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REVIEW

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Major heavy metals and human gut microbiota composition: a systematic review with nutritional approach

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Abstract

Background The human gut microbiota has a critical role in several aspects of host homeostasis, such as immune development, metabolism, nutrition, and defense against pathogens during life. It can be sensitive to xenobiotics including drugs, diet, or even environmental pollutants, especially heavy metals (HMs). The findings of some previous studies are heterogeneous due to the inclusion of various types of study (human, and animal studies) and wide exposures (phthalate, bisphenol A, HMS, etc.), and no comprehensive systematic review has investigated the association between HMs exposure and human gut microbiota composition. Therefore, we carried out a systematic review of human observational studies to examine this association.

Main body of the abstract PubMed, Scopus, ISI Web of Science, and Google Scholar were searched using Medical Subject Headings (MeSH) and non-MeSH terms. Eventually, 12 studies for arsenic (As), lead (Pb), mercury (Hg), and cadmium (Cd) were included in this study. No eligible study was found for Aluminium.

Short conclusion The findings showed exposure to HMs disturbs the composition of gut microbiota and can lead to dysbiosis. Exposure to high levels of As, Pb, and Hg increased the abundance of *Collinsella* as pathobionts. Evidently, it is related to leaky gut, oxidative stress, and several diseases such as inflammatory bowel disease and cancers. Probiotic treatment and nutritional strategies such as high fiber intake and following antioxidant-rich diets should be considered in terms of HMs exposure.

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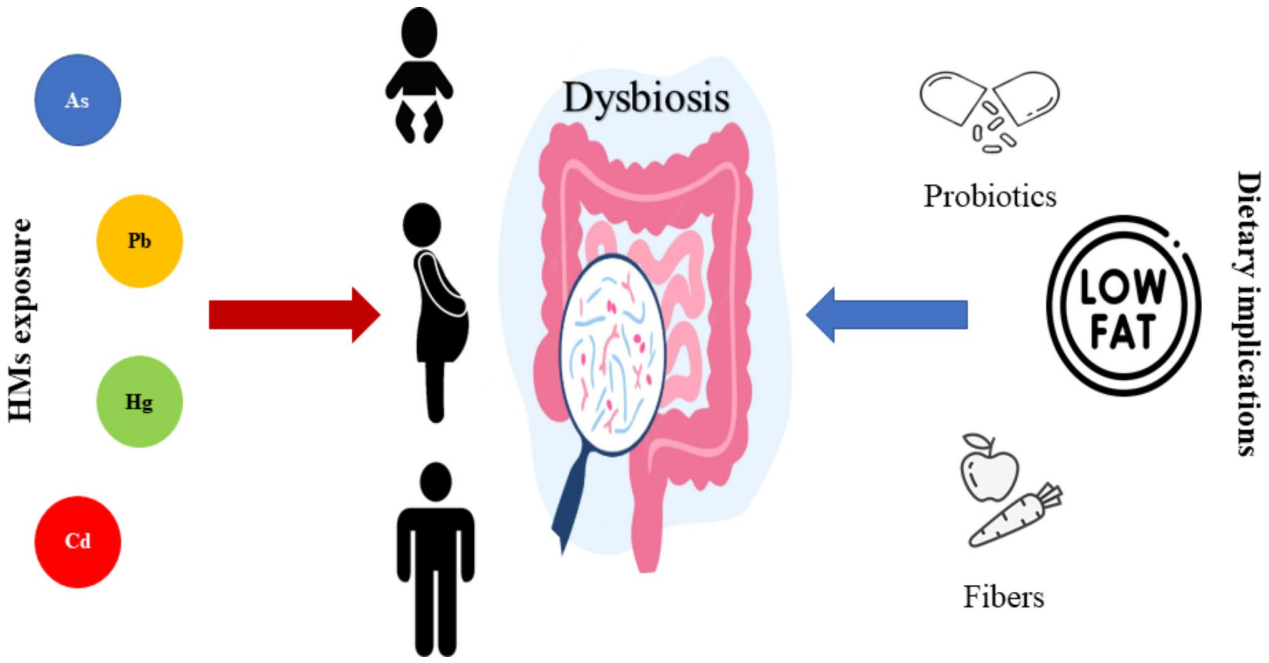
Graphical Abstract



Keywords Heavy metal, Gut, Microbiota, Nutrition, Systematic review

Introduction

Human microbiota includes all existing microbes (eukaryotes, archaea, bacteria, and viruses) in certain parts of the body such as the mouth, airways, genitourinary system, skin, and especially the intestine [1]. Disruption in the balance of the gut microbiome, i.e. dysbiosis, can lead to several diseases including inflammatory bowel diseases, cancers, diabetes mellitus, obesity, liver, and kidney diseases [2–4]. Diet, medications, and other environmental factors have a key role in shaping the composition of the intestinal microbiome, although genetics provides the background context [5, 6].

Pollution with heavy metals (HMs) such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) is a persistent universal issue and can lead to dysbiosis [7]. Humans are exposed to HMs through environmental pollution, food contamination, dental care, and industrial, agricultural, and, occupational operations [8]. Organisms absorb pollutants faster than the rate at which they are excreted or catabolism [9]. Dysbiosis caused by HMs exposure may affect physiological and metabolic functions, and contribute to inflammation and the development of various diseases in the host [10, 11]. It is important to consider exposure to HMs in special periods of life such as early pregnancy because HMs are strong neurotoxins [12].

The effects of metal exposure on the gut microbiota have been examined on various species [13]. A study on mice showed that As exposure (10 mg/L) for 4 weeks disrupts the gut microbiota and metabolic profiles [14]. A review demonstrated that phthalates, HMs, bisphenol A, and particulate matter may alter the intricate microbiota–gut–brain axis, thereby, affecting neurological and mental health [9]. Many reviewed studies showed that exposure to HMs can change the diversity and structure of the gut microbiota [11, 15]. However, the findings are not homogeneous and there is no comprehensive systematic review that has investigated this association in humans. Therefore, the purpose of this systematic review was to determine the relation between major heavy metal exposure and alteration of human gut microbiota composition.

Methods

This review was conducted according to the guidelines for systematic reviews of observational studies [16]. The review question was defined using the PECO/PICO approach (participants, exposure, comparator, and outcome) [17, 18].

Search strategy

Electronic databases including PubMed, Scopus, ISI Web of Science, and Google Scholar were searched to

find the relevant human observational studies by MR, and no language limitations or restrictions were applied. The literature search was run using the Medical Subject Headings (MeSH) and non-MeSH terms without restrictions up to October 2023. Terms including: ("Heavy metal" OR Cadmium OR Arsenic OR Lead OR mercury OR Aluminium) AND ("Gut Microbiome OR Gut Flora OR Intestinal Microbiome OR Gut microbiota composition OR "gastrointestinal microbiome" OR dysbiosis). Also, we searched the references of the retrieved articles manually.

Eligibility criteria

Screening for eligible studies was done for the article's title, abstract, and full text by two independent researchers (MR and NR). The inclusion criteria for studies were: cohort, cross-sectional, or case-control human studies that investigated the association between main HMs (Cd, As, Pb, Hg, and aluminium) and human gut microbiota composition. Interventional, animal, in-vivo, and in-vitro studies; editorials, letters, review articles, or meeting abstracts; studies with insufficient reported data and study protocols were excluded.

Data extraction

Data extraction was done by BF and YH through recording the following items: author name, year of publication, country where the study was done, sample size, age of participants, design of the observational study, type of heavy metal and its dosage, exposure duration for cohort studies, method for heavy metal assessment, gut microbiota assessment, gut microbiota composition changes, and effects of HMs on human health outcomes.

Assessment of quality

The quality of each study was evaluated using the Newcastle Ottawa Scale (NOS) [19]. Two independent authors (BF and NR) assessed the quality of the included studies, and the third author resolved any disagreements. The NOS has three sections including selection, comparability, and assessment of exposure or outcome, each section containing several items related to the quality of studies. For each prospective cohort and case-control study, the NOS considers a maximum of 9 points, and 10 points for cross-sectional studies. Studies that achieved an NOS score of 6 or higher in our study were considered to be high-quality publications (Supplemental Tables 1 & 2).

Results

Study selection

We identified 24,219 records after excluding duplicates. Then articles were screened, and 61 articles remained for assessing the full-texts. Finally, we included 12 studies in the present systematic review. Figure 1 illustrates the selection process for studies.

Study characteristics

The articles in this systematic review addressed four major HMs, As ($n=5$) [20–24], Pb ($n=5$) [21, 25–28], Hg ($n=4$) [21, 29–31], and Cd ($n=1$) [21]. There were no studies on aluminum exposure and gut microbiota composition.

The existing study designs were cross-sectional ($n=6$), cohort ($n=4$), Longitudinal ($n=1$), and case-control studies ($n=1$). Most studies were done in the US, but others were from China, Nepal, and Bangladesh. Of the included studies, 4 evaluated HMs during pregnancy, 3 measured HMs in infants or children, 1 measured in both infantile and pregnancy periods and 4 evaluated HMs in adults.

Most studies used Inductively Coupled Plasma Mass Spectrometry (ICP-MS) for the assessment of HMs in drinking water or biological specimens including blood, urine, feces, teeth, and toenail. Also, atomic absorption spectrometry, cold vapor atomic fluorescence spectrophotometer, direct mercury analyzer, and gas chromatography were other methods used.

For determining gut microbiota composition, studies used DNA extraction, 16 S rRNA gene sequencing/profiling, and polymerase chain reaction (PCR) ($n=10$) or metagenomic sequencing ($n=2$) based on collected feces specimens of children or adults.

Study quality assessment

The included studies had NOS scores ranging from 4 to 9. According to the score of 6 as the median for a total score of NOS, 7 articles had a score of ≥6, considered high-quality studies (Supplemental Tables 1 & 2).

Heavy metals and gut microbiota composition

Arsenic

Five studies were conducted on As in Nepal ($n=1$) [20], the United States (USA) ($n=2$) [21, 23], Bangladesh ($n=2$) [22, 24]. These included articles were published between 2017 and 2020. Three studies on infants and children and two on adults examined the outcomes. The study designs were cohort ($n=2$), cross-sectional ($n=2$), and nested case-control ($n=1$). These articles included 724 participants in total, ranging from 42 to 249 participants per study. Three studies had high quality. More details are presented in Table 1, Supplemental Tables 1 & 2.

Among the studies that measured As exposure, 2 measured arsenic levels in urine, 2 in the water, and 1 in toenail. Brabec et al. reported that high exposure to As compared undetected level has increased *Bacillaceae* and decreased *Erysipelotrichales* in Mahuawa and increased

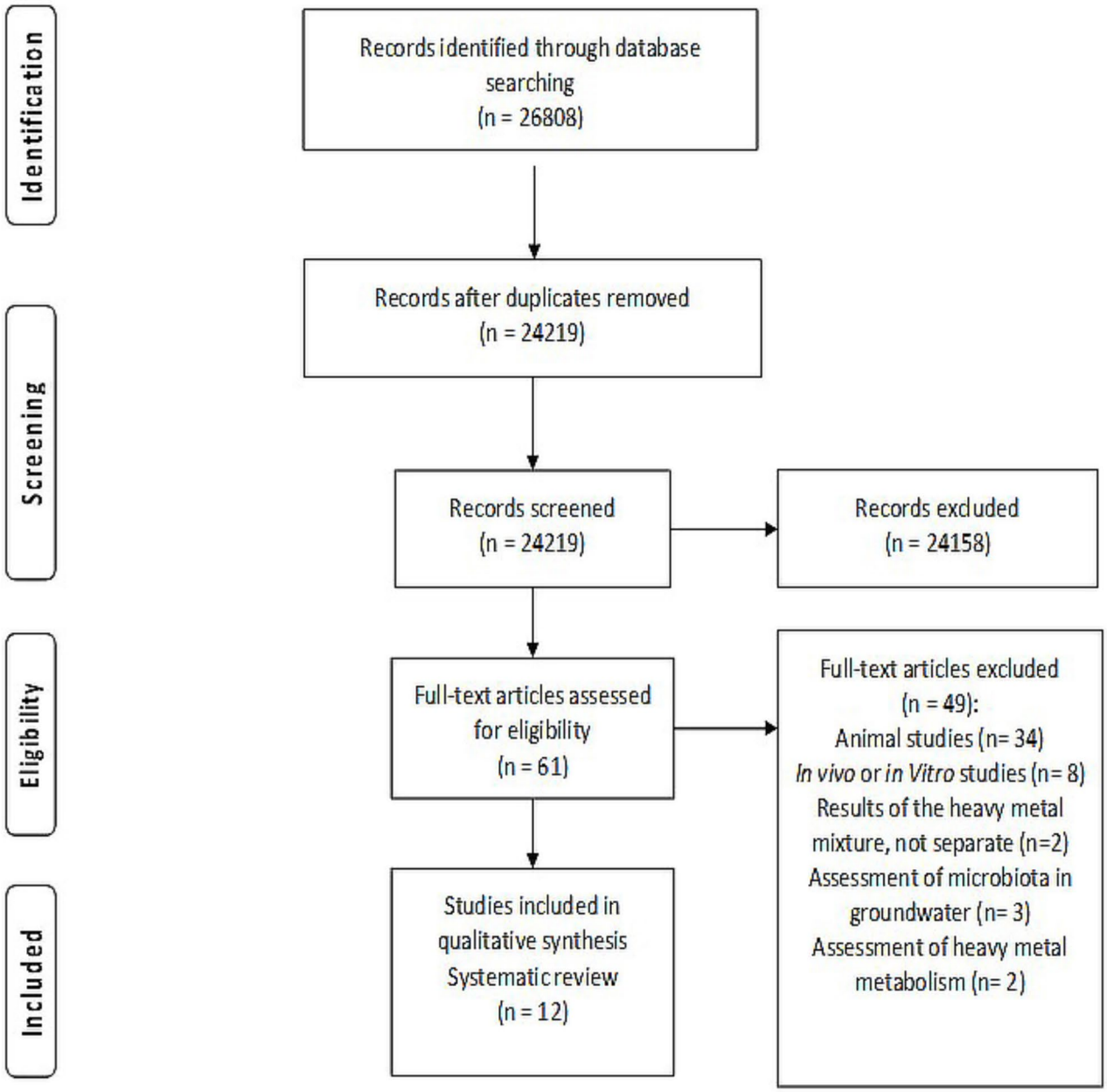


Fig. 1 Flow diagram of the study selection process

Collinsella in Ghanashyampur. Moreover, moderate As level showed reduced *Erysipelotrichi* class in Mahuawa, and increased *Lactobacillus*, and decreased *Gammaproteobacteria* and *Erysipelotrichaceae* in Ghanashyampur [20]. Elevated phylum *Proteobacteria* and class *Gammaproteobacteria* in a high level of As vs. low level, was represented in another study [24]. One study reported that As levels in adults were negatively associated with *Catenibacterium* (*Erysipelotrichaceae* family) [20]. Urinary As levels had an indirect and direct association with *Ruminococcus* in adults and infants, respectively. Also, association with *Clostridiaceae* was negative in both groups [20, 23]. Brabec et al. found adults' urinary As levels had a negative (*Haemophilus* & *Luteimonas*) and positive (*Desulfovibrionaceae*, member genus *Bilophila*, *Succinovibrio*) association with some members of *Proteobacteria* phylum [20]. Another study illustrated water arsenic exposure was related to *Proteobacteria*, *Enterobacteriaceae* family, and predominantly As resistant *Escherichia coli* directly [24]. There was a positive relationship between As levels in infants' toenail and *Bifidobacterium* at high concentrations of zinc [21]. However, another study that measured As in infants' urine showed a negative association with *Bifidobacterium*. Moreover, a

Table 1 Overview of the included studies in the systematic review

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
Eggers et al. -2023	North America	Cohort	123(74/49)	9.7 y	Pb	9–11 y	ICP-MS (maternal's B)	2nd trimesters	MS (child's F)	-	**Alistipes**: putredinis (-) indistinctus (-) **Bacteroides**: caccae (-) intestinalis (-) coprocola (+) **Bifidobacterium**: adolescentis (-) **Coprococcus**: catus (-) **Ruminococcus**: gnavus (-) callidus (-)	-	Child sex, Child's age at time of F sample collection, Mother's SES during pregnancy, Mother's age at birth, Mother's BMI during pregnancy, Microbiome analysis batch
								3rd trimesters			**Alistipes**: indistinctus (-) **Bacteroides**: coprocola (+) finegoldii (+) **Bifidobacterium**: bifidum (-) longum (-) **Eubacterium**: eligens (+)		

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
Zeng et al. (2022)	China	Cross-sectional	70 (38/32)	4.6 y	Pb	-	ICP-MS		DNA extraction & 16S rRNA gene sequencing & PCR	-	Proteobacteria (NR)		Age, Sex, Parental education levels, Children contact with e-waste, Home used as e-waste workshop, Family monthly income
							(U)		(F)		Bacteroidetes (NR)		
								H **vs** L			Firmicutes (NR)		
											Tenericutes (NR)		
							GFAAS				Proteobacteria (NR)		
							(B)				Bacteroidetes (NR)		
								H **vs** L			Firmicutes (NR)		
											Tenericutes (NR)		
Yang et al.	china	Cross-sectional	33 (14 /19)	41.5	THg, MeHg	-	DMA-80, Acid digestion & CVAFS, Ethylation & GC-CVAFS (F)		DNA extraction & MS	↔ Firmicutes	-	-	-
-2022				y				H **vs** L	(F)	↔ Bacteroidetes			
										↔ Actinobacteria			
										↔ Fusobacteria			
										↓Gammaproteobacteria class			
								H **vs** L		↑Desulfovibrio ↑Methanogens			
								(through rice consumption)		↓ Proteobacteria			
								L (fish consumption) **vs** L (rice consumption)		↑ Actinobacteria			

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
										↑Desulfovibrio ↑Methanogens			
Brabec et al. (2020)	Nepal	Cross-sectional	42 (17/25)	42	As	-	Hybrid generation/ AAS	1) Undetected	16S rRNA gene sequencing & PCR	**2 vs 1**:	Family Bacillaceae (+)	-	-
	(Mahuawa)			y			(U)		(F)	↓ Erysipelotrichi class			
										3 vs 1:	**Erysipelotrichaceae family**:		
										↑ bacillaceae	Catenibacterium (-)		
										↓ Erysipelotrichales			
										3 vs 2:	**Firmictutes phylum**:		
								2) Moderate		NR	Ruminococcus (-)		
								3) High			Clostridiaceae (-)		
	Nepal							1) Undetected		**2 vs 1**:	**Proteobacteria phylum**:		
	(Ghanashyampur)									↑ Lactobacillus	Haemophilus (-)		
										↓ ɣ-proteobacteria	Luteimonas (-)		
										↓ Erysipelotrichaceae	Desulfovibrionaceae (+)		
										3 vs 1:	member genus Bilophila (+)		
										↑collinsella	Succinovibrio (+)		
								2) Moderate		**3 vs 2**:			
								3) High		NR			
Sitarik et al. (2020)	USA	Cohort	143 (70/73)	1 m	Pb	7 m	(LA-ICP-MS)	2nd Trimester	16S rRNA gene sequencing (bacterial) & ITS2 (fungal) sequencing & PCR	-	Collinsella (+)		Exact age at F sample collection, Child race, Tooth type, Attrition, Batch
							(T)		(F)		several Bacteroides OTUs (-)		
											Aspergillus (-)		
											Saccharomyces (+)		

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
											Candida:		
											parapsilosis (-)		
											Malassezia:		
											restricta (+)		
											globose (+)		
											Collinsella (+)		
											several Bacteroides OTUs (-)		
											Candida:		
								3rd Trimester			*Parapsilosis* (-)		
								Postnatal			several Bacteroides OTUs (-)		
											Aspergillus (-)		
											Malassezia:		
											restricta (+)		
											globose (+)		
				6 m		12 m		2nd Trimester			Bilophila (+)		
											several Bacteroides OTUs (-)		
											Saccharomyces (-)		
											Malassezia:		
											restricta (+)		
											globose (+)		
								3rd Trimester			Bilophila (+)		
											several Bacteroides OTUs (-)		
								Postnatal			several Bacteroides OTUs (-)		
											Penicillium (-)		
											Malassezia:		
											restricta (+)		
											globose (+)		
Laue et al. (2020)	USA	Cross-sectional study on cohort population	179 (99/80)	2.5 m		-	ICP-MS		DNA extraction & 16S rRNA gene sequencing		Bifidobacterium (at	-	All metal/ metalloid exposures and covariates

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
					As		(infant's toenail)	Moderate levels	(infant's F)		high concentrations of zinc) (+)		
					Cd						Bifidobacterium (+)		
					Pb						Bifidobacterium (Ø)		
											Bifidobacterium (Ø)		
					Hg								
Wu et al. (2019)	Bangladesh	Cohort	249 (102/147)	48.6 y	As	22 m	High-resolution ICP-MS	Moderate levels	DNA extraction	-	Class RF3 (Ø)	Atherosclerosis	Age, BMI, Sex, Education, Smoking status,
							(Wa)	(Wa)	& 16S rRNA gene sequencing & PCR (F)		Order ML615J-28 (Ø)		
							GFAAS (U)				Class Epsilonproteobacteria (Ø)		
								Moderate levels			Order Campylobacterales(Ø)		
								(U)			Genus Anaerostipes(Ø)		
											Genus Faecalibacterium (Ø)		
Eggers et al. (2019)	USA	Cross -sectional	696 (297/399)	18 y ≤	Pb	-	ICP-MS	H vs L	DNA extraction & 16S rRNA gene sequencing & PCR	-	Phylum	-	Age, BMI, Sex, Education, Smoking, Creatinine,
							(U)		(F)		Proteobacteri (+)		, Antibiotic use, Race/Ethnicity, Fiber
											Order		consumption, Urbanicity, Indoor pet ownership
											Burkholderiales (+)		
Rothenberg et al.	USA	Longitudinal	24	Early gestation		Late gestation	CVAFS, Ethylation-GC-CVAFS	Early gestation	16S rRNA gene profiling	-	Collinsella (+)	-	Longitudinal trends gestational

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
-2019						(9 m)	after alkaline digestion-solvent extraction, GC-CVAFS		(Maternal's F)		Lachnoclostridium (+)		period, vitamin D supplementation
					MeHg		(H, F, B,Mec)				Ruminococcaceae_ ucg013 (+)		status
											Ruminococcaceae_ ucg002 (-)		
								Late gestation			Lachnospiraceae_ nk4a136 (+)		
											Faecalibacterium (+)		
											Parabacteroides (+)		
								Early gestation			phylum *Bacteroidetes* (-)		
											Prevotella_9 (+)		
					IHg						Collinsella (+)		
											Ruminococcaceae_ ucg013 (+)		
								Late gestation			phylum Bacteroidetes (Ø)		
											Parabacteroides (+)		
											Megasphaera (+)		
Hoen et al. (2018)	USA	Cohort	204 (118/81)	At birth	As	6 w	ICP-MS	Maternal used WW	DNA extraction & 16S rRNA gene sequencing	-	genus Ruminococcus (+)	-	Infant feeding type, USG
							(Infant's U)		(F)		phylum Firmicutes (+)		
								infant's U			family Clostridiaceae (-) genera Bacteroides (-)		
											Bifidobacterium (-)		
											genera Lactobacillus (±)		
											Dorea (±)		
Dong et al. (2017)	Bangladesh	Nested case-control	50 (26/24)	4.5 y	As	-	ICP-MS		DNA extraction & 16S rRNA gene sequencing & PCR	↑↑phylum Proteobacteria	Proteobacteria (+)	-	Age, BMI, Sex

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
							(maternal used Wa)		(child's FF)	↑class Gammaproteobacteria	Enterobacteriaceae family (+)		
								H **vs** L		↔ order Enterobacteriales	predominantly As resistant E. coli (+)		
Rothenberg et al. -2016	USA	Cross-sectional	17(pregnant)	≥ 18 y	Hg	-	CVAFS, GC-CVAFS		16S rRNA gene profiling	-	**Firmicutes (+)**:	-	-
									(F)		Subdoligranulum		
											Unclassified B9304 Lachnospiraceae		
											Unclassified 00jsh Ruminococcaceae		
											Unclassified 76946 Ruminococcaceae		
								MeHg			Unclassified 02cp1 Ruminococcaceae		
								(F)			Unclassified 02fdk Ruminococcaceae		
											Unclassified B1957		
											Ruminococcaceae		
											Firmicutes (-):		
								IHg			Unclassified 00bd9 Lachnospiraceae		
								(F)			Moryella		
							Thermal decomposition & AAS				**Firmicutes (+)**:		
											Faecalibacterium		
											Subdoligranulum		
											Unclassified 0065e Clostridiales		
								THg			Unclassified 62248 Erysipelotrichaceae		

Table 1 (continued)

First Author (Year)	Country	Study design	Sample size (male/female)	Mean age/ Age range	Type of heavy metal	Time of exposure	Heavy metal assessment	Comparison	Gut microbiota assessment	Effect on gut microbiota (categorical)	Effect on gut microbiota (continuous)	Health outcomes	Adjustments
								(H)			Unclassified 00r39 Peptostreptococcaceae Unclassified 009c6 Ruminococcaceae		

AAS: Atomic absorption spectrometry, As: Arsenic, BMI: body mass index, B: blood, CVAFS: Cold Vapor Atomic Fluorescence Spectrophotometer, Cd: Cadmium, DMA-80: Direct Mercury Analyzer 80, F: Feces, FF: Fresh feces, GFAAS: Graphite furnace atomic absorption spectroscopy, GC: Gas chromatography, H: hair, Hg: mercury, H: Highest, ICP-MS: Inductively coupled plasma mass spectrometry, IHg: Inorganic mercury, ITS2: Internal transcribed spacer 2, L: Lowest, LA-ICP-MS: Laser ablation–inductively coupled plasma–mass spectrometry, MeHg: Methyl mercury, m: Month, MS: Metagenomic sequencing, Mec: Meconium, NR: not reported, Pb: Lead, PCR: Polymerase chain reaction, SES: Socio-economic status, THg: total Hg, T: teeth, U: urine, USG: Urine specific gravity, Wa: Water, WW: well water, y: Year

positive and negative association with phylum *Firmicutes* and genera *Bacteroides* was found, respectively [23].

Lead

There were five studies on Pb in different regions, including USA ($n=3$) [21, 27, 28], North America ($n=1$) [25], and China ($n=1$) [26] that were published from 2019 to 2023. Most of the existing studies had an age range of 1 month to 9.7 years, however, one of them included adults. The total population of these cohort ($n=2$) and cross-sectional ($n=3$) studies was 1211 ranging from 70 to 696. The quality of 4 studies was high (Table 1, Supplemental Tables 1 & 2).

Eggers et al. (2023) showed Pb exposure, measured in maternal blood, in the second trimester is related to the decrease of *Alistipes putredinis*, *Bacteroides caccae* & *intestinalis*, *Coprococcus catus*, and *Ruminococcus gnavus*. Also, after using Microbial Co-Occurrence Analysis (MiCA) reduction of *Bifidobacterium adolescentis* and *Ruminococcus callidus* was observed. In the third trimester, they found a decrease of *Bifidobacterium bifidum* & *longum* and elevation of *Bacteroides finegoldii* and *Eubacterium eligens*. An increment of *Bacteroides coprocola* and a reduction of *Alistipes indistinctus* were reported in both trimesters [25]. Two studies didn't report any significant association [21, 26]. Another cohort study that measured lead exposure in baby teeth illustrated that second and third trimester lead levels were positively associated with *Collinsella* abundance at 1 month of age, as well as *Bilophila* abundance at 6 months of age. Furthermore, in utero and postnatal lead levels were negatively associated with several *Bacteroides* OTUs, at both ages. Higher lead exposure in the second and third trimesters was related to lower *Candida parapsilosis*, and in the second trimester and postnatal period also negatively correlated with *Aspergillus* abundance at 1 month old. There was a positive association between lead levels with *Malassezia restricta* & *globose* abundances in the second trimester and postnatally at both 1-month and 6-month ages. In the second trimester positive and negative association with *Saccharomyces* was found at 1 month and 6 month of age, respectively. Additionally, at 6 months of age, postnatal lead exposure reversely correlated with *Penicillium* abundance [27]. Finally, a Cross-sectional study demonstrated higher lead levels in adult urine have a direct relation with Phylum *Proteobacteri* and Order *Burkholderiales* [28].

Mercury

Four studies were conducted in the USA ($n=3$) [21, 30, 31] and China ($n=1$) [29]. The publication year of these studies was between 2016 and 2022 and they examined infants, adults, and pregnant women. Three studies were cross-sectional, and one was longitudinal. There were 253

participants in these studies, which ranged from 17 to 179 participants. Just 2 studies had high quality (Table 1, Supplemental Tables 1 & 2).

These studies measured Hg in feces, toenail, hair, blood, and meconium. Yang et al. revealed high Hg exposure (THg and MeHg), through rice consumption, is associated with *Gammaproteobacteria* class and *Proteobacteria* reversely and with *Desulfovibrio* and *Methanogens* directly. Also, low Hg exposure through fish intake vs. rice intake showed an increased abundance of *Actinobacteria*, *Desulfovibrio*, and *Methanogens* [29]. Laue et al. found no significant correlation between Hg and *Bifidobacterium* [21]. There was a positive association between Methyl mercury (MeHg) and Inorganic mercury (IHg) with *Collinsella* (early gestation) and *Parabacteroides* (late gestation) in another study. MeHg in early gestation was associated with *Lachnoclostridium*, *Ruminococcaceae_ucg013* positively, and with *Ruminococcaceae_ucg002* negatively. Furthermore, they found a direct relation with *Lachnospiraceae_nk4a136* and *Faecalibacterium* in late gestation. Phylum *Bacteroidetes* (negative), and *Prevotella_9* (positive) in early gestation and *Ruminococcaceae_ucg013* and *Megasphaera* (positive) in late gestation were correlated with IHg [30]. Rothenberg et al. (2016) reported that *Firmicutes* with MeHg and THg (positive) and IHg (negative) have a relationship [31].

Cadmium

Only one cross-sectional study in 2020 that was conducted in the USA, evaluated Cd in infants' toenail and their composition of gut microbiota. This study involved 179 infants, and its quality was high. It showed that there is a positive association between moderate levels of Cd and *Bifidobacterium* [21].

Discussion

In the present study, we reviewed major HMs exposure and alteration of human gut microbiota composition in different periods of life (adulthood, pregnancy, infancy, and childhood). Most included studies were from the USA and had evaluated As and Pb. A high number of participants belonged to Pb exposure studies. Different specimens such as urine, feces, blood, hair, nail, and water were used for the measurement of heavy metal exposure mainly by using the ICP-MS method. Almost all studies used the same method for determining gut microbiota composition. Of 12 studies, 7 were scored high quality.

Findings show that exposure to HMs disturbs gut microbiota composition and can lead to dysbiosis, although results were not homogeneous. Exposure to environmental pollutants such as HMs can damage to the intestinal epithelial barrier and cause loss of immune and microbial homeostasis [32]. A review study reported that exposure to metals in humans or animals can change the composition, structure, diversity, and homogeneity of gut microbiota. Moreover, it indicated that the specific modifications reported are not homogeneous, which is in line with our study [11]. Ghosh et al. demonstrated that HMs exposure impairs the metabolic activity of the microbiome and causes inflammatory responses and cellular damage [33]. The toxic effect of HMs exposure in animal models revealed modifications in the composition and function of gut bacteria, which are linked to metabolite changes, ultimately leading to disease conditions [34]. Recent research has shown that gut bacteria with the host signaling system through metabolites, can regulate intestinal immunity and barrier defense [35]. The mechanisms underpinning this microbiota-mediated defense against environmental pollutants are still being investigated. The main role of gut microbiota in maintaining gut homeostasis is to neutralize the toxicity of HMs. Therefore, using probiotics and their metabolites may hold great promise in treating pollutant-induced gut barrier dysfunction [36].

Exposure to high levels of all metals listed, except Cd, caused an increased abundance of one of the pro-inflammatory bacteria named *Collinsella* [37]. The genus *Collinsella* belongs to the family *Coriobacteriaceae* and is considered as pathobionts. It is associated with type 2 diabetes, rheumatoid arthritis, cholesterol metabolism, and leaky gut [38]. It can affect on metabolism by altering cholesterol absorption in the gut, decreasing glycogenesis in the liver, and increasing triglyceride synthesis [39]. Collinsella reduces the expression of tight junction proteins in enterocytes and induces leaky gut, both of which are features associated with metabolic endotoxemia [40]. An assessment of the US population showed that dietary fiber intake is inversely related to blood concentrations of HMs [41]. Low dietary fiber may contribute to the overgrowth of Collinsella and alter the fermentation pattern in the gut microbiota [38]. Therefore, increased intake of fiber can help to modulation of gut microbiota composition.

Exposure to As increased some pathogenic bacteria associated with inflammation such as *Collinsella*, *Proteobacteria*, and *Enterobacteriaceae*. *Bifidobacterium* is mostly non-pathogenic bacteria, and some strains are known as probiotics [42]. We found that As can reduce it although one of the included studies revealed that the elevation of *Bifidobacterium* is in concomitant high concentrations of As with zinc. This finding may be due to the presence of zinc. Moreover, an included study showed direct and indirect association of infant urine arsenic with *Firmicutes* and *Bacteroides*, respectively. *Firmicutes* and *Bacteroidetes* are major phyla of the colon, that can be related to obesity, and cancer [43].

Pb exposure during second trimester led to decreased both good and bad microbiota and an increment of two pathogen fungi (*Malassezia restricta* & *globose*). Some species of *Malassezia* can cause seborrheic dermatitis, pityriasis versicolor, and folliculitis, and can aggravate atopic dermatitis [44]. In third trimester, a reduction of *Bifidobacterium bifidum* & *longum* was observed. Also, an increase of pathogens including *Bilophila*, *Collinsella* (both trimesters), *Proteobacteri*, *Burkholderiales* (adult), *Malassezia restricta* & *globose*, and a decrease of *Penicillium* (Postnatal) was revealed through studies. Liu et al. revealed Pb can impair the gut barrier; which causes microbial metabolites such as bile acids and short-chain fatty acids (SCFAs) enter the intrahepatic circulation and induce multiple systematic lesion in animal and human [45]. Another study on mice illustrated Pb exposure can strongly affect on metabolic functions and gut microbiome toxicity [46].

Regarding the exposure to mercury and cadmium, a general conclusion cannot be made because the data are too inconclusive. Only one study demonstrated that exposure to low levels of Hg through fish consumption compared to rice, was associated with the elevation of three bacteria (*Actinobacteria*, *Desulfovibrio*, *Methanogens*). The primary pathway for human exposure to MeHg is fish consumption unlike providing essential nutrients [47]. Even at low levels, organic Hg (including MeHg) has high toxicity because it can pass the blood brain barrier and cause central nervous system disorders [48]. *Desulfovibrio* has emerged as pathobionts contribute to not only gut disorders but also extraintestinal diseases such as Parkinson's [49]. Also, Methanogens are emerging pathogens related to brain and muscular abscesses, dysbiosis, metabolic disorders, and colon cancer [50]. Both in vivo and in vitro research have demonstrated that exposure to Cd has various detrimental effects on the microbiome. These effects include structural alterations, increased permeability, and interference with the synthesis of bile acids, SCFAs, and amino acids [51]. Exposure to the combination of cadmium with other toxins can increase gut microbiota toxicity. As a result, this exposure may lead to dysfunction in multiple organs in different model organisms and humans [52].

Type of specimen, different age groups, bacterial species diversity in basal microbiota, type of HMs, some individual conditions (stress, food intake, etc.), living location, exposure level, and time are reasons for the heterogeneity of included studies results. There are various pathways to human exposure to HMs including foods, air, water, and soil [8]. Nevertheless, Pb exposure is mainly through air pollutants, to Hg through soil, and to As through water [53]. These provide insights into how xenobiotics may influence the composition of microbiomes and how hosts with distinct microbiomes may respond differently to xenobiotics.

The gut microbial community has evolved with its host over a lifespan and has benefits for it through several mechanisms, including digestion, detoxification, production of nutrients, protection against pathogens, and regulation of the immune system [54]. HMs through gut lining injury and its leak can increase oxidative stress, and inflammation, have cytotoxic, genotoxic, and carcinogenic effects following gut dysbiosis, and lead to some diseases [34]. Hence, enough intake of dietary fiber especially wheat bran and pectin, antioxidant-rich food sources, treatment with probiotics and prebiotics, and following a low to moderate fat diet may be effective strategies for preventing HMs toxicity and gut dysbiosis [55–58]. Furthermore, we should consider micronutrients deficiency (Iron, zinc, etc.) in particular in high-risk groups such as pregnant women and children [59, 60]. Rawee et al. in a review study demonstrated that iron deficiency plays a crucial role in the damaging effects of HMs exposure in patients with chronic kidney disease and iron supplementation might be a strategy to combat these detrimental effects [61]. Another study reported that zinc supplement can reduce the harmful effects of Cd in zebrafish model [62]. Therefore, the risk of HMs exposure can be mitigated by consuming a diet rich in essential nutrients, vitamins, protein, bioactive peptides, and various anti-oxidant-rich phytochemicals [63].

The present study has some strengths and limitations. It is the first systematic review study that considers nutritional applications with regard to HMs and microbiome. Most included studies were recently published with high quality. Albeit, some studies adjusted age, sex, body mass index, and education, only one study had adjusted other metals' exposure. It is needed to adjust potential confounders for all studies. We could not reach conclusive results because the age range, various types of specimens, exposure levels, and geographical areas were heterogeneous. Also, the number of included studies for each metal was limited. Most of the included studies had a cross-sectional design, which was not able to confirm the temporal precedence between the exposure and the outcome.

Conclusion

HMs exposure in different ways induces alterations that can lead to microbial dysbiosis. Changes in the microbiota composition and production of related metabolites may have a major impact on human health. There is a need to conduct future review studies with enough included studies on each HMs and more homogenous information. Our findings elucidate the necessity to support limiting environmental HMs contamination and the implementation of nutritional plans including more

access to probiotics, prebiotics, antioxidant-rich foods, healthy and low-fat products, and treatment of micronutrients deficiency through national and international policies.

Supplementary Information

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Supplementary Material 1

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MR, BF, YH, NR and RA contributed to the study conception, design, data interpretation, and the drafting of the manuscript. All authors approved the final manuscript for submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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