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Prenatal exposure to metals and autism spectrum disorder: Current status and future directions

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Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with genetic and environmental contributors to etiology. Many metals have the potential to be neurotoxic, and their exposures are widespread. The field of metals exposure and ASD research is emerging, and in this review article, we assess the current state of the literature, with emphasis on the previous 2 years. Epidemiology studies are discussed with respect to exposure timing, exposure matrix, and outcome assessment. Toxicology studies are described for exposure dosing and timing, as well as behavioral and molecular outcomes. Further epidemiological and toxicological investigations can identify the timing and importance of metals as ASD risk factors and uncover biological mechanisms for risk mitigation and therapeutic strategies.

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1. Autism spectrum disorder and etiologic factors

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by deficits in social communication and interaction as well as restrictive, repetitive patterns of behavior, interests, or activity [1]. ASD affects 1 in 54 U.S. children and is 4.3 times more prevalent in boys [2] and poses a substantial public health burden with lifelong social and economic consequences to affected individuals and their communities [3]. Between 1990 and 2019, the social lifetime costs of ASD in the United States exceeded $7 trillion [4]. Although changes in diagnostic practices and cultural awareness may have contributed to increased ASD prevalence over time, much of this increase is unexplained, suggesting ASD incidence is increasing [5,6]. Prevention through identification of modifiable risk factors for ASD could curtail increasing ASD prevalence and its costly consequences.

The etiology of ASD includes genetic and environmental risk factors [7]. Parental factors associated with the risk of ASD include advanced age, aspects of metabolic syndrome and diabetes, nutritional factors, infections, time between pregnancies, and medication use during pregnancy [7–9]. Adverse pregnancy outcomes and perinatal exposure to air pollution and heavy metals are also associated with ASD [7–9]. Important neurodevelopment occurs during the fetal period [10], and exposure to environmental insults, including metals, *in utero* likely plays a role in ASD etiology [7,9,11]. Toxicological mechanisms implicated in ASD include immune dysregulation, hyperserotonemia, mitochondrial dysfunction, and oxidative stress [11].

Women of childbearing age in the United States experience widespread exposure to metals with higher concentrations among pregnant than nonpregnant women [12,13]. Metals can be characterized as trace essential (e.g. Co, Cu, Fe, Mn, Mo, Se, and Zn) and possibly essential (e.g. organic As, Cr, Ni, and Sn) if they are required by the human body in small quantities. Harm can occur for those that are deficient or for those that are too highly exposed [14]. Other metals are considered trace nonessential metals (e.g. Pb, Cd, and Hg), as they have no normal physiologic role in the human body and no levels are required for normal function. Many metals are known neurotoxicants [15], and emerging evidence suggests they may have a role in ASD specifically. In the following sections, we review recent evidence from epidemiologic and toxicologic studies linking metals to ASD and ASD-related phenotypes.

2. Metals exposures and ASD: epidemiologic evidence

Epidemiologic studies of metals exposure and ASD are emerging as a promising area of research (Table 1).

Table 1 Metals exposure and autism spectrum disorder in epidemiology studies in the last 2 years.

Reference	Study design	Population	Exposure and timing	Exposure matrix	Accounted for metals co-exposures	Neurodevelopmental outcome	Main findings
McCanlies, 2019 [21]	Case–control	537 cases: children aged 2–5 years with ASD 414 age-, sex-, and region-matched typically developing controls ascertained from birth records	Parental occupational exposure to metals (general) assigned by industrial hygienists based on reported job title and duties, no information on timing of exposure	Occupational history	No	ASD diagnosis	Occupational metals exposure in mothers or fathers (separately analyzed) was not associated with odds of ASD
Fruh, 2019 [16]	Cohort	1006 mother–child pairs from Project Viva, a US-based cohort	Maternal erythrocyte lead concentration measured in second trimester	Blood	Yes Mn, Hg	SDQ in mid-childhood (median 7.7 years), rated by parent and teacher separately	1 IQR (0.6 μg/dL) increase in maternal erythrocyte lead associated with 0.18 (95% CI: 0.03–0.33) point higher parent-rated emotional problems subscore 1 IQR increase associated with 0.72 (95% CI: 0.16–1.27) point higher parent-rated total score among girls Associations between maternal erythrocyte lead and total score or other subscales were not significant for parent- or teacher-rated SDQ
Long, 2019 [29]	Case–control	Participants of the Historic Birth Cohort at Statens Serum Institute born between 1995 and 1999 with sufficient amniotic fluid samples: 37 cases with ASD 50 controls frequency-matched on child age, gender, and maternal age	Concentration of Fe, Cu, Zn, Se, Cr, Mn, As, Cd, and Pb in amniotic fluid sample measured via inductively coupled plasma mass spectrometry	Amnionic fluid	Mixed Individual exposures PCA mixture exposure	ASD diagnosis	Large individual effect sizes that failed to meet statistical significance: 1 μg/L increase in As has OR of 1.50 (95% CI: 0.92–2.42) 1 μg/L increase in Pb has OR of 1.30 (95% CI: 0.66–2.58) Principal component one, associated with perfluoroalkyl substances, Cu, Fe, and estrogenic activity, moderately inversely associated with ASD with OR = 0.1 (FDR q = 0.10)
Doherty, 2020 [18]	Cohort	371 participants in the New Hampshire Birth Cohort Study	As, Cu, Mn, Pb, Se, Zn measured in: Maternal toenail at 27 weeks' gestation (reflects periconception/early pregnancy) Maternal toenail at 4 weeks postpartum (reflects mid-pregnancy) Infant toenail at 6 weeks (reflects late pregnancy/ early neonatal exposure)	Toenail	Yes	Total SRS-2 score at 3 years	Children with both high As and Se in infant toenails had highest SRS score (greater deficits), children with low As and high Se had lowest SRS score Higher Mn in male infant toenail associated with higher SRS-2 score No associations found for metals measured in maternal toenail at either time point and SRS-2 score

Frye, 2020 [20]	Case–control	27 cases with ASD (13 with neurodevelopmental regression) 7 typically developing controls	Pb, Ni, Cr, Mg, Mn, Cu, Zn, Sr, Sn, and Ba measured in deciduous (baby) teeth	Teeth	No	ASD diagnosis VABS SRS ABC	In unadjusted analysis, cases had lower Ni, Cu, and Cu-to-Zn ratio during the prenatal period and lower Cu during the early postnatal period No significant associations for other metals and case status
Strain, 2021 [17]	Cohort	1237 mother–child pairs from Seychelles Child Development Study, a population with high fish consumption	Total mercury (primarily representing MeHg) measured from maternal hair at birth	Hair	No	SRS-2 and SCQ at 7 years	1 IQR increase in maternal hair MeHg was associated with 0.05 fewer points (better score) on square-root SCQ ($p = 0.04$), although this was not significant after adjusting for multiple testing Maternal hair MeHg was not associated with SRS-2 score
Jedynak, 2021 [19]	Cohort	708 mother–child pairs from five European cohorts	As, Cd, Cs, Co, Cu, Pb, Mn, Hg, and Mo measured in maternal blood collected during pregnancy or cord blood	Blood	Yes	SDQ between 3 and 7 years of age, externalizing and internalizing subscores only	In LASSO model with all exposures, Cu was associated with externalizing behavior. 1 IQR higher blood Cu concentration (μg/dL) associated with a 0.9 (95% CI: 0.82–0.99) times lower probability of SDQ externalizing score increasing by one unit. Other metals were not associated with SDQ externalizing score

ASD, autism spectrum disorder; Mn, manganese; Hg, mercury; SDQ, Strengths and Difficulties Questionnaire; IQR, interquartile range; Fe, iron; Cu, copper; Zn, zinc; Se, selenium; Cr, chromium; As, arsenic; Cd, cadmium; Pb, lead; PCA, principal component analysis; SRS-2, Social Responsiveness Scale; OR, odds ratio; FDR, false discovery rate; Mn, manganese; Ni, nickel; Mg, magnesium; Sr, strontium; Sn, tin; Ba, barium;,; VABS, Vineland Adaptive Behavior Scale; ABC, aberrant behavior checklist; MeHg, methylmercury; SCQ, Social Communication Questionnaire; Cs, cesium; Co, cobalt; Mo, molybdenum.

For example, in 1006 mother–child pairs from a Massachusetts cohort, maternal erythrocyte Pb concentrations during the second trimester were associated with mid-childhood scores on the Strengths and Difficulties Questionnaire (SDQ; Box 1) [16]. An interquartile range (IQR) increase in maternal Pb blood concentration was associated with a 0.18 (95% confidence interval [CI]: 0.03–0.33) point increase in the parent-rated emotional problems subscale of the SDQ and a 0.72 (95% CI: 0.16–1.27) point increase on the parent-rated SDQ total score among girls [16]. Maternal hair collected at birth provided untimed prenatal methylmercury (MeHg) exposure in 1237 mother–child pairs from a population with high fish consumption and MeHg exposure [17]. An IQR increase in MeHg was nominally associated with a 0.05-point decrease in Social Communication Questionnaire (SCQ; Box 1) score at 7 years of age. The authors hypothesized that the neurodevelopmental benefits of fish consumption associated with polyunsaturated fatty acids outweighed the negative effects of MeHg, and evidence of interaction was suggestive.

In a North American cohort of 371 children, maternal toenail clippings measured metals exposure at 27 weeks' gestation, reflecting periconceptional and early pregnancy exposure [18]. These were paired with maternal toenail clippings at 4 weeks postpartum, reflecting middle and late pregnancy exposure, and infant toenail clippings at 6 weeks, reflecting perinatal exposure. An IQR increase in perinatal exposure to Mn measured via infant toenail was suggestively associated with 0.09-point increase in the Social Responsiveness Scale (SRS-2; Box 1) score. Infants with the highest infant toenail levels of both As and Se metals had the highest SRS-2 scores, and infants with low As and high Se had the lowest SRS-2 scores, although this was not statistically significant. In a pooled analysis of 708 mother–child pairs across five European cohorts, maternal blood metals measures between 14 and 27 weeks' gestation or cord blood at birth were tested in an exposome-wide association study of ASD with 39 other chemicals [19]. An IQR increase in $\log_2$ blood Cu concentration was associated with a 0.9 (95% CI: 0.82–0.99) times lower probability of the SDQ externalizing behavior score increasing by one unit. Complex exposure timing and mixture issues influence the potential for replication testing across studies, the available sample sizes within studies, the testing of non-linear dose-response relationships, and the testing of interactions between essential and non-essential metals.

Biomarkers reflecting a perinatal exposure history can be efficiently implemented in retrospective case–controls studies of ASD using biosamples collected at birth or in childhood. Progressive laser ablation of infant decidual teeth can provide repeated metals exposure measures at trimester resolution. In a small case–control study, increased prenatal Cu and Cu-to-Zn ratio exposure measured in infant decidual teeth was associated with increased Vineland Adaptive Behavioral Scales (VABS; Box 1) communication subscale score [20]. In a Dutch nested case–control study of 37 ASD cases and 50 matched controls, biobank amniotic fluid samples collected during screening or diagnostic amniocentesis were analyzed for antenatal metals exposure. Individually, amniotic As and Pb levels were suggestively associated with ASD with odds ratios (ORs) of 1.5 and 1.3, respectively. In a sensitivity analysis to account for co-exposures, principal component 1, associated with perfluoroalkyl substances, Cu, Fe, and estrogenic activity, was inversely associated with ASD (OR = 0.1, q = 0.1), possibly suggesting selection bias from a competing risk such as miscarriage. Parental occupational history between 3 months prepregnancy and birth was recently used as a semiquantitative measure of metals exposure in a population-based retrospective case–control study of ASD in California with 537 cases and 414 matched controls, although no association was found [21]. Limited power due to small sample size and low metals exposure among participants could explain the inconsistency of statistically significant findings, despite appreciable or even large effect sizes. The heterogeneity of study designs complicates meta-analysis to improve power or replicate results.

A variety of molecular endpoints can be used to understand ASD, although not all techniques have been extended to metals. For example, in primary human

Box 1. Questionnaires in recent neurobehavioral research.

Social Responsiveness Scale, second edition (SRS-2): Identifies the presence and severity of social impairment within the autism spectrum and differentiates it from that which occurs in other disorders in individuals aged 2.5 years or older. Higher scores reflect greater social impairment.

Social Communication Questionnaire (SCQ): A tool to screen for autism spectrum disorders, based on the Autism Diagnostic Interview for ages 4+ years with mental development levels of age 2+ years. Higher scores reflect greater communication and social impairments.

Vineland Adaptive Behavior Scales, second edition (VABS): A semistructured interview to aid the diagnosis of autism spectrum disorders and intellectual and developmental disabilities and delays in those aged 0–90 years. Higher scores reflect greater functioning.

Strengths and Difficulties Questionnaire (SDQ): A behavioral screening questionnaire for children aged 3–16 years with subscales covering emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Higher scores reflect greater difficulties, except for the prosocial subscale. Importantly, the SDQ does not discriminate between ASD and other psychiatric disorders [16], thus the specificity of SDQ findings to ASD must be confirmed.

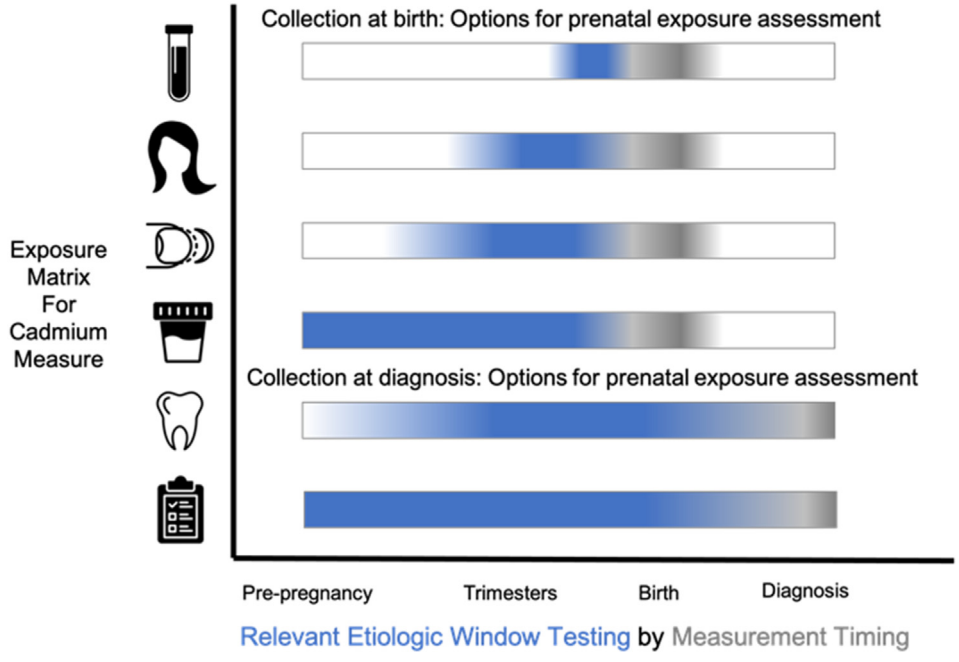
peripheral blood mononuclear cells taken during adolescence, the same study that evaluated metals exposure in deciduous teeth found prenatal Zn and Mn and postnatal Ni and Sr were associated with mitochondrial dysfunction and prenatal Mn and Pb and postnatal Mn with decreased glycolysis (Sn, increased glycolysis) in ASD cases with regression [20]. Future human research on metals and ASD may consider molecular intermediates, including ASD gene expression [22], Shank3 protein expression [23], epigenetics [24], neuroinflammation [25], metabolomics [26], neuroimaging [27], and neuroendocrine hormone levels [28]. Including molecular intermediates in epidemiology research can contribute evidence for causality or mechanism between metals and ASD.

Recent epidemiology studies of metals exposure and ASD vary greatly by metal(s) assayed, exposure matrix, timing of exposure measure, ASD outcome measure, and timing of outcome assessment. A range of metals have assayed in various matrices, including maternal and fetal toenail [18], blood [19], deciduous teeth [20], or amniotic fluid [29] (Figure 1). Metal concentrations are typically quantified using highly parallel mass spectrometry techniques with simultaneous measures of multiple metals. However, which metals are analyzed depends on *a priori* hypotheses, detection rates, the metals' half-lives, and the ability to faithfully model mixtures. Each matrix–metal biomarker combination reflects a unique exposure timing and history, even for metals measured at the same time point. Case–control studies use ASD diagnosis as the outcome, whereas neurobehavioral questionnaires are more common in cohort studies to reveal subclinical outcomes or progression. Less commonly studied in humans are neuroanatomic or molecular endpoints. The existence of few biomarker-based prospective, longitudinal studies of metals exposure and ASD assessment makes current findings difficult to interpret and limits the ability to replicate findings in independent cohorts or meta-analyses. Considerable progress has been made in leveraging the strengths and weaknesses of various metal–matrix combinations to triangulate the timing and nature of potential etiologic exposures. Given the heterogeneity of ASD as a health outcome, epidemiological investigation informed by advanced exposure assessment provides a way forward to understand and prevent ASD.

3. Metals exposures and ASD: toxicologic evidence

Experimental animal models are used to understand human disease based on conserved genetic features, molecular pathways, and behavioral patterns, which are of particular interest in recent ASD research [30] (Table 2). Modeling ASD in model organisms can be difficult because diagnosis is based on a collection of human social and attention behaviors, and there is no single objective biomarker for ASD. Behavioral

Figure 1



Measurement timing and relevant etiologic window testing by metals exposure matrix in epidemiologic study designs. For illustrative purposes, we highlight exposure and biosample half-life information for the metal cadmium specifically, and we highlight measures taken at birth or postnatal. The exposure matrices from top to bottom are blood, hair, toenail clippings, urine, tooth, and questionnaire.

Table 2 Recent metals exposure and autism spectrum disorder behavioral phenotypes in toxicology studies.

Reference	Model system	Exposure	Outcome	Main findings
Chen, 2019 [32]	C57BL/6 J mice (only male offspring)	Gestational day 9.5 to postnatal day 21 via osmotic pump: 1.2 ng/day Pb or Pb/BDE209 (a PBDE) mixture	Three-chambered social testing (sociability), marble burying (repetitive behavior, perseverative/impulsive behavior), grooming (repetitive behavior)	Pb and Pb/BDE209 mice buried more marbles than controls ($P < 0.001$) No differences in sociability, grooming between treatment groups
Zhang, 2019 [33]	C57BL/6 J mice	F0 generation: for period of 1, 3, or 5 months before mating and during pregnancy via drinking water: 0, 1, 10, or 100 μg/L Cd F1 generation: continued 0, 1, 10, or 100 μg/L Cd in drinking water until postnatal week 10	At 8–9 weeks of age: open-field test (anxiety), Morris water maze (spatial learning and memory)	Mice exposed to 100 μg/L for 5 months had lower distance traveled in center zone and time spent in central zone, no significant differences for mice exposed to lower doses or for shorter periods
Tartaglione, 2020 [34]	Wistar rats	4 weeks before breeding until postnatal day 23 via drinking water: 50 mg/L (5 mg Pb/kg body weight per day) Pb	At juvenile/adult stage: open-field test (locomotor activity), Y-maze (spatial working memory and explorative activity), elevated plus maze (anxiety), novel object recognition (recognition memory), Morris water maze (spatial learning and memory)	Pb-exposed rats entered fewer total arms in Y-maze ($P = 0.02$) and took more time to reach target quadrant ($P < 0.01$) in Morris water maze. Female Pb-exposed rats visited open arms of elevated plus maze less ($P < 0.01$) and spent less time there ($P < 0.01$) No difference in open-field test performance
Lian, 2021 [35]	267 wild-born harbor seal pups in central California admitted for stranding or maternal separation	Total Hg measured in hair (partly lanugo hair grown *in utero*) and blood	Response to tactile stimulation, movement, swimming, interactions with other seals, and feeding ability scored from 1 (normal) to 4 (most abnormal) while in ICU and pool (less critical)	Hg in whole blood negatively associated with response to tactile stimulation ($P < 0.001$) and movement ($P < 0.001$) in ICU stage Hg in hair and in blood associated with response to tactile stimulation ($P = 0.01$ for hair, $P = 0.002$ for blood), and Hg in blood associated with movement ($P = 0.04$) in pool stage Hg in hair or blood not associated with swimming behavior, interaction with other seals, or feeding behavior

PBDE, polybrominated diphenyl ethers; Hg, mercury; Pb, lead;,; F0, parental generation; F1, offspring generation.

hallmarks of ASD related to deficits in social communication and interaction and restricted or repetitive interests, however, are face valid constructs in animal models [31]. For example, in mice, increased marble burying or self-grooming behaviors are measures of repetitive or stereotyped behaviors, and sociability assays test for deficits in social interaction. Zebrafish is a popular and efficient ASD model, although studies of metals have yet to be published [30]. Alternative neuroanatomical or molecular endpoints can also be more readily assessed in model organisms to reveal the underlying mechanisms of ASD-like behaviors.

In C57BL/6 J mice male offspring, perinatal exposure to a low dose of Pb (1.2 ng/day) or a mixture of Pb and BDE209 (0.12 ng/day), a flame retardant, led to an increase in stereotyped repetitive behavior and spatial learning impairment [32]. Decreased hippocampal neurogenesis was also observed in the Pb-exposed groups. BDE209 exposure alone did not produce statistically significant differences, suggesting Pb drove the mixture effects. The Pb/BDE209 mixture, however, did produce a synergistic increase in proinflammatory cytokine production, highlighting the importance of studying mixtures of various compositions. Offspring of C57BL/6 J mice randomly assigned to 100 μg/L Cd exposure, a human-relevant dose, through drinking water for 5 months before mating and then continually exposed *in utero* until PND 70 had increased signs of anxiety [33]. Other evidence of neurotoxicity included

altered liver function and increased corticosterone among females of the same exposure group. Recent results in mice indicate deleterious neurobehavioral outcomes consistent with ASD characteristics in humans can occur at doses relevant to current human metals exposure.

Male and female offspring of Wistar rats exposed to 50 mg/L Pb through drinking water for 4 weeks before mating continually exposed until PND 23 exhibited less explorative behavior in adolescence and spatial learning impairment compared with vehicle controls [34]. Exposed female offspring had lower spatial learning efficiency and recognition memory, higher anxiety, and altered glutaminergic receptor distribution at the postsynapse on PND 23. In 267 rehabilitated seal pups, whole blood Hg was negatively associated with response to tactile stimulation and movement in the intensive care unit (ICU) stage of recovery [35]. Hg measured in lanugo hair, partially reflecting gestational exposure, was inversely associated with response to tactile simulation and movement in the pool recovery stage. Female pups had higher levels of hair and blood Hg. These results in male and female animals underscore sex as an important factor in the relationship between metals and ASD.

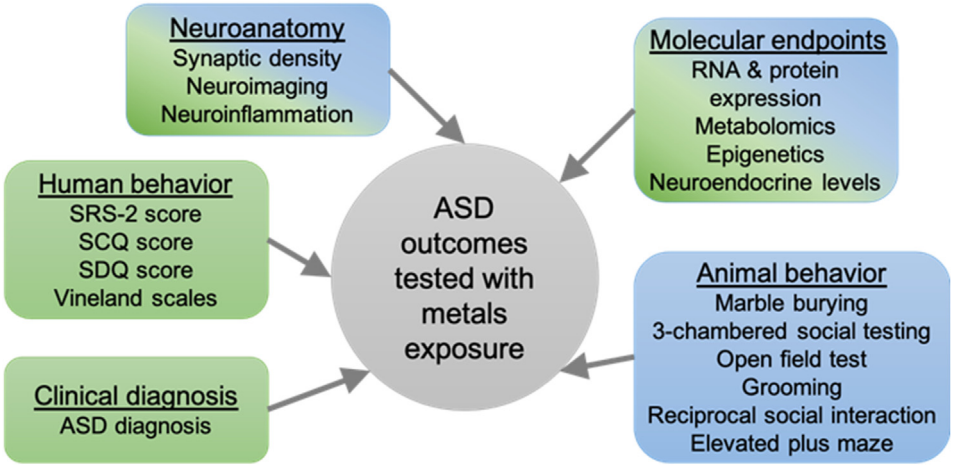
Common animal models applied to ASD and metals research include mouse and rat rodent models. Importantly, many previous toxicology studies were conducted in male animals only. Metals can have sex-dependent effects on the developing brain [36], and future work should continue to consider female animals. Animal toxicology studies assess behaviors related to ASD and neurobehavioral development, such as repetitive or social behaviors. Including molecular and neuroanatomical outcomes in animal studies allows for additional comparison to human research. For example, perinatal Pb exposure in mice caused elevated proportions of hippocampal oligodendrocytes at 5 months of age as well as altered gene expression, measured using single cell RNA sequencing [37]. Higher throughput toxicological models include primary cells, model organs, or cell lines that can stand in for relevant tissues in organisms affected by disease. For example, rat brain hippocampal cell culture models treated with metal mixtures had altered synapsis, apoptotic nuclei, dendritic fragmentation, altered expression of synaptic receptors, and altered Shank scaffold protein expression [38]. Continuing to link molecular factors, anatomy, and behavior in metal toxicology studies will provide mechanistic insights that inform and complement human ASD etiology studies.

Emerging translational molecular and neuroanatomic biomarkers of neurotoxicity [39] and synaptic function [40] may also provide insight into ASD. Prior studies have emphasized the use of metal exposure levels that are comparable to humans. The recent toxicology work reviewed here maintained continuous exposure before mating, through gestation, and during weaning; thus, narrowing in on the etiologic time window is difficult. Successful methods development in animal toxicology research on air pollution and ASD [41] can be extended to metals. The complexity of exposure mixtures is especially challenging in animal studies, requiring large sample sizes or higher throughput next-generation toxicology screens with ASD-relevant endpoints. Animal and *in vitro* toxicology studies are essential to understanding the mechanistic neurotoxicity of metals, and the specificity to ASD is an exciting application.

4. Summary and future directions

Metals exposure and ASD research is complex and requires multiple study approaches. *In vivo* toxicology studies have tremendous scientific merit to provide

Figure 2



Triangulation of evidence for metals in ASD across model systems and ASD-relevant endpoints. Green represents evidence available in human studies, and blue represents evidence available in animal studies.

longitudinal sampling of disease target tissues, a causal framework, and multiple measures in one experiment (exposure, pathology, and behavior). However, they are limited in their ability to translate across species to human ASD [42]. Similarly, epidemiology studies provide evidence that is directly relevant to humans; however, they are often limited to ascertaining exposure in peripheral or surrogate tissues [42]. Thus, the advantages and tradeoffs of toxicology and epidemiology methods are complementary. To gain a complete picture of the role of metals in ASD, it is essential that we continue to assess and combine findings across fields (Figure 2).

There is emerging, although modest, evidence linking prenatal metals exposure to ASD. Few studies have been conducted, and the question is technically challenging to investigate [11,43]. To build on this evidence, future epidemiologic studies require advanced planning and expertise. To test an association between pregnancy exposure to metals and postnatal ASD diagnoses requires longitudinal sampling or advanced retrospective exposure assessment. Exposure assessment for each metal relies on noninvasive biosampling or biomarker measures with unique challenges related to the sample matrix and the metal's half-life [44]. In addition, pregnant women are exposed to mixtures of environmental factors simultaneously that complicate analysis and increase the dimensionality of treatments in toxicological studies [45]. Higher throughput toxicant screening assays with ASD-relevant endpoints will be especially important for efficiently considering mixtures. Heterogeneity in ASD phenotypes complicates outcome ascertainment in epidemiological or animal model settings [46,47]. Susceptibility to metals toxicity could vary by nutritional status or genetic variability in metals processing. Future research can include genetic susceptibility to ASD or to metals toxicity in metals research [48]. Finally, exposure to many metals is associated with likelihood of miscarriage, which may result in underestimation or even reversal of associations between metals exposures and postnatal outcomes [49]. As new studies become available, the breadth of available literature will expand. For example, a prospective cohort study of pregnant women with high levels of mercury exposure in Suriname will have neurodevelopmental examinations conducted on children (N = 992) in the next several years [50]. Similarly, enriched-risk ASD sibling studies in the United States will add prenatal metals exposure assessments [51,52]. Risk assessment in neurotoxicology is particularly complex [53]. Further epidemiological and toxicological investigations can identify the timing and importance of environmental risk factors and uncover biological mechanisms for risk mitigation and therapeutic strategies and appropriate risk communication.

Authors' contributions

M.D.F. and K.M.B. conceptualized the article. R.H. performed the literature review and developed the tables. K.A.C. and K.M.B. drafted the article. K.M.B. developed the figures. R.H. and M.D.F. edited the article. M.D.F. provided funding.

Declaration of competing interest

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

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* of special interest
** of outstanding interest

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