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Review Article

The Association of Heavy Metals in Breast Milk and Health Outcomes of Infants: A Systematic Review

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Abstract

Introduction: The early stages of life are vulnerable to exogenous chemical exposures because of infants' rapid development and incomplete metabolic activities. Emerging evidence suggests that heavy metals in breast milk may be linked to the poorest developmental outcomes. This systematic review was designed to summarize the association between heavy metal exposure in breast milk and health outcomes in infants.

Methods: PubMed, ScienceDirect, Web of Science, Scopus, and Google Scholar were searched to extract original animal and human studies published until December 2024, with no date restrictions. Irrelevant and duplicate studies were screened out, and data extraction was performed. The quality of the included articles and the risk of bias were assessed using the OHAT and the Newcastle-Ottawa scale tools.

Results: Firstly, 5019 studies were retrieved via the search strategy, and 8 articles (3 animal and 5 observational studies (3 cross-sectional and 2 cohort)) were included in this review. Except for one case, all of the included animal and human studies indicated that heavy metal exposure in breast milk was significantly associated with negative health outcomes in infants. Of the three human studies evaluating the effects of mercury exposure on infants' health, two found that mercury impairs neurodevelopmental performance and induces oxidative stress. Other included studies also reported that cadmium exposure through breast milk was associated with oxidative DNA damage, and lead exposure negatively influenced the mental development of the offspring.

Conclusion: Our findings demonstrated that heavy metal exposure in breast milk can negatively impact health outcomes in infants. Future well-designed human studies with large sample sizes are warranted to clearly establish these findings.

Introduction

The essential nutrients in maternal milk are vital for infants' optimal growth and development. Several factors, including maternal diet, socioeconomic conditions, and environmental factors, affect human milk and result in changes in its composition.[1] The environment contains heavy metals from natural Earth processes and from anthropogenic activities worldwide, such as vehicle emissions, mining, and pesticide use.[2] As a result, the human body can be exposed to heavy metals through the digestive system, inhalation, and skin, and these metals can be released into the placenta or breast milk.[3] Evidence shows that even low levels of heavy metals can have toxic effects on humans.[4]

Based on extensive research, preterm birth, intrauterine growth retardation, and poor cognitive development are among the unfavorable birth outcomes linked to maternal exposure to heavy metals such as cadmium (Cd), chromium, lead (Pb), and mercury (Hg) during pregnancy.[3] Hg, one of the naturally occurring metals widespread in the environment, can be transferred to the developing fetus during pregnancy through the placenta or after delivery through breast milk, and cause a wide range of adverse health effects for the fetus and infant.[5-7] Diet, particularly seafood, is a major source of Hg exposure.[8] In addition, lead contamination during pregnancy seems to result in abortions, premature births, and fetal death.[9]

Several in vivo studies investigated the association between maternal milk heavy metal levels and neonatal and fetal exposure to these metals, and developmental

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consequences, neurodevelopmental status, organ weight (kidney and spleen), motor coordination, learning disabilities, sleep problems, hormone synthesis, and behavioral problems.[3,9-11] In the present systematic review, we summarized the results and outcomes of available in vivo trials and observational studies on the effects of neonatal exposure to heavy metals to further clarify the importance of the pregnancy period and breastfeeding for infant or offspring health and development. Therefore, this review aimed to evaluate the association between heavy metals in breast milk and infant health outcomes.

Methods

Data sources and search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline served as the foundation for the current systematic review.[12] PubMed, Web of Sciences, Scopus databases, and Google Scholar were searched using the following keywords: ("heavy metal (mesh)" OR cadmium OR mercury OR lead) AND ("breast milk (mesh)" OR "human milk (mesh)") AND (infant (mesh) OR neonatal OR infancy OR baby OR child* OR newborn). The search was limited to December 2024. The PubMed search strategy is presented in Supplementary Table 1.

Eligibility criteria

Original full-text articles in English that addressed the association of heavy metals exposure via breast milk and the health outcomes of neonates and newborns were included in the present review. The PICOS (Population (infants), Intervention (heavy metals exposure), Comparison (without heavy metals exposure), Outcome (the health outcomes of neonates and newborns, such as developmental indicators), and Study Design (case-control, cross-sectional, cohort, and animal studies)) criteria were used for the definition of research questions and eligibility criteria. Both animal and human studies were eligible for this review. Letters, editorial commentary, review articles, and studies for which the full text was not available were excluded.

Study selection and Data extraction

Two independent authors screened the titles and abstracts of the articles against the eligibility criteria, after removing duplicates. The full text of the screened studies was screened in the next step to extract the required data, including the first author's name, study location, and study design, the offspring's age, type of species, type of heavy metal, duration of exposure, year of publication, sample size, and findings related to the association

Table 1. Characteristics of the include human studies.

First author / Years	Country/ Study design	Sample size/ Age of children	Heavy metal /Exposure duration	Heavy metal exposure route	Studied parameters	Adjusted covariates	Findings in infants
Al-saleh et al. 2013 [15]	Saudi Arabia/ Cross-sectional	155 women and their infants/ 2.5–12.8 months	Hg/	Hg through maternal milk	8-OHdG and MDA were measured as biomarkers of oxidative stress	NR	Increased urine MDA levels in babies were linked to mercury in breast milk, but not 8-OHdG.
Al-saleh et al. 2016 [20]	Saudi Arabia/ Cross-sectional	944 mothers and their infants/2.5-12.5 months	Hg/NR	Hg through maternal milk	Neurodevelopment tests, including DDST-II and PEDS	z score weight for age, location, z score weight for length, infant health status, father's work, mother and infant age, mother's taking medication, father's smoking status,	Hg levels in breast milk are significantly correlated with neurodevelopmental tests in crude analysis, which was not observed in the adjusted model.
Kippler et al. 2012 [16]	Bangladesh/ Cross-sectional	96 breast-fed infants/3 months	Cd/3 months	Cd through maternal milk	8-oxodG as an oxidative DNA damage	Age, socioeconomic status, body weight, urinary arsenic, and calcium, magnesium, and copper in breast milk	Cd exposure was positively associated with urinary 8-oxodG.
Marques et al. 2014 [11]	Brazil/Cohort	96 children and their mothers/<5 years of age	Pb/NR	Heavy metal exposure during pregnancy and lactation	The MDI is based on the age of walking and the age of talking, and the Bailey scales tests.	NR	The MDI was negatively affected by breast-milk Pb.
Valent et al. 2013 [18]	Italy/Cohort	606 women and their infants/18 months	Hg/NR	Hg exposure during pregnancy and lactation	BSID-III	The child's sex, birth weight, gestational age, maternal intelligence quotient, maternal age at delivery, BMI before pregnancy, weight gain, marital status at delivery, socioeconomic index, size of the home, cigarettes smoked, and alcohol intake during pregnancy, breastfeeding history, and time of BSID-III testing.	At 18 months, there was no correlation between the amount of mercury exposure and the performance of neurodevelopmental.

Cd: cadmium, Hg: mercury, Pb: lead, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, MDA: malondialdehyde, DDST-II: Denver Developmental Screening Test II, PEDS: Parents' Evaluation of Developmental Status, BSID-II: the Bayley Scales of Infant Development-II, SMS: Social Maturity Scale, CBCL: Child Behavior Checklist, 8-oxodG: 8-oxo-7,8-dihydro-20 -deoxyguanosine, MDI: Mental development index, NR: Not reported

between maternal heavy metal exposure and infant health.

Quality Assessment of studies and risk of bias

We evaluated the quality of cross-sectional and cohort studies using the Newcastle-Ottawa scale.[13] The Newcastle-Ottawa scale has eight items across three domains, with a maximum score of nine. A score of 7-9 indicates high quality, 4-6 indicates significant risk, and 0-3 indicates very high bias risk. The Office of Health Assessment and Translation (OHAT) recommendations were followed for evaluating the possibility of bias in animal research.[14] Selection, confounding, performance, attrition/exclusion, detection, and selective reporting bias are the six categories of biases covered by the 11 questions in the OHAT tool. The answers are (1) "definitely low risk of bias," (2) "probably low risk of bias," (3) "probably high risk of bias," and (4) "definitely high risk of bias."

Results

Selection of studies

In total, 5019 publications were identified after primary database searching. After removing duplicate articles and screening based on title and abstract, 4893 articles were excluded. In the next step, 126 potential relevant papers were selected for full-text evaluation, of which 118 were excluded because they studied the association between circulating heavy metals and infants' health or examined the effects of other sources of heavy metal exposure on infants' health. As shown in Table 1, finally, 8 articles met the study criteria.[11,15-21] Of the 8 included articles, 7 were initially identified through electronic searches, and 1 through citation mining. Figure 1 presents the PRISMA flow diagram.

Characteristics of the included studies

Characteristics of the included human and animal studies are comprehensively described in Tables 1 and 2, respectively. The included studies comprised both animal and observational studies. Various health effects of Hg, Cd, and Pb exposures during breastfeeding were examined in the aforementioned studies. As presented in Table 1, half of the included studies (4 studies)[11,18,20,21] measured the association between heavy metal exposure in breast milk and neurodevelopmental status. The remaining studies evaluated heavy metal exposure in breast milk and DNA damage and oxidative stress markers (3 studies),[15-17] and testicular development and steroidogenesis (1 study).[19]

Findings of the human studies

A human study found that Hg exposure via breast milk was associated with neurodevelopmental delay among children in the crude analysis but not in the adjusted model.[20] Additionally, elevated levels of malondialdehyde (MDA) in infants' urine were linked to mercury in breast milk.[15] However, the findings of an included cohort study showed that Hg exposure via breast milk was not associated with infants' neurodevelopmental performance at 18 months.[18] Another cohort study

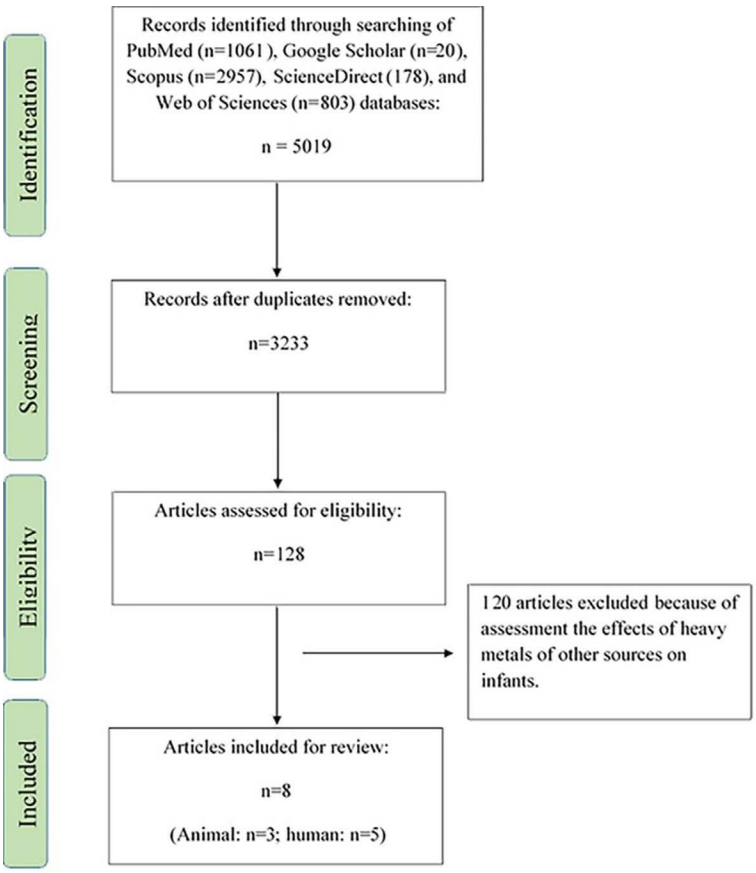

Figure 1. PRISMA flow diagram for the process of finding literature and choosing studies

Table 2. Characteristics of the include animal studies.

First author/ Years	Country/ Study design	Studied animals	Treatment/Dose of treatment	Exposure duration	Heavy metal exposure route	Assessed organs	Findings in offspring
Pillet et al. 2005 [17]	Canada/In vivo (trial)	23-28 days Sprague-Dawley female rats	Cd/0 ppb (control), 10 ppb or 5 ppm Cd as CdCl2 in drinking water	28 days	Cd through maternal milk	Spleen, thymus, liver, and kidneys	-Decreased body, kidney, and spleen weights of weaned females -Lower hepatic metallothionein-1 mRNA levels -Reduced cytotoxic activity of splenic NK-cells -Inhibited the proliferative response of Con A-stimulated thymocytes
Sakamato et al. 2002 [21]	Japan/ In vivo (trial)	7 weeks old Wistar female rats	MeHg/0 ppb (control), 5 ppm MeHg in chow diet during gestation and lactation	30 days	MeHg during gestation and through maternal milk	Brain	-Focal cerebellar dysplasia, a learning handicap in the passive avoidance response test, a marked impairment in motor coordination in the rotarod test, and a decrease in the heterotopic placement of Purkinje cells and granule cells during lactation -Suggesting that MeHg transport by milk was limited.
Wang et al. 2013 [19]	China/In vivo (trial)	CD1 male mice 8 to 10 weeks old	Pb/0 pb (control), 200 or 2000 ppm	21 days	Pb through maternal milk	Testis	-Testis weight was significantly decreased -The level of serum and testicular Testosterone was reduced -Important enzymes for the manufacture of testosterone, P450scc, P45017a, and 17b-HSD, have down-regulated expression in the testes. -The level of serum and testicular Testosterone remained decreased in adult offspring -The number of spermatozoa was reduced

Cd: cadmium, MT-1: metallothionein-1, MeHg: methyl mercury, Pb: lead, NR: NK-cell: 17β-HSD: 17β-hydroxysteroid dehydrogenase, Natural killer cell, Not reported

indicated that the mental development index in infants was negatively affected by Pb in breast milk.[11] In addition, Cd exposure was associated with urinary 8-hydroxy-2′-deoxyguanosine (8-oxodG) in infants.[16]

Findings of the animal studies

In an animal study by Sakamoto et al., offspring were exposed to Hg during gestation and lactation. They showed that on the day of delivery, the content of mercury in the babies' brains was 1.4 times higher than in the mothers'. Furthermore, at 5 and 6 weeks of age, MeHg-exposed rats demonstrated localized cerebellar dysplasia, a learning deficit in the passive avoidance response test, and severe impairment of motor coordination in the rotarod test as compared with controls. However, the concentration of MeHg in the offspring's brain decreased rapidly to 1/5 of the level at birth during the nursing period, indicating that MeHg transport via milk was restricted. These abnormalities may be caused by the effect of high accumulation of MeHg in the brain during the gestation period.[21] Another animal study also revealed that after offspring exposure to Pb through maternal milk, testis weight was decreased, the levels of serum and testicular Testosterone were reduced, the expression of P450scc, P45017a, and 17β-hydroxysteroid dehydrogenase, key enzymes for Testosterone synthesis, was inhibited in testes, and the number of spermatozoa was reduced. Serum and testicular testosterone levels remained decreased in adult offspring.[19] In addition, Pillet et al. reported that Cd exposure decreased body, kidney, and spleen weights in weaned females, lowered hepatic metallothionein-1 mRNA levels, reduced cytotoxic activity of splenic NK cells, inhibited the proliferative response of Con A-stimulated thymocytes, and disrupted testicular development and steroidogenesis in male offspring.[17]

The quality of articles and risk of bias assessment

Using the Newcastle-Ottawa scale, the two independent authors evaluated the quality of the chosen publications according to the following standards (Tables 3 and 4): representativeness of cases (1 score), sample size (1 score), response rate (1 score), ascertainment of the screening (2 score), comparability (1 scores), assessment of outcomes (2 scores), and statistical analyses (1 scores). Of the included observational studies, two cohort studies[11,18] had a quality score of 7, and three cross-sectional studies had a quality score of 8 [15,16,20]. Two animal studies were at high risk of bias[17,21], and one study was at probably low risk of bias (Table 5).[19]

Discussion

In the present systematic review, the current evidence regarding heavy metal exposure during breastfeeding and its effect on infants' health outcomes was summarized. Most of the reviewed studies support an association between exposure to Hg, Cd, and Pb via breast milk and worse health outcomes in infants. Al-Saleh et al. conducted a cross-sectional survey and reported a negative association between exposure to Hg via maternal milk and neurodevelopmental performance in infants.[20] However, Valent et al. demonstrated that there was no correlation between neurodevelopmental status and the level of mercury exposure during nursing. [18] While another cross-sectional study reported that Hg levels in breast milk were related to the excretion of urinary MDA, in a dose-dependent manner.[15] The results of the in vivo study included in this review showed that, compared with Hg exposure during gestation or through dietary intake, Hg levels in the brains of rats were reduced during the breastfeeding period, and neurodevelopmental deficits were not increased after Hg exposure during breastfeeding; these suggest that Hg transport via milk was lower than via the placenta or the diet.[21] In a recent systematic review, Heng et al. assessed the connection between children's neurodevelopment in low- and middle-income nations and exposure to heavy metals from any source. They

Table 3. Quality assessment of the included cohort studies by the Newcastle-Ottawa scale

Quality assessment criteria													
	Selection				Comparability			Outcomes					
Study ID	Representativeness of exposed cohort?		Selection of the non-exposed cohort?	Ascertainment of exposure?		Demonstration that the outcome of interest was not present at the start of the study?	Comparability of cohorts based on the design or analysis controlled for confounders		Assessment of outcome?		Was the follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts		Overall Quality Score (Maximum = 9)
	Truly representative	Somewhat representative	Drawn from the same community as the exposed cohort	Secured records	Structured interview	yes	The study controls for the age and gender of the child	Study controls for other factors	Independent blind assessment	Record linkage	yes	Complete follow-up on all subjects accounted for	Subjects lost to follow-up are unlikely to introduce bias- number lost less than or equal to 20%, or the description of those lost suggests no difference from those followed.	
Valent /2013 [18]	*		*		*	*	*	*	-	*	*	*	-	7
Marques et al. 2014 [11]	*		*	*		*	NS	NS	*		*	*	-	7

*, Acceptable; S, not stated

Table 4. The included cross-sectional studies' quality assessment by the Newcastle-Ottawa scale

Quality assessment criteria																					
	Selection													Comparability		Outcomes					
	Representativeness of the sample				Sample size		Non-respondents				Ascertainment of the exposure					Assessment of the outcome			Statistical test		
Study ID	Truly representative of the average in the target population	Somewhat representative of the average in the target population	Selected group of users	No description of the sampling strategy	Justified and satisfactory	Not justified	Comparability between respondents' and non-respondents' characteristics is established, and the response rate is satisfactory	The response rate is unsatisfactory, or the comparability between respondents and non- respondents is unsatisfactory	No description of the response rate or the characteristics of the responders and the non-responders		Validated measurement tool	Non-validated measurement tool, but the tool is available or described	No description of the measurement tool	The study controls for the most important factor	The study controls for any additional factor	Independent blind assessment	Record linkage	Self-report	No description	The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented	The statistical test is not appropriate, not described, or incomplete	Overall Quality Score (Maximum = 10)
Al-Saleh/ 2015 [20]	*				*		*				**					**			*		8
Al-Saleh/ 2013 [15]	*				*		*				**			NS	NS	**			*		8
Kippler/ 2012 [16]	*				*		*				**					**			*		8

*, Acceptable; NS, not stated

showed that there was conflicting or scant evidence linking postnatal exposure to mercury to poorer child outcomes.[22] Heng et al. summarized the studies conducted in low- and middle-income countries, whereas the neurotoxic effects of mercury have been extensively reported in high-income settings.[23-25] In most countries, eating fish is the primary cause of non-occupational mercury exposure. However, eating fish offers a variety of vital nutrients crucial for a child's neurodevelopment [26] and is associated with better neurodevelopmental outcomes.[27-29] Because of the collinearity of fish consumption and Hg exposure, it is difficult to disentangle these negative and positive effects. However, according to a several earlier studies, high levels of mercury in cord blood were linked to poorer cognitive development only in infants whose mothers ate fewer than 3 servings of fish per week during pregnancy.[24,30-33] Liop et al. also found that the PUFA status affected the relationship between mercury and neuropsychological development; children with lower n-3 PUFA levels or a higher n-6/n-3 PUFA ratio showed lower motor scale scores as mercury exposure increased.[32] This is an important consideration when making recommendations on fish consumption that advise promoting fish with low Hg as optimal choices for pregnant and lactating women

Table 5. The included animal studies' risk of bias assessment by the OHAT tool

CATEGORY	QUESTIONS	Wang 2013	Sakamato 2002	Pillet 2005
Selection Bias	1. Was there sufficient randomization of the exposure level or delivered dose?	++	-	-
	2. Was the distribution of study groups sufficiently hidden?	+	-	-
Performance Bias	3. Were all study groups subjected to the same experimental conditions?	++	+	+
	4. During the study, were the human volunteers and research staff blinded to the study group?	-	-	-
Attrition/ Exclusion Bias	5. Was there no attrition or exclusion from analysis in the outcome data?	++	+	++
Detection Bias	6. Is the exposure characterization reliable?	+	++	++
	7. Is the outcome assessment reliable?	++	++	++
Selective Reporting Bias	8. Did all measured results get reported?	++	++	++
Other Sources of Bias	9. Were there no further possible risks to internal validity (e.g., researchers followed the study protocol and statistical procedures were appropriate)?	++	+	+
Overall risk of bias		+	-	-

Risk of bias response options for individual items:
++ Definitely low risk of bias -- Definitely high risk of bias
+ Probably low risk of bias - Probably high risk of bias

and their infants.

Regarding other heavy metals, some included studies reported a negative association between Pb and Cd exposure and adverse health outcomes among infants. Marques et al., demonstrated in a cohort study that Pb exposure via breast milk was negatively associated with the mental development index.[11] Moreover, findings from an included animal study indicated that Pb exposure via breast milk results in decreased testis weight, disrupts testicular development, and impairs testosterone synthesis in male offspring.[19] It has been demonstrated that prenatal exposure to lead harms neurodevelopment.[34,35] Also, Pb exposure is identified as a substantial risk factor for attention-deficit hyperactivity disorder in children in several cross-sectional studies.[36,37] Based on the included studies' reports, Cd had negative effects on oxidative stress status in exposed infants. For example, Kippler et al. reported that early-life Cd exposure through breast milk was associated with urinary 8-oxodG levels in infants.[16] Moreover, the results of the in vivo study included in this review showed that Cd via maternal milk leads to lower hepatic metallothionein-1 mRNA levels, and decreased cytotoxic activity of the spleen.[17] In a systematic study, Heng et al. showed reliable evidence that exposure to Pb in the postnatal period is linked to poorer neurodevelopmental outcomes, in contrast Cd exposure had conflicting effects on children.[22]

Due to their rapid growth, high rates of cell division and metabolism, and immature defensive mechanisms against reactive oxygen species, infants are more susceptible to oxidative DNA impairment than adults.[38,39] It is demonstrated that Cd and Hg reduce antioxidant activity, inhibit the electron transport chain, and increase mitochondrial ROS formation.[15,40] Oxidatively damaged Deoxyguanosine triphosphate in the mitochondria, is one source of urine 8-oxodG.[41] Cadmium has been demonstrated to decrease the production and activity of 8-hydroxyguanine glycosylase, which is the enzyme that repairs DNA's 8-oxodG excision.[42] Therefore, up-regulation of oxidative DNA damage repair pathways, such as nucleotide excision repair, which results in the creation of 8-oxodG, may be the cause of the correlation between cadmium exposure and elevated urine 8-oxodG levels in babies.[16] As the amount of mercury in breast milk increased, MDA levels in the infant's urine similarly rose, indicating that the mother's exposure to mercury may have induced lipid peroxidation. Long-term mercury exposure is probably the cause of oxidative DNA damage.[15] Recent observations revealed a strong positive association between newborns' urine 8-oxodG and MDA levels, suggesting that lipid peroxidation may affect DNA damage.[43,44] These results imply that MDA can form adducts with deoxyadenosine and Deoxyguanosine in DNA,[45] with the quantity of 8-oxodG formed in DNA equal to the amount of lipid peroxidation assessed as MDA.[46] These findings show that exposure to mercury and cadmium among nursing moms can cause oxidative stress in nursing babies and may contribute to the pathophysiology of numerous health issues, especially during neurodevelopment. Therefore, we must have solid facts to direct policies and programs regarding heavy metal exposure during the prenatal and postnatal periods due to the baby's brain's vulnerability to heavy metal exposure. However, some studies did not report a significant association between Hg exposure via breast milk and developmental delay in children, which may be due to short exposure time, insufficient follow-up duration, and failure to control for possible confounding factors such as other sources of heavy metal exposure. Moreover, some of the included studies possibly had a high risk of bias; their findings should be considered with a degree of caution.

The current review has certain limitations. First, there's a chance that research on exposure to heavy metals and neurodevelopment that didn't provide noteworthy findings won't be published. Second, the heterogeneity across studies, heavy metals, exposure measurement techniques, and the different neurodevelopmental

evaluation scales that were employed prevented us from doing a meta-analysis. Moreover, this study was not registered in the PROSPERO database.

Conclusion

The research on the relationship between breast milk exposure to heavy metals and baby health outcomes was summarized in this systematic review. The findings demonstrated that heavy metal exposure, such as Hg, Cd, and Pb, can have worse neurodevelopmental outcomes and induce oxidative stress in breastfeeding infants. However, there is still emphasis on the beneficial effects of breast milk, and the advantages of breastfeeding for the baby, the mother, and the community have been reiterated by the American Academy of Pediatrics.[1] Breastfeeding should therefore not be discouraged, but the sources of heavy metal exposure for mothers and babies should be found and removed.

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Writing–Review & Editing: Roghayeh Molani-Gol, Leila Nikniaz

Competing Interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not for- profit sectors.

Data Availability Statement

If requested, data is accessible via email to the corresponding author.

Ethical Approval

Not Applicable.

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