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Review

Exposure to metal mixtures and adverse pregnancy and birth outcomes: A systematic review

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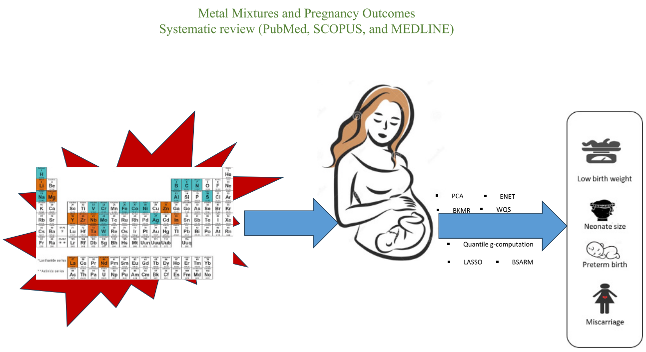
HIGHLIGHTS

- Our study reviews 34 epidemiological studies on multiple metals exposure and pregnancy outcomes.
- The review revealed a broad assessment of toxic, essential, and rare earth metals.
- Metals exert a more substantial impact on critical pregnancy outcomes when analyzed collectively rather than individually.
- The review revealed additive, antagonistic, and synergistic interactions among metal mixtures on pregnancy outcomes.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Prenatal exposure to metal mixtures is associated with adverse pregnancy and birth outcomes like low birth weight, preterm birth, and small for gestational age. However, prior studies have used individual metal analysis, lacking real-life exposure scenarios.
Objectives: This systematic review aims to evaluate the strength and consistency of the association between metal mixtures and pregnancy and birth outcomes, identify research gaps, and inform future studies and policies in this area.
Methods: The review adhered to the updated Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist, along with the guidelines for conducting systematic reviews and meta-analyses of observational studies of etiology (COSMOS-E). Our data collection involved searching the PubMed, MEDLINE, and SCOPUS databases. We utilized inclusion criteria to identify relevant studies. These chosen studies underwent

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thorough screening and data extraction procedures. Methodological quality evaluations were conducted using the NOS framework for cohort and case-control studies, and the AXIS tool for cross-sectional studies.

Results: The review included 34 epidemiological studies, half of which focused on birth weight, and the others investigated neonate size, preterm birth, small for gestational age, miscarriage, and placental characteristics. The findings revealed significant associations between metal mixtures (including mercury (Hg), nickel (Ni), arsenic (As), cadmium (Cd), manganese (Mn), cobalt (Co), lead (Pb), zinc (Zn), barium (Ba), cesium (Cs), copper (Cu), selenium (Se), and chromium (Cr)) and adverse pregnancy and birth outcomes, demonstrating diverse effects and potential interactions.

Conclusion: In conclusion, this review consistently establishes connections between metal exposure during pregnancy and adverse consequences for birth weight, gestational age, and other vital birth-related metrics. This review further demonstrates the need to apply mixture methods with caution but also shows that they can be superior to traditional approaches. Further research is warranted to deeper understand the underlying mechanisms and to develop effective strategies for mitigating the potential risks associated with metal mixture exposure during pregnancy.

1. Introduction

Adverse pregnancy and birth outcomes, such as miscarriages, low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA), are a significant public health concern because they are associated with an increased risk of maternal and neonatal morbidity and mortality (Amadi et al., 2017; Iliodromiti et al., 2017; Kabiri et al., 2020). These outcomes can also have long-term consequences on a child's health and development, such as cognitive impairment and stunting (Black et al., 2008; Imdad and Bhutta, 2013; WHO, 2014). In addition, poor birth outcomes have been linked to an increased risk of chronic diseases in adulthood, such as cardiovascular disease, hypertension, obesity, and diabetes (Bianchi and Restrepo, 2022).

Several modifiable risk factors have been associated with adverse birth outcomes, including poor maternal nutrition, maternal smoking and alcohol consumption, and maternal exposure to environmental toxins (Stillerman et al., 2008). Environmental metals, such as lead (Pb), cadmium (Cd), and mercury (Hg), have been identified as potential risk factors for adverse effects on pregnant women and the developing fetus, including reproductive disorders, low birth weight, reduced birth length, reduced head and chest circumferences, and poor mental development (Gull et al., 2018). Heavy metals are discharged into the environment from a wide array of sources (Sherene, 2010). Human are exposed to these metals through different pathways, encompassing occupational routes (such as mining, smelting, foundries, and electronic waste recycling), unplanned exposures, and inadvertent activities (like consuming contaminated food and water, as well as inhaling polluted air) (Alissa and Ferns, 2011; Basu et al., 2023; Takyi et al., 2021). These metals can cross the placenta and accumulate in fetal tissues, potentially causing damage to developing organs and systems (Amegah et al., 2021; Thompson and Bannigan, 2008).

The effects of metals on pregnancy and birth outcomes have been widely studied (Lin et al., 2018; Sun et al., 2019; Wai et al., 2017), and recent review papers have provided a comprehensive summary of this issue (Amegah et al., 2021; Khanam et al., 2021; Milton et al., 2017; Quansah et al., 2015). While previous studies have linked single metal exposure with adverse birth outcomes, it is crucial to recognize that exposure to multiple pollutants concurrently provides a more accurate representation of real-world exposure. To address this issue, there has been a shift toward using mixture analysis to better understand the health impacts of exposure to multiple pollutants (Suk et al., 2002b), since this may exert a joint and potential interactive effect on health outcomes.

The National Institute of Environmental Health Sciences (NIEHS) has been a leader in this effort, promoting the use of mixture analysis in environmental health research (Carlin et al., 2013; Suk et al., 2002a). To facilitate this, researchers have developed a range of statistical methods to help handle the complexity of mixture analysis. These methods include Bayesian kernel machine regression (BKMR) (Bobb et al., 2015), quantile-based g-computation (Keil et al., 2020), principal component analysis (PCA) (Abdi and Williams, 2010), and least absolute shrinkage and selection operator (LASSO) (Ranstam and Cook, 2018).

The issue of metal mixture exposure during pregnancy and its potential impact on birth outcomes has garnered growing attention, leading to a surge in published studies within this domain (Lee et al., 2021b; Michael et al., 2022a; Rahman et al., 2021a; Signes-Pastor et al., 2019). Nevertheless, a systematic review of the emerging evidence has not been undertaken so far. It would be advantageous to conduct an all-encompassing review of the existing literature to assess the robustness and uniformity of the connection between metal mixtures and pregnancy as well as birth outcomes. This review could help identify areas where research is lacking and offer insights for forthcoming studies and policy considerations in this realm.

2. Methods

The protocol for this review was registered with the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) database (Booth et al., 2011) and assigned a registration number CRD42023422903. The review was performed according to the updated version of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA 2020) checklist (Page et al., 2021) and followed the guidance on conducting systematic reviews and meta-analyses of observational studies of etiology (COSMOS-E) (Dekkers et al., 2019).

2.1. Eligibility criteria

To establish eligibility criteria for inclusion in our review, we utilized the Participants/Population, Exposure, Comparator, Outcome, and Study design (PECOS) framework. The structured eligibility criteria using the PECOS framework are as follows:

Participants/population:

- Participants in the studies must be adult pregnant women.

Exposure:

- Studies must assess a minimum of three different metals, in accordance with the NIEHS mixture definition (Suk et al., 2002a).
- Metals should be analyzed individually at the level of human biological samples.

Comparator:

- Not applicable in this review

Outcome:

- The outcome measures must be pregnancy or birth outcomes (birth weight (BW), estimated fetal weight (EFW), abdominal circumference (AC), femur length (FL), head circumference (HC), biparietal diameter (BPD), birth length (BL), ponderal index (PI), preterm birth (PTB), small for gestational age (SGA), and miscarriage.

Study design:

- Studies eligible for inclusion must be primary investigations.
- The acceptable study designs include cohort, case-control, or cross-sectional designs.
- Multipollutant statistical methodology must be employed, rather than the conventional regression approach.

Additional Exclusions:

- Non-peer-reviewed publications and conference abstracts are excluded from consideration to ensure the reliability of evidence.
- Studies involving multiple pregnancies or prenatal conditions such as HIV infection, syphilis infection, preeclampsia, gestational diabetes, in vitro fertilization (IVF)-assisted pregnancies, or any other conditions linked to elevated risks of adverse pregnancy outcomes are also excluded from the review.

2.2. Information sources and search strategy

For this systematic review, we conducted a comprehensive search of three major databases: PubMed, Medline, and Scopus. We utilized a combination of keywords and Boolean operators to identify relevant articles related to the association between heavy metal exposure and adverse birth outcomes. The following search terms were used: (“heavy metals” OR “metals “OR “pollutant” OR “toxic element” OR “metalloid” OR “arsenic” OR “cadmium” OR “mercury” OR “lead” OR “cobalt” OR “zinc” OR “manganese” OR “iron” OR “nickel” OR “chromium”) AND (“Stillbirth” OR “perinatal death” OR “spontaneous abortion” OR “miscarriage” OR “preterm birth” OR “birth weight” OR “low birth weight” OR “small for gestational age” OR “intrauterine growth retardation” OR “birth outcome” OR “adverse birth outcome” OR “adverse pregnancy outcome” OR “pregnancy outcome”) AND (“mixture*” OR “multipollutant*” OR “multiple metals” OR “multimetal*” OR “joint effect*” OR “joint association*” OR “joint exposure*” OR “overall effect*” OR “overall association*” OR “overall exposure*” OR “joint and individual” OR “copollutant*” OR “coexposure*” OR “combined metal*” OR “mixed metal*” OR “principal component analysis” OR “exploratory factor analysis” OR “Bayesian Kernel Machine Regression” OR “Least Absolute Shrinkage and Selection Operator” OR “penalized regression*” OR “Weighted Quantile Sum” OR “quantile-based g-computation” OR “quantile g-computation”). The search was limited to peer-reviewed journal articles published in English from 1998, when NIEHS first funded mixture research (Chemical Mixtures in Environmental Health, 1998), to May 10th, 2023. The same search strategy was applied to all three databases. The search was conducted on 10th May 2023 for all three databases and updated on 31st July 2023 by rerunning the search strategies using the same databases. The search terms were selected based on their relevance to the topic and included variations in heavy metals, adverse birth outcomes, and methods used to evaluate the joint effects of multiple pollutants. The full search strategy and results are presented in supplementary Table S1.

2.3. Selection process

Search results were screened based on the title, abstract, and full-text eligibility criteria. All citations retrieved from the three major databases were exported into EndNote referencing manager (version 8; Clarivate Analytics; Pennsylvania, PA, USA). We then proceeded to remove duplications through both manual procedures and by using the deduplication function in EndNote to ensure that each article was only counted once. We subsequently screened article titles and abstracts following the inclusion criteria to exclude any articles that were irrelevant to the research question. The full text of studies that passed the abstract and title screening were retrieved using the “find full text” function in EndNote and further screened in detail against the inclusion and exclusion criteria. The entire screening process was conducted independently by two reviewers to ensure that each article was screened objectively. Any discrepancies between the two reviewers were resolved through consensus. The search results from each database and the screening process are presented in the PRISMA flow chart (Haddaway et al., 2022) (Fig. 1), which provides a clear overview of the number of articles identified, screened, and included in the final review.

2.4. Data extraction

Data from eligible studies were extracted independently by two investigators (II and MSD) into a purposefully designed data collection form. The data collection sheet included the following information: author name and year of publication, study location, study design, study population, metals evaluated, biological media used for metal analysis, outcomes studied, mixture analysis methods used, covariates, and summary of main findings. These data were extracted to provide a summary of the study's basic characteristics, determine the exposure assessment and analysis methods used in the studies, identify the different types of adverse birth outcomes associated with heavy metal exposure, determine the degree of adjustment for confounding factors, and provide an overview of the study's key results. Any discrepancies between the two reviewers were resolved through discussion and consensus.

2.5. Assessment of the studies

2.5.1. Study quality assessment

We assessed the methodological quality of the included studies using two qualitative tools. The first tool was the Newcastle–Ottawa Quality Assessment Scale (NOS) for Case–Control and Cohort Studies, which can be accessed online at (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) [accessed on 18 May 2023]. The second tool was the AXIS Appraisal tool for Cross-Sectional Studies developed by Downes et al. (2016). The NOS consists of three main categories: selection, comparability, and ascertainment of exposure or outcome. II and MSD applied the NOS to assess the quality of eligible cohort and case–control studies, with a maximum score of 9. Each numbered item within the selection and outcome/exposure categories could receive a maximum of one star, while comparability could receive a maximum of two stars. Studies scoring $\geq$7 were considered high quality (Quansah et al., 2015) (Tables S2 and S3). In addition, we used the AXIS critical appraisal tool to evaluate the quality of cross-sectional studies. The AXIS tool comprises 20 components, including seven related to quality of reporting (1, 4, 10, 11, 12, 16, and 18), seven related to study design quality (2, 3, 5, 8, 17, 19, and 20), and six related to the potential introduction of biases in the study (6, 7, 9, 13, 14, and 15) (Downes et al., 2016) (Table S4).

2.5.2. Risk of bias assessment

A high-quality study may still have an important risk of bias (Higgins et al., 2023). To assess bias risk in each of the included studies, we utilized the adapted Office of Health Assessment and Translation (OHAT) approach developed by the National Institutes of Environmental Health Sciences National Toxicology Program (Ohat, 2019). This OHAT risk of bias tool encompasses key criteria such as exposure assessment, outcome assessment, and confounding, as well as other criteria like selection bias, attrition/exclusion bias, selective reporting bias, conflicts of interest, and other potential sources of bias. We evaluated each of these bias domains and assigned a rating of low, probably low, probably high, or high risk based on our analysis of study-specific details and

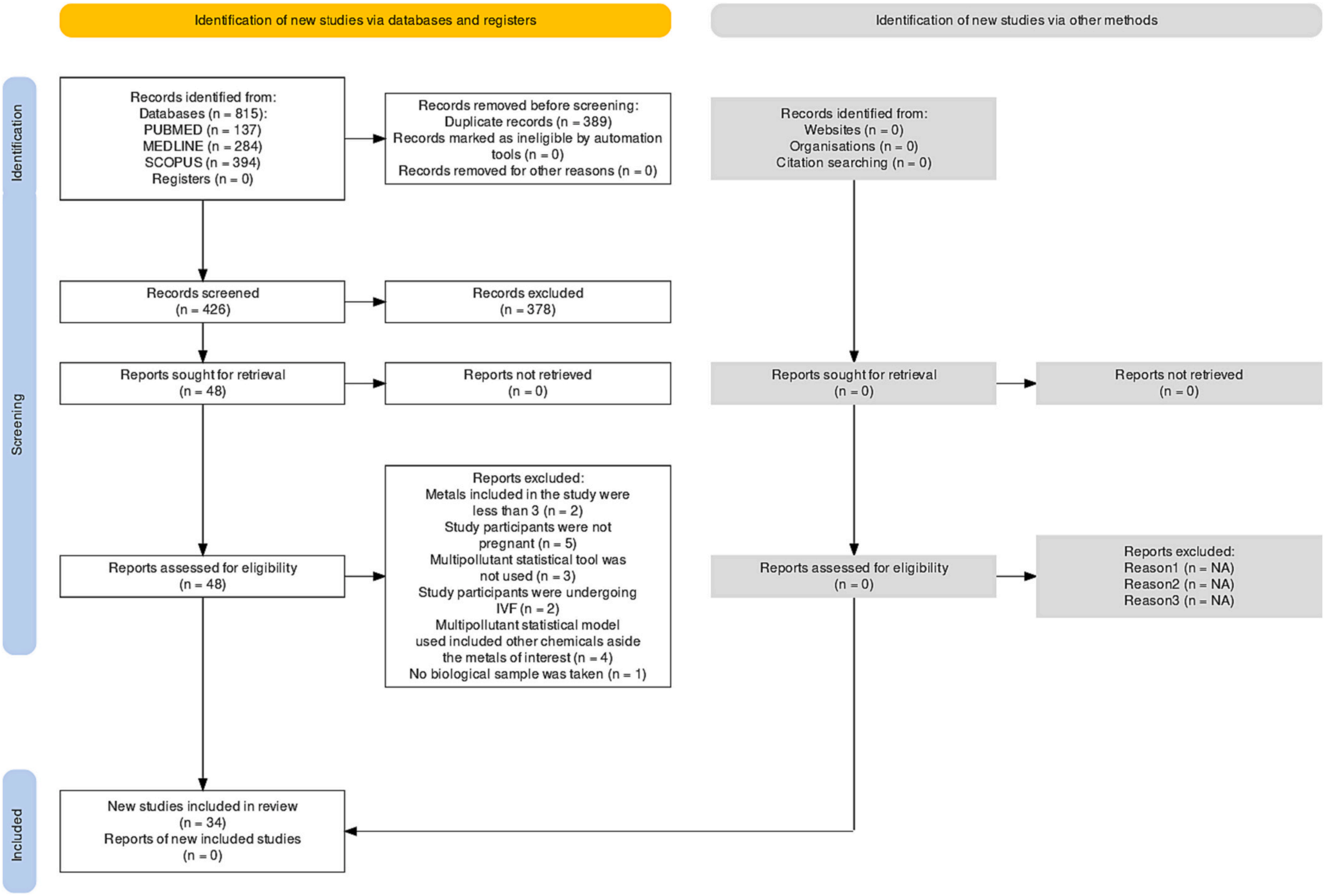

Fig. 1. PRISMA flow diagram depicting the sequential process of selecting peer-reviewed articles for inclusion in the systematic review.
(Source: Haddaway et al. (2022).)

responses to a set of relevant questions (Ohat, 2019).

2.6. Data synthesis and analysis

Due to the lack of consistency in the statistical methods employed in the mixture analysis among the included studies, conducting a meta-analysis, which was originally intended, became unfeasible. Furthermore, there is currently no existing method capable of quantitatively assessing the findings from studies employing diverse multipollutant approaches (Yim et al., 2023). As a result, we opted to conduct a separate review and synthesis of the literature for each specific birth outcome using a narrative synthesis approach.

3. Results

3.1. Study selection

A peer-reviewed literature search across three databases (PUBMED, MEDLINE, and SCOPUS) yielded a total of 815 articles. After removing duplicates (n = 389), the remaining 426 articles underwent an initial screening based on their title and abstract. As a result, 378 articles were excluded, leaving 48 articles for full-text screening. Of these, 14 articles were further excluded for various reasons, including the inclusion of fewer than three metals of interest (n = 2) (Al-Saleh et al., 2015; Govarts et al., 2020), the study participants were not pregnant (n = 5) (Bloom et al., 2015; Cao et al., 2022; Cassidy-Bushrow et al., 2019; Eaves et al., 2023; Li et al., 2022), articles did not use any multipollutant statistical tool (n = 3) (Bloom et al., 2015; Cabrera-Rodríguez et al., 2018; Shih et al., 2021), study participants were undergoing IVF (n = 2) (Cao et al., 2022; Li et al., 2022), articles included other chemicals aside from the metals of interest in their multipollutant statistical analysis (n = 4) (Gokoel et al., 2021; Govarts et al., 2016; Kalloo et al., 2020; Yim et al., 2023) and articles did not take biological samples (n = 1) (Keil et al., 2021). Furthermore, relevant information from the included articles was extracted and used for this systematic review (n = 34) (Fig. 1).

3.2. Study characteristics

For this review, a total of 34 studies met the inclusion criteria. The majority of these studies were conducted in China (n = 14), followed closely by the USA (n = 8), Bangladesh (n = 3), Puerto Rico (n = 2), and one study each from Japan, the Republic of Korea, Israel, Australia, Canada, and Rhode Island. In addition, one study combined data from the USA and Puerto Rico (Howe et al., 2022). Among the included studies, the majority (n = 23) utilized a prospective cohort design, while six studies employed a nested case-case control design (Hou et al., 2019; Kim et al., 2018; Liu et al., 2022; Ren et al., 2022; Wang et al., 2022; Xu et al., 2022). The remaining five studies were cross-sectional in nature (Kao et al., 2023; Kim et al., 2020b; Lazarevic et al., 2022; Lu et al., 2022; Michael et al., 2022b). The sample sizes of the included studies ranged from 148 participants (Xu et al., 2022) to 93,739 participants (Takatani et al., 2022).

The majority of the studies included in this analysis utilized data from ongoing prospective cohort studies. These studies included the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) (Ashrap et al., 2020; Ashrap et al., 2021), Rhode Island Child Health Study (RICHS) (Deyssenroth et al., 2018), Guangxi Birth Cohort Study (GBCS) (Hou et al., 2019), Maternal and Developmental Risks from

Environmental and Social Stressors (MADRES) (Howe et al., 2021; Howe et al., 2020), Maternal-Infant Research on Environmental Chemicals (MIREC) (Hu et al., 2021), LIFECODES birth cohort (Kim et al., 2020a; Kim et al., 2018), Australian Maternal Exposures to Toxic Substances (AMETS) study (Lazarevic et al., 2022), Mothers and Children's Environmental Health (MOCEH) study (Lee et al., 2020), Beijing Birth Cohort (BBC) (Ren et al., 2022), New Hampshire Birth Cohort Study (NHBCS) (Signes-Pastor et al., 2019), Japan Environment and Children's Study (JECS) (Takatani et al., 2022), Maoming Birth Cohort Study (MBCS) (Wang et al., 2022), PRogramming of Intergenerational Stress Mechanisms (PRISM) pregnancy cohort (Zhang et al., 2022), Hangzhou Birth Cohort Study (HBCS) (Zhao et al., 2020), and the National Institute of Child Health and Human Development (NICHD) Fetal Growth Study (Zilversmit Pao et al., 2019), and the Jiangsu Birth Cohort (JBC) (Dou et al., 2022).

Although the National Institute of Environmental Health Sciences (NIEHS) provided initial funding for mixture research in 1998 (Chemical Mixtures in Environmental Health, 1998), studies specifically focusing on the effects of metal mixtures on pregnancy and birth outcomes were first published in 2018 (Deyssenroth et al., 2018; Kim et al., 2018). Since then, the number of publications in this field has steadily grown, and in 2022, it experienced a six fold increase (Fig. 2). Several journals actively contributed to the field of research. Notably, Environmental International made 11 contributions, while Environmental Research published 6 papers. Additionally, the International Journal of Hygiene and Safety, Chemosphere, and Environmental Epidemiology each made 2 significant contributions to the field.

Two studies stood out by evaluating the highest number of metals, examining a combination of 56 metals (Chen et al., 2021; Huang et al., 2021). On the other hand, the smallest metal combination examined in studies included only 3 metals (Lee et al., 2020; Signes-Pastor et al., 2019; Zilversmit Pao et al., 2019). Among the studies, the majority (n = 31) assessed a combination of both toxic and essential metals, while three studies (Kao et al., 2023; Lee et al., 2020; Zilversmit Pao et al., 2019) focused solely on toxic metals. In terms of biological medium for metal exposure assessment, blood was the most frequently utilized (n = 13), followed by urine (n = 12). In addition, three publications (Ashrap et al., 2021; Lazarevic et al., 2022; Zhao et al., 2020) employed both blood and urine samples for their assessments. Other biological media utilized were maternal hair (n = 1) (Ren et al., 2022), toenail clippings (n = 2) (Deyssenroth et al., 2018; Signes-Pastor et al., 2019), meconium (n = 1) (Kao et al., 2023), and serum (n = 2) (Chen et al., 2021; Hou et al., 2019). A total of 59 unique metals were investigated in the studies, with Cd being the most frequently studied metal (n = 29), followed by Pb (n = 27), As (n = 25), and Mn (n = 21). All of the studies we considered used inductively coupled plasma mass spectrometry (ICPMS) to measure metals in different biological media, with one exception: the study by Kim et al. (2020b), which utilized graphite furnace atomic absorption spectrometry (GFAAS) to measure metals in maternal whole blood.

The included studies examined pregnancy and birth outcomes, which were classified into six main groups: 1) birth weight, 2) preterm birth, 3) neonate size, 4) small for gestational age, 5) miscarriage and 6) placental characteristics. Among these categories, birth weight was the most extensively studied outcome (n = 17), followed by neonate size (n = 11), preterm birth (n = 9), small for gestational age (n = 4), miscarriage (n = 1), and placental characteristics (n = 1) (Fig. 3). BKMR, WQS, PCA, and ENET were the mixture analysis methods most commonly used in the studies. Table 1 provides a summary of the characteristics of the included studies.

3.3. *Assessment of studies*

3.3.1. *Quality assessment*

All the articles included in this review were assessed for quality using the Newcastle–Ottawa scale for cohort and case–control studies and the AXIS tool for cross-sectional studies. Out of the 23 cohort study articles, 11 achieved a score of 8 out of 9, indicating high quality. The remaining 12 articles scored 7 out of 9 on the quality assessment. Consequently, all the studies were considered to be of high quality based on these evaluations (Table S2). Similarly, all 6 case–control study articles obtained a score of 8 out of 9, indicating high quality (Table S3). Furthermore, the cross-sectional studies included in this review achieved scores ranging from 13 (Michael et al., 2022b) to 15 (Kim et al., 2020b) out of 20 (Table S4).

3.3.2. *Risk of bias assessment*

All the studies included in this review were generally considered to have a low risk of bias in the key domains. Specifically, in the selection domain, all studies were rated as probably low risk. In addition, except for one study, which received a rating of probably low risk in the attrition/exclusion domain, all other studies were assessed as having a low risk of bias in the remaining domains (Table 2).

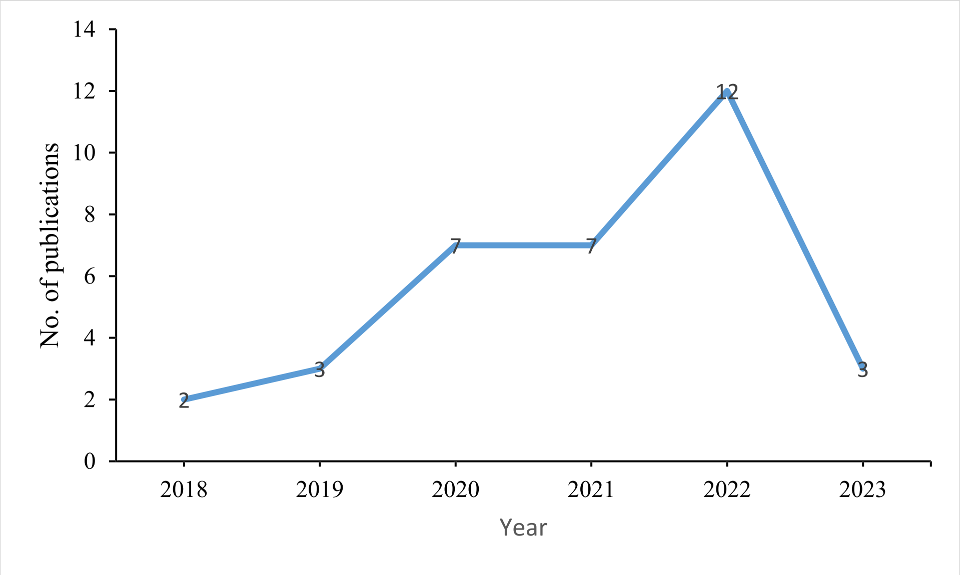

Fig. 2. Annual scientific production.

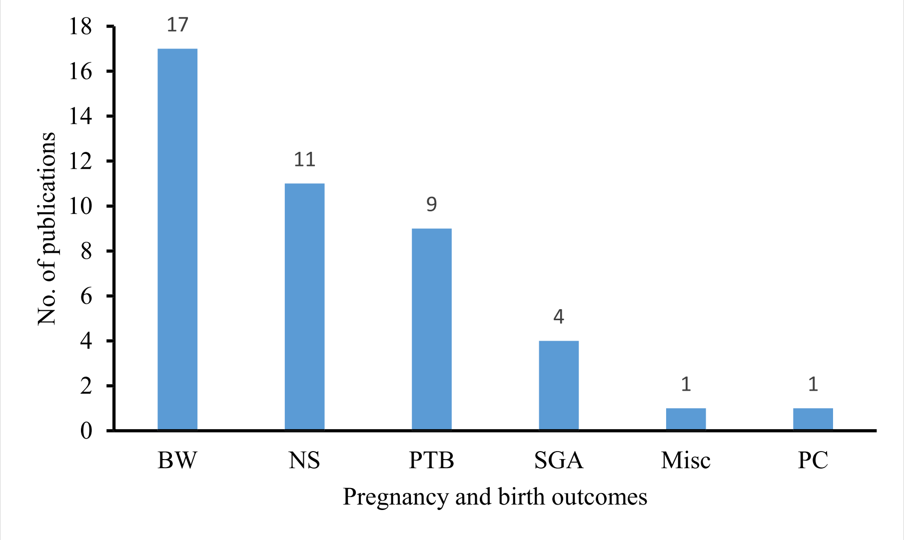

Fig. 3. Summary of included studies that reported various pregnancy and birth outcomes. Abbreviations: BW – birth weight; NS – neonate size; PTB – preterm birth; SGA – small for gestational age; Misc – miscarriage; PC – placental characteristics. NB: Some studies reported more than one outcome.

3.4. *Narrative synthesis of study outcomes*

3.4.1. *Birth weight*

Out of the 34 studies analyzed in this review, 17 studies investigated the impact of exposure to metal mixtures on birth weight (Chen et al., 2021; Hou et al., 2019; Howe et al., 2020; Howe et al., 2022; Hu et al., 2022; Hu et al., 2021; Kao et al., 2023; Kim et al., 2020b; Lazarevic et al., 2022; Lee et al., 2020; Michael et al., 2022b; Rahman et al., 2021b; Signes-Pastor et al., 2019; Takatani et al., 2022; Wu et al., 2023; Yang et al., 2020; Zhang et al., 2022). Four of these studies were conducted in the USA (Howe et al., 2020; Rahman et al., 2021b; Signes-Pastor et al., 2019; Zhang et al., 2022), six studies were conducted in China (Hou et al., 2019; Hu et al., 2022; Kao et al., 2023; Kim et al., 2020b; Wu et al., 2023; Yang et al., 2020), and one study each was conducted in Bangladesh (Chen et al., 2021), Australia (Lazarevic et al., 2022), Canada (Hu et al., 2021), Korea (Lee et al., 2020), Israel (Michael et al., 2022b), and Japan (Takatani et al., 2022). In addition, one study pooled data from the USA and Puerto Rico (Howe et al., 2022). Of these studies, most ($n = 12$) were prospective cohort studies, with one being a nested case–control study (Hou et al., 2019) and four being cross-sectional studies (Kao et al., 2023; Kim et al., 2020b; Lazarevic et al., 2022; Michael et al., 2022b). The researchers employed various mixture analysis methods, including BKMR ($n = 12$), WQS ($n = 2$), ENET ($n = 2$), PCA ($n = 2$), BSARM ($n = 1$), LASSO ($n = 1$), and quantile g-computation ($n = 1$).

Among the studies conducted in the USA, Howe et al. (2020) utilized BKMR to investigate the impact of a complex mixture of metals (Cd, Co, Hg, Ni, Mo, Pb, Sb, Sn, Tl) in maternal urine samples collected in early pregnancy on birth weight for gestational age (BW for GA) in a predominantly lower-income Hispanic pregnancy cohort in Los Angeles, California. The primary analysis focused on seven metals previously associated with fetal growth. The results of the primary analysis revealed that Hg and Ni had the strongest associations with BW for GA. Hg showed an inverse linear association with a difference of −0.11 standard deviations (SD) in BW for GA (95 % credible interval (CI): −0.31, 0.09), while Ni showed a positive association with a difference of 0.10 SD in BW for GA (95 % CI: −0.16, 0.35) at low-to-moderate concentrations, with a potential interaction between the two. In exploratory analysis, Sb ranked highest as a predictor of BW for GA, followed by Hg and Ni. Rahman et al. (2021b) utilized data from 1391 mother-infant pairs from Project Viva enrolled from 1999 to 2002 in eastern Massachusetts. The authors measured 11 metals (As, Ba, Cd, Cs, Cu, Mg, Mn, Pb, Se, Zn, and Hg) in maternal 1st-trimester erythrocytes and abstracted birth weight from their medical records. The BKMR analysis showed that an IQR increase in As was associated with a lower birth weight of −0.08 (95 % CI: −0.19, 0.03), −0.13 (95 % CI: −0.20, −0.0004), and −0.13 (95 % CI: −0.24, −0.01) SDs (1 SD = 567.0 g) when the concentrations of Cd, Mn, Pb, Zn, and Hg were fixed at the 25th, 50th, and 75th percentiles, respectively, in males. In addition, As and Mn showed a synergistic association with birth weight in males, in whom an IQR increase in As was associated with 25.3 g (95 % CI: −79.9, 29.3), 47.9 g (95 % CI: −98.0, 2.1), and 72.2 g (95 % CI: −129.8, −14.7) lower birth weight when Mn concentrations were at the 25th, 50th, and 75th percentiles, respectively. Similarly, using BKMR, Signes-Pastor et al. (2019) found an inverse relationship between Pb and BW, especially among females exposed to lower concentrations of the other metals (As, Mn, and Pb). Zhang et al. (2022) examined the joint effects of prenatal exposure to a panel of 12 metals (As, Ba, Cd, Co, Cr, Cs, Cu, Mn, Ni, Pb, Sb, and Zn) and maternal nutrition on birth weight for gestational age (BWGA) z scores among an urban US population. This study was conducted using participants from the PRogramming of Intergenerational Stress Mechanisms (PRISM) pregnancy cohort, an ongoing longitudinal study designed to examine the effects of environmental exposures and psychosocial determinants on child development. Metals associated with the BWGA z score in males and females were identified using both multivariable linear regression models and Bayesian Kernel Machine Regression (BKMR) models. The results of their analysis revealed that three metals (Co, Ni, and Pb) were associated with the BWGA z score in male infants, while five metals (Ba, Cs, Cu, Ni, and Zn) were associated with the BWGA z score in female infants. Furthermore, Howe et al. (2022) conducted a study in which they combined data from the United States and Puerto Rico ($n = 1002$) from three cohorts (MADRES, NHBCS, and PROTECT) participating in the Environmental Influences on Child Health Outcomes (ECHO) Program. The primary objectives of the study were to enhance statistical power and encompass a broader range of exposure. The researchers utilized BKMR to assess the association between seven metals (Cd, Co, Hg, Mo, Ni, Sb, Sn) measured in maternal urine samples collected during pregnancy and birth weight for gestational age z scores (BW for GA). The findings from the pooled BKMR analysis revealed inverse and linear associations between Sb, Hg, and Sn and BW for GA, while a positive linear association was found for Ni. The inverse association between Sb and BW for GA was observed in both males and females, as well as across all three cohorts. However, the effect was most pronounced in MADRES, which predominantly

Table 1
Summary of the various studies included in the systematic review.

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
Ashrap et al. (2020)	Puerto Rico	Prospective Cohort	Pregnant Women, (n = 812)	As, Ba, Be, Cd, Co, Cr, Cs, Cu, Hg, Mn, Ni, Pb, Ti, U, V, Zn	Blood	ICPMS	PTB (overall and spontaneous), SGA, LGA	ENET and Metal Risk Score, BKMR	Maternal Age, Maternal Education Level, Prepregnancy BMI, Exposure to Second-Hand Smoking	1. ENET models identified Pb and Zn, as important predictors of preterm birth 2. The odds ratio (OR) for preterm birth comparing the highest vs. lowest tertiles of ERS was 2.13 (95 % CI = 1.12, 5.49, p = 0.02). 3. BKMR models indicated that all three metal groups (Zn, Pb, and Mn) were likely associated with preterm birth, with Zn having the highest posterior inclusion probability (condPIP = 0.83)
Ashrap et al. (2021)	Puerto Rico	Prospective Cohort	Pregnant Women, (n = 847)	As, Ba, Be, Cd, Co, Cr, Cs, Cu, Hg, Mn, Ni, Pb, Ti, U, V, Zn, Mo, Pt, Sb, Sn, and W	Urine and Blood	ICPMS	Preterm birth, gestational age	ERSs using Ridge regression	Maternal age, maternal education level, prepregnancy BMI, exposure to second-hand smoking	1. All the examined ERSs constructed for urine (SG-corrected), blood, and two integrated multimedia biomarkers (MMB) were significantly associated with increased odds of preterm birth, with odds ratios ranging from 1.83 to 2.00 2. When analyzing ERS models, which combine multiple metal biomarkers, the odds ratios (ORs) for preterm birth were higher compared to individual metals. The ORs ranged from 2.83 to 5.17 for urine, blood, MMBICC, and MMBWQS ERSs.
Chen et al. (2021)	Bangladesh	Prospective Cohort	Mother-infant pairs (n = 745)	Be, Na, Mg, K, Ca, Rb, Sr, Cs, Ba, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Li, Al, Ga, As, B Se, Zr, Nb, Mo, Ag, Cd, Sn, Hf, Ta, W, Hg, Tl, Pb, Bi, Th, and U	Umbilical cord serum	ICPMS	Birth weight	BKMR and WQS	Age, BMI, age of marriage, maternal and spouse education level, family income level, and second-hand smoking exposure	1. BKMR showed potential interactive associations between Li and the other elements (Mn, Co, Cu, Se, Y, and Er) 2. WQS showed that for each unit increment of ERS, birth weight decreased by 64.73 g, with a 95 % confidence interval of (−86.75, −42.71), and a p value of 1.23 × 10ˆ(−8)
Deyssenroth et al. (2018)	Rhodes Island	Prospective Cohort	Mother-infant pairs (n = 195)	Ag, Al, As, Cd, Co, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, Sb, Se, Sn, U, V, Zn	Toenails	ICPMS	SGA	WQS and BKMR	Infant gender, maternal ethnicity, maternal BMI and maternal smoking status during pregnancy	1. WQS - for every unit increase in the derived metal mixture index, there was a 2.7-fold increase in the odds

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
										of being classified as SGA, OR = 2.73, (95 % CI: 1.04, 7.18). 2. BKMR - showed that SGA status was positively associated with As and Cd, while inversely associated with Ni
Hou et al. (2019)	China	Nested case–control	Mother-infant pairs (LBW = 246), (NBW = 406)	Al, As, Ba, Ca, Cd, Cr, Co, Cu, Mn, Mg, Mo, Ni, Fe, Pb, Rb, Se, Sn, Sb, Sr, Ti, V, and Zn	Serum	ICPMS	LBW	ENET	Maternal age, height and weight, gestational age, education level, and drinking and smoking (both prepregnancy and during pregnancy)	ENET - multimetal model demonstrated improved predictive accuracy for LBW compared to single metal models, as evidenced by a higher AUC value.
Howe et al. (2021)	USA	Prospective Cohort	Hispanic pregnancy women (n = 188)	As, Ba, Cd, Hg, Mo, Sn, Co, Ni, Sb, Tl	Urine	ICPMS	EFW, AC, FL, HC, BPD	BKMR	Prepregnancy weight, race, ethnicity, birth country, smoking status during the pregnancy, education level, and prenatal vitamin use.	An increase in Mo from the 25th to 75th percentile was associated with a 0.114 SD (approximately 7.4 g) higher EFW. On the other hand, an increase in Ba from the 25th to 75th percentile was associated with a −0.076 SD (approximately 4.9 g) lower EFW.
Howe et al. (2020)	USA	Prospective cohort	Lower-income Hispanic pregnancy women (n = 262)	As, Cd, Co, Hg, Ni, Tl, Pb, Mo, Sb, and Sn	Urine	ICPMS	BW	BKMR	Prepregnancy weight, race, ethnicity, and birth country	Hg and Ni ranked highest as predictors of BW for GA. An inverse linear association was estimated for Hg, whereas a positive association was estimated for Ni at low-to-moderate concentrations. A potential interaction between Hg and Ni was also identified.
Howe et al. (2022)	USA and Puerto Rico	Prospective cohort	Pooled sample from 3 cohorts (MADRES = 350, NHBCS = 184, and PROTECT = 468) (n = 1002)	Sb, Cd, Co, Hg, Mo, Ni, and Sn	Urine	ICPMS	BW for GA	BKMR	Maternal education, parity, maternal smoking during the pregnancy, second-hand smoke exposure during pregnancy, maternal prepregnancy BMI,	Sb, Hg, and Sn were inversely and linearly associated with BW for GA, while a positive linear association was identified for Ni
Hu et al. (2021)	Canada	Cohort	pregnant women (n = 1857)	As, Cd, Hg, Mn, Pb	Blood	ICPMS	BW	BKMR	Maternal age, race, education, smoking status, BMI, GA	Higher levels of Pb associated with a reduction in BW. Specifically, an increase in log2-transformed Pb from the 25th to the 75th percentile was associated with a posterior mean reduction of 47 g in BW.
Huang et al. (2021)	Bangladesh	Prospective cohort	Pregnant women (n = 745)	Li, Be, B, Na, Mg, Al, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Rb,	Cord blood	ICPMS	PTB	ENET and BKMR	Maternal age, marriage age, maternal BMI categories, maternal education level, paternal education level,	BKMR - When Ti, As, and Ba concentrations simultaneously increased from the 10th to the 90th

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
				Sr, Y, Zr, Nb, Mo, Ag, Cd, Sn, Sb, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Hg, Tl, Pb, Bi, Th, U					second-hand smoking, and family income level	percentile, the risk of preterm birth steadily increased ENET - Higher ERS was associated with higher probability of preterm birth
Kao et al. (2023)	Taiwan (People's Republic of China)	CS	Mother-infant pairs (n = 526)	Hg, Pb, Cd, and As	Meconium	ICPMS	BW, BL, HC	BKMR	Maternal educational level, age at delivery, reproductive history, and smoking habit, amalgam fillings, and fish consumption during the pregnancy	BKMR - Negative associations of the metal mixture with the birth weight, birth length, and head circumference, with an especially stronger association of the metal mixture with birth weight.
Kim et al. (2020a)	USA	Prospective cohort	Pregnant women (n = 390)	As, Ba, Be, Cd, Cr, Cu, Pb, Hg, Mn, Mo, Ni, Se, Sn, Tl, W, U, and Zn	Urine	ICPMS	AC, HC, FL, and EFW	PCA	Maternal age, race, education, type of health insurance, prepregnancy body mass index (BMI), self-reported tobacco use during pregnancy, self-reported alcohol use during pregnancy, parity, assisted reproductive technology (ART), and sex of neonate	PC 3 comprised of arsenic, mercury, and tin was inversely associated with head circumference z score (β = −0.14, 95 % CI = −0.23, −0.05) and the combined EFW and BW z score (β = −0.10, 95 % CI = −0.19, −0.01)
Kim et al. (2018)	USA	Nested case–control	Pregnant women, (cases n = 99) vs (controls n = 291)	As, Ba, Be, Cd, Cr, Cu, Pb, Hg, Mn, Mo, Ni, Se, Sn, Tl, W, U, and Zn	Urine	ICPMS	PTB	ENET and PCA	Maternal age, race/ethnicity, education, health insurance provider, prepregnancy BMI, self-reported tobacco and alcohol use during pregnancy, parity, use of assisted reproductive technology (ART), self-reported multivitamin use during pregnancy, and sex of the neonate	1. PC1: high loadings from toxic Cd, Mn, and Pb was not significantly associated with overall PTB or any subtype of PTB. 1. PC2: high loadings from Cu, Se, and Zn. showed a significant association with an increased risk of overall PTB and spontaneous PTB. 3. PC3: high loadings from As, Hg, and Sn did not show any significant associations with PTB.
Kim et al. (2020b)	China	CS	Pregnant women in informal e-waste recycling site (n = 314), vs unexposed site ((n = 320)	Pb, Cd, Cr, and Mn	Blood	GFAAS	BW, BL, HC, BMI, and PI	BKMR	Maternal age, maternal education, maternal occupation, maternal prepregnancy BMI, gravidity, environmental tobacco smoke (ETS), and neonate sex	Increased concentration of four metals from the 25th to the 75th percentile was associated with a decrease in the PI, HC, and BMI but not with BW
Lazarevic et al. (2022)	Australia	CS	Nonsmoking pregnant women (n = 166)	Cd, Cs, Li, Pb, Rb, Se, Sr, Zn, Sb, Cu, Mn, U, As, Ba, Co, Ni, Tl, and Sn	Blood and urine	ICPMS	BW, BL, HC, and PI	Bayesian structured additive regression model (BSARM)	Prepregnancy BMI gestational weight gain, maternal age, primiparity, level of education gross household income, place of residence, iron and folic acid supplementation, pregnancy vitamin use,	An increase in log blood Cs from the 25th to 75th percentile was associated with a reduction in birth weight of 124 g (90 % credible interval: −240 to −3 g)

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
									residential distance to, and medium–high trophic level fish consumption	
Lee et al. (2021a)	Bangladesh	Cohort study	Pregnant women (n = 1088)	As, Cd, Mn, Pb	Umbilical cord blood	ICPMS	Neonate size	BKMR	Maternal age, maternal BMI, infant sex, household income, secondhand smoke exposure during pregnancy, daily tea intake during pregnancy, study site, birth weight, birth length head circumference and gestational age at birth	There was a negative association between the metal mixtures and infant length and infant head circumference when the metals were above the 60th and 55th percentiles, respectively when compared to their median values. The association becomes stronger as the concentration of the metals increases.
Lee et al. (2020)	Republic of Korea	Prospective cohort study	Pregnant women (n = 719)	Hg, Pb and Cd	Maternal blood	ICPMS	BW	PCA and SPCA	Maternal age, Maternal education, Maternal pre pregnancy BMI, weight gained during pregnancy, gestational age, infant sex and parity	SPCA - exposure to Hg and Pb combined was associated with reduced birth weight (−55.32 g [95 % CI: −99.01 g to −11.64 g] birthweight reduces per a unit increase in both Hg and Pb.
Liu et al. (2022)	China	Nested case–control study	Pregnant women (n = 7187)	V, Cr, Co, Ni, Cu, Ga, Ag, Ba, Th, U, Zn, As, Rb, Sr, Cd, Cs, Tl, and Pb,	Maternal urine	ICPMS	PTB	ENET, WQSR AND BKMR	Maternal age, Infant gender, prepregnancy BMI, Parity, maternal education level, passive smoking during pregnancy, folic acid supplementation during pregnancy, gestational diabetes, hypertension during pregnancy	**ENET -** V, Cr, Zn, Ba, Cu, U, Ga, Ag, and Th were positively associated with PTB however V had the highest magnitude (most important metal). **WQSR** - all the metals combined showed positive association with PTB, with Cr and V the main driving mixture effect force on PTB. **BKMR -** In addition to confirming that the joint effect of the metal mixture increases the possibility of PTB, it furthermore highlighted an interaction between Zn and Cu resulting in positive association with PTB
Lu et al. (2022)	China	CS	Pregnant women (N = 195)	As, Ba, Cd, Ce, Co, Cs, Cu, Fe, Ga, Gd, Hg, Mn, Ni, Pb, Pr, Rb, Re, Sr, V, and Zn	Whole blood	ICPMS	Miscarriage	BKMR, WQS, GWQS	Maternal age, BMI, gestational age, history of pregnancies, history of miscarriages, parity, education, occupation, personal income, family income, smoking during pregnancy and alcohol consumption during pregnancy	**BKMR -** positive association between barium and miscarriage while copper and rubidium exposure revealed negative association. This was confirmed by WQS and GWQS. Barium was the most influential/weighted

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
										element to have a positive association with miscarriage. **GWSQ** - the mixture of only essential trace elements was negatively associated with miscarriage
Michael et al. (2022b)	Israel	CS	Pregnant women (n = 975)	As, Cd, Cr, Hg, Ni, Pb, Se, and Tl	Maternal urine	ICPMS	Anthropometric birth outcomes (BW, BL, HC)	BKMR	Maternal age, newborn gender, parity, tobacco exposure during pregnancy, socioeconomic status, geographic area, and creatinine concentration	**BKMR -** birthweight was negatively associated with Chromium and thallium but positively associated with nickel. Additionally, the birth length was negatively associated with chromium levels.
Rahman et al. (2021b)	USA	Prospective cohort	Pregnant women (n = 1391)	As, Ba, Cd, Cs, Cu, Mg, Mn, Pb, Se, Zn, and Hg.	Maternal blood	ICPMS	Birth outcomes (BW, BL, and HC)	BKMR	Maternal age, education, prepregnancy BMI, household income, smoking status, race/ethnicity, parity	As was associated with lower infant BW; higher concentration of Zn was also associated with larger infant female HC; higher concentration of Mn was associated with BL. Additionally, AS and Mn showed a synergistic association with male infant BW, while Pb and Zn showed an antagonistic relationship with male infant HC.
Ren et al. (2022)	China	Nested case–control study	Case control pop (n = 509), mothers with preterm babies (n = 87), control (n = 422)	Pb, Hg, As, Cd, Zn, Fe, Cu, and Se	Maternal hair	ICPMS	PTB	BKMR	Maternal age, ethnicity, prepregnancy height and weight, parity, education level, residence area, husband smoking status, passive smoking status, folate intake and the start time of folate supplementation, vaginitis status, habitual aquatic food intake	Exposure to a mixture of EDM (Pb, Hg, As and Cd) after controlling for all covariates had positive association with tPB and sPB while exposure to NTM (Zn, Fe, Cu and Se) resulted in decrease tPB and sPB risk. However, Fe was the most influential NTM with PIP of 0.716 followed by Zn (PIP: 0.563), Cu (PIP: 0.428) with the least influencer being Se (PIP: 0.287)
Signes-Pastor et al. (2019)	USA	cohort study	maternal-infant pairs (n = 989)	As, Mn and Pb	Maternal toenails	ICPMS	HC, FL, & BW	BKMR	Maternal age, smoked cigarette during pregnancy, maternal highest educational level, maternal BMI, infant sex.	Higher toenail As concentration was associated with decrease head circumference among male infants and an increase infant length and weight among female. The effect of the As on birth outcome was not modified by other metals in the mixture. Lower

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
										concentration of Mn was positively ass with female infant head circumference and higher concentrations was negatively associated. Furthermore a mixture of Pb with lower conc of other metals is associated with reduced head circumference, weight and length mostly in infant females.
Takatani et al. (2022)	Japan	Cohort study	Pregnant women (n = 93,739)	Pb, Cd, Hg, Se, and Mn	Maternal blood	ICPMS	Birth size (BW, BL, HC, CC)	Quantile g-computation and BKMR	Infant sex, gestational duration, maternal age at delivery, parity, pregnancy complications and mode of delivery	Quantile g-computation - Exposure to a mixture of Pb, Se, Cd and Hg decreased infant weight, length, head and chest circumference with lead being the strongest negative influencer, a quartile increase in the mixed metals reduce infant birth weight by 17.87 g, infant length by 0.04 cm, head circumference by 0.01 and chest circumference by 0.07 cm. on the other hand Manganese increases infant weight, length, head and chest circumference. BKMR established the effect of these metal mixtures on birth size to be additive.
Wang et al. (2022)	China	Nested case–control study	pregnant women (preterm infants (515), full term infants (595))	Na, Mg, K, Ca, Si, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Sr, Sn, Al, As, Y, Cd, Sb, Ce, Tl, Pb, and U	Cord blood	ICPMS	PTB	BKMR with probit link function	Gestational age, maternal age, pre pregnancy BMI, mother's education, annual household income, parity, baby's gender, delivery type and passive smoking	PTB decreases when pregnant women are exposed to mixture of K, Pb, Sb, Si, Sr, Ti and Zn. In addition, this decrease is largely influenced by Zn and Sr, however the protective effect of them (Zn and Sr) are reduced in the presence of higher levels concentration of Sb
Xu et al. (2022)	China	Nested case–control study	Pregnant women (74 full term birth; 74 cases, SPB)	B, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Rb, Sr, Mo, Sn, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Al, As, Cd, Sb, Ba, Hg, Pb, Li, Ti, Ge, Ag, Cs, U,	Maternal blood	ICPMS	Spontaneous PTB	BKMR	Age, BMI, education, occupation, residence, gravidity, parity, spontaneous abortion history, folic acid use, medication use, passive smoking, infant sex, fasting blood collection and sampling time	1. There was an association between the metal mixtures (Mn, Fe, Cu, Nd, Hg and Pb) and SPB risk. 2. There was an antagonistic effect on SPB risk between Cu and Mn with the other 4 metals fixed at median. 3. Additionally, a synergistic

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
										effect with mixture exposure between Mn and Nd with the other 4 metals fixed at median and SPB risk
Dou et al. (2022)	China	Cohort study	Maternal-infant pairs (1275)	Pb, As, Cd, Hg, Cr, V, Tl, and Ba	Maternal urine	ICPMS	EFW, HC, AC, FL	WQSR	Maternal birthdate, socioeconomic characteristics, smoking and drinking during pregnancy, maternal weight and height before pregnancy, maternal age	WQS = showed evidence of the significant association between metal mixtures and EFW at 34–36 weeks of gestation, and the relationship was mainly driven by Cr (30.41 %), Pb (23.92 %), and Tl (15.60 %)
Hu et al. (2022)	China	Prospective cohort study	Pregnant women (discovery; n = 1849) and (replication; n = 7255)	Al, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Rb, Sr, Cd, Cs, Ba, Tl, and Pb	Maternal urine	ICPMS	BW	ENET and LASSO	Maternal age, education, annual household income, active smoking, second-hand tobacco smoke exposure, alcohol consumption, and folic acid supplement use during pregnancy	ENET - V, Fe, Mn, Cs, and Ba were negatively associated with BW Z score, Co, Zn, and Sr showed positive associations.
Wu et al. (2023)	China	Cohort study	Pregnant women (n = 2394)	As, Cd, Co, Cr, Mo, Ni, Pb, Sb, Se, and Tl	Maternal urine	ICPMS	BW for GA	BKMR	Maternal age, prepregnancy weight, marital status, educational level, geographic living, smoking and drinking histories of pregnant women	BKMR = Tl, Ni, and Cd ranked among the top three predictors of BW for GA in girls. High Tl concentrations decreased the positive relationship between Cd and BW for GA and strengthened the negative association between Ni and BW for GA.
Yang et al. (2020)	China	Cohort study	Pregnant women (n = 734)	U, Cu, Pb, Se, Ba, Tl, Mn, Ni, Sr, As, Zn, Cd, V, Cr, Al, Co	Umbilical cord blood	ICPMS	BW	WQSR	Alcohol consumption, smoking, passive smoking during pregnancy, maternal age, education level, annual household income level, prepregnancy BMI, maternal weight gain, gestational weeks	Exposure to the metal mixtures reduced the birth weight z score with the major contributions to this negative effect being Cu (39.7 %), Ni (18.3 %), Mn (14.0 %) and Cd (13.1 %)
Zhang et al. (2022)	USA	Prospective cohort study	Pregnant women (n = 526)	As, Ba, Cd, Co, Cr, Cs, Cu, Mn, Ni, Pb, Sb and Zn	Maternal urine	ICPMS	Birth weight for gestational age (BWGA) z score	BKMR	Maternal race, maternal highest education, smoking during pregnancy, BMI, age at delivery and city of residency	BKMR - Co, Ni and Pb were negatively associated with BWGA Z score in infant males. Ba, Cs, Cu, Ni and Zn however had a negative association with BWGA Z score in females.
Zhao et al. (2020)	China	Cohort study	Pregnant women (n = 483)	As, Cd, Co, Cr, Mn, Ni, Pb, Se, Sn, Sr and Tl,	Maternal blood and urine	ICPMS	Placental weight, chorionic disc area, chorionic disc eccentricity, placental thickness, placental fetal birth weight ratio and birth weight	ENET and unpenalized regression	Maternal age at conception, maternal education, second hand smoke in pregnancy, parity, household income per year, pre pregnancy BMI, fetal gender and gestational duration at delivery	A unit increase in natural log transformed urine creatinine corrected (cc) Cd levels was associated with the reduction in placental weight by 7.2 g (95 % CI: −14–0.4). Blood Cd was also negatively associated with placental weight. Mediation analysis furthermore

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Table 1 (*continued*)

Author name & year	Location	Study design	Study population	Metals evaluated	Biological media for metals analysis	Metal detection methods	Outcome(s) studied	Mixture analysis method	Covariates	Main findings
										demonstrated that urine cc-Cd levels was associated with a decrease in infant weight by 21.3 g through the reduction in placental weight
Zilversmit Pao et al. (2019)	USA	Cohort study	Pregnant women (n = 1569)	Pb, Hg and Cd	Maternal blood	ICPMS	SGA	WQS	Education, ethnicity/race and income, depression and perceived stress, birth weight, gestational age, sex of the infant, marital status, parity, Age, maternal weight gain during the entire pregnancy	The combined effect of the 3 metals studied did not have any significant association with SGA
Zhao et al. (2023)	China	Cohort study	Pregnant women (n = 1081)	Be, Ti, Co, Fe, Mg, Mn, Ni, V, Mo, As, Cu, Ga, Rb, Se, Sr, Sb, Sn, Ag, Cd, W, Ba, Cs, Sm, Pb, Tl, U, Al, Cr, and Zn.	Maternal urine	ICPMS	PTB	ENET and BKMR	Maternal age, maternal education level, number of past pregnancies, and passive smoke exposure	ENET = Mg, Cu, Sn, Co, Tl, and Ti were positively associated with PTB, whereas Cs, Rb, and Mo were negatively associated with PTB. BKMR = joint effect of three “harmful” metals on PTB when all metals were at or above their 55th percentile compared with their median values

Abbreviations: ICPMS (Inductively coupled plasma mass spectrometry), GFAAS (graphite furnace atomic absorption spectrometry), As (Arsenic), Ba (Barium), Be (Beryllium), Cd (Cadmium), Co (Cobalt), Cr (Chromium), Cs (Cesium), Cu (Copper), Hg (Mercury), Mn (Manganese), Ni (Nickle), Pb (Lead), Ti, (Thallium), U (Uranium), V (Vanadium), Zn (Zinc), SGA (small for gestational age), LGA (large for gestational age), ENET (Elastic Net), BKMR (Bayesian Kernel Machine regression), ERS (Environmental risk score), BMI (Body mass index), Mo (molybdenum), Pt (Platinum), Sb (antimony), Sn (tin), W (tungsten), MMB (multimedia biomarker) ICC (intraclass correlation coefficient), WQS (weighted quantile sum regression), SG (specific gravity), OR (odds ratio), Na (Sodium), Mg (Magnesium), K (Potassium), Ca (Calcium), Rb (rubidium), Sr (strontium), Cs (cesium), Fe (Iron), Sc (Scandium), Y (yttrium), La (Lanthanum), Ce (cerium), Pr (praseodymium), Nd (neodymium), Sm (samarium), Eu (europium), Gd (gadolinium), Tb (terbium), Dy (dysprosium), Ho (holmium), Er (erbium), Tm (thulium), Yb (ytterbium), Lu (lutetium), Li (Lithium), Al (aluminum), Ga (gallium) B (Boron), Se (Selenium), Zr (zirconium), Nb (niobium), Ag (silver), Hf (hafnium), Ta (tantalum), Bi (bismuth), Th (thorium), CI (confident interval), LBW (low birth weight), NBW (normal birth weight) AUC (area under the curve), EFW (estimated fetal weight), AC (abdominal circumference), FL (femur length), HC (head circumference), BPD (biparietal diameter), SD (standard deviation), BW (birth weight), GA (gestational age), PTB (preterm birth), CS (cesarean section), PCA (Principal component analysis), ART (assisted reproductive technology), BL (birth length), PI (ponderal index), PC (Principal component), ETS (environmental tobacco smoke), Ge (germanium), SPCA (supervised principal analysis), WQSR (weighted quantile sum regression), GWQS (group weighted sum regression), NTM (nutritional trace metal(loids), EDM (endocrine disrupting metal(loids), tPB (total preterm birth), sPB (spontaneous preterm birth), PIP (posterior inclusion probabilities), BWGA (birth weight for gestational age), BSARM (Bayesian structured additive regression models), ICPMS (Inductively coupled plasma mass spectrometry), GFAAS (Graphite furnace atomic absorption spectrometry.

Table 2

Heat map of risk of bias assessment rating for included studies.

		Bias domains							
		Key criteria			Other criteria				
		Detection		Confounding	Selection	Attrition/ exclusion	Selective Reporting	Conflict of interest	Other Sources
Study	Design	Exposure	Outcome						
Ashrap et al. (2020)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Ashrap et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Chen et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Deyssenroth et al. (2018)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Dou et al. (2022)	Cohort	🟩	🟩	🟩	▩	▩	🟩	🟩	🟩
Hou et al. (2019)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Howe et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Howe et al. (2020)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Howe et al. (2022)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Hu et al. (2022)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Hu et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Huang et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Kao et al. (2023)	CS	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Kim et al. (2020a)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Kim et al. (2018)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Kim et al. (2020b)	CS	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Lazarevic et al. (2022)	CS	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Lee et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Lee et al. (2020)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Liu et al. (2022)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Lu et al. (2022)	CS	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Michael et al. (2022)	CS	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Rahman et al. (2021)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Ren et al. (2022)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Signes-Pastor et al. (2019)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Takatani et al. (2022)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Wang et al. (2022)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Wu et al. (2023)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Xu et al. (2022)	CC	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Yang et al. (2020)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Zhang et al. (2022)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Zhao et al. (2020)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Zhao et al. (2023)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Zilversmit Pao et al. (2019)	Cohort	🟩	🟩	🟩	▩	🟩	🟩	🟩	🟩
Legend									
Risk of bias rating	🟩 Low	▩ Probably low	🟨 Probably high	🟥 High					

Abbreviations; CC = Case-control; CS = Cross-sectional.

consisted of a low-income Hispanic population in Los Angeles.

In China, six studies investigated the effects of metal mixtures on birth weight (BW) (Hou et al., 2019; Hu et al., 2022; Kao et al., 2023; Kim et al., 2020b; Wu et al., 2023; Yang et al., 2020). Hou et al. (2019) specifically conducted a case–control study nested in the Guangxi Birth Cohort Study (GBCS), which is an ongoing multicenter prospective cohort study in China. They measured the total concentrations of 22 serum metals in 246 cases of low birth weight (LBW) and 406 cases of normal birth weight (NBW), serving as controls. The authors used an elastic net (ENET) regression model to select multiple metals associated with the risk of LBW. The multimetal compound exposure model revealed that 15 metals, selected using the ENET model, showed a significant association with an elevated risk of LBW (OR = 5.14, 95 % CI: 2.81–9.40). Furthermore, a positive association was observed between lower levels of serum cobalt (Co) and LBW, while lower levels of serum titanium (Ti) showed a negative association with LBW, particularly in pregnancies beyond 13 weeks of gestational age. In addition, both Co and Ti demonstrated nonlinear dose–response relationships with LBW. In a study conducted by Yang et al. (2020), the WQSR model was employed to estimate the relationships between a mixture of 16 metals and the birthweight z score. The analysis utilized 736 cord blood samples collected from a Chinese birth cohort study. The findings indicated a negative association between the estimated metal mixtures and the overall birthweight z score [β (95 % CI): −0.31 (−0.42, −0.20)]. Furthermore, the study identified the major contributors to the mixture index as Cu accounting for 39.7 %, Ni accounting for 18.3 %, Mn accounting for 14.0 %, and Cd accounting for 13.1 %. Similarly, Hu et al. (2022) conducted a two-stage analysis within two prospective cohorts situated in Wuhan, China, to assess the relationship between 18 metals and BW. The study encompassed a prenatal cohort (referred to as the discovery cohort; n = 1849) and the Healthy Baby Cohort (HBC) (referred to as the replication cohort; n = 7255). The authors applied two penalized regression models, i.e., elastic net regression for main effects and lasso for hierarchical interactions, to identify important mixture components associated with BW. Within the prenatal cohort, 8 metals were identified to be associated with z scores for birth weight using elastic net regression, and the findings were replicated in the HBC. Specifically, five of these metals (V, Mn, Fe, Cs, and Ba) showed negative associations with birth weight, whereas the other three metals (Co, Zn, and Sr) showed positive associations. In the same vein, Wu et al. (2023) utilized BKMR to estimate the association of individual metals or metal mixtures and birth weight for gestational age (BW for GA). The model showed a sex-specific relationship between prenatal exposure to metal mixtures and BW for GA with a significant negative association in girls and a nonsignificant positive association in boys. Alternatively, one study assessed the associations between birth outcomes and living in a community with a history of informal e-waste recycling (Kim et al., 2020b). The researchers analyzed maternal whole blood samples from pregnant women in Guiyu, an informal e-waste recycling area (n = 314), as well as from an unexposed control site called Haojiang (n = 320), to measure levels of Pb, Cd, Cr, and Mn at the time of delivery. Using BKMR, the cumulative impact of all 4 metals did not show any significant association with BW. In Taiwan, a region within the People's Republic of China, Kao and colleagues conducted a cross-sectional study in 2023 to explore the links between a combination of Hg, Pb, Cd, and As levels measured in meconium and various birth outcomes, including birth weight (BW) (Kao et al., 2023). The study findings demonstrated a negative relationship between the metal mixture and BW. Specifically, the concentrations of Hg and Pb in the meconium exhibited a linear inverse relationship with BW, with Hg identified as the most significant contributor to the overall mixture effect.

In a study conducted in Bangladesh, Chen et al. (2021) employed both BKMR and WQS regression models to evaluate the effects of a metal mixture on BW. The analysis involved examining fifty-six elements in umbilical cord serum from 745 mother-infant pairs in Bangladesh. The findings from the BKMR analysis demonstrated a significant negative relationship between six metals (Li, Mn, Cu, Co, Y, and Er) and BW. Conversely, higher levels of Se exhibited a positive association with BW. In addition, an exposure risk score (ERS) was developed by calculating the weighted sum of the elements using the mean weight of elements from the WQS regression. The ERS reflected the average contributions of Li (48 %), Er (21 %), Co (16 %), Cu (7 %), Mn (7 %), and Y (1 %), with a higher ERS indicating an increased exposure to risk elements. The results obtained from the WQS revealed that with each increase in ERS, BW decreased by 64.73 g [95 % CI: (−86.75,−42.71), P = 1.23 × 10–8]. This effect was more pronounced among individuals with a high ERS [b = −21.73, 95 % CI: (−31.16,−12.31), Ptrend = 7.21 × 10–6]. In a comparable cross-sectional study carried out in Western Australia (n = 166), Lazarevic et al. (2022) observed that an increase in log blood Cs between the 25th and 75th percentile was linked to a decrease in BW of 124 g (90 % credible interval: −240 to −3 g). In a Canadian study, Hu et al. (2021) conducted an analysis quantifying the concentrations of 21 chemicals from five classes of endocrine disrupting chemicals (EDCs), which included organochlorine compounds (OCs), metals, perfluoroalkyl substances (PFAS), phenols, and phthalate metabolites. The study utilized a mixture of five metals (As, Cd, Hg, Mn, and Pb) to assess their association with BW using BKMR. The findings of the study revealed that among the components of the metal mixture, Pb emerged as the primary contributor to the adverse effect on BW. For instance, an increase in the log2-transformed Pb levels from the 25th to the 75th percentile was associated with a posterior mean reduction of −47 g in birth weight, while holding the other components in the metal mixture constant at their median levels (q.fixed = 0.5).

Three studies were conducted to examine the effects of a mixture of metals on BW in Korea (Lee et al., 2020), Israel (Michael et al., 2022b), and Japan (Takatani et al., 2022). The Korean study conducted by S. Lee et al. (2020) aimed to investigate the impact of prenatal exposure to various environmental pollutants (such as heavy metals, bisphenol, phthalates, and air pollutants) on BW. The concentrations of three heavy metals (Hg, Pb, and Cd) were measured in maternal blood samples. Using a supervised principal component analysis (SPCA) model, the study found that exposure to nitrogen dioxide (NO_2) during early pregnancy and combined exposure to mercury and lead during late pregnancy were negatively associated with BW. Specifically, for each increase in the corresponding component, birth weight decreased by 46.63 g (95 % CI: −90.65 g to −2.62 g) and 55.32 g (95 % CI: −99.01 g to −11.64 g), respectively. In a study conducted by Michael et al. (2022b), BKMR was employed to examine the associations between eight heavy metals (As, Cd, Cr, Hg, Ni, Pb, Se, and Ti) detected in maternal urine samples collected on the day of delivery and BW. The results indicated that Cr and Ti showed negative associations with BW, with Cr being identified as the most influential metal in predicting weight. On the other hand, a positive association between Ni and BW was suggested. Similarly, Takatani et al. (2022) conducted a study utilizing both quantile g-computation and BKMR models to assess the combined effect of five metals (Pb, Cd, Hg, Se, and Mn) measured in the blood of pregnant women participating in the Japan Environment and Children's Study (JECS) (n = 93,739) on BW. The quantile g-computation analysis revealed that a quartile increase in the concentrations of the mixed metals led to a reduction in BW by 17.87 g, with Pb identified as the strongest contributor to the mixture effect. The BKMR analysis indicated that the metals exhibited an additive effect rather than a synergistic effect (Table S5).

3.4.2. Neonate size

In this review, a total of 11 studies examined the association between exposure to metal mixtures and neonate size. Among these studies, four were conducted in the United States (Howe et al., 2021; Kim et al., 2020a; Rahman et al., 2021b; Signes-Pastor et al., 2019), while the remaining six studies were conducted in various countries: Taiwan (China) (Kao et al., 2023), China (Dou et al., 2022; Kim et al., 2020b), Australia (Lazarevic et al., 2022), Bangladesh (Lee et al., 2021a), Israel (Michael et al., 2022b), and Japan (Takatani et al., 2022). Various parameters were utilized as proxies for assessing neonate size, including estimated fetal weight (EFW), abdominal circumference (AC), femur length (FL), head circumference (HC), biparietal diameter (BPD), birth length (BL), and ponderal index (PI). Six of these were cohort studies, and the remaining four were cross-sectional in design. Of the 10 studies included in the review, seven employed BKMR as the primary method for analyzing the mixture effects. One study utilized both BKMR and quantile g-computation methods (Takatani et al., 2022), while the remaining studies employed PCA (Kim et al., 2020a) and BSARM (Lazarevic et al., 2022), respectively.

Howe et al. (2021), Kim et al. (2020a), Rahman et al. (2021b), and Signes-Pastor et al. (2019) all employed a cohort study design to assess metal mixture exposure and fetal size in the USA. Among these studies, three (Howe et al., 2021; Rahman et al., 2021b; Signes-Pastor et al., 2019) utilized BKMR as the method for analyzing the mixtures, while Kim et al. (2020a) employed PCA as the analysis method for the mixtures. The study by Howe et al. (2021) investigated the impact of a mixture of six metals (As, Ba, Cd, Hg, Mo, Sn) on fetal size in mid-pregnancy in the MADRES Study. They utilized fetal biometry measurements (EFW, AC, HC, BPD, FL) obtained during routine anatomy ultrasounds and restricted analyses to fetal measurements obtained between 18 and 22 weeks gestation. The results of the BKMR analysis revealed that Mo ranked highest among the metals as a predictor of EFW, showing a positive linear association. An increase in Mo from the 25th to 75th percentile was associated with a 0.114 SD higher EFW, equivalent to approximately 7.4 g higher EFW. On the other hand, Ba showed an inverse linear association with EFW. An increase in Ba from the 25th to 75th percentile was associated with a −0.076 SD lower EFW, equivalent to an approximately 4.9 g smaller EFW. Further analysis showed that Mo consistently had the highest contribution to the associations with other fetal measures (AC, FL, HC, BPD), while Ba had the highest contribution to associations with AC and BPD only. Rahman et al. (2021b) and Signes-Pastor et al. (2019) evaluated the impact of metal mixtures on HC and BL using data from the Project Viva and New Hampshire Birth Cohort Study (NHBCS), respectively. Both studies employed BKMR as the method for analyzing the mixtures, but there were differences in the metals measured and the sample sources. In Rahman et al. (2021b), 11 metals (As, Ba, Cd, Cs, Cu, Mg, Mn, Pb, Se, Zn, and Hg) in maternal blood were measured. They discovered a positive association between Mn and BL, indicating that higher Mn levels were linked to longer birth lengths. In addition, Zn was found to be associated with a larger HC in newborns. On the other hand, Signes-Pastor et al. (2019) focused on three metals (As, Mn, and Pb) measured in maternal toenails. Their findings revealed a complex relationship between Mn and HC. At lower concentrations, Mn showed a positive association with HC in newborns. However, at higher concentrations, especially among female infants, Mn exhibited a negative association with HC. Kim and colleagues conducted an analysis on the LIFECODES birth cohort, examining the impact of 17 urinary metals, both individually and as a mixture, on fetal growth measures. The researchers utilized ultrasound to assess abdominal circumference (AC), head circumference (HC), and femur length (FL), which were then used to estimate fetal weight (EFW) at approximately 26 and 35 weeks of gestation (Kim et al., 2020a). The results of their PCA revealed that the PCA component that comprised arsenic, mercury, and tin was associated with a decreased HC z score (−0.14 [95 % CI, −0.23, −0.05]).

Four studies conducted in China (Kao et al., 2023; Kim et al., 2020b), Australia (Lazarevic et al., 2022), and Israel (Michael et al., 2022b) employed a cross-sectional design to examine the associations between metal mixture exposure and neonate size. Three of these studies (Kao et al., 2023; Kim et al., 2020b; Michael et al., 2022b) utilized BKMR to assess the impact of metal mixtures on neonate size measures, including birth length (BL), head circumference (HC), and ponderal index (PI). In contrast, Lazarevic et al. (2022) utilized the Bayesian Structured Additive Regression Model (BSARM) for their analysis. In the study by Kao et al. (2023) in Taiwan, a region within China, the authors measured the levels of metals (Hg, Pb, Cd, and As) in meconium samples. Their findings revealed negative associations between the metal mixture and both BL and HC. Among the metals, Pb concentration emerged as the most influential factor in these associations. Similarly, among e-waste workers in China, Kim et al. (2020b) found that cumulative exposure to metals (Pb, Cd, Cr, and Mn) was related to lower HC, BMI, and PI. In contrast, Lazarevic et al. (2022) employed the Bayesian Structured Additive Regression Model (BSARM) and reported no significant associations between mixtures of chemicals and measures of neonatal growth, including BL, HC, and PI. This finding was based on their analysis of neonates who participated in the Australian Maternal Exposures to Toxic Substances (AMETS) study.

Among Bangladeshi children, Lee et al. (2021a) assessed the association between metal mixtures (As, Cd, Mn, Pb) in umbilical cord blood and neonate size using BKMR. The results of their study found a significant negative association between metal mixtures and BL and HC when all metal concentrations were above the 60th and 55th percentiles, respectively, compared with the median. Similarly, a study conducted in Japan by Takatani et al. (2022) analyzed the effects of metal mixtures (Pb, Se, Cd, Hg, and Mn) on neonate size using a quantile g-computation approach. The results showed that Pb, Se, Cd, and Hg were associated with decreased BL, HC, and CC. On the other hand, Mn was associated with an increase in these metrics. Among all the metals, Pb had the strongest effect in reducing all birth size measurements. Following a similar line of investigation, Dou et al. (2022) utilized the weighted quantile sum (WQS) model to evaluate the overall effect of 8 metals (Pb, Cd, Hg, As, Cr, V, Tl and Ba) on fetal growth during pregnancy. The authors used data of maternal-infant pairs ($n = 1275$) from the Jiangsu Birth Cohort (JBC) in China. The results of their analysis showed that maternal exposure to metal mixtures was significantly associated with reduced EFW at 34–36 weeks of gestation, and this association was mainly driven by Cr (30.41 %), Pb (23.92 %), and Tl (15.60 %) (Table S6).

3.4.3. *Preterm birth*

Out of the 34 studies included in this review, nine specifically investigated on the effect of metal exposure on preterm birth. Of this number ($n = 9$), five were conducted in China (Liu et al., 2022; Ren et al., 2022; Wang et al., 2022; Xu et al., 2022; Zhao et al., 2023), two in Puerto Rico (Ashrap et al., 2020; Ashrap et al., 2021) and one each in the USA (Kim et al., 2018) and Bangladesh (Huang et al., 2021). A nested case–control study design was used in five out of the nine studies, while the remaining four used a prospective cohort study design. Notably, five of the studies (Ashrap et al., 2020; Huang et al., 2021; Kim et al., 2018; Liu et al., 2022; Wang et al., 2022) employed a combination of multipollutant analytical tools to estimate the association between toxic exposure and preterm birth. Among these multipollutant analytical methods, BKMR was the most commonly used ($n = 7$), followed by ENET ($n = 5$), WQRS ($n = 1$), PCA ($n = 1$), and ERS ($n = 1$).

Of the studies conducted in China, Wang et al. (2022) utilized BKMR to assess the association between concentrations of elements in maternal cord blood and preterm birth. Out of the 14 elements examined, only 7 (K, Pb, Sb, Si, Sr, Tl, and Zn) with $PIP > 0.5$ were included in the model. The analysis of the model indicated that the risk of preterm birth decreased significantly with increasing concentrations of the element mixture when InC (interaction contrast) was larger than the median. However, an antagonistic effect was observed between Sb and Zn as well as Sb and Sr when interacting with each other. Similarly, Ren et al. (2022) employed BKMR to investigate the association between levels of trace element mixtures in hair and PTB. The model analysis revealed that hair nutritional trace metal(loid)s (NTMs) (Zn, Fe, Co, and Se) exhibited a significant, monotonous, and inverse association with the risk of spontaneous preterm birth (SPB) after controlling for covariates and endocrine disrupting metal(loid)s [EDMs; Pb, Hg, As, and Cd]. Among these hair NTMs, Fe had the highest contribution to the association with a posterior inclusion probability (PIP) of 0.716, followed by Zn (PIP of 0.563). Furthermore, a mixture of hair EDMs (Pb, Hg, As, Cd) showed a positive association with both term preterm birth (tPB) and SPB after adjusting for covariates and NTMs. Once again, Liu et al. (2022) conducted a study to investigate the associations between maternal exposure to multiple metals and preterm birth (PTB) using maternal urine. The study employed three statistical tools, namely, BKMR, WQSR, and ENET, to estimate the metal mixtures and their impact on PTB. Using ENET, 9 metals (V, Cr, Zn, Ba, Cu, U, Ga, Ag, and Th) were positively associated with PTB, with V exhibiting the strongest association ($B = 0.23$). WQSR analysis indicated a positive combined effect of metal mixtures on PTB (OR: 1.44, 95 % CI: 1.32–1.57), with Cr ($weight = 0.41$) and V ($weight = 0.32$) having the highest weights among the metals. BKMR analysis further confirmed the positive association between metal mixtures and PTB. The model highlighted the nonlinear relationship of V and Cu with PTB, as well as the potential interaction between Zn and Cu. Furthermore, Xu et al. (2022) employed BKMR to explore the associations between maternal exposure to a mixture of six metals (Mn, Fe, Cu, Nd, Hg, and Pb) during early pregnancy and the risk of spontaneous preterm birth (SPB). The study observed a positive association between the metal mixture and the risk of SPB. Specifically, Cu and Nd showed significantly positive effects on the risk of SPB when the other four metals were fixed at the 25th, 50th, and 75th percentiles. The study also observed an antagonistic effect between Cu and a high concentration of Mn when the other four metals were fixed at the median, while a synergistic effect was observed between Mn and a high concentration of Nd. Similarly, Zhao et al. (2023) conducted a cohort study to evaluate the mixture effect of maternal urinary metal(loid) exposure and the risk of preterm birth in the Tibetan Plateau, China. The researchers used both ENET and BKMR to explore the joint associations. The results of their study revealed that Mg, Cu, and Sn were the main metal(loid)s positively associated with PTB, with Mg being the dominant metal(loid) associated with PTB in a J-shape.

Ashrap et al. (2021) conducted a study in Puerto Rico to assess the association between metal mixtures in pregnant women's urine and blood, integrated multibiological media usage, and birth outcomes. The study identified Pb as the most significant contributor to blood ERS as well as the two integrated multimedia biomarkers of ERS. Individuals with high ERS in the 3rd tertile exhibited increased odds of PTB compared to individuals with low ERS in the 1st tertile, with a 2.8-fold (95 % CI, 1.68–6.25) increase for blood ERS, a 3.9-fold (95 % CI, 2.34–11.42) increase for multimedia biomarkers composed using ICC, and a 5.2-fold (95 % CI, 2.34–11.42) increase for multimedia biomarkers composed using WQS. The four ERSs demonstrated comparable predictive performance (AUC, 0.64–0.68) when urine was examined with specific gravity-corrected concentrations. Another study conducted by the same group in Puerto Rico in 2020 (Ashrap et al., 2020) investigated the effects of exposure to metals and metalloids among pregnant women and birth outcomes. From this study, Pb and Zn had nonzero weights of 0.057 ($OR = 1.06$) and 0.011 ($OR = 1.01$), respectively, and were selected as important predictors of PTB. The ERS was constructed using these metals (Pb and Zn). The odds ratio (OR) for preterm birth comparing the highest versus the lowest tertile of ERS was 2.13 (95 % CI $= 1.12–5.49$, $p = 0.02$). Furthermore, the study demonstrated that Pb and Zn exhibited a positive linear relationship with preterm birth (PTB) at higher levels, and the overall trend for Mn was also positive and generally linear. However, there was no interaction observed between the different metals and their association with PTB.

In the United States of America, a study conducted by Kim et al. (2018) aimed to examine the associations between 17 urinary trace metals among pregnant women and PTB. Among the 17 urinary trace metals studied, Cu (copper) was identified as the most significant metal associated with PTB using ENET. In addition, a principal component (PC) composed of Cu, Se, and Zn was found to be associated with increased odds of overall and spontaneous PTB. One study conducted in Bangladesh investigated the mixed effects of elements on PTB using ENET and BKMR statistical tools (Huang et al., 2021). The study highlighted the cord blood levels of Ti as the most important predictor of PTB, followed by As and Ba. The study showed that a simultaneous increase in Ti, As, and Ba levels from the 10th to 90th percentile steadily increased the risk of PTB (OR = 1.54, 95 % CI: 1.08–2.18) compared to women with concentrations at the 50th percentile. Furthermore, using BKMR, the study identified a synergistic interaction between As and Ba on the risk of PTB (Table S7).

3.4.4. *Small for gestational age*

In this review, three articles investigated the effects of metal exposure on small for gestational age (SGA). All articles utilized a cohort study design, with one conducted in Puerto Rico (Ashrap et al., 2021), one in the USA (Zilversmit Pao et al., 2019) and the other on Rhodes Island (Deyssenroth et al., 2018). The included studies employed various multipollutant statistical methods, including WQS, BKMR, ENET, and ERS ridge regression. The study by Ashrap et al. (2021) in Puerto Rico examined the mixed effects of metals and metalloids on birth outcomes, including SGA. The authors conducted measurements of metal concentrations in both urine and blood samples. They then utilized the intraclass-correlation coefficient (ICC) and weighted quantile sum (WQS) approaches to integrate exposure estimates from the paired urine and blood biomarkers into multimedia biomarkers (MMBs). Furthermore, ridge regression was employed to construct environmental risk scores (ERSs) as weighted summary measures of the effects of metals. The weights used in the ERSs were derived from regression coefficients obtained from models assessing the association between metal mixtures and the specific outcome of interest. The study found that all 10 metal mixtures studied (Co, Cs, Cu, Mn, Ni, Zn, As, Cd, Hg, and Pb) were associated with SGA. The ERSs, which included metal exposure in urine, blood, and multimedia biomarker groupings, were significantly associated with lower birth z scores. However, the ORs of SGA obtained from MMBs were found to be greater than those derived from using only urine or blood biomarkers. Similarly, Deyssenroth et al. (2018) examined intrauterine multimetal exposure and SGA in Rhode Island. Using WQS analysis, the authors observed a 2.7-fold increase in the odds of SGA status (OR = 2.73, 95 % CI [1.04, 7.18]) for a unit increase in metal mixture exposure. The predominant metals in the mixture were As (44.4 %) and Cd (17.8 %). Additionally, a metal mixture predominated by Ni (23.6 %) and Al (22.3 %) was significantly associated with decreased odds of SGA status (OR = 0.24, 95 % CI [0.08, 0.76]). The results from WQS analysis were confirmed by BKMR. In contrast, Zilversmit Pao et al. (2019) conducted a study in the USA using the WQS model and found no significant association between metals (Pb, Hg, and Cd) and SGA outcomes (Table S8).

3.4.5. *Other outcomes*

The other outcomes of interest identified in this review were miscarriage and placental changes. These two studies were conducted in China, one as a cohort study and the other as a cross-sectional study. Among the two studies, one utilized ENET and unpenalized regression to assess the effect of metal mixture exposure on placental characteristics (Zhao et al., 2020), while the other employed BKMR, WQS, and GWQS to examine the impact of metal mixture exposure on miscarriage (Lu et al., 2022).

Regarding the study on placental characteristics by Zhao et al. (2020), an equal number of metals were measured in maternal urine and blood. Out of the 11 urine metals analyzed, the ENET model selected Cd and Se as having an effect on placental weight. Further analysis using the unpenalized regression model revealed that an increase in one unit (natural-logarithm (ln)-transformed urine creatinine corrected (CC)) Cd levels was associated with a reduction in placental weight of −7.2 g (95 % confidence interval (CI): −14.0, −0.4). Similarly, blood Cd and Co were also retained, and further unpenalized effect estimates demonstrated an inverse association with placental weight (β = −7.5, 95 % CI: −17.0, 1.9) and Co (β = −11.1, 95 % CI: −24.1, 1.9). To assess the effect of the metal mixture on the placental fetal birth weight ratio (PFR), Cd and Co were selected by the ENET model. Further unpenalized estimates showed inverse associations with PFR (β = −0.3, 95 % CI: −0.6, 0.01) and (β = −0.32, 95 % CI: −0.72, 0.09).

Lu et al. (2022) also investigated the joint association between trace elements and miscarriage. Using the BKMR model, they identified Ba as being positively associated with spontaneous abortion, while copper and rubidium exhibited a negative association with miscarriage. WQS analysis highlighted a general positive association between mixed metal elements and miscarriage (OR: 1.71; 95 % CI: 1.07, 2.78), with barium (75.7 %) having the highest weighted element, indicating its major contribution to miscarriage. Similarly, the GWQS results also indicated that the toxic trace element group dominated by barium was significantly associated with increased odds ratios (OR: 2.71; 95 % CI: 1.74, 4.38) of miscarriage. Additionally, a negative association was observed between the essential trace element group and miscarriage (OR: 0.32; 95 % CI: 0.18, 0.54), with rubidium contributing the most to this result (Table S9).

4. Discussion

4.1. *Summary of results*

To the best of our knowledge, this systematic review represents the first comprehensive evaluation of the association between multi-metal exposure and pregnancy and birth outcomes. Through a meticulous search process, we identified a total of 34 epidemiological studies utilizing prospective cohort, cohort-based case–control, and cross-sectional designs to investigate the relationship between exposure to metal mixtures and the risk of adverse pregnancy and birth outcomes. The insights gained from this review underscore the heterogeneous impacts of metal mixtures on pregnancy and birth outcomes, observed across various populations and exposure scenarios. Overall, the majority of the included studies reported significant associations, consistently indicating that metal mixtures are associated with an elevated risk of low birth weight (LBW), reduced neonate size, preterm birth (PTB), small for gestational age (SGA), and miscarriage. Furthermore, our review identified specific metals within the mixtures that contributed more strongly to these health risks, emphasizing their significance as risk drivers. In addition, several studies within our review highlighted the presence of potential, synergistic, and antagonistic interactions among metal mixtures. However, it is important to note that some studies reported null associations with certain birth outcomes, and in some cases, associations were observed in the opposite direction, particularly with essential metals. These discrepancies may be attributed to the diverse metals analyzed and the varied methods employed across the studies, contributing to the heterogeneity of the results.

4.2. *Comparison with previous studies*

Our comprehensive review of metal mixture exposure is consistent with prior research, revealing substantial associations that align with studies focusing on the impact of individual metal exposures on adverse pregnancy and birth outcomes. For instance, systematic reviews and meta-analyses conducted by Amegah et al. (2021) and Khoshhali et al. (2020) revealed a correlation between cadmium exposure and an increased risk of low birth weight (LBW). In addition, by Dack et al. (2021) highlighted that higher-quality studies reported a negative association between mercury exposure and birth weight. Similarly, Quansah et al. (2015) demonstrated that environmental arsenic exposure was significantly associated with reduced birth weight and an elevated risk of spontaneous abortion.

In addition, a meta-analysis conducted by Wang et al. (2020) provided quantitative evidence supporting the relationship between prenatal Pb exposure and reduced birth weight. In our review, consistent patterns emerged regarding birth weight (BW), with the majority of studies (16 out of 17) reporting a strong association between metal mixture exposure and BW. Only one study reported a null association. Various metals, including mercury (Hg), nickel (Ni), arsenic (As), cadmium (Cd), manganese (Mn), cobalt (Co), lead (Pb), zinc (Zn), barium (Ba), cesium (Cs), copper (Cu), selenium (Se), and chromium (Cr), were identified as significant risk factors in this association. These findings provide further support to the existing body of research emphasizing the potential risks associated with both individual metal exposures and the combined effects of metal mixtures on pregnancy and birth outcomes.

However, in contrast to the aforementioned associations, a systematic review and meta-analysis by Khoshhali et al. (2020) did not find a significant relationship between maternal exposure to Cd and birth length or head circumference. Similarly, Dack et al. (2021) reported no strong evidence of an association between mercury exposure and birth length or head circumference. In our analysis, we identified both positive and negative associations between metal mixtures and neonate size measures, such as estimated fetal weight (EFW), abdominal circumference (AC), femur length (FL), head circumference (HC), biparietal diameter (BPD), birth length (BL), and ponderal index (PI). While metals such as molybdenum (Mo), manganese (Mn), zinc (Zn), and lead (Pb) consistently emerged as significant predictors of neonate size, the specific associations varied across studies. Interestingly, the majority of studies (8 out of 11) indicated links between metal mixtures and reduced neonate size measurements, suggesting that exposure to specific combinations of metals may contribute to growth restriction and smaller neonate size.

In a recent review by Wu et al. (2022), maternal exposure to lead (Pb), cadmium (Cd), chromium (Cr), cobalt (Co), and manganese (Mn) was found to correlate with an increased risk of preterm birth (PTB). Our findings align with this, as we observed a consistent association between metal mixture exposure and higher odds of PTB, supported by seven out of the nine studies included in our analysis. Regarding small for gestational age (SGA), two systematic reviews and meta-analyses by Amegah et al. (2021) and Habibian Sezavar et al. (2022) found that maternal exposure to Cd increased the risk of SGA. We found consistent evidence indicating that exposure to various metal mixtures, including cobalt (Co), cesium (Cs), copper (Cu), manganese (Mn), nickel (Ni), zinc (Zn), arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb), is associated with an increased risk of SGA.

These comparisons with previous studies provide valuable support for the associations found in our review. The consistent findings across multiple studies reinforce the potential risks posed by both individual metal exposures and the combined effects of metal mixtures on pregnancy and birth outcomes.

4.3. Biological plausibility

The mechanisms through which metals impact pregnancy and fetal health are well documented (Eaves et al., 2023; Sultana et al., 2017). The developing fetus is especially susceptible to the adverse effects of metals due to its rapid rate of cell division and differentiation (Taylor et al., 2014). The placenta, a vital organ during pregnancy, serves as the central controller of the intrauterine environment (Burton and Jauniaux, 2015). The dysregulation of critical biological pathways within the placenta serves as a key factor underlying the biological mechanisms linking metal exposure to adverse pregnancy outcomes.

In laboratory animals, prenatal arsenic exposure causes spontaneous abortion by defective implantation or zygote development and aneuploidy or through aberrant placental vasculogenesis and placental insufficiency (He et al., 2007). Experimental studies have demonstrated that metal(loid)s alter maternal and placental hormones, including estradiol, progesterone, testosterone, and thyroid stimulating hormone (TSH), among others (Iavicoli et al., 2009). For example, Cd and Hg exposure stimulate progesterone production, while Hg and Pb reduce plasma testosterone levels in experimental animals (Badger et al., 1998; Davis et al., 2001). Cadmium can also alter the secretory patterns of pituitary hormones, including TSH (Lafuente et al., 2003). Moreover, experimental studies have provided evidence that cadmium could impair placental circulation, inhibiting the transport of nutrients from the mother to the fetus. Furthermore, combined exposure to inorganic arsenic (iAs) and Cd has been observed to exhibit a synergistic effect in stimulating the expression of crucial gene biomarkers in placental JEG-3 cells (Adebambo et al., 2015). These cells serve as a valuable model for assessing cellular responses to exposures during pregnancy, emphasizing the significance of conducting mixture analysis to comprehensively understand the effects of combined exposures (Adebambo et al., 2015).

Epidemiological studies have also provided evidence that metals including but not limited to Cd, Pb, Hg, As, Cu, and Se have the potential to induce oxidative stress, inflammation, endocrine disruption, and epigenetic modifications. These biological effects can contribute to a broad spectrum of adverse pregnancy and birth outcomes through the disruption of normal placental functioning, impairment of nutrient transport to the fetus, the development of preeclampsia, and interference with hormonal activities (Eaves et al., 2023; Kim et al., 2019; Paithankar et al., 2021; Valko et al., 2005). For instance, oxidative stress is strongly linked to placental aging and has been implicated in various adverse pregnancy outcomes, such as spontaneous preterm birth, stillbirth, miscarriage, and intrauterine growth retardation (IUGR) (Sultana et al., 2017). In pregnant women, the accumulation of Cd in the placenta has been found to result in the inhibition of trophoblastic invasion, reduced steroidogenesis, and altered regulation of essential nutritive metals. These effects can have detrimental impacts on both fetal and maternal health (Esteban-Vasallo et al., 2012). Another study suggested that metal(oids) alter maternal hormones, including corticotropin-releasing hormone (CRH), sex-hormone binding globulin (SHBG), estriol (E3), progesterone, and testosterone (Rivera-Núñez et al., 2021). Similarly, Eaves et al. (2023) revealed that metal mixtures have the potential to affect birth weight through specific pathways in the placenta. In particular, placental inflammation-related pathways involving Eukaryotic Initiation Factor 2 (EIF2) and Nuclear Factor kappa-light-chain-enhancer of Activated B Cells (NF-kB) signaling, as well as gene expression changes in DNA Methyl Transferase 1 (DNMT1) associated with epigenetic processes, were identified as key mechanisms influenced by metal exposure (Eaves et al., 2023).

4.4. Statistical methods for analyzing effects of metal mixtures

Humans are consistently exposed to a multitude of chemical pollutants simultaneously. Nevertheless, many previous epidemiological studies have employed single pollutant models to evaluate the impact of these chemicals on human health, despite the limitations associated with this approach (Guan et al., 2012; Wai et al., 2017). For example, in single pollutant models, it is not clear if an observed association reflects the effect of the analyzed pollutant or if it acts as a surrogate for another pollutant possibly originating from the same source. Furthermore, these single-pollutant models fall short in capturing the complexity and interactions among various exposures. Attempting to employ mutual regression by analyzing the health effects of multiple pollutants together in a regression model is in many cases not meaningful because of the usually high correlation between these pollutants (Stafoggia et al., 2017). As a result, researchers are increasingly turning to more advanced statistical methods to explore the health impacts of exposure mixtures. These methods are known to accurately assess both the individual and joint effects of multiple correlated exposures on human health (Billionnet et al., 2012).

Across the studies included in this review, the most frequently employed analytical methods for handling exposure mixtures include BKMR, PCA, ENET, and WQSR. Less frequently used methods include LASSO, and quantile-based g-computation. The BKMR is a supervised, semi-parametric method that flexibly model the relationship between a large number of exposure variables/mixture components and a particular health outcome (Bobb et al., 2015). The BKMR uses a kernel function to estimate the combined effects of a mixture of pollutants of interest, examine potential interactions between pollutants, potential non-linear and non-additive effects between pollutants while adjusting for possible confounding factors (Bobb et al., 2018; Valeri et al., 2017). In addition, a hierarchical variable selection extension is incorporated to address collinearity in the mixture components, allowing the incorporation of prior knowledge about the mixture's structure (Bobb et al., 2015). The hierarchical variable selection approach allows estimating the posterior inclusion probability for each exposure (Stafoggia et al., 2017). This helps in identifying which components of a mixture are responsible for health effects. However, BKMR often requires a large sample size due to its non-parametric property (Bobb et al., 2018; Gibson et al., 2019). In contrast, PCA is an unsupervised dimension reduction technique widely employed. Its primary objective is to capture the maximum amount of total variance within the data while using a reduced number of components (Gibson et al., 2019). While PCA remains a popular choice, it has its limitations. These include yielding an orthogonal solution, which may not accurately represent real-world exposure patterns if they are not independent. Furthermore, PCA does not provide assurance of an easily interpretable solution, and it requires the researcher to make decisions regarding the number of components to retain for further analysis (Gibson et al., 2019; Stafoggia et al., 2017). The WQSR is another supervised mixture analysis method that initially involves categorizing all exposures, typically into quartiles. Then, a single index is created to summarize these exposures, and it's calculated as a weighted average of the categorized exposures (Stafoggia et al., 2017). The index, representing the exposure mixture as a whole, is then used in a generalized linear model to estimate associations with health outcomes. The main limitation of this method is that it assumes that all exposures have a consistent impact on the outcome in the same direction (directional homogeneity assumption). Therefore, it's suitable for situations where all the exposures are expected to influence the investigated health outcome in a similar manner, which may not be a reasonable assumption when both toxic and essential metals are being evaluated (Yim et al., 2022). In addition, WQSR also assumes the individual exposures have linear and additive effects. To overcome the limitations of WQSR, a quantile g-computation method is employed. This approach relaxes the assumptions of directional homogeneity, linearity, and additivity that are inherent in WQSR (Keil et al., 2020). Penalized methods including LASSO, ridge regression, and ENET are also utilized in estimating the effects of pollutant mixture on health outcomes. LASSO performs automatic variable selection by shrinking the coefficients of irrelevant variables to zero, while ridge regression reduces the sum of squared coefficients, leading to non-zero coefficients that are smaller or equal in magnitude compared to those obtained through traditional regression (Stafoggia et al., 2017). ENET combines the LASSO and ridge regression methods and performs better than LASSO, while still achieving a similar level of sparsity in representation (Zou and Hastie, 2005).

Despite the availability of a wide range of mixture analysis techniques, there is still not a single method that can answer all the questions. Therefore, well-defined research questions should guide the selection of the best statistical method for analyzing the effect of chemical mixtures. For example, questions such as (1) “Are there specific exposure patterns in the study population?” (2) “Which are the toxic agents in the mixture?” (3) “Are mixture members acting synergistically?” and (4) “What is the overall effect of the mixture?” play a crucial role in determining the appropriate approach. In cases involving complex research questions that cannot be addressed by a single mixture analysis technique, employing more than one method may be necessary, maximizing the different strengths of each tool and enhancing the comprehensiveness of the analysis (Gibson et al., 2019).

4.5. Strengths, limitations and future directions

Our study possesses several notable strengths. First, it is the first systematic review to comprehensively analyze a large number of studies that have investigated prenatal exposure to multiple metals and its association with a wide range of pregnancy and birth outcomes. Notably, these studies employed various innovative and robust statistical methods. Second, the majority of the studies included in this review sourced their data from ongoing large-scale prospective cohort studies, encompassing diverse populations and controlling for important confounders such as maternal age and smoking, among others. Third, our study strictly adhered to preestablished methods outlined in a predefined protocol. We conducted extensive searches across multiple databases, including reference lists of relevant studies and reviews. The eligibility of studies was independently assessed by two authors using a predefined set of criteria. Additionally, our review followed the updated PRISMA guidelines (Page et al., 2021) and incorporated the recommended approach for conducting systematic reviews and meta-analyses of observational studies of etiology (COSMOS-E) (Dekkers et al., 2019). These rigorous methodologies enhance the reliability and validity of our findings.

In the context of this review, it is essential to acknowledge several potential limitations that warrant consideration. Firstly, it's notable that a significant proportion of the studies included into this analysis were carried out within wealthy countries in North America and Asia, mostly, United States and China, respectively. While these studies provide valuable insights, the overrepresentation of these countries might introduce geographical bias and potentially restrict the broad applicability of the findings on a global scale. To enhance the robustness and relevance of the outcomes, it is imperative to expand the scope of research to encompass middle and lower-income countries. These regions may exhibit unique patterns of metal concentrations and sources of exposure, due to diverse industrial activities, environmental regulations, and socioeconomic contexts. By including a broader spectrum of countries, the study can capture a more comprehensive representation of real-world scenarios and further elucidate potential variations in dose-response relationships. In essence, the inclusion of more diverse geographical locations within the study would provide a more holistic understanding of the relationship between metal mixture exposure and adverse pregnancy outcomes, accommodating the intricacies of different environmental contexts and socioeconomic factors that influence metal exposure dynamics. Second, the heterogeneity in biomarkers and the use of different statistical methods to measure metals and analyze associations presented challenges in directly comparing results across all studies. This variation in methodologies should be taken into account when interpreting the overall findings. Third, most of the included studies measured metal concentrations at a single time point, which limits the ability to assess susceptible windows of exposure. To address potential intraindividual variations in metal concentrations and identify critical periods of susceptibility, it is important for future studies to incorporate repeated measures of multiple metal exposures, an aspect that has rarely been explored. This approach is recommended to enhance the understanding of temporal relationships between metal exposure and adverse pregnancy outcomes. Fourth, it is worth noting that the vast majority of studies included in this review utilized a single biological medium to assess metal exposure. However, only one study (Ashrap et al., 2021) stood out by integrating exposure estimates from both urine and blood biomarkers, creating a multimedia biomarker (MMB) approach. Notably, this MMB approach yielded higher odds ratios (ORs) for small for gestational age (SGA) compared to using only urine or blood biomarkers. This finding suggests that future studies should consider adopting an integrated approach that combines exposure estimates from multiple biological media. Such an approach is considered to provide a more comprehensive estimate of the body burden of exposure, surpassing the limitations associated with relying solely on a single biological medium for exposure estimation (Levin-

Schwartz et al., 2021; Levin-Schwartz et al., 2020). Lastly, it's worth highlighting that while our initial intention was to undertake a meta-analysis, we faced a notable constraint. Presently, there exists a limitation in effectively synthesizing findings from studies that investigate the health consequences of multiple pollutants through a single meta-analysis technique (Yim et al., 2023). This can be attributed to the complex nature of chemical mixtures and their varied effects. However, it's important to emphasize that given the growing body of literature in this domain, it becomes imperative for future research to prioritize the development of specialized meta-analysis methods tailored specifically for exploring the health impacts of chemical mixtures. Such advancements hold the potential to significantly enhance our understanding of this field and facilitate more informed and evidence-based decision-making. By addressing this methodological challenge, researchers can better grasp the nuanced relationships between various pollutants and their collective impact on health outcomes. This, in turn, will contribute to a more comprehensive comprehension of the intricate interactions within chemical mixtures and the subsequent implications for public health and policy formulation.

4.5.1. *Conclusions*

In summary, the comprehensive synthesis of research within this review sheds light on the potential hazards linked to prenatal exposure to combinations of metal elements, impacting a variety of pregnancy outcomes. Our review consistently establishes connections between metal exposure during pregnancy and adverse consequences for birth weight, gestational age, and other vital birth-related metrics. These findings underscore the necessity of comprehending the collective repercussions of multiple metals and the complexities inherent in evaluating their combined effects. This review further demonstrates the need to apply mixture methods with caution but also shows that they can be superior to traditional approaches. It is evident that more research is required to unveil the underlying mechanisms driving these associations and to formulate effective strategies aimed at mitigating the potential hazards tied to metal exposure during pregnancy. This calls for a deeper exploration into the intricate interplay of metal exposures and their influence on maternal and fetal well-being. Ultimately, these conclusions underscore the significance of ongoing endeavors aimed at minimizing environmental metal exposure. By doing so, we can safeguard the health of both mothers and their developing infants, ensuring healthier pregnancy outcomes and contributing to the overall well-being of our communities.

List of abbreviations

AC	abdominal circumference
BKMR	Bayesian Kernel Machine Regression
BL	birth length
BW	birth weight
BWGA	birth weight for gestational age
COSMOS-E	conducting systematic reviews and meta-analyses of observational studies of etiology
EFW	estimated fetal weight
ENET	elastic net
ERS	environmental risk score
GA	gestational age
HC	head circumference
IVF	invitro fertilization
LBW	low birth weight
LGA	large for gestational age
NBW	normal birth weight
NIEHS	National Institute of Environmental Health Sciences
NOS	Newcastle - Ottawa Quality Assessment Scale
PCA	principal component analysis
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
PROSPERO	Prospective Register of Ongoing Systematic Reviews
PTB	preterm birth
SGA	small for gestational age

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Ibrahim Issah: Conceptualization, Methodology, Software. **Ibrahim Issah and Mabel S. Duah**: Data curation, Writing- Original draft preparation: Visualization, Investigation. **Julius N. Fobil and John Arko-Mensah**: Supervision. **Thomas P. Agyekum and Serwaa A. Bawua**: Writing- Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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