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Associations of Metals and Neurodevelopment: a Review of Recent Evidence on Susceptibility Factors

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Abstract

Purpose of Review Epidemiologic evidence exists that many metals are associated with adverse neurobehavioral effects in young children, including lead (Pb), methylmercury (meHg), manganese (Mn), and arsenic (As) (Antunes dos Santos et al. J Trace Elem Med Biol. 38:99–107; Tolins et al. Ann Glob Health. 80(4):303–14; Vollet et al. Curr Environ Health Rep. 3(4):392–404; Bellinger Curr Opin Pediatr. 20(2):172–7). Importantly, chemical insult can vary depending on host factors and exposure circumstance. This systematic review summarizes the recent literature investigating modifying factors of the associations between metals and neurodevelopment, including immutable traits (sex or genetics) or exposure conditions (timing or co-exposures).

Recent Findings Of the 53 studies included in this review, the number investigating the modification of exposure effects was as follows: 30 for sex, 21 for co-exposures, 12 for timing of exposure, and six for genetic modifiers. Sex-specific effects of metal-neurobehavioral associations were inconclusive for all metals, likely due to the heterogeneity of outcome domains assessed and the exposure time points measured. Seven studies evaluated both sex and exposure timing as modifying factors using deciduous teeth or other biomarkers with repeated measures to characterize metals exposure over time. Only five studies used statistical methods for mixtures to evaluate associations of more than two metals with neurobehavioral domains.

Summary Despite the expansion of research on susceptibility to the neurodevelopmental effects of metals exposure, considerable gaps remain. This work remains critical, as characterizing susceptible subpopulations can aid in identifying biological mechanisms and is fundamental for the protection of public health.

Keywords Metals · Neurodevelopment · Lead · Mercury · Arsenic · Manganese · Children

Introduction

In the USA, one in six children lives with a developmental disability and prevalence continues to rise [1]. While the etiology of cognitive and behavioral dysfunctions is complex, evidence supports the substantial involvement of environmental factors, even at low doses [2, 3]. Many metals and metalloids (hereafter collectively referred to as metals) are

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ubiquitous in the environment, commonly co-occur, and target the developing central nervous system [4]. Among the most prevalent environmental metals with neurotoxic potential are lead (Pb), methyl-mercury (meHg), arsenic (As), and manganese (Mn) [5–8]. Considerable epidemiologic evidence exists that these metals are associated with adverse neurobehavioral effects in young children, with more evidence for some (Pb, meHg) than for others (Mn, As) [3, 9–11]. Because neurodevelopment during the prenatal period and early life is a dynamic and complex process of critically timed events, chemical insult can not only have profound impacts but can also vary by immutable traits (sex or genetics) or exposure conditions (timing or co-exposures). Identifying susceptibility factors and other modifiers is important for understanding potential biological mechanisms and for the protection of vulnerable subpopulations.

This review surveys the recent literature on modifiers of the associations between metals and childhood neurobehavior. Mounting evidence suggests that the structure and functioning of many areas of the developing brain are sexually dimorphic [12], and some epidemiologic studies have reported sex-specific associations between individual metals and neurobehavioral outcomes [13, 14]. The differential expression of genes relating to metals' toxicokinetics or toxicodynamics also has potential to alter the association between metals and neurobehavior [15, 16]. Co-exposure to other metals can produce synergistic or antagonistic effects [17••, 18]. Exposure timing also plays an important role, because the time at which the toxic insult interferes with the neurodevelopmental cascade can determine the extent of damage and the ensuing phenotype [19••, 20••, 21].

Methods

Our review encompasses epidemiologic studies that measured exposure to As, Hg, Mn, and/or Pb and evaluated cognitive and other behavioral outcomes in early childhood, up to a mean age of 8 years. We performed our search in PubMed using the following keywords: ("child," "childhood," "children," "infant," "pregnant," "in utero," "prenatal," "postnatal," "school," "maternal exposure") AND ("neurodevelopment," "neurobehavior," "cognition," "behavior," "intelligence," "hyperactivity," "ADHD," "attention deficit," "disruptive behavior disorders", "executive function") AND ("manganese" OR "arsenic" OR "lead" OR "mercury" OR "methylmercury"). The search was restricted to English language studies of humans and publication during the past 5 years (Nov 2014–Nov 2019). We included studies that reported results from cognitive (Table 1) or other behavioral (social, personality, affective, or behavioral control) (Table 2) outcomes and investigated modification by at least one of the following: sex, genetics, co-exposure to other metals (including through fish consumption or smoking status), or exposure timing. Studies that evaluated these factors in stratified models, as interactions, or using statistical models for mixtures (e.g., Bayesian kernel machine regression, weighted quantile sum regression-based methods, and principal component analysis or other clustering methods) were included. We excluded studies that adjusted for multiple metals as confounders only (i.e., did not examine interaction, stratification, or mixtures effects) and those that reported only autism spectrum disorder, motor outcomes, or unadjusted associations. The selection of studies can be viewed in Fig. 1, which follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Lead and Neurodevelopment

The inverse association between Pb exposure and child neurological performance has been consistently demonstrated for IQ, for which no known safe level of exposure exists [8, 75]. Prior literature reporting on sex-specific effects of the association between Pb and neurobehavioral outcomes has been inconclusive [76]. In the past 5 years, Pb research has focused on blood levels < 5 μg/dL and has included novel biomarkers such as tooth dentine and placenta. Studies assessing Pb and childhood neurodevelopment have measured a variety of exposure windows and outcomes, making comparisons across studies challenging. Sex-specific findings were inconclusive across study outcomes, potentially due to the domain-specific nature of these sex-specific effects and the varying domains examined among studies.

Cognitive Outcomes

Nine studies within our review parameters evaluated the effect of Pb and modifiers of metal co-exposure on cognitive outcomes among children [17••, 22–25, 26•, 27••, 28, 34••]. In a cohort study from Korea, late pregnancy maternal blood Pb (BPb) was associated with reduced cognition at 6 months among infants with lower prenatal iron intake (< 15.1 mg/day), compared with infants with sufficient prenatal iron intake (≥ 15.1 mg/day) [22]. In a cross-sectional study of 7–12-year-old Brazilian children, Pb neurotoxicity was enhanced by higher toenail Mn [23]. On the other hand, a cross-sectional study among 6–8-year-old Uruguayan children reported marginal evidence for an antagonistic interaction between hair Mn and BPb [24]. In a Spanish cohort, an adverse synergistic interaction between placental Pb and As was reported for general cognitive scores at 4–5 years old [26•]. Rodrigues et al. evaluated pairwise interactions of Pb with Mn and As in relation to cognitive scores among 20–40-month-olds in Bangladesh and reported a negative Pb-As interaction in Pabna, where Pb levels were lower (median < LOD of 3.3 μg/dL) [25]. Another study within the same districts

Table 1 Summary of recent studies including modifiers (sex, co-exposures, exposure timing, genetic polymorphisms) of associations between lead, methyl mercury, arsenic, or manganese and child cognition

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
Lead (Pb) and cognitive outcomes										
Shah-Kulkarni 2016 [22]	Prospective cohort	965	Korea	6 months–3 years	Korean version of Bayley Scales of Infant Development II (K-BSID-II)	Maternal blood	Prenatal	Mean in the early and late gestational periods = 1.29 and 1.27 μg/dL, respectively	Iron intake, exposure timing	Late pregnancy Pb associated with decrease in 6-month MDI ($\beta = -1.61$, $p = 0.12$) for GLM models. Lower prenatal iron intake (< 15.1 mg/day) intensified the adverse association of late pregnancy Pb on 6-month MDI [$\beta = -2.53$ (95% CI = − 4.87, − 0.19)] vs. higher prenatal iron intake [≥ 15.1 mg/day: $\beta = 1.16$ (− 3.35, 5.67)]. No evidence of association for early pregnancy within mixed model analysis.
Menezes-Filho 2018 [23]	Cross-sectional	225	Brazil	7–12 years	Wechsler Abbreviated Scale for Intelligence (WASI).	Blood	7–12 years	BPb: median (25th, 75th percentiles): 1.15 (0.6–2.1 μg/dL)	Mn	Pb associated with decrease in total IQ: [β (p-value) = − 8.61 (0.004)]. Higher toenail Mn (> 0.84 μg/g) intensified the adverse association of Pb on total IQ [− 8.70 (0.04)] compared with lower toenail Mn [− 6.80 (0.17)].
Frndak 2019 [24]	Cross-sectional	345	Uruguay	6–8 years	Woodcock-Muñoz tests of cognitive abilities (W-M), Cambridge Neuropsychological Test Automated Battery (CANTAB), Bender-Gestalt Task, and Wechsler (WISC-IV) block design task	Blood	6–8 years	Mean (SD) = 4.1 (2.1) μg/dL	Mn	Pb associated with greater likelihood of belonging to poorer performing cognitive profile [OR (95% CI) = 1.28 (1.01, 1.61)]. Little evidence for interaction between linear Pb and hair Mn [OR-interaction = 0.94 (0.88, 1.00)].
Rodrigues 2016 [25]	Cross-sectional (primary analysis)	524	Bangladesh	20–40 months	Bayley Scales of Infant Development (BSID-III)	Blood	20–40 months (primary analysis)	20–40 months: median (IQR) in Sirajdikhan: 7.6 (5.5, 10.4) μg/dL. Median (IQR) in Pabna: < LOD (< LOD, 3.8) μg/dL	Mn, As	Pb associated with decreased cognitive scores in Sirajdikhan ($\beta = -0.17$, $p = 0.05$). In Pabna, Pb-water As interaction term: $p = 0.003$.
Valeri 2017 [17••]	Prospective cohort	825	Bangladesh	20–40 months	Bayley Scale of Infant and Toddler Development Third Edition	Cord blood	Prenatal	Mean ± SD (μg/dL): 1.8 ± 1.9 Pabna; 6.0 ± 1.89 Sirajdikhan	As, Mn	Adverse effect of the mixture all above the 60th percentile (BKMR analyses). Ln-Pb associated with reduced raw cognitive score [per IQR (1.4 μg/dL): −0.1 (−0.2, −0.03)] standard deviations when As and Mn at median.
Freire 2018 [26•]	Prospective cohort	302	Spain	4–5 years	McCarthy Scales of Children's Abilities (MSCA)	Placenta	Prenatal	16.6% > LOD; median, 25th, 75th: < LOD of 6.500 ng/g	As, Mn, Hg, Cd sex	No association between detectable Pb and MSCA continuous outcomes. Significant interaction between As and Pb ($p = 0.02$)
Levin-Schwartz 2019 [27••]	Prospective cohort	393	Mexico	6–9 years	RVP from CANTAB: percentage of correct responses and latency	Blood	Prenatal	2nd trimester mean (SD), range: 3.68 + 2.59 (0.84–17.81) μg/dL.	Cd, cesium, chromium,	No effect estimates reported (joint weighted quantile sum regression (JWQS) and

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
								3rd trimester mean (SD), range: 3.83 + 2.88 (0.02–28.25) μg/dL	As, antimony	meta-weighted quantile sum regression (MWQS)): Pb was among the largest contributor to the JWQS and MWQS models associated with the delay to the correct response in the RVP.
Kordas 2015 [28]	Cross-sectional	92	Uruguay	13–42 months	Bayley Scales of Infant Development (BSID-III)	Blood	13–42 months	Mean (SD), range: 5.8 (2.9), 2.4–15.5 μg/dL	Cd, Mn, As	Used latent class analysis to cluster participants based on metal exposure to Mn, Pb, As, Cd, no association found with BSID scores in Uruguayan preschool children.
Silver 2016 [29]	Prospective cohort	315	China	Newborn 6 weeks	Infant sensory function (measured by auditory brainstem response or ABR) and grating visual acuity (VA)	Maternal and cord blood	Mid- and late--pregnancy	GM mid-pregnancy 2.4 (2.5) μg/dL	Exposure timing	Higher categorical late pregnancy Pb (Pb > 3.8 μg/dL or Pb = 2–3.8 μg/dL) was associated with reduced mean VA scores [8.5% lower (95% CI 2.4–14.7%) and 7.2% lower (95% CI 1.1–13.3%); p-trend = 0.009] and higher mean ABR central-to-peripheral ratios (4.6 and 3.2% higher; p-trend = 0.002) compared with the Pb < 2 μg/dL.
Desrochers-Couture 2018 [30]	Prospective cohort	609	Canada	3–4 years	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) at 3–4 years	Maternal and cord blood	Prenatal childhood (3–4 years)	Mean ± SD (range)—1st trimester: 0.62 ± 1.6 μg/dL (0.16–4.14); 3rd trimester 0.59 ± 1.7 (0.14–3.93); cord blood: 0.76 ± 1.7 (0.08–3.52); child blood: 0.70 ± 1.7 (0.14–5.49)	Sex exposure timing	Cord Pb associated with reduced performance IQ among boys [β (95% CI) = −3.28 (−5.31, −1.18) vs. girls (3.44 (0.82, 5.98)]. No association between cord Pb and WPPSI-III scores.
Taylor 2017 [31•]	Prospective cohort	235; 4251	UK	4 or 8 years	WPPSI and WISC-III	Maternal and cord blood	Prenatal (1st trimester) 30 months (secondary analysis)	Mean ± SD: prenatal Pb: 3.67 ± 1.46 μg/dL (n = 4251) Mean ± SD: childhood Pb: 4.22 ± 3.12 μg/dL (n = 235)	Sex	Among boys, Pb weakly associated with reduced IQ [VIQ: β (95% CI) = −0.15 (−0.90, 0.60), PIQ: −0.42 (−1.19, 0.35), and total IQ: −0.29 (−1.02, 0.44)], while among girls, Pb weakly associated with increased IQ [VIQ: 0.71 (0.11, 1.32), PIQ: 0.57 (−0.11, 1.24), total IQ: 0.73 (0.13, 1.33)]; sex-Pb interaction terms for VIQ, PIQ, and total IQ (p = 0.071, 0.065, 0.033). No evidence of moderating effect of prenatal Pb between child Pb and child IQ.
Fruh 2019 [32]	Prospective cohort	1006	USA	7.8 ± 0.8 years (mean age)	Behavior Rating Inventory of Executive Functions (BRIEF) and Strengths and	Maternal blood	Prenatal	Mean maternal erythrocyte Pb concentration:	Sex	Pb associated with worse BRIEF Global Executive Composite (GEC) scores [per IQR (0.6

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
					Difficulties Questionnaire (SDQ)			1.2 μg/dL (interquartile range [IQR] 0.8–1.5 μg/dL) (~0.4 μg/dL whole blood)		μg/dL) increase, parent-rated: β (95% CI) = 0.73 (−0.06, 1.52), teacher-rated: 0.42 (−0.39, 1.23)] and BRIEF plan/organize [parent-rated: 0.85 (0.12, 1.59)]. Generally, Pb more strongly associated with outcomes among girls: parent-rated behavioral regulation [1.03 (0.01, 2.04)], GEC [1.17 (0.06, 2.28)], plan organize [1.05 (0.11, 1.98)] vs. boys: [0.51 (−0.63, 1.66), 0.47 (−0.58, 1.51), 0.70 (−0.34, 1.74)]. No evidence for effect modificaQon based on sex-Pb interaction terms.
Barg 2018 [33]	Cross-sectional	206	Uruguay	6.7 ± 0.5 years (mean age)	Behavior Rating Inventory of Executive Functions (BRIEF); Conners' Rating Scale (CRS); teacher rated	Blood	6.7 ± 0.5 years (mean age)	Mean BPb: 4.2 ± 2.1 μg/dL	Sex	1% higher prevalence ratio on the inhibit subscale of the BRIEF scores [per 1 μg/dL in blood Pb, PR (95% CI) = 1.01 (1.00, 1.03)]; Among girls [inhibition: 1.02 (1.00, 1.05), behavioral regulation: 1.03 (1.00, 1.05)]; among boys [inhibition: 1.00 (0.98, 1.01), behavioral regulation: 0.99 (0.97, 1.01)].
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months	Denver Developmental Screening Test II (DDST-II): social contact, language skills	Breast milk, blood, urine	2–12 months	Median (range), breast milk: 47.13 (12.29–329.91) μg/L maternal blood: 2.11 (0.10–9.48) μg/dL maternal urine: 5.57 (0.00–56.78) μg/L	Pb, Mn, meHg, DDT + metabolites, Se	No association of Pb in single exposure or mixed exposure analysis (PCA) on DDST-II outcomes.
Methyl mercury (meHg) and cognitive outcomes										
Strain 2015 [35]	Prospective cohort	1265	Seychelles	20 months	BSID-II MacArthur Bates Communicative Development Inventories (CDI) Infant Behavior Questionnaire-Revised	Maternal hair collected at delivery	Prenatal	Mean (SD) THg: 3.92 (±3.46) ppm	Fatty acids	Null associations between prenatal MeHg and neurodevelopmental outcomes. For PDI, MeHg-PUFAs interaction term: $p < 0.05$. Increasing MeHg associated with lower PDI but only in children of mothers with higher n-6/n-3. Among mothers with higher n-3 PUFAs, increasing MeHg associated with higher PDI.
Golding 2017 [36]	Prospective cohort	2062	England	8 years	Short form of WISC: FSIQ, VIQ, PIQ	Maternal blood	Prenatal	Median THg: 1.86 μg/L	Sex fish consumption	Null associations between THg and FSIQ for all children [β (95% CI) = 0.61 (−0.06, 1.29)]; among fish-eating mothers, THg associated with increased FSIQ [0.84 (0.13, 1.56)] vs. non-fish

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
										eaters [−2.22 (−5.00, 0.56)]. Hg-fish consumption interaction term in binary models: $p < 0.05$. No sex differences.
Hibbeln 2019 [37]	Prospective cohort	1569 to 2224	England	School years: 4, 7, 9, 13; age 8	11 scholastic outcomes (spelling, reading, mathematics, comprehension, reasoning)	Maternal blood	Prenatal 1st trimester	Not reported	Beneficial nutrients from fish consumption	Inverse associations between THg and 6-year scores among mothers who did not eat fish [science reasoning: β (95% CI) = −0.29 (−0.68, 0.10), math reasoning: −0.96 (−2.05, 0.13)] vs. mothers who ate fish [science reasoning: 0.14 (0.01, 1.12), math reasoning: 0.13 (−0.21, 0.48)]. Hg-fish consumption interaction term: $p < 0.05$.
Llop 2017a [38]	Prospective cohort	1362	Spain	4–5 years	MSCA	Cord blood	Prenatal	GM (95% CI) THg: 8.8 (8.4, 9.2) μg/L	Fish consumption	A doubling in CB-Hg associated with higher scores in most of the MSCA scales. Inverse associations for CB-Hg among children whose mothers consumed < 3 weekly servings of fish during the first trimester of pregnancy for the perceptive-manipulative scale [β (95% CI) = −1.20 (−2.62, 0.22)] and general cogniQve scale [−3.06 (−6.37, 0.24)]. Hg-fish consumption interaction term: $p < 0.05$.
Xu 2016 [39]	Prospective cohort	344	USA	5 weeks	NICU Network Neurobehavioral Scale (NNNS)	Maternal blood 2nd trimester and birth cord blood	Prenatal	GM (95% CI) maternal THg (μg/L): 16 weeks: 0.7 (0.6–0.7) 26 weeks: 0.6 (0.5–0.6) Delivery: 0.6 (0.5–0.7) GM cord THg: 0.7 (0.6–0.8) μg/L	Sex Total PCBs	Sex differences between maternal blood THg and asymmetric reflex [girls (0.05 (0.10)] vs. boys [−0.13 (0.12)], but not associaQons using cord blood THg. Hg-PCB interaction term on special handling scale: maternal THg ($p = 0.03$) and cord BTHg ($p = 0.07$), without PUFA adjustment; among those with higher PCBs (> 61.1 ng/g lipid), Hg associated with less need for special handling.
Jacobson 2015 [40]	Prospective cohort	282	Canada	8–14 years	WISC-IV IQ	Cord blood maternal hair current hair current blood	Prenatal childhood	Mean (SD): Cord THg: 21.8 (17.5) μg/L Maternal hair THg: 4.9 (2.8) μg/g Child's current hair THg: 6.9 (6.5) μg/g Current blood THg: 4.7 (4.7) μg/L	PCB-153, selenium, DHA exposure timing	No interaction ($p > 0.20$) between Hg and: current PCB-153, cord Pb, cord selenium, or cord DHA. Prenatal THg associated with lower WISC scores [overall IQ: β (95% CI) = −0.17 (−0.31, −0.02), verbal comprehension: −0.15 (−0.30, −0.004), perceptual reasoning: −0.18 (−0.30, −0.06)]. Null

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
										associations of THg measured in childhood and IQ [overall IQ: 0.16 (−0.03, 0.36)].
Marques 2015 [41]	Prospective cohort	294	Brazil	6 and 24 months	BSID Age of walking Age of talking	Hair	Prenatal postnatal	Median (min, max) hair THg (μg/g): Birth: girls: 0.8 (0.1–2.0); boys: 0.8 (0.3–2.0) 6 months: girls: 0.8 (0.3–2.0); boys: 1.0 (0.5–1.9) 24 months: girls: 1.8 (0.6–5.4); boys: 1.7 (0.6–5.7)	Exposure timing	Beta estimates not reported. Interaction between exposure group and time of outcome borderline significant ($p = 0.09$). Children in highest THg exposure group had more with < 80 IQ at 24 months than at 6 months.
Jeong 2017 [42]	Prospective cohort	553	South Korea	60 months	IQ, VIQ, PIQ from WPPSI-R, Korean language version	Maternal blood 3rd trimester	Prenatal	GM (GSD) THg: 3.14 (± 1.66) μg/L Tertiles: 1.9 (± 1.5); 3.2 (± 1.1); 5.2 (± 1.3) μg/L	Fish consump-tion	A doubling of maternal blood THg associated with a 2.4-point reduction in verbal and FSIQ [β (95% CI) = −2.48 (−4.21, −0.75), −2.40 (−4.28, −0.53), respecQvely]. A doubling of Hg with increasing tertiles of fish consumption associated with worse VIQ [T1: −0.64 (−3.83, 2.56), T2:−2.54 (−5.85, 0.77), T3: −3.72 (−6.42, −1.02)].
Barbone 2019 [43]	Prospective cohort	1083	Italy, Sloveni-a, Croatia, Greece	18 months	BSID-III composite scores	Maternal hair and blood cord blood, breast milk	Prenatal postnatal	Median THg: Maternal hair: 704 ng/g Maternal blood: 2.4 ng/g Cord blood: 3.6 ng/g Breast milk: 0.6 ng/g	Exposure timing	Strongest associations for THg measured in maternal hair: positively associated with several domains including language composite score [β (95% CI) = 0.55 (0.05, 1.05)] and receptive communication scaled score [0.12 (0.02, 0.22)].
Freire 2018 [26•]	Prospective cohort	302	Spain	4–5 years	McCarthy Scales of Children's Abilities (MSCA)	Placenta	Prenatal	Median: 0.025 ng/g wet weight 25th and 75th percentiles: 0.02 and 12.95 ng/g wet weight	Mn, Pb, As, Cd Sex Breastfeeding Smoking during pregnancy	Detected vs. non-detected Hg associated with increased odds of poorer performance in the verbal function of posterior cortex [β (95% CI) = 2.43 (1.07, 5.52)]. Dose-response for Hg tertiles and odds of poorer scores for verbal function of posterior cortex. Inverse associations of Hg with the general cognitive score among boys [−1.04 (−5.81, 3.74)], but not girls [1.61 (−5.90, 9.09)]; Hg-sex interaction term: $p = 0.04$. The positive effect of Mn on cognitive function was increased among children with Hg co-exposure.
Kim 2018 [44]	Prospective cohort	476 to 1076	South Korea	6, 12, 24, and 36 months	BSID-II test: MDI	Maternal and cord blood	Prenatal	GM (10th; 90th percentiles) THg: maternal blood: early	Exposure timing	Associations were strongest for early pregnancy THg measurements and early MDI

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
								pregnancy: 3.3 μg/L (1.8; 5.9); late pregnancy: 3.0 μg/L (1.7; 5.6); cord blood: 5.1 μg/L (2.9; 8.9)		outcomes [e.g., 6-month MDI ($\beta = -0.49$, $p = 0.03$)].
Wang 2019 [45]	Prospective cohort	286	China	3 days (NBNA) 18 months (BSID)	Neonatal Behavioral Neurological Assessment (NBNA) and BSID-III	Cord blood	Prenatal	GM: 2.0 μg/L THg Range: 0.2–11.9 μg/L Median: 1.9 μg/L	Sex DHA	THg associated with reduced NBNA [β (95% CI) = −0.07 (−0.14, −0.002)], BSID scores [cognitive: −0.39 (−1.17, 0.40), language: −0.19 (−1.02, 0.63)]. Among boys, stronger Hg associations for NBNA total [−0.18 (−0.34, −0.02) vs. girls −0.07 (−0.16, 0.03); Hg-sex interaction term: $p < 0.05$]. Among low DHA (< 45.54 μg/mL), stronger associations between Hg and NBNA total [−0.14 (−0.26, −0.02) vs. high DHA −0.06 (−0.16, 0.03)]. Hg-DHA interaction term: $p < 0.05$.
Tatsuta 2018 [46]	Prospective cohort	1016	Japan	18 months	BSID-II: MDI and PDI	Cord blood	Prenatal	Median (5–95 percentiles) THg: Maternal hair (μg/g): urban: 2.0 (0.9–4.4), coastal: 2.6 (0.9–6.0) Cord blood (ng/g): urban: 10.0 (4.2–22.4), coastal: 16.0 (5.6–39.3)	Sex	Null associations between THg and MDI. No effect measure modification by sex for Hg-MDI associations [boys: β (p-value) = −0.04 (0.44), girls: −0.02 (0.73)]. Hg-PDI association differed by sex [boys: −0.12 (0.008), girls: 0.02 (0.62)].
Engstrom 2016 [47]	Prospective cohort	1313	Seychelles	15–32 months	BSID-II	Maternal hair	Prenatal	Mean (SD) THg: 3.94 (± 3.47) ppm	Genetic polymorphisms	Among rs11075290 genotypes CC, hair THg associated with worse scores on MDI [compared to CC genotype, TT genotype: $\beta = 1.92$, CT genotype: $\beta = 0.27$, $p = 0.04$].
Wahlberg 2018 [48••]	Prospective cohort	935	Seychelles	15–32 months	BSID-II MDI and PDI	Maternal hair and blood cord blood	Prenatal	Hg median (25th, 75th) THg: maternal hair: 2.9 ppm (1.4, 5.1); maternal blood: 15.8 μg/L (10.8, 22.8); cord blood: 30.15 μg/L (20.0, 43.9)	Genetic polymorphisms	Among GSTP1 rs1695 GG carriers, 1 ppm hair Hg increase associated with a 1.5 point decrease on MDI ($p < 0.05$).
Snoj Tratnik 2017 [49]	Prospective cohort	361	Slovenia and Croatia	18 months	BSID-III	Cord blood maternal hair maternal blood	Prenatal	GM (min, max) THg (ng/g) Cord blood: 2.05 (1.87, 2.25) Maternal hair: 582 (490–691)	Genetic polymorphisms	THg weakly associated with reduced points on the cognitive scale for both CBHg [β (95% CI) = −1.41 (−3.47, 0.66)] and maternal hair Hg [−1.12 (−3.08, 0.84)]. Among e4 carriers, CBHg associated with reduced

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
								Maternal blood: 2.36 (2.1–2.66)		cognitive score [CBHg: −5.4 (−10.7, 0.19) vs. referent carriers: −0.49 (−2.76, 1.78)]; maternal blood, among e4 carriers only: −4.02 (−8.54, 0.50); Hg-e4 carrier interaction term: $p < 0.05$
Julvez 2019 [50]	Prospective cohort	1723	England	8.5 years average	Short form WISC-III: FSIQ, VIQ, PIQ	Cord tissue	Prenatal	25.2 (SD, 12.7) ng/g; corresponds to a cord blood mercury concentration of 2.70 μg/L	Genetic polymorphisms	An increase in cord Hg weakly associated with higher points on FSIQ [β (95% CI) = 2.6 (−1.1, 6.4)], VIQ [2.9 (−0.9, 6.80)], and PIQ [1.6 (−2.6, 5.7)]. New interacQng SNPs were discovered in relation to superoxide dismutase 2, ATP binding cassette subfamily A member 1, and metallothionein 1 M genes. Progesterone receptor rs1042838 minor alleles revealed a negative association of mercury exposure with IQ..
Llop 2017b [51••]	Three prospective birth cohorts	2639	Seychelles Spain Italy and Greece	14–30 months	BSID-I, II, and III	Cord blood and/or maternal hair	Prenatal	Mean (SD) THg maternal hair (μg/g): Seychelles 1: 5.8 (3.7) Seychelles 2: 3.9 (3.5) Spain: NA PHIME Italy: 1.0 (1.0) PHIME Greece: 1.4 (1.1) Mean (SD) THg cord blood (μg/L): Seychelles 1: 39.3 (25.5) Seychelles 2: NA Spain: 11.3 (9.8) PHIME Italy: 5.6 (4.8) PHIME Greece: 7.5 (5.8)	Genetic polymorphisms	Per 1 ppm prenatal THg increase and BSID score [β (95% CI)] among each genotype: CYP3A7 rs2257401 GG + GC: MDI: 2.9 (1.53, 4.27), CYP3A5 rs776746 AA + AG: MDI: 2.51 (1.04, 3.98) CYP3A4 rs2740574 GG + AG: MDI: 2.31 (0.12, 4.50). Interaction between the CYP3A genes and THg ($p < 0.05$) in European cohorts only.
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months	Denver Developmental Screening Test II (DDST-II): social contact, language skills; Parents' Evaluation of Developmental Status (PEDS): learning and behavior problems	Breast milk, maternal blood	2–12 months	Median (range), breast milk: 1.4 (1.1–2.1) μg/L; mom blood: 0.5 (0.1–1.0) μg/L	Pb, Mn, DDT + metabolites, Se	No association of MeHg in individual or PCA analyses. MeHg-Se interaction insignificant.
Arsenic (As) and cognitive outcomes										
Valeri 2017 [17••]	Prospective cohort	825	Bangladesh	20–40 months	BSID-III (Cognitive and Language Domains)	Cord blood	Prenatal	Total as mean (SD), range in Pabna: 1.0 (2.2), 0.1–27.7 μg/dL Total as mean (SD), range in Sirajdikhan: 0.4 (1.9), 0.1–7.4 μg/dL	Mn, Pb	BKMR results: Positive association between As and cognitive score, but less pronounced at high levels of Mn. As-cognitive score associations from linear regression: Pabna: β (95% CI) = 0.07 (−0.08, 0.23), Sirajdikhan: −0.02 (−0.06, 0.06).

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
Rodrigues 2016 [25]	Cross-sectional (primary analysis), prospective cohort (sensitivity analyses)	524	Bangladesh	20–40 months	Bayley Scales of Infant Development (BSID-III)	Water	20–40 months (primary analysis), prenatal and 1 1 month postpartum (sensitivity analyses)	Median (IQR): 20–40 months: Sirajdikhan: 1.5 (LOD, 21.6) μg/L; Pabna: 25.7 (4.4, 130) μg/L] Prenatal: Sirajdikhan: 1.3 (LOD, 1.9) μg/L; Pabna: 26.5 (5.3, 81) μg/L 1 month postpartum: Sirajdikhan: 0.8 (LOD, 1.9) μg/L; Pabna: 31 (5.9, 120) μg/L	Mn, Pb	Significant associations only observed in Pabna: Primary (cross-sectional, 20–40-month water As) Analysis (Pabna): β (p-value) = −0.06, (0.05) Prenatal water As (Pabna): −0.09, (0.006) 1 month water As (Pabna): −0.05(0.17).
Freire 2018 [26•]	Prospective cohort	302	Spain	4–5 years	McCarthy Scales of Children's Abilities (MSCA)	Placenta	Prenatal	22.2% above LOD (0.23 ng/g)	Mn, Pb, Hg, Cd, sex, breastfeeding, smoking during pregnancy	Placenta As associated with reduced scores on global executive function [β (95% CI) = −5.52 (−9.73, −1.32)] and verbal execuQve funcQon [−6.54 (−10.83, −2.25)] and increased odds of scoring low on quantitative subarea [OR (95% CI) = 2.92 (1.19, 7.15)] and working memory [2.47 (0.96, 6.32)]. Total As-Pb interaction term: p = 0.02. No other significant interactions.
Levin-Schwartz 2019 [27••]	Prospective cohort	393	Mexico	6–9 years	RVP from CANTAB: percentage of correct responses and latency to a correct response	Maternal blood	Prenatal	Total as mean (SD), range: 2nd trimester: 0.92 (1.46), 0.28–27.52 μg/L 3rd trimester: 0.94 (0.74), 0.27–7.31 μg/L	Cd, cesium, chromium, Pb, antimony	No effect estimates reported (WQS extensions used for mixtures approach): Tri3 As identified as one of top 3 metals associated with reduced accuracy of RVP. Neither Tri2 nor Tri3 As ranked highly in relation to RVP latency.
Kordas 2015 [28]	Cross-sectional	92	Uruguay	13–42 months	Bayley Scales of Infant Development (BSID-III) (cognitive and language domains)	Hair	13–42 months	Total as mean (SD), range: 0.2 (1.0), 0.01–9.6 μg/g hair	Cd, Mn, Pb	Used latent class analysis to cluster participants based on metal exposure to Mn, Pb, As, and Cd. No association with BSID scores.
Wang 2018 [52]	Prospective cohort	892	China	3 days	Neonatal Behavioral Neurological Assessment (NBNA)	Cord blood serum	Prenatal	Total As median (IQR): 0.73 (0.28, 2.04) μg/L	Sex	CB-As associated with increased odds for low overall NBNA scores (< 37) [OR (95% CI) = 1.90 (1.62, 2.23)]. No As-sex interaction: $p > 0.10$.
Signes-Pastor 2019 [53••]	Cross-sectional	361	Spain	4–5 years	McCarthy Scales of Children's Abilities (MSCA)	Spot urine, SG adjusted	4–5 years	Speciated As (iAs + MMA + DMA) Median (IQR): 4.85 (2.74–7.54) μg/L	Sex	As weakly associated with reduced general cognition: [β (95% CI) = −0.86 (−2.43, 0.71)]. Among boys, As inversely associated with quantitative index [−2.59 (−5.36, 0.17)] and working

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
										memory [(−2.56 (−5.36, 0.24)]. As-sex interaction term: $p < 0.10$.
Desai 2018 [54•]	Cross-sectional	328	Uruguay	5–8 years	Woodcock-Munoz Cognitive Battery	First-void urine, SG-adjusted	5–8 years	Speciated As (iAs + MMA + DMA) Median (range): 11.9 (1.4–93.9) μg/L	Folate intake (tertiles) %MMA (median cutoff 9.42%) Sex	Null overall associations of As and outcomes. Some significant associations observed within certain strata of folate intake or %MMA, but inconsistent directions of associations (both protective and adverse effects observed depending on the subtest and stratum). No As-sex interactions: $p > 0.05$.
Zhou 2020 [55]	Cross-sectional	296	China	~7–8 years	Wechsler Intelligence Scale for Children-Chinese Revised (WISC-CR)	Spot urine (SG-adjusted)	Childhood	Total As median (IQR): Unadjusted T-As: 26.05 (12.88, 43.80) μg/L SG-adjusted T-As: 25.70 (12.81, 43.23) μg/L.	Sex	As not significantly associated with FSIQ, VIQ or PIQ in full sample or in sex-stratified analyses. Multi-element model, FSIQ: all: [β (95% CI) = 1.12 (−0.74, 2.98), $p = 0.24$]. Among girls, As associated with a 2-point increase in IQ: [2.1 (−1.05, 5.24), p = 0.19]. The associaQon was not as strong among boys: [0.78 (−1.60, 3.16), $p = 0.52$].
Manganese (Mn) and cognitive outcomes										
Menezes-Filho 2018 [23]	Cross-sectional	225	Brazil	7–12 years	IQ with Wechsler Abbreviated Scale of Intelligence (WASI)	Hair, toenails	7–12 years	Median (25th, 75th percentiles), hair: 0.74 (0.50, 1.32) μg/g; toenails: 0.85 (0.51, 1.77) μg/g	BPb	No interaction between Mn and BPb (though some evidence that high toenail Mn (> 0.84 μg/g) enhances the adverse association of Pb on IQ)
Gunier 2015 [56]	Prospective cohort	197	USA	6, 12, and/or 24 months	Bayley Scales of Infant Development (BSID-II)	Tooth dentine	Prenatal, postnatal	GM (GSD) as 55Mn:43Ca AUC, prenatal: 0.47 (1.5) [~0.04 mg Mn/g dentin]; postnatal: 0.14 (2.8)	BPb maternal Fe sex exposure timing	Among girls whose mothers had lower hemoglobin levels, 2-fold increase in prenatal Mn associated with 10.5 point decrease (95% CI: −16.2, −4.8). Two-fold increase in postnatal Mn associated with ~ 1 point decrease in MDI at 6 and 12 months; association stronger in girls [−1.5 (−2.4, −0.6)]. No association at 24 months.
García-Chimalpopoca 2019 [57]	Cross-sectional	265	Mexico	7–11 years	Verbal learning and memory with Children's Auditory Verbal Learning Test-2 (CVLT-2)	Hair	7–11 years	Mean (SD): 5.04 (7.47) μg/g	BPb Sex Age at evaluation	MnH third tertile (3.96 to 48 μg/g) associated with an average of 5- to 9-point decrease in verbal learning and memory scores. No interaction with BPb, sex, or age at evaluation.
Mora 2015 [58]	Prospective cohort	248	USA	7, 9, 10.5 years	Wechsler Intelligence Scale for Children (WISC-IV): IQ	Tooth dentine	Prenatal postnatal	GM (GSD), prenatal: 0.46 (1.48); postnatal: 0.14 (2.47) $^{55}Mn:^{43}Ca$ AUC × 10^4	BPb Sex Exposure timing	Prenatal and postnatal Mn associated with better cognition and memory among boys only, but in the presence of high Pb,

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
										prenatal Mn associated with worse cognition and memory.
Carvalho 2018 [59]	Cross-sectional	70	Brazil	7–12 years	Inhibition: inhibitory control and cognitive flexibility; word generation: verbal fluency; list memory: verbal learning and memory	Hair	7–12 years	Median (range): 11.5 (0.5–55.7) μg/g	Sex	MnH associated with lower verbal memory scores [free recall after interference: β (95% CI) = −1.8 (−3.4, −0.2); delayed effect: −2.0 (−3.7, −0.2)]. Stronger adverse associaQons in boys on 2 verbal memory subtests and in girls on 1 subtest.
Claus Henn 2017 [60]	Prospective cohort	224	USA	2 years	Bayley Scales of Infant Development (BSID-II)	Maternal, umbilical cord blood	Prenatal	Median (25th, 75th percentiles) in maternal and cord blood, respectively: 24.0 (19.5, 29.7) and 43.1 (33.5, 52.1) μg/L	Sex	IQR increase in maternal blood Mn associated with −3.0 (95% CI −5.3, −0.7) points on MDI. No association with cord Mn and no clear evidence of Mn-sex interaction.
Haynes 2018 [61]	Cross-sectional	106	USA	7–9 years	IQ with Wechsler Intelligence Scale for Children-IV (WISC-IV)	Hair, blood	7–9 years	GM (GSD), hair: 360 (2.2) ng/g; blood: 10 (1.3) μg/L	Sex	MnH associated with 1–2-point decreases in IQ that were similar for boys and girls but attenuated after adjustment for Pb, cotinine, and blood Mn.
Oulhote 2014 [62]	Cross-sectional	375	Canada	6–13 years	California Verbal Learning Test Children's Version (CVLT C), Conners' Continuous Performance Test II (CPT II), Digit Span, Santa Ana Test, Wechsler Abbreviated Scale of Intelligence (WASI): attention, memory, IQ	Hair, drinking water	6–13 years	Mean (range), water: 99 (1–2701) μg/L; hair: 1.4 (0.1–20.7) μg/g	Sex	1 SD increase in hair Mn associated with 24% SD decrease in memory, 25% SD decrease in attention. 1SD increase in water Mn associated with 14% SD decrease in memory. No sex-specific effects.
Bouchard 2018 [63]	Cross-sectional	259	Canada	6–14 years	Wechsler Intelligence Scale for Children (WISC-IV): IQ	Drinking water, hair, toenails, saliva	6–14 years	GM, hair: 2.0 mg/g, toenails: 0.3 mg/g, saliva supernatant: 1.1 mg/L; water: < 0.03 to 1046 mg/L	Sex	Toenail Mn associated with reduced IQ scores in girls [for a 10-fold increase in Mn, β (95% CI) = −5.65 (−10.97, −0.32)]; in boys, water Mn associated with better PIQ scores: [2.66 (0.44, 4.89)].
Mora 2018 [64•]	Prospective cohort	355	Costa Rica	1 year	Bayley Scales of Infant Development (BSID-III)	Maternal hair, blood, urinary ethylenethio-urea (ETU; mancozeb metabolite)	Prenatal	Median (25th, 75th percentiles), hair: 1.7 (0.9, 4.1) μg/g; blood: 24.0 (20.3, 28.0) μg/L; ETU: 3.3 (2.4, 4.9) μg/L	Sex exposure timing	Among girls, higher hair Mn associated with lower cognitive scores [β (95% CI) = −3.0 (−6.1, 0.1)]; null among boys. AssociaQon in girls stronger in the second half of pregnancy than first. Null associations for blood Mn.
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months (mean 7 months)	Denver Developmental Screening Test II (DDST-II): social contact, language skills	Breast milk, mother's blood, mother and infant urine	2–12 months (mean 7 months)	Median (range), breast milk: 16 (7–32) μg/L; mom blood: 14 (5–47) μg/L; infant urine: 3 (1–22) μg/L; mom urine: 2 (0.1–23) μg/L	Pb, meHg, DDT + metabolites	Using PCA analysis, no associations with social contact or language skills on DDST-II.
Claus Henn 2018 [20••]	Prospective cohort	138	Mexico	6–16 years		Tooth dentine	2nd trimester through	Median (25th, 75th percentiles), as	Sex BPb	Prenatal tooth Mn associated with better visual-spatial scores at low

Table 1 (continued)

Reference	Study design	Sample size	Study location	Age at outcome	Specific outcome	Exposure metric	Exposure timing	Exposure Level	Modifier	Key main findings
					Wide Range Assessment of Visual Motor Abilities (WRAVMA)		early childhood	55Mn:43Ca across all time points: 1.2E−3 (6.8E−4, 2.0E−3)	Exposure timing	Pb level; postnatal tooth Mn associated with worse visual-spatial scores among boys.
Freire 2018 [26•]	Prospective cohort	302	Spain	4–5 years	Cognition with McCarthy Scales of Children's Abilities (MSCA) and MSCA subareas, e.g., executive function	Placenta	Prenatal	Median (25th, 75th percentiles): 64 (51, 82) ng/g	As, Pb, Hg, Cd, sex, breastfed, smoking during pregnancy	A 10% increase in placental Mn levels associated with 1.10-fold increased odds [OR (95% CI) = 1.10 (1.01, 1.19)] of scoring lower on perceptual-performance skills, but lower odds of poorer quantitative skills [0.90 (0.83, 0.97)]. Antagonistic Mn-Hg interaction.
Frndak 2019 [24]	Cross-sectional	345	Uruguay	6–8 years	Cognitive functioning with Woodcock-Muñoz tests of cognitive abilities (W-M), Cambridge Neuropsychological Test Automated Battery (CANTAB), Bender-Gestalt Task, and Wechsler (WISC-IV) block design task	Hair	6–8 years	Median (5th, 95th percentiles): 0.8 [0.3, 4.1] ppb (ng/g)	BPb	Little evidence for interaction between linear BPb and hair Mn: OR-interaction = 0.94 (0.88, 1.00).
Kordas 2015 [28]	Cross-sectional	92	Uruguay	13–42 months	Bayley Scales of Infant Development (BSID-III)	Hair	13–42 months	Mean (SD): 1 (1.4) μg/g	Pb, As, Cd	Used latent class analysis to cluster participants based on metal exposure to Mn, Pb, As, and Cd. No association found with BSID scores.
Rodrigues 2016 [25]	Prospective cohort	524	Bangladesh	20–40 months	Bayley Scales of Infant Development (BSID-III)	Drinking water	1st trimester; 1, 12, 20–40 months	Range of medians: 464–1150 μg/L	Water As, BPb, exposure timing	Null associations for water Mn with cognitive scores and no evidence of differences by exposure timing or of interaction with As or Pb.
Valeri 2017 [17••]	Prospective cohort	825	Bangladesh	20–40 months	Bayley Scales of Infant Development (BSID-III)	Umbilical cord blood	Prenatal	Mean (range), Sirajdikhan: 54 (12–886) μg/L; Pabna: 97 (17–3031) μg/L	Pb, As	BKMR results: ln-Mn associated with decrease cognitive score [per IQR (13.2 μg/dL): β (95% CI) = 0.3 (−0.5, −0.1) SDs], when As and Pb are at median. Higher levels (> 60th percenQle) of Mn, As, and Pb associated with worse scores.
Zhou 2020 [55]	Prospective cohort	296	China	~7–8 years	Cognition (WISC-Chinese revised)	Umbilical cord blood, urine	Prenatal; childhood (urine)	GM (GSD), cord: 29.29 (1.48) μg/L; urine: 0.66 (3.81) μg/L	Sex exposure timing	Urine Mn positively associated with higher performance IQ scores, particularly in girls [β (95% CI) = 1.3 (0.03, 2.6)].

reported joint adverse effects of a mixture of As, Pb, and Mn measured in cord blood on 2–3-year Bayley Scales of Infant Development (BSID) scores using Bayesian kernel machine regression (BKMR) [17••]. Pb was the most neurotoxic component of the mixture among children from one study site with higher BPb levels (mean 6.0 μg/dL), while Pb-BSID associations were largely null at the other study site, with lower Pb concentrations (mean 1.8 μg/dL). No interaction between Pb and other metals was observed [17••]. In a Mexico-based study also evaluating a mixture of metals, maternal BPb and cadmium (Cd) contributed the most to a reduction in executive function and rapid visual processing in 6–9-year-olds using weighted quantile sum regression (WQS)–based models [27••]. One study evaluating As, Cd, Mn, and Pb and BSID scores among 13–42-month-olds observed null results using latent class analysis [28].

Two other prospective cohort studies examined exposure at multiple time points in relation to Pb and cognition. In rural China, maternal BPb measured in late pregnancy was associated with decrements in auditory and visual sensory outcomes among 6-week-olds, whereas the association was weaker for BPb measured in early pregnancy and for cord BPb [29]. Among a Canadian cohort of 3–4-year-old children, no association was found between cognitive scores and prenatal maternal or concurrent child BPb concentrations [30].

Sexual dimorphism of the Pb-cognition association was explored in four studies. Two studies reported stronger adverse associations between prenatal BPb and IQ among boys, compared with girls, in Canadian preschoolers (3–4 years old) [30] and in preschool- to school-age children from the UK [31•]. In contrast, two studies suggested stronger adverse associations among girls compared with boys between Pb and executive function measured at 6–8 years [32, 33]. Maternal BPb was associated with poorer ability to plan/organize and worse performance on overall executive function related behavior among girls in the USA, although interaction terms provided little evidence of effect modification by sex [32]. Concurrent BPb levels were also marginally associated with poorer ability to inhibit inappropriate responses among first-grade Uruguayan girls [33].

Other Behavioral Outcomes

Within our review parameters, eight studies assessed the relationship between Pb and non-cognitive behavioral outcomes [19••, 32, 33, 34••, 65••, 66–68]. A prospective Korean study reported sex- and time-specific associations between early life BPb and total, internalizing and externalizing problems in 2–5-year-old children. Boys were more susceptible to prenatal Pb exposure, while girls were more susceptible to postnatal exposure [65••]. In contrast, a US study of 6–8-year-old children reported stronger associations between maternal BPb and behavioral difficulties among girls compared with boys [32]. Horton et al. evaluated dentine Pb and metals co-exposures and investigated potential windows of susceptibility in a Mexican birth cohort using reverse distributed lag models and lagged weighted quantile sum regression: Pb exposure measured at the 8- to 12-month time point was most strongly associated with increased anxiety and internalizing symptoms assessed at 8–11 years [19••]. A cross-sectional study of 7–12-year-old Brazilians found suggestive evidence of synergistic interaction between Mn and Pb with total internalizing and externalizing behavior problems [66]. Additionally, Arbuckle et al. reported stronger adverse associations between Pb and behavioral difficulties among 6–11-year-old children whose mothers smoked during pregnancy compared with those that did not [67].

When considering Pb-ADHD associations, two studies reported sex-specific findings. The association between early childhood BPb (< 4 years; 5–10 μg/dL vs. < 5 μg/dL) and 7–12-year-olds diagnosed with ADHD in a US cohort was stronger among boys than girls [68]. In contrast, childhood BPb was modestly associated with hyperactivity scores among girls but not boys in a Uruguayan cross-sectional study of first graders [36].

Mercury and Neurodevelopment

Historically, the neurotoxic effects of high level meHg exposure on nervous system outcomes in children have been well described from unfortunate circumstances of mass poisoning events in the 1950s and 1970s in Japanese and Iraqi populations, respectively [77, 78]. The symptoms of prenatal meHg poisoning in these populations included speech difficulty, movement problems meeting criteria for diagnosis of cerebral palsy, primitive reflexes, seizures, and mental retardation [78]. In populations with moderate exposure to meHg from consumption of large predatory sea life, meHg biomarkers at birth have been associated with decrements in memory, attention, language, and visual-motor skills in childhood [79]. In recent years, results from epidemiologic research on low-level meHg exposure and children's neurodevelopment remain mixed, likely due to the heterogeneity of fish and rice consumption patterns across populations [80, 81]. Fish consumption particularly complicates the associations between meHg and neurobehavioral outcomes because associated co-exposures may be beneficial (e.g., selenium, poly-unsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA)) or deleterious (e.g., polychlorinated biphenyls (PCBs)) for neurodevelopment. Most recent studies have utilized prospective birth cohorts, in which meHg exposure was consistently associated with adverse neurobehavioral scores in Asian populations, but less consistently in European and North American populations. All studies used blood or hair total Hg as a surrogate for meHg exposure.

Table 2 Summary of recent studies including modifiers (sex, co-exposures, exposure timing, genetic polymorphisms) of associations between lead, mercury, arsenic, or manganese and non-cognitive behavioral outcomes in children

Reference	Study design	Sample size	Study location	Age	Outcomes	Exposure metric	Exposure timing	Exposure level	Modifier	Key main findings
Lead (Pb) and other behavioral outcomes										
Horton 2018 [19••]	Prospective cohort	133	Mexico	8–11 years	Behavior Assessment System for Children (BASC-2)	Tooth dentine	2nd trimester through early childhood	Not reported	Exposure timing Mn and Zn	Reverse distributed lag models and lagged WQS results: Postnatal Pb, especially 8-12 months, associated with increased behavioral problems [e.g., SD change in BASC score per SD increase in log postnatal Pb, 10-month Pb and overall behavioral problems: β (95% CI) = 0.22 (0.06, 0.38); 10 month Pb and hyperactivity: 0.19 (0.02, 0.37)]. Increased anxiety symptoms at 8–12-month window driven by the metal mixture and dominated by Pb.
Fruh 2019 [32]	Prospective cohort	1006	USA	7.8 ± 0.8 years (mean age)	Behavior Rating Inventory of Executive Functions (BRIEF); Strengths and Difficulties Questionnaire (SDQ)	Maternal blood	Prenatal	Mean maternal erythrocyte lead concentration: 1.2 μg/dL; interquartile range (IQR) 0.8–1.5 μg/dL.	Sex	Pb associated with increased emotional problems [per IQR (0.6 μg/dL) increase: β (95% CI) = 0.18 (0.03, 0.33)]. Stronger effects for girls across most subscales; example: Pb and parentrated total difficulties [0.72 (0.16, 1.27)] vs. boys [0.16 (−0.38, 0.70)]. No Pb-sex interaction.
Barg 2018 [33]	Cross-sectional	206	Uruguay	6.7 ± 0.5 years (mean)	Behavior Rating Inventory of Executive Functions (BRIEF); Conners' Rating Scale (CRS); teacher rated	Blood	6.7 ± 0.5 years (mean age)	Mean (SD) BPb: 4.2 (2.1) μg/dL	Sex	Pb associated with increased prevalence ratio of BRIEF inhibit subscale [PR (95% CI) = 1.01 (1.00, 1.03)]. Pb not associated with CRS subscales. Sex-specific prevalence ratios for associations between Pb and hyperactivity higher in girls [1.02 (1.00, 1.04)] vs. boys [0.99 (0.97, 1.01); Pb-sex interaction: $p < 0.05$].
Joo 2018 [65••]	Prospective cohort	1751	Korea	5 years	Korean Child Behavior Checklist: Korean version of CBCL 1.5–5	Maternal, cord, and child blood	Prenatal; maternal blood in early and late pregnancies, cord blood and 2-, 3-, and 5-year-old children's blood.	μg/dL: early pregnancy (GM ± SD): 1.3 ± 1.5; late pregnancy: 1.2 ± 1.6; cord blood: 0.9 ± 1.6; Child blood 2 years.: (1.6 ± 1.5); 3 years: (1.4 ± 1.4); 5 years: (1.3 ± 1.4)	Sex exposure timing	Sex-specific findings for associations of Pb and total behavioral problems differed by exposure timing. Stronger associations of late pregnancy Pb and total behavioral problems in boys [β (95% CI) = 3.0 (0.6, 5.5) vs. girls: 0.4 (−2.1, 2.9); Pb-sex interaction: p=0.1]. Stronger associations of 2-year and 5-year Pb and total behavioral problems in girls [girls: 3.8 (1.3, 6.4) vs.

Table 2 (continued)

Reference	Study design	Sample size	Study location	Age	Outcomes	Exposure metric	Exposure timing	Exposure level	Modifier	Key main findings
										boys: 0.2 (−1.9, 2.3); interacQon: p=0.04] and [5.7 (0.4, 11.0) vs. boys: 1.37 (−2.1, 4.8); interaction: p=0.1], respectively.
Rodrigues 2018 [66]	Cross-sectional	165	Brazil	7–12 years	Child Behavior Check List (CBCL) by parents: behavior, attention	Blood	7–12 years	Mean (range) BPb: 1.2 (0.2–15.6) μg/dL	Mn	Null associations between Pb and raw total CBCL score [β (95% CI) = −0.74 (−5.3, 3.8)]. Suggestive evidence of synergistic Pb-Mn interaction.
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months	Parents' Evaluation of Developmental Status (PEDS): learning and behavior problems	Maternal blood and urine, infant urine, breast milk	2–12 months	Mean (± SD) BPb: 2.4 (1.7) μg/dL	meHg, Mn, DDT + metabolites	Combination of Pb-maternal urine, Mn-breast milk, Mn-blood, and Se-blood correlated with delayed PEDS scores [principal component analysis, RR (95% CI) = 0.42 (0.18, 1.02)].
Arbuckle 2016 [67]	Cross-sectional	1080	Québec	6–11 years	Strengths and Difficulties Questionnaire (SDQ) outcomes; emotional symptoms, hyperactivity/inattention, and a total difficulties score with borderline and abnormal scores grouped together and compared with children with normal scores; parent-reported learning disability	Blood	6–11 years	GM BPb: 0.9 μg/dL	Maternal smoking	Pb associated with increased odds of hyperactivity/inattention [OR (95% CI) = 2.8 (1.5, 5.2)]. Interaction between prenatal smoking and Pb for total difficulties score [OR (95% CI) = 10.6 (2.8, 39.7) vs. 2.0 (1.4, 2.8) if mother did not smoke during pregnancy].
Ji 2018 [68]	Prospective cohort	1479	USA	7.4–12 years	ADHD (as determined by the ICD-9 and ICD-10 codes)	Blood	0–4 years	Mean (± SD) BPb: 2.2 ± 1.6 μg/dL	Sex	Associations of Pb and odds of any ADHD diagnosis for children with 5–10 μg/dL Pb vs. children with < 5 μg/dL Pb were stronger among boys [(OR (95% CI) = 2.5 (1.5, 4.3)] than girls [0.7 (0.3, 1.7)].
Methyl mercury (meHg) and other behavioral outcomes										
Ng 2015 [69]	Prospective cohort	166	Taiwan	2 years	Items on the Child Behavior Checklist (CBCL 1.5/5 Chinese version)	Cord blood	Prenatal	Cord blood THg (μg/L): Median: 12.0 (min 1.53; max 47.1)	Genetics sex	Among APOE ε4 carriers, stronger inverse associations between CBHg (> 12 μg/L) and behavioral outcomes (total problems, total internalizing, emotionally reactive, anxious/depressed). Stronger inverse associations among male APOE ε4 carriers, except between Hg and anxiety, and where associations were strongest among female APOE ε4 carriers.
Patel 2019 [70••]	Prospective cohort	389	USA	2–8 years (BASC)	Behavioral Assessment System for Children (BASC-2) and	Maternal blood cord blood	Prenatal (16, 26 weeks gestations	THg median: 0.67 μg/L	Exposure timing sex	Per 1 μg/L increase in mean maternal THg: BASC anxiety: β (95% CI) = 0.71 (−0.12,

Table 2 (continued)

Reference	Study design	Sample size	Study location	Age	Outcomes	Exposure metric	Exposure timing	Exposure level	Modifier	Key main findings
				8 years (SCAS)	Spence Children's Anxiety Scales (SCAS)		and delivery)			1.54); 2-fold increase 16-week THg and BASC anxiety score: 0.83 (0.05, 1.62) points.
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months	Parents' Evaluation of Developmental Status (PEDS): learning and behavior problems	Breast milk, maternal blood	2–12 months	Median (range), breast milk: 1.4 (1.1–2.1) μg/L; mom blood: 0.5 (0.1–1.0) μg/L	Pb, Mn, DDT + metabolites, Se	No association of MeHg in individual or PCA analyses. No MeHg-Se interaction.
Arsenic (As) and other behavioral outcomes										
Rodriguez-Barranco 2016 [71]	Cross-sectional	261	Spain	6–9 years	3 tests from the Behavioral Assessment and Research System (BARS): Simple Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT); AULA Test; Child Behavior Check List (CBCL); Teacher's Report Form (TRF)	Total As in first-void urine (unadjusted; urinary Cr included as a covariate in statistical models)	6–9 years	Median (IQR): 1.17 (0.50–1.93) μg/L	Sex	SAT latency: β (95% CI) = 3.58 (0.37, 6.79), RTT latency: 12.31(3.51, 21.11), AULA impulsivity omission errors: 0.57 (0.07, 1.07), AULA inattention omission errors: 0.50 (0.03, 0.97). No significant associations for CBCL or TRF. No significant As-sex interactions.
Manganese (Mn) and other behavioral outcomes										
Al-Saleh 2019 [34••]	Cross-sectional	206	Saudi Arabia	2–12 months	Parents' Evaluation of Developmental Status (PEDS): learning and behavior problems	Breast milk, maternal blood and urine, infant urine	2–12 months	Median (range), breast milk: 16 (7–32) μg/L; mom blood: 14 (5–47) μg/L; mom urine: 2 (0.1–23) μg/L; infant urine: 3 (1–22) μg/L	Pb, meHg, DDT + metabolites	Combination of Mn-breast milk, Mn-blood, Se-blood, and Pb-maternal urine correlated with delayed PEDS scores (principal component analysis, RR (95% CI) = 0.42 (0.18, 1.02).
Horton 2018 [19••]	Prospective cohort	133	Mexico	8–11 years	Behavior Assessment System for Children (BASC-2): internal and externalizing symptoms	Tooth dentine	2nd trimester through early childhood	Median (25th, 75th percentiles), as 55Mn:43Ca across all time points: 1.2E−3 (6.8E−4, 2.0E−3)	Zn, Pb exposure timing	Reverse distributed lag models and lagged WQS results: Prenatal Mn protects against externalizing behavior [SD change in BASC score per SD increase in log Mn at birth, β (95% CI) = −0.15 (−0.24, −0.07)]. Postnatal Mn associated with more anxiety and internalizing behaviors [6-month Mn and anxiety symptoms: 0.18 (0.09, 0.27)]. Joint exposure with Pb, Zn at 12 months associated with more anxiety.
Ode 2015 [72]	Case-control	166 cases, 166 controls	Sweden	5–17 years	ADHD diagnosis with DSM criteria	Umbilical cord serum	Birth	Median (range): 4.1 (1.3–39) μg/L	Se	No association of Mn with ADHD; no interaction with Se.
Rodrigues 2018 [25]	Cross-sectional	165	Brazil	7–12 years		Hair, toenails, blood	7–12 years	Median (range), hair: 0.73	BPb	Toenail Mn associated with more externalizing behavioral

Table 2 (continued)

Reference	Study design	Sample size	Study location	Age	Outcomes	Exposure metric	Exposure timing	Exposure level	Modifier	Key main findings
					Child Behavior Check List (CBCL) by parents: behavior, attention			(0.16–8.79) μg/g, toenails: 0.84 (0.15–13.30) μg/g, blood: 8.98 (1.51–40.43) μg/L		problems: β (95% CI) = 10.29 (1.9, 19.6) points per 10-fold Mn increase. Suggestive evidence of synergistic Mn-Pb interaction.
Carvalho 2018 [59]	Cross-sectional	70	Brazil	7–12 years	Conners' Abbreviated Teacher Rating Scale: inattention, hyperactivity	Hair	7–12 years	Median (range): 11.5 (0.5–55.7) μg/g	Sex	Hair Mn associated with worse behavior [β (95% CI) = −6.6 (−12.0, −1.3) points per 10-fold increase; no sex-specific effects.
Menezes-Filho 2014 [73]	Cross-sectional	70	Brazil	7–12 years	Child Behavior Check List (CBCL) by parents: behavior, attention	Hair	7–12 years	Median (range): 12 (0.5–55.7) μg/g	Sex	Girls' total externalizing behavior and inattention associated with Log-MnH: β (95% CI) = 8.85 (2.44, 15.25) and 4.03 (1.50, 6.56); no association in boys.
Oulhote 2014 [62]	Cross-sectional	375	Canada	6–13 years	Parent- and teacher-reported Conners' Rating Scales: hyperactivity	Hair, drinking water	6–13 years	Mean (range), water: 99 (1–2701) μg/L; hair: 1.4 (0.1–20.7) μg/g	Sex	Using SEM with both hair and drinking water Mn; no association with hyperactivity and no sex-specific effects.
Tinkov 2019 [74]	Case-control	90 cases, 90 controls	Russia	4–10 years	ADHD diagnosis using ICD-10 criteria	Hair	4–10 years	Median (25th, 75th percentiles), cases: 0.21 (0.14, 0.32); controls: 0.29 (0.18, 0.40) μg/g	Sex, age	Lower hair Mn levels in ADHD cases, with girls having ~25% lower Mn, and preschool having lower Mn than primary school kids.
Mora 2018 [64•]	Prospective cohort	355	Costa Rica	1 year	Bayley Scales of Infant Development (BSID-III): social-emotional scores	Maternal hair, blood, urinary ethylene--thiourea (ETU; mancozeb metabolite)	Prenatal	Median (25th, 75th percentiles), hair: 1.7 (0.9, 4.1) μg/g; blood: 24.0 (20.3, 28.0) μg/L; ETU: 3.3 (2.4, 4.9) μg/L	Sex, exposure timing	Among girls, higher ETU associated with lower (worse) social-emotional scores [β (95% CI) per 10-fold increase = −7.4 (−15.2, 0.4) points]. Among boys, higher hair Mn associated with lower social-emotional scores [−4.6 (−8.5, −0.8)]. AssociaQon in boys stronger for second half of pregnancy than first; in girls, stronger in first half. Null associations for blood Mn.
Mora 2015 [58]	Prospective cohort	248	USA	7, 9, 10.5 years	Behavior Assessment System for Children (BASC-2), Conners' ADHD/Diagnostic and Statistical Manual Scales (CADS)	Tooth dentine	Prenatal, postnatal	GM (GSD), prenatal: 0.46 (1.48); postnatal: 0.14 (2.47) ^{55}Mn:^{43}Ca AUC × 10^4	BPb, sex, exposure timing	Prenatal Mn associated with more parent-reported internalizing problems, fewer teacher-reported inattention at age 7, among those with lower prenatal Pb (< 0.8 μg/dL). Postnatal Mn associated with more internalizing, externalizing, and hyperactivity problems in girls and boys.

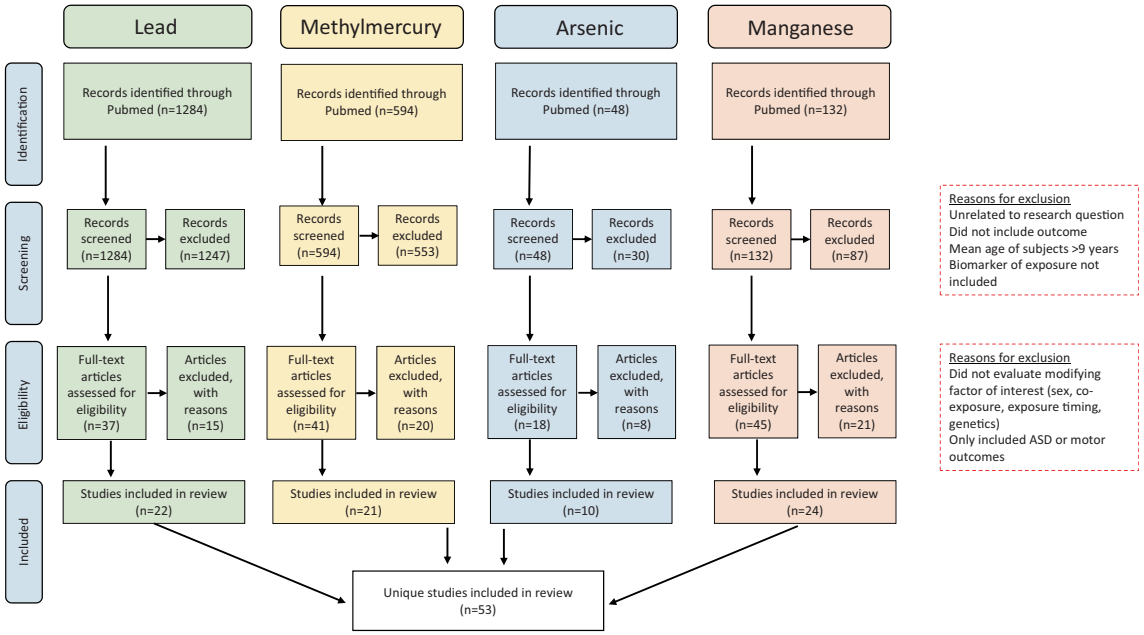

Fig. 1 Study selection flowchart

Cognitive Outcomes

Seven studies investigated effect measure modification of the association between prenatal Hg and cognition by co-exposures related to fish consumption, reporting beneficial [35–39], malign [42], or null [40] effects. One study in the Seychelles reported that gestational PUFA concentrations significantly modified the association of maternal hair Hg and 20-month BSID scores: the association was only adverse among children born from mothers with higher serum n-6:n-3 PUFA ratios (> 4.5), compared with children born from mothers with lower ratios (< 3.5), consistent with the proinflammatory properties of n-6 PUFAs [35]. In a study of 5-year-old South Koreans, increased maternal fish consumption enhanced inverse associations between third trimester maternal blood Hg and IQ [42]. In an Arctic population that regularly consumes beluga meat, cord blood Hg (CBHg) was associated with poorer 8–14-year-old IQ, but no interaction was found between Hg and other common pollutants (cord blood PCB-153 or Pb) or nutrients (cord blood selenium or DHA) from fish consumption [40]. In a US population, co-exposure to PCBs was evaluated when estimating the association between prenatal Hg and cognition in newborns: among infants with higher PCBs (> 61.6 ng/g lipid), maternal blood and CBHg were associated with less need for special handling, indicative of a calmer temperament. However, authors did not report whether this interaction persisted after adjustment for fish consumption [39]. In 4–5-year-old Spanish children, detectable placenta Hg was associated with worse general cognition only among boys [26•]. Interaction between Hg and Mn was significant, whereby the inverse association between placental Hg and verbal function was less pronounced among participants with higher placental Mn, suggesting protective Mn effects [26•]. None of these studies used statistical methods for mixtures.

Four studies evaluated exposure timing, either by evaluating multiple biomarkers that captured different exposure periods [41, 43] or by using the same biomarker across multiple time points [40, 44]. Kim et al. measured prenatal blood Hg at three time points (12–20 and 28–40 weeks gestation, birth) and assessed neurodevelopment at multiple ages (6, 12, 24 and 36 months) in South Korean children. Inverse associations with 6-month outcomes were strongest for maternal blood Hg collected during early pregnancy (12–20 weeks) [44]. Jacobson et al. measured hair and blood Hg at prenatal and childhood time points, but only CBHg was associated with poorer IQ assessed at 8–14 years of age [40].

Four studies investigated sex-specific effects of the Hg-cognition association [26•, 36, 45, 46]. One Asian study reported stronger inverse associations of prenatal Hg with newborn cognitive scores among boys [52], while another reported null findings for associations with 18-month BSID MDI scores [46]. A US study reported worse asymmetric reflex among newborn boys with increasing maternal blood Hg levels, as compared with positive findings among girls, although estimates were weak, especially after adjustment for fish consumption [39].

Cohort studies in the Seychelles [47, 48••], England [50] and near the Adriatic Sea [49, 51••] reported gene-environment interactions. In the Seychelles, inverse associations of prenatal Hg and 18–20-month BSID scores were reported for maternal hair, maternal blood, and CBHg among carriers of specific glutathione related gene variants [48••] as well as for maternal hair Hg among carriers of specific ATP-

binding cassette transporters [47]. Snoj Tratnik et al. reported adverse associations between cord and maternal blood Hg and 18-month BSID scores, among children with at least one ApoE ε4 allele [49]. In an analysis combining three prospective cohorts from the Seychelles, Spain, Italy, and Greece, maternal hair Hg and CBHg were associated with higher 14–30-month BSID scores among carriers with high CYP3A activity alleles [51••].

Other Behavioral Outcomes

Only three studies investigated the association of meHg with non-cognitive behaviors, one reporting null findings [34••] and the others reporting adverse associations with anxiety [69, 70••]. Ng et al. evaluated genetics and sex as modifiers of the Hg-behavior association in Taiwanese 2-year-olds: among APOE ε4 carriers, stronger inverse associations between CBHg (> 12 μg/L) and behavioral outcomes were seen in boys, except between Hg and anxiety, where associations were strongest among female APOE ε4 carriers [69]. Patel et al. investigated sex and exposure timing (maternal blood at 16 and 26 weeks gestation and delivery, cord blood at birth) as modifiers in a US cohort of 2–8-year-olds: 16-week maternal Hg was most strongly associated with worse anxiety scores among boys compared with girls, while maternal Hg at delivery was most strongly associated with anxiety among girls [70••].

Arsenic and Neurodevelopment

The neurotoxic evidence for As exposure in children has been recently described by a meta-analysis of studies published between 2000 and 2012, which reported that a 50% increase in As exposure was associated with a reduction of 0.4 full-scale IQ points in children between 5 and 15 years of age [9]. Additionally, decrements were greater for verbal IQ than performance IQ [9]. However, less consistent evidence exists for low-level As concentrations (< 100 μg/L) in association with neurodevelopment [11]. Over the past 5 years, most studies on As and neurodevelopment have evaluated cognitive outcomes. While several studies have observed adverse effects of As exposure on child cognition, with some evidence of synergistic interactions with Pb, results have generally been inconsistent. Potential explanations include the different life stages examined, unmeasured confounding from fish or seafood consumption, and the various As exposure metrics used, which can reflect different As species. For example, while water As primarily reflects inorganic As (iAs), total blood and urinary As can reflect a combination of iAs, arsenobetaine (which is non-toxic and derived entirely from fish and seafood), and monomethyl (MMA) and dimethyl (DMA) arsenicals (derived from metabolized iAs or dietary sources, such as rice, fish, and seafood) [82, 83].

Cognitive Outcomes

Five studies meeting our review criteria examined the impacts of As and modifying metal co-exposures on child cognition [17••, 25, 26•, 27••, 28]. One small study clustered participants based on their concentrations of hair As, hair Cd, hair Mn, and BPb using latent class analysis and examined these clusters in relation to BSID scores at 13–42 months, but results were null [28]. Two larger studies were conducted in the same population in Bangladesh and evaluated BSID scores at 20–40 months. For both studies, As associations were most apparent in a subset of participants living in a region with high water As levels (range 4.4–130 μg/L) [17••, 25]. Rodrigues et al. used a cross-sectional study and traditional linear regression and reported inverse associations between water As and cognitive scores as well as a synergistic relationship with BPb, in which As neurotoxicity was enhanced at higher BPb concentrations. In sensitivity analyses, stronger associations were observed for water As measured in the prenatal period, as compared with 20–40 months of age. No significant associations were observed for water As at 1 month of age, possibly due to breastfeeding, as As levels in breast milk are low regardless of maternal consumption of As-contaminated drinking water [84]. Valeri et al. evaluated total As in cord blood as part of a mixture with Mn and Pb using BKMR [17••]. In contrast with the findings for water As [25], a suggestive protective relationship was observed between cord blood As and cognitive scores, possibly due to unmeasured confounding from seafood consumption [17••]. This unexpected finding was less pronounced at higher levels of Mn [17••]. Two studies examined the impacts of prenatal As exposure and co-exposures on cognitive outcomes in school-age children, and both observed adverse effects [26•, 27••]. One study was conducted in Mexico and measured total As in both second and third trimester maternal blood, which were evaluated as part of a larger mixture using a WQS approach (Cd, cesium, chromium, Pb, antimony) [27••]. Of the two time points evaluated, only third trimester As contributed to reduced executive function at 6–9 years of age [27••]. Consistent with this finding, a study in Spain observed an inverse association between placental As and executive function scores at 4–5 years of age. A significant interaction was also identified between As and Pb, indicating that this As-executive function association was more pronounced among children with high placental Pb [26•]. An inverse association between placental As and quantitative abilities was also reported [26•].

Six studies investigated sex-specific associations, although the majority reported no difference between boys and girls [26•, 52, 53••, 54•, 71]. In a cross-sectional study of 4–5-year-old children in Spain, speciated urinary As (iAs +

MMA + DMA) was marginally associated with worse working memory for boys only [53••]. A cross-sectional study in Uruguay also evaluated associations between speciated urinary As (iAs + MMA + DMA) and cognitive outcomes at 5–8 years of age [54•]. Although they did not observe sex differences, urinary As was significantly associated with several subtests of the Woodcock-Muñoz Cognitive Battery within certain strata of dietary folate and urinary %MMA levels [54•]. However, the directions of the associations differed by subtest and were inconsistent within the folate and %MMA strata. A cross-sectional study of 7–8-year-old children in China also examined the relationship between total urinary As concentrations and cognitive outcomes by sex, but results were null, possibly due to unmeasured confounding from seafood consumption [55]. Finally, a cross-sectional study of 6–9-year-old Spanish children reported an inverse association between total urinary As and measures of attention [71]. Possible sex differences were examined, but none was observed.

Other Behavioral Outcomes

While limited, there is also some evidence that As may adversely impact non-cognitive behavioral outcomes. A cross-sectional study of 6–9-year-old Spanish children observed an inverse association between total urinary As and measures of attention, and there were no interactions with sex [71].

Manganese and Neurodevelopment

Manganese is an essential nutrient required for growth and neurodevelopment, but in excess is a potent neurotoxicant [85]. An ideal exposure range has not been identified, particularly for children, and it is unclear at what level Mn becomes toxic rather than beneficial [86–88]. In high excess, Mn neurotoxicity in adults is well described in occupational studies as manganism, a parkinsonian-like syndrome involving motor (kinetic tremor, bradykinesia, specific gait disturbances) and neuropsychological (diminished concentration, working memory, spatial orientation) symptoms [89–91]. However, less is known about how Mn affects the developing brain. Over the past 5 years, studies on modifying factors of the Mn-neurodevelopment association have been conducted around the world using drinking water and various matrices, including placenta and teeth, to estimate exposure. Results generally support adverse effects of Mn, with suggestive evidence for effect modification by sex and exposure timing. There is also evidence of interaction between Mn and other metals, although much remains to be understood given the heterogeneity in exposure metrics, route, levels, timing, and composition of the mixture.

Cognitive Outcomes

Eleven studies evaluated metal co-exposures as modifiers of the Mn-cognition association, with most studies examining pairwise interactions of Mn with another metal [20••, 23–25, 26•, 56–58]. About half of these studies reported no modification of Mn associations [23, 25, 28, 34••, 57], while the other half reported some modification or joint effect [17••, 20••, 24, 26•, 56, 58]. In a prospective Bangladeshi study of a mixture of cord blood Mn, As, and Pb using BKMR, Mn was associated with lower 20–40-month BSID-III cognitive scores and contributed to a decline in scores with increasing levels (> 60th percentile) of the metal mixture [17••]. Another prospective study reported a beneficial association of placental Mn on cognition and executive function in 4–5-year-old Spanish children, which was stronger among children with detectable placental Hg even after adjustment for fish intake [26•]. Three other prospective studies used tooth dentine as a biomarker of early life exposure, all of which reported modification of Mn associations [20••, 56, 58]. Prenatal Mn was associated with lower 6- and 12-month BSID-II mental development index scores, but only among girls whose mothers had lower iron [56]. No Mn-Pb interactions were found, but in the same cohort, Mora et al. estimated beneficial prenatal Mn associations with cognition and memory at 7 years, which appeared harmful in the presence of higher BPb (≥ 0.8 μg/dL) [58]. This was consistent with findings from Mexico City, where prenatal dentine Mn was estimated to have beneficial effects on 6–16-year visuospatial abilities only at low dentine Pb levels [20••].

Twelve studies examined sex-specific associations of Mn with cognition. Six studies reported no or inconclusive evidence of sexual dimorphism [26•, 57, 59–62]. Most of these were cross-sectional analyses of school-age children, with only two prospective studies investigating prenatal exposure in relation to 24-month BSID-II score [60] and 4–5-year McCarthy Scales scores [26•]. Four studies with a range of participant ages from 12 months to 10.5 years reported adverse associations among girls and/or beneficial or null associations among boys [56, 58, 63, 64•]. In contrast, a study of 7–8-year-old Chinese children reported positive associations between urine Mn and IQ, which were stronger among girls [55], and in a prospective study in Mexico, early postnatal tooth Mn was associated with worse 6–16-year visuospatial abilities among boys only [20••].

Exposure timing was evaluated in six studies [20••, 25, 55, 56, 58, 64•]. Two studies of tooth dentine Mn both reported beneficial associations of prenatal Mn and harmful associations of postnatal Mn on cognition, memory, and visuospatial abilities in 6–16-year-old children [20••, 58]. This is somewhat consistent with a Costa Rican study, in which maternal hair Mn concentrations measured in the second half of pregnancy, compared with the first half, were more strongly

associated with lower cognitive scores among girls [64•]. In Bangladesh, null associations were reported between 20- and 40-month cognitive scores and drinking water Mn measured both in gestation and early life [25]. In China, urine Mn in 7–8-year-old children, but not cord blood Mn, was associated with better IQ scores [55].

Other Behavioral Outcomes

Ten studies examined modifiers of the association between Mn and non-cognitive behaviors. Four studies evaluated co-exposures [19••, 34••, 58, 66]. Mostly adverse Mn associations and either synergistic or joint effects with Pb [34••, 66] or with Pb and Zn [19••] were reported. The exception was in a US prospective study of Mexican-American children, in which postnatal dentine Mn was associated with worse behaviors at 7 years, but associations were not modified by BPb, perhaps due to the low levels (median BPb 0.8 μg/dL) [58]. In a prospective cohort in Mexico City, co-exposure of dentine Mn with Pb and Zn at 12 months was associated with more anxiety in 8–11-year-olds [19••]. In a cross-sectional study of mother-infant pairs in Saudi Arabia, principal component analysis was used to find that the combination of breast milk Mn, Pb in maternal urine, and Mn and Se in maternal blood at delivery was correlated with lower parent-rated learning and behavior performance in 2–12-month infants [34••].

Five studies examined sex-specific Mn associations on behavioral outcomes [58, 59, 62, 64•, 73]. Two studies were from a cross-sectional evaluation of 7–12-year-old Brazilian children, in which hair Mn was adversely associated with girls', but not boys', inattention and externalizing behavior scores [73], whereas sex-specific associations were not seen with teachers' ratings of hyperactivity [59]. The lack of sex-specific Mn associations with hyperactivity was also reported in a cross-sectional study of 6–13-year-old Canadian children exposed to Mn in drinking water [62] and in a prospective cohort of Mexican-American children in relation to early life Mn and 7-year behavioral scores [58].

Three studies evaluated exposure timing, two of which used tooth dentine as a metric of Mn exposure. In a Mexico City cohort, protective associations were reported for prenatal dentine Mn against externalizing behavior in 8–11-year-olds while postnatal Mn was associated with more anxiety and internalizing behaviors [19••]. In Mexican-American children in the USA, however, both prenatal and postnatal Mn measures were associated with worse 7-year internalizing and externalizing behaviors [58]. In Costa Rica, the negative association between maternal hair Mn and 12-month BSID social-emotional scores in boys was stronger in the second half of pregnancy than during the first half [64•].

Finally, two case-control studies on ADHD differed in their findings. In Swedish 5–17-year-olds, neither main effect of umbilical cord serum Mn nor interaction with Se was found in relation to ADHD [72]. In contrast, lower hair Mn levels were reported in 4–10-year-old ADHD cases, where girls had even lower levels than boys (− 25%) [74].

Conclusions

As our interest in understanding susceptibility factors grows, research examining modifiers of the associations between Pb, meHg, As, and Mn and children's neurobehavior is also expanding. Of the modifiers examined, sex was most commonly investigated. However, the evidence for sex-specific effects was mixed for all four metals, likely due in part to heterogeneity in the timing of exposure, neurobehavioral domains assessed, and ages of the participants at time of outcome assessment. Seven studies, however, evaluated both multiple exposure windows and sex-specific effects for Pb [65••], Hg [70••], or Mn [20••, 55, 56, 58, 64•]. More research examining multiple exposure time points together with sex-specific effects could help characterize sexually dimorphic relationships.

Although few studies evaluated exposure timing, potential windows of susceptibility were identified for Pb [19••, 29, 30, 65••], Hg [40, 44], As [25, 27••], and Mn [19••, 20••, 56, 58, 64•]. The majority of recent research also measured outcomes at only one time point and the time frame between exposure and outcome assessment was short. Yet effects of environmental exposures on neurodevelopment could span across childhood and early adulthood [21]. Thus, while more challenging and resource-intensive, studies measuring both exposures and outcomes at multiple time points are warranted.

Despite recent expansions to the literature on co-exposures that include studies using statistical mixtures methods to investigate joint exposure [17••, 19••, 27••, 28, 34••], research remains limited. Similarly, recent research on genetic modifiers, investigated in only five of the reviewed meHg studies [47, 48••, 49, 50, 51••], is sparse. Both of these areas represent ripe opportunities for future work.

In summary, our understanding of susceptibility to the neurodevelopmental effects of metals exposure is growing, but considerable gaps remain. Many studies conducted to date may not have been specifically designed to evaluate effect modification and may therefore lack statistical power. Larger prospective studies ($n > 500$) designed to address susceptibility factors may help unravel the complexity in metals-neurodevelopment associations. As we progress toward investigating the effects of the exposome, it is imperative that modifying factors be more fully examined. Characterizing susceptible subpopulations is critical for identifying biological mechanisms and is fundamental for the protection of public health.

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Compliance with Ethical Standards

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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