The Association between Exposure to Environmental Toxicants and Childhood Autism: A Mini Review

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Abstract

Background: Autism spectrum disorder is a condition of interrupted neuronal development marked by limitations in communication, social behavior, and tenacity to repetitions. This mini review examined evidence published between 1961-2023 to determine the association between autism and heavy metal exposure. **Methods**: The PubMed and EBSCO essentials electronic databases were searched for studies available in the English language only. Systematic reviews and Animal studies were excluded. **Results**: Out of 9,431 initial database hits, seven (7) studies were included in the review. The data synthesis revealed no significant association between Autism and Heavy metals exposure in 67% (Arsenic and Lead), 75% (Manganese), 80% (Mercury and Cadmium), and 100% (Nickle) of the reviewed studies. Furthermore, there was no significant association between autism and sea-fish consumption status in 100% of reviewed studies. **Conclusion**: There is no consistent evidence to suggest an association between autism and heavy metals exposure or sea-fish consumption status. More elaborate umbrella reviews are needed to confirm this finding.

Key words: Autism, Child, Environmental, Heavy metals, Mother, Toxicants

1. Introduction

Pregnancy and breastfeeding are vulnerable periods for embryos, fetuses, and infants. Maternal exposure to toxic chemicals in the environment can result in an accumulation of the substances in maternal blood (Skogheim et al., 2021). Some toxicants can pass the placental barrier and accumulate in amniotic fluid before crossing the embryo's underdeveloped blood-brain barrier to cause developmental mutations in neurons (Long et al., 2019). The toxicants might also pass into the breast milk during breastfeeding and cause interruptions in neuronal development in breastfed infants (Martín-Carrasco et al. 2023).

Autism spectrum disorder is a condition of interrupted neuronal development marked by limitations in communication, social behavior, and tenacity to repetitions (Miani et al., 2021). It manifests during infancy or childhood (Campbell et al., 2024). The prevalence of autism spectrum disorder has been on the rise from 0.6% in 2000 to about 4% in 2021 (Bolte et al., 2019; Skogheim et al., 2021). Male children are more affected by the condition at a 5:1 male to female ratio (Dickerson et al, 2017; Tsirgiotis et al., 2024). Numerous studies on the genetic component of autism spectrum disease have led to the identification of mutations in genetic materials involved in disrupting neuronal development (Miani et al., 2021). Furthermore, environmental toxicants have been identified as probable causes of 55% of autism spectrum disorders, compared to 37% attributed to spontaneous genetic variables (Duque-Cartagena et al., 2024; Long et al., 2019).

Environmental toxicants such as Mercury (Hg), Lead (Pb), Cadmium (Cd), and Arsenic (As) are naturally occurring in the environment (Ding et al., 2023). Furthermore, man-made activities such as mining, the use of fossil fuels, and manufacturing contribute to the widespread distribution of toxicants (Skogheim et al., 2021). The aforementioned environmental toxicants in addition to Nickel (Ni) and Manganese (Mn) have been Associationed to neuronal mutations (Ijomone et al., 2020). The contamination of water sources by waste effluents from the manufacturing industry exposes humans to lead, cadmium, nickel, and manganese, while contaminated sea fish is the primary source of human exposure to mercury and arsenic (Khellaf et al., 2023; Papadopoulou et al., 2019). The literature would imply that riverside communities that have polluted water resources and depend heavily on seafood like fish and shellfish may be at risk.

The biomarkers of prenatal exposure to environmental toxicants are observable in maternal and umbilical cord blood taken after delivery. Nonetheless, the expected vulnerability window for many health outcomes is often in the first half of pregnancy (Long et al., 2019). Amniotic fluid provides another matrix for biomarkers, but it is only obtainable through an invasive technique called amniocentesis. To ensure the safety, accuracy, and less invasiveness of research investigations, some studies have proposed hair as another viable biological matrix for assessing environmental exposure to environmental toxicants (Aljumaili et al., 2023). Hair samples have an advantage over blood samples since they can be more easily collected for analysis (Ali et al., 2023). Furthermore, hair can provide more detailed information regarding long-term exposure than blood or plasma, where biomarkers are often altered by homeostasis (Čargonja et al., 2023). Nevertheless, one notable limitation of hair analysis studies is the use of hair treatment (Domingues et al., 2016). This review summarized recently published evidence concerning the association between maternal exposure to environmental toxicants and autism spectrum disorder based on published results involving blood, amniotic fluid, hair

specimen, and seafood consumption status (a proxy qualitative estimation matrix, Golding et al., 2018).

2. Methods

This review was conducted in line with the provisions of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Using keywords, the search strategy was formulated in line with the PICO framework (Pollick et al., 2018). The PICO is an acronym, where "P" stands for population, "I" stands for Intervention/exposure, "C" stands for comparison, and "O" stands for the outcome (Pollick et al., 2018). Keywords related to the PICO research variables were combined with Boolean operators to generate a search string that was applied to PubMed and EBSCO essentials databases. The search was limited to free full-text studies published in the English language from 1961 to 2023. The search string used for the database search was: (Maternal OR Pregnant OR Infant OR Child*) AND (Environment* OR Toxic* OR "Heavy metals") AND (Autism OR "Autism Spectrum Disorder"). The review was conducted in January 2024. To ensure quality, evidence of ethical approval was a major inclusion criterion. The included studies satisfied the inclusion criteria expressed in table 1.

Table 1: Development of search strategy

Variables	**Keywords**
Population	Maternal OR Mother OR Infant OR Child*
Intervention/exposure	Environment* OR toxic* OR "Heavy metals"
Comparison	No exposure
Outcome	Autism OR "Autism spectrum disorder"
Search strategy	(Maternal OR Pregnant OR Infant OR Child*) AND (Environment* OR Toxic* OR "Heavy metals") AND (Autism OR "Autism spectrum disorder")
limiters	English language studies only, 1961-2023, free full text articles
Databases	PubMed and EBSCO essentials
Inclusion criteria	Case-control, Prospective analytical, Longitudinal analytical studies, Specimen for heavy metal analysis (child hair, maternal and child blood), and Ethical Approval for study clearly expressed.
Exclusion criteria	Systematic Reviews and Meta-analysis, animal studies

Data extracted from the included studies data such as author, year of publication, aim, sample size, sampling method, laboratory method, data analysis method, results, and

conclusion. The extracted demographic data of participants were maternal age, maternal smoking status, maternal seafood consumption status, child age, and child biological sex. Analysis of collected demographic data was done using descriptive statistics. Narrative analyses were applied to the synthesis of evidence concerning the association between heavy metal exposure and childhood autism).

3. Results

Figure 1 shows the study selection process. A total of 9,431 studies were identified during the initial database search (PubMed, n = 5,615; EBSCO essentials, n = 3816). During article screening, 9,380 studies were excluded for non-relevant titles and another 38 duplicate studies were removed. The remaining 13 studies were passed through an eligibility check and 5 Systematic reviews and 1 animal study were excluded. A final 4 eligible studies were included in the review.

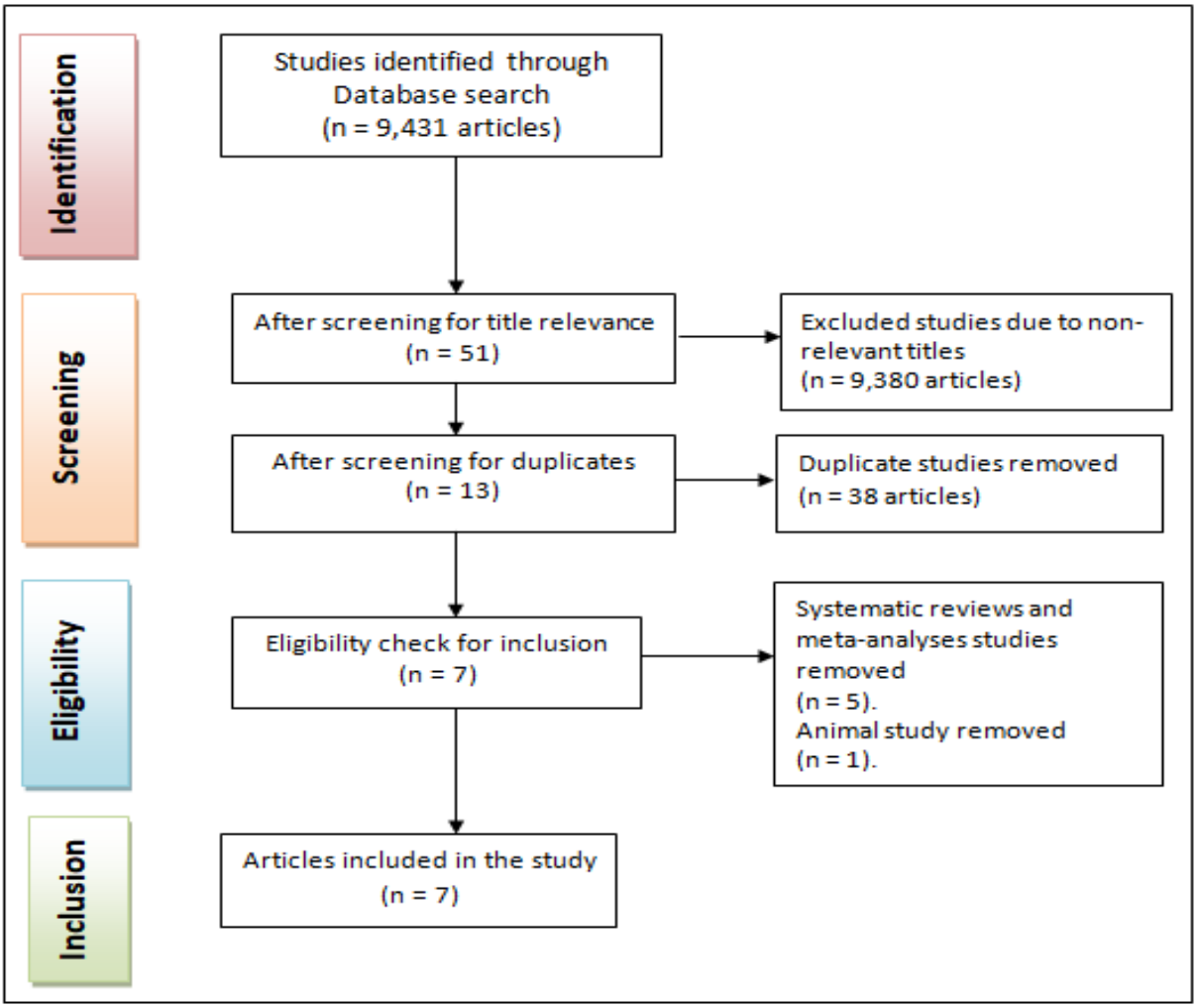

Figure 1: The Study selection process

Table 2 summarizes the demographic profile of the study participants. The included studies comprised 3,871 mothers and 4,231 children (2,883 autism cases and 1,348 controls). Both the Case and Control groups had more boys than girls. Furthermore, there were more sea-fish consumers in both the case and control groups.

Table 2: Demographic profile of participants

Author	Skogheim et al. (2021)		Goldi ng et al. (2018)	Long et al. (2019)		Rahbar et al. (2021)		Domin gues et al. (2016)	Mohamed et al. (2015)		Filo n et al. (202 0)
	Cas es	Cont rols		Cas es	Cont rols	Case s	Cont rols		Case s	Con trols	
N	397 Mo the r-chil d pair s	1034 Moth er-child pairs	2230 moth er-child pairs all with ASD	75 mo the r-chil d pair s	135 moth er-child pairs	30 chil dren	30 child ren	21 cases and 19 control s, childre n	100 chil dren	100 chil dre n	30 case s and 30co ntro l, chil dren
Matern al age											
Mean (SD)	29. 6 (4.9 4)	30.1 (4.43)		34	35						
<35						23 (79. 3)	25 (89.3)				
>35						6 (20. 7)	3 (10.7)				
Smokin g in Pregna											

ncy, n (%)											
No	332 (83.6)	901 (87.1)									
Yes	65 (16.4)	133 (12.9)									
Seafood consumption, n (%)											
No			285 (12.8)			3 (10.0)	3 (10.0)		0 (0)	11 (15.7)	
Yes			1945 (87.2)			27 (90.0)	27 (90.0)		70 (100)	59 (84.3)	
Child sex, n (%)											
Girl	61 (15.4)	329 (31.8)		13 (17.3)	26 (19.3)				16 (16)	26 (26)	
Boy	336 (84.6)	705 (68.2)		62 (82.7)	109 (80.7)				84 (84)	74 (74)	

N = sample size, n = frequency, % = percentage

Table 3 summarizes the findings from the included studies. For Mercury (Hg), 4 out of 5 studies (80%) found no significant association between Mercury exposure and autism. For Lead (Pb), 4 out of 6 studies (67%) found no significant association between Lead exposure and autism. For Cadmium, 4 out of 5 studies (80%) found no significant association between Cadmium exposure and autism. For Arsenic (As), 4 out of 6 studies (67%) found no significant association between Arsenic exposure and autism. For Nickel (Ni), 2 out of 2 studies (100%) found no significant association between Nickel exposure and autism. For Manganese (Mn), 3 out of 4 studies (75%) found no significant

association between Manganese exposure and autism. For sea-fish consumption, 3 out of 3 studies (100%) found no significant association between Sea fish consumption and autism.

Table 3: Study synthesis

Author	Skogheim et al.	Golding et al.	Long et al. [2]	Rahbar et al.	Domingues et al.	Mohamed et al.	Filon et al.
Year of publication	2021	2018	2019	2021	2016	2015	2020
Country	Norway	Avon, UK	Denmark	Pakistan	Italy	Egypt	Poland
Aim	Association between mid-pregnancy maternal levels of toxic metals and childhood autism.	Association between prenatal mercury exposure through fish eating and childhood autism.	Association between Amniotic fluid heavy metal levels and childhood autism.	Association between blood levels of heavy metals and Autism among childrn	Association between hair levels of heavy metals and Autism among children	Association between hair levels of heavy metals and Autism among children	Association between hair levels of heavy metals and Autism among children
Study design	Prospective cohort	Longitudinal	Case-control	Matched case-control	Case-control	Matched case-control	Case-control
Sample size	397 ASD cases and 1034 controls	1945 Sea-fish eating mothers and 285 non-sea-fish eating mothers	75 ASD cases and 135 controls	30 ASD Cases and 30 controls	21 ASD cases and 19 controls	100 ASD cases and 100 controls	30 ASD Cases and 30 controls

		all with an ASD child					
Sampling method	Census of children born on or after 2002 and 2 years old.	Census of mothers with and ASD child and those without an ASD child	Census of mothers with ASD children and those without	Purposive	Purposive	purposive	purposive
Specimen tested	Maternal blood at 17 weeks gestation	Maternal blood at 9-13 weeks of gestation.	Amniotic fluid at birth	Child blood	Hair	Hair	Hair
Laboratory method	Inductively coupled plasma-sector field mass spectrometry (ICP-SFMS)	Inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS)	Inductively coupled plasma mass spectrometry (ICP-MS)	NR	Inductively coupled plasma optical emission spectrometry (ICP-OES)	Electro-thermal Atomic Absorption Spectrometer (EAAS) with automatic auto sampler	X-ray micro-analyzer
Data analysis method	Odds ratio (OR) risk estimation	Adjusted Odds ratio risk estimate	T test	Odds Ratio risk estimation		T test	Mann Whitney U test

Hg	-	-		-	-	+	
Pb	-		-	-	-	+	+
Cd	+		-	-	-	-	
As	+		-	-	-	-	+
Ni					-	-	
Mn	+		-	-	-		
Sea-fish consumption		-		-		-	
Conclusion	Maternal exposure to high levels of As, Cd, and Mn were associated with a higher chance for ASD	No significant association between prenatal blood Hg levels and autism among mothers who ate sea-fish.	The presence of heavy metals in Amniotic fluid indicates that they can cross the placenta barrier.	There was no significant difference in child heavy metal blood levels between Cases and Controls.	There was no significant difference in child heavy metal blood levels between Cases and Controls.	There were significantly higher heavy metals (Hg and Pb) concentrations in the hair of cases compared to controls.	There were significantly higher heavy metals (As and Pb) concentrations in the hair of cases compared to controls.

ASD = Autism Spectrum Disorder, NR = Not reported, - = no association, + = significant association.

4. Discussion

Mercury is a poisonous element that accumulates in the liver, kidneys, and nervous system (Szabat et al., 2019). Humans are widely exposed to Mercury through the consumption of contaminated sea fish (Nyarko et al., 2023). This review found no significant association between Mercury exposure and autism. This finding corroborates three previous studies that found no association between mercury and autism (McKean et al., 2015; Van-Wijngaarden et al., 2013; Yau et al., 2014). This finding disagreed with two other studies that suggest an association between Mercury and autism (Geier et al., 2012; Ijomone et al., 2020). The human body has mechanisms that try to maintain homeostasis by eliminating toxic substances.

Lead is a non-essential metal with no known physiological role in the human body (Ijomone et al., 2020). At a blood level of 10 µg/dL, alterations in brain health can occur (Kim et al., 2013). Lead has been named as a cause of autism (Nakhaee et al., 2023). Nevertheless, this review found no significant association between Lead exposure and autism. This finding disagreed with two previous studies that found an association between Lead and autism (Qin et al., 2018; Grump et al., 2017). This finding would imply that biological systems may have a way of curtailing the cellular impact of Lead.

Cadmium is a heavy metal that is harmful to humans as it damages the kidneys at a dose between 350 and 3500 mg (Szabat et al., 2019). This study found no significant association between Cadmium exposure and autism. This finding is noteworthy as Cadmium was a suspected developmental neurotoxin before 2009 (European Food Safety Authority, 2009). This finding corroborates a review that demonstrated that autism spectrum disorder cases in industrialized countries had significantly lower concentrations of Cadmium compared to the general population (Lam et al., 2016). This finding disagrees with a previous review that found an association between Cadmium and autism (Liu et al., 2019). This finding would suggest that the impact of cadmium exposure is debatable.

Arsenic is an inorganic element that is toxic to humans (Skogheim et al., 2021). This study found no significant association between Arsenic exposure and autism. This finding corroborates two prospective studies that found no associations between prenatal arsenic exposure and autism (Forms et al., 2014; Long et al., 2019). This finding disagreed with two reviews that found a significant association (Modabbernia et al., 2017; Rossignol et al., 2014). The Association between Arsenic and autism is therefore not consistent.

Nickel is a heavy metal known to be toxic to humans as it has negative consequences on the kidney, lungs, liver, and brain (Ijomone et al., 2020). This study found no significant association between Nickel exposure and autism. This finding corroborates two previous studies that noted no significant association between Nickel exposure and Autism (Blaurock-Busch et al., 2011; Skalny et al., 2017). This finding disagreed with two studies that found an association between Nickel exposure and autism (Al-Farsi et al., 2013; Roberts et al., 2013). This finding would suggest that the impact of Nickel may be modified by biochemical means.

Manganese is an essential metal with useful physiological functions but excess exposure can interrupt brain function (Ijomone et al., 2020). This study found no significant association between Manganese exposure and autism. This finding corroborates one study that found no association between Manganese exposure and Autism (De-Palma et al., 2012). The finding disagreed with a study that supported an association between Manganese exposure and autism (Arora et al., 2017). The finding would imply that although Manganese could be ingested as a component of mineral capsules, the human body mechanism eliminates the excesses to limit its impact.

Sea fish is known to be rich in omega-3 (Gialloreti et al., 2019). Some studies have implied that sea fish consumption could expose pregnant women and children to heavy metals (Ijomone et al., 2020). This review found no significant association between sea-fish consumption and autism. This finding corroborates a pivotal study that found no association between sea-fish consumption and autism (Oken & Bellinger, 2008). This finding disagrees with studies that implied an association between sea-fish consumption and autism (Lyall et al., 2013; Sullivan et al., 2014). This finding would suggest that there is no strong evidence to conclude that sea fish consumption by pregnant women increase the likelihood of their children having autism.

Limitations

The search strategy was limited to English language studies. Although it imposed some publication bias on the review, it was done because the researcher is fluent in the English language. Furthermore, because this review was a student project and there was no library support on access to paid articles, the search was limited to free full-text research in PubMed and EBSCO essentials. Other databases, like CINHAL, SCOPUS, PsychInfo, and EMBASE were not explored.

The strength of this review is that it provides a middle ground between findings in research on child's hair, maternal blood, amniotic fluid, and sea fish eating status.

5. Conclusion

This literature review focused on association between autism and heavy metal exposure. After synthesis of evidence, this study found that there is no strong evidence of significant association between autism and heavy metal exposure. The global implication of this study is that eating Sea-fish should not be discouraged among pregnant women.

Acknowledgement: None to declare

Funding and Support: This study received no funding or financial support from any organization.

Authors' Contributions: Based on their contributions to the manuscript, all of the authors are eligible to get credit for this study. This study was conceptualized by SB-D, AE, and CE. The literature search was carried out by SB-D and CE. All authors contributed to the interpretation of the data and writing of the final manuscript.

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Compliance with Ethical Standards
Ethics **A**pproval: This review was exempted from University of Port Harcourt Nigeria IRB review and approval.

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