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Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance?

Dufault RJ *et al*. Higher rates of autism/ADHD in United States

Abstract

In the United States, schools offer special education services to children who are diagnosed with a learning or neurodevelopmental disorder and have difficulty meeting their learning goals. Pediatricians may play a key role in helping children access special education services. The number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. Children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for children under the developmental delay and other health impaired (OHI) categories increased by 184% and 83% respectively. Although student enrollment in American schools has remained stable since 2006, the percentage distribution of children receiving special education services nearly tripled for the autism category and quadrupled for the developmental delay category by 2021. Allowable heavy metal residues remain persistent in the American food supply due to food ingredient manufacturing processes. Numerous clinical trial data indicate heavy metal exposures and poor diet are the primary epigenetic factors responsible for the autism and attention deficit hyperactivity disorder epidemics. Dietary heavy metal exposures, especially inorganic mercury and lead may impact gene behavior across generations. In 2021, the United States Congress found heavy metal residues problematic in the American food supply but took no legislative action. Mandatory health warning labels on select foods may be the only way to reduce dietary heavy metal exposures and improve child learning across generations.

Key Words: Lead exposure; Mercury; Oxidative stress; Methylation patterns; Epigenetic inheritance; Autism

Dufault RJ, Crider RA, Deth RC, Schnoll R, Gilbert SG, Lukiw WJ, Hitt AL. Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance? *World J Clin Pediatr* 2022; In press

Core Tip: Heavy metal residues are pervasive in the food supply and allowed by the Code of Federal Regulations because of food ingredient manufacturing processes. Children fed food with heavy metal residues may bioaccumulate inorganic mercury and lead in their blood and exhibit symptoms of autism or attention deficit/hyperactivity-disorder. Prenatal dietary exposures to heavy metals may impact gene activity in children and create learning difficulties requiring special education services. Educators see an increase in the prevalence of autism and developmental delay with cases doubling or tripling since 2006. Food quality issues may be impacting epigenetic inheritance of autism and related disorders.

INTRODUCTION

The special education system in the United States began developing in the 1970s and is mandated by Congress through the Individuals with Disabilities Education Act (IDEA). This act is codified in title 20 of the Code of Federal Regulations and governs how states must meet the educational needs of students between the ages of 3 and 21 who are developmentally impaired, either cognitively or intellectually, and have difficulty learning in the general education classroom. IDEA requires states to provide a free and appropriate public education to each disabled student at no cost to the parents. Through IDEA, the United States Department of Education is authorized to provide federal funding to states in the form of grants which are distributed each year and based on the child count or number of children in each state in need of special education services[1]. The funding is used by states to pay for special education teachers who provide academic services, school psychologists, occupational therapists, transportation, classroom aides, instructional materials, and parent education[2].

Under IDEA, there are 13 disability categories states must use to determine student eligibility for special education and related services[3]. Young children with autism are found eligible for services under different disability categories depending on their age and dominant behaviors[4]. Typical disability categories used to determine eligibility for children exhibiting symptoms of autism include Autism, Developmental Delay,

Speech/Language Impairment, or OHI if attention deficit hyperactivity disorder (ADHD) is a co-morbid condition[5]. In a 2009 review of the literature, Yerys *et al*[6] estimated 30% of children with autism also meet diagnostic criteria for ADHD and another 20% of children with autism exhibit subthreshold clinical symptoms for ADHD. This review provides up-to-date analyses of the prevalence data for disability categories made available to the public by the United States government. Etiology of autism and ADHD and future trends will be discussed from an epigenetic perspective.

CURRENT AUTISM AND ADHD PREVALENCE IN THE UNITED STATES

Medical researchers at the United States Center for Disease Control (CDC) and Prevention have been monitoring the prevalence of autism and developmental disabilities in eight-year-old children living in select communities in up to eleven states since 2000. Between 2000 and 2002, the estimated autism prevalence among eight-year-old children living in these communities was one in 150 or 6.7/1000[7]. By 2018, the autism prevalence in eight-year-old children living in these communities had increased to one in 44 or 23/1000[7]. Autism was 4.2 times more prevalent in boys than girls[7]. CDC researchers collect their autism prevalence data through federal contracts with community medical and educational service providers in CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.

Our review of the data collected by CDC's ADDM network revealed the prevalence of autism among children aged 8 years has increased 70% from 2000 to 2018[8]. Although the increase over the entire period is substantial, more noteworthy is the fact that the rate of change is increasing. From 2000 to 2010, the rate of change was 1.6/1000 per 2-year measurement period. From 2012 to 2018, the rate of change nearly doubled as it increased to 2.7/1000 per 2-year measurement period. Table 1 clearly shows these changes.

The CDC has not set up a network to track ADHD prevalence in any age group or community, however, periodically, the agency studies the prevalence of ADHD using data gathered from the National Health Interview Survey (NHIS)[9]. The most recent

analysis of the NHIS data (n = 146457) was conducted by Xu *et al*[10] who found a significant increase in the prevalence of ADHD in a representative sample of United States children aged 4-17 with 14% of boys and 6.3% of girls given the diagnosis in 2015-2016.

Public policy and medical researchers can better understand the magnitude of the problem of autism and ADHD across the United States by studying the special education data collected by the United States Department of Education each year. Newschaffer *et al*[11] first used this data set to determine increasing autism and ADHD prevalence over time in United States children between the ages of 6 and 17 from 1992 to 2001. ADHD prevalence trends can be determined by tracking the children receiving special education services under the OHI category[11,12]. Dufault *et al*[12] reviewed the special education data set available for the years 2005-2010 and found the number of children in the United States between the ages 6-21 receiving services under the IDEA categories of autism and OHI increased 91% and 26% respectively. We conducted an assessment and analysis of the special education data currently available at the United States Department of Education for the years 2006[13], 2011[14], and 2021[15] in preparation for this review and present our results in Table 2.

The overall number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. The number of children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for children with developmental delay and OHI increased by 184% and 83% respectively. These increases should be alarming to policymakers, teachers, parents, and others who are responsible for educating these learning-disabled children in classrooms across the country given the stable student enrollment in public schools during the last fifteen years. The National Center for Education Statistics (NCES) reported a total enrollment of 49.5 million children in public elementary and secondary schools in grades pre-k to 12 during the fall of 2021 (16). Prior to the COVID pandemic, public school enrollment in grades pre-k to 12 ranged from 49.5 million students in the fall of 2010 to 50.8 million students in the

fall of 2019[16]. The NCES created Figure 1 to provide a visual representation of the student enrollment trends in the United States since 2003[17].

While student enrollment in United States schools has remained stable since the early 2000s, our data shows the percentage distribution of children receiving special education services in the autism disability category has nearly tripled between 2006 and 2021. The percentage distribution of children receiving special education services in the developmental delay category has quadrupled over the same period. Figure 2, created using the data in Table 2, shows the burden of care required for children in special education disability categories associated with ADHD and autism compared to all other disability categories in 2006 and 2021. The burden of care for American children with autism or ADHD related special education services has increased dramatically between 2006-2021 even as student enrollment remains stable.

Data collected through the ADDM network and analyzed by CDC medical researchers reveal autism prevalence rates in the United States vary by geographic location[7]. Dufault *et al*[12] analyzed autism prevalence data from the United States and Italy and proposed a macroepigenetic model to explain why autism prevalence may vary across geographic regions depending on nutrition deficits in the population under study, exposure to organophosphate (OP) pesticides, and the influence of various dietary factors known to impact gene expression. Such dietary factors may include high intake of high fructose corn syrup (HFCS) and exposures to heavy metal residues from the consumption of processed foods[12]. Dietary epigenetic factors vary between countries due to policies and regulations that determine allowable exposures to heavy metal and pesticide residues in food and food ingredients[18].

A recent review of the literature indicates the primary epigenetic factors involved in the development of autism and ADHD worldwide are poor diet and exposures to heavy metals[18]. Recent clinical trial data collected from cohort studies around the world show mercury and/or lead are the most common heavy metal exposures of concern in children with autism and ADHD[19-28].

SOURCES OF HEAVY METAL EXPOSURES IN THE US FOOD SUPPLY

Ingredients in the American food supply with allowable lead, arsenic, and mercury residues are abundant[29]. The allowed heavy metal residues are based on the individual food ingredient manufacturing processes. For example, food colors made from petroleum[30] are expected to contain trace amounts of heavy metals because petroleum is extracted from beneath the earth's crust where heavy metals are found[29]. The United States Food and Drug Administration (FDA) therefore has a process in place to ensure the petroleum-based food colors do not contain more than the "allowable" levels of inorganic mercury (≤ 1 ppm Hg), lead (≤ 10 ppm Pb), and arsenic (≤ 3 ppm As)[31]. FDA regulations require manufacturers to test and certify each batch of food coloring to ensure the allowable levels of heavy metals are not exceeded[31]. All food colors requiring FDA certification are referred to as "certified food colors".

In addition to certified food colors, other food ingredients may contain various levels of heavy metal residues. Some preservatives and a few food colors exempt from the FDA certification requirements have legally allowable levels of arsenic, lead, cadmium, or inorganic mercury[29]. Corn sweetener products such as HFCS may also be at risk of mercury contamination due to their manufacturing process which may involve the use of mercury cell chlor-alkali products[32-34] or the direct application of mercuric chloride onto the corn starch at the front end of the refining process[35]. Vegetable oils risk heavy metal contamination from a variety of sources including the use of fertilizers and pesticides during farming and the use of process aids (*e.g.,* phosphoric acid, citric acid) during refining[36]. The use of phosphoric acid may introduce up to 10 ppm Pb and 1 ppm As while the use of citric acid may introduce up to 1 ppm Pb during the vegetable oil refining process[36].

The risk of heavy metal exposure in humans from eating foods containing heavy metal residues was first demonstrated by Khan *et al*[37] who found heavy metal concentrations in foodstuffs significantly correlated with the same heavy metals detected in human blood. Wells *et al*[38] analyzed data (n = 1770 for non-fish eaters, n = 5427 for fish/seafood eaters) from the CDC's National Health and Nutrition

Examination Survey (NHANES) and verified mercury exposure from non-fish food occurs in the American population through the consumption of vegetable oil, an ingredient found in many processed foods. In another study using NHANES data (n = 11354), Raehsler *et al*[39] determined a diet high in ultra-processed foods[40], such as a gluten-free diet, may lead to significantly higher levels of mercury, cadmium, and lead in blood.

Vegetable oils, HFCS, and corn syrup solids are common ingredients used in the ultra-processed food supply[41]. The United States Department of Agriculture (USDA) provides estimates of the annual per capita dietary intake of corn sweeteners ("sugar") and vegetable oils ("fat") *via* the Food Availability (Per Capita) Data System[42]. We were able to extract the most current data available from the system to determine the average American consumed 21.6 pounds per year of HFCS in 2019 and 36 pounds per year vegetable oil ("salad and cooking oils") in 2010[42]. Unfortunately, the USDA does not analyze corn sweeteners or vegetable oil products to determine heavy metal residue levels. The USDA also does not track "corn syrup solid" consumption trends. Corn syrup solids and vegetable oils are the primary ingredients in many baby formula food products[43,44].

In 2019, the United States Congress investigated consumer reports alleging elevated levels of toxic heavy metals in the American baby food supply[45]. In response, seven of the largest baby food manufacturers provided internal documents and baby food test results to Congress[45]. After reviewing the manufacturers' information, the United States Congress issued a report in February 2021 that included the following findings: Arsenic, lead, and cadmium residues were present in baby foods made by all the responding companies and mercury residues were detected by the one company that tested for it[45]. The mercury levels were reported at higher concentrations many times higher than allowed under existing regulations[45]. The United States Congress issued a second report in September 2021 with the recommendation that baby food manufacturers should "voluntarily find substitutes for ingredients that are high in toxic heavy metals"[46].

In addition to the United States Congressional reports, we identified a few other studies conducted to determine heavy metal exposures in baby formula or baby foods. Dabeka and McKenzie[47] measured total mercury levels in 150 infant formula products sold in Canada in 2003. Using the measurement method available at the time, mercury concentrations in 76% of the samples fell below the limit of detection[47]. There were, however, clear cases of low-level mercury contamination (up to 1.5 ng/g) in individual lots of powdered formula[47]. In a sample size of 87, Martins *et al*[48] identified median total mercury concentrations of 0.50 ug/kg in baby formula analyzed in Portugal. In a more recent study, Gardener *et al*[49] analyzed 564 baby food (including infant formula, cereals, meals, juices, snacks) products for cadmium and lead. While lead was only detected in 37% of the samples, cadmium was detected in 57% of the samples collected from the United States food supply[49].

The multiple findings of heavy metal residues in the food supply are important because children diagnosed with symptoms of autism have difficulty metabolizing and excreting heavy metals from their bloodstream due to their biologically embedded epigenome[18]. In the most recent study, Hassan *et al*[50] found higher aluminum, mercury, and lead levels in the blood of children with autism (n = 73) compared to children serving in a healthy age- and sex- matched control group (n = 73). The finding of higher aluminum in this case-control study is alarming because a novel laboratory experiment recently showed significant synergism in the toxicity of aluminum and mercury when added together in a culture of human brain cells[51]. Alabdali *et al*[52] demonstrated the levels of mercury and lead in the blood of children with autism correlate with the severity of their symptoms to include social and cognitive impairment. The synergistic neurotoxic damage caused by dietary inorganic mercury, lead, and cadmium exposures was recently demonstrated in a study conducted on rats[53]. Co-exposures to specific heavy metals cause more extensive damage to brain cells. When studied alone, however, mercury exposure is a significant factor in the development of autism. In agreement with Alabdali *et al*[52], Mostafa *et al*[54] also found mercury levels were significantly higher ($P < 0.001$) in the blood of children with autism

(n = 84) compared to the healthy matched controls (n = 84). There was also a significant (P < 0.0001) and positive linear relationship between mercury in the blood of children with autism and symptom severity[54].

Children diagnosed with ADHD bioaccumulate lead in their blood because of dietary calcium and zinc deficits or losses, in conjunction with lead exposures[18]. In an analysis of NHANES data gathered between 1976-1980 (n = 2926), Mahaffey *et al*[55] found an inverse relationship exists between lead in blood and dietary calcium intake. More recently, Gulson *et al*[56] found a positive association between lead content in the diets of 108 children over a 5-year period and the lead concentration in their blood. There was also a statistically significant inverse relationships between dietary zinc and calcium and lead levels in the children's blood[56]. As dietary zinc and calcium levels increased, the blood lead levels decreased[56]. Lead exposure has historically been recognized by governments and public health agencies to adversely impact child neurodevelopment. According to the CDC, no safe level of lead in blood has been identified and even low levels of lead in blood can negatively impact child intelligence and ability to learn[57].

ETIOLOGY OF AUTISM AND ADHD: AN EPIGENETIC PERSPECTIVE ON HEAVY METAL EXPOSURES AND POOR DIET

Food ingredients with allowable lead, arsenic, cadmium, and mercury residues may impact gene behavior by synergistically interfering with heavy metal excretion[58]. For example, in addition to being a source of lead, arsenic, and mercury exposure, the food color tartrazine (yellow 5) has been shown to negatively impact zinc status of children with ADHD[59,60]. Lower levels of zinc may downregulate metallothionein (MT) gene expression, thereby further reducing heavy metal detoxification and elimination[58,61], especially in children with autism[61,62]. The MT gene promotes the synthesis of the MT protein which is zinc dependent because it requires up to seven zinc atoms per molecule[63]. Hundreds of molecules bind together to make a MT protein strand. With adequate zinc reserves, the MT transporter protein prevents heavy metal accumulation as it continuously swaps zinc for lead, mercury, arsenic, or cadmium as part of the

body's metal detoxification and elimination process[64]. Dietary zinc is therefore crucial for supporting the body's effort to rid itself of harmful metals that create conditions for oxidative stress and the development of various disease conditions[65]. The more zinc deficient a child is, or becomes because of his/her diet, the more likely he/she will accumulate heavy metals in his bloodstream due to the disruption in MT gene activity[58]. Zinc is an important macromineral; it is a dietary element needed by the body in copious amounts. Food ingredients, such as yellow 5, that are a source of heavy metal exposure and lead to zinc loss may be eliminated from the food supply to improve child health and learning outcomes.

Another example of a food ingredient that can disrupt macromineral homeostasis in humans is HFCS[58,66]. In a study conducted by the USDA, Milne and Nielsen fed eleven men a mixed Western diet for four 42-d dietary periods[66]. When fed a high fructose diet, the men showed significant calcium ($P < 0.007$) and phosphorus ($P < 0.005$) losses, especially when dietary magnesium intake was low[66]. In their conclusion, Milne and Nielsen[66] suggested further studies are needed to see if a high fructose diet with the accompanied calcium loss and low dietary magnesium lead to the development of osteoporosis. With respect to child health, there is a need to conduct other studies. Because HFCS consumption may lead to calcium losses, its overconsumption by children may result in the bioaccumulation of lead stores in the body[55,56]. More research needs to be done to determine if HFCS consumption adversely impacts children with ADHD or autism by contributing to calcium losses and the bioaccumulation of lead.

The calcium losses that resulted from the consumption of HFCS is a finding of concern especially when the average American consumed 21.6 pounds of HFCS in 2019. Calcium is required by the body in copious amounts to conduct important processes. For example, the paraoxonase (PON1) gene relies on calcium to synthesize the PON1 enzymes that break down and detoxify the metabolites of OP pesticides[67]. PON1 gene expression varies in children with autism and ADHD[68] and can be inhibited by dietary factors such as fructose and heavy metal (*e.g.*, lead, inorganic mercury, or cadmium)

intake[67,69,70]. Children with autism and ADHD have nutrient poor diets and are thus thought to be more susceptible to the neurotoxic effects of OP pesticide exposure especially when concurrently exposed to heavy metals[18,68]. A search of the literature did not yield even one study on humans to determine the effect of concurrent or co-exposures to multiple xenobiotic agents found in the food supply.

However, Zhou *et al*[71] conducted a recent case-control study on pregnant rats to determine if low concurrent exposures to lead, cadmium, and inorganic mercury *via* diet resulted in adverse outcomes among the pups. The low dose exposures to the heavy metals induced damage to several organs including brain tissue in both the dosed rats and their pups[71]. The heavy metal concentration in blood and brain tissue significantly increased in a dose dependent manner[71]. Zhou *et al*[71] also observed significant increases in oxidative stress, intracellular free calcium, and cell apoptosis in the brain tissue of the cases compared to the controls. Learning and memory deficits and sensory perception issues were also observed in the behavior of the prenatally dosed pups along with the histopathological changes in hippocampus morphology[71]. This is the first study showing dietary low-level lead, cadmium, and inorganic mercury co-exposures in rats are a relevant model for evaluating human dietary heavy metal exposure levels that adversely impact child neurobehavior and development[71]. Zhou *et al*[71] also identified changes in the behavior of select genes in select organs in response to the concurrent heavy metal exposures. Figure 3 shows the updated epigenetic model for how autism and ADHD may develop in children because of concurrent exposures to heavy metals in the food supply.

Dietary nutritional deficits, exposures to food ingredients that induce macromineral imbalances, and heavy metal exposures may impact gene behavior through a variety of mechanisms such as histone or DNA methylation[72,73]. Methylation patterns in the cellular environment may change under conditions of oxidative stress which simply means the cell contains too many molecules made up of reactive oxygen species (ROS). The primary ROS (molecular species) are hydrogen peroxide, superoxide anion, hydroxyl radical. When the cell does not contain enough of the molecules (antioxidants)

it needs to neutralize the ROS, it is under oxidative stress and the DNA or RNA methylation pattern can change along with gene behavior. The formation of ROS and the development of oxidative stress can be induced by the presence of heavy metals (*e.g.,* inorganic mercury, lead) in the cellular environment.

As heavy metals accumulate in red blood cells, oxidative stress occurs, and methylation patterns may change. Oxidative stress caused by heavy metal exposure may be alleviated with the introduction of nutrients that serve as antioxidants. Examples of such nutrients include zinc[74] and selenium[75]. It is important to reduce dietary heavy metal intake and improve diet to prevent the bioaccumulation of heavy metals in the blood cells of children who exhibit symptoms associated with autism and/or ADHD[18]. In addition to creating conditions for symptomatic autism and ADHD in childhood[18], heavy metal exposures can create changes in DNA methylation patterns that impact child neurodevelopment in the womb[76-79] and contribute to adverse health outcomes in adulthood[79]. DNA methylation is an important regulator of gene expression; a methyl group which is a molecule made up of one carbon and three hydrogen atoms (CH_3) attaches to DNA and serves as a switch to turn a gene on or off from one generation to the next for better or worse.

EMERGING TRANSGENERATIONAL EPIGENETIC INHERITANCE PATTERNS MAY EXPLAIN INCREASING AUTISM AND ADHD

Changes in methylation patterns and gene behavior that occur in response to heavy metal exposures and nutritional factors are common in the development of disease conditions across generations[80]. The term used to describe these cross generational changes in methylation patterns is "transgenerational epigenetic inheritance [80]." Methylation patterns on genes vary among humans and can be modified by useful or harmful dietary factors[80]. For example, folate and vitamins B6 and B12 are useful dietary factors that induce the formation of the methyl donor (CH_3) in DNA methylation[80]. Conversely, prenatal inorganic mercury exposure may be a harmful dietary factor because it has been shown to induce changes in methylation levels of the

PON1 gene that persist into early childhood[78]. Cardenas *et al*[78] showed changes in methylation levels of PON1 in cord blood from mercury exposures could be used to predict lower cognitive scores in childhood. These findings are not surprising in the child neurodevelopment field of study because we know suppression of the PON1 gene and/or the bioaccumulation of heavy metals create conditions for oxidative stress which is a hallmark feature of autism[81,82] along with impaired or decreased DNA methylation capacity[12]. The emerging evidence strongly suggests DNA methylation patterns altered by dietary stimuli may be stable or passed on to the next generation and this is of great concern[83].

Changes in DNA methylation patterns during pregnancy, infancy, and adult life can lead to the inheritance of disease conditions such as obesity and diabetes[83]. Ando *et al*[84] recently conducted a rat study and found changes in DNA methylation patterns on a specific gene led to the development of insulin resistance and hyperlipidemia in offspring when pregnant rats were fed a diet consisting of 20% HFCS[84]. This transgenerational epigenetic inheritance of metabolic abnormalities observed in rats has not yet been studied in humans to determine which gene(s) may be impacted by the consumption of HFCS[84]. In the case of autism and ADHD however, the literature strongly supports the idea that changes in DNA methylation patterns from prenatal exposures to lead and mercury may lead to the inheritance of the same methylation patterns in human offspring[76].

Bozack *et al*[76] investigated the epigenome-wide associations of maternal heavy metal measurements in blood (n = 361) with cord blood DNA methylation (n = 361) and persistent DNA methylation changes in mid-childhood (n = 333, 6-10 years). Of the twelve metals studied, Bozack *et al*[76] found evidence that prenatal exposures to lead and manganese are associated with changes in cord blood DNA methylation patterns which may persist in children when measured at mid-childhood[76]. In a separate meta-analysis of epigenome-wide association studies involving the cord blood of 2477 children, Neumann *et al*[77] found evidence that DNA methylation at birth is strongly associated with the development of ADHD ($P = 1 \times 10^{-7}$).

Persistent DNA methylation changes resulting from prenatal mercury exposures (n = 321) were observed in a study of epigenome-wide methylation patterns conducted by Cardenas *et al*[78]. Among male children, prenatal mercury exposures were associated with cord blood methylation at the PON1 gene locus and lower cognitive test scores measured in early childhood[78]. Cord blood DNA methylation levels at the PON1 gene locus is widely known to be associated with lower PON1 gene activity[78]. In a commentary citing elements of the macroepigenetic model, Dufault and Gilbert[85] explain that because male children have lower PON1 gene activity, prenatal mercury exposure associated with cord blood methylation at the PON1 gene may explain why autism impacts males more often than females. This observation is relevant; CDC reported the finding that autism was 4.2 times more prevalent in boys than girls in 2018[7].

PERSPECTIVES ON FUTURE RESEARCH AND ACTIONS

Research evidence presented in a recent review suggests heavy metal exposures are among the most significant environmental agents impacting human health[86]. Prenatal exposures to lead, inorganic mercury and other heavy metals can induce developmental epigenetic programming in the human population[86]. Research evidence provided in this review supports the idea that food quality issues are impacting epigenetic inheritance. Fortunately, developmental epigenetic modifications, including methylation patterns, may be reversible. More research is needed to identify what intervention measures can be taken to lower dietary heavy metal exposures in children and whether such measures may reverse methylation patterns and gene behaviors.

Switching to a healthy diet and eliminating the intake of ultra-processed foods is currently one intervention used to reduce heavy metals in blood and improve behaviors and learning among children with autism or ADHD[18]. In the current political environment, interventions for mitigating climate change are on the rise along with the trend towards adopting a plant-based animal product alternative (PB-APA) diet[87]. Unfortunately, PB-APA foods tend to be ultra-processed so this trend to increase ultra-

processed food intake may have detrimental effects on children. It is important to ensure these "ultra-processed" PB-APA foods do not contribute to child heavy metal exposures. Studies need to be conducted to determine whether the ultra-processed PB-APA food products and the ingredients they are made of are at risk of heavy metal contamination.

The impact of specific food ingredients on macro and micro mineral balance in the human body needs further study. To date only two food ingredients are known to create mineral imbalances: yellow 5 (tartrazine) and HFCS. There are many more ingredients commonly found in the ultra-processed food supply that could impact mineral balance. Yellow 6 is similar to yellow 5 with the same allowable lead, inorganic mercury, and arsenic residue levels in each manufactured batch; its overconsumption may also lead to zinc loss. A case-control study could be designed to determine the impact of yellow 5 and/or yellow 6 intake on zinc balance, methylation patterns, and MT gene activity levels. Determining how mineral imbalances and dietary exposures to heavy metals impact DNA methylation and gene expression in children with autism or ADHD would be useful.

The mechanisms by which heavy metals bioaccumulate in children with autism and/or ADHD are poorly understood. Dietary factors such as zinc, calcium, and HFCS intake could be key to understanding how dietary heavy metals bioaccumulate in a child's blood. Intervention studies could be designed to consider pre-post intervention dietary intake (survey intake of whole foods and dairy *vs* ultra-processed foods including those with HFCS, vegetable oils, food colors, preservatives), pre-post intervention heavy metal exposures (heavy metal measurements in blood), pre-post intervention DNA methylation patterns, pre-post intervention gene activity levels (*e.g.*, PON1, MT). Instructions for creating a healthy diet intervention that reduces dietary heavy metal exposures are available[18].

With autism and ADHD prevalence climbing at alarming rates with each successive generation it is clear more must be done to reduce dietary heavy metal exposures and improve child nutrition. Unfortunately, until advancements are made on the

epigenomic front, we can only moderate the increasing autism and ADHD prevalence through the introduction of policies and laws that eliminate exposures to certain harmful food ingredients and reduce dietary exposures to heavy metal residues.

The United States Congress has taken an excellent first step in collecting heavy metal residue data from food manufacturers[45,46]. Decisive action is needed now to address the autism and ADHD epidemic in the United States. Ethical considerations need to guide the decision making among Congressional members. We must acknowledge what we know and what we don't know about the contaminants in the food supply. In the case of lead and inorganic mercury, we known there is no safe level of exposure, and any exposure is harmful to the developing fetus[88]. With the knowledge that widespread heavy metal contamination exists in the United States food supply, Congress could now choose to ban food ingredients with allowable heavy metals. Alternatively, Congress could mandate warning labels on foods that contain ingredients with allowable heavy metal residues. At least warning labels would serve to inform consumers and expectant parents of the health risks associated with eating food ingredients with allowable lead and inorganic mercury residues.

There is compelling evidence to suggest that mandatory health warning labels do encourage consumers to adopt more healthful purchasing behaviors[89]. Song *et al*[89] conducted a meta-analysis of the impact of color-coded and warning nutrition labelling schemes on consumer behavior. Of the 134 studies analyzed, the traffic light labelling system, nutrient warning, and health warning labels were the most effective front-of-package labeling methods for influencing consumers' purchasing choices[89]. Health warning labels reduced consumers' perception of the healthfulness of less healthful products while increasing their perceived disease risk from eating unhealthful products[89].

Mandatory health warning labels on foods containing ingredients with allowable heavy metal residues would direct parent purchasing behaviors away from unhealthful food products in the United States free market system. Movement away from the consumption of these foods could lead to significant reductions in child heavy metal

exposures. Without any changes in United States food safety law, however, unabated dietary exposures to inorganic mercury and lead will continue to occur because of the adulterated American food supply. Autism and ADHD prevalence will continue to rise as transgenerational epigenetic inheritance becomes the norm.

CONCLUSION

The American food supply is contaminated with allowable heavy metals in specific food ingredients. Americans continue to be exposed to inorganic mercury and lead over time which can impact the national epigenome. The United States Congress has confirmed heavy metal exposures are occurring in American children due to contaminants in the food supply. We are seeing sustainable and alarming increases in autism and ADHD prevalence with cases doubling or tripling in one generation. Congress may act now to mandate the health warning label on foods containing food ingredients with allowable heavy metal residues before child intellectual development and learning erodes any further.

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SIMILARITY INDEX

PRIMARY SOURCES

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