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Autism and Environmental Influences

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Abstract

Autism is a neurobiological spectrum disorder manifesting with challenges in socialization, communication, and repetitive behaviors. The Center of Disease Control estimates that 1:54 children have autism. Autism includes extremely gifted individuals and those who are severely challenged. Males are diagnosed four times the rate of girls. It is generally agreed that no one factor causes autism, there is a genetic component, and that autistic brains differ from neurotypical brains as determined by imaging studies. This literature review investigated research behind environmental factors that may contribute to autism such as exposure to chemicals, pesticides, pollution, and toxins found in products. Autism severity ranges from those who are extremely gifted to those who are non-verbal, and severely cognitively and behaviorally challenged in their daily lives. The cause of disorder is inconclusive and warrants further investigation regarding how environmental factors impact autism spectrum disorder.

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CHAPTER I: INTRODUCTION

Autism Spectrum Disorder (ASD), a commonly recognized developmental disorder, is on the rise in the United States and globally. In the year 2000, 1:150 children had autism. Fast forward to 2020 and statistics indicates that 1:54 people have ASD, based on the most up-to-date information posted on the Center of Disease Control (CDC) website. In comparison, four boys are diagnosed for every girl. What is causing this rise in ASD diagnosis?

The causes contributing to this increase are not only genetic, but environmental factors also have been identified as a contributing factor to this growing disorder (Shibata et al., 2013). Specifically, circumstantial evidence links differences in brain imaging from exposure to environmental factors such as lead, ethyl alcohol, aluminum, and methyl mercury in those with comorbid autism and allergies linked to common risk factors (Shibata et al., 2013). Other environmental factors worth considering include allergies, maternal smoking, birth order and asthma. There appears to be a link between autism and environmental factors that may help explain this rise in autism over the last decade.

Autism is defined as a neurobiological spectrum disorder manifesting with challenges in socialization, communication, and ritualistic behavioral patterns. It is suggested that many children with autism share neurodevelopmental symptoms, delays, and comorbidities. This disorder has no specific cause, but scientists have noted possible genetic components and differences in brain development. The consistently increasing rate is puzzling. It is not known whether the increase is due to more knowledge about the disorder and better diagnostic practices, or whether other potential causes could account for this unprecedented growth in a childhood disorder (Shibata et al., 2013).

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria, those with autism have deficits in communication and restricted interests and repetitive behaviors. “A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome” (CDC.gov., 2020). This “spectrum” ranges from those who are extremely gifted to those who are non-verbal, and severely cognitively and behaviorally challenged in their daily lives.

Autism occurs among people of all races and socioeconomic groups but is identified in boys four times greater than in girls. Autism is an important health concern, citing environmental and genetic factors. However, specific factors are not clearly stated. While genetic links have been documented, environmental factors need to be further studied and carefully considered. It is important and essential that researchers determine the etiology to protect our children and their futures.

A Mother’s Experience

My son, whom I’ll refer to as Henry to protect his identity, was diagnosed with Autism Spectrum Disorder (ASD) at the early age of 21 months. Henry started physical therapy because he appeared to have low muscle tone. We had been waiting for him to walk and when he finally did, he was nearly two years old. We still sensed that something seemed a bit off. He stared out the window for extended periods of time. He hyper-focused on certain things, such as the way objects moved. He especially enjoyed watching the trees being jostled by the wind. When this happened, he got very excited and put his hands up in the air in tight, clenched fists making somewhat of a jerking motion. He enjoyed spinning in circles most of all; underneath the fan repeating his movement coordinated with it. He spun most anything he could find. Instead of

playing with his cars, he turned them over and watched the spinning wheels. So much spinning. He took the food out the pantry and stacked cans and boxes in huge uneven towers, but they didn't fall. So much stacking. So much spinning. Oh, and so many explosive diapers! What did this mean?

During this time in my life, 12 years ago, I was uncertain where to turn and what this meant for our family. I turned to doctors for advice, only to discover that autism was a life-long disorder. I received no definitive answer to my question, "Where did this come from?" My personal experience with autism has challenged me to study the connection between the development of autism and to what degree environmental factors potentially contribute to this mysterious condition.

Finally, we received Henry's diagnosis from Fraser, one of the most renowned autism providers in Minnesota. I can admit that the diagnosis was not something I would wish on anyone. As a young mother with her firstborn child, at just 21 months, we walked into the facility. We entered an empty room with empty walls. I read that limited visual stimulation is good for people with autism, but the room seemed sterile and uninviting to me. We sat for hours as strangers observed our child, as if they might know him better than we do. What would this observation prove? Would it help him? If he is diagnosed, what will change? Will he ever be able to talk? He just started walking last week. I was still not sure if he could hear me. What would that mean for him? Those were the thoughts that reigned through my head. If I only knew then what I know now. Of course, I know that my son is an amazing human being. And now I can admit that this process has taught me so much about life and what is important. After all, according to the CDC, a diagnosis and early intervention is key to establishing positive outcomes in the autism world. Diagnosis can lead to treatment and services that open-up so many doors

and possibilities. There is no cure for autism, but is it treatable? Some believe children can respond to therapies, supplements, vitamins, or magnesium. I invested a lot of time trying to find answers to these questions. I have seen slow and steady progress, but not monumental gains.

To answer my previous questions, Yes. My son talks. Sometimes he doesn't stop talking. Yes. My son is successful. You see, Henry is now 13-years-old. He has received multiple therapies since his diagnosis at 21-months. He has received occupational therapy, hippotherapy, aquatic therapy, and speech therapy. We tried hyperbaric oxygen therapy (HBOT). We even tried special vitamins. Henry has been to many medical doctors, natural doctors, and chiropractors. Some of them believe that autism has a gut-brain connection. What does the research say? Henry's allergy tests around the age of three showed an intolerance to both gluten and dairy, commonly linked to people on the autism spectrum. What does that mean? Do food additives have anything to do with autism? What about monosodium glutamate (MSG)? We put Henry on a gluten free/dairy free diet. This diet has helped a lot with his digestion. How do gluten and dairy contribute to autism? How could we explain the unfairness that other kids could enjoy a multitude of foods and not Henry? Was he missing out? I didn't want him to miss anything that other kids got to do. It didn't seem fair. Through the years, Henry became very knowledgeable about what he could and could not eat. He knows that his stomach will hurt if he eats gluten. Does this all connect to something bigger that I cannot wrap my head around? That everything in Henry's life connects to autism certainly seems far over my head.

Why is it that boys are so much more likely to have autism than girls? Does autism have to do with a defect with the X-chromosome? Autism is so complex due to the many contributing factors that since it's discovery in 1943, scientists continue to have unanswered questions. Why

has there been a diagnostic explosion of children with autism over the last decade? There must be an explanation.

Should we not be living near powerlines? Do we need to stay away from Round-Up? What about artificial dye? Does it cause hyperactivity? Is it linked to autism? What is all the hype about vaccines anyway? Is there any truth to this assumption? Do food coloring or additives affect the behavior of children on the autism spectrum? Does the amount of Vitamin D affect autism? What if our children have an underlying condition or a genetic predisposition? Do environmental factors contribute to any of this? What if I am parenting all wrong? I have so many questions, and the answers are not in a book. Or are they? Can I figure this out on my own? Who could help me?

According to the National Institute of Mental Health, autism is a known neurodevelopmental disorder that impairs social interaction, communication, and repetitive behaviors. and Twenty to 30% of children diagnosed with autism have experienced regression between the ages of 18 and 24 months. However, a larger percentage present autism characteristics from birth. I am not certain where our autism journey began. I cannot pinpoint the day or the time. There wasn't an *AHA!* moment. Was it present from birth? Perhaps. Did he experience regression? I don't think so. I do believe that due to research and data collection, someday we will know more about this condition.

My 13 years of living with autism led me to become a special education teacher to help children like my own son reach their full potential. I absolutely love working with families and children with autism spectrum disorder. I am fascinated by the individuality each child presents. I can't help but wonder if there is something more I can do?

"It is possible that there are several causes of autism since, to date, aberrant findings have not been present in 100% of the subjects in any study. It is first important to assess the incidence and prevalence data to get timelines that might help determine the major causes of autism" (Ratajczak 2010). The ever-growing rise of autism leads me to believe that more studies must be done to understand the reason for the increase. Parents shouldn't have to wonder "what if?" Are environmental factors involved in autism? This literature review will explore these questions: What factors in addition to genetics contribute to autism? What evidence supports the theory that the rise in autism is caused by environmental factors? If ASD is caused by environmental factors, what is the specific impact?

Is there an environmental component responsible for the increased rate of autism? More children are diagnosed with autism spectrum disorder than ever before, which has led some researchers to refer to the disorder as an epidemic. The severity of autism for each person varies but the disorder is defined by deficits or delays in three major areas: social interaction, communication, and repetitive behaviors. "Research has suggested that there are multiple risk factors related to the pathogenesis of ASD" (Bjorklund et al., 2018, p. 234). Initial autism studies suggested a genetic predisposition. Recent neurobiological studies point to ways exposure to various toxic metals and environmental pollutants affect the brain. Environmental toxins are a concern for public health (Bjorklund et al., 2018). The mixture of pollutants and metals may disrupt the nervous system processes and result in the impairments and behavioral problems known as autism.

There has been limited evidence documenting a link between autism and environmental factors, however, there are undocumented anecdotal claims. Research focused on the development of autism is quite complicated due to the vast number of causes believed to result in

this epidemic. Autism causes may include a genetic make-up that is triggered by an environmental factor. For example, environmental toxins can cause birth defects or a weakened immune system. Lead, arsenic, and mercury are widespread in the environment and often ingested and inhaled from an array of sources. These widely used toxins are also known to affect the immune system (Bjorklund et al., 2018). In what way could these external factors be the cause of autism?

CHAPTER II: LITERATURE REVIEW

Autism and Environmental Influences

To locate literature for this thesis, searches of ERIC, EBSCO, PubMed, Springer Link, and National Center for Biotechnology Information, U.S. National Library of Medicine (NCBI), This list was narrowed by only reviewing published empirical studies articles from peer-reviewed journals that focused on autism, it's environmental etiology and addressed the guiding questions. The key words used in these searches included "autism and etiology," "environmental causes and autism," "autism and toxins", "autism and chemicals," "prenatal autism," "autism and pollution" and "autism and vaccines."

Environmental Influences

Many environmental factors may contribute to an autism diagnosis. The structure of this chapter is to break down those possible causative environmental factors. This review analyzes potential environmental influences of autism. Specific research needs to address autism etiology from both genetic and environmental perspectives.

Mercury and Aluminum

Mercury is one of the most noted environmental pollutants according to the World Health Organization (Bjorklund et al., 2018). Three forms of Mercury exist in the environment: elemental mercury, inorganic mercury compounds, and organic mercury compounds (Kern et al., 2016). All forms of mercury are known to be toxic and some of these forms are found in foods such as fish, artificial food sweetener, high fructose corn syrup, and in dental amalgams. Mercury is also found in the atmosphere and has been linked to autism but is an unavoidable source. Atmospheric mercury directly enters the bloodstream when inhaled. The trend to connect mercury to autism gained attention due to the similarity of symptoms between mercury

poisoning and autism (Ng et al., 2017). Mercury poisoning affects the brain and nervous system, resulting in mood swings, irritability, and decreased coordination and cognitive functions. The relationship between autism and mercury has been a much debated topic.

Studies measured mercury in hair samples, blood, urine, teeth, and nails with inconsistent findings. It was noted that mercury has a short half-life and that blood and hair analysis were likely unreliable. "Ecological studies have demonstrated an association between environmentally released mercury emissions and significant increases in autism rates, which may be related to residential distance from mercury pollution sources" (Ng et al., 2017, pg. 2). The US Environmental Protection Agency concluded that all forms of mercury are toxic (Ng et al., 2017).

Kern et al., (2016) reviewed 91 studies in a mega analysis that examined the relationship between mercury and autism. The studies were completed between 1999 and 2016 and the results suggested that mercury was both a direct and indirect risk factor in the autism epidemic. Data showed that 74% of the studies supported a link between mercury and an autism diagnosis. It was further revealed that brain auto-antibodies correlated with the mercury levels in children with autism (Kern et al., 2016). The findings also concluded that mercury in air pollution and maternal mercury fillings were also risk factors for autism. The findings pointed to limited government action in reducing mercury exposure that created a toxic environment. In 2012 the FDA devised a plan to eliminate mercury-filled amalgams among more sensitive groups of people but neglected to release it under the United States Department of Health & Human Services (Kern et al., 2016). Overall, it was found that autism severity was more prevalent when mercury levels were higher and children with autism were more susceptible to heavy metals than neurotypical children. This study urged a change in government policy; however, extensive

research compared the mercury and autism relationship with conflicting evidence. Therefore, the theory that mercury caused or contributed to autism was inconclusive.

Mold, Umar, King and Exley (2017) studied the environmental toxin, aluminum, and its impact on brain tissue in the autistic population. While previous studies have examined hair, blood, or urine, this study looked at the brain tissue of five donors (four male, one female) with autism.

Brain tissue was examined at the Oxford Brain Bank with samples collected from various portions of the cortex from five subjects who were between the ages of 15-50 diagnosed with autism using the Autism Diagnostic Interview-Revised. All subjects had extremely elevated levels of aluminum, with a higher content in the four males compared to the female (Mold, Umar, King and Exley, 2017). The findings documented one of the highest recorded levels of aluminum found in the brain. The researchers questioned why a 15-year-old boy had significantly elevated levels of aluminum in his tissue?

This study illustrated how the aluminum crossed the blood-brain barrier and was found in the extracellular and intracellular locations, including the microglia. The microglia make up 10-15% of brain cells. The microglia are the primary defense of the central nervous system. High aluminum content eventually will compromise the microglia, resulting in a dysfunction.

Conclusively, Mold, Umar, King and Exley (2017) realized their measurements were extremely high and attributed that to autism. However, the study was limited due to the small sample size of its donors.

Valproate

Valproate is a medication used to treat epilepsy, bipolar disorder, or migraine headaches and may can cause adverse effects for offspring if women when taken during pregnancy. It is

possible that prenatal exposure to this medication may influence the developing brain and nervous system placing children at risk for autism spectrum disorders. Christensen, et al. (2013) reviewed 5,437 children identified with autism (using the International Statistical Classification of Diseases Tenth Revision criteria) from a sample of 655,615 children in the registration system born in Denmark between 1996 to 2006 for up to 14 years. The Danish Data Protection Agency and a Danish Regional Ethical Committee reviewed the subjects. Finally, the children were considered if their mother had filled a prescription for an antiepileptic drug. The Cox hazard regression method was used to estimate the prevalence autism spectrum disorder in the subjects against the control group. The team identified 2,644 children exposed to antiepileptic drugs with 508 specifically exposed to Valproate.

Mothers who used Valproate while pregnant had children with autism at rate of 4.42% compared with a risk of 2.55% for those who stopped before conception. Other antiepileptic drugs were evaluated but resulted in no potential risk for autism. In conclusion, mothers who used Valproate during pregnancy had an increased risk for bearing a child with autism (Christensen, et al. 2013).

Animal studies also showed increased repetitive behavior and less socialization in the pregnancy stages in animals when exposed to Valproate. Christensen, et al. (2013) believed that valproate may alter functioning of neurotransmitters causing oxidative stress, delayed cognitive development or malformation in the offspring of women using it during pregnancy. The risk of valproate was less than 5% but should be advised to those using it maternally balanced with the benefits to determine risk factors. Valproate and autism must be studied further, and the medical community should alert mothers about the potential association (Christensen, et al., 2013).

Authors Persico and Merelli (2014) reviewed studies related to the effects of environmental toxins. exposure to sodium valproate, pesticides, and heavy metals in utero. They found that genetic variants seemingly accounted for 50% of ASD cases which left ample room to suggest that environmental factors may have a casual relationship. Researchers studied case reports, patient cohort studies and investigations and the findings were eye-opening.

One substance, VPA (sodium valproate), has been linked to Fetal Anticonvulsant Syndrome. Epidemiologic and experimental studies documented an increase in disorders such as Autism, ADHD, and dyspraxia. A rodent study determined a hazard ratio of 2.9% to 5.2% in those with autism spectrum disorder. VPA caused increased oxidative stress, acid folic deficiency and interference with pathways and neurodevelopmental genes such as WNT, FZD-5, GFRA-2, and GATA (Persico and Merelli, 2014).

Exposure to organophosphates (pesticides) and insecticides through the placenta via breast milk, breathing, and food showed vulnerability to neurodevelopmental deficits and inflammatory imbalances. The result was impaired pathway disruption altering neuronal connectivity which affected attention, receptive language, social cognition, and behavioral brain regions. Inflammatory imbalances were also a result of prenatal exposure to pesticides (Persico and Merelli, 2014).

Heavy metals such as mercury, thimerosal, and lead produced multisystem damage through the placenta (Persico and Merelli, 2014). This viewpoint has been highly controversial, however, a cohort of ASD children may have hypersensitivity due to their genetic make-up. Exposure to these metals along with a genetic NLGN3 mutation could be responsible for a small number of regressive forms of autism in children (Persico and Merelli, 2014). The theory that vaccines caused autism has been debunked, but the vaccine controversy continues. The

thimerosal component in an influenza vaccine was removed in 1999. Animal models showed that thimerosal affected the central nervous system. This, in turn, caused oxidative stress and affected motor learning (Persico and Merelli, 2014).

Persico and Mendelli (2014) concluded that a gene variant may be more susceptible to thimerosal, activating the immune system during prenatal exposure. The environmental factors sodium valproate, pesticides and heavy metals may also trigger the genetic variant causing susceptibility to autism. Persico and Mendelli (2014) did not perform original research with human or animal subjects. In summary, they believed that due to the complexity of autism spectrum disorder, it was unrealistic to believe there was only one underlying cause (Persico and Merelli, 2014).

In addition to valproic acid, Karimi (2017) suggested that maternal prenatal medication use could be a risk factor contributing to 46% of an increase in fetal autism. They noted that previous studies showed a connection between the usage of antidepressants by mothers in relation to autism. Mathew et al. (2018) looked at SSRI's used to treat depression. They found between a 1.4-1.8-fold increase in mothers taking this medication. Acetaminophen has also been examined in relation to autism in the womb. Two studies found that "earlier and more frequent use during pregnancy" was associated with higher risk (Mathew, et al., 2018). Overall, evidence suggested a combination of factors, again inconclusive. Further studies should be completed to clarify potential risks versus benefits.

Influenza

Does maternal influenza cause autism? In animal experiments, given the human influenza virus, offspring exhibited autistic-like behaviors (Zerbo, 2013). Therefore, a case-controlled study reviewed and assessed data from groups of 538 children with autism and 163 children with

developmental delays look for autism-related associations. The children's ASD diagnosis was confirmed using standardized instruments: The Mullen Scale of Early Learners, Vineland Adaptive Behavior Scales and the Autism Diagnostic Interview-Revised. The Autism Diagnostic Observation Schedules-Generic (Zerbo, 2013), which had not been used in previous studies of this nature, was included. Parents completed the Social Communication Questionnaire and subjects who scored higher on than the cut off completed the Autism Diagnostic Observation. Children were between the ages of 24 and 60 months, lived with one biological parent and were born in California. Children were divided into categories using the state birth file and random selection: those with autism, those with autism and developmental delays and those in the general population. Siblings were not included in this analysis. Fever during pregnancy was noted in 18% of mothers of children with autism compared with 15% of the mother controls. The influenza occurred more frequently in the winter than in the fall as typically found in California.

Autism was not associated with influenza, however, both autism and developmental delays were associated with fever during pregnancy. Rates were lower among mothers who reported the use of fever-reducing medications and higher for mothers who did not. It was interesting to note that fewer mothers of children with autism received the influenza vaccine compared with those in the general population. However, because the vaccine dates were not noted, the authors suggested that the results be considered with caution. The overall results showed that the fever-reducing medication used while pregnant could eliminate the association between maternal fever with autism (Zerbo, 2013).

Air Pollution

Air pollution has been associated with many diseases, but how it affects mental health is not known. Studies show an increase in disease rates, but the effect on mental health needs to be

examined further (Chen et al., 2018). Western countries have found connections between air pollution and autism, but no such study has been completed in developing countries. One study addressed the long-term connection of three air pollutants with a diagnosis of ASD in Shanghai, China. Researchers Chen et al., (2018) revealed a connection between autism and exposure to three air pollutants during the first three years of life in the case-controlled study looking at particulate matter. Particulate matter is a complex toxic substance that is recognized to cause health issues, influence the brain and possibly the MET gene, a gene that is responsible for making protein, is important for neurodevelopment. Could the association between pollutants and this gene influence autism during critical stages of development?

The focus of the study in June 2014 included three air pollutants PM_1, $PM_{2.5}$ and PM_{10} amongst 84.934 12-year-old children who were selected and screened for ASD in the first stage. Pediatricians later confirmed the autism diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V). The children were administrated the Social Communication Questionnaire (SCQ), where an SCQ score of > 15 met the criteria for an autism diagnosis. The questionnaire administered in the second stage confirmed the initial results. Pediatric specialists interviewed and selected stage three participants. The final stage interviewed 711 children who completed the Weschler Intelligence Scale for Children-Revised (WISC-R). A total of 124 ASD children and 1240 healthy controls ages three through twelve were selected. There were more males (77%) than females (23%) (Chen et al., 2018).

Exposures to PM_1, $PM_{2.5}$ and PM_{10} showed an increased risk of ASD as stronger links were present during the second and third years of life. Concentrations of these air pollutants were measured using satellite based-prediction and conditional regression models. Data analysis determined the associations between the air pollutants and autism. The first year of life showed

less significant findings than the second and third years, but exposure during these three years of life significantly increased the risk factor. It is known that babies breathe more air during the second and third years of life which may have led to these results. Could the amount of air intake influence the adverse effects that contributed to autism?

Another significant finding was that families of those with ASD were more likely to have other mental health problems (Chen et al., 2018). The exact onset date of ASD was unknown and was hard to pinpoint in many cases, which was one of the limitations of this study. Future studies should examine low income/high pollution countries to determine the health effects of PM pollution. Overall, the study provided evidence that particulate matter should be studied further in connection with autism and other mental health-related disorders (Chen et al., 2018).

Fluoride

Strunecka and Strunecky (2019) reviewed the impact of fluoride and how it affected autism. They agreed with other researches who believed that the cause of autism was multifactorial including both genetics and the environment. Fluoride was not currently accepted as a potential cause of autism, but study results demonstrated that fluoride contributed effects to factors such as inflammation, mitochondrial dysfunction and oxidative stress which are coincidentally the same symptoms observed in people with autism (Stunecka and Strunecky, 2019).

Fluoride reacts when mixed with aluminum tetrafluoride, however it has been regarded as nontoxic by the CDC. Fluoride is found in water, food, and cosmetics, among other daily used things (Strunecka and Strunecky, 2019). One may question why it has been linked to neurological and psychiatric behaviors since the 1930's if there was no harm. A medical review proved that 500 people were affected from drinking fluoridated water when it appeared in 1977.

Fluoride has also been documented as neurotoxic to humans, specifically for those in China where there is naturally high fluoride occurrence. This high fluoride incidence was prevalent in autistic children. Japan, a country that uses a school-based mouth rinse program also reported an increased incidence of children with ASD. Seventy-three Egyptian children who used fluoride were compared to 73 typical children. They also were reported to have mitochondrial dysfunction (Strunecka and Strunecky 2019).

The Strunecka and Strunecky 2019 review found neurotoxicity evidence from in fluoride from 315 laboratories around the world. The review was limited due to availability of reports; however, the data sounded an alarming warning about fluoride use. In countries with a high incidence of ASD documentation noted higher fluoride usage. The toxicity remained unclear, but fluoride is not required as an essential nutrient and may very possibly harm the brain development of children. Future studies should monitor the effects of those born after fluoride was removed from drinking water to confirm or negate this suggestion.

Allergens

Rzhentsky et al., 2014 conducted research to clarify whether there was a link between autism and allergies. Japanese children in Kanazawa City were examined using the Autism Screening Questionnaire, consideration of environmental factors, and known allergies. The authors studied 1407 children ages three through five years at the preschool and kindergarten levels (Rzhentsky et al., 2014).

Initially families completed questionnaires that investigated characteristics, family environment, birth order, and allergic symptoms. Then 1407 children were analyzed by medical doctors using questionnaires seeking information about allergic diseases such as asthma and nasal allergy. This questionnaire screened for autism considering social skills, communication,

and attention to detail. Environmental factors were analyzed, and dichotomized results based on categories were noted with scores greater or lower than eight. Statistical tests analyzed the data (Rzhentsky et al., 2014).

The data revealed a higher prevalence of autism in boys (80%) and an increased number of firstborn children. The study linked ASD and nasal allergies. The author "speculated" that the central nervous system played a role and that allergies were connected to "reciprocal social interaction," "language and communication," and "stereotyped behaviors," which also are a larger subset of autism symptomology (Rzhentsky et al., 2014). Overall, the study showed that there was a closer relationship between allergy and autism than previously determined. However, the authors concluded that there was limited sample data related to asthma, and little consistency between ASD and maternal smoking, or the nasal allergy connection and suggested that further research should be completed.

Food Allergy

Food allergy may be a casual factor in autism. Seventy-six percent of autistic people suffer from gastrointestinal problems (Khakzad et al., 2012). Some people believe that allergies may contribute to autism, but research is limited. Some proponents believe that a gluten and casein free diet helps those on the autism spectrum. Both autism and allergies occur in the first years of life and anecdotal records indicate that behaviors improved after the elimination of certain foods.

Khakzad et al. (2012) studied 39 Iranian children (25 boys and 14 girls) between the ages of 1.6 and 8.5 and evaluated them following six months of an elimination diet. Behavioral changes were collected each month using the Childhood Autism Rating Scale (CARS) scores. A standard exam screened children for allergy symptoms and differentiated them by whether

additional family members also had symptoms. Children did not receive any allergy medications during the time of testing.

The allergy testing began with a skin prick test (SPT) followed by a serum IgE of ten foods common to locals in the Iran. The skin prick test was examined for egg whites, oranges, peanuts, tomatoes, tuna fish, walnuts, eggplant, melons, grapes, and cow milk. The children were re-evaluated with a questionnaire. The results of the SPT test showed that 3/39 of the SPT's were positive and 2/3 children reacted to peanuts. IgE levels increased by 56.4% and 46.6% of the children had atopic allergies (Khakzad et al., 2012).

The CARS scale results showed a decreasing trend in negative behaviors throughout the study, although the numbers were not significant. Since autism is known to have multiple causes, it was not possible to conclude that allergies were the primary cause. The Khakzad hypothesis was that allergies played some role in the increased prevalence of the disorder. Based on the study, researchers believed it was a risk factor. The results showed positive effects for children's behaviors. They theorized that if the children had a dysregulated immune system, the allergens must have altered their behavior. Researchers hope that studies will be conducted to analyze food allergens on a larger scale related to autism behaviors in children.

Artificial Food Color

Artificial food color (AFC) has been linked to autism and other disorders such as attention-deficit/hyperactivity disorder (ADHD). The effects of artificial food dye have been studied since 1500 B.C., starting in Ancient Egypt. The Food and Drug Administration Food Advisory Committee reviewed the behavioral controversy related to artificial food dyes. The FDA decided to not ban colored dyes or require a warning label noting potential harm. The committee decided further research was needed to make such conclusions (Arnold et al., 2012).

There are seven certified food colors used in the United States with two others approved for limited usage. The US separates the dye food coloring into two groups: synthetically made and naturally made. Testing is not required. This is different from Europe (Arnold et al., 2012).

Parents and educators continue to debate whether food coloring affects children's behavior and contributes to learning problems. Dr. Benjamin Feingold suggested the idea that this was a problem in 1973 and 1977 (Arnold et al., 2012). Dr. Feingold proposed that food dye was linked to behavior problems in children and completed observations of children considering food dye intake along with other flavorings. His results indicated sensitivity in children (Arnold et al., 2012). Dr. Feingold created a diet eliminating two food additives that he thought were linked to hyperactivity claiming 60-70% of children improved after starting his diet (Arnold et al., 2012). He later authored a book, *Why Your Child is Hyperactive*? Although many parents adopted this belief and followed his lead, it was determined in 1982 that more studies were needed to be done to solidify the link between hyperactivity and food additives.

In one sample study reviewed, 150 of 200 children improved when artificial food colors were eliminated from their diets (Arnold et al., 2012). In another study, 22 of 34 children reacted with sleep restlessness and irritability after artificial food coloring was reintroduced to their diet. Landmark studies were completed in 2004 and 2007 with preschool children, using an elimination diet for two weeks followed by reintroducing food coloring the next week. Children were classified as hyperactive based on a behavior scale and criteria from the *Diagnostic and Statistical Manual, fourth edition* (DSM-IV) (Arnold et al., 2012). Children were classified as hyperactive based on a behavior scale and criteria from the *Diagnostic and Statistical Manual, fourth edition* (DSM-IV) (Arnold et al., 2012). Results indicated hyperactivity, but no association with a diagnosis of attention deficit hyperactivity disorder (ADHD). Overall, there was a small

effect for all children that resulted in changes in the United Kingdom public health system. A committee heard testimonies for two days from experts who discussed food coloring and ADHD. The committee agreed 93% that additional studies were needed (Arnold et al., 2012).

ADHD, a dimensional diagnosis, can be difficult to separate from a typical child with other risk factors. Many studies investigated ADHD and results indicated that genetics supported the best documented cause; specifically indicating that up to 80% of twins shared a replicable gene that is heritable. However, this percentage could lead to the belief that the remaining percentage was environmental, but this belief could also indicate susceptibility in the inherited genes causing the disruption (Arnold et al., 2012).

Studies of fertilized foods such as fruits and vegetables examined nutrient content and artificial food coloring. Increased food processing changes the nutrient make-up of the food One study examined 10 hyperactive children and 10 healthy children on an additive free diet. After the elimination diet, half of the children a commercial drink containing tartrazine. The behavior observations showed changes in urine zinc in the hyperactive children. The study questioned what other nutrients might be wasted because zinc is an essential part of brain functioning (Arnold et al., 2012).

More food color studies were completed since 2007 and all researchers agreed that because evidence was not strong enough and data was flawed the impact of food coloring on ADHD remains inconclusive. Some studies used blinding that was imperfect. Others used the DSM-IV criteria, but it was not followed correctly (Arnold et al., 2012). Another flaw in these studies was the use of multiple food colorings, making it hard to pinpoint the specific AFC effects.

It is understood that both ADHD and ASD are multifactorial and that many unknowns

exist in both disorders. In addition to artificial food coloring causes could be related to gene vulnerability. The incidence of both ADHD and autism have dramatically increased over the last 20 years. Children experience more life stressors, environmental, educational, and chemical changes that could affect both disorders.

Additional research should be completed to enhance the artificial food coloring study. Elimination studies using multiple dyes should be completed to determine which specific food colors may cause hyperactivity in children. Arnold et al. (2012) suggested that the interaction between nutrients, medication and AFC's should be studied. Additionally, population samples must be larger to provide persuasive evidence that influences the FDA, especially since food coloring has already been approved for use in the United States. Because of the approval, some believe that the artificial food coloring is no longer an issue and does not need to be studied, while others believe that the results are too concerning to dismiss. Arnold et al. (2012) believed that because childhood obesity was on the rise, making food more attractive was not significantly important and food coloring was not the main cause of ADHD. He posited that it was a contributing factor affecting the nutrients manifested in younger children contributing to the overall problems in public health. Autism was not factored in this study but should be addressed in future studies related to food coloring and behavior. Arnold et al. (2012) suggested that children's exposure to food coloring additives be minimal due to the inconclusive results.

High Fructose Corn Syrup

The autism rate is growing tremendously in the United States, but why isn't it growing at such a large rate in Italy? Dufault et al. (2012) investigated the discrepancy in autism rates between the United States and Italy. A gene variant (PON1) has been shown to be linked in the United States to autism, but not in Italy. A previous study reviewed by Dufault et al. (2012)

attributed the gene variation connected to high fructose corn syrup. Italians seldom use high fructose corn syrup while it is consumed by Americans at an average of 35.7 pounds per year. The belief was that the gene interacted with certain environmental factors. Researchers investigated foods more likely to be consumed by Americans through information provided by the U.S. Department of Agriculture.

Dufault et al. (2012) conducted a literature review on these studies that investigated and reviewed gene-environmental interactions that potentially cause autism. The review consisted of the expanded Mercury Toxicity Model that compared differences in the gene variation PON1 in the United States with Italy. Environmental factors such as diet influence genes, exposing them to toxic substances, one of which is high fructose corn syrup. High fructose corn syrup is not consumed in Italy to the degree it is within the United States. High fructose corn syrup has trace amounts of mercury that is also in food coloring and processed foods. The consumption of high fructose corn syrup can lead to mineral imbalances causing oxidative stress. Children with autism who have a zinc deficiency struggle to excrete heavy metals. The study found that autism behaviors might be associated with the prenatal diet and use of high fructose corn syrup in the United States. More research is required; however, dietary changes should be made to eliminate the toxic exposure to high fructose corn syrup according to the Mercury Toxicity Model.

Excitotoxins

Monosodium glutamate (MSG) was discovered by Lucas and Newhouse in 1957. Later, John Olney found that MSG caused destruction in the neurons of animals and thus coined the term *excitotoxin* to describe how the neurons became overstimulated. Neuroscientists found that the brain has a large amount of glutamate receptors and this stimulation created destruction in the

brain. Glutamate, the largest neurotransmitter in the brain, plays a significant role in the developing nervous system (Blaylock, 2008).

Pathological and biological changes may be the results of foodborne *excitotoxin* additives. Many parents have noted a connection between their child's diet and symptoms of autism spectrum disorder. Additive studies were reviewed by Russell L. Blaylock, MD (2012) suggested links to glutamate, aspartate and quinolinic acid in the brains of people with autism. First, glutamate from MSG affected the fetal brain and created lesions that disrupted the function (Blaylock 2009). Glutamate additives found in toddler food among others can affect a child's brain during the first two years of life. When rats and mice took glutamate additives orally, they were found with lesions in the brain, oxidative stress, and behavioral changes. Humans are five times more sensitive to MSG than rats and mice. In addition, one study found that children with autism had a deficit in glutamic acid decarboxylase (GAD) which affected the cognitive areas of the brain (Blaylock, 2009).

Other areas addressed in Blaylock's review included aluminum and fluoride which were mentioned previously. Aluminum was found in water and additionally accumulated in the brain and caused inflammation. Fluoride accumulated in the hippocampus. Fluoride was not only found in drinking water, but also baby formula and processed foods (Blaydock, 2009).

Blaydock's foodborne excitotoxin review is alarming. Food additives such as MSG and neurotoxins are shown to cause disruption in the brain during initial stages of development suggested in cases of autism spectrum disorder. With this evidence, why are we not vigilant about this growing disorder? Diet appears to play a role in this complex condition known as autism spectrum disorder. The role of food additives, such as MSG, must be looked at more deeply to determine a potential link with autism.

Mycotoxins

Fungal infections have been shown to be common in the immunocompromised population. Mycotoxin, a natural contaminant, comes from mold or fungi can be found in foods such as cereals, grains, or spices. Some think there may be a correlation between mycotoxins and autism (Duringer et al., 2016). One pilot study looked at 54 children, with a median age of 12.4 years to determine a possible link. Boys were a larger majority and 25 had autism, while 29 were controls. The children were from six counties in Washington and a substantial proportion were verbal children (Duringer et al., 2016).

Autism diagnosis was confirmed using the DSMI-IV criteria and affirmed by the children's clinicians. Parents completed questionnaires that included Individualized Education Plan (IEP) information, background information, language proficiency and medication usage. Additionally, IQ scores were obtained to determine cognitive levels. Urine samples in a four ounce cup were collected from the children selected. They were frozen and transported to Oregon State University where they were analyzed (Duringer et al., 2016).

Screening was completed for 87 mycotoxins. Nine out of 54 children tested positive for at least one mycotoxin via the urine biomarkers. There was no specific difference between the control group and the children with an autism diagnosis. The primary mycotoxin was zearalenone, produced by fusarium species, often used in animals' feed that infects cereals (Zhang et al., 2018). The geographic area did not seem to be a factor in detection. Overall, there was no correlation between mycotoxins and autism. Future studies should include samples from children in utero to collect a more specific mycotoxin load. A larger, more enhanced sample and technique would improve detection of mycotoxins. Food intake should be considered with

caution as mycotoxins have documented health effects on children, however, there has not been a significant link between autism and these mycotoxins (Duringer et al., 2016).

Domoic Acid

Another neurotoxin known as domoic acid has been shown to cause amnesic shellfish poisoning. It can cause memory loss and brain damage when consumed and shares similarities with those who have an autism spectrum disorder. Amnesic shellfish poisoning is caused when consuming shellfish or whole fish. Because of the variation in exposure across geographic locations, it is interesting to know that autism prevalence is higher in areas across the coasts where people are more likely to consume fish. In addition, metals and pollution are also linked to seafood (Lahvis, 2017). Could domoic acid be a potential autism risk factor as well?

Lahvis, 2017, reviewed studies that revealed that young animals were likely more sensitive to domoic acid than adults. In addition, one report revealed that infants are over 40 times more sensitive to domoic acid than adults regarding toxicity. The limit of 20 mg/kg in seafood protects adults, but this is concerning in areas along the European and Asian coasts because the limit is exceeded which occasionally closes the shellfish harvest (Lahvis, 2017). Much like MSG, the toxic effects of domoic acid imbalances the brain and causes excitotoxicity, over-exciting neurons and causing seizure activity. The domoic acid-induced behaviors are quite like those of autism including impairments in social behavior, one of the hallmark characteristics, and seizure activity. Domoic acid was also shown to affect males at a greater rate than females, also common in autism spectrum disorders.

Because rodents are raised in cages, they make a poor comparison with humans who have large living spaces and are free to change their environment. Lahvis instead reviewed studies of California sea lions since they have more freedom to adapt their environment and roam. The sea

lions also displayed effects from the domoic acid by exhibiting repetitive behaviors, swimming in circles, displaying aggression, and rocking. These behaviors were similar to the rodent's exposure to the domoic acid.

Continued should target the toxicity of domoic acid. Consumption limits need to be altered to protect children in the developing stages of life. Studies should be completed with free roaming animals to better compare human effects specifically comparing the autism community. In addition, a specific drug known to reverse the effects of kainic acid was noted to diminish the autism characteristics. Kainic acid is a toxin comparable to domoic acid and therefore, this MgLuR5 antagonistic drug, which promised a 'cure' should be further investigated in relation to helping children with adverse autism symptoms (Lahvis, 2017).

Genetics

Autism causes are poorly understood, but evidence is rising to suggest that environmental factors contribute to the diagnosis. Sporadic studies link chemicals or viruses, but not enough rigorous investigations exist. The Childhood Autism Risks from Genetics and Environment (CHARGE) study currently in process, evaluated chemical and biological markers. The study began by considering developmental assessments and medical information.

Evidence thus far suggested that a minimum of 40% of those who received an autism diagnosis were linked to an environmental cause. Environmental factors associated with autism included prenatal exposure to thalidomide, valproic acid, or rubella (Hertz-Picciotto et al., 2006). Results showed a genetic factor with twins and in families. This was documented in previous case-controlled studies. Studies have also shown factors related to the prenatal origin of autism. CHARGE studies the connection between prenatal and early childhood to determine if exposures to infectious agents can be determined from the available records and samples.

The CHARGE study compares immune function in regressive autism with those who have early onset. Medical records, blood measurements determining metal exposures, and genetic susceptibility are charted by the CHARGE study to determine the causes of autism and developmental delay, both genetically and environmentally. This study hopes to understand the causes of autism and reduce the incidence through the investigation of etiologic factors. Researchers would like to collaborate with the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) to incorporate opportunities for possible replication and data pooling (Hertz-Picciotto, 2006).

Vitamin D Deficiency

Vitamin D deficiency is a world-wide concern, specifically in areas with limited sunshine. Many studies have indicated that vitamin D deficiency is common among children with mental health concerns, asthma, and diabetes, and pregnant women. Over the last 20 years, people have been advised to stay inside to avoid the sun, according to healthcare providers (Bener et al., 2014). Could Vitamin D deficiency contribute to the disorder known as autism? One study looked at the association and the risk factors.

Between 2011 and 2013, a case-controlled study evaluated 508 children that included 254 children with autism and 254 controls. Informed parental consent was provided, and data was collected from semi-structured assessments, family history, body mass index (BMI), and clinical manifestations. Those taking Calcium or Vitamin D were eliminated. History of sunblock use in puberty, those with epilepsy, and those who used an epilepsy drug were also eliminated. Healthy subjects were matched based on their age, gender, and ethnicity (Bener et al., 2014).

Next, blood samples were collected and stored in serum at -70 degrees Celsius. The samples were separated into four main categories labeled severe, moderate, mild, and normal

(Bener et al., 2014). The children were screened during this period where they completed a history, medical exam, and a questionnaire. The evaluation was completed based on age, location, and income by doctors and other healthcare professionals. Statistical analysis determined differences between the two groups.

The results revealed that 14.2% of autistic children had a severe deficiency in Vitamin D and that 8.35% of the control group also demonstrated a severe deficiency. In addition, 43.7% of autistic children had moderately deficient vitamin D levels. In the control group 37% demonstrated a moderate deficiency. Mild levels of deficiency were found in 28.3% of autistic children. Lastly, 13.8% of the autistic children produced adequate levels of vitamin D compared with only 17.3% of the control group. The results showed significant differences in Vitamin D levels for children with ASD than the children compared to the controls (Bener et al., 2014).

This was the first study of its kind to consider the impact of Vitamin D on ASD. Vitamin D deficiencies and its relationship to health is not well understood. However, it was revealed that Vitamin D deficiency was higher in children with autism than those in the control group. Prescribing Vitamin D supplements during infancy was suggested as a strategy to lower the of autism rates based on this study.

Fragrances

Fragrances, a mixture of chemicals and hormone disruptors, were investigated by Sealey et al. in 2015. The researchers previously studied ninety-one fragrances and found that they had the potential to cause neurological damage, specifically toxic effects on the neuroblastoma cell lines. Such damage was shown by decreased levels of oxytocin (OXY) and vasopressin (AVP) neurons, which is common in children with autism. Based on the results, researchers created a new study targeting three fragrances that resulted in significant impairment. Impairments were

also found in the mothers of autistic children as well as those in animals. The study found that this was also more prevalent among males (Sealey et al., 2015). The hypothesis was that chemical mixtures had different effects on brain development. To make this determination the testing examined neuroblastoma cell lines from humans. The study sought to determine whether there were differences in the neuroblastoma cell lines between genders using immunohistochemistry. Each experiment was performed at least 10 times with male and female neuroblastoma seeded and cultured on glass slides, incubated, washed several times, and mounted onto glass coverslips. The slides were analyzed blindly by four different observers at two distinct locations (Sealey et al., 2015).

The study found that changes in cellular diameter, length, thinning, and abnormal neurons were vastly higher when the neuroblastoma cells were exposed to any of the three fragrances. The male neuroblastoma cells showed that ~50% of cells were depleted, but the female cells were not. However, both genders showed significant changes in abnormal proliferation and thinning (Sealey et al., 2015).

Overall, the AVRP and OXYR neurons were reduced especially among males, but also among females. Exposure to concentrations of the fragrances showed more changes in the receptors of males more than females. This experiment may provide a potential link to autism, and certainly portrays a male bias. Fragrances should be further studied. This study showed the male bias and the depletion of neurons and cytotoxic effects that linked fragrances to autism development (Sealey et al., 2015).

Electromagnetic Fields

There are so many electronics constantly around us, it is hard to imagine a world without them. The increase in usage over the years has raised a red flag to some about the hazards to

health conditions and the indirect link to DNA and gene altercations (Ahuja et al., 2013). With the significant rise in electromagnetic field usage, via cell phone use, some wonder whether this may be another environmental health concern disrupting the nervous system and leading to disorders such as autism.

Ahuja et al., 2013, reviewed several studies concerning electromagnetic fields and autism. One study found abnormal white matter in the brain. Another study looked at large changes in 444 genes compared to the typical controls. Yet another study found abnormalities in the frontal cortex region of adults with autism. These electromagnetic fields can affect the large population of developing children that including those in utero.

EMFs can play a positive role and promote healing in some instances, such as cancer; however, people have wondered about the negative health effects for children living near powerlines. Some studies have linked genetic changes such as Alzheimer's disease to the power lines. High frequency electromagnetic fields can affect sensitive brain systems and cause oxidative stress (Ahuja et al., 2013).

Researchers are beginning to recognize that EMFs can alter DNA and phenotypes, possibly contributing to autism. This is particularly crucial in the first trimester of development. Ahuja et al., 2013, believed EMFs should be examined *in vivo* and *in vitro* altercations in genes related to autism.

Ultrasound

Is there a relationship between autism diagnosis and ultrasound or is it a coincidence that both have increased in the last decade? Ultrasound is to determine fetal health and used in most pregnancies. Some authors believed that the two are linked, but many other factors in the

environment could contribute to this phenomena. Abramowicz (2012) believed that the link must be evaluated.

Older studies have documented the negative effects of ultrasound in the developing fetus, but these studies have been disregarded (Abramowicz, 2012). One study that contained 123 variables found only two significant points which included infant grasp and tonic neck reflex. These are not defining characteristics of autism. Another study found no common links between routine exposure to ultrasound and deficits in school-aged children. A large study of 4900+ children indicated only lower scores in the physical education for boys. No other associations with prenatal exposure to ultrasound were noted (Abramowicz, 2012). Ultrasounds are typically completed in the second trimester of pregnancy. The number of ultrasounds has also not contributed to increased autism.

Perinatal outcomes were evaluated in a large study encompassing 41 studies that included 16 controlled, 13 cohort, and 12 case-controlled looking at the link between ultrasound and autism. The results indicated little association that linked ultrasound with brain changes in those with autism (Abramowicz, 2012). It was possible that the autism prevalence was the result of more enhanced diagnosis. Studies have found that children with autism have altered brain growth, but is there any link to ultrasound? These studies pointed to "no," but the results were not identifiably clear. Larger studies should be done to consider more links with between ultrasound and autism (Abramowicz, 2012).

Secondhand Smoke

Is secondhand smoke associated with autism? Smoking has been linked to behavioral disorders in children. Smoke is one of the primary environmental factors considered as a potential autism cause, along with air pollutants and pesticides (Khalil et al., 2018). In a National

Health and Nutrition survey, secondhand smoke was shown to be more common in males than females. Secondhand smoke exposure causes health and behavioral problems.

In 2011 and 2012, the CDC Data Resource Center sponsored by Material and Child Health Bureau studied 56,710 children aged two through twelve that included 2.4 % with an autism diagnosis and 24% with exposure to secondhand smoke (Khalil et al., 2018). Parents were randomly selected via telephone to answer questions about whether their child had an autism spectrum disorder. Yes/No questions were also asked regarding secondhand smoke exposure. Data also include factors such as the mother's mental health, age, child's age, weight, full-term or premature, ethnicity, and education level of the parents.

The study results found that children with autism had higher exposure to secondhand smoke (30% vs. 24% typically). Developing children with autism also had younger mothers with a lower education status and poor mental health status (Khalil et al., 2018). A significant finding was that secondhand smoke was associated with autism in boys, 48% chance higher, but not with females. It was a crucial factor for boys as it was previously studied and suggests the association with autism. Smoke has been shown to impact neurodevelopment (Khalil et al., 2018). Interestingly, gender differences have been mentioned in many of the studies reviewed. Nicotine, an endocrine disruptor, can change hormone levels upon exposure which may be reason for this gender variation. Further studies should be done to understand this revelation. In addition, parental mental health, particularly that of the mother should be considered another potential contributing factor due to the impact on brain development by maternal stress.

The results may be less reliable due to the manner in which the survey was conducted. Secondhand smoke was considered associated with ASD, not a causal factor. Smoking should be evaluated to consider mothers who smoke during pregnancy. Smoking is associated with autism

and thus should be forbidden for mothers. These efforts could possibly reduce the chances of autism spectrum disorder.

Physical Environment

One interesting study looked at the physical environment of those with autism spectrum disorder. Is it possible that toxins mixed with genetics resulted in autism? Powerlines, pesticides, and chemicals have been reviewed resulting in inconclusive findings. Could a detox from the environment change anything? Ten children aged three through twelve, with an autism diagnosis confirmed by the Autism Diagnostic Observation Schedule (ADOS), changed their sleeping environment to sleeping in a cleaner environment for two weeks and were reevaluated using behavioral scales (Faber, 2015).

The study took place in Duquesne University in Pittsburg, Pennsylvania following consent from the children's caretaker. The children slept in a clean room between May and October 2010 and completed routine activities during the day. When arriving at the cleanroom, at a modified hospital room, children typically spent around ten hours and wore only silk and cotton clothing (Faber, 2015). The room contained filters and air purifiers and an ultraviolet water purification system in the bathroom. Testing was performed using a Handheld Airborne Particle Counter (Faber, 2015). Researchers recorded sleep behaviors and a psychologist monitored the family.

The children's blood was drawn by a phlebotomist in their home, stored for two hours, and separated for testing at Duquesne University Pittsburg, Pennsylvania. They analyzed the children's serum, red blood cells, and plasma and processed in Agilent Mass Hunter software for analysis then exported in Microsoft Excel in addition to glutathione analysis (Faber, 2015).

The Behavioral rating scales were completed before and after the experiment. The scales included the Pervasive Development Disorder (PDD) Behavioral Inventory, Aberrant Behavior Checklist, Gilliam Autism Rating Scale-2, Autism Treatment Evaluation Checklist, Childhood Autism Rating Scale, and the Social Communication Questionnaire (Faber, 2015). The children who participated in the clean room experiment improved in expressive language, and socialization and maintained the skills following exposure to the clean environment. Half of the children (five) had decreased oxidative glutathione (Faber, 2015). It was also noted that younger children detoxed quicker than older children indicating possible psychological effects. The small number of children in the study (10) limited the ability to generalize the results to a larger population. It would be ideal to have a larger study over a longer period of time.

Parental Age

The age of parents who have children with autism has been previously studied, with confusing, misunderstood, and conflicting results. Some studies indicated little to no risk while other studies showed that parental age was associated with autism, so why is there confusion? King et al. (2009) investigated changes in the risk factors of autistic children ay associating parental age with autism for children born between the years of 1992 and 2000 in California. From over four million birth records at the California Birth Master Files and Department of Developmental Services (DDS), 18,731 matched with an autism diagnosis. DDS provides services to those with autism, but not other related diagnoses such as pervasive developmental disorder or high functioning autism (Asperger's Syndrome) which skewed the data. Parental age data was missing on 8% of birth records. Three analyses were conducted using a regression scale and pooled together. The mean maternal age of was 26.9 in 1992 and increased to 27.7 in

2000. The mean paternal age was 29.6 and increased to 30.6 in 2000, detailing vast increases in age over the eight year study.

The King et al. (2009) study found a probable risk factor for autism when assessing age of parents at conception but understanding biological factors may contribute to the association and thus further research must be done regarding exposure to environmental factors. California was the only state analyzed so future studies should extend to the rest of the country and world to determine whether parental age is a risk factor for autism.

Melatonin

A vast number of environmental factors linked to autism. It is interesting to note that many are linked to a melatonin deficiency that starts in the mother. Melatonin protects against oxidative stress. May individuals with autism have low-levels of melatonin and is a factor in neurodevelopmental growth in children (Braam et al., 2016).

Braam et al. (2016) used 66 participants in a study related to melatonin at the Ethical Committee of Maastrick University in the Netherlands. One participant in this group withdrew. Five cases did not receive their samples to complete. This study used mothers of patients who primarily had sleep disorders and autistic phenotypes. In addition, 15 women who worked at the clinic with no relationship to autism served as the controls. Questionnaires that included medical history and coffee use and a urine sample with instructions were mailed to the homes. Collected samples were mailed back to the clinic. These samples were then stored at 20 degrees Celsius. Six different urine levels were measured in the mothers of children with autism. Significantly lower levels of 6-M were found in most of the autism. Drinking coffee was not a differential factor (Braam et al., 2016).

This was the first evidence to link melatonin as a factor that contributed to autism. As autism is a co-morbid condition it is therefore linked to other environmental and genetic factors. Conclusively, it may be beneficial for children to supplement with melatonin to enhance brain development. This phenomenon should be further investigated and studied according to the authors (Braam et al., 2016).

Diabetes

Gestational diabetes and obesity may be associated with autism spectrum disorder and other developmental and health disorders. Is this an important risk factor to note? One study looked at 2734 children in Boston between the years 1998 and 2014. Within 24-72 hours postpartum, the study used a constructed interview and medical records with an abstraction form. The children received care at the facility and had their records reviewed and diagnoses confirmed by the *International Classification of Diseases Ninth Revision*. Medical Records identified Pregestational and Gestational diabetes. Most of the children were identified with autism spectrum disorder by pediatric specialists. The study examined the association with both diabetes and obesity in children with autism, some with additional diagnosis of ADHD and DD (Li et al., 2016).

The study was a prospective birth cohort and a meta-analysis. The study showed a slight increase in maternal obesity related to autism. It also concluded significant risk with combined obesity and diabetes. Gestational diabetes was not shown as significant but had a slightly elevated risk. The small sample size results indicated that this study needs to be addressed on a larger scale. A limitation was that the diagnosed children may have been misclassified because both the ASD and developmental disability diagnoses may have been tentative and other risk factors including genetics may have been unknown (Li et al., 2016).

CHAPTER III: DISCUSSION AND CONCLUSION

Autism spectrum disorders are complex and can be a puzzle to so many affected. Evidence suggested that autism is possibly clustered among families. There was some evidence to support environmental influences, but many remain undocumented. Clusters have been linked to California, Texas, North Carolina, and Utah (Rzhetsky et al., 2014).

Ng et al. (2017) reviewed many factors associated with autism from the years 2003 through 2013. The research reviewed over 50,000 publications and eliminated many, resulting in 315 worldwide articles that studied physiological, chemical, nutritional, and social factors associated with autism. Mercury, cadmium, lead, arsenic, and aluminum were reviewed and most commonly linked to autism. A vast majority of the studies occurred within the United States, United Kingdom, Australia, or Japan (Mold, Umar, King, and Exley, 2017). Whether an environmental cause or contributed to an autism diagnosis, the link to environmental influences in autism remains inconclusive. The information considered was impressive, but lack of consistency and limited sample sizes continued to be barriers and further studies were suggested as noted by Kern et al., 2016 and Mold, Umar, King and Exley, 2017.

Mercury levels measured in hair, blood, urine, teeth, and nails resulted in inconsistent findings. Another study examined the distance a subject lived from a location with mercury pollution such as a powerplant. Inconsistent results were found in mercury studies and the connection to autism. The studies had many conflicting results, once again resulting in further studies investigating a link.

Air pollution and drinking water were also taken into account. Five investigations took place in California (Chen et al., 2018). The results connected prenatal exposure to air pollutants and children with autism spectrum disorder. Cardiovascular disease found in subjects exposed to

air pollution triggers oxidative stress, also common in children living with autism spectrum disorder (Chen et al., 2018). Living near a freeway was possibly linked to autism. The study of pesticides in the air and water in connection to autism is emerging, but again, further studies were recommended to determine whether there is a significant connection (Chen et al., 2018 and Strunecka and Strunecky, 2019).

Medication taken by mothers was a possible marker of autism. Antidepressants were a large concern especially in the 1980's. Two case-controlled studies reviewed a minimal relationship with mothers taking prenatal antidepressants. Interestingly, the final review noted pregnancy complications in eleven studies with four cohorts. One review indicated that autism was associated with a variety of pregnancy-related complications (Ng et al., 2017).

Typically, there are disease clusters that are shown to be more defined in certain areas of the globe geographically. It was difficult to decipher clusters of autism and other developmental disorders. Findings based on the collective research data suggested the cause of autism appeared to be multifactorial and interrelated (Ahuja et al., 2013).

Interestingly, many of the environmental factors have been linked to having a large impact for boys. People believe that girls are typically diagnosed later in life, that autism is more difficult to spot in girls; that girls somehow can hide their "autism" more. Others believe it is displayed differently in girls. It seems that researchers should consider biology in relation to these studies. Many of the environmental factors such as the toxins, resulted in increased autism at greater rates with boys. These studies have shown that biological factors play a part in autism along with genetics (such as gene interaction) and chromosomes. The study between genders and their make-up regarding autism and how it is linked at a higher rate in boys needs to be

considered with more detail. In addition, it is apparent that genetics play a role in addition to environment.

A great study is continuing with the group from CHARGE (Zerbo, et al., 2013 and Herz-Picciotto et al., 2016). They are continuing to build an infrastructure to investigate autism and other disorders to help understand and determine the growing rates of autism. The current study mentioned in this paper emphasized both genetic and environmental factors. Researchers addressed biological markers, immune response, and gene expression and continue to study medical records and questionnaires about pesticides and other household products (Hertz-Picciotto et al., 2006). Most importantly, the specimen bank compares biochemical profiles of those with autism to those within the general population. The CHARGE study (Zerbo, et al., 2013 and Herz-Picciotto et al., 2016) is currently limited due a geographic area in California. Studies need continue research in the United States and across the globe to help identify environmental causes at a deeper level while considering genetic variants, y chromosome links, brain pathways, and other genetic variants that may contribute to the predisposition of autism in boys (Hertz-Picciotto et al., 2006).

Other environmental factors that may influence autism and link to genetic variables studied in this literature review included pesticides (Persico and Merelli, 2014 and Khalil et al., 2018), lead (Shibata et al., 2013), medication (Christensen, et al., 2013), and various toxins (Bjorklund et al., 2018). Environmental toxins can add to birth defect, and weaken the immune system (Blaylock, 2008). Ongoing research should be at the top of the list due to this overwhelming increase in the prevalence of autism and to foresee the potential connection in the development of autism and intellectual disabilities. Inflammatory imbalances were also a result of prenatal exposure to pesticides (Blaylock, 2008).

Heavy metals were shown to influence the placenta. There was an increase in heavy metals in blood and urine of children with autism. They demonstrated hypersensitivity due to genetic make-up. The results showed that metals mixed with a genetic NLGN3 mutation may result in autism (Persico and Merelli, 2014). Thimerosal, mentioned above, also may cause oxidative stress. Oxidative stress affects motor learning and in addition a gene variant may be more susceptible to thimerosal. Thimerosal may have dangerous effects on the immune system (Persico and Merelli, 2014). Again, genetic make-up could influence this. Vaccines have been eliminated as a cause of autism, but mercury is known to be neurotoxic. It is linked to air pollutants, amalgams, seafood, and other foods such as high-fructose corn syrup. Eating foods with high fructose corn syrup has been shown to impact children with attention deficit disorder and autism spectrum disorder (Ng et al., 2017). Mercury also has toxic effects on brain cells, depleting glutathione. Glutathione has shown up in many of these studies (Faber, 2015). It is important to note that glutathione seems to play a key role in the makeup of autism, but other environmental factors contribute.

The environmental factors sodium valproate and pesticides, in addition to heavy metals, may also trigger the same genetic variant causing susceptibility to autism. The make-up and complexity of autism is growing. It is so peculiar and complicating to identify. Many of these studies have possible links and seem to show some sort of underlying genetic cause that is triggered by something in the environment. The cause is something that we are unable to pinpoint. I believe there is no one direct influence. People are all made up differently, with different genes and different environmental experiences that contribute to how autism affects them. Someone may be more susceptible to autism based on their genetic make-up.

It is important for my colleagues to know that autism falls on a large spectrum. There are high functioning kids who present as neurotypical, but they still need to know their brain works differently than others. These studies illustrate that children with autism have brains that function differently. We cannot expect children with autism all to think the same way, just as we should not expect any other child to produce the same thoughts or ideas. It is important to see where students are coming from. They just may be able to teach their teachers something worthwhile.

My son is just one of many children diagnosed with an autism spectrum disorder. How it looks for him is not the same in how it looks in others. I have considered many possible factors and there is some evidence of possible causative factors, but there is no direct link. Autism clearly comes from a variety of sources. I am hopeful that people will find more compelling evidence and research will continue to determine relevant factors. As a teacher, I have seen children with autism grow a lot over one year in the educational process. I have also seen children regress. There is no exact marker that says a child will or will not learn or progress. I do believe every child deserves a chance to reach their full potential. It takes time to discover how each child with autism learns, but I believe all children can learn. I also want my colleagues to know that each families background is different, and all are doing what they can to help their children. I know I have tried many things for my child. Some strategies produced big results; some have produced no results.

Since its discovery in 1944, autism remains a mystery. Children with autism not only attend school but have additional therapies and schedules that can make parents lives stressful and difficult. Parents try to do what is best for their child with the resources and knowledge they have been given. I truly believe that there is a multitude of information that needs to be studied and have hope that more evidence and information about autism will be discovered.

Why is autism growing at such an alarming rate? It is hard to say, vast research has been completed, but evidence is limited. I know that genetics and environment are being studied in relation to autism. Clinicians, researchers, teachers, universities, government, and parents have a key role to play in advocating and assisting children on the autism spectrum. Continued research and advocacy must be done for the autism community. One child with autism is one child with autism. The etiology of autism is yet to be found.

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