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REVIEW

Critical period of exposure to mercury and the diagnostic of autism spectrum disorder: A systematic review

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Abstract

Autism spectrum disorder (ASD) is characterized by repetitive behaviors and deficits in social interaction. Its etiology is not completely clear, but both genetic and environmental factors contribute to and influence its development and course. The increased number of autism cases in recent years has been strongly associated with increased exposure to heavy metals. Mercury (Hg) has gained prominence in the scientific literature as a result of its presence as an urban pollutant and well-described neurotoxicity. This review assessed the relationship between Hg exposure in the pre- and post-natal period and ASD. The systematic review identified observational clinical studies and pre-clinical trials in journals indexed in the PubMed, Embase, ProQuest, and LILACS databases. The aim of this study was to investigate the association between exposure to Hg and ASD and to define the critical period of exposure. A total of 57 articles were selected for this review, with 35 articles (61.40%) identifying a positive association between ASD and Hg, while 22 articles (38.60%) did not find the same outcome. The biological samples most used to analyze Hg body burdens were hair (36.84%) and blood (36.84%). Most case–control studies found an increase in Hg levels in individuals with ASD who were exposed to a polluted environment in the post-natal period. Taken together, the studies suggest that these patients have a deficient detoxification system, and this could worsen the symptoms of the disorder. However, new studies addressing the influence of Hg on the post-natal nervous system and its relationship with ASD should be carried out.

KEYWORDS
autistic, heavy metals, mercury, neurodevelopment, neurotoxicity, risk factor

Abbreviations: ADDM, autism and developmental disabilities monitoring; ADI-R, revised diagnostic interview for autism; ADOS-G, program diagnostic observation of autism–generic; ASD, autism spectrum disorder; ATEC, autism treatment assessment list; CARS, childhood autism rating scale; CDC, center for disease control and prevention; DSM, diagnostic and statistical manual of mental disorders; EtHg, ethylmercury; Hg, mercury; ICD, international classification of diseases; ICP-MS, inductively coupled plasma mass spectrometry; MeHg, methylmercury; MgCl2, mercuric chloride; MRI, brain magnetic resonance imaging; MT, metallothionein; M-CHAT, modified children's autism checklist; NOS, Newcastle–Ottawa Scale; SCQ, social communication questionnaire; SHANK3, multiple ankyrin repeat domains 3; SRS, social responsiveness scale; TRI, toxic release inventory; Zn, zinc.

Bruna Bittencourt Netto and Elica Pizzolo da Silva contributed equally to this work.

This Review is part of the special issue "Autism Spectrum Disorder".

1 | INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a deficit in behavioral and social interaction, associated with repetitive attitudes and restrictive interests (Hodges et al., 2020). The prevalence of ASD has dramatically increased in recent years and globally is estimated to be at approximately 1/100 cases (Zeidan et al., 2022). In 2000, the prevalence was 1 autistic child in every 150 children, whereas in 2020, it increased to 1 in 36 live births in the United States, and the rate was 4.2 times higher among boys than among girls (Maenner et al., 2023). In addition, this increase has led to strained health services and a mandate for a greater inclusion of autistic individuals in society. However, because the pathophysiology of ASD is still not very well defined, the genetic and environmental factors that may cause this comorbidity have yet to be fully elucidated (Chiarotti & Venerosi, 2020).

Factors that contribute to ASD are complex and include the environment, genetics, and biological influences (Almandil et al., 2019). To date, ASD etiology has been associated with about 800 genes (Butler et al., 2015). High prevalence of ASD is inherent to individuals with fragile X syndrome and mutations in chromosome 22, leading to the malfunction of the SH3 and multiple ankyrin repeat domains 3 (SHANK3) gene (Waye & Cheng, 2018). Regarding environmental factors, advanced parental age (Hultman et al., 2011), childbirth complications (trauma, ischemia, and hypoxia; Hultman et al., 2002), maternal obesity (Krakowiak et al., 2012), and toxicant exposures, such as heavy metals (Kalkbrenner et al., 2014), are significant risk factors for ASD.

Another factor implicated in the increased risk of ASD is micronutrient deficiency, both during pre-natal and post-natal periods. Dietary deficiencies, such as a lack of zinc, are associated with alterations in neurological functions and neuronal maturation (Faber et al., 2009; Wuehler et al., 2005). Around 50% of children with ASD have a zinc deficiency, and this seems to be implicated in adverse effects on behavior and the overall health of individuals (Faber et al., 2009; Wuehler et al., 2005).

Furthermore, neurodevelopment can be negatively affected when there is a zinc deficiency or exposure to heavy metals such as mercury (Hg; Dufault et al., 2009). This is because these factors can induce epigenetic changes that interfere with the expression of the zinc-dependent metallothionein (MT) gene, which is the protein that enables the excretion of heavy metals from the body (Dufault et al., 2012). Another way in which MT's function can be altered is by specific heavy metals such as lead, copper, cadmium, silver, bismuth, and Hg, which are capable of displacing the Zn atom in the MT molecule. Consequently, this protein is unable to bind to the heavy metals present in the body and transport them for excretion (Coyle et al., 2002).

Researchers using animal models have shown that zinc deficiency, along with oxidative stress, leads to brain damage because together they cause disruption of the blood–brain barrier (Noseworthy & Bray, 2000). Another study demonstrated that maternal zinc supplementation can prevent common deficits associated with ASD in an animal model of ASD (Vyas et al., 2020). Finally, zinc deficiency is indirectly related to the glutamatergic system, as it interacts with Shank proteins, which regulate synapses in this system (Vyas et al., 2020). The corticostriatal glutamatergic pathway has been associated with the repetitive behaviors observed in individuals with ASD, and not coincidentally, these patients exhibit increased striatal activity (Langen et al., 2009, 2014).

Exposure to heavy metals has gained prominence, mainly caused by the increased concentration of these elements in urban areas and their neurotoxic effects characteristic of neurodevelopmental diseases (Modabbernia et al., 2017). Hg is the most cited metallic element among many other factors that can influence the continuous neuronal cytotoxicity evidenced in ASD, especially in its most available organic form, methylmercury (MeHg) (Blaurock-Busch et al., 2011; Ijomone et al., 2020). MeHg is formed after a reaction of metallic Hg with organic molecules in the aquatic environment. Consumption of MeHg occurs by ingestion of fish and consumption from polluted water (Kern et al., 2016). Furthermore, there is evidence that this heavy metal can cause loss of neuronal connectivity through a direct insult and neuroinflammatory process, a mechanism shared in ASD etiology (Kern et al., 2012).

Another organic molecular form of Hg is ethylmercury (EtHg). Thimerosal, which contains EtHg, has been used as a preservative in medicines, cosmetics, and vaccines. It is worth mentioning that there is no relationship between vaccination or thimerosal and ASD, as previously demonstrated by a meta-analysis study (Taylor et al., 2014). EtHg and MeHg cause similar neural toxicities, such as local oxidative stress and changes in mitochondrial permeability, culminating in cell death (Dórea et al., 2013; Migdal et al., 2010).

As a result of the increased number of ASD cases in recent years, there has also been a growing effort to identify potential triggering factors that could be avoided or treated. One of the most researched aspects has been the cumulative effect of Hg in biological systems and its potential to cause oxidative stress and neuroinflammation. Therefore, addressing this relationship was deemed important for improving the understanding of the risk associated with Hg and elucidating modifiable risk factors for ASD. Thus, this systematic review assesses the vulnerability to exposure to Hg in the pre- and post-natal period and its relationship with ASD.

2 | MATERIALS AND METHODS

The present systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines, as stated in a prospective protocol (Supplemental Digital Content 1). International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42021229805.

2.1 | Literary search strategy

This systematic review of clinical studies was conducted with an overview of Hg, MeHg, and EtHg exposure and its relationship to the development of ASD. The studies were identified by searching international and national databases, including PubMed/National Library of Medicine, PsycINFO, and EMBASE (Ovid) databases. The research was restricted to the years 1985–2021. No language or publication restrictions have been applied. The search strategy is presented in Supplemental Digital Content 2.

2.2 | Eligibility criteria

Original peer-reviewed articles and abstracts were included without language and year restrictions that addressed ASD and Hg. We omitted review articles, in vitro studies, and studies that did not include the terms ASD or Hg.

2.3 | Screening

A total of 339 articles were included in the primary screening, and 57 articles were included in the review (Figure 1). Besides, a detailed description of screening, article selection, and data extraction is presented in Supplemental Digital Content 2.

2.4 | Article selection

The titles and abstracts were mainly screened for eligibility by four authors (BBN, EPS, CLG, and DD). A detailed description of article selection is presented in Supplemental Digital Content 2.

2.5 | Data extraction

The data were extracted from the comprehensively reviewed journal articles methodically. The extracted variables included were selected as follows: study design, research type, sample/sex, age, type of biological sample analyzed, the method used to analyze, type of derivative Hg compound, period of Hg exposure, type of Hg exposure, ASD diagnostic method, and the relationship between Hg and ASD (Supplemental Digital Content 3).

Furthermore, a summary table of articles was structured, analyzing the evidence regarding the positive or negative relationship between ASD and Hg exposure (Table 1). For this, several factors were examined, such as study model, study type, analyzed structure,

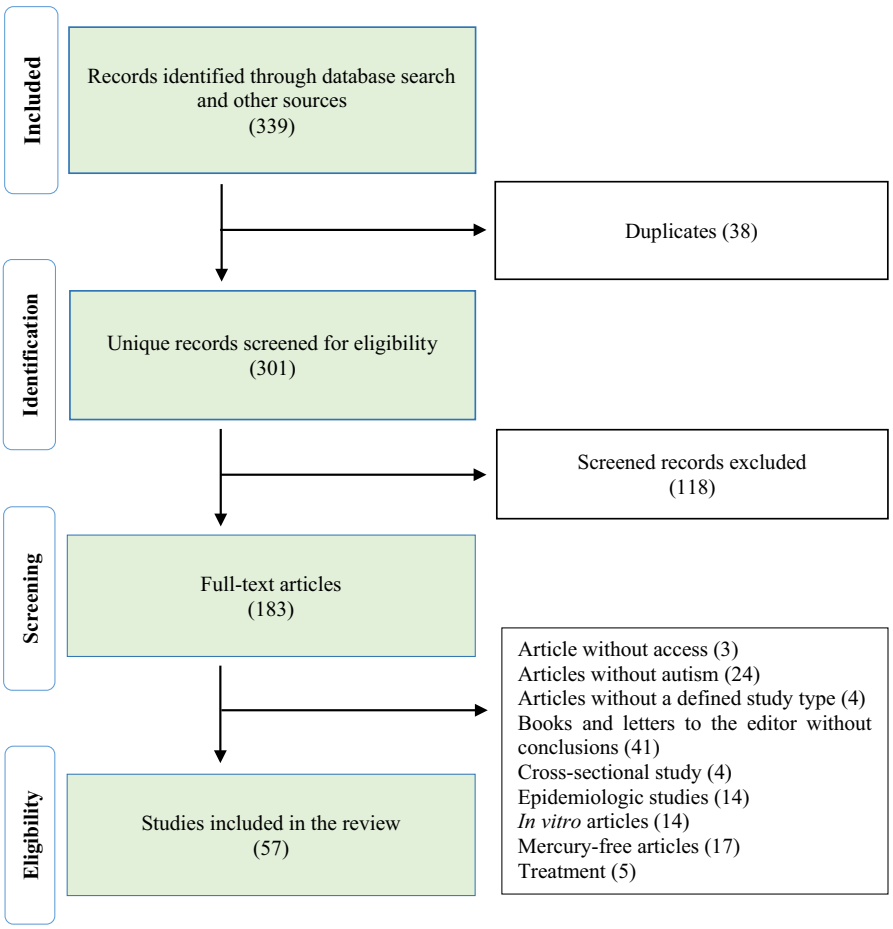

FIGURE 1 Flowchart of study selection.

TABLE 1 Summary of articles relating signs of autism and exposure to mercury.

Factors	Evidence of a positive relationship between autism and Hg *n* (%)	Evidence of a negative relationship between autism and Hg *n* (%)
Study model		
Animal	8 (14.03)	3 (5.26)
Human	27 (47.37)	20 (35.09)
Type of study		
Cohort study	2 (3.51)	3 (5.26)
Case–control study	25 (43.86)	16 (28.07)
Preclinical study	8 (14.03)	3 (5.26)
Structure analyzed		
Urine	5 (8.77)	4 (7.02)
Hair	14 (24.56)	7 (12.28)
Blood	10 (17.54)	11 (19.30)
Brain	5 (8.77)	3 (5.26)
Teeth	2 (3.51)	1 (1.75)
Kidney	1 (1.75)	1 (1.75)
Nails	1 (1.75)	-
Liver	1 (1.75)	-
Exposure markers		
Average levels of toxic metals	27 (47.37)	19 (33.33)
Urinary porphyrin concentration	2 (3.51)	3 (5.26)
Metallothionein (MT) and Anti-MT	-	1 (1.75)
Inflammatory process	2 (3.51)	-
Unmentioned and others	5 (8.77)	2 (3.51)
Exposed compound form		
Organic	1 (1.75)	4 (7.02)
Inorganic	10 (17.54)	3 (5.26)
All the forms mentioned above	24 (42.10)	15 (26.32)
Exposure period		
Pre-natal and post-natal	11 (19.30)	8 (14.03)
Post-natal	22 (38.60)	8 (14.03)
Pre-natal	2 (3.51)	5 (8.77)
Type of exposure		
Medical exposure to thimerosal vaccine or antibiotics	9 (15.79)	5 (8.77)
Dental exposure to amalgam	3 (5.26)	3 (5.26)
Exposure to the diet of fish consumption	5 (8.77)	8 (14.03)
Environmental exposure to pollutants or contaminated water	24 (42.10)	9 (15.79)

exposure marker, form of the exposed compound, exposure period, and type of exposure. The analysis of evidence was conducted through a basic calculation of the percentage of each studied factor in relation to the total number of articles analyzed.

2.6 | Quality assessment of the included studies

The quality of case–control and cohort studies included was assessed using the 9-star Newcastle–Ottawa Scale (9-star NOS). For the pre-clinical studies included, the adapted 9-star NOS was used. The full score was 9 stars, studies with scores of 7–9 stars have the lowest risk of bias and represent the highest quality, studies with scores of 4 to 6 stars have a moderate risk of bias and quality, and studies with scores less than 4 stars have the highest risk of bias and the lowest quality (Saghazadeh et al., 2017; Saghazadeh & Rezaei, 2017a, 2017b). Two authors (BBN and EPS) separately assessed study quality, and discrepancies were resolved by a third author (CLG). A detailed description of these scales is presented in Supplemental Digital Content 4.

3 | RESULTS

3.1 | Selection of studies and identification

A total of 57 articles were identified in this search; 35 articles intimated a positive relationship between Hg and ASD, while 22 articles did not reach the same conclusion. Only 11 pre-clinical studies were selected for analysis compared to 46 studies with autistic people. The predominant clinical study design was case–control (41 articles), followed by cohort studies (5 articles). Seven pre-clinical studies in animal models performed socio-behavioral and/or post-mortem brain analysis that included tissues from the hippocampus, amygdala, cortex, evaluation of neurotransmitters, and neural morphology. The majority of the clinical studies informed on the concentration of Hg in blood, urinary, hair, and dental amalgams, as shown in Table 1. Regarding the association between exposure to Hg and the development of ASD, the articles evaluated which form of exposure was related to its bodily accumulation. Among the means of exposure were vaccines containing thimerosal, dietary exposures caused by the consumption of seafood, and environmental exposures to atmospheric pollutants or contaminated water, or all of these considered as general exposure. It is important to highlight that from the 57 studies selected, 14 studies assessed thimerosal present in vaccines and antibiotics, which contain low doses of Hg. Among these 14 studies, 9 provided positive evidence for the association between Hg and ASD, while 5 presented negative evidence. However, most of them did not provide the relationship between the specific dose and time during which Hg was administered and risk for ASD.

Most studies used inductively coupled plasma mass spectrometry (ICP-MS) to quantify the concentration of Hg in biological fluids. ICP-MS is an analytical technique that evaluates several elements in a single sample with the ability to detect very low thresholds. The

diagnosis of ASD and assessment of symptom severity in the studies were achieved primarily through the International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), Revised Diagnostic Interview for Autism (ADI-R), Program Diagnostic Observation of Autism–Generic (ADOS-G), Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), Social Communication Questionnaire (SCQ), Autism Treatment Assessment List (ATEC), and Modified Children's Autism Checklist (M-CHAT).

The 9-star NOS tool was used to assess the studies' quality. NOS is an ongoing collaboration between the Universities of Newcastle, Australia, and Ottawa, Canada. It was developed to assess the quality of non-randomized studies with its design, content, and ease of use. In the present systematic review, 34 studies were evaluated as having high methodological quality (≥7 stars), 20 had a moderate methodological quality (between 6 and 4 stars), and only 3 had a low methodological quality (<4 stars), as detailed in Supplemental digital contents 3 and 4.

3.2 | Blood

Of the 57 articles selected, only 21 articles evaluated the relationship between Hg levels in blood samples and ASD. An association was found in 10 studies, while the other 11 failed to demonstrate a similar outcome (Table 1). Mostafa et al. (2016) considering all forms of exposure, studied a group of individuals with ASD, diagnosed by the DSM-IV, containing 62 boys and 22 girls aged between 3 and 10 years, with an age-matched control group containing 60 boys and 24 girls. ASD children had significantly higher blood Hg levels than neurotypical children. The level correlated linearly and positively with the severity of the disorder. A similar result was shown by Qin et al. (2018), evaluating environmental pollution and dietary exposure, where 34 ASD children (20 boys and 14 girls) aged between 3 and 5 years had higher accumulated levels of several heavy metals, including Hg, compared to unaffected children in the control group.

In contrast, Berman et al. (2008), in a pre-clinical study with SJL/J mice, concluded that neonatal exposure to thimerosal did not significantly alter Hg blood, brain, and kidney levels. No complex behavioral deficit or abnormal somatic growth of brain structures was observed after exposure to thimerosal, concluding that there was no influence of vaccine Hg on the etiology of neurodevelopmental disorders, especially ASD. Yau et al. (2014) analyzed the concentration of Hg in maternal serum in mid-pregnancy and neonatal blood shortly after birth, which were environmentally exposed to Hg. Three groups of children were studied: 84 children with ASD, 49 children with intellectual deficits, and 159 controls from the general population. The results of maternal and neonatal blood Hg levels did not reach statistical significance to conclude a relationship between this element and ASD prevalence. However, the authors stated that there is a need for additional studies that address a larger sample size and a covariate measurement for the proper association between Hg and ASD.

3.3 | Urine

From the 57 articles selected, only 9 articles analyzed the concentration of this metal in the urine. While 5 articles demonstrated that there was a relationship between ASD and urinary Hg, another 4 did not show the same result (Table 1). The methods of analysis of urinary material varied among them; while some measured Hg directly in the sample, others measured the levels of urinary porphyrins associated with Hg intoxication. Kern et al. (2011) compared the level of these urinary biomarkers in 20 children with ASD and 20 control children, aged 2–13 years, who received routine childhood vaccines. ASD individuals had increased levels of urinary porphyrins, intimating a possible association between this heavy metal and ASD. Blaurock-Busch et al. (2011) analyzed heavy metal levels in urine and hair by ICP-MS, considering all forms of exposure. The study included 25 ASD children (22 boys and 3 girls), aged between 3 and 9 years, and 25 control children. Hair and urine Hg levels were higher in autistic individuals, indicating that previous and immediate exposure to Hg was higher in children with ASD.

On the other hand, Wright et al. (2012) carried out a case–control study composed of a group diagnosed with ASD through the ICD-10, ADI-R, and ADOS-G with 54 participants (42 boys and 12 girls) and another control group composed of siblings of these children (42), children from regular schools (121), and children from special schools (34), with the aim of testing possible changes in the Hg concentrations in the patient's urine, taking into account the number of amalgams. No statistically significant differences were found in creatinine-corrected urinary Hg between groups compared with control, neurotypical children, and siblings, regardless of whether or not the analysis was controlled for age, sex, and amalgam fillings. Urinary porphyrins undergo specific changes in the pattern of excretion associated with prolonged exposure to Hg; thus, Woods et al. (2010) measured and compared urinary porphyrin and urinary Hg concentrations in 117 neurotypical children and 100 children with ASD, who could have been exposed to all forms of contamination. Several porphyrins were associated with ASD, but no differences were found between the neurotypical and the affected groups with respect to urinary Hg levels.

3.4 | Hair

Among the 57 articles, only 21 searched for a relationship between Hg levels in hair and ASD. Of these, 14 studies found this association, while 7 studies did not show it (Table 1). Yassa (2014) addressed potential environmental risk factors for ASD, such as pregnancy-related information and environmental exposures to toxins, through a questionnaire. They measured the concentration of Hg in hair and blood of ASD and neurotypical children aged between 3 and 10 years. In addition to observing higher levels of heavy metals in ASD, they also showed that by decreasing blood metal concentrations with chelating agents, ASD symptoms were attenuated. The work included an ASD group of 53 boys and 22 girls and a control

group of 31 boys and 27 girls, ages 3 to 7. In both groups, 100 mg of hair was collected and analyzed by ICP-MS. The analysis showed that Hg concentrations were significantly higher in children with ASD compared to control children.

Gil-Hernández et al. (2020) conducted a case–control study on 108 children (ages 2–6 years), 54 children with ASD and 54 without associated pathologies, with the same environmental exposure, vaccines, and without amalgams. In addition to measuring Hg in hair, the article also reported urinary Hg levels. There were no significant differences between the level of Hg in both hair and urine of children with ASD and neurotypical children. Kern et al. (2007) compared the level of sulfhydryl-reactive metals, including Hg, in the hair of 90 children, 45 diagnosed with ASD and 45 neurotypical, considering environmental exposure, food, and vaccines. Although the group with ASD had mean Hg values slightly below the other group's values, the statistical difference did not reach statistical significance, concluding that there was no association between Hg and ASD.

3.5 | Brain

Examining the eight articles that analyzed brain structures to verify the relationship between Hg exposure and ASD, only five met the association criteria, while three did not reach the same result (Table 1). These eight studies were carried out in animals exposed to Hg and later behaviorally tested to evaluate autistic-like behaviors. Olczak et al. (2011) documented that administration of thimerosal in the early post-natal period caused neurobehavioral impairments and neurochemical changes in the brain, depending on the dose and sex. In this study, 42 rats (21 males and 21 females) were exposed to thimerosal based on pediatric vaccination schedules. This led to locomotor and social impairments compatible with ASD and dopaminergic alterations characteristic of neurocognitive disorders. Another study addressed the interaction between three risk factors for ASD, genetics, sex, and exposure to MeHg during the pre-and post-natal period in rats (Biamonte et al., 2014). After the proposed periods, the animals underwent behavioral tests and their brains, kidneys, and livers were dissected for analysis. A subtoxic dose of MeHg did not cause an ASD-like phenotype in exposed animals; however, at higher MeHg exposures, loss of sociability and increasingly restricted behaviors were identified in male mice.

Gadad et al. (2015) in a preclinical study failed to note an association between Hg and ASD when analyzing exposure to thimerosal-containing vaccines in rhesus monkeys. This article included 79 rhesus monkeys across 6 groups: 16 primates in the control group, 12 in the pediatric vaccination schedule of the 1990s, 12 in the quadruplicate vaccination schedule, 12 in the group exposed only to thimerosal-containing vaccines, 26 in a vaccine group against measles, mumps, and rubella, and 12 Rhesus monkeys in a group following the 2008 vaccination schedule. Using behavioral tests and later anatomopathological evaluation, the authors concluded that no cellular or neuronal alterations were inherent to the cerebellum, hippocampus, and amygdala in animals after vaccination schedules. Furthermore, there were no alterations in social behavior, and there were no significant differences in negative behaviors (e.g., stereotyping) between animals in the control and experimental groups. Zhang et al. (2012) examined whether developmental exposure to mercuric chloride (HgCl2) induced TEA-like behavior in offspring derived from a cross between behaviorally normal mice (B6) and TEA-like BTBR mice (B6BF1 offspring). The animals underwent several behavioral tests and neuroinflammation measurements. Exposure to Hg during development increased the social capacity of the female offspring. However, it did not change the social behavior of the male offspring, and cytokine levels were not altered on post-natal day 21 or 70, suggesting that neuroinflammation was not induced in this exposure scenario. Table 1 brings the summary of data that state a positive or negative relationship between Hg and ASD.

3.6 | Relationship between pre-natal and post-natal exposure to Hg and ASD

Among the 57 studies selected, 30 had a case–control studies design that analyzed environmental exposure, especially post-natal, and ASD. Of these, 20 were positively associated with environmental heavy metal pollution and ASD. Pre-natal and peri-natal exposures to air pollutants have been shown to adversely affect childbirth outcomes and may contribute to the prevalence of ASD. Mainly, post-natal exposures to environmental factors such as air pollutants, contaminated water (Alabdali et al., 2014; Biamonte et al., 2014), and thimerosal (Li, Qu, et al., 2014) have been shown to adversely affect developmental parameters and may contribute to the prevalence of ASD in humans and animal models. Furthermore, it is important to highlight that the consumption of seafood during the gestational period by mothers and during early childhood by children appears to be significantly associated with the development of ASD. Therefore, the high levels of Hg in these individuals are mainly caused by a change in the ability to excrete Hg (Blanchard et al., 2011). However, some studies present controversial results, as no changes were observed in relation to metal levels in urine, blood, and hair after environmental exposure to metals, whether through air pollution or fish consumption (Gil-Hernández et al., 2020; Ip et al., 2004; Kern et al., 2007; Rahbar et al., 2013).

4 | DISCUSSION

To understand the pathophysiological process of neurodevelopmental diseases, it is essential to know the critical period of exposure to possible risk factors (Rice & Barone, 2000). During pregnancy, the placenta, in one of its roles, prevents the passage of pathogenic mediators, thus protecting the fetus (Caserta et al., 2013). However, this barrier cannot prevent the transfer of several pollutants (Hamid et al., 2019). Therefore, the developing fetus and infant are at potential risk of environmental toxic effects as a result of their immature system (Amaya et al., 2013).

During the gestational period, excessive consumption of teratogenic drugs, family genetics, and maternal clinical pathologies are factors that have been proven to cause fetal harm (Wang et al., 2017). The initial months of embryogenesis are the most sensitive to neurotoxic actions from external factors, especially in the first trimester, when the neuronal tube is developing. Changes during this process can lead to severe brain damage causing deformations and dysfunction in motor and neurocognitive systems (Copp & Greene, 2010; Santos et al., 2007). In the perinatal period, factors associated with maternal and fetal complications during childbirth include preeclampsia and fetal distress (Wang et al., 2017). After birth, the neonatal brain continuously develops for an extended period of time (Adlard et al., 2014). Nonetheless, with suboptimal hepatic metabolism and incomplete blood–brain barrier formation, the infant remains vulnerable to exposure to environmental toxins, mainly via breastfeeding (Grzunov Letinić et al., 2016; Jain & Lacy, 2005).

Environmental pollutants are toxic substances that reach the environment through anthropogenic or natural sources (Abalaka et al., 2020). Among these pollutants are heavy metals, which in recent years have been a great focus of attention because of their increased environmental levels and the threat to the health of both children and adults (Annamalai & Namasivayam, 2015). Heavy metals can reach the human body by inhalation, ingestion, and dermal exposure (Ab Razak et al., 2015). Health problems caused by heavy metals occur secondary to their accumulation in various organs, including the central nervous system, impairing the function and structure of signaling pathways, perturbing the physiology of the organism, and contributing to DNA damage (Amadi et al., 2019; Rehman et al., 2018; Tchounwou et al., 2012). In addition, the accumulation of these compounds, especially Hg, in children with ASD, compared with neurotypical children, provides a possible positive neuropathological relationship between them (Yassa, 2014).

The duration of exposure is a parameter that varies widely among studies, ranging from chronic exposures through amalgams and pollution to acute exposures, such as consumption of contaminated fish and vaccines. Developmental changes associated with post-natal environmental exposure are already well documented, such as learning difficulties, limb deformities (Eto, 2000), microcephaly (Kondo, 2000), neuronal atrophy, migration-affected neurons, underdevelopment of brain regions (Harada, 1978), and when there is exposure in the pre-natal period, there is a delay in global development (Ramirez et al., 2003). Children's exposure to Hg through amalgam fillings, a smaller type of exposure, increases urinary Hg levels but does not appear to cause cognitive and behavioral changes (Bellinger et al., 2006; DeRouen et al., 2006). Finally, there is exposure to Hg through vaccines and medications, although some studies have studied the relationship between vaccines and autism, high-quality ecological and cohort studies have not found evidence to support this type of statement (Gerber & Offit, 2009; Parker et al., 2004). Interestingly, even after some countries have removed thimerosal from the vaccination program, autism rates are increasing year after year (Madsen et al., 2003; Stehr-Green et al., 2003). The Hg is not biodegradable, can be toxic even at low concentrations, primarily to young children (Al Osman et al., 2019; Hsueh et al., 2017), and persist in the environment and organisms through bioaccumulation (Abeysinghe et al., 2017).

Interestingly, when analyzing the data obtained, patients with an autistic phenotype have difficulty metabolizing/detoxifying Hg, culminating in high levels in both urine and blood (Kern et al., 2011; Yalçın et al., 2020). Furthermore, changes in the intestinal permeability of these atypical individuals may contribute to greater absorption of toxic substances (Khaled et al., 2016; Lakshmi Priya & Geetha, 2011; Sasser et al., 1978). Interestingly, studies have demonstrated that children with autism have a greater use of antibiotics, which contributes to the dysregulation of the intestinal microbiota, and consequently impacts the excretion of Hg (Adams et al., 2003; Konstantareas & Homatidis, 1987).

According to Woods (1996), higher urinary levels of Hg are correlated with higher levels of Hg in tissues and, furthermore, they are related to the severity of neurobehavioral deficits (Geier & Geier, 2006). The chemical Hg forms explain their differences in toxicity, effects, absorption, and target organ predilection (Aaseth et al., 2018). Although elemental Hg can be ingested without causing significant problems, when converted into inorganic Hg, it becomes toxic (Bernhoft, 2012; Bjørklund et al., 2018; Magos & Clarkson, 2006; Rice et al., 2014). Furthermore, organic forms of Hg are even more toxic than inorganic forms (Ijomone et al., 2020), especially those linked to the alkyl chemical group (EtHg and MeHg), with a high affinity for lipid-rich organs such as the brain (Sweet & Zelikoff, 2001). The primary source of exposure to MeHg, for example, is through oral ingestion, where the gastrointestinal wall is the entry point for this metal into the systemic bloodstream (Vázquez et al., 2014).

Upon reaching the gastrointestinal tract, bacteria and yeast can convert inorganic Hg into organic MeHg (Dufault et al., 2009). This compound, when transported into the bloodstream, is distributed throughout various tissues and can cross the blood–brain and placental barriers, potentially impacting neurodevelopment (Dufault et al., 2009; Gonzalez-Estecha et al., 2015). Once deposited in the brain, MeHg returns to its inorganic state, leading to cerebral oxidative stress and neuronal impairment (Dufault et al., 2009).

The exposure period varies widely among studies, but according to the findings, there are a greater number of studies showing that the post-natal period is when stronger evidence is found, suggesting a potential relationship between Hg and ASD. This may occur as a result of the vulnerability of infants who are still in development and also because of the deficit in heavy metal excretion in individuals with ASD. The Hg from sources such as dietary intake can cause damage to the central nervous system in adults, leading to cognitive decline (Siblerud et al., 2019). It can also adversely affect the neurodevelopment of infants and children during the pre-natal period (Clarkson, 1997; Oken & Bellinger, 2008), impacting various neurological functions. This is because Hg can be transferred pre-natally via the placenta to the fetus or post-natally, in addition to environmental exposure (Dorea, 2004; Esteban-Vasallo et al., 2012), leading to deleterious effects that alter the structure and functionality of the nervous system, which can persist throughout life,

such as in the case of ASD (Sanfeliu et al., 2003). Interestingly, childhood Hg poisoning known as acrodynia or "pink disease," caused by excessive exposure to Hg, highlights the vulnerability of children compared to adults (Lai et al., 2016; Shandley & Austin, 2011). Shandley and Austin (2011), investigating the Hg-ASD hypothesis using a cohort of descendants (1086 children and 1366 grandchildren) of acrodynia survivors, concluded that there is a hereditary and genetic basis for the Hg-ASD relationship. They observed a significantly higher prevalence of autism among the grandchildren of disease survivors compared to the general population (Shandley & Austin, 2011).

The heavy metal excretion system appears to be compromised in individuals with ASD. Interestingly, previous studies have identified that individuals with ASD have lower zinc levels and alterations in the MT protein (Adams et al., 2009; Faber et al., 2009; Li, Qu, et al., 2014; Yasuda et al., 2011). Thus, the system appears to be compromised in these patients and this demonstrates a potential contribution to the pathophysiology of the disorder (Blaylock, 2009; Faber et al., 2009; Kidd, 2002) since the MT proteins and zinc play an important role in protecting not only against heavy metals but also against free radicals and inflammation (Coyle et al., 2002). Moreover, other factors are involved in the maintenance of high metal levels in the body of ASD patients (D. Geier et al., 2012; Kaur et al., 2021; Ye et al., 2017). Kern et al. (2013) demonstrated that ASD children show decreased glutathione (GSH) reserve capacity, an enzyme that plays an important role in the detoxification of xenobiotics and can also prevent damage caused by oxidative stress. Interestingly, it has been observed that exposure to Hg inhibits the development of the brain's GSH antioxidant system, thus contributing to oxidative damage. Besides, epigenetic alterations such as DNA methylation and histone alterations can contribute to metal toxicity, leading to brain damage (Bjørklund et al., 2017; Stojsavljević et al., 2023). However, it is important to remember that not all children exposed to Hg develop ASD. Thus, the idea emerges that there must be exposure associated with a genetic and physiological sensitivity to Hg, such as descendants of acrodynia survivors, (Shandley & Austin, 2011) or impaired metal excretion systems, leading to increased levels of Hg in the body (Bernard et al., 2001).

As analyzed in pre-clinical studies, there is a higher prevalence of changes in specific brain region morphology in individuals with ASD (Bachevalier, 1994). Brain magnetic resonance imaging (MRI) scans indicate increased total brain volume (Nordahl et al., 2011) and changes involving this disorder's limbic and cerebellar systems (Lee et al., 2003). In addition, dysfunctions predominate in the temporal lobe regarding the functional impairment of structures (Bigler et al., 2007). The temporal lobe is closely connected with frontal, parietal, limbic, and associative sensory systems (Bota et al., 2015), thus, is related to the clinical symptoms present in ASD (cognitive and emotional deficit) (Apicella et al., 2013).

Socioeconomic characteristics and contact with maternal environmental toxins before and during pregnancy were evaluated through questionnaires to investigate the differences between mothers with autistic children and mothers with neurotypical children. Despite having neurodevelopmental benefits, consuming fish subtypes has been reported to be associated with higher rates of Hg in the umbilical cord (Julvez et al., 2016). In fact, Adams et al. (2007) showed that the concentration of Hg in the dental structure of autistic children compared to neurotypical children had significantly higher levels and that this structure is an adequate representation of the accumulation of Hg during the fetal period (Adams et al., 2007).

When analyzing the risk of environmental contamination in populations living in the vicinity of plants and factories that used coal, a positive correlation was found between the increase in cases of ASD and the consequent atmospheric concentration of Hg (the primary residue of this industrial activity; Blanchard et al., 2011). Palmer et al. (2009) found similar results when collecting information on chemical releases by major industrial facilities and ASD rates in nearby areas, factors that had a significant association. Similarly, Dickerson et al. (2015) showed findings suggestive of the association between the proximity of urban residences to industrial facilities and a higher prevalence of ASD.

Other limitations of this study are the lack of variability between the sex of the participants, the most extensive male samples, the mean age, and the country of origin. Among the inclusion criteria in the articles, some admitted only autistic children, and others included children within the spectrum of autistic disorder. There was also diversity in the choice of screening and diagnosis methods; as the definition of ASD is broad, it would be ideal to use the most updated version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) to diagnose cases, but most studies used the DSM-IV (not being the most inclusive) or assessed the severity of the disorder with other clinical scales. Considering the possible heterogeneity of ASD etiology, confounding variables such as medications, nutritional status, socioeconomic status, maternal age, lifestyle, diet, and other exposures were not always included. In this systematic review, of the 57 articles evaluated by the NOS, 34 represented high methodological quality with a lower risk of bias, 20 had a moderate risk of bias and quality, and only 3 had the highest risk of bias and low quality. No meta-analysis was applied, as the studies did not provide specific numbers of exposure times or dose concentrations of exposures. Furthermore, the studies are not equivalent to each other, and it is not possible to compare them through meta-analysis, as the studies present different periods of exposure (pre-natal and post-natal) as well as different types of exposure (dental amalgam and consumption of seafood, pollutants, and thimerosal).

5 | CONCLUSION

After analyzing the results, we concluded that Hg plays a role in the heterogeneity of ASD etiology, mainly when exposure occurs in the post-natal period. Based on the case–control studies selected in this review, there was an increase in the levels of Hg present in the blood, hair, and urine of children diagnosed with ASD and exposed to an environment with high levels of air and

water pollution of Hg. This can be explained, at least in part, by the impairment in GSH antioxidant system in addition to the deficiency of MT protein, which is responsible for the toxic metal excretion, enabling an increase in oxidative stress and inflammation, making the spectrum characteristics more severe. In addition, oral intake of antibiotics leads to changes in the intestinal flora, which is responsible for converting Hg into MeHg, a metabolite capable of overcoming body barriers and causing damage to fetal development, as well as brain oxidative stress and neuronal damage, contributing to the autistic phenotype. However, the results are controversial, since some of the studies found a positive relationship between Hg levels and autism and others did not. Therefore, pre-clinical research using animal models of ASD could clarify the influence of Hg in the pre- and post-natal period elucidating the molecular mechanisms that permeate brain changes in ASD. Finally, it is also crucial to investigate the excretory system, which appears to be altered in these patients.

AUTHOR CONTRIBUTIONS

Diogo Dominguini: Conceptualization; data curation; formal analysis; investigation; methodology; project administration. **Bruna Bittencourt Netto:** Investigation; methodology. **Elica Pizzolo da Silva:** Investigation; methodology; writing – original draft. **Maiara de Aguiar da Costa:** Visualization; writing – review and editing. **Luciane Bisognin Ceretta:** Supervision. **Victória Linden Rezende:** Writing – original draft. **Sofia Januário Bolan:** Visualization; writing – original draft. **Michael Aschner:** Supervision. **Cinara Ludvig Gonçalves:** Conceptualization; investigation; methodology; supervision; validation; visualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests to disclose related to the submission of this manuscript. Michael Aschner has served as an expert witness in litigation on the role of heavy metals in ASD. This systematic review was conducted to identify the effects of Hg in the pre- and post-natal period based on the recent scientific literature.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.16076.

DATA AVAILABILITY STATEMENT

All research data will be available through prior contact with the researchers.

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