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Gastrointestinal Symptoms in Children with Autism

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An abstract of a thesis submitted to the faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in the Hubert Department of Global Health
2018

Abstract

Gastrointestinal Symptoms in Children with Autism
by M. Elizabeth Jaramillo M.S. CCC-SLP

Background: The classification and defining symptomology of autism has, historically, been controversial. Once considered a mental health disorder, today autism is known as a complex neurodevelopmental disorder with a heterogeneous presentation. It is diagnosed based on observation of hallmark behavioral symptoms. Comorbid conditions have been increasingly recognized. Gastrointestinal complications are perhaps among the most common co-occurring conditions. The etiology and pathophysiology of autism remains unknown and immeasurable. There has been much debate over whether symptomatic epidemiology may help us understand the pathophysiology and intervention options for children with autism.

Objective: This study aims to describe the change in the proportion of reported gastrointestinal symptoms among children with autism in a U.S.-based nationally representative sample, over the past decade. This study poses the question; does the association between gastrointestinal symptoms and autism stay constant from 2007 to 2016 in the National Health Interview Survey Data?

Methods: This secondary data analysis will produce descriptive statistics, including frequencies, unadjusted and adjusted odds ratios, calculated per individual year from 2007 to 2016 of the National Health Interview Survey Sample Child data. Autism prevalence as well as age distribution across the decade was also calculated. Variables that represent gastrointestinal symptoms are referred to digestive allergy, stomach illness and diarrhea/colitis, and defined by the survey question.

Results: This study cannot definitively conclude that there is not a pattern in the proportion of reported gastrointestinal symptoms (digestive allergies, stomach illness, and diarrhea/colitis) among children with autism, from 2007 to 2016 in the NHIS data. Based on odds ratios, the odds of having any of the three gastrointestinal symptoms hovered almost or right above significant over the decade, when compared to children without autism. Based on linear regression models, age and sex did not have an effect on the association between any of the three gastrointestinal variables and autism.

Conclusion: A gastrointestinal pathophysiology specific to autism may be plausible and children with autism may perhaps experience a higher incidence of gastrointestinal symptoms than children without autism. However, the connection between the gut-brain-axis and autism remains poorly understood. The results of this study show an oscillation in the significance of the likelihood of digestive allergies, stomach illness or diarrhea/colitis among children with autism, compared to those without. These results imply that there is insufficient evidence for the need for health care recommendations or interventions that target autism-specific gastrointestinal symptoms.

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Gastrointestinal Symptoms in Children with Autism

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INTRODUCTION

Overview

Autism is diagnosed based on behavioral symptoms, including social withdrawal, repetitive behaviors, and communication deficits. However, the ascertainment of diagnosis and classification of symptoms have historically been challenging due to the heterogenous presentation of the condition and lack of a definitive biological test. Since it was first described in the early 1940's, there has been debate over whether certain symptoms are primary symptoms of the condition or comorbidities. This debate becomes impactful as it shapes a working definition of autism, how it is diagnosed and may even indicate which symptoms may have implications for the physiology and etiology of autism. Some common comorbid symptoms for autism include sleep disturbance, intellectual disability, gastrointestinal complications, seizures and others. Autism prevalence has been on an upward trend as the definition of autism evolves.

The profiles of children with autism diagnosis may also evolve along with our understanding of symptoms and the growth of the autistic population. While the increase in prevalence may be due to an organic increase in autism incidence, there may be other influential systematic factors as well. Changes in the profiles, or in the overall population of children with autism, may have far reaching implications. These implications include a change in diversity of comorbidities, severity of cases, demands for quantity and types of health care services, average age may skew younger, needs for life-course focused services, and changes in research priorities.

Gastrointestinal symptoms are perhaps one of the most common types of comorbidities among children with autism. There are many theories of autism etiology that propose a plausible yet incompletely understood bidirectional pathway between the gut (including the gastrointestinal system, along with both the enteric nervous system and key components of the immune system which are intimately involved in its functioning) and the central nervous system (which is responsible for our behaviors, emotions, communication and learning). Hence, symptoms of the gastrointestinal system may influence, and be influenced by, symptoms of the central nervous system.

Background

The history of autism research is riddled with controversy and inconclusive findings. Autism was recognized as a mental health disorder in the early 1900's. The term 'autism' was first used to describe social withdrawal among patients believed to have schizophrenia. By the mid 1900's infantile autism was classified as separate from schizophrenia (Fombonne, 2003). In the 1970's there was controversy in the research community regarding the primary symptoms and etiology of autism (Panksepp, 1979). Despite advances in autism research, particularly in genetics and neuroimaging, there continues to be controversy and inconclusive findings.

Currently, autism is considered a complex neurodevelopmental disorder with heterogeneous presentations. There is no known genetic or biological marker of the disorder, rather it is diagnosed based on observable symptoms. The main symptoms are social withdrawal, communication deficits and repetitive behavior (P. Whiteley, & Shattock, P., 2002). Social withdrawal includes deficits in reciprocal social interaction and lack of eye contact.

Repetitive behavior classically includes a need for following established routines and repetitive hand movements. Communication deficits are marked by a difficulty learning a rule-based symbolic system and theory of mind (Baron-Cohen, 2000). While these hallmark symptoms are behavioral, each child may be unique in his or her expression of these and other symptoms.

Diagnostic terms that fall under the umbrella of autism spectrum disorders are Asperger Syndrome, Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS), and Autistic Disorder. Asperger Syndrome is considered a less severe condition on the spectrum with respect to language learning skills and functional impact. Asperger Syndrome was folded into Autistic Disorder in the 2013, 5th revision of the Diagnostic and Statistical Manual of Mental Disorders manual (DSM-V). Children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) exhibit symptoms associated with Autistic Disorder but do not meet the full diagnostic criteria (Akshoomoff, Corsello, & Schmidt, 2006).

Autism is a life-long condition for which there is no known cure. The onset of autistic symptoms typically occurs around age 3, but symptoms can begin to show as early as 6 to 18 months and continue to manifest through a child's school age years (Lyall, 2017) and beyond. Cases that present with more severe symptoms tend to be identified more readily and diagnosed at younger ages (Lyall, 2017). Additionally, more children are being diagnosed at younger ages as the impact of early intervention on long-term outcomes is recognized.

Theories of Etiology

Many theories for the etiology of autism have been proposed, yet the cause remains poorly understood (Autism Spectrum Disorder, National Library of Medicine-PubMed Health).

Autism research has become increasingly multidisciplinary, with input from fields such as genetics, epidemiology, demography, neuroanatomy and neurophysiology, molecular biology, immunology, and gastroenterology. Theories mainly point towards either environmental, genetic, or organic causes, or a combination of these. Some predominant theories of autism etiology include the extreme male brain theory (S. Baron-Cohen, 2002), leaky gut theory (Cass et al., 2008; White, 2003), opioid peptide excess theory (Panksepp, 1979), and the toxic metal body burden theory (Adams et al., 2009). In general, these are concerned with biochemical imbalances and exaggerated immune responses. This review does not touch upon studies related to neurophysiology and neuroimaging. The leaky gut theory and other theories related to gastrointestinal complications and the gut's connection to the brain will be discussed in further in this paper.

In the 1960's, autism was thought to be a psychosocial condition caused by lack of maternal nurturing, referred to as "refrigerator mothers" theory, which has since been definitively debunked (DeMyer, Hingtgen, & Jackson, 1981) (Fombonne, 2003). After this hypothesis was ruled out, an environmental toxicant seemed to be a more likely cause. Autism was feared, although now disproven, to be an adverse effect of the Measles Mumps Rubella vaccine (MMR), typically given to children at age two – the age at which autism typically manifests (Fombonne, 2008; Nelson & Bauman, 2003). Similarly, others thought Autism could perhaps be caused by thimerosal, a mercury-based stabilizer used in vaccines, but which was never used in the MMR vaccine (Nelson & Bauman, 2003). Thimerosal was removed from all vaccines in 2003 in the United States; however, the incidence of autism has continued to increase, further suggesting no correlation (Adams et al., 2009). As of yet, no environmental

risk factor has been definitively determined to cause autism (Adams et al., 2009; Fombonne, 2003).

When scientists noticed similarities in symptoms between children with autism and children with mercury poisoning, researchers began to explore a potential correlation between levels of toxic metals and autism severity (Adams et al., 2009). Studies have found higher levels of mercury in children with autism through urinary tests after administration of chelation medication and in their baby teeth (Adams et al., 2009; J. Bradstreet, 2003). While several studies have found statistically significant correlations between autism or autism severity and toxic metal body burden, this correlation has not yet established causation and is not yet fully understood (Adams et al., 2009; Hertz-Picciotto, 2010).

Another hypothesis is that of genetic etiology; however, like with environmental toxicants, genetics has not been able to explain trends in the condition. Genetics may have become a more popular research focus due to the lack of biological or physiological markers that would be expected in the case of other etiological explanations (P. Whiteley, & Shattock, P., 2002). Correlations of autism with conditions of known genetic etiology, such as Down's syndrome, may influence researchers to look for genetic etiology (P. Whiteley, & Shattock, P., 2002). Some researchers have hypothesized a more complex interaction between genetic factors and environmental components that are not related to nurturing (Adams et al., 2009; Ghalichi, Ghaemmaghami, Malek, & Ostadrahimi, 2016; Lyall, 2017).

The opioid excess theory, similar to other metabolic-based theories, suggests that peptides from dietary intake are incompletely metabolized and allowed to pass through the intestinal lining and the blood-brain barrier into the brain where they mimic naturally occurring

opioids (P. Whiteley, & Shattock, P., 2002). It was first developed after observations of similarity in symptoms of children with autism and laboratory animals who have been administered low doses of morphine (Panksepp, 1979). These peptides, derived from casein and gluten-containing foods, have an effect on neuro-activity which influence psychological and behavioral symptoms (P. Whiteley, & Shattock, P., 2002). The opioid excess theory is supported by research that looks at the biochemistry of autism and the efficacy of exclusionary diet interventions (P. Whiteley, & Shattock, P., 2002). Yet, this theory has not drawn any conclusive findings.

The immune system has been implicated in many theories and studies regarding the etiology of autism, from ones related to dietary intake to maternal influences during gestation. Some researchers suggest that children with autism may have too few regulatory or suppressor T Cells. These T Cells are crucial for the maintenance of immunological tolerance. A reduced level of regulatory T Cells may lead to exaggerated immune responses in children with autism (Autism Speaks). Studies of the immune system during pregnancy in mice are proposing that cytokines and T Cells, which can cross the placenta, may affect fetal neurodevelopment and influence autism-like characteristics. (Autism Speaks).

Rationale for Increase in Prevalence

The estimated prevalence of autism increased from nearly 0.1% in 1997 to 2.2% in 2014. 2010-2012 was the first time that the ADDM surveillance network did not see an increase in autism prevalence among 8-year-olds. However, straddling that same time frame, from 2011-2014, NHIS reported a higher rate of autism than ADDM, at 2.2% among 3 to 17-year-olds (Lyall,

2017). While these numbers represent U.S. population data, researchers estimate the same trend in growth globally (Wright, 2017). Global trends may be difficult to measure as the majority of the world's children live in developing countries which lack access to appropriate diagnostic tools and epidemiological data is sparse. Factors that may account for this rise in prevalence include changes in diagnostic criteria, funding availability, and an increase in community awareness through public service campaigns and public policy.

In 1980, The Diagnostic and Statistical Manual of Mental Disorders (DSM-II) included a diagnosis for autism if a child met all of 6 criteria. By 1987, the DSM-III edition specified 16 symptoms of which children had to meet 8 to qualify with the diagnosis (Wright, 2017). In 1994, the fourth edition of the DSM criteria (DSM-IV) included Asperger Syndrome in autism. Most recently, in 2013 the DSM-5 edition collapsed the diagnosis for Asperger, Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS), and autism into one diagnosis (Wright, 2017). The Centers for Disease Control and Prevention estimates that the changes from DSM-4 to DSM-5 criteria may cause future diagnosis prevalence to decrease (Maenner et al., 2014).

There has been a substantial increase in community awareness of autism (Lyall, 2017). In 1991, after the Individuals with Disabilities Education Act (IDEA) legislation called for free and appropriate public education for all, the U.S. department of Education recognized autism as a possible diagnosis qualifying a child for special education services (IDEA, U.S. Department of Education). Along with policy and awareness, the rate of diagnosis is heavily linked to education-related spending and availability of health resources (Akshoomoff et al., 2006). The availability of free intervention services in the school system and awareness of the benefits of

early intervention, spurred more resource investment for autism and likely increased the number of parents and practitioners who sought the school-based diagnosis. More recently, a popular public service campaign called *Learn the Signs, Act Early* raised awareness for the benefits of earlier identification and intervention (Learn the Signs, December 17, 2017).

An influx of funding for research and resources for early identification and services has been substantial. The Combating Autism Act of 2006 allotted $1 billion to autism research (M. D. King & Bearman, 2011). The Centers for Disease Control and Prevention increased funding for autism research from $2.1 million in 2002 to $16.7 million in 2005 (M. D. King & Bearman, 2011). The National Institutes of Health increased their funding for autism five-fold, from $22 million to $108 million between 1997 to 2006 (M. D. King & Bearman, 2011).

The theory of diagnostic substitution explains the increase in prevalence of autism as an effect of conditions that would normally have been present being labeled as autism as opposed to other developmental delays. As autism has increased, there has been a decrease in diagnosis of other conditions that were previously more popular. There is a decrease of prevalence of intellectual disability and other developmental disabilities (M. D. King & Bearman, 2011).

Changing Profiles of Autism Population

Epidemiological research has aimed to describe the changing profiles of children diagnosed with autism. Changes in characteristics within the group of children diagnosed with autism may or may not be associated with changes in the disorder itself. Presumably, changing profiles are due mostly to systematic changes related to diagnostic practices, availability of intervention services and increased awareness of the condition. Characteristics that may

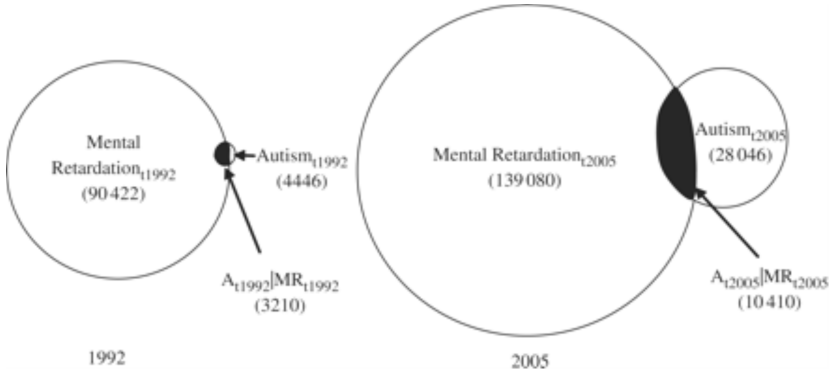
influence a changing profiles include a family's social economic status (Durkin et al., 2010), gender, severity of symptoms, presence of comorbid conditions, and age at diagnosis. In light of the recent changes in autism diagnostic criteria and rising prevalence, researchers have sought to identify health risks associated with autism (Boyle et al., 2011).

Comorbidities

Children with developmental delays, in general, have higher rates of concurrent medical conditions and unmet health care needs compared to children who are typically developing (Schieve, 2012). This is also the case with autism. Concurrent medical conditions among children with developmental delays make their health care needs more complex. Therefore, it is important to consider potential comorbid conditions when addressing healthcare needs of children with autism. Common comorbid conditions include, anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), gastrointestinal complications, sleep disturbances and epilepsy (Autism Speaks, Treatment). About one third of children with autism have various epileptic conditions (Fombonne, 2003; P. Whiteley, & Shattock, P., 2002). More than half of adults with autism may suffer from psychological comorbidities such as anxiety and depression (Preibmann, 2017). Among the most common cooccurring conditions are gastrointestinal discomfort, particularly chronic constipation, inflammatory bowel, esophageal reflux, abdominal pain, chronic diarrhea, and bloating (Ghalichi, Ghaemmaghami, et al., 2016). Children with autism may be about 1.8 times more likely to have food allergies and 3.5 times more likely to have chronic diarrhea or colitis than children without autism (Autism Speaks, Treatment).

Intellectual disability used to be considered a potential cause of communication deficits, however now we consider it a comorbidity that is not as frequently seen. As we look back to 1992 the proportion of children with autism who had intellectual disability was much larger despite a smaller population with autism (M. King & Bearman, 2009). Fast forward to 2005, the proportion of children with autism and intellectual disability decreases despite the increase in both autism and intellectual disability (M. King & Bearman, 2009).

INTELLECTUAL DISABILITY: FROM PRIMARY SYMPTOM TO LESS COMMON COMORBIDITY



The changing diagnostic world in California between 1992 and 2005. The number of cases of autism and MR both expand, though the proportion of autism cases is increasing at a much greater rate. As this is happening, the rate of co-morbidity within the autism population is decreasing, though the number of co-morbid cases is increasing, as is co-morbidity within the population with MR. Represented in the non-shaded portion of the MR circles is MR*, the number of cases of MR without co-morbidity.

King, M., & Bearman, P. (2009). Diagnostic change and the increased prevalence of autism. *International journal of epidemiology*, *38*(5), 1224-1234. Used with permission from Oxford University Press.

Figure A The changing prevalence of Mental Retardation and Autism from 1992 to 2005.

This change may influence the types of services the evolving population of children with autism will need, how we phenotype children with autism, and which new research directions may be more important. Research conclusions about kids with autism that were true for the

group in 1992 may not apply to the group in 2005. Studies published prior to 2005 that look at the prevalence of comorbid conditions, such as intellectual disability, may be less relevant to the children diagnosed with autism today because of changes in screening and diagnostic practices (M. King & Bearman, 2009).

Scientists have used concurrent conditions as leads to etiology. For example, scientist began to differentiate autism from other psychosocial conditions based on observations that seizures were common among children with autism (Fombonne, 2003). As we look at symptoms or characteristics among kids with autism, the proportion or frequency at which we see a characteristic may inform our conclusions of whether that characteristic may be randomly co-occurring, strongly associated, or perhaps even causative.

Conclusion

A first step in unraveling this issue is to determine the change in prevalence, if any, of gastrointestinal complications among children with autism over time. **This study aims to describe the change in the proportion of gastrointestinal symptoms among children with autism in a U.S.-based nationally representative sample, over the past decade. This study poses the question; does the association between gastrointestinal symptoms and autism stay constant from 2007 to 2016 in the National Health Interview Survey Data?**

If all else is held constant, but autism prevalence is truly increasing, we would expect a similar proportion of gastrointestinal complications through time. This relationship can be modified by many factors. Some key factors include autism severity or phenotype, socio-economic status and age. Some of these factors we cannot control for due to lack of variables in

this data set. There is no system to measure severity or phenotype of autism yet, and certainly not in this data set. This analysis will allow us to understand their concurrent health risks. Furthermore, an increase in the proportion of gastrointestinal complications may inform future research priorities and the need for gastrointestinal intervention. In order to better serve children with autism, it is imperative to achieve a better understanding of their complex health needs.

Gastrointestinal Complications in children with Autism

Since the 1970's, various researchers have looked at gastrointestinal complications among children with autism. The earliest article found in this literature review was published in 1976. It presents indications of "bacterial action and malabsorption" through urine 4-hydroxyhippuric acid testing in children with autism (Lis, 1976). 42 years later, researchers continue inquiring into this relationship. The gastrointestinal microbiome is known to be associated with diseases in humans, including neurodevelopmental conditions such as autism (Barko, McMichael, Swanson, & Williams, 2018). The pathophysiology implied in this association is not completely understood but is based on the reciprocity between the enteric and the central nervous systems (Campion, Ponzo, Alessandria, Saracco, & Balzola, 2018). The interplay between the gastrointestinal tract and the central nervous system involves neural, hormonal, immune and microbe-derived metabolic products (Cristiano et al., 2018). Understanding these pathways may lead to an understanding of the pathophysiology of autism and of potential treatments that target inflammatory process and gut microbiota (Cristiano et al., 2018).

Is there an Increased prevalence of GI in ASD?

There is a broad range of data regarding the prevalence of gastrointestinal symptoms among children with autism, as reported in studies since 2011 through more recent years. The range of prevalence of reported gastrointestinal symptoms has been reported anywhere between 9% to 91% in different autistic populations (Buie et al., 2010; Williams et al., 2011). A

cross-sectional case-control study reported gastrointestinal symptoms were higher in children with autism (70%) than in controls (typically developing= 28%; developmental delay= 42%) based on the Childhood Autism Risks from Genetics and the Environment (CHARGE) which sampled 24-60 month old children, with 50 participants in each group, in California between 2003 and 2011 (Chaidez, Hansen, & Hertz-Picciotto, 2014). Children with autism are more than 3.5 times more likely to suffer chronic diarrhea or constipation than are their typically developing peers, based on National Health Interview Survey data from 2006 to 2010, which samples children under 17 in 4 regions of the U.S. through a cross-sectional study design (Schieve, 2012). More recent articles, including a meta-analysis, document a range of 20% to 85% of gastrointestinal symptoms in children with autism, based on parent reports (Calderoni et al., 2016; McElhanon, McCracken, Karpen, & Sharp, 2014).

Explanations for variability in estimates

The broad range of estimates of prevalence of gastrointestinal symptoms among children with autism may be due to various factors that are mentioned in the literature or observable when analyzing the literature. Literature reviews commonly mention a lack of precision in nomenclature as a salient limitation in research on gastrointestinal issues or etiology theories (Buie et al., 2010). There are many potential types of gastrointestinal symptoms and they tend to be difficult to measure. For example, one study included a large variety of symptoms defined as, “abdominal pain, pain on stooling, constipation, gaseousness/bloating, diarrhea, sensitivity to foods, as well as vomiting and difficulty swallowing” (Chaidez et al., 2014). This inconsistency in definition of terms and data collection

may cause inaccuracies. The wide range in the estimates is dependent on definition of GI symptoms and demographic and clinical characteristics of ASD samples (Calderoni et al., 2016). Also, research articles may look at different gastrointestinal symptoms across and within studies.

They are based on parent report

Estimates of gastrointestinal symptom prevalence may vary greatly across studies because these symptoms are typically diagnosed based on patient, or in the case with children, parent report. Data collected through subject report tends to be susceptible to bias. For the case of these variables however, a greater bias may be more likely in reports from parents with children with complex health needs as opposed to from parents of typically developing children. This becomes a concern when comparing results between the group of children with autism and a control group that is typically developing. Studies may also pull data from medical chart review, which may or may not have been originally based on parent reports during clinic visits (Chaidez et al., 2014).

Which confounding variables are controlled?

Which variables are controlled for during statistical analysis of gastrointestinal symptom prevalence may impact the range of the estimate. Most studies control for age, gender and socioeconomic status variables. Gastrointestinal complications may have additional confounders such as medications with potential gastrointestinal side effects. Although few studies in this literature review mentioned controlling for medications, one study concluded that the findings remained that children with autism frequent gaseousness/bloating,

constipation diarrhea, and sensitivity to foods regardless of which variables were controlled" (Chaidez et al., 2014).

Who of ASD have GI?

There may be a correlation between gastrointestinal symptoms and autism severity. Specifically, children with more severe autism report greater occurrence of gastrointestinal symptoms than children with less severe autism (Adams JB, 2011). The first article to address this issue in 2011, found children with autism had a 42% odd of gastrointestinal symptoms compared to 12% in non-autistic siblings, from data in the Autism Genetic Resource Exchange (Wang, Tancredi, & Thomas, 2011).

Severity of autistic symptoms may be an indicator for use of gluten free diet. Children with developmental regression may have more severe autism symptoms (Rubenstein et al., 2018). Children with more severe autism may try more interventions (Patten, 2013; Rubenstein et al., 2018). Children with developmental regression and no gastrointestinal symptoms were more likely to use a gluten-free diet than children with developmental regression and also gastrointestinal symptoms (Rubenstein et al., 2018). In children with autism, a gluten-free diet may be used more frequently to reduce autism symptoms than to reduce gastrointestinal symptoms.

Other potential risk factors for autism and gastrointestinal symptoms that are mentioned in the literature include sex, age, socio-economic status, intellectual disability and genetics. Researchers have speculated over the effect of gender on associations between autism and other risk factors (Dworzynski K, 2012). While there is speculation of other factors

that define a subgroup of children with autism who have greater risk for gastrointestinal symptoms, we don't know if there is in fact a subgroup or how to identify this group (Buie et al., 2010).

Hypothesized Gastrointestinal-related Pathophysiology of Autism

Why might children with autism have higher GI?

Potential explanations for the higher incidence of gastrointestinal complications in children with autism as compared to typically developing children may be due to the general increase in medical attention and a higher rate of overall health complications in children with special needs. Children with special health care needs, or who have some kind of developmental delay tend to have higher rates of comorbid conditions compared to typically developing children (Schieve, 2012). However, a potential increased incidence may also be explained by the pathophysiology of autism.

Intestinal mucoepithelial microbiota

The role of gut microflora in the pathogenesis of gastrointestinal complications in individuals with ASD is not well understood. A 2005 study conducted in the U.K. analyzed fecal samples of 58 children with autism, and two control groups. This study found that children with autism had more Clostridium histolyticum bacteria, a recognized toxin-producer, in their gut (Parracho et al., 2010). This study proposes dietary treatment to manage this bacterium and ameliorate the reported gastrointestinal discomfort. Children who had this imbalance in gut

bacteria were cited to have had a history of antibiotic use early in life and pre- and probiotic use (Parracho et al., 2010).

One study surveyed gene expression and the mucoepithelial microbiota in intestinal biopsies of children with gastrointestinal complications with and without autism. The pathophysiology of gastrointestinal complications in children with autism may be explained through the relationship between gut microbiota and intestinal gene expression (Williams et al., 2011). This study found "impairment of the primary pathway for carbohydrate digestion and transport in enterocytes," was associated with expression of the "intestinal transcription factor, CDX2" (Williams et al., 2011).

The most recent research claims that "gut-microbe-brain axis" or the "microbiota-gut-brain-axis" is a more accurate term than the "gut-brain axis" to describe the relationship between the gastrointestinal system and the brain (Kim, N 2018). Researchers are recognizing that microbiota have for a long time formed a symbiotic relationship with humans. Microbiota are important for better health and also play a role in disease. They even impact human evolution (Kim, YK 2018; Yang, 2018). In recent literature, reference to the gut microbiome implies also the genetics of the microbes and their interaction with their human host (Yang, 2018). The microbiome acts on the gastrointestinal system, Perhaps the newest trend in gut-related treatments for autism, after antibiotics and gluten-free diets, is the use of probiotics and fecal microbiota transplant (Kim N, 2018; Kim YK, 2018).

Immune System and ASD

Immunity plays a pivotal role in the neurodevelopment of central and peripheral nervous systems, regulating neuronal proliferation, synapse formations and plasticity, along with removing apoptotic neurons, but also actively participating in many neurological activities" (Bjorklund et al., 2016). As observed by many researchers and clinicians, children with autism often present with immune function loss. Allergies are one indication of involvement of the immune system in autism (Bjorklund et al., 2016). Children with autism often present with immune tolerance loss, namely environmental and food allergies (Bjorklund et al., 2016). One study reported that IgE (Immunoglobulin-E) levels were 36% higher in children with autism compared to 6% in the control group (Lucarelli, Pappas, Welchons, & Augustyn, 2017). "Immunologic aberrations beyond IgE have been reported in individuals with autism but a direct cause-and-effect relationship between immune dysfunction and autism has yet to be proven" (T. Buie et al., 2010). These preliminary findings are not yet completely understood (T. Buie et al., 2010).

Currently, there is no evidence as to whether immune disorders are causative of ASD or if ASD causes immune dysfunction (Bjorklund et al., 2016; (Buie et al., 2010). A review reported that studies have consistently shown "marked pan-enteric infiltration of lymphocytes and eosinophils in the gut mucosa"(Buie et al., 2010). Some researchers speculate a chronic inflammatory process in some children with autism with enterocolitis, and mucosal infiltration by immune cells along the length of the gastrointestinal tract.

Celiac Disease and ASD

Some studies report a possible connection between autism and Celiac Disease (Craig A. Erickson, 2005). However, there is insufficient evidence of a physiological similarity or association between the two conditions (T. Buie, 2013). Currently, the association between autism and celiac disease is still under debate (Calderoni et al., 2016). Some studies report that autism is associated with higher risk for positive celiac disease serology (Ludvigsson, Reichenberg, Hultman, & Murray, 2013). However, another study (Pavone et al) looked at 11 children with autism and found no celiac disease. Two studies published by Batista et al and Pavone et al both found that there was no evidence for a link between celiac disease and autism disorder. Half of children with ASD who screened positive for Celiac Disease had no symptoms or risk factors related to CD when they performed the serological screening (Calderoni et al., 2016). And of 120 children with celiac disease and found no autistic behaviors (T. Buie, 2013).

Instead of having celiac or gluten intolerance, kids with autism may have a genetic-based condition that leads to excess in peptides from poor digestion of gluten or casein. This excess in peptides in turn may lead to maladaptive behaviors and other symptoms common in autism (Elder, Kreider, Schaefer, & de Laosa, 2015; Reichelt & Knivsberg, 2009; Rubenstein et al., 2018). Some researchers have hypothesized that we will see a difference in celiac disease prevalence based on what year the autism sample is drawn (particularly in the US) based on the increase in prevalence of autism and the change in this group due to awareness and diagnostic practices (T. Buie, 2013).

An association between ASD and CD cannot be excluded. A comparison between studies is complex because of different screening methods for CD, different populations which will have a different prevalence of CD in their non ASD population, severity and age of ASD group, ASD diagnostic methods and criteria, size of ASD and CD groups (Calderoni et al., 2016).

Metabolic Disorders

Other popular theories, such as the "leaky gut" theory or the gut microbiota theory, propose a difference in the body's absorption of gluten or casein proteins. Ultimately these theories all attempt to explain how metabolic toxins reach the brain and impact brain function to in turn alter mood and behavior. In a study from 2013, reported that 43% of 21 cases with autism had increased gut permeability, while none of the 42 controls presented with increased permeability (T. Buie, 2013) Another postulated theory is that there is an abnormality in the mucosal lining of the digestive track. "In children with autism, studies have consistently shown marked pan-enteric infiltration of lymphocytes and eosinophils in the gut mucosa"(Buie et al., 2010). Some experts have proposed that toxins or abnormal gut bacteria may trigger or worsen autism. As treatment, many scientists hypothesize that altering gut microbiota with specific diets or antibiotics may help treat neurodevelopment disorders including autism and hyperactivity (Cryan, 2015).

Behavior and the gastrointestinal system in autism

Gastrointestinal disturbance may contribute to behavioral impairment (Williams et al., 2011). This relationship is not clearly understood. We do not know if autism is causative of

gastrointestinal symptoms or vise-versa. Or if other factors related to autism contribute to increased gastrointestinal symptoms. For instance, an autistic child may have food preferences that limit his or her diet to the point of causing constipation or other abdominal discomfort. At this point, there is not sufficient evidence for a gastrointestinal condition specific for autism (Buie et al., 2010).

Medical recommendations for the treatment of gastrointestinal symptoms in children with Autism is largely the same as those without Autism, with some minor notes of caution. Health care providers are to be aware of potential abnormal presentation of gastrointestinal symptoms that includes aberrant behaviors as expression of GI discomfort. Potential nutritional assessment may be recommended for children who have selective eating behaviors (Barnhill, 2018).

Among children with autism, those with GI symptoms (abdominal pain, gaseousness, diarrhea, constipation) scored higher on 4/5 of the ABC subscales (irritability, social withdrawal, stereotypy and hyperactivity) (Chaidez et al., 2014). Parents were asked open ended questions regarding GI symptoms. The most frequently reported food sensitivity was dairy/casein (14% ASD, 6.6% DD and 5.3% TD) (Chaidez et al., 2014). The most common reason for food restrictions in children with autism was the child's own food selectivity, followed by GI symptoms (Chaidez et al., 2014). Constipation and food selectivity are attributed to behavioral characteristics of children with autism that relate to preference for routine, ritualistic tendencies, and insistence on sameness, rather than on underlying GI pathology (Chaidez et al., 2014).

Language and the gastrointestinal system

There is scant literature on the potential connection between effects of the gastrointestinal system on language or social communication development. In 1998, an article was published and later retracted from the Lancet, titled, “Non-specific colitis with ileal lymphonodular hyperplasia was described in 12 children with a history of behavioral and language regression and GI symptoms that were felt to be specific to autism”.

Developmental regression is a symptom often observed in children with autism. A child may appear to have typical development, and at age 2 experience loss of expressive language skills along with a loss of interest in social engagement. This often spurs and assessment for autism and other developmental delays. Regression may be an indicator for autism severity. Children who use gluten free diet as autism intervention are more likely to have had developmental regression, and thus more severe autistic behavioral and linguistic symptoms. Parents report using dietary intervention to target the behavioral symptoms in autism. These behavioral symptoms are related to cognitive function, which may imply language delay. However, the connection between the gut and language development or social communication has not been studied and is poorly understood.

Conclusion

While the cause of autism and its physiology remain elusive, the international research community has produced many articles on gastrointestinal complications among children with

autism. This has spurned the generation of theories associating dietary intake to cognitive function and behavioral symptoms. These theories that link metabolic function to autism's behavioral symptoms are not unprecedented. For instance, newborns are now routinely screened for Phenylketonuria (PKU), a metabolic disorder that, if left untreated has profound cognitive and behavioral ramifications (P. Whiteley et al., 2010). However, in the case of autism spectrum disorders no pathophysiological mechanism or even causal relationship has been established.

The prevalence of gastrointestinal symptoms in children with autism is not known with certainty, nor do we know if it is significantly higher than in the general population (Buie et al., 2010). Few estimates of GI symptoms in the typically developing population are available for comparison (Chaidez et al., 2014). Researchers have speculated that perhaps we will see a difference in the prevalence of Celiac Disease based on what year the autism sample was drawn (particularly in the US) (Calderoni et al., 2016). A review from 2014 stated that the "connection between GI problems and autism is not yet resolved, and research provides conflicting findings "(Chaidez et al., 2014). With a myriad of inconclusive and inconsistent research, there remains no evidence to support any one theory or aberrant physiological process.

METHODS

This descriptive analysis uses the 2007-2016 National Health Interview Survey's (NHIS) Child Sample survey data to analyze the proportion of gastrointestinal issues among children with autism compared to children without autism in the U.S. population. This research is not human subjects research because information has been de-identified, and the data is made publicly available; therefore, this study is exempt from IRB review.

Instrument and Data

This project will use the NHIS (National Health Interview Survey), which is a cross-sectional survey designed by the Centers for Disease Control and Prevention National Center for Health Statistics and administered annually by the U.S. Census Bureau. It surveys non-military and non-institutionalized individuals, both citizens and non-citizens, residing in the U.S. It uses a multi-stage probability design which incorporates geographic regions and families within households as sampling units through various sampling stages. The four geographic regions include the Northeast, Midwest, South and West.

Information is collected on one adult and one child per family, or sampling unit, via hour-long in-person interviews are conducted each year over four interview quarters. The information collected from this interview is not corroborated with medical records but rather based on caregiver report. Respondents for the child sample survey could be a parent, grandparent, aunt/uncle, brother/sister, other relative, legal guardian, foster parent, or other non-relative. A large majority of respondents identified themselves as a parent (92% in 2007).

NHIS has included a question about autism in the child sample questionnaire since 1997, providing 20 years of data. The analysis in this paper used data that straddled two major changes in how the autism question was presented. In 2010 and prior, the question referred to "autism", while in 2011 and after the question referred to "autism/autism spectrum disorders," yet remained part of a checklist of disorders. From 2013 to 2014 additional changes were made, including further expanding the wording, autism became a stand-along question, it was placed in a different order in the questionnaire, and respondents were asked about current diagnosis as well as history of a diagnosis. The most recent wording of the question defines autism as, "Autism, Asperger's, Pervasive Developmental Disorder-not otherwise specified, or Autism Spectrum Disorder." The changes in prevalence over time may be influenced by these changes in the survey questions, as represented in Figure B, where the blue vertical lines indicate time-period when changes to survey questions were made. The NHIS data shows an increase in autism prevalence from 2007 to 2016, which is consistent with prevalence trends reported elsewhere. After the changes between years 2013 and 2014, the NHIS data better matched the data from the Autism and Developmental Disabilities Monitoring (ADDM) network data which is collected via medical record extraction. Among 8 year-olds in the U.S, the autism prevalence in 2014 was 16.8 per 1,000 (one in 59) according to the Morbidity and Mortality Weekly Report (MMWR) released April of 2018 (Baio et al., 2018).

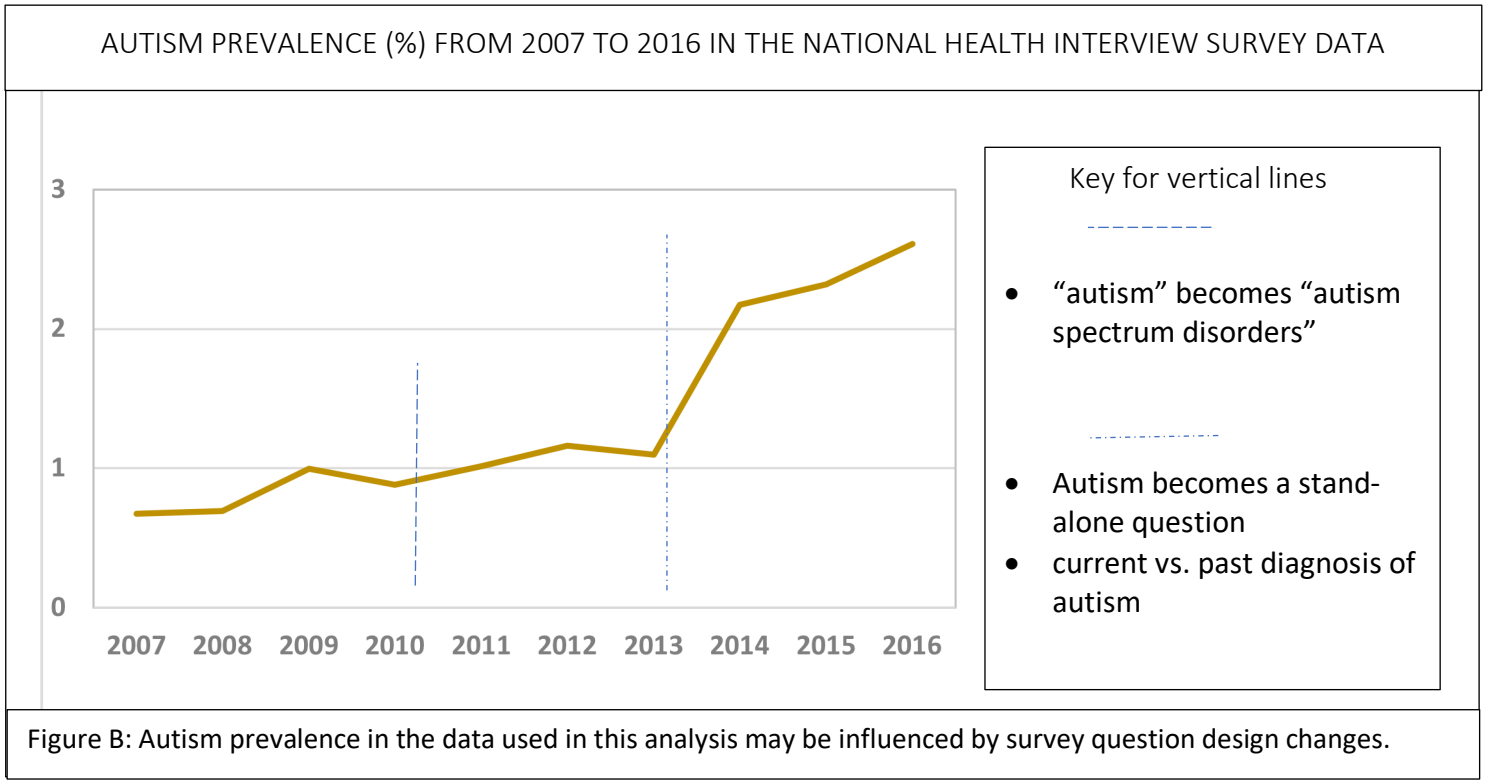


Figure B: Autism prevalence in the data used in this analysis may be influenced by survey question design changes.

Procedures

The NHIS child sample files were downloaded and extracted directly from the Centers for Disease Control, National Centers for Health Statistics (https://www.cdc.gov/nchs/nhis). This complex survey data analysis generated descriptive statistics, including frequencies and chi-square analysis, using survey procedures in SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

The use of survey procedures indicates to the SAS software to account for weights in the computations. Weights provide a quantification of that representation. They are the inverse of

the probability that an element is selected from the sampling frame. Complex design means we have clusters (naturally occurring) and strata (researcher defined). Different size clusters or strata lead to different weights. This creates a random denominator for the variance estimate. Degrees of freedom are calculated based on number of primary sampling units (PSUs) which inflates the variance estimation. Not accounting for weights in the analysis of survey data would cause the estimator to be imprecise. It was necessary to use SAS survey procedures to invoke the application of survey weights in statistical calculations.

This analysis includes all children in the data files from ages 3 to 17 from 2007 through 2016. Data previous to 2007 was not used because this study focuses on recent trends. Additionally, incompatibility of data file type prior to 2007 prevented use of early survey years. The scope of this study was limited to children from 3-17 years old due to historical age limits of autism diagnosis for children under 3 years of age. No further exclusion criteria were used for this analysis. The weighted sample size mean across the ten years was 73,830.090. The unweighted sample size mean across the ten years was 11,643. Non-response and “don’t know” responses were coded out of the analysis as missing values because the low frequencies interfere with SAS’s ability to compute chi-squared analysis. There were no implausible values in the data sets.

Frequencies were used to estimate the proportion of each gastrointestinal variable (digestive allergies, stomach illness, and diarrhea/colitis) among a second variable, autism (current autism diagnosis). These three gastrointestinal variables were the only ones available in all ten years of the data. Three additional gastrointestinal variables were available only in the 2007 dataset. Frequencies were generated from individual survey years without pooling. This

was done through the macro statement, which called each of the survey years from a dataset repository file. Pooling survey years into a combined data set would have inflated the sample size artificially and not allowed for the analysis over time.

The frequency procedure was also used to compute odds ratios which were then graphed by year on a logarithmic scale. The odds ratios are used to summarize the association between two binary (two outcomes: yes or no) variables, such as autism and a gastrointestinal variable. While there are many potential effect measures that can be reported for associations between binary variables, odds ratios were used because the survey which collected the data was a cross-sectional design. Furthermore, the odds ratios provide a good estimation of relative risk for rare conditions such as autism. The prevalence of autism used in this study was 2.6% at its highest in the 2016 dataset.

Additional analysis was conducted to further explore the relationship between autism and the three gastrointestinal variables. First, descriptive data was also generated for the prevalence of the gastrointestinal variable among children with any type of developmental delay. The distribution of age among children with autism was described across two age groups, 3 to 10 and 11 to 17-year-olds. Lastly three linear regression analyses were conducted on the 2016 data, to explore the effect of age and sex on the association between each of the three gastrointestinal variables and autism. This analysis produced adjusted odds ratios.

Variables

Variables that were used in this analysis included autism and three gastrointestinal variables. There was variation in the autism variables across survey years. Years 2007 - 2013 included a question that asked if the child *currently has* an autism diagnosis. Years 2014 - 2016 included two questions; if the child had *ever had*, and if the child *currently* has an autism diagnosis. For this analysis, the autism variable was defined as "currently has autism, Asperger's, PDD or autism spectrum disorder," per caregiver report. Autism cases are defined by a "yes" answer to this question. Respondents answer based on a standardized administration of survey questions. The information in this survey was not further corroborated through medical record extraction or developmental assessments. Children may have undergone diagnosis using different diagnostic tools or screeners and through various settings.

Three variables were used to represent "gastrointestinal symptoms" in this analysis. Digestive allergy is defined as, "sampled child had food/digestive allergy, in the past 12 months". Stomach illness is defined as, "Sampled child had stomach illness with vomiting/ diarrhea, 2-week reference period." Diarrhea/colitis is defined as, "Sampled child had frequent diarrhea/colitis, past 12 months." The NHIS administered these questions in a standardized manner from 2007 to 2016.

AUTISM AND GASTROINTESTINAL VARIABLES IN THE NHIS[3] CHILD SAMPLE DATA, 2007-2016		
VARIABLE	SURVEY YEARS	SURVEY QUESTION
Autism[2]	All[1]	Sampled child *currently* has autism, Asperger's, PDD or autism spectrum disorder
Digestive Allergy[2]	All	sampled child had food/digestive allergy, past 12 months
Stomach Illness[2]	All	Sampled child had stomach illness with vomiting/ diarrhea, 2-week reference period
Diarrhea/Colitis[2]	All	Sampled child had frequent diarrhea/colitis, past 12 months
Abdominal pain[2]	2007	Had abdominal pain, past 12 months
Acid Reflux[2]	2007	Had acid reflux, past 12 months
Constipation[2]	2007	Had recurring constipation, past 12 months

[1] The Autism variable was present in all survey years, but question format changed. Refer to Appendix A for detailed description of autism question formats. Refer to Figure B for the impact of question format changes on autism prevalence.
[2] Variables are categorical, binary, and based on respondent report. Over 90% of respondents identified as biological parents.
[3] National Health Interview Survey

Table 1: This analysis used variables from the National Health Interview Survey Child Sample Data. All variables are defined by the format in which they were asked to participants in the survey questionnaire.

RESULTS

Frequencies and Rao-Scott Chi-Square for each of three GI variables

When looking at digestive allergy, with a 12-month reference period, the data ranged from 0.8% to 17.0% in the autism group. In 2008, the estimated prevalence was 0.8%, which was much lower than the frequency in the general population. This data point is not consistent with the other study years, leading to concerns about data quality. The data was verified through a closer look at the 2008 data set and determined to be an anomaly. Based on odds ratios, the risk of digestive allergy among children with autism fluctuates, with some years appearing significant and others not. From 2014 to 2016, the survey question regarding autism did not change across distinct survey administrations and the prevalence of autism continued to increase. In these three years, the reported frequency of digestive allergy shows a downward slope, that in 2016 becomes a non-significant difference between the autistic and non-autistic groups. Digestive allergy among children without autism nearly doubled, from 3.6% to 6.1%.

Interestingly, stomach illness with vomiting/diarrhea with a 2-week reference period was very high in 2007 (19.5%) with a substantial drop to 2009 (6.3%). From 2010 to 2014 the prevalence fluctuated around 10%. By 2015, the frequency of stomach illness is not statistically significantly different in children with autism compared to those without. In children without autism, the prevalence of stomach illness remained between 4.5% and 6% throughout the decade.

Frequent diarrhea/colitis, with a 12-month reference period decreased over the decade among children with autism. At its highest, the prevalence was 9.6% in 2007, and 2.0% in 2011. However, the prevalence oscillated with similar rates in 2008 (4.6%) and 2016 (4.9%). Based on odds ratios, frequent diarrhea/colitis was variable prior to 2013. From 2013 to 2016, the odds ratios remained constant at about 1, indicating a weak association of diarrhea/colitis in children with autism.

Unadjusted Odds Ratios for Gastrointestinal Variables among children with autism compared to those without, National Health Interview Survey Child Sample Data, 2007 – 2016

Year	Digestive	CI upper	CI Lower	Stomach	CI upper2	CI Lower3	Diarrhea	CI upper4	CI Lower5
2007	3.0337	1.2197	7.5456	4.7974	2.0193	11.3972	9.5846	3.8949	23.5858
2008	0.1837	0.0249	1.3551	2.6156	1.1365	6.0197	3.4654	0.9251	12.9822
2009	3.4446	1.5655	7.5792	1.0623	0.4134	2.7294	8.4164	2.3179	30.5602
2010	2.4315	1.1917	4.9613	1.8417	0.8241	4.1159	8.1601	3.1713	20.9973
2011	2.843	1.6043	5.0381	2.0178	1.0469	3.8893	1.4029	0.4976	3.955
2012	2.5844	1.073	6.0866	1.6959	0.7484	3.8429	5.8398	2.5318	13.4701
2013	1.8293	0.9051	3.6973	2.0903	0.9966	4.3844	2.6442	0.9925	7.0447
2014	3.7145	2.2706	6.0766	1.747	1.0059	3.034	2.7291	0.9757	7.6335
2015	2.0567	1.2615	3.3531	0.5996	0.2686	1.325	2.3674	0.659	8.5045
2016	1.4267	0.7445	2.734	1.197	0.6352	2.2554	3.0445	1.4594	6.3512

Gastrointestinal variables are defined based on how they were asked in the NHIS child sample questionnaire. Digestive= sampled child had food/digestive allergy, past 12 months. Stomach= Sampled child had stomach illness with vomiting/ diarrhea, 2-week reference period. Diarrhea= Sampled child had frequent diarrhea/colitis, past 12 months

Table 2: Table representation of unadjusted odds ratios for digestive allergies, stomach illness and diarrhea/colitis in the National Health Interview Survey Child Sample data.

Reported Frequency and Unadjusted Odds Ratios for Food/Digestive Allergy over a 12-month reference period among children with autism compared to those without, National Health Interview Survey Child Sample Data, 2007-2016

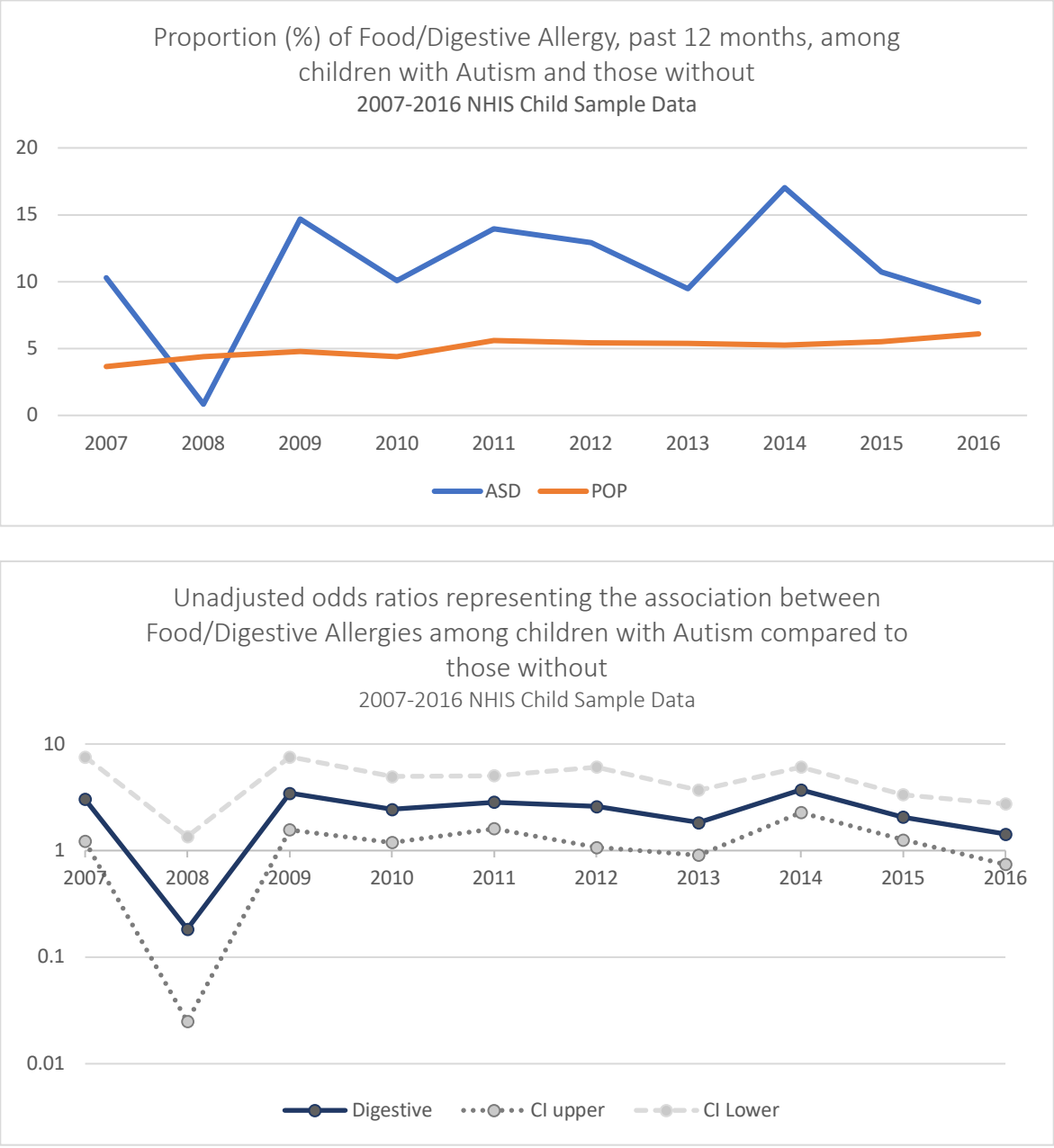


Figure C: The top graph is a in the prevalence of reported digestive allergies among kids with autism compared to those without, from 2007 to 2016, in the National Health Interview Survey. The bottom figure is the plotted unadjusted odds ratios for digestive allergies in children with autism compared to those without. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016.

Reported Frequency and Unadjusted Odds Ratios for Stomach Illness with Vomiting/Diarrhea, over a 2-week reference period among children with autism compared to those without, National Health Interview Survey Child Sample Data, 2007-2016

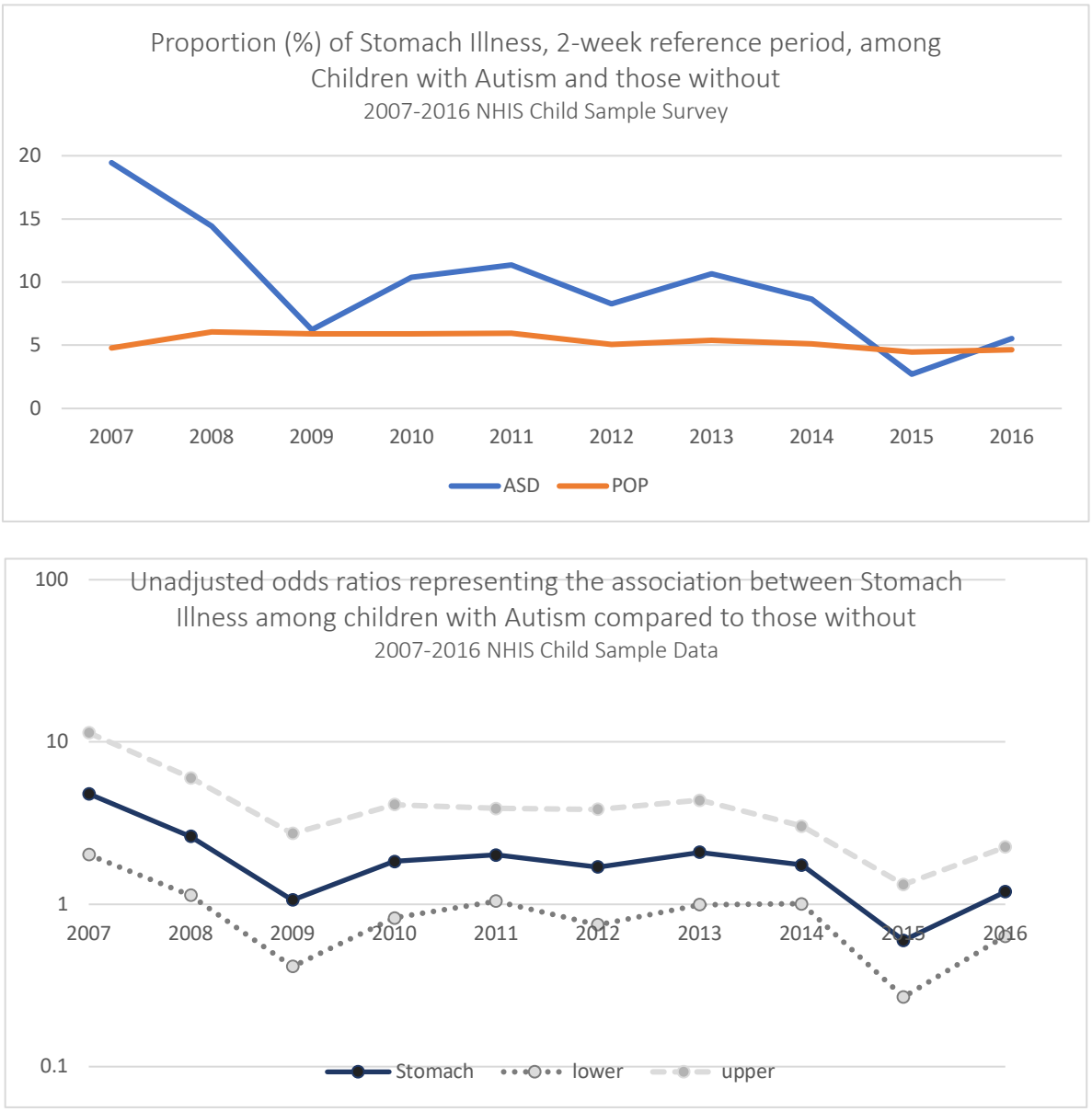
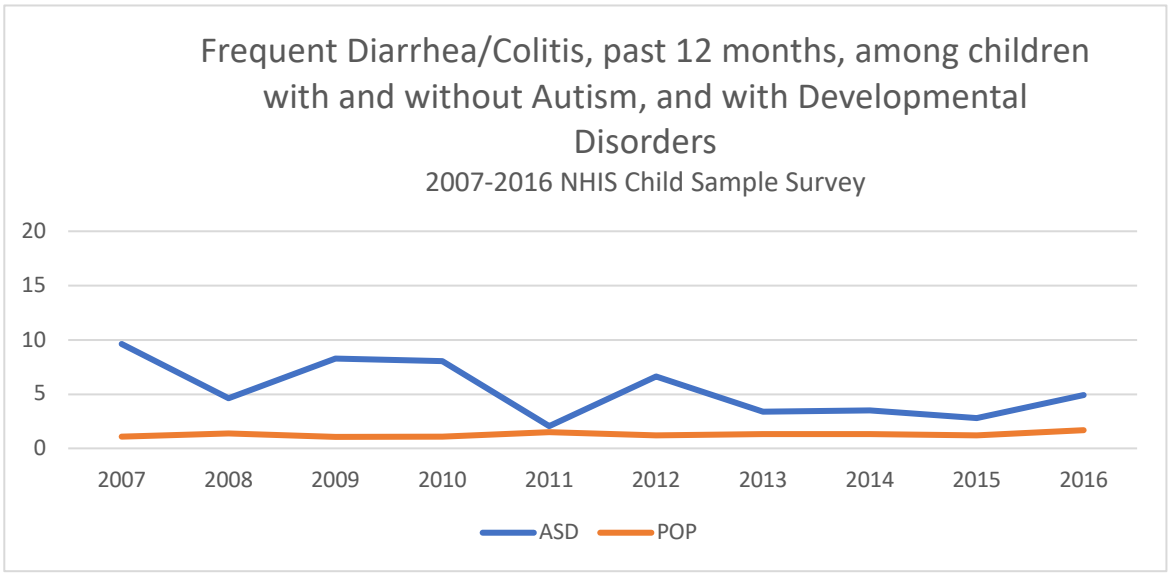


Figure D: The top graph is a in the prevalence of reported stomach illness among kids with autism compared to those without. The bottom figure is the plotted unadjusted odds ratios for stomach illness in children with autism compared to those without. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016.

Reported Frequency and Unadjusted Odds Ratios for Diarrhea/Colitis over a 12-month reference period among children with autism compared to those without, National Health Interview Survey Child Sample Data, 2007-2016



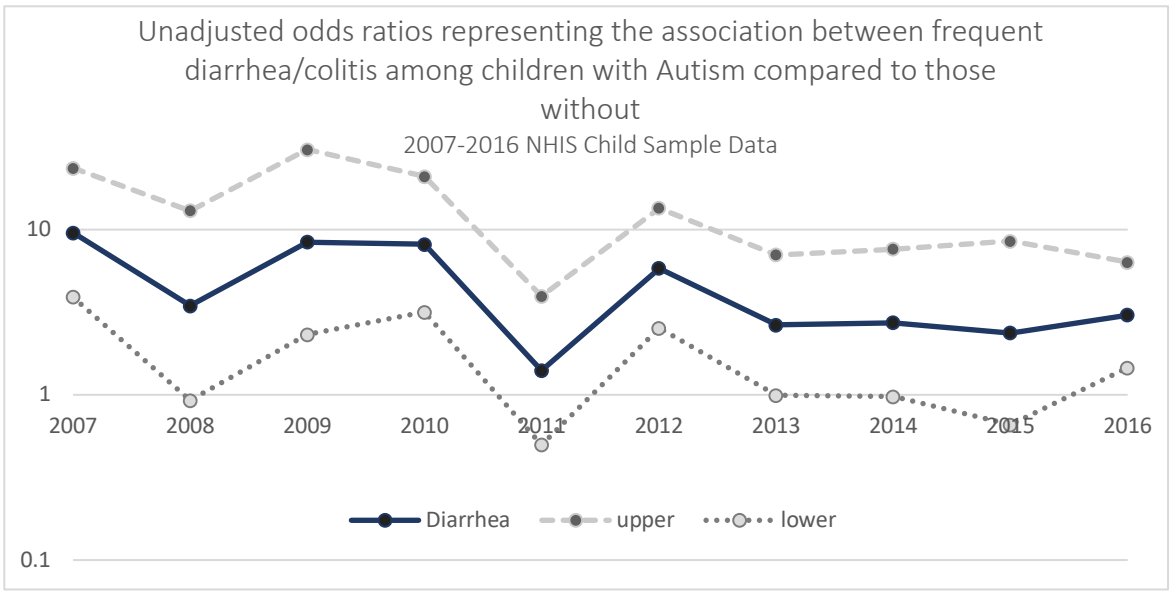


Figure E: The top graph is a in the prevalence of reported diarrhea/colitis among kids with autism compared to those without. The bottom figure is the plotted unadjusted odds ratios for diarrhea/colitis in children with autism compared to those without. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016.

The change in the GI variables among children with autism from 2007 to 2016 may be more variable compared to those without autism because the size of the group with autism is much smaller than those without. It could also be more variable because children with any type of developmental disorder may receive more medical attention which could lead to greater awareness of gastrointestinal symptoms.

Logistic Regression

The following data are results of a logistic regression analysis for the 2016 NHIS Child Sample dataset. Three separate logistic regression analyses were computed for each of the three gastrointestinal variables; digestive allergy, stomach illness and diarrhea/colitis for the year 2016. In each analysis, the gastrointestinal variables are the “Y” variable (dependent variable) and autism is the “X” variable (explanatory variable).

The percent change from the crude odds ratios to the adjusted odds ratios for all three gastrointestinal variables, namely digestive allergy, stomach illness and diarrhea/colitis, in the NHIS Child Sample 2016 data were not greater than 10%, therefore there is no evidence of confounding by the covariates of sex (male, female) and age (3-10, 11-17).

Logistic Regression Model for Autism and **Digestive Allergies**, Adjusting for Sex and Age NHIS Child Sample Data 2016			
	Estimate	95% CI	Percent Change
Crude OR	1.43	(0.74, 2.73)	
Age	1.42	(0.79, 2.81)	< - 0.1%
Sex	1.44	(0.75, 2.75)	< 0.1%
Full (Age & Sex)	1.43	(0.72, 2.82)	0.0%

Table 3: Crude and adjusted odds ratios for digestive allergies and autism. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016. Age is coded as 3-10 or 11-17-year-olds with 3-10 being the reference group.

Logistic Regression Model for Autism and **Stomach Illness**, Adjusting for Sex and Age NHIS Child Sample Data 2016			
	Estimate	95% CI	Percent Change
Crude OR	1.197	(0.6, 2.25)	
Age	1.20	(0.64, 2.25)	0.25%
Sex	1.20	(0.63, 2.28)	0.25%
Full (Age & Sex)	1.20	(0.63, 2.28)	0.25%

Table 4: Crude and adjusted odds ratios for stomach illness and autism. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016. Age is coded as 3-10 or 11-17-year-olds with 3-10 being the reference group.

Logistic Regression Model for Autism and **Diarrhea/Colitis**, Adjusting for Sex and Age NHIS Child Sample Data 2016			
	Estimate	95% CI	Percent Change
Crude OR	3.04	(1.45, 6.35)	
Age	3.03	(1.45, 6.35)	-0.33%
Sex	2.83	(1.34, 5.95)	-6.91%
Full (Age & Sex)	2.82	(1.33, 5.95)	-7.23%

Table 5: Crude and adjusted odds ratios for diarrhea/colitis and autism. The variables in this data are defined based on the National Health Interview Survey Child Sample data, from 2007 to 2016. Age is coded as 3-10 or 11-17-year-olds with 3-10 being the reference group.

The year 2007 had three additional gastrointestinal variables which were not asked in any other year; abdominal pain, acid reflux, and constipation. As with food/digestive allergy, stomach illness and diarrhea/colitis for 2007, the frequencies of the additional variables were higher among children with autism.

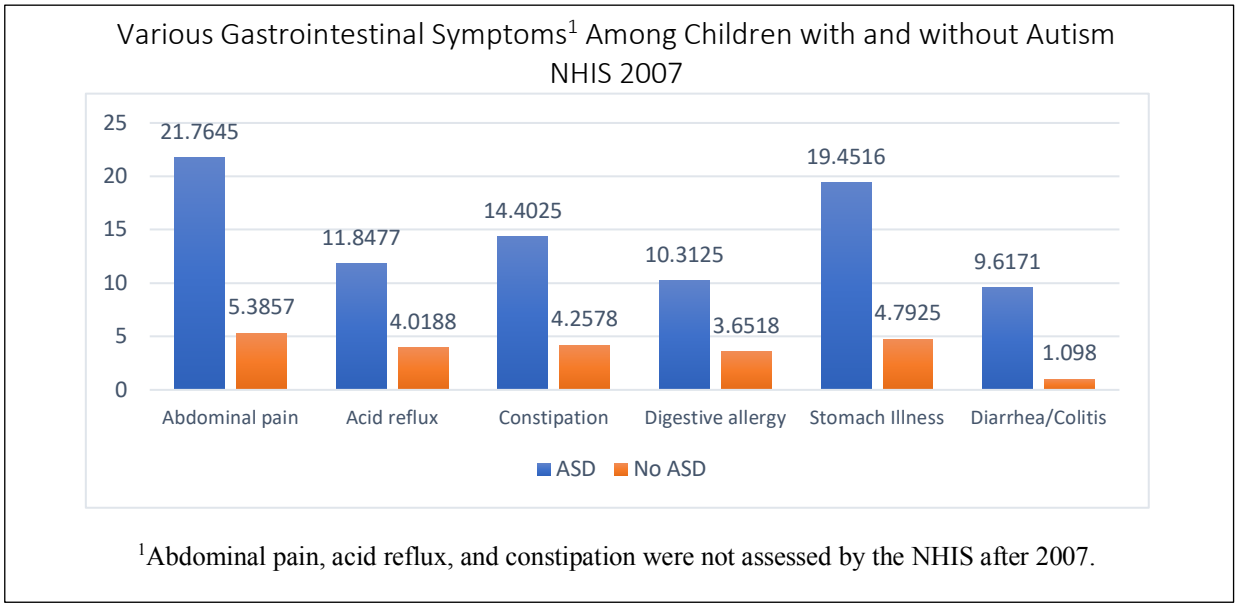


Figure F: The survey data from year 2007 had three additional gastrointestinal variables.

Summary

Despite an increase in autism prevalence, there is not a consistent pattern in frequencies of gastrointestinal symptoms among children with autism in the NHIS data from 2007-2016. Certainly, some symptoms may be more sensitive and specific for an underlying gastrointestinal pathology, but this is beyond the scope of this research. There may also have been more gastrointestinal symptoms in children with autism ten years ago, and as the

prevalence of autism has increased, the proportion of children with gastrointestinal symptoms may be getting closer to the rate in the general population. This is challenging to interpret as children with autism show a more varied trend in reported gastrointestinal symptoms. Findings related to the association between gastrointestinal symptoms and autism, based on odds ratios for individual survey years, oscillate over time. The difference between the two populations may be as related to reporting as it is to differences in symptom prevalence. This data is not conclusive in terms of there being more gastrointestinal complications in children with autism compared to those without.

DISCUSSION

Strengths

There are several key strengths to this study design. The NHIS is an in-person interview which has high response rates compared to online or over the phone interviews. High response rates decrease sampling bias. Furthermore, the NHIS is a nationally representative survey which gives us a larger sample size. This is important statistically because it adds power to the findings. Most studies conducted on gastrointestinal issues in children with autism use small sample sizes. While those studies may still add information to the body of knowledge, it is important to have robust statistical power in order to be able to generalize our results to the population.

Limitations

The National Health Interview Survey provides cross-sectional data which limits our analysis of causality and temporality. This survey is also limited to a non-institutionalized and non-military population residing in the United States. Children who are most severe are most likely to be institutionalized and are excluded from the sampling frame. Furthermore, autism is a rare condition and the survey design did not include oversampling of autism. As we divide it into subgroups for further statistical analysis the sample size becomes smaller. As mentioned previously, there were questionnaire changes in 2014 (Zablotsky, Black, Maenner, Schieve, & Blumberg, 2015) that may decrease the under-estimation bias of autism prevalence but make comparisons across survey years difficult. As seen in the 2007 data, there were inconsistencies in

which questions were asked over survey years. This analysis was limited to the availability of gastrointestinal variables and their consistency across the ten years.

This study lacks nuance in the break-down of gastrointestinal complications and digestive food allergies. These can be classified as toxic, meaning that anyone who is exposed to some level of a substance will have an adverse reaction, or as non-toxic. Non-toxic reactions can be allergic if they are mediated by the immune system or they can be idiosyncratic/food intolerance (T. Buie et al., 2010). For the purposes of this study, we cannot verify that what is reported as "digestive food allergies" were actually mediated by the immune system or not, but rather they were some kind of adverse reaction, either toxic or non-toxic reactions. It is also based on a parent's diagnostic acumen of an adverse reaction as allergic in the event medical care has not been sought for these complaints. It is unclear to what degree parent-reports from other sources reflect true food allergies versus food sensitivities, and this is likely true for the NHIS data as well (Chaidez et al., 2014). Furthermore, we are limited by the lack of specific information regarding types of foods and types of adverse reactions observed by parents when they indicated on the NHIS that the child had a "digestive food allergy".

NHIS data does not provide clinical confirmation of diagnoses and medical conditions. This means that we are unable to crosscheck diagnosis for ascertainment of cases. We are also limited in obtaining nuanced information about individual cases, such as severity of symptoms, from the NHIS data. We do not have qualitative data to better understand the impact of perceptions of autism and gastrointestinal symptoms on how questions were answered.

Although parents tend to have high reliability when asked questions about the health of their children, this data is limited to answers provided by respondents. Respondent report may

be influence by their awareness of gastrointestinal symptoms, perceived social desirability, and their ability to recall information. Families with medically complex children may be more in-tune with the healthcare needs of their child. Particularly, if families believe that children with autism may have increased gastrointestinal symptoms, they may attribute greater significance to these symptoms. Increased awareness may lead to increased reporting of frequency. This data is susceptible to bias from parents' ability to accurately recall data or misrepresentation of data based on perceived social desirability. Education and standardization, in general, is needed to ensure that it is clear what symptoms, parents and health care providers are referring to. Standardized definitions of adverse reactions to foods need to be established with parents and health care providers, as well as among research studies on the adverse food reactions in individuals with autism (T. Buie et al., 2010).

Future Research

Therapies based on *gut-brain theories* have gained popularity for children with autism. Understanding the pathophysiology between the gut and the autistic brain may help us determine more effective treatments and be able to provide more clear recommendations for care. There are many theories of pathophysiology which provide ample opportunity for research.

Population-based and parent-reported data places many limitations on research. We may benefit from developing better and more sensitive tools for measuring symptom-based variables in populations which have limited communicative capacity, emotional/behavioral disturbance, or generally populations with developmental delays. More effective ways of

extracting data, such as subjective accounts of various gastrointestinal symptoms or behavioral symptoms in children, may yield data that is more sensitive to the nuances of the conditions being studied.

Another area of study may be to consider differences in the effects of various dietary interventions on gastrointestinal or behavioral symptoms as well as nutritional status. Future research may consider nutritional and feeding health of children with autism with a reported history of developmental regression who are on gluten-free or other dietary interventions.

A mixed methods approach to this research topic may provide further insight to autism symptomology. Qualitative research can lead to a more nuanced understanding of children's and families' experiences with autism along with potential gastrointestinal symptoms. This may allow us to consider which interventions families use and believe to be effective. Additionally, qualitative data will increase our understanding of parent's perceptions of gastrointestinal symptoms, and how they learn about autism and gastrointestinal comorbidity.

CONCLUSION

The gut-brain connection may plausibly be where the pathophysiology of autism lies, but trends in gastrointestinal symptoms in children with autism are insufficient to inform theories of etiology and pathophysiology or justify use of dietary interventions. The associations between three gastrointestinal variables (digestive allergies, stomach illness, diarrhea/colitis), tended to hover around and right above not-significant. Overall, the data is insufficient, and we cannot conclude that there is a pattern in the change of prevalence of these gastrointestinal variables among children with autism, compared to those without in the NHIS data over the past decade. This data must be interpreted with caution due to the many potential confounding variables for which we may not be able to control, as well as limitations in the data.

This research is challenging due to lack of standardized definitions used in research and clinical practice relating to gastrointestinal symptoms, and perhaps also autism. As with patients without autism, those with autism can present with various gastrointestinal issues. However, perhaps gastrointestinal conditions can present atypically in some children with autism. Children with autism may be more likely to express gastrointestinal discomfort through maladaptive behaviors (T. Buie et al., 2010). Nonetheless, there is no evidence that children with autism have significantly different proportion of gastrointestinal symptoms than they did a decade ago despite potential changes in the autism population.

These inconclusive results and limitations in defining and measuring gastrointestinal symptoms in children with autism may indicate a need for an improved methodology to gauge symptoms in children with autism. It may be beneficial to develop a method of communication, or a communication aid such as a picture chart or assistive technology, for children with autism

to understand and quantify physical discomfort and gastrointestinal symptoms. Such a tool may help increase the accuracy of reported concerns for both individual care and research purposes.

Responsible translation of the results of scientific inquiry is an important role of public health. The use of non-evidence-based, and potentially harmful, interventions among children with autism can be prevented through community education. The provision of nutritional guidelines and the development of recommendations for gastrointestinal care, may help caregivers avoid the pitfalls of non-evidence-based practices and be beneficial to the overall health of this vulnerable population.

APPENDIX A

Expanded Definitions of Gastrointestinal Complications

Chronic constipation, Chronic diarrhea, Gastroesophageal Reflux Disease

Constipation, when chronic, can become a serious medical concern. It can be caused by insufficient fiber intake, side-effect of medications, sensory or behavioral issues related to toileting. It can also be caused by anatomic, neurological, metabolic, or gut motility issues. Treatment may include dietary modifications or medications (Autism Speaks, Treatment).

Chronic diarrhea can be caused by intestinal infection, immune dysfunction, inflammatory bowel diseases (Crohn's or ulcerative colitis), irritable bowel syndrome, celiac disease (gluten intolerance), food allergies, lactose intolerance or excessive consumption of certain foods. It can lead to stomach discomfort, dehydration, and poor nutrient absorption (Autism Speaks, Treatment).

Gastroesophageal reflux disease, or GERD, is a condition in which stomach acid moves into the esophagus and causes irritation. Signs of GERD may include hoarseness, chronic sore throat, cough or heartburn, dental erosions, food refusal or disturbed sleep (Autism Speaks, Treatment).

Irritable Bowel Disease or Inflammatory Bowel Disease (IBD)

Irritable Bowel Disease is a chronic condition that results in inflammation and ulcers in the gastrointestinal tract. Crohn's Disease is a type of IBD in which chronic inflammation may cause diarrhea and eventually scar tissue that narrows the intestine and slows food moving

through the intestine. A second type of IBD is Ulcerative Colitis, in which inflammation may cause loss of the lining of the colon (Irritable Bowel, PubMed)

Gut-brain axis and the gut microbiota

The gut-brain axis is a biochemical network between the central nervous system and the gastrointestinal tract (PsychSceneHub, 2017). The enteric nervous system, sometimes referred to as the second brain, is a pathway of over 100 million nerves embedded in two layers along the digestive tract running from the esophagus to the rectum. There is a complex interplay between the 'second brain', or the enteric nervous system and our central nervous system, termed the gut-brain axis. An irritated intestine sends signals to the central nervous system which can then trigger a mood change. Likewise, a negative emotional state such as typical life stress can trigger diarrhea, changes in appetite, nausea, pain or irritation of the bowel. The enteric system and the central nervous system, are thought to have a greater influence on each other than what science currently understands (Carabotti, 2015).

The gut-brain axis is influenced by the gut microbiota, or the microbial community that resides in the gut. We may think of our bodies as "self-sufficient individuals" when in fact we are each more of a "super-complex ecosystem" (Montiel-Castro, Gonzalez-Cervantes, Bravo-Ruiseco, & Pacheco-Lopez, 2013). While some bacteria in our gut may be harmful to our health, some form symbiotic relationships with our bodies by helping us absorb nutrients from food intake, stave off disease, metabolizing complex lipids and polysaccharides, and modulating intestinal motility. Furthermore, gut microbiota has influenced the evolution of our immune

system (Kelly & Mulder, 2012; Montiel-Castro et al., 2013). The epithelium lining of the gut is the main point of contact between bacteria and the gut, as well as the immune system. Exposure of bacteria to the immune cells helps in the healthy development of the immune system, but excessive exposure can cause an inflammatory response (Kelly & Mulder, 2012). Hence, a healthy balance between protection from the bacteria by lining of the gut and exposure to bacteria is important for optimal health. Mucin and Immunoglobulins (IgA, IgM, IgE) help in controlling the exposure of the gut to bacteria and other antigens (Kelly & Mulder, 2012). The composition of gut microbiota is diverse and unique to each individual (Montiel-Castro et al., 2013). It is influenced mostly by environment, including diet (Kelly & Mulder, 2012). The bacteria that reside in our gut is postulated to influence our brain, and perhaps even our behavior. "It is not evident that the bidirectional signaling between the gastrointestinal tract and the brain, mainly through the vagus nerve, the so called 'microbiota-gut-vagus-brain axis,' is vital for maintaining homoeostasis and it may be also involved in the etiology of several metabolic and mental dysfunctions/disorders," (Montiel-Castro et al., 2013).

Food Allergy, Food Intolerance and Food Sensitivity

Food sensitivity is a general term for food intolerance but may also refer to food allergies. Food allergies occur when dietary intake triggers an immune response, usually within a short time after consuming a certain food (PubMed Health, Food Allergies). Foods that trigger an allergic reaction in one person may not trigger another, and they can be developed at any age (PubMed Health, Food Allergies). Food allergies are not very common, and immune responses can be mild or severe. Immune response can affect the nose, mouth and throat as

well as the gut and intestines. Food allergies can cause skin rash or hives, sudden blood pressure changes, and breathing difficulties. Typical allergens include soy, nuts, fruits and seafood.

Food intolerance is a less serious condition limited to digestive problems and is not immune mediated. It is caused by a difficulty in digesting a particular food which leads to symptoms such as intestinal gas, abdominal pain, headache, reflux, or diarrhea. Common triggers of food intolerance include caffeine, gluten, dairy, sulfites, MSG and others (Kubala, 2018).

Immune System: Allergies and immunoglobulins (IgE)

Immunoglobulins, also referred to as antibodies, are proteins which function as part of the immune system to protect the body against pathogens such as viruses and bacteria (WebMD, Immunoglobulin). The gastrointestinal tract is the largest immune organ in the body, containing up to 80% of the immunoglobulin producing cells in the body.

T-cells, also called "Adaptive" immune "T" cells or T-lymphocytes, are a type of white blood cell that is made by stem cells in the bone marrow. They help protect the body from infection and may help fight cancer (Autism Speaks, Immune). Immune T cells can sometimes attack the own body's cells, a process called "autoimmunity." (Autism Speaks, Immune). "Immune T cells also can over-react to otherwise harmless substances, such as pollen, and produce allergies. Usually these potentially errant responses by immune T cells are kept under control by 'regulatory T cells." Regulatory T cells are produced by the Foxp3 gene," (Autism Speaks, Immune).

Casein and Gluten

"Casein" and "gluten" are proteins commonly mentioned in autism research. Casein is a family of phosphoproteins commonly found in mammalian milk. 80% of cow's milk and 20% of human milk is comprised of casein protein. Casein is a source of amino acids, carbohydrates, calcium and phosphorous. Since the mid 2010's, researchers have sought evidence linking casein intake to behavioral, cognitive or social function in autistic children (PubMed Health, Gluten). Gluten is a general name for proteins found in wheat (PubMed Health, Gluten). Some gastrointestinal symptoms potentially related to gluten allergy or gluten sensitivity include gas, bloating, diarrhea, and constipation.

Celiac Disease

Celiac Disease, also called Gluten Intolerance, is a serious autoimmune disorder occurring in genetically predisposed people where ingestion of gluten triggers an immune response against the villi of the small intestine. This response damages the villi, affecting their ability to absorb nutrients (Johns Hopkins, What is). Celiac disease treatment consists of a life-long avoidance of gluten. Symptoms include diarrhea, abdominal pain, nausea, fatigue, and weight loss (Johns Hopkins, What is). Prevalence of celiac disease in the western population is about 1% (Calderoni et al., 2016).

Non-celiac Gluten Sensitivity

Non-celiac gluten sensitivity has been linked to neuro-psychiatric disorders, such as autism, schizophrenia and depression (Lionetti et al., 2015). While there are cases described of psychosis, including poor speech, apathy, lethargy, irritability, abdominal pain and hallucinations related to dietary intake of gluten, with absence of celiac disease and gluten allergy, this connection is still not well understood or documented (Lionetti et al., 2015). The pathogenic mechanisms that cause non-celiac gluten sensitivity are not well understood, yet non- celiac gluten sensitivity is thought to be caused by a non-immunological and non-allergic process (Elli et al., 2015). Non-Celiac gluten sensitivity is a diagnosis of exclusion (Elli et al., 2015).

Gluten-related disorders have an estimated global prevalence of around 5% (Elli et al., 2015). This includes celiac disease, wheat allergy, and non-celiac gluten sensitivity. Celiac Disease is diagnosed through serology and duodenal biopsies, and wheat allergy is diagnosed through laboratory and functional assays. However, non-celiac gluten sensitivity is only recently being recognized as a condition and is diagnosed through exclusion of other conditions (Elli et al., 2015). Despite a growing market for gluten-free products, a gluten free diet is often viewed as a lifestyle choice rather than a dietary treatment.

TERMS

Casein: is a protein found in dairy products

GFD: Gluten Free Diet defined as the “purposeful restriction of gluten or carbohydrates from a child’s diet. Not all GFD exclude all carbohydrates, and some diets that exclude casein are used with GFD’s (Rubenstein et al., 2018).

Celiac: Gluten-sensitive enteropathy is a genetically linked autoimmune disorder in which eating certain types of grain-based foods triggers an immune response that causes damage to the small intestine (Ghalichi, Ghaemmaghami, et al., 2016). Celiac disease is a specific immune response.

Gluten: a large protein found in wheat, rye, barley, and malt.

Leaky Gut: a genetic condition in children with ASD that leads to gluten or casein creating and excess of peptides, causing behavioral symptoms common to ASD (Rubenstein et al., 2018). Disruption of mucosal lining of the gut and abnormal carbohydrate digestive enzyme activity lead to malabsorption of large proteins (gluten, gliadin, casein) that cause inflammation and act like neuropeptides which alter neurologic function (Ghalichi, Ostadrahimi, Malek, & Ghaemmaghami, 2016).

Chelation: The bonding of ions to metals. A process used to aid the body in excreting toxic metals such as lead.

Socioeconomic gradient: seen in low, middle and high-income countries, a phenomenon that as household income increases, the risk of death and negative health outcomes decrease.

Sensitivity: Considered an immune response but does not have a clear serologic marker.

Allergy: causes anaphylactic response and has serologic antibody response. Immune regulated response.

Intolerance: individuals are unable to digest something, such as a carbohydrate,

Appendix C: Frequency tables for reported gastrointestinal symptoms and autism in the National Health Interview Survey Child Sample Data from 2007 to 2016.

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2007 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	48885	21623	0.0796	0.0349	10.3125	4.2890
	2 No	48	425151	68234	0.6920	0.1104	89.6875	4.2890
	Total	55	474036	72497	0.7716	0.1163	100.0000	
2 No	1 Yes	285	2226206	174800	3.6236	0.2759	3.6518	0.2781
	2 No	7320	58735546	1216864	95.6048	0.3001	96.3482	0.2781
	Total	7605	60961752	1247660	99.2284	0.1163	100.0000	
Total	1 Yes	292	2275091	179247	3.7032	0.2813		
	2 No	7368	59160697	1222785	96.2968	0.2813		
	Total	7660	61435788	1258183	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2007 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	94887	37741	0.1292	0.0514	19.4516	6.7173
	2 No	50	392925	62876	0.5350	0.0845	80.5484	6.7173
	Total	57	487812	73334	0.6643	0.0987	100.0000	
2 No	1 Yes	427	3496149	250076	4.7607	0.3154	4.7925	0.3176
	2 No	8903	69453836	1344156	94.5751	0.3322	95.2075	0.3176
	Total	9330	72949985	1423380	99.3357	0.0987	100.0000	
Total	1 Yes	434	3591036	251157	4.8899	0.3163		
	2 No	8953	69846761	1352280	95.1101	0.3163		
	Total	9387	73437797	1432608	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2007 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	46755	19441	0.0761	0.0314	9.6171	3.8473
	2 No	49	439410	70492	0.7150	0.1137	90.3829	3.8473
	Total	56	486165	73504	0.7911	0.1178	100.0000	
2 No	1 Yes	87	669443	91704	1.0893	0.1472	1.0980	0.1481
	2 No	7519	60301596	1234964	98.1197	0.1734	98.9020	0.1481
	Total	7606	60971039	1247752	99.2089	0.1178	100.0000	
Total	1 Yes	94	716198	94007	1.1654	0.1500		
	2 No	7568	60741006	1243147	98.8346	0.1500		
	Total	7662	61457204	1258616	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2008 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	1	3954	3954	0.0064	0.0064	0.8369	0.8409
	2 No	61	468514	76659	0.7580	0.1240	99.1631	0.8409
	Total	62	472468	76761	0.7644	0.1242	100.0000	
2 No	1 Yes	347	2693943	181707	4.3583	0.2832	4.3919	0.2855
	2 No	6881	58645636	1313454	94.8774	0.3109	95.6081	0.2855
	Total	7228	61339579	1351176	99.2356	0.1242	100.0000	
Total	1 Yes	348	2697897	181780	4.3647	0.2833		
	2 No	6942	59114150	1316200	95.6353	0.2833		
	Total	7290	61812047	1354154	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2008 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	10	73933	28521	0.1001	0.0387	14.4398	5.2185
	2 No	57	438076	75358	0.5934	0.1021	85.5602	5.2185
	Total	67	512009	80575	0.6936	0.1094	100.0000	
2 No	1 Yes	521	4443597	240606	6.0192	0.3079	6.0612	0.3100
	2 No	8219	68868405	1466989	93.2873	0.3254	93.9388	0.3100
	Total	8740	73312002	1529260	99.3064	0.1094	100.0000	
Total	1 Yes	531	4517530	242865	6.1193	0.3117		
	2 No	8276	69306481	1469866	93.8807	0.3117		
	Total	8807	73824011	1530844	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2008 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	4	21696	13727	0.0351	0.0222	4.6160	2.8927
	2 No	59	448326	75797	0.7245	0.1222	95.3840	2.8927
	Total	63	470022	76857	0.7596	0.1239	100.0000	
2 No	1 Yes	98	845756	104522	1.3668	0.1679	1.3772	0.1692
	2 No	7136	60564497	1342832	97.8737	0.2097	98.6228	0.1692
	Total	7234	61410253	1351508	99.2404	0.1239	100.0000	
Total	1 Yes	102	867452	105261	1.4018	0.1690		
	2 No	7195	61012823	1346891	98.5982	0.1690		
	Total	7297	61880275	1356076	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2009 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	17	105009	40165	0.1708	0.0651	14.6984	5.0530
	2 No	91	609416	83174	0.9912	0.1340	85.3016	5.0530
	Total	108	714425	93228	1.1620	0.1497	100.0000	
2 No	1 Yes	442	2894971	201885	4.7086	0.3148	4.7640	0.3186
	2 No	8607	57872714	1057784	94.1294	0.3505	95.2360	0.3186
	Total	9049	60767685	1097291	98.8380	0.1497	100.0000	
Total	1 Yes	459	2999980	210850	4.8794	0.3284		
	2 No	8698	58482130	1066254	95.1206	0.3284		
	Total	9157	61482110	1108206	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2009 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	46087	21097	0.0624	0.0285	6.2535	2.7890
	2 No	105	690896	91725	0.9350	0.1228	93.7465	2.7890
	Total	112	736983	94263	0.9974	0.1261	100.0000	
2 No	1 Yes	610	4322336	250734	5.8495	0.3255	5.9084	0.3295
	2 No	10421	68832998	1223126	93.1531	0.3589	94.0916	0.3295
	Total	11031	73155334	1268309	99.0026	0.1261	100.0000	
Total	1 Yes	617	4368423	252302	5.9119	0.3274		
	2 No	10526	69523894	1231503	94.0881	0.3274		
	Total	11143	73892317	1279152	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2009 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	5	58086	35810	0.0943	0.0581	8.2534	4.7602
	2 No	102	645696	84933	1.0487	0.1364	91.7466	4.7602
	Total	107	703782	92618	1.1431	0.1486	100.0000	
2 No	1 Yes	101	643667	86618	1.0455	0.1386	1.0575	0.1402
	2 No	8959	60220746	1087149	97.8115	0.2000	98.9425	0.1402
	Total	9060	60864413	1099202	98.8569	0.1486	100.0000	
Total	1 Yes	106	701753	90734	1.1398	0.1449		
	2 No	9061	60866442	1096351	98.8602	0.1449		
	Total	9167	61568195	1109879	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2010 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	11	61794	19756	0.1004	0.0322	10.0677	3.2230
	2 No	83	551993	72299	0.8968	0.1170	89.9323	3.2230
	Total	94	613787	73257	0.9972	0.1188	100.0000	
2 No	1 Yes	409	2682000	156588	4.3575	0.2373	4.4014	0.2396
	2 No	8711	58253775	1058740	94.6453	0.2622	95.5986	0.2396
	Total	9120	60935775	1105893	99.0028	0.1188	100.0000	
Total	1 Yes	420	2743794	156994	4.4579	0.2382		
	2 No	8794	58805768	1063451	95.5421	0.2382		
	Total	9214	61549562	1109941	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2010 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	8	68511	26182	0.0919	0.0351	10.3994	3.7491
	2 No	91	590287	75842	0.7917	0.1016	89.6006	3.7491
	Total	99	658798	80403	0.8836	0.1077	100.0000	
2 No	1 Yes	619	4380989	201289	5.8759	0.2589	5.9283	0.2606
	2 No	10546	69518431	1218894	93.2405	0.2692	94.0717	0.2606
	Total	11165	73899420	1264054	99.1164	0.1077	100.0000	
Total	1 Yes	627	4449500	200485	5.9678	0.2575		
	2 No	10637	70108718	1223101	94.0322	0.2575		
	Total	11264	74558218	1267956	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2010 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	6	49713	22129	0.0807	0.0359	8.0453	3.4524
	2 No	89	568199	70780	0.9229	0.1151	91.9547	3.4524
	Total	95	617912	73373	1.0037	0.1190	100.0000	
2 No	1 Yes	113	646543	75290	1.0502	0.1214	1.0608	0.1226
	2 No	9010	60301094	1099133	97.9462	0.1659	98.9392	0.1226
	Total	9123	60947637	1106117	98.9963	0.1190	100.0000	
Total	1 Yes	119	696256	78598	1.1309	0.1264		
	2 No	9099	60869293	1101791	98.8691	0.1264		
	Total	9218	61565549	1110186	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2011 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	18	105932	27948	0.1707	0.0450	14.3993	3.5161
	2 No	122	629745	68790	1.0146	0.1116	85.6007	3.5161
	Total	140	735677	74324	1.1853	0.1206	100.0000	
2 No	1 Yes	573	3426217	183473	5.5200	0.2814	5.5862	0.2846
	2 No	9821	57907040	935569	93.2947	0.3021	94.4138	0.2846
	Total	10394	61333257	975672	98.8147	0.1206	100.0000	
Total	1 Yes	591	3532149	185313	5.6907	0.2840		
	2 No	9943	58536785	934777	94.3093	0.2840		
	Total	10534	62068934	975144	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2011 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	14	85479	26961	0.1148	0.0362	11.3565	3.3329
	2 No	128	667207	70175	0.8959	0.0950	88.6435	3.3329
	Total	142	752686	75530	1.0107	0.1022	100.0000	
2 No	1 Yes	709	4401143	203581	5.9097	0.2404	5.9701	0.2421
	2 No	11989	69318803	978661	93.0796	0.2492	94.0299	0.2421
	Total	12698	73719946	1070190	98.9893	0.1022	100.0000	
Total	1 Yes	723	4486622	205151	6.0245	0.2419		
	2 No	12117	69986010	977887	93.9755	0.2419		
	Total	12840	74472632	1069051	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2011 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	4	15089	7600	0.0243	0.0122	2.0510	1.0338
	2 No	136	720588	73976	1.1601	0.1199	97.9490	1.0338
	Total	140	735677	74324	1.1844	0.1205	100.0000	
2 No	1 Yes	155	902728	96077	1.4533	0.1523	1.4707	0.1540
	2 No	10250	60477884	966335	97.3624	0.1864	98.5293	0.1540
	Total	10405	61380612	979251	98.8156	0.1205	100.0000	
Total	1 Yes	159	917817	96180	1.4776	0.1524		
	2 No	10386	61198472	966401	98.5224	0.1524		
	Total	10545	62116289	978790	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2012 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	14	103426	42823	0.1680	0.0696	12.9292	4.8406
	2 No	135	696514	70769	1.1313	0.1156	87.0708	4.8406
	Total	149	799940	81341	1.2993	0.1329	100.0000	
2 No	1 Yes	568	3301819	182490	5.3629	0.2832	5.4335	0.2879
	2 No	10212	57465727	967699	93.3378	0.3272	94.5665	0.2879
	Total	10780	60767546	1003723	98.7007	0.1329	100.0000	
Total	1 Yes	582	3405245	187414	5.5309	0.2914		
	2 No	10347	58162241	966591	94.4691	0.2914		
	Total	10929	61567486	1004024	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2012 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	11	71144	27601	0.0967	0.0376	8.3054	3.0947
	2 No	145	785457	82236	1.0678	0.1119	91.6946	3.0947
	Total	156	856601	85557	1.1645	0.1166	100.0000	
2 No	1 Yes	630	3686034	203693	5.0110	0.2694	5.0700	0.2721
	2 No	12473	69016839	1062368	93.8245	0.2840	94.9300	0.2721
	Total	13103	72702873	1092655	98.8355	0.1166	100.0000	
Total	1 Yes	641	3757178	202358	5.1077	0.2677		
	2 No	12618	69802296	1065327	94.8923	0.2677		
	Total	13259	73559474	1094424	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2012 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	9	53767	21305	0.0872	0.0346	6.6084	2.4941
	2 No	142	759853	78007	1.2327	0.1271	93.3916	2.4941
	Total	151	813620	81928	1.3199	0.1335	100.0000	
2 No	1 Yes	134	728236	83521	1.1814	0.1354	1.1972	0.1373
	2 No	10658	60101601	999868	97.4988	0.1920	98.8028	0.1373
	Total	10792	60829837	1002410	98.6801	0.1335	100.0000	
Total	1 Yes	143	782003	85521	1.2686	0.1387		
	2 No	10800	60861454	1000634	98.7314	0.1387		
	Total	10943	61643457	1003459	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2013 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	16	72590	24033	0.1179	0.0388	9.4602	3.0022
	2 No	125	694727	75157	1.1283	0.1238	90.5398	3.0022
	Total	141	767317	78412	1.2462	0.1285	100.0000	
2 No	1 Yes	578	3285504	165013	5.3359	0.2614	5.4032	0.2650
	2 No	9945	57520747	972923	93.4179	0.2943	94.5968	0.2650
	Total	10523	60806251	998340	98.7538	0.1285	100.0000	
Total	1 Yes	594	3358094	166427	5.4538	0.2623		
	2 No	10070	58215474	968218	94.5462	0.2623		
	Total	10664	61573568	996831	100.0000			

Frequency of reported stomach illness and autism in the NHIS Child Sample 2013 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	11	86240	31551	0.1174	0.0429	10.6711	3.5838
	2 No	136	721922	75130	0.9832	0.1030	89.3289	3.5838
	Total	147	808162	82750	1.1006	0.1131	100.0000	
2 No	1 Yes	676	3925823	215083	5.3465	0.2778	5.4060	0.2805
	2 No	12026	68694345	1024160	93.5529	0.2934	94.5940	0.2805
	Total	12702	72620168	1073774	98.8994	0.1131	100.0000	
Total	1 Yes	687	4012063	219231	5.4639	0.2827		
	2 No	12162	69416267	1023916	94.5361	0.2827		
	Total	12849	73428330	1074447	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2013 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	26231	12642	0.0426	0.0206	3.4000	1.6105
	2 No	135	745273	77175	1.2092	0.1261	96.6000	1.6105
	Total	142	771504	78524	1.2518	0.1286	100.0000	
2 No	1 Yes	130	799459	88587	1.2971	0.1438	1.3136	0.1454
	2 No	10402	60061613	995816	97.4511	0.1780	98.6864	0.1454
	Total	10532	60861072	999182	98.7482	0.1286	100.0000	
Total	1 Yes	137	825690	89462	1.3397	0.1455		
	2 No	10537	60806886	996586	98.6603	0.1455		
	Total	10674	61632576	997648	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2014 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	33	234220	50025	0.3810	0.0808	17.0313	3.3841
	2 No	203	1141013	101610	1.8561	0.1616	82.9687	3.3841
	Total	236	1375233	108672	2.2372	0.1710	100.0000	
2 No	1 Yes	576	3147213	197389	5.1197	0.2966	5.2369	0.3039
	2 No	10254	56949976	952767	92.6431	0.3486	94.7631	0.3039
	Total	10830	60097189	1014826	97.7628	0.1710	100.0000	
Total	1 Yes	609	3381433	204446	5.5007	0.3050		
	2 No	10457	58090989	968343	94.4993	0.3050		
	Total	11066	61472422	1037305	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2014 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	22	122730	33220	0.1878	0.0503	8.6442	2.1941
	2 No	221	1297065	103742	1.9850	0.1553	91.3558	2.1941
	Total	243	1419795	110718	2.1729	0.1640	100.0000	
2 No	1 Yes	590	3284309	223863	5.0263	0.3121	5.1379	0.3182
	2 No	10966	60638365	977773	92.8008	0.3361	94.8621	0.3182
	Total	11556	63922674	1065063	97.8271	0.1640	100.0000	
Total	1 Yes	612	3407039	229572	5.2141	0.3181		
	2 No	11187	61935430	996234	94.7859	0.3181		
	Total	11799	65342469	1087927	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2014 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	8	47862	23836	0.0778	0.0385	3.4694	1.6980
	2 No	229	1331667	107148	2.1649	0.1699	96.5306	1.6980
	Total	237	1379529	109020	2.2427	0.1715	100.0000	
2 No	1 Yes	133	781625	96283	1.2707	0.1538	1.2999	0.1572
	2 No	10707	59350278	999368	96.4866	0.2226	98.7001	0.1572
	Total	10840	60131903	1014090	97.7573	0.1715	100.0000	
Total	1 Yes	141	829487	99368	1.3485	0.1579		
	2 No	10936	60681945	1018280	98.6515	0.1579		
	Total	11077	61511432	1036560	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2015 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	24	158954	37606	0.2576	0.0607	10.7077	2.3643
	2 No	215	1325531	127372	2.1483	0.2058	89.2923	2.3643
	Total	239	1484485	135989	2.4059	0.2190	100.0000	
2 No	1 Yes	577	3317593	194281	5.3767	0.3138	5.5093	0.3209
	2 No	9356	56900662	969046	92.2174	0.3696	94.4907	0.3209
	Total	9933	60218255	980554	97.5941	0.2190	100.0000	
Total	1 Yes	601	3476547	201242	5.6343	0.3240		
	2 No	9571	58226193	975850	94.3657	0.3240		
	Total	10172	61702740	988001	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2015 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	9	41365	16920	0.0629	0.0257	2.7135	1.0672
	2 No	236	1483035	133041	2.2543	0.2011	97.2865	1.0672
	Total	245	1524400	136817	2.3172	0.2067	100.0000	
2 No	1 Yes	512	2870286	173857	4.3630	0.2506	4.4665	0.2557
	2 No	10128	61392464	981686	93.3198	0.3074	95.5335	0.2557
	Total	10640	64262750	1026009	97.6828	0.2067	100.0000	
Total	1 Yes	521	2911651	175324	4.4259	0.2526		
	2 No	10364	62875499	990569	95.5741	0.2526		
	Total	10885	65787150	1033703	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2015 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	7	41092	26434	0.0665	0.0427	2.7616	1.7342
	2 No	233	1446883	132298	2.3411	0.2127	97.2384	1.7342
	Total	240	1487975	136034	2.4076	0.2186	100.0000	
2 No	1 Yes	128	714985	83542	1.1569	0.1349	1.1854	0.1382
	2 No	9814	59599406	978013	96.4355	0.2566	98.8146	0.1382
	Total	9942	60314391	981453	97.5924	0.2186	100.0000	
Total	1 Yes	135	756077	89052	1.2234	0.1437		
	2 No	10047	61046289	985359	98.7766	0.1437		
	Total	10182	61802366	989275	100.0000			

Frequency of reported digestive allergy and autism in the NHIS Child Sample 2016 Data

Table of Ever Told Autism by Digestive Allergy								
Ever Told Autism	Digestive Allergy	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	26	144313	44793	0.2339	0.0717	8.4762	2.4971
	2 No	208	1558263	178665	2.5260	0.2701	91.5238	2.4971
	Total	234	1702576	187748	2.7599	0.2813	100.0000	
2 No	1 Yes	548	3656508	223117	5.9272	0.3296	6.0955	0.3369
	2 No	8443	56330707	1514349	91.3129	0.4018	93.9045	0.3369
	Total	8991	59987215	1595369	97.2401	0.2813	100.0000	
Total	1 Yes	574	3800821	226719	6.1612	0.3295		
	2 No	8651	57888970	1577771	93.8388	0.3295		
	Total	9225	61689791	1665038	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2016 Data

Table of Ever Told Autism by Stomach Illness								
Ever Told Autism	Stomach Illness	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	15	94713	31846	0.1441	0.0475	5.5206	1.6475
	2 No	221	1620902	174441	2.4669	0.2463	94.4794	1.6475
	Total	236	1715615	187782	2.6111	0.2639	100.0000	
2 No	1 Yes	460	2978411	200821	4.5330	0.2907	4.6545	0.2967
	2 No	9150	61010993	1645601	92.8559	0.3590	95.3455	0.2967
	Total	9610	63989404	1701291	97.3889	0.2639	100.0000	
Total	1 Yes	475	3073124	205119	4.6772	0.2921		
	2 No	9371	62631895	1709748	95.3228	0.2921		
	Total	9846	65705019	1772018	100.0000			

Frequency of reported diarrhea/colitis and autism in the NHIS Child Sample 2016 Data

Table of Ever Told Autism by Diarrhea/Colitis								
Ever Told Autism	Diarrhea/Colitis	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent	Row Percent	Std Err of Row Percent
1 Yes	1 Yes	9	84005	31497	0.1360	0.0505	4.9340	1.6645
	2 No	225	1618571	175136	2.6211	0.2621	95.0660	1.6645
	Total	234	1702576	187748	2.7572	0.2810	100.0000	
2 No	1 Yes	149	1006525	112099	1.6300	0.1726	1.6762	0.1771
	2 No	8850	59041987	1562221	95.6129	0.3156	98.3238	0.1771
	Total	8999	60048512	1595511	97.2428	0.2810	100.0000	
Total	1 Yes	158	1090530	116149	1.7660	0.1767		
	2 No	9075	60660558	1627360	98.2340	0.1767		
	Total	9233	61751088	1665303	100.0000			

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