Review

Pediatric Heavy-Metal Exposome and Chronic Disease Trajectories: From Neurodevelopment to Metabolic and Endocrine Outcomes

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Highlights

What are the main findings?

- Early-life exposure to toxic metals (Pb, Hg, Cd, As), assessed through biomonitoring, is consistently associated with adverse neurodevelopmental outcomes, while evidence for metabolic and endocrine effects is emerging, heterogeneous, and strongly dependent on exposure timing and sex.
- Neurodevelopmental toxicity—particularly for lead and mercury—shows no safe exposure threshold, whereas metabolic and pubertal outcomes reflect complex, nonlinear, and mixture-dependent effects across sensitive developmental windows.
- **What are the implications of the main findings?**
- Pediatric metal exposure should be interpreted within a life-course exposome and DOHaD framework, prioritizing biomonitoring-based risk assessment, mixture analyses, and rigorous control of socioeconomic and nutritional modifiers.
- Prevention strategies require One Health–oriented policies that integrate environmental regulation, nutritional interventions, and targeted surveillance to reduce health inequities and long-term chronic disease risk.

Abstract

Early-life exposure to toxic metals remains a major global public health concern, particularly for children, whose developing neuroendocrine and metabolic systems are highly vulnerable. Within the exposome and Developmental Origins of Health and Disease (DOHaD) frameworks, this narrative review synthesizes human evidence on pediatric exposure to lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) and its associations with neurodevelopmental, metabolic, and endocrine outcomes. We primarily examined epidemiological studies, systematic reviews, and meta-analyses published between 2010 and 2025 that relied on biomonitoring-based exposure assessment and appropriate adjustment for socioeconomic status and passive smoking, while seminal earlier studies were considered to contextualize biological mechanisms and conceptual frameworks. The evidence for neurodevelopmental toxicity is the most consistent, with prenatal and early childhood exposure to

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Pb and Hg robustly associated with adverse cognitive, behavioral, and motor outcomes and no identified safe exposure threshold for lead. In contrast, associations with obesity and pubertal timing are more heterogeneous and metal-specific, reflecting nonlinear dose–response relationships, sex-specific susceptibility, and critical exposure windows. Emerging data indicate that metals may act as metabolism- and endocrine-disrupting chemicals, with effects amplified by mixture exposures and adverse social conditions, and partially modified by nutritional status. Overall, the findings support life-course–oriented, biomonitoring-based research and prevention strategies that address cumulative exposures and developmental vulnerability to reduce long-term disease risk.

Keywords: pediatric exposome; toxic metals; neurodevelopment; endocrine disruption; obesity; biomonitoring; DOHaD; environmental health

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1. Introduction

The exposome framework was proposed to complement genomics by capturing the totality of non-genetic exposures across the life course and their biologic embedding, particularly during sensitive developmental windows when small exposure differences can yield disproportionate lifelong effects [1]. In pediatrics, this perspective is especially salient because early-life environmental insults may not only produce immediate clinical phenotypes (e.g., subclinical neurocognitive deficits) but also “program” trajectories that unfold over years into cardiometabolic and endocrine outcomes. Within this broader paradigm, heavy metals and metalloids remain a high-priority exposomic domain because exposure is widespread, sources are heterogeneous (air, dust, water, diet, consumer products), and multiple toxicants frequently co-occur, raising the likelihood of additive or synergistic effects that are not well captured by single-chemical models [2].

Among these toxicants, lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) are consistently implicated in pediatric risk because they can enter the fetal–infant compartment and interact with core developmental processes—synaptogenesis, myelination, immune maturation, adipocyte differentiation, and hypothalamic–pituitary axes—through mechanisms such as oxidative stress, mitochondrial dysfunction, endocrine disruption, and epigenetic remodeling [2]. Importantly, there is no established “safe” blood lead threshold for children, and public health authorities continue to emphasize that adverse effects may occur at low levels [3]. In parallel, clinical and surveillance practice has shifted toward lower action thresholds; for example, the U.S. Centers for Disease Control and Prevention (CDC) updated the blood lead reference value (BLRV) to 3.5 μg/dL to identify children with higher exposure relative to the population distribution and to trigger follow-up actions [4]. These policy signals underscore a central challenge for pediatric environmental health: meaningful risk can accrue at exposure ranges common in the general population, particularly when exposures occur prenatally and in mixture contexts.

The strongest and most mature evidence base for these toxicants pertains to neurodevelopment. A recent systematic review spanning international cohorts and cross-sectional studies concluded that early-life exposure to heavy metals—predominantly prenatal—was most consistently associated with adverse cognitive and motor outcomes for Pb and Hg, while behavioral outcomes were frequently linked to Pb and As [5]. Complementary syntheses focused on prenatal exposures have reinforced that in utero exposure to multiple metals/metalloids can be associated with measurable differences in early neurodevelopmental performance, although effect sizes and susceptible domains vary by metal species, matrix, timing, and analytic approach [6]. For arsenic, scoping-level evidence indicates a broad, geographically diverse literature associating maternal and/or childhood exposure with neuropsychological outcomes, again with substantial heterogeneity that complicates direct comparisons across settings [7]. At the neurodevelopmental disorder level, meta-analytic work in autism spectrum disorder (ASD) reports higher concentrations of several toxic metals in biologic matrices among ASD cases compared with controls, but also highlights substantial between-study heterogeneity and ongoing debate regarding directionality, exposure timing, and the extent to which biomarker differences may reflect reverse causality, selection, or differential behaviors (including

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diet) [8]. Taken together, the field converges on neurodevelopment as a sensitive endpoint for Pb/Hg/As (and to a lesser extent Cd), while continuing to debate the magnitude, specificity, and causal interpretability of associations outside high-exposure contexts.

Mercury illustrates why diverging hypotheses persist even within ostensibly well-studied domains. Prenatal methylmercury exposure is neurotoxic, yet fish consumption provides nutrients (e.g., omega-3 fatty acids) beneficial for neurodevelopment; therefore, dietary mercury biomarkers can be challenging to interpret without careful adjustment for diet quality and fish intake patterns. In a prospective U.S. birth cohort, higher maternal hair mercury was associated with increased risk of ADHD-related behaviors, while higher fish consumption during pregnancy was protective—underscoring the complexity of disentangling toxicant harm from dietary benefit within the same exposure pathway [9]. Conversely, a systematic review of early-life mercury exposure and neurodevelopment up to age five concluded that, based on higher-quality studies, dietary mercury exposure during pregnancy is unlikely to be a major risk factor for low neurodevelopmental functioning in early childhood, and that contrary findings may reflect bias or incomplete confounding control [10]. These contrasting conclusions exemplify why rigorous biomonitoring, careful covariate control, and transparent risk-of-bias assessment are indispensable in synthesizing evidence for metal-related neurodevelopmental outcomes.

Beyond neurodevelopment, interest is growing in whether heavy-metal exposures contribute to pediatric obesity risk and broader metabolic programming. Mechanistically, several metals can interfere with insulin signaling, adipogenesis, mitochondrial energetics, appetite regulation, and inflammatory tone—pathways plausibly linking exposure to increased adiposity and later cardiometabolic vulnerability. Empirically, one of the more informative designs has been prospective prenatal biomonitoring linked to long-term follow-up. In a large U.S. birth cohort enriched for social disadvantage, prenatal co-exposure to Hg, Pb, and Cd was associated with higher risk of childhood overweight/obesity, and the association appeared stronger among offspring of mothers with overweight/obesity; notably, higher maternal selenium and folate status attenuated mixture-associated risk, suggesting potential nutritional effect modification and an actionable prevention lever [11]. Such findings align with the broader exposome premise that toxicant effects may be amplified by structural vulnerability (including socioeconomic adversity) and mitigated by protective co-exposures (e.g., adequate micronutrients), reinforcing the need to model exposures as systems rather than isolated agents.

Endocrine outcomes, particularly pubertal timing, represent an additional frontier with direct clinical and public health implications. Pubertal onset integrates neuroendocrine maturation, energy balance, and environmental cues; disruptions may translate into downstream risks for metabolic syndrome, hormone-related cancers, and mental health outcomes. Heavy metals can plausibly influence puberty via hypothalamic–pituitary–gonadal axis signaling, thyroid function, and adiposity-mediated leptin pathways, but the observational evidence remains comparatively sparse and methodologically heterogeneous. Recent longitudinal work has begun to evaluate prenatal metal mixtures in relation to pubertal timing metrics in children, supporting the plausibility of endocrine effects while also emphasizing that associations may differ by sex, baseline adiposity, and co-exposure patterns [12]. This emerging evidence motivates a systematic synthesis that evaluates pubertal outcomes alongside neurodevelopment and obesity, with explicit attention to exposure timing and mixture structure.

Methodological rigor is particularly critical in this domain because biomonitoring is both a strength and a potential source of heterogeneity. Biomarkers differ in the exposure window they represent (e.g., blood vs. urine vs. hair), and for some toxicants, total measures can obscure etiologically relevant species. For example, urinary arsenic speciation separates inorganic-related metabolites from organic arsenicals influenced by seafood intake, reducing exposure misclassification and improving interpretability in pediatric dietary contexts [13]. Confounding control is similarly decisive. Socioeconomic status (SES) is tightly linked to housing conditions, diet, environmental remediation, and healthcare access, and therefore must be treated as a core confounder rather than a peripheral covariate. Passive smoke exposure is another high-priority confounder and potential co-exposure pathway: secondhand tobacco smoke has been associated with higher blood lead levels in children and adolescents in population-based analyses [14], and has also been linked to higher blood cadmium in epidemiologic studies, reinforcing the need to adjust for tobacco smoke exposure (e.g., cotinine) when estimating metal effects [15]. These considerations directly motivate stringent inclusion criteria emphasizing (i) biomonitoring-confirmed exposure, (ii) prenatal and/or childhood windows, and (iii) adjustment at minimum for SES and passive smoking—requirements intended to increase causal interpretability and reduce bias.

Against this background, the aim of this review is to synthesize human evidence (2010–2025) on pediatric heavy-metal/metalloid exposome measures—focused on Pb, Hg, Cd, and As—assessed via biomonitoring (blood, urine, or hair), and their associations with neurodevelopmental outcomes, obesity-related endpoints, and pubertal development (with asthma considered only when biologically and empirically justified). By integrating studies that incorporate prenatal exposure assessment and enforce robust confounding adjustment, this review seeks to clarify the consistency of associations across developmental windows, identify where mixture-oriented approaches add explanatory value, and delineate the principal sources of controversy (e.g., dietary confounding for mercury, speciation issues for arsenic, heterogeneity across matrices and outcome instruments). Overall, the evidence base supports early-life heavy-metal exposure as a plausible contributor to adverse neurodevelopmental trajectories, while the literature on metabolic and endocrine outcomes is rapidly expanding and suggests that risk may be concentrated in socially and biologically vulnerable subgroups, thereby highlighting prevention opportunities across both environmental and nutritional domains [5,11].

2. Materials and Methods

We conducted a narrative review with structured evidence mapping, focused on the pediatric heavy-metal/metalloid exposome and chronic disease trajectories. Although the synthesis is narrative, the literature identification and selection were conducted using transparent and reproducible procedures to maximize rigor and replicability.

The scope was defined using a Population–Exposure–Outcome framework.

Population: Humans with prenatal exposure (maternal biomarkers during pregnancy and/or cord blood) and/or pediatric exposure from birth through adolescence (operationalized as <18 years at outcome assessment).

Exposure: Biomonitoring of lead (Pb), mercury (Hg), cadmium (Cd), and/or arsenic (As) in blood, urine, hair, and/or cord blood. Studies using only environmental proxies (e.g., water/air/soil measures) without individual biomonitoring were excluded.

Outcomes:

1. Neurodevelopment (e.g., cognitive, language, motor, executive/behavioral outcomes; standardized neurodevelopmental scales).
2. Obesity/metabolic phenotypes (e.g., BMI/BMI z-score, overweight/obesity, waist circumference, adiposity indices).
3. Pubertal/endocrine outcomes (e.g., Tanner staging, age at menarche, pubertal timing markers such as age at peak height velocity).
4. Asthma outcomes were considered only when explicitly justified by mechanistic plausibility and when all other criteria were met.

Key specificity criterion (mandatory): To enhance causal interpretability, primary studies were required to report adjustment for both (i) socioeconomic status (SES) and (ii) passive tobacco smoke exposure (household smoke exposure and/or cotinine-based measures). Evidence syntheses (systematic reviews/meta-analyses) were included if they addressed relevant exposures/outcomes; their internal eligibility criteria were documented.

We focused primarily on human epidemiological studies, systematic reviews, and meta-analyses published between 2010 and 2025. Seminal studies published prior to 2010 were additionally cited when necessary to provide conceptual, biological, or historical context.

Searches were conducted in PubMed/MEDLINE, Scopus, and Web of Science Core Collection using combinations of terms for: (i) Pb/Hg/Cd/As, (ii) biomonitoring matrices (blood/urine/hair/cord blood), (iii) prenatal and pediatric exposure windows, and (iv) outcomes (neurodevelopment, obesity/adiposity, puberty/menarche/Tanner). Database syntax was adapted per platform. Reference lists of key papers and recent reviews were hand-searched to identify additional relevant studies.

Findings were synthesized narratively and organized by outcome domain (neurodevelopment; obesity/metabolic; pubertal/endocrine), then by metal and exposure window (prenatal vs postnatal) and biomatrix. Emphasis was placed on consistency of directionality, dose–response patterns, mixture findings, and sources of heterogeneity (matrix choice, outcome instruments, dietary confounding for mercury, arsenic speciation, and effect modification by sex or adiposity).

Ethical approval was not required because this review used published, de-identified data and involved no new human participant recruitment or intervention.

3. Biological Rationale and Windows of Susceptibility

Early-life exposure to toxic metals and metalloids can influence health across the life course through mechanisms consistent with the Developmental Origins of Health and Disease (DOHaD) framework, which posits that biological systems are highly plastic during early development and that environmental perturbations during sensitive periods can permanently shape organ structure and physiological regulation [16,17]. Lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) are of particular concern in pediatric populations because they are ubiquitous, can cross the maternal–fetal interface, and converge on shared molecular pathways—oxidative stress, inflammation, endocrine disruption, mitochondrial dysfunction, and epigenetic remodeling—capable of influencing neurodevelopmental, metabolic, and pubertal/endocrine trajectories [18–20].

3.1. Windows of Susceptibility Across Development

Windows of susceptibility denote developmental periods during which exposure produces quantitatively larger or qualitatively different effects due to rapid cellular proliferation, differentiation, and neuroendocrine maturation. For the outcomes prioritized in this review, the most biologically relevant windows include:

Periconception and early gestation, encompassing implantation and placentation, when exposures may disrupt placental development and establish persistent epigenetic marks with long-term consequences [16,17].

Mid-to-late gestation, characterized by accelerated fetal brain growth, neuronal migration, synaptogenesis, and early organization of endocrine axes; metals crossing the placenta during this phase may alter neurodevelopmental substrates and hormonal set points [18,21].

Infancy and early childhood, a period of continued myelination, synaptic pruning, immune maturation, and adipose tissue expansion, during which toxicant exposure may influence cognition and energy balance regulation [19,22].

Late childhood and puberty, marked by reactivation of the hypothalamic–pituitary–gonadal (HPG) axis and dynamic changes in thyroid and growth hormone signaling; exposures during this window may shift pubertal timing and body composition trajectories [23,24].

Accordingly, timing is a critical determinant of toxicity: identical biomarker concentrations may have distinct biological implications depending on whether they reflect exposure during placentation, early brain development, metabolic programming, or pubertal transition [16,17].3.2. Placental Transfer and the Maternal–Fetal Interface as a Mechanistic Hub

3.2. Placental Transfer and the Maternal–Fetal Interface as a Mechanistic Hub

A major biological rationale for including prenatal exposure derives from the capacity of Pb, Hg, Cd, and As to cross the placenta and to disrupt placental structure and function. The placenta is an active endocrine and immunologic organ that regulates nutrient transport, inflammatory signaling, and fetal growth. Prenatal arsenic exposure, for example, has been associated with increased placental oxidative stress and inflammation, supporting a pathway through which fetal development may be altered independently of postnatal exposure [25]. Epidemiologic evidence further links prenatal and early-life arsenic exposure with adverse neuropsychological outcomes, reinforcing the relevance of in utero windows [26,27].

Similar placenta-centered mechanisms have been proposed for Pb, Hg, and Cd, including interference with metal transporters, oxidative injury, altered steroidogenesis, and dysregulation of placental hormones, which may collectively influence fetal organogenesis and long-term disease susceptibility [18,28]. Importantly, placental vulnerability is modulated by maternal nutritional status and co-exposures, suggesting that micronutrients such as selenium, iron, folate, and calcium may modify metal toxicity through competitive transport, antioxidant defenses, and methylation capacity [16,17].

A central biological justification for including prenatal exposures is the capacity of these metals/metalloids to reach the fetus via placental transfer and to perturb placental function itself. The placenta is not merely a passive barrier; it is an endocrine and immunologic organ that regulates nutrient transport, inflammatory signaling, and fetal growth trajectories. Maternal exposures to arsenic, for example, have been associated with increased placental oxidative stress and inflammation, supporting a plausible pathway through which fetal development may be affected even before postnatal exposure occurs [20]. Arsenic exposure is widely recognized as capable of initiating in utero exposure through placental transfer, and a growing epidemiologic literature links prenatal/childhood arsenic with neuropsychological endpoints [21,22]. Similar placenta-centered mechanisms are biologically plausible for Pb, Hg, and Cd: altered transport proteins, oxidative injury, and endocrine disturbances may influence both fetal organ development and the "starting point" for postnatal health trajectories. Because placental biology is sensitive to maternal nutrition and co-exposures, it also provides a framework for effect modification: micronutrient status (e.g., selenium, folate, iron, calcium) and inflammatory context may attenuate or amplify metal-related risk through competition for transport pathways, antioxidant capacity, and methylation potential [16,17].

3.3. Shared Molecular Pathways Linking Metals to Neurodevelopment

Neurodevelopment is a central endpoint in pediatric environmental health because the developing brain is particularly sensitive to toxic perturbations and has limited compensatory capacity. Across metals, several convergent mechanisms have been described, as stated in table 1. These overlapping pathways help explain heterogeneity across observational studies while supporting a coherent biological basis for metal-associated neurodevelopmental impairment.

Table 1. Key biological mechanisms linking early-life exposure to toxic metals with neurodevelopmental outcomes.

Mechanism	Biological relevance	Supporting evidence
Oxidative stress and neuroinflammation	Can disrupt neuronal differentiation, synaptic formation, and circuit refinement. For arsenic, oxidative stress is a well-established mechanism of developmental neurotoxicity.	[27,29]
Mitochondrial dysfunction and impaired energy metabolism	particularly relevant for neurons given their high metabolic demands	[18]
Disruption of neuroendocrine and stress-response systems	Including altered hypothalamic–pituitary–adrenal (HPA) axis signaling; lead exposure has been associated with changes in cortisol regulation that may influence cognition and behavior.	[21,30]

Epigenetic remodeling	Whereby early-life exposures induce persistent changes in DNA methylation and chromatin structure, acting as a form of "biological memory" that links early exposure to long-term neurodevelopmental outcomes	[31,32]
Sex-specific susceptibility	Reflecting differences in neuroendocrine milieu and brain maturation timing; sex-dependent neurodevelopmental effects of lead have been reported in both experimental and epidemiologic studies.	[21,30].

3.4. Metabolic Programming: From Early Toxicant Exposure to Obesity Risk

The inclusion of obesity and metabolic outcomes is grounded in DOHaD-based concepts of metabolic programming, whereby early exposures influence adipocyte differentiation, appetite regulation, insulin sensitivity, and systemic inflammatory tone [16,17]. Pb, Hg, Cd, and As may contribute to obesogenic trajectories through: endocrine interference, including disruption of thyroid hormones, glucocorticoids, and sex steroids, which regulate basal metabolic rate and adiposity distribution [19,20]; chronic low-grade inflammation and oxidative stress, promoting insulin resistance and adipose tissue dysfunction [18]; epigenetic and mitochondrial mechanisms, which may predispose individuals to inefficient metabolic responses in later nutritional environments [31,32]; mixture effects, as metals often co-occur and converge on shared metabolic pathways, resulting in additive or synergistic impacts not captured by single-metal analyses [33]; longitudinal studies increasingly report associations between prenatal metal exposure profiles and childhood adiposity indices, supporting the biological plausibility of early windows influencing later metabolic risk [34].

3.5. Endocrine Disruption and Pubertal Timing: Nonlinearity and Diverging Observations

Pubertal timing represents an integrative endocrine outcome regulated by the coordinated activity of the hypothalamic–pituitary–gonadal (HPG) axis, adiposity-related metabolic signals (notably leptin), thyroid hormone function, and broader psychosocial and environmental contexts. This complex neuroendocrine integration renders pubertal development particularly sensitive to environmental perturbations during critical developmental windows [35].

Several toxic metals and metalloids are biologically plausible contributors to altered pubertal timing due to their endocrine-disrupting properties, even at low, environmentally relevant exposure levels. Cadmium has been extensively characterized as a metalloestrogen capable of activating estrogen receptor–mediated signaling through metal–ligand interactions, independent of endogenous estradiol. Experimental and mechanistic studies demonstrate that cadmium can bind to estrogen receptor α and trigger downstream transcriptional activity, supporting its potential role in pubertal dysregulation [36].

Epidemiologic evidence linking metal exposures to pubertal outcomes is notably heterogeneous, a pattern that is biologically credible given several modifying factors. First, dose- and timing-dependent nonlinearity is a recognized feature of endocrine systems, whereby low-dose exposures may elicit qualitatively different effects compared with higher doses, and prenatal, early childhood, or peripubertal exposures may influence distinct regulatory pathways. Second, sex-specific susceptibility is critical, as pubertal signaling pathways, hormonal milieus, and developmental trajectories differ substantially between girls and boys; consequently, the same exposure may delay pubertal onset in one sex while accelerating it in the other. Third, adiposity functions both as a mediator and an effect modifier, since body fat influences pubertal timing through leptin and insulin signaling, and metals that disrupt metabolic regulation may indirectly alter pubertal progression [35,37].

Empirical data support an association between lead exposure and altered pubertal development. Prenatal blood lead concentrations have been associated with a later age at menarche in girls in prospective cohort analyses [38]. Similarly, prenatal and early childhood lead exposure has been linked to delayed pubertal onset and progression in longitudinal cohorts, including studies conducted in urban Latin American populations, underscoring the relevance of early-life exposure in vulnerable settings [39].

Broader narrative and systematic reviews examining endocrine-disrupting chemicals, including metals and metalloids, consistently report inconsistent directions and magnitudes of association with pubertal timing. These reviews emphasize exposure window, sex, baseline nutritional status, and outcome definition as primary sources of heterogeneity rather than methodological inconsistency alone [40]. Collectively, these patterns justify a narrative synthesis approach that explicitly stratifies evidence by developmental timing, sex, and pubertal endpoint, rather than assuming a uniform biological effect across populations and exposure contexts.

3.6. Why Mixtures and Social Context Matter Biologically

Neurodevelopment represents one of the most sensitive biological domains to environmental exposures, given the tightly regulated sequence of cellular proliferation, migration, synaptogenesis, myelination, and synaptic pruning that occurs from early gestation through adolescence. These processes are orchestrated by finely balanced molecular and endocrine signals, rendering the developing brain particularly vulnerable to disruption by toxic metals during defined windows of susceptibility [41].

Several metals and metalloids—including lead, mercury, arsenic, and cadmium—are well-established developmental neurotoxicants. Mechanistically, these elements can cross the placental barrier and, in some cases, the immature blood–brain barrier, allowing direct interaction with neural progenitor cells and developing neuronal circuits. Proposed mechanisms include oxidative stress induction, mitochondrial dysfunction, interference with calcium-dependent signaling, disruption of neurotransmitter systems (particularly dopaminergic and glutamatergic pathways), and epigenetic modifications affecting gene expression critical for neurodevelopment [42,43].

Timing of exposure is a key determinant of neurodevelopmental impact. Prenatal exposure may alter early brain patterning and neuronal differentiation, while postnatal and early childhood exposures may interfere with synaptic refinement and cognitive maturation. Importantly, adverse neurodevelopmental outcomes have been documented even at low-level exposures previously considered safe, supporting the concept of non-threshold effects for certain neurotoxic metals [44].

Epidemiologic studies consistently associate early-life lead exposure with deficits in cognitive function, attention, executive performance, and academic achievement across childhood and adolescence. Longitudinal cohort studies have demonstrated inverse associations between prenatal or early childhood blood lead levels and intelligence quotient (IQ), with effects persisting into later life stages [45]. Similar, though less extensively characterized, associations have been reported for prenatal arsenic and mercury exposure, particularly in relation to language development, memory, and psychomotor performance [46].

Systematic reviews and meta-analyses reinforce these findings, highlighting the robustness of associations between early-life metal exposure and neurodevelopmental impairment while also emphasizing heterogeneity driven by exposure assessment methods, outcome definitions, socioeconomic context, and co-exposures. Importantly, several reviews underscore that combined exposures—rather than isolated metals—may better reflect real-world conditions and could exert additive or synergistic neurotoxic effects [47].

Collectively, the strong biological plausibility, consistency of epidemiologic evidence, and support from mechanistic and experimental data position neurodevelopment as a critical endpoint for evaluating the health impacts of prenatal and early-life exposure to toxic metals. These characteristics further justify a life-course–oriented narrative synthesis that integrates exposure timing, neurodevelopmental domain, and population vulnerability.

3.7. Metabolic Programming and Cardiometabolic Risk

The concept of metabolic programming originates from developmental biology and DOHaD, positing that early-life environmental influences can alter the trajectory of energy balance regulation, adipocyte differentiation, and insulin sensitivity, thereby shaping long-term metabolic health. Toxic metals are biologically plausible contributors to this process because they can interfere with endocrine signaling, cellular energetics, inflammatory pathways, and nutrient–hormone networks that regulate body composition and metabolic homeostasis [48,49].

Animal and mechanistic studies have demonstrated that heavy metals can influence adipogenesis and glucose–lipid metabolism. For example, some toxicants alter adipocyte differentiation and mitochondrial function, while others perturb thyroid and steroid hormone signaling, all of which are central to metabolic set points established early in life. Although the bulk of mechanistic evidence originates from experimental models, these pathways provide a plausible framework linking early exposures to later metabolic outcomes.

Epidemiological evidence for associations between early-life metal exposure and obesity/metabolic risk in humans is evolving but somewhat inconsistent. A systematic review of childhood obesity, trace elements, and heavy metals reported that perturbations in metal homeostasis may be linked to increased oxidative stress, inflammatory responses, and dysregulated carbohydrate and lipid metabolism, all of which plausibly contribute to risk for adiposity and cardiometabolic disorders [50]. Cross-sectional data from U.S. children and adolescents identified associations between urinary and blood metal measures and obesity, with evidence of gender-specific effects and nonlinear relationships, though the direction and magnitude of associations varied by metal species and analytic model [51]. These mixed findings reflect the complexity of metabolic outcomes, the influence of co-exposures, and the difficulty of interpreting cross-sectional data in regard to temporality.

Prospective birth cohort studies provide deeper insight. Some report that prenatal exposure to Pb, Hg, and Cd is associated with later measures of overweight or obesity in childhood, though effect estimates and directions differ between studies, and not all analyses reach statistical significance after adjustment for confounders [13,48,49]. For instance, data from NHANES suggests that in adolescents (6–18 years), higher blood lead and cadmium levels are inversely associated with waist circumference, but these measurements do not necessarily reflect early-life exposures and may be influenced by postnatal metabolic and behavioral factors [13].

Adding complexity, analyses that consider metal mixtures—rather than single metals—indicate that patterns of multiple concurrent exposures may be more indicative of metabolic perturbation than individual metals alone, with some metals correlating with higher risk of excess weight and others showing inverse or neutral associations [18,51]. This aligns with the idea that metabolic programming is multifactorial, with potential interactive effects among metals, nutrients, and social determinants of health.

Taken together, the current body of evidence supports biological plausibility for metals influencing metabolic trajectories, yet the epidemiological patterns are heterogeneous. This heterogeneity underscores the need for longitudinal studies with rigorous biomonitoring, adjustment for socioeconomic and lifestyle confounders, and thoughtful modeling of mixtures, to more precisely characterize how early exposures may contribute to obesity and cardiometabolic risk over the life course.

4. Exposure Assessment in Pediatric Populations

Accurate exposure assessment is a cornerstone of pediatric environmental health research, particularly when evaluating the long-term health effects of toxic metals. In children, exposure assessment presents unique methodological challenges due to rapid developmental changes, age-dependent toxicokinetics, and ethical constraints that limit invasive sampling. Consequently, biomonitoring-based measures—including blood, urine, and hair concentrations—are widely regarded as the most reliable approach for quantifying internal dose in pediatric populations [52].

4.1. Blood Biomarkers

Blood concentrations are the most commonly used biomarkers for assessing exposure to several toxic metals, particularly lead and mercury. Blood lead levels (BLLs) are considered the gold standard for evaluating recent and cumulative exposure during childhood and have been extensively used in epidemiologic studies linking lead exposure to neurodevelopmental, behavioral, and metabolic outcomes [53]. For mercury, whole blood or erythrocyte mercury reflects recent exposure and is especially informative in populations with dietary fish consumption [54].

However, blood measurements are limited by their relatively short biological half-lives for certain metals and may not fully capture historical or prenatal exposures unless repeated measures or cord blood samples are available. Cord blood, in particular, provides a valuable proxy for in utero exposure and has been widely used in birth cohort studies assessing developmental outcomes [55].

4.2. Urinary Biomarkers

Urinary biomarkers are commonly employed to assess exposure to cadmium and inorganic arsenic species. Urinary cadmium reflects cumulative body burden due to its long biological half-life and renal accumulation, making it particularly useful for evaluating chronic low-level exposure [56]. For arsenic, speciation analysis of urinary metabolites (inorganic arsenic, monomethylarsonic acid, dimethylarsinic acid) is critical to distinguish toxic exposure from non-toxic organic arsenic derived from seafood [57].

Interpretation of urinary biomarkers requires careful adjustment for urine dilution, typically using creatinine or specific gravity. In pediatric studies, this adjustment is essential due to age-related variability in hydration status and muscle mass [58].

4.3. Hair Biomarkers

Hair analysis offers a non-invasive method for assessing exposure to certain metals, notably mercury and arsenic, and can provide an integrated measure of exposure over weeks to months. This approach has been used in pediatric and prenatal studies to reconstruct exposure timelines, particularly when repeated biological samples are not feasible [59]. Nonetheless, hair measurements are susceptible to external contamination, variability in hair growth rates, and methodological heterogeneity, which limit comparability across studies and necessitate rigorous laboratory protocols [60].

4.4. Considerations for Pediatric and Prenatal Exposure Assessment

Exposure assessment in pediatric populations must account for critical windows of susceptibility, including prenatal life, infancy, and early childhood, during which toxicokinetics and biological vulnerability differ substantially from those of adults. Prenatal exposure is typically assessed using maternal blood, urine, or hair during pregnancy, as well as cord blood at delivery, each reflecting different exposure windows [55,61].

Furthermore, high-quality pediatric exposure studies routinely adjust for socioeconomic status and passive tobacco smoke exposure, both of which are strong determinants of metal exposure and potential confounders of health outcomes. Failure to account for these factors can result in biased effect estimates and spurious associations [62].

Overall, while biomonitoring provides a robust framework for exposure assessment in pediatric populations, careful consideration of biomarker selection, exposure timing, and confounding structure is essential for valid inference regarding the health effects of toxic metals.

5. Neurodevelopmental Trajectories

Neurodevelopmental trajectories reflect the cumulative and dynamic influence of genetic, social, and environmental factors acting across sensitive developmental periods. Exposure to toxic metals during prenatal life, infancy, and early childhood has been consistently implicated as a determinant

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of altered cognitive, behavioral, and neuropsychological outcomes. These effects are best understood within a life-course framework, recognizing that early insults may exert persistent or delayed effects that unfold over time rather than manifesting immediately [63].

5.1. Prenatal Exposure and Early Neurodevelopment

Prenatal life constitutes a critical window of vulnerability for neurodevelopment, as neuronal proliferation, migration, and early synaptogenesis are highly active during gestation. Several birth cohort studies have demonstrated that prenatal exposure to lead, mercury, and arsenic, assessed through maternal or cord blood biomarkers, is associated with adverse neurodevelopmental outcomes in infancy and early childhood.

Prospective cohort data from Europe, North America, and Asia indicate that higher prenatal blood lead concentrations are associated with lower cognitive scores, impaired psychomotor development, and subtle deficits in attention and executive functioning during early childhood [64,65]. Importantly, these associations are often observed at exposure levels below historically accepted safety thresholds, supporting the absence of a clear neurotoxic threshold for lead.

Prenatal mercury exposure, particularly in the form of methylmercury, has similarly been associated with adverse neurodevelopmental outcomes, including language delay and reduced cognitive performance. Although fish consumption complicates exposure assessment, biomonitoring-based studies using maternal or cord blood mercury provide evidence that neurodevelopmental effects are detectable even in populations without overt poisoning [66].

For arsenic, emerging evidence from prenatal cohorts suggests associations with altered cognitive and motor development, although findings are more heterogeneous. Variability in arsenic speciation, exposure sources, and nutritional context likely contributes to inconsistency across studies [67].

5.2. Postnatal and Early Childhood Exposure

Postnatal exposure during infancy and early childhood represents an additional critical period for neurodevelopment, coinciding with rapid synaptic refinement, myelination, and cortical maturation. Blood lead levels measured in early childhood have been repeatedly associated with deficits in IQ, attention, working memory, and academic achievement later in childhood and adolescence [68].

Cross-sectional and longitudinal studies using biomonitored lead and cadmium concentrations in children demonstrate associations with neurobehavioral outcomes, including increased risk of attention-deficit/hyperactivity disorder–related symptoms and poorer executive functioning. Although cadmium has been less extensively studied than lead, available data suggest potential neurodevelopmental toxicity at low exposure levels, particularly when exposure occurs early in life [69].

5.3. Cognitive, Behavioral, and Executive Function Outcomes

Neurodevelopmental effects of metal exposure extend beyond global cognitive measures to encompass specific domains such as attention regulation, impulse control, memory, and behavior. Several studies report associations between early-life metal exposure and increased externalizing behaviors, emotional dysregulation, and impaired executive function, which may persist into adolescence [70].

Systematic reviews and meta-analyses consistently identify lead as the metal with the strongest and most consistent evidence for adverse neurodevelopmental effects. A quantitative meta-analysis published in the last decade confirmed a dose–response relationship between blood lead levels and cognitive impairment in children, reinforcing earlier pooled analyses while incorporating more recent cohorts [71].

5.4. Sex-Specific and Socioeconomic Modifiers

Sex-specific susceptibility has emerged as an important modifier of neurodevelopmental effects. Several studies report stronger associations between metal exposure and neurodevelopmental outcomes in boys, while others observe heightened vulnerability in girls, depending on the outcome assessed and the exposure window. These differences likely reflect sex-dependent neuroendocrine signaling, brain maturation timing, and behavioral expression [72].

Socioeconomic status (SES) is a critical contextual factor influencing both exposure and vulnerability. Children from lower-SES backgrounds often experience higher metal exposure due to housing conditions, environmental contamination, and nutritional factors, while simultaneously facing reduced access to protective resources. Studies that rigorously adjust for SES and passive smoking consistently demonstrate that metal exposure exerts independent neurodevelopmental effects, although residual confounding remains a concern [73].

5.5. Evidence from Systematic Reviews and Meta-Analyses

Over the past two decades, an expanding body of systematic reviews and meta-analyses has synthesized epidemiological evidence linking early-life exposure to toxic metals with adverse neurodevelopmental outcomes. These evidence syntheses provide critical insight into the consistency, magnitude, and heterogeneity of observed associations across populations, exposure windows, and neurodevelopmental domains, complementing narrative frameworks of developmental neurotoxicity [5].

Lead (Pb) remains the most extensively studied and consistently implicated metal in relation to child neurodevelopment. A high-quality meta-analysis by Xu et al. quantitatively evaluated the association between blood lead levels and intelligence in children, demonstrating a robust inverse relationship across a wide exposure range [74]. The pooled estimates confirmed significant IQ decrements per incremental increase in blood lead concentration, with a steeper slope at lower exposure levels, thereby reinforcing the absence of a safe neurodevelopmental threshold for lead exposure. These findings corroborate earlier pooled analyses while incorporating more recent population-based cohorts and improved exposure characterization.

Systematic reviews focusing on prenatal exposure further strengthen the evidence base. Reviews synthesizing birth cohort studies consistently report associations between prenatal lead exposure—assessed via maternal or cord blood biomarkers—and reduced mental development indices, impaired executive functioning, and behavioral dysregulation in offspring [71, 75]. These associations are biologically plausible given the heightened vulnerability of neurodevelopmental processes during early and mid-gestation, including neuronal proliferation, migration, and early circuit formation.

Beyond lead, evidence for other toxic metals has expanded in recent years. A systematic review and meta-analysis evaluating early-life exposure to cadmium, arsenic, and manganese reported that prenatal cadmium exposure was significantly associated with lower full-scale IQ, while arsenic exposure showed negative but more heterogeneous associations with cognitive and psychomotor outcomes [76]. The authors highlighted substantial between-study heterogeneity driven by differences in biomarker matrices (blood versus urine), exposure sources, geographic context, and nutritional status, but concluded that cadmium exposure in utero represents a credible neurodevelopmental risk factor.

Neurobehavioral outcomes have also been examined through quantitative syntheses. A meta-analysis assessing heavy metal exposure and attention-deficit/hyperactivity disorder (ADHD) found that children diagnosed with ADHD had significantly higher blood lead concentrations compared with controls, supporting a positive association between lead exposure and ADHD diagnosis or symptom severity [77]. Evidence for mercury and cadmium was less consistent, largely reflecting fewer high-quality longitudinal studies and variability in outcome definitions.

With respect to autism spectrum disorder (ASD), a recent and comprehensive systematic review and meta-analysis by Ding et al. synthesized evidence on cadmium, lead, arsenic, and mercury exposure measured in biological matrices, including blood and hair [78]. The analysis demonstrated significantly higher concentrations of multiple toxic metals among children with ASD compared with neurotypical controls. Although causal inference remains limited due to the observational design of included studies, the consistency of elevated metal burdens across matrices and regions supports a contributory role of toxic metals within a multifactorial etiologic framework.

Collectively, systematic reviews and meta-analyses converge on several key conclusions: (i) lead exposure exhibits the strongest and most consistent association with adverse neurodevelopmental outcomes, particularly cognitive and behavioral domains; (ii) cadmium shows emerging and increasingly consistent evidence of prenatal neurotoxicity; (iii) arsenic and mercury demonstrate heterogeneous but concerning associations, likely modified by exposure timing, dose, and population context; and (iv) neurobehavioral disorders such as ADHD and ASD show reproducible associations with higher metal burdens, although residual confounding and reverse causation remain important limitations. Taken together, these quantitative syntheses provide strong support for a role of early-life exposure to toxic metals in shaping adverse neurodevelopmental trajectories, underscoring the need for longitudinal studies with repeated biomonitoring, rigorous control of socioeconomic confounders, and harmonized neurodevelopmental assessments.

6. Metabolic Outcomes and Obesity Risk

Metabolic health in pediatric populations encompasses a range of outcomes including adiposity, insulin resistance, dyslipidemia, and metabolic syndrome. Early-life exposure to toxic metals has been investigated as a potential contributor to altered metabolic trajectories and increased risk of obesity. Toxic metals such as lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) may interfere with endocrine signaling, mitochondrial function, adipogenesis, and inflammatory pathways, all of which are central to metabolic regulation [79].

6.1. Prenatal and Early-Life Metal Exposure and Childhood Adiposity

Several epidemiological studies indicate that prenatal and early postnatal exposure to toxic metals is associated with altered adiposity trajectories in childhood. Evidence from prospective birth cohorts suggests that in utero exposure to metal mixtures, assessed using maternal or cord blood biomarkers, is associated with increased risk of overweight and obesity during childhood and adolescence. These associations appear to be modified by nutritional status, sex, and socioeconomic context, underscoring the multifactorial nature of metabolic programming [80].

Systematic reviews and meta-analyses synthesizing observational evidence across age groups, including pediatric populations, report heterogeneous associations between individual metals and obesity-related outcomes. Lead exposure has frequently shown inverse associations with body mass index (BMI) and obesity, whereas mercury and arsenic have been more consistently linked to increased adiposity. Cadmium demonstrates variable associations, potentially reflecting differences in exposure assessment (blood versus urine), timing of exposure, and underlying nutritional or inflammatory status [79].

Importantly, studies applying mixture-based analytical approaches, such as weighted quantile sum regression or Bayesian kernel machine regression, suggest that combined exposure to multiple metals may exert additive or synergistic effects on adiposity, which are not captured when metals are evaluated individually [81].

6.2. Insulin Resistance and Glucose Homeostasis

Beyond adiposity, toxic metals have been implicated in disruptions of glucose metabolism and insulin signaling. Experimental and epidemiological evidence indicates that arsenic and cadmium may impair insulin sensitivity through mechanisms involving oxidative stress, mitochondrial dysfunction, and interference with insulin receptor signaling pathways. In pediatric populations, higher urinary or blood concentrations of arsenic and cadmium have been associated with elevated fasting insulin levels and markers of insulin resistance, even after adjustment for BMI and socioeconomic confounders [82].

Although most evidence linking metals to insulin resistance derives from cross-sectional studies, findings are biologically coherent and supported by mechanistic data. Early-life exposure may prime metabolic tissues toward reduced insulin responsiveness, increasing susceptibility to dysglycemia later in life, particularly in obesogenic environments [83].

6.3. Lipid Metabolism and Metabolic Syndrome Components

Alterations in lipid metabolism represent another potential consequence of pediatric metal exposure. Observational studies have reported associations between blood or urinary metal concentrations and dyslipidemia markers, including elevated triglycerides and reduced high-density lipoprotein cholesterol. Lead and arsenic exposure have been linked to adverse lipid profiles in children and adolescents, suggesting early perturbation of cardiometabolic risk pathways [84].

While the prevalence of overt metabolic syndrome is low in childhood, subclinical clustering of metabolic risk factors may already be evident in metal-exposed populations. These early alterations may track into adulthood, consistent with a life-course model of metabolic disease development.

6.4. Endocrine Disruption and Metabolic Programming

Toxic metals may influence metabolic outcomes through endocrine-disrupting properties. Several metals can interfere with thyroid hormone signaling, glucocorticoid regulation, and adipokine secretion, thereby affecting energy balance, growth, and pubertal-metabolic interactions. Disruption of these hormonal axes during sensitive developmental windows may result in long-lasting metabolic consequences, even in the absence of overt toxicity [85].

Epigenetic mechanisms have also been proposed as mediators linking early metal exposure with later metabolic dysfunction. Altered DNA methylation patterns in genes involved in adipogenesis, glucose transport, and lipid metabolism have been observed in relation to cadmium and lead exposure, providing a potential molecular substrate for persistent metabolic effects [86].

6.5. Synthesis and Knowledge Gaps

Collectively, available evidence suggests that early-life exposure to toxic metals contributes to altered metabolic trajectories characterized by changes in adiposity, insulin sensitivity, and lipid metabolism, as shown in table 2. Associations are metal-specific, context-dependent, and influenced by exposure timing, sex, nutritional status, and co-exposures. While causal inference remains limited by the predominance of cross-sectional designs and residual confounding, the convergence of epidemiological, experimental, and mechanistic data supports a contributory role of toxic metals in pediatric metabolic programming.

Table 2. Integrated summary of evidence linking pediatric heavy-metal exposures across windows of susceptibility with neurodevelopmental, metabolic/obesity, and pubertal outcomes.

Metal	**Exposure Window**	**Neurodevelopmental Outcomes**	**Metabolic / Obesity Outcomes**	**Pubertal / Endocrine Outcomes**
Lead (Pb)	Prenatal	Reduced IQ, cognitive delay, behavioral dysregulation [63,75]	Increased risk of childhood overweight and obesity in birth cohorts [80]	Delayed menarche and altered pubertal timing [72]
	Early childhood	Executive dysfunction, attention deficits, ADHD symptoms [68,77]	Inverse or null associations with obesity in cross-sectional studies [81]	Slower pubertal progression in some cohorts [72]
Mercury (Hg)	Prenatal	Impaired language and cognitive performance, especially in fish-consuming populations [66]	Positive associations with adiposity in meta-analyses [79]	Sex-specific alterations in pubertal markers reported [72]
	Early childhood	Mixed evidence for cognition after	Positive associations with	Limited evidence; endocrine

		adjustment for nutrition [66]	BMI and adiposity [79]	disruption biologically plausible [85]
Cadmium (Cd)	Prenatal	Lower full-scale IQ and neurodevelopmental scores (systematic review evidence) [76	Increased risk of childhood overweight in cohort and mixture analyses [80,81]	Potential estrogen-like and endocrine-disrupting effects [86]
	Early childhood	Limited pediatric data; suggestive neurotoxicity [69]	Inverse or null associations with obesity in population studies [79]	Sparse evidence; mechanistic plausibility exists [86]
Arsenic	Prenatal	Heterogeneous associations with cognitive and motor outcomes [70,76]	Associations with adiposity and metabolic dysregulation [79,80]	Delayed pubertal timing reported in some cohorts [31]
	Early childhood	Reduced cognitive performance in exposed pediatric populations [70]	Associations with dyslipidemia and metabolic alterations [84]	Endocrine disruption hypothesized but understudied [85]

Future research should prioritize longitudinal studies with repeated biomonitoring, standardized metabolic outcome assessments, and mixture-based analytical frameworks to better elucidate causal pathways and identify critical windows of susceptibility.

7. Endocrine Outcomes and Pubertal Timing

The endocrine system plays a central role in coordinating growth, metabolic regulation, and pubertal maturation during childhood and adolescence. Increasing epidemiological and experimental evidence indicates that exposure to toxic metals during critical developmental windows may disrupt endocrine signaling pathways, leading to alterations in pubertal timing and hormonal trajectories. These effects are of particular concern given the sensitivity of the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes to environmental perturbations during early life [87].

7.1. Biological Plausibility of Endocrine Disruption by Metals

Several toxic metals exhibit endocrine-disrupting properties through diverse mechanisms, including interference with hormone synthesis, receptor binding, signal transduction, and epigenetic regulation of endocrine genes. Lead, cadmium, mercury, and arsenic have been shown to alter steroidogenesis, thyroid hormone homeostasis, and glucocorticoid signaling in experimental models [88]. Cadmium, in particular, has been characterized as a “metalloestrogen,” capable of activating estrogen receptors and mimicking estrogenic effects even at low exposure levels [89].

Disruption of endocrine signaling during development may result in long-lasting alterations due to organizational effects on neuroendocrine circuits. Animal studies demonstrate that early-life metal exposure can permanently modify gonadotropin-releasing hormone (GnRH) neuron development, pituitary responsiveness, and peripheral hormone secretion, providing mechanistic support for epidemiological observations in humans [90].

7.2. Lead Exposure and Pubertal Development

Lead exposure has been the most extensively studied metal in relation to pubertal timing. Large population-based studies have consistently reported associations between higher blood lead concentrations and delayed pubertal onset, particularly in girls. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) demonstrated that girls with higher blood lead levels experienced later menarche and delayed breast and pubic hair development, even after adjustment for socioeconomic status and nutritional factors [91].

Similar Findings have been reported in longitudinal cohorts, where childhood lead exposure was associated with slower progression through Tanner stages and altered gonadotropin and sex steroid levels [92]. These effects are biologically plausible given lead's capacity to disrupt calcium-dependent signaling, impair gonadotropin secretion, and interfere with ovarian steroidogenesis.

7.3. Cadmium and Estrogenic Effects on Puberty

Cadmium exposure has attracted increasing attention due to its estrogen-mimicking properties and its tendency to accumulate in biological tissues. Epidemiological studies suggest that prenatal and early-life cadmium exposure may be associated with altered pubertal timing, although findings are somewhat inconsistent. Some cohort studies report earlier breast development and menarche in girls with higher cadmium exposure, while others suggest delayed pubertal milestones, potentially reflecting differences in exposure timing, dose, and co-exposures [93].

Experimental evidence supports cadmium's capacity to activate estrogen receptor–dependent pathways and disrupt normal endocrine feedback mechanisms. These findings raise concern that cadmium exposure during sensitive developmental periods may contribute to dysregulated pubertal maturation and long-term reproductive consequences [94].

7.4. Mercury, Arsenic, and Thyroid-Related Pathways

Mercury and arsenic have been less consistently linked to pubertal timing but are recognized disruptors of thyroid hormone homeostasis, which plays a permissive role in growth and pubertal development. Prenatal and childhood mercury exposure has been associated with altered thyroid hormone levels in observational studies, with potential downstream effects on growth velocity and pubertal progression [95].

Arsenic exposure, particularly from contaminated drinking water, has been associated with delayed puberty and altered sex hormone levels in highly exposed populations. Studies conducted in South Asia and Latin America report associations between arsenic biomarkers and delayed menarche, reduced testosterone levels in boys, and impaired growth, although confounding by nutrition and socioeconomic factors remains a challenge [96].

7.5. Sex-Specific Vulnerability and Life-Course Implications

Sex-specific differences in endocrine disruption are a recurrent theme in the literature. Differential susceptibility may arise from sex-dependent hormone milieus, timing of pubertal maturation, and interactions between metals and sex steroid receptors. Several studies report stronger associations between metal exposure and pubertal delay in girls, while others identify heightened vulnerability in boys for specific hormonal outcomes [97].

Alterations in pubertal timing have important life-course implications, as both early and delayed puberty have been associated with increased risks of cardiometabolic disease, reproductive disorders, and mental health outcomes later in life. Thus, metal-induced endocrine disruption during childhood may represent a critical pathway linking early environmental exposures to long-term health trajectories [98].

8. Cross-Cutting Issues and Controversies

Despite substantial progress in understanding the developmental toxicity of metals, several cross-cutting issues and unresolved controversies continue to shape interpretation of the evidence. These challenges span exposure assessment, causal inference, biological complexity, and implications for risk assessment and public health policy.

8.1. Low-Dose Effects and Nonlinear Dose–Response Relationships

One of the most persistent controversies concerns the existence of safe exposure thresholds for toxic metals. Accumulating evidence, particularly for lead, supports the presence of nonlinear dose–response relationships, with proportionally greater adverse effects observed at lower exposure levels. This phenomenon challenges traditional toxicological assumptions that “the dose makes the poison” and complicates regulatory decision-making [99]. Similar concerns have been raised for cadmium and arsenic, where endocrine and neurodevelopmental effects may occur at exposure levels previously considered negligible.

8.2. Mixtures and Cumulative Exposures

Real-world exposures rarely occur in isolation. Children are simultaneously exposed to multiple metals and other environmental contaminants, raising important questions about mixture effects, additivity, synergy, or antagonism. Epidemiological studies increasingly suggest that combined exposure to metals such as lead, cadmium, mercury, and arsenic may produce effects that differ in magnitude or direction from single-metal models [100]. However, methodological limitations—including collinearity, limited statistical power, and lack of standardized mixture modeling approaches—have hindered definitive conclusions.

8.3. Timing, Windows of Susceptibility, and Life-Course Perspective

Another central issue is the identification of critical windows of susceptibility. Evidence increasingly indicates that prenatal exposure, early postnatal life, and peripubertal periods may differ in vulnerability depending on the outcome assessed. Discrepant findings across studies may reflect differences in exposure timing rather than true inconsistencies. Life-course epidemiology frameworks emphasize that early endocrine or neurodevelopmental perturbations may remain latent until later developmental stages, complicating causal attribution [101].

8.4. Sex-Specific Effects and Effect Modification

Sex-specific susceptibility remains an area of active debate. While biological plausibility for sex-dependent effects is strong—given differences in hormonal milieu, growth trajectories, and neurodevelopmental timing—epidemiologic findings are not always concordant. Some studies report stronger associations in boys, others in girls, and some show opposing directions of effect. These inconsistencies may reflect outcome-specific mechanisms, differential exposure patterns, or limited power for sex-stratified analyses [102].

8.5. Residual Confounding and Socioeconomic Context

Residual confounding continues to challenge causal inference in observational studies of metal exposure. Socioeconomic status, nutrition, housing quality, psychosocial stress, and co-exposures are intricately linked to both exposure and developmental outcomes. Although many studies adjust for key confounders, unmeasured or imperfectly measured factors may bias results. Nonetheless, the consistency of associations across diverse settings argues against confounding as the sole explanation [103].

8.6. Implications for Risk Assessment and Policy

These cross-cutting issues have important implications for environmental health policy. Traditional risk assessment approaches, which often rely on single-chemical evaluations and assume linear dose–response relationships, may underestimate risk during sensitive developmental windows. Growing recognition of low-dose effects, mixture toxicity, and life-course vulnerability has prompted calls for more precautionary regulatory frameworks, particularly for protecting pregnant women and children [104]. Collectively, these controversies underscore the need for integrative research strategies that combine longitudinal cohort studies, advanced exposure modeling, mechanistic insights, and harmonized outcome assessment. Addressing these challenges is essential for translating scientific evidence into effective prevention and policy actions

9. Implications for Prevention and Research

The evidence synthesized in this review has important implications for prevention, public health policy, and future research directions. Because pediatric exposure to toxic metals occurs at the interface of environmental, social, nutritional, and biological systems, effective strategies must be integrative, life-course oriented, and equity-focused.

9.1. One Health Framework and Policy Integration

A One Health framework provides a unifying paradigm to address pediatric metal exposure by integrating human health, environmental protection, and societal determinants. Toxic metals such as lead, mercury, cadmium, and arsenic originate from shared sources across ecosystems, including contaminated water, soil, food chains, industrial emissions, and household environments. Policy interventions targeting a single exposure source are therefore unlikely to be sufficient [105]. Coordinated actions across environmental regulation, food safety, housing policy, and occupational standards are required to reduce cumulative exposure, particularly during pregnancy and early childhood [106].

Recent policy initiatives emphasize prevention at the population level, including stricter regulation of contaminants in infant foods and drinking water. However, substantial heterogeneity persists across countries, and regulatory thresholds often lag behind emerging evidence indicating adverse effects at very low exposure levels [107].

9.2. Biomonitoring and Exposure Surveillance

Biomonitoring remains a cornerstone of prevention and research. Measurement of metals in blood, urine, hair, and, in some contexts, deciduous teeth provides objective indicators of internal dose and cumulative exposure. Population-based biomonitoring programs have been instrumental in documenting exposure disparities and temporal trends, particularly for lead [108]. Expanding biomonitoring capacity in low- and middle-income countries is essential, as these regions often face higher exposure burdens but lack systematic surveillance [109].

Longitudinal biomonitoring across multiple developmental windows would allow improved characterization of critical exposure periods and facilitate evaluation of intervention effectiveness.

9.3. Nutritional Interventions and Modifiers of Toxicity

Nutritional status plays a key role in modulating metal absorption, distribution, and toxicity. Adequate intake of essential micronutrients—such as iron, calcium, zinc, selenium, and folate—may reduce gastrointestinal absorption of toxic metals or mitigate downstream biological effects. Epidemiologic studies suggest that iron and calcium sufficiency may attenuate lead absorption in children, while selenium status may modify mercury toxicity [110].

Emerging evidence also indicates that prenatal nutritional status may influence susceptibility to metal-associated metabolic and neurodevelopmental outcomes, highlighting nutrition as a potentially modifiable intervention target [111]. However, high-quality trials evaluating nutritional interventions as preventive strategies remain limited.

9.4. Environmental Justice and Vulnerable Populations

Metal exposure disproportionately affects socioeconomically disadvantaged populations due to residential proximity to pollution sources, older housing, unsafe water infrastructure, and limited access to health care. These disparities underscore the importance of embedding environmental justice principles into prevention strategies [112]. Policies that reduce exposure at the source may yield the greatest benefits for vulnerable populations, while individual-level interventions alone risk exacerbating inequities [113].

9.5. Research Gaps and Methodological Priorities

Several critical research gaps remain. First, there is a need for longitudinal cohort studies integrating repeated biomonitoring with standardized neurodevelopmental, metabolic, and endocrine assessments [114]. Second, real-world exposure scenarios involve mixtures of metals and other environmental contaminants, yet mixture-focused epidemiologic studies remain relatively scarce [115].

Third, mechanistic research linking low-dose exposure to endocrine and metabolic disruption across developmental stages is needed to support causal inference. Finally, harmonization of exposure metrics and outcome definitions would enhance comparability across studies and strengthen evidence synthesis [116].

9.6. Translational and Policy-Relevant Research

Future research should explicitly aim to inform policy and clinical practice. This includes evaluating the effectiveness of regulatory interventions, community-based exposure reduction programs, and prenatal or early-life screening strategies. Translational research that bridges epidemiology, toxicology, and implementation science will be essential to move from evidence to action [117–119]. These implications reinforce the urgency of preventing pediatric metal exposure and advancing research strategies that are interdisciplinary, preventive, and equity-oriented.

10. Conclusions

This narrative review synthesizes epidemiological and mechanistic evidence linking pediatric exposure to toxic metals—lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As)—with long-term neurodevelopmental, metabolic, and endocrine outcomes across the life course. Framed within the exposome and Developmental Origins of Health and Disease (DOHaD) paradigms, the findings underscore that early-life exposure to these ubiquitous environmental toxicants represents not a transient insult, but a biologically consequential process capable of shaping chronic disease trajectories from childhood into adulthood.

The evidence base for neurodevelopmental toxicity is the most robust and mature. Across diverse populations and study designs, prenatal and early childhood exposure to lead and mercury consistently predict adverse cognitive, motor, and behavioral outcomes, including deficits in executive function and increased risk of attention-related disorders. Critically, the absence of a demonstrable safe threshold for blood lead levels reinforces the conclusion that even low-level exposures—well below historical regulatory benchmarks—pose meaningful risks during sensitive periods of brain development. These findings firmly position neurodevelopment as a sentinel outcome of early-life metal exposure.

In contrast, metabolic and endocrine outcomes represent an emerging but rapidly evolving frontier. Toxic metals act as metabolism-disrupting chemicals and endocrine disruptors through mechanisms that include impaired insulin signaling, altered adipogenesis, mitochondrial dysfunction, and interference with steroid and thyroid hormone pathways. Epidemiologic evidence linking metals to obesity, insulin resistance, and pubertal timing remains heterogeneous and metal-specific: lead often shows inverse associations with adiposity, whereas mercury and arsenic are more consistently associated with increased adiposity and metabolic dysfunction. Pubertal timing, in particular, emerges as an integrative endocrine endpoint characterized by sex-specific effects, nonlinear dose–response relationships, and strong dependence on exposure timing and baseline adiposity. These complexities do not weaken the evidence base; rather, they reflect the biological reality of endocrine regulation during development.

A central insight reinforced throughout this review is the inadequacy of single-chemical models to reflect real-world exposure. Children are exposed to complex mixtures of metals and other environmental contaminants, often simultaneously and across multiple developmental windows. Increasing evidence indicates that these mixtures can exert additive or synergistic effects that are not predictable from individual exposures alone. A life-course exposome approach is therefore essential to capture cumulative and interactive risks, particularly in vulnerable populations.

Methodological rigor emerges as a prerequisite for valid inference. Accurate exposure assessment depends on appropriate biomonitoring matrices—blood for recent Pb and Hg exposure, urine for Cd and inorganic As, hair for chronic Hg exposure—and, critically, on proper arsenic speciation to distinguish toxic inorganic forms from benign dietary sources. Equally important is rigorous adjustment for key confounders, especially socioeconomic status and passive tobacco smoke exposure, without which associations may be biased or misinterpreted. Recognition of low-dose and nonlinear effects further challenges traditional threshold-based risk assessment frameworks.

This review also highlights that vulnerability to metal toxicity is socially patterned rather than evenly distributed. Socioeconomic disadvantage amplifies exposure and susceptibility through intersecting pathways involving housing quality, nutrition, psychosocial stress, and access to health care. Conversely, nutritional status—particularly adequate intake of iron, calcium, selenium, and folate—may mitigate absorption and biological impact of metals, identifying nutrition as a plausible and equity-oriented intervention target.

Looking forward, the field must prioritize longitudinal, biomonitoring-based studies that integrate mixture analyses, standardized outcome assessment, and life-course perspectives. Prevention strategies should be grounded in One Health principles, combining environmental regulation, nutritional interventions, housing policy, and targeted surveillance in high-risk communities. Regulatory frameworks must evolve to account for low-dose toxicity, sensitive windows of susceptibility, and cumulative exposures rather than isolated agents.

Pediatric exposure to toxic metals represents a preventable determinant of lifelong health. By integrating exposome science, developmental biology, and social context, this body of evidence calls for a paradigm shift—from reactive management of disease to proactive protection of early development. Protecting children from metal exposure is not only an environmental imperative; it is an investment in neurodevelopmental potential, metabolic health, and intergenerational equity.

These findings support the need for early-life prevention strategies and stricter regulatory thresholds for metal exposure

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Abbreviations

The following abbreviations are used in this manuscript:

ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
As	Arsenic
BMI	Body Mass Index
Cd	Cadmium
DOHaD	Developmental Origins of Health and Disease
EDCs	Endocrine-Disrupting Chemicals
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GnRH	Gonadotropin-Releasing Hormone
HPA	Hypothalamic–Pituitary–Adrenal (axis)
HPG	Hypothalamic–Pituitary–Gonadal (axis)
Hg	Mercury
IQ	Intelligence Quotient
LMICs	Low- and Middle-Income Countries
NHANES	National Health and Nutrition Examination Survey

Pb	Lead
SES	Socioeconomic Status
WHO	World Health Organization

References

1. Wild, C.P. The exposome: from concept to utility. Int. J. Epidemiol. 2012, 41, 24–32.
2. von Stackelberg, K.; Guzy, E.; Chu, T.; Claus Henn, B. Exposure to mixtures of metals and neurodevelopmental outcomes: a multidisciplinary review using an adverse outcome pathway framework. Risk Anal. 2015, 35, 971–1016.
3. World Health Organization. Lead poisoning and health. WHO Fact Sheet; updated 2024.
4. Centers for Disease Control and Prevention (CDC). CDC's Blood Lead Reference Value. CDC; updated 2021 Oct 28.
5. da Silva, A.S.; Santos, A.; et al. Neurodevelopmental outcomes associated with early-life exposure to heavy metals: a systematic review. Int. J. Environ. Res. Public Health 2025, 22, 1308.
6. Su, R.; Jiang, Y.; Li, W.; Ding, W.; Feng, L. Effects of prenatal arsenic, cadmium, and manganese exposure on neurodevelopment in children: a systematic review and meta-analysis. Medicina 2025, 61, 1143.
7. Notario-Barandiaran, L.; Compañ-Gabucio, L.M.; Bauer, J.A.; Vioque, J.; Karagas, M.R.; Signes-Pastor, A.J. Arsenic exposure and neuropsychological outcomes in children: a scoping review. Toxics 2025, 13, 542.
8. Ding, M.; Shi, S.; Qie, S.; Li, J.; Xi, X. Association between heavy metals exposure (cadmium, lead, arsenic, mercury) and child autistic disorder: a systematic review and meta-analysis. Front. Pediatr. 2023, 11, 1169733.
9. Sagiv, S.K.; Thurston, S.W.; Bellinger, D.C.; Amarasiriwardena, C.; Korrick, S.A. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. Arch. Pediatr. Adolesc. Med. 2012, 166, 1123–1131.
10. Dack, K.; Fell, M.; Taylor, C.M.; et al. Prenatal mercury exposure and neurodevelopment up to the age of 5 years: a systematic review. Int. J. Environ. Res. Public Health 2022, 19, 1976.
11. Huang, W.; Igusa, T.; Wang, G.; Buckley, J.P.; Hong, X.; et al. In-utero co-exposure to toxic metals and micronutrients on childhood risk of overweight or obesity: new insight on micronutrients counteracting toxic metals. Int. J. Obes. 2022, 46, 1435–1445.
12. Katagiri, M.; et al. Prenatal exposure to toxic metals and pubertal timing in children: a prospective cohort study. Environ. Res. 2025, 279, 120892.
13. Signes-Pastor, A.J.; Vioque, J.; Navarrete-Muñoz, E.M.; Carey, M.; García de la Hera, M.; et al. Concentrations of urinary arsenic species in relation to rice and seafood consumption among children living in Spain. Environ. Res. 2017, 159, 69–75.
14. Obeng, A.; Roh, T.; Aggarwal, A.; Uyasmasi, K.; Carrillo, G. The contribution of secondhand tobacco smoke to blood lead levels in US children and adolescents: a cross-sectional analysis of NHANES 2015–2018. BMC Public Health 2023, 23, 1129.
15. Jung, S.Y.; et al. Association between secondhand smoke exposure and blood lead and cadmium concentration in community dwelling women: the fifth Korea National Health and Nutrition Examination Survey (2010–2012). BMJ Open 2015, 5, e008218.
16. Gluckman, P.D.; Hanson, M.A. Developmental origins of health and disease. N. Engl. J. Med. 2004, 359, 61–73.
17. Lacagnina, S. The developmental origins of health and disease (DOHaD). Front. Endocrinol. 2019, 10, 853.
18. Gundacker, C.; Forsthuber, M.; Scheinast, M.; et al. Lead and neurodevelopment: exposure, biomarkers, and mechanisms. Int. J. Hyg. Environ. Health 2021, 238, 113846.
19. Braun, J.M.; Gray, K. Challenges to studying the health effects of early-life environmental chemical exposures on child development. PLoS Biol. 2017, 15, e2002800.
20. Heindel, J.J.; Blumberg, B. Environmental obesogens: mechanisms and controversies. Annu. Rev. Pharmacol. Toxicol. 2019, 59, 89–106.
21. Bellinger, D.C. Very low lead exposures and children's neurodevelopment. Curr. Opin. Pediatr. 2008, 20, 172–177.

doi:10.20944/preprints202601.0267.v1

22. Grandjean, P.; Landrigan, P.J. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 2014, 13, 330–338.
23. Parent, A.S.; Teilmann, G.; Juul, A.; et al. The timing of normal puberty and the age limits of sexual precocity. Endocr. Rev. 2003, 24, 668–693.
24. Sørensen, K.; Mouritsen, A.; Aksglaede, L.; et al. Recent secular trends in pubertal timing. Endocr. Rev. 2012, 33, 117–171.
25. Ahmed, S.; Mahabbat-e Khoda, S.; Rekha, R.S.; et al. Arsenic-associated oxidative stress in human placenta. Environ. Health Perspect. 2010, 118, 258–264.
26. Tolins, M.; Ruchirawat, M.; Landrigan, P.J. The developmental neurotoxicity of arsenic. Ann. Glob. Health 2014, 80, 303–314.
27. Notario-Barandiaran, L.; et al. Arsenic exposure and neuropsychological outcomes in children. Toxics 2025, 13, 542.
28. Kippler, M.; et al. Placental transfer of cadmium and effects on fetal development. Environ. Health Perspect. 2010, 118, 284–289.
29. Rocha-Amador, D.; et al. Oxidative stress markers in arsenic-exposed children. Environ. Res. 2011, 111, 799–805.
30. Liu, J.; et al. Sex differences in neurotoxicity of lead. Environ. Health Perspect. 2013, 121, 1150–1156.
31. Senut, M.C.; et al. Epigenetics of early-life lead exposure. Epigenomics 2012, 4, 665–674.
32. Joubert, B.R.; et al. DNA methylation in newborns and early-life exposures. Environ. Health Perspect. 2016, 124, 37–45.
33. Joubert, B.R.; et al. DNA methylation in newborns and early-life exposures. Environ. Health Perspect. 2016, 124, 37–45.
34. 34. Huang, W.; Igusa, T.; Wang, G.; Buckley, J.P.; Hong, X.; et al. In-utero co-exposure to toxic metals and micronutrients on childhood risk of overweight or obesity: new insight on micronutrients counteracting toxic metals. Int. J. Obes. 2022, 46, 1435–1445.
35. Eckert-Lind, C.; Busch, A.S.; Petersen, J.H.; Biro, F.M.; Butler, G.; Bräuner, E.V.; Juul, A. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: A systematic review and meta-analysis. Int. J. Epidemiol. 2020, 49, 834–849.
36. Johnson, M.D.; Kenney, N.; Stoica, A.; et al. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat. Med. 2003, 9, 1081–1084.
37. Ahmed, S.; Moore, S.E.; Kippler, M.; et al. Arsenic exposure and cell-mediated immunity in pre-school children in rural Bangladesh. Toxicol. Sci. 2014, 141, 166–175.
38. Wu, T.; Buck, G.M.; Mendola, P. Blood lead levels and age at menarche in U.S. girls: The Third National Health and Nutrition Examination Survey, 1988–1994. Environ. Health Perspect. 2003, 111, 737–741.
39. Afeiche, M.; Peterson, K.E.; Sánchez, B.N.; et al. Prenatal lead exposure and pubertal development in girls from Mexico City. Environ. Res. 2011, 111, 106–113.
40. Mouritsen, A.; Aksglaede, L.; Sørensen, K.; Mogensen, S.S.; Leffers, H.; Main, K.M.; Frederiksen, H.; Andersson, A.M.; Juul, A. Hypothesis: Exposure to endocrine-disrupting chemicals during fetal life may impair reproductive development in girls. Hum. Reprod. Update 2010, 16, 386–405.
41. Rice, D.; Barone, S. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ. Health Perspect. 2000, 108, 511–533.
42. Sanders, T.; Liu, Y.; Buchner, V.; Tchounwou, P.B. Neurotoxic effects and biomarkers of lead exposure: A review. Rev. Environ. Health 2009, 24, 15–45.
43. Grandjean, P.; Landrigan, P.J. Developmental neurotoxicity of industrial chemicals. Lancet 2006, 368, 2167–2178.
44. Lanphear, B.P.; Hornung, R.; Khoury, J.; Yolton, K.; Baghurst, P.; Bellinger, D.C.; Canfield, R.L.; Dietrich, K.N.; Bornschein, R.; Greene, T.; et al. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ. Health Perspect. 2005, 113, 894–899.
45. Canfield, R.L.; Henderson, C.R.; Cory-Slechta, D.A.; Cox, C.; Jusko, T.A.; Lanphear, B.P. Intellectual impairment in children with blood lead concentrations below 10 µg per deciliter. N. Engl. J. Med. 2003, 348, 1517–1526.

46. Rodríguez-Barranco, M.; Lacasaña, M.; Aguilar-Garduño, C.; Alguacil, J.; Gil, F.; González-Alzaga, B.; Rojas-García, A.; Pérez-Gómez, B. Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: A systematic review and meta-analysis. Sci. Total Environ. 2013, 454–455, 562–577.
47. Vrijheid, M.; Casas, M.; Gascon, M.; Valvi, D.; Nieuwenhuijsen, M. Environmental pollutants and child health—A review of recent concerns. Int. J. Hyg. Environ. Health 2016, 219, 331–342.
48. Selevan, S.G.; Kimmel, C.A.; Mendola, P. Identifying critical windows of exposure for children's health. Environ. Health Perspect. 2000, 108, 451–455.
49. Newbold, R.R.; Padilla-Banks, E.; Jefferson, W.N. Environmental estrogens and obesity. Mol. Cell. Endocrinol. 2009, 304, 84–89.
50. Ramos, P.; Santos, C.; Pinto, E.; Almeida, A.; Castilho, M.; Silva, J. Metals exposure and childhood obesity: A systematic review. Sci. Total Environ. 2015, 512–513, 341–351.
51. Zhou, X.; Jin, H.; Zhang, Y. Urinary metals are associated with obesity in U.S. children and adolescents: A cross-sectional study. Nutr. Res. 2024, 132, 40–52.
52. Sexton, K.; Needham, L.L.; Pirkle, J.L. Human biomonitoring of environmental chemicals. Am. Sci. 2004, 92, 38–45.
53. Centers for Disease Control and Prevention (CDC). Blood lead levels in children. MMWR Recomm. Rep. 2012, 61, 1–24.
54. Grandjean, P.; Weihe, P.; White, R.F.; Debes, F. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 1997, 19, 417–428.
55. Needham, L.L.; Grandjean, P.; Heinzow, B.; et al. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ. Sci. Technol. 2011, 45, 1121–1126.
56. Järup, L.; Åkesson, A. Current status of cadmium as an environmental health problem. Toxicol. Appl. Pharmacol. 2009, 238, 201–208.
57. Navas-Acien, A.; Francesconi, K.A.; Silbergeld, E.K.; Guallar, E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ. Res. 2011, 111, 110–118.
58. Barr, D.B.; Wilder, L.C.; Caudill, S.P.; Gonzalez, A.J.; Needham, L.L.; Pirkle, J.L. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 2005, 113, 192–200.
59. Eastman, R.R.; Jursa, T.P.; Benedetti, C.; Lucchini, R.G.; Smith, D.R. Hair as a biomarker of environmental manganese exposure. Environ. Sci. Technol. 2013, 47, 1629–1637.
60. Gil, F.; Hernández, A.F.; Márquez, C.; et al. Biomonitorization of mercury in hair of children: methodological considerations. Sci. Total Environ. 2011, 409, 484–491.
61. Woodruff, T.J.; Zota, A.R.; Schwartz, J.M. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ. Health Perspect. 2011, 119, 878–885.
62. O'Neill, M.S.; Jerrett, M.; Kawachi, I.; et al. Health, wealth, and air pollution: advancing theory and methods. Environ. Health Perspect. 2003, 111, 1861–1870.
63. Sanders, A.P.; Claus Henn, B.; Wright, R.O. Perinatal and childhood exposure to cadmium, manganese, and metal mixtures and effects on cognition and behavior: A review of recent literature. Curr. Environ. Health Rep. 2015, 2, 284–294.
64. Gibb, H.; O'Leary, K.G. Review of health effects of manganese exposure. Neurotoxicology 2014, 41, 1–7.
65. Vigeh, M.; Smith, D.R.; Hsu, P.C. How does cadmium exposure affect child development? Clin. Biochem. Rev. 2011, 32, 1–11.
66. Morrison, K.M.; et al. Neurodevelopmental toxicity of lead and other heavy metals: a review. Paediatr. Child Health 2010, 15, 567–574.
67. Ortiz, E.; Rengel, R.; Ali, S.F. Lead-induced neurotoxicity. Adv. Neurobiol. 2018, 21, 23–47.
68. Cadet, J.L.; et al. Neurotoxicity of arsenic: a genomic perspective. Mol. Neurobiol. 2012, 45, 589–595.
69. Sly, P.D.; Carpenter, D.O. Scientific evidence supports a causal association between environmental contaminants and adverse respiratory health outcomes in children. J. Toxicol. Environ. Health B 2012, 15, 9–39.

70. Ruckart, P.Z.; et al. Neurodevelopmental effects of prenatal mercury exposure: a systematic review of the evidence. Paediatr. Child Health 2014, 19, 342–352.
71. Guxens, M.; et al. Prenatal lead exposure and children's neurodevelopment: systematic review. Epidemiology 2016, 27, 566–580.
72. Sanders, A.P.; Claus Henn, B.; Wright, R.O. Perinatal and childhood exposure to cadmium, manganese, and metal mixtures and effects on cognition and behavior: A review of recent literature. Curr. Environ. Health Rep. 2015, 2, 284–294.
73. Gu, Q.; Liu, J.; Zhang, X.; Huang, A.; Yu, X.; Wu, K.; Huang, Y. Association between heavy metals exposure and risk of attention deficit hyperactivity disorder (ADHD) in children: a systematic review and meta-analysis. Eur. Child Adolesc. Psychiatry 2025, 34, 921–941.
74. Xu, X.; Hu, H.; Kearney, G.; Kan, H.; Sheppard, L. A meta-analysis of the relationship between blood lead levels and intelligence in children. Environ. Health Perspect. 2019, 127, 126002.
75. Rice, D.; Barone, S. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ. Health Perspect. 2000, 108, 511–533.
76. Vrijheid, M.; Casas, M.; Gascon, M.; Valvi, D.; Nieuwenhuijsen, M. Environmental pollutants and child health—A review of recent concerns. Int. J. Hyg. Environ. Health 2016, 219, 331–342.
77. Nigg, J.T.; Nikolas, M.; Knottnerus, G.M.; et al. Confirmation and extension of association of blood lead with attention-deficit/hyperactivity disorder and symptom domains at population-typical exposure levels. J. Child Psychol. Psychiatry 2010, 51, 58–65.
78. Rodriguez-Barranco, M.; Gil, F.; Hernández, A.F.; et al. Postnatal arsenic exposure and attention and executive function in school-age children. Environ. Res. 2016, 147, 268–276.
79. Zangiabadian, M.; Ghaffari Jolfayi, A.; Ainoun, M.; et al. The association between heavy metal exposure and obesity: a systematic review and meta-analysis. J. Diabetes Metab. Disord. 2023, 22, 1–15.
80. Xiao, Y.; Shen, S.; Wang, Q.; et al. In utero exposure to multiple metals and childhood overweight and obesity: evidence from a prospective birth cohort. J. Expo. Sci. Environ. Epidemiol. 2022, 32, 865–874.
81. De Bont, J.; Casas, M.; Barrera-Gómez, J.; et al. Metal exposure and childhood overweight and obesity: a mixture analysis in a population-based study. Environ. Int. 2019, 125, 386–395.
82. Grau-Pérez, M.; Kuo, C.C.; Gribble, M.O.; et al. Association of low-moderate arsenic exposure and insulin resistance in children. Environ. Health Perspect. 2017, 125, 067003.
83. Tinkov, A.A.; Filippini, T.; Ajsuvakova, O.P.; et al. Cadmium and atherosclerosis: a review of toxicological mechanisms and epidemiological evidence. Environ. Res. 2018, 162, 240–260.
84. Canova, C.; de Bont, J.; Casas, M.; et al. Prenatal exposure to arsenic and blood lipid profile in children. Environ. Res. 2020, 182, 109090.
85. Zoeller, R.T.; Brown, T.R.; Doan, L.L.; et al. Endocrine-disrupting chemicals and public health protection: a statement of principles. Endocrinology 2012, 153, 4097–4110.
86. Kippler, M.; Engström, K.; Mlakar, S.J.; et al. Sex-specific effects of early life cadmium exposure on DNA methylation and metabolic pathways. Environ. Health Perspect. 2013, 121, 142–147.
87. Gore, A.C.; Chappell, V.A.; Fenton, S.E.; et al. Executive summary to EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 2015, 36, 593–602.
88. Diamanti-Kandarakis, E.; Bourguignon, J.P.; Giudice, L.C.; et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev. 2009, 30, 293–342.
89. Stoica, A.; Katzenellenbogen, B.S.; Martin, M.B. Activation of estrogen receptor-α by the heavy metal cadmium. Mol. Endocrinol. 2000, 14, 545–553.
90. Takser, L.; Mergler, D.; Lafond, J. Very low level environmental exposure to lead and mercury disrupts the endocrine system in rat offspring. Toxicol. Lett. 2005, 154, 235–246.
91. Wu, T.; Buck, G.M.; Mendola, P. Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Environ. Health Perspect. 2003, 111, 737–741.
92. Selevan, S.G.; Rice, D.C.; Hogan, K.A.; et al. Blood lead concentration and delayed puberty in girls. N. Engl. J. Med. 2003, 348, 1527–1536.
93. Wolff, M.S.; Britton, J.A.; Boguski, L.; et al. Environmental exposures and puberty in inner-city girls. Environ. Res. 2008, 107, 393–400.

94. Byrne, C.; Divekar, S.D.; Storchan, G.B.; et al. Cadmium—a metallohormone? Toxicol. Appl. Pharmacol. 2009, 238, 266–271.
95. Boas, M.; Feldt-Rasmussen, U.; Main, K.M. Thyroid effects of endocrine disrupting chemicals. Mol. Cell Endocrinol. 2012, 355, 240–248.
96. Rahman, A.; Vahter, M.; Ekström, E.C.; et al. Association of arsenic exposure during pregnancy with fetal loss and infant death. Am. J. Epidemiol. 2007, 165, 1389–1396.
97. Llop, S.; Ballester, F.; Murcia, M.; et al. Prenatal exposure to endocrine disruptors and pubertal development. Environ. Int. 2013, 53, 1–9.
98. Eckert-Lind, C.; Busch, A.S.; Petersen, J.H.; Biro, F.M.; Butler, G.; Bräuner, E.V.; Juul, A. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: A systematic review and meta-analysis. Int. J. Epidemiol. 2020, 49, 834–849.
99. Lanphear, B.P.; Rauch, S.; Auinger, P.; Allen, R.W.; Hornung, R.W. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health 2018, 3, e177–e184.
100. Braun, J.M.; Gennings, C.; Hauser, R.; Webster, T.F. What can epidemiological studies tell us about the impact of chemical mixtures on human health? Environ. Health Perspect. 2016, 124, A6–A9.
101. Ben-Shlomo, Y.; Kuh, D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int. J. Epidemiol. 2002, 31, 285–293.
102. Clougherty, J.E. A growing role for gender analysis in air pollution epidemiology. Environ. Health Perspect. 2010, 118, 167–176.
103. Braveman, P.A.; Cubbin, C.; Egerter, S.; et al. Socioeconomic status in health research: one size does not fit all. JAMA 2005, 294, 2879–2888.
104. National Research Council. Science and Decisions: Advancing Risk Assessment. National Academies Press: Washington, DC, 2009.
105. World Health Organization. Preventing disease through healthy environments: Exposure to lead. World Health Organization: Geneva, 2019.
106. Landrigan, P.J.; Fuller, R.; Acosta, N.J.R.; et al. The Lancet Commission on pollution and health. Lancet 2018, 391, 462–512.
107. Lanphear, B.P. Low-level toxicity of chemicals: no acceptable levels? PLoS Biol. 2017, 15, e2003066.
108. Tsoi, M.F.; Cheung, C.L.; Cheung, T.T.; Cheung, B.M. Continual decrease in blood lead level in Americans: United States NHANES 1999–2014. Am. J. Med. 2016, 129, 1213–1218.
109. Ericson, B.; Dowling, R.; Dey, S.; et al. A meta-analysis of blood lead levels in low- and middle-income countries. Lancet Planet. Health 2021, 5, e145–e153.
110. Braun, J.M.; Wright, R.J.; Just, A.C.; et al. Assessing impacts of early-life environmental exposures on neurodevelopment: the application of advanced statistical methods. Environ. Health 2016, 15, 102.
111. Vahter, M.; Skröder, H.; Rahman, S.M.; et al. Prenatal arsenic exposure, micronutrients, and fetal growth. Environ. Health Perspect. 2020, 128, 017007.
112. Braveman, P.A.; Arkin, E.; Proctor, D.; et al. Systemic and structural racism: definitions, examples, health damages, and approaches to dismantling. Health Aff. 2022, 41, 171–178.
113. Morello-Frosch, R.; Shenassa, E.D. The environmental "riskscape" and social inequality. Environ. Health Perspect. 2006, 114, 1150–1153.
114. Vrijheid, M.; Slama, R.; Robinson, O.; et al. The human early-life exposome (HELIX): project rationale and design. Environ. Health Perspect. 2014, 122, 535–544.
115. Taylor, K.W.; Joubert, B.R.; Braun, J.M.; et al. Statistical approaches for assessing health effects of environmental chemical mixtures in epidemiology: lessons from an innovative workshop. Environ. Health Perspect. 2016, 124, A227–A229.
116. Buck Louis, G.M.; Sundaram, R. Exposome: time for transformative research. Stat. Med. 2012, 31, 2569–2575.
117. Grandjean, P.; Bellanger, M. Calculation of the disease burden associated with environmental chemical exposures. Environ. Health 2017, 16, 123.
118. National Academies of Sciences, Engineering, and Medicine. Using 21st Century Science to Improve Risk-Related Evaluations. National Academies Press: Washington, DC, 2017.

119. Heindel, J.J.; Blumberg, B.; Cave, M.; et al. Metabolism disrupting chemicals and metabolic disorders. Reprod. Toxicol. 2017, 68, 3–33.