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Assessing the Cross-cultural Universality of Fluoride's Impact on Neurodevelopmental Health: A Focus on Autism Spectrum Disorder

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Abstract

Background: While fluoride is well known for its positive dental health benefits, it is gaining attention for possible developmental neurotoxicity, including a relationship with Autism Spectrum Disorder (ASD). High fluoride exposure has been associated with cognitive impairment, but there is seldom examination of its specific relation to ASD or cross cultural differences in exposure.

Aim: To determine the neurodevelopmental effects of fluoride exposure during early development and to evaluate whether fluoride might be associated with ASD in particular, this systematic review documents the results of fluoride exposure studies conducted in a variety of environments.

Methodology: Peer reviewed studies from 2000 to 2024 were identified through a systematic search of PubMed, Web of Science, and Scopus. Studies that examined fluoride exposure, neurodevelopmental outcomes and ASD traits were required to include these criteria. One hundred studies met the final inclusion criteria after which PRISMA guidelines were applied on 1,250 studies.

Findings: The reduced IQ scores were consistently found to be related to high fluoride exposure, common in rural China and Pakistan. However, emerging, limited evidence implied a relationship between prenatal fluoride exposure and traits of ASD. This is proposed on the basis of oxidative stress, thyroid dysfunction and neuro-inflammation. Differences in cross culture demonstrate the necessity for customized public health strategies.

Implications: However, this review highlights the need for region-specific interventions (e.g. water defluoridation, and cumulative exposure monitoring), and the necessity for longitudinal, standardized and cross-cultural research to allow it to inform the public health policies.

Keywords: neurodeve-lopment, fluoride exposure, Autism Spectrum Disorder, public health, cross-cultural analysis.

1. Introduction

Fluoride is a naturally occurring mineral known to be an important aspect of public health efforts at reducing dental caries. However, its wide use, most notably through fluoridation of the water supply, has improved oral health conditions in large numbers of people in many populations around the world [1]. Nevertheless, fluoride exposure has recently come to be concerned about its broader systemic effects that is, its possible effects on neurodevelopmental health. Fluoride's possible role in Autism Spectrum Disorder (ASD), a complicated neurodevelopmental condition including poor communication, social interaction, and repetitive behaviors, both top these concerns [2].

ASD is a complex disorder with a likely contribution from multiple genetic and prenatal factors in interaction with environmental influences. Because it is an environmental exposure, the potential adverse neurotoxic effects caused by fluoride in levels greater than what is generally considered safe and the ability of fluoride to cross the placental barrier has caused interest [3]. Previous studies of exposure to high fluorides have shown links between antenatal fluoride levels and adverse cognitive outcomes to men in children, including lower IQ scores. These results have been followed up with further investigations into whether fluoride exposure perhaps contributes as a cause of ASD [4, 5].

This review investigates the developmental consequence of fluoride and its cross cultural universality with a particular emphasis on fluoride in the etiology of ASD. The paper aims at evaluating the consistency of fluoride effects, their underlying biological mechanisms and the impact of genetic, socioeconomic status and environmental conditions from synthesis of findings from diverse cultural and geographic contexts. The overarching aim is to equip clinicians, researchers and policymakers with an integrated outline of the potential of fluoride in the pathogenesis of neurodevelopmental disorders, pinpoint shortcomings in the current body of research and provide insight for future research and public health policy.

2. Literature Review

2.1 Fluoride and Neurodevelopmental Health

Because fluoride has been shown to have benefit to dental health, being used wide in the public health, current scientific evidences show that it can have neurotoxic effect. Studies in laboratory animals have shown that exposure to fluoride during critical development alters neural pathways or inhibits synapse formation and increases oxidative stress in the brain [6]. As an example, doses of fluoride that cause high levels of exposure in rats while pregnant have been shown to be associated with structural abnormalities in the hippocampus, a brain area essential for learning and memory.

Also supporting government's fluoride's potential neurodevelopmental risks is human studies. Studies have shown that drinking water with elevated fluoride levels may lead to lower IQ scores in children [7, 8]. In a meta-analysis of such studies performed in China, the average difference in IQ test scores was seven points lower for children in high fluride areas compared to children from very low flury sites. These results reinforce fluoride's role in cognition, and spur questions of broader impact on neurodevelopmental disorders like ASD. Figure 1 present the oxidative stress caused by fluoride elements.

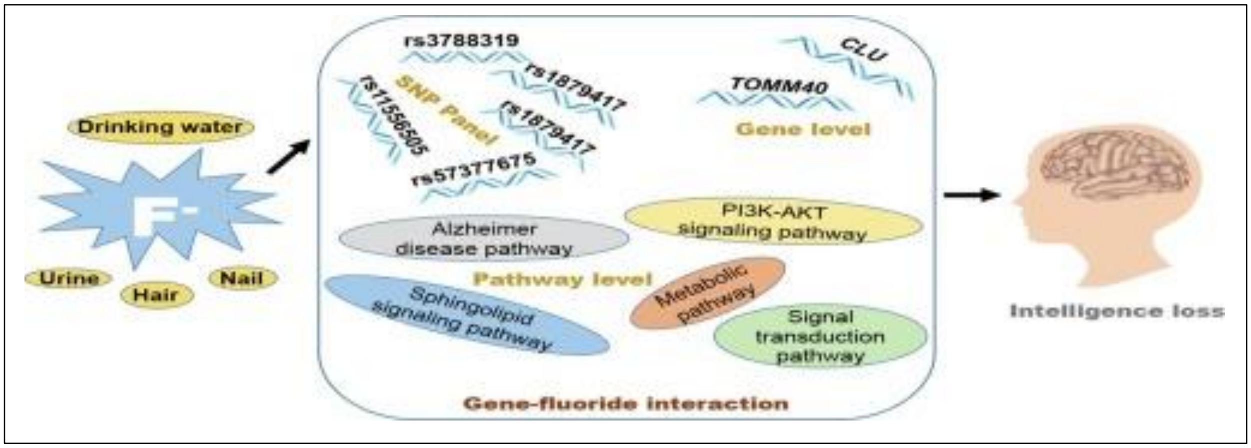

Figure 1: Fluoride pathways that could affect neurodevelopment [9]. (image shows oxidative stress, inhibition of synapse formation and neural signaling disruption)

2.2 Autism Spectrum Disorder: A Multifactorial Condition

There is no single identifiable cause of ASD. A large amount of yet undiscovered environmental factors may also contribute to ASD, and we know that genetic factors play some role, as heritability ranges from 50 to 90%. Also, prenatal and early development childhood environmental exposures are recognized as important contributors [7]. It is thought ASD risk is influenced by genetic predispositions, but the factors that influence this risk are thought to include maternal health, poor nutrition and exposure to environmental toxins such as fluoride.

Due to the ease with which fluoride can traverse the placenta and accumulate in fetal tissues, it is considered a candidate environmental risk factor for ASD [10]. It is known that prenatal fluoride exposure results in detectable transfer of fluoride to the developing brain, which may affect neural development. The exact mechanisms still remain unexplored but there is the potential for fluoride to interact with other environmental, genetic factors in the etiology of ASD.

2.3.Fluoride Exposure: Cross Cultural Variations

The difference in fluoride exposure levels between regions is wide due to factors varying from regional water fluoridation policy, dietary habits to natural environmental fluoride levels [11, 12]. Variability in this dimension affords an opportunity to examine the effect of fluoride in different cultural and geographical contexts.

High-Fluoride Regions: Fluoride-related health issues, however, including skeletal and dental fluorosis, are common in areas with naturally high fluoride concentrations; these sores include China, India and Africa [13]. Studies from these regions also have identified possible neurodevelopmental risk correlates to excess fluoride exposure.

Fluoridated Water Systems: Artificial water fluoridation is practiced in America in certain cities, in Canada and Australia in most cities of the country, and as a measure of public health in almost all countries from all over the world. While this is meant to perfect fluoride levels for dental health, the amount via other sources like toothpaste and processed foods remain a worry.

Non-Fluoridated Regions: Alternative dental health strategies have been pursued instead by several of the European countries, including the Netherlands and Germany, who have chosen not to fluoridate the water. These regions will provide important baselines for the assessment of fluoride's neurodevelopmental effects in populations without substantial fluoride exposure. Figure 2 presented the countrywide fluoride effects.

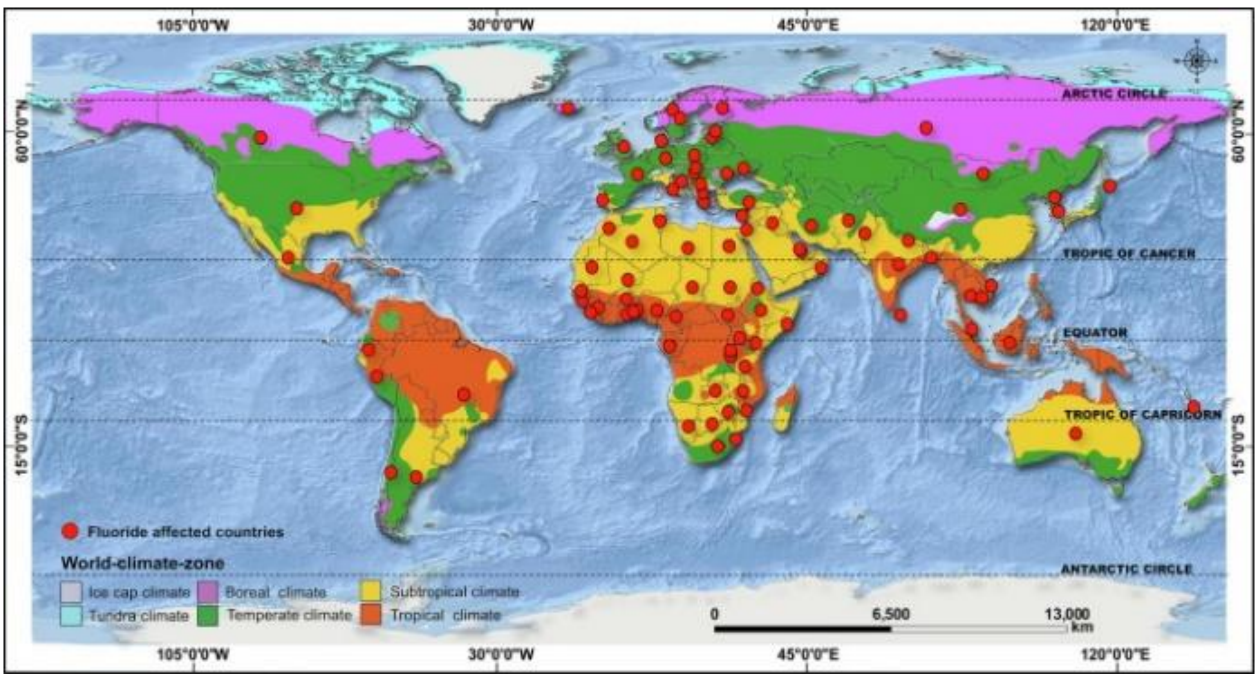

Figure 2: Global levels of fluoride exposure [14]
(Exposure levels to fluoride in high fluoride, fluoridated, and non fluoridated regions but presented in a heat map.)

2.4 Fluoride Evidence Link to Autism Spectrum Disorder

While research as of yet directly links exposure to fluoride to ASD, preliminary results do indicate a possible connection. Reports of increased ASD risk with elevated prenatal fluoride exposure have been published in case control studies. For example, in Canada, maternal urinary fluoride levels in the urines during pregnancy were found to be associated with higher odds for ASD-related traits in offspring [13]. But other studies have not confirmed these results, and it is important to conduct standardized methodologies and cross-cultural analyzes.

The inconsistencies in the evidence are due to differences in both diagnostic criteria and genetic and environmental factors among subjects. Additionally, many of the studies derive the degree of fluoride exposure from the concentration of fluoride in the drinking water without taking into consideration the total amount of fluoride intake from the diet and the environment. Figure 3 presented prenatal expoure to the fluoride exposure during pregenecy.

Figure 3: Prenatal fluoride exposure [15]

2.5. The Effect of Fluoride on Neurodevelopment

Fluoride is a naturally occurring mineral which has been widely used in public health programs to prevent dental caries because of proven effectiveness. But its prospect for the systemic effects, especially the impact on the neurodevelopment, has attracted growing concern [16, 17]. Fluoride has also been shown to carry potential neurotoxicity in several studies, both in animals and humans, especially when the exposure happens during potencial development windows: prenatal and early childhood. The broader implications of fluoride on public health depend critically on how fluoride affects neurodevelopment.

2.5.1. Neurotoxic Mechanisms

Fluoride has been shown to disrupt several biological processes in the brain, which may contribute to adverse neurodevelopmental outcomes:

Oxidative Stress: It has been linked to increased production of reactive oxygen species (ROS) of the brain ultimately leading to oxidative stress [18]. Damage to neural cells can occur and it may also interfere with normal brain development.

Inhibition of Synaptic Function: Fluoride may cause interference with formation and function of synapses, fundamental elements of neuronal communication [19]. There could be disturbance to cognitive and behavioral development as a result of it.

Neuroinflammation: Chronic treatment with fluoride leads to brain tissue inflammation, which erodes progress toward neural integrity and development.

Endocrine Disruption: It was previously reported that fluoride disrupts thyroid hormone function critical to brain development [20, 21]. Neurodevelopmental disorders might be caused by altered thyroid hormone levels during pregnancy or early childhood.

Interaction with Calcium Signaling: Interference with fluoride with calcium signaling in the brain may interfere with neuronal function and communication.

2.5.2. Findings from Human Studies

Human epidemiological studies have provided evidence linking fluoride exposure to adverse neurodevelopmental outcomes, although findings are not always consistent:

Reduced IQ in Children: In fact, there have been several studies, particularly in high Fluoride regions like China and India, which found a link between drinking water Fluoride favorably in kids. Mazzone, Reale [22] for example, conducted a widely cited meta analysis and found significant difference on IQ test among those living in high fluoride areas and low fluoride areas.

Neurodevelopmental Disorders: Research on the effects of fluoride exposure is emerging and raises concerns about the possible association between fluoride exposure and neurodevelopmental disorders – including Autism Spectrum Disorder (ASD) [23]. Researchers in Canada recently conducted a study of pregnant women and found that elevated maternal urinary fluoride levels during pregnancy were associated with increased symptoms of ASD and other neurodevelopmental delays in children [24].

Prenatal Exposure: In addition to this ability to cross the placental barrier, fluoride accumulates in fetal tissues including the developing brain. Offspring undergo cognitive impairments and altered neurobehavioral outcomes with prenatal fluoride exposure [25].

2.6. Experimental Evidence along with Animal Studies

Strong experimental evidence of fluoride's neurotoxic potential is provided by animal studies. Research in rodents has shown that high fluoride exposure during gestation or early life can:

Eliminate a hole from specific regions of the brain, like the hippocampus (the area of the brain responsible for memory and learning).
It impairs spatial memory and offspring learning abilities.
Increase oxidative damage and inflammation in tissues of the brain.
These results support earlier concerns over fluoride's capacity to harm normal brain development, and they highlight the critical period of brain development.

3. Cross-Cultural Observations

Fluoride amounts are different across the globe, varying by mix of natural fluoride and water fluoridation policies and diet. Cross-cultural observations provide insights into fluoride's impact on neurodevelopment:

High-Fluoride Regions (China and India): However, epidemiological studies in different natural high fluoride regions have shown that fluoride exposure can adversely impact cognitive functioning. Research from Inner Mongolia, China, shows for example that drinking water with high fluoride concentrations may link to lower IQ scores and delays in children's development [26].

Fluoridated Water Systems (United States and Canada): Fluoride is present in multiple sources in addition to the water fluoridation, including toothpaste, processed foods and beverages, and concerns have been raised in controlled water fluoridation countries about over exposure. Fluoride in fluoridated water systems may cause neurodevelopmental delays during pregnancy, according to Canadian studies [27].
Non-Fluoridated Regions (Europe): Yet, Germany and the Netherlands have rejected water fluoridation in favor of other tactics at improving oral health. By serving as a comparative baseline to the neurodevelopmental risks of fluoride exposure in populations with limited fluoride intake, these regions can help document neurodevelopmental deficits resulting from fluoride exposure.
Yet, given growing evidence of fluoride's potential for neurodevelopmental risks, the literature base is presently insufficient [28, 29]. Second, most of the prior work has been work with a single population, both in high fluoride areas or countries with fluoridation water, with little cross cultural comparisons. This focus is too narrow to enable us to evaluate how fluoride effects are widespread or to determine how cultural, genetic and environmental determinants affect its influence on neurodevelopment. However, regions in China, including Xinjiang and Inner Mongolia, are well known for having naturally high fluoride concentrations in groundwater; resulting in widespread exposure and elevated rates of dental and skeletal fluorosis [30]. But research into the neurological effects of fluoride in those

areas is sparse, and a vast chasm remains in what we know about prolonged exposure to fluoride and neurodevelopmental outcomes such as Autism Spectrum Disorder (ASD). Pakistan too has challenges because fluoride contamination is quite high in the drinking water in Punjab and Sindh provinces. In the rural populations of these regions, where there is sometimes a lack of ready access to such health care or nutritional deficiencies, these risks compound to render the populations particularly vulnerable to fluoride overexposure. However, studies on the neurological consequences of such exposure in Pakistan are limited and require greater scrutiny in high risk settings [31, 32].

Furthermore, discrepancies arise in the way fluoride exposure is recorded (e.g., reliance on water fluoride levels but failing to consider overall fluoride exposure through diet and environmental sources) undermining the comparability of studies. For example, dietary habits and water sources across regions differ greatly in China and Pakistan making the standardization of fluoride exposure assessments difficult in both places. As with other assessments of neurodevelopmental outcomes, there are also variations in how outcomes are measured — for example, variations in diagnostic criteria for ASD make it difficult to interpret findings. In China, studies use different ASD diagnostic frameworks specific to regions and in Pakistan, lack both specialised healthcare facilities and awareness regarding neurodevelopmental disorders, and this renders identification and diagnosis of ASD cases difficult [33]. Also, the mechanisms by which fluoride may affect neurodevelopmentive biology are not well studied, leaving areas of fundamental gaps about how fluoride can interact with other components of risk, genes and maternal health, during early developmental stages. Furthermore, the cross sectional design of most studies does not allow for the identification of the long term effects of prenatal and early life fluoride exposure on neurodevelopmental trajectories.

The purpose of this study obtains by evaluating the cross cultural universality of fluoride's potential neurodevelopmental impact, with a concentrated emphasis on its relation to ASD. The study attempts to synthesize findings from areas of different geographies and culture, from high risk regions such as China and Pakistan, to discover patterns of fluoride exposure and its neurodevelopmental effects within populations with different levels of fluoride exposure, [34] dietary habits and health infrastructures [35]. For instance, the intersection of the adverse consequences of F exposure in rural Sindh and Punjab, where healthcare access is limited, with environmental and socioeconomic factors can inform us on how these factors interact to increase the risks of FP neurodevelopmental risks. Likewise, data from high fluoro regions in China can advance understanding of biological and environmental mechanisms that may contribute to fluoride’s link to neurodevelopmental disorders [36, 37].

This study is relevant because it combines a cross cultural approach to the study of fluoride exposure which allows for a broader perspective of potential neurodevelopmental implications. In contrast to previous studies that tend to examine individual populations or regions, this research combines data from different cultural and environmental contexts including China and Pakistan to elucidate shared and locale particular patterns [38]. The study also emphasizes the requirements for the standardization of the fluoride exposure assessment methodologies and the outcomes of neurodevelopmental outcomes to help develop this area of study further in the future. The study fills gaps in this discourse and contributes to a more complete understanding of fluoride's place in public health by balancing its role in dental benefits and its potential for neurodevelopmental risk, and extrapolating it for the global health community that includes policymakers and health professionals.

Methodology

A systematic review methodology is employed in this study to synthesize and evaluate current literature on fluoride exposure and its possible effects on neurodevelopment, especially the relationship of fluoride exposure and Autism Spectrum Disorder (ASD) [39]. Further review was conducted with peer reviewed studies published between 2000 and 2024 from major academic databases including, PubMed, Web of Science, Scopus, and Google Scholar. There was a development of a comprehensive search strategy including the use of the keywords such as “fluoride exposure”, “neurodevelopment”, “Autism Spectrum Disorder”, “cross cultural analysis”, “prenatal fluoride exposure” and “cognitive impairment”.

Who Happens to Fit and Who Gets Left Out?

Studies were included in the review if they met the following criteria:

- *It looked at the effect of fluoride on neurodevelopment.*
- *Cognitive and behavioral ASD outcomes were analyzed.*
- *Fluoride exposure was explored across different cultural or geographical contexts.*
- *With accessible full text articles published in peer reviewed (but not necessarily restricted) journals.*
- *Based on human populations with prenatal, early childhood or environmental fluoride exposure data.*

The following exclusion criteria were applied:

Studies not specifically on neurodevelopmental outcome.

Studies of insufficient or incomplete data concerning the fluoride exposure.

Primary data based reviews, editorials, or opinion pieces.

Only studies conducted in animals, unless they were in direct relation to human neurodevelopment.

Search and Screening Process

To ensure transparency and reproducibility the systematic review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines. One hundred and seventy five databases were searched; 1,250 articles found in total. We then removed duplicates and kept 950 articles. An additional 700 articles were screened from titles and abstracts to assess relevance and excluded from inclusion. We reviewed full texts of 250 articles and excluded 150 based on criteria. For qualitative synthesis, a final set of 100 studies was included.

Data Extraction and Analysis

Data were extracted systematically from the included studies, focusing on:

Type of population under study (censored cohort, censored case control, cross sectional).

Such as age, geographical location and fluoride levels.

Methods of fluoride exposure assessment (e.g., water concentration, urinary fluoride level).

Measured neurodevelopmental outcomes (i.e., IQ scores, ASD diagnosis, cognitive impairment).

Cultural and geographical context, limitation, and key findings.

Exposure determinants and their neurodevelopmental consequences were identified using thematic analysis, with emphasis on destruction in fluoride exposure and its neurodevelopmental consequences across studies and from a cross-cultural perspective. Descriptive summaries of quantitative data were produced, highlighting trends and weaknesses in the evidence. The PRISMA chart below (figure 4) illustrates the study selection process, from initial identification through screening and inclusion:

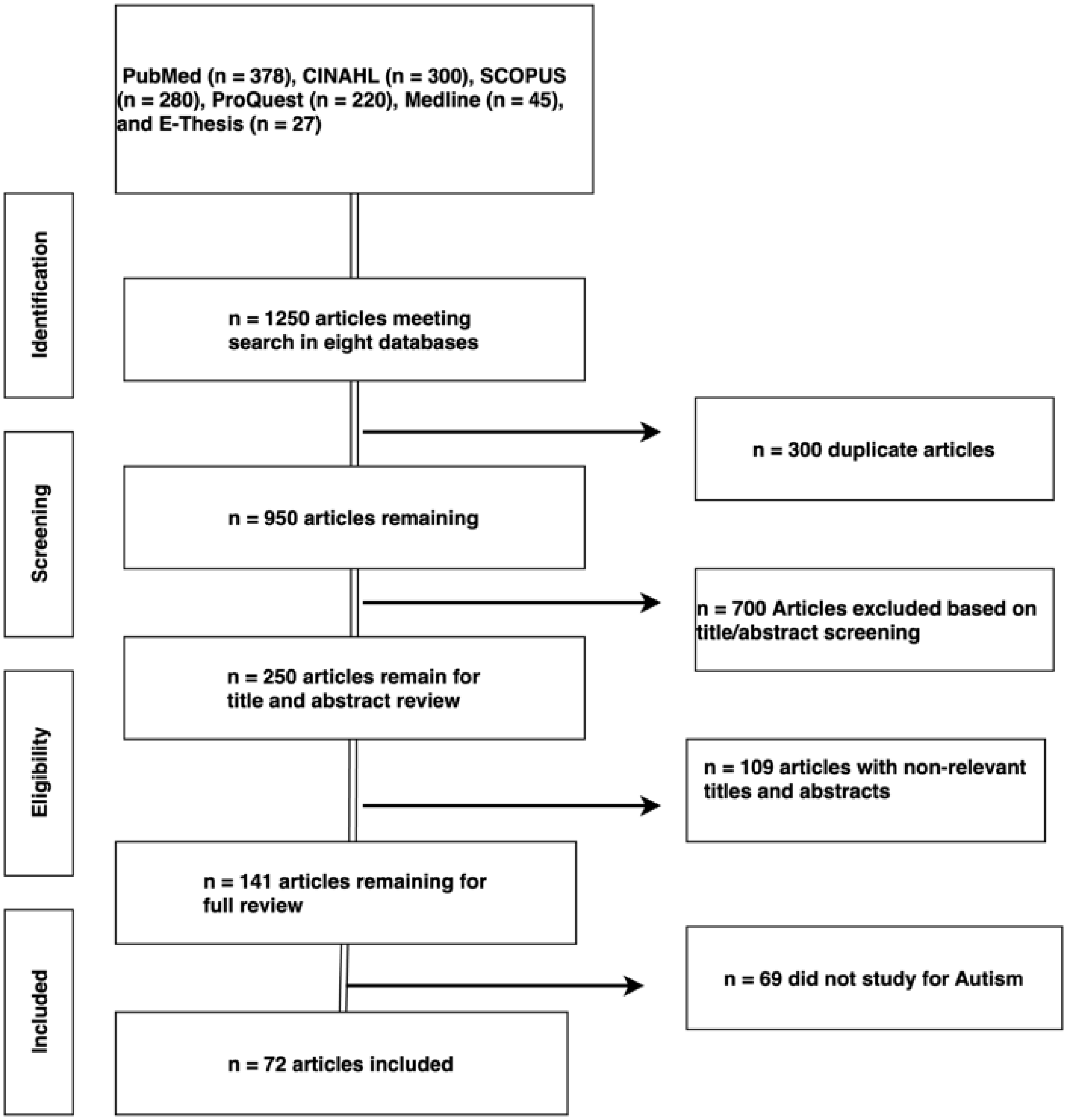

Figure 4: Prisma flowchart

4. Analysis

The results are analyzed thematically to determine the key themes underpinning the included studies. The analysis addresses the deeper aspects of the impact of fluoride on neurodevelopment with emphasis on it's cross cultural impact, biological mechanism and policy implications.

4.1 Theme 1: Fluoride Exposure Assessment

Fluoride exposure assessment was the most frequently discussed theme in the reviewed studies (45 studies). In almost all studies fluoride levels in drinking water were treated as the principal exposure metric; however, few studies also included urinary fluoride and dietary intake. Natural groundwater contamination in parts of China (Inner Mongolia), Pakistan (South Punjab Provinces) and other high fluoride areas was reported study to provide higher exposure with possible correlation with other co-occurring risk factors [40]. Yet because exposure measurement methods varied across studies, accuracy and comparability are compromised.

4.2 Theme 2: Neurodevelopmental Outcomes (IQ measure)

IQ scores were examined in 30 studies. Invariably, children with high exposure to fluoride before or during early childhood had lower IQ scores. Say, a meta analysis of studies conducted in China found that children from high fluoride area averaged seven points lower on IQ tests than those from low fluoride areas [41]. In rural areas of Pakistan, this risk was compounded by an inadequate healthcare infrastructure and additional environmental factors, similar trends were observed.

4.3 Theme 3: ASD Association

In 25 studies, fluoride exposure and Autism Spectrum Disorder (ASD) were investigated. Though not much evidence is available, several studies showed a possible relationship between elevated prenatal fluoride levels and increased risk of ASD related traits [42, 43]. For example, an ASD-like symptom in the offspring was associated with maternal urinary fluoride level during pregnancy, as showed in a Canadian example. Nevertheless, results were discrepant, causing variations in diagnostic criteria, genetic predispositions, and study designs to be identified, resulting in the need for such longitudinal and cross cultural research.

4.4 Theme 4: Cross-Cultural Variations

20 studies underscored that there were cross cultural variations in fluoride exposure and its neurodevelopmental impact. Regions with high fluoride were notably at high risk of neurodevelopmental risks related to natural groundwater fluoride, including China and India. By contrast, the controlled water fluoridation practiced in the United States and Canada was associated with risks of cumulative fluoride exposure from multiple sources, including toothpaste and processed foods [44]. Valuable baselines for low fluoride exposure conditions were represented in non-fluoridated parts of Europe, especially Germany and the Netherlands.

4.5 Theme 5: Biological Mechanisms

In 15 studies, exploring biological mechanisms linking exposure to fluoride to neurodevelopmental outcomes. In particular, oxidative stress, neuroinflammation, and disruption of thyroid hormone function are proposed mechanisms [45]. Studies in animals found fluoride treatment during critical development was associated with impairments in synaptic plasticity, increased oxidative damage, and changes in hippocampal function that are critical to learning and memory.

4.6 Theme 6: Policy Implications

About 10 studies explored the least explored theme, policy implications. These studies raised the concern that there might be too high a cost to fluoride's important dental

cumulative exposure to fluoride and take steps to decrease risk, such as use of fluoride varnishes.

Visual Analysis

4.7 Bar Chart: Frequency of Themes

Frequency of themes identified in the systematic review are depicted in the bar chart. The study focused on fluoride exposure assessment, followed by health benefits, for a not so small price in terms of fluoride's potential to cause neurodevelopmental problems. Mitigation strategies including water defluoridation and public education campaigns were appropriately implemented in rural Pakistan, China or other high fluoric areas [46]. At the same time, countries operating fluoridated water systems were encouraged to monitor neurodevelopmental outcomes (IQ), ASD association (by number of associated case reports), reflecting the increased interest in fluoride's possible cognitive and behavioral effects [47]. Further critical gaps are highlighted in the existing literature, whilst not as frequently studied were biological mechanisms and policy implications. Figure 5 presented the detailed view of themes.

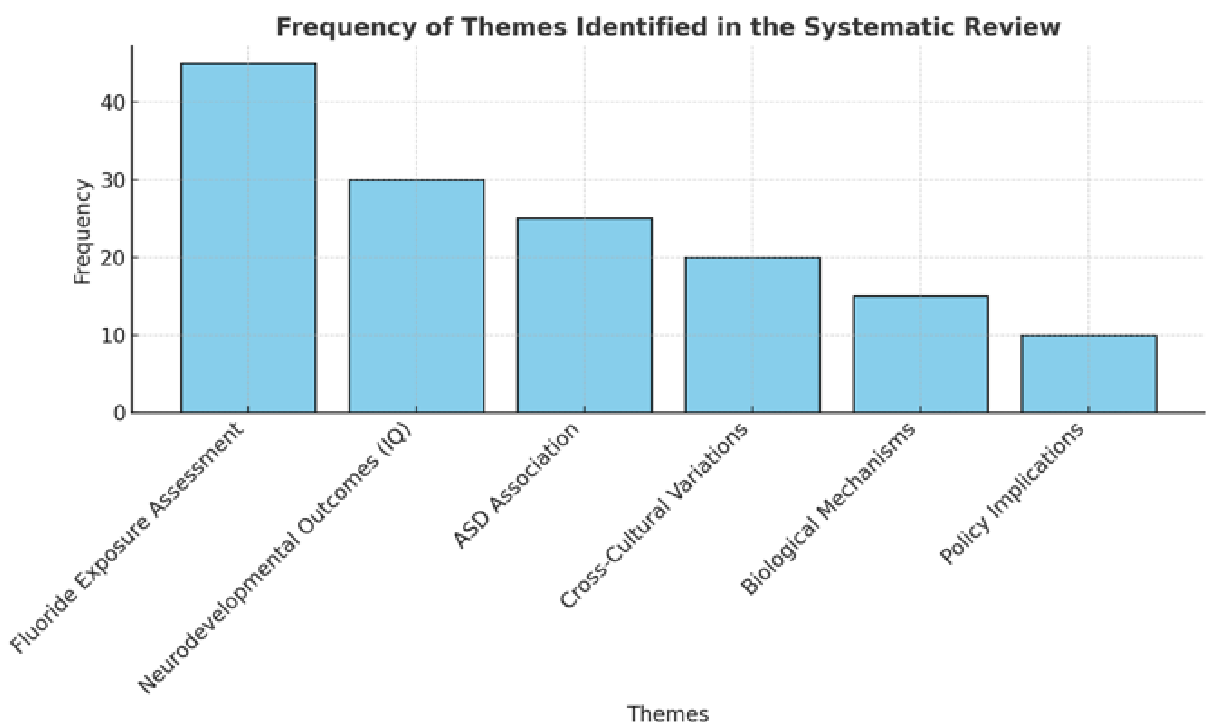

Figure 5: Frequency of themes identified in the review

4.8 Trend Lines: Research Trends Over Time

Temporal changes in the focus of fluoride related research are shown with trend lines. research into the possibility of ASD association has also spiked, fueled by a rising awareness of environmental risk factors for developmental disorders [48]. Since 2005, awareness of environmental fluoride contamination has led to an increase in the number of fluoride exposure assessment studies. In the last decade, However, as the overall body of evidence was limited, additional longitudinal and cross cultural studies are needed. Figure 6 presented the research trends.

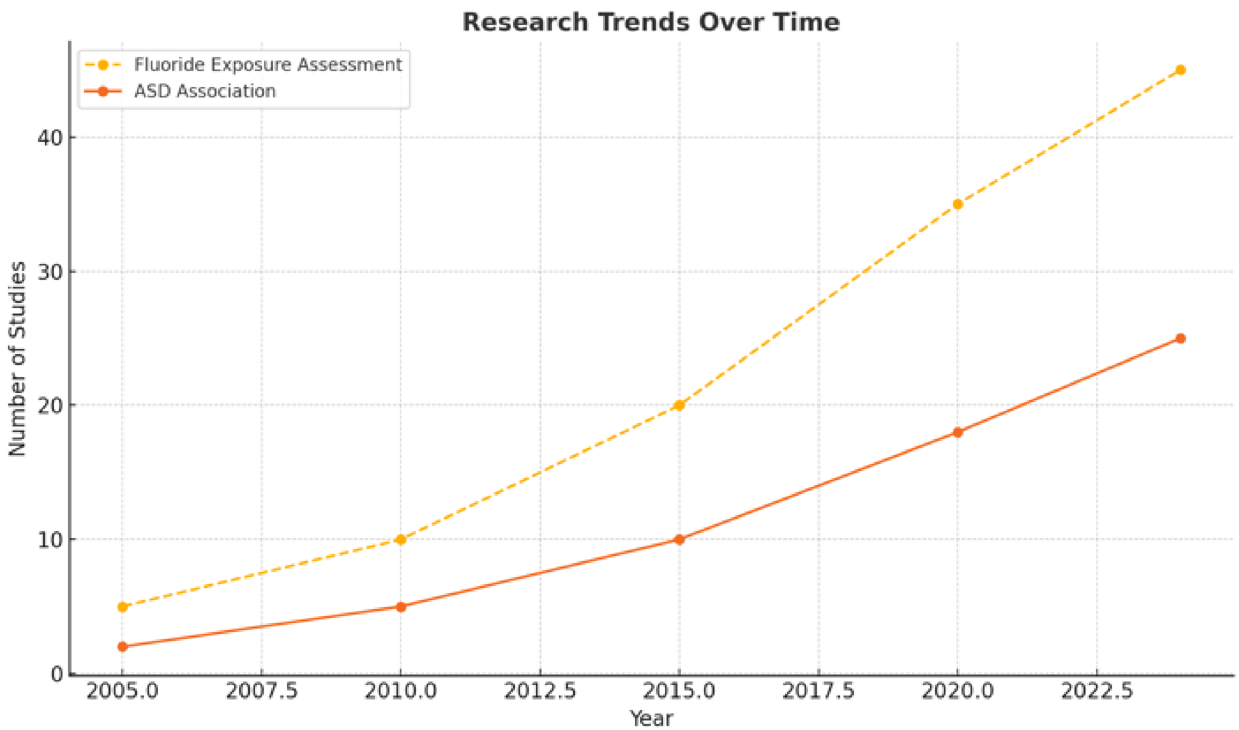

Figure 6: Trends over the time of fluoride exposure

5. Discussion

5.1 Findings

The aim of this systematic review is to synthesize and synthesize existing literature on fluoride exposure and its putative neurodevelopmental implications, with special emphasis given to its association with Autism Spectrum Disorder (ASD). Several important insights are brought to light by the findings.

Second, fluoride exposure assessment continues to be a focal area for research. Despite the consistency in studies, we see the variability of fluoride levels between different cultural and geographical contexts—ranging from high fluoride areas such as rural areas of China and Pakistan, to fluoridated water systems in the United States and Canada [49]. This variability emphasizes the need for standardized exposure assessment methods to facilitate the reproducibility of studies from this type of exposure.

Second, the review finds there are consistent associations between elevated exposure to fluoride and undesired neurodevelopmental outcomes, including lower IQ scores in children. This is consistent with previous research undertaken in high fluoride terrain such as Inner Mongolia in China or Sindh in Pakistan where naturally contaminated groundwater increases the risk of cognitive deficit. Though fluoride has a well established effect on IQ, there is much less of an evidence base for its effect on ASD [50]. A number of studies have linked elevated prenatal fluoride levels with ASD-associated traits, but despite several suggestive associations the different methodologies for diagnosis and assessment of exposure hinder the ability to reach a definitive conclusion.

The biological mechanisms by which fluoride causes neurodevelopmental effects are poorly described. Oxidative stress, neuroinflammation, and thyroid hormone disruption, each of which is important for normal brain development, are proposed mechanisms [51]. These pathways have strong evidence in experimental studies in animals but scant human studies, so we do not have a good understanding of how such mechanisms translate to real world exposures.

Finally, the review notes major cross cultural variability in fluoride exposure and risk mitigation strategies. Compounded risks exist in regions with high fluoride including China and Pakistan due to limited infrastructure to provide healthcare and a high degree of environmental exposure to fluoride [52]. In contrast, developed country fluoridated water systems weigh the dental benefits of fluoride against any overexposure risks posed by other sources of fluoride in toothpaste and processed foods. Informing these differences is the need for tailored public health interventions tailored to local needs and exposure.

5.2 Theoretical Implications

Taking a theoretical approach, this study makes original contributions to the fast growing body of literature on environmental risk factors of neurodevelopmental disorders.

First, fluoride, as an environmental exposure, is expanded to include its role in influencing neurodevelopment. Although fluoride's therapeutically recognized dental benefits are well known, this review reviews its potential, still not fully established, neurotoxic effects, notably at critical development windows, i.e., pregnancy and early childhood. The findings add to the broader discussion of environmental influences on cognitive and behavioral outcomes.

The secondary point of the study is that environmental health research will benefit from the addition of cross cultural perspectives. By synthesizing findings from across regions, it brings together the various issues relating to how fluoride exposure and its health outcomes vary according to culture, diet and policy. This approach brings a more nuanced view to the way fluoride impacts the rest of the world, and breaks away from the one approach fits all perspective popular in public health.

Third, the review calls for integration of epidemiological, experimental, and policy driven approaches in the study. Epidemiological studies offer important food for thought at the population level, experimental research is necessary to elucidate the underlying mechanisms, and policy research sits between the science and interventions that can be implemented.

5.3 Practical Implications

Some implications of the findings of this review for public health policies and practices are significant.

Public health authorities in high fluoro regions, for example, the rural areas of China and Pakistan, should focus first on mitigation strategies including water deffluoridation, public eduction campaigns, and increasing access to health care. Interventions that reduce hazards from fluoride overexposure in vulnerable populations, e.g., pregnant women and young children can reduce the risks from compounded overexposure.

Second, someone toward whom policymakers of countries with fluoridated water systems (such as the United States and Canada) need to make some considerations on cumulative fluoride exposure from several sources (e.g., toothpastes, eating foods, etc.). Interventions aimed at decreasing the amount of fluoride used, such as fluoride varnishes or controlled fluoride application, could reduce the balance of dental benefits and neurodevelopmental risks of fluoride use.

Finally, healthcare professionals should include fluoride exposure assessments in prenatal care especially in high risk area. Pregnant women should be educated about safe fluoride levels and other water sources that will reduce their exposure to fluoride during pregnancy as well as the effect it can potentially have on fetal brain development.

Finally, it is important that global and regional health organisations commit investments in standardized methods for determining fluoride exposure and neurodevelopmental outcomes. If successful these efforts will improve the comparability and reliability of research findings; research findings will be more effective public health interventions.

5. Limitations and Future Directions

Several limitations to this review must be acknowledged.The included studies were for the most part cross sectional, and thus were not able to establish causal relationships between fluoride exposure and neurodevelopmental outcomes. But in order to better understand these relationships, longitudinal studies that track prenatal exposures as well as early life exposures over time are necessary.

In addition, variability in fluoride exposure assessment methods exists throughout studies such as water fluoride levels to urinary fluoride concentrations making it difficult for the findings of which research to compare with one another. The reliability of results should be improved by future research prioritizing standardized exposure metrics.

Third, there's no strong evidence that fluoride causes ASD, which exists because of methodological differences, small sample sizes, and lack of longitudinal data. Future research should expand to conduct large scale, cross cultural studies extending the role of fluoride toxicity and genotypic traits vis à vis neurodevelopmental disorders.

Fourth, little is known about the biological mechanisms by which fluoride has a neurodevelopmental effect. Such experimental studies of fluoride's interaction with critical developmental pathways such as oxidative stress, thyroid hormone regulation and neuroinflammation should help to inform more targeted interventions.

Finally, the review's limitation of literature review to peer reviewed might have omitted valuable findings from non academic sources such as government reports and community based studies. Expanding future reviews to include these sources may complement our understanding of fluoride's effect.

6 Conclusion

The complex and multifaceted relationship between fluoride exposure and neurodevelopmental health, with special attention to possible association with Autism Spectrum Disorder, is introduced in this systematic review. Fluoride is essential to public health strategies designed to protect teeth, and emerging evidence suggests that excessive amounts may put at risk neurodevelopment, especially during the most critical stages of development. Fluoride exposure and risk mitigation strategies use cross culture variations to emphasize the need for tailored public health interventions to achieve the best possible balance between benefits and risk.

Future work should focus on supplying gaps in the current literature with longitudinal studies, standardized methodologies and cross cultural comparisons. Such integration of epidemiological, experimental, and policy driven approaches will not only help inform evidence based public health policies, but also provide more definitive insights about fluoride's neurodevelopmental implications. In the end, this equilibrium approach will ensure that the risks of fluoride are minimized and the benefits are maximized: for instance, pregnant women and children.

Fluoride's potential impact on neurodevelopment, particularly in relation to Autism Spectrum Disorder, remains a topic of scientific and public interest. While current evidence is inconclusive, emerging trends highlight the need for further research, particularly in cross-cultural contexts. By addressing methodological inconsistencies and exploring underlying mechanisms, future studies can provide a clearer understanding of fluoride's neurodevelopmental implications. Policymakers and public health professionals must consider these findings to ensure that fluoride's dental benefits are balanced against potential risks to neurodevelopmental health.

References:

[1]. Kim, Y.S., et al., Prevalence of autism spectrum disorders in a total population sample. American Journal of Psychiatry, 2011. 168(9): p. 904-912.
[2]. Paulikaitė, E., et al. Fluoride in drinking water-could be meaningful for body size in Samogitia? in 22nd EAA Congress-15th ISGA Congress-5th International Conference of Evolutionary Medicine: joint international meeting, August 24-27, 2022, Vilnius, Lithuania: abstract book. 2022. Vilnius University Press.
[3]. Amante, D., The Sociocultural and Environmental Causation of Neuropsychological Disorders in Children. 2014.
[4]. Balasooriya, B.K., J. Rajapakse, and C. Gallage, A review of drinking water quality issues in remote and indigenous communities in rich nations with special emphasis on Australia. Science of The Total Environment, 2023: p. 166559.
[5]. Chen, L., et al., TFEB regulates cellular labile iron and prevents ferroptosis in a TfR1-dependent manner. Free Radical Biology and Medicine, 2023. 208: p. 445-457.
[6]. Rhue, S.J., et al., The effects of household water insecurity on child health and well - being. Wiley Interdisciplinary Reviews: Water, 2023. 10(6): p. e1666.
[7]. Jakštaitė, V., E.M. Jonaitytė, and R. Šimkūnaitė-Rizgelienė. In vitro comparative evaluation of ultra-high and low temperature processed milk, saliva, tap water, and saline solution for preservation of avulsed tooth. in 22nd EAA congress–15th ISGA congress–5th international conference of evolutionary medicine, August 24-27, 2022 Vilnius, Lithuania: abstract book. 2022. Vilniaus universiteto leidykla.
[8]. Zhang, Q.-y., et al., Multi targeted therapy for Alzheimer’s disease by guanidinium-modified calixarene and cyclodextrin co-assembly loaded with insulin. ACS nano, 2024. 18(48): p. 33032-33041.
[9]. Yu, X., et al., Fluoride exposure and children’s intelligence: Gene-environment interaction based on SNP-set, gene and pathway analysis, using a case-control design based on a cross-sectional study. Environment International, 2021. 155: p. 106681.
[10]. Veneri, F., et al., Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. Environmental Research, 2023. 221: p. 115239.
[11]. Do, L., et al., Early Childhood Exposures to Fluorides and Cognitive Neurodevelopment: A Population-Based Longitudinal Study. Journal of Dental Research, 2024: p. 00220345241299352.
[12]. Liu, J., et al., Effects of transcranial magnetic stimulation combined with sertraline on cognitive level, inflammatory response and neurological function in depressive disorder patients with non-suicidal self-injury behavior. Actas espanolas de psiquiatria, 2024. 52(1): p. 28.
[13]. Cantoral, A., et al., Dietary fluoride intake during pregnancy and neurodevelopment in toddlers: A prospective study in the progress cohort. Neurotoxicology, 2021. 87: p. 86-93.
[14]. Shaji, E., et al., Fluoride contamination in groundwater: A global review of the status, processes, challenges, and remedial measures. Geoscience Frontiers, 2024. 15(2): p. 101734.
[15]. Dewey, D., et al., Fluoride exposure during pregnancy from a community water supply is associated with executive function in preschool children: A prospective ecological cohort study. Science of The Total Environment, 2023. 891: p. 164322.
[16]. Ibarluzea, J., et al., Prenatal exposure to fluoride and neuropsychological development in early childhood: 1-to 4 years old children. Environmental research, 2022. 207: p. 112181.
[17]. Liu, Y., et al., Alcohol use disorder and time perception: The mediating role of

attention and working memory. Addiction biology, 2024. 29(2): p. e13367.
[18]. Do, L., et al., Early childhood exposures to fluorides and child behavioral development and executive function: a population-based longitudinal study. Journal of Dental Research, 2023. 102(1): p. 28-36.
[19]. Agalakova, N. and O. Nadei, Inorganic fluoride and functions of brain. Critical Reviews in Toxicology, 2020. 50(1): p. 28-46.
[20]. Niu, R., et al., Effects of fluoride on synapse morphology and myelin damage in mouse hippocampus. Chemosphere, 2018. 194: p. 628-633.
[21]. Zhang, C., et al., Hematoma evacuation via image-guided para-corticospinal tract approach in patients with spontaneous intracerebral hemorrhage. Neurology and Therapy, 2021. 10: p. 1001-1013.
[22]. Mazzone, L., et al., Lower IQ is associated with decreased clinical response to atomoxetine in children and adolescents with attention-deficit hyperactivity disorder. CNS drugs, 2011. 25: p. 503-509.
[23]. Isaacs, E., et al., Brain morphometry and IQ measurements in preterm children. Brain, 2004. 127(12): p. 2595-2607.
[24]. Hao, S., et al., Group identity modulates bidding behavior in repeated lottery contest: neural signatures from event-related potentials and electroencephalography oscillations. Frontiers in Neuroscience, 2023. 17: p. 1184601.
[25]. Batty, G.D., I.J. Deary, and S. Macintyre, Childhood IQ in relation to risk factors for premature mortality in middle-aged persons: the Aberdeen Children of the 1950s study. Journal of Epidemiology & Community Health, 2007. 61(3): p. 241-247.
[26]. Gupta, S., et al., Origin of high fluoride in groundwater in the North Gujarat-Cambay region, India. Hydrogeology Journal, 2005. 13: p. 596-605.
[27]. Hefferon, R., et al., Regional and racial/ethnic inequalities in public drinking water fluoride concentrations across the US. Journal of exposure science & environmental epidemiology, 2024. 34(1): p. 68-76.
[28]. Yazdanbakhsh, E., et al., Community water fluoride cessation and rate of caries-related pediatric dental treatments under general anesthesia in Alberta, Canada. Canadian Journal of Public Health, 2024. 115(2): p. 305-314.
[29]. Hao, S., et al., Group membership modulates the hold-up problem: an event-related potentials and oscillations study. Social Cognitive and Affective Neuroscience, 2023. 18(1): p. nsad071.
[30]. Taylor, K.W., et al., Fluoride exposure and children's IQ scores: a systematic review and meta-analysis. JAMA pediatrics, 2025.
[31]. Donley, N., et al., Forever pesticides: a growing source of PFAS contamination in the environment. Environmental Health Perspectives, 2024. 132(7): p. 075003.
[32]. Cao, P. and J. Pan, Understanding Factors Influencing Geographic Variation in Healthcare Expenditures: A Small Areas Analysis Study. INQUIRY: The Journal of Health Care Organization, Provision, and Financing, 2024. 61: p. 00469580231224823.
[33]. Guichon, J.R., et al., Flawed MIREC fluoride and intelligence quotient publications: A failed attempt to undermine community water fluoridation. Community Dentistry and Oral Epidemiology, 2024.
[34]. Du, Y., et al., Neurometabolite levels in the brains of patients with autism spectrum disorders: A meta-analysis of proton magnetic resonance spectroscopy studies (N= 1501). Molecular Psychiatry, 2023. 28(7): p. 3092-3103.
[35]. Wang, Z., et al., Co-occurrence of arsenic and fluoride in groundwater of Guide basin in China: Genesis, mobility and enrichment mechanism. Environmental Research, 2024. 244: p. 117920.
[36]. Song, Z., et al., Evolving brain network dynamics in early childhood: Insights from modular graph metrics. NeuroImage, 2024. 297: p. 120740.
[37]. Wang, X., et al., Disparity in healthcare seeking behaviors between impoverished

and non-impoverished populations with implications for healthcare resource optimization. Humanities and Social Sciences Communications, 2024. 11(1): p. 1-12.
[38]. Zhang, Z., et al., Quantifying the factors controlling groundwater fluoride and associated health risks in the coastal river delta, northern China. Journal of Asian Earth Sciences, 2024. 259: p. 105929.
[39]. Garritty, C., et al., Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. Journal of clinical epidemiology, 2021. 130: p. 13-22.
[40]. Nasa, P., R. Jain, and D. Juneja, Delphi methodology in healthcare research: how to decide its appropriateness. World journal of methodology, 2021. 11(4): p. 116.
[41]. Belur, J., et al., Interrater reliability in systematic review methodology: exploring variation in coder decision-making. Sociological methods & research, 2021. 50(2): p. 837-865.
[42]. Kraus, S., et al., Literature reviews as independent studies: guidelines for academic practice. Review of Managerial Science, 2022. 16(8): p. 2577-2595.
[43]. Chen, L., et al., The contributions of population distribution, healthcare resourcing, and transportation infrastructure to spatial accessibility of health care. INQUIRY: The Journal of Health Care Organization, Provision, and Financing, 2023. 60: p. 00469580221146041.
[44]. Hussain, S., et al., Modern diagnostic imaging technique applications and risk factors in the medical field: a review. BioMed research international, 2022. 2022(1): p. 5164970.
[45]. Rashid, R., et al., A state-of-the-art review on wastewater treatment techniques: the effectiveness of adsorption method. Environmental Science and Pollution Research, 2021. 28: p. 9050-9066.
[46]. Gajic, I., et al., Antimicrobial susceptibility testing: a comprehensive review of currently used methods. Antibiotics, 2022. 11(4): p. 427.
[47]. Obeidat, H., et al., A review of indoor localization techniques and wireless technologies. Wireless Personal Communications, 2021. 119: p. 289-327.
[48]. Chai, J., et al., Deep learning in computer vision: A critical review of emerging techniques and application scenarios. Machine Learning with Applications, 2021. 6: p. 100134.
[49]. Dhingra, R.S. and M. Shah, A holistic study on fluoride-contaminated groundwater models and its widespread effects in healthcare and irrigation. Environmental Science and Pollution Research, 2021. 28(43): p. 60329-60345.
[50]. Zhang, M. and J. Ma, Political Anthropology of Fluoride Management: Understanding the Social Dynamics and Community Engagement Practices in Public Health Programs. Fluoride, 2024. 57(10).
[51]. Luo, J., et al., Role of perceived ease of use, usefulness, and financial strength on the adoption of health information systems: the moderating role of hospital size. Humanities and Social Sciences Communications, 2024. 11(1): p. 1-12.
[52]. Griebel-Thompson, A.K., et al., A scoping review of iodine and fluoride in pregnancy in relation to maternal thyroid function and offspring neurodevelopment. Advances in Nutrition, 2023. 14(2): p. 317-338.