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Perinatal Metal and Metalloid Exposures and Offspring Cardiovascular Health Risk

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Abstract

Purpose of Review—Toxic metal exposures have been associated with cardiovascular disease in adults and growing evidence suggests metal exposures also adversely affect cardiovascular phenotypes in childhood and adolescence. However, to our knowledge, the influence of perinatal metals exposure, particularly metal mixtures, in relation to cardiovascular-related outcomes have not been comprehensively reviewed.

Recent findings—We summarized 17 contemporary studies (2017–2021) that investigated the impact of perinatal metal exposures on measures of cardiovascular health in children. Accumulating evidence supports a potential adverse impact of perinatal Pb exposure on BP in children. Fewer recent studies have focused on perinatal As, Hg, and Cd; thus, the cardiovascular impacts of these metals are less clear. Studies of metal mixtures demonstrate that interactions between metals may be complex and have identified numerous understudied elements and essential metals, including Mo, Co, Ni, Se, Zn, and Mn, which may influence cardiovascular risk.

Summary—A key question that remains is whether perinatal metals exposure influences cardiovascular health into adulthood. Comparisons across studies remain challenging due to several factors, including differences in the timing of exposure/outcome assessments and exposure biomarkers, as well as variability in exposure levels and mixture compositions across populations. Future studies longitudinally investigating trajectories of cardiovascular outcomes could help determine the influence of perinatal metals exposure on long-term effects of clinical relevance in

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later life and whether interventions, which reduce metals exposures during this key developmental window, could alter disease development.

Keywords

Cardiovascular; Metals; Mixtures; Children's health; Perinatal; Childhood

Introduction

Cardiovascular diseases (CVD) contribute to a third of all deaths and are the leading cause of premature death worldwide [1]. The importance of environmental agents in the development of CVD has become increasingly clear [2, 3]. Toxic metals and metalloids (referred to as metals hereafter) are of particular concern, as exposures are widespread, and a growing body of evidence has linked metal exposures to CVD and related outcomes [4]. Lead (Pb) and cadmium (Cd) have been particularly well-studied; there is now sufficient evidence that exposure to these metals reflect important risk factors for CVD [5]. Two systematic reviews recently concluded that arsenic (As), copper (Cu), and mercury (Hg) may also contribute to the development of CVD [3, 4]. Given the high prevalence of metal exposures, even small effects on cardiovascular health may translate to a substantial increase in the number of CVD cases.

Although CVD typically manifests in adulthood, atherosclerosis begins early in life [6]. Potentially relevant mechanisms for CVD [7–9] including increased oxidative stress, inflammation, and endothelial dysfunction contribute to pathogenesis and may initiate and accelerate atherosclerosis in early childhood and across the life course [10–12]. Identifying modifiable environmental factors in childhood that influence subsequent cardiovascular risk is therefore key for designing public health interventions that reduce the lifelong burden of CVD.

The perinatal period can be especially influential for CVD development later in life, as it reflects an important developmental window during which environmental stressors may interfere with fetal and early postnatal programming [13]. Fundamental developmental events impacted during this period include nephrogenesis, cardiomyocyte proliferation and maturation, coronary vascularization, the development and maturation of the immune system, and the development of the hypothalamic–pituitary–adrenal axis [13]. Disruption of these processes can have long-lasting and potentially irreversible impacts on cardiovascular health [13]. A growing number of studies have reported that toxic metal exposures during the prenatal and early postnatal periods adversely affect cardiovascular phenotypes in childhood and adolescence. To our knowledge, perinatal metals exposure in relation to cardiovascular health related outcomes in children have not been comprehensively reviewed; therefore, we sought to compile the recent literature and update information previously included as part of reviews of developmental toxicity of metals [2, 4, 14–18]. Our objective was to synthesize the primary epidemiologic literature describing the influence of contemporary exposures to metals during the perinatal period on early-life cardiovascular risk factors in order to identify critical knowledge gaps and to inform prevention efforts and health policy.

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Methods

Our scoping review focused on peer-reviewed, original articles published between January 1, 2017, and December 1, 2021, encompassing approximately the past 5 years. We searched the PubMed (MEDLINE) and Web of Science databases to identify studies that explored the relationship between perinatal metals exposure and offspring cardiovascular health risk. Only publications written in English were reviewed.

Articles were eligible if they had examined perinatal metals exposure, defined as occurring and/or measured during the period of a normal pregnancy. We included studies with exposure measurements taken during pregnancy, as well as studies that collected samples at birth or in the postpartum period that reflect pre-/perinatal exposures (e.g. metals measured in maternal toenail samples collected within ~ six months postpartum) [19, 20]. Our search terms allowed for the inclusion of studies that performed metals exposure assessment specifically in the pre-conception period, but none was identified. We excluded studies that only examined metals exposure beyond the perinatal period, such as during childhood, adolescence, or adulthood.

We focused our review on epidemiological studies, excluding case reports, ecologic studies, reviews and meta-analyses, or animal and/or experimental studies, but citing these studies where applicable, e.g., to provide additional background, fill in gaps in our knowledge, i.e., mechanistic understanding, or supporting evidence for potential future research directions. We did not limit our search by age or timing of outcome assessment, as we were interested to learn whether any recent studies had been conducted to explore perinatal metals exposure in relation to later life outcomes related to cardiovascular health. We anticipated that children and adolescents would be the primary focus of this review on perinatal exposures and that we might not identify longer-term studies of clinical CVD endpoints that typically manifest later in adulthood. Therefore, we focused our search broadly on cardiovascular risk factors that would be measurable in younger populations, including blood pressure (BP), blood lipids, measures of cardiovascular function such as echocardiogram, heart rate variability, endothelial function, cardiovascular-related ultrasound measures (e.g. carotid intima media thickness), and biomarkers previously associated with cardiovascular health, including biospecimen measures of endothelial function, inflammation, and oxidative stress. A list of our search terms and numbers of articles retrieved with each search are included as supplemental material (Table S1).

Three reviewers simultaneously identified articles from our search (172 from PubMed and 845 from Web of Science from the time period of January 1, 2017 to December 1, 2021). The abstract and title of each article were reviewed and where there was doubt about their inclusion, the full text was reviewed. Initial review of each article for fit within the inclusion criteria was based primarily on whether (1) it was a human study, (2) the exposure was to a metal or metal mixture during the perinatal period, (3) the outcome was assessed in perinatally exposed offspring (with outcomes measured anytime from infancy through late adolescence), and (4) the outcome was of a cardiometabolic nature. Papers investigating metals exposures in relation to medical treatments (e.g. chemotherapy) were not included in those reviewed. Any disagreement among the reviewers was resolved by

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discussion with a senior investigator. The following information was recorded in tables from each selected study, including author, publication year, title, name and location of the study, sample size, study population, year at study baseline, exposure assessment method, metal concentration(s), outcomes, covariates, and key findings. As a scoping review, quality assessment of the retrieved articles was not conducted. The details of reviewed articles were provided in two tables, with Table 1 providing details of studies of individual or co-exposures to metals and Table 2 detailing the metal mixtures studies, solely due to the need to provide additional details related to differences in statistical methodology used to analyze mixtures.

Results

Between 2017 and 2021, seventeen unique studies were published from nine cohorts on single, dual or multiple metal exposures in the perinatal period and their relationship to cardiovascular risk factors in children (Tables 1 and 2). Over half of the published studies ($n = 9$) were conducted in North America from three US cohorts ($n = 5$) and two cohorts in Mexico ($n = 4$). The remaining eight studies were conducted in various cohorts located in Europe ($n = 4$) and Asia ($n = 4$). Study sample size ranged from 176 to 1277 mother–child pairs.

Nine studies reported findings on a single metal exposure: As ($n = 2$), Cd ($n = 1$), Pb ($n = 3$), or Hg ($n = 3$) (Table 1). Of the remaining seven studies, two reported findings on co-exposures and five reported on mixtures. In the mixture studies, the most frequently measured metals included Pb (assessed in all 5 studies), followed by As and Cd (4 studies) and cobalt (Co), Cu, manganese (Mn), and selenium (Se) (3 studies) (Table 2). The most commonly used mixture analysis method was Bayesian kernel machine regression (BKMR; $n = 3$). One study used Least Absolute Shrinkage and Selection Operator (LASSO) in addition to BKMR [21••] and another used deletion-substitution-addition (DSA) [22••].

Metal concentrations were determined most frequently in biomarkers, including blood ($n = 8$), urine ($n = 6$), and toenail samples ($n = 2$) (Tables 1, 2, S2). Two European consortium studies used either maternal blood samples obtained in pregnancy or infant cord blood samples as an indicator of prenatal metals exposures [22••, 23•]. A third study investigated cord blood Pb levels at birth, in addition to prenatal maternal blood samples [24•], while another used both cord blood total Hg levels in addition to current child blood samples [25•] We did not identify any studies that measured placental metals in relation to our outcomes of interest. One study utilized filter-based samples of particulate matter (PM2.5) components, which were linked to individuals using maternal residential address (Table 2) [21••]. The most investigated outcomes of interest included BP ($n = 13$), lipid levels ($n = 6$), and inflammatory markers ($n = 4$) (Tables 1 & 2).

Arsenic

In recent years, mounting evidence has supported a role for As exposure in CVD mortality and morbidity, but the majority of studies have focused on highly exposed adult populations [26, 27] While relatively few studies have been prospectively designed to examine the effects of perinatal As exposure on cardiovascular health, those that have suggest that

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As may influence early cardiovascular risk factors, such as BP and vascular changes, as described below. Some of the earliest evidence of a possible link between in utero As exposure and CVD came out of a set of autopsy case reports from young children who lived in Antofogasta, Chile, a region that experienced a period of high-level As contamination of the public water supply from 1958 to 1970 [28, 29]. These As-exposed children all exhibited vascular lesions, and death from acute myocardial infarction was recorded in two cases. Further ecological work from this region found that young adult men who were born during the period of highest As contamination had nearly three times the rate of acute mortality from myocardial infarction compared to the general population of Chile [30]. Prior studies of children exposed to relatively high levels of As in utero and early in life from Mexico and Bangladesh have provided additional evidence linking As exposure to elevated BP, cardiac hypertrophy, carotid intima media thickness and plasma asymmetric dimethylarginine, a marker of oxidative stress [31–33].

In the past 5 years, we identified three studies that have explored the association specifically between perinatal As exposure and measures and/or biomarkers related to cardiovascular health [34, 35]. One study of 500 mother–child pairs in the US-based New Hampshire Birth Cohort Study (NHBCS) observed positive associations between maternal prenatal urinary As and infant plasma markers, intercellular adhesion molecule (ICAM1) and vascular adhesion molecule (VCAM1), which have been associated with inflammation and endothelial dysfunction in adult populations (Table 1) [34, 36]. Furthermore, maternal levels of VCAM1 appeared to mediate the association between prenatal As and infant cord ICAM1 levels, suggesting that As may, at least in part, alter these infant markers via maternally regulated mechanisms [34]. A study of pregnant women in the US-based Navajo Birth Cohort also support a potential role for As in maternal inflammatory regulation, as authors observed an association between maternal As exposure and elevated maternal levels of oxidative stress marker urinary 8-isoprostaglandin F2a during pregnancy [37]. Since biomarkers were not assessed in offspring, the potential influence of As on children's oxidative stress could not be determined. A second study, also conducted in the NHBCS, explored co-exposure to Pb and As at two perinatal timepoints, periconceptional/early prenatal and mid-pregnancy, in relation to child BP around age 5 years (Table 1). While associations were null for As and BP, early prenatal Pb levels were related to child BP and these results are further described below [35].

More recently, Chen et al. investigated three exposure windows (in utero/early childhood, mid-childhood, current/adolescence) in relation to BP among Bangladeshi adolescents [38•]. Investigators reported that a doubling of in utero/early childhood As exposure, defined as maternal urinary As measured from one year prior to birth until age 5, was associated with a 0.7 mmHg (95% CI: 0.5, 1.4) greater SBP at ages 14–17 years [38•]. Current As exposure, measured in urine at the time of assessment, was also associated with greater SBP. While one limitation of this study is that in utero As exposure cannot be differentiated from early childhood exposure, interestingly, childhood exposure from ages 5–12 was not associated with changes in BP in adolescence, highlighting the potential importance in utero/early life, as well as current, exposures. Another study, also conducted in Bangladeshi adolescents but did not meet our inclusion criteria, observed that compared to those who drank from wells with lower As levels (≤ 50 μg/L), individuals who reported drinking exclusively from water

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sources with high levels of As (> 50 μg/L) had poorer endothelial function, an important cardiovascular risk factor [39•]. Overall, while some evidence among children exposed to high levels of As points to possible early life impacts on cardiovascular risk factors, much less is understood about the influence of lower levels of perinatal As exposure on child cardiovascular risk and potential consequences for later life health.

Lead

Epidemiological studies have consistently supported a role for Pb in CVD among adults over the past several decades. Summary evidence presented in a recent systematic review and meta-analysis of 37 studies reported that Pb exposure was associated with increased risks of CVD, coronary heart disease, and stroke [4, 5]. Despite the accumulating evidence among adults, exploration of the influence of early life Pb on cardiovascular health has remained somewhat limited. Two studies conducted prior to our search criteria time period, one from Mexico City, MX and another from rural New York, US, both reported associations between prenatal Pb exposure and elevated BP in later childhood [40, 41]. However, a third study that also preceded our inclusion period from Bangladesh did not find an association between prenatal Pb exposure and child BP, although an association with kidney volume was identified, which could potentially impact later life renal and cardiovascular health [42].

We identified five contemporary studies in children that examined associations between Pb exposure and cardiovascular health measures, such as BP and lipid profiles. Three of these studies, based in Mexico City within the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) and Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) cohorts, measured prenatal Pb levels in maternal blood samples [24•, 43•, 44]. Within PROGRESS, Sanders et al. examined the joint effect of gestational age at birth and prenatal Pb exposure on BP at 4 to 6 years of age in 565 children (Table 1) [43•]. Compared to children born to women with blood Pb levels < 2.5 μg/dL, children born to women with blood Pb≥ 2.5 μg/dL had 1.6 mmHg higher systolic BP (SBP) per each week reduction in gestational age [43•]. A positive association also was observed for Pb and SBP among children born > 37 weeks, but the magnitude of the association was smaller, suggesting that while Pb exposure may adversely influence BP in children, this association may be more pronounced in those born prematurely.

In a study of 323 5–6-year-old children enrolled in the NHBCS, Farzan et al. examined child BP in relation to perinatal co-exposure to Pb and As at two timepoints, during the periconceptional/early prenatal period and in mid-pregnancy, based on maternal toenail samples collected at ~ 24–28 weeks gestation and ~ 6 weeks postpartum (Table 1) [35]. In co-exposure models where toenail Pb and As were modeled jointly, maternal early prenatal toenail Pb was associated with increases in child SBP (β: 0.58 mmHg, 95% CI: 0.05, 1.11), whereas prenatal As was not [35]. No apparent associations were observed for Pb or As measured in toenails collected at 6 weeks postpartum. Stronger associations between prenatal Pb and SBP were observed among boys, compared to girls. These results suggest the potential sensitivity of the early prenatal window for Pb exposure, particularly for boys, compared to girls and to exposures later in pregnancy.

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Recent literature suggests that the association of Pb and some cardiovascular risk predictors may also differ in children compared to adults. In a study by Liu et al. of 369 children enrolled in the ELEMENT cohort, researchers observed significantly lower total cholesterol and low-density lipoprotein cholesterol (LDL-c) levels at ages 10–18 years old for offspring of mothers with prenatal blood Pb levels greater or equal to 5 ;g/dL, compared to offspring of mothers with blood Pb < 5 ;g/dL (Table 1) [44]. These associations were limited only to boys, with no associations observed among girls. These findings were inconsistent with prior studies of adults and adolescents that reported positive associations between Pb and lipid levels [45–48]. The authors hypothesized that such early prenatal Pb exposure could lead to reductions in total cholesterol and LDL-c via impaired cholesterol regulation and oxidative stress. In a later study, PROGRESS investigators explored associations of perinatal and childhood Pb exposure with multiple markers of metabolic syndrome, including lipid levels and BP, in 601 mother-child dyads (Table 1) [24•]. Similar to the findings of Liu et al., higher prenatal blood Pb was associated with significantly lower levels of child triglycerides (TG), and lower diastolic BP (DBP) [24•]. While these findings are inconsistent with prior findings among adults, they are consistent with findings from the ELEMENT cohort study and suggest that Pb exposure may have differential effects on cardiovascular and metabolic health measures in children compared to adults. However, it is worth noting that similar associations between Pb and lipids were not reported in another PROGRESS cohort study by Kupsco et al. which examined prenatal metal mixtures in relation to a panel of cardiometabolic outcomes (Table 2) [49••].

Overall, these recent studies indicate that perinatal Pb exposure may differentially influence CVD-related risk factors in children. Perinatal Pb exposure was associated with elevated child BP in two of the four studies that examined it, consistent with what has been observed in adult populations, but lower DBP in the most recent PROGRESS study. Pb also was unexpectedly associated with lower blood lipid levels in children, warranting further investigation of these associations in other study populations, as well as changes in BP over time to investigate whether such effects may persist into adulthood.

Cadmium

Cadmium has been strongly associated with cardiovascular health effects in adults, but few studies have investigated whether perinatal exposure to this toxic metal influences cardiovascular risk factors in children [5, 50, 51]. To our knowledge, only two studies, one from Greece and another of As-Cd co-exposures in Bangladesh, investigated perinatal Cd exposure in relation to cardiovascular-related biomarkers or health outcomes in recent years [52]. In the Rhea cohort, Chatzi and colleagues examined the association of maternal urinary Cd, measured ~ 13 weeks of gestation and a panel of cardiometabolic measures in 515 children at age 4, including BP, lipids, and biomarkers leptin and C-reactive protein (Table 1). Prenatal Cd exposure was not associated with any of the cardiometabolic measures in this analysis [52]. These results are consistent with two earlier cross-sectional studies in Bangladesh and Thailand of similarly aged children, which found no association of Cd exposure with BP, but potential adverse impacts on kidney function [53, 54]. Conversely, in a contemporary study of children from the MiniMAT trial in Bangladesh, Ahktar et al. found that both prenatal and childhood Cd exposure were positively associated with

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greater SBP and DBP, and prenatal Cd exposure was also related to reduced high-density lipoprotein (HDL) (Table 1). Interestingly, this study accounted for As co-exposure, which was not associated with any changes in BP. As described below, mixtures analyses found some evidence that Cd alone may be related to altered BP [55••], while others found that Cd may interact with other metals to influence children's cardiovascular health outcomes [56•], indicating that co-exposures and context may play an important role, particularly when examining Cd (Table 2).

Given the strong epidemiological evidence supporting a role for Cd in cardiovascular morbidity and mortality in adults [5, 50, 51], it is somewhat surprising that few studies have investigated this relationship in children. However, it is possible Cd exposures in early life may set the stage for later life health. This hypothesis is supported by two recent experimental studies in mice, which both reported similar findings indicating that maternal in utero Cd exposure induces cardiovascular changes and metabolic syndrome limited to adult female offspring and corresponding changes in the transcription of genes related to CVD, oxidative stress and cellular energy balance [57, 58]. While there is little epidemiological evidence of whether these relationships exist in humans, together these experimental studies provide compelling evidence to support a potential role for prenatal Cd exposure in programming of delayed cardiometabolic health effects in adulthood [57, 58].

Mercury

Hg is a widespread contaminant of concern and some limited evidence has suggested potential cardiovascular effects in adults, including cardiovascular mortality, acute myocardial infarction, coronary heart disease, carotid atherosclerosis and elevated BP [59–64]. A recent meta-analysis reported associations between chronic Hg exposure and multiple fatal and non-fatal cardiovascular outcomes in adults; they found that heterogeneity was largely due to differences in exposure levels [3]. Similarly, a handful of studies over the past two decades published prior to our review period examined early life Hg exposure to measures of cardiovascular health in childhood, but findings have been largely inconsistent. Two studies in fish-consuming populations, one conducted in the Seychelles which used maternal hair samples as a biomarker of methyl-Hg exposure and another in the Faroe Islands that measured methyl-Hg in cord blood, observed positive associations between prenatal methyl-Hg levels and higher BP in childhood [65, 66]. However, two large prospective studies, one from the Avon Longitudinal Study of Parents and Children (ALSPAC) and another from the US-based Project Viva study, examined maternal blood Hg levels during pregnancy with childhood BP and found inconsistent or no associations [67, 68]. Others have observed positive associations between Hg and other cardiovascular risk factors, including children's heart rate variability, but no associations with BP [69–71].

Within the last 5 years, three studies have further investigated the influence of perinatal Hg exposure on offspring cardiovascular health [23•, 72•]. In a study of 395 children enrolled in the NHBCS, researchers explored Hg exposure during the prenatal period and at multiple time points in childhood in relation to BP at 5–6 years of age (Table 1) [72•]. Neither early prenatal nor mid-gestation Hg exposure, as measured by maternal toenail levels, were associated with child BP. However, both child toenail Hg at age 3 and urine Hg at age 5–6

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were each associated with higher DBP and mean arterial pressure in children, suggesting that while perinatal Hg exposure may not influence child BP, early to mid-childhood may be a sensitive window [72•]. A second study from the European HELIX Project investigated the influence of maternal fish consumption and perinatal Hg levels in maternal blood and infant cord blood samples on a suite of cardiometabolic measures in 805 children ages 6–12 years (Table 1) [23•]. Maternal fish consumption during pregnancy was positively correlated with Hg blood levels. Children born to mothers with medium to high fish consumption had significantly higher HDL cholesterol levels compared to those born to mothers with lower fish intakes. However, neither fish consumption nor Hg biomarker levels were associated with child BP or triglycerides. In a third study of 604 children originally enrolled in a birth cohort study in Hong Kong Hg was linked to heart rate variability (Table 1). Prenatal methyl-Hg, measures in cord blood samples was associated with decreased heart rate variability, as indicated by several parameters, but current blood Hg in children was not associated with any of these measurements, suggesting that prenatal exposure is of importance for cardiac autonomic function.

Given inconsistencies across studies, it is difficult to draw conclusions about the potential role of perinatal Hg in child cardiovascular health. Further exploration of dose-related effects and potential windows of vulnerability over pregnancy and early childhood may shed light on some of the differences in the current literature. Additional investigation into exposure biomarker differences across studies may also be helpful, however, the majority of studies utilized blood or hair/toenail samples, which primarily reflect methyl-Hg levels [73]. The potential nutritional benefits of fish consumption, as well as correlated intake of other seafood, also must be considered against the increased risk of Hg exposure with increased fish intake when investigating adverse cardiovascular health effects. It is also possible that unmeasured/residual confounding from fish consumption could in part explain some of the discrepancies observed between studies.

Metal Mixtures

Humans are exposed to numerous environmental chemicals simultaneously, but previous studies investigating metal impacts on cardiovascular risk have mainly applied single-chemical approaches [74, 75]. Recognizing this research gap, the number of studies evaluating the cardiovascular impact of metal mixtures exposure has increased in recent years. We identified five studies that focused on perinatal metal mixtures exposure and their association with cardiovascular risk factors in childhood (Table 2) [21••, 22••, 49••, 55••, 56•]. Zanobetti et al. evaluated the association of maternal exposure to airborne pollutants (including particle mass with diameter < 2.5 ;m [PM2.5], black carbon [BC], aluminum [Al], silicon [Si], potassium [K], calcium [Ca], titanium [Ti], iron [Fe], magnesium [Mg], sulfur [S], As, Cu, zinc [Zn], bromine [Br], Pb, vanadium [V], nickel [Ni], sodium [Na], and chlorine [Cl]) with BP at a mean age of 30 h among 1,311 mother-infant pairs in a Boston-area pregnancy cohort [21••]. The adaptive LASSO selected S, Ni, Zn, and Cl as important elements for SBP, and Ni, Zn, S, Si, As, Cu, and Pb for DBP. Findings from BKMR were similar to the LASSO results, identifying Ni and Zn as the most influential mixture components for BP. The other US-based study by Zhang et al. examined how in utero exposure to multiple metals (Pb, Hg, Cd, Se, and Mn), measured in maternal blood samples

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between 24 and 72 h after delivery as a proxy for third trimester exposure, was associated with SBP and DBP between 3 and 15 years of age among 1,194 mother–child dyads in an urban, low-income, minority birth cohort [56•]. Using BKMR, no joint association was observed. However, both hierarchical variable selection procedure in BKMR and single metal analysis found that two essential elements (Se and Mn) to be inversely associated with SBP than heavy metals [56•]. Potential interactions were also reported between Mn and Cd in relation to childhood BP; a stronger inverse association was identified between Mn and child SBP at higher levels of Cd.

Two studies have evaluated the impact of in utero exposure to metal mixtures on BP at 4 years of age or above. Howe et al. analyzed data from 176 mother–child pairs from the Rhea study in Greece [55••] and employed Bayesian Varying Coefficient Kernel Machine Regression and BKMR to determine the relationship between maternal exposure to 8 metals (Mg, Co, Se, molybdenum [Mo], As, Cd, antimony [Sb], and Pb), measured in urine, and BP trajectories and elevated BP at age 11, respectively. At age 4, maternal exposure to Mo and Co during pregnancy were associated with a J-shaped increase in SBP and DBP, and Cd associated with lower DBP. An interaction between Mo and Pb was also detected for BP. Furthermore, prenatal exposure to Co and Mo were found to be associated with lower per-year increases in BP from ages 4 to 11, while Mg was associated with higher per-year increases in BP. At age 11, prenatal Mo and Pb were associated with J-shaped elevated BP, suggesting that maternal exposure to Mo or Pb within the mixture was most consistently associated with childhood BP. The study by Kupsco et al. in PROGRESS cohort study participants ($N = 609$) in Mexico reported inverse joint association between maternal exposure to a mixture of 11 metals (As, Cd, Co, chromium [Cr], cesium [Cs], Cu, Mn, Pb, Sb, Se, and Zn) during pregnancy and SBP at 4 to 6 years of age in the BKMR analysis [49••].

Warembourg et al. utilized an exposome approach, which considers all the exposures to which an individual is subjected in a given time period. This analysis included a mixture of prenatal and postnatal exposures, including a panel of metals, in addition to outdoor and indoor exposures, chemical contaminants and water disinfection by-products [22••] Pooling data from 1,277 children from 6 longitudinal European birth cohorts, the authors investigated associations between multiple prenatal ($n = 89$) and postnatal ($n = 128$) environmental exposures (including As, Cd, Co, Cs, Cu, Hg, Mn, Mo, Pb, and thallium [Tl]) and BP among children aged 6 to 11 years [22••]. To examine the joint impact of these exposures on childhood BP, they conducted exposome-wide association study (ExWAS) analyses and using a DSA algorithm, which were performed separately for prenatal and postnatal exposures. While Co measured during childhood was associated with higher DBP, none of the metals measured prenatally was identified as influential factors for child BP.

Of these, only 1 study by Kupsco et al. assessed how prenatal exposure to a metal mixture (As, Cd, Co, Cr, Cs, Cu, Mn, Pb, Sb, Se, and Zn) was associated with CVD risk factors other than BP, such as TG, non-HDL cholesterol, leptin, and adiponectin using BKMR in a subset of the PROGRESS birth cohort ($N = 411$) [49••]. While in utero exposure to the metal mixture was jointly associated with higher non-HDL cholesterol and adiponectin levels in children, an inverse joint relationship was shown for the leptin concentration. In single metal

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analyses, higher Se was associated with lower TG, and higher Sb and As were associated with lower leptin. No interactions were found among the metals. Overall, these studies suggest that prenatal exposure to metal mixtures influence on CVD risk factors, mainly BP, among the offspring. However, results for specific metals were inconsistent possibly due to differing metal concentrations (see metal concentrations, Supplemental Table S2), diverse metal combinations within each mixture, and differences in when the outcome was assessed.

Discussion

It is becoming clear that perinatal exposure to metals is associated with adverse effects on child cardiovascular health and development, yet the implications for long term health remain to be fully examined. Growing evidence, including the highlighted studies from the last 5 years, suggests that both individually and as mixtures, toxic metals may have adverse impacts on BP, lipids, and other cardiovascular risk factors beginning in childhood. Given these associations of metals with early-life cardiovascular risk factors, longer term effects are anticipated, though not yet well delineated in the literature. In this review, we summarized 16 contemporary studies which investigated the impact of perinatal metal exposures on measures of cardiovascular health in children. Accumulating evidence supports a potential adverse impact of perinatal Pb exposure on BP in children, consistent with prior findings in adults [5], while Pb's role in lipid homeostasis among children requires further investigation. For As, numerous previous studies suggest possible early life impacts on cardiovascular risk factors among children exposed to high As concentrations, but less is known for populations exposed to lower concentrations. As fewer studies have focused on Hg and Cd, the potential cardiovascular impacts of these metals are currently less clear. Recent studies have also failed to clarify whether the perinatal period is a particularly sensitive window for Hg exposure, although many of the existing studies observed a relationship between perinatal and/or childhood Hg exposures and children's BP, as well as heart rate variability. While only one study has reported associations between Cd and cardiovascular measures in childhood, emerging data indicate that perinatal Cd may also have delayed cardiometabolic effects, emphasizing the importance of long-term follow up studies to capture outcomes with longer latency periods. Lastly, studies of perinatal metal mixtures have revealed previously overlooked elements, such as Mo, Co, and Ni, which may impact child BP and essential metals, like Se, Zn, and Mn, which may also play a role in later cardiovascular risk. While few elements were commonly identified in relation to BP across these mixture analyses, together these studies clearly demonstrate that interactions between metals may be complex and dose-dependent.

While all the recent studies we reviewed were prospective, due to the nature of our question, few studies longitudinally investigated cardiovascular trajectories in childhood or the longer-term impacts of perinatal metals exposures across the lifecourse. A key question that remains is whether the observed associations of perinatal metals exposure with measures of cardiovascular health in childhood will persist into adulthood and have long-term effects of clinical relevance in later life. Indeed, there is evidence to indicate that subclinical measures of children's cardiovascular health, including BP, lipids, and carotid intima media thickness, may inform later cardiovascular risk [7–9, 76–85]. However, more information is needed to better predict who may be at greater risk over time and understand whether interventions

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to reduce exposures in childhood could slow or reverse disease development. Translational work in this area will be critical to guiding epidemiological studies by providing mechanistic insights, identifying metals-disrupted pathways and thus improving our ability to identify susceptible populations and potentially intervene prior to adverse health consequences.

It is also important to consider the timing of exposure assessment in pregnancy, as particular periods of development may be more sensitive to lower levels of metals. Future studies should consider collecting biospecimens across gestation to explore whether there may be periods of heightened susceptibility, given that cardiovascular health could be impacted at various points in pregnancy, from early prenatal epigenetic programming and organogenesis to the later gestational period during which establishment of fetal hormonal signaling pathways occurs [86, 87]. It is possible that differences in timing of assessment and biomarker of exposure could explain in part some differences across studies and susceptibility among children versus adults should be further explored. Future studies which incorporate placental metal concentrations will also be important for determining if the placenta's ability to act as a partial barrier to certain metals (e.g., Cd) may protect the developing fetus from downstream effects on cardiometabolic health [88].

A limitation of the current review is that somewhat few studies have been published with relatively current levels of exposure and, while the trends observed are suggestive, direct comparison across studies is difficult, given the different biomarkers and exposure levels for each of the metals that were explored. A further complication is that among mixtures studies, mixture compositions are highly variable across populations, as levels of metals will vary by study environment, context, exposure biomarker, and timing of exposure assessment, making comparability across studies a challenge. Various substrates may reflect short- or long-term exposures, distinct metal species, and overall exposures to metals more or less accurately. Furthermore, individual species of a metal may represent disparate sources of exposure. Primary routes of exposure can differ between metals and for a given metal, among populations. Additionally, some relationships between metals are likely non-linear and interactions between metals can become complex, particularly as one begins to investigate the combined effects of essential nutrients and toxic elements on a particular health effect. Furthermore, while the majority of the reviewed studies accounted for other established sources of metal exposures, such as maternal smoking or secondhand smoke exposure fish/seafood consumption, it is possible that differences in how these variables were measured or included in the analysis may account for some variability across studies. Inclusion of additional sources of exposure (e.g. water intake, additional dietary, or environmental sources) should be considered in future studies when possible. Lastly, renal function was not measured in most studies, which could influence excretion of metals and may be related to some cardiovascular outcomes, such as blood pressure.

Conclusions

CVD remains a critical public health issue, as its prevalence has doubled over the last three decades [89]. Potential interventions to protect public health are more crucial than ever and insights into modifiable environmental factors, like metals exposures, could have positive effects on this troubling trend. Pregnancy, in particular, may be a critical opportunity

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for intervention, as women may be more receptive to lifestyle and/or dietary changes that could help protect the long-term health of their child [90, 91]. Although awareness of the dangers of metals exposures has grown, exposures to toxic elements remain widespread via food, water, and air [92, 93]. As growing evidence of the health effects of metals exposures continues to emerge in both adults and children, a deeper understanding of the potential long-term health effects from perinatal exposures is essential to establishing regulatory guidelines and improving cardiovascular health outcomes for decades to come.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of the included studies of individual metal exposures or co-exposure models

Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
Arsenic										
Farzan et al., 2017; Maternal and infant inflammatory markers in relation to prenatal arsenic exposure in a US pregnancy cohort	New Hampshire, USA	563 mothers; 500 paired infants	Mean maternal age at enrollment: 31.2 years	New Hampshire BIrth Cohort Study; ongoing recruitment since January 2009	Prospective cohort	Arsenic [As] levels measured in maternal urine samples at gestational weeks (GW) 24–28	Mean (SD) Maternal urinary As (μg/L): 5.78 (13.34)	Maternal and infant Inflammation levels measured by plasma and cord blood samples markers: MCP1, TNFalpha, ICAM1, VCAM1	Enrollment age, education, maternal smoking and/or second hand smoke exposure during pregnancy, urinary creatinine, and batch assignment	Maternal arsenic exposure during pregnancy was positively associated with infant cord blood levels of ICAM and VCAM. A dose response relationship was found between maternal urinary As and maternal VCAM. Maternal VCAM and ICAM mediated the relationship between arsenic and infant VCAM and ICAM
Chen et al., 2019; Early life and adolescent arsenic exposure from drinking water and blood pressure in adolescence	Araihazar, Bangladesh	726 adolescents	Mean age at child assessment: 14.75 years	Health Effects of Arsenic Longitudinal Study (HEALS)	Prospective cohort	Arsenic [As] levels repeatedly measured in maternal urine from 1 year prior to birth (in utero) to < 5 years; in maternal urine from 5 to 12 years; in child urine at time of recruitment 14–17 years	Mean (SD) maternal urine As from 1 year prior to birth (in utero) to < 5 years (μg/g creatinine): 264.5 (247.5) Mean (SD) maternal urine As from 5 to 12 years (μg/g creatinine): 235.6 (234.2) Mean (SD) child urine As at 14–17 years (μg/g creatinine): 158.4 (207.1)	Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in adolescents 14–17 years of age	Sex, age at time of assessment, BMI	Every doubling of urinary As at time of assessment (current exposure) and maternal urinary As (in utero/ early childhood) was positively associated with a difference of 0.7 mmHg (95% CI: 0.1, 1.3) and 0.7 mmHg (95% CI: 0.05, 1.4) in SBP, respectively. Associations were stronger in adolescents with

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
										a BMI above the median than those below the median. No associations were observed for DBP. BKMR identified current urinary As as a significant contributor to SBP and DBP independent of other concurrent blood levels of Cd, Pb, Mn, and Se
Stratakis et al., 2020; Association of Fish Consumption and Mercury Exposure During Pregnancy With Metabolic Health and Inflammatory Biomarkers in Children	5 European countries (France, Greece, Norway, Spain, and the UK)	805 mother–child pairs	Mean maternal age at study inclusion or delivery: 31.3 years; Mean child age 8.4 years; 91.2% of sample was of White race/ethnicity	HELIX Project (Consortium of 5 European cohorts: UK (BIB cohort), France (EDEN cohort), Spain (INMA cohort), Norway (MoBa cohort), Greece (Rhea cohort)); Enrollment between 2003 and 2009, studies conducted between 2003and 2016	Prospective cohort	Prenatal Hg levels measured in either maternal whole blood (mid-pregnancy for MoBa & RHEA cohorts; late pregnancy for BiB cohort or in infant cord blood samples (INMA cohort)). Estimated Hg exposure also was assessed by reported fish intake during pregnancy (FFQ categorized as low (< 1x/week), medium (1–3x/week), and high (> 3x/week))	Median (IQR) Maternal Hg or infant cord:2.5 μg/L (1.5–4.2)	Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in children ages 6–12 years. Child levels of high-density lipoprotein (HDL) cholesterol and triglyceride levels were assessed in serum	Maternal age, pre-pregnancy BMI, parity, maternal/parental educational level, and child's race/ethnicity. Effect modification by maternal educational level, gestational diabetes, and child sex	Maternal mercury concentrations and fish intake during pregnancy were positively correlated (Spearman r = 0.2, no *p*-value given). Children with medium and high maternal fish intake had significantly higher HDL cholesterol levels than children with low maternal fish intake. No significant association was found between medium or high maternal fish intake and child SBP, DBP, or triglyceride levels

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
Farzan et al., 2021; Prenatal and postnatal mercury exposure and blood pressure in childhood	New Hampshire, US	395 children; *n* = 301 maternal prenatal (GW 24—28) and/or *n* = 322 postpartum (6 weeks) toenail measurements	Mean maternal age at enrollment: 30.9 years;. Mean child age at time of assessment: 5.5 years	New Hampshire Birth Cohort Study; ongoing recruitment since January 2009	Prospective cohort	Mercury [Hg] levels measured in maternal toenail clippings collected at gestational week (GW) 24–28 and 6 weeks postpartum. Children's Hg levels were measured in toenail clippings at 3 years of age and in urine samples at 5–6 years of age	Mean (SD) Child 3-year toenail Hg: 0.055 μg/g (0.087); Mean (SD) Child 5–6 year urine Hg: 0.071 μg/L (0.119); Mean (SD) Maternal GW 24–28 toenail Hg: 0.129 μg/g (0.139) Maternal 6 week postpartum toenail Hg: 0.128 μg/g (0.157)	Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in children 5–6 years of age	Child age, sex, height, weight, birth weight, gestational age and maternal smoking during pregnancy and educational attainment. Additional adjustment for urine specific gravity was included in models with urine biomarkers only	Higher child mercury exposure was associated with higher DBP (toenail β: 0.53 mmHg; 95% CI: 0.02, 1.07, p = 0.06 urine β: 0.48 mmHg; 95% CI: 0.10, 0.86, p = 0.01) and higher MAP (toenail β: 0.67 mmHg; 95% CI: 0.002, 1.33, p = 0.049 urine β: 0.55 mmHg; 95%CI: 0.10, 1.01, p = 0.02). When stratified by sex, stronger associations were observed in males, but did not reach statistical significance
Chan et al., 2021; Prenatal methylmercury exposure is associated with decreased heart rate variability in children	Hong Kong, China	604 children, enrolled as part of prior birth cohort study	Mean maternal age at enrollment: Not reported; Mean (SD) child age at time of assessment: 8.1 (0.9) years	Hong Kong Birth Cohort, enrolled between July 2000–December 2001 at Prince of Wales Hospital	Prospective cohort	Cord blood and current whole blood total Hg concentration were used as biomarkers of prenatal and recent MeHg exposure. Recent child fish consumption was measured by FFQ (estimate kg/ month)	Mean (SD) infant cord blood Hg (nmol/L): 50.12 (23.9); current mean (SD) whole blood Hg (nmol/L): 15.94 (9.94)	Heart rate variability (HRV), resting heart rate (RHR) and blood pressure in children 7–8 years of age	Child sex, age, body mass index, gestational age at birth, maternal smoking and alcohol consumption during pregnancy, and maternal hypertension during pregnancy. Additional adjustment for recent fish intake was included as a sensitivity analysis	Prenatal MeHg exposure was associated with multiple measures of decreased HRV. Recent blood Hg showed no association with any outcomes Adjustment of recent fish consumption further increased the significance and magnitude of the adverse associations of MeHg
Lead										

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
Sanders et al., 2018; "Prenatal lead exposure modifies the effect of shorter gestation on increased blood pressure in children"	Mexico City, Mexico	565 mother–child pairs	Mean (SD) maternal age: 27.6(5.6) years; mean (SD) child age at time of assessment: 4.8(0.6) years	PROGRESS; enrolled between 2007 and 2011	Prospective cohort	Lead [Pb] levels measured in maternal blood at 2nd trimester visit	Mean (SD) Maternal Pb (βg/dL): 3.7 (2.7)	Systolic and diastolic blood pressure of child (avg. 2 measurements) between 4 and 6 years of age	Maternal SES, tobacco smoke at home and child age, height, sex	Increased blood Pb levels were associated with higher systolic BP measurements in children with shorter gestational ages
Liu et al. 2019; "Prenatal Lead Exposure, Type 2 Diabetes, and Cardiometabolic Risk Factors in Mexican Children at Age 10–18 Years"	Mexico City, Mexico	369 mother–child pairs	Mean (SD) maternal age: 26.7 (5.6) years; mean (SD) child ageat time of assessment: 13.7 (1.9)	ELEMENT; enrolled between 1997 and 2003	Prospective cohort	Lead [Pb] levels measured in maternal blood at 1st trimester visit	Mean (95% CI) Maternal Pb (βg/dL): 4.3 (4.0–4.6)	Fasting glucose serum sample, insulin serum sample, lipids serum sample (triglycerides, total cholesterol, HDL-C, LDL-C) between 10 and 18 years of age (peripubertal)	Maternal age, marital status, education, smoking history and child age, sex, BMI, number of siblings at birth	Increased Pb concentrations were associated with decreased total cholesterol scores (B = − 0.76, 95% CI: − 1.38, − 0.13) and decreased LDL scores (B = − 0.96, 95% CI: − 1.59, − 0.33). Association only remained in males after adjusting for child sex
Wang et al., 2021; "Associations between prenatal and postnatal lead exposure and preschool children humoral and cellular immune responses"	Wuhan, China	394 mother–child pairs	Mean (SD) maternal age: 28.98 (3.54) years; child age caetgories at time of assessment: < 36 months (10.91%), 36–48 months (82.23%), > 48 months (6.85%)	Wuhan Medical and Healthcare Center for Women and Children birth cohort; enrolled between 2013 and 2015	Prospective cohort	Lead [Pb] levels in maternal urine at third trimester; normalized to urine creatinine	Mean (SD) Maternal Pb (βg/g): 5.82 (6.47)	Biomarkers of immune cytokines and T lymphocytes via child blood serum at age 3 years	Maternal age, parity, passive smoking, education and child sex	Increased prenatal Pb exposure is associated with reductions in two anti-atherosclerotic cytokines IL-4 (B = − 5.62, 95%: − 10.44, − 0.80) and IL-10 (B = − 5.93, 95%: − 11.82, − 0.03)
Muciño-Sandoval et al., 2021; "Prenatal and Early Childhood Exposure to Lead and Repeated Measures of	Mexico City, Mexico	601 mother–child dyads	Mean (SD) maternal age: 27.1 (5.5) years; no average child age reported	PROGRESS birth cohort in Mexico enrolled between 2007 and 2011	Prospective cohort	Prenatal Lead [Pb] levels in maternal blood at 2nd and 3rd trimester visit & cord blood, and bone (patella and	Median (IQR) 2nd trimester Pb (μg/dL): 2.9 (1.9–4.4). Median (IQR) 3rd trimester Pb (μg/dL): 3.1 (2.0–4.8). Median (IQR)	Metabolic syndrome: biomarkers (fasting glucose, HbA1C) via blood, lipids (triglycerides, total	Maternal: age, SES, parity. Child: sex, size for gestational age, age	Children with higher prenatal Pb exposure had lower odds of higher total cholesterol, compared to children with lower prenatal

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
Metabolic Syndrome Risk Indicators From Childhood to Preadolescence”						tibia) at 1 month postpartum. Postnatal Pb in child blood samples at ages 1/2/4 years	Umbilical cord Pb (μg/dL): (1.4–3.7). Median (IQR) patella Pb (μg/dL): 3.4 (1.3–8.9). Median (IQR) tibia Pb (μg/dL): 3.0 (1.1–7.5)	cholesterol, HDL, LDL) via blood, anthropometric measures (BMI, waist circumference, body fat%), systolic and diastolic blood pressure between ages 6 to 12 years		Pb exposure (OR = 0.53, 95% CI: 0.31–0.99) & (OR = 0.67, 95% CI: 0.43–1.02, results in table reported as “marginal significance”). Children with higher prenatal Pb exposure had lower odds of high triglycerides (OR = 0.65, 95% CI: 0.44–0.95), high diastolic BP (OR = 0.60, 95% CI: 0.37–0.98), compared to children with lower prenatal Pb exposure
Cadmium										
Chatzi et al., 2018; “Associations of prenatal exposure to cadmium with child growth, obesity, and cardiometabolic traits”	Heraklion, Greece	515 mother–child pairs	Mean (SD) maternal age: 29.8 (5.0) years; mean (SD) child age at time of assessement: 4.2 (0.2) years)	Rhea Cohort; recruited between 2007 and 2012	Prospective cohort	Cadmium [Cd] levels in maternal urine during pregnancy; Median (IQR) 13 (12–15) weeks of gestation	Median (IQR) Maternal Cd (μg/L): 0.5 (0.3–0.7)	Weight, height, waist circumference, skinfold thickness, systolic and diastolic blood pressure of child (avg. 5 measurements), lipids (total cholesterol, HDL-C), CVD biomarkers (leptin, C-reactive protein) measured at age-4-year examination	Maternal age, education, national origin, parity, pre-pregnancy BMI, gestational diabetes, tobacco smoking, pollutant exposure and child sex, gestational age at birth, weight, breastfeeding duration	Cd concentrations and change in BP measures (systolic [B = 0.01, 95%: −0.14, 0.16]; diastolic: [B = 0.04, 95%: −0.06, 0.13]), lipids (total [B = − 3.07, 95%: −8.79, 2.64]; HDL: [B = −0.07, 95%: −2.43, 2.28]), and CVD biomarkers (CRP [B = −11.1, 95%: −33.0, 18.0]; Leptin: [B = 0.6, 95%: −15.0, 10.0]),

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
										were not statistically significantly associated (null)
Co-exposure to two metals										
Farzan et al., 2018; “Prenatal lead exposure and elevated blood pressure in children”	New Hampshire, USA	323 mother–child pairs	Mean maternal age: 31.3 years; Mean child age at time of assessment: 5.5 years	New Hampshire Birth Cohort Study; ongoing recruitment since January 2009	Prospective cohort	Arsenic [As] and lead [Pb] levels in maternal toenails at 24–28 weeks gestation and 6 weeks postpartum	Mean (SD) prenatal maternal toenail Pb (μg/g): 0.3 (0.6); Mean (SD) postpartum maternal toenail Pb (μg/g): 0.3 (1.4); Mean (SD) prenatal maternal toenail As: 0.1 μg/g (0.1); Mean (SD) postpartum maternal toenail As: 0.1 μg/g (0.1)	Systolic and diastolic blood pressure of child (avg. 5 measurements)	Maternal tobacco use during pregnancy and child sex, age, height, weight	Prenatal Pb concentrations were associated with increased systolic BP for children (B = 0.58, 95% CI = 0.05, 1.11). Postpartum Pb was not associated with child BP. There was no significant associations between prenatal or postpartum arsenic exposure and child’s systolic blood pressure or diastolic blood pressure
Akhtar et al. 2021; “A longitudinal study of rural Bangladeshi children with long-term arsenic and cadmium exposures and biomarkers of cardiometabolic diseases”	Matlab, Bangladesh	540 mother–child pairs	Maternal age not reported; Mean child age at time of assessment: 8.9 years	Multiple micronutrient supplementation (MINIMat) trial; enrolled 2001–2003	Prospective cohort	Arsenic [As] and cadmium [Cd] levels measured in maternal urine at 8 weeks gestation; normalized to urine creatinine	Median (IQR) Cd (μg/g): 0.58 (0.31, 0.96); As (μg/L): 76.07 (37.62, 218.64): maternal urine AS: Median, 76.07 μg/L	Systolic and diastolic blood pressure measured at two time points (4.5 years and 9 years of age). Lipids (total cholesterol, triglycerides, HDL-C, LDL-C), and metabolic biomarkers (glucose, a1C, adipokines, eGFR) measured in child blood serum at 9 years	Maternal educational level, food supplementation, micronutrient supplementation and child SES, sex, age, height-for-age z-score, BMI-for-age z-score	Increased Cd concentrations were associated with increased systolic BP (exact B not given). Increased Cd concentrations were associated with decreased HDL scores (B = − 1.22, 95% CI: − 2.02, − 0.42). Association remained when accounting for Cd-As interaction. CVD

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Author, year of publication; title	Location	Sample Size	Study population characteristics	Year at baseline, study name if available	Study design	Exposure(s)	Metal concentrations	Outcome	Covariates	Key findings
										biomarkers (Leptin) not associated with Cd concentrations. Maternal As exposure was not associated with child total cholesterol at age 9 or with child blood pressure at either time point. A negative association was found between maternal arsenic exposure and child HDL levels at age 9 (β = − 1.02, 95% CI: 1.56, − 0.48, p < 0.001)

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Table 2

Summary of the included studies using mixture analysis methods

Author, year of publication; title	Location	Year at baseline; study name if available	Study population	Metals or metalloids included	Exposure	Outcomes	Mixture analysis method(s)	Covariates	Key findings
Kupsco et al. 2019; "Prenatal metal concentrations and childhood cardio-metabolic risk using Bayesian Kernel Machine Regression to assess mixture and interaction effects"	Mexico City, Mexico	2007; PROGRESS cohort	548 mother–child pairs	As, Cd, Co, Cr, Cs, Cu, Mn, Pb, Sb, Se, and Zn	Maternal blood samples (2nd trimester)	SBP, DBP, cardio-metabolic risk score, TG, HbA1c, non-HDL-C, leptin, and adiponectin at 4–6 years of age	BKMR	Maternal age, education, socioeconomic status, parity, environmental tobacco smoke, and date of follow-up visit (for HbA1c, global risk score, non-HDL cholesterol, SBP and DBP outcomes only). Birth weight, gestational age, sex, and pre-pregnancy BMI included as covariates in sensitivity analyses	•Inverse joint effect of metal mixture on SBP was observed • Higher Se was associated with lower TG • Sb and As were associated with lower leptin • No interaction among the metals or nonlinear responses detected
Warembourg et al. 2019; "Early-Life Environmental Exposures and Blood Pressure in Children"	Europe (United Kingdom, France, Spain, Lithuania, Norway, Greece)	NA; HELIX European consortium	1,277 mother–child pairs	As, Cd, Co, Cs, Cu, Hg, Mn, Mo, Pb, and Tl (out of 89 prenatal exposures)	Maternal blood samples	SBP and DBP at 6 to 11 years	DSA	Cohort, maternal age, maternal education level, maternal pre-pregnancy BMI, parity, parental country of birth, child age, child sex, and child height in the multi-exposure linear regression models	•The DSA method selected 5 and 2 prenatal exposures for SBP and DBP in childhood, respectively • None of these exposures included prenatal exposure to metals
Zanobetti et al. 2020; Ambient particle component and newborn blood pressure in Project Viva	Massachusetts, USA	1999; Project Viva	1,131 mother-infant pairs	Al, Si, K, Ca, Ti, Fe, Mg, As, Cu, Zn, Br, Pb, V, Ni, and Na (in addition to PM2.5, BC, S, and Cl)	The PM2.5 components measured at the Harvard Supersite linked to each mother's residential address	SBP and DBP at a mean age of 30 h	LASSO and BKMR	Maternal age, third-trimester maternal BP, race/ethnicity, and educational level; infan's postnatal age and birth weight, infant state at BP, median neighborhood income, same day temperature, and sine and cosine terms of day of year	•For SBP, the adaptive LASSO selected S, Ni, Zn, and Cl • Using BKMR, these components have a linear dose–response relationship with the outcome, with Ni and Zn showing the highest PIPs • Ni and S were associated with higher SBP, whereas Zn and Cl were associated with lower SBP. Only Ni and Zn were significantly associated with BP • For DBP, the adaptive LASSO selected Ni, Zn, S, Si, As, Cu, and Pb • The BKMR analysis indicated Ni and Zn as the most influential components

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Author, year of publication; title	Location	Year at baseline; study name if available	Study population	Metals or metalloids included	Exposure	Outcomes	Mixture analysis method(s)	Covariates	Key findings
									•Ni was positively associated with DBP, whereas Zn was inversely associated with the outcome. Other associations were suggestive
Howe et al., 2021; "Prenatal metal mixtures and child blood pressure in the Rhea mother–child cohort in Greece"	Heraklion, Greece	2007; Rhea Cohort	176 mother–child pairs	Mg, Co, Se, Mo, As, Cd, Sb, and Pb	Maternal urine samples	SBP and DBP at 4 and 11 years of age, BP change from ages 4 to 11, and elevated BP at 11 years of age	BKMR	Maternal age, maternal education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, child's sex, child's age, and child's height	•Mo and Co were associated with increased SBP and DBP at baseline (age 4). J-shaped associations were identified • Cd was inversely associated with DBP at baseline (age 4) • Co was associated with lower per-year increases in both SBP and DBP from ages 4 to 11 • Mo was associated with lower per-year increases in DBP from ages 4 to 11 • Mg was associated with higher per-year increases in both SBP and DBP from ages 4 to 11, but not with BP at baseline (age 4) • Mo and Pb were associated with BP at age 11 (J-shaped) • A possible synergistic interaction between Mo and Pb was shown for BP at ages 4 and 11
Zhang et al., 2021; "In Utero exposure to heavy metals and trace elements and childhood blood pressure in a US urban, low-income, minority birth cohort"	Boston, USA	2002; Boston Birth Cohort	1,194 mother–child pairs	Pb, Hg, Cd, Se, and Mn	Maternal blood samples (2nd trimester)	Child SBP and DBP between 3 and 15 years of age	BKMR	Maternal age, at delivery, race/ethnicity, educational level, pre-pregnancy body mass index, and cigarette smoking history	•No joint association observed • The hierarchical variable selection indicated that essential elements (highest conditional PIP for Se) were more strongly associated with SBP than heavy metals (largest conditional PIP for Pb) • In the BKMR individual analysis, Se and Mn were inversely associated with child SBP percentiles; no association found for DBP • In utero exposure to Mn and Cd interacted with each other in relation to child blood pressure

Al, aluminum; *As*, arsenic; *BC*, black carbon; *BKMR*, Bayesian kernel machine regression; *BMI*, body mass index; *BP*, blood pressure; *Br*, bromine; *Ca*, calcium; *Cd*, cadmium; Cl, chlorine; *Co*, cobalt; *Cs*, cesium; *Cu*, copper; *DBP*, diastolic blood pressure; *DSA*, deletion-substitution-addition algorithm; *Fe*, iron; *Hg*, mercury; *K*, potassium; *LASSO*, Least Absolute Shrinkage and Selection Operator; *Mg*, magnesium; *Mn*, manganese; *Mo*, molybdenum; *NA*, not applicable; *Na*, sodium; *Ni*, nickel; *Pb*, lead; *PIP*, posterior inclusion probability; *PM2.5*, particle mass with diameter < 2.5 μm; *S*, sulfur; *Sb*, antimony; *SBP*, systolic blood pressure; *Se*, selenium; *Si*, silicon; *Ti*, titanium; *Tl*, thallium; *V*, vanadium; *Zn*, zinc