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Dietary Approaches to the Treatment of Autism Spectrum Disorders

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Dietary Approaches to the Treatment of Autism Spectrum Disorders

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Each person whose signature appears below certifies that this doctoral project in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Psychology.

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CONTENT

ABSTRACT OF THE DOCTORAL PROJECT

Dietary approaches to the treatment of autism spectrum disorders

by

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This chapter reviews the literature surrounding autism spectrum disorders (ASD) and their relation to gastrointestinal (GI), behavioral, neurological, and immunological functioning. Individuals with ASDs often have poor GI health, including bowel motility issues, autoimmune and/or other adverse responses to certain foods, and lack of necessary nutrient absorption. These issues may be caused or exacerbated by restrictive behavioral patterns (e.g., preference for sweet and salty foods and/or refusal of healthy foods). Those individuals with GI issues tend to demonstrate more behavioral deficits (e.g., irritability, agitation, hyperactivity) and also tend to have an imbalance in overall gut microbiome composition, thus corroborating several studies that have implicated brain—gutpathways as potential mediators of behavioral dysfunction.

We examine the literature with regard to dietary approaches for ASD treatment, including elimination diets of either gluten or casein, complex carbohydrates, a ketogenic diet, and a low oxalate diet. We also explore the research examining dietary supplements such as fatty acids, pro- and prebiotics, vitamins, minerals, glutathione, phytochemicals, and hormones. The research on dietary approaches to treating ASDs is limited and the results are mixed. However, a few approaches, such as the gluten-free/casein-free diet, fatty acid supplementation, and pre/probiotics have generally demonstrated improved GI

and behavioral symptoms. Given that GI issues seem to be over-represented in ASD populations, and that GI issues have been associated with a number behavioral and neurological deficits, dietary manipulation may offer a cheap and easily-implemented approach to improve the lives of those with ASDs.

Keywords: neurodevelopment, neurological disorders, gastrointestinal dysfunction, eating behaviors, gut-brain axis, nutraceuticals

CHAPTER ONE

OVERVIEW OF AUTISM SPECTRUM DISORDERS

Prevalence and Common Features

Autism spectrum disorders (ASDs) are characterized by sustained deficits with social communication/interactions and repetitive/restricted behavioral patterns that may interfere with the activities of daily living. Approximately 60 million people are affected world-wide by ASDs. The Autism and Developmental Disabilities Monitoring Network estimates that the prevalence among 8-year-old children has increased from approximately one in 150 children during the years 2000 to 2002 to one in 68 children during the years 2010 to 2012. According to the Centers for Disease Control and Prevention, about one in 59 children currently have a diagnosis of ASD (Baio et al., 2018). This increase in ASD diagnoses may be at least partially due to the relatively recent inclusion of milder disorders, such as Asperger syndrome and pervasive developmental disorder, along with autism in the *Diagnostic and Statistical Manual of Mental Disorders-5*'s definition of an ASD. Other contributors to the increase in ASD diagnoses may include changes in referral practices and public awareness but may also include increased exposure to environmental risk factors. A number of ASD-related behavioral, neurological, immunological, and gastrointestinal (GI) features have been described.

ASD symptoms often gradually manifest within the first two or three years of life. About 50% of parents first notice the ASD-related symptoms by 1.5 years of age, whereas about 80% notice something unusual by 2 years (Courchesne, et al. 2007; Landa,

2008). From an early age, individuals with ASDs tend to lack social—emotional reciprocity. Rather than reflecting, commenting, sharing feelings, and generally participating in a conversation, they may be more prone to simply requesting or labeling. Although adults can develop compensatory strategies to overcome these challenges, they may still suffer from the anxiety and effort of continuously evaluating appropriate social interactions.

Individuals with ASDs may also experience delayed language, speech comprehension deficits, echoed speech, superfluous language, or even a complete lack of language development. Others may have an impaired ability to communicate with others, despite possessing vocabulary or grammar skills. Nonverbal behaviors essential to communication (e.g. eye contact, gestures, facial expressions, body orientation, and speech intonation) are often diminished, absent, or atypical relative to cultural standards.

In addition to social interaction and communication deficits, individuals with ASD often display restricted and/or repetitive behaviors such as finger flicking, continuously using the same objects, repetitive speech, and rigidity to routine. This may manifest differently depending on the age of the individual. Deviance from a structured routine may cause distress, as they maintain these patterns of behavior with abnormal intensity. Symptoms of distress may include shutting down communication, aggression, tantrums, and/or self-injurious behavior (Kawicka & Regulska-Ilow, 2013). Other common features include intellectual disability, temporal processing deficits, affective disorders (e.g., anxiety, depression), attention deficit disorders (with or without hyperactivity), oppositional defiant disorders, sleep disorders, epilepsy, and Tourette syndrome and/or related disorders, and increased incidence of metabolic disorders such

as phenylketonuria (Allman, 2011; Bejerot, Eriksson, & Mörtberg, 2014; Manzi, et al., 2008; Simonoff, et al., 2008; Zafeiriou, Ververi, & Vargiami, 2007).

Several neuroanatomical features have been described, including an excess of neurons (perhaps resulting from lack of normal apoptosis / pruning during the brain's development; Courchesne, et al. 2007; Lewis, et al., 2013), ectopic neuronal arrangement (perhaps resulting from abnormal neuronal migration during the brain's development), and abnormal synaptic development (Bear, et al., 2008; Kelleher & Bear 2008). Interestingly, a pattern of brain overgrowth early in life followed by slower-than-normal growth has been described in some ASD individuals (Geschswind, 2009) that would be consistent with diminished normal early pruning. These characteristics have been specifically associated with communication dysfunction of the brain's neural networks (Wickelgren, 2005), specifically in the so-called mirror neuron network, which consists of widespread cortical neurons that spike when an individual performs an action and when others perform a similar action. This network has been hypothesized to modulate imitation, empathy, social awareness, and communication. Other studies have suggested neurochemical imbalances in excitatory / inhibitory neurotransmitters and/or their receptors (Kumar & Sharma, 2016; McTighe, et al., 2013; Nikvarz, et al., 2017; Persico & Bourgeron, 2006; Wei, et al., 2012*)* and impaired mitochondrial functioning (Evangeliou, et al., 2003).

Finally, ASDs have also been associated with a number of inflammatory / immunological factors, including increased expression of pro-inflammatory cytokines and increased activation of microglia in the brain (Marchezan, et al., 2018; Onore, et al., 2012; Rossignol & Frye, 2014). In some cases, increased severity of these symptoms has

been associated with more severe behavioral deficits. Presumably, maternal exposure to infectious agents or environmental toxins during pregnancy can lead to early overactivation of the fetal immune system, leading to problems with nervous system development (Patterson, 2011).

Potential Causes and Risk Factors

Autism and other ASDs have been associated with a number of environmental and genetic risk factors. For example, some evidence suggests that environmental insults during gestation (e.g., infections and/or exposure to teratogens such as drugs and pollution) may play a role in the development of ASDs (Ornoy, et al., 2015; Lee, et al., 2015; Atladóttir, et al., 2010). Some studies have reported significantly higher levels of heavy metals in ASD children compared to matched controls (Al-Farsi et al., 2013; El-Ansary et al., 2017). However, other studies have reported lower levels of heavy metals or no significant differences between ASD individuals and controls (Skalny et al., 2017; Tschinkel, et al., 2018).

The high degree of heritability (Freitag, et al., 2010; Miles, 2011; Morrow, et al., 2008; Steyaert & De La Marche, 2008; Sutcliffe, 2008) suggests a strong genetic influence, and genetic disorders such as Fragile X syndrome have a strong association with ASDs and related behavioral symptoms. Links between ASDs and schizophrenia have also been suggested, especially in individuals with abnormalities on chromosome 1 (i.e., 1q21.1 deletion syndrome; Kirov, 2015). Postmortem analyses of brains from ASD individuals has recently shown a significant decrease in RNA editing, especially with synaptic genes across several brain regions, and similar patterns of dysregulated RNA

editing were observed in the brains of Fragile X individuals (Tran, et al., 2018).

Simply having a Y chromosome seems to be one of the greatest risk factors for a diagnosis of ASD, in that they occur about twice as often in males when intellectual disabilities are also present, and more than 5x as often without intellectual disabilities (Newschaffer, et al., 2007). One main hypothesis for this phenomenon suggests that females require a greater etiologic load to display impairments consistent with an ASD diagnosis (Robinson, et al., 2013). For example, in a subject pool that presented with ASDs and/or developmental/intellectual disabilities, Jacquemont and colleagues (2014) reported that females had more deleterious autosomal variants (copy number and single nucleotide) than males. A higher number of these deleterious variants was associated with lower performance IQ. The authors hypothesized that increased mutational burden (more deleterious variants) and worse presentation of symptoms (lower IQ scores) are required for females to meet ASD threshold. Another study demonstrated that females with ASD have more problems with social interaction, communication, externalizing behavioral problems, irritability, feelings of lethargy, and lower IQ / language processing abilities compared to ASD males of the same age range, and that the differences grew larger with age (Frazier, et al., 2014).

However, some studies have not corroborated ASD-related sex differences in social communication, cognitive functioning, or adaptive behaviors (Dean et al., 2014; Reinhardt, Wetherby, & Schatschneider, 2015). Furthermore, one study reported that young ASD females had significantly better social skills than young ASD males (Head, McGillivray, & Stokes, 2014), but that this may be due to general female behavioral traits/tendencies in maintaining social relationships (e.g., empathy and care taking).

Eating Behaviors

Problems with eating can decrease the quality of nutrient intake and GI health in those with ASDs (Kral, et al., 2013; Ranjan & Nassar, 2015). Excessive rigidity regarding routines in individuals with ASDs can lead to extreme reactions to foods (particularly regarding texture) and/or rituals around food packaging, presentation, preparation, and/or eating patterns. Therefore, it is not surprising that children with ASD were reported to consume a significantly lower volume of food compared to their non-ASD siblings (Nadon, et al., 2010). In one study, at least 78% of ASD children omitted one or more food groups and displayed problematic mealtime behaviors, such as pushing away food, turning away their head, crying, leaving the table, making negative statements, and/or displaying aggression towards caregivers (Sharp et al., 2018). Schreck, Williams, and Smith (2004) reported that children with ASDs generally accepted a relatively narrow range of presented food options and refused food significantly more often than children without ASDs, but that they were more likely to accept food that was paired with specific preferred utensils. Similarly, Bandini and colleagues (2010) reported that children with ASDs refused more foods and had a smaller food repertoire than typically developing children of the same age range. These findings can be partially explained by behavioral rigidity and intolerance to new foods. However, it is not clear how much of an effect their medications, such as stimulants prescribed for attention deficits and/or hyperactivity, may play a role in this reduced food intake. Furthermore, motor behaviors in individuals with ASDs, such as weak sucking, tongue thrusting, and poor lip closure, can further affect eating patterns and reactions to food (Geraghty et al., 2010). For example, caregivers reported that children with ASDs required more supervision during mealtimes because they had tendencies to gag, vomit, cough, or choke

(Nadon, et al., 2010).

Interestingly, an fMRI study reported a significantly positive correlation between taste reactivity and response to sweeter tastes versus neutral tastes in the primary gustatory cortex of children with ASDs compared to typically developing children, and that children with ASDs who reported more taste-related symptoms had a greater cortical response (Avery et al., 2018). Nevertheless, caregiver education can positively impact the eating behaviors of children with ASDs. For example, parents of 3—6-year-old children in Japan were provided education on factors contributing to food selectivity and approaches for coping with problems of selective eating (Miyajima, et al., 2017). By the end of the study, the range of acceptable foods significantly increased.

Characteristics of Gastrointestinal Dysfunction

Individuals with ASDs seem to be more susceptible to GI issues, such as chronic abdominal pain, impaired peristaltic reflexes, bowel motility disorders (e.g., constipation and/or chronic loose stools), and/or bloating. Compared to ASD children without GI symptoms, ASD children with GI symptoms are more likely to be irritable, agitated, socially withdrawn, lethargic, hyperactive, and/or non-compliant (Afzal, et al., 2003; Berding & Donovan, 2018; Horvath & Perman, 2002; Ibrahim, et al., 2009; Kawicka & Regulska-Ilow, 2013; Kazek, et al., 2010; McElhanon, et al., 2014).

Constipation seems to be most strongly correlated with dairy intake, indicating that specific foods may be incongruent with the GI makeup of ASD individuals. Individuals with ASD that experience diarrhea, loose stools, and/or gaseousness tend to exhibit lower than normal activity of digestive enzymes such as disaccharidase, lactase, maltase, sucrase, palatinase, and glucoamylase, as well as higher pancreatobiliary fluid

output following secretin stimulation. Furthermore, protein intake that is significantly higher than the recommended dietary allowance is associated with increased bowel motility issues.

Endoscopic examination has revealed increased blood flow (hyperemia) consistent with gastroesophageal reflux (e.g., esophageal swelling, gastritis duodenitis, and colitis). Other tests have indicated incomplete digestion of dietary gluten and casein, low levels of gastric acid, excessive levels of abnormal gut bacteria, increased intestinal permeability ("leaky gut"), increased absorption of incompletely hydrolyzed peptides, and elevated serotonin concentrations in the GI associated with GI inflammation (Bandini, et al., 2010; Graf-Myles, et al., 2013; Herndon, et al., 2009; Kawicka & Regulska-Ilow, 2013; Levy, et al., 2007; Patrick & Ames, 2014; Sharp, et al., 2013; Veenstra-VanderWeele, et al., 2012; Xia, et al., 2010). These GI-related symptoms, combined with restricted and rigid eating patterns / food preferences, can lead to inefficient and/or ineffective nutrient absorption (Bandini, et al., 2010; Kawicka & Regulska-Ilow, 2013; Xia, et al., 2010). Indeed, some studies have reported significant differences in nutrient intake between children with and without ASDs (Graf-Myles, et al., 2013; Herndon, et al., 2009; Levy, et al., 2007; Sharp et al., 2013; Xia, et al., 2010).

For example, Schreck and colleagues (2004) reported that children with ASDs generally consume fewer vegetables, fruits, and starches than children without ASDs. Others have demonstrated inadequate consumption of dietary fiber, minerals such as potassium, iron, zinc, magnesium, and calcium (Herndon, et al., 2009; Graf-Myles, et al., 2013; Meguid, et al., 2017; Neumeyer, et al., 2018) and vitamins such as the retinoids (vitamin A), riboflavin (vitamin B_2), folate/folic acid (vitamin B_9), ascorbic acid (vitamin

C), cyanocobalamin (vitamin B_{12}), and vitamin D (Bandini, et al., 2010; Berding & Donovan, 2018; Graf-Myles, et al., 2013; Herndon, et al., 2009; Kawicka & Regulska-Ilow, 2013; Meguid, et al., 2017; Neumeyer, et al., 2018; Xia et al., 2010). Other studies have reported higherthanaverage consumption of calories from monosaturated fats (perhaps due to a preference for crunchy/crispy/fried snacks; Berding & Donovan, 2018; Graf-Myles, et al., 2013; Sharp, et al., 2013) and niacin (vitamin B_3; Xia, et al., 2010).

Physical ramifications of imbalanced nutrient intake include reports of scurvy, presumably caused by a paucity of fruits and vegetables in the diet (Saavedra, et al., 2018) as well as lower bone mass density scores in males with ASD (Neumeyer, et al., 2018). Children with ASDs are also more likely to be obese, presumably due to increased preference for snack foods and/or decreased ability to exercise from poor motor skills, low muscle-tone, and/or unstable posture (Curtin, et al., 2010; Kazek, et al., 2010).

Mechanisms of Gastrointestinal Dysfunction

The brain and the gut can interact via multiple pathways, including those mediated by the vagus nerve, immuneresponses, and metabolites (Desbonnet, et al., 2015; Dinan, et al., 2015; Foster & McVey Neufeld, 2013; Liu, Cao, & Zhang, 2015; Rogers, et al., 2016). Many of the GI issues that children with ASD endorse seem to be associated with “leaky gut.” Normally, the small intestinal mucosa acts a luminal barrier to prohibit substances from entering the bloodstream. However, in individuals with ASDs, this luminal barrier is impaired, allowing larger molecules that normally cannot cross the membrane, to pass via various ways through the compromised membrane (White, 2003). These enterocolitis specific issues seem to mediate the neurobehavioral features observed

in children with ASD (Ibrahim, et al., 2009).

The gut contains a microbial collection composed of various bacteria, viruses, and fungi that develops and grows during infancy. Changes in gut microbiota composition can impact cognitive behaviors (e.g., depression, anxiety, increased stress levels), but these symptoms may also be reversed by replacing beneficial microbes in the gut through probiotic supplementation (Berding & Donovan, 2018; Liu, Cao, & Zhang, 2015). Hoban and colleagues (2017) recently showed that gut microbes can regulate the expression of microRNA in the amygdala and prefrontal cortex, providing at least one mechanism but which the microbiota could influence cognition, affect, and behavior.

Interestingly, there is often an overall imbalance in the gut microbe composition of individuals with ASDs. A healthy gut normally contain species of *Bifidobacteria*, *Lactobacillus*, *Prevotella*, *Coprococcus*, and *Veillonellaceae*, which help to break down carbohydrates and control the expression of inflammatory cytokines (e.g., TNF-α), but Mezzelani and colleagues (2015) reported that individuals with ASDs tend to have decreased levels of these bacteria. Deficiencies in beneficial gut microbes, which may be attributed to the poor dietary patterns often exhibited by individuals with ASDs, can foster the growth of potentially harmful bacterial species such as *Clostridia*, *Desulfovibrio*, and *Bacteroides*. It is therefore not surprising that these species are found more often in stool samples of individuals with ASDs than those without ASDs (Berding & Donovan, 2018; Kantarcioglu, Kiraz, & Aydin, 2017; Kang, et al., 2013; Kushak, et al., 2017; Rose, et al., 2018). Lipopolysaccharides (LPS) are endotoxins found in Gram-negative bacteria (e.g., *Desulfovibrio* and *Bacteroides*) that can disrupt the blood—brain barrier and interfere with neuroimmunological communication, and such pathways have

been found to be disrupted in individuals with ASD (Jyonouchi, et al., 2005; Mezzelani, et al., 2015). Prenatal exposure to bacterial LPS via maternal infections that occur during pregnancy may also play a role in the development of ASDs (Kirsten, et al., 2018).

Other potential explanations for the GI issues observed in individuals with ASD include autoimmune responses against the gut epithelium and/or allergic reactions / sensitivities to certain foods. Specifically, chronic gastritis is associated with an increased number of lymphoid aggregates in the mucosa and an increased number of local immune defense cells. Cow's milk (for example) may cause an allergic reaction, which results in an antigen induced distal constipation (Afzal, et al., 2003). Whether caused by poor diet, gut microbiome imbalances, or auto-immune / allergic responses, chronic inflammation in the GI is also associated with inflammation in other organs, including the brain (Horvath & Perman, 2002).

Current Treatment Options

The overarching treatment goal for individuals with ASDs is to increase quality of life, including functional independence, increased social interaction, and improved language skills. Improvements in these areas of life will often reduce stress for both the individual and the family, but specific treatment goals depend on the range and severity of impairment. Generally, higher IQ and earlier intervention have both been associated with better overall outcomes. As reviewed by Poleg and colleagues (2019), most treatments available are tailored towards behavioral impairments and psychoeducation (Poleg, et al., 2019; Seida, et al., 2009). Perhaps due to the widely variable nature of ASD symptoms, no specific treatment strategy has been proven as reliably effective (Smith &

Iadarola, 2015). Behavioral intervention and positive support will not “cure” ASDs but can mask or reduce the presentation of ASD symptoms.

Similarly, no pharmaceutical treatments have been shown to reliably improve the social and language problems central to a diagnosis of ASD. However, overall brain function, repetitive behaviors, and comorbid / secondary symptoms such as attention deficits, hyperactivity, irritability, depression, and/or anxiety have been targets of pharmaceutical intervention. Over 50% of children with an ASD diagnosis are prescribed psychoactive drugs such as antipsychotics (e.g., risperidone and apriprazole), antidepressants (e.g., serotonin / norepinephrine reuptake inhibitors), stimulants (e.g., methylphenidate, norepinephrine reuptake inhibitors), antihypertensives (e.g., beta-blockers, guanfacine), depressants (e.g., GABAergic drugs), and hormones (e.g., oxytocin, vasopressin) (Oswald & Sonenklar, 2007; Doyle & McDougle, 2012*;* Ji & Findling, 2015; Sanchack & Thomas; Frye, 2018). However, one recent study that assessed a cohort of Danish ASD children born between 1992 and 2011 reported that only about 30% of the sample used ADHD medications (e.g., methylphenidate), antipsychotics (e.g., risperidone), antidepressants (e.g., sertraline), and/or hormones (e.g., melatonin) (Rasmussen, et al., 2018). These data suggest regional differences in either ASD diagnoses, symptom presentation, and/or treatment protocols.

One recent study found that post-natal administration of an antidiabetic drug (pioglitazone) improved ASD-like social impairments in a rat model of autism (prenatal LPS exposure; Kirsten, et al., 2018). Unfortunately, although certain psychoactive drugs may provide some relief from symptoms such as repetitive behaviors (e.g., antidepressants), irritability, aggression, self-injurious behaviors (e.g., antipsychotics), or

attention deficits / hyperactivity (e.g., stimulants, antihypertensives) (Johnson & Myers, 2007; Ji & Findling 2016; Leskovec, Rowles, & Findling, 2008), individuals with ASDs (and children in general) can often respond atypically. Additionally, these drugs have a number of unpleasant and/or harmful side effects, including weight gain, lethargy, and dyskinesias (Williamson, 2017).

CHAPTER TWO

DIETARY APPROACHES TO TREATMENT

The relative lack of efficacy for either behavioral or pharmaceutical treatment strategies for ASDs has led to an increased interest in the use of complementary or alternative medicine in the treatment of autism (Alanazi, 2013; Nath, 2017; Sathe, et al., 2017). The beneficial effects of dietary interventions for neurological disorders and injuries have been reported many times. For example, papers from our laboratory have demonstrated improvements in neuropathology and/or behaviors in mouse studies of irradiation (Dulcich, et al., 2013) and Alzheimer's disease (Hartman, et al., 2006) and in human studies of recovery from coronary artery bypass surgery (Ropacki, et al., 2013) and stroke (Bellone, et al., 2018). Due in part to the lack of available empirically validated therapies, there has been an increasing trend toward using similar treatment strategies in children with ASD (Christison & Ivany, 2006). In a study conducted by Hall and Riccio (2012), parents commonly resorted to trying elimination diets (e.g., gluten-free/casein-free) and/or dietary supplements including probiotics, omega-3 fatty acids, and melatonin.

Elimination Diets

Based on the hypothesis that some ASD symptoms are at least partly caused by dietary hypersensitivities that may be exacerbated by the GI issues mentioned above, "elimination diets" aim to improve behavioral symptoms by restricting intake of the

problem-causing component(s) (Christison & Ivany, 2006; Kawicka & Regulska-Ilow, 2013).

Casein and Gluten

Dietary proteins such as casein, which is found in milk, and the glutens, which are found in grains such as wheat, rye, and barley, have been linked to heightened inflammatory and immune responses (Buie, 2013; Jyonouchi, Sun, & Itokazu, 2002). In a study by Jyonouchi and colleagues (2005), ASD children expressed more proinflammatory cytokines and LPS (endotoxins produced by pathogenic microbial intestinal flora) after the consumption of cow's milk or gliadin (a component of wheat gluten). Similarly, casein and gluten can induce expression of immunoglobulin A and G antibodies in subsets of individuals with ASDs, which could exacerbate symptoms (Lau, et al., 2013; Marí-Bauset, et al., 2014).

Another explanation behind some of the atypical behavior observed in children with ASD is the "excess opioid" hypothesis, which proposes that gluten and casein are metabolized in the gut into short-chain peptides called gluteomorphins and caseomorphins (respectively) that are structurally similar to endorphins and have opiate agonist properties. Normally, the small intestinal mucosa acts as a luminal barrier to prohibit such metabolites from entering the bloodstream. However, in ASD individuals with increased intestinal permeability ("leaky gut") due to inflammation, this luminal barrier is impaired, potentially allowing these "exorphin" (exogenous opioid) metabolites into the bloodstream and ultimately into the brain to activate opiate receptors (Christison & Ivany, 2006; Geraghty, et al., 2010; Horvath & Perman, 2002; Mezzelani, et al., 2014;

Saad, et al., 2015; White, 2003).

Regardless of the specific mechanisms by which these dietary proteins may exacerbate ASD symptoms, some evidence suggests that reducing their consumption may help. Ghalichi and colleagues (2016) conducted a randomized controlled trial in which children with ASD were assigned to a gluten-free diet or their regular diet. Those in the "gluten-free" group exhibited a significant decrease in GI symptoms and stereotyped behaviors, with slightly improved communication and social interaction, whereas those who maintained a regular diet actually showed a significant increase in their GI symptoms after six weeks. Another study (Lucarelli et al., 1995) reported that, compared to controls, ASD children had higher levels of casein-specific antibodies, and that their ASD symptoms seemed to improve after eight weeks on the cow's milk elimination diet. However, some studies have shown no significant differences in intestinal permeability and behavioral symptoms between individuals who were on a gluten-/casein-free diet and those who were not (Harris & Card, 2012; Navarro, et al., 2015), and a systemic review by the Cochrane group suggested that there is little hard evidence for the effectiveness of casein- and gluten-free diets in ASDs, but that only large-scale, randomized trials would yield more conclusive data (Millward, et al., 2008).

Specific Carbohydrate Diet

The specific carbohydrate diet eliminates complex carbohydrates (e.g., sugars, grains, starches, and dairy), allowing only those requiring minimal digestion. Nutrients in the diet come from monosaccharides (e.g., fruit, some vegetables, honey, meat, eggs, natural cheeses, homemade yogurt, nuts, soaked lentils, and beans). The idea behind the

diet is that complex carbohydrates take longer to break down and digest in the GI system, thereby becoming a foundation for pathogenic intestinal microflora to breed (Gotschall, 2004; Kawicka & Regulska-Ilow, 2013; Geraghty, et al., 2010).

Individuals with colonic and ileocolonic Crohn's disease who followed the diet for nearly three years found that their symptoms generally improved (Kakodkar, et al., 2015). Although these individuals did not have ASDs, their GI symptoms were similar to those found in individuals with ASDs, so the results may be generalizable across populations. In a 2018 case study, Barnhill and colleagues (2018) observed a 4-year-old male who was diagnosed with ASD and followed the specific carbohydrate diet for four months. He showed significant improvement in stool consistency and level of irritability when passing stool. His symptoms, including sensory, repetitive, and ritualistic behaviors, receptive and expressive language problems, and learning and memory also significantly improved.

Ketogenic Diet

The ketogenic diet (and the similar modified Atkins diet) which generally prescribes low-carbohydrate, moderate protein, and high-fat intake, forces the metabolism of ketones rather than glucose, and its overall effects include increased blood ketones, reduced blood glucose, and improved mitochondrial function (Ruskin, et al., 2013). The diet has shown some effectiveness in treating individuals with refractory epilepsy (which is more common in individuals with ASD than those without) and other neurological disorders. Indeed, one study administered a ketogenic diet to ASD children who presented with seizures and found that the sample showed an overall decrease in seizures along with

improved learning ability and social skills (Napoli, Dueñas, & Giulivi, 2014).

Animal models of ASDs have yielded some promising results using the ketogenic diet. For example, Ruskin and colleagues (2013) assessed the BTBR mouse model of ASD, which has severely reduced interhemispheric communication due an absent corpus callosum and a diminished hippocampal commissure and displays behaviors similar to those seen in humans with ASDs (abnormal social interactions, play behaviors, and vocalizations). They reported that the ketogenic diet increased sociability, decreased repetitive behaviors, and improved social communication. Another mouse study (Ruskin, Murphy, Slade, & Masino, 2017) that examined the offspring of C57B1/6 mice given an infection during pregnancy reported that male, but not female, offspring exhibited behavioral patterns similar to those seen in humans with ASDs, and that a ketogenic diet attenuated these behaviors. Other studies using rodent models of autism have yielded mixed results. For example, the diet significantly improved sociability in glut3$^{+/-}$, but not wild-type, mice, and significantly improved spatial cognition in wild-type, but not glut3$^{+/-}$, mice (Dai, et al., 2017). Kasprowska-Liśkiewicz and colleagues (2017) also demonstrated increased social interaction, but no differences in locomotor activity, anxiety, or working memory, in male Long-Evans rats, and that the administration of exogenous ketones did not affect social behavior.

Human studies have also demonstrated some modest improvements from the ketogenic diet. For example, the study mentioned above (Napoli, Dueñas, & Giulivi, 2014) not only reported fewer seizures, but also improved learning ability and social skills. Additionally, Evangeliou and colleagues (2003) implemented the ketogenic diet in 18 children with autistic behavior for six months. They reported significant improvement

in two subjects, average improvement in eight subjects, and minor improvement in eight subjects, with the individuals on the lower end of the ASD spectrum showing the most improvement. In a study comparing a modified Atkins / ketogenic diet to a gluten-/casein-free diet, El-Rashidy and colleagues (2017) found that a ketogenic diet improved cognition and sociability significantly more than the gluten-free/casein-free diet. Finally, a case study of a 6-year-old ASD patient with glucose hypometabolism showed that one month of a ketogenic diet improved hyperactivity, attention span, abnormal reactions to stimuli, communication skills, fear, anxiety, and emotional reactions (Zarnowksa, et al., 2018).

Low Oxalate Diet

One study reported a 3x higher concentration of plasma oxalate and more than a 2.5x higher concentration of urinary oxalate than the recommended value in urine among a sample of children with ASD compared to healthy peers (Konstantynowicz, et al., 2012). High concentrations of oxalates are found in spinach, beets, cocoa, black tea, and certain fruits, grains and nuts. Related compounds such as oxalic acid, in conjunction with GI system dysfunction, have been linked to impaired neurological development and abnormalities in the nervous system (Kawicka & Regulska-Ilow, 2013; Cristiano, et al., 2018). However, there have been no empirical studies demonstrating the effectiveness of a low oxalate diet on individuals with ASD.

Supplements

In addition to eliminating problem-causing compounds (e.g., certain proteins, carbohydrates, oxalates) from the diet, some studies suggest that supplementing the diet with beneficial compounds may improve ASD symptoms.

Fatty Acids

Insufficient omega-3 fatty acid intake has been implicated in the abnormal development of the nervous system (Kawicka & Regulska-Ilow, 2013), and children with ASDs often have decreased plasma levels of phospholipid fatty acids (Geraghty et al., 2010). Thus, a reduced omega-3 index (the proportion of omega-3 fatty acids to the total amount of fatty acids in the brain) may be a biomarker for ASDs, because neurons should be rich in polyunsaturated fatty acids to ensure normal development, membrane fluidity, and functional properties.

Nevertheless, there have been mixed reviews regarding the results of omega-3 fatty acid supplementation (Kawicka & Regulska-Ilow, 2013). Parellada and colleagues (2017) found that children aged 5—17 years who supplemented their diets with omega-3 fatty acids for approximately two months showed a significant improvement in social motivation as reported by parents. Another study that provided supplemental omega-3 fatty acids for three months showed a significant improvement of atypical sensory processing from baseline (again, as reported by parents; Boone, et al., 2017). They also found increased levels of long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which promote healthy brain development.

The administration of omega-3 fatty acids along with vitamin B_{12} has also been found to increase the growth of a Gram-positive bacterium (*Staphylococcus*) and reduce survival of a Gram-negative bacterium (*Clostridia*; Alfawaz, et al., 2018). Another combination study administered medium chain triglycerides (which also improve fatty acid levels) along with a ketogenic diet and gluten-free diet to children with ASD for three months (Lee, et al., 2018). The combination of multiple dietary therapies showed significant improvement in core features of ASD and symptom severity.

A meta-analysis conducted by Cheng and colleagues (2017) suggested that omega-3 fatty acid supplementation in ASD children induced only borderline improvements in hyperactivity, but significant improvements in stereotypic behavior. When Agostoni and colleagues (2017) reviewed studies on omega-3 fatty acid supplementation across developmental psychopathologies, they found mixed effects on ASD, with non-significant trends for beneficial effects on impaired behavior.

A fatty acid-like compound derived from the cannabis plant may also offer some relief from ASD symptoms. Since cannabidiol (CBD) has anticonvulsive, sedative, hypnotic, antipsychotic, anti-inflammatory, and neuroprotective properties, it may benefit individuals with ASDs (Anderson, et al., 2017; Gu, 2017; Poleg, et al., 2019). For example, one study demonstrated that CBD reduced seizures by 70% in a mouse model of an epileptic disorder (Dravet syndrome), and when administered in low doses, significantly increased social interaction (Kaplan, et al., 2017).

Pro- and Pre-biotics

Probiotics are live microorganisms (e.g., *Lactobacillus, Bifidobacterium spp.*) that naturally occur in certain (often fermented) foods such as yogurt and sauerkraut or can be added to the diet via supplemental capsules (Kałużna-Czaplińska & Błaszczyk, 2012). Prebiotics are compounds in (often high fiber) foods that selectively promote the growth and colonization of healthy gut probiotics. Improving gut health via ingestion of dietary probiotics may ameliorate some of the gut-related issues associated with the ASDs (Doenyas, 2018; Hsiao, et al., 2013).

Probiotics have been shown to alleviate GI dysfunction, which is commonly associated with ASD, by a number of mechanisms (Geraghty, et al., 2010). For example, probiotics may reduce gut permeability and reconstruct or stabilize the intestinal barrier via increased mucin production (Anderson, et al., 2010; Berding & Donovan, 2018). They also produce digestive enzymes that metabolize potentially toxic / irritating compounds (such as casein and the glutens; Lindfors, et al., 2008), synthesize antioxidants that protect the gut from pathogens (Kałużna-Czaplińska & Błaszczyk, 2012), and modulate immune responses. Supplemental consumption of beneficial probiotic bacteria such as *Lactobacillus* can normalize the gut microbiome and influence social/sensory/cognitive behaviors (Patusco & Ziegler, 2018). A probiotic mixture of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* species attenuated elevated levels of *Clostridia* and reversed persistent ASD-like behaviors induced by propionic acid (a neurotoxin) in young male golden Syrian hamsters (El-Ansary, et al., 2018). In another study using a rodent model of ASDs, Shank3b -/- mice were administered *Lactobacillus*, resulting in fewer unsocial/aggressive behaviors in males, and fewer stereotypical

repetitive behaviors in both males and females (Tabouy, et al., 2018).

In a double-blind, placebo-controlled, crossover-designed feeding sample, a sample of 17 ASD subjects took a probiotic (*Lactobacillus plantarum WCSF1)* for 12 weeks. The supplement significantly increased *Lactobacilli* and *Enterococci* bacteria and reduced *Clostridia* bacteria in the gut and significantly decreased behavioral and emotional disturbances (Parracho, et al., 2010). The first study to evaluate prebiotic supplementation in ASD demonstrated that a galacto-oligosaccharide, in combination with a gluten-free/casein-free diet, improved beneficial bacteria growth, and increased gut microbiota diversity (Grimaldi, et al., 2018).

Vitamins

These organic compounds are essential nutrients that play a wide role in general life functions. Insufficient consumption of vitamins can lead to a number of psychiatric issues (Mehl-Madrona & Cornish, 2008) and can potentially exacerbate the issues already present in the ASDs. A recent literature review found mixed results on the overall effectiveness of vitamin supplementation in ASD populations, most likely due to the heterogeneity of methodological aspects (e.g., type of vitamin, dosage, sample size, treatment duration; Gogou & Kolios, 2017). Nevertheless, several studies have been published that suggest therapeutic potential for supplementing with certain vitamins.

For example, vitamin B_6 (pyridoxine) is involved in the synthesis of serotonin, dopamine, and norepinephrine (Gogou & Kolios, 2017), and has been shown to improve behavioral symptoms, sleep, and GI symptoms (Adams & Holloway, 2004; Adams, et al., 2011; Xia, et al., 2010). Individuals with ASD often have less vitamin B_9 (folic acid) in

their cerebrospinal fluid because autoantibodies block folic acid synthesis by binding to folate receptors and inhibiting folate transport. Therefore, dietary supplementation with folic acid has been suggested for ASD individuals with cerebral folate deficiency syndrome. In one recent study, Alfawaz and colleagues (2018) reported that dietary supplementation with vitamin B_{12} (cobalamin) or omega-3 fatty acid equally alleviated ASD-like symptoms in a rat model of ASD (neurotoxic propionic acid administration). Methyl B_{12} (methylcobalamin) administration has also induced improvements in methylation, antioxidant capacity, and clinician-rated global symptoms in an ASD sample (Hendren, et al., 2016).

Individuals with ASD were also reported to have lower levels of vitamin C (ascorbic acid), suggesting that supplementation may provide some benefit (Adams & Holloway, 2004). Some ASD individuals have even presented with scurvy (a symptom of vitamin C deficiency), presumably caused by a paucity of fruits and vegetables in the diet (Saavedra & Cacchiarelli, 2018). Maternal vitamin deficiencies (e.g., vitamin D) during pregnancy may increase the infant's risk of developing an ASD, suggesting that prenatal supplementation may also provide some benefit (Adams & Holloway, 2004; Kawicka & Regulska-Ilow, 2013). Furthermore, vitamin D deficiencies in individuals with ASDs may exacerbate symptoms. Patrick and Ames (2014) proposed that vitamin D supplementation could lower the elevated levels of serotonin and the associated GI inflammation in ASD subjects.

Minerals

These inorganic compounds are essential nutrients that play a wide role in general life functions. Like vitamin B6, magnesium has been implicated in improving behavioral symptoms, sleep, and gastrointestinal symptoms (Adams & Holloway, 2004; Adams et al., 2011; Xia et al., 2010) and is also involved in serotonin, dopamine, and norepinephrine synthesis (Gogou & Kolios, 2017). Zinc has been implicated in neuronal genesis, plasticity, fetal growth, cellular differentiation and reproduction, tissue repair, and immunity. Adams and Holloway (2004) reported a significantly lower zinc to copper ratio in children with ASD, suggesting that increasing levels zinc (and/or reducing levels of copper) may aid this population. In corroboration of this idea, the administration of zinc reversed the effects of impaired vocalization and improved social behavior in a rodent model of autism (prenatal valproic acid exposure; Cezar, et al., 2018).

Glutathione

Oxidative stress is a common biomarker in ASD populations and is congruent with GI dysfunction. Lower antioxidant capacity has been implicated as a potential contribution to ASD pathophysiology and social impairment. Glutathione is an antioxidant molecule synthesized in the liver that has been reported as deficient in ASD populations (Yui, et al., 2017). Although glutathione has poor oral bioavailability, ingestion of *N*-acetylcysteine (NAC), which is metabolized to one of its precursors (L-cysteine), can replenish glutathione levels. NAC supplementation has demonstrated mixed results. Although it seems to increase levels of glutathione in ASD individuals (Ghanizadeh & Moghimi-Sarani, 2013; Nikoo, et al., 2015; Wink et al., 2016), a recent

study in which NAC was administered to subjects with ASDs for six months reported no significant improvements in sociability or repetitive behaviors compared to controls (Dean, et al., 2017). However, NAC seemed to improve the effects of Risperidone treatment on irritability and hyperactivity in ASD subjects (Ghanizadeh & Moghimi-Sarani, 2013; Nikoo et al., 2015).

Phytochemicals

Sulforaphane is an organosulfur phytochemical (meaning that it is an organic plant-derived compound that contains sulfur) found in cruciferous vegetables such as broccoli seeds and sprouts. It has a number of reported physiological effects, including antioxidant/anti-inflammatory properties (Bent et al., 2018). It has also been found to regulate the expression of cytoprotective responses through long-lasting mediation of a transcription factor, making it a potentially efficient dietary therapeutic (Panjwani, Liu, & Fahey, 2018).

One study (Singh, et al., 2014) examined whether dietary treatment with sulforaphane might reduce the severity of socially impaired behavior among a sample of young males with ASD. After an 18-week period, they found that the sample's social interactions, aberrant behavior, and verbal communication significantly improved, with symptoms starting to change around one month after initiating treatment. In a 2018 study, Bent and colleagues investigated whether treating a sample of ASD adolescents with sulforaphane would improve behavioral impairments and metabolic output. They found that social communication and symptom severity significantly improved, and that metabolites involved in oxidative stress, amino acid/gut microbiome, neurotransmitters,

hormones/stress response, and sphingomyelin metabolism were significantly different in the ASD sample. In a study of subjects who took sulforaphane for a few years, there was considerable improvement, and subjects reported that it worked better than pharmacological interventions such as aripiprazole and levetiracetam (Lynch et al., 2017). However, one recent study (Fahey, et al., 2017) reported that a significant number of subjects in a study of individuals without ASDs experienced upset stomach while taking sulforaphane supplements. Finally, prenatal administration of another phytochemical, resveratrol (a stilbenoid found in grapes, berries, nuts, etc.) was reported to prevent social impairments in a valproic acid exposure rodent model of ASDs (Bambini, et al., 2014).

Hormones

Secretin is a hormone that stimulates pancreatic secretion and inhibits gastric acid secretion, thereby maintaining the pH of the intestinal luminal fluid in the GI system. Individuals with ASDs tend to produce lower levels of this hormone, so their gastric acid secretion is higher and pancreatic secretion is lower, which increases luminal acidity and permeability (White, 2003). Therefore, secretin supplementation may be a viable therapeutic agent to improve GI dysfunction in individuals with ASDs. One case study found a significant improvement in diet and behavioral symptoms after a six-month intravenous administration of secretin (Pallanti, et al., 2017). However, other studies have concluded that secretin showed no improvement in the core features of ASDs after single or multiple doses (Krishnaswami, McPheeters, & Veenstra-VanderWeele, 2011; Williams, Wray, & Wheeler, 2012).

Melatonin is a hormone secreted by the pineal gland, GI system, lungs, renal cortex, and retina and is responsible for regulating circadian rhythm, GI motility, and influencing immune and reproductive systems (Gagnon & Godbout, 2018). The secretion pattern of melatonin is different in individuals with ASDs, which could explain the common symptom of sleep problems, and administration of melatonin can show improvements in sleep disturbances (Cuomo, et al., 2017; Damiani, Sweet, & Sohoni, 2014; Rossignol & Frye, 2011). Mothers of children with ASDs have been reported to have lower levels of melatonin in their urine compared to mothers of control children, suggesting that parental melatonin levels could be a potential contributor to the development of ASDs in their offspring (Braam, et al., 2018). Finally, the GI system has a high concentration of melatonin, and it exerts both excitatory and inhibitory effects on the gut muscles and modulates inflammatory responses. Although there is no empirical evidence of melatonin alleviating GI issues in ASD populations, its role in the GI system may lead to future research developing this theory.

CHAPTER THREE

CONCLUSION

Although there has been extensive research on the symptoms and potential causes of ASDs, the role of GI dysfunction is an emerging topic of interest. Not only do individuals with ASDs display rigid food eating patterns, but they are more likely to suffer from GI issues such as diarrhea, constipation, and irritable bowel syndrome. Ultimately, the diets discussed throughout this chapter may ameliorate, at least partially, both GI and behavioral impairments. Dietary approaches are not considered a significant treatment for "curing" ASD. Rather, they provide a potential alternative to alleviate GI dysfunction commonly experienced by individuals with ASD. Dietary approaches may be cheaper, easier to implement, and better tolerated with fewer side effects than pharmaceutical interventions. In addition, individuals adhering to these diets may also experience reductions in dysfunctional behavior. However, as mentioned previously, these dietary approaches should not substitute evidenced based cognitive and behavioral interventions developed for ASD. Dietary modifications can be a supplementation to an already established treatment plan as it shows to at least improve overall physical health and target eating behaviors which contribute to nutrition deficiencies in ASD. Future research should also determine whether these diets can be generalizable in different populations and whether they are feasible in different settings (areas with fewer resources, lower socio-economic areas, countries with different dietary restrictions).

REFERENCES

Adams J.B., Audhya T., McDonough-Means S., Rubin R.A., Quig D., Geis E, Gehn E, Loresto M, Mitchell J, Atwood S, Barnhouse S, Lee W (2011) Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutr Metab 8:34

Adams JB, Holloway C (2004) Pilot Study of a Moderate Dose Multivitamin/Mineral Supplement for Children with Autistic Spectrum Disorder. J Altern Complement Med 10:1033–1039

Afzal N, Murch S, Thirrupathy K, Berger L, Fagbemi A, Heuschkel R (2003) Constipation with acquired megarectum in children with autism. Pediatrics 112:939–942

Agostoni C, Nobile M, Ciappolino V, Delvecchio G, Tesei A, Turolo S, Crippa A, Mazzocchi A, Altamura CA, Brambilla P (2017) The role of omega-3 fatty acids in developmental psychopathology: A systematic review on early psychosis, autism, and ADHD. Int J Mol Sci 18:1–25.

Al-Farsi YM, Waly MI, Al-Sharbati MM, Al-Shafaee MA, Al-Farsi OA, Al-Khaduri MM, Gupta I, Ouhtit A, Al-Adawi S, Al-Said MF, Deth RC (2013) Levels of Heavy Metals and Essential Minerals in Hair Samples of Children with Autism in Oman: a Case–Control Study. Biol Trace Elem Res 151:181–186

Alanazi AS (2013) The role of nutraceuticals in the management of autism. Saudi Pharm J 21:233–243

Alfawaz H, Bhat RS, Al-Mutairi M, Alnakhli OM, Al-Dbass A, Alonazi M, Al-Mrshoud M, Hasan IH, El-Ansary A (2018) Comparative study on the independent and combined effects of omega-3 and vitamin B12 on phospholipids and phospholipase A2 as phospholipid hydrolyzing enzymes in PPA-treated rats as a model for autistic traits. Lipids Health Dis 17:1–7.

Allman MJ (2011) Deficits in Temporal Processing Associated with Autistic Disorder. Front Integr Neurosci 5:1–2

Anderson C, Evans V, DeMarse T, Febo M, Johnson C, Carney P (2017) Cannabidiol for the Treatment of Drug-Resistant Epilepsy in Children: Current State of Research. J Pediatr Neurol 15:143–150

Anderson RC, Cookson AL, McNabb WC, Kelly WJ, Roy NC (2010) Lactobacillus plantarum DSM 2648 is a potential probiotic that enhances intestinal barrier function. FEMS Microbiol Lett 309:184–192

Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET (2010) Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 40:1423–1430

Avery JA, Ingeholm JE, Wohltjen S, Collins M, Riddell CD, Gotts SJ, Kenworthy L, Wallace GL, Simmons WK, Martin A (2018) Neural correlates of taste reactivity in autism spectrum disorder. NeuroImage Clin 19:38–46

Baio J (2018) Prevalence of autism spectrum disorder among children aged 8 years — Autism and developmental disabilities monitoring network, 11 Sites, USA, 2014.

Bandini LG, Anderson SE, Curtin C, Cermak S, Evans EW, Scampini R, Maslin M, Must A (2010) Food selectivity in children with autism spectrum disorders and typically developing children. J Pediatr 157:259–264.

Barnhill K, Devlin M, Moreno HT, Potts A, Richardson W, Schutte C, Hewitson L (2018) Brief Report: Implementation of a Specific Carbohydrate Diet for a Child with Autism Spectrum Disorder and Fragile X Syndrome. J Autism Dev Disord 0:0

Bear MF, Dölen G, Osterweil E, Nagarajan N (2008) Fragile X: Translation in Action. Neuropsychopharmacology 33:84–87.

Bejerot S, Eriksson JM, Mörtberg E (2014) Social anxiety in adult autism spectrum disorder. Psychiatry Res 220:705–707

Bellone JA, Murray JR, Jorge P, Fogel TG, Kim M, Wallace DR, Hartman RE (2018) Pomegranate supplementation improves cognitive and functional recovery following ischemic stroke: A randomized trial. Nutr Neurosci:1–6

Bent S, Lawton B, Warren T, Widjaja F, Dang K, Fahey JW, Cornblatt B, Kinchen JM, Delucchi K, Hendren RL (2018) Identification of urinary metabolites that correlate with clinical improvements in children with autism treated with sulforaphane from broccoli. In: Molecular Autism, pp 1–12. Molecular Autism.

Berding K, Donovan SM (2018) Diet Can Impact Microbiota Composition in Children With Autism Spectrum Disorder. Front Neurosci 12:1–16

Boone KM, Gracious B, Klebanoff MA, Rogers LK, Rausch J, Coury DL, Keim SA (2017) Omega-3 and -6 fatty acid supplementation and sensory processing in toddlers with ASD symptomology born preterm: A randomized controlled trial. Early Hum Dev 115:64–70.

Braam W, Ehrhart F, Maas APHM, Smits MG, Curfs L (2018) Low maternal melatonin level increases autism spectrum disorder risk in children. Res Dev Disabil 82:79–89

Buie T (2013) The relationship of autism and gluten. Clin Ther 35:578–583

Cezar LC, Kirsten TB, da Fonseca CCN, de Lima APN, Bernardi MM, Felicio LF (2018) Zinc as a therapy in a rat model of autism prenatally induced by valproic acid. Prog Neuropsychopharmacol Biol Psychiatry 84:173–180

Cheng YS, Tseng PT, Chen YW, Stubbs B, Yang WC, Chen TY, Wu CK, Lin PY (2017) Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: A meta-analysis of randomized controlled trials. Neuropsychiatr Dis Treat 13:2531–2543.

Christison GW, Ivany K (2006) Elimination diets in autism spectrum disorders: any wheat amidst the chaff? J Dev Behav Pediatr 27:S162-71

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J (2007) Mapping early brain development in autism. Neuron 56:399–413.

Cristiano C, Lama A, Lembo F, Mollica MP, Calignano A, Mattace Raso G (2018) Interplay Between Peripheral and Central Inflammation in Autism Spectrum Disorders: Possible Nutritional and Therapeutic Strategies. Front Physiol 9

Cuomo BM, Vaz S, Lee EAL, Thompson C, Rogerson JM, Falkmer T (2017) Effectiveness of Sleep-Based Interventions for Children with Autism Spectrum Disorder: A Meta-Synthesis. Pharmacother J Hum Pharmacol Drug Ther 37:555–578

Curtin C, Anderson SE, Must A, Bandini L (2010) The prevalence of obesity in children with autism: A secondary data analysis using nationally representative data from the National Survey of Children's Health. BMC Pediatr 10:0–4.

Dai Y, Zhao Y, Tomi M, Shin B-C, Thamotharan S, Mazarati A, Sankar R, Wang EA, Cepeda C, Levine MS, Zhang J, Frew A, Alger JR, Clark PM, Sondhi M, Kositamongkol S, Leibovitch L, Devaskar SU (2017) Sex-Specific Life Course Changes in the Neuro-Metabolic Phenotype of Glut3 Null Heterozygous Mice: Ketogenic Diet Ameliorates Electroencephalographic Seizures and Improves Sociability. Endocrinology 158:936–949

Damiani JM, Sweet B V., Sohoni P (2014) Melatonin: an option for managing sleep disorders in children with autism spectrum disorder. Am J Health Syst Pharm 71:95–101

Dean M, Kasari C, Shih W, Frankel F, Whitney R, Landa R, Lord C, Orlich F, King B, Harwood R (2014) The peer relationships of girls with ASD at school: comparison to boys and girls with and without ASD. J Child Psychol Psychiatry 55:1218–1225

Dean OM, Gray KM, Villagonzalo K-A, Dodd S, Mohebbi M, Vick T, Tonge BJ, Berk M (2017) A randomised, double blind, placebo-controlled trial of a fixed dose of N -

acetyl cysteine in children with autistic disorder. Aust New Zeal J Psychiatry 51:241–249

Desbonnet L, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD, Cotter PD, Dinan TG, Cryan JF (2015) Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. Brain Behav Immun 48:165–173

Dinan TG, Stilling RM, Stanton C, Cryan JF (2015) Collective unconscious: How gut microbes shape human behavior. J Psychiatr Res 63:1–9

Doenyas C (2018) Dietary interventions for autism spectrum disorder: New perspectives from the gut-brain axis. Physiol Behav 194:577–582

Doyle CA, McDougle CJ (2012) Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. Dialogues Clin Neurosci 14:263–279

Dulcich MS, Hartman RE (2013) Pomegranate supplementation improves affective and motor behavior in mice after radiation exposure. Evidence-based Complement Altern Med 2013:940830

El-Ansary A, Bacha A Ben, Bjørklund G, Al-Orf N, Bhat RS, Moubayed N, Abed K (2018) Probiotic treatment reduces the autistic-like excitation/inhibition imbalance in juvenile hamsters induced by orally administered propionic acid and clindamycin. Metab Brain Dis 33:1155–1164

El-Ansary A, Bjørklund G, Tinkov AA, Skalny A V., Al Dera H (2017) Relationship between selenium, lead, and mercury in red blood cells of Saudi autistic children. Metab Brain Dis 32:1073–1080

El-Rashidy O, El-Baz F, El-Gendy Y, Khalaf R, Reda D, Saad K (2017) Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study. Metab Brain Dis 32:1935–1941

Evangeliou A, Vlachonikolis I, Mihailidou H, Spilioti M, Skarpalezou A, Makaronas N, Prokopiou A, Christodoulou P (2003) Application of a Ketogenic Diet in Children With Autistic Behavior: Pilot Study. J Child Neurol 18:113–118.

Fahey JW, Wade KL, Wehage SL, Holtzclaw WD, Liu H, Talalay P, Fuchs E, Stephenson KK (2017) Stabilized sulforaphane for clinical use: Phytochemical delivery efficiency. Mol Nutr Food Res 61:1–10.

Foster JA, McVey Neufeld KA (2013) Gut-brain axis: How the microbiome influences anxiety and depression. Trends Neurosci 36:305–312 Bambini V, Zanatta G, Della Flora Nunes G, Mueller de Melo G, Michels M, Fontes-Dutra M, Nogueira Freire V,

Riesgo R, Gottfried C (2014) Resveratrol prevents social deficits in animal model of autism induced by valproic acid. Neurosci Lett 583:176–181

Frazier TW, Georgiades S, Bishop SL, Hardan AY (2014) Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. J Am Acad Child Adolesc Psychiatry 53:329-40.e1-3

Freitag CM, Staal W, Klauck SM, Duketis E, Waltes R (2010) Genetics of autistic disorders: review and clinical implications. Eur Child Adolesc Psychiatry 19:169–178

Frye RE (2018) Social Skills Deficits in Autism Spectrum Disorder: Potential Biological Origins and Progress in Developing Therapeutic Agents. CNS Drugs 32:713–734

Gagnon K, Godbout R (2018) Melatonin and Comorbidities in Children with Autism Spectrum Disorder. Curr Dev Disord Reports 5:197–206

Geraghty ME, Bates-Wall J, Ratliff-Schaub K, Lane AE (2010) Nutritional Interventions and Therapies in Autism: A Spectrum of What We Know: Part 2. ICAN Infant, Child, Adolesc Nutr 2:120–133.

Geschwind DH (2009) Advances in Autism. Annu Rev Med 60:367–380.

Ghalichi F, Ghaemmaghami J, Malek A, Ostadrahimi A (2016) Effect of gluten free diet on gastrointestinal and behavioral indices for children with autism spectrum disorders: a randomized clinical trial. World J Pediatr 12:436–442

Ghanizadeh A, Moghimi-Sarani E (2013) A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. BMC Psychiatry 13:196

Gogou M, Kolios G (2017) The effect of dietary supplements on clinical aspects of autism spectrum disorder: A systematic review of the literature. Brain Dev 39:656–664

Gottschall E (2004) Digestion-gut-autism connection: the Specific Carbohydrate Diet. Med Verit J Med Truth 1:261–271

Graf-Myles J, Farmer C, Thurm A, Royster C, Kahn P, Soskey L, Rothschild L, Swedo S (2013) Dietary Adequacy of Children with Autism Compared with Controls and the Impact of Restricted Diet. J Dev Behav Pediatr 34:449–459

Grimaldi R, Gibson GR, Vulevic J, Giallourou N, Castro-Mejía JL, Hansen LH, Leigh Gibson E, Nielsen DS, Costabile A (2018) A prebiotic intervention study in children with autism spectrum disorders (ASDs). Microbiome 6:1–13.

Gu B (2017) Cannabidiol provides viable treatment opportunity for multiple neurological pathologies of autism spectrum disorder. Glob Drugs Ther 2:1–4

Hall SE, Riccio CA (2012) Complementary and alternative treatment use for autism spectrum disorders. Complement Ther Clin Pract 18:159–163

Harris C, Card B (2012) A pilot study to evaluate nutritional influences on gastrointestinal symptoms and behavior patterns in children with Autism Spectrum Disorder. Complement Ther Med 20:437–440

Hartman RE, Shah A, Fagan AM, Schwetye KE, Parsadanian M, Schulman RN, Finn MB, Holtzman DM (2006) Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol Dis 24:506–515

Head AM, McGillivray JA, Stokes MA (2014) Gender differences in emotionality and sociability in children with autism spectrum disorders. Mol Autism 5:1–9.

Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S (2016) Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. J Child Adolesc Psychopharmacol 26:774–783

Herndon AC, DiGuiseppi C, Johnson SL, Leiferman J, Reynolds A (2009) Does nutritional intake differ between children with autism spectrum disorders and children with typical development? J Autism Dev Disord 39:212–222

Hoban AE, Stilling RM, M Moloney G, Moloney RD, Shanahan F, Dinan TG, Cryan JF, Clarke G (2017) Microbial regulation of microRNA expression in the amygdala and prefrontal cortex. Microbiome 5:102

Hoban AE, Stilling RM, M Moloney G, Moloney RD, Shanahan F, Dinan TG, Cryan JF, Clarke G (2017) Microbial regulation of microRNA expression in the amygdala and prefrontal cortex. Microbiome 5:102.

Horvath K, Perman JA (2002) Autism and gastrointestinal symptoms. Curr Gastroenterol Rep 4:251–258.

Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155:1451–1463

Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ (2009) Incidence of Gastrointestinal Symptoms in Children With Autism: A Population-Based Study. Pediatrics 124:680–686

Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, Beckmann JS, Rosenfeld JA, Eichler EE (2014) A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet 94:415–425

Ji NY, Findling RL (2016) Pharmacotherapy for mental health problems in people with intellectual disability. Curr Opin Psychiatry 29:103–125

Johnson CP, Myers SM (2007) Identification and Evaluation of Children With Autism Spectrum Disorders. Pediatrics 120:1183–1215

Jyonouchi H, Geng L, Ruby A, Zimmerman-Bier B (2005) Dysregulated innate immune responses in young children with autism spectrum disorders: Their relationship to gastrointestinal symptoms and dietary intervention. Neuropsychobiology 51:77–85.

Jyonouchi H, Sun S, Itokazu N (2002) Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. Neuropsychobiology 46:76–84.

Kakodkar S, Farooqui AJ, Mikolaitis SL, Mutlu EA (2015) The Specific Carbohydrate Diet for Inflammatory Bowel Disease: A Case Series. J Acad Nutr Diet 115:1226–1232.

Kałuzna-Czaplińska J, Błaszczyk S (2012) The level of arabinitol in autistic children after probiotic therapy. Nutrition 28:124–126.

Kałuzna-Czaplińska J, Błaszczyk S (2012) The level of arabinitol in autistic children after probiotic therapy. Nutrition.

Kałużna-Czaplińska J, Błaszczyk S (2012) The level of arabinitol in autistic children after probiotic therapy. Nutrition 28:124–126

Kang D-W, Park JG, Ilhan ZE, Wallstrom G, Labaer J, Adams JB, Krajmalnik-Brown R (2013) Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. PLoS One 8:e68322

Kantarcioglu AS, Kiraz N, Aydin A (2016) Microbiota-Gut-Brain Axis: Yeast Species Isolated from Stool Samples of Children with Suspected or Diagnosed Autism Spectrum Disorders and In Vitro Susceptibility Against Nystatin and Fluconazole. Mycopathologia 181:1–7

Kaplan JS, Stella N, Catterall WA, Westenbroek RE (2017) Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A 114:11229–11234

Kasprowska-Liśkiewicz D, Liśkiewicz AD, Nowacka-Chmielewska MM, Nowicka J, Małecki A, Barski JJ (2017) The ketogenic diet affects the social behavior of young male rats. Physiol Behav 179:168–177

Kawicka A, Regulska-Ilow B (2013) How nutritional status, diet and dietary supplements can affect autism. A review. Rocz Państwowego Zakładu Hig 64:1–12

Kazek B, Jamroz E, Grzybowska-chlebowczyk U, Kajor M (2010) Gastrointestinal disturbances in patients with autistic spectrum disorders. Neurol Dziecięca 19:27–31.

Kelleher RJ, Bear MF (2008) The autistic neuron: troubled translation? Cell 135:401–406

Kirov G (2015) CNVs in neuropsychiatric disorders. Hum Mol Genet 24:R45-9

Kirsten TB, Casarin RC, Bernardi MM, Felicio LF (2018) Pioglitazone abolishes autistic-like behaviors via the IL-6 pathway. PLoS One 13:1–14.

Konstantynowicz J, Porowski T, Zoch-Zwierz W, Wasilewska J, Kadziela-Olech H, Kulak W, Owens SC, Piotrowska-Jastrzebska J, Kaczmarski M (2012) A potential pathogenic role of oxalate in autism. Eur J Paediatr Neurol 16:485–491

Kral TVE, Eriksen WT, Souders MC, Pinto-Martin JA (2013) Eating behaviors, diet quality, and gastrointestinal symptoms in children with autism spectrum disorders: A brief review. J Pediatr Nurs 28:548–556

Krishnaswami S, McPheeters ML, Veenstra-VanderWeele J (2011) A Systematic Review of Secretin for Children With Autism Spectrum Disorders. Pediatrics 127:e1322–e1325

Kumar H, Sharma B (2016) Memantine ameliorates autistic behavior, biochemistry & blood brain barrier impairments in rats. Brain Res Bull 124:27–39

Kushak RI, Winter HS, Buie TM, Cox SB, Phillips CD, Ward NL (2017) Analysis of the Duodenal Microbiome in Autistic Individuals: Association With Carbohydrate Digestion. J Pediatr Gastroenterol Nutr 64:e110–e116

Landa RJ (2008) Diagnosis of autism spectrum disorders in the first 3 years of life. Nat Clin Pract Neurol 4:138–147.

Lau NM, Green PHR, Taylor AK, Hellberg D, Ajamian M, Tan CZ, Kosofsky BE, Higgins JJ, Rajadhyaksha AM, Alaedini A (2013) Markers of Celiac Disease and Gluten Sensitivity in Children with Autism. PLoS One 8:6–11.

Lee BK, Magnusson C, Gardner RM, Blomström Å, Newschaffer CJ, Burstyn I, Karlsson H, Dalman C (2015) Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun 44:100–105

Lee RWY, Corley MJ, Pang A, Arakaki G, Abbott L, Nishimoto M, Miyamoto R, Lee E, Yamamoto S, Maunakea AK, Lum-Jones A, Wong M (2018) A modified ketogenic gluten-free diet with MCT improves behavior in children with autism spectrum disorder. Physiol Behav 188:205–211

Leskovec TJ, Rowles BM, Findling RL (2008) Pharmacological treatment options for autism spectrum disorders in children and adolescents. Harv Rev Psychiatry 16:97–112

Levy SE, Souders MC, Ittenbach RF, Giarelli E, Mulberg AE, Pinto-Martin JA (2007) Relationship of Dietary Intake to Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders. Biol Psychiatry 61:492–497.

Lewis JD, Theilmann RJ, Townsend J, Evans AC (2013) Network efficiency in autism spectrum disorder and its relation to brain overgrowth. Front Hum Neurosci 7:845

Lindfors K, Blomqvist T, Juuti-Uusitalo K, Stenman S, Venäläinen J, Mäki M, Kaukinen K (2008) Live probiotic Bifidobacterium lactis bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. Clin Exp Immunol 152:552–558.

Liu X, Cao S, Zhang X (2015) Modulation of Gut Microbiota-Brain Axis by Probiotics, Prebiotics, and Diet. J Agric Food Chem 63:7885–7895

Lucarelli S, Zingoni AM, F F, O G, Frediani T, Zingoni AM, Ferruzzi F, Giardini O, Quintieri F, Barbato M, D'Eufemia P, Cardi E (1995) Food allergy and infantile autism. Panminerva Med 37:137–141.

Lynch R, Diggins EL, Connors SL, Zimmerman AW, Singh K, Liu H, Talalay P, Fahey JW (2017) Sulforaphane from Broccoli Reduces Symptoms of Autism: A Follow-up Case Series from a Randomized Double-blind Study. Glob Adv Heal Med 6:2164957X1773582

Manzi B, Loizzo AL, Giana Grazia G, Curatolo P (2008) Autism and metabolic diseases. J Child Neurol 23:307–314

Marchezan J, Winkler Dos Santos EGA, Deckmann I, Riesgo RDS (2018) Immunological Dysfunction in Autism Spectrum Disorder: A Potential Target for Therapy. Neuroimmunomodulation 903:1–20

Marí-Bauset S, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M (2014) Evidence of the gluten-free and casein-free diet in autism spectrum disorders: A systematic review. J Child Neurol 29:1718–1727.

McElhanon BO, McCracken C, Karpen S, Sharp WG (2014) Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. Pediatrics 133:872–883

McTighe SM, Neal SJ, Lin Q, Hughes ZA, Smith DG (2013) The BTBR Mouse Model of Autism Spectrum Disorders Has Learning and Attentional Impairments and Alterations in Acetylcholine and Kynurenic Acid in Prefrontal Cortex. PLoS One 8.

Meguid NA, Anwar M, Bjørklund G, Hashish A, Chirumbolo S, Hemimi M, Sultan E (2017) Dietary adequacy of Egyptian children with autism spectrum disorder compared to healthy developing children. Metab Brain Dis 32:607–615

Mehl-Madrona L, Cornish S (2008) The Role of Vitamins and Minerals in Psychiatry. Integr Med Insights 3:33–423.

Mezzelani A, Landini M, Facchiano F, Raggi ME, Villa L, Molteni M, De Santis B, Brera C, Caroli AM, Milanesi L, Marabotti A (2015) Environment, dysbiosis, immunity and sex-specific susceptibility: A translational hypothesis for regressive autism pathogenesis. Nutr Neurosci 18:145–161

Miles JH (2011) Autism spectrum disorders-a genetics review. Genet Med 13:278–294

Millward C, Ferriter M, Calver SJ, Connell-Jones GG (2008) Gluten- and casein-free diets for autistic spectrum disorder. Cochrane Database Syst Rev:1–29.

Miyajima A, Tateyama K, Fuji S, Nakaoka K, Hirao K, Higaki K (2017) Development of an intervention programme for selective eating in children with autism spectrum disorder. Hong Kong J Occup Ther 30:22–32

Morrow EM et al. (2008) Identifying autism loci and genes by tracing recent shared ancestry. Science (80-) 321:218–223

Nadon G, Feldman DE, Dunn W, Gisel E (2011) Mealtime problems in children with Autism Spectrum Disorder and their typically developing siblings: A comparison study. Autism 15:98–113.

Napoli E, DueÃ±as N, Giulivi C (2014) Potential Therapeutic Use of the Ketogenic Diet in Autism Spectrum Disorders. Front Pediatr 2:1–9

Nath D (2017) Complementary and Alternative Medicine in the School-Age Child With Autism. J Pediatr Heal Care 31:393–397

Navarro F, Pearson DA, Fatheree N, Mansour R, Hashmi SS, Rhoads JM (2015) Are “leaky gut” and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders? Nutr Neurosci 18:177–185

Neumeyer AM, Cano Sokoloff N, McDonnell EI, Macklin EA, McDougle CJ, Holmes TM, Hubbard JL, Misra M (2018) Nutrition and Bone Density in Boys with Autism Spectrum Disorder. J Acad Nutr Diet 118:865–877

Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM, Rice CE, Schendel D, Windham GC (2007) The Epidemiology of Autism Spectrum Disorders. Annu Rev Public Health 28:235–258

Nikoo M, Radnia H, Farokhnia M, Mohammadi M-R, Akhondzadeh S (2015) N-Acetylcysteine as an Adjunctive Therapy to Risperidone for Treatment of Irritability in Autism. Clin Neuropharmacol 38:11–17

Nikvarz N, Alaghband-Rad J, Tehrani-Doost M, Alimadadi A, Ghaeli P (2017) Comparing Efficacy and Side Effects of Memantine vs. Risperidone in the Treatment of Autistic Disorder. Pharmacopsychiatry 50:19–25

Onore C, Careaga M, Ashwood P (2012) The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun 26:383–392

Ornoy A, Weinstein-Fudim L, Ergaz Z (2015) Prenatal factors associated with autism spectrum disorder (ASD). Reprod Toxicol.

Oswald DP, Sonenklar NA (2007) Medication Use Among Children with Autism Spectrum Disorders. J Child Adolesc Psychopharmacol.

Pallanti S, Lassi S, La Malfa G, Campigli M, Di Rubbo R, Paolini G, Cesarali V (2005) Short report: Autistic gastrointestinal and eating symptoms treated with secretin: A subtype of autism. Clin Pract Epidemiol Ment Heal. 1:24.

Panjwani AA, Liu H, Fahey JW (2018) Crucifers and related vegetables and supplements for neurologic disorders: what is the evidence? Curr Opin Clin Nutr Metab Care.

Parellada M, Llorente C, Calvo R, Gutierrez S, Lázaro L, Graell M, Guisasola M, Dorado ML, Boada L, Romo J, Dulin E, Sanz I, Arango C, Moreno C (2017) Randomized trial of omega-3 for autism spectrum disorders: Effect on cell membrane composition and behavior. Eur Neuropsychopharmacol 27:1319–1330

Parracho HMRT, Gibson GR, Knott F, Bosscher D, Kleerebezem M (2010) A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. Int J Probiotics Prebiotics 5:69–74

Patrick RP, Ames BN (2014) Vitamin D hormone regulates serotonin synthesis. Part 1: Relevance for autism. FASEB J.

Patterson PH (2011) Maternal infection and immune involvement in autism. Trends Mol Med.

Patusco R, Ziegler J (2018) Role of Probiotics in Managing Gastrointestinal Dysfunction in Children with Autism Spectrum Disorder: An Update for Practitioners. Adv Nutr 9:637–650

Persico AM, Bourgeron T (2006) Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. Trends Neurosci.

Poleg S, Golubchik P, Offen D, Weizman A, Daniel O, Weizman A (2019) Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. Prog Neuro-Psychopharmacology Biol Psychiatry 89:90–96.

Ranjan S, Nasser JA (2015) Nutritional Status of Individuals with Autism Spectrum Disorders: Do We Know Enough? Adv Nutr An Int Rev J 6:397–407

Rasmussen L, Bilenberg N, Thomsen Ernst M, Abitz Boysen S, Pottegård A (2018) Use of Psychotropic Drugs among Children and Adolescents with Autism Spectrum Disorders in Denmark: A Nationwide Drug Utilization Study. J Clin Med 7:10.

Reinhardt VP, Wetherby AM, Schatschneider C, Lord C (2015) Examination of Sex Differences in a Large Sample of Young Children with Autism Spectrum Disorder and Typical Development. J Autism Dev Disord.

Robinson EB, Lichtenstein P, Anckarsäter H, Happé F, Ronald A (2013) Examining and interpreting the female protective effect against autistic behavior. Proc Natl Acad Sci 110:5258–5262

Rogers GB, Keating DJ, Young RL, Wong M-L, Licinio J, Wesselingh S (2016) From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol Psychiatry 21:1–11

Ropacki S, Patel SM, Hartman RE (2013) Pomegranate Supplementation Protects against Memory Dysfunction after Heart Surgery: A Pilot Study. Evidence-Based Complement Altern Med 2013:1–8

Rose DR, Yang H, Serena G, Sturgeon C, Ma B, Careaga M, Hughes HK, Angkustsiri K, Rose M, Hertz-Picciotto I, Van de Water J, Hansen RL, Ravel J, Fasano A, Ashwood P (2018) Differential immune responses and microbiota profiles in children with autism spectrum disorders and co-morbid gastrointestinal symptoms. Brain Behav Immun 70:354–368

Rossignol DA, Frye RE (2011) Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol 53:783–792

Rossignol DA, Frye RE (2014) Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front Physiol 5:150

Ruskin DN, Svedova J, Cote JL, Sandau U, Rho JM, Kawamura M, Boison D, Masino SA (2013) Ketogenic Diet Improves Core Symptoms of Autism in BTBR Mice. PLoS One 8:4–9.

Ruskin DN, Murphy MI, Slade SL, Masino SA (2017) Ketogenic diet improves behaviors in a maternal immune activation model of autism spectrum disorder. PLoS One 12:e0171643

Saad K, Eltayeb AA, Mohamad IL, Al-Atram AA, Elserogy Y, Bjørklund G, El-Houfey AA, Nicholson B (2015) A Randomized, Placebo-controlled Trial of Digestive Enzymes in Children with Autism Spectrum Disorders. Clin Psychopharmacol Neurosci 13:188–193

Saavedra MJ, Aziz J, San Román NC (2018) Scurvy due to restrictive diet in a child with autism spectrum disorder. Case report. Arch Argent Pediatr 116:684–687

Sanchack KE, Thomas CA (2016) Autism Spectrum Disorder: Primary Care Principles. Am Fam Physician 94:972–979

Sathe N, Andrews JC, McPheeters ML, Warren ZE (2017) Nutritional and Dietary Interventions for Autism Spectrum Disorder: A Systematic Review. Pediatrics 139:e20170346

Schreck KA, Williams K, Smith AF (2004) A comparison of eating behaviors between children with and without autism. J Autism Dev Disord 34:433–438.

Seida JK, Ospina MB, Karkhaneh M, Hartling L, Smith V, Clark B (2009) Systematic reviews of psychosocial interventions for autism: An umbrella review. Dev Med Child Neurol 51:95–104.

Sharp WG, Berry RC, McCracken C, Nuhu NN, Marvel E, Saulnier CA, Klin A, Jones W, Jaquess DL (2013) Feeding problems and nutrient intake in children with autism spectrum disorders: A meta-analysis and comprehensive review of the literature. J Autism Dev Disord 43:2159–2173.

Simonoff E, PICKLES A, CHARMAN T, CHANDLER S, LOUCAS T, BAIRD G (2008) Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. J AM ACAD CHILD ADOLESC PSYCHIATRY 47:921–929.

Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, Zimmerman AW (2014) Sulforaphane treatment of autism spectrum disorder (ASD). Proc Natl Acad Sci 111:15550–15555

Skalny A V., Simashkova N V., Klyushnik TP, Grabeklis AR, Radysh I V., Skalnaya MG, Nikonorov AA, Tinkov AA (2017) Assessment of serum trace elements and electrolytes in children with childhood and atypical autism. J Trace Elem Med Biol 43:9–14

Smith T, Iadarola S (2015) Evidence Base Update for Autism Spectrum Disorder. J Clin Child Adolesc Psychol 44:897–922

Steyaert JG, De La Marche W (2008) What's new in autism? Eur J Pediatr 167:1091–1101.

Sutcliffe JS (2008) Insights into the pathogenesis of autism. Science (80-) 321:208–209

Tabouy L, Getselter D, Ziv O, Karpuj M, Tabouy T, Lukic I, Maayouf R, Werbner N, Ben-Amram H, Nuriel-Ohayon M, Koren O, Elliott E (2018) Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders. Brain Behav Immun 73:310–319

Tran SS, Jun H-I, Bahn JH, Azghadi A, Ramaswami G, Van Nostrand EL, Nguyen TB, Hsiao Y-HE, Lee C, Pratt GA, Martínez-Cerdeño V, Hagerman RJ, Yeo GW, Geschwind DH, Xiao X (2019) Widespread RNA editing dysregulation in brains from autistic individuals. Nat Neurosci 22:25–36

Tschinkel S, Fabiana P, Bjørklund G, Conón LZZ, Chirumbolo S, Nascimento VA (2018) Plasma concentrations of the trace elements copper, zinc and selenium in Brazilian children with autism spectrum disorder. Biomed Pharmacother 106:605–609

Veenstra-VanderWeele J et al. (2012) Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior. Proc Natl Acad Sci 109:5469–5474

Wei H, Dobkin C, Sheikh AM, Malik M, Brown WT, Li X (2012) The therapeutic effect of memantine through the stimulation of synapse formation and dendritic spine maturation in autism and fragile X syndrome. PLoS One 7:e36981

White JF (2003) Intestinal Pathophysiology in Autism. Exp Biol Med:639–649.

Wickelgren I (2005) Neurology. Autistic brains out of synch? Science (80-) 308:1856–1858

Williams K, Wray JA, Wheeler DM (2012) Intravenous secretin for autism spectrum disorders (ASD). Cochrane database Syst Rev:CD003495

Williamson E (2017) Medical therapies for children with autism spectrum Disorder—An Update. Comp Eff Rev 189

Wink LK, Adams R, Wang Z, Klaunig JE, Plawecki MH, Posey DJ, McDougle CJ, Erickson CA (2016) A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Mol Autism 7:26

Xia W, Zhou Y, Sun C, Wang J, Wu L (2010) A preliminary study on nutritional status and intake in Chinese children with autism. Eur J Pediatr 169:1201–1206.

Yui K, Tanuma N, Yamada H, Kawasaki Y (2017) Decreased total antioxidant capacity has a larger effect size than increased oxidant levels in urine in individuals with autism spectrum disorder. Environ Sci Pollut Res 24:9635–9644

Zafeiriou DI, Ververi A, Vargiami E (2007) Childhood autism and associated comorbidities. Brain Dev 29:257–272.

Żarnowska I, Chrapko B, Gwizda G, Nocuń A, Mitosek-Szewczyk K, Gasior M (2018) Therapeutic use of carbohydrate-restricted diets in an autistic child; a case report of clinical and 18FDG PET findings. Metab Brain Dis 33:1187–1192