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Mercury and neurodevelopmental disorders in children: A systematic review

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ABSTRACT

Mercury is a toxic metal which can cross the placenta and the blood-brain barrier and cause the disruption of various cellular processes. Studies have investigated mercury exposure and neurodevelopmental disorders; therefore, a critical and rigorous analysis of this evidence is required. The objective of this review was to evaluate the available scientific evidence on the effects of mercury exposure during the prenatal and postnatal periods and its relationship with the development of neurobehavioral disorders.

A systematic search of the MEDLINE and ScienceDirect databases was conducted; the results were presented in tables and narrative synthesis. Only 31 studies met the eligibility criteria. Overall, the evidence on the effects of mercury exposure and neurodevelopmental disorders in children is limited. Learning disabilities, autism, and attention deficit hyperactivity disorder were some of the reported potential effects.

Keywords: *mercury; neurodevelopmental disorders; autism spectrum disorder; attention deficit hyperactivity disorder.*

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INTRODUCTION

Prenatal development includes the growth and development of the internal organs of the fetus, and is involved in several subsequent health outcomes.[1] This period is complemented by the postnatal period, where the fetus becomes a newborn, and its nutrition will depend exclusively on breast milk.[2] Therefore, both environments are critical for the optimal development of children.[1,2] However, aspects related to environmental pollution have been shown to trigger undesirable effects in children exposed during these periods.[1]

Mercury (Hg), the only liquid metal that is found worldwide, is one of the heavy metals that has aroused interest in this field in recent years.[3,4] In its elemental form, Hg is found in nature as sulfides or also bound to other minerals.[5,6] Apart from its element state, Hg can be found in its inorganic form, mainly in tailings from industrial and gold mining operations.[7,8] When released into the environment, Hg is transformed into its organic form by bacteria present in aquatic sediments, mainly into methylmercury. This is the main source of exposure among humans since, due to its ability to be biomagnified and bioaccumulated by the marine food chain, Hg is found at a higher level in predatory fish, which account for a high percentage of the human diet.[8-11]

The high intake of fish contaminated with mercury entails a high health risk for pregnant women due to Hg's ability to cross the placenta and the blood-brain barrier, potentially affecting fetal and early childhood development and during and even into adolescence.[12,13] These age groups are mainly affected by the inability to mitigate the harmful effects of Hg. A potential relationship has been reported between (prenatal and postnatal) exposure to Hg and the presence of some neurodevelopmental disorders, such as autism spectrum disorder, attention deficit hyperactivity disorder, reduced IQ, and language disorders.[14,15]

Therefore, given the potential complications associated with Hg exposure, several health agencies have attempted to counteract its effects; for example, the United States Environmental Protection Agency recommends blood Hg levels should be below 5.8 µg/L.[16] However, despite the implementation of these measures, there are still reports suggesting possible neurodevelopmental effects in children associated with Hg exposure; therefore, a critical and rigorous analysis of the evidence on this issue is required. For this reason, the objective of this review was to evaluate the available scientific evidence on the effects of Hg exposure during the prenatal and postnatal periods and its relationship with the development of neurodevelopmental disorders.

METHODS

A systematic review was performed following the guidelines of the PRISMA statement.

Search strategy

A systematic electronic search of the MEDLINE (via PubMed) and ScienceDirect databases was performed. Search strategies adapted to each database were used, with the following keywords and terms: "neurodevelopmental disorders" (MeSH) OR "brain" (Mesh) OR "cognitive skills" OR memory OR alertness OR language OR fine motor skills. To obtain the most current evidence, the search was filtered to include only the past 5 years. The last search was performed on May 5, 2021 (*Supplementary material 1*).

Study selection

The studies that met the following inclusion criteria were selected: a) Hg levels in pregnant women and newborn infants; b) Hg levels in biological matrices: blood, urine, umbilical cord blood/tissue, placenta and/or hair; c) studies that assessed the association between Hg and the development of neurobehavioral disorders in children (2–12 years of age). All animal reports, book chapters, reviews, conference abstracts, and letters to the editor were excluded.

All studies obtained were stored in the Rayyan platform[17] and, after removing duplicates, titles and abstracts were examined independently by 2 reviewers, considering the eligibility criteria. Then, the full texts of all articles considered relevant in the first stage were obtained and reviewed, and compliance with the eligibility criteria was determined in order to make a final decision. In case of disagreement between the reviewers, a third collaborator participated in the selection process until they reached an agreement. The reasons for the exclusion of full-text articles are described in the *Supplementary material 2*.

Assessment of methodological quality

The studies included in this review were assessed using the Joanna Briggs Institute (JBI) checklist.[18] This tool does not establish a cut-off point; a higher score indicates better quality.

This process was carried out independently by 2 reviewers and, in case of disagreement, a third reviewer participated in the process until they reached a consensus.

Data extraction and analysis

The following data were extracted: general study characteristics (authors, year, country, sample size) and aspects related to Hg exposure and its impact on neurodevelopment (type of sample, pre- and postnatal Hg levels, tests performed, tests used, and main outcomes). Given the degree of heterogeneity among the studies, findings were described using tables and a narrative synthesis of the evidence was performed.

RESULTS

Study selection

A total of 2299 studies were identified. After removing duplicates, 2263 titles/abstracts were reviewed. Then, the full texts of 50 studies were reviewed and 31 studies were finally selected for review (*Figure 1*).

Characteristics and methodological quality of included studies

Included studies were published between 2016 and 2021; most were cohort studies, followed by case-control studies. The sample size ranged from 60 to 38 581 participants. Most studies were conducted in the United States, Spain, and South Korea. In relation to the methodological quality, the mean study score was 7.3 ± 0.7 for cohort studies and 7 ± 0.7 for case-control studies (*Table 1*).

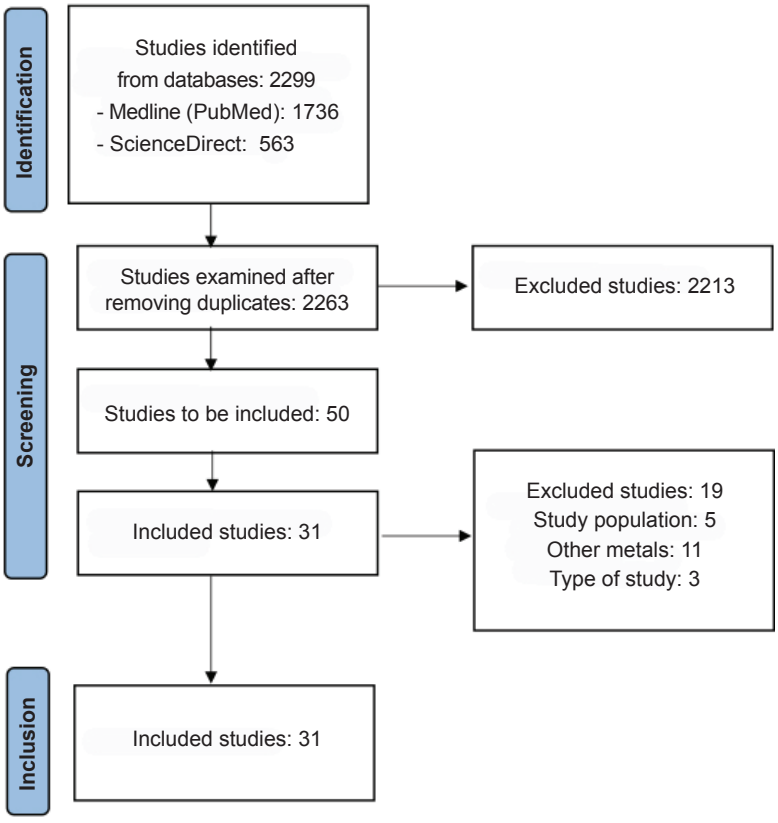
Mercury and neurodevelopmental disorders in children

All of the studies included in this review assessed the effects of Hg on the neurological system of children; 18 focused on the effects of Hg exposure on neurodevelopment[12–14,16,19–32] and 13, on behavioral disorders.[8,15,33–41]

Mercury and its effects on child neurodevelopment

Four studies assessed the effect of pre- and postnatal exposure to Hg,[12–14,25] 8 in the

Figure 1. Study selection process



prenatal period[19,20,26–30,32] and 6 in the postnatal period[16,21–24,31] (*Table 2*). Participants' age ranged from 16 months to 5 years old. Two studies used the Wechsler Intelligence Scale for Children (WISC) to assess cognitive skills,[12,14] while the other 2 used the Bayley Scales of Infant and Toddler Development, versions II and III (BSID-II/III).[13,22] According to Lee et al.[12] and Jeong et al.,[15] pre- and postnatal Hg exposure had a negative effect on the intellectual and the verbal development of participants, respectively; while Kim et al.,[13] found a reduction in the psychomotor development of infants. However, Barbone et al.,[25] did not find a relationship between these variables.

Eight studies focused on Hg exposure during the prenatal period in a population aged 0 months to 8 years old. For the assessment of neurodevelopment impairment, only 2 studies used the same instrument (BSID-III),[28,32] while the others used the WISC-III,[26] the Malawi tool (MDAT),[19] the Neonatal Behavioral Neurological Assessment (NBNA),[28] the McCarthy scale (MSCA),[29] and the Speech and Language Assessment Scale (SLAS).[30]

In addition, Strain et al.,[20] administered the Clinical Evaluation of Language Fundamentals, fifth edition (CELF-5), the Kaufman Brief Intelligence Test 2 (KBIT-2), the Boston Naming Test (BNT), the Trail Making and Finger Tapping test (FT), and the Woodcock Johnson-III Tests of Achievement (WJ-III).

Nyanza et al. observed that prenatal Hg exposure at or above permissible levels was associated with an overall neurological and language development impairment in infants. A similar finding was reported by Wang et al. and Freire et al.[19,28,29] However, other authors found no relationship between these variables.[20,26,27,30,32]

Six studies were included in the review that assessed the effect of postnatal Hg exposure in a population of children aged 2 to 10 years. The tests and scales used by these studies included the Denver Developmental Screening Test II (DDST-II), the Test of Nonverbal Intelligence (TONI), the Bayley III scale, the Beck Anxiety Inventory (BAI), the Montreal Cognitive Assessment (MoCa), the WISC-IV, the intelligence quotient test, the McCarthy Scales of Children's Abilities (MSCA), and the basic generic scales of the Pediatric Quality of Life Inventory (PedsQL).[16,21–24,31]

As reported by Al-Saleh et al., methylmercury levels in breastfeeding mothers were associated with decreased general intelligence scores in children, an event that was also observed in the study by Feng et al., who found that Hg levels in children's hair were associated with a reduced IQ.[21,24] Barbone et al., indicated that high concentrations of methylmercury in the hair of mothers were related to poor motor performance in their children.[22] However, the studies by Da Cunha et al., Llop et al., and Hsueh et al., found no adverse effects in relation to postnatal Hg exposure and neurodevelopment in children.[16,23,31]

Effects of mercury exposure and neurobehavioral disorders in children

Cases of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) seem to be on the rise worldwide. The etiology of these disorders has been associated with Hg exposure in the pre- and postnatal periods.[42,43] Among included studies, 7 analyzed the involvement of Hg in ASD,[34,35,37,38,40,41,44] 4 in ADHD,[8,33,36,45] 1 in both ASD and ADHD,[15] and 1 in behavioral conditions[39] (*Table 3*).

Exposure to mercury and autism spectrum disorders

One of the selected studies assessed prenatal and postnatal Hg exposure and the development of ASD[40] and 5 analyzed postnatal exposure.[34,37,38,41,44,46]

According to Ryu et al., prenatal and postnatal Hg exposure was significantly related to autistic behaviors in 5-year-old children followed-up from birth.[40] In relation to postnatal exposure, Gump et al. and Li et al., reported that there was a relationship between Hg levels in children and their symptoms of autism.[37,38] However, more recently, Gil-Hernandez et al. did not find an association between Hg neurotoxicity and the etiopathogenesis of ASD.[44]

In addition, the use of thimerosal (organomercurial compound) as a preservative in vaccines administered during early childhood has been a controversial topic. In this regard, Geier et al., have reported a potential relationship between increased exposure to Hg in the form of thimerosal and the development of ASD in children.[34,41,46] However, they suggest that further high-quality studies are required, which should include populations other than that of the United States, to determine whether there is an association between thimerosal and ASD.

Table 1. Characteristics and quality of included studies

Author and year	Type of study	Country	Sample size	Biological sample	Methodological quality
Al-Saleh et al. 2020	Cohort	Saudi Arabia	82	Urine, blood, breast milk, and hair	7/11
Barbone et al. 2020	Cohort	Italy	53	Hair	8.5/11
Barbone et al. 2019	Cohort	Italy, Slovenia, Croatia	1308	Hair, umbilical cord blood	7/11
Barry et al. 2020	Case-control	Saudi Arabia	Controls: 30 ADHD cases: 30	Saliva	7.5/10
Da Cunha et al. 2020	Cohort	Brazil	535	Vaccines	7/11
Feng et al. 2020	Cohort	China	314	Hair	7.5/11
Freire et al. 2018	Cohort	Spain	302	Placenta	7.5/11
Geier et al. 2018	Case-control	United States of America	3486	Mercury	7/10
Geier et al. 2017	Case-control	United States of America	Controls: 15 216 ASD cases: 164	Vaccines	7/10
Geier et al. 2016	Case-control	United States of America	Controls: 11 783 ASD cases: 73	Vaccines	6.5/10
Gil-Hernández et al. 2020	Case-control	Spain	Controls: 5 ASD cases: 57	Hair and urine	6.5/10
Gump et al. 2017	Cohort	United States of America	203	Blood	7/11
Hsueh et al. 2017	Case-control	Taiwan	Controls: 89 Cases: 89	Blood	7/10
Jeong et al. 2017	Cohort	South Korea	553	Blood	8.5/11
Julvez et al. 2019	Cohort	United Kingdom	1723	Blood	6.5/11
Karatela et al. 2017	Cohort	New Zealand	278	Fingernails	6.5/11
Kim et al. 2020	Cohort	South Korea	451	Maternal serum	8.5/11
Lee et al. 2021	Cohort	South Korea	502	Blood	8/11
Li et al. 2018	Case-control	United States of America	Controls: 184 ASD cases: 180	Blood	6.5/10
Llop et al. 2020	Cohort	Spain	1252	Hair and blood	8.5/11
Lozano et al. 2021	Cohort	Spain	731	Hair	6.5/11
Lygre et al. 2018	Cohort	Norway	19 220	Dental amalgams	7/11
Nyanza et al. 2021	Cohort	North Adriatic coast	257	Umbilical cord blood	7/11
Ništević et al. 2019	Cohort	Tanzania	439	Blood	6.5/11
Prpić et al. 2017	Cohort	Croatia	257	Umbilical cord blood	7/11
Ryu et al. 2017	Cohort	South Korea	458	Blood	6.5/11
Skogheim et al. 2021	Case-control	Norway	Controls: 1034 ADHD cases: 705, ASD cases: 397	Umbilical cord blood	8.5/10
Strain et al. 2021	Cohort	Seychelles	1237	Hair	8/11
Tabatadze et al. 2018	Case-control	United States of America	Controls: 35 ADHD cases: 35	Hair	6.5/10
Vejrup et al. 2018	Cohort	Norway	38 581	Seafood	7.5/11
Wang et al. 2019	Cohort	China	286	Umbilical cord blood	7.5/11

ADHD: attention deficit hyperactivity disorder.
ASD: autism spectrum disorder.

Table 2. Effects of mercury exposure on the neurodevelopment of children aged 0 to 12 years

Author and year	Age	Prenatal Hg level	Postnatal Hg level	Tests and/or instruments	Main outcomes
Nyanza et al. 2021	6–12 mo	1.2 µg/L (range: 0.8–1.7)	Not reported	MDAT	For every 1 µg/L increase in total Hg in maternal blood, the prevalence rate of language impairment increased by 5%. Sex-stratification analyses revealed significant associations between increased prenatal Hg exposure and language impairment in children.
Lee et al. 2021	4 and 6 yo	GM: 2.49 ± 1.56 µg/L	4 yo: 1.98 ± 1.8 µg/L (GM) 6 yo: 1.63 ± 1.58 µg/L (GM)	KEDI-WISC K-WAIS	Hg levels at 6 years of age had a greater impact on children's intelligence quotient than at 4 years of age. Thus, an increase in 1 unit of Hg in the blood was associated with a decrease of 0.319 in children's intelligence quotient at 6 years of age.
Strain et al. 2021	7 yo	3.91 ± 3.47 ppm	Not reported	CELF-5 KBIT-2 BNT FT WJ-III	Prenatal MeHg levels did not show a significant effect on language, cognition, executive, motor and psychomotor function tests, as well as on academic achievement, behaviors, and social communication in study children.
Al-Saleh et al. 2020	5–8 yo	Not reported	Total mercury in maternal blood: 0.5 ± 0.190 µg/L Breast milk: 1.307–0.125 µg/L	TONI DDST-II	Lower scores in the TONI were associated with higher maternal MeHg levels. Early Hg exposure, measured in infants' urine, showed an adverse association with children's performance in the nonverbal IQ test and the integration of visual and motor skills. The methylmercury level in maternal blood was inversely associated with children's nonverbal intelligence quotient.
Barbone et al. 2020	3–18 mo	Not reported	Total Hg in the mother: 0.83–1.24 Total Hg in children: 0.89–1.08 ppm MeHg in the mother: 0.63–0.98 ppm MeHg in children: 0.45–0.72 ppm	DDST-II	No significant differences were observed in the comparison between children with low performance in at least an area of the DDST-II and the others compared to mercury levels. Children whose mothers had a hair MeHg level > 1 ppm were 47% more likely to have lower fine motor performance compared to children whose mothers had MeHg levels < 1 ppm.
Da Cunha et al. 2020	24 and 36 mo	Not reported	Thimerosal/vaccines	BSID-III BAI MoCa	Initially, children who received more doses of thimerosal-containing vaccines showed a lower level of language and motor development compared to children who received 0–3 doses. However, a multivariate analysis did not confirm such association.

Feng et al. 2020	8–10 yo	Not reported	1.53 µg/g (0.21–12.6 µg/g)	WISC-IV IQ	Statistically significant associations were found between hair Hg levels and an intelligence quotient below 80. The authors found that the odds of children having an IQ < 80 increased 1.58-fold when hair Hg levels increased by 1 µg/g. That is to say, children's intelligence quotient will decrease by approximately 1 point when the hair Hg level increases by 1 µg/g.
Kim et al. 2020	0, 6, 12, 24, and 36 mo	3.41 µg/L(GM) (GM)	5.35 µg/L	BSID-II	Prenatal Hg exposure adversely affects infant neurological development and is associated with rapid growth during the first 3 years.
Llop et al. 2020	4–5 yo	Not reported	Hair levels: 1.38 ± 1.42 µg/g	MSCA	No adverse effects on child neuropsychological development associated with postnatal Hg exposure were observed in 4-year-old children, although some children had Hg levels above the permissible value of > 1 µg/g.
Barbone et al. 2019	16–20 mo	Maternal blood: 3.2 ± 3.4 ng/g	Breast milk: 0.4 ± 1.2 ng/g	BSID-III	No associations were found between maternal Hg levels and cognitive, motor, and language skills in study children.
Julvez et al. 2019	8 yo	25.2 ± 12.7 ng/g	Not reported	WISC-III	Hg levels in umbilical cord tissue were not associated with cognitive development in study children.
Ništević et al. 2019	18 ± 2 mo	1.41 - 5.61 ng/g	Not reported	BSID-III	No correlation was found between cord blood Hg T levels and infant neurodevelopmental scores at 18 months of age.
Wang et al. 2019	0–18 mo	Maternal blood: 0.18–11.85 µg/L	Not reported	NBNA BSID-III	Prenatal exposure to low levels of Hg was associated with a significant decrease in neonatal neurobehavioral development. Girls had significantly higher scores on the BSID-III cognitive, language, and motor scales than boys. Cord blood Hg levels were associated with an increased odds of higher scores on behavioral and active tone aspects. The sex-Hg interaction indicated that females tended to be more susceptible to the detrimental effects of prenatal Hg exposure in terms of language development.
Freire et al. 2018	4–5 yo	0.016–12.953 ng/g	Not reported	MSCA	Hg found in placenta was associated with an increased odds of worse performance on posterior cortex verbal function in the study children. Hg found in placenta was associated with a 3.85 fold increased odds of lower scores on verbal memory skills. In addition, some cognitive subareas involved in executive and verbal functions, quantitative skills, and motor skills were identified and appear to be affected by Hg exposure.

Vejrup et al. 2018	5 yo	Dietary Hg: 1.48 ± 0.97 µg/day Hg in maternal blood: 1.0 µg/L	Not reported	SLAS	No associations were found between prenatal Hg exposure through seafood consumption and language and communication skills in the study children.
Hsueh et al. 2017	Controls: 6.15 ± 0.29 yo Cases: 5.87 ± 0.19 yo	Not reported	Controls: 9.58 ± 2.36 µg/L Cases: 6.83 ± 0.68 µg/L	PedsQL scale	Children's blood mercury levels were not associated with delays in physical, social, psychosocial, emotional, and academic development.
Jeong et al. 2017	5 yo	Maternal blood: 3.14 ± 1.66 µg/L	Blood of children: 1st quartile: 1.87 µg/L 2nd quartile: 3.18 µg/L 3rd quartile: 5.23 µg/L	WPPSI-R	Children's verbal intelligence quotient was negatively associated with maternal blood Hg levels during late pregnancy.
Prpić et al. 2017	18 mo	Exposed: > 5.8 µg/L Not exposed: < 5.8 µg/L	Not reported	BSID-III	No correlation was found between cord blood Hg T levels and infant neurodevelopmental at 18 months of age.

Hg: mercury.
Hg T: total mercury.
MeHg: methylmercury.
mo: months old.
yo: years old.
GM: geometric mean.
MDAT: Malawi Development Assessment Tool.
KEDI-WISC: Wechsler Intelligence Scale for Children.
K-WAIS: Korean Wechsler Adult Intelligence Scale.
CELF-5: Clinical Evaluation of Language Fundamentals, fifth edition.
KBIT-2: Kaufman Brief Intelligence Test 2nd edition.
BNT: Boston Naming Test.
FT: Finger Tapping and Trail Making test.
WJ-III: Woodcock-Johnson III Tests of Achievement.
TONI: Test of Nonverbal Intelligence.
DDST-II: Denver Developmental Screening Test II.
BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition.
BAI: Beck Anxiety Inventory.
MoCa: Montreal Cognitive Assessment.
WISC-IV: Wechsler Intelligence Scale for Children, fourth edition.
IQ: intelligence quotient test.
MSCA: McCarthy Scales of Children's Abilities adapted to the Spanish population.
WISC-III: Wechsler Intelligence Scale for Children, third edition.
NBNA: Neonatal Behavioral Neurological Assessment.
SLAS: Speech and Language Assessment Scale.
WPPSI-R: Korean version of the Wechsler Preschool and Primary Scale of Intelligence-Revised.
PedsQL: basic generic scales of the Pediatric Quality of Life Inventory.

Table 3. Effects of mercury exposure and behavioral disorders in children aged 0 to 12 years

Author and year	Age	Prenatal Hg level	Postnatal Hg level	Diagnosis and/or behavioral tests	Main outcomes
Lozano et al. 2021	9 and 11 yo	Not reported	0.89 µg/g (GM)	CBCL, ANT, CTRS	Older children with total Hg levels in hair had worst scores on the internalizing and total problems (emotional and behavioral) scales of the CBCL. Although Hg T levels in hair were not significantly related to ADHD scores, a significant decrease was observed in children aged 9–11 years.
Skogheim et al. 2021	2 yo	Control: 1.39 µg/L ADHD cases: 1.17 µg/L ASD cases: 1.17 µg/L	Not reported	ADHD and ASD	Increased gestational Hg levels were associated with a lower risk of attention deficit hyperactivity disorder and autism spectrum disorder in children.
Barry et al. 2020	6–7 yo	Not reported	Cases: 6.58 ± 0.94 µg/L Controls: 4.41 ± 0.43 µg/L	ADHD	No association found between Hg levels in saliva and the development of ADHD.
Gil-Hernández et al.*2020*	2–6 yo	Not reported	Controls: Urine: 0.33 ± 0.42 µg/L Hair: 13 ± 12.68 µg/g Cases: Urine: 0.54 ± 0.78 µg/L Hair: 8.26 ± 10.57 µg/g	ASD	No significant association found between Hg levels (urine and hair) and the development of ASD.
Geier et al. 2018	2, 4, 6, and 15 mo	Not reported	12.5–25 µg Hg/vaccine	ASD, psychomotor disorder, and neurodevelopmental disorder	Thimerosal exposure showed a higher risk for ASD, psychomotor disorder, and neurodevelopmental disorder than the corresponding controls (vaccines without thimerosal).
Geier et al. 2017	8 yo	Not reported	Case-control: 12.5 µg Hg/dose of hepatitis B vaccine	ASD	Cases diagnosed with atypical autism were observed to be significantly more likely than controls to have received increasing doses of Hg-containing vaccines (hepatitis B) in the first 6 months of life. Therefore, the authors suggest that the mercurial component (thimerosal), used as a preservative in many vaccines, is significantly associated with an increased risk for autism.
Lygre et al. 2018	3 and 5 yo	Mothers with dental amalgams	Not reported	ADHD symptoms	Prenatal exposure to Hg from dental amalgams in the mothers was not associated with the development of ADHD symptoms in children at 3 and 5 years of age.
Tabatadze et al. 2018	6–8 yo	Not reported	Controls: 0.20 ± 0.6 µg/g Cases: 1.29 ± 1.2 µg/g	ADHD	High Hg levels were significantly associated with the development of ADHD in children.
Li et al. 2018	Cases: 5.06 ± 1.3 7 yo Controls: 6.12 ± 1.6 9 yo	Not reported	Controls: 13.47 ± 17.24 µg/L Cases: 55.59 ± 52.56 µg/L	ASD	Children with ASD had significantly higher Hg levels than controls; however, the study did not assess the association between these two variables.

Gump et al. 2017	9–11 yo	Not reported	0.46 ± 1.02 µg/L	ASQ	Increased Hg levels were associated with a greater spectrum of autism symptoms, specifically in children with continuous low vagal withdrawal during acute stress. However, no evidence of simple associations between blood Hg levels and neurodevelopmental/ psychological impairment was reported.
Karatela et al. 2017	9 yo	Not reported	Median: 0.02 µg/g	CBCL	Approximately 21% of children had total Hg levels above the EPA recommendations (1 µg/g). No significant association was found between Hg and total scores in behavioral aspects; however, a significant association was observed between total Hg and aggressive behavior in children.
Ryu et al. 2017	0, 2, 3, and 5 yo	Beginning of pregnancy: 3.53 ± 1.55 µg/L (GM) End of pregnancy: 3.30 ± 1.68 µg/L (GM)	Umbilical cord: 5.52 ± 1.57 µg/L 2 yo: 2.35 ± 1.75 µg/L 3 yo: 2.16 ± 1.65 µg/L	ASD	Hg levels at the end of pregnancy, in umbilical cord blood, and at 2 and 3 years of age were significantly associated with autistic behaviors at 5 years old.
Geier et al.	Cases: 4.2 yo Controls: 3.9 yo	Not reported	Thimerosal/ vaccines	ASD	The risk of autism decreased significantly as the amount of Hg exposure from vaccines also decreased.

Hg T: total mercury; mo: months old; yo: years old.

GM: geometric mean.

ADHD: attention deficit hyperactivity disorder.

ASD: autism spectrum disorder.

CBCL: Child Behavior Checklist.

ANT: Attention Network Test.

CTRS: Conners' Teacher Rating Scale-Revised.

ASQ: Autism Spectrum Quotient.

EPA: United States Environmental Protection Agency.

Exposure to mercury and attention deficit hyperactivity disorder in children

The 5 studies included in this section assessed the effect of postnatal Hg exposure and the development of ADHD.[8,33,36,39,45] Tabatadze et al., observed that high levels of Hg in children were significantly associated with the development of ADHD.[45] Karatela et al., indicated a significant relationship between total Hg levels and aggressive behavior in children.[39] Lozano et al., reported a decrease in emotional and behavioral indices in children with high Hg levels; however, they did not find a relationship with the development of ADHD.[8] On their side, Barry et al., found no association between Hg levels in saliva and the development of ADHD.[33] Similarly, Lygre et al., did not observe an association between Hg and ADHD. This study assessed mothers' dental amalgams as a source of exposure.[36]

On their side, Skogheim et al., found a negative association between Hg levels and ADHD in the prenatal period and suggested that high Hg levels were associated with a lower risk of ADHD and ASD in children.[15]

DISCUSSION

The main findings of this review suggest that the current evidence on the effects of pre- and postnatal Hg exposure and its incidence on neurodevelopmental and neurobehavioral

disorders is limited. However, some reports suggest that Hg may probably be associated with some neurodevelopmental disorders in children. In this regard, these findings are similar to those reported by Dzwilewski et al.,[47] whose review summarized the available evidence of the impact of prenatal and postnatal exposure to chemicals, such as Hg, on delays or impairments in language development. However, results were inconclusive due to the heterogeneity of studies. Similarly, Sharma et al.,[48] found associations between Hg exposure, neurodevelopment and neurotoxicity in children and adults; however, they mentioned the need for further studies to verify such relationship.

Some reports suggest that there is a relationship between the presence of thimerosal in vaccines and the risk for ASD and ADHD; however, these results must be interpreted in context, considering the limitations of each study. Likewise, it is worth considering that some reports in the bibliography suggest that it has not been possible to demonstrate that thimerosal in vaccines is related to the presence of neurodevelopmental disorders. In this regard, Yoshimasu et al.,[49] conducted a meta-analysis of studies that assessed the effect of postnatal exposure to Hg, including thimerosal in vaccines, on the development of ASD and ADHD. They concluded that thimerosal exposure did not show an association with an increased risk for ASD or ADHD, although these disorders could be related to environmental exposure. Similarly, Modabbernia et al., conducted an analysis of systematic reviews and meta-analyses and concluded that the current evidence suggests that neither vaccination nor thimerosal exposure is related to a risk for ASD, but that other factors—such as advanced parental age, complications during pregnancy and childbirth—are strongly associated with ASD.[50]

Therefore, considering the importance of vaccination as a public health measure, especially in the prevention of diseases in children and adolescents, and the low thimerosal doses received by vaccinated subjects, the recommendations by the World Health Organization and health authorities should be followed, which consider that the evidence available to date supports thimerosal use based on the risk-benefit balance.

Among the practical implications of this review, we aimed to make the scientific and medical community aware of the potential risks faced by children exposed to Hg in the pre- and postnatal periods, considering that the evidence obtained in recent years points to neurodevelopmental disorders and increased neurobehavioral disorders. This may be interpreted as a warning sign in regions with high Hg contamination, such as those near gold mining areas, where in most cases Hg is discharged into the environment with little or no restrictions. Therefore, health care providers should consider the fact that exposure to environmental contaminants, such as Hg, is another potential triggering factor for nervous system diseases, particularly when signs and/or symptoms are observed in children. Likewise, the process of taking the medical history should be used to inquire about the history of possible environmental exposures, which will contribute to an early diagnosis and timely treatment.

CONCLUSION

There is limited evidence on prenatal and postnatal Hg exposure and its effects on neurodevelopment. However, reported effects include impaired cognitive and language functions, as well as an association with the development of ASD and ADHD. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2838_Act_Ealo-Tapia_Anexo.pdf

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