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REVIEW ARTICLE

Re-thinking the link between exposure to mercury and blood pressure

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Abstract

Hypertension or high blood pressure (BP) is a prevalent and manageable chronic condition which is a significant contributor to the total global disease burden. Environmental chemicals, including mercury (Hg), may contribute to hypertension onset and development. Hg is a global health concern, listed by the World Health Organization (WHO) as a top ten chemical of public health concern. Most people are exposed to some level of Hg, with vulnerable groups, including Indigenous peoples and small-scale gold miners, at a higher risk for exposure. We published a systematic review and meta-analysis in 2018 showing a dose–response relationship between Hg exposure and hypertension. This critical review summarizes the biological effects of Hg (both organic and inorganic form) on the underlying mechanisms that may facilitate the onset and development of hypertension and related health outcomes and updates the association between Hg exposure (total Hg concentrations in hair) and BP outcomes. We also evaluated the weight of evidence using the Bradford Hill criteria. There is a strong dose–response relationship between Hg (both organic and inorganic) exposure and BP in animal studies and convincing evidence that Hg contributes to hypertension by causing structural and functional changes, vascular reactivity, vasoconstriction, atherosclerosis, dyslipidemia, and thrombosis. The underlying mechanisms are vast and include impairments in antioxidant defense mechanisms, increased ROS production, endothelial dysfunction, and alteration of the renin–angiotensin system. We found additional 16 recent epidemiological studies that have reported the relationship between Hg exposure and hypertension in the last 5 years. Strong evidence from epidemiological studies shows a positive association between Hg exposure and the risk of hypertension and elevated BP. The association is mixed at lower exposure levels but suggests that Hg can affect BP even at low doses when co-exposed with other metals. Further research is needed to develop robust conversion factors among different biomarkers and standardized measures of Hg exposure. Regulatory agencies should consider adopting a 2 µg/g hair Hg level as a cut-off for public health regulation, especially for adults older than child-bearing age.

Keywords Mercury · Hypertension · Mechanism · Animal studies · Epidemiology · Narrative review

Introduction

Hypertension, or high blood pressure (BP), is one of the most common and manageable chronic conditions, and it contributes substantially to the total burden of disease worldwide. According to the World Health Organization (WHO), an estimated 1.28 billion adults aged 30–79 years have hypertension. Hypertension has long been recognized as a leading risk factor for cardiovascular diseases (CVDs), which affect millions globally and leads to many morbidities and fatalities (Forouzanfar et al. 2017). The WHO estimates that 17.9 million people died from CVDs in 2019, representing 32% of all global deaths (Abbafati et al. 2020). Among other major modifiable risk factors for CVD, including cigarette smoking, diabetes mellitus, and lipid abnormalities, high BP is associated with the strongest evidence for causation and has a high prevalence of exposure (Fuchs and Whelton 2020).

The prevalence of hypertension in adults aged 30–79 years was 32% in women and 34% in men (Zhou et al. 2021). The prevalence of hypertension varies across countries and regions, with higher rates observed in low- and middle-income countries. Hypertension prevalence is highest throughout central and eastern Europe, central Asia, Oceania, southern Africa, and some countries

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in Latin America and the Caribbean (Zhou et al. 2021). Many of these regions overlap with regions where fisheries and aquaculture have increased over the last two-to-three decades (Food and Agriculture Organization 2020). Many populations in regions with a high prevalence of hypertension also have fish and seafood as a staple food (Food and Agriculture Organization 2020).The etiology of hypertension is complex and multifactorial (Carretero and Oparil 2000). Recognized modifiable risk factors include unhealthy diets (high in salt, saturated fat, and trans fats, low in fruits and vegetables), physical inactivity, consumption of tobacco and alcohol, and being overweight or obese. Non-modifiable risk factors include a family history of hypertension, 65 years of age and older, and co-existing diseases such as diabetes or kidney disease (Carretero and Oparil 2000). Besides the traditional risk factors for hypertension, exposure to environmental chemicals may also play an important role (Abhyankar et al. 2012; Eum et al. 2008; Houston 2011; Navas-Acien et al. 2007). It is likely that their contribution has been underestimated (Fuller et al. 2022).

Mercury (Hg) is a chemical pollutant that is of concern to human health worldwide. The WHO has listed Hg as one of its top ten chemicals of public health concern (World Health Organization 2020). Human biomonitoring studies have established that most people worldwide are exposed to some amount of Hg and that there are notable vulnerable groups (e.g., Indigenous peoples and artisanal and small-scale gold miners (ASGM)) (Basu et al. 2018).

Hg released into the environment can contaminate water bodies and accumulate in aquatic ecosystems. This poses a risk to different fish species and other wildlife, affecting biodiversity and ecosystem health. This, in turn, poses a significant population health risk, particularly in coastal regions where fish and seafood are staple food. Workers in industries such as ASGM and chlor-alkali production are at a higher risk of occupational Hg exposure, including Hg poisoning. Chronic Hg exposure could potentially lead to an increased risk of hypertension, diabetes, CVDs, and certain types of cancer, posing a significant global burden on human health (Basu et al. 2023; Ha et al. 2017).

Although the health impacts of Hg have been primarily focused on its neurotoxicity, especially the effects of prenatal exposure on the neurodevelopment of children and youth, there is increasing evidence that exposure to Hg is a risk factor for hypertension and CVDs (Ha et al. 2017; Basu et al. 2023). The dose–response relationship between Hg exposure and CVDs and the possible underlying mechanisms were reported over 10 years ago (Houston 2011; Roman et al. 2011). We have published two systematic reviews and meta-analyses showing the significant relationship between hypertension, CVDs, and Hg exposure in the last five years (Hu et al. 2018, 2021), and more evidence has emerged since.

This study is a critical review carried out through database searches, synthesis of the evidence, and critical interpretation of the findings. This narrative review approach is useful for topics that require a meaningful synthesis of research evidence that may be complex or broad and that require detailed, nuanced description and interpretation (Sukhera 2022). The pathophysiology of hypertension is complex and involves processes that include inflammation, oxidative stress, endothelial dysfunction, altered activation of hormones that regulate salt, and water excretion by the kidney (such as those in the renin–angiotensin–aldosterone system), excessive activation of the sympathetic nervous system, or plaque buildup in the arteries (Harrison et al. 2021). Also, Hg is distributed in multiple organs and involves multiple pathways related to different health outcomes. Therefore, this study aims to review the dose–response of Hg at the tissue and organ level and the underlying mechanisms that can potentially contribute to hypertension onset reported in animal studies, update the latest epidemiological evidence between Hg exposure and hypertension, and critically evaluate the weight of evidence on Hg exposure as a risk factor for hypertension. Therefore, some key evidence of Hg's impact on other health outcomes, such as CVD, with similar or related pathophysiology to hypertension from both animal and human studies was also summarized (less extensively) to add the weight of evidence that the association observed in epidemiology between Hg and hypertension is likely to be a cause–effect relationship.

Mercury speciation, toxicology and biomarkers

Hg is ubiquitously found in natural elements like soils, coal, and minerals. Its release into the atmosphere occurs naturally through geological actions, like volcanic eruptions, as well as through human activities, such as coal burning, waste incineration, and metal processing (ATSDR 2022; Driscoll et al. 2013). There are three forms of Hg: elemental (Hg^0), inorganic (Hg^{1+}, mercurous Hg, and Hg^{2+} mercuric Hg), and organic. Organic Hg occurs when Hg is combined with carbon. Common types of organic Hg include methylmercury (MeHg/CH_3Hg^+), ethylmercury ($EHgC_2H_5Hg^{1+}$), and dimethylmercury (C_2H_6Hg) (Clarkson and Magos 2006).

For the general populations, exposure to organic Hg primarily occurs via the consumption of larger fish species, where MeHg is biomagnified and predominates (Lin et al. 2021; Driscoll et al. 2013). MeHg is absorbed by marine species and biomagnified (Lin et al. 2021). MeHg exposure can commence during fetal development through cord blood and can persist via breast milk transmission to infants (Sundseth et al. 2017). Approximately 90–95% of MeHg is absorbed by the gastrointestinal tract. Major targets of

MeHg-induced toxicity include the brain, reproductive system, and cardiovascular system (Government of Canada 2008; National Research Council (US) 2000). MeHg commonly forms bonds with sulfhydryl (thiol) groups and selenohydryl (selenol) groups (Ajsuvakova et al. 2020). Demethylating MeHg to Hg^{2+} can occur in the gastrointestinal tract (Nakamura et al. 1977; Rowland 1988) and the liver (Suzuki et al. 1984; Uchikawa et al. 2016). Hg^{2+} is then excreted in the feces and urine (Ballatori and Clarkson 1982; Yasutake et al. 1989). MeHg demethylation by gut flora had been indicated as the major elimination route. Typically, 90% or more of the Hg derived from a MeHg dose is excreted in feces as inorganic Hg (Ishihara 2000). Pope and Rand (2021) used data collected from 37 adult volunteers who consumed three fish meals with known MeHg concentrations and developed a PBPK model to estimate the metabolism and elimination rate of MeHg. They found that by day 50, 46 and 51% of the dose in the adult man and woman, respectively, was removed via biotransformation in the gut lumen, representing 73% of the total eliminated MeHg in each case. Overall, the whole-body half-life of MeHg is approximately 70–80 days (Government of Canada 2008; National Research Council (US) 2000). More recent human studies showed that the half-life of MeHg was 46.9, 38.9, and 31.5 days and steady-state blood MeHg of 2.6, 2.6, and 2.3 µg/l in men, women, and children, respectively, and gut microbiota can affect the elimination of MeHg and hence accounts for the individual variability (Pope and Rand 2021).

Additionally, the general population encounters inorganic Hg exposure to a lesser extent, often originating from sources like dental amalgams (ATSDR 2022; Park and Zheng 2012). Exposure to elemental Hg may occur within the general population through various means, including inhalation of vapors in ambient air, ingestion, and dental or medical procedures (Park and Zheng 2012). Workers in industries, such as ASGM, dental amalgam preparation, fluorescent light bulb manufacturing, chlor-alkali production, and thermometers and barometers manufacturing, may come into contact with Hg^0 or other Hg-containing substances (Aubrac et al. 2022; Driscoll et al. 2013). Lipophilic Hg^0 is rapidly distributed throughout the body to target the kidneys and brain. Excretion commonly occurs through exhalation, sweat, or saliva. Alternatively, Hg^0 can be oxidized in erythrocytes to form Hg^{2+}, which is then eliminated in the feces and urine (Ballatori and Clarkson 1982; Yasutake et al. 1989). Overall, the whole-body half-life of Hg^0 is approximately 58 days (Government of Canada 2008; National Research Council (US) 2000).

Finally, inorganic Hg in both Hg^{1+} and Hg^{2+} forms are formed through the oxidation of Hg^0 or demethylation of MeHg in the tissues of animals or plants. The absorption rate of inorganic Hg is low at around 5%, and the major target organ of Hg^{2+} is the kidneys; at high doses, Hg^{2+} can result in kidney failure and gastrointestinal damage (Government of Canada 2008; National Research Council (US) 2000). Hg^{2+} is eliminated in the feces and urine (Ballatori and Clarkson 1982; Yasutake et al. 1989). The whole-body half-life of Hg^{2+} is approximately 1–2 months (Government of Canada 2008; National Research Council (US) 2000).

Hg exposure can be assessed in two major ways. The first approach involves estimating external dose by measuring Hg concentrations in various mediums, such as food, air, or water, and then multiplying the concentrations by the corresponding frequency of exposure. The second method focuses on estimating the body burden of Hg by analyzing biological samples such as hair, urine, blood, nails, cord tissues, or placenta (Basu et al. 2023; Ha et al. 2017). Pharmacokinetics models have been developed to predict the body burden of Hg in various tissues from external doses of Hg exposure for both inhaled Hg vapor (Jonsson et al. 1999; Leggett et al. 2001) and MeHg (Carrier et al. 2001; Wang and Wang 2015). These models provide quantifiable parameters for exposure, absorption, distribution, metabolism, and excretion, thereby allowing for a more robust comparison between studies reporting different Hg exposure sources and doses.

Measurements of total Hg in blood and urine can be used as biomarkers of total exposure to all forms of Hg without additional information on the magnitudes of exposure to any specific forms of Hg. MeHg concentration in whole blood or total Hg concentration in red blood cells or hair are preferred biomarkers for MeHg exposure. Inorganic Hg in blood (or plasma/serum) and inorganic Hg or total Hg in urine are considered biomarkers of exposure to inorganic forms of Hg (ATSDR 2022).

Conversion ratios or equations are published to quantify the numeric relationships among various Hg biomarkers. The WHO recommends a hair-to-blood ratio of 250 for the conversion of hair Hg levels (in µg/g) to those in whole blood (in µg/L) (Joint FAO/WHO Expert Committee on Food Additives 2004). Although this ratio is widely adopted, there is literature suggesting that there is vast inter-individual variation (Liberda et al. 2014; Singh et al. 2023; Yaginuma-Sakurai et al. 2012). Hg concentrations in toenails (in µg/g) and in urine (µg/L) could be converted to hair Hg (in µg/g) using a regression model (Ohno et al. 2007).

Animal studies on mercury and hypertension

To establish the cause–effect relationship between Hg exposure and hypertension, we searched the literature for animal dosing studies. We found 17 major studies published between 1983 and 2023 investigating the relationship between Hg exposure and hypertension using rodent models (Table 1). Different strains of rats were used, and the Hg

Table 1 Characteristics of published rodent studies which assess blood pressure included in the review

Reference	Species	Exposure route	Co-exposure or interaction with other metals	Dose	Form	Outcome	Total exposure = (dose × length × weight (assume 300 g)) For drinking water assume 30 ml/day
Carmignani et al. (1983)	Sprague–Dawley rats	Drinking water		50 µg/ml for 320 days	Inorganic	No significant change in BP	Total exposure = 50 µg/ml × 30 ml/day × 320 days = **420,000 µg**
Carmignani et al. (1992)	Wistar rats	Drinking water		200 µg/ml for 180 days	Inorganic	Increase in arterial BP	Total exposure = 200 µg/ml × 30 ml/day × 180 days = **1,080,000 µg**
Machado et al. (2007)	Wistar rats	Intravenous injection		680 ng/kg/BW/day	Inorganic	SBP/DBP increase	Total exposure = 680 ng × 1 day × 0.3 kg = 204 ng = **0.204 µg**
Simões et al. (2016)	Wistar rats	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	Diastolic arterial BP increase	Initial dose = 4.6 µg/kg × 0.3 kg = 1.38 µg Subsequent doses = 0.07 µg/kg/day × 0.3 kg × 30 days = 0.63 µg Total exposure 30 days = 1.38 µg + 0.63 µg = **2.01 µg**
Rizzetti et al. (2017b)	Wistar rats	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 or 60 days	Inorganic	SBP increase after 60 days only	Total exposure 30 days = **2.01 µg** Total exposure 60 days = **2.64 µg**
Bello et al. (2023)	Wistar rats	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	SBP/DBP increase	Total exposure 30 days = **2.01 µg**
Schereider et al. (2021)	Wistar rats (female)	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	No significant change in SBP	Total exposure 30 days = **2.01 µg**
Vassallo et al. (2019)	Spontaneously hypertensive rats [Wistar rats (control)]	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	SBP increase in spontaneously hypertensive rats only	Total exposure 30 days = **2.01 µg**

Table 1 (continued)

Reference	Species	Exposure route	Co-exposure or interaction with other metals	Dose	Form	Outcome	Total exposure = (dose × length × weight (assume 300 g)) For drinking water assume 30 ml/day
Fardin et al. (2020)	Spontaneously hypertensive rats	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	SBP increase	Total exposure 30 days = **2.01 µg**
Simões et al. (2020)	Spontaneously hypertensive rats [Wistar rats (control)]	Intramuscular injections		Initial dose of 4.6 µg/kg and subsequent doses of 0.07 µg/kg/BW/day for 30 days	Inorganic	SBP increase in spontaneously hypertensive rats only	Total exposure 30 days = **2.01 µg**
Tamashiro et al. (1986)	Spontaneously hypertensive rats [Wistar rats (control)]	Injection		5 mg/kg/BW/day for 10 days	Methyl	NA	Total exposure = 5 mg/kg × 10 days × 0.3 kg = 15 mg = **15,000 µg**
Wakita (1987)	Wistar rats	Subcutaneous injection Oral gavage		5 mg/kg 11 times for 13 days (acute) 0.5 mg/kg/BW/day (chronic) for 23–28 days	Methyl	SBP increase following cessation	Total exposure acute = 5 mg/kg × 11 times × 0.3 kg = 16.5 mg = **16,500 µg** Total exposure chronic = 0.5 mg/kg × 23–28 days × 0.3 kg = 3.45–4.2 mg = **3450–4200 µg**
Grotto et al. (2009)	Wistar rats	Oral gavage		100 µg/kg/BW/day for 100 days	Methyl	SBP increase	Total exposure = 100 µg/kg × 100 days × 0.3 kg = **3000 µg**
Grotto et al. (2011)	Wistar rats	Oral		Contaminated fish for 84 days [uncontaminated fish (control)]	Methyl	SBP increase	N/A
Wildemann et al. (2015a)	Wistar rats	Drinking water		7, 14, 29, 57, 357, 2000, 4000, 8000 µg/kg/BW/day for 28 days 4, 7, 14, 29, 57, 357, 1607 µg/kg/BW/day for 28 days	Inorganic Methyl	MeHg caused SBP/DBP increase	4 µg/kg × 28 days × 0.3 kg = **33.6 µg** 7 µg/kg × 28 days × 0.3 kg = **588 µg** 14 µg/kg × 28 days × 0.3 kg = **1176 µg** 29 µg/kg × 28 days × 0.3 kg = **2436 µg** 57 µg/kg × 28 days × 0.3 kg = **4788 µg** 357 µg/kg × 28 days × 0.3 kg = **2998.8 µg** 1607 µg/kg × 28 days × 0.3 kg = **13,498.8 µg** 2000 µg/kg × 28 days × 0.3 kg = **16,800 µg** 4000 µg/kg × 28 days × 0.3 kg = **33,600 µg** 8000 µg/kg × 28 days × 0.3 kg = **67,200 µg**

Table 1 (continued)

Reference	Species	Exposure route	Co-exposure or interaction with other metals	Dose	Form	Outcome	Total exposure = (dose × length × weight (assume 300 g)) For drinking water assume 30 ml/day
Wildemann et al. (2015b)	Wistar rats	Drinking water	Yes	57 or 357 µg/kg/BW/day for 28 days 29 or 357 µg/kg/BW/day for 28 days	Inorganic Methyl	MeHg alone caused SBP increase	29 µg/kg × 28 days × 0.3 kg = **2436 µg** 57 µg/kg × 28 days × 0.3 kg = **4788 µg** 357 µg/kg × 28 days × 0.3 kg = **2998.8 µg**
Wildemann et al. (2016)	Wistar rats	Drinking water	Yes	357 or 4000 µg/kg/BW/day for 28 days 7 or 357 µg/kg/BW/day for 28 days	Inorganic Methyl	Inorganic Hg increased DBP MeHg alone caused SBP/DBP increase	7 µg/kg × 28 days × 0.3 kg = **588 µg** 29 µg/kg × 28 days × 0.3 kg = **2436 µg** 357 µg/kg × 28 days × 0.3 kg = **2998.8 µg** 4000 µg/kg × 28 days × 0.3 kg = **33,600 µg**

dose was administered by drinking water, oral gavage, or intramuscular injection. The exposure duration ranged from 13 to 320 days. More studies (13) used inorganic Hg than MeHg (7). Most of them (14/17) found a significant relationship between Hg treatment and increased BP.

To support the observed cause–effect relationships, we reviewed other studies reporting Hg distribution to the cardiovascular system, its effects and the underlying mechanisms. We group the findings under the following sections: Hg distribution in organs related to hypertension development, structural changes, functional changes, and factors that affect hypertension.

Hg distribution in organs related to hypertension development

Many organs are involved in the development of hypertension. Three, which we will cover here, are the 1) heart, 2) kidneys, and 3) liver. Evaluating Hg distribution in each is important to understanding Hg-induced hypertension. There are scarce data on the distribution of Hg in human tissues. Work conducted on a victim of Minamata disease following the Minamata disaster in Japan has revealed high levels of inorganic Hg in the liver and kidneys. Lower levels of Hg were observed in the brain. However, approximately 50% of it was MeHg (Marumoto et al. 2020). Studies from non-polluted regions with larger sample sizes also found inorganic Hg in the brain and kidney and additional Hg deposits in the thyroid and pancreas (Pamphlett 2021).

Here, we will focus on the findings of Hg distribution in rodent models. In rats following Hg^0 vapor exposure, Hg has been measured in the heart, kidneys, and liver (Iranmanesh et al. 2013). Following MeHg exposure in rats, Hg was found in the heart, liver, and kidneys as either inorganic Hg or MeHg. Following thimerosal exposure in rats, Hg was found in the heart, liver, and kidneys as MeHg, inorganic Hg, or ethylmercury (Rodrigues et al. 2010). Thimerosal has also been found in similar organs following exposure in mice (Carneiro et al. 2014). Interestingly, spontaneously hypertensive rats exposed to 5 mg/kg/BW/day over 10 days had higher Hg levels in their kidneys and liver compared to control Wistar rats (Tamashiro et al. 1986). Overall, elemental, inorganic, and organic forms of Hg can be found in the heart, liver, and kidneys directly or via metabolism to alternate Hg forms.

Two key factors determine Hg distribution in these critical areas: 1) age and 2) sex. First, age plays an important role in Hg accumulation. In a study, two groups of rats, young (10 weeks old) and old (36 months old), were sacrificed, and the number of trace elements in various organs was analyzed. Researchers found that old rats had significantly more Hg in their livers and blood than young rats (Rakic et al. 2020). Similar results were found in a Harbour Seal study

where Hg in the liver and heart significantly increased with age, probably due to bioaccumulation (Marino et al. 2011). In humans, a similar trend has been observed, in which inorganic Hg increases with age. However, it was reported that the peak in inorganic Hg began to decrease in multiple organs in individuals older than 80 years old (Pamphlett 2021). Second, sex is a factor that can alter Hg toxicokinetics. Whole-body clearance of Hg is potentially faster in females than in males (Thomas et al. 1987). In C57BL/6N mice 5 min after treatment with MeHgCl, the level of Hg in the kidneys of females was significantly lower. This led to significantly less Hg in the urine of females at 24 h and significantly more Hg in the liver and blood of females (Hirayama and Yasutake 1986). Moreover, male Wistar rats (Bello et al. 2023; Simões et al. 2016, 2020), but not females (Schereider et al. 2021), show changes in BP following inorganic Hg exposure. This sexual dimorphism is potentially caused by lower renal organic anion transport 1 (Oat1) and Oat3 levels in females, as Oat1 and Oat3 are transporters involved in the renal uptake of Hg (Hazelhoff et al. 2012).

Structural changes

Changes in heart and kidney weight have been extensively studied following Hg exposure. Two early studies examined the structural effect of MeHg and $HgCl_2$ in early postnatal rats. Here, MeHg and $HgCl_2$ were administered in varying doses (1 and 2.5 mg/kg/BW/day) starting from P1 until wean (Bartolome et al. 1984; Slotkin et al. 1985). In $HgCl_2$-treated rats, researchers observed a slight increase in heart and kidney weight at early postnatal, which gradually decreased; this was followed by a slight decrease in heart weight compared to the controls (Bartolome et al. 1984). In MeHg-treated rats, similar effects on heart and kidney weights were observed (Slotkin et al. 1985). In a long-term generational study conducted in rats, the parents' generation was given 0, 0.1, 0.5, and 2.5 ppm MeHgCl and bred to create F1 progeny. F1 was later bred to generate F2. Significant increases in the weight of the hearts and kidneys were observed in the Fl and F2 offspring following 2.5 ppm treatment (Verschuuren et al. 1976a, b).

Changes in collagen and elastin have also been observed in $HgCl_2$-exposed rodents across multiple studies. Rats given 1 mg/kg/BW/day $HgCl_2$ for 12 weeks had an increase in total collagen and elastin in the heart muscle (Olczyk et al. 1994). This effect was also observed after a shorter exposure period. Here, rats exposed to 1.23 mg/kg/BW/day $HgCl_2$ for 28 days also had increased collagen deposits in the aorta (Arbi et al. 2021).

More severe heart malformations have been observed following in utero exposure to Hg. MeHg, Hg^0, and Hg^{2+} all readily distribute into the heart and kidneys of prenatally exposed offspring resulting in congenial deformities (Feng et al. 2004; Rutkiewicz and Basu 2013; Yoshida et al. 1986). Embryonic mice treated with 7.5 mg/kg/BW/day MeHg from embryonic day 5.5 (E5.5) to E10.5 had significantly thinner ventricular walls. Moreover, total heart volume was significantly lower at E14.5 following treatment with MeHg (Qiu et al. 2022). Hamsters injected with a single dose (15 mg/kg/BW) of mercuric acetate were sacrificed at E12. The embryos showed ventral wall defects and pericardial cavity distention (Gale 1980). Outside of rodent models, a reduction in the thickness of the ventricular walls has been observed in multiple species, including chickens (Ronconi-Krüger et al. 2022) and fish (Weis and Weis 1977).

Functional changes

Apart from structural changes, alterations in force generated by contracting papillary muscles have also been observed. Papillary muscles are located in the ventriculus of the heart and contract during systole. Female rat papillary muscles treated with varying concentrations of $HgCl_2$ showed that lower concentrations (1 µM) could increase contracting papillary force, while higher concentrations of $HgCl_2$ (5–10 µM) would decrease contracting papillary force. Potentially by modulating Ca^{2+} release from the sarcoplasmic reticulum (Oliveira et al. 1994; Oliveira and Vassallo 1992; Vassallo et al. 1999). The sarcoplasmic reticulum is an organelle within smooth muscle cells that releases Ca^{2+} to trigger the contraction of the muscle fibers. Excessive Ca^{2+} release from vascular smooth muscle cells has been associated with vasoconstriction, which could potentially influence hypertension development.

Similar results were observed following exposure of isolated atria to $MeHgOH^-$. At lower concentrations (0.5 and 2 ppm), MeHg increased the frequency of contractions, while at high concentrations (>2 ppm), MeHg decreased the frequency of contractions (Su et al. 1979). Overall, MeHg seems to induce a biphasic effect on muscle contraction (Ottolini et al. 2019).

Factors that influence the onset of hypertension

Multiple studies in rodents have linked Hg exposure to increased hypertension risk. For example, chronic MeHgCl exposure caused a significant increase in SBP 42 days after cessation (Wakita 1987). Grotto et al. found in a series of experiments that exposure to MeHgCl (100 µg/kg/BW/day) (Grotto et al. 2009) or MeHg-contaminated fish (Grotto et al. 2011) significantly increased SBP over time. Similar results were seen at even lower doses observed by Wildemann et al. (2015a, b). Here, rats were exposed to MeHg or $HgCl_2$ for 4 weeks. The researchers observed that 7 µg/kg/BW/day MeHg and above significantly increased SBP relative to control, while 14 µg/kg/BW/day MeHg and above significantly

increased diastolic blood pressure (DBP) relative to control. This effect was not seen following treatment with $HgCl_2$ (Wildemann et al. 2015a).

While many studies have shown no effect of $HgCl_2$ on BP (Carmignani et al. 1983; Schereider et al. 2021; Wildemann et al. 2015a) other studies have found a relationship between $HgCl_2$ and hypertension (Bello et al. 2023; Machado et al. 2007). Male Wistar rats were given $HgCl_2$ for 180 days; this caused an increase in systemic arterial BP (Carmignani et al. 1992). Similar results were observed in an in vivo model of hypertension called the spontaneously hypertensive rat model. Here, rats were exposed to an initial dose of 4.6 µg/kg/BW $HgCl_2$ and subsequent doses of 0.07 µg/kg/BW/day $HgCl_2$ for 4 weeks. The researchers found that $HgCl_2$ accelerated the development of hypertension marked by increased SBP while increasing reactive oxygen species (ROS) production in mesenteric resistance arteries (Fardin et al. 2020). However, a follow-up study showed that non-spontaneously hypertensive (normotensive) rats do not show the same phenomenon (Simões et al. 2020). However, they do show increased mean arterial pressure and heart rate after 30 days of $HgCl_2$ exposure (Simões et al. 2016), and increased SBP after prolonged exposure (60 days) (Rizzetti et al. 2017b). Sex differences also contribute to MeHg-induced BP impairments. MeHgCl 5 mg/kg/BW/day was administered over 10 days to spontaneously hypertensive rats. Male spontaneously hypertensive rats experienced more toxicity, indicated by higher rates of mortality, larger weight loss, and earlier neurologic signs (Tamashiro et al. 1986). Overall, some studies found that even low doses of inorganic Hg can cause changes in SBP/DBP in rodent models (Bello et al. 2023; Machado et al. 2007; Rizzetti et al. 2017b; Simões et al. 2020). In the studies summarized in the current review, MeHg can also affect BP, but this has been studied at high dosage experiments (Grotto et al. 2009; Wakita 1987). In the three studies that evaluated the effect of both MeHg and inorganic Hg on BP at various dosages, two major conclusions were established: 1) MeHg-exposed rats had increased BP at multiple doses and 2) inorganic Hg showed fewer cardiovascular effects than MeHg (Wildemann et al. 2015a, b, 2016).

Hypertension is influenced by a wide range of factors and CVDs, many of which are interconnected and contribute to the disease's onset and progression. Other factors that influence the onset of hypertension are various, including 1) vasoconstriction, 2) atherosclerosis, 3) dyslipidemia, and 4) thrombosis. Vascular reactivity refers to the ability of blood vessels to change their diameter and ultimately alter blood flow. Vasoconstriction is a type of vascular reactivity where blood vessels are narrowed due to the contraction of smooth muscle cells. This can contribute to or be caused by hypertension onset (Giles et al. 2012). Multiple factors contribute to vascular reactivity. Angiotensin, 5-HT (serotonin), and ACh (acetylcholine) are all critical molecules, and their role will be highlighted below.

First, angiotensin is a hormone that can cause vasoconstriction by binding to receptors on smooth muscle cells of blood vessels. Second, 5-HT is a neurotransmitter and vasoconstrictor that also binds to receptors located on smooth muscle cells. Finally, ACh is a neurotransmitter that acts on endothelial cells to promote the release of nitric oxide (NO). In smooth muscle cells, NO increases the concentration of cyclic guanosine monophosphate (cGMP), which ultimately causes vasodilation. Multiple studies have found that $HgCl_2$ alters vascular reactivity in both the peripheral nervous system (PNS) and the central nervous system (CNS).

In the rat aorta, $HgCl_2$ was shown to cause oxidative stress via NAPDH oxidation, resulting in decreased NO production, leading to endothelial dysfunction, and enhanced vascular reactivity following phenylephrine exposure (a drug used for vasoconstriction) (Cordeiro et al. 2019). Similar $HgCl_2$-induced impairments have been observed in rat aortic rings (Lemos et al. 2012), and isolated rat tail vascular bed (Da Cunha et al. 2000).

In the CNS, MeHg exposure for 3 weeks in a rodent model promoted angiotensin-induced vasoconstriction in isolated basilar arterial. Similarly, ACh-induced relaxation in the basilar arterial rings was decreased in MeHg-treated mice (Islam et al. 2016). In another study, L-NAME (NO synthase inhibitor) was added to basilar arteries isolated from both control and $HgCl_2$-treated rats. L-NAME caused enhanced 5-HT-induced vasoconstriction. This indicates that the presence of NO normally counteracts the vasoconstrictive effects of 5-HT in these arteries. However, inhibition of NO production causes enhanced vasoconstriction in Hg-treated rats (Wiggers et al. 2016).

Atherosclerosis is the thickening or hardening of arteries where plaques, which consist of cholesterol and other substances form. This results in reduced blood flow which could potentially contribute to or be caused by hypertension development (Poznyak et al. 2022). At the beginning of atherosclerotic plaque formation, a critical step is the adhesion of monocytes to endothelial cells and the subsequent migration and transformation of monocytes into macrophages.

An in vitro model found that MeHg treatment significantly induced the adhesion of monocytes to human microvascular endothelial cells and increased pro-inflammatory cytokines and NF-κB activation (Fowler et al. 2021). In vivo studies have shown a similar relationship between MeHg and atherosclerosis. Here, atherosclerosis-prone apolipoprotein E (ApoE) knockout mice were compared to atherosclerosis-resistant C57BL/6 mice. Following surgery to induce atherosclerosis the mice were split into 1) control or 2) MeHg drinking water (20 ppm). They found that atherosclerosis lesions were more extensive in the aorta and carotid sites

of MeHg-treated ApoE knockout mice and MeHg-treated C57BL/6 control mouse line (Silva et al. 2020).

Dyslipidemia is characterized by abnormal levels of lipids including cholesterol and triglycerides in the blood. Dyslipidemia impairs levels of low-density lipoprotein (LDL), commonly referred to as "bad" cholesterol, and high-density lipoprotein (HDL), commonly referred to as "good" cholesterol. High levels of cholesterols can contribute to atherosclerotic plaque formation and potentially hypertension development (Otsuka et al. 2016).

MeHg exposure (20 ppm) in ApoE knockout mice elevated total cholesterol (TC), LDL, and HDL levels (Roque et al. 2021). This is consistent with a study using both Swiss and C57BL/6 mice treated with high-dose MeHg (40 ppm) for 21 days, which showed that MeHg-treated mice had high total HDL and non-HDL (including LDL) plasma levels (Moreira et al. 2012). Overall, MeHg (at high doses) seems to lead to dyslipidemia in rodent models.

Lipid-lowering drugs may present as a potential rescue for MeHg-induced hypercholesterolemia. A study using Swiss mice treated with 40 ppm MeHg and Probucol (a lipid-lowering drug) prevented the development of hypercholesterolemia (Moreira et al. 2012).

Thrombosis occurs when a blood clot forms and obstructs blood flow. Procoagulant factors that trigger platelet activation may contribute to hypertension by increasing the risk of blood clots, narrowing blood vessels, and promoting inflammation. One procoagulant factor that has been linked to hypertension is thrombin. In human erythrocytes, exposure to 0.25–5 μM $HgCl_2$ for 1–48 h resulted in increased thrombin generation (Lim et al. 2010). Furthermore, in rats, 1.148 mg/kg/BW/day $HgCl_2$ for 28 days caused enhanced platelet activation (Arbi et al. 2017). In combination, these results suggest that Hg can promote procoagulant factors leading to platelet activation and potentially blood clot formation.

Mechanism of Hg-induced hypertension

It is well established that Hg binds to thiol and seleno groups of proteins with high affinity and disrupts the structure and activity of enzymes, transporters, and other proteins dependent on functional thiol and seleno groups. Therefore, adverse outcomes are often caused by multiple mechanisms, including intracellular calcium homeostasis, mitochondrial function, oxidative stress, and neurotransmitter release (Kang et al. 2021).

The most studied mechanism is the effects of Hg on oxidative stress and mitochondrial dysfunction. $HgCl_2$ is known to increase the formation of reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and superoxide anion (O_2^-), through the NAPDH oxidase enzyme (Cordeiro et al. 2019; Rizzetti et al. 2017a). Another potential contributor to ROS production is via the electron transport chain, which has been well studied in neurons, but evidence for this outside of the CNS is lacking (Mori et al. 2007). In this review, we will focus on the studies related directly to CVDs only. MeHg can also trigger mitochondrial membrane potential disruption (Nishimura et al. 2019), decrease mitochondrial function in cardiomyocytes (Truong et al. 2015), and cause mitochondrial damage in the myocardium (Arbi et al. 2021). Disruptions in mitochondrial potential and function were seen in conjunction with increased ROS production (Nishimura et al. 2019; Truong et al. 2015).

Thiol depletion can also contribute to ROS formation through the inactivation of antioxidant defense molecules, including superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) [see review, (Ajsuvakova et al. 2020)]. Wiggers et al. (2008) showed that only EC-SOD was significantly changed in the rat aorta following $HgCl_2$ exposure (Wiggers et al. 2008). Other studies which have investigated cardiovascular dysfunction and $HgCl_2$/MeHg exposure have seen reductions in general SOD (Jindal et al. 2011; Zhang et al. 2013). Hg has an affinity for GSH, to form the Hg-GSH complex (Ballatori and Clarkson 1982). As a result, this complex reduces the total amount of GSH, which has been observed in multiple models of cardiovascular dysfunction across both inorganic and organic forms of Hg (Ghizoni et al. 2017; Jindal et al. 2011; Karaboduk et al. 2015; Zhang et al. 2013). Finally, multiple cardiac models have also shown decreased CAT levels following $HgCl_2$ exposure (Karaboduk et al. 2015; Zhang et al. 2013).

Multiple protective agents have been employed to rescue impaired antioxidant homeostasis following Hg exposure. First, in rat myocardial tissues, both MeHg and $HgCl_2$ caused decreased levels of GSH and SOD, which was rescued by co-treatment with melatonin, which is known to detoxify ROS (Jindal et al. 2011). Second, vitamin E has been proposed in multiple papers to alleviate Hg-induced cardiotoxicity (Jin et al. 2012; Karaboduk et al. 2015); via increased SOD, CAT, and GPx levels (Karaboduk et al. 2015). Finally, multiple forms of selenium have been shown to have beneficial effects on both MeHg and $HgCl_2$-induced toxicity dependent on dosage (Jin et al. 2012; Karaboduk et al. 2015). Selenite (a form of selenium) could similarly raise SOD, CAT, and GPx levels in rodents following $HgCl_2$ exposure (Karaboduk et al. 2015).

We propose that Hg toxicity is mediated through three major mechanisms: 1) endothelial cell dysfunction, 2) alteration of the renin–angiotensin system, and 3) inflammation. We summarize the potential effects and the underlying mechanisms of Hg on the cardiovascular system in Fig. 1 and discuss the details of each mechanism below.

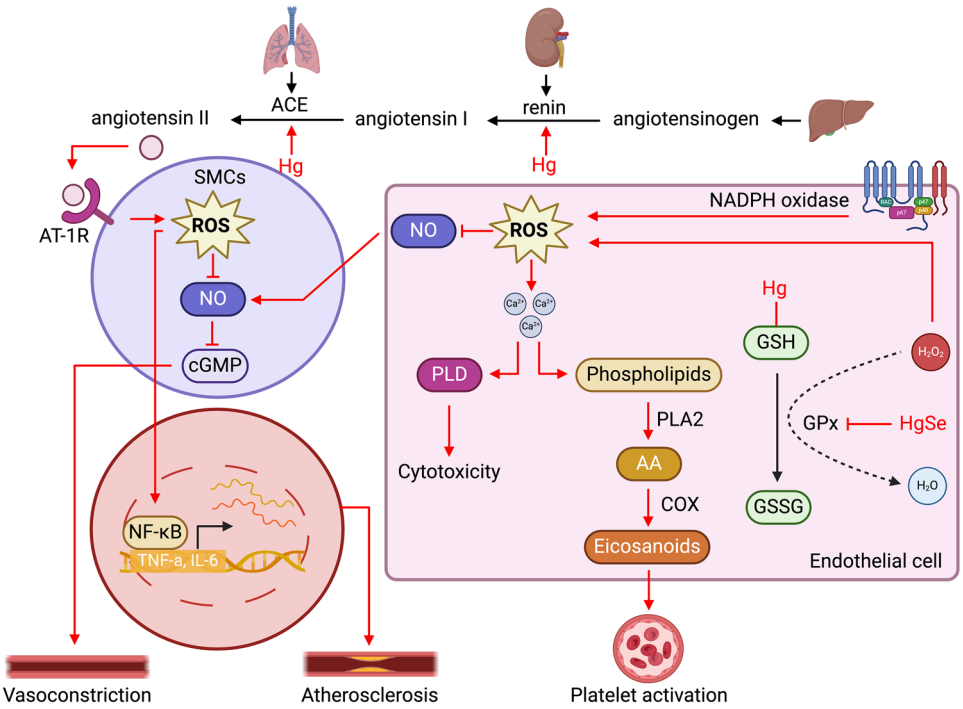

Fig. 1 The proposed mechanism by which mercury (Hg) effects the cardiovascular system. Hg is able to enhance an ACE and renin. These are released from the kidney and lungs respectively and ultimately result in increased angiotensin II which has been shown to trigger ROS formation in vascular smooth muscle cells. This inhibits NO and cGMP contributing to vasoconstriction. ROS production can trigger NF-kB leading to transcription of pro-inflammatory cytokines and atherosclerosis. In vascular endothelial cells, Hg forms complexes with GSH and selenium inhibiting ROS reduction. Furthermore, NAPDH oxidase generates ROS which have been shown to trigger increased intracellular Ca^{2+}; this has been shown to lead to cytotoxicity and eicosanoid production. Abbreviations: AA, arachidonic acid; ACE, angiotensin I-converting enzyme; Ca^{2+}, calcium; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; GPx, glutathione peroxidase; GSH, glutathione; GSSG, oxidized glutathione; H_2O, water; H_2O_2, hydrogen peroxide; Hg, mercury; HgSe, mercury selenide; IL-6, interleukin 6; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PLA2, phospholipase A2; PLD, phospholipase D; ROS, reactive oxygen species; TNF-a, tumor necrosis factor alpha. Created with BioRender.com

Endothelial dysfunction

Lipid peroxidation is a process that occurs when free radicals and ROS oxidize polyunsaturated fatty acid (PUFA) chains of cell membrane lipids. This process generates reactive lipid peroxides, including malondialdehyde (MDA), contributing to cellular damage. Increased levels of MDA have been readily observed following exposure to both MeHg and $HgCl_2$ (Jindal et al. 2011; Vassallo et al. 2019). Rats exposed to MeHg via contaminated fish had a significantly increased SBP over time combined with a significant increase in plasma MDA (Grotto et al. 2011).

As introduced previously, NO is a molecule produced by endothelial cells that acts as a vasodilator. In smooth muscle cells, NO increases the concentration of cGMP, which ultimately causes vasodilation. Multiple studies have found that NO is reduced following both $HgCl_2$ and MeHg. An in vitro experiment using aortic rings exposed to $HgCl_2$ showed increased ROS production and reduced downstream NO (Lemos et al. 2012). Furthermore, a dose-dependent decrease in NO production has also been observed in a culture of human endothelial cell, EA.hy926, following MeHg (0.1–10 µM) exposure (Van Dao et al. 2016). Other models of Hg-induced toxicity have observed similar effects (Cordeiro et al. 2019; Da Cunha et al. 2000; Lemos et al. 2012). However, it is important to note that contradictory studies have observed increased NO production following acute MeHg exposure to induce vasodilation (Omanwar et al. 2013).

In vascular endothelial cells, $HgCl_2$, MeHg, and thimerosal were shown to cause an intracellular Ca^{2+} influx caused by ROS formation and diminished thiols. This Ca^{2+} influx activates PLD in a dose-dependent manner. Overall, this leads to endothelial cell dysfunction and eicosanoid production (Hagele et al. 2007; Peltz et al. 2009). Calcium chelating agents, when co-administered with either MeHg, HgCl2, or thimerosal, were able to attenuate PLD activation (Peltz et al. 2009). Ca^{2+} and thiol depletion are also involved in the Hg-induced activation of the phospholipase A2 (PLA2) pathway. This pathway begins with PLA2

cleaving arachidonic acid (AA) from cell membrane phospholipids. AA can then be metabolized through the COX pathway, which converts AA into various prostaglandins and thromboxanes. These molecules play important roles in inflammation and platelet aggregation (Hagele et al. 2007; Mazerik et al. 2007, 2008). MeHgCl stimulates TXA_2 and prostacyclin (PGI2) in the heart under in vitro conditions, and this effect was inhibited by both thromboxane synthetase and phospholipase A2 inhibitors (Ally et al. 1993). $HgCl_2$ was shown to increase thromboxane A2 (TXA_2) following decreased NO. TXA_2 is known to contribute to platelet aggregation and vasoconstriction (Cordeiro et al. 2019).

Alteration of the renin–angiotensin system

Hg can alter the renin–angiotensin system by enhancing angiotensin I-converting enzyme (ACE 1) and renin 2. These are released from the kidney and lungs, respectively, and ultimately result in increased angiotensin II, which has been shown to trigger ROS formation in vascular smooth muscle cells, which inhibits NO and cGMP, contributing to vasoconstriction. Chronically $HgCl_2$-treated rats showed increased plasma angiotensin I-converting enzyme (ACE), which is a potential contributing factor in angiotensin II formation (Carmignani et al. 1992). Other studies have shown increased plasma renin and a simultaneous BP increase following MeHgCl exposure; this could further promote angiotensin II synthesis (Wildemann et al. 2016). Furthermore, downstream angiotensin II is known to decrease NO synthesis via ROS formation. In the aortic ring, $HgCl_2$ exposure caused increased vasoconstriction and angiotensin II, ultimately reducing NO synthesis (Lemos et al. 2012). Similar results have been observed in rats where an initial dose of 4.6 µg/kg/BW $HgCl_2$ and subsequent doses of 0.07 µg/kg/BW/day $HgCl_2$ were given for 30 days. Left coronary arteries had increased NO production triggered by increased O_2^- (Furieri et al. 2011). Enhanced Rho-kinase activity and inhibition of NO have also been observed in mice following 21 days of 40 ppm MeHg (Islam et al. 2016).

Angiotensin II receptor (AT-1R) may play a critical role in this pathway. Angiotensin II decreases NO by binding to the AT-IR on the surface of vascular smooth muscle cells. This activates ROS, which then scavenges NO or indirectly limits NO synthase (Fig. 1). Co-treatment with losartan, an AT-1 receptor blocker, prevented the deleterious effects of $HgCl_2$ on vascular reactivity and oxidative stress (Rizzetti et al. 2018).

Inflammation

ROS production following Hg exposure can trigger NF-kB, leading to the transcription of pro-inflammatory cytokines (TNF-a and IL-6) and atherosclerosis (Baiyun et al. 2018). ROS are also critical to triggering the cytoprotective pathway Keap1/Nrf2. Kelch-like ECH-associated protein 1 (Keap1) contains a cysteine residue that Hg can bind to. Under stress conditions, electrophiles and ROS bind to Keap1, which causes nuclear factor erythroid 2-related factor 2 (Nrf2) to migrate from the cytoplasm into the nucleus, leading to transcription of glutamate–cysteine ligase (GCL) and antioxidant defense enzymes (Ni et al. 2010; Toyama et al. 2007; Wang et al. 2009). However, decreased Nrf2 and decreased downstream antioxidant targets (HO-1 and NQO1) were observed following $HgCl_2$ exposure in liver cells, potentially due to the crosstalk between Nrf2 and NF-κB (Baiyun et al. 2018; Zhang et al. 2017).

Luteolin is a natural antioxidant, and co-administration of luteolin and $HgCl_2$ in Wistar rats has been shown to rescue histopathological alterations and oxidative stress infected by $HgCl_2$ alone. Luteolin can elevate Nrf2 levels and inhibit NF-kB. Overall, it prevents inflammation and oxidative stress caused by $HgCl_2$ alone (Baiyun et al. 2018).

Brief summary

In the sections above, we highlighted the potential relationship between various forms of Hg on hypertension development. At the organ and tissue level, Hg has been shown to cause structural and functional changes. Moreover, we emphasize the multi-faceted impact of Hg on cardiovascular health, including its effects on vascular reactivity, vasoconstriction, atherosclerosis, dyslipidemia, and thrombosis. At the cellular and molecular levels, we highlight the similarity in the ability of both inorganic and organic Hg to induce impairments in antioxidant defense mechanisms, leading to increased ROS production, which causes endothelial dysfunction and alteration of the renin–angiotensin system, leading to inflammation, and resulting in vasoconstriction. While both inorganic Hg and MeHg have been reported to have similar effects at the cellular and molecular levels, as highlighted above, key differences exist. Mainly, limited cellular uptake and intracellular distribution limit the role of inorganic Hg. This is primarily due to its lack of lipophilicity. This may provide some insight into why MeHg has more extensive cardiovascular effects, which was highlighted in multiple rodent studies (Wildemann et al. 2015a, b, 2016).

The significance of these findings lies in the comprehensive understanding of Hg's impact on organ, tissue, cellular, and molecular functioning leading to cardiovascular dysfunction. Overall, clarifying the molecular initiating event is critical to understanding and effectively treating Hg-induced cardiovascular dysfunction. A summary of these effects is presented in the form of an adverse outcome pathway in Fig. 2.

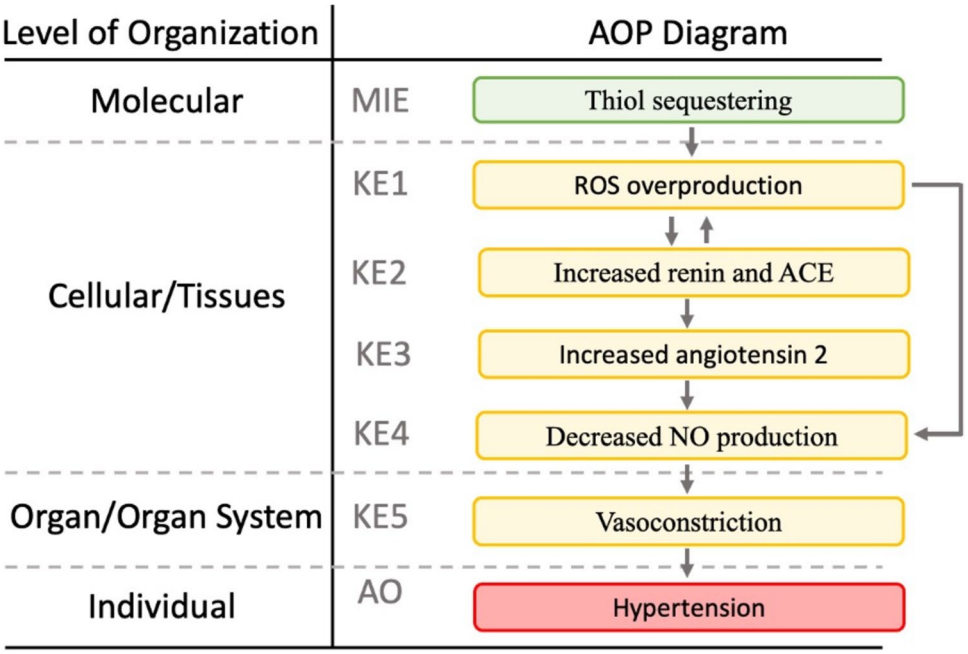

Fig. 2 Adverse outcome pathway (AOP) of MeHg exposure and hypertension onset. Abbreviations: AO, adverse outcome; AOP, adverse outcome pathway; KE, key event; MIE, molecular initiating event

Population studies on mercury and hypertension

Our 2018 systematic review included 29 studies, a significant positive association between Hg and BP was identified, and a non-linear dose–response relationship is plausible for both SBP as a continuous measurement or hypertension (defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) (Hu et al. 2018). We recommended that hair Hg at 2 µg/g be considered as a potential candidate regulatory value for international agencies [e.g., the WHO and the Environmental Protection Agency (EPA)] to update their guidelines on Hg exposure (Hu et al. 2018).

In this review, we aim to update the systematic review and elaborate on the following key aspects: 1) investigate how the source and type of Hg exposure and the use of different biomarkers influence the association between Hg and hypertension; 2) identify populations at higher risk due to increased exposure duration, elevated doses, or exposure during vulnerable life stages; 3) explore how simultaneous exposure to Hg and other heavy metals might interact, potentially amplifying or mitigating Hg's impact on BP; 4) examine the interaction between Hg exposure and dietary factors, e.g., omega-3 fatty acids and selenium, and how these might modulate the association between Hg and hypertension; 5) understand the relationship between Hg exposure and health conditions related to hypertension, as well as broader cardiovascular health outcomes. Finally, we weigh the evidence of causality and discuss the potential regulatory value of Hg and public health recommendations to reduce the health burden associated with Hg exposure.

Update on literature published since 2018

Using the same search criteria, we found 16 new studies reporting findings on the relationship between Hg exposure and hypertension in different populations between 2018 and 2024 (Table 2). Most of the studies (9) were from the United States, 3 were from China, and the rest were from South Korea, Canada, Kazakhstan, and Brazil. The sample size ranged from 84 to 8371 participants. Five studies reported urinary Hg to reflect inorganic Hg exposure (Bulka et al. 2019; Farzan et al. 2021; Shinetova et al. 2020; Wang et al. 2021; Nunes et al. 2022), the rest of the studies reported MeHg or total Hg exposures measured in blood. At least nine of these studies could potentially provide additional information on the dose–response relationship between Hg exposure, BP, and hypertension. The rest of the studies are not eligible for dose–response meta-analysis due to several reasons: 1) the study participants are pregnant women only (Liu et al. 2019; Louopou et al. 2020; Wang et al. 2020), 2) the biomarker reported in the study cannot be converted to hair Hg (Ma et al. 2022, 2023; Nunes et al. 2022), and 3) lack of quantitative Hg exposure data (Guo et al. 2022b).

In five out of the nine studies, the highest exposed group had average Hg levels equal to or above 2 µg/g hair Hg (Bulka et al. 2019; Farzan et al. 2021; Kim et al. 2019; Shinetova et al. 2020; Wang et al. 2021). These five studies all reported a positive association between Hg and either SPB/DBP or hypertension. Two studies investigated residents of industrially polluted areas (Kim et al. 2019; Shinetova et al. 2020), and the remaining three investigated general populations. Four of the studies used urinary Hg as a biomarker of

Table 2 Characteristics of studies published after 2018 and included in the review

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Bulka et al. (2019)	USA	General population	Yes	54.8	52.7	1088	Urine (µg/h)	Inorganic	GM 17.8	HPT	130/85 mmHg, BP medication		Age, gender, race/ethnicity, family income: poverty ratio, total caloric intake, educational attainment, smoking status, alcohol consumption, physical activity status, survey cycle, and BMI
Kim et al. (2019)	South Korea	Population living in mercury polluted regions		≈65	31.6	7822	Blood (µg/L)	Total	Mean 5.2 (SD: 4.5)	HPT	140/90 mmHg, BP medication	Measured with standard mercury sphygmomanometers	Age, sex, smoking status, alcohol drink, and income

Table 2 (continued)

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Liu et al. (2019)	USA	Pregnant women	Yes	28.3	0	1274	RBC (µg/L)	Total	(range: 0.3, 27.8)	HPT	140/90 mmHg		Age at delivery (continuous), self-reported race (black, nonblack), education (below high school, high school, college or above), parity (nulliparous, multiparous), pregnancy body mass index (continuous), and smoking status during pregnancy (never, former, current)
Louopou et al. (2020)	Canada	Pregnant women		31.9	0	1817	Blood (µg/L)	Methyl		HPT, BP	140/90 mmHg, BP medication	Average of 2 readings using a mercury sphygmomanometer	Age, BMI, fish consumption, weight gain, coffee intake, education, household income, ethnicity, parity, multiple child pregnancy, maternal smoking

Table 2 (continued)

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Shinetova et al. (2020)	Kazakhstan	Population living in mercury polluted regions		54	56	84	Urine (μg/L)	Inorganic	GM 2.5 (SD: 0.9)	HPT	130/85 mmHg, BP medication	Medical records	
Wang et al. (2020)	China	Pregnant-women	Yes	20–30	0	854	Blood (μg/L)	Total	Case Median 1.52 (IQR: 0.97, 2.36) Control Median 1.49 (IQR: 0.96, 2.08)	HPT	140/90 mmHg	Medical records	Pre-pregnancy BMI, education, household monthly income per capita, and gestational age
Yao et al. (2020)	USA	General population	Yes	8-17	50.9	7076	Blood (μg/L)	Total/ Methyl	Mean 0.44	BP	NA	Average of three measurements with standard mercury sphygmomanometer	
Desai et al. (2021)	USA	General population	Yes	12.5	49.8	1642	Blood (μg/L)	Total	Median 0.37	BP	NA	Average of three measurements with standard mercury sphygmomanometer	Age, sex, race, BMI, total energy intake, cycle, education of household head, and income to poverty ratio

Table 2 (continued)

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Farzan et al. (2021)	USA	General population		5.5	48.6	395	Urine (μg/L)	Inorganic	Mean 0.07	BP	NA	Average of five measurements with	Age, height, weight; child sex, birth weight, gestational age; maternal education and smoking during pregnancy; and urine specific gravity
Wang et al. (2021)	USA	General population	Yes	49.4	0	1317	Urine (μg/L)	Inorganic	Mean 1.2	BP	NA	Average of 2 readings using a mercury sphygmomanometer	Age at baseline, race/ethnicity, study site, specific gravity (log-transformed), education, smoking status, alcohol drinking, physical
Xu et al. (2021)	USA	Occupational population	Yes	>30	74	957	Blood (μg/L)	Total		HPT, BP	140/90 mmHg, BP medication	Average of two measurements	Age, sex, race, education, income, BMI

Table 2 (continued)

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Guo et al. (2022a, b)	USA	General population	Yes	≥20	49.6	8371	Blood (μg/L)	Total	GM 3.90	BP	NA	Average of second- and third-time measurements in 5 min interval using standard mercury sphygmomanometer	Age, gender, smoking status
Ma et al. (2022)	China	Pregnant women	Yes	30	0	438	Plasma (μg/L)	Total	Case Median 0.33	HPT	140/90 mmHg	Medical records	Maternal age at enrollment, gestational age at blood sample collection, household income, pre-pregnancy BMI, parity, passive smoking, and gestational diabetes mellitus
Nunes et al. (2022)	Brazil	General population		59	42	112	Urine (μg/g creatinine)	Inorganic	Median	BP	NA		Age, sex, BMI, smoking and alcohol consumption

Table 2 (continued)

Reference	Population	Exposure route	Co-exposure or interaction with other metals	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Mercury concentration	Outcome	Definition of HPT	Blood pressure measurement	Variables adjusted for
Tang et al. (2022)	USA	Asian population	Yes	>20	47.3	1422	Blood (μg/L)	Total/ Methyl	Mean 1.95	HPT, BP	130/80 mmHg, BP medication	Average of three measurements with standard mercury sphygmomanometer	Age, sex, education, annual household income, cotinine level, alcohol use, BMI, omega-3 fatty acids and selenium
Ma et al. (2023)	China	Prenatal exposure		5–6	51.6	2535	Maternal serum (μg/L)	Total	GM 1.03	HPT, BP	NA	Average of 3 measurements using electronic sphygmomanometer	Maternal age, maternal education, monthly family income, parity, smoking during pregnancy and family history of hypertension. child age, BMI, child sex and feeding patterns

BMI, body mass index; BP, blood pressure; HPT, hypertension; GM, geometric mean; IQR, inter-quartile range; SD, stan study

Hg exposure, while one used blood Hg (Kim et al. 2019). In the other four studies, the average Hg level in the highest exposed group was below the cut-off (Desai et al. 2021; Tang et al. 2022; Xu et al. 2021; Yao et al. 2020). Three studies reported no or inverse association between Hg, BP, or hypertension (Desai et al. 2021; Xu et al. 2021; Yao et al. 2020), while one study reported a positive association in a subgroup of participants (Non-Hispanic Asian) and no association in the rest of the study populations (Tang et al. 2022). All four studies were from the US, and three were based on the NHANES (Desai et al. 2021; Tang et al. 2022; Yao et al. 2020).

The findings of the nine additional studies reconfirmed our conclusion on the overall association between Hg exposure, BP, and hypertension. Hair Hg 2 µg/g was a reasonable cut-off for the association between Hg exposure, BP, and hypertension. The shape of the dose–response relationship curve may be worth revisiting as well. However, several uncertainties and research gaps remain. First, evidence suggesting no or an inverse association at a lower dose (<1 µg/g hair Hg) is the most abundant, followed by a clear positive association from higher end exposure (>5 µg/g hair Hg), and the least evidence with inconsistent findings from medium-exposed populations. Second, the population exposed to low, medium, and high Hg was likely to be heterogeneous. Many of the studies with low Hg exposure participants were likely from the few national biomonitoring studies, e.g., NHANES, or other studies conducted in populations consuming a typical "western" diet that consists of only a small amount of fish and seafood. Participants with higher end exposure were either residents living close to industrial contaminated sites or workers being exposed occupationally. The medium-exposed participants were likely coastal or Indigenous populations who were exposed to MeHg through fish and seafood consumption. Besides the heterogeneity in the number of studies available and study population by exposure doses, several other key factors may influence the relationship between Hg exposure, BP, and hypertension.

In the following sections, we will investigate how the source and type of Hg exposure and the use of different biomarkers influence the association between Hg and hypertension and discuss the effects of different confounding factors.

Sources, forms, and biomarkers of mercury exposure

One main challenge to establishing a robust dose–response relationship is that Hg exists in various chemical forms, and each of these forms is characterized by distinct exposure sources, target organs, toxicological properties, and metabolic pathways. With currently available epidemiology studies, it is not feasible to elaborate on whether Hg exposure from different sources or different forms of Hg, affects BP following the same or similar pathways. However, for public health purposes, scientists would like to explore if Hg's impact on BP or hypertension is similar, given that all populations are exposed to a certain level/dose of Hg, regardless of its source and form. Furthermore, many of the epidemiology studies assess Hg exposure with biomarkers, which adds another layer of uncertainty to estimating the overall relationship between Hg, BP, and hypertension.

It is important to delineate the impact of biomarkers in two aspects. First, whether the association between Hg and BP is consistent within the same study measuring different biomarkers, and second, whether the association remains similar across different studies measuring different biomarkers with similar exposure levels. As for the impact of exposure sources and forms of Hg, most scientists are mainly interested in comparing the associations between MeHg exposure from fish and seafood and inorganic Hg exposure from occupational sources at moderate to higher end exposure. Four underlining assumptions are needed to support the investigation of these associations. First, urinary Hg primarily reflects exposure to inorganic Hg, e.g., exposure from mining. Second, hair Hg or blood MeHg primarily reflects exposure to MeHg, e.g., from fish and seafood consumption. Third, blood total Hg reflects exposure to all forms of Hg. Finally, different biomarkers are convertible.

Evidence from different biomarkers in the same study population

Several studies reported more than one biomarker for the same participants, including hair and blood Hg (Bautista et al. 2009; Choi et al. 2009; Valera et al. 2011a), blood and urinary Hg (Kobal et al. 2004; Park et al. 2013), and hair and urinary Hg (Goodrich et al. 2013; Rajaee et al. 2015; Siblerud 1990). These studies covered a wide range of Hg exposure levels and were from both general population and occupational exposures. Generally, when comparing the BP between high-exposure and low-exposure groups classified by different biomarkers within the same study, the estimates were always in the same direction and with similar magnitudes. For example, it was estimated that SBP was 3.4 mmHg (95% CI: −0.5 to 7.3) higher in the high-exposure group measured by hair Hg and 2.7 mmHg (95% CI: −1.2 to 6.6) higher measured by blood Hg (Bautista et al. 2009). The differences in SBP were −2.0 mmHg (95% CI: −3.1 to −0.9) and -3.2 mmHg (95% CI: −5.2 to −1.2) between exposure groups defined by blood and urinary Hg, respectively (Park et al. 2013). The corresponding estimates were 1.2 mmHg (95% CI: −5.7 to 8.1) and 1.0 mmHg (95% CI: −3.9 to 5.9) between exposure groups defined by hair and urinary Hg (Rajaee et al. 2015). The results were similar in the other studies identified for DBP, with two exceptions in the occupational setting. One was that the result from

blood Hg was opposite to urinary Hg, which is the preferred biomarker for miners exposed to inorganic Hg (Kobal et al. 2004). The other was between hair and urinary Hg among dentists (Goodrich et al. 2013). In general, the association between Hg exposure and BP was consistent across three major biomarkers (hair, blood, and urinary Hg) in the non-occupational populations, given the same or similar exposure level. Therefore, it is reasonable to synthesize evidence from different studies using different biomarkers with proper conversion. Hair Hg level seems to be an appropriate biomarker for the comparison across studies.

Evidence from different biomarkers in populations with similar exposure levels

The association between Hg exposure and BP was examined thoroughly in both the United States (US) population and the Indigenous population with high fish consumption, including Inuit living in the Arctic. Hg exposure in the US general population is low regardless of which biomarkers were measured (Bautista et al. 2009; Desai et al. 2021; Mordukhovich et al. 2012; Mozaffarian et al. 2012; Park et al. 2013; Vupputuri et al. 2005; Xu et al. 2021; Yao et al. 2020). Also, regardless of the biomarkers used and the study design, no or inverse association between Hg, BP, or hypertension has been reported in the US general population consistently. These studies contribute substantially to the body of literature investigating Hg exposure and BP at lower doses (less than 2 µg/g hair Hg or equivalent), and the findings were relatively homogenous as many of them were using the National Nutrition and Health Examination Survey. On the other hand, Indigenous populations are generally exposed to Hg higher than 2 µg/g hair Hg or equivalent through their traditional diet (Houde et al. 2022; Pirkle et al. 2016). Blood Hg (Hu et al. 2017; Valera et al. 2009, 2011b, 2013) and hair Hg (Choi et al. 2009; Fillion et al. 2006; Valera et al. 2011a) were commonly assessed in these populations to reflect their dietary exposure to MeHg. Positive associations between Hg exposure and BP outcomes were consistently reported in these studies, except for one that reported no significant association among 313 Inuit adults in northern Canada (Valera et al. 2013). Studies from the Nordic population (Daneshmand et al. 2016; Pedersen et al. 2005; Virtanen et al. 2012a, b) and South Korea (Eom et al. 2014; Hong et al. 2013; Kim et al. 2019; Nguyen and Kim 2022; Park and Choi 2016) in general fell into moderate Hg exposure, and they generally showed positive associations.

The consistent associations observed within populations with similar exposure levels suggest that, although the use of different biomarkers may introduce variations to the estimated magnitudes of association between Hg exposure and BP outcomes to a certain extent, it is unlikely to change the direction and significance of the association within a given exposure range. The differences in association reported between the US population and other populations with higher dietary Hg exposure suggest that Hg exposure level is a more important factor influencing the association between Hg exposure and BP outcomes.

Evidence of population exposed to different sources and forms of mercury

Since the studied populations are exposed to varying sources of Hg that are in different forms, the studies reported in the literature often assessed Hg exposure using different biomarkers. For instance, individuals exposed to inorganic Hg via mining activities typically exhibit considerably higher Hg exposure levels compared to those exposed to MeHg through fish consumption. Conversely, individuals who consume minimal or no fish typically show notably lower Hg exposure levels. In this context, observed disparities in the associations between Hg exposure and BP outcomes could be attributed to variations in either Hg exposure levels, in sources or forms, or both.

Therefore, in this review, we focused on evaluating the associations reported within populations exposed to comparable levels of either inorganic Hg or MeHg. This approach aimed to mitigate potential confounding factors arising from dissimilar exposure levels, allowing for a more accurate and balanced assessment of the associations between these distinct forms of Hg and their respective health outcomes.

At the higher end of Hg exposure, Hg miners from Slovenia in the 1970s had an average annual urinary Hg level of over 26 µg/L, certain residents of Minamata, Japan, and Amazon, Brazil could have a hair Hg level over 30 µg/g (Fillion et al. 2006; Yorifuji et al. 2010). All three studies reported a positive association with similar magnitudes, with odds ratio comparing the highest to lowest exposure groups 2.1, 2.5, and 3.8, respectively. In a moderate exposure scenario, individuals with dental amalgam had hair Hg 1.4 µg/g and an average of 5.7 mmHg higher in SPB, compared to those without (Siblerud 1990). In populations exposed to similar MeHg from fish intake (Daneshmand et al. 2016; Hong et al. 2013; Hu et al. 2017; Park and Choi 2016). The estimated differences in SBP comparing high–to-low-exposure groups in these studies were also similar, ranging from 2.0 to 4.4 mmHg.

At the low end of Hg exposure, it is difficult to distinguish the sources and contributions of different Hg forms to the overall exposure. Also, given that null or inverse associations were consistently reported in populations with hair Hg below 2 µg/g (Hu et al. 2018), it can be assumed that populations with low Hg exposure should have no concern about effects on BP, regardless of the form of Hg.

Brief summary

In summary, the associations observed remained largely consistent across various biomarkers, both within the same study population/participants and among populations with similar exposure levels. Additionally, when comparing populations exposed to broadly similar levels of Hg but differing in the forms and sources, the associations exhibited remarkable similarity. This consistency in associations across diverse biomarkers and exposure scenarios suggests the plausibility of establishing a dose–response relationship between Hg exposure and BP outcomes, using either measured or converted hair Hg concentrations.

Populations at higher risk

Since exposure dose is the driving factor of the association between Hg and hypertension, it is worth identifying the population groups that are more at risk due to their dietary habits, occupation, or geographical location. Monitoring and addressing Hg exposure in such populations are crucial for mitigating health risks associated with long-term Hg exposure.

Coastal populations and fishing communities are at risk of elevated Hg exposure due to fish and marine mammal consumption as Hg biomagnifies through the food chain (Driscoll et al. 2013; Lavoie et al. 2013). This includes Indigenous populations and communities reliant on subsistence fishing (ATSDR 2022). Workers in industries such as mining, smelting, or manufacturing products involving Hg are at risk of higher exposure due to direct Hg contact (ATSDR 2022; Driscoll et al. 2013). Individuals involved in small-scale gold mining often use Hg to extract gold from ore, leading to substantial exposure through inhalation or skin contact (ATSDR 2022; Esdaile and Chalker 2018). Certain regions might have higher levels of Hg exposure due to natural deposits, industrial pollution, or mining activities. Residents in such affected areas are at higher risk of Hg exposure as well (ATSDR 2022; Aubrac et al. 2022). Certain traditional medicines and cosmetic products might contain Hg as an ingredient, and as a result, consumers of these products may be exposed to Hg (Bastiansz et al. 2022).

In addition to the populations with a higher risk of elevated Hg exposure, certain populations may be more sensitive to the adverse effects of Hg due to various factors. Certain groups of individuals are sensitive to any stressor, e.g., the elderly and individuals with the existing health conditions. Hg exposure may exacerbate their health conditions through various pathways. Some individuals may have genetic variations affecting their ability to metabolize or excrete Hg efficiently, leading to increased susceptibility to Hg toxic effects (Andreoli and Sprovieri 2017). Several recent studies suggest that Hg exposure is related to hypertensive disorders of pregnancy or postpartum BP. However, results on this topic are inconsistent, and more research is needed (Dantas et al. 2022; Liu et al. 2019; Louopou et al. 2020; Ma et al. 2022; Wang et al. 2020). Exposure to Hg during crucial early developing stages, e.g., fetus and infants, may also have additional long-term adverse effects.

Hg crosses the placental barrier and accumulates in fetal tissues, especially the developing brain. Evidence suggests that prenatal exposure may lead to long-term unfavorable neurological and cardiovascular outcomes (Counter and Buchanan 2004; Davidson et al. 2004; Gallego-Viñas et al. 2019). Several studies reported prenatal Hg exposure was associated with alterations in BP in children or adolescents (Farzan et al. 2021; Ma et al. 2023; Sørensen et al. 1999; Thurston et al. 2007). Among these two studies were from highly exposed populations—Seychelles and the Faroe Islands (Sørensen et al. 1999; Thurston et al. 2007). Negative findings (no association) or partial associations (significant results in certain subgroups) were reported as well (Grandjean et al. 2004; Gregory et al. 2016; Kalish et al. 2014; Valera et al. 2011b, 2012). The mixed findings observed suggest the possibility of a dose-dependent relationship between prenatal Hg exposure and BP during childhood.

Mixed findings were reported for postnatal exposure as well. Two studies reported a positive significant association (Farzan et al. 2021; Poursafa et al. 2014), and interestingly, the association observed in prenatal exposure in Seychelles and the Faroe Islands became null in children and adolescent with postnatal exposure assessment (Grandjean et al. 2004; Valera et al. 2011b, 2012). This variability in results suggests that high fish intake or other public health interventions during childhood may play a crucial role in mitigating the adverse effect of prenatal Hg exposure to BP outcomes. It is also worth clarifying whether prenatal and postnatal exposure to Hg influences BP similarly.

Chemical mixtures and interaction with other heavy metals

The most commonly studied Hg chemical mixtures in animals are Hg and lead (Pb) and Hg and cadmium (Cd). Co-exposure to Hg and Pb has been studied in rats. Here, rats were exposed to a mixture of Hg^{2+}, Pb, and MeHg for 4 weeks via drinking water. Exposure to MeHg alone raised SBP and pulse pressure, while exposure to the mixture had no effect relative to control. Potentially because Hg^{2+} and Pb work as an antagonist of MeHg (Wildemann et al. 2015a, b). Similar results were observed in a follow-up study whereby MeHg-induced hypertension was not seen following exposure to Hg^{2+}, Pb, and MeHg chemical mixtures (Wildemann et al. 2016).

Co-exposure of Hg and Cd has also been extensively studied. As highlighted previously, exposure to $HgCl_2$ alone

has been shown to increase collagen and elastin in the heart muscle (Olczyk et al. 1994). Here, co-exposure to both Cd and $HgCl_2$ for 28 days leads to further collagen deposition (Arbi et al. 2021). A study in rabbits showed that following both $HgCl_2$, Cd, and $HgCl_2$ + Cd exposure TC was elevated, while HDL and LDL were lowered; suggesting that both Cd and Hd can also contribute to dyslipidemia (Ali et al. 2020).

Silver nanoparticles (SiNPs) are a more recent area of study. A recent study exposed human cardiomyocytes to MeHg and SiNPs. This caused enhanced ROS production and lowered SOD and GPx (Yang et al. 2018). Overall, studies that assess co-exposure to multiple chemicals may more accurately replicate real-world toxicant exposure and may clarify epidemiological results.

Many of the human studies investigated the association between mixtures of heavy metals and cardiovascular outcomes using biomonitoring data with different matrices of biomarkers (e.g., blood, urine, and serum) and various statistical methods. The available evidence suggests a positive association between hypertension (or increased BP) and the concurrent exposure of Hg with other metals, particularly Pb, arsenic, and Cd (Bulka et al. 2019; Park and Choi 2016; Poursafa et al. 2014; Shiue 2014; Yao et al. 2021). This co-exposure to heavy metals was reported to be related to other metabolic conditions (Bulka et al. 2019; Yao et al. 2021; Nunes et al. 2022; Qu et al. 2022; Shiue 2014; Poursafa et al. 2014; Rotter et al. 2015), heart diseases, and mortality, as well (Yao et al. 2021). A good proportion of the positive findings were from low Hg populations, e.g., the US population (Bulka et al. 2019; Guo et al. 2022a; Park and Choi 2016; Shiue 2014; Yao et al. 2021). This underscored the importance of the chemical mixture approach in assessing Hg's toxic effect at exposure levels relevant to general populations, which are likely to be well below regulatory values. Nonetheless, these findings need to be confirmed with further high-quality prospective studies and in other populations with similar biomonitoring data. There are studies showing either no association from heavy metal mixtures or the positive association was attributed primarily to metals other than Hg (Desai et al. 2021; Guo et al. 2022b; Liu et al. 2022; Mordukhovich et al. 2012; Nunes et al. 2022; Qu et al. 2022; Rotter et al. 2015).

Interaction with omega-3 fatty acids and selenium

Certain foods and nutrients, on the other hand, interact with Hg, either directly or indirectly, to mitigate Hg's adverse effect on BP. Omega-3 fatty acids and selenium are the two most investigated nutrients, which could potentially counteract Hg's adverse effect due to their anti-inflammatory and anti-oxidative properties. Furthermore, selenium can bind with Hg and form less toxic complexes. It is reasonable to assume that most of the findings in this section were more relevant to MeHg exposure, although studies might report blood total Hg or other Hg exposure biomarkers.

Omega-3 fatty acids

The interaction between omega-3 fatty acids and Hg on BP can be investigated through two approaches. First, by synthesizing studies that directly address their interaction, and second, by comparing studies that reported Hg exposure from fish consumption against those with similar Hg exposure from other sources. One common approach to investigating the direct interaction was to stratify the study participants by Hg and omega-3 fatty acids (fish consumption) levels and then compare the outcome of interest among different categories. No clear interaction between Hg and omega-3 fatty acids on hypertension was observed (Virtanen et al. 2012b). The protective effect of omega-3 fatty acids on hypertension was attenuated by Hg (Xun et al. 2011).

More studies were available reporting the interaction on other cardiovascular or metabolic outcomes, e.g., stroke, coronary heart disease (Downer et al. 2017; Guallar et al. 2002; Virtanen et al. 2005; Wennberg et al. 2012), and blood cholesterol (Smith et al. 2009). Except for Downer 2017, the rest studies reported consistently that Hg was associated with an increased risk of cardiovascular outcomes, while omega-3 fatty acids were inversely associated with these outcomes, with the two effects offsetting each other.

In summary, the epidemiological evidence on the interaction between Hg and omega-3 fatty acids in relation to hypertension is not as clear as it is for other cardiovascular outcomes, such as myocardial infarction. More studies specifically focused on BP outcomes are needed. Additionally, most studies examining the interaction between Hg and omega-3 have stratified their exposures into high or low categories based on the distribution within the study population. This leaves uncertainty about the precise levels at which the interaction begins. More studies with Hg exposure at or around 2 μg/g hair mercury will help to better quantify such interaction. Furthermore, it remains unclear whether Hg and omega-3 interact by regulating the same or similar pathways with offsetting effects on hypertension or if they work individually through separate pathways, ultimately resulting in an offsetting effect. More experimental studies on that perspective will shed light on the underlying mechanism.

Selenium

The approach to examine the interaction between selenium and Hg is similar to that for omega-3 fatty acids. Significant interactions between selenium and Hg were reported in two studies at moderate-to-high Hg exposure levels, with mean hair Hg of 12 μg/g and mean blood Hg of 7.8 μg/L,

respectively (Afridi et al. 2014; Hu et al. 2017). The findings are inconclusive in populations with low Hg exposures. No interaction was observed in two studies in the US population (Downer et al. 2017; Mozaffarian et al. 2012). However, the potential offsetting effect between Hg and selenium cannot be completely ruled out for two reasons. First, Hg may not have any adverse effect at such an exposure level. Second, most of the US population has adequate selenium intake; Hg may exhibit certain adverse effects on BP in selenium-depleted populations. Another study reported a three-way interaction between omega-3 fatty acids, selenium, and Hg on hypertension in a 20-year follow-up study (Xun et al. 2011). In that study, the protective effect of omega-3 fatty acids on hypertension was most pronounced in the high selenium, low Hg group and was most diminished in the low selenium, high Hg group. This finding provides indirect evidence of an interaction between Hg and selenium in relation to hypertension (Xun et al. 2011).

Similar to the interaction between Hg and omega-3 fatty acids, more epidemiological studies with varying levels of Hg and selenium exposures are needed. These studies should aim to first confirm the presence of such an interaction and second to quantify the exact dose at which this interaction starts. More mechanism studies are needed to understand how Hg and selenium interact on various biological pathways associated with BP outcomes. It is also important to investigate whether omega-3 fatty acids and selenium interact with inorganic and organic forms of Hg similarly. Understanding this distinction could provide valuable insights into the mechanisms of their interaction and their potential impact on health outcomes.

Besides that, several unique features of selenium are worth considering for future studies. First, there are different forms of selenium compounds, and animal studies suggest that the effectiveness of each compound in reducing Hg toxicity is different (Magos et al. 1981; Yamashita et al. 2013). More human studies are needed to understand the impact of selenium intake from different sources on their health implications. Second, in populations in which fish and seafood are their primary source of selenium intake, certain indexes such as the selenium/Hg ratio were proposed to guide fish choice (Barone et al. 2021; Gochfeld and Burger 2021; Ralston et al. 2008). Third, selenium may exhibit a toxic effect on certain health outcomes at a high dose (EFSA Panel on Nutrition et al. 2023).

Mercury exposure and conditions related to hypertension

There has been a recognized pattern of hypertension co-existing with other risk factors, such as obesity, elevated blood glucose, and unfavorable blood cholesterol levels (Huang 2009). These combined conditions substantially elevate the likelihood of developing diabetes, heart disease, stroke, or all three (Mottillo et al. 2010). If the association between Hg exposure and hypertension is not coincidental, it is expected that Hg exposure would demonstrate correlations with other metabolic conditions and CVDs. The present review provides some key references from this perspective without a comprehensive literature search and quality assessment.

There is evidence suggesting that Hg levels are significantly higher among individuals with type-2 diabetes compared with those without; however, the association between Hg exposure and type-2 diabetes is not conclusive (Ghorbani Nejad et al. 2022; Guo et al. 2023; Roy et al. 2017). There is increasing evidence outlining the positive association between Hg exposure and adverse blood cholesterol profiles (Cho 2017; Farkhondeh et al. 2020; Park et al. 2016; Sohn et al. 2020; Xu et al. 2023). A systematic review and meta-analysis identified a positive association between Hg exposure and obesity (Jeon and Park 2023). Another systematic review and dose–response meta-analysis from our group revealed that chronic exposure to Hg was associated with an increased risk of all-cause mortality and fatal/nonfatal IHD (Hu et al. 2021). The risk of multiple cardiovascular endpoints starts to increase consistently at a hair Hg concentration of 2 μg/g (Hu et al. 2021).

These findings strongly suggest that the link between Hg exposure and hypertension is not coincidental. There is a growing indication that Hg exposure might serve as a notable risk factor not just for hypertension but also for other metabolic conditions, CVDs, and even mortality. However, the emerging evidence was largely from biomonitoring data from the US and Korean populations. More high-quality prospective studies from populations with different Hg exposure levels are needed to solidify these associations and draw a more robust conclusion.

Weight of evidence for causality

The plausibility of the association between Hg exposure and BP outcomes was evaluated with the Bradford Hill criteria (Fedak et al. 2015; Hill 1965). Upon comprehensive evaluation of all evidence identified in the current review, alongside previous reviews and peer-reviewed articles, hypertension, SBP, and DBP were discussed as one outcome. Criteria 1, Strength of association—the available evidence suggested a moderate-to-strong magnitude (strength) of association between Hg exposure and BP, especially at hair Hg over 2 μg/g or equivalent. Criteria 2, Consistency—the available evidence suggested the association was consistent in several ways: 1) the association observed in the same population or population with similar exposure levels were consistent, 2) the association observed from different biomarkers were

consistent, and 3) the association observed for hypertension, SBP, and DBP were consistent. Criteria 3, Specificity—Hg appeared to be involved in multiple mechanism pathways and play a role in multiple metabolic risk factors. The association between Hg exposure and BP was not specific. Criteria 4, Temporality—most epidemiological studies currently available are cross-sectional. However, there are also plenty of prospective studies suggesting a positive association between Hg exposure and BP outcomes. Criteria 5, Biological gradient and plausibility—significant dose–response relationship between Hg exposure and BP outcomes were reported. In vitro, in vivo, and animal studies provided supportive evidence on various pathways that are linked to BP outcomes. Criteria 6, Coherence—mechanistic studies provide supporting evidence to epidemiological studies. Criteria 7, Experiment —experimental evidence from animal studies is conclusive. Experimental evidence in human exposure was rare, although studies investigating Minimata disease or comparing populations living within and outside of Hg-polluted areas may be considered quasi-experiment evidence. Criteria 8, Analogy—the evidence suggesting interactions between omega-3 fatty acids, selenium, and Hg provides certain insight into the mechanism of association between Hg exposure and BP.

Conclusion

This review has presented conclusive evidence on the cause–effect of Hg exposure and hypertension in animal studies, including the mechanistic studies that provide supportive evidence on this association. Strong evidence from epidemiological studies shows that Hg exposure is associated with an increased risk of hypertension and elevated SBP/DBP with a dose–response relationship. The association between Hg exposure and BP is mixed at lower exposure levels; however, increasing evidence suggests that Hg can play a role in BP outcomes co-exposed with other metals, even at low doses. The availability of evidence is also uneven across three forms of Hg (elementary, inorganic, and organic) and different biomarkers. Based on biomarker conversion, a dose–response relationship was derived, assuming that different forms of Hg exhibit similar toxic effects on BP outcomes.

Further research to develop more robust conversion factors among different biomarkers and standardized/harmonized measures of Hg exposure will help to better understand the association between Hg and BP. For risk management purposes, a practical framework is lacking to integrate mechanism and epidemiological studies to derive a robust regulatory value on Hg's toxic effect on cardiovascular endpoints. The current evidence continues to support the proposed 2 μg/g hair Hg or equivalent as the cut-off level for public health regulation. Regulatory agencies should consider adopting this level, specifically for adult men or women older than child-bearing age.

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Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflict of interest None of the authors has a conflict of interest to declare.

Authorship X.F.H., A.L., and H.M.C. conceived the study. X.F.H. and A.L. performed the literature searches. X.F.H. and A.L. screened articles for inclusion. X.F.H., A.L., and H.M.C. wrote the first draft of the manuscript. All authors revised the manuscript and approved the final version.

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References

Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M et al (2020) Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Abhyankar LN, Jones MR, Guallar E, Navas-Acien A (2012) Arsenic exposure and hypertension: a systematic review. Environ Health Perspect 120:494–500. https://doi.org/10.1289/ehp.1103988

Afridi HI, Kazi TG, Talpur FN, Kazi A, Arain SS, Arain SA et al (2014) Interaction between essential elements selenium and zinc with cadmium and mercury in samples from hypertensive patients. Biol Trace Elem Res 160(2):185–196. https://doi.org/10.1007/s12011-014-0048-y

Ajsuvakova OP, Tinkov AA, Aschner M, Rocha JBT, Michalke B, Skalnaya MG et al (2020) Sulfhydryl groups as targets of mercury

toxicity. Coord Chem Rev 417. https://doi.org/10.1016/J.CCR.2020.213343
Ali S, Awan Z, Mumtaz S, Hafiz &, Shakir A, Ahmad F et al (2020) Cardiac toxicity of heavy metals (cadmium and mercury) and pharmacological intervention by vitamin C in rabbits. Environ Sci Pollut Res Int. https://doi.org/10.1007/s11356-020-09011-9/Published
Ally A, Buist R, Mills P, Reuhl K (1993) Effects of methylmercury and trimethyltin on cardiac, platelet, and aorta eicosanoid biosynthesis and platelet serotonin release. Pharmacol Biochem Behav 44:555–563. https://doi.org/10.1016/0091-3057(93)90166-Q
Andreoli V, Sprovieri F (2017) Genetic aspects of susceptibility to mercury toxicity: an overview. Int J Environ Res Public Health 14. https://doi.org/10.3390/ijerph14010093
Arbi S, Bester MJ, Pretorius L, Oberholzer HM (2021) Adverse cardiovascular effects of exposure to cadmium and mercury alone and in combination on the cardiac tissue and aorta of Sprague–Dawley rats. J Environ Sci Health A Tox Hazard Subst Environ Eng 56:609–624. https://doi.org/10.1080/10934529.2021.1899534
Arbi S, Oberholzer HM, Van Rooy MJ, Venter C, Bester MJ (2017) Effects of chronic exposure to mercury and cadmium alone and in combination on the coagulation system of Sprague-Dawley rats. Ultrastruct Pathol 41:275–283. https://doi.org/10.1080/01913123.2017.1327909
ATSDR (2022) Toxicological profile for mercury (Draft for Public Comment). U.S. Department of Health and Human Services, Public Health Services, Atlanta, GA
Aubrac G, Bastiansz A, Basu N (2022) Systematic review and meta-analysis of mercury exposure among populations and environments in contact with electronic waste. Int J Environ Res Public Health 19. https://doi.org/10.3390/ijerph191911843
Baiyun R, Li S, Liu B, Lu J, Lv Y, Xu J et al (2018) Luteolin-mediated PI3K/AKT/Nrf2 signaling pathway ameliorates inorganic mercury-induced cardiac injury. Ecotoxicol Environ Saf 161:655–661. https://doi.org/10.1016/J.ECOENV.2018.06.046
Ballatori N, Clarkson TW (1982) Developmental changes in the biliary excretion of methylmercury and glutathione. Science (1979) 216:61–63. https://doi.org/10.1126/science.7063871
Barone G, Storelli A, Meleleo D, Dambrosio A, Garofalo R, Busco A et al (2021) Levels of mercury, methylmercury and selenium in fish: insights into children food safety. Toxics 9:1–14. https://doi.org/10.3390/toxics9020039
Bartolome J, Whitmore WL, Slotkin TA (1984) Effects of neonatal mercuric chloride administration on growth and biochemical development of neuronal and non-neuronal tissues in the rat: comparison with methylmercury. Toxicol Lett 22:101–111. https://doi.org/10.1016/0378-4274(84)90052-3
Bastiansz A, Ewald J, Saldaña VR, Santa-Rios A, Basu N (2022) A systematic review of mercury exposures from skin-lightening products. Environ Health Perspect 130. https://doi.org/10.1289/EHP10808
Basu N, Bastiansz A, Dórea JG, Fujimura M, Horvat M, Shroff E et al (2023) Our evolved understanding of the human health risks of mercury. Ambio 52:877–896. https://doi.org/10.1007/s13280-023-01831-6
Basu N, Horvat M, Evers DC, Zastenskaya I, Weihe P, Tempowski J (2018) A state-of-the-science review of mercury biomarkers in human populations worldwide between 2000 and 2018. Environ Health Perspect 126. https://doi.org/10.1289/EHP3904
Bautista LE, Stein JH, Morgan BJ, Stanton N, Young T, Nieto FJ (2009) Association of blood and hair mercury with blood pressure and vascular reactivity. WMJ 108:250–252. https://doi.org/10.1038/nbt.3121.ChIP-nexus
Bello KAS, Wilke MCB, Simões RP, Landim-Vieira M, Langa P, Stefanon I et al (2023) Chronic exposure to mercury increases arrhythmia and mortality post-acute myocardial infarction in rats. Front Physiol 14. https://doi.org/10.3389/FPHYS.2023.1260509
Bulka CM, Persky VW, Daviglus ML, Durazo-Arvizu RA, Argos M (2019) Multiple metal exposures and metabolic syndrome: a cross-sectional analysis of the National Health and Nutrition Examination Survey 2011–2014. Environ Res 168:397–405. https://doi.org/10.1016/j.envres.2018.10.022
Carmignani M, Boscolo P, Artese L, Del Rosso G, Porcelli G, Felaco M et al (1992) Renal mechanisms in the cardiovascular effects of chronic exposure to inorganic mercury in rats. Br J Ind Med 49:226–232. https://doi.org/10.1136/OEM.49.4.226
Carmignani M, Finelli VN, Boscolo P (1983) Mechanisms in cardiovascular regulation following chronic exposure of male rats to inorganic mercury. Toxicol Appl Pharmacol 69:442–450. https://doi.org/10.1016/0041-008X(83)90267-3
Carneiro MFH, Oliveira Souza JM, Grotto D, Batista BL, de Oliveira Souza VC, Barbosa F (2014) A systematic study of the disposition and metabolism of mercury species in mice after exposure to low levels of thimerosal (ethylmercury). Environ Res 134:218–227. https://doi.org/10.1016/J.ENVRES.2014.07.009
Carretero OA, Oparil S (2000) Essential hypertension. Part I: definition and etiology. Circulation 101:329–335. https://doi.org/10.1161/01.CIR.101.3.329
Carrier G, Bouchard M, Brunet RC, Caza M (2001) A toxicokinetic model for predicting the tissue distribution and elimination of organic and inorganic mercury following exposure to methyl mercury in animals and humans. II. Application and validation of the model in humans. Toxicol Appl Pharmacol 171:50–60. https://doi.org/10.1006/taap.2000.9113
Cho YM (2017) Fish consumption, mercury exposure, and the risk of cholesterol profiles: findings from the Korea National Health and Nutrition Examination Survey 2010–2011. Environ Health Toxicol 32:e2017014. https://doi.org/10.5620/eht.e2017014
Choi AL, Weihe P, Budtz-Jorgensen E, Jorgensen PJ, Salonen JT, Tuomainen T-PP et al (2009) Methylmercury exposure and adverse cardiovascular effects in Faroese Whaling men. Environ Health Perspect 117:367–372. https://doi.org/10.1289/ehp.11608
Clarkson TW, Magos L (2006) The toxicology of mercury and its chemical compounds. Crit Rev Toxicol 36:609–662. https://doi.org/10.1080/10408440600845619
Cordeiro ER, Filetti FM, Simões MR, Vassallo DV. 2019. Mercury induces nuclear estrogen receptors to act as vasoconstrictors promoting endothelial denudation via the PI3K/Akt signaling pathway. Toxicol Appl Pharmacol 381:114710; https://doi.org/10.1016/J.TAAP.2019.114710.
Counter SA, Buchanan LH (2004) Mercury exposure in children: a review. Toxicol Appl Pharmacol 198:209–230. https://doi.org/10.1016/j.taap.2003.11.032
Da Cunha V, Souza HP, Rossoni LV, França AS, Vassallo DV (2000) Effects of mercury on the isolated perfused rat tail vascular bed are endothelium-dependent. Arch Environ Contam Toxicol 39:124–130. https://doi.org/10.1007/S002440010001/METRICS
Daneshmand R, Kurl S, Tuomainen T-P, Virtanen JK (2016) Associations of serum n-3 and n-6 PUFA and hair mercury with the risk of incident stroke in men: the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). Br J Nutr 115:1851–1859. https://doi.org/10.1017/S0007114516000982
Dantas ADO, De CTDSDS, Câmara VDM, Santos ADSE, Asmus CIRF, Vianna ADS (2022) Maternal mercury exposure and hypertensive disorders of pregnancy: a systematic review. Rev Bras De Ginecol Obstet 44:1126–1133. https://doi.org/10.1055/s-0042-1760215
Davidson PW, Myers GJ, Weiss B (2004) Mercury exposure and child development outcomes. Pediatrics 113:1023–1029
Desai G, Niu Z, Luo W, Frndak S, Shaver AL, Kordas K (2021) Low-level exposure to lead, mercury, arsenic, and cadmium, and blood

pressure among 8–17-year-old participants of the 2009–2016 National Health and Nutrition Examination Survey. Environ Res 197. https://doi.org/10.1016/j.envres.2021.111086

Downer MK, Martínez-González MA, Gea A, Stampfer M, Warnberg J, Ruiz-Canela M et al (2017) Mercury exposure and risk of cardiovascular disease: a nested case-control study in the PREDIMED (PREvention with MEDiterranean Diet) study. BMC Cardiovasc Disord 17:9. https://doi.org/10.1186/s12872-016-0435-8

Driscoll CT, Mason RP, Chan HM, Jacob DJ, Pirrone N (2013) Mercury as a global pollutant: sources, pathways, and effects. Environ Sci Technol 47:4967–4983. https://doi.org/10.1021/es305071v

EFSA Panel on Nutrition NF and FA (NDA), Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst K-I et al (2023) Scientific opinion on the tolerable upper intake level for selenium. EFSA J 21:e07704. https://doi.org/10.2903/j.efsa.2023.7704

Eom S-Y, Choi S-H, Ahn S-J, Kim D-WD-K, Kim D-WD-K, Lim J-A et al (2014) Reference levels of blood mercury and association with metabolic syndrome in Korean adults. Int Arch Occup Environ Health 87:501–513. https://doi.org/10.1007/s00420-013-0891-8

Esdaile LJ, Chalker JM (2018) The mercury problem in artisanal and small-scale gold mining. Chem A Eur J 24:6905–6916. https://doi.org/10.1002/chem.201704840

Eum KD, Lee MS, Paek D (2008) Cadmium in blood and hypertension. Sci Total Environ 407:147–153. https://doi.org/10.1016/j.scitotenv.2008.08.037

Fardin PBA, Simões RP, Schereider IRG, Almenara CCP, Simões MR, Vassallo DV (2020) Chronic mercury exposure in prehypertensive SHRs accelerates hypertension development and activates vasoprotective mechanisms by increasing NO and H_2O_2 production. Cardiovasc Toxicol 20:197–210. https://doi.org/10.1007/S12012-019-09545-6/FIGURES/6

Farkhondeh T, Afshari R, Mehrpour O, Samarghandian S (2020) Mercury and atherosclerosis: cell biology, pathophysiology, and epidemiological studies. Biol Trace Elem Res 196:27–36. https://doi.org/10.1007/s12011-019-01899-w

Farzan SF, Howe CG, Chen Y, Gilbert-Diamond D, Korrick S, Jackson BP et al (2021) Prenatal and postnatal mercury exposure and blood pressure in childhood. Environ Int 146. https://doi.org/10.1016/j.envint.2020.106201

Fedak KM, Bernal A, Capshaw ZA, Gross S (2015) Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol 12:1–9. https://doi.org/10.1186/s12982-015-0037-4

Feng W, Wang M, Li B, Liu J, Chai Z, Zhao J et al (2004) Mercury and trace element distribution in organic tissues and regional brain of fetal rat after in utero and weaning exposure to low dose of inorganic mercury. Toxicol Lett 152:223–234. https://doi.org/10.1016/j.toxlet.2004.05.001

Fillion M, Mergler D, Passos CJS, Larribe F, Lemire M, Guimarães JRD (2006) A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. Environ Health 5:29. https://doi.org/10.1186/1476-069X-5-Received

Food and Agriculture Organization (2020) The state of world fisheries and aquaculture 2020. https://www.fao.org/state-of-fisheries-aquaculture/2020/en

Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L et al (2017) Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA 317:165–182. https://doi.org/10.1001/JAMA.2016.19043

Fowler J, Tsui MTK, Chavez J, Khan S, Ahmed H, Smith L et al (2021) Methyl mercury triggers endothelial leukocyte adhesion and increases expression of cell adhesion molecules and chemokines. Exp Biol Med 246:2522–2532. https://doi.org/10.1177/15353702211033812

Fuchs FD, Whelton PK (2020) High blood pressure and cardiovascular disease. Hypertension 75(2):285–292. https://doi.org/10.1161/HYPERTENSIONAHA.119.14240. Epub 2019 Dec 23. PMID: 31865786; PMCID: PMC10243231

Fuller R, Landrigan PJ, Balakrishnan K, Bathan G, Bose-O'Reilly S, Brauer M et al (2022) Pollution and health: a progress update. Lancet Planet Health 6:e535–e547. https://doi.org/10.1016/S2542-5196(22)00090-0

Furieri LB, Galán M, Avendaño MS, García-Redondo AB, Aguado A, Martínez S et al (2011) Endothelial dysfunction of rat coronary arteries after exposure to low concentrations of mercury is dependent on reactive oxygen species. Br J Pharmacol 162:1819–1831. https://doi.org/10.1111/J.1476-5381.2011.01203.X

Gale TF (1980) Cardiac and non-cardiac malformations produced by mercury in hamsters. Bull Environ Contam Toxicol 726–732

Gallego-Viñas G, Ballester F, Llop S (2019) Chronic mercury exposure and blood pressure in children and adolescents: a systematic review. Environ Sci Pollut Res 26:2238–2252. https://doi.org/10.1007/s11356-018-3796-y

Ghizoni H, de Souza V, Straliotto MR, de Bem AF, Farina M, Hort MA (2017) Superoxide anion generation and oxidative stress in methylmercury-induced endothelial toxicity in vitro. Toxicol in Vitro 38:19–26. https://doi.org/10.1016/J.TIV.2016.10.010

Ghorbani Nejad B, Raeisi T, Janmohammadi P, Mehravar F, Zarei M, Dehghani A et al (2022) Mercury exposure and risk of type 2 diabetes: a systematic review and meta-analysis. Int J Clin Pract 2022. https://doi.org/10.1155/2022/7640227

Giles TD, Sander GE, Nossaman BD, Kadowitz PJ (2012) Impaired vasodilation in the pathogenesis of hypertension: focus on nitric oxide, endothelial-derived hyperpolarizing factors, and prostaglandins. J Clin Hyperten 14:198. https://doi.org/10.1111/J.1751-7176.2012.00606.X

Gochfeld M, Burger J (2021) Mercury interactions with selenium and sulfur and the relevance of the Se: Hg molar ratio to fish consumption advice. Environ Sci Pollut Res 28:18407–18420. https://doi.org/10.1007/s11356-021-12361-7.Mercury

Goodrich JM, Wang Y, Gillespie B, Werner R, Franzblau A, Basu N (2013) Methylmercury and elemental mercury differentially associate with blood pressure among dental professionals. Int J Hyg Environ Health 216:195–201. https://doi.org/10.1016/j.ijheh.2012.03.001

Government of Canada (2008) Human health risk assessment of mercury in fish and health benefits of fish consumption. https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/human-health-risk-assessment-mercury-fish-health-benefits-fish-consumption.html. Accessed 27 Feb 2020

Grandjean P, Murata K, Budtz-Jørgensen E, Weihe P (2004) Cardiac autonomic activity in methylmercury neurotoxicity: 14-Year follow-up of a Faroese birth cohort. J Pediatr 144:169–176. https://doi.org/10.1016/j.jpeds.2003.10.058

Gregory S, Iles-Caven Y, Taylor CM, Golding J, Hibbeln JR (2016) Are prenatal mercury levels associated with subsequent blood pressure in childhood and adolescence? The Avon prebirth cohort study. BMJ Open 6. https://doi.org/10.1136/bmjopen-2016-012425

Grotto D, De Castro MM, Barcelos GRM, Garcia SC, Barbosa F (2009) Low level and sub-chronic exposure to methylmercury induces hypertension in rats: nitric oxide depletion and oxidative damage as possible mechanisms. Arch Toxicol 83:653–662. https://doi.org/10.1007/S00204-009-0437-8/FIGURES/4

Grotto D, Valentini J, Serpeloni JM, Monteiro PAP, Latorraca EF, De Oliveira RS et al (2011) Evaluation of toxic effects of a diet containing fish contaminated with methylmercury in rats mimicking the exposure in the Amazon riverside population.

Environ Res 111:1074–1082. https://doi.org/10.1016/J.ENVRES.2011.09.013

Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gómez-Aracena J, Kark JD, Riemersma RA, Martín-Moreno JM, Kok FJ et al (2002) Mercury, fish oils, and the risk of myocardial infatction. N Engl J Med 347:1747–1754. https://doi.org/10.1056/NEJMoa020157 [pii]

Guo X, Li N, Wang H, Su W, Song Q, Liang Q et al (2022a) Combined exposure to multiple metals on cardiovascular disease in NHANES under five statistical models. Environ Res 215. https://doi.org/10.1016/j.envres.2022.114435

Guo X, Su W, Li N, Song Q, Wang H, Liang Q et al (2022b) Association of urinary or blood heavy metals and mortality from all causes, cardiovascular disease, and cancer in the general population: a systematic review and meta-analysis of cohort studies. Environ Sci Pollut Res 29:67483–67503. https://doi.org/10.1007/s11356-022-22353-w

Guo Y, Lv Y, Liu X, Wang G (2023) Association between heavy metal mercury in body fluids and tissues and diabetes mellitus: a systematic review and meta-analysis. Ann Transl Med 11:114. https://doi.org/10.21037/atm-22-6404

Ha E, Basu N, Bose-O'Reilly S, Dórea JG, McSorley E, Sakamoto M et al (2017) Current progress on understanding the impact of mercury on human health. Environ Res 152:419–433. https://doi.org/10.1016/j.envres.2016.06.042

Hagele TJ, Mazerik JN, Gregory A, Kaufman B, Magalang U, Kuppusamy ML et al (2007) Mercury activates vascular endothelial cell phospholipase D through thiols and oxidative stress. Int J Toxicol 26:57–69. https://doi.org/10.1080/10915810601120509

Harrison DG, Coffman TM, Wilcox CS (2021) Pathophysiology of hypertension: the mosaic theory and beyond. Circ Res 128:847–863. https://doi.org/10.1161/CIRCRESAHA.121.318082/ASSET/CCB9929F-2796-40B1-919B-CBA056777917/ASSETS/IMAGES/LARGE/CIRCRESAHA.121.318082.FIG03.JPG

Hazelhoff MH, Bulacio RP, Torres AM (2012) Gender related differences in kidney injury induced by mercury. Int J Mol Sci 13:10523–10536. https://doi.org/10.3390/IJMS130810523

Hill AB (1965) The environment and disease: association or causation? Proc R Soc Med 58:295–300. https://doi.org/10.1016/S0079-7421(08)60562-9

Hirayama K, Yasutake A (1986) Sex and age differences in mercury distribution and excretion in methylmercury-administered mice. J Toxicol Environ Health 18:49–60. https://doi.org/10.1080/15287398609530847

Hong D, Cho SH, Park SJ, Kim SY, Park SB (2013) Hair mercury level in smokers and its influence on blood pressure and lipid metabolism. Environ Toxicol Pharmacol 36:103–107. https://doi.org/10.1016/j.etap.2013.03.007

Houde M, Krümmel EM, Mustonen T, Brammer J, Brown TM, Chételat J et al (2022) Contributions and perspectives of indigenous peoples to the study of mercury in the Arctic. Sci Total Environ 841:156566. https://doi.org/10.1016/j.scitotenv.2022.156566

Houston MC (2011) Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. J Clin Hypertens 13:621–627. https://doi.org/10.1111/j.1751-7176.2011.00489.x

Hu XF, Eccles KM, Chan HM (2017) High selenium exposure lower the odds ratios for hypertension, stroke, and myocardial infarction associated with mercury exposure among Inuit in Canada. Environ Int 102:200–206. https://doi.org/10.1016/j.envint.2017.03.002

Hu XF, Lowe M, Chan HM (2021) Mercury exposure, cardiovascular disease, and mortality: a systematic review and dose–response meta-analysis. Environ Res 193:110538. https://doi.org/10.1016/j.envres.2020.110538

Hu XF, Singh K, Chan LHM (2018) Mercury exposure, blood pressure, and hypertension: a systematic review and dose–response meta-analysis. Environ Health Perspect 126. https://doi.org/10.1289/EHP2863/SUPPL_FILE/EHP2863.SMCONTENTS.508.PDF

Huang PL (2009) A comprehensive definition for metabolic syndrome. Dis Model Mech 2:231–237. https://doi.org/10.1242/dmm.001180

Iranmanesh M, Fatemi SJA, Golbafan MR, Dahooee BF (2013) Treatment of mercury vapor toxicity by combining deferasirox and deferiprone in rats. Biometals 26:783–788. https://doi.org/10.1007/S10534-013-9656-9

Ishihara N (2000) Excretion of methyl mercury in human feces. Arch Environ Health 55:44–47. https://doi.org/10.1080/00039890009603384

Islam MZ, Van Dao C, Shiraishi M, Miyamoto A (2016) Methylmercury affects cerebrovascular reactivity to angiotensin II and acetylcholine via Rho-kinase and nitric oxide pathways in mice. Life Sci 147:30–38. https://doi.org/10.1016/J.LFS.2016.01.033

Jeon J, Park K (2023) Mercury exposure is associated with obesity: a systematic review and meta-analysis. Korean J Commun Nutr 28:192–205

Jin X, Hidiroglou N, Lok E, Taylor M, Kapal K, Ross N et al (2012) Dietary selenium (Se) and Vitamin E (VE) supplementation modulated methylmercury-mediated changes in markers of cardiovascular diseases in rats. Cardiovasc Toxicol 12:10–24. https://doi.org/10.1007/S12012-011-9134-Y/FIGURES/12

Jindal M, Garg GR, Mediratta PK, Fahim M (2011) Protective role of melatonin in myocardial oxidative damage induced by mercury in murine model. Hum Exp Toxicol 30:1489–1500. https://doi.org/10.1177/0960327110391685/ASSET/IMAGES/LARGE/10.1177_0960327110391685-FIG2.JPEG

Joint FAO/WHO Expert Committee on Food Additives (2004) Safety evaluation of certain food additives and contaminants. Sixty-first meeting of JECFA

Jonsson F, Sandborgh-Englund G, Johanson G (1999) A compartmental model for the kinetics of mercury vapor in humans. Toxicol Appl Pharmacol 155:161–168. https://doi.org/10.1006/taap.1998.8585

Kalish BT, Rifas-Shiman SL, Wright RO, Amarasiriwardena CJ, Jayawardene I, Gillman MW et al (2014) Associations of prenatal maternal blood mercury concentrations with early and mid-childhood blood pressure: a prospective study. Environ Res 133:327–333. https://doi.org/10.1016/j.envres.2014.06.004

Kang P, Shin HY, Kim KY (2021) Association between dyslipidemia and mercury exposure in adults. Int J Environ Res Public Health 18(2):775. https://doi.org/10.3390/ijerph18020775

Karaboduk H, Uzunhisarcikli M, Kalender Y (2015) Protective effects of sodium selenite and vitamin E on mercuric chloride-induced cardiotoxicity in male rats. Arch Biol Technol 58:229–238. https://doi.org/10.1590/S1516-8913201400339

Kim JW, Kim BG, Park JW, Yi JW, Kim J Il, Hong YS (2019) A study of relationship between blood mercury concentration and hypertension in residents living in old mine fields and related factors. Ann Occup Environ Med 31. https://doi.org/10.35371/AOEM.2019.31.E6

Kobal AB, Horvat M, Prezelj M, Briški AS, Krsnik M, Dizdarevič T et al (2004) The impact of long-term past exposure to elemental mercury on antioxidative capacity and lipid peroxidation in mercury miners. J Trace Elem Med Biol 17:261–274. https://doi.org/10.1016/S0946-672X(04)80028-2

Lavoie RA, Jardine TD, Chumchal MM, Kidd KA, Campbell LM (2013) Biomagnification of mercury in aquatic food webs: a worldwide meta-analysis. Environ Sci Technol 47:13385–13394. https://doi.org/10.1021/es403103t

Leggett RW, Munro NB, Eckerman KF (2001) Proposed revision of the ICRP model for inhaled mercury vapor. Health Phys 81:450–455. https://doi.org/10.1097/00004032-200110000-00010

Lemos NB, Angeli JK, de Faria TO, Ribeiro Junior RF, Vassallo DV, Padilha AS et al (2012) Low mercury concentration produces vasoconstriction, decreases nitric oxide bioavailability and increases oxidative stress in rat conductance artery. PLoS One 7:49005. https://doi.org/10.1371/JOURNAL.PONE.0049005

Liberda EN, Tsuji LJSS, Martin ID, Ayotte P, Dewailly E, Nieboer E (2014) The complexity of hair/blood mercury concentration ratios and its implications. Environ Res 134:286–294. https://doi.org/10.1016/j.envres.2014.08.007

Lim KM, Kim S, Noh JY, Kim K, Jang WH, Bae ON et al (2010) Low-level mercury can enhance procoagulant activity of erythrocytes: a new contributing factor for mercury-related thrombotic disease. Environ Health Perspect 118:928–935. https://doi.org/10.1289/EHP.0901473

Lin H, Ascher DB, Myung Y, Lamborg CH, Hallam SJ, Gionfriddo CM et al (2021) Mercury methylation by metabolically versatile and cosmopolitan marine bacteria. ISME J 15:1810–1825. https://doi.org/10.1038/s41396-020-00889-4

Liu T, Zhang M, Guallar E, Wang G, Hong X, Wang X et al (2019) Trace minerals, heavy metals, and preeclampsia: findings from the Boston birth cohort. J Am Heart Assoc 8. https://doi.org/10.1161/JAHA.119.012436

Liu W, Yu L, Ye Z, Wang X, Qiu W, Tan Q et al (2022) Assessment for the associations of twenty-three metal(loid)s exposures with early cardiovascular damage among Chinese urban adults with five statistical methods: Insight into assessing health effect of multipollutant exposure. Chemosphere 307. https://doi.org/10.1016/j.chemosphere.2022.135969

Louopou RC, Trottier H, Arbuckle TE, Fraser WD (2020) Dental amalgams and risk of gestational hypertension in the MIREC study. Pregnancy Hypertens 21:84–89. https://doi.org/10.1016/j.preghy.2020.04.015

Ma J, Zhang H, Zheng T, Zhang W, Yang C, Yu L et al (2022) Exposure to metal mixtures and hypertensive disorders of pregnancy: a nested case-control study in China. Environ Pollut 306. https://doi.org/10.1016/j.envpol.2022.119439

Ma Y, Liang C, Wang Z, Wang X, Xie L, Tao S et al (2023) Association between prenatal metals exposure and blood pressure in 5–6 years children: a birth cohort study. Environ Res 219:114974. https://doi.org/10.1016/j.envres.2022.114974

Machado AC, Padilha AS, Wiggers GA, Siman FDM, Stefanon I, Vassallo DV (2007) Small doses of mercury increase arterial pressure reactivity to phenylephrine in rats. Environ Toxicol Pharmacol 24:92–97. https://doi.org/10.1016/J.ETAP.2007.02.005

Magos L, Peristianis GC, Clarkson TW, Brown A, Preston S, Snowden RT (1981) Comparative study of the sensitivity of male and female rats to methylmercury. Arch Toxicol 48:11–20

Marino KB, Hoover-Miller A, Conlon S, Prewitt J, O'Shea SK (2011) Quantification of total mercury in liver and heart tissue of Harbor Seals (*Phoca vitulina*) from Alaska USA. Environ Res 111:1107–1115. https://doi.org/10.1016/J.ENVRES.2011.07.010

Marumoto M, Sakamoto M, Marumoto K, Tsuruta S, Komohara Y (2020) Mercury and selenium localization in the cerebrum, cerebellum, liver, and kidney of a minamata disease case. Acta Histochem Cytochem 53:147. https://doi.org/10.1267/AHC.20-00009

Mazerik JN, Hagele T, Sherwani S, Ciapala V, Butler S, Kuppusamy ML et al (2007) Phospholipase A 2 activation regulates cytotoxicity of methylmercury in vascular endothelial cells. Int J Toxicol 26:553–569. https://doi.org/10.1080/10915810701707759

Mazerik JN, Mikkilineni H, Kuppusamy VA, Steinhour E, Peltz A, Marsh CB et al (2008) Mercury activates phospholipase A2 and induces formation of arachidonic acid metabolites in vascular endothelial cells. 17:541–557. https://doi.org/10.1080/15376510701380505

Mordukhovich I, Wright RO, Hu H, Amarasiriwardena C, Baccarelli A, Litonjua A et al (2012) Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the Normative Aging Study. Environ Health Perspect 120:98–104. https://doi.org/10.1289/ehp.1002805

Moreira EL, De oliveira J, Dutra MF, Santos DB, Gonçalves CA, Goldfeder EM et al (2012) Does methylmercury-induced hypercholesterolemia play a causal role in its neurotoxicity and cardiovascular disease? Toxicolog Sci 130:373. https://doi.org/10.1093/TOXSCI/KFS252

Mori N, Yasutake A, Hirayama K (2007) Comparative study of activities in reactive oxygen species production/defense system in mitochondria of rat brain and liver, and their susceptibility to methylmercury toxicity. Arch Toxicol 81:769–776. https://doi.org/10.1007/S00204-007-0209-2

Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P et al (2010) The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol 56:1113–1132. https://doi.org/10.1016/j.jacc.2010.05.034

Mozaffarian D, Shi P, Morris JS, Grandjean P, Siscovick DS, Spiegelman D et al (2012) Mercury exposure and risk of hypertension in US men and women in 2 prospective cohorts. Hypertension 60:645–652. https://doi.org/10.1161/HYPERTENSIONAHA.112.196154

Nakamura I, Hosokawa K, Tamura H, Miura T (1977) Reduced mercury excretion with feces in germfree mice after oral administration of methyl mercury chloride. Bull Environ Contam Toxicol 17:528–533. https://doi.org/10.1007/BF01685974

National Research Council (US) (2000) Toxicological effects of methylmercury. https://doi.org/10.17226/9899

Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ (2007) Lead exposure and cardiovascular disease—a systematic review. Environ Health Perspect 115:472–482. https://doi.org/10.1289/ehp.9785

Nguyen HD, Kim MS (2022) The effects of a mixture of cadmium, lead, and mercury on metabolic syndrome and its components, as well as cognitive impairment: genes, MicroRNAs, transcription factors, and sponge relationships: the effects of a mixture of cadmium, lead, and mercury on metabolic syndrome and its components, as well as cognitive impairment: genes, MicroRNAs, transcription factors, and sponge relationships. Biol Trace Elem Res. https://doi.org/10.1007/s12011-022-03343-y

Ni M, Li X, Yin Z, Jiang H, Sidoryk-Wegrzynowicz M, Milatovic D et al (2010) Methylmercury induces acute oxidative stress, altering Nrf2 protein level in primary microglial cells. Toxicol Sci 116:590–603. https://doi.org/10.1093/TOXSCI/KFQ126

Nishimura A, Shimoda K, Tanaka T, Toyama T, Nishiyama K, Shinkai Y et al (2019) Depolysulfidation of Drp1 induced by low-dose methylmercury exposure increases cardiac vulnerability to hemodynamic overload. Sci Signal 12:1920. https://doi.org/10.1126/SCISIGNAL.AAW1920/SUPPL_FILE/AAW1920_SM.PDF

Nunes FL da S, Lima SCVC, Lyra C de O, Marchioni DM, Pedrosa LFC, Barbosa Junior F et al (2022) The impact of essential and toxic elements on cardiometabolic risk factors in adults and older people. J Trace Elem Med Biol 72. https://doi.org/10.1016/j.jtemb.2022.126991

Ohno T, Sakamoto M, Kurosawa T, Dakeishi M, Iwata T, Murata K (2007) Total mercury levels in hair, toenail, and urine among women free from occupational exposure and their relations to renal tubular function. Environ Res 103:191–197. https://doi.org/10.1016/j.envres.2006.06.009

Olczyk K, Kucharz EJ, Glowacki A (1994) Influence of chronic mercury poisoning upon the connective tissue in rats. I. Effect of

mercuric chloride on glycosaminoglycan levels in tissues, serum and urine. Cent Eur J Public Health 2:77–79
Oliveira EM, Vassallo DV (1992) Effects of mercury on the contractility of isolated rat cardiac muscle. Braz J Med Biol Res 25:1037–1040
Oliveira EM, Vassallo DV, Sarkis JJF, Mill JG (1994) Mercury effects on the contractile activity of isolated heart muscle. Toxicol Appl Pharmacol 128:86–91. https://doi.org/10.1006/TAAP.1994.1183
Omanwar S, Saidullah B, Ravi K, Fahim M (2013) Modulation of vasodilator response via the nitric oxide pathway after acute methyl mercury chloride exposure in rats. Biomed Res Int. https://doi.org/10.1155/2013/530603
Otsuka T, Takada H, Nishiyama Y, Kodani E, Saiki Y, Kato K et al (2016) Dyslipidemia and the risk of developing hypertension in a working-age male population. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 5. https://doi.org/10.1161/JAHA.115.003053
Ottolini M, Hong K, Sonkusare SK (2019) Calcium signals that determine vascular resistance. Wiley Interdiscip Rev Syst Biol Med 11:e1448. https://doi.org/10.1002/WSBM.1448
Pamphlett R (2021) The prevalence of inorganic mercury in human cells increases during aging but decreases in the very old. Scient Rep 11:1–8. https://doi.org/10.1038/s41598-021-96359-8
Park JD, Zheng W (2012) Human exposure and health effects of inorganic and elemental mercury. J Prev Med Public Health 45:344–352. https://doi.org/10.3961/jpmph.2012.45.6.344
Park S, Choi N-K (2016) Associations of blood heavy metal levels with intraocular pressure. Ann Epidemiol 26:546–550. https://doi.org/10.1016/j.annepidem.2016.07.002
Park SJ, Yeum KJ, Choi B, Kim YS, Joo NS (2016) Positive correlation of serum HDL cholesterol with blood mercury concentration in metabolic syndrome Korean men (analysis of KNANES 2008–2010, 2013). J Endocrinol Invest 39:1031–1038. https://doi.org/10.1007/s40618-016-0459-z
Park SK, Lee S, Basu N, Franzblau A (2013) Associations of blood and urinary mercury with hypertension in U.S. adults: the NHANES 2003–2006. Environ Res 123:25–32. https://doi.org/10.1016/j.envres.2013.02.003
Pedersen EB, Jørgensen ME, Pedersen MB, Siggaard C, Sørensen TB, Mulvad G et al (2005) Relationship between mercury in blood and 24-h ambulatory blood pressure in greenlanders and Danes. Am J Hypertens 18:612–618. https://doi.org/10.1016/j.amjhyper.2004.11.022
Peltz A, Sherwani SI, Kotha SR, Mazerik JN, O'Connor Butler ES, Kuppusamy ML et al (2009) Calcium and calmodulin regulate mercury-induced phospholipase D activation in vascular endothelial cells. Int J Toxicol 28:190–206. https://doi.org/10.1177/1091581809338077/ASSET/IMAGES/LARGE/10.1177_1091581809338077-FIG2.JPEG
Pirkle CM, Muckle G, Lemire M (2016) Managing mercury exposure in northern Canadian communities. Can Med Assoc J 188:1015–1023. https://doi.org/10.1503/cmaj.151138
Pope Q, Rand MD (2021) Variation in methylmercury metabolism and elimination in humans: physiological pharmacokinetic modeling highlights the role of gut biotransformation, skeletal muscle, and hair. Toxicol Sci 180:26–37. https://doi.org/10.1093/TOXSCI/KFAA192
Poursafa P, Ataee E, Motlagh ME, Ardalan G, Tajadini MH, Yazdi M et al (2014) Association of serum lead and mercury level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study. Environ Sci Pollut Res 21:13496–13502. https://doi.org/10.1007/s11356-014-3238-4
Poznyak AV., Sadykhov NK, Kartuesov AG, Borisov EE, Melnichenko AA, Grechko AV et al (2022) Hypertension as a risk factor for atherosclerosis: cardiovascular risk assessment. Front Cardiovasc Med 9. https://doi.org/10.3389/FCVM.2022.959285
Qiu Q, Huang Y, Zhang B, Huang D, Chen X, Fan Z et al (2022) Noninvasive dual-modality photoacoustic-ultrasonic imaging to detect mammalian embryo abnormalities after prenatal exposure to methylmercury chloride (MMC): a mouse study. Environ Health Perspect 130. https://doi.org/10.1289/EHP8907
Qu Y, Lv Y, Ji S, Ding L, Zhao F, Zhu Y et al (2022) Effect of exposures to mixtures of lead and various metals on hypertension, pre-hypertension, and blood pressure: a cross-sectional study from the China National Human Biomonitoring. Environ Pollut 299. https://doi.org/10.1016/j.envpol.2022.118864
Rajaee M, Sánchez BN, Renne EP, Basu N (2015) An investigation of organic and inorganic mercury exposure and blood pressure in a small-scale gold mining community in Ghana. Int J Environ Res Public Health 12:10020–10038. https://doi.org/10.3390/ijerph120810020
Rakic A, Milovanovich ID, Trbovich AM, Stefanović S, Nikolić D, Janković S et al (2020) Trace elements in different tissues in aging rats. J Trace Elem Med Biol 62:126604. https://doi.org/10.1016/J.JTEMB.2020.126604
Ralston NVC, Ralston CR, Blackwell JL, Raymond LJ (2008) Dietary and tissue selenium in relation to methylmercury toxicity. Neurotoxicology 29:802–811. https://doi.org/10.1016/j.neuro.2008.07.007
Rizzetti DA, da Silva TM, Escobar AG, Piagette J, Peçanha FM, Vassallo DV et al (2018) Mercury-induced vascular dysfunction is mediated by angiotensin II AT-1 receptor upregulation. Environ Res 162:287–296. https://doi.org/10.1016/J.ENVRES.2018.01.026
Rizzetti DA, Martín Á, Corrales P, Fernandez F, Simões MR, Peçanha FM et al (2017a) Egg white-derived peptides prevent cardiovascular disorders induced by mercury in rats: role of angiotensin-converting enzyme (ACE) and NADPH oxidase. Toxicol Lett 281:158–174. https://doi.org/10.1016/j.toxlet.2017.10.001
Rizzetti DA, Torres JGD, Escobar AG, da Silva TM, Moraes PZ, Hernanz R et al (2017b) The cessation of the long-term exposure to low doses of mercury ameliorates the increase in systolic blood pressure and vascular damage in rats. Environ Res 155:182–192. https://doi.org/10.1016/J.ENVRES.2017.02.022
Rodrigues JL, Serpeloni JM, Batista BL, Souza SS, Barbosa F (2010) Identification and distribution of mercury species in rat tissues following administration of thimerosal or methylmercury. Arch Toxicol 84:891–896. https://doi.org/10.1007/S00204-010-0538-4
Roman HA, Walsh TL, Coull BA, Dewailly É, Guallar E, Hattis D et al (2011) Evaluation of the cardiovascular effects of methylmercury exposures: current evidence supports development of a dose–response function for regulatory benefits analysis. Environ Health Perspect 119:607–614. https://doi.org/10.1289/ehp.1003012
Ronconi-Krüger N, Pinheiro J, Simioni C, Nazari EM (2022) Methylmercury toxicity during heart development: a combined analysis of morphological and functional parameters. Cardiovasc Toxicol 22:962–970. https://doi.org/10.1007/S12012-022-09772-4/FIGURES/5
Roque CR, Sampaio LR, Ito MN, Pinto D V., Caminha JSR, Nunes PIG et al (2021) Methylmercury chronic exposure affects the expression of DNA single-strand break repair genes, induces oxidative stress, and chromosomal abnormalities in young dyslipidemic APOE knockout mice. Toxicology 464:152992. https://doi.org/10.1016/J.TOX.2021.152992
Rotter I, Kosik-Bogacka D, Dołęgowska B, Safranow K, Lubkowska A, Laszczyńska M (2015) Relationship between the concentrations of heavy metals and bioelements in aging men with metabolic syndrome. Int J Environ Res Public Health 12:3944–3961. https://doi.org/10.3390/ijerph120403944

Rowland IR (1988) Interactions of the gut microflora and the host in toxicology. Toxicol Pathol 16

Roy C, Tremblay P-Y, Ayotte P (2017) Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature. Environ Res 156:747–760. https://doi.org/10.1016/j.envres.2017.04.038

Rutkiewicz J, Basu N (2013) Methylmercury egg injections: part 1—tissue distribution of mercury in the avian embryo and hatchling. Ecotoxicol Environ Saf 93:68–76. https://doi.org/10.1016/J.ECOENV.2013.04.008

Schereider IRG, Vassallo DV, Simões MR (2021) Chronic mercury exposure induces oxidative stress in female rats by endothelial nitric oxide synthase uncoupling and cyclooxygenase-2 activation, without affecting estrogen receptor function. Basic Clin Pharmacol Toxicol 129:470–485. https://doi.org/10.1111/BCPT.13655

Shinetova L, Akparova A, Bekeyeva S (2020) The relationship between cytokine profile and hypertension among the mercury-exposed residents of Temirtau Region in Central Kazakhstan. Iran J Public Health 49

Shiue I (2014) Higher urinary heavy metal, arsenic, and phthalate concentrations in people with high blood pressure: US NHANES, 2009–2010. Blood Press 23:363–369. https://doi.org/10.3109/08037051.2014.925228

Siblerud RL (1990) The relationship between mercury from dental amalgam and the cardiovascular system. Sci Total Environ 99:23–35

Silva JL, Leocádio PCL, Reis JM, Campos GP, Capettini LSA, Foureaux G et al (2020) Oral methylmercury intoxication aggravates cardiovascular risk factors and accelerates atherosclerosis lesion development in ApoE knockout and C57BL/6 mice. Toxicol Res 37:311–321. https://doi.org/10.1007/S43188-020-00066-X

Simões MR, Azevedo BF, Fiorim J, Freire DD, Covre EP, Vassallo DV et al (2016) Chronic mercury exposure impairs the sympathovagal control of the rat heart. Clin Exp Pharmacol Physiol 43:1038–1045. https://doi.org/10.1111/1440-1681.12624

Simões RP, Fardin PBA, Simões MR, Vassallo DV, Padilha AS (2020) Long-term mercury exposure accelerates the development of hypertension in prehypertensive spontaneously hypertensive rats inducing endothelial dysfunction: the role of oxidative stress and cyclooxygenase-2. Biol Trace Elem Res 196:565–578. https://doi.org/10.1007/S12011-019-01952-8/FIGURES/7

Singh K, Blechinger S, Pelletier L, Karthikeyan S, St-Amand A, Liberda EN et al (2023) Characterizing variability in total mercury hair:blood ratio in the general Canadian population. Environ Res 224:115491. https://doi.org/10.1016/j.envres.2023.115491

Slotkin TA, Pachman S, Bartolome J, Kavlock RJ (1985) Biochemical and functional alterations in renal and cardiac development resulting from neonatal methylmercury treatment. Toxicology 231

Smith KM, Barraj LM, Kantor M, Sahyoun NR (2009) Relationship between fish intake, n-3 fatty acids, mercury and risk markers of CHD (National Health and Nutrition Examination Survey 1999–2002). Public Health Nutr 12:1261–1269. https://doi.org/10.1017/S1368980008003844

Sohn SH, Heo HC, Jo S, Park C, Sakong J (2020) The association between mercury concentrations and lipid profiles in the Korean National Environmental Health Survey (KoNEHS) cycle 3. Ann Occup Environ Med 32:e19. https://doi.org/10.35371/aoem.2020.32.e19

Sørensen N, Murata K, Budtz-Jørgensen E, Weihe P, Grandjean P, Sorensen N et al (1999) Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age. Epidemiology 10:370–375. https://doi.org/10.1097/00001648-199907000-00006

Su JY, Chen W, Seattle WW (1979) The effect of methylmercury on isolated cardiac tissues. Am J Pathol 95:753

Sukhera J (2022) Narrative Reviews: Flexible, Rigorous, and Practical. J Grad Med Educ 14(4):414–417. https://doi.org/10.4300/JGME-D-22-00480.1

Sundseth K, Pacyna JM, Pacyna EG, Pirrone N, Thorne RJ (2017) Global sources and pathways of mercury in the context of human health. Int J Environ Res Public Health 14. https://doi.org/10.3390/ijerph14010105

Suzuki T, Yonemoto J, Satoh H, Naganuma A, Imura N, Kigawa T (1984) Normal organic and inorganic mercury levels in the human feto-placental system. J Appl Toxicol 4:249–252. https://doi.org/10.1002/JAT.2550040507/FORMAT/PDF

Tamashiro H, Arakaki M, Akagi H, Hirayama K, Smolensky MH (1986) Methylmercury toxicity in spontaneously hypertensive rats (SHR). Bull Environ Contam Toxicol 668–673

Tang J, Zhu Q, Xu Y, Zhou Y, Zhu L, Jin L et al (2022) Total arsenic, dimethylarsinic acid, lead, cadmium, total mercury, methylmercury and hypertension among Asian populations in the United States: NHANES 2011–2018. Ecotoxicol Environ Saf 241. https://doi.org/10.1016/j.ecoenv.2022.113776

Thomas D, Fisher H, Sumler M, Mushak P, Hall LL (1987) Sexual differences in the excretion of organic and inorganic mercury by methyl mercury-treated rats. Environ Res

Thurston SW, Bovet P, Myers GJ, Davidson PW, Georger LA, Shamlaye C et al (2007) Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood? Neurotoxicology 28:924–930

Toyama T, Sumi D, Shinkai Y, Yasutake A, Taguchi K, Tong KI et al (2007) Cytoprotective role of Nrf2/Keap1 system in methylmercury toxicity. Biochem Biophys Res Commun 363:645–650. https://doi.org/10.1016/J.BBRC.2007.09.017

Truong J, Mailloux RJ, Chan HM (2015) Impact of methylmercury exposure on mitochondrial energetics in AC16 and H9C2 cardiomyocytes. Toxicol in Vitro 29:953–961. https://doi.org/10.1016/J.TIV.2015.03.016

Uchikawa T, Kanno T, Maruyama I, Mori N, Yasutake A, Ishii Y et al (2016) Demethylation of methylmercury and the enhanced production of formaldehyde in mouse liver. J Toxicol Sci 41:479–487. https://doi.org/10.2131/JTS.41.479

Valera B, Dewailly É, Poirier P (2013) Association between methylmercury and cardiovascular risk factors in a native population of Quebec (Canada): a retrospective evaluation. Environ Res 120:102–108. https://doi.org/10.1016/j.envres.2012.08.002

Valera B, Dewailly É, Poirier P (2009) Environmental mercury exposure and blood pressure among Nunavik inuit adults. Hypertension 54:981–986. https://doi.org/10.1161/HYPERTENSIONAHA.109.135046

Valera B, Dewailly E, Poirier P (2011a) Impact of mercury exposure on blood pressure and cardiac autonomic activity among Cree adults (James Bay, Quebec, Canada). Environ Res 111:1265–1270. https://doi.org/10.1016/j.envres.2011.09.001

Valera B, Dewailly E, Poirier P, Counil E, Suhas E (2011b) Influence of mercury exposure on blood pressure, resting heart rate and heart rate variability in French Polynesians: a cross-sectional study. Environ Health 10:99. https://doi.org/10.1186/1476-069X-10-99

Valera B, Muckle G, Poirier P, Jacobson SW, Jacobson JL, Dewailly E (2012) Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. Neurotoxicology 33:1067–1074

Van Dao C, Islam MZ, Sudo K, Shiraishi M, Miyamoto A (2016) MARCKS is involved in methylmercury-induced decrease in cell viability and nitric oxide production in EA.hy926 cells. J Vet Med Sci 78:1569. https://doi.org/10.1292/JVMS.16-0249

Vassallo DV, Simões MR, Giuberti K, Azevedo BF, Junior RFR, Salaices M et al (2019) Effects of chronic exposure to mercury

on angiotensin-converting enzyme activity and oxidative stress in normotensive and hypertensive rats. Arq Bras Cardiol 112:374. https://doi.org/10.5935/ABC.20180271

Vassallo DV, Moreira CM, Oliveira EM, Bertollo DM, Veloso TC (1999) Effects of mercury on the isolated heart muscle are prevented by DTT and cysteine 1

Verschuuren HG, Kroes R, Den Tonkeaar EM, Berkvens JM, Helleman PW, Rauws AG et al (1976a) Toxicity of methylmercury chloride in rats II. Reproduction study. Toxicology 6:97–106. https://doi.org/10.1016/0300-483X(76)90011-1

Verschuuren HG, Kroes R, Den Tonkelaar EM, Berkvens JM, Helleman PW, Rauws AG et al (1976b) Toxicity of methylmercury chloride in rats I. Short-term study. Toxicology 6:85–96. https://doi.org/10.1016/0300-483X(76)90010-X

Virtanen JK, Laukkanen JA, Mursu J, Voutilainen S, Tuomainen T-P (2012a) Serum long-chain n-3 polyunsaturated fatty acids, mercury, and risk of sudden cardiac death in men: a prospective population-based study. PLoS One 7:e41046. https://doi.org/10.1371/journal.pone.0041046

Virtanen JK, Nyantika AN, Kauhanen J, Voutilainen S, Tuomainen T-P (2012b) Serum long-chain n-3 polyunsaturated fatty acids, methylmercury and blood pressure in an older population. Hypertens Res 35:1000–1004. https://doi.org/10.1038/hr.2012.80

Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen T-P, Korhonen MJ et al (2005) Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arterioscler Thromb Vasc Biol 25:228–233. https://doi.org/10.1161/01.ATV.0000150040.20950.61

Vupputuri S, Longnecker MP, Daniels JL, Guo X, Sandler DP (2005) Blood mercury level and blood pressure among US women: Results from the National Health and Nutrition Examination Survey 1999–2000. Environ Res 97:195–200. https://doi.org/10.1016/j.envres.2004.05.001

Wakita Y (1987) Hypertension induced by methyl mercury in rats. Toxicol Appl Pharmacol 89:144–147. https://doi.org/10.1016/0041-008X(87)90185-2

Wang L, Jiang H, Yin Z, Aschner M, Cai J (2009) Methylmercury toxicity and Nrf2-dependent detoxification in astrocytes. Toxicol Sci 107:135–143. https://doi.org/10.1093/TOXSCI/KFN201

Wang X, Karvonen-Gutierrez CA, Herman WH, Mukherjee B, Harlow SD, Park SK (2021) Urinary heavy metals and longitudinal changes in blood pressure in midlife women: the Study of Women's Health across the nation. Hypertension 78:543–551. https://doi.org/10.1161/HYPERTENSIONAHA.121.17295

Wang X, Wang W-X (2015) Physiologically based pharmacokinetic model for inorganic and methylmercury in a marine fish. Environ Sci Technol 49:10173–10181. https://doi.org/10.1021/acs.est.5b02301

Wang Y, Wang K, Han T, Zhang P, Chen X, Wu W et al (2020) Exposure to multiple metals and prevalence for preeclampsia in Taiyuan, China. Environ Int 145:106098. https://doi.org/10.1016/j.envint.2020.106098

Weis P, Weis JS (1977) Methylmercury teratogenesis in the killifish, *Fundulus heteroclitus*. Teratology 16:317–325. https://doi.org/10.1002/TERA.1420160311

Wennberg M, Stromberg U, Bergdahl IA, Jansson J-HH, Kauhanen J, Norberg M et al (2012) Myocardial infarction in relation to mercury and fatty acids from fish: a risk-benefit analysis based on pooled Finnish and Swedish data in men. Am J Clin Nutr 96:706–713. https://doi.org/10.3945/ajcn.111.033795

Wiggers GA, Furieri LB, Briones AM, Avendaño MS, Peçanha FM, Vassallo DV et al (2016) Cerebrovascular endothelial dysfunction induced by mercury exposure at low concentrations. Neurotoxicology 53:282–289. https://doi.org/10.1016/J.NEURO.2016.02.010

Wiggers GA, Peçanha FM, Briones AM, Pérez-Girón JV., Miguel M, Vassallo DV et al (2008) Low mercury concentrations cause oxidative stress and endothelial dysfunction in conductance and resistance arteries. Am J Physiol Heart Circ Physiol 295. https://doi.org/10.1152/AJPHEART.00430.2008

Wildemann TM, Mirhosseini N, Siciliano SD, Weber LP (2015a) Cardiovascular responses to lead are biphasic, while methylmercury, but not inorganic mercury, monotonically increases blood pressure in rats. Toxicology 328:1–11. https://doi.org/10.1016/J.TOX.2014.11.009

Wildemann TM, Siciliano SD, Weber LP (2016) The mechanisms associated with the development of hypertension after exposure to lead, mercury species or their mixtures differs with the metal and the mixture ratio. Toxicology 339:1–8. https://doi.org/10.1016/J.TOX.2015.11.004

Wildemann TM, Weber LP, Siciliano SD (2015b) Combined exposure to lead, inorganic mercury and methylmercury shows deviation from additivity for cardiovascular toxicity in rats. J Appl Toxicol 35:918–926. https://doi.org/10.1002/JAT.3092

World Health Organization (2020) 10 chemicals of public health concern. https://www.who.int/news-room/photo-story/photo-story-detail/10-chemicals-of-public-health-concern

Xu J, Engel LS, Rhoden J, Jackson WB, Kwok RK, Sandler DP (2021) The association between blood metals and hypertension in the GuLF study. Environ Res 202. https://doi.org/10.1016/j.envres.2021.111734

Xu W, Park SK, Gruninger SE, Charles S, Franzblau A, Basu N et al (2023) Associations between mercury exposure with blood pressure and lipid levels: a cross-sectional study of dental professionals. Environ Res 220:115229. https://doi.org/10.1016/j.envres.2023.115229

Xun P, Hou N, Daviglus M, Liu K, Morris JS, Shikany JM et al (2011) Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med 270:175–186. https://doi.org/10.1111/j.1365-2796.2010.02338.x

Yaginuma-Sakurai K, Murata K, Iwai-Shimada M, Nakai K, Kurokawa N, Tatsuta N et al (2012) Hair-to-blood ratio and biological half-life of mercury: experimental study of methylmercury exposure through fish consumption in humans. J Toxicol Sci 37:123–130. https://doi.org/10.2131/jts.37.123

Yamashita M, Yamashita Y, Ando T, Wakamiya J, Akiba S (2013) Identification and determination of selenoneine, 2-Selenyl-Nα, Nα, Nα-Trimethyl-L-Histidine, as the major organic selenium in blood cells in a fish-eating population on remote Japanese Islands. Biol Trace Elem Res 156:36–44. https://doi.org/10.1007/s12011-013-9846-x

Yang X, Feng L, Zhang Y, Hu H, Shi Y, Liang S et al (2018) Co-exposure of silica nanoparticles and methylmercury induced cardiac toxicity in vitro and in vivo. Sci Total Environ 631–632:811–821. https://doi.org/10.1016/J.SCITOTENV.2018.03.107

Yao B, Lu X, Xu L, Wang Y, Qu H, Zhou H (2020) Relationship between low-level lead, cadmium and mercury exposures and blood pressure in children and adolescents aged 8–17 years: an exposure-response analysis of NHANES 2007–2016. Sci Total Environ 726. https://doi.org/10.1016/j.scitotenv.2020.138446

Yao X, Steven Xu X, Yang Y, Zhu Z, Zhu Z, Tao F et al (2021) Stratification of population in NHANES 2009–2014 based on exposure pattern of lead, cadmium, mercury, and arsenic and their association with cardiovascular, renal and respiratory outcomes. Environ Int 149. https://doi.org/10.1016/j.envint.2021.106410

Yasutake A, Hirayama K, Inoue M (1989) Mechanism of urinary excretion of methylmercury in mice. Arch Toxicol 63:479–483

Yorifuji T, Tsuda T, Kashima S, Takao S, Harada M (2010) Long-term exposure to methylmercury and its effects on hypertension in Minamata. Environ Res 110:40–46. https://doi.org/10.1016/j.envres.2009.10.011

Yoshida M, Yamamura Y, Satoh H (1986) Distribution of mercury in guinea pig offspring after in utero exposure to mercury vapor during late gestation. Arch Toxicol 58:225–228. https://doi.org/10.1007/BF00297110

Zhang H, Tan X, Yang D, Lu J, Liu B, Baiyun R et al (2017) Dietary luteolin attenuates chronic liver injury induced by mercuric chloride via the Nrf2/NF-κB/P53 signaling pathway in rats. Oncotarget 8:40982. https://doi.org/10.18632/ONCOTARGET.17334

Zhang J, Lu S, Wang H, Zheng Q (2013) Protective role of Aralia elata polysaccharide on mercury(II)-induced cardiovascular oxidative injury in rats. Int J Biol Macromol 59:301–304. https://doi.org/10.1016/J.IJBIOMAC.2013.04.047

Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA et al (2021) Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. The Lancet 398:957–980. https://doi.org/10.1016/S0140-6736(21)01330-1