL) cholesterol/low HDL cholesterol, high BP, diabetes, obesity, smoking, and increasing age. Measures of subclinical atherosclerosis provide the opportunity to assess the pathogenesis of vascular disease at an earlier stage. PAD is an indicator of atherosclerosis and is measured by the ankle brachial index, which is the ratio of BP between the posterior tibia artery and the brachial artery. An ankle brachial index of less than 0.9 is typically indicative of the presence of PAD. Prior toxicological studies have reported that Pb can increase atheromatous plaque formation in pigeons, increase arterial pressure, decrease heart rate and blood flow, and alter cardiac energy metabolism and conduction (Prentice and Kopp, 1985; Revis et al., 1981).

4.8.1 Epidemiologic Studies of Atherosclerosis and Peripheral Artery Disease

A limited number of studies have evaluated the effects of biomarkers of Pb exposure and atherosclerosis. The 2013 Pb ISA (U.S. EPA, 2013) described an association between BLLs and both intimal medial thickening (IMT) and atherosclerotic plaque presentation in an occupational study, among those with high concentrations of blood Pb (~25 μg/dL) (Poręba et al., 2011). Recent studies further expand the knowledge base for the relationship between Pb biomarkers and atherosclerosis and PAD. Study-specific details, including BLLs, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 4-13. These details include standardized results as well as those that could not be standardized based on the information provided in each paper.

A study published since the 2013 Pb ISA evaluated diabetic patients in China (Wan et al., 2021). This study evaluated the association between common carotid artery (CCA) plaques and BLLs. When comparing the highest quartile of BLLs (≥3.7 μg/dL) with the lowest quartile of BLLs (≤1.8 μg/dL), there were increased odds (OR: 1.53 [95% CI: 1.29, 1.82]) of CCA plaque. The diameter of the CCA did not appear related to BLLs (Figure 4-16).

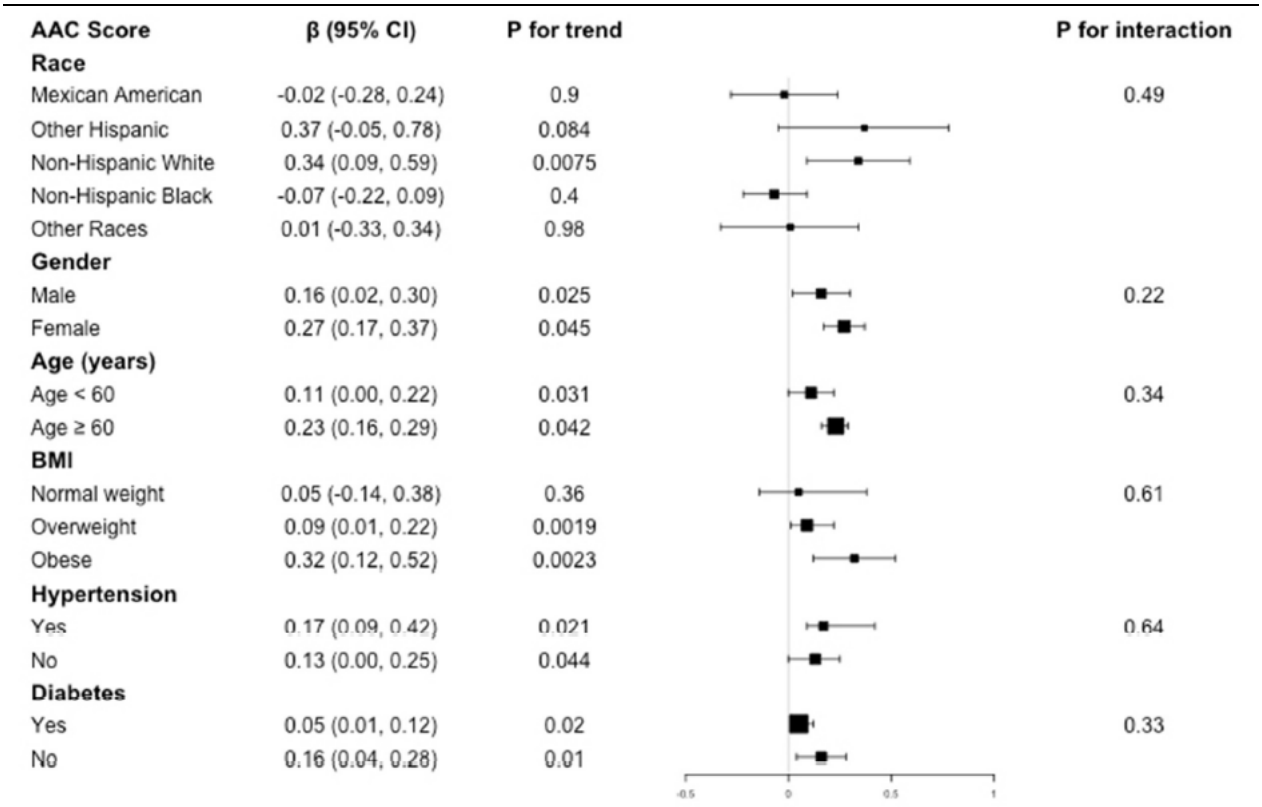
Another recent analysis described the association between hemodynamic measures (peripheral BP, central BP, and time-dependent hemodynamics), which assess arterial stiffness, and BLLs among a Flemish population (Yu et al., 2020). Blood Pb was collected at least once during the study period (1985 to 2005), and participants were followed for a median of 9.4 years. BLLs within this population were relatively low (GM: 2.93 μg/dL, IQR: 1.8–4.7). At the final follow-up, trained personnel assessed measures of arterial stiffness. Overall, measures of peripheral BP or central BP were not associated with BLLs. However, for every doubling of BLLs, several measures of time-dependent hemodynamics were elevated, including augmentation ratio (1.74% [95% CI: 0.95, 2.53%]), augmentation index (3.03% [95% CI: 1.56, 4.50]), forward pulse peak time (6.62% [95% CI: 2.21, 11.0%]), backward PP amplitude (1.02 mmHg [95% CI: 0.02, 2.02 mmHg]), and reflection index (3.98% [95% CI: 1.71, 6.24%]). However, the association with aortic pulse wave velocity (aPWV) was null (0.14 ms [95% CI: −0.08, 0.35 ms]), and age appeared to be a major component of increases in aPWV (Figure 4-18). The sum of these results from this study indicates an association between relatively low BLLs and evidence of atherosclerosis (Table 4-13).



Panel A: pulse wave velocity was only standardized to a heart rate of 60 beats per minute; Panel B: the associations were fully adjusted.
Source: Yu et al. (2020).

Figure 4-18 Association between aortic pulse wave velocity with blood Pb levels and age.

A large Korean study evaluated the association between BLLs and coronary artery stenosis (CAS), which is the blockage or narrowing of the arteries that supply blood to the heart (Kim et al., 2021). This study performed a coronary computerized tomography (CT) angiography and classified participants with CAS if they had ≥25% stenosis. Overall, each 1 µg/dL increase in BLL was associated with increased odds of CAS (OR: 1.14 [95% CI: 1.02, 1.26]). Many studies of atherosclerosis focus on calcification or blockage of the coronary artery, but a recent NHANES analysis focused on abdominal aortic calcification (AAC) (Qin et al., 2021). AAC is a marker of subclinical atherosclerosis and a predictor of future CVD events. Lateral lumbar spine images, using the Kauppila score system were used to score the AAC severity on a scale from 0 to 24, and a total AAC score >6 was considered to be substantial calcification of the abdominal aorta. Overall, each one-unit increase in BLLs corresponded to a 0.15-unit increase (95% CI: 0.02, 0.27) in total AAC score and an 11% increase in severe AAC (OR: 1.11 [95% CI: 1.00, 1.22]). There were no differences in association when stratified by race, sex, age, BMI, hypertension, or diabetic status (Figure 4-19).



AAC = abdominal aortic calcification; BLL = blood lead level; BMI = body mass index; CI = confidence interval; P = p-value.
Source: Qin et al. (2021).

Figure 4-19 Stratified associations between abdominal aortic calcification score and blood Pb levels.

The 2013 Pb ISA described epidemiologic studies assessing the relationship between biomarkers of Pb exposure and prevalent PAD. An NHANES (1999–2002) analysis observed an increasing trend in the odds of PAD with increasing concurrent BLLs (Muntner et al., 2005). Another NHANES (1999–2000) analysis also indicated a trend of increasing odds of PAD with increasing quartiles of concurrent BLLs, among adults >40 years (Navas-Acien et al., 2004). However, these results were not statistically significant for any quartile of Pb exposure. To date, no recent studies evaluating biomarkers of Pb exposure and PAD have been conducted for inclusion in the current review.

4.8.2 Toxicological Studies of Atherosclerosis

In the 2013 Pb ISA, a study in rats demonstrated that Pb exposure increased the aortic media thickness, media-lumen ratio, and medial collagen content (Zhang et al., 2009). Since the publication of that document, Xu et al. (2015) reported a statistically significant increase in proliferating cell nuclear antigen in cardiac tissue ($p \leq 0.05$) in rats exposed to Pb up to 12 or 40 days. This result potentially indicates increased cellular division and/or DNA repair following exposure to Pb, which is relevant given

that increased cellular proliferation plays a role in atherosclerotic plaque growth. Moreover, in the 40-day exposure group, these authors reported a statistically significant increase in the diameter of the cells of the aorta, as well as changes in the shape (i.e., loss of curvature) of the aortic internal elastic lumen relative to control animals. The blood Pb concentrations in this study were 19.3 μg/dl on day 12 and 24.6 μg/dl on day 40 (Xu et al., 2015). Additional details for the animal toxicological studies discussed in this section can be found in Table 4-14 of this ISA.

4.8.3 Integrated Summary of Atherosclerosis

At the time of the 2013 Pb ISA, there were few studies examining the relationship between biomarkers of Pb exposure and measures of atherosclerosis and PAD. Overall, these studies were mixed, with some indicating an association between BLLs and IMT or an increase in the odds of PAD prevalence, while others did not indicate a relationship between BLLs and prevalent PAD. Recent epidemiologic evidence indicates a consistent positive association between markers of atherosclerosis and Pb exposure. Atherosclerotic evidence is measured differently between the included studies, but further supports the notion of an association between BLLs and plaque formation. While there is strong evidence that markers of atherosclerosis increase with age, BLLs also appear to play a substantial role. The toxicological evidence from the previous and current ISA is limited but supports epidemiologic studies demonstrating a positive association between Pb exposure and markers of atherosclerosis. More specifically, there is animal toxicological evidence of morphological changes in the aorta consistent with the potential for atherosclerosis. Taken together, there is evidence from both epidemiologic and toxicological studies to support an association between biomarkers of Pb exposure and makers of atherosclerosis development.

4.9 Cerebrovascular Disease

Cerebrovascular disease describes a group of conditions involving the cerebral blood vessels that result in transient or permanent disruption of blood flow to the brain. These conditions include stroke, transient ischemic attack, and subarachnoid hemorrhage. Both hypertension and atherosclerosis are risk factors for cerebrovascular disease and the mechanisms for these outcomes also apply to cerebrovascular disease. Very few studies have examined the effects of Pb exposure on cerebrovascular disease.

4.9.1 Epidemiologic Studies of Cerebrovascular Disease

The 2013 Pb ISA (U.S. EPA, 2013) described a limited number of epidemiologic studies that examined associations between Pb exposure and cerebrovascular disease. Two previous prospective epidemiologic studies evaluated mortality from stroke(Khalil et al., 2009; Menke et al., 2006). In an

NHANES analysis, Menke et al. (2006) indicated that increases in BLLs were associated with an increase in stroke mortality, although the association was imprecise. In contrast, Khalil et al. (2009) reported a null association between BLLs and stroke mortality. In a cross-sectional study in Taiwan, Lee et al. (2009) reported an association between increased intracranial and extracranial stenosis (>50%) and urine Pb concentrations but not blood Pb concentrations.

In a recent small case-control analysis (n = 88), Mousavi-Mirzaei et al. (2020) evaluated acute ischemic stroke in relation to BLLs among patients in Iran. Cases (n = 44) of acute ischemic stroke were matched to controls (n = 44) based on age, sex, occupation, opium addiction, and sampling time. Participants in this study had relatively high BLLs (median: 6.38 µg/dL, IQR: 1.75−34.87). There was an association between increased BLLs and increased risk of acute ischemic stroke (OR: 1.04 [95% CI: 1.02, 1.07] for a 1 µg/dL increase in blood Pb). Study-specific details, including BLLs, study population characteristics, potential confounders, and select results are highlighted in Table 4-15. Study details in Table 4-15 include standardized results as well as results that could not be standardized based on the information provided in each paper There were no animal toxicological studies at BLLs ≤30 µg/dL that examined the relationship between Pb exposure and cerebrovascular disease.

4.9.2 Summary of Cerebrovascular Disease

Few studies have examined the relationship between biomarkers of Pb exposure and cerebrovascular disease. A small amount of evidence was presented in the 2013 Pb ISA suggesting an association between Pb exposure and stroke mortality or stenosis in the intracarotid system. Since the publication of these prior documents, however, very little additional epidemiologic information can be added to the current evidence base. Moreover, there were no relevant animal toxicological studies at BLLs ≤30 µg/dL. Thus, the evidence to suggest an association between Pb exposure and cerebrovascular disease is limited.

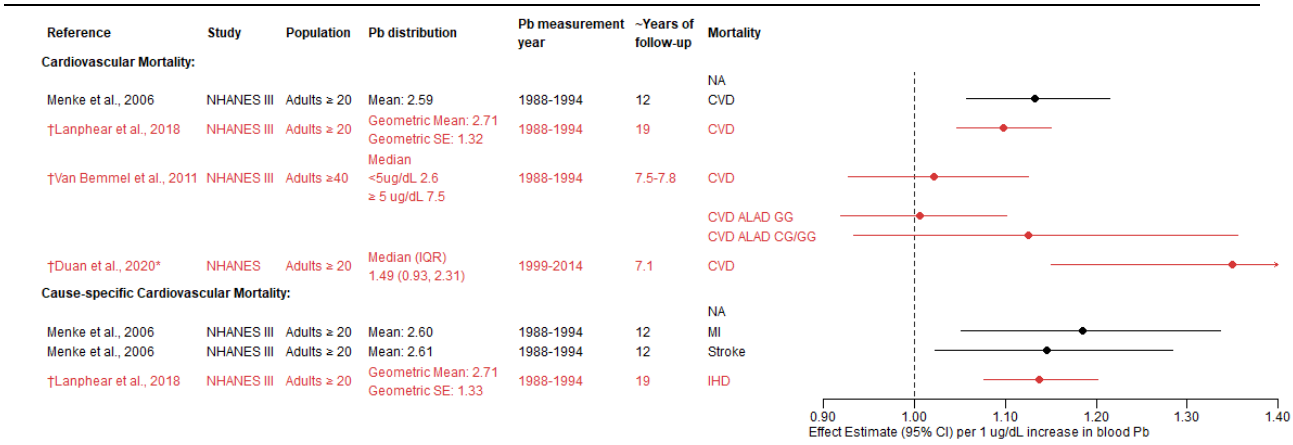
4.10 Cardiovascular Mortality

4.10.1 Epidemiologic Studies of Cardiovascular Mortality

Studies that examine the association between biomarkers of Pb exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for Pb-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects. Several epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) strengthened the evidence presented in the 2006 Pb AQCD (U.S. EPA, 2006) indicating an association between Pb biomarkers of exposure and cardiovascular mortality. The strongest evidence came from multiple prospective cohort

studies that observed consistent positive associations with CVD mortality across different populations, while also using different model specifications and approaches to control for a wide range of potential confounders. The majority of cohort studies evaluated in the 2013 Pb ISA utilized blood Pb data from NHANES II and III, which was then linked prospectively to mortality data, with between 8–16 years of follow-up (Menke et al., 2006; Schober et al., 2006; Lustberg and Silbergeld, 2002). Additional prospective cohort studies, specifically among older adults, reported that CVD mortality was associated with Pb measured in blood (Khalil et al., 2009).

Notably, adult BLLs may be representative of contributions from both recent Pb exposures and mobilization of legacy Pb from bone, therefore it remains unclear as to what extent either recent, past, or cumulative Pb exposures contribute to the observed associations with cardiovascular mortality. Because of the rapid decline in ambient air Pb concentrations and population BLLs that corresponded with the phase out of leaded gasoline, participants of NHANES II (1976–1980) and NHANES III (1988–1994) likely had higher past Pb exposures compared with exposure at the time of blood collection—further complicating the determination of BLLs that might contribute to the observed associations. Recent studies continue to provide evidence of consistent positive associations between exposure to Pb and CVD mortality (Figure 4-20). Study-specific details, including biomarker Pb levels, study population characteristics, confounders, and select results from these studies, are highlighted in Table 4-16.



ALAD = δ-aminolevulinic acid dehydratase; ALAD GG and ALAD CG/GG = variants of δ-aminolevulinic acid dehydratase; CI = confidence interval; CVD = cardiovascular disease; IHD = Ischemic heart disease; IQR = Interquartile range MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; Pb = lead; T# = tertile #.
Note: †Red text: Studies published since the 2013 Pb ISA, Black text: Studies included in the 2013 Pb ISA.
Effect estimates are standardized to a 1 µg/dL increase in blood Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval.
*Study estimated relative risk.

Figure 4-20 Associations between blood Pb level and cardiovascular mortality.

In an analysis of the NHANES III cohort, Lanphear et al. (2018) reported that a 1 μg/dL increase in BLLs was associated with hazard ratios (HRs) of 1.10 (95% CI: 1.05, 1.15]) for CVD mortality and 1.14 [95% CI: 1.08, 1.20]) for IHD mortality. Lanphear et al. (2018) extended the average follow-up time of the Menke et al. (2006) analysis of the same NHANES III cohort by over 7 years (from ~12 to ~19 years), resulting in a substantial increase in observed cardiovascular deaths (766 versus 1,801). Several other recent studies that analyzed NHANES cycles reported associations of similar magnitude for CVD mortality (Duan et al., 2020; Ruiz-Hernandez et al., 2017; Aoki et al., 2016; van Bemmel et al., 2011). Specifically, van Bemmel et al. (2011), Ruiz-Hernandez et al. (2017), and Cook et al. (2022) assessed cohorts using NHANES III data with similar results. Aoki et al. (2016) evaluated the relationship between CVD mortality and BLLs with additional control for either hemoglobin or hematocrit values using NHANES (1999–2010) data with mortality follow-up through 2011. A 10-fold increase in BLLs was associated with an RR of 1.26 (95% CI: 0.91, 1.78). However, when BLLs were hemoglobin-corrected (see details below), there was a greater increase in magnitude and precision in predicting CVD mortality, compared with the association with whole blood Pb alone (RR: 1.46 [95% CI: 1.06, 2.01]). Similar results were obtained when evaluating hematocrit-corrected whole BLLs and CVD mortality (RR: 1.44 [95% CI: 1.05, 1.98]).

Duan et al. (2020) evaluated the relationship between CVD mortality and BLLs using NHANES (1999–2014) with mortality follow-up through 2015. Here, a 1 μg/dL increase in BLLs was associated with an RR of 1.39 (95% CI: 1.28, 1.51). Both Aoki et al. (2016) and Obeng-Gyasi et al. (2021) also relied on more recent NHANES blood Pb data, 1999–2010 and 1999–2008, respectively. Because of the phaseout of leaded paint and gas, these more recent NHANES studies will capture populations potentially less affected by the earlier period of elevated Pb exposure. . It is expected, however, that these populations would still have had a substantial period of elevated BLLs in early life due to the gradual decline in BLLs over time.

A number of studies have additionally evaluated either hemoglobin- or hematocrit-corrected BLLs and mortality. Aoki et al. (2016) used six 2-year NHANES cycles (1999–2010) linked with mortality data through the end of 2011 (median follow-up time: 6.2 years) to evaluate the association between whole BLLs, hematocrit-corrected and hemoglobin-corrected BLLs, and CVD mortality among subjects >40 years of age at baseline. Hematocrit- or hemoglobin-corrected whole blood Pb was calculated by dividing whole blood Pb by either hematocrit or hemoglobin, respectively. To make the results more comparable with whole blood Pb, the values were multiplied by the weighted arithmetic mean of either hematocrit or hemoglobin (Aoki et al., 2017). In models assessing whole BLLs (not corrected for either hematocrit or hemoglobin), every 10-fold increase in whole BLLs was associated with an RR of 1.26 (95% CI: 0.91, 1.78) for cardiovascular mortality. Results were similar when controlling for hematocrit (RR: 1.35 [95% CI: 0.98, 1.86]) or hemoglobin (RR: 1.35 [95% CI: 0.98, 1.87]) as a covariate in the model. However, the association was stronger in terms of both magnitude and precision when evaluating hematocrit-corrected (RR: 1.44 [95% CI: 1.05, 1.98]) or hemoglobin-corrected (RR: 1.46 [95% CI: 1.06, 2.01]) whole BLLs. Another study (Lin et al., 2011), also examined BLLs corrected

for hemoglobin. Lin et al. (2011) examined Taiwanese adults with end-stage renal disease with relatively high (mean: 11.5 µg/dL) BLLs. To correct for hemoglobin, the authors used the following equations, for males: BLL × 14/hemoglobin concentration; for females: BLL × 12/hemoglobin concentration. The hemoglobin-corrected blood Pb results were similar in magnitude (HR: 7.35 [95% CI: 1.64, 33.33]) than the noncorrected blood Pb values (HR: 9.71 [95% CI: 2.11, 23.26]) when comparing the highest tertile (>12.64 µg/dL) with the lowest tertile (<8.51 µg/dL).

A recent re-analysis of NAS data (Weisskopf et al., 2015), expanded on a similar analysis (Weisskopf et al., 2009) which was presented in the 2013 Pb ISA. In the re-analysis, special considerations for selection bias were taken. Specifically, the authors created four different models, which controlled for different covariates, additional markers for SES, and restricted by age (Table 4-16). In this analysis, the authors restricted the sample (Model 3 and Model 4) to participants that were ≤45 years at the start of the NAS study, since cardiovascular disease-related deaths would be relatively rare in the younger population. This study indicated a positive association with CVD (HR: 2.23 [1.02, 4.84]) and IHD (HR: 4.60 [1.26, 16.8]) when comparing the highest tertile (>31 µg/g) of patella Pb to the lowest tertile (<20 µg/g), in the model restricting the age of participants to participants ≤45 years at the start of the NAS study. No associations were observed without the age restriction or with blood or tibia Pb.

In a recent study, Hollingsworth and Rudik (2021) implemented a quasi-experimental design to examine the effect of the phase out of leaded gasoline in automotive racing on mortality rates in older adults. Comparing time periods prior to and after the phaseout of leaded gasoline in professional racing series (i.e., the National Association for Stock Car Auto Racing [NASCAR] and the Automobile Racing Club of America [ARCA]), the authors used a difference-in-differences technique to estimate county-level changes in air Pb concentrations, elevated BLL prevalence among children, and mortality rates in race counties and counties bordering race counties relative to control counties. A detailed discussion of results for air Pb concentrations and BLLs is presented in Appendix 2, Section 2.4.1. In short, there were substantial declines in both air Pb concentrations and the prevalence of children with elevated BLLs associated with the phaseout of leaded gasoline. The authors also reported significant declines in cardiovascular mortality rates over this same period. Specifically, in the period following de-leading of gasoline, there was an estimated decline in annual age-standardized cardiovascular mortality rates of 37 deaths per 100,000 in race counties and 12 deaths per 100,000 in border counties. Additionally, there was a similar decline for IHD-related deaths, with 53 deaths per 100,000 in race counties and 20 deaths per 100,000 in border counties. Similar to the exposure results, the mortality estimates appear to demonstrate a distance gradient. The difference-in-difference approach controls for spatially varying confounders by estimating the difference in mortality rates in adjoining years in the same county and controls for temporally varying confounders by taking the difference of those differences between locations. The authors additionally adjust for potential confounders that may vary spatially and temporally (e.g., unemployment rate and quantity of Toxic Release Inventory [TRI] lead emissions). Hollingsworth and Rudik (2021) did not adjust for potential co-pollutant exposures but provides evidence that there is no differential effect of leaded and unleaded races on other co-pollutant concentrations (i.e., CO, VOCs,

PM_{10}, $PM_{2.5}$, NO_2, and O_3) in the weeks leading up to and following the race. However, because the mortality rates are an annual measure, there is remaining uncertainty regarding potential differential trends in the long-term average of other pollutants that could be correlated with the phaseout of leaded gasoline in NASCAR and ARCA.

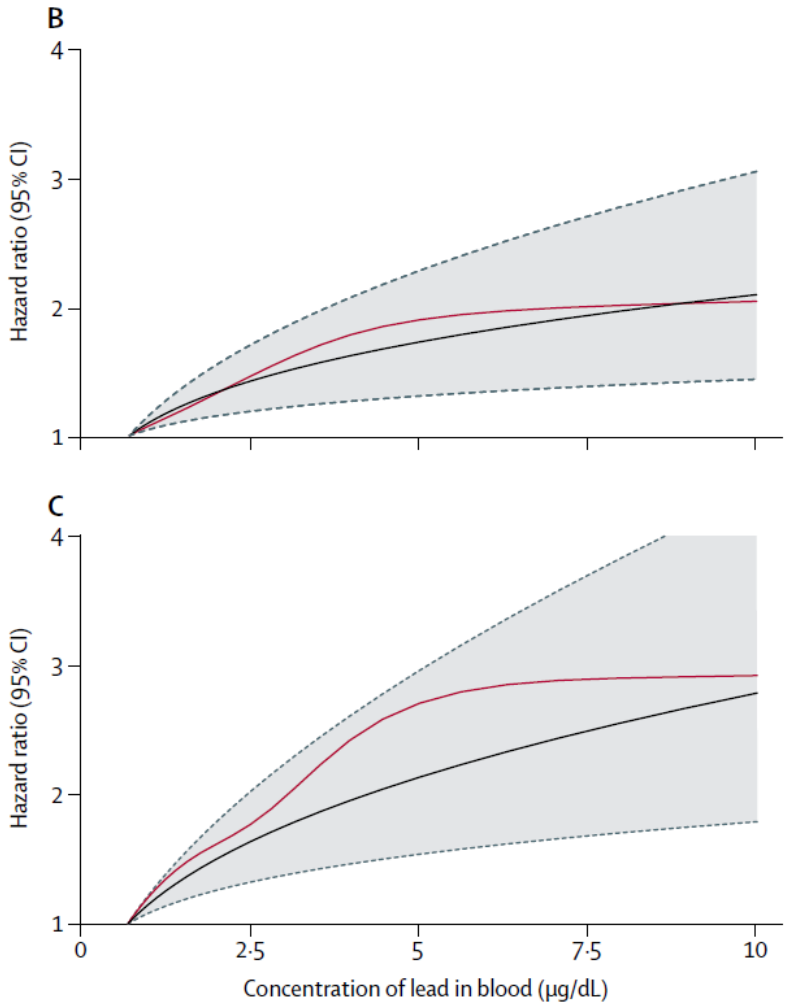
Several analyses evaluated metal chelation therapy as a treatment for those with atherosclerotic plaques and evaluated subsequent mortality outcomes in the Trial to Assess Chelation Therapy (TACT) study. The TACT study was a randomized control trial (RCT) with a 2 × 2 factorial design evaluating chelation therapy with ethylenediaminetetraacetic acid (EDTA) plus the use of high dose oral vitamins. The factorial group results indicated that a combination of EDTA and high-dose vitamins was associated with a reduction in clinically important cardiovascular events, especially for cardiovascular deaths, MI, or stroke (Lamas et al., 2014). In the same trial, the findings indicated that diabetic patients ≥50 years, had a reduction (6% versus 9% HR: 0.63 [95% CI: 0.35, 1.13]) in cardiovascular death following EDTA chelation therapy (Escolar et al., 2014). Although these studies suggest a clear association between chelation therapy and a reduction in cardiac deaths, these studies did not measure BLL pre and post chelation making the potential role of Pb unclear, as compared to other divalent ions that are chelated by EDTA.

Additionally, a recent meta-analysis (Chowdhury et al., 2018) evaluated several metal biomarkers, including BLLs, and evaluated the overall association between BLLs and CHD, specifically including studies of CHD mortality. It included studies with cohort, case-control, or nested-case-control study designs. As described in Section 4.4, this analysis provided evidence of an increased risk of CHD mortality associated with increasing BLLs (Figure 4-20).

4.10.1.1 Dose-Response Relationship

An examination of the dose-response relationship between biomarkers of Pb exposure and cardiovascular mortality helps to further evaluate the continuum of effect between biomarkers of Pb exposure and cardiovascular outcomes. Because of differences in exposure historically, it is expected that adult BLLs would be influenced by historical Pb exposures. Therefore, studies examining a single blood Pb measurement in adulthood may not fully capture the true effect of biomarkers of Pb exposure and cardiovascular mortality.

Several recent studies, however, have summarized mortality outcomes over a range of blood Pb values. Lanphear et al. (2018) extended the follow-up period of the Menke et al. (2006) study and evaluated the dose-response relationship among the same population. Using a five-knot restricted cubic spline analysis, this study generally indicated a supralinear dose-response relationship between BLLs and CVD and IHD mortality. The authors also stated that this dose-response relationship was steeper (HRs were larger in magnitude) at lower blood Pb concentrations. Overall, this study reported increased risk of CVD or IHD mortality among those with BLLs <5 µg/dL (Figure 4-21).



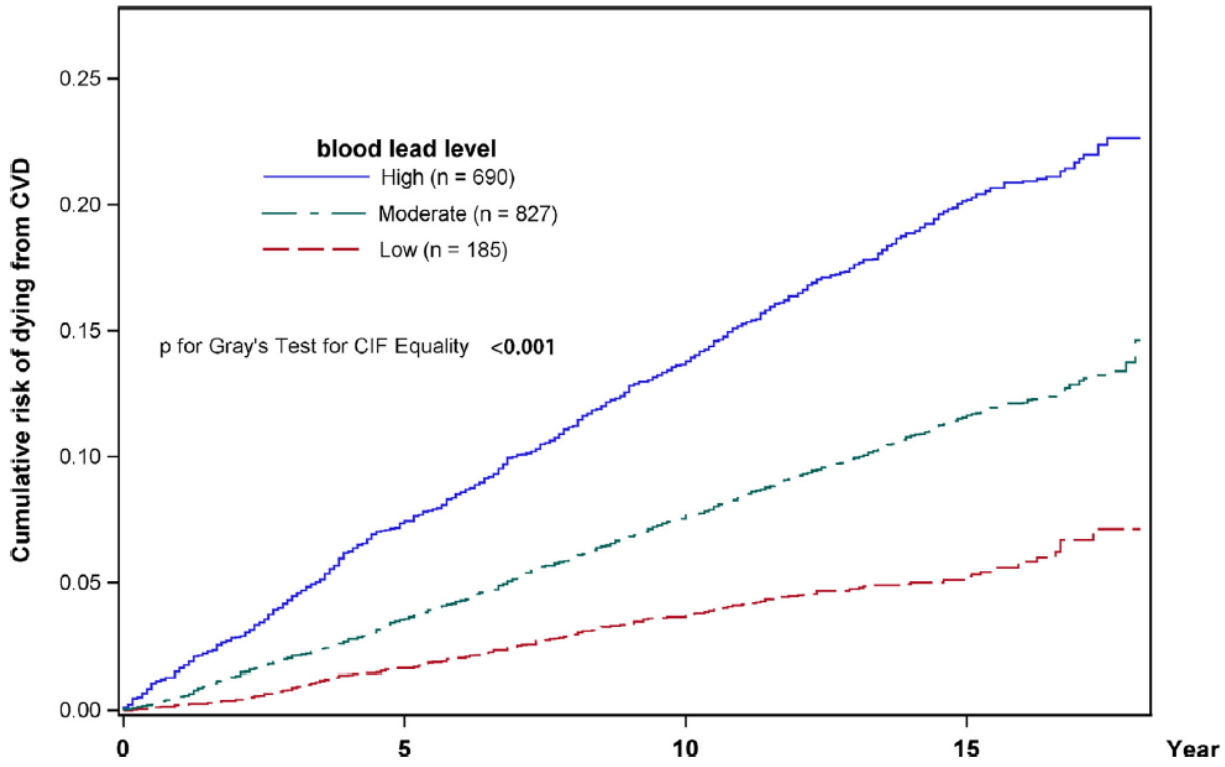
CI = confidence interval.
Note: Restricted cubic spline (5 knots) (red lines) and adjusted HRs (black lines) with 95% CIs (hatched lines) for (B) cardiovascular disease mortality and (C) IHD mortality.
Source: Adapted from Lanphear et al. (2018).

Figure 4-21 Dose-response relationship between blood Pb levels and cardiovascular and ischemic heart disease mortality.

These results are similar to other assessments of the dose-response relationship described in previous assessments of Pb, including the 2006 Pb AQCD (U.S. EPA, 2006) along with the 2013 Pb ISA (U.S. EPA, 2013). In the original evaluation of the NHANES III data and mortality, Menke et al. (2006) noted a similar linear shape of the dose-response curve. Specifically, the dose-response relationship was steeper at lower blood Pb concentrations.

A similar NHANES III (1988–1994) analysis evaluated total CVD, heart disease (CVD diagnosis codes excluding stroke), and MI deaths through 2010 (Cook et al., 2022). This study indicated a greater risk of CVD mortality among those with the highest BLLs (≥6.23 µg/dl for men and ≥3.74 µg/dl for

women) (Figure 4-22). Similar patterns were reported for heart disease and MI mortality. The results of this analysis provide no evidence of a threshold below which an association between blood Pb and mortality does not exist, at least within the blood Pb ranges within this study (10th percentile: 1.0 µg/dl, 90th percentile: 6.7 µg/dl). A sensitivity analysis evaluated BLLs continuously. In the model, a 1-unit increase in log-transformed BLLs was associated with an 8% (HR: 1.08 [95% CI: 1.00, 1.16]) increase in total CVD mortality risk and a 9% (HR: 1.09 [95% 1.02, 1.16]) increase in heart disease risk. However, there was no reported increased risk of acute MI mortality associated with a 1-unit increase in log-transformed BLLs (HR: 0.95 [95% CI: 0.84, 1.08]).



CIF = cumulative incidence function; CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey.
Source: Cook et al. (2022).

Figure 4-22 Cumulative incidence function of cardiovascular mortality by blood Pb level, National Health and Nutrition Examination Survey III (1988–1994).

4.10.1.2 At-Risk Populations

Several recent analyses of biomarkers of Pb exposure and cardiovascular mortality have evaluated EMM or stratification of the relationship by specific parameters such as sex, genetic factors,

stress, and behavior factors like smoking, whereas other analyses have primarily focused on populations or lifestages that may be particularly vulnerable to premature mortality associated with biomarkers of Pb exposure. The differences observed in at-risk populations are described below.

4.10.1.2.1 Effect measure modification

Ruiz-Hernandez et al. (2017) used NHANES III (1988–1994) and three 2-year NHANES cycles (1999–2004) linked with mortality data—through the end of 1996 for the NHANES III cohort and through the end of 2006 for the NHANES 1999–2004 cohort data—to assess the relationship between BLLs and CVD and CHD mortality. This study showed that in fully adjusted models, there were increases in both CVD mortality (relative risk [RR]: 1.19 [95% CI: 1.07, 1.31]) and CHD mortality (RR: 1.24 [95% CI: 1.10, 1.41]) for each doubling of BLLs. The RRs for both CVD and CHD mortality were stronger among women compared with men and among never-smokers compared with ever-smokers. Despite a higher mean BLL in the NHANES III (1988–1994) cohort, the RR was 1.17 (95% CI: 1.06, 1.29) compared with 1.43 (95% CI: 1.16, 1.78) in 1999 to 2004.

van Bemmel et al. (2011) investigated a smaller subset of NHANES III (1988–1994) subjects. This study specifically evaluated EMM of the relationship between BLLs and cardiovascular mortality by polymorphisms in ALAD. A critical mechanism of Pb toxicity is its ability to interact and inhibit key enzymes, such as ALAD, in the heme biosynthetic pathway. This analysis identified a null association between elevated BLLs (>5 μg/dL) and cardiovascular mortality. When further stratified by ALAD variant, this study continued to observe null associations of elevated BLLs (>5 μg/dL) among both $ALAD^{GG}$ variants for cardiovascular mortality (HR: 1.01 [95% CI: 0.92, 1.10]) and among $ALAD^{CG/CC}$ variants (HR: 1.13 [95% CI: 0.93, 1.36]).

In a more recent analysis, (Obeng-Gyasi et al., 2021) evaluated whether the association between BLLs and CVD mortality was modified by AL, a measure of cumulative stress. This study used NHANES (1999–2008) data linked to mortality data through 2014. First, the study indicated that higher BLLs were associated with a higher AL index. There was also an increased risk of CVD mortality among those with BLLs ≥1.55 μg/dL (median) (HR: 2.35 [95% CI: 1.77, 2.93]), when compared with those below the median BLL. This study also indicated that the interaction between BLLs and AL was significant ($p = 0.014$) but did not present stratified results.

Evidence of EMM is in direct contrast to stratified analyses presented in the previous Pb ISA. Menke et al. (2006) demonstrated that there were no interactions between BLLs and other adjusted variables, when comparing the 80th percentile (4.92 μg/dL) with the 20th percentile (1.46 μg/dL) of BLLs. Specifically, the association between BLLs and cardiovascular mortality was positive but not different when stratified by age, race, sex, urban/rural residence, smoking, BMI, and comorbid conditions (hypertension, diabetes, low kidney function). However, Lanphear et al. (2018) indicated EMM by age, in the same NHANES population, but with longer follow-up. Specifically, individuals ≥50 years old had

greater HRs for cardiovascular disease mortality (HR: 2.93 [95% CI: 1.60, 5.36] vs. HR: 2.08, [95% CI: 1.35, 3.19]) and for IHD mortality (HR: 4.68 [95% CI: 2.42, 9.05] vs. HR: 2.46, [95% CI: 1.51, 4.01]). Additionally, the HR for cardiovascular disease mortality was higher in smokers (HR: 2.19 [95% CI: 1.47, 3.26]), compared to non-smokers (HR: 1.32 [95% CI: 0.86, 2.05]).

4.10.1.2.2 Specific Populations

Several recent analyses have focused on the analysis of biomarkers of Pb exposure and cardiovascular mortality among certain populations with comorbid conditions or at specific lifestages. Lin et al. (2011) evaluated the relationship between BLLs and mortality among patients on maintenance hemodialysis in a relatively short (~18 months of follow-up) prospective cohort in Taiwan. Study subjects had a relatively high average BLL (mean: 11.5 μg/dL), which is higher than the general Taiwanese population (mean: 7.7 μg/dL). It is suspected that hemodialysis patients may experience higher BLLs because their kidneys may no longer be able to excrete Pb from the body due to a total loss of renal function (see Appendix 5: Renal Effects). There was an increased HR among those in the third tertile of BLLs (>12.64 μg/dL) for cardiovascular mortality (HR: 9.71 [2.11, 23.26]), compared with the first tertile of BLLs (<8.51 μg/dL). Additionally, when considering hemoglobin-corrected blood Pb values, the association between the highest and lowest tertile was smaller in magnitude (HR: 4.98 [95% CI: 1.86, 13.33]) compared with whole blood Pb measurements, but was still imprecise (both measurements had large confidence intervals).

4.10.2 Summary of Cardiovascular Mortality

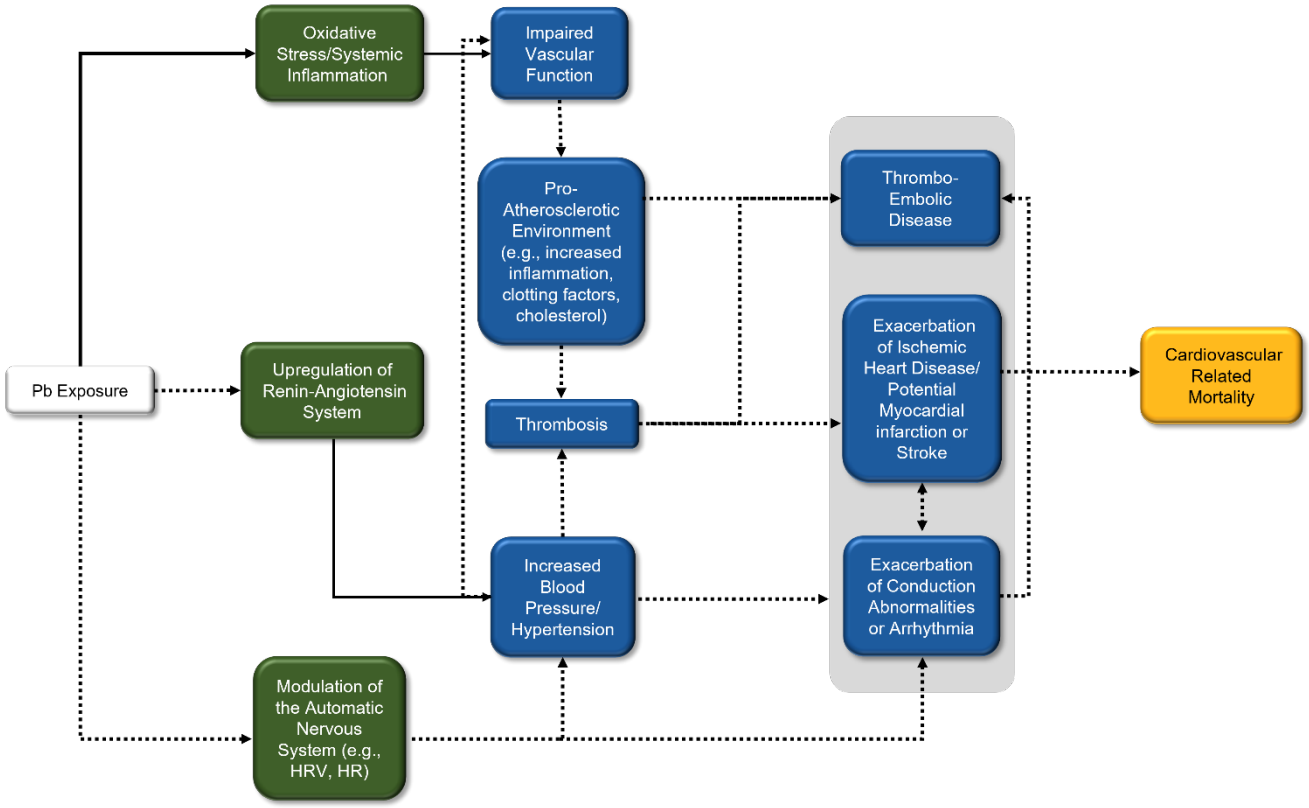
The CVD mortality results in this review supported and expanded on findings from both the 2006 Pb AQCD, which included NHANES mortality studies (Schober et al., 2006; Lustberg and Silbergeld, 2002), and the 2013 Pb ISA, which included an NHANES mortality study (Menke et al., 2006) and non-NHANES cohort analyses (Khalil, 2010; Khalil et al., 2009; Weisskopf et al., 2009). Several of the most recent NHANES analyses (Duan et al., 2020; Lanphear et al., 2018; Ruiz-Hernandez et al., 2017; Aoki et al., 2016) further strengthen the evidence provided within the 2013 Pb ISA, by including a wide range of potential confounders and further consideration of a dose-response relationship. Furthermore, the most recent NHANES analyses provide evidence of an association between BLLs and mortality at lower mean population blood Pb concentrations (mean or median blood Pb range between 1.49 and 3.2 μg/dL) (Duan et al., 2020; Lanphear et al., 2018; Ruiz-Hernandez et al., 2017; Aoki et al., 2016). Despite the differences observed within the studies, associations between increased concentrations of Pb biomarkers and mortality were generally observed (Figure 4-23, Table 4-16).

There still remains uncertainty regarding the relative contributions of recent, past, and cumulative Pb exposure for the relationship between BLLs and cardiovascular mortality. The more recent NHANES

analyses evaluate cycles as recent as 2015 and continue to observe strong associations between increasingly lower levels of blood Pb and cardiovascular mortality; however, these analyses still contain populations greatly influenced by high historic Pb exposure. Additionally, further confounder control, such as the inclusion of Cd concentrations in blood or urine, can also reduce the uncertainty noted in the 2006 Pb AQCD. van Bemmel et al. (2011) reported null associations between BLLs and cardiovascular mortality. However, despite using data from NHANES III, the authors were not able to sufficiently account for all confounders, and were limited to a smaller sample size, given their study hypothesis. The cohort of Taiwanese hemodialysis patients provided evidence that there may be subsets of the population at an increased risk of Pb-related cardiovascular mortality, compared with the general population (Lin et al., 2011). Taken together, despite differences in the design, methods, and considerations across studies, associations between elevated levels of Pb biomarkers and increased mortality risk were generally observed.

4.11 Biological Plausibility

Sections 4.1 to 4.10 of this appendix describe the cardiovascular health effects associated with exposure to Pb from epidemiologic and animal toxicological studies. Informed largely by the animal toxicological evidence presented in these sections, as well as in previous ISAs and AQCDs, this section describes the biological pathways that potentially underlie the cardiovascular associations observed in epidemiologic studies. Figure 4-23 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events associated with exposures to Pb at concentrations observed in epidemiologic studies (e.g., IHD, MI). Note that the role of biological plausibility in contributing to the weight-of-evidence causality determinations reached in the current Pb ISA are discussed in Section 4.12.



HR = heart rate; HRV = heart rate variability; Pb = lead.
Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color-coded (gray, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in this Pb ISA are discussed in Section 4.12.

Figure 4-23 Potential biological pathways for cardiovascular effects following exposure to Pb.

Considering the available health evidence, Figure 4-26 shows plausible pathways connecting Pb exposure to the apical events reported in epidemiologic studies. The first potential pathway begins with oxidative stress leading to impaired vascular function, systemic inflammation, a pro-atherosclerotic environment, and increases in BP. The second potential pathway involves Pb perturbation of the RAAS leading to increases in BP and impaired vascular function. The third potential pathway involves modulation of the ANS leading to increases in BP and exacerbation of conduction abnormalities and arrythmia. Once these pathways are initiated, there is evidence from in vitro and in vivo toxicological studies that exposure to Pb may result in a series of pathophysiological responses that could lead to cardiovascular events such as IHD, MI, and stroke, and thus, possible cardiovascular mortality.

As noted above, one potential pathway for Pb exposure to result in the associations reported in epidemiologic studies is through the induction of oxidative stress and inflammation. Exposure to Pb can

stimulate the production of ROSs in the blood, heart, and/or vasculature (Simões et al., 2015; Dewanjee et al., 2013; Farmand et al., 2005; Ni et al., 2004; Attri et al., 2003; Courtois et al., 2003; Vaziri et al., 1999; Gonick et al., 1997) For example, Pb exposure in rats resulted in increased levels of superoxides and hydrogen peroxide in human coronary endothelial cells. Similarly, Vaziri et al. (1999) demonstrated increased plasma and cardiac levels of the oxidative stress marker 3-nitrotyrosine following Pb exposure in rats.

Pb exposure resulting in the production of ROSs is important because several studies have demonstrated a role for Pb-induced oxidative stress in impaired vascular function (Simões et al., 2015; Dursun et al., 2005; Attri et al., 2003; Gonick et al., 1997; Vaziri et al., 1997; Khalil-Manesh et al., 1994; Khalil-Manesh et al., 1993). Impaired vascular function is often the result of impaired functioning of the endothelium, which maintains the normal balance of mediators that promote vasorelaxation (e.g., nitric oxide) and vasoconstriction (e.g., endothelin-1). Animal toxicological studies demonstrate that exposure to Pb results in altered vascular function (Nunes et al., 2015; Gaspar and Cordellini, 2014; Silveira et al., 2010; Zhang et al., 2007; Skoczynska and Stojek, 2005), including impairment that would be consistent with greater vasoconstriction (Simões et al., 2015; Gaspar and Cordellini, 2014) or decreased vasodilation (Silveira et al., 2010; Zhang et al., 2007). Toxicological studies have also demonstrated that Pb-induced oxidative stress results in impaired vascular function through the inactivation or downregulation of vasodilators such as nitric oxide and/or soluble guanylate cyclase, thereby increasing the potential for vasoconstriction (Gonçalves-Rizzi et al., 2016; Dursun et al., 2005; Attri et al., 2003; Gonick et al., 1997; Vaziri et al., 1997; Khalil-Manesh et al., 1994; Khalil-Manesh et al., 1993). For example, Pb-induced ROSs can inactivate or sequester the vasodilator nitric oxide (Malvezzi et al., 2001; Vaziri et al., 1999), and inhibition of nicotinamide adenine dinucleotide phosphate oxidase was able to block Pb-enhanced contraction of cultured rat aorta cells in response to the vasoconstrictor 5 hydroxytryptamine (Zhang et al., 2005).

Continuing along this potential pathway, impaired vascular function also promotes plaque formation potentially leading to atherosclerosis. In addition to its hallmark feature of impaired vasodilation, impaired vascular function is further characterized by decreased vascular integrity, increased expression of adhesion molecules, and cytokine upregulation (Lind et al., 2021). In total, this increases the potential for atherosclerotic disease and formation of thrombi (i.e., blood clots). Following Pb exposure, toxicological studies have demonstrated that Pb induces markers of systemic inflammation in blood (Fernandez-Cabezudo et al., 2007; Iavicoli et al., 2006; Chen et al., 2004; Dyatlov and Lawrence, 2002; Miller et al., 1998; Heo et al., 1997; Heo et al., 1996), as well as increases in C-reactive protein in cardiac tissue (Roshan et al., 2011). In addition, Pb was also found to induce interleukin (IL)-8, which mediated vessel intima hyperplasia in human endothelial cells (Zeller et al., 2010). Similarly, Pb exposure in rats increased aortic media thickness, media-lumen ratio, and medial collagen content (Zhang et al., 2009). Exposure to Pb also promoted thrombus formation in rats (Shin et al., 2007), as well as cellular perforations and membrane blebbing in endothelial cells (van Strijp et al., 2023). In agreement with these toxicological studies demonstrating Pb-induced inflammation, an epidemiologic study found that higher

BLLs in children were correlated with higher serum levels of IL-4 (Lutz et al., 1999), which can stimulate the liver to produce additional coagulation factors and further the pro-atherosclerotic environment. Moreover, as discussed in the metabolic effects appendix (Section 9.2), exposure to Pb can also result in the upregulation of cholesterol, another key contributor to developing atherosclerosis. Taken together, evidence of a pro-atherosclerotic environment is important given that atherosclerosis can lead to plaque and thrombosis (i.e., clot) formation. If dislodged, those plaques could obstruct blood flow to the heart or stimulate intravascular clotting (Karoly et al., 2007), both of which could result in acute myocardial ischemia. If the dislodged plaque obstructs blood flow to the brain, there is potential for stroke.

Impaired vascular function (e.g., resulting from Pb-induced oxidative stress) can also lead to increases in BP through vasoconstriction. Increases in BP may then exacerbate IHD or heart failure through conduction abnormalities or arrythmias, and further impair vascular function. For example, in patients with high BP, changes in arterial shear stress due to changes in blood flow (i.e., laminar versus turbulent) are associated with impaired vascular function (Khder et al., 1998), which, as noted above, could lead to a worsening of IHD or heart failure. Importantly, there are numerous studies demonstrating that Pb can increase measures of BP: (Nunes et al., 2015; Xu et al., 2015; Fioresi et al., 2014; Mohammad et al., 2010; Zhang et al., 2009; Badavi et al., 2008; Grizzo and Cordellini, 2008; Reza et al., 2008; Bravo et al., 2007; Robles et al., 2007; Heydari et al., 2006; Bagchi and Preuss, 2005; Nakhoul et al., 1992). In addition, a toxicological study has demonstrated that Pb exposure can result in conduction abnormalities and potential arrythmia (Reza et al., 2008).

The second pathway by which Pb exposure may result in the cardiovascular associations reported in epidemiologic studies is through activation of the RAAS, which is responsible for fluid homeostasis and BP regulation. Exposure of experimental animals to Pb increases ACE activity; plasma kininase II; kininase I; and kallikrein activities in plasma, aorta, heart, and kidney, as well as renal angiotensin II positive cells (Rodríguez-Iturbe et al., 2005; Sharifi et al., 2004; Carmignani et al., 1999). These changes can result in increases in BP, which as noted above, could lead to worsening of IHD or heart failure potentially through conduction abnormalities, arrythmia, and/or impaired vascular function. Additional information on the effect of Pb on the RAAS system is discussed in the renal effects appendix. This summary includes a discussion of Pb accumulation in the kidney resulting in cellular damage, thereby increasing the potential for RAAS disfunction (see Appendix 5).

The third pathway by which Pb exposure may result in the cardiovascular associations reported in epidemiologic studies is through modulation of the ANS. As noted in the nervous system appendix, Pb can deposit in the brain where it causes cellular damage and altered neurological function (see Appendix 3). Similarly, it has also been shown that exposure to Pb can modulate autonomic tone (e.g., increased sympathetic tone) to the heart and vasculature, possibly through stimulation of the P2X4 and P2X7 receptors in satellite glial cells (Zhu et al., 2019; Zhu et al., 2018). Shifts toward increased sympathetic nervous system tone may result in increases in heart rate and BP as well as decreases in vascular function, which as mentioned above, could exacerbate IHD and/or heart failure. It is therefore

important to note evidence from animal toxicological studies for increases in heart rate (Simões et al., 2011; Badavi et al., 2008; Lai et al., 2002) and changes in HRV consistent with a shift toward increased sympathetic tone (Zhu et al., 2019; Shvachiy et al., 2018; Zhu et al., 2018; Geraldes et al., 2016) following Pb exposure. Similarly, evidence from an animal toxicological study suggests that Pb exposure can result in conduction abnormalities or arrhythmia (Reza et al., 2008). Conduction abnormalities or arrhythmia could exacerbate IHD and/or HF. Taken together, there are potential pathways by which ANS modulation may lead to worsening of IHD or HF, thereby increasing the risk for mortality.

When considering the available evidence presented throughout this appendix, there are plausible pathways connecting Pb exposure to the cardiovascular associations reported in epidemiologic studies (Figure 4-26). Thus, these proposed pathways provide biological plausibility for the associations reported in epidemiologic studies between Pb and IHD, MI, stroke, and therefore, mortality.

4.12 Summary and Causality Determination

A large body of health evidence published since the 2013 Pb ISA continues to demonstrate a causal relationship between exposure to Pb and cardiovascular health effects. The 2013 Pb ISA concluded that the evidence supported a causal relationship between exposure to Pb and hypertension and increased BP in adults, as well as between Pb exposure and CHD (based largely on epidemiologic studies of CVD-related mortality). For other cardiovascular-related outcomes, the evidence was suggestive of but not sufficient to infer a causal relationship for subclinical atherosclerosis and inadequate to infer the presence or absence of a relationship with cerebrovascular disease (Table 4-2). More recent studies greatly expand the evidence base discussed in the 2013 Pb ISA and serve to strengthen the support for relationships between exposure to Pb and a number of cardiovascular-related health effects. In particular, there is substantially more evidence of hypertension, increases in BP, and cardiovascular-related mortality following exposure to Pb. Moreover, there is additional health evidence for effects such as changes in cardiac electrophysiology (e.g., ECG measures of cardiac depolarization, repolarization, and HRV), arrythmia, and markers of atherosclerosis. *Thus, in the current ISA, the evidence supports a causal relationship between exposure to Pb and cardiovascular effects and cardiovascular-related mortality*.[6] After a brief discussion of the health evidence and key uncertainties found in the 2013 Pb ISA, the rest of this summary and causal determination section discusses the health evidence and rationale for the causal determination reached in this Pb ISA. This discussion will rely upon the framework for causality determinations described in the preamble to the ISAs (U.S. EPA, 2015). Key health evidence supporting this determination is also summarized in Table 4-2.

[6]The current ISA follows the approach of more recent ISAs, including the 2019 Particulate Matter and 2020 Ozone ISAs, in making a single causality determination for cardiovascular effects. Additional information regarding this decision can be found in Section 4.1 of this appendix.

In the 2013 Pb ISA, the strongest evidence for an effect of Pb on cardiovascular outcomes was on BP and CVD-related mortality. Prospective epidemiologic studies clearly supported the relationship between biomarkers of Pb exposure and hypertension incidence and changes in BP (U.S. EPA, 2013). The prospective evidence was supported by meta-analyses that underscored the consistency and reproducibility of Pb-associated increases in BP and hypertension and epidemiologic studies that adjusted for a wide range of potential confounders to reduce uncertainty due to potential unmeasured confounding (U.S. EPA, 2013). With respect to cardiovascular-related mortality, the previous Pb ISA (U.S. EPA, 2013) described longitudinal studies in adult cohorts in a number of locations reporting that biomarkers of Pb exposure were associated with risk of mortality from MI, IHD, or CHD, with the strongest of these associations being with MI mortality. In addition, epidemiologic studies reviewed in the 2013 Pb ISA included some evidence of a positive association between exposure to Pb and changes in cardio electrophysiology (e.g., changes in HRV and QT interval) and atherosclerotic plaque formation. Key uncertainties noted with respect to the epidemiologic evidence from the last review included inconsistent evidence for BP changes in children and uncertainty in the level, timing, frequency, and duration of Pb exposure contributing to the reported cardiovascular effects in adults. That is, given the appreciable history of exposure in decades past (see Appendix 2, Section 2.4.1), and that Pb accumulates in the body over a lifetime, the extent to which past Pb exposures contribute to the BLLs and positive associations reported in epidemiologic studies remains uncertain.

In the 2013 Pb ISA, animal toxicological studies provided supporting evidence and biological plausibility for the associations observed in epidemiologic studies, particularly with respect to BLLs and changes in BP and/or hypertension. Increases in BP following exposure to Pb were generally reported in animal toxicological studies. The previous ISA further noted toxicological studies indicating the production of oxidative stress species that could inactivate the vasodilator, nitric oxide, which could potentially lead to increased vasoconstriction, and thus, increases in BP. Animal toxicological studies discussed in the last review also provided at least some evidence that exposure to Pb may contribute to a pro-atherosclerotic environment and result in changes in HRV.

More recent studies greatly expand the evidence base from the 2013 Pb ISA and serve to strengthen support for the relationship between exposure to Pb and cardiovascular effects in adults. In particular, the strongest evidence continues to be Pb's effect on increases in BP. Numerous additional epidemiologic studies published since the last review report positive associations between measures of Pb in the body and increases in BP. Nationally representative cross-sectional studies in countries including the United States and Canada reported positive associations between increases in BLLs and changes in SBP, DBP, or both (Huang, 2022; Qu et al., 2022; Everson et al., 2021; Teye et al., 2020; Obeng-Gyasi et al., 2018; Lee et al., 2016a; Hara et al., 2015; Bushnik et al., 2014; Hicken et al., 2013; Zota et al., 2013b; Scinicariello et al., 2011). These nationally representative studies of adult cohorts (with most participants born before 1970, some in the 1930s) generally reported positive increases in BP (mmHg) with mean BLLs ~1.5– 3 µg/dL. Consistent with these nationally representative studies, smaller cross-sectional studies generally reported positive associations between measures of Pb burden and changes in BP (Yan

et al., 2022; Chung et al., 2020; Wang et al., 2020; Guo et al., 2019; Gambelunghe et al., 2016; Ettinger et al., 2014) within a slightly larger range of mean BLLs within each study (~1.5– 8.5 μg/dL). While not all studies reported positive associations with SBP or DBP (e.g., [(Yu et al., 2020; Ettinger et al., 2014)]), the generally positive cross-sectional results were consistent with a longitudinal analysis in a small Bangladeshi cohort. This study indicated there was an annual increase in SBP associated with the largest quartile of baseline BLLs compared with the lowest quartile Bulka et al. (2019). The majority of recent analyses consider a wide range of confounders including demographics, comorbid conditions, antihypertensive medication use, and other co-exposures to metals such as Cd. In addition, an extensive amount of literature also considered effect measure modifiers, including, sex, age, and race, among others. Combined with epidemiologic results from the previous ISA and AQCDs, there is clear and substantial evidence that increasing body Pb levels is associated with increases in measures of BP. However, uncertainty remains regarding the role of extensive historical exposure (magnitude, duration, timing) of these cohorts.

The epidemiologic associations summarized above are coherent with animal toxicological studies published since the 2013 Pb ISA that examined BP. BLLs in these animal studies were ≤30 μg/dL, and most of these studies reported that in animals exposed to Pb, there were increases in BP when compared with control treated animals (Zhu et al., 2019; Shvachiy et al., 2018; Zhu et al., 2018; Nunes et al., 2015; Silva et al., 2015; Xu et al., 2015; Fioresi et al., 2014; Gaspar and Cordellini, 2014). It should be noted that although these studies found some measure of BP at some time point to be increased following exposure to Pb, there was variability among studies with respect to which measure of BP increased (e.g., SBP or DBP) and the timing of those increases. Moreover, there was a single animal toxicological study in rats that reported no changes in measures of BP following a Pb drinking water exposure (Wildemann et al., 2015). Nonetheless, when considered in total, these animal toxicological studies provide clear evidence for exposure to Pb resulting in increases in measures of BP. These animal toxicological studies are coherent with, and provide support for, the mostly positive associations reported in epidemiologic studies between body Pb levels and BP increases.

As noted above, a number of prospective cohort studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) and in the 2006 Pb AQCD (U.S. EPA, 2006) indicated positive associations between Pb biomarkers of exposure and cardiovascular mortality. Moreover, the results of these previously reviewed studies remained positive when controlling for a wide range of potential confounders. Since the publication of the 2013 Pb ISA, additional evidence of cardiovascular-related mortality has been reported. In an analysis of the NHANES III cohort, a 1 μg/dL increase in BLLs was associated with HRs of 1.10 (95% CI: 1.05, 1.15) for CVD mortality and 1.14 (95% CI: 1.08, 1.20) for IHD mortality (Lanphear et al., 2018). Consistent with these results, additional studies analyzing NHANES cycles reported associations of similar magnitudes between BLLs and CVD-related mortality (Duan et al., 2020; Ruiz-Hernandez et al., 2017; Aoki et al., 2016; van Bemmel et al., 2011). These more recent studies also reported that associations between BLLs and CVD-related mortality remained positive after accounting for risk factors such as physical activity, serum cholesterol, (Lanphear et al., 2018; Ruiz-Hernandez et al., 2017) and Cd

levels in blood or urine (Aoki et al., 2016) (Table 4-16). In addition, Duan et al. (2020) specifically evaluated NHANES participants enrolled in cycles between 1999 and 2014 (mortality data included through 2015), with ~7 years of mortality follow-up. Although some members of this population may have had lower Pb exposures due to the phaseout of leaded gasoline, especially when compared with studies assessing adults in NHANES II (1976–1980) and NHANES III (1988–1994), the vast majority of the participants were born well before the phaseout.

Epidemiologic studies of mortality are consistent not only with the large amount of evidence for changes in BP and hypertension described above, but also with evidence of associations between blood or bone Pb levels and other cardiovascular outcomes. Studies using the NAS cohort of older adult men indicated an association between patella Pb levels and incident IHD (Ding et al., 2019; Ding et al., 2016). Additionally, a series of 10-year CVD risk evaluations using KNHANES data observed increased 10-year CVD risk with increasing BLLs (Nguyen et al., 2021; Park and Han, 2021; Choi et al., 2020; Cho et al., 2016). These studies are also consistent with a series of NAS analyses presented in the 2013 Pb ISA indicating an association between bone Pb levels and a prolonged QT interval (Eum et al., 2011; Park et al., 2009; Cheng et al., 1998). Recent studies among children are less consistent than those in adults. However, there is some evidence to support clinically relevant changes in HRV (Halabicky et al., 2022) and increases in SBP and TPR (Gump et al., 2011) following an acute stressor.

Toxicological studies evaluated in the 2013 Pb ISA demonstrated increased incidence of arrhythmia, atrioventricular block, and a prolonged ST segment interval in Pb-exposed animals (Reza et al., 2008). That said, an additional toxicological study published since the last review reported no change in the PR, QRS, or QT segments in Pb-exposed rats (Wildemann et al., 2015). Similarly, although more limited and/or mixed, there is at least some epidemiologic and animal toxicological evidence for changes in heart rate and HRV (Section 4.7) and potential indicators of atherosclerosis following exposure to Pb. Notably, a toxicological study published since the 2013 Pb ISA reported a statistically significant increase in the diameter of the cells of the aorta, as well as changes in the shape (i.e., loss of curvature) of the aortic internal elastic lumen in Pb-exposed rats, relative to control rats. This study also reported a statistically significant increase in proliferating cell nuclear antigen in rat cardiac tissue in Pb-exposed rats ($p \leq 0.05$), potentially consistent with the type of cellular proliferation that is involved in atherosclerotic plaque growth (Xu et al., 2015). Moreover, these results are consistent with a study discussed in the 2013 Pb ISA demonstrating increased aortic media thickness, media-lumen ratio, and medial collagen content following exposure to Pb (Zhang et al., 2009).

In support of epidemiologic studies reporting positive associations between BLLs and CVD-related mortality, animal and in vitro toxicological evidence provides plausible pathways by which exposure to Pb could lead to serious CVD-related outcomes such as IHD, MI, and/or stroke. In brief, one such pathway posits that exposure to Pb resulting in oxidative stress and systemic inflammation could potentially lead to impaired vascular function, a pro-atherosclerotic environment, and increases in BP. Importantly, there is animal toxicological evidence demonstrating all these effects following exposure to

Pb (Section 4.8). In addition, these effects, in particular atherosclerosis and increases in BP, can set the stage for an MI or stroke that could result in mortality. More information on this and other potential pathways can be found in Section 4.11, in which each potential pathway is described in detail. Several recent epidemiologic studies have been published further supporting this association. Many of the epidemiologic studies evaluated in this appendix utilize data from large population-based health surveys (e.g., NHANES). Due to the higher prevalence of cardiovascular disease in older populations, most available studies examine populations born before the phaseout of leaded gasoline. Although some members of these study populations may have had lower Pb exposures due to the phaseout of leaded gasoline, especially when compared with studies assessing adults who participated in older studies, such as NHANES II (1976–1980) and NHANES III (1988–1994), the vast majority of participants across older and more recent studies were born well before the phaseout. It is also important to note that Pb in blood at a particular time point may be reflective of more recent exposures, or due to mobilization of Pb from bone stores. While uncertainty remains regarding the role of extensive historical exposure (magnitude, duration, timing) in health outcomes assessed in these cohorts, there is still sufficient evidence that supports the use of blood Pb as a valid and reliable biomarker for assessing associations of Pb with long-term effects, such as cardiovascular disease and mortality (Ruiz-Hernandez et al., 2017).

The collective evidence is sufficient to conclude that there is a *causal relationship* between Pb exposure and cardiovascular effects and cardiovascular-related mortality. Evidence from epidemiologic studies indicates consistent associations between Pb biomarkers and cardiovascular endpoints such as BP (Section 4.3.1.1), hypertension (Section 4.3.1.2), and mortality (Section 4.10). This evidence was further supported by experimental animal studies (Section 4.3.2, Section 4.11). Studies relying on bone biomarkers to assess Pb exposure provided consistent evidence for an association between cumulative exposures and chronic health outcomes, such as hypertension and premature mortality. Evidence of this effect was further supported by cross-sectional studies primarily evaluating concurrent BLL levels and cardiovascular health effects. It is also important to note that Pb in blood at a particular time point may be reflective of more recent exposures, or due to mobilization of Pb from bone stores. While uncertainty remains regarding the role of extensive historical exposure (magnitude, duration, timing) in health outcomes assessed in these cohorts, there is still sufficient evidence that supports the use of blood Pb as a valid and reliable biomarker for assessing associations of Pb with long-term effects, like mortality (Ruiz-Hernandez et al., 2017). While much of the evidence between Pb biomarkers and cardiovascular effects is consistent, some specific cardiovascular outcomes are examined in relatively few studies, and the results across these studies are inconsistent (see Sections 4.7–4.9). Furthermore, uncertainties remain regarding the timing, frequency, and duration of the Pb exposures that contribute to cardiovascular health effects. Yet, even after the consideration of these uncertainties, the overall evidence base strongly indicates that exposure to Pb is associated with numerous cardiovascular effects including increases in BP and cardiovascular-related mortality.

Table 4-2 Summary of evidence indicating a causal relationship between Pb exposure and cardiovascular effects and cardiovascular-related mortality

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Generally consistent evidence from epidemiologic studies of BP in adults	Epidemiologic studies consistently demonstrating increases in at least some measure of BP and Pb biomarkers	Hara et al. (2015) Hicken et al. (2012) Hicken et al. (2013) Obeng-Gyasi et al. (2018) Scinicariello et al. (2011) Teye et al. (2020) Zota et al. (2013b) Everson et al. (2021) Huang (2022) Obeng-Gyasi (2019) Tsoi et al. (2021) Lee et al. (2016a) Bushnik et al. (2014) Qu et al. (2022) Lopes et al. (2017a) Chung et al. (2020) Yan et al. (2022) Gambelunghe et al. (2016) Bulka et al. (2019)	Mean blood Pb: ~1.0 to 3 µg/dL
Generally consistent evidence from epidemiologic studies of hypertension	Epidemiologic studies consistently demonstrating increases in incident hypertension risk with Pb biomarkers Mostly positive associations between prevalent hypertension and Pb biomarkers	Gambelunghe et al. (2016) Zheutlin et al. (2018) Huang (2022) Tsoi et al. (2021) Miao et al. (2020) Scinicariello et al. (2011) Lee et al. (2016b) Lee et al. (2016a) Choi et al. (2018) Qu et al. (2022) Lopes et al. (2017a)	Mean blood Pb: ~2.5–5 µg/dL Mean bone Pb: ~20 (tibia) – 27 (patella) µg/g Mean blood Pb: ~1.5–3.5 µg/dL
Generally consistent evidence from epidemiologic studies of cardiovascular mortality	Epidemiologic studies consistently demonstrating increases in cardiovascular mortality risk with Pb biomarkers	Menke et al. (2006) Lanphear et al. (2018) van Bemmel et al. (2011) Cook et al. (2022) Ruiz-Hernandez et al. (2017) Duan et al. (2020) Aoki et al. (2016) Obeng-Gyasi et al. (2021) Lin et al. (2011)	Mean blood Pb: ~1.5–3.2 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Generally consistent evidence from epidemiologic studies of ischemic heart disease	Mostly positive associations between incident IHD and Pb biomarkers	Jain et al. (2007) Ding et al. (2016) Ding et al. (2019)	Mean blood Pb: ~6.5 µg/dL Mean bone (patella) Pb: ~30 µg/g Mean bone (tibia) Pb: ~23 µg/
	Mostly positive associations between estimates of 10-yr CHD risk and Pb biomarkers	Cho et al. (2016) Choi et al. (2020) Park and Han (2021) Nguyen et al. (2021)	Mean blood Pb: ~3 µg/dL
Generally consistent evidence from epidemiologic studies of cardiac function	Mostly positive associations between left ventricle structure/function and Pb biomarkers	Yang et al. (2017) Lind et al. (2012) Chen et al. (2021)	Mean blood Pb: ~2–5 µg/dL
Limited evidence from epidemiologic studies for changes in HRV	A single study reported a change in HRV following a stress response in children	Halabicky et al. (2022)	Mean blood Pb: ~3–6 µg/dL
Limited evidence from epidemiologic studies for atherosclerosis	A small number of studies demonstrated development of atherosclerosis within different populations	Wan et al. (2021) Kim et al. (2021) Qin et al. (2021)	Mean blood Pb: 1.5–3 µg/dL
Consistent evidence from animal toxicological studies of BP	Animal toxicological studies consistently demonstrating increases in at least some measure of BP	Fioresi et al. (2014) Nunes et al. (2015) Xu et al. (2015) Silva et al. (2015) Shvachiy et al. (2018) Gaspar and Cordellini (2014) Zhu et al. (2018) Zhu et al. (2019)	Mean blood Pb: ~8–30 µg/dL
Limited evidence from animal toxicological studies for changes in HRV	A small number of studies demonstrated changes in at least some measure of HRV (e.g., LF)	Shvachiy et al. (2018) Zhu et al. (2018) Zhu et al. (2019)	Mean blood Pb: ~24–28 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Limited but consistent evidence from animal toxicological studies for structural changes consistent with the development of atherosclerosis	A single animal toxicological study reported an increase in the aortic media thickness, media-lumen ratio, and medial collagen content following Pb exposure	Zhang et al. (2009)	Mean blood Pb: ~28 µg/dL
	A single animal toxicological study reporting an increase in the diameter of the cells of the aorta, changes in the shape of the aortic internal elastic lumen, and an increase in proliferating cell nuclear antigen in rat cardiac tissue	Xu et al. (2015)	Mean blood Pb: ~20–25 µg/dL
Biological Plausibility	A few well-defined potential pathways by which exposure to Pb could reasonably result in the health outcomes reported in epidemiologic studies	Section 4.11	NA

BP = blood pressure; CHD = coronary heart disease; HRV = heart rate variability; IHD = ischemic heart disease; LF = low frequency; NA = not available; Pb = lead; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

4.13 Evidence Inventories – Data Tables to Summarize Study Details

Table 4-3 Epidemiologic studies of Pb exposure and blood pressure

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cross-Sectional Studies					
Hara et al. (2015) United States NHANES 2003–2010 Cross-sectional	NHANES n = 12,725 ≥20 yr Average individual born ~1957	Blood Pb (ICP-MS) (µg/dL) GM (IQR): See Figure 4-4 Age at measurement: Mean (SD) Black Women: 48.31 (6.8) Hispanic Women: 48.1 (16.8) White Women: 53.0 (8.4) Black Men: 47.7 (16.9) Hispanic Men: 46.1 (6.8) White Men: 53.1 (18.6)	BP (SBP, DBP, PP, MAP)	Linear models adjusted for ethnicity, sex, age, BMI, heart rate, hematocrit, serum total calcium γ-glutamyltransferase, cotinine, dietary sodium to potassium intake ratio, college education, antihypertensive drug treatment	BP change (mmHg) per doubling of blood Pb See Figure 4-4[b]
Hicken et al. (2012) United States NHANES 2005–2008 Cross-sectional	NHANES n =10,971 ≥20 yr Average individual born ~1963	Blood Pb (ICP-MS) (µg/dL) Mean (Median) See Figure 4-6 Age at measurement Mean (SD) White Men: 45.6 (15.8) Black Men: 40.6 (14.4) White Women: 47.3 (16.7) Black Women: 42.4 (15.1)	BP (SBP, DBP, PP)	Linear regression adjusted for age, BMI, heavy alcohol use, smoking status, diabetes diagnosis, antihypertensive medication use, and dietary intake of sodium, calcium, and potassium	Change in BP (mmHg) See Figure 4-6[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Hicken et al. (2013) United States NHANES 2005–2008 Cross-sectional	NHANES n = 4,470 Nonpregnant adults (>20 yr) Average individual born ~1962	Blood Pb (ICP-MS) (µg/dL) Mean (SD) lack: 1.9 (2.2) White: 1.7 (0.9) Age at measurement: Mean (SD) Black: 42.2 (16.4) White: 47.1 (10.8)	BP (SBP, DBP)	Linear regression adjusted for race/ethnicity, age, sex, high school education, family poverty, hematocrit, BMI, heavy alcohol use, smoking status, and diabetes	BP (mmHg) per doubling of blood Pb[b] SBP Black 3.2 (1.5, 5.0) High Depression 5.6 (2.0, 9.2) Low Depression 1.8 (0.2, 3.5) White 1.0 (−0.3, 2.4) High Depression 1.2 (−0.5, 2.9) Low Depression 1.0 (–0.6, 2.6) DBP Black 1.8 (0.7, 2.8) White 0.9 (0.1, 1.8)
Obeng-Gyasi et al. (2018) United States 2007–2010 Cross-sectional	NHANES n = 12,153 ≥20 yr Average individual born ~1958	Blood Pb (ICP-MS) (µg/dL) Mean (SD) Q1 (0–2): 1.09 (0.01) Q2 (2–5): 2.78 (0.02) Q3 (5–10): 6.40 (0.10) Q4 (>10): 16.11 (1.40) Age at measurement Mean (SD): Q1: 44.25 (0.32) Q2: 56.05 (0.54) Q3: 54.77 (1.13) Q4: 47.56 (2.56)	BP (SBP, DBP)	Linear regression adjusted for age, sex, race/ethnicity, BMI, antihypertensive medication	BP (mmHg) and ln-blood Pb[b,c] DBP 0.268 (0.079, 0.458) SBP 0.052 (−0.233, 0.458)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Scinicariello et al. (2010) United States NHANES III 1988–1994 Cross-sectional	NHANES III n =6,016 ≥17 yr Average individual born ~1963, ~1949, and in or before ~1931	Blood Pb (GFAAS) (µg/dL) Mean (SE) Overall, 2.99 (0.09) NH White 2.87 (0.09) NH Black 3.59 (0.20) Mexican American 3.33 (0.11) Age at measurement: 17–39 47% 40–59 30.9% ≥60 22.1%	BP (SBP, DBP)	Multivariable linear regression adjusted for age, sex, education, smoking status, alcohol intake, BMI, serum creatinine levels, serum calcium, glycosylated hemoglobin, and hematocrit	BP (mmHg) and blood Pb SBP NH White 0.707 (0.216, 1.199) NH Black 1.615 (1.007, 2.223) Mexican American 0.471 (0.062, 0.879) DBP NH White −0.094 (−0.741, 0.553) NH Black 1.261 (0.716, 1.805) Mexican American 0.414 (−0.001, 0.83) Significant interactions with blood Pb and ALAD genotype observed in relation to SBP for NH white and NH Black individuals
Scinicariello et al. (2011) United States NHANES 1999–2006 Cross-sectional	NHANES n =16,222 ≥20 yr with blood Pb ≤10 µg/dL Average individual born ~1959	Blood Pb (ICP-MS) (µg/dL) Mean (SE) See Figure 4-5 Age at measurement: Mean (SE) White men: 47.14 (0.37) White women: 49.64 (0.36) Black men: 42.86 (0.37) Black women: 45.10 (0.42) Mexican-American men: 37.64 (0.48) Mexican-American women: 40.67 (0.65)	BP (SBP, DBP, PP)	Multivariable logistic and linear regression models adjusted for age, BMI, self-reported diabetes alcohol ingestion, smoking status, education, serum creatinine, serum total calcium, sodium, hematocrit, and blood Cd	BP (mmHg) and twofold increase in blood Pb[b] See Figure 4-5

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Teye et al. (2020) United States NHANES 1999–2016 Cross-sectional	NHANES n = 30,467 20–79 yr Average individual born ~1965	Blood Pb (ICP-MS)[d] (µg/dL) Median (IQR) NH White Men: 1.50 (0.99, 2.29) Women: 1.06 (0.69, 1.60) NH Black Men: 1.60 (1.00, 2.60) Women: 1.11 (0.71, 1.77) Hispanic Men: 1.58 (0.99, 2.43) Women: 0.95 (0.62, 1.51) Other race Men: 1.54 (1.05, 2.39) Women: 1.16 (0.75, 1.79) Age at measurement Mean age NH white men: 46.37 NH white women: 47.00 NH Black men: 43.09 NH Black women: 43.28 Hispanic men: 39.67 Hispanic women: 40.51 Other men: 42.92 Other women: 43.54	BP (SBP, DBP)	Linear regression adjusted for age/ethnicity, age, gender, education level, BMI, and PIR	BP (mmHg)[e] SBP NH White: 0.34 (0.11, 0.57) NH Black: 0.67 (0.29, 1.05) Hispanic: 0.10 (−0.01, 0.21) Other: 0.44 (−0.51, 1.39) DBP NH White: 0.38 (0.19, 0.57) NH Black: 0.36 (0.06, 0.66) Hispanic: −0.08 (−0.21, 0.05) Other: 0.27 (−0.15, 0.69)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Zota et al. (2013b) United States 1999–2008 Cross-sectional	NHANES n =8,194 40–65 yr Average individual born ~1953	Blood Pb (ICP-MS) (μg/dL) GM 1.69 Geometric SE (GSE) 0.02 Quintiles GM (GSE) Q1: 0.76 (0.01) Q2: 1.25 (0.00) Q3: 1.67 (0.00) Q4: 2.25 (0.01) Q5: 3.88 (0.03) Age at measurement Mean: 50.9 SE: 0.15	BP (SBP, DBP)	Logistic and linear regression adjusted for age, educational attainment, race/ethnicity, smoking, alcohol consumption, marital status, and antihypertensive medication use	OR (Q5 vs. Q1)[b] Elevated SBP (≥140 mmHg) All participants: 1.23 (0.92, 1.65) Low AL: 1.14 (0.79, 1.66) High AL: 1.40 (0.99, 1.97) Elevated DBP (≥90 mmHg) All participants: 1.77 (1.25, 2.50) Low AL: 1.46 (0.80, 2.68) High AL: 2.28 (1.33, 3.91) BP change (mmHg, Q5 vs. Q1) SBP All participants: 0.36 (−1.07, 2.33) Low AL: 0.67 (−1.24, 2.58) High AL: 1.60 (−0.62, 3.82) DBP All participants: 1.76 (0.75, 2.78) Low AL: 1.72 (0.62, 2.95) High AL: 2.01 (0.24, 3.79)
Everson et al. (2021) United States NHANES 1999–2004 Cross-sectional	NHANES n =2,413 20–59 yr Average individual born ~1962	Blood Pb (ICP-MS) (μg/dL) Median: 1.5 Age at measurement: Range 20–59 yr	BP (SBP, DBP)	Linear regression models adjusted for age, age2, race, sex, BMI, and smoking status	BP (mmHg) SBP 0.73 (0.03, 1.44) DBP 0.41 (−0.10, 0.92)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Huang (2022) United States NHANES 1999–2018 Cross-sectional	NHANES n = 32,289 ≥20 yr Average individual born ~1958	Blood Pb (ICP-MS) (μg/dL) Mean (SD) 1.73 (1.71) Age at measurement Mean (SD) 49.68 (18.04)	BP (SBP, DBP)	Linear regression models adjusted for age, sex, race, education, family income poverty ratio, BMI, alcohol use, and smoking	BP (mmHg) SBP All 0.30 (0.19, 0.42) Men Mexican American 0.01 (−0.13, 0.34) Other Hispanic 0.07 (−0.31, 0.45) NH White 0.44 (0.22, 0.66) NH Black 0.37 (0.07, 0.67) Other Race 0.49 (−0.04, 1.03) Women Mexican American 0.14 (−0.28, 0.57) Other Hispanic 0.84 (−0.15, 1.83) NH White 0.63 (0.22, 1.04) NH Black 0.99 (0.48, 1.50) Other Race 0.49 (−0.35, 1.34) DBP All 0.23 (0.14, 0.32) Men Mexican American 0.08 (−0.11, 0.26) Other Hispanic −0.20 (−0.51, 0.11) NH White 0.40 (0.22, 0.58) NH Black 0.26 (0.00, 0.51) Other Race 0.05 (−0.37, 0.48) Women Mexican American 0.08 (−0.25, 0.40) Other Hispanic 0.42 (−0.30, 1.14) NH White 0.74 (0.41, 1.07) NH Black 0.80 (0.40, 1.20) Other Race 0.16 (−0.47, 0.79)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Obeng-Gyasi (2019) United States NHANES 2009–2016 Cross-sectional	NHANES young adults (18–44 yr) (n = 7,730), middle-aged adults (45–65 yr) (n = 5,744) Average individual born ~1981 and ~1957	Blood Pb (ICP-MS) (µg/dL) mean (SE): young adults: 1.03 (0.026) Middle-aged adults: 1.62 (0.044)	BP (SBP, DBP)	Logistic regression adjusted for sex, BMI, income, ethnicity, alcohol consumption, and smoking	OR (above/below 5 µg/dL)[b] SBP >120 mmHg Young adults: 1.21 (1.07, 1.38) Middle-aged adults: 1.32 (1.14, 1.52) DBP >80 mmHg Young adults: 1.32 (1.10, 1.58) Middle-aged adults: 1.16 (0.98, 1.38)
Tsoi et al. (2021) United States NHANES 1999–2016 Cross-sectional	NHANES N = 39,477 adults ≥20 Average individual born ~1960	Blood Pb ICP-MS (µg/dL) Median 1.30 Q1 <0.89 Q2 0.89–1.30 Q3 1.30–2.10 Q4 ≥2.10 Age at measurement: Mean (SE) Hypertensive 54.08 (0.23) yr Non-hypertensive 39.87 (0.19) yr	BP (SBP)	Multivariable linear regression adjusted for age, sex ethnicity, waist circumference, PIR, education, ever cigarette smoking, diabetes, and stage 3–5 chronic kidney diseases	SBP (mmHg) For every doubling of blood Pb[b] 0.52 (0.19, 0.86)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lee et al. (2016a) South Korea KNHANES IV (2008–2009), V (2010–2012), and VI (2013) Cross-sectional	Korean NHANES n = 11,797 ≥19 yr Average individual born in or before ~1991	Blood Pb (GFAAS with Zeeman correction) (μg/dL) GM (95% CI) Male: 2.396 (2.362, 2.430) Female: 1.919 (1.889, 1.949) Age at measurement ≥19 yr	BP (SBP, DBP)	Linear models adjusted for sex, age, residence area, education level, smoking, drinking status, BMI, physical activity, serum creatinine, and hemoglobin	BP (mmHg) doubling of blood Pb[b] SBP All 0.73 (0.09, 1.36) Male: 0.30 (−0.53, 1.14) Female: 1.08 (0.26, 1.90) DBP: All 0.71 (0.29, 1.13) Male: 0.59 (0.01, 1.17) Female: 0.80 (0.28, 1.33)
Bushnik et al. (2014) Canada 2007–2011 Cross-sectional	Canadian Health Measures Survey n = 4,550 Nonpregnant individuals aged 40–79 Average individual born ~1954	Blood Pb (ICP-MS) (μg/dL) Mean 1.64 (1.58–1.71) Age at measurement: mean: 55.4	BP (SBP, DBP)	Linear regression adjusted for age, sex, education, smoking, alcohol, physical activity, BMI, non-HDL cholesterol, diabetes, chronic kidney disease, family history of high BP, antihypertension medication use	BP (mmHg) SBP See Figure 4-11 DBP See Figure 4-12

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Qu et al. (2022) China 2017–2018 Cross-sectional	China National Human Biomonitoring Study n = 11,037 ≥18 yr Average individual born ~1969	Blood Pb (ICP-MS) (μg/dL)[f] Quartiles Q1: <1.59 Q2: 1.59–2.24 Q3: 2.24–3.21 Q4: ≥3.21 Age at measurement Range 18–79	BP change (SBP, DBP)	Multiple linear regression adjusted for sex, age, BMI, regions, education, smoking status, alcohol consumption, family history of hypertension, residence area, rice consumption, red meat consumptions, vegetable consumptions, FBG, TC, HDL-C, urinary arsenic levels, and blood Cd levels	BP Change (mmHg)[b] SBP Q2 vs. Q1 1.36 (0.25–2.47) Q3 vs. Q1 1.38 (−0.25–3.00) Q4 vs. Q1 4.72 (2.70–6.74) DBP Q2 vs. Q1 1.06 (0.23–1.90) Q3 vs. Q1 1.94 (0.79–3.09) Q4 vs. Q1 4.42 (3.02–5.83)
Lopes et al. (2017a) Cambè, Brazil 2011 Cross-sectional	n = 948 Adults 40 yr and older, randomly sampled from census tracts in the region Average individual born ~1956	Blood Pb (ICP-MS) (μg/dL) GM (95% CI): 1.97 (1.90–2.04) 10th percentile: 0.74 90th percentile: 6.03 Age at measurement: Mean: 54.5 yr	BP (DBP, SBP)	Multiple linear regression adjusted for age, sex, race, income, education, antihypertensive medication, total cholesterol, triglycerides, glycemia, smoking, alcohol consumption, and BMI	Change in BP (mmHg) (10th vs. 90th percentile) SBP no association (all CIs ranged between 0 and 0) DBP 0.005 (0.002, 0.008)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Chung et al. (2020) Taiwan recruited 2010–2011 and 2015–2016 Cross-sectional	n = 770 Community residents living near an electric arc furnace (EAF) Average individual born ~1953	Blood Pb (ICP-MS) (µg/dL) GM (IQR) Distance from EAF <500 m: 2.41 (1.22–6.19) 500–1000m: 2.26 (1.16–4.83) 1000–1500 m: 2.12 (1.05–4.67) 1500–2000 m: 2.23 (0.98–4.31) >2000m: 2.03 (1.03–4.31) Age at measurement: Median 60	BP (SBP, DBP)	General linear models adjusting for age, sex, ethnicity, living near the main road and smoking	Change in BP (mmHg)[b,c] SBP: 1.43 (0.34, 2.52) DBP: 0.69 (0.01, 1.37)
Wang et al. (2020) China Cross-sectional	n = 816 Adults 40–75, residing in area for >15 yr, and subsisting on rice and vegetables grown in the polluted (Cd concentration >0.2 mg/kg) or unpolluted (Cd concentration <0.05 mg/kg) area	Blood (ICP-MS) (µg/dL)[f] Median (IQR) Polluted 3.54 (2.42–4.89) Unpolluted 2.61 (1.70–3.84) Age at measurement: mean (SD) Polluted area Hypertensive: 60.32 (8.08) Normotensive: 55.61 (8.52) Unpolluted area Hypertensive: 59.92 (9.19) Normotensive: 56.86 (9.22)	BP (SBP, DBP)	Linear regression adjusted for age, gender, smoking status, and BMI	BP (mmHg) and Blood Pb[b] See Figure 4-2 and Figure 4-3

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Zhang et al. (2010) Boston, MA August 1991 and December 2001 Cross-sectional	NAS n = 619 Elderly men (mostly white) Average individual born ~1933	Bone Pb (K-XRF) (µg/g) Median (IQR) Wild type HFE Tibia: 8 (12–27) Patella: 26 (17–37) *C282Y* HFE Tibia: 20 (14–27) Patella: 25 (17–37) *H63D* HFE Tibia: 19 (14–26) Patella: 27 (19–37) Age at measurement Mean: 67	BP (PP)	Linear mixed-effects regression models with repeated measurements adjusted for age, education, alcohol intake, smoking, daily intakes of calcium, sodium, and potassium, total calories, family history of hypertension, diabetes, height, heart rate, HDL, total cholesterol, HDL ratio, and waist circumference	PP (mmHg) Tibia Pb Wild Type HFE: 0.29 (−0.46, 1.05) *H63D* HFE: 2.54 (0.12, 4.96) *C282Y* HFE: 0.68 (−1.33, 2.70) Any HFE variant: 2.23 (0.23, 4.23) Patella Pb Wild Type HFE: 0.14 (−0.33, 0.61) *H63D* HFE: 1.53 (−0.005, 3.11) *C282Y* HFE: 0.29 (−0.15, 0.73) Any HFE variant: 1.49 (0.16, 2.82)
Weaver et al. (2008) South Korea 1999–2001 Cross-sectional	n = 652 current and former Pb workers Average individual born ~1957	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 30.9 (16.7) Bone (Patella) Pb (K-XRF) (µg/g) Mean (SD): 75.1 (101.1) Age at measurement: Mean: 43.3, SD: 9.8	BP (SBP)	Multivariable linear regression adjusted for age, sex, BMI, diabetes, antihypertensive and analgesic medication use, Pb job duration, tobacco, and alcohol use	SBP (mmHg)[e] Blood Pb 0.1007 (0.02, 0.18) Patella Pb 0.059 (−0.08, 0.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Elmarsafawy et al. (2006) Boston, MA Participants' first visit after 1991 Cross-sectional	NAS n = 471 Elderly men (mostly white) Average individual born ~1924	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 6.6 (4.3) Bone (K-XRF) (µg/g) Mean (SD): Tibia: 21.6 (12.0) Patella: 31.7 (18.3) Age at measurement Mean: 67	BP (SBP)	Multivariable linear regression adjusted for age, BMI, family history of hypertension, smoking, dietary sodium intake, and cumulative alcohol ingestion No control for potential confounding SES factors	SBP (mmHg) Tibia Low Ca^{2+} group (<800 mg/d): 4.00 (1.05, 6.95) High Ca^{2+} group (>800 mg/d): 1.90 (0.10, 3.70)
Yan et al. (2022) Port-au-Prince, Haiti 2019–2021 Cross-sectional	Haitian CVD Cohort Study n = 2,504 General population ≥18 living in Port-au-Prince Average individual born ~1980	Blood Pb (LeadCare II Blood Level Analyzer) (µg/dL) (Pb measurement device had high limit of detection (3.3 µg/dL), and only 71% of the population had quantifiable blood Pb values) GM: 4.73 Geometric SE: 1.62 Age at measurement Median: 40 yr	BP (SBP, DBP)	Multivariable linear regression models adjusted for age, sex, BMI, smoking status, alcohol use, physical activity, income, and use of antihypertensive medication	BP (mmHg)[b] SBP Q2 vs. Q1 0.62 (−1.46, 2.70) Q3 vs. Q1 1.73 (−0.24, 3.70) Q4 vs. Q1 2.42 (0.36, 4.49) ≥3.3 µg/dL vs. <3.3 µg/dL 1.65 (0.05, 3.24) ≥5 µg/dL vs. <5 µg/dL 1.16 (−0.35, 2.68) DBP Q2 vs. Q1 0.19 (−1.26, 1.64) Q3 vs. Q1 1.16 (−0.25, 2.57) Q4 vs. Q1 1.96 (0.56, 3.37) ≥3.3 µg/dL vs. <3.3 µg/dL 1.16 (0.04, 2.27) ≥5 µg/dL vs. <5 µg/dL: 0.96 (−0.1, 2.02)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xu et al. (2021) United States 2011–2013 Cross-sectional	GuLF Study Cohort n = 957 ≥21 yr Average individual born in or before ~1991	Blood Pb (ICP-MS) (µg/dL) Median: 0.09 75th percentile: 0.19 Maximum: 33.8 Age at measurement: ≥21 yr	BP (SBP, DBP)	Multiple linear regression adjusted for age, sex, race, educational attainment, and household income	BP (mmHg) SBP Q2 vs. Q1 1.19 (−1.73, 4.11) Q3 vs. Q1 0.54 (−2.48, 3.55) Q4 vs. Q1 −0.96 (−4.13, 2.22) DBP Q2 vs. Q1 0.21 (−1.81, 2.24) Q3 vs. Q1 0.26 (−1.84, 2.35) Q4 vs. Q1 −0.01 (−2.21, 2.19)
Perlstein et al. (2007) Boston, MA 1991–1997 Cross-sectional	NAS n = 593 Elderly men (mostly white) Average individual born ~1927	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD) Overall: 6.12 (4.03) Q1: 2.3 (0.8) Q2: 3.9 (0.3) Q3: 5.4 (0.5) Q4: 7.4 (0.6) Q5: 12.4 (4.4) Tibia (K-XRF) (µg/g) Median: 19 Mean (SD) Q1: 7.4 (3.2) Q2: 14.1 (1.4) Q3 18.9 (1.4) Q4 24.9 (2.2) Q5 40.9 (14)	BP (PP)	Multiple linear regression adjusted for age, height, race, heart rate, waist circumference, diabetes, family history of hypertension, education level achieved, smoking, alcohol intake, fasting plasma glucose, and ratio of total cholesterol to HDL cholesterol	PP (mmHg)[b] Tibia Pb (above/below median): 4.2 (1.9, 6.50) Tibia Pb (mean difference) Q5 vs. Q1: 2.58 (−1.15, 6.48) Blood Pb (mean difference) Q5 vs. Q1: −1.49 (−4.93, 1.94)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ettinger et al. (2014) Ghana, South Africa, Seychelles, Jamaica, and the United States 2010–2011 Cross-sectional	Modeling the Epidemiologic Transition Study (METS) n = 150 (30 randomly selected from each site) Young adults (25–45) of African descent Average individual born ~1975	Blood Pb (ICP-MS) (µg/dL) GM: 1.55 (95% CI: 1.30, 1.85); Median 1.66 (95% CI: 1.34, 1.93) 75th: 2.6 Max: 31.82 Age at measurement (years): Mean (SD): Males: 34.7 (6) Females: 35.2 (6.2)	BP (SBP, DBP)	Logistic regression adjusted for age, sex, site location, education, paid employment, marital status, smoking, alcohol use, fish intake (percent body fat in models not assessing models of BMI)	OR above/below median (1.66 µg/dL)[b] High SBP (≥130 mmHg) 1.69 (0.55, 5.15) High DBP (≥85 mmHg) 2.20 (0.59, 8.16)
Guo et al. (2019) China 2015 Cross-sectional	n = 145 Males free of cardiovascular disease (including angina pectoris, MI, and thrombus) Average individual born ~1976	Blood Pb (ICP-MS) (µg/dL) mean (SD): 8.50 (3.77) Median: 7.85 75th: 10.08 Max: 28.17 Age at measurement (years): mean (SD): 39 (12)	BP (SBP, DBP)	Linear (log-transformed) and logistic regression adjusting for age	Linear regression (log-transformed) (mmHg)[b] SBP: 7.28 (−7.68, 22.24) DBP: 4.34 (−7.12, 15.80) OR above/below median (7.85 µg/dL)[b] SBP >134 mmHg: 2.28 (1.01, 5.12) DBP >84 mmHg: 1.55 (0.70, 3.40)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort Studies					
Gambelunghe et al. (2016) Malmö Sweden 1991–1994, re-examination 2007–2012 Cohort with cross-sectional component	Malmö Diet and Cancer Study (MDCS-CC) n = 4,452 Aged 46–67 living in Malmö Sweden Average individual born ~1935	Blood Pb (ICP-MS) (µg/dL) Mean: 2.8 Max: 25.8 Quartile Means Q1: 1.5 Q2: 2.2 Q3: 2.8 Q4: 4.7 Age at measurement (years): Mean: 57	BP (SBP, DBP)	Linear regression adjusted for sex, age, smoking, alcohol, waist circumference, education	BP differences (mmHg) (Q4 vs. Q1+Q2+Q3)[b,e] SBP: 1.8 (0.5, 3.1) SBP: Smokers 3.9 (1.6, 6.2) SBP Never-smokers: 0.6 (−1.5, 2.7) Males: 2.1 (0.3, 3.9) Females: 1.5 (−0.4, 3.4) ≤57 yr: 2.4 (1.2, 3.6) >57 yr: 1.3 (−0.6, 3.2) DBP: 1.4 (0.6, 2.2) DBP Smokers:1.6 (0.7, 2.5) DBP Never-smokers: 1.1 (−0.05, 2.2) Males: 1.7 (0.9, 2.5) Females: 1.1 (0.2, 2.0) ≤57 yr: 1.4 (0.7, 2.1) >57 yr: 1.5 (0.75, 2.5)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Bulka et al. (2019) Bangladesh Participants were randomized between April 2006 and August 2009, BP measurements taken at baseline, and every 2 yr for a total of 6 yr Cohort	Bangladesh Vitamin E and Selenium Trial (BEST) n = 255 Participants from the trial were from randomized sample of those taking part of the placebo arm of the BEST study Average individual born ~1976, ~1965, ~1952	Blood Pb (whole) (ICP-MS) (µg/dL) Median 8.5 Age at measurement 25–37 yr (88/255) 38–46 yr (82/255) 47–64 yr (85/255)	BP (SBP, DBP, PP)	Mixed-effects regression models adjusting for manganese, selenium, age, sex, site, smoking, educational duration, creatine-corrected urinary arsenic, diabetes, BMI, antihypertensive medication use	Yearly change in BP (mmHg) (4th quartile vs. 1st quartile)[b] SBP: 1.16 (95% CI: 0.21, 2.11) DBP: 0.53 (95% CI: −0.10, 1.16) PP: 0.63 (95% CI: −0.08, 1.34)
Glenn et al. (2006) South Korea 1997–2001 Cohort	n = 575 Pb-exposed workers Average individual born ~1956	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Females Visit 1: 20.3 (9.6) Visit 2: 20.8 (10.8) Visit 3: 19.8 (10.7) Males Visit 1: 35.0 (13.5) Visit 2: 36.5 (14.2) Visit 3: 35.4 (15.9) Age at measurement: Range 18–67 yr	BP (SBP)	Multivariable models using generalized estimating equations were used in longitudinal analyses adjusted for visit number, baseline age, baseline age squared, baseline lifetime alcohol consumption, baseline BMI, sex, baseline BP-lowering medication use, alcohol consumption	SBP (mmHg) Model 1 (short-term) Blood Pb (longitudinal): 0.009 (0.002, 0.02) Blood Pb (concurrent): 0.008 (−0.001, 0.02) Model 4 (short and longer-term, controls for tibia Pb) Blood Pb (longitudinal): 0.009 (0.002, 0.02) Blood Pb (concurrent): 0.01 (0.001, 0.019)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Yu et al. (2020) Belgium Blood Pb collected in 1985–2005, arterial stiffness measured a median of 9.4 yr later Cohort	Cadmium in Belgium study n = 267 Average individual born ~1958	Blood Pb (ETAAS) (µg/dL) GM (IQR): 2.93 (1.8–4.7) Age at measurement Mean: 37 yr	Central and Peripheral BP	Linear multivariable models adjusting for sex, enrollment characteristics (age, BMI, smoking, drinking, serum total to HDL-C ration, plasma glucose, eGFR (estimated from serum creatinine), SES), the time interval between measurement of exposure biomarkers and hemodynamic assessment, and antihypertensive drug treatment at enrollment and follow-up	Per doubling of Pb concentration[b] Peripheral Systolic Pressure: 2.41 (−0.38, 5.20) Diastolic Pressure: 0.50 (−1.07, 2.07) PP: 1.91 (−0.32, 4.14) Central Systolic Pressure: 2.65 (−0.17, 5.46) Diastolic Pressure: 0.42 (−1.18, 2.02) PP: 2.23 (−0.03, 4.48) Similar results when controlling for baseline urinary Cd

AL = allostatic load; ALAD = δ-aminolevulinic acid dehydratase; BEST = Biomonitoring of Environmental Status and Trends; BMI = body mass index; BP = blood pressure; *C282Y* HFE = mutant of the HFE wildtype; Ca^{2+} = calcium ion(s); Cd= cadmium; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; EAF = electric arc furnace; eGFR = estimated glomerular filtration rate; ETAAS = electrothermal atomic absorption spectrometry; FBG = fasting blood glucose; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; GSE = geometric standard error; GuLF = Gulf Long-Term Follow-up; HDL-C = high-density lipoprotein cholesterol; *H63D* HFE = mutant of the HFE wildtype; HFE = hemochromatosis gene; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; KNHANES = Korea National Health and Nutrition Examination Survey; K-XRF = K-shell X-ray fluorescence; LF = low frequency; MAP = mean arterial pressure; MDCS-CC = cardiovascular cohort of the Malmö Cancer and Diet Study; METS = Modeling the Epidemiologic Transition Study; MI = myocardial infarction; mo = month(s); NAS = Normative Aging Study; NH = non-Hispanic; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIR = poverty-income ratio; PP = pulse pressure; Q = quartile; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; SES = socioeconomic status; TC = total cholesterol; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Increment unclear.

[d]Blood Pb analysis method unclear, assumed based on data source.

[e]Confidence intervals estimated based on reported p values.

[f]Original results reported in µg/L.

Table 4-4 Epidemiologic studies of Pb exposure and hypertension

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Teye et al. (2020) United States NHANES 1999–2016 Cross-sectional	NHANES n = 30,467 20–79 yr Average individual born ~1965	Blood Pb ICP-MS[c] (µg/dL) NH white men: 1.89 NH white women: 1.30 NH Black men: 2.20 NH Black women: 1.49 Hispanic men: 2.18 Hispanic women: 1.30 Other men: 1.93 Other women: 1.42 Age at measurement: NH white men: 46.37 NH white women: 47.00 NH Black men: 43.09 NH Black women: 43.28 Hispanic men: 39.67 Hispanic women: 40.51 Other men: 42.92 Other women: 43.54	Hypertension (SBP ≥140 mmHg, DBP ≥90, use of antihypertensive medication)	Race/ethnicity, age, gender, education level, BMI, and PIR	OR (95% CI): 1.002 (0.983, 1.021)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Huang (2022) United States NHANES 1999–2018 Cross-sectional	NHANES n = 32,289 ≥20 yr Average individual born ~1958	Blood Pb (ICP-MS) (µg/dL) Mean (SD): 1.73 (1.71) Age at measurement (years): Mean (SD): 49.68 (18.04)	Hypertension (SBP ≥130 mmHg, DBP ≥80, use of antihypertensive medication, or self-reported hypertension)	Linear regression models adjusted for age, sex, race, education, family income poverty ratio, BMI, alcohol use, and smoking	Hypertension (OR) All 1.01 (0.99, 1.03) Women 1.03 (0.99, 1.07) Men 1.01 (0.99, 1.03) Mexican American 0.99 (0.96, 1.02) Other Hispanic 1.01 (0.95, 1.06) NH White 1.03 (1.00, 1.06) NH Black 1.02 (0.98, 1.06) Other race 1.04 (0.97, 1.11) BMI ≥30 1.00 (0.97, 1.03) BMI 25–30 1.00 (0.98, 1.03) BMI ≤25 1.03 (1.00, 1.06)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Tsoi et al. (2021) United States NHANES 1999–2016 Cross-sectional	NHANES n = 39,477 Adults ≥20 Average individual born ~1960	Blood Pb ICP-MS (µg/dL) Median: 1.30 Q1: <0.89 Q2: 0.89–1.30 Q3: 1.30–2.10 Q4: ≥2.10 Age at measurement Mean (SE) Hypertensive: 54.08 (0.23) yr Non-hypertensive: 39.87 (0.19) yr	Hypertension (SBP ≥130 mmHg, DBP ≥80, use of antihypertensive medication, or self-reported hypertension)	Multivariable logistic regression adjusted for age, sex ethnicity, waist circumference, PIR, education, ever cigarette smoking, diabetes, and stage 3–5 chronic kidney diseases	OR[b] For every doubling of blood Pb All 1.09 (1.04, 1.14) Male 1.10 (1.05, 1.16) Female 1.04 (0.97, 1.11) Mex. American 0.98 (0.89, 1.08) Other Hispanic 1.07 (0.93, 1.23) NH White 1.12 (1.05, 1.19) NH Black 1.06 (0.99, 1.15) Other ethnicity 1.10 (0.95, 1.28) Quartiles (All) Q2 vs. Q1 1.15 (1.04, 1.26) Q3 vs. Q1 1.17 (1.05, 1.31) Q4 vs. Q1 1.21 (1.07, 1.36)
Miao et al. (2020) United States NHANES 1999–2016 Cross-sectional	NHANES n = 30,762 ≥20 yr Average individual born ~1978, ~1958, or before ~1947	Whole Blood Pb (GFAAS with Zeeman correction) (1999–2002) and ICP-MS (2003–2016) (µg/dL) mean (SE) Male: 1.50 (0.02) Female: 1.07 (0.01) Age at measurement (years): 20–39 36.5% 40–59 38.9% ≥60 24.6%	Uncontrolled hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg or antihypertension medication use) and uncontrolled hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg regardless antihypertension medication use)	Logistic regression adjusted for age, sex, race/ethnicity, ratio of family income to poverty, education, smoking status, serum cotinine, alcohol intake, BMI, and menopausal status among females	OR (95% CI) Uncontrolled hypertension vs. non-hypertension: Male: 1.037 (1.015, 1.060) Female: 1.020 (0.970, 1.074) Uncontrolled Hypertension vs. Controlled Hypertension Male: 1.157 (1.080, 1.239) Female: 1.109 (1.020, 1.205) Uncontrolled hypertension vs. Controlled and Non-hypertension: Male: 1.062 (1.036, 1.088) Female: 1.056 (1.011, 1.102)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Scinicariello et al. (2011) United States NHANES 1999–2006 Cross-sectional	NHANES n = 16,222 Blood Pb ≤10 µg/dL Average individual born ~1959	Blood Pb (ICP-MS) (µg/dL) Percentile: 10th: <0.7 90th: 3.5–10 Age at measurement (years): Mean (SE) White males: 47.14 (0.37) White females: 49.64 (0.36) Black males: 42.86 (0.37) Black females: 45.10 (0.42) Mexican-Am males: 37.64 (0.48) Mex-Am females: 40.67 (0.65)	Hypertension prevalence (SBP ≥140 mmHg, DBP ≥90, use of antihypertensive medication)	Multivariable logistic and linear regression models. Confounders: age, BMI, self-reported diabetes alcohol ingestion, smoking status, education, serum creatinine, serum total calcium, sodium, hematocrit, and blood Cd	Prevalence OR (90th vs. 10th percentile)[b] All: 1.26 (0.98, 1.61) White males: 1.20 (0.74, 1.96) White females: 1.07 (0.69, 1.66) Black males: 2.69 (1.08, 6.72) Black females: 1.04 (0.50, 2.16) Mex-Am males: 1.03 (0.23, 4.59) Mex-Am females: 0.67 (0.37, 1.20)
Hara et al. (2015) United States NHANES 2003–2010 Cross-sectional	NHANES n = 12,725 ≥20 yr Average individual born ~1957	Blood Pb (ICP-MS) (µg/dL) GM (IQR): Females Black: 1.37 (0.88–2.10) Hispanic: 1.21 (0.80–1.78) White: 1.22 (0.80–1.86) Males Black: 1.86 (1.20–2.85) Hispanic: 1.94 (1.25–2.83) White: 1.73 (1.16–2.57) Age at measurement: mean (SD) Black females: 48.31 (6.8) Hispanic females: 48.1 (16.8) White females: 53.0 (8.4) Black males: 47.7 (16.9) Hispanic males: 46.1 (6.8) White males: 53.1 (18.6)	Hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg or the use of antihypertensive medication)	Logistic models adjusted for ethnicity, sex, age, BMI, heart rate, hematocrit, serum total calcium γ-glutamyltransferase, cotinine, dietary sodium to potassium intake ratio, college education, antihypertensive drug treatment	OR (95% CI) for doubling blood Pb[b] All: 0.95 (0.90, 1.01) Females: 0.95 (0.87, 1.04) Black: 0.82 (0.67, 0.99) Hispanic: 0.86 (0.72, 1.04) White: 1.06 (0.94, 1.21) Males: 0.95 (0.87, 1.02) Black: 1.00 (0.84, 1.20) Hispanic: 0.84 (0.71, 0.99) White: 0.99 (0.89, 1.10)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lee et al. (2016b) Korea KNHANES 2007–2013 Cross-sectional	KNHANES n = 8,493 ≥20 yr Average individual born ~1981, ~1961, or before ~1950	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Quartiles Q1: 0.206–1.539 Q2: 1.540–2.056 Q3: 2.057–2.716 Q4: 2.717–24.532 Age at measurement: 20–39 (58.8%) 40–59 (34.9%) ≥60 (6.3%)	Prehypertension prevalence (DBP 80–89 mmHg or SBP 120–139 mmHg and the absence of any current treatment or diagnosis of hypertension)	Logistic regression adjusted for age, sex, education, occupation, income, residence, smoking, alcohol consumption, exercise level, serum creatinine clearance, chronic disease, and antihypertensive medication	OR[b] (95% CI): Q2 vs. Q1 1.24 (1.04, 1.48) Q3 vs. Q1 1.27 (1.06, 1.52) Q4 vs. Q1 1.30 (1.07, 1.60)
Lee et al. (2016a) KNHANES 2008–2013 Cross-sectional	KNHANES n = 11,797 ≥19 yr Average individual born in or before ~1991	Blood Pb (GFAAS with Zeeman correction) (µg/dL) GM (95% CI) Male: 2.396 (2.362, 2.430) Female: 1.919 (1.889, 1.949)	Hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) and Prehypertension (SBP ≥120 mmHg or DBP ≥80 mmHg)	Logistic models adjusted for sex, age, residence area, education level, smoking, drinking status, BMI, physical activity, serum creatinine, and hemoglobin	OR for doubling blood Pb[b] Hypertension All: 1.09 (0.98, 1.22) Male: 0.92 (0.80, 1.07) Female: 1.29 (1.10, 1.51) Prehypertension All: 1.09 (0.99, 1.21) Male: 0.98 (0.85, 1.12) Female: 1.21 (1.06, 1.38)
Choi et al. (2018) South Korea KNHANES 2013 Cross-sectional	KNHANES n = 1,350 19–64 yr Average individual born ~1989, ~1978, ~1968, ~1958, ~1951	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean 2.01 SE 0.025 Age at measurement: 19–29 (23.1%) 30–39 (22.7%) 40–49 (21.9%) 50–59 (22.1%) 60–64 (10.1%)	Hypertension prevalence (SBP >140 mmHg, or DBP >90 mmHg, or use of antihypertensive medication)	Logistic regression adjusting for age, sex, smoking, and BMI	OR[d] (95% CI) Curry intake: 1.108 (0.827, 1.484) Non-curry intake: 1.399 (1.054, 1.857)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Qu et al. (2022) China 2017–2018 Cross-sectional	China National Human Biomonitoring Study n = 11,037 18–79 yr Average individual born ~1969	Blood Pb (ICP-MS) (μg/dL)[e] Quartiles Q1: <1.59 Q2: 1.59–2.24 Q3: 2.24–3.21 Q4: ≥3.21	Prehypertension (SBP 120–139, DBP 80–89), hypertension (Chinese guideline: SBP ≥140, or DBP ≥90), elevated BP (2017 ACC/AHA: SBP 120–129, DBP <80), stage 1 hypertension (2017 ACC/AHA: SBP 130–139, DBP 80–89)	Logistic regression adjusted for sex, age, BMI, regions, education, smoking status, alcohol consumption, family history of hypertension, residence area, rice consumption, red meat consumptions, vegetable consumptions, FBG, TC, HDL-C, urinary arsenic levels, and blood Cd levels	OR[b] (95% CI) Prehypertension Q2 vs. Q1: 1.24 (1.04–1.47) Q3 vs. Q1: 1.27 (1.02–1.59) Q4 vs. Q1: 1.56 (1.22–1.99) Hypertension Q2 vs. Q1: 1.23 (0.96–1.56) Q3 vs. Q1: 1.49 (1.12–1.96) Q4 vs. Q1: 2.33 (1.67–3.24) Elevated BP Q2 vs. Q1: 1.00 (0.77–1.31) Q3 vs. Q1: 1.10 (0.83–1.47) Q4 vs. Q1: 1.18 (0.88–1.57) Stage 1 Hypertension Q2 vs. Q1: 1.35 (1.10–1.65) Q3 vs. Q1: 1.35 (1.04–1.77) Q4 vs. Q1: 1.75 (1.31–2.33)
Bushnik et al. (2014) Canada 2007–2011 Cross-sectional	Canadian Health Measures Survey n = 4,550 Nonpregnant individuals aged 40–79 Average individual born ~1954	Blood Pb (ICP-MS) (μg/dL) Mean: 1.64 (1.58–1.71) Age at measurement: Mean: 55.4	Hypertension: SBP ≥140, or DBP ≥90, or use of antihypertensive medication, or health care provider diagnosis of hypertension	Logistic regression adjusted for age, sex, education, smoking, alcohol, physical activity, BMI, non-HDL cholesterol, diabetes, chronic kidney disease, family history of high BP, antihypertension medication use	OR Age 40–79: 0.02 (0.00, 0.43) Age 40–54: 0.01 (0.00, 0.20) Age 55–79: 0.01 (0.00, 1.00) Male: 0.00 (0.00, 0.91) Female: 0.02 (0.00, 0.60) *Results correspond to linear model. Concentration response function for splines not shown. Authors indicated no relationship between hypertension and BLL

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wang et al. (2020) China Cross-sectional	n = 816 Adults 40–75, residing in area for >15 yr, and subsisting on rice and vegetables grown in the polluted (Cd concentration >0.2 mg/kg) or unpolluted (Cd concentration <0.05 mg/kg) area	Blood Pb (ICP-MS) (μg/dL) Median (IQR) Polluted: 3.54 (2.4–4.89) Unpolluted: 2.61 (1.70–3.84) Age at measurement: Mean (SD) Polluted area Hypertensive: 60.32 (8.08) Normotensive 55.61 (8.52) Unpolluted area Hypertensive: 59.92 (9.19) Normotensive 56.86 (9.22)	Hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg, self-reported physician diagnosis, or current use of antihypertensive medication)	Logistic regression adjusted for age, gender, smoking status, and BMI	OR[b] (95% CI) See Figure 4-2 and Figure 4-3
Lopes et al. (2017a) Cambè, Brazil 2011 Cross-sectional	n = 948 adults 40 yr and older, randomly sampled from census tracts in the region Average individual born ~1956	Blood Pb (ICP-MS) (μg/dL) GM: 1.97 (95% CI:1.90–2.04) Age at measurement: Mean: 54.5 yr	Hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg or current antihypertensive medication)	Logistic regression adjusted for age, sex, race, income, education, antihypertensive medication, total cholesterol, triglycerides, glycemia, smoking, alcohol consumption, and BMI	OR 1.079 (1.026, 1.136)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xu et al. (2021) United States 2011–2013 Cross-sectional	GuLF Study Cohort n = 957 Adults ≥21 Average individual born in or before ~1991	Blood Pb (ICP-MS) (µg/dL) Median: 0.09 75th percentile: 0.19 Maximum: 33.8 Age at measurement: ≥21 yr	Hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg or current antihypertensive medication)	Multivariable Poisson regression adjusted for age, sex, race, educational attainment, and household income	Prevalence Ratio (PR) Q2 vs. Q1: 0.96 (0.73,1.25) Q3 vs. Q1: 0.91 (0.71, 1.17) Q4 vs. Q1: 0.86 (0.66, 1.12) BMI ≥30 Q2 vs. Q1: 1.05 (0.78, 1.42) Q3 vs. Q1: 1.09 (0.82, 1.45) Q4 vs. Q1: 1.14 (0.84, 1.55) BMI <30 Q2 vs. Q1: 0.89 (0.52, 1.52) Q3 vs. Q1: 0.81 (0.50, 1.31) Q4 vs. Q1: 0.82 (0.50, 1.32)
Weaver et al. (2008) South Korea 1999–2001 Cross-sectional	n = 652 current and former Pb workers Average individual born ~1957	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 31.9 (14.8) Patella Pb (K-XRF) (µg/g) Mean (SD): 75.1 (101.1) Age at measurement: Mean: 43.3, SD: 9.8	Hypertension (SBP >140 mmHg, DBP >90 mmHg; and/or use of antihypertensive medications; or physician diagnosis)	Logistic regression models adjusted for age, sex, BMI, diabetes, antihypertensive and analgesic medication use, Pb job duration, work status, tobacco, and alcohol use	Quantitative results not reported. None of the examined Pb exposure metrics (blood, patella, and logarithmic (ln)-transformed patella) were significantly associated with hypertension

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Elmarsafawy et al. (2006) Boston, MA 1991 Cross-sectional	NAS n = 471 Elderly men (mostly white) Average individual born ~1924	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 6.6 (4.3) Bone (K-XRF) (µg/g) Mean (SD) Tibia: 21.6 (12.0) Patella: 31.7 (18.3) Age at measurement Mean: 67	Hypertension (SBP ≥160 mmHg, DBP ≥95 mmHg; and/or physician diagnosis with current use of antihypertensive medications)	Logistic regression models adjusted for age, BMI, family history of hypertension, history of smoking, dietary sodium intake, and cumulative alcohol ingestion	OR (95% CI) Low Ca^{2+} group (<800 mg/d): Blood: 1.02 (1.00, 1.03) Tibia: 1.02 (1.00, 1.03) Patella: 1.01 (1.00, 1.01) High Ca^{2+} group (>800 mg/d): Blood Pb: 1.01 (0.99, 1.02) Tibia Pb: 1.02 (1.00, 1.05) Patella Pb: 1.01 (1.00, 1.02)
Gambelunghe et al. (2016) Malmö, Sweden 1991–1994, re-examination 2007–2012 Cohort	Malmö Diet and Cancer Study (MDCS-CC) n = 4,452 aged 46–67 living in Malmö Sweden Average individual born ~1935	Blood Pb (ICP-MS) (µg/L) All: 2.8 Max: 25.8 Age at measurement: Mean: 57 Range: 46–67	Hypertension (SBP ≥140 mmHg, or DBP ≥90 mmHg, or antihypertensive medication use)	Logistic regression adjusted for sex, age, smoking, alcohol, waist circumference, education	OR (Q4 vs. Q1+Q2+Q3)[b] All: 1.3 (1.1, 1.5) Smokers: 1.5 (1.2, 1.8) Never-smokers: 0.96 (0.7, 1.3) ≤57 yr: 1.5 (1.2, 1.9) >5 yr: 1.3 (0.9, 1.4) Male: 1.20 (0.60, 1.5) Female1.4 (1.1, 1.7) At Follow-up Antihypertensive medication use: 1.0 (0.8, 1.2) High BP: 1.0 (0.7, 1.3)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Zheutlin et al. (2018) Boston, MA 1986–2013 Cohort	NAS n = 475 Male volunteers aged 21 to 80 yr (bone Pb measurement started in 1991, resistant hypertension assessed starting at visit prior to first bone measurement) Average individual born ~1931	Blood Pb (GFAAS with Zeeman correction) (μg/dL) Median (IQR): 5.0 (3.4–8.0) Bone (K-XRF) (μg/g) Median (IQR) Tibia: 20.0 (13.0–28.5) Patella: 27.0 (18.0–40.0) Age at measurement: 67.9 (63.2–72.6)	Incident resistant hypertension (inadequate control) (SBP ≥140 mmHg, DBP ≥90 mmHg) while taking ≥3 antihypertensive medications, or adequate control (SBP <140 mmHg, DBP <90 mmHg) while taking ≥4 antihypertensive medications	Poisson regression with robust error variation adjusting for age, race/ethnicity, education attainment, income level, BMI, family history of hypertension, and cigarette smoking	RR Tibia: 1.12 (1.01, 1.25) Patella: 1.04 (0.96, 1.13) Blood: 1.02 (0.97, 1.08)

ACC = American College of Cardiologists; AHA = American Heart Association; BLL = blood lead level; BMI = body mass index; BP = blood pressure; Ca^{2+} = calcium ion; Cd = cadmium; CI = confidence interval; DBP = diastolic blood pressure; FBG = fasting blood glucose; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; GuLF = Gulf Long-Term Follow-up; HDL-C = high-density lipoprotein cholesterol; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; KNHANES = Korea National Health and Nutrition Examination Survey; LF = low frequency; MDCS-CC = cardiovascular cohort of the Malmö Cancer and Diet Study; Mex-Am = Mexican-American; NAS = Normative Aging Study; NH = non-Hispanic; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PIR = poverty-income ratio; Pb = lead; Q = quartile; PR = prevalence ratio; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TC = total cholesterol; K-XRF = K-shell X-ray fluorescence; yr = year(s).

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Blood Pb analysis method unclear, assumed based on data source.

[d]Confidence intervals estimated based on reported p values.

[e]Original results reported in μg/L.

Table 4-5 Epidemiologic studies of Pb exposure and blood pressure and hypertension among children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Zhang et al. (2012) Mexico City, Mexico 1994–2003 Follow-up 2008–2010 Cohort	Early Life Exposures in Mexico to Environmental Toxicants project n = 457 mother-child pairs Average individual born ~1973	Cord Blood (AAS) (µg/dL) Mean (SD): 5.51 (3.45) Bone (K-XRF) (µg/g) Median (IQR) Tibia: 9.3 (3.3–16.1) Patella: 11.6 (4.5–19.9) Age at measurement Mean (SD): 25.6 (5.4)	BP (SBP, DBP) in children Age at outcome Mean (SD): 10.7 (2.4)	Multiple regression models and generalized estimating equations (log linear for cord blood, linear for concurrent blood and maternal bone) adjusted for maternal education, birth weight, BMI, sex, and child concurrent age	Difference in BP (mmHg) Cord Blood SBP All: 0.23 (−0.14, 0.60) DBP All: 0.23 (−0.03 0.49) Tibia SBP All: 0.74 (−0.10, 1.58) SBP Female: 1.62 (0.54, 2.71) SBP Male: −0.26 (−1.52, 1.00) DBP All: 0.35 (−0.36, 1.07) DBP Female: 1.24 (0.23, 2.25) DBP Male: −0.64 (−1.57, 0.30) Patella SBP All: 0.28 (−0.45, 1.00) DBP All: 0.14 (−0.59, 0.88)
Gump et al. (2005) Oswego, NY (born at a single hospital in New York from 1991–94) Cohort	Oswego Children's Study n = 122 children aged 9.5 yr Average individual born ~1990	Cord blood (ETAAS) (µg/dL) Mean (SD): 2.97 (1.75) Child blood (ETAAS and ASV) (µg/dL) Mean (SD): 4.62 (2.51) Age of child blood Pb measurement Mean: 2.6	BP (SBP, DBP) and TPR in children Age at outcome 9.5	Linear regression models examined the adjusted for HOME score, SES, birth weight, child BMI, and child sex	Baseline BP (mmHg) per 1 µg/dL increase in cord blood Pb[b] SBP: 12.16 (2.44, 21.88) DBP: 8.45 (−0.45, 17.35) TPR, dyne-s/cm^5 no association, results NR Relationship of blood Pb with change in z-score for outcome (post and prestress) per 1 µg/dL increase in childhood blood Pb SBP: −0.009 (−0.074, 0.055) DBP: 0.069 (−0.001, 0.138) TPR, dyne-s/cm^5 0.088 (0.024, 0.152)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Gump et al. (2007) Oswego, NY (born at a single hospital in New York from 1991–94) Cohort	Oswego Children's Study n = 122 children aged 9.5 yr Average individual born ~1990	Cord blood (ETAAS) (µg/dL) Mean (SD): 2.97 (1.75) Child blood (ETAAS and ASV) (µg/dL) Mean (SD): 4.62 (2.51) Age of child blood Pb measurement (years): Mean: 2.6	BP (SBP) and TPR in children Age at outcome 9.5	Linear regression models adjusting for the same covariates as in Gump et al. (2005). Separate models testing whether Pb is a mediator of SES associations (Sobel test) and whether Pb moderates SES associations (Pb-SES interaction)	Blood Pb was a mediator of the SES-TPR relationship SES alone: −0.62 dyne-s/cm^5 ($p < 0.05$) SES with Blood Pb: −0.40 dyne-s/cm^5 ($p > 0.10$), change in R2 attributable to SES: −55.3% Blood Pb was a potential moderator of the SES-TPR relationship. Blood Pb × SES interaction: p = 0.07 Blood Pb was a moderator of SES-SBP relationship Pb × SES interaction: p = 0.007
Kupsco et al. (2019) Mexico City, Mexico 2007–2011 Cohort	Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) birth study n = 548 Mother/child pairs Maternal blood tested for metals in second trimester, children assessed at age 4–6 Average individual born ~1981	Maternal Blood (ICP-MS) (µg/dL) Mean: 3.7, SD: 2.7 Range 0.75–18 Max: 18 Age at measurement (years): 28 (5.6)	BP (SBP, DBP) Age at Outcome: Mean (SD): 4.8 (0.55) Range: 4–6.8	Linear regression adjusted for birth weight, gestational age, prepregnancy BMI, education, socioeconomic status, parity, environmental tobacco smoke	BP (mmHg) per 1 ln unit increase in maternal blood Pb[c] SBP: −0.05 (−0.09, 0.07) DBP: 0 (−0.23, 0.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Skröder et al. (2016) Bangladesh (2002- 2004) Cohort	Maternal and Infant Nutrition Interventions, Matlab n = 1,511 (gestational week [GW] 14); 713 (GW 30) Mother-child pairs Eyr-Pb measured at GW14 and GW30, children assessed at age 4.5 Average individual born ~1977	Maternal Blood (Eyr-Pb) (ICP-MS) (µg/kg) GW: 14 Median: 73 95th: 172 GW: 30 Media: 86 95th : 506 Age at measurement: Mean (SD): 26 (6)	BP (SBP, DBP) Age at Outcome Mean: 4.5 yr	Linear regression adjusted for sex, birth weight, season of birth, age at outcome measurements, height for age z-score, maternal BMI at GW8, parity, SES, and supplementation group	BP (mmHg) per µg/kg Eyr-Pb[c] GW14: SBP: 0.042 (−0.058, 0.14) DBP: −0.0058 (−0.090, 0.077) GW30: SBP: 0.042 (−0.090, 0.17) DBP: 0.072 (−0.039, 0.18)
Gump et al. (2011) Oswego, NY Cross-sectional	n = 140 children ages 9–11 yr	Blood (ICP-MS) (µg/dL) GM: 1.01 Q1: 0.14–0.68 Q2: 0.69–0.93 Q3: 0.94–1.20 Q4: 1.21–3.76	BP (SBP), TPR	Linear regression adjusted for sex, SES, BMI, and age	Change in SBP (mmHg) across quartiles in response to acute stress[c,d] Q1: 5.30, Q2: 7.33, Q3: 7.07, Q4: 7.23, p for trend = 0.31 Change in TPR (%) across quartiles in response to acute stress[c,d] Q1: 2.91, Q2: 8.18, Q3: 9.55, Q4: 9.51, p for trend = 0.03

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Factor-Litvak et al. (1996) Kosovo (when part of Yugoslavia) January 1st, 1984-July 31st, 1986 Cross-sectional	Yugoslavia Prospective Study n = 281 from two towns (Kovoska Mitrovica [Exposed town] and Pristina [Unexposed town 25 miles south]) Average individual born ~1980	Blood (GFAAS) (µg/dL) Exposed Town Mean (SD): 37.3 (12.0) Range: 9.5- 76.4 Unexposed Town Mean (SD): 8.7 (2.8) Range: 4.1- 20.2	BP (SBP, DBP)	Linear regression adjusted for ethnic group, birth order (and height, BMI, and sex for SBP and waist circumference for DBP)	BP (mmHg) per 1 µg/dL blood Pb SBP: 0.054 (−0.024, 0.13) DBP: 0.042 (−0.010, 0.090)
Lu et al. (2018) Guiyu (e-waste exposed), Haojiang (reference) China 2016 Cross-sectional	n = 590 children (aged 3–7) residing in either Guiyu or Haojiang China Average individual born ~2011	Blood (GFAAS) (µg/dL) Median Exposed: 7.14 Unexposed: 3.91 Age at measurement Mean (SD) Exposed: 4.52 (0.86) Unexposed 4.40 (1.04)	BP (SBP, DBP) Age at Outcome Mean (SD) Exposed: 4.52 (0.86) Unexposed: 4.4 (1.04)	Linear regression adjusted for outdoor activities, family member smoking, parent education and diet (including cooking oil, picky eating, sweetmeat consumption, salted products, vegetable and fruit consumption, dairy products, bean products, marine products), age, sex, BMI, and family history of diseases (hypertension, diabetes, obesity)	Ln-transformed Blood Pb and BP (mmHg)[c] SBP: −0.30 (−2.6, 2.00) DBP: −2.11 (−4.38, 0.17)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ahn et al. (2018) Korea KNHANES 2010–2016 Cross-sectional	KNHANES n = 1,776 Adolescents (10–18 yr) Average individual born ~1999	Blood (GFAAS with Zeeman background correction (µg/dL) GM (95% CI): 1.19 (1.17–1.22) Age at measurement: Range: 10–18 yr	BP (SBP, DBP) Prehypertension (SBP 120–140 mmHg, DBP 80–90 mmHg)	Linear and logistic regression adjusted for sex, age, residence area, smoking status, drinking status, BMI, year of measurement, physical activities, hemoglobin, and serum creatinine	Mean difference (mmHg) for doubling blood Pb[c] DBP: −0.680 (−1.561, 0.221) SBP: −0.0999 (1.098, 0.898) Prehypertension (OR [95% CI]) for doubling blood Pb[c] 0.906 (0.629, 1.305)
Xu et al. (2017) United States NHANES 1999–2012 Cross-sectional	NHANES n = 11,662 Adolescents 12–19 participating in NHANES Average individual born ~1990	Blood (ICP-MS)[c] (µg/dL) Mean (SD) 1.17 (1.20) Q1: <0.6 Q2: 0.6–0.9 Q3: 0.0–1.34 Q4: >1.34 Age at measurement Range: 12–19 yr	BP (SBP, DBP)	Linear models adjusted for age, sex, PIR, waist circumference, serum cotinine, physical activity and NHANES cycle	BP (mmHg) (Q4 vs. Q1)[c] SBP: 0.001 (−0.001, 0.004) DBP: 0.001 (−0.006, 0.008)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Yao et al. (2020) United States 2007–2016 Cross-sectional	NHANES n = 7,076 Children and adolescents Average individual born ~1999	Blood (ICP-MS) (µg/dL) Mean: 0.67 Q1: <0.46 Q2: 0.46–0.65 Q3: 0.65–0.96 Q4: >0.96 Age at measurement Mean (SD): 11.99 (2.88)	BP (SBP, DBP) High BP (self (or parent) reported hypertension diagnosis or antihypertension medication use for those ≥16, or SBP >120 mmHg or DBP >80)	Linear or logistic regression adjusted for age, sex, race/ethnicity, BMI, cycle, serum cotinine levels, hematocrit, annual family income, and intake of calcium, sodium, and potassium	BP (Regression coefficient) for log-transformed blood Pb[b,c] SBP All: −0.48 (−1.07, 0.11) Male: −0.55 (−1.35, 0.25) Female: −0.53 (−1.41, 0.35) Mexican American: −0.10 (−1.06, 0.86) Other Hispanic: −1.77 (−3.46, −0.08) White: −0.27 (−1.21, 0.67) Black: 0.17 (−0.15, 1.65) DBP All: 0.75 (−1.01, 1.49) Male:1.16 (−0.13, 2.45) Female: 0.24 (−1.01, 1.49) Mexican American: 1.12 (−0.49, 2.73) Other Hispanic: −0.86 (−2.53, 0.81) White: 1.99 (0.58, 3.40) Black: −2.30 (−4.38, −0.22) High BP (OR) Q4 vs. Q1 All: 0.89 (0.62–1.27) *Change in BP associated with a twofold increase in blood Pb was calculated by dividing the regression coefficient by $\log_2$ €

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Desai et al. (2021) NHANES 2009–2016 Cross-sectional	NHANES n = 1,642 participants aged 8–17 yr Average individual born ~2000	Blood Pb (ICP-MS) (µg/dL) Median: 0.57 ^{9}5th percentile: 1.6 Age at measurement Median: 152 mo (~12.7 yr)	BP (SBP, DBP, PP)	Multivariate linear regression models adjusted for age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio	BP (mmHg) SBP: −0.351 (−1.391, 0.689) DBP: −0.078 (−1.365, 1.209) PP: −0.273 (−1.781, 1.235)
Zhang et al. (2021) Boston, MA (United States) Baseline 2002–2013, follow-up through 2018 Cohort	Boston Birth Cohort n = 1,194 mother-child pairs Average individual born ~1980	Maternal red blood Pb (measured 24–72 hr postdelivery, ICP-MS) (µg/dL) Median: 2.42 ^{7}5th percentile: 3.68 Max: 24.8 Age at measurement (age at delivery) Mean (SD): 27.7 (6.5)	BP (SBP) percentile (based on child age, sex, and height according to the 2017 American Academy of Pediatric Clinical Practice Guideline) Age at outcome Median (IQR): 8.4 (6.2–10.6)	Multivariate linear regression models adjusting for maternal age, race/ethnicity, educational level, prepregnancy BMI, and smoking history	Difference in child SBP percentile[c] Quartiles Q2 vs. Q1: 0.92 (−3:13, 4.97) Q3 vs. Q1: 1.39 (−2:85, 5.64) Q4 vs. Q1: −0.62 (−4.97, 3.74) Per 1 µg/dL increase in blood Pb 0.142 (−0.673, 0.958)

AAS = atomic absorption spectrometry; ASV = anodic stripping voltammetry; BMI = body mass index; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; ETAAS = Electrothermal Atomic Absorption Spectrometry with Zeeman background correction; Eyr = erythrocyte; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; GSD = geometric standard deviation; GW = gestational week; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; KNHANES = Korea National Health and Nutrition Examination Survey; mo = month(s); Mex-Am = Mexican American; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; PIR = poverty-income ratio; PP = pulse pressure; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; Q = quartile; SBP = systolic blood pressure; SD = standard deviation; SES = socioeconomic status; TPR = total peripheral resistance; Pb = lead; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Confidence intervals estimated based on reported standard errors.

[c]Unable to be standardized.

[d]Confidence intervals not provided and unable to calculate based on given information.

Table 4-6 Animal toxicological studies of Pb exposure and blood pressure/hypertension

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Fioresi et al. (2014)	Rat (Wistar) Control (tap water), M, n = 9–12 100 ppm group, M, n = 9–12	Age 2 mo to 3 mo	100 ppm Pb acetate in drinking water for 30 d	<0.5 µg/dL for control 13.6 ± 1.07 µg/dL for 100 ppm group	SBP, measured weekly from 0 to 4 wk MAP, DBP, ACE activity measured post 30-d exposure
Gaspar and Cordellini (2014)	Rat (Wistar) Control (tap water), M, n = 15 8500 ppm group, M, n = 20	In utero to PND 22	Pregnancy day 0: females divided into tap water and 500 ppm Pb acetate in drinking water groups. Exposure lasted through pregnancy. At birth, pups were exposed to Pb (or control) through nursing. Pups were weaned at 22 d	<5 µg/dL at all times for tap water 19.98 ± 6.31 – PND 52 13.15 ± 0.97 – PND 70 11.17 ± 2.11 – PND 100	SBP weekly measurements starting at PND 23 to PND 100
Nunes et al. (2015)	Rat (Wistar) Control (Distilled water), M, n = 5 100 ppm Pb acetate group, M, n = 5	2 mo old rats exposed for 30 d	100 ppm Pb acetate in drinking water for 30 d	NR for control 8.4 µg/dL for 100 ppm	SBP measured post 30 d exposure for 28 d

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Silva et al. (2015)	Rat (Wistar) Control (distilled water) M, n = 6 100 ppm Pb acetate group M, n = 6	3 mo old rats exposed for 15 d	100 ppm Pb acetate in drinking water for 15 d	12.3 ± 2 µg/dL	SBP measured weekly
Wildemann et al. (2015)	Rat (Wistar) Control (tap water), M, n = 6 357 or 1607 µg/kg BW/d, M, n = 5 per group	Unknown start age for 4 wk	Tap water with 0.2% nitic acid, or 357 or 1607 µg/kg BW/d Pb acetate in drinking water for 4 wk	1.4 ± 1.2 µg/L for tap water/ 0.2% nitic acid (0.14 ± 0.12 µg/dL) 17 ± 7 µg/L for 357 µg/kg BW/d Pb acetate (1.7 ± 0.7 µg/dL) 86 ± 29 µg/L for 1607 µg/kg BW/d Pb acetate (8.6 ± 2.9 µg/dL)	DBP, PP, SBP all measured post 4-wk exposure
Xu et al. (2015)	Rat (Sprague Dawley) Control 1, M/F, n = 6 1% PB acetate group 12 d, M/F, n = 15 1% PB acetate group 40 d, M/F, n = 15	6–7-wk-old rats exposed for 12 or 40 d	Distilled water for 40 d or 1% Pb acetate in drinking water for 12 or 40 d	Day 12: 193.3 µg/L (19.33 µg/dL) Day 40: 245.9 µg/L (24.59 µg/dL)	DBP, SBP, measured intermittently from 0–40 d

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Shvachiy et al. (2018)	Rat (Wistar) Control, M/F, n = 8 0.2% Pb acetate, intermittent Pb group, M/F, n = 9 0.2% Pb acetate, permanent Pb group, M/F, n = 9	In utero to 28 wk	Pregnant Wistar rats were given 0.2% Pb acetate in drinking water or tap water. After a 21 d weaning period, pups were either continuously exposed to Pb acetate in drinking water until 28 wk or were given 8 wk of Pb abstinence and then exposed until 28 wk with Pb acetate	18.8 ± 2.0 µg/dL for intermittent exposure 24.4 ± 4.9 µg/dL for continuously exposed	DBP, MAP, Baroreceptor Reflex, Chemoreceptor Reflex, SBP, all measured 2-hr post 28-wk exposure
Zhu et al. (2018)	Rat (Sprague Dawley) Control (distilled water), M, n = 10 0.5 g/L Pb acetate, M, n = 10	In utero to 1 yr	Female rats were given either 0 or 500 mg/L Pb acetate for 10 d before mating. Male offspring continued receiving 0 or 500 mg/L Pb acetate for 1 yr	0.28 ± 0.02 mg/L (28 ± 2 µg/dL)	SBP, DBP measured post 1-yr exposure

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Zhu et al. (2019)	Rat (Sprague Dawley) Control (distilled water), M, n = 100 0.5 g/L Pb acetate, M, n = 10	In utero to 1 yr	Female rats were given either 0 or 0.5 g/L Pb acetate for 10 d before mating. Male offspring continued receiving 0 or 0.5 g/L Pb acetate for 1 yr	0.27 ± 0.02 mg/L (27 ± 2 µg/dL)	SBP, DBP measured post 1-yr exposure

ACE = angiotensin-converting enzyme; BLL = blood lead level; BW = body weight; d = day(s); DBP = diastolic blood pressure; F = female; M = male; MAP = mean arterial pressure; NR = not reported; Pb = lead; PND = postnatal day; PP = pulse pressure; SBP = systolic blood pressure; yr = year(s); wk = week(s).

Table 4-7 Epidemiologic studies of Pb exposure and coronary and ischemic heart disease

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Jain et al. (2007) Boston, MA 1991–2001 Cohort	NAS n = 837 elderly men (mostly white) Average individual born ~1933	Blood (GFAAS with Zeeman correction) (μg/dL) Non-cases Mean (SD): 6.2 (4.3) Range: 0 to 35 Cases Mean (SD): 7.0 (3.8) Range: 1.0 to 20.0 Bone (K-XRF) (μg/g) Patella Non-cases Mean (SD): 30.6 (19.7) Range: −10 to 165 Cases Mean (SD): 36.8 (20.8) Range: 5.0 to 101 Tibia Pb Non-Cases Mean (SD): 21.4 (13.6) Range: −3 to 126 Cases Mean (SD): 24.2 (15.9) Range: −5 to 75 Age at measurement Mean 67	IHD (MI or angina pectoris)	Cox proportional hazards models adjusted for age, BMI, education, race, smoking status, pack-years smoked, alcohol intake, history of diabetes mellitus and hypertension, family history of hypertension, DBP, SBP, serum triglycerides, serum HDL, and total serum cholesterol	BLL ≥5 μg/dL[b] Per 1 SD increase in Pb biomarker OR over 10-yr follow-up: 1.73 (1.05, 2.87) Ln (blood Pb) OR: 1.45 (1.01, 2.06) Ln (patella Pb) OR: 2.64 (1.09, 6.37) Ln (tibia Pb) OR: 1.84 (0.57, 5.90)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ding et al. (2016) Boston 1991 through 2011 participants followed up to 20 yr Cohort	NAS n = 589 Elderly men (mostly white) Average individual born ~1935	Bone (K-XRF) (µg/g) Mean (SD) No CHD Patella: 29.2 (16.1) Tibia 20.2 (12.5) CHD Patella: 32.1 (18.8) Tibia: 22.6 (13.5) Age at measurement: Mean: 66 Range: 48–96	Incident Coronary Heart Disease (MI, angina pectoris or CHD deaths)	Cox regression adjusted for age, smoking status, BMI, and the ratio of total cholesterol to HDL-C level	HR (twofold increase in blood Pb)[b] Bone (Patella) 1.36 (1.15, 1.61) At least one minor allele in VDR *rs1544410 (Bsm1)* 1.65 (1.31, 2.08) *rs731236 (Taq1)* 1.61 (1.29, 2.02) *rs7975232 (Apa1)* 1.28 (1.04, 1.57) *rs1073581 (Fok1)* 1.47 (1.17, 1.83) *rs757343 (Tru91)* 1.48 (1.18, 1.85) At least one minor allele in ALAD *rs1833435* 1.11 (0.79, 1.55) No minor allele in HFE *rs1799945 (H63D)* 1.41 (1.15, 1.73) *rs1800562 (C282Y)* 1.36 (1.13, 1.64) No minor allele HMOX1 *rs2071746* 1.51 (1.07, 2.14) *rs5995098* 1.63 (1.23, 2.14) At least one minor allele in HMOX1 *rs2071749* 1.51 (1.22, 1.86) No minor allele in APOE *rs429358* 1.43 (1.17, 1.76) *rs449647* 1.29 (1.05, 1.60) *rs7412* 1.34 (1.10, 1.64) At least one minor allele in APOE *rs7412* 1.53 (1.07, 2.19) No minor allele in AGT *rs699* 2.17 (1.50, 3.12) *rs5046* 1.53 (1.27, 1.94) *rs5050* 1.36 (1.09, 1.69) At least one minor allele in AGT

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					rs50501.41 (1.03, 1.94) No minor allele in angiotensin II receptor type 1 *rs12695908* 1.43 (1.20, 1.74) No minor allele in glutathione S-transferase pi 1 *rs1695* 1.39 (1.10, 1.76) GRS 1 2.27 (1.50, 3.42) GRS 2 2.77 (1.78. 4.31)
Ding et al. (2019) Boston, MA United States August 1991- June 2011 Mean (SE) 8.52 (5.75) yr of follow-up Cohort	NAS n = 594 elderly men (mostly white) without CHD at baseline Average individual born ~1935	Bone (K-XRF) (μg/g) Mean (SD) CHD Patella: 32.2 (18.9) Tibia: 22.6 (13.5) Non-CHD Patella: 29.4 (18.9) Tibia: 20.9 (13.2) Age at measurement Mean (SD) CHD: 65.5 (6.2) Non-CHD: 66.5 (7.5)	Incident Coronary Heart Disease (MI, angina pectoris or CHD deaths)	Cox proportional hazards adjusting for BMI, total energy intake, smoking status, TC to HDL ratio, education level, and occupation	HR (95 % CI) for twofold increase in Bone Pb[b] Patella 1.30 (1.09, 1.56) Tibia 1.25 (1.06, 1.48) Prudent Diet Patella Low: 1.64 (1.27, 2.11) High: 1.07 (0.86, 1.34) Tibia Low: 1.24 (0.96, 1.59) High: 1.26 (1.02, 1.55) Western Diet: Patella Low: 1.35 (1.05, 1.72) High 1.27 (0.96, 1.61) Tibia Low: 1.43 (1.14, 1.80) High: 1.08 (0.86, 1.34)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Tonelli et al. (2018) Canada Participant recruited between March 2005 and November 2012 Cohort (year of follow-up)	n = 1,278 Patients on incident hemodialysis Average individual born ~1946	Plasma Pb (ICP-MS) (µg/dL) Deciles 1: 0.06 2: 0.19 3: 0.28 4: 0.35 5: 0.44 6: 0.55 7: 0.68 8: 0.83 9: 1.08 10: 1.74	Cardiovascular event (acute MI, percutaneous coronary angioplasty, coronary artery bypass grafting, heart failure, and stroke or transient ischemic attack)	Logistic regression adjusting for age, sex, race/ethnicity, unemployment prior to dialysis, year dialysis initiated, dialysis duration, predialysis care, arteriovenous access, comorbidities (AF, MI, BMI, cancer, cerebrovascular disease, CHF, lung disease, diabetes, dementia, hypertension, liver disease, PVD, psychiatric disease, substance misuse), albumin, and creatinine. *All variables were considered candidate variables and were included based on stepwise regression results	OR[b] Cardiovascular events: NR Authors indicate a null relationship between blood Pb deciles and all-cardiovascular events, results not reported
Cho et al. (2016) South Korea 2008–2019 Cross-sectional	KNHANES n = 5,361 Participants in KNHANES aged 20–70 y Average individual born ~1973	Blood (GFAAS with Zeeman correction) (µg/dL) Males Mean (SE): 2.81 (0.32) Q1: 0.71–2.13 Q2: 2.13–2.70 Q3: 2.70–3.52 Q4: 3.52–26.51 Females Mean (SE): 2.04 (0.02) Q1: 0.42–1.49 Q2: 1.49–1.95 Q3: 1.95–2.51 Q4: 2.51–9.59 Age at measurement (years): Mean (SE) Males: 39.3 (0.30)	>10% increase in 10-yr CHD Risk (FRS) based on age, gender, SBP, total cholesterol, and HDL-C)	Logistic regression adjusted for BMI, triglycerides, and LDL-C	OR[b] (95% CI): Males Q2 vs. Q1: 1.59 (1.03, 2.46) Q3 vs. Q1: 2.31 (1.52, 3.50) Q4 vs. Q1: 3.13 (2.9, 4.69) Females Q2 vs. Q1: 1.84 (0.61, 5.55) Q3 vs. Q1: 1.43 (0.44, 4.59) Q4 vs. Q1: 0.88 (0.26, 2.97)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Females: 40.9 (0.30)			
Choi et al. (2020) Korea 2016–2017 Cross-sectional	KNHANES n = 2,424 Participants in KNHANES aged 40–80 yr Average individual born ~1956	Blood (GFAAS with Zeeman correction) (µg/dL) Pb distribution NR	10-yr atherosclerotic cardiovascular disease (ASCVD) risk	Multiple linear regression analysis adjusting for age, income, job type, physical activity, location, and sleep	Linear increase in 10-yr ASCVD risk score (Q4 vs. Q1)[b,c] Males: 0.117 (0.01, 0.23) Urban: 0.133 (0.01, 0.25) Rural: 0.079 (−0.15, 0.31) <7 hr sleep: 0.097 (−0.03, 0.23) >7 hr sleep: 0.183 (0.01, 0.36) Females: 0.072 (−0.00, 0.15) Urban: 0.038 (−0.05, 0.12) Rural: 0.212 (0.05, 0.38) <7 hr sleep: 0.110 (0.016, 0.20) >7 hr sleep: 0.021 (−0.09, 0.13)
Park and Han (2021) South Korea KNHANES VII-1 (2017) Cross-sectional	KNHANES n = 1,929 ≥20 y Average individual born in or before ~1997	Blood Pb (GFAAS with Zeeman correction (µg/dL) Distribution: NR	10%–20% and >20% increase in 10-yr CVD risk estimated using FRS	Logistic regression adjusted for SBP, HDL cholesterol, and total cholesterol	OR (<10% increase in 10-yr CVD risk as referent)[b,c,d] Males 10%–20% 10 yr CVD risk (vs. <10%): 2.407 (1.885, 3.075) >20% 10 yr CVD risk (vs. <10%): 2.847 (2.020, 4.011) Females 10%–20% 10 yr CVD risk (vs. <10%): 1.051 (0.676, 1.633) >20% 10 yr CVD risk (vs. <10%): 0.706 (0.188, 2.659)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Nguyen et al. (2021) South Korea KNHANES IV (2009), V (2010–2012), VI (2013), and VII (2016–2017) Cross-sectional	KNHANES n = 9,602 ≥20 y Average individual born ~1965	Serum Pb (GFAAS with Zeeman correction (µg/dL) GM (95% CI) 2.02 (2.00–2.03) Age at measurement Mean (SD) Males: 47.76 (15.25) Females: 46.87 (15.16)	10-yr CVD risk estimated using FRS	Multivariable models adjusted for serum cotinine, age group, sex, high-risk drinking, physical activity, BMI, family history of CVDs, diabetes or dyslipidemia, and type 2 diabetes. *Assume linear regression, but not specified	Linear increase in 10-yr CVD risk score (log_2 transformed blood Pb)[b] 0.104 (0.016, 0.214)
Ochoa-Martínez et al. (2018) San Luis Potosi Mexico 2015–2016 Cross-sectional	Women living in communities with a high-risk of environmental Pb contamination n = 175 Average individual born ~1967	Blood Pb (GFAAS) (µg/dL) mean (SD) 11.5 (9.0) Tertiles T1: <3.5 T2: 3.6–9.0 T3: >9.1 Age at measurement: mean (SD): 48.5 (18.0)	Predictive CVD biomarkers [asymmetric dimethylarginine (ADMA), FABP4, adiponectin, and chemerin]	Linear regression controlling for age, weight, waist circumference, hip circumference, SBP, DBP, BMI, body fat %, visceral fat %, glucose, triglycerides, total cholesterol, HDL-C, LDL-C	Predictive CVD biomarkers[b] ADMA (µmol/L): T2: 0.51 (−0.25, 0.69) T3: 0.75 (0.15, 1.85) FABP4 (ng/mL): T2: 11.0 (−15.0, 16.0) T3: 27.5 (10.0, 34.5) Adiponectin (µg/mL): T2: 9.50 (−17.0, 21.0) T3: 12.5 (−7.5-, 18.0) Chemerin (ng/mL): T2: 195 (−75.0, 275) T3: 220 (−25, 300)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wan et al. (2021) China May-August 2018 Cross-sectional	Environmental Pollutant Exposure and Metabolic Diseases in Shanghai (METAL study) n = 4,234 Average individual born ~1951	Blood (AAS) (μg/dL) Median (IQR): 2.6 (1.8–3.6) Age at measurement Median (IQR): 67 (62–72) yr	Presence of CVD (Self-reported diagnosis by a physician, including CHD, MI or stroke)	Linear or logistic regression adjusting for age, sex, duration of diabetes, education status, current smoking, BMI, HbA1c, dyslipidemia, hypertension	OR (95% CI) (4th vs. 1st quartile of Blood Pb)[b] 1.44 (1.17, 1.76)

AAS = atomic absorption spectrometry; ADMA = asymmetric dimethylarginine; AF = atrial fibrillation; AGT = angiotensinogen; ALAD = δ-aminolevulinic acid dehydratase; APOE = apolipoprotein E; ASCVD = atherosclerotic cardiovascular disease; BLL = blood lead level; BMI = body mass index; *C282Y* HFE = mutant of the HFE wildtype; CHD = congenital heart disease; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; FABP4 = adipocyte fatty acid-binding protein 4; FRS = Framingham risk score; GFAAS = graphite furnace atomic absorption spectrometry; GRS = genetic risk score; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HFE = hemochromatosis gene; HMOX1 = heme oxygenase-1; HR = hazard ratio; ICP-MS = inductively coupled plasma mass spectrometry; IHD = ischemic heart disease; IQR = interquartile range; KNHANES = Korea National Health and Nutrition Examination Survey; K-XRF = K-shell X-ray fluorescence; LDL-C = low-density lipoprotein cholesterol; METAL = Environmental Pollutant Exposure and Metabolic Diseases in Shanghai ; MI = myocardial infarction; NR = not reported; OR = odds ratio; Pb = lead; PVD = peripheral vascular disease; Q = quartile; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; T# = tertile #; TC = total cholesterol; VDR = vitamin D receptor; yr = year(s).

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Confidence intervals estimated from standard error.

[d]Increment unclear.

Table 4-8 Epidemiologic studies of Pb exposure and cardiac function

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Schwartz (1991) United States 1976–1980 Cross-sectional	NHANES II n = 9,932 Average individual born ~1931	Blood- Method NR Distribution NR	Left ventricle hypertrophy (based on body habitus, BMI, and tricep skinfold)	Logistic regression adjusting for age, sex, and race	OR 1.028 (1.009, 1.048)
Yang et al. (2017) Belgium baseline 1985–2000; follow-up: 2005–2010 Median follow-up 11.9 yr Cohort	Cadmium in Belgium study n = 179 Average individual born ~1953	Blood (ETAAS with Zeeman correction) (µg/dL) GM 4.14 Age at measurement Mean: 39.1	Left ventricle structure and function	Linear regression adjusting for measures at the time of the echocardiography including age, sex, MAP, heart rate, BMI, fasting plasma glucose, total to HDL cholesterol ratio, serum creatinine, γ-glutamyltransferase, smoking, and antihypertensive medication class	For each doubling of blood Pb[b,c] LV Structure LVMI, g/m^2 −1.399 (−4.504,1.707) End diastolic diameter, cm −0.064 (−0.134, −0.006) RWT 0.0065 (−0.0031, 0.0162) Systolic LV Function Ejection fraction, % 0.190 (−1.293, 1.675) GLS, % −0.497 (−0.957, −0.038) RLS, % −0.784 (−1.482, −0.087) RLS rate, (s-1) −0.071 (−0.124, −0.019) RRS, % −2.316 (−4.748, −0.115) RRS rate, (s-1) −0.135 (−0.292, 0.022) Diastolic LV Function E peak, cm/s 1.308 (−1.120, 3.736) E/A ratio −0.036 (−0.085, 0.014) e' peak, cm/s −0.188 (−0.494, 0.118 (E/e' ratio 0.172 (−0.133, 0.477)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lind et al. (2012) Uppsala, Sweden Cross-sectional	Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study n = 993 Elderly (70 yr) individuals	Blood (ICP-MS) (µg/dL) Median (IQR): 1.72 (1.22, 2.28)	Left ventricle structure	Linear regression adjusting for sex, BP, antihypertensive medication, diabetes, and BMI	Per ln-transformed unit increase in serum Pb[b] LVMI, g/m^2 −0.7–3 –(2.20, 0.74) RWT 0.011 (−0.001, 0.022)
Chen et al. (2021) Guangdong province China 2018 Cross-sectional	n = 486 Preschool children (aged 2–6) from two towns with similar SES but different Pb exposure Average individual born ~2013	Blood (GFAAS) (µg/dL) Median (IQR): Exposed: 4.51 (3.70–5.67) Reference: 3.98 (3.25–4.84) Age at measurement Mean (SD): Exposed: 4.74 (0.84) Reference: 4.75 (1.01)	Left ventricle structure and function	Linear regression adjusted for gender, age, BMI, e-waste contamination w/ in 50 m of residence, residence as workplace, distance of residence from road, family member daily smoking, monthly household income, maternal work associated with e-waste, duration of outdoor play, child contact with e-waste, washing hands before eating, nail biting habit, chewing pencil habit, yearly canned food consumption, yearly fruit/vegetable consumption, yearly iron rich food consumption, yearly marine product consumption, and yearly salted food consumption	Ln-transformed parameters per one-unit increase in blood Pb[b] IVS, cm −0.004 (−0.007, 0.001) LV posterior wall, mm −0.001 (−0.003, 0.001) Ejection fraction, % 0.001 (−0.002, 0.001)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Gump et al. (2005) Oswego, NY (born at a single hospital in New York from 1991–94) Cohort	Oswego Children's Study n = 122 children aged 9.5 yr Average individual born ~1990	Cord blood (ETAAS) (µg/dL) Mean (SD): 2.97 (1.75) Child blood (ETAAS and ASV) (µg/dL) Mean (SD): 4.62 (2.51) Age of child blood Pb measurement Mean 2.6	Stroke volume, cardiac output	Multivariate linear regression adjusted for HOME score, SES, birth weight, child BMI, child sex	Cord BLL No association, results not reported Childhood BLL Stroke volume, mL −0.069 (−0.124, −0.015) Cardiac output, L/min −0.056 (−0.113, 0.001)
Gump et al. (2011) Oswego, NY Cross-sectional	n = 140 children ages 9–11 yr	Blood (ICP-MS) (µg/dL) GM 1.01 Q1: 0.14–0.68 Q2: 0.69–0.93 Q3: 0.94–1.20 Q4: 1.21–3.76	Stroke volume, cardiac output	Linear regression models adjusted for sex, SES, BMI, and age	Change in Stroke Volume (%) across quartiles in response to acute stress[b,d] Q1: 2.23, Q2: 0.91, Q3: −3.47, Q4: −0.89, p for trend = 0.04 Change in Cardiac Output (%) across quartiles in response to acute stress[b,d] Q1: 3.26, Q2: 1.19, Q3: −2.31, Q4: −0.20, p for trend = 0.05

A = peak late diastolic velocity; ASV = anodic stripping voltammetry; BLL = blood lead level; BMI = body mass index; BP = blood pressure; E = peak early diastolic velocity; e' = peak early diastolic mitral annular velocity; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; GLS = global longitudinal strain; GM = geometric mean; GSD = geometric standard deviation; HDL = high-density lipoprotein; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; IVS = interventricular septum; LV = left ventricular; LVMI = left ventricular mass index; MAP = mean arterial pressure; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; Pb = lead; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; RLS = regional longitudinal strain; RRS = regional radial strain; RWT = relative wall thickness; SD = standard deviation; SES = socioeconomic status; Q = quartile.

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Corrected for regression dilution bias using quintile method.

[d]Confidence intervals not provided and unable to calculate based on given information.

Table 4-9 Animal toxicological studies of cardiac function

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)[c]	Endpoints Examined
Wildemann et al. (2015)	Rat (Wistar) Control (tap water), M, n = 6	Unknown start age for 4 wk	Tap water with 0.2% nitic acid, or 357 or 1607 µg/kg BW/d Pb acetate in drinking water for 4 wk	1.4 ± 1.2 µg/L for tap water/ 0.2% nitic acid (0.14 ± 0.12 µg/dL)	Stroke volume and cardiac output post 4-wk exposure
	357 or 1607 µg/kg BW/d, M, n = 5 per group			17 ± 7 µg/L for 357 µg/kg BW/d Pb acetate (1.7 ± 0.7 µg/dL) 86 ± 29 µg/L for 1607 µg/kg BW/d Pb acetate (8.6 ± 2.9 µg/dL)	
Silva et al. (2015)	Rat (Wistar) Control (distilled water) M, n = 6	3 mo old rats exposed for 15 d	100 ppm Pb acetate in drinking water for 15 d	12.3 ± 2 µg/dL	Force generation in LV papillary muscle following pulse stimulation post 15-d exposure
	100 ppm Pb acetate group M, n = 6				Time to peak tension and 90% relaxation post 15-d exposure Inotropic force following calcium or isoproterenol stimulation post 15-d exposure

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)[c]	Endpoints Examined
Fioresi et al. (2014)	Rat (Wistar) Control (tap water), M, n = 9–12 100 ppm group, M, n = 9–12	Age 2 mo to 3 mo	100 ppm Pb acetate in drinking water for 30 d	<0.5 µg/dL for control 13.6 ± 1.07 µg/dL for 100 ppm group	LVSP and RVSP, left and right diastolic pressure all measured post 30 d exposure Isometric contraction force, time to peak contraction, and relaxation rates in LV papillary muscle post 30 d exposure Contractile force following calcium treatment in LV papillary muscle 30 d post exposure

BW = body weight; d = day(s); LV = left ventricular; LVSP = right ventricular systolic pressure; M = male; mo = month(s); Pb = lead; RVSP = right ventricular systolic pressure; wk = week(s).

Table 4-10 Animal toxicological studies of Pb exposure and endothelial dysfunction

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Gaspar and Cordellini (2014)	**Rat (Wistar)** Rat (Wistar) Control (tap water), M, n = 8 500 ppm group, M, n = 6	In utero to PND 22	Pregnancy day 0: females divided into tap water and 500 ppm Pb acetate in drinking water groups. Exposure lasted through pregnancy. At birth, pups were exposed to Pb (or control) through nursing. Pups were weaned at 22 d.	<5 µg/dL at all time points for tap water 19.98 ± 6.31 – PND 52 13.15 ± 0.97 – PND 70 11.17 ± 2.11 – PND 100	Vascular reactivity in aortic rings post exposure at PND 23, 52, 70, and 100
Nunes et al. (2015)	**Rat (Wistar)** Control (distilled water), M, n = 16 100 ppm Pb acetate treatment, M, n = 16 5–8 rats from control or 100 ppm group for other treatments (e.g., phenylephrine in control or Pb-treated mice)	2-mo-old rats exposed for 30 d	100 ppm Pb acetate in drinking water for 30 d.	NR for control 8.4 µg/dL for 100 ppm	Vascular reactivity in aortic rings measured post 30-d exposure

BLL = blood lead level; d = day(s); M = male; NR = not reported; Pb = lead; PND = postnatal day.

Table 4-11 Epidemiologic studies of Pb exposure cardio electrophysiology and arrythmia

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cheng et al. (1998) Boston, MA NAS August 1991 and December 1995 Cross-sectional	NAS n = 750 Elderly men (mostly white) Average individual born ~1925	Blood Pb (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 5.79 (3.44) Bone (K-XRF) (µg/g) Mean (SD): Patella: 30.82 (19.19) Tibia: 22.9 (13.36) Age at measurement Mean (SD): 67.81 (7.27)	ECG conduction (QTc, QRSc)	Linear regression adjusted for age and DBP. Model for QTc additionally adjusted for alcohol intake and BMI. Model for QRSc additionally adjusted for fasting glucose level.	QTc (msec) Bone (Patella) Pb <65 yr: 3.00 (0.16, 5.84) >65 yr: 0.39 (−1.05, 1.83) Tibia Pb <65 yr: 5.03 (0.83, 9.22) >65 yr: 1.41 (−0.67, 3.49 QRSc (msec) Patella Pb <65 yr: 2.23 (0.10, 4.36) >65 yr: −0.11 (−1.07, 0.85) Tibia Pb <65 yr: 4.83 (1.83, 7.83) >65 yr: −0.83 (−2.21, 0.56) No association with blood Pb
Eum et al. (2011) Boston, MA NAS 1989 and 1996 Cohort	NAS n = 600 Elderly men (mostly white) Average individual born ~1925	Blood (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 5.8 (3.6) Bone (K-XRF) (µg/g) Mean (SD): Patella: 30.3 (17.7) Tibia: 21.6 (12.0) Tibia Quartiles: Q1: <16 Q2: 16.0–23 Q3: >23	ECG conduction (QTc, QRSc)	Linear regression adjusted for age, education, smoking, BMI, albumin-adjusted serum Ca^{2+}, and diabetes status at baseline, years between ECG tests, and QT-prolongation drugs at the time of ECG measurement.	Bone (Tibia) Pb[b] Adjusted 8-yr change QTc (Q1 reference) Q1: 7.49 (1.22, 13.75) msec Q3: 7.94 (1.42, 14.45) msec p for trend = 0.03 QRSc (Q1 reference) Q2: 0.52 (−3.60, 4.65) msec Q3: 5.94 (1.66, 10.22) msec p for trend = 0.005

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Age at measurement: Mean 67			No associations with patella or blood Pb
Park et al. (2009) Boston, MA NAS August 1991 and December 1995 Cross-sectional	NAS n = 613 Elderly men (mostly white) Average individual born ~1925	Blood (GFAAS with Zeeman correction) (µg/dL) Median (IQR): 5 (4–7) Bone (K-XRF) (µg/g) Median (IQR) Patella: 26 (18–37) Tibia: 19 (14–27) Age at measurement Mean 67	QTc interval	Linear regression models adjusted for age, BMI, smoking status, serum Ca^{2+}, and diabetes. No SES indicator was considered.	QTc interval (msec) 0.433 (−0.253, 1.12) Patella Pb: 1.389 (0.068, 2.711) Tibia Pb: 2.192 (0.227, 4.158)
Jing et al. (2019) United States NHANES III 1988–1994 Cross-sectional	NHANES n = 7,179 Participants without self-reported history of MI (or ECG results indicating MI), without a history of CHF Average individual born ~1934, ~1936, ~1932, ~1935	Blood (GFAAS) (µg/dL) GM Men: 4.10 Women: 2.93 Age at measurement: Mean (SD) Men T1: 57.12 (0.51) T2: 55.42 (0.53) T3: 57.00 (0.65) Women T1: 59.01 (0.64) T2: 55.88 (0.62) T3: 59.45 (0.98)	Ventricular arrhythmia (QRS-T angle) Spatial QRS-T angle estimated using a 12-Pb ECG.	Multivariate weighted logistic regression adjusting for impaired fasting glucose, hypertension, poverty index, age, race, and smoking status.	One-unit increase in log of blood Pb[b] OR (95% CI) (3rd vs. 1st tertile) Men: 1.35 (1.05, 1.74) Women: 1.05 (0.82, 1.36)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Park et al. (2006) Boston, MA 2000–2004 Cross-sectional	NAS n = 413 Elderly men (mostly white) Average individual born ~1935	Bone (K-XRF) (μg/g) Median (IQR) Tibia: 19 (11–28) Patella (measured within 6 mo of HRV): 23 (15–34) Estimated Patella (accounting for time difference): 16.3 (10.4–25.8) Age at measurement: Mean: 67	HRV	Linear regression models adjusted for age, cigarette smoking, alcohol consumption, room temperature, season (Model 2) BMI, fasting blood glucose, HDL-C, triglyceride, use of β-blockers, Ca^{2+} channel blockers, and/or ACE inhibitors. No SES indicator was considered.	HRV Tibia HF: −0.529 (−2.265, 1.206) nu LF: 0.529 (−1.206, 2.265) nu Log LF/HF: 1.941 (−6.941, 10.824) % Corrected Patella HF: −0.39 (−2.013, 1.234) nu LF: 0.39 (−1.234, 2.013) nu Log LF/HF: 1.948 (−6.136, 10.032) Effect estimates were more pronounced among those with greater # metabolic abnormalities.
Gump et al. (2011) Oswego, NY Cross-sectional	n = 140 Children aged 9–11 yr	Blood (ICP-MS) (μg/dL) GM: 1.01 Q1: 0.14–0.68 Q2: 0.69–0.93 Q3: 0.94–1.20 Q4: 1.21–3.76	Heart rate	Linear regression adjusted for sex, SES, BMI, and age.	Change in heart rate (beats/min) across quartiles in response to acute stress[b,c] Q1: 0.91, Q2: 0.19, Q3: 0.86, Q4: 0.58, p for trend = 0.85 No association between Pb levels and baseline cardiovascular levels
Gump et al. (2017) New York	Environmental Exposures and Child Health Outcomes study n = 203 Children aged 9–11	Blood (ICP-MS) (μg/dL) Mean (SD): 0.98 (0.61) Range: 0.19–3.25	Heart rate variability	Linear regression adjusted for sex, race, age, and SES.	No association between BLLs and HRV. Results not shown (p > 0.25)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Environmental Exposures and Child Health Outcomes					
Halabicky et al. (2022) Jintan, China Children aged 3–5 in 2004–2005 wave, aged 11–12 in 2011–2013 wave Cohort	China Jintan Child Cohort Study n = 408 Average individual born ~2000	Whole blood (GFAAS) (µg/dL) Median (IQR) 3–5 yr: 6.4 (4.9–8.0) 11–13 yr: 2.9 (2.3–3.6) Age at measurement: 3–5 and 11–13 yr	HRV in children during a stress test Age at outcome ~12	General linear models adjusted for parental occupation, child sex, serum Fe, crowded neighborhood *No baseline HRV measurement and no adjustment for BMI or physical activity. Serum Fe less precise measure of iron status opposed to ferritin or transferrin.	Change in planning phase HRV per log-transformed increase in blood Pb[b] 3–5 yr Pb 0.03 (−0.02, 0.09) 12 yr Pb −0.04 (−0.16, 0.07) Change in speaking phase HRV per log-transformed increase in blood Pb[b] 3–5 yr Pb: 0.06 (0.01, 0.12) 12 yr Pb: −0.05 (−0.18, 0.08)

ACE = angiotensin-converting enzyme; BLL = blood lead level; BMI = body mass index; Ca^{2+} = calcium ion(s); CHF = congestive heart failure; CI = confidence interval; DBP = diastolic blood pressure; ECG = electrocardiogram; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; HDL = high-density lipoprotein; HF = high-frequency power in normalized units; HRV = heart rate variability; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; K-XRF = K-shell X-ray fluorescence; LF = low-frequency; MI = myocardial infarction; mo = month(s); NAS = Normative Aging Study; NHANES = National Health and Nutrition Examination Survey; nu = normalized units; OR = odds ratio; Pb = lead; Q = quartile; QRSc = corrected QRS duration; QTc = corrected QT interval; SD = standard deviation; SES = socioeconomic status; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Confidence intervals not provided and unable to calculate based on given information

Table 4-12 Animal toxicological studies of Pb exposure and cardiac electrophysiology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Fioresi et al. (2014)	Rat (Wistar) Control (tap water), M, n = 9–12 100 ppm group, M, n = 9–12	Age 2 mo to 3 mo	100 ppm Pb acetate in drinking water for 30 d	<0.5 µg/dL for control 13.6 ± 1.07 µg/dL for 100 ppm group	Heart rate post 30-d exposure
Wildemann et al. (2015)	Rat (Wistar) Control (tap water), M, n = 6 357 or 1607 µg/kg BW/d, M, n = 5 per group	Unknown start age for 4 wk	Tap water with 0.2% nitic acid, or 357 or 1607 µg/kg BW/d Pb acetate in drinking water for 4 wk	1.4 ± 1.2 µg/L for tap water/ 0.2% nitic acid (0.14 ± 0.12 µg/dL) 17 ± 7 µg/L for 357 µg/kg BW/d Pb acetate (1.7 ± 0.7 µg/dL) 86 ± 29 µg/L for 1607 µg/kg BW/d Pb acetate (8.6 ± 2.9 µg/dL)	Heart rate measured baseline and post 4-wk exposure PR and QRS interval post 4-wk exposure

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Shvachiy et al. (2018)	Rat (Wistar) Control, M/F, n = 8 0.2% Pb acetate, intermittent Pb group, M/F, n = 9 0.2% Pb acetate, permanent Pb group, M/F, n = 9	In utero to 28 wk	Pregnant Wistar rats were given 0.2% Pb acetate in drinking water or tap water. After a 21-d weaning period, pups were either continuously exposed to Pb acetate in drinking water until 28 wk or were given 8 wk of Pb abstinence and then exposed until 28 wk with Pb acetate	18.8 ± 2.0 µg/dL for intermittent exposure 24.4 ± 4.9 µg/dL for continuously exposed	Heart rate, HF, LF, LF/HF measured 24-hr post 28-wk exposure
Zhu et al. (2018)	Rat (Sprague Dawley) Control (distilled water), M, n = 100 0.5 g/L Pb acetate, M, n = 10 M, n = 100 0.5 g/L Pb acetate, M, n = 10	In utero to 1 yr	Female rats were given either 0 or 500 mg/L Pb acetate for 10 d before mating. Male offspring continued receiving 0 or 500 mg/L Pb acetate for 1 yr	0.28 ± .02 mg/L (28 ± 2 µg/dL)	Heart rate, HF, LF, LF/HF measured post 1-yr exposure
Zhu et al. (2019)	Rat (Sprague Dawley) Control (distilled water), M, n = 100 0.5 g/L Pb acetate, M, n = 10	In utero to 1 yr	Female rats were given either 0 or 0.5 g/L Pb acetate for 10 d before mating. Male offspring continued receiving 0 or 0.5 g/L Pb acetate for 1 yr	0.27 ± 0.02 mg/L (27 ± 2 µg/dL)	HF, LF, LF/HF, heart measured post 1-yr exposure

BLL = blood lead level; BW = body weight; d = day(s); F = female; HF = high-frequency; LF = low-frequency; M = male; mo = month(s); Pb = lead; PR = prevalence ratio; wk = week(s); yr = year(s).

Table 4-13 Epidemiologic studies of Pb exposure and atherosclerosis and peripheral artery disease

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wan et al. (2021) China May-August 2018 Cross-sectional	METAL study n = 4,234 Average individual born ~1951	Blood (AAS) (μg/dL) Median (IQR) 2.6 (1.8–3.6) Age at measurement Median (IQR): 67 (62–72) yr	CCA plaques and diameter	Linear or logistic regression adjusting for age, sex, duration of diabetes, education status, current smoking, BMI, HbA1c, dyslipidemia, hypertension	OR (4th vs. 1st quartile of Blood Pb)[b] 1.53 (1.29, 1.82)
Yu et al. (2020) Belgium Blood Pb collected in 1985–2005, arterial stiffness measured a median of 9 yr later Cohort	Cadmium in Belgium n = 267 Average individual born ~1958	Blood (ETAAS) (μg/dL) GM (IQR): 2.93 (1.8–4.7) Age at measurement: Mean 37 yr	Arterial stiffness Hemodynamic measures	Linear multivariable models adjusting for sex, enrollment characteristics (age, BMI, smoking, drinking, serum total to HDL-C ration, plasma glucose, eGFR (estimated from serum creatinine), SES), the time interval between measurement of exposure biomarkers and hemodynamic assessment, and antihypertensive drug treatment at enrollment and follow-up	Time-dependent hemodynamics per doubling of Pb concentration[b] Augmentation ratio, % 1.74 (0.95, 2.53) Augmentation index, % 3.03 (1.56, 4.50) Pressure amplification −0.06 (−0.08, −0.04) Pulse wave velocity, m/s 0.14 (−0.08, 0.35) Forward pulse peak time, ms 6.62 (2.21, 11.0) Backward pulse peak time, ms 1.02 (−1.31, 3.35) Forward PP amplitude, mmHg −0.43 (−1.92, 1.06) Backward PP amplitude, mmHg 1.02 (0.02, 2.02) Reflection index, %: 3.98 (1.71, 6.24)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Kim et al. (2021) South Korea 2011–2018 Cross-sectional	n = 2,193 Adults ≥2 yr of age who completed voluntary medical examinations at the Chonnam National University Hwasun Hospital Average individual born ~1961	Whole blood Pb (GFAAS) (µg/dL) Mean (Median) All participants: 2.71 (2.53) Men: 2.98 (2.78) Women: 2.18 (2.03) Age at measurement: Mean (SD): 53.5 (8.3) Range: 23–81	Moderate to severe CAS (≥25% stenosis)	Logistic regression adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, BMI, regular exercise, smoking, and alcohol drinking	OR All participants: 1.14 (1.02, 1.26) Men: 1.13 (1.01, 1.27) Women: 1.10 (0.86, 1.41)
Qin et al. (2021) United States NHANES 2013–2014 Cross-sectional	NHANES n = 1,503 ≥40 yr Average individual born ~1960	Blood (ICP-MS) (µg/dL)[c] Mean (SD): 1.45 (1.31) Q1: 0.16–0.80 Q2: 0.81–1.21 Q3: 1.22–1.84 Q4: 1.85–24.6 Age at measurement Mean: 52.7	AAC score (0–24 for total score), and severe AAC (AAC score >6)	Linear or logistic regression adjusted for sex, age, race, education, BMI, BP, creatinine, A1c, uric acid, serum calcium, serum phosphorus, total cholesterol, cotinine, hemoglobin, hydroxy-vitamin D, hypertension, diabetes	Change in AAC score Per µg/dL increase in blood Pb 0.15 (0.02, 0.27) Q2 vs. Q1: 0.58 (0.15, 1.02) Q3 vs. Q1: 0.60 (0.14, 1.07) Q4 vs. Q1: 0.99 (0.50, 1.48) OR Per µg/dL increase in blood Pb 1.11 (1.00, 1.22) Q2 vs. Q1: 1.68 (0.86, 3.25) Q3 vs. Q1: 2.15 (1.10, 4.19) Q4 vs. Q1: 3.72 (1.94, 7.12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Muntner et al. (2005) United States NHANES 1999–2002 Cross-sectional	NHANES n = 9,961 Average individual born ~1954 Or Average individual born in or before ~1983	Blood (GFAAS) (µg/dL) Mean (95% CI): 1.64 (1.59–1.68) Q1: <1.06 Q2: 1.06–1.63 Q3: 1.63–2.47 Q4: ≥2.47 Age at measurement Mean NR	PAD	Logistic regression models adjusted for age, race/ethnicity, sex, diabetes mellitus, BMI, cigarette smoking, alcohol consumption, high school education, health insurance status	OR (95% CI) (vs. 1st quartile)[b] Q2: 1.00 (0.45, 2.22) Q3: 1.21 (0.66, 2.23) Q4: 1.92 (1.02, 3.61)
Navas-Acien et al. (2004) United States 1999–2000 Cross-sectional	NHANES n = 2,125 participants, age ≥40 yr, Average individual born in or before ~1960	Blood (GFAAS) (µg/dL) Q1: <1.45 Q2: 1.45–2.07 Q3: 2.07–2.90 Q4: >2.90	PAD	Logistic regression adjusted for age, sex, race, education, BMI, alcohol intake, hypertension, diabetes, hypercholesterolemia, eGFR, C-reactive protein, self-reported smoking status, serum cotinine and Cd	OR (95% CI) (vs. 1st quartile)[b] Q2: 1.63 (0.50–5.27) Q3: 1.77 (0.55–5.63) Q4: 2.52 (0.75–8.51)

AAC = abdominal aortic calcification; AAS = atomic absorption spectrometry; BMI = body mass index; BP = blood pressure; CAS = coronary artery stenosis; CCA = common carotid artery; Cd = cadmium; CI = confidence interval; eGFR = estimated glomerular filtration rate; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; METAL = Environmental Pollutant Exposure and Metabolic Diseases in Shanghai; mo = month(s); NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; PAD = peripheral artery disease; Pb = lead; PP = pulse pressure; Q = quartile; SD = standard deviation; SES = socioeconomic status; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Unable to be standardized.

[c]Results reported as ng/dL but assumed to be ug/dL based on data source (NHANES).

Table 4-14 Animal toxicological studies of Pb exposure and atherosclerosis

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Xu et al. (2015)	Rat (Sprague Dawley) Control 1, M/F, n = 6 1% PB acetate group 12 d, M/F, n = 15 1% PB acetate group 40 d, M/F, n = 15	6–7-wk old rats exposed for 12 or 40 d	Two control groups given distilled water for 12 or 40 d. Two 1% Pb acetate groups exposed for 12 or 40 d	Day 12: 193.3 µg/L (19.33 µg/dl) Day 40: 245.9 µg/L (24.59 µg/L)	Cardiovascular histology measured at 12 and 40 d

BLL = blood lead level; d = day(s); F = female; M = male; Pb = lead; wk = week(s).

Table 4-15 Epidemiologic studies of Pb exposure and cerebrovascular disease

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Menke et al. (2006) United States NHANES III 1988–1994, mortality follow-up in 2001 Cohort	NHANES III n = 13,946 Average individual born ~1946	Blood (GFAAS with Zeeman correction) (µg/dL) Mean: 2.58 Tertiles: T1: <1.93 T2: 1.94–3.62 T3: ≥3.63 Age at measurement Mean: 44.4 yr	Stroke mortality	Cox proportional hazard regression analysis adjusted age, race/ethnicity, sex, urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus, hypertension, GFR category	HR: 1.15 (1.02, 1.28)
Khalil et al. (2009) Baltimore, MD and Monongahela Valley, PA Blood Pb measured 1990–1991, mortality follow-up for ~12 yr Cohort	Study of Osteoporotic Fractures n = 533 women, ages 65–87 yr Average individual born ~1921	Blood (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 5.3 (2.3) Range: 1–21 Age at measurement (Mean): 70	Stroke mortality	Cox proportional hazards regression analysis adjusted for age, clinic, BMI, education, smoking, alcohol intake, estrogen use, hypertension, total hip bone mineral density, walking for exercise, and diabetes	HR (95% CI) (≥8 µg/dL blood Pb)[b]: 1.13 (0.34, 3.81)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Mousavi-Mirzaei et al. (2020) Birjand, Iran 2016–2017 Case-control	n = 88 (44 cases, 44 controls matched on age and sex, occupation, opium addiction, and sampling time) Average individual born ~1944	Blood (GFAAS) (µg/dL) Median (IQR): 6.38 (1.75–34.87) Age at measurement Mean (SD): 71.95 (11.37)	Acute ischemic stroke	Logistic regression controlling for lipid profile and fasting blood sugar	OR (95% CI): 1.04 (1.02, 1.07)

BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; GFAAS = graphite furnace atomic absorption spectrometry; GFR = glomerular filtration rate; HR = hazard ratio; IQR = interquartile range; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; SD = standard deviation; T# = tertile #; yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.
[b]Unable to be standardized.

Table 4-16 Epidemiologic studies of Pb exposure and cardiovascular mortality

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lustberg and Silbergeld (2002) United States NHANES II 1976–1980, mortality follow-up in 1992 Cohort	NHANES II n = 4,190, aged 30–74 Average individual born ~1924	Blood (GFAAS with Zeeman correction)[b] (µg/dL) Mean (SD): 14.0 (5.1) Median: 13 Tertiles T1: <10 T2: 10–19 T3: 20–29 Age at measurement: Mean (SD) 54.1 (13.2)	Circulatory mortality	Cox proportional hazard regression analysis adjusted for age, sex, location, education, race, income, smoking, BMI, exercise	HR[c] T2 vs. T1 1.27 (0.97, 1.57) T3 vs. T1 1.74 (1.25, 2.40)
Schober et al. (2006) United States NHANES III 1988–1994, mortality follow-up in 2006 ~8.5 yr of follow-up Cohort	NHANES III n = 9,686, ≥40 yr Average individual born in or before ~1951	Blood (GFAAS with Zeeman correction) (µg/dL) T1: <5 (median 2.6) T2: 5–9 (median 6.3) T3: ≥10 (median 11.8) Age at measurement: ≥40 yr	CVD mortality	Cox proportional hazard regression analysis adjusted for sex, age, race/ethnicity, smoking, education level. Did not evaluate BMI nor comorbidities	HR (95% CI)[c]: CVD T3 vs. T1 1.55 (1.16, 2.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Menke et al. (2006) United States NHANES III 1988–1994, mortality follow-up in 2001 ~12 yr of follow-up Cohort	NHANES III n = 13,946, ≥20 yr. Average individual born ~1946	Blood (GFAAS with Zeeman correction) (µg/dL) Mean: 2.58 Tertiles: T1: <1.93 T2: 1.94–3.62 T3: ≥3.63 Age at measurement Mean: 44.4 yr	CVD, MI, and stroke mortality	Cox proportional hazard regression analysis adjusted age, race/ethnicity, sex, urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus, hypertension, GFR category	HR (95% CI): CVD: 1.13 (1.06, 1.22) MI: 1.19 (1.05, 1.34) Stroke: 1.15 (1.02, 1.28)
Lanphear et al. (2018) United States 1988–1994 mortality follow-up in 2011 ~19 yr of follow-up (IQR 17.6–21.0 yr) Cohort	NHANES III n = 14,289 ≥ 20 yr. Average individual born ~1947	Blood (GFAAS with Zeeman correction) (µg/dL) GM: 2.71 Geometric SE: 1.31 10th percentile: 1.0 90th percentile: 6.7 Age at measurement: Mean: 44.1 yr	CVD, and IHD mortality	Cox proportional hazards regression analysis adjusting for age, sex, household income, ethnic origin, BMI, smoking status, alcohol consumption, physical activity, concentration of Cd in urine, BP, healthy eating index tertiles, HbA1c, and serum cholesterol	HR (95% CI) CVD: 1.10 (1.05, 1.15) IHD: 1.14 (1.08, 1.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
van Bemmel et al. (2011) United States 1988–1994, follow-up through 2007 ~7 yr of follow-up for those with low blood Pb ~7 yr of follow-up for those with high blood Pb Cohort	NHANES III n = 3,349 adult age ≥40 yr Average individual born ~1932	Blood (GFAAS with Zeeman correction) (µg/dL) Median: <5 µg/dL: 2.6 ≥5 µg/dL: 7.5 Age at measurement Mean <5 µg/dL: 57 ≥5 µg/dL: 61	CVD mortality	Cox proportional hazards adjusting for age, education, sex, smoking status, and race/ethnicity	HR (95% CI): CVD All: 1.02 (0.93, 1.13) $ALAD^{GG}$: 1.01 (0.92, 1.10) $ALAD^{CG/GG}$: 1.13 (0.93, 1.37)
Cook et al. (2022) United States Baseline 1988–1994, mortality follow-up through 2010 (2 yr of follow-up) Cohort	NHANES III n = 15,036 adults ≥19 y Average individual born in or before ~1972	Blood Pb (GFAAS) (µg/dL) Quartiles Men: Q1: <2.63 Q2 and Q3: 2.63–6.23 Q4: ≥6.23 Women: Q1: <1.38 Q2 and Q3: 1.38–3.74 Q4: ≥3.74 Age at measurement: ≥1 yr	Heart disease mortality (ICD-10 I00-I13 I20-I22, I24, I25-I28, I25.1-I25.9, I30-I31, I33, I34-I38, I40, I42-I51, I70-I78), MI mortality (I21-I22), and CVD mortality (heart disease mortality plus I60-I69 (cerebrovascular disease)	Multivariate Cox model adjusted for age, gender, race/ethnicity, family income, alcohol drinking, cigarette smoking, BMI, physical activity, and self-reported health status at baseline	HR (95% CI)[c]: CVD mortality Q2 & Q3 vs. Q1: 1.10 (0.84, 1.43) Q4 vs. Q1: 1.35 (1.03, 1.77) Per 1 µg/dL increase in log-transformed Pb: 1.08 (1.00, 1.16) Heart disease mortality Q2 & Q3 vs. Q1: 1.37 (1.04, 1.81) Q4 vs. Q1: 1.60 (1.21, 2.13) Per 1 µg/dL increase in log-transformed Pb: 1.09 (1.02, 1.16) MI mortality Q2 & Q3 vs. Q1: 1.73 (1.08, 2.79) Q4 vs. Q1: 1.45 (0.90, 2.32) Per 1 µg/dL increase in log-transformed Pb: 0.95 (0.84, 1.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ruiz-Hernandez et al. (2017) United States Baseline 1988–1994 and 1999–2004, mortality follow-up through 1996 and 2006 Cohort	NHANES III and NHANES n = 15,421 age ≥40yr Average individual born in or before ~1951	Blood (µg/dL) 1988–1994 (GFAAS with Zeeman correction) Mean: 3.2 1999–2004 (ICP-MS) Mean: 1.9 Age at measurement: ≥40 yr	CVD and CHD mortality	Poisson regression adjusting for age, sex, race, smoking status, physical inactivity, obesity, hypertension, diabetes, high total cholesterol, low HDL cholesterol, lipid lowering medication, survey period, and log-transformed urinary Cd concentrations	RR (95% CI) for twofold increase in blood Pb[c] CVD: 1.19 (1.07, 1.31) CHD: 1.24 (1.10, 1.41)
(Duan et al., 2020) United States 1999–2014, follow-up through end of 2015 ~7 yr of follow-up Cohort	NHANES n = 18,602 Age ≥20 yr Average individual born ~1960	Blood (ICP-MS) (µg/dL)[d] Median (IQR) 1.49 (0.93, 2.31) Age at measurement: Mean (SD): 45.9 (0.3)	CVD mortality	Poisson regression analyses adjusted for: sex, age, ethnicity, education, PIR, cotinine category, BMI, physical activity, hypertension, and diabetes	RR (95% CI) CVD: 1.35 (1.15, 1.59)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Aoki et al. (2016) United States 1999–2010, follow-up through end of 2011 ~6 yr of follow-up Cohort	NHANES n = 18,602 age ≥40 yr Average individual born ~1947	Blood (ICP-MS) (µg/dL) Mean (SE): 1.73 (0.02) Age at measurement Mean (SE): 57.5 (0.2)	CVD mortality	Cox proportional hazards (using age during follow-up as the time scale) adjusting for race, Hispanic origin, sex, alcohol consumption, blood Cd, serum iron, C-Reactive Protein (CRP), and serum calcium	RR (95% CI) for 10-fold increase in blood Pb[c] Overall: 1.26 (0.91, 1.78) Control for hematocrit: 1.35 (0.98, 1.86) Control for hemoglobin: 1.35 (0.98, 1.87) Hematocrit-corrected: 1.44 (1.05, 1.98) Hemoglobin-corrected: 1.46 (1.06, 2.01)
Obeng-Gyasi et al. (2021) United States Baseline 1999–2008, mortality follow-up through 2014 Cohort	NHANES n = 28,852 adults ≥20 yr Average individual born in or before ~1983	Blood Pb (ICP-MS) (µg/dL) Median: 1.55 Age at measurement: ≥20 yr	CVD mortality	Multivariate Cox model adjusting for sex, BMI, smoking, alcohol consumption, country of birth, and income *No adjustment for age	HR (≥1.55 µg/dL Blood Pb)[c]: 2.35 (1.77, 2.93)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lin et al. (2011) Taiwan Years not reported Cohort (18 mo of follow-up)	n = 927 Taiwanese adult patients with end-stage renal disease on hemodialysis for >6 mo, age >18	Baseline blood Pb (ETAAS) (µg/dL) Mean: 11.5 Median: 10.4 T1: <8.51 µg/dL T2: 8.51–12.64 µg/dL T3: >12.64 µg/dL Age at measurement Mean (SD): 55.2 (13.5)	CVD mortality	Multivariate Cox model adjusting for age, previous cardiovascular diseases (stroke, MI, PVD, CHF), education level, hemodialysis vintage, using fistula, normalized protein catabolic rate, hemoglobin, serum albumin, creatinine, cardiothoracic ratio, and logarithmic transformation of high-sensitivity CRP	HR (95% CI) (T1: Referent)[c] CVD T2: 3.70 (2.06, 6.48) T3: 9.71 (2.11, 23.26) Hemoglobin-corrected: CVD T2: 3.52 (0.51, 6.33) T3: 7.35 (1.64, 33.33)
Weisskopf et al. (2009) United States Baseline biomarkers collected an average of 8 yr prior to death Cohort	NAS n = 835 Mostly white elderly men Average individual born in or before ~1940	Blood Pb (GFAAS) (µg/dL) Mean (SD): 5.6 (3.4) Bone Pb (KXRF) (µg/g) Patella Pb Mean (SD): 31.2 (19.4) Tertiles: T1: <20 T2: 20–31 T3: >31 Tibia Pb Mean (SD): 21.8 (13.6) Age at measurement: Mean (SD): 67 (7) (13.5)	CVD and IHD mortality	Multivariate Cox models. Model 1 was adjusted for age at biomarker measurement, smoking, and education. Model 2 included covariates from Model 1 as well as mother and father's occupation, mother and father's education, occupation at NAS entry, and salary at NAS entry. Model 3 includes all of Model 2 covariates but is restricted to men ≤ 45 at study inception. Model 4 is the same as Model 3, but includes inverse probability of attrition rates, as described in the study	HR (95% CI) (3rd vs. 1st tertile)[c] Patella Pb: All men in study (n = 835) Model 1: CVD: 1.46 (0.86, 2.48) IHD: 2.01 (0.86, 4.68) Model 2: CVD: 1.45 (0.83, 2.53) IHD: 2.11 (0.87, 5.13) Men ≤ 45 at study inception (n = 637) Model 3: CVD: 2.23 (1.02, 4.84) IHD: 4.60 (1.26, 16.8) Model 4: CVD: 2.47 (1.23, 4.96) IHD: 3.09 (1.61, 16.8) No associations reported between blood Pb and tibia Pb concentrations with mortality

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Khalil et al. (2009) Baltimore, MD and Monongahela Valley, PA Blood Pb measured 1990–1991, mortality follow-up for ~12 yr Cohort	Study of Osteoporotic Fractures n = 533 Women, ages 65–87 yr Average individual born ~1921	Blood (GFAAS with Zeeman correction) (µg/dL) Mean (SD): 5.3 (2.3) Range: 1–21 Age at measurement (Mean): 70	CVD, and CHD mortality	Cox proportional hazards regression analysis adjusted for age, clinic, BMI, education, smoking, alcohol intake, estrogen use, hypertension, total hip bone mineral density, walking for exercise, and diabetes	HR (95% CI) (≥8 µg/dL blood Pb)[c]: CVD: 1.78 (0.92, 3.45) CHD: 3.08 (1.23, 7.70)
Hollingsworth and Rudik (2021) United States 1999-2016 Quasi-experimental design	Elderly population (≥65 yr) Assessed the change in deaths (National Vital Statistics System) occurring among this age group before and after the phaseout of leaded gasoline in professional racing (NASCAR, ARCA). Compared mortality rates in race counties to bordering counties Average individual born in or before ~1942	County-level blood Pb measurements in children	CVD and IHD mortality	Difference-in-difference approach controlling for SES at the county level (median income, unemployment rates, percent minority population), TRI Pb emissions data	Decline in age-standardized mortality rate per 100,000 population CVD: Race counties: 37 Border counties: 12 IHD: Race counties: 53 Border counties: 20

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

ARCA = Automobile Racing Club of America; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; Cd = cadmium; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; GFR = glomerular filtration rate; GM = geometric mean; HDL = high-density lipoprotein; HR = hazard ratio; ICD = International Classification of Diseases; ICP-MS = inductively coupled plasma mass spectrometry; IHD = ischemic heart disease; IQR = interquartile range; K-XRF = K-shell X-ray fluorescence; MI = myocardial infarction; mo = month(s); NAS = Normative Aging Study; NASCAR = National Association for Stock Car Auto Racing; NHANES = National Health and Nutrition Examination Survey; Pb = lead; PIR = poverty-income ratio; PVD = peripheral vascular disease; Q = quartile; RR = relative risk; SD = standard deviation; SE = standard error; T# = tertile #; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Pb analysis method assumed based on data source, not reported in paper.

[c]Unable to be standardized.

[d]Units assumed to be µg/dL (written as µg/L in the paper).

4.14 References

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