The American Journal of Clinical Nutrition 120 (2024) 240–256

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Report of a Meeting

Food, nutrition, and autism: from soil to fork

Melissa Maitin-Shepard [1], Perrie O'Tierney-Ginn [2], Aletta D Kraneveld [3,4], Kristen Lyall [5], Daniele Fallin [6], Manish Arora [7], Alessio Fasano [8,9], Noel T Mueller [10], Xiaobin Wang [11], Laura E Caulfield [12], Aisha S Dickerson [10], Rochellys Diaz Heijtz [13], Tomo Tarui [14], Jeffrey B Blumberg [15], Calliope Holingue [16], Rebecca J Schmidt [17], Johan Garssen [3], Katherine Almendinger [18], Pi-I Debby Lin [19], Dariush Mozaffarian [20,*]

[1] *MMS Health Strategies, LLC, Alexandria, VA, United States;* [2] *Mother Infant Research Institute, Tufts Medical Center, Boston, MA, United States;* [3] *Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, the Netherlands;* [4] *Center for Neurogenomics and Cognitive Research, VU University, Amsterdam, the Netherlands;* [5] *AJ Drexel Autism Institute, Drexel University, Philadelphia, PA, United States;* [6] *Rollins School of Public Health, Emory University, Atlanta, GA, United States;* [7] *Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States;* [8] *Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, MA, United States;* [9] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, United States;* [10] *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [11] *Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [12] *Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [13] *Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden;* [14] *Department of Pediatrics, Hasbro Children's Hospital, Warren Alpert Medical School of Brown University, Providence, RI, United States;* [15] *Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, United States;* [16] *Center for Autism Services, Science and Innovation, Kennedy Krieger Institute and Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [17] *Department of Public Health Sciences, the MIND Institute, University of California Davis, Davis, CA, United States;* [18] *Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [19] *Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, United States;* [20] *Food is Medicine Institute, Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, United States*

ABSTRACT

Food and nutrition-related factors have the potential to impact development of autism spectrum disorder (ASD) and quality of life for people with ASD, but gaps in evidence exist. On 10 November 2022, Tufts University's Friedman School of Nutrition Science and Policy and Food and Nutrition Innovation Institute hosted a 1-d meeting to explore the evidence and evidence gaps regarding the relationships of food and nutrition with ASD. This meeting report summarizes the presentations and deliberations from the meeting. Topics addressed included prenatal and child dietary intake, the microbiome, obesity, food-related environmental exposures, mechanisms and biological processes linking these factors and ASD, food-related social factors, and data sources for future research. Presentations highlighted evidence for protective associations with prenatal folic acid supplementation and ASD development, increases in risk of ASD with maternal gestational obesity, and the potential for exposure to environmental contaminants in foods and food packaging to influence ASD development. The importance of the maternal and child microbiome in ASD development or ASD-related behaviors in the child was reviewed, as was the role of discrimination in leading to disparities in environmental exposures and psychosocial factors that may influence ASD. The role of child diet and high prevalence of food selectivity in children with ASD and its association with adverse outcomes were also discussed. Priority evidence gaps identified by participants include further clarifying ASD development, including biomarkers and key mechanisms; interactions among psychosocial, social, and biological determinants; interventions addressing diet, supplementation, and the microbiome to prevent and improve quality of life for people with ASD; and mechanisms of action of diet-related factors associated with ASD. Participants developed research proposals to address the priority evidence gaps. The workshop findings serve as a foundation for future prioritization of scientific research to address evidence gaps related to food, nutrition, and ASD.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BPA, bisphenol-A; CHARGE, CHildhood Autism Risks from Genetics and Environment; CI, confidence interval; ECHO, Environmental influences on Child Health Outcomes; GEMMA, Genome; Environment, Microbiome and Metabolome in Autism; MAMP, microbe-associated molecular pattern; OR, odds ratio; PCB, polychlorinated biphenyl; SNAP, Supplemental Nutrition Assistance Program; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

* Corresponding author.
E-mail address: Dariush.Mozaffarian@tufts.edu (D. Mozaffarian).

https://doi.org/10.1016/j.ajcnut.2024.04.020
Received 16 May 2023; Received in revised form 18 April 2024; Accepted 22 April 2024; Available online 25 April 2024

Keywords: autism, autism spectrum disorder, environmental exposures, folic acid, food selectivity, microbiome, nutrition, obesity, Special Supplemental Nutrition Program for Women, Infants, and Children, WIC

Introduction

Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental condition characterized by difficulties with social communications and interactions and restrictive or repetitive patterns of behaviors and interests [1] (We recognize that there are multiple terminologies and preferences related to autism/ASD. This article uses terminology consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [1] and the *International Classification of Diseases, 11th Revision* [2]). There is currently no biological marker for ASD. In the United States, ASD is estimated to affect 1 in 36 school-age children and is diagnosed 3.8 times more frequently in boys than girls [3]. Although ASD occurs in people in all racial and ethnic groups, in the United States it is more prevalent among non-Hispanic Black, Hispanic, and non-Hispanic Asian or Pacific Islander children [3].

The significant rise in ASD prevalence in the last half century is at least partially due to changes in diagnostic practice and increases in community awareness, although a true increase in ASD cannot be ruled out [4]. The increase in ASD prevalence correlates with other changes, including a large increase in obesity prevalence [5], greater intake of processed foods and other dietary changes [6], including an increased ω-6 to ω-3 fatty acid ratio [7], folic acid fortification [8], and an increase in the rate of cesarean deliveries [9]. However, although associations between some of these factors and development of ASD exist, they may not all be causal relationships [10]. Furthermore, ASD has multiple causal contributors, and existing evidence suggests the cause may vary across those with the diagnosis [4].

ASD is extremely heterogenous, and there are multiple etiologic pathways of development. Although some individuals may be genetically predisposed to develop ASD, social and environmental factors also play a role [4,11]. A subset of ASD has an inflammatory component and involves alterations in the gut–brain axis [12,13]. The immune system and gut microbiome, which is significantly impacted by diet [14], are programmed during fetal development and early childhood, making these time periods particularly critical for addressing factors that may influence ASD development [15,16]. Prospective human and animal studies are important for clarifying the mechanisms underlying ASD development.

Complex relationships exist among maternal preconception, prenatal, and postnatal diet and human milk feeding practices; early childhood diet and nutrition; maternal and child gut microbiome; and development of neurodevelopmental conditions such as ASD [4,17]. Given the potential for diet and nutrition-related factors to impact—or be impacted by—ASD development, particularly during critical early life developmental periods, relationships between diet and nutrition-related factors and ASD prevention, treatment, and quality of life outcomes should be targets for future study.

Meeting Goals

On 10 November 2022, the Tufts University Friedman School of Nutrition Science and Policy and the Tufts University Food and Nutrition Innovation Institute hosted a 1-d meeting in Boston, MA to explore the current state of the evidence and evidence gaps regarding the relationships between food, nutrition, and ASD. The full-day, in-person meeting, which was attended by ~30 of the United States' and the world's leading scientific experts on the topic, was co-chaired by Perrie O'Tierney-Ginn (Tufts Medical Center), Aletta Kraneveld (Utrecht University), Daniele Fallin (Emory University), and Kristen Lyall (Drexel University) and convened with support from the Bia-Echo Foundation. The mission of the Bia-Echo Foundation (https://biaecho.org/) is to create a multiplying effect across new frontiers in reproductive longevity and equality, criminal justice reform, and a healthy and livable planet [18].

The goals of the meeting were to discuss current knowledge, share ongoing research, identify new research needs, and consider the potential for future cross-collaborations. The meeting featured presentations on the existing evidence for the role of prenatal and early childhood nutrition in ASD; mechanisms, pathways, and biological processes; social influences and considerations; and research design and data sources. The presentations were followed by breakout groups to identify outstanding research questions and develop potential research proposals. Figure 1 provides a conceptual framework of selected influences of food and nutrition on ASD that were reviewed during the meeting (inner circles), together with priority areas for future research (outer circle), also discussed at the meeting.

This meeting report summarizes the presentations and deliberations from the meeting. Given the breadth of topics related to food, nutrition, and ASD, the meeting was unable to comprehensively address all issues. This meeting report is not intended to be a comprehensive review of evidence related to food, nutrition, and ASD, and systematic literature reviews were not conducted in the development of this meeting report. Instead, our article highlights key findings and takeaways from the scientific presentations and discussion at the expert meeting, along with research recommendations. A limitation of the conclusions and recommendations presented in this meeting report is that they are based on the meeting presentations and discussion and reflect the views of the experts in attendance; they may not reflect the full body of evidence or the views of all experts. In addition, the meeting report may not include all comments made at the scientific meeting or represent the views of any single meeting participant, host, or sponsor.

Existing Evidence for the Role of Nutrition in ASD

The meeting included presentations and discussion on the state of the evidence regarding the relationships with ASD development and food and nutrition-related factors, with a focus on prenatal factors that may relate to etiology, including dietary intake, folic acid supplementation, the microbiome, obesity, and food-related environmental exposures. Some of these presentations also described the mechanisms, pathways, and biological processes linking these factors and ASD development.

Diet and immune system health

The gastrointestinal tract, immune system, and brain development are closely related and play key roles in ASD development. A resilient immune system has the capacity to adapt to challenges by establishing, maintaining, and regulating an appropriate immune response and is important for proper brain development [19,20].

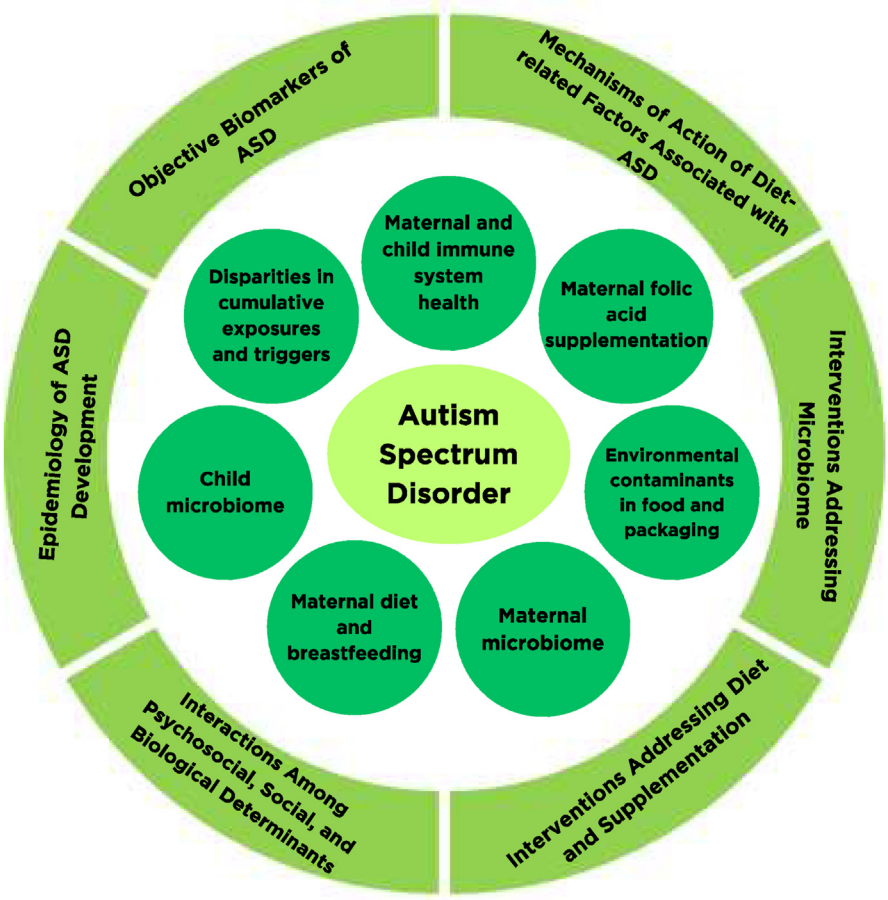

FIGURE 1. A conceptual framework of selected influences of food and nutrition on ASD (inner circles) reviewed in the meeting, together with priority areas for future research (outer circle). For example, risk appears related to environmental contaminants from foods and food packaging like metals, pesticides, and nonpersistent and persistent organic compounds, whereas disparities in cumulative exposures and triggers accrue from structural disparities in environmental exposures and psychosocial triggers. ASD, autism spectrum disorder.

The gut microbiota in early life influences immune cell development and function throughout the body, a relationship that is crucial for immune homeostasis [21]. As ~70% to 80% of the body's immune cells originate in the mucosal immune system of the gut, the immune system requires good nutrition to function properly [22]. The general mechanism by which gut microbiota in the gut lumen communicate with and regulate immune cells in distant immune organs was recently described by Schlechte et al. [21]. In short, gut microbes in the intestinal mucosa train immune cells that can recirculate to other body compartments to participate in the systemic and central nervous system immune system [23]. Microbe-associated molecular patterns (MAMPs) via the circulation can bind to pattern recognition receptors on immune cells throughout the body (so-called long distant MAMP signals) [24,25]. In addition, gut microbes can produce a variety of immune-active metabolites, such as short chain fatty acids, that can communicate with systemic immune cells through the circulation [26]. Neuroimmune mechanisms from microbe-produced neurotransmitters or indirectly induced production of neuroendocrine peptide hormones can also impact systemic and central nervous system immune cell function [27,28]. Microbial extracellular vesicles have also been demonstrated to have remote effects on the immune system [29].

In a healthy state, the immune system is programmed to protect against disease. In this state, the gut microbiota is well-balanced, epithelial cells provide a tight mechanical barrier, goblet cells are active against pathogenic invaders, and immune cells are trained and ready to respond to potentially offending moieties from the surrounding environment [30–32]. In contrast, a poorly programmed immune system responds either too weakly or too strongly, increasing vulnerability to conditions such as ASD in genetically susceptible individuals. Appropriate immune system development in early life protects against impaired growth; infections; allergies; chronic inflammatory disorders such as diabetes, obesity, and cardiovascular disease; and impaired cognition and behavior, including development of ASD [33].

With respect to T lymphocytes, an imbalance in Th1 and Th17 cells at the expense of Th2 and regulatory T cells is reported in ASD. A preclinical study using the maternal immune activation murine model for ASD demonstrated that the enhanced intestinal permeability and proinflammatory cytokines in the brain were reduced by blocking T cell recirculation [34]. In relation to the gut–brain axis in ASD, a recent article from Morton et al. [35] strongly supports the long distance immune effects of gut microbiota.

The immune system changes throughout the lifespan, and early life and older adulthood are sensitive periods of vulnerability [36]. Th1 cell development increases and then decreases over the lifespan in a bell-shaped curve, whereas Th2 cell development follows an opposing

curve. Unbalanced immune phenotypes, such as Th1 and Th17/Th2 and Treg ratio disbalances, may be associated with brain–behavior disorders, including ASD [36].

Specific dietary components, including oligosaccharides, microbes, and amino acids, can promote a fit and resilient immune system [37], potentially influencing development of conditions such as ASD [38]. Therefore, immunomodulation through dietary interventions aimed at resilience and inflammation management may influence development of brain disorders such as ASD [39,40]. A diet associated with reduced ASD risk may vary by individual, and timing for dietary interventions is critical. Early life interventions are likely to be the most effective [10,41,42]. Development of early biomarkers of ASD risk could support identification of a need for intervention.

Folic acid

The relationship between maternal folic acid intake during pregnancy and the periconceptional period and development of ASD was described by several meeting participants. Randomized trials in the 1990s showed that periconceptional folic acid supplementation can reduce neural tube defects by 70% [43]. Although folic acid fortification policies have decreased the prevalence of neural tube defects [44], many females of childbearing age—and particularly those from vulnerable populations—still have insufficient folic acid intake [45,46].

Folic acid supplementation in early pregnancy also provides behavioral and developmental benefits for the offspring [47–51]. In particular, research shows that maternal folic acid supplementation is associated with reduced risk of ASD development. The CHildhood Autism Risks from Genetics and Environment (CHARGE) population-based case-control study involving 429 children with ASD and 278 typically developing children found that use of vitamins containing folic acid near conception and intake of folic acid from food and supplement sources was associated with reduced prevalence of ASD [52,53]. Similarly, the Markers of Autism Risk in Babies—Learning Early Signs prospective pregnancy cohort study involving 241 younger siblings of children with ASD found that maternal intake of prenatal vitamins near conception was associated with ~50% reduced ASD occurrence in at-risk infants [54]. These findings have been replicated in several large prospective birth cohort studies [55–59]. However, the results of meta-analyses are mixed, with some finding ~50% to 60% reduced risk of ASD and some finding no association [60–64].

There are several possible reasons for the inconsistent findings regarding the relationship between maternal folic acid intake and child ASD development. Research from case-control and prospective studies shows a U-shaped dose–response relationship, with both high and low levels of folic acid intake being associated with increased ASD risk [65]. Of note, most studies compared low and high folate intake and did not analyze excess folate intake as a separate group. When folate subtypes were considered, a higher concentration of unmetabolized folic acid, a synthetic form of folate, but not the natural form typically found in foods, was associated with greater risk of ASD in Black children [66].

Timing of folic acid intake is also critical. The strongest relationship with folic acid intake and ASD risk is during the first month of pregnancy or shortly after conception [53–55,62,67], when epigenetic reprogramming occurs. However, some studies show an association from ≤2 y before pregnancy and after the first trimester [59]. Although use of prenatal vitamins, which contain folic acid, is relatively high among pregnant people in the United States (~78%–92%), gaps remain, with only 55% to 60% of pregnant people reporting use during the critical periods of the first month of pregnancy or first trimester [68].

Inconsistencies in findings regarding the relationship between folic acid supplementation and ASD could also point to interactions of nutritional, genetic, and environmental factors. For example, the association could be influenced by differences in baseline nutritional status, with evidence suggesting a stronger relationship if the mother is not well-nourished during pregnancy [59]. There is also evidence of a stronger association between folic acid supplementation and development of ASD when either the mother or the child has a gene variant associated with less efficient folate metabolism [52,53], and when the mother is exposed to environmental contaminants, with folic acid intake potentially attenuating an increased likelihood of ASD development or symptom severity triggered by environmental contaminants, such as pesticides, air pollution, or phthalates [69–71]. Data from the Boston Birth Cohort also found an association with adequate maternal folate levels and reduced adverse metabolic effects of prenatal exposure to toxic metals [72,73] and maternal smoking [74]. Meeting participants suggested that the most effective strategies to address environmental risks for ASD would combine folic acid supplementation with a reduction in environmental exposures.

Speakers explored potential mechanisms underlying the relationship between folic acid intake and ASD development. Folic acid supplementation may impact ASD development through an impact on DNA methylation [75], which prepares the fetus to adapt to a new environment [76,77]. Nutrition and other environmental impacts could play important roles at key points of development. As folate is a methyl donor, the amount of methyl donors available could play a role in the development of ASD. In both human and animal experimental studies, environmental contaminants affect DNA methylation, and supplemental folic acid has been shown to reverse DNA methylation changes [78–80]. In mice, folate supplementation also countered the DNA hypomethylation in offspring [79]. Near conception, a critical period for folic acid supplementation, dynamic DNA methylation changes occur, in which the methylome is erased and re-established [81,82]. Epigenetic reprogramming prepares the developing fetus for its environment. Placenta epigenetic changes can serve as biomarkers of early gestational events and the biologic pathways that are altered. Based on differences in methylation in the placenta, genetic variation, oxidative stress, and inflammation may all be involved in the mechanistic pathways through which folic acid intake impacts ASD development [83–85].

Future research can improve understanding of the relationships between folic acid intake and ASD development. Animal studies can help to further elucidate the mechanisms, but other animals' brains metabolize folate differently than human brains, reducing the transferability of the results. Although it would be unethical to conduct a randomized trial in humans involving withholding folic acid supplements, future research could test the effects of different amounts, types, and timing of maternal folic acid intake on offspring ASD development.

Microbiome and diet in ASD development

Several speakers described relationships among diet, the gut microbiome, and development of ASD. The human microbiome—bacteria, archaea, fungi, and viruses—serves many essential functions, including fermenting energy substrates, training the immune system, preventing growth of harmful species, producing vitamins, and developing hormones that direct fat storage [86]. Emerging evidence suggests microbial imbalances in both mother and child may be involved in ASD development.

Early life antibiotic use influences microbial composition, often resulting in a proinflammatory profile that can influence later development of chronic immune diseases including allergies and brain disorders [87]. One of the first human studies to suggest a potential gut–ASD connection was an uncontrolled, open-label trial that found 10 children with ASD symptoms treated with the antibiotic vancomycin had improved ASD symptoms short-term that waned long-term [88]. Although other case-control studies have found mixed results, the most recent well-conducted studies found that children with ASD have a different microbiome composition than those without ASD [89], lower prevalence of Bifidobacterium species, and greater prevalence of potentially pathogenic Clostridium-related species [89]. Several potential mechanisms may underlie the microbiome–ASD association. A primary hypothesis is that an overabundance of pathobionts and gram-negative bacterial species containing endotoxins cross the gut barrier and produce inflammatory molecules, which cross the blood-brain barrier and result in neurological effects.

Preclinical studies using genetic, environmental, and idiopathic mouse models of ASD have shown that probiotic supplementation with *L. reuteri* starting at weaning reduces social deficits [90,91]. The beneficial effects of *L. reuteri* involve effects on the vagus nerve and oxytocinergic and dopaminergic signaling in the brain [90,91]. Additional factors such as premature delivery, cesarean section, and the environment may affect patterns of intestinal microbial colonization. Infant exposure to microbes occurs during labor and vaginal delivery. Mother-to-newborn microbial transfer is altered by cesarean section delivery, which has been linked to higher risk of ASD [92]. A Brazilian birth cohort found that infants born by cesarean section have a distinct microbiome structure compared with infants delivered vaginally [93,94]. At 3 mo of age, cesarean-delivered infants have higher relative abundance of pathobionts (e.g., Clostidrium) and lower relative abundance of commensal bacteria (e.g., Bifidobacterium and Bacteroides), compared with vaginally-delivered infants. A similar pattern of microbial colonization has been observed in children with ASD [95]. Birth by cesarean section is associated with a 26% to 33% increased risk of ASD and higher risk of other neurodevelopmental conditions, such as attention-deficit/hyperactivity disorder (ADHD) [92]. It was noted during the meeting that the increase in cesarean births over the past couple of decades may be contributing to a microbiome-dependent increase in ASD prevalence, although other factors could explain the association between cesarean birth and ASD.

Given that ASD may be established in the first 3 y of life [96], influences of microbiota are likely critical during this time period [97]. Meeting participants suggested that longitudinal studies of mother–infant pairs that examine their microbiomes early in life, prior to manifestation of ASD symptoms, could help determine potential causal microbiome–ASD associations. The influence of dietary preferences should be considered as part of this research.

The causal potential of the microbiota in ASD has been suggested from murine studies transferring fecal gut microbiota from individuals with ASD into germ-free mice, resulting in behavioral and molecular changes relevant to this condition [98]. The link of gut microbiota composition and function to ASD symptoms has been corroborated in human studies [99,100], including an uncontrolled, open-label trial of 40 children with ASD in which fecal transplantation from healthy donors correlated with improvements in gastrointestinal symptoms and behavioral measures [101]. The findings from these animal studies and small, nonrandomized human studies suggest that the microbiome may not only be involved in ASD pathogenesis but could also inform ASD-related behaviors.

The evidence on whether a disrupted infant microbiome can be restored to prevent ASD development was reviewed. A preliminary, nonrandomized observational study found that giving infants delivered by cesarean section their mother's own milk with the mother's fecal microbiota helped restore some microbes lost during delivery [102]. The infants receiving the fecal microbiota had higher beneficial Bacteroidales and Bifidobacteria and lower Clostridiales and potential pathogens at 1 to 3 mo of age [102]. A recent longitudinal study examining the developmental profile of fecal microbiota and metabolome in infants with and without a family history of ASD (first- or second-degree relatives) during the critical first 3 y of life revealed altered gut microbiota composition and functionality at 5 mo of age (i.e., before any dietary changes might occur). Infants with a family history of ASD (siblings of children with ASD) exhibited lower levels of beneficial Bifidobacterium species and γ-aminobutyric acid, alongside increased abundance of Clostridium-related species [103]. Notably, these microbiota changes preceded atypical neurodevelopmental trajectories in the elevated-likelihood group, suggesting a potential role for the gut microbiota in later emerging behavioral variability. The absence of major perinatal risk factors, such as preterm birth and antibiotic exposure, in this infant cohort suggests a role for host genetic factors in the early life differences in gut microbiota of infants with elevated likelihood of developing ASD. Recent studies indicate that high-confidence ASD risk genes are expressed in both the developing brain and gut [104], suggesting that genetic variants linked to behavioral symptoms in ASD may contribute to an atypical gut microbiota through alterations in the host gut environment.

A small, nonrandomized trial also found that vaginal seeding may restore some bacterial taxa at 1 mo of age to infants born via cesarean delivery [105]. However, recent results from a small trial ($n = 20$) found that vaginal microbiome seeding *decreases* microbial diversity and alters microbiome composition in cesarean section infants at day 3 and day 30 [106]. As vaginal seeding carries risks and not all studies have found benefits, the American College of Obstetricians and Gynecologists does not recommend vaginal seeding outside of research [107]. Participants suggested the need for a large randomized controlled trial to further understand risks and benefits of vaginal seeding.

Human milk feeding provides benefits for a healthy gut microbiota composition and development of a resilient immune system. Human milk has many components that work together to promote optimal immunonutrition. In preclinical studies, human milk oligosaccharides are beneficial for brain development, potentially through gut microbiome effects [108]. Free amino acids present in human milk have anti-inflammatory capacity and can interact with unique immune system and nerve receptors. The microbes that colonize the infant gut are critical to metabolism of human milk. Human milk oligosaccharides feed infant gut microbes, particularly Bifidobacteria, important for reducing inflammation and strengthening the immune system [109]. Although no studies have reported the impact of maternal diet on the mother's own milk quality in relationship to development of ASD, ongoing research is focused on interrelationships among maternal diet, human milk composition, and immune system health.

Impact of maternal obesity

Another topic of focus was the impact of maternal obesity during pregnancy on the offspring's neurodevelopment [110]. It was noted that maternal obesity, defined as prepregnancy BMI $\geq$30 kg/m^2, affects 29% of pregnancies in the United States [111]. Large-scale national registry studies have reported that maternal obesity is associated with

an increased risk of neurodevelopmental disorders in the offspring, including a 1.5- to 2-fold risk of ASD [110,112–121].

Although the specific mechanisms through which maternal obesity increases risk for neurodevelopmental disorders are unknown [114], human brain imaging studies and animal model studies suggest an intrauterine origin of altered fetal brain development [122,123]. The offspring of pregnancies affected by obesity have been shown to have structural and functional alterations in the brain, including a smaller hippocampus in school-age boys, but not girls [122,123], and altered white matter integrity in both children and adults [124]. In animal models of diet-induced obesity during pregnancy, maternal obesity affected offspring intrauterine brain development, including increased neural progenitor proliferation, altered neuronal differentiation and maturation, and altered DNA methylation patterns [125–128].

Participants discussed several research needs related to maternal obesity and development of ASD, including the relative influences of prepregnancy maternal weight, maternal weight management during pregnancy, and the child's BMI trajectory after birth and the impact of maternal bariatric surgery on ASD risk. Participants also suggested future research examining the influence of birth order on ASD risk. Given that females typically gain weight during their reproductive years [129], they may be more likely to begin a subsequent pregnancy at a higher weight than prior pregnancies. The impact of interpregnancy weight and weight gain and of paternal obesity on outcomes related to ASD development could also be topics for future study.

Food-related toxic chemical exposures

Humans are exposed to chemicals from a variety of food system sources, including through agricultural practices (additives to soil, such as fertilizers, and use of pesticides), food processing (contaminants introduced during harvesting and animal husbandry), and food packaging and transportation. Many of these chemical exposures have neurotoxic consequences and act through diverse pathophysiological pathways in the immune, gut–brain, and endocrine systems, interacting with genetic factors, thus altering the neurodevelopment of neural circuitry and synapses, cell migration, and connectivity [130]. Contaminants discussed include metals, pesticides, and nonpersistent and persistent organic compounds.

Metals that are toxic to humans occur both naturally and through industrial processes. Metals are present in air, soil, and water and can enter the food chain at multiple points from cultivation to processing, packaging, and cooking-related activities. Most biomarkers of metal exposure are measured in matrices such as blood, urine, and hair that capture exposure from multiple sources, an advantage when considering neurological and behavioral impairments [131–135].

Several toxic metals are implicated in the etiology of ASD, including mercury, lead, zinc, and copper [136,137]. A systematic review and meta-analysis examining the link between toxic metals and ASD found 48 relevant case-control studies measuring levels of toxic metals (antimony, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) in whole blood, plasma, serum, red cells, hair, and urine [138], finding several metals were differently present in cases versus controls, but patterns were not consistent across populations.

Many of the active ingredients of pesticides and related agricultural chemicals target living organisms through their nervous systems. A 2014 review comprising 7 epidemiological studies noted that all studies documented an association across all classes of pesticides and ASD risk, with several associations reaching significance [139]. These effects were the largest for exposures in weeks 1 to 7 of pregnancy and postnatally in weeks 4 to 12 [140]. A more recent case-control study drawing on data from the CHARGE study found that proximity to organophosphates during pregnancy was associated with a 60% increase in ASD risk [141]. This risk was amplified for exposures during the third trimester (odds ratio [OR]: 2.0; 95% confidence interval [CI]: 1.1, 3.6), and exposures to chlorpyrifos during the second trimester (OR: 3.3; 95% CI: 1.5, 7.4). Pyrethroid insecticide exposure immediately prior to conception or during the third trimester posed an increased risk for both ASD and developmental delays, with ORs ranging from 1.7 to 2.3.

Compounds found in food packaging, such as phthalates and bisphenol-A (BPA), have been studied in the context of ASD. The role of phthalates in ASD was recently summarized across 7 studies, inclusive of 5 human studies, 3 case-control in design, and 2 cohort studies [142]. One cohort and 2 case-control studies reported an association between phthalates and ASD. Concerning BPA, the published literature is mostly characterized by smaller case-control studies and conflicting findings, reporting associations ranging from none to substantial links with clinical ASD and ASD-related traits [143,144]. BPA has been removed from many children's products, but the toxicity of its replacements is not fully understood.

Organic compounds resistant to environmental degradation accumulate in the environment and food chains for decades with the potential to negatively influence human health [139]. The Stockholm Convention on Persistent Organic Pollutants was ratified in 2001 with the aim of prohibiting these pollutants worldwide. A review summarized the evidence of the potential association between ASD and ASD-relevant phenotypes and persistent organic pollutants for 3 major agents: dichlorodiphenyltrichloroethane, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers [145]. Collectively, these agents have shown adverse endocrine, immune, and neurodevelopmental effects in humans [146]. Studies on PCBs have focused on cognitive skills, demonstrating negative effects on intellectual, motor, and verbal outcomes of relevance to ASD [147,148]. A recent larger case-control study also found that exposure to organochlorine compounds during pregnancy was associated with ASD [149].

Social Influences and Considerations

The meeting featured presentations and discussion about social influences and considerations related to ASD development across the life course. Presentations focused on the relationships between participation in maternal and early childhood nutrition assistance programs and child neurodevelopmental outcomes; the potential impacts of a combination of discrimination, nutritional, and other factors on ASD development; and food selectivity in children with ASD.

Participation in the Special, Supplemental Nutrition Program for Women, Infants, and Children (WIC) and child neurodevelopment

One presentation focused on the relationships between participation in WIC and child neurodevelopmental outcomes, such as development of ASD and related conditions. WIC is a nutrition program for low-income pregnant and postpartum females, infants, and children up to age 5 who are at "nutrition risk." Nutrition risk is defined by statute as including "detrimental or abnormal nutritional conditions detectable by biochemical or anthropometric measures, other documented nutritionally related medical conditions, dietary deficiencies that impair or endanger health, or conditions that predispose persons to inadequate nutritional patterns or nutritionally related medical conditions" [150]. Components of WIC include prescriptions for specific types of

nutritious foods, lactation promotion and support, and referrals to other health and social services.

The results of 5 studies examining WIC participation and child development and cognitive outcomes were presented. The studies found little evidence of an association between WIC participation and these outcomes. No studies specifically examined the impact of the 2009 WIC food package update on child development outcomes, including ASD [151]. However, an earlier study based on 2000–2004 data found that US states with highest WIC participation have lower rates of ASD [152].

A large systematic review examined the relationships between WIC participation and maternal and child health outcomes. The study compared WIC participants with income-eligible nonparticipants and found moderate strength of evidence that WIC participation reduces preterm birth, infant low birth weight, and infant mortality and increases child diet quality, child healthy food group intake, and household healthy food purchasing patterns. It found low strength of evidence that WIC participation increases adherence to recommendations for gestational weight gain, maternal diet quality, preventive care visits, immunizations (for maternal and child participation), child nutrient intake, and child cognitive development (for maternal participation) and has no effect on initiation of human milk feeding, introduction of solid foods prior to 4 mo of age, and communication and adaptive behavior (for maternal WIC participation) [151]. Meeting participants noted that findings of benefits for WIC participation differ from those of the Supplemental Nutrition Assistance Program (SNAP), which provides low-income individuals with cash equivalent to purchase food, with few limitations, whereas WIC provides participants with specific foods regardless of cost. In contrast to WIC, there is much less evidence that SNAP participation improves diet quality [153].

Participants noted that WIC participation addresses income-related health disparities, with equivalent impacts across racial and ethnic subgroups for most outcomes [151,154]. Research to assess the feasibility of developmental screenings, referrals, and increased linkages with Head Start and home visiting programs is ongoing.

Food selectivity in ASD

The meeting explored approaches to managing food selectivity, an issue affecting 46% to 89% of children with ASD [155]. Participants noted that although there is no well-defined definition of food selectivity, it generally involves a combination of food refusal and limited food preferences. A core reason for the food refusal is sensory difficulty. Challenges relate to difficulties with texture, taste, food presentation, olfactory sensitivity, and temperature [156]. Although it was noted that feeding difficulties also occur in typically developing children, they are 5 times as common and often more pronounced in children with ASD [157]. A participant noted that a sudden increase in selective eating could allow for early ASD identification and intervention. Difficulties with food selectivity among children with ASD often persist into adolescence [158].

Confounding by child diet presents methodologic challenges for case-control and cross-sectional ASD studies. Given that feeding challenges are much more common in children with ASD, differences in the microbiome between children with and without ASD could be explained by differences in diet because diet has a major impact on the microbiome. A study that attempted to control for diet in childhood did not find an ASD–microbiome association [159]. However, this study only examined the microbiome after the onset of ASD symptoms. It was noted that these findings may suggest that the genetic and behavioral manifestations of ASD promote the reduction of dietary diversity, and the differences in the gut microbiome between children with ASD and typically developing children may be due to ASD-related dietary preferences, rather than differences in the gut microbiome causing ASD. Participants suggested that future studies examining the microbiome before onset of ASD symptoms could help to better discern the direction of the relationship. The influence of dietary preferences could also be analyzed in future studies examining the microbiome and ASD risk.

Food selectivity is associated with several adverse outcomes, including problematic behaviors, impacts on other family members, poor diet quality, micronutrient deficiencies, and related health outcomes. Challenging behaviors include refusal to come to or stay at the table to eat, parental stress, and adverse influences on the diets of other family members [160]. As the preferred foods are typically less healthy options, food selectivity can lead to poor diet quality, micronutrient deficiencies, higher BMI, and related adverse health outcomes [161]. Common micronutrient deficiencies include vitamin A, vitamin B6, vitamin B12, folate, vitamin C, vitamin D, calcium, iron, zinc, magnesium, and ω-3 fatty acids [161]. Micronutrient deficiencies are associated with adverse health and neurodevelopmental outcomes [162].

Speakers recommended a framework for addressing food selectivity in ASD that is centered around the family and focused on creating trusted parent–child relationships. Suggested strategies for addressing food selectivity in children with ASD include eliciting parental concerns, providing parental education and behavior supports, considering cultural influences of food eating behaviors, increasing child exposure to food options, expanding family food preferences, and utilizing interdisciplinary treatment teams [158,163–166]. Professionals to involve in the interdisciplinary management of food selectivity include occupational therapists, who can address sensory integration difficulties; speech-language pathologists, who can address oral–motor difficulties; dietitians, who can develop individualized diet plans; behavioral therapists, who can address behavioral difficulties; and medical professionals, who can address micronutrient deficiencies [165]. It was suggested that behavioral interventions targeting food selectivity in children with ASD should focus on building healthy habits for the entire family before addressing any sensory issues in the child with ASD.

Cumulative risk through multiple factors

It was noted that many environmental factors associated with ASD occur disproportionately in low-income communities. Thus, many underresourced families are exposed to a disproportionate burden of pollution and other toxicants in areas permanently impaired by environmental damage or economic disinvestment [167]. Race-based housing segregation policies dating to the 1930s have had lasting effects that create correlations between race and geographic areas disproportionately impacted by lead-based paint, environmental contaminants, and food deserts [168–170].

A framework of ASD development based on genetic susceptibility and exposure to an environmental trigger was presented. The framework posits that genetic and environmental factors result in changes in brain development that impact brain function and subsequently cognitive function. Changes in cognitive function lead to behavioral manifestations related to social interaction and communication, including lowered intelligence quotient, ADHD, hearing loss, and nervous system damage [11,171]. Specific windows of opportunity for the environmental trigger include preconception and pregnancy (particularly the first trimester), infancy, and early childhood. For example, nutrition-related factors including inadequate calcium and folate intake can have particularly adverse impacts during the first

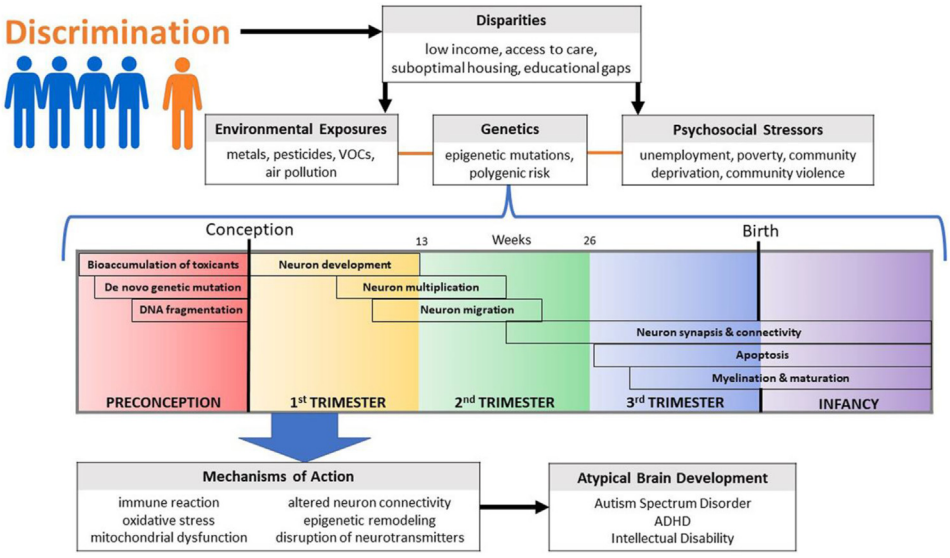

FIGURE 2. A conceptual illustration of joint environmental and psychosocial stressors across differing time points and potential modes of action for atypical neurodevelopment. ADHD, attention-deficit/hyperactivity disorder; VOC, volatile organic compound. Figure reproduced with permission from Dickerson et al. [11].

trimester of pregnancy. Lead can be stored in bone preconception and metabolized during pregnancy. Toxicants can transfer to the child through human milk. Environmental triggers can also include psychosocial stress. These deficiencies and exposures are more common in certain vulnerable populations [11,171].

A multifactor framework, such as that shown in Figure 2 [11], highlights that discrimination, such as through neighborhood segregation, leads to disparities in environmental exposures and psychosocial triggers. These, in turn, can lead to ASD and other neurodevelopmental disorders or subclinical outcomes. Racial, ethnic, and socioeconomic disparities exist in ASD diagnosis in children [172].

Speakers and participants discussed options for improving ASD-related outcomes in the context of social determinants. Community-based participatory research was recommended to identify and develop the best intervention strategies for environmental exposures relevant to specific communities. It was noted that research involving disadvantaged communities is increasingly focused on improving resilience and utilizing public health interventions.

To address delays in ASD diagnosis in low-income communities, it was suggested that brief ASD screenings could be integrated into well-child visits, with referrals to psychologists or other specialists for individuals with abnormal findings. However, participants noted that a follow-up visit with a specialist could incur a long waiting period and require additional time and costs, presenting particular challenges for people in low-income communities who may not be able to afford the cost sharing required for a follow-up visit, the necessary time off from work, transportation, or other social barriers.

Data Sources for ASD Research

The meeting included presentations and discussion on research design and data sources that may be useful for future ASD research. Although there are many ASD epidemiologic and genetic studies with available data, and data from several were presented at the meeting, we provide 3 specific examples, 2 of which are single prospective studies, and the third is a consortium of ASD studies: Genome, Environment, Microbiome and Metabolome in Autism (GEMMA) Project; the Autism Longitudinal Study in the Boston Birth Cohort; and the Environmental influences on Child Health Outcomes (ECHO) study.

The GEMMA Project

The GEMMA (EU Horizon 2020 project: https://www.gemma-project.eu) project is an at-risk longitudinal, observational,

prospective birth cohort for modeling personalized treatments and primary prevention of ASD [173]. The study team, which has 14 European and 2 United States partners, is enrolling a total of 2400 subjects, including 600 at-risk infants, their ASD-affected sibling, and both parents. The study examines prenatal, perinatal, and postnatal events and uses preclinical, clinical, and multiomics analyses. Preclinical analyses include, for example, studies in which stools from children with ASD and typically developing children from the same household are transplanted into mice. Clinical analyses and observational studies involve monitoring children for development of ASD and implementing an interventional arm using a symbiotic formulation when indicators of ASD are present. Multiomics analyses involve microbiome, metabolome, proteome, genome, epigenetic, and lipidomic assessments modeled through artificial intelligence, including machine learning and neural networking to develop a predictive model of ASD development in genetically at-risk infants and to implement personalized interventions for those affected by ASD.

GEMMA addresses the desire expressed by meeting participants for prospective cohort studies that reflect the multidimensional model of ASD development. Meeting participants also expressed an interest in research that moves from examining correlations with ASD development to identification of causal factors and use of a personalized medicine approach. GEMMA's involvement with multiple stakeholders also reflects meeting participants' recommendations for a multidisciplinary approach to ASD research, prevention, and treatment, including involving dietary factors.

Autism Longitudinal Study in the Boston Birth Cohort

The Autism Longitudinal Study in the Boston Birth Cohort [174] was established to improve understanding of the early life factors that impact the chance of developing ASD and other developmental disabilities and how these early life factors shape the developmental trajectory of ASD and developmental disabilities across life stages. Launched in 1998 to assess the environmental and genetic determinants of preterm birth, the Boston Birth Cohort is based at Boston Medical Center, the largest safety net hospital in the greater Boston area, serving predominantly urban, low-income, and Medicaid patients. As of November 2022, the Boston Birth Cohort was ongoing and consisted of ~8700 mother–child pairs. About 60% of participants are Black and 25% are Hispanic. The study design involves multilevel data collection, including a standard questionnaire, in-person study visits and measurements, maternal and child biospecimen collections, review of electronic medical records, and screening for food insecurity and social determinants of health.

Research using the Boston Birth Cohort has been instrumental in identifying relationships between ASD development or associated disorders and a range of early life factors, including maternal obesity, diabetes, and dyslipidemia; maternal and cord metabolome; maternal immune activation, placental inflammation, and preterm birth; maternal intake of micronutrients, including folate, selenium, and vitamin B12; fetal and infant growth; and in utero exposure to acetaminophen [65,66,110,175–184].

Meeting participants suggested that future research could attempt to replicate study findings or improve understanding of mechanisms. Animal studies could also help to increase understanding of the extent to which folate circulating in the blood equates with folate in the brain, which may more directly impact ASD risk.

ECHO study

The ECHO study was launched in 2016 to investigate the influence of early life exposures on child health and development [185]. Of the 69 participating cohorts, 13 have an ASD diagnosis or trait. Participating cohorts reflect the general population of pregnant or postpartum females or oversample those at higher risk of ASD. It was noted that ECHO presents a rich data set to examine questions related to the relationship between diet, microbiome, and ASD risk.

Research Gaps

The second half of the meeting involved 2 series of breakout sessions to identify, discuss, and begin to address research gaps. In the first set of breakout sessions, participants were assigned to 1 of 4 breakout groups. Each group was instructed to identify 3 to 4 research gaps related to the relationships between food, nutrition, and ASD development. Meeting participants then discussed and voted on the overall research priorities.

Table 1 lists the evidence gaps identified by meeting participants, with the research needs determined to be highest priority indicated by

TABLE 1
Evidence gaps identified by meeting participants.

Epidemiology and Biomarker Evidence Gaps
- Assess the epidemiology of ASD through the life course, with a particular emphasis on the first 1000 d, including preconception, pregnancy, and early life.[1]
  - Research should consider the impacts of maternal and paternal nutrition; the maternal oral, vaginal, and fecal microbiome; and other factors on the child's development and identify biomarkers for ASD screening or intervention targets.
- Identify biomarkers of ASD as well as developmental resilience in mothers and children.[1]
- Improve screening and diagnosis of ASD or identification of ASD risk prior to school age.

Environmental and Social Influences Evidence Gaps
- Conduct multidisciplinary research on psychosocial, social, and biological determinants of ASD risk.
- Identify interactions among multiple ASD risk factors, including diet, exposure to pollution or other toxins, and social factors, and their impact on ASD development.[1]
- Examine the impact of a multipronged maternal environmental intervention during pregnancy on offspring ASD risk.[1]
  - The intervention should consider the impact of diet and other factors.
- Use translational and other multidimensional research to assess the extent to and ways in which maternal diet impacts ASD risk.[1]
- Identify social influences and barriers to a healthy diet for individuals with ASD or families with a child with ASD.
  - Research should seek to identify the measures or outcomes that matter most to individuals with ASD and their families.
- Evaluate racial/ethnic, geographic, and other disparities in ASD risk, assessment, diagnosis, care, and outcomes, including risk factors related to maternal and child nutrition.
- Determine the impacts of soil components and soil-related policies on food-based interventions for ASD prevention and treatment.

Quality of Life and Life Course Timing Intervention Evidence Gaps
- Conduct research aimed at improving quality of life for people with ASD across the life course through impacts on diet, supplementation, and targeting the microbiome.[1]
- Identify the optimal life course windows for specific dietary interventions based on microbiome, behavioral, and other considerations.[1]
- Conduct a randomized controlled trial assessing the impact of *Bifidobacteria infantis* supplementation at birth on ASD prevention.

Mechanisms, Pathways, and Biological Processes Evidence Gaps
- Investigate the mechanisms of action of interventions to treat detrimental gut and brain-related ASD problems using human and animal studies.[1]
- Assess the role of the placenta in the communication between the maternal microbiome and the fetal brain using human and animal models.[1]

Abbreviation: ASD, autism spectrum disorder.
[1] Priority research topic identified by meeting participants.

a superscript 1. Evidence gaps identified are categorized into epidemiology and biomarkers; environmental and social influences; quality of life and life course timing interventions; and mechanisms, pathways, and biological processes. Epidemiology and biomarker evidence gaps focused on the epidemiology of ASD through the life course, with a particular emphasis on the preconception, pregnancy, and early life periods; biomarkers of ASD and of developmental resilience; and improvements in ASD diagnosis and risk factor identification earlier in life. Environmental and social influence evidence gaps focused on the psychosocial, social, and biological determinants of ASD risk, including interactions among diet and other risk factors; impacts of maternal diet on ASD risk and dietary and environmental interventions during pregnancy; social influences and barriers to a healthy diet for individuals and families affected by ASD; nutrition-related disparities in ASD risk, assessment, diagnosis, and care; and the impacts of soil components or related policies on food-based interventions related to ASD. Quality of life and life course timing interventions included interventions involving diet, supplementation, and targeting the microbiome aimed at improving quality of life for people with ASD; identification of optimal life course windows for dietary interventions; and a randomized controlled trial on the impact of early life pre/pro/synbiotic supplementation on ASD prevention. Mechanistic and biological process evidence gaps include mechanisms of action of interventions to treat detrimental gut and brain-related ASD symptoms and the role of the placenta in the communication between the maternal gut microbiome and the fetal brain. Although not noted in Table 1, participants suggested that all research proposals should consider disparities in ASD development and risk factors.

Opportunities for Future Research

Following the identification of evidence gaps, meeting participants discussed in small groups potential research proposals to address the priority evidence gaps, and group leaders presented and led discussions on the research proposals. Brief descriptions of the potential research proposals developed by meeting participants are presented in Table 2. Research proposals focus on the epidemiology and biomarkers relevant to the development of ASD during the first 1000 d, including fetal development and infant/child life; multipronged interventions throughout the life course that address outcomes of interest to people with ASD and their families; identification of holobiont-interactive drivers in ASD (the holobiont is a human and its microbes, including those found in the gut microbiome); and interactions among environmental and social factors that impact ASD risk.

TABLE 2
Research proposals developed during scientific meeting by participants to address evidence gaps.

Topic	Study overview	Study description
Epidemiology and biomarkers of the first 1000 d	A large prospective cohort study focused on the epidemiology and biomarkers relevant to the development of ASD during the first 1000 d (including fetal development and the first 2 y of life).	The study would oversample families with a child with ASD. The study design would include robust tissue and biospecimen collection from the mother and father, follow the offspring through childhood, and include long-term follow-up on adolescent and adult outcomes. The study would attempt to identify potential biomarkers for screening and later interventions. People with ASD, their families, and other stakeholder groups would be involved in the study design to ensure it addresses outcomes of interest.
Multipronged ASD interventions tailored to the life course	A 3-part study aimed at designing, prioritizing, and testing multipronged interventions throughout the life course that address outcomes of interest to people with ASD and their families.	The first aim would involve qualitative participatory research with people with ASD and their families and other stakeholders to identify outcomes of interest to them at various life stages. Reviews could then identify and prioritize interventions that address the outcomes. The second aim would be to develop an intervention for each period in the life course in partnership with the ASD community. The specific plans for the intervention would be adapted to the population and time period of interest. The third aim would be to assess the feasibility, implementation, and early efficacy of each intervention, piloting work for future fully powered trials.
Identification of external holobiont-interactive drivers and mechanisms	A 2-part study focused on identification of holobiont[1]-interactive drivers in ASD.	The study would enroll couples in geographic areas with both high and low rates of ASD. The first aim would be to identify external factors, including maternal dietary and environmental exposures, that affect the gut microbiome during pregnancy and drive ASD in at-risk children. Data collection would include longitudinal collection of biospecimens from the mother, father, and any siblings; assessment of diet and medication use by the mother or father; surveillance to identify environmental pollutants and environmental and microbial aspects of the home environment; and follow-up after birth, including brain imaging. The second aim would be to investigate the mechanisms by which the identified external factors influence brain development of the fetus prenatally, with an emphasis on the role of the placenta, and perinatally, with an emphasis on birth modality. The study would use animal models to improve understanding of how maternal environmental and nutritional factors influence brain development in utero, specifically considering the role of the maternal gut microbiome. Mice with a gene mutation known to increase ASD risk would be inoculated

(*continued on next page*)

TABLE 2 (*continued*)

Topic	Study overview	Study description
		with human gut microbiome influenced by identified environmental and nutritional components, and fetal brain development would be examined at multiple stages in pregnancy. The study would examine impacts on the maternal vaginal microbiome and the maternal and paternal gut microbiomes; placental development and function; fetal brain development and sex differences; in utero inflammation; behavior and cognition of the offspring, including any sex differences; and development of the offspring microbiome, including any differences by sex or mode of birth. The study could be followed by maternal dietary intervention studies to address the detrimental effects of the identified environmental, nutritional, and microbial components that negatively influence the holobiont during pregnancy.
Interactions of environmental and social factors	A 3-part study focused on the interactions among environmental and social factors that impact ASD risk.	The study would focus on populations at high risk of ASD and consider the microbiome, diet quality, probiotic use, and exposure to pollutants. The first aim would be to examine the interactions among these and other social and environmental factors that impact ASD risk. The second aim would involve identification and measurement of social and environmental biomarkers of ASD development. In the third aim, observational data from the first 2 parts would be used to develop interventions to address the identified social and environmental ASD risk factors.

Abbreviation: ASD, autism spectrum disorder.
[1] The holobiont is a human and its microbes, including those found in the gut microbiome.

Conclusion

The substantial increase in ASD prevalence over the past half century correlating with dietary changes and other related factors motivates increased research on the relationships among these and other genetic, environmental, and social factors that may play a role in ASD development. Future research can target key prenatal and early life developmental periods and identify biomarkers of elevated ASD risk. Human and animal studies can also improve understanding of the pathways of ASD development and identification of interventions to reduce ASD risk and severity and improve outcomes for individuals and families affected by ASD.

This meeting report summarized key research on the relationships between diet and nutrition-related factors and ASD development presented at a 1-d scientific workshop. The workshop findings serve as a foundation for future prioritization of scientific research to address evidence gaps related to food, nutrition, and ASD. In particular, future scientific meetings or calls for proposals can help to further refine and address the evidence gaps.

Acknowledgments

We thank the following meeting participants for their input and contributions during the discussions, the identification and prioritization of evidence gaps, and development of research proposals to address the priority evidence gaps: Jorge E. Chavarro, Professor of Nutrition and Epidemiology, Harvard T.H. Chan School of Public Health; Sizi Chen, Product Partner, FoundersX Ventures; Martha Forero, Assistant Professor, Department of Public Health and Community Services, Tufts University School of Dental Medicine; Cheryl S. Rosenfeld, Professor, Biomedical Sciences, University of Missouri; Christina Sakai, Associate Professor of Pediatrics, Tufts University School of Medicine; Tammy Scott, Research Assistant Professor, Friedman School of Nutrition Science and Policy, Tufts University; Nicole Shanahan, Founder and President, Bia-Echo Foundation; and Katie Stebbins, Executive Director, Food & Nutrition Innovation Institute. We also thank Kirsten Deuman for her research assistance.

Author contributions

The authors' responsibilities were as follows – MMS: had primary responsibility for writing the article. PO-G, ADK, KL, DM: had primary responsibility for the planning of the meeting on which this report is based; all authors: provided content for and/or edits to the article; and all authors: read and approved the final manuscript.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Melissa Maitin-Shepard reports financial support and travel were provided by Tufts University. Aletta D Kraneveld reports travel was provided by Tufts University Friedman School of Nutrition Science and Policy. Aletta Kraneveld reports a relationship with European Commission that includes: funding grants. Kristen Lyall reports a relationship with Campbell Soup Company that includes: consulting or advisory. Dani Fallin reports travel and writing assistance were provided by Tufts University. Manish Arora reports a relationship with Linus Biotechnology Inc that includes: board membership, employment, and equity or stocks. Alessio Fasano reports a relationship with 9 Meters Biopharma, Inc. that includes: consulting or advisory. Alessio Fasano reports a relationship with Alba Therapeutics Corp that includes: equity or stocks. Alessio Fasano reports a relationship with FARE (Food Allergy Research & Education) that includes: consulting or advisory. Alessio Fasano reports a relationship with Food Is Good, Inc. that includes: consulting or advisory. Alessio Fasano reports a relationship with GlaxoSmithKline that includes: consulting or advisory. Alessio Fasano reports a relationship with Mead Johnson Nutrition that includes: speaking and lecture fees. Alessio Fasano reports a relationship with MilkWayLife Sciences, LLP that includes: consulting or advisory. Alessio Fasano reports a relationship with Nemysis, LTD that includes: consulting or advisory. Alessio Fasano reports a

relationship with Ono Pharmaceutical Co Ltd that includes: consulting or advisory. Alessio Fasano reports a relationship with Precidiag Inc that includes: consulting or advisory. Alessio Fasano reports a relationship with Seed Health, Inc. that includes: consulting or advisory. Alessio Fasano reports a relationship with Topas Therapeutics that includes: consulting or advisory. Alessio Fasano reports a relationship with Viome Life Sciences that includes: consulting or advisory. Alessio Fasano reports a relationship with Vulcan Biologics that includes: consulting or advisory. Noel Mueller reports a relationship with Tiny Health Inc. that includes: board membership and equity or stocks. Aisha S. Dickerson reports financial support was provided by National Institute of Environmental Health Sciences. Aisha S. Dickerson reports financial support was provided by National Institutes of Health Office of the Director. Aisha S. Dickerson reports a relationship with Interagency Autism Coordinating Committee that includes: board membership. Rochellys Diaz Heijtz reports financial support was provided by Karolinska Institute Department of Neuroscience. Rochellys Diaz Heijtz reports a relationship with Karolinska Institute Department of Neuroscience that includes: employment and funding grants. Jeffrey B. Blumberg reports financial support was provided by Tufts University Friedman School of Nutrition Science and Policy. Jeffrey B. Blumberg reports a relationship with Bragg Live Food Products, LLC that includes: consulting or advisory. Jeffrey Blumberg reports being on the scientific advisory board or a consultant for Bragg Live Food Products, LLC; California Prune Board; California Walnut Commission; Cranberry Institute; Good Pharma, LLC; Guiding Stars Licensing Co.; January.ai; Kroger Co.; and Segterra Inc. all outside the submitted work. Rebecca J Schmidt reports financial support was provided by National Institutes of Health. Johan Garssen reports financial support, administrative support, and travel were provided by Utrecht University. Johan Garssen reports financial support, administrative support, and travel were provided by Danone Nutricia Research. Johan Garssen reports a relationship with Utrecht University that includes: employment, funding grants, and non-financial support. Dariush Mozaffarian reports a relationship with National Institutes of Health that includes: funding grants. Dariush Mozaffarian reports a relationship with Gates Foundation that includes: funding grants. Dariush Mozaffarian reports a relationship with The Rockefeller Foundation that includes: funding grants. Dariush Mozaffarian reports a relationship with Vail Innovative Global Research that includes: funding grants. Dariush Mozaffarian reports a relationship with Kaiser Permanente Fund at East Bay Community Foundation that includes: funding grants. Dariush Mozaffarian reports a relationship with Acasti Pharma Inc that includes: consulting or advisory. Dariush Mozaffarian reports a relationship with Barilla that includes: consulting or advisory. Dariush Mozaffarian reports a relationship with Beren Therapeutics that includes: board membership. Dariush Mozaffarian reports a relationship with Brightseed that includes: board membership. Dariush Mozaffarian reports a relationship with Calibrate that includes: board membership and equity or stocks. Dariush Mozaffarian reports a relationship with Elysium Health that includes: board membership. Dariush Mozaffarian reports a relationship with Filtricine that includes: board membership. Dariush Mozaffarian reports a relationship with HumanCo that includes: board membership and equity or stocks. Dariush Mozaffarian reports a relationship with Instacart that includes: board membership. Dariush Mozaffarian reports a relationship with January Inc that includes: board membership. Dariush Mozaffarian reports a relationship with Perfect Day that includes: board membership. Dariush Mozaffarian reports a relationship with Tiny Organics that includes: board membership. Dariush Mozaffarian reports a relationship with Day Two that includes: board membership. Dariush Mozaffarian reports a relationship with Discern Dx that includes: board membership. Dariush Mozaffarian reports a relationship with Season Health that includes: board membership. Dariush Mozaffarian reports a relationship with UpToDate that includes: consulting or advisory.

Funding

Support for the development of this report and the scientific meeting on which it is based was provided by a grant to Tufts University from the Bia-Echo Foundation. The sponsor had no involvement in the planning or execution of the meeting or the development of this report.

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th ed, 2013.
[2] World Health Organization, ICD-11: International Classification of Diseases, 11th Revision [Internet] [cited 17 April, 2023]. Available from: https://icd.who.int/en.
[3] M.J. Maenner, Z. Warren, A. Robinson Williams, E. Amoakohene, A.V. Bakian, D.A. Bilder, et al., Prevalence and characteristics of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring network, 11 sites, United States, 2020, MMWR Surveill. Summ 72 (2) (2023) 1–14, https://doi.org/10.15585/mmwr.ss7202a1.
[4] K. Lyall, L. Croen, J. Daniels, M.D. Fallin, C. Ladd-Acosta, B.K. Lee, et al., The changing epidemiology of autism spectrum disorders, Annu. Rev. Public Health 38 (2017) 81–102, https://doi.org/10.1146/annurev-publhealth-031816-044318.
[5] A. Sanyaolu, C. Okorie, X. Qi, J. Locke, S. Rehman, Childhood and adolescent obesity in the United States: a public health concern, Glob. Pediatr. Health 6 (2019) 2333794X19891305, https://doi.org/10.1177/2333794x19891305.
[6] F. Juul, N. Parekh, E. Martinez-Steele, C.A. Monteiro, V.W. Chang, Ultra-processed food consumption among US adults from 2001 to 2018, Am. J. Clin. Nutr. 115 (1) (2022) 211–221, https://doi.org/10.1093/ajcn/nqab305.
[7] J.J. DiNicolantonio, J. O'Keefe, The importance of maintaining a low omega-6/omega-3 ratio for reducing the risk of autoimmune diseases, asthma, and allergies, Mo, Med. 118 (5) (2021) 453–459.
[8] M. Quinn, J. Halsey, P. Sherliker, H. Pan, Z. Chen, D.A. Bennett, et al., Global heterogeneity in folic acid fortification policies and implications for prevention of neural tube defects and stroke: a systematic review, EClinicalMedicine 67 (2024) 102366, https://doi.org/10.1016/j.eclinm.2023.102366.
[9] C.M. Angolile, B.L. Max, J. Mushemba, H.L. Mashauri, Global increased cesarean section rates and public health implications: a call to action, Health Sci. Rep. 6 (5) (2023) e1274, https://doi.org/10.1002/hsr2.1274.
[10] L. Emberti Gialloreti, L. Mazzone, A. Benvenuto, A. Fasano, A.G. Alcon, A. Kraneveld, et al., Risk and protective environmental factors associated with autism spectrum disorder: evidence-based principles and recommendations, J. Clin. Med. 8 (2) (2019) 217, https://doi.org/10.3390/jcm8020217.
[11] A.S. Dickerson, A.S. Dickerson, Prenatal socioenvironmental exposures and autism spectrum disorder: a web of confusion, Child Dev. Perspect. 17 (1) (2023) 32–38, https://doi.org/10.1111/cdep.12472.
[12] H.E. Vuong, E.Y. Hsiao, Emerging roles for the gut microbiome in autism spectrum disorder, Biol. Psychiatry 81 (5) (2017) 411–423, https://doi.org/10.1016/j.biopsych.2016.08.024.
[13] P. Ashwood, S. Wills, J. Van de Water, The immune response in autism: a new frontier for autism research, J. Leukoc. Biol. 80 (1) (2006) 1–15, https://doi.org/10.1189/jlb.1205707.
[14] R.K. Singh, H.W. Chang, D. Yan, K.M. Lee, D. Ucmak, K. Wong, et al., Influence of diet on the gut microbiome and implications for human health, J. Transl. Med. 15 (1) (2017) 73, https://doi.org/10.1186/s12967-017-1175-y.
[15] Y.E. Borre, G.W. O'Keeffe, G. Clarke, C. Stanton, T.G. Dinan, J.F. Cryan, Microbiota and neurodevelopmental windows: implications for brain disorders, Trends Mol. Med. 20 (9) (2014) 509–518, https://doi.org/10.1016/j.molmed.2014.05.002.

[16] A. Kim, C.R. Zisman, C. Holingue, Influences of the immune system and microbiome on the etiology of ASD and GI symptomology of autistic individuals, Curr. Top. Behav. Neurosci. 61 (2023) 141–161, https://doi.org/10.1007/7854_2022_371.
[17] C. Zhong, J. Tessing, B.K. Lee, K. Lyall, Maternal dietary factors and the risk of autism spectrum disorders: a systematic review of existing evidence, Autism Res 13 (10) (2020) 1634–1658, https://doi.org/10.1002/aur.2402.
[18] Bia-Echo Foundation, Bia-Echo: The creative spirit and life force behind our human capacity will inspire long-lasting and sustainable progress [Internet] [cited 30 October, 2023]. Available from: https://biaecho.org/.
[19] H. Renz, P.G. Holt, M. Inouye, A.C. Logan, S.L. Prescott, P.D. Sly, An exposome perspective: early-life events and immune development in a changing world, J. Allergy Clin. Immunol. 140 (1) (2017) 24–40, https://doi.org/10.1016/j.jaci.2017.05.015.
[20] A.A. Te Velde, T. Bezema, A.H.C. van Kampen, A.D. Kraneveld, B.A. 't Hart, H. van Middendorp, et al., Embracing complexity beyond systems medicine: a new approach to chronic immune disorders, Front. Immunol. 7 (2016) 587, https://doi.org/10.3389/fimmu.2016.00587.
[21] J. Schlechte, I. Skalosky, M.B. Geuking, B. McDonald, Long-distance relationships - regulation of systemic host defense against infections by the gut microbiota, Mucosal Immunol 15 (5) (2022) 809–818, https://doi.org/10.1038/s41385-022-00539-2.
[22] S.P. Wiertsema, J. van Bergenhenegouwen, J. Garssen, L.M.J. Knippels, The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies, Nutrients 13 (3) (2021) 886, https://doi.org/10.3390/nu13030886.
[23] V. Cerovic, S.A. Houston, C.L. Scott, A. Aumeunier, U. Yrlid, A.M. Mowat, et al., Intestinal CD103$^-$ dendritic cells migrate in lymph and prime effector T cells, Mucosal Immunol 6 (1) (2013) 104–113, https://doi.org/10.1038/mi.2012.53.
[24] M.L. Balmer, C.M. Schürch, Y. Saito, M.B. Geuking, H. Li, M. Cuenca, et al., Microbiota-derived compounds drive steady-state granulopoiesis via MyD88/TICAM signaling, J. Immunol. 193 (10) (2014) 5273–5283, https://doi.org/10.4049/jimmunol.1400762.
[25] C.B. Hergott, A.M. Roche, E. Tamashiro, T.B. Clarke, A.G. Bailey, A. Laughlin, et al., Peptidoglycan from the gut microbiota governs the lifespan of circulating phagocytes at homeostasis, Blood 127 (2) (2016) 2460–2471, https://doi.org/10.1182/blood-2015-10-675173.
[26] W. Yang, Y. Cong, Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases, Cell. Mol. Immunol. 18 (4) (2021) 866–877, https://doi.org/10.1038/s41423-021-00661-4.
[27] L.H. Morais, H.L. Schreiber 4th, S.K. Mazmanian, The gut microbiota-brain axis in behaviour and brain disorders, Nat. Rev. Microbiol. 19 (4) (2021) 241–255, https://doi.org/10.1038/s41579-020-00460-0.
[28] P.A. Muller, M. Schneeberger, F. Matheis, P. Wang, Z. Kerner, A. Ilanges, et al., Microbiota modulate sympathetic neurons via a gut-brain circuit, Nature 583 (7816) (2020) 441–446, https://doi.org/10.1038/s41586-020-2474-7.
[29] T. Lajqi, N. Köstlin-Gille, S. Hillmer, M. Braun, S.A. Kranig, S. Dietz, et al., Gut microbiota-derived small extracellular vesicles endorse memory-like inflammatory responses in murine neutrophils, Biomedicines 10 (2) (2022) 442, https://doi.org/10.3390/biomedicines10020442.
[30] T. Pelaseyed, J.H. Bergström, J.K. Gustafsson, A. Ermund, G.M.H. Birchenough, A. Schütte, et al., The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system, Immunol. Rev. 260 (1) (2014) 8–20, https://doi.org/10.1111/imr.12182.
[31] M. Zhang, C. Wu, The relationship between intestinal goblet cells and the immune response, Biosci. Rep. 40 (10) (2020), https://doi.org/10.1042/bsr20201471. BSR20201471.
[32] N. Shi, N. Li, X. Duan, H. Niu, Interaction between the gut microbiome and mucosal immune system, Mil. Med. Res. 4 (2017) 14, https://doi.org/10.1186/s40779-017-0122-9.
[33] S.D. Bilbo, J.M. Schwarz, Early-life programming of later-life brain and behavior: a critical role for the immune system, Front. Behav. Neurosci. 3 (2009) 14, https://doi.org/10.3389/neuro.08.014.2009.
[34] A. Butera, R. De Simone, R.L. Potenza, M. Sanchez, M. Armida, D. Campanile, et al., Effects of a gut-selective integrin-targeted therapy in male mice exposed to early immune activation, a model for the study of autism spectrum disorder, Brain Behav. Immun. 115 (2024) 89–100, https://doi.org/10.1016/j.bbi.2023.09.024.
[35] J.T. Morton, D.M. Jin, R.H. Mills, Y. Shao, G. Rahman, D. McDonald, et al., Multi-level analysis of the gut-brain axis shows autism spectrum disorder-associated molecular and microbial profiles, Nat. Neurosci. 26 (7) (2023) 1208–1217, https://doi.org/10.1038/s41593-023-01361-0.
[36] B. van't Land, G. Boehm, J. Garssen, Breast milk: components with immune modulating potential and their possible role in immune mediated disease resistance, in: R. Watson, S. Zibadi, V. Preedy (Eds.), Dietary Components and Immune Function, Nutrition and Health, Humana Press, Totowa, NJ, 2010, pp. 25–41, https://doi.org/10.1007/978-1-60761-061-8_2.
[37] C.E. Childs, P.C. Calder, E.A. Miles, Diet and immune function, Nutrients 11 (8) (2019) 1933, https://doi.org/10.3390/nu11081933.
[38] A. Meltzer, J. Van de Water, The role of the immune system in autism spectrum disorder, Neuropsychopharmacology 42 (1) (2017) 284–298, https://doi.org/10.1038/npp.2016.158.
[39] J. Marchezan, E.G.A. Winkler Dos Santos, I. Deckmann, R.D.S. Riesgo, Immunological dysfunction in autism spectrum disorder: a potential target for therapy, Neuroimmunomodulation 25 (5–6) (2018) 300–319, https://doi.org/10.1159/000492225.
[40] C. Doenyas, Dietary interventions for autism spectrum disorder: new perspectives from the gut-brain axis, Physiol. Behav. 194 (2018) 577–582, https://doi.org/10.1016/j.physbeh.2018.07.014.
[41] T.S. Dong, A. Gupta, Influence of early life, diet, and the environment on the microbiome, Clin. Gastroenterol. Hepatol. 17 (2) (2019) 231–242, https://doi.org/10.1016/j.cgh.2018.08.067.
[42] M. Bragg, J.E. Chavarro, G.B. Hamra, J.E. Hart, L.P. Tabb, M.G. Weisskopf, et al., Prenatal diet as a modifier of environmental risk factors for autism and related neurodevelopmental outcomes, Curr. Environ. Health Rep 9 (2) (2022) 324–338, https://doi.org/10.1007/s40572-022-00347-7.
[43] MRC Vitamin Study Research Group, Prevention of neural tube defects: results of the Medical Research Council Vitamin Study, Lancet 338 (8760) (1991) 131–137, https://doi.org/10.1016/0140-6736(91)90133-A.
[44] Centers for Disease Control and Prevention, Spina bifida and anencephaly before and after folic acid mandate–United States, 1995-1996 and 1999-2000, MMWR Morb. Mortal. Wkly. Rep. 53 (17) (2004) 362–365.
[45] T.L. Cheng, K.B. Mistry, G. Wang, B. Zuckerman, X. Wang, Folate nutrition status in mothers of the Boston Birth Cohort, sample of a US urban low-income population, Am. J. Public Health. 108 (6) (2018) 799–807, https://doi.org/10.2105/ajph.2018.304355.
[46] A. Osterhues, N.S. Ali, K.B. Michels, The role of folic acid fortification in neural tube defects: a review, Crit. Rev. Food Sci. Nutr. 53 (11) (2013) 1180–1190, https://doi.org/10.1080/10408398.2011.575966.
[47] J. Steenweg-de Graaff, S.J. Roza, E.A. Steegers, A. Hofman, F.C. Verhulst, V.W. Jaddoe, et al., Maternal folate status in early pregnancy and child emotional and behavioral problems: the Generation R Study, Am. J. Clin. Nutr. 95 (6) (2012) 1413–1421, https://doi.org/10.3945/ajcn.111.030791.
[48] C. Roth, P. Magnus, S. Schjølberg, C. Stoltenberg, P. Surén, I.W. McKeague, et al., Folic acid supplements in pregnancy and severe language delay in children, JAMA 306 (14) (2011) 1566–1573, https://doi.org/10.1001/jama.2011.1433.
[49] W. Schlotz, A. Jones, D.I.W. Phillips, C.R. Gale, S.M. Robinson, K.M. Godfrey, Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring, J. Child Psychol. Psychiatry 51 (5) (2010) 594–602, https://doi.org/10.1111/j.1469-7610.2009.02182.x.
[50] J. Julvez, J. Fortuny, M. Mendez, M. Torrent, N. Ribas-Fitó, J. Sunyer, Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort, Paediatr. Perinat. Epidemiol. 23 (3) (2009) 199–206, https://doi.org/10.1111/j.1365-3016.2009.01032.x.
[51] S.J. Roza, T. van Batenburg-Eddes, E.A.P. Steegers, V.W.V. Jaddoe, J.P. Mackenbach, A. Hofman, et al., Maternal folic acid supplement use in early pregnancy and child behavioural problems: the Generation R study, Br. J. Nutr. 103 (3) (2010) 445–452, https://doi.org/10.1017/s0007114509991954.
[52] R.J. Schmidt, R.L. Hansen, J. Hartiala, H. Allayee, L.C. Schmidt, D.J. Tancredi, et al., Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism, Epidemiology 22 (4) (2011) 476–485, https://doi.org/10.1097/ede.0b013e31821d0e30.
[53] R.J. Schmidt, D.J. Tancredi, S. Ozonoff, R.L. Hansen, J. Hartiala, H. Allayee, et al., Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study, Am. J. Clin. Nutr. 96 (1) (2012) 80–89, https://doi.org/10.3945/ajcn.110.004416.
[54] R.J. Schmidt, A.M. Iosif, E. Guerrero Angel, S. Ozonoff, Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings, JAMA Psychiatry 76 (4) (2019) 391–398, https://doi.org/10.1001/jamapsychiatry.2018.3901.
[55] P. Surén, C. Roth, M. Bresnahan, M. Haugen, M. Hornig, D. Hirtz, et al., Association between maternal use of folic acid supplements and risk of autism

spectrum disorders in children, JAMA 309 (6) (2013) 570–577, https://doi.org/10.1001/jama.2012.155925.
[56] J.M. Braun, T. Froehlich, A. Kalkbrenner, C.M. Pfeiffer, Z. Fazili, K. Yolton, et al., Brief report: are autistic-behaviors in children related to prenatal vitamin use and maternal whole blood folate concentrations? J. Autism Dev. Disord. 44 (10) (2014) 2602–2607, https://doi.org/10.1007/s10803-014-2114-x.
[57] J. Steenweg-de Graaff, A. Ghassabian, V.W.V. Jaddoe, H. Tiemeier, S.J. Roza, Folate concentrations during pregnancy and autistic traits in the offspring. The Generation R Study, Eur. J. Public Health 25 (3) (2015) 431–433, https://doi.org/10.1093/eurpub/cku126.
[58] E.A. DeVilbiss, C. Magnusson, R.M. Gardner, D. Rai, C.J. Newschaffer, K. Lyall, et al., Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort: population based cohort study, BMJ 359 (2017) j4273, https://doi.org/10.1136/bmj.j4273.
[59] S.Z. Levine, A. Kodesh, A. Viktorin, L. Smith, R. Uher, A. Reichenberg, et al., Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring, JAMA Psychiatry 75 (2) (2018) 176–184, https://doi.org/10.1001/jamapsychiatry.2017.4050.
[60] L. Iglesias Vázquez, J. Canals, V. Arija, Review and meta-analysis found that prenatal folic acid was associated with a 58% reduction in autism but had no effect on mental and motor development, Acta Paediatr 108 (4) (2019) 600–610, https://doi.org/10.1111/apa.14657.
[61] X. Liu, M. Zou, C. Sun, L. Wu, W. Chen, Prenatal folic acid supplements and offspring's autism spectrum disorder: a meta-analysis and meta-regression, J. Autism Dev. Disord. 52 (2) (2022) 522–539, https://doi.org/10.1007/s10803-021-04951-8.
[62] K.K. Brieger, K.M. Bakulski, C.L. Pearce, A. Baylin, J.F. Dou, J.I. Feinberg, et al., The association of prenatal vitamins and folic acid supplement intake with odds of autism spectrum disorder in a high-risk sibling cohort, the Early Autism Risk Longitudinal Investigation (EARLI), J. Autism Dev. Disord. 52 (6) (2022) 2801–2811, https://doi.org/10.1007/s10803-021-05110-9.
[63] M. Wang, K. Li, D. Zhao, L. Li, The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders in children: a meta-analysis, Mol. Autism. 8 (2017) 51, https://doi.org/10.1186/s13229-017-0170-8.
[64] B.Q. Guo, H.B. Li, D.S. Zhai, S.B. Ding, Association of maternal prenatal folic acid intake with subsequent risk of autism spectrum disorder in children: a systematic review and meta-analysis, Prog. Neuropsychopharmacol. Biol. Psychiatry 94 (2019) 109650, https://doi.org/10.1016/j.pnpbp.2019.109650.
[65] R. Raghavan, A.W. Riley, H. Volk, D. Caruso, L. Hironaka, L. Sices, et al., Maternal multivitamin intake, plasma folate and vitamin B_{12} levels and autism spectrum disorder risk in offspring, Paediatr. Perinat. Epidemiol. 32 (1) (2018) 100–111, https://doi.org/10.1111/ppe.12414.
[66] R. Raghavan, J. Selhub, L. Paul, Y. Ji, G. Wang, X. Hong, et al., A prospective birth cohort study on cord blood folate subtypes and risk of autism spectrum disorder, Am. J. Clin. Nutr. 112 (5) (2020) 1304–1317, https://doi.org/10.1093/ajcn/nqaa208.
[67] M. Bjørk, B. Riedel, O. Spigset, G. Veiby, E. Kolstad, A.K. Daltveit, et al., Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero, JAMA Neurol 75 (2) (2018) 160–168, https://doi.org/10.1001/jamaneurol.2017.3897.
[68] J.F. Dou, L.Y.M. Middleton, Y. Zhu, K.S. Benke, J.I. Feinberg, L.A. Croen, et al., Prenatal vitamin intake in first month of pregnancy and DNA methylation in cord blood and placenta in two prospective cohorts, Epigenetics Chromatin 15 (1) (2022) 28, https://doi.org/10.1186/s13072-022-00460-9.
[69] R.J. Schmidt, V. Kogan, J.F. Shelton, L. Delwiche, R.L. Hansen, S. Ozonoff, et al., Combined prenatal pesticide exposure and folic acid intake in relation to autism spectrum disorder, Environ. Health Perspect. 125 (9) (2017) 097007, https://doi.org/10.1289/ehp604.
[70] A.J. Goodrich, H.E. Volk, D.J. Tancredi, R. McConnell, F.W. Lurmann, R.L. Hansen, et al., Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder, Autism Res 11 (1) (2018) 69–80, https://doi.org/10.1002/aur.1885.
[71] Y. Oulhote, B. Lanphear, J.M. Braun, G.M. Webster, T.E. Arbuckle, T. Etzel, et al., Gestational exposures to phthalates and folic acid, and autistic traits in Canadian children, Environ. Health Perspect. 128 (2) (2020) 27004, https://doi.org/10.1289/ehp5621.
[72] G. Wang, J. DiBari, E. Bind, A.M. Steffens, J. Mukherjee, R.E. Azuine, et al., Association between maternal exposure to lead, maternal folate status, and intergenerational risk of childhood overweight and obesity, JAMA Netw. Open 2 (10) (2019) e1912343, https://doi.org/10.1001/jamanetworkopen.2019.12343.
[73] G. Wang, J. DiBari, E. Bind, A.M. Steffens, J. Mukherjee, T.R. Bartell, et al., In utero exposure to mercury and childhood overweight or obesity: counteracting effect of maternal folate status, BMC Med 17 (1) (2019) 216, https://doi.org/10.1186/s12916-019-1442-2.
[74] B. Zhang, X. Hong, H. Ji, W.Y. Tang, M. Kimmel, Y. Ji, et al., Maternal smoking during pregnancy and cord blood DNA methylation: new insight on sex differences and effect modification by maternal folate levels, Epigenetics 13 (5) (2018) 505–518, https://doi.org/10.1080/15592294.2018.1475978.
[75] K.S. Crider, T.P. Yang, R.J. Berry, L.B. Bailey, Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role, Adv. Nutr. 3 (1) (2012) 21–38, https://doi.org/10.3945/an.111.000992.
[76] P. Hajkova, S. Erhardt, N. Lane, T. Haaf, O. El-Maarri, W. Reik, et al., Epigenetic reprogramming in mouse primordial germ cells, Mech. Dev. 117 (1–2) (2002) 15–23, https://doi.org/10.1016/s0925-4773(02)00181-8.
[77] D.M. Maatouk, L.D. Kellam, M.R.W. Mann, H. Lei, E. Li, M.S. Bartolomei, et al., DNA methylation is a primary mechanism for silencing postmigratory primordial germ cell genes in both germ cell and somatic cell lineages, Development 133 (17) (2006) 3411–3418, https://doi.org/10.1242/dev.02500.
[78] A. Baccarelli, V. Bollati, Epigenetics and environmental chemicals, Curr. Opin. Pediatr. 21 (2) (2009) 243–251, https://doi.org/10.1097/mop.0b013e32832925cc.
[79] D.C. Dolinoy, D. Huang, R.L. Jirtle, Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development, Proc. Natl. Acad. Sci. U. S. A. 104 (32) (2007) 13056–13061, https://doi.org/10.1073/pnas.0703739104.
[80] J. Zhong, O. Karlsson, G. Wang, J. Li, Y. Guo, X. Lin, et al., B vitamins attenuate the epigenetic effects of ambient fine particles in a pilot human intervention trial, Proc. Natl. Acad. Sci. U. S. A. 114 (13) (2017) 3503–3508, https://doi.org/10.1073/pnas.1618545114.
[81] Y. Zhu, J.A. Gomez, B.I. Laufer, C.E. Mordaunt, J.S. Mouat, D.C. Soto, et al., Placental methylome reveals a 22q13.33 brain regulatory gene locus associated with autism, Genome Biol 23 (1) (2022) 46, https://doi.org/10.1186/s13059-022-02613-1.
[82] Y. Zhu, C.E. Mordaunt, D.H. Yasui, R. Marathe, R.L. Coulson, K.W. Dunaway, et al., Placental DNA methylation levels at *CYP2E1* and *IRS2* are associated with child outcome in a prospective autism study, Hum. Mol. Genet. 28 (16) (2019) 2659–2674, https://doi.org/10.1093/hmg/ddz084.
[83] S.A. Smallwood, G. Kelsey, De novo DNA methylation: a germ cell perspective, Trends Genet 28 (1) (2012) 33–42, https://doi.org/10.1016/j.tig.2011.09.004.
[84] Z.D. Smith, M.M. Chan, K.C. Humm, R. Karnik, S. Mekhoubad, A. Regev, et al., DNA methylation dynamics of the human preimplantation embryo, Nature 511 (7511) (2014) 611–615, https://doi.org/10.1038/nature13581.
[85] H. Guo, P. Zhu, L. Yan, R. Li, B. Hu, Y. Lian, et al., The DNA methylation landscape of human early embryos, Nature 511 (7511) (2014) 606–610, https://doi.org/10.1038/nature13544.
[86] F. Bäckhed, H. Ding, T. Wang, L.V. Hooper, G.Y. Koh, A. Nagy, et al., The gut microbiota as an environmental factor that regulates fat storage, Proc. Natl. Acad. Sci. U. S. A. 101 (44) (2004) 15718–15723, https://doi.org/10.1073/pnas.0407076101.
[87] N.A. Ottman, H. Smidt, W.M. de Vos, C. Belzer, The function of our microbiota: who is out there and what do they do? Front. Cell. Infect. Microbiol. 2 (2012) 104, https://doi.org/10.3389/fcimb.2012.00104.
[88] R.H. Sandler, S.M. Finegold, E.R. Bolte, C.P. Buchanan, A.P. Maxwell, M.L. Väisänen, et al., Short-term benefit from oral vancomycin treatment of regressive-onset autism, J. Child Neurol. 15 (7) (2000) 429–435, https://doi.org/10.1177/088307380001500701.
[89] L.K.H. Ho, V.J.W. Tong, N. Syn, N. Nagarajan, E.H. Tham, S.K. Tay, et al., Gut microbiota changes in children with autism spectrum disorder: a systematic review, Gut Pathog 12 (2020) 6, https://doi.org/10.1186/s13099-020-0346-1.
[90] S.A. Buffington, G.V. Di Prisco, T.A. Auchtung, N.J. Ajami, J.F. Petrosino, M. Costa-Mattioli, Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring, Cell 165 (7) (2016) 1762–1775, https://doi.org/10.1016/j.cell.2016.06.001.
[91] M. Sgritta, S.W. Dooling, S.A. Buffington, E.N. Momin, M.B. Francis, R.A. Britton, et al., Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder, Neuron 101 (2) (2019) 246–259.e6, https://doi.org/10.1016/j.neuron.2018.11.018.
[92] T. Zhang, A. Sidorchuk, L. Sevilla-Cermeño, A. Vilaplana-Pérez, Z. Chang, H. Larsson, et al., Association of cesarean delivery with risk of neurodevelopmental and psychiatric disorders in the offspring: a systematic review and meta-analysis, JAMA Netw. Open 2 (8) (2019) e1910236, https://doi.org/10.1001/jamanetworkopen.2019.10236.

[93] N.T. Mueller, H. Shin, A. Pizoni, I.C. Werlang, U. Matte, M.Z. Goldani, et al., Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome, Sci. Rep. 6 (2016) 23133, https://doi.org/10.1038/srep23133.
[94] N.T. Mueller, H. Shin, A. Pizoni, I.C. Werlang, U. Matte, M.Z. Goldani, et al., Delivery mode and the transition of pioneering gut-microbiota structure, composition and predicted metabolic function, Genes (Basel) 8 (12) (2017) 364, https://doi.org/10.3390/genes8120364.
[95] N.T. Mueller, M.G. Dominguez-Bello, L.J. Appel, S.K. Hourigan, 'Vaginal seeding' after a caesarean section provides benefits to newborn children: FOR: does exposing caesarean-delivered newborns to the vaginal microbiome affect their chronic disease risk? The critical need for trials of 'vaginal seeding' during caesarean section, BJOG 127 (2) (2020) 301, https://doi.org/10.1111/1471-0528.15979.
[96] C. Lord, M. Elsabbagh, G. Baird, J. Veenstra-Vanderweele, Autism spectrum disorder, Lancet 392 (10146) (2018) 508–520, https://doi.org/10.1016/s0140-6736(18)31129-2.
[97] J. Roswall, L.M. Olsson, P. Kovatcheva-Datchary, S. Nilsson, V. Tremaroli, M.C. Simon, et al., Developmental trajectory of the healthy human gut microbiota during the first 5 years of life, Cell Host Microbe 29 (5) (2021) 765–776.e3, https://doi.org/10.1016/j.chom.2021.02.021.
[98] G. Sharon, N.J. Cruz, D.W. Kang, M.J. Gandal, B. Wang, Y.M. Kim, et al., Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice, Cell 177 (6) (2019) 1600–1618.e17, https://doi.org/10.1016/j.cell.2019.05.004.
[99] D.W. Kang, J.B. Adams, D.M. Coleman, E.L. Pollard, J. Maldonado, S. McDonough-Means, et al., Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota, Sci. Rep. 9 (1) (2019) 5821, https://doi.org/10.1038/s41598-019-42183-0.
[100] D.W. Kang, J.B. Adams, A.C. Gregory, T. Borody, L. Chittick, A. Fasano, et al., Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study, Microbiome 5 (1) (2017) 10, https://doi.org/10.1186/s40168-016-0225-7.
[101] N. Li, H. Chen, Y. Cheng, F. Xu, G. Ruan, S. Ying, et al., Fecal microbiota transplantation relieves gastrointestinal and autism symptoms by improving the gut microbiota in an open-label study, Front. Cell. Infect. Microbiol. 11 (2021) 759435, https://doi.org/10.3389/fcimb.2021.759435.
[102] K. Korpela, O. Helve, K.L. Kolho, T. Saisto, K. Skogberg, E. Dikareva, et al., Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores normal gut microbial development: a proof-of-concept study, Cell 183 (2) (2020) 324–334.e5, https://doi.org/10.1016/j.cell.2020.08.047.
[103] S. Zuffa, P. Schimmel, A. Gonzalez-Santana, C. Belzer, J. Knol, S. Bölte, et al., Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder, Transl. Psychiatry. 13 (1) (2023) 257, https://doi.org/10.1038/s41398-023-02556-6.
[104] B. Niesler, G.A. Rappold, Emerging evidence for gene mutations driving both brain and gut dysfunction in autism spectrum disorder, Mol. Psychiatry. 26 (5) (2021) 1442–1444, https://doi.org/10.1038/s41380-020-0778-5.
[105] M.G. Dominguez-Bello, K.M. De Jesus-Laboy, N. Shen, L.M. Cox, A. Amir, A. Gonzalez, et al., Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer, Nat. Med. 22 (3) (2016) 250–253, https://doi.org/10.1038/nm.4039.
[106] N.T. Mueller, M.K. Differding, H. Su, J. Wang, S. Levy, V. Deopujari, et al., Maternal bacterial engraftment in multiple body sites of cesarean section born neonates after vaginal seeding-a randomized controlled trial, mBio 14 (3) (2023) e0049123, https://doi.org/10.1128/mbio.00491-23.
[107] American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with Kurt R, MD Wharton, L Meredith, MD Birsner, Vaginal Seeding [Internet]. Committee Opinion No. 725. Nov 2017. Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/11/vaginal-seeding. (Accessed 14 April 2023).
[108] C.A. Moubareck, Human milk microbiota and oligosaccharides: a glimpse into benefits, diversity, and correlations, Nutrients 13 (4) (2021) 1123, https://doi.org/10.3390/nu13041123.
[109] R.P. Singh, J. Niharika, K.K. Kondepudi, M. Bishnoi, J.M.R. Tingirikari, Recent understanding of human milk oligosaccharides in establishing infant gut microbiome and roles in immune system, Food Res. Int. 151 (2022) 110884, https://doi.org/10.1016/j.foodres.2021.110884.
[110] M. Li, M.D. Fallin, A. Riley, R. Landa, S.O. Walker, M. Silverstein, et al., The association of maternal obesity and diabetes with autism and other developmental disabilities, Pediatrics 137 (2) (2016) e20152206, https://doi.org/10.1542/peds.2015-2206.
[111] A.K. Driscoll, E.C.W. Gregory, Increases in prepregnancy obesity: United States, 2016-2019, NCHS Data Brief, 2020, pp. 1–8, 392.
[112] C.H. Andersen, P.H. Thomsen, E.A. Nohr, S. Lemcke, Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children, Eur. Child Adolesc. Psychiatry. 27 (2) (2018) 139–148, https://doi.org/10.1007/s00787-017-1027-6.
[113] L. Dodds, D.B. Fell, S. Shea, B.A. Armson, A.C. Allen, S. Bryson, The role of prenatal, obstetric and neonatal factors in the development of autism, J. Autism Dev. Disord. 41 (7) (2011) 891–902, https://doi.org/10.1007/s10803-010-1114-8.
[114] T. Tarui, A. Rasool, P. O'Tierney-Ginn, How the placenta-brain lipid axis impacts the nutritional origin of child neurodevelopmental disorders: focus on attention deficit hyperactivity disorder and autism spectrum disorder, Exp. Neurol. 347 (2022) 113910, https://doi.org/10.1016/j.expneurol.2021.113910.
[115] S.L. Matias, M. Pearl, K. Lyall, L.A. Croen, T.V.E. Kral, D. Fallin, et al., Maternal prepregnancy weight and gestational weight gain in association with autism and developmental disorders in offspring, Obesity (Silver Spring) 29 (9) (2021) 1554–1564, https://doi.org/10.1002/oby.23228.
[116] G.C. Windham, M. Anderson, K. Lyall, J.L. Daniels, T.V.E. Kral, L.A. Croen, et al., Maternal pre-pregnancy body mass index and gestational weight gain in relation to autism spectrum disorder and other developmental disorders in offspring, Autism Res 12 (2) (2019) 316–327, https://doi.org/10.1002/aur.2057.
[117] K.J. Varcin, J.P. Newnham, A.J.O. Whitehouse, Maternal pre-pregnancy weight and autistic-like traits among offspring in the general population, Autism Res 12 (1) (2019) 80–88, https://doi.org/10.1002/aur.1973.
[118] K.D. Getz, M.T. Anderka, M.M. Werler, S.S. Jick, Maternal pre-pregnancy body mass index and autism spectrum disorder among offspring: a population-based case-control study, Paediatr. Perinat. Epidemiol. 30 (5) (2016) 479–487, https://doi.org/10.1111/ppe.12306.
[119] B.G. Moss, D.C. Chugani, Increased risk of very low birth weight, rapid postnatal growth, and autism in underweight and obese mothers, Am. J. Health Promot. 28 (3) (2014) 181–188, https://doi.org/10.4278/ajhp.120705-quan-325.
[120] L.C. Reynolds, T.E. Inder, J.J. Neil, R.G. Pineda, C.E. Rogers, Maternal obesity and increased risk for autism and developmental delay among very preterm infants, J. Perinatol 34 (9) (2014) 688–692, https://doi.org/10.1038/jp.2014.80.
[121] P. Krakowiak, C.K. Walker, A.A. Bremer, A.S. Baker, S. Ozonoff, R.L. Hansen, et al., Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders, Pediatrics 129 (5) (2012) e1121–e1128, https://doi.org/10.1542/peds.2011-2583.
[122] X. Ou, K.M. Thakali, K. Shankar, A. Andres, T.M. Badger, Maternal adiposity negatively influences infant brain white matter development, Obesity (Silver Spring) 23 (5) (2015) 1047–1054, https://doi.org/10.1002/oby.21055.
[123] X. Li, A. Andres, K. Shankar, R.T. Pivik, C.M. Glasier, R.H. Ramakrishnaiah, et al., Differences in brain functional connectivity at resting state in neonates born to healthy obese or normal-weight mothers, Int. J. Obes. (Lond.) 40 (12) (2016) 1931–1934, https://doi.org/10.1038/ijo.2016.166.
[124] J. Verdejo-Román, L. Björnholm, R.L. Muetzel, F.J. Torres-Espínola, J. Lieslehto, V. Jaddoe, et al., Maternal prepregnancy body mass index and offspring white matter microstructure: results from three birth cohorts, Int. J. Obes. (Lond). 43 (10) (2019) 1995–2006, https://doi.org/10.1038/s41366-018-0268-x.
[125] G.Q. Chang, V. Gaysinskaya, O. Karatayev, S.F. Leibowitz, Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity, J. Neurosci. 28 (46) (2008) 12107–12119, https://doi.org/10.1523/jneurosci.2642-08.2008.
[126] M.D. Niculescu, D.S. Lupu, High fat diet-induced maternal obesity alters fetal hippocampal development, Int. J. Dev. Neurosci. 27 (7) (2009) 627–633, https://doi.org/10.1016/j.ijdevneu.2009.08.005.
[127] E.K. Stachowiak, M. Srinivasan, M.K. Stachowiak, M.S. Patel, Maternal obesity induced by a high fat diet causes altered cellular development in fetal brains suggestive of a predisposition of offspring to neurological disorders in later life, Metab. Brain Dis. 28 (4) (2013) 721–725, https://doi.org/10.1007/s11011-013-9437-8.
[128] N.M. Grissom, C.T. Herdt, J. Desilets, J. Lidsky-Everson, T.M. Reyes, Dissociable deficits of executive function caused by gestational adversity are linked to specific transcriptional changes in the prefrontal cortex, Neuropsychopharmacology 40 (6) (2015) 1353–1363, https://doi.org/10.1038/npp.2014.313.
[129] Y.C. Yang, C.E. Walsh, M.P. Johnson, D.W. Belsky, M. Reason, P. Curran, et al., Life-course trajectories of body mass index from adolescence to old age: racial and educational disparities, Proc. Natl. Acad. Sci. U. S. A. 118 (17) (2021) e2020167118, https://doi.org/10.1073/pnas.2020167118.

[130] P. Grandjean, P.J. Landrigan, Neurobehavioural effects of developmental toxicity, Lancet Neurol 13 (3) (2014) 330–338, https://doi.org/10.1016/s1474-4422(13)70278-3.
[131] A.P. Sanders, B. Claus Henn, R.O. Wright, Perinatal and childhood exposure to cadmium, manganese, and metal mixtures and effects on cognition and behavior: a review of recent literature, Curr. Environ. Health Rep 2 (3) (2015) 284–294, https://doi.org/10.1007/s40572-015-0058-8.
[132] B. Claus Henn, B.A. Coull, R.O. Wright, Chemical mixtures and children's health, Curr. Opin. Pediatr. 26 (2) (2014) 223–229, https://doi.org/10.1097/mop.0000000000000067.
[133] L.S. Jackson, Chemical food safety issues in the United States: past, present, and future, J. Agric. Food Chem. 57 (18) (2009) 8161–8170, https://doi.org/10.1021/jf900628u.
[134] A. Borchers, S.S. Teuber, C.L. Keen, M.E. Gershwin, Food safety, Clin. Rev. Allergy Immunol. 39 (2) (2010) 95–141, https://doi.org/10.1007/s12016-009-8176-4.
[135] A. Maher, A. Nowak, Chemical contamination in bread from food processing and its environmental origin, Molecules 27 (17) (2022) 5406, https://doi.org/10.3390/molecules27175406.
[136] N. Zaks, C. Austin, M. Arora, A. Reichenberg, Elemental dysregulation in psychotic spectrum disorders: a review and research synthesis, Schizophr. Res. 233 (2021) 64–71, https://doi.org/10.1016/j.schres.2021.06.015.
[137] P. Curtin, C. Austin, A. Curtin, C. Gennings, M. Arora, (for the Emergent Dynamical Systems Group), K. Tammimies, et al., Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder, Sci. Adv. 4 (5) (2018) eaat1293, https://doi.org/10.1126/sciadv.aat1293.
[138] A. Saghazadeh, N. Rezaei, Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury, Prog. Neuropsychopharmacol. Biol. Psychiatry. 79 (Pt B) (2017) 340–368, https://doi.org/10.1016/j.pnpbp.2017.07.011.
[139] S. Bölte, S. Girdler, P.B. Marschik, The contribution of environmental exposure to the etiology of autism spectrum disorder, Cell. Mol. Life Sci. 76 (7) (2019) 1275–1297, https://doi.org/10.1007/s00018-018-2988-4.
[140] A.E. Kalkbrenner, R.J. Schmidt, A.C. Penlesky, Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence, Curr. Probl. Pediatr. Adolesc. Health Care. 44 (10) (2014) 277–318, https://doi.org/10.1016/j.cppeds.2014.06.001.
[141] J.F. Shelton, E.M. Geraghty, D.J. Tancredi, L.D. Delwiche, R.J. Schmidt, B. Ritz, et al., Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study, Environ. Health Perspect. 122 (10) (2014) 1103–1109, https://doi.org/10.1289/ehp.1307044.
[142] M. Ejaredar, E.C. Nyanza, K. Ten Eycke, D. Dewey, Phthalate exposure and childrens neurodevelopment: a systematic review, Environ. Res. 142 (2015) 51–60, https://doi.org/10.1016/j.envres.2015.06.014.
[143] M.H. Rahbar, H.M. Swingle, M.A. Christian, M. Hessabi, M. Lee, M.R. Pitcher, et al., Environmental exposure to dioxins, dibenzofurans, bisphenol A, and phthalates in children with and without autism spectrum disorder living near the Gulf of Mexico, Int. J. Environ. Res. Public Health. 14 (11) (2017) 1425, https://doi.org/10.3390/ijerph14111425.
[144] E.P. Harris, H.A. Allardice, A.K. Schenk, E.F. Rissman, Effects of maternal or paternal bisphenol A exposure on offspring behavior, Horm, Behav. 101 (2018) 68–76, https://doi.org/10.1016/j.yhbeh.2017.09.017.
[145] B.S. Ye, A.O.W. Leung, M.H. Wong, The association of environmental toxicants and autism spectrum disorders in children, Environ. Pollut. 227 (2017) 234–242, https://doi.org/10.1016/j.envpol.2017.04.039.
[146] I. Hertz-Picciotto, H. Park, M. Dostal, A. Kocan, T. Trnovec, R. Sram, Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development, Basic Clin. Pharmacol. Toxicol. 102 (2) (2008) 146–154, https://doi.org/10.1111/j.1742-7843.2007.00190.x.
[147] S.L. Schantz, J.J. Widholm, D.C. Rice, Effects of PCB exposure on neuropsychological function in children, Environ. Health Perspect. 111 (3) (2003) 357–576, https://doi.org/10.1289/ehp.5461.
[148] P.W. Stewart, E. Lonky, J. Reihman, J. Pagano, B.B. Gump, T. Darvill, The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children, Environ. Health Perspect. 116 (10) (2008) 1416–1422, https://doi.org/10.1289/ehp.11058.
[149] K. Lyall, L.A. Croen, A. Sjödin, C.K. Yoshida, O. Zerbo, M. Kharrazi, et al., Polychlorinated biphenyl and organochlorine pesticide concentrations in maternal mid-pregnancy serum samples: association with autism spectrum disorder and intellectual disability, Environ. Health Perspect. 125 (3) (2017) 474–480, https://doi.org/10.1289/ehp277.
[150] D.R. Whitford, WIC Nutrition Risk Criteria [Internet], in: WIC Policy Memorandum 2011-5, May 20, 2011. Available from: https://www.fns.usda.gov/wic/nutrition-risk-criteria. (Accessed 14 April 2023).
[151] L.E. Caulfield, W.L. Bennett, S.M. Gross, K.M. Hurley, S.M. Ogunwole, M. Venkataramani, et al., Maternal and child outcomes associated with the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), Report No.: 22-EHC019, Agency for Healthcare Research and Quality (US), Rockville, MD, 2022, https://doi.org/10.23970/ahrqepccer253.
[152] R.J. Shamberger, Autism rates associated with nutrition and the WIC program, J. Am. Coll. Nutr. 30 (5) (2011) 348–353, https://doi.org/10.1080/07315724.2011.10719978.
[153] T. Andreyeva, S. Tripp, M.B. Schwartz, Dietary Quality of Americans by Supplemental Nutrition Assistance Program Participation Status A Systematic Review, Am J Prev Med 49 (4) (2015) 594–604, https://doi.org/10.1016/j.amepre.2015.04.035.
[154] M. Venkataramani, S.M. Ogunwole, L.E. Caulfield, R. Sharma, A. Zhang, S.M. Gross, et al., Maternal, infant, and child health outcomes associated with the Special Supplemental Nutrition Program for Women, Infants, and Children: a systematic review, Ann. Intern. Med. 175 (10) (2022) 1411–1422, https://doi.org/10.7326/m22-0604.
[155] J.R. Ledford, D.L. Gast, Feeding problems in children with autism spectrum disorders, Focus Autism Other Dev. Disabl. 21 (3) (2006) 153–166, https://doi.org/10.1177/10883576060210030401.
[156] P.G. Williams, N. Dalrymple, J. Neal, Eating habits of children with autism, Pediatr. Nurs. 26 (3) (2000) 259–264.
[157] W.G. Sharp, R.C. Berry, C. McCracken, N.N. Nuhu, E. Marvel, C.A. Saulnier, et al., 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 (9) (2013) 2159–2173, https://doi.org/10.1007/s10803-013-1771-5.
[158] L.G. Bandini, C. Curtin, S. Phillips, S.E. Anderson, M. Maslin, A. Must, Changes in food selectivity in children with autism spectrum disorder, J. Autism Dev. Disord. 47 (2) (2017) 439–446, https://doi.org/10.1007/s10803-016-2963-6.
[159] C.X. Yap, A.K. Henders, G.A. Alvares, D.L.A. Wood, L. Krause, G.W. Tyson, et al., Autism-related dietary preferences mediate autism-gut microbiome associations, Cell 184 (24) (2021) 5916–5931.e17, https://doi.org/10.1016/j.cell.2021.10.015.
[160] C. Curtin, K. Hubbard, S.E. Anderson, E. Mick, A. Must, L.G. Bandini, Food selectivity, mealtime behavior problems, spousal stress, and family food choices in children with and without autism spectrum disorder, J. Autism Dev. Disord. 45 (10) (2015) 3308–3315, https://doi.org/10.1007/s10803-015-2490-x.
[161] Y. Shmaya, S. Eilat-Adar, Y. Leitner, S. Reif, L. Gabis, Nutritional deficiencies and overweight prevalence among children with autism spectrum disorder, Res. Dev. Disabil. 38 (2015) 1–6, https://doi.org/10.1016/j.ridd.2014.11.020.
[162] F.E. Viteri, H. Gonzalez, Adverse outcomes of poor micronutrient status in childhood and adolescence, Nutr. Rev. 60 (5 Pt 2) (2002) S77–S83, https://doi.org/10.1301/00296640260130795.
[163] C.T. Lukens, A.H. Silverman, Systematic review of psychological interventions for pediatric feeding problems, J. Pediatr. Psychol 39 (8) (2014) 903–917, https://doi.org/10.1093/jpepsy/jsu040.
[164] W.G. Sharp, T.L. Burrell, D.L. Jaquess, The Autism MEAL Plan: a parent-training curriculum to manage eating aversions and low intake among children with autism, Autism 18 (6) (2014) 712–722, https://doi.org/10.1177/1362361313489190.
[165] K. Peterson, V. Ibañez, Food selectivity and autism spectrum disorder: guidelines for assessment and treatment, Teach. Except. Child. 50 (6) (2018) 322–332, https://doi.org/10.1177/0040059918763562.
[166] K.A. Schreck, K. Williams, Food preferences and factors influencing food selectivity for children with autism spectrum disorders, Res. Dev. Disabil. 27 (4) (2006) 353–363, https://doi.org/10.1016/j.ridd.2005.03.005.
[167] R.D. Bullard, Sacrifice zones: the front lines of toxic chemical exposure in the United States, Environ. Health Perspect. 119 (6) (2011) A266.
[168] K.T. Jackson, Crabgrass Frontier: The Suburbanization of the United States, Oxford University Press, New York, 1987.
[169] E.K. Lee, G. Donley, T.H. Ciesielski, I. Gill, O. Yamoah, A. Roche, et al., Health outcomes in redlined versus non-redlined neighborhoods: a systematic review and meta-analysis, Soc. Sci. Med. 294 (2022) 114696, https://doi.org/10.1016/j.socscimed.2021.114696.
[170] M. Li, F. Yuan, Historical redlining and food environments: a study of 102 urban areas in the United States, Health Place 75 (2022) 102775, https://doi.org/10.1016/j.healthplace.2022.102775.
[171] A.S. Dickerson, S. Frndak, M. DeSantiago, A. Mohan, G.S. Smith, Environmental exposure disparities and neurodevelopmental risk: a review,

Curr. Environ. Health Rep. 10 (2) (2023) 73–83, https://doi.org/10.1007/s40572-023-00396-6.
[172] B.S. Aylward, D.E. Gal-Szabo, S. Taraman, Racial, ethnic, and sociodemographic disparities in diagnosis of children with autism spectrum disorder, J. Dev. Behav. Pediatr. 42 (8) (2021) 682–689, https://doi.org/10.1097/dbp.0000000000000996.
[173] J. Troisi, R. Autio, T. Beopoulos, C. Bravaccio, F. Carraturo, G. Corrivetti, et al., Genome, Environment, Microbiome and Metabolome in Autism (GEMMA) study design: biomarkers identification for precision treatment and primary prevention of autism spectrum disorders by an integrated multi-omics systems biology approach, Brain Sci 10 (10) (2020) 743, https://doi.org/10.3390/brainsci10100743.
[174] C. Pearson, T. Bartell, G. Wang, X. Hong, S.A. Rusk, L. Fu, et al., Boston Birth Cohort profile: rationale and study design, Precis. Nutr. 1 (2) (2022) e00011, https://doi.org/10.1097/pn9.0000000000000011.
[175] B.Y. Park, R. Yao, E. Tierney, M. Brucato, X. Hong, G. Wang, et al., The association between maternal lipid profile after birth and offspring risk of autism spectrum disorder, Ann. Epidemiol. 53 (2021) 50–55.e1, https://doi.org/10.1016/j.annepidem.2020.08.009.
[176] A.S.E. Lee, Y. Ji, R. Raghavan, G. Wang, X. Hong, C. Pearson, et al., Maternal prenatal selenium levels and child risk of neurodevelopmental disorders: a prospective birth cohort study, Autism Res 14 (12) (2021) 2533–2543, https://doi.org/10.1002/aur.2617.
[177] R. Raghavan, M.D. Fallin, X. Hong, G. Wang, Y. Ji, E.A. Stuart, et al., Cord and early childhood plasma adiponectin levels and autism risk: a prospective birth cohort study, J. Autism Dev. Disord. 49 (1) (2019) 173–184, https://doi.org/10.1007/s10803-018-3688-5.
[178] C. Holingue, M. Brucato, C. Ladd-Acosta, X. Hong, H. Volk, N.T. Mueller, et al., Interaction between maternal immune activation and antibiotic use during pregnancy and child risk of autism spectrum disorder, Autism Res 13 (12) (2020) 2230–2241, https://doi.org/10.1002/aur.2411.
[179] Y. Ji, R.E. Azuine, Y. Zhang, W. Hou, X. Hong, G. Wang, et al., Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood, JAMA Psychiatry 77 (2) (2020) 180–189, https://doi.org/10.1001/jamapsychiatry.2019.3259.
[180] R. Raghavan, B.B. Helfrich, S.R. Cerda, Y. Ji, I. Burd, G. Wang, et al., Preterm birth subtypes, placental pathology findings, and risk of neurodevelopmental disabilities during childhood, Placenta 83 (2019) 17–25, https://doi.org/10.1016/j.placenta.2019.06.374.
[181] A.A. Panjwani, Y. Ji, J.W. Fahey, A. Palmer, G. Wang, X. Hong, et al., Maternal dyslipidemia, plasma branched-chain amino acids, and the risk of child autism spectrum disorder: evidence of sex difference, J. Autism Dev. Disord. 50 (2) (2020) 540–550, https://doi.org/10.1007/s10803-019-04264-x.
[182] A.A. Panjwani, Y. Ji, J.W. Fahey, A. Palmer, G. Wang, X. Hong, et al., Maternal obesity/diabetes, plasma branched-chain amino acids, and autism spectrum disorder risk in urban low-income children: evidence of sex difference, Autism Res 12 (10) (2019) 1562–1573, https://doi.org/10.1002/aur.2177.
[183] M. Brucato, C. Ladd-Acosta, M. Li, D. Caruso, X. Hong, J. Kaczaniuk, et al., Prenatal exposure to fever is associated with autism spectrum disorder in the Boston Birth Cohort, Autism Res 10 (11) (2017) 1878–1890, https://doi.org/10.1002/aur.1841.
[184] R. Raghavan, B. Zuckerman, X. Hong, G. Wang, Y. Ji, D. Paige, et al., Fetal and infancy growth pattern, cord and early childhood plasma leptin, and development of autism spectrum disorder in the Boston Birth Cohort, Autism Res 11 (10) (2018) 1416–1431, https://doi.org/10.1002/aur.2011.
[185] E.A. Knapp, A.M. Kress, C.B. Parker, G.P. Page, K. McArthur, K.K. Gachigi, et al., The Environmental influences on Child Health Outcomes (ECHO)-wide cohort, Am. J. Epidemiol. 192 (8) (2023) 1249–1263, https://doi.org/10.1093/aje/kwad071.