

# Nutritional Epidemiology Research in the Field of Autism Spectrum Disorders—A Review

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## ABSTRACT

Autism Spectrum Disorders (ASD) is a heterogeneous condition with a complex and unresolved epi-genetic etiology in which the contribution of maternal diet and children's feeding problems raise increasing interest. Nutritional epidemiology research applied to ASD offers the perspective of a better understanding of its etiology and the possibility of implementing prevention strategies.

## Keywords

Autism Spectrum Disorders, Nutritional Epidemiology, dietary pattern, maternal diet, dietary behaviour disorders,

## Introduction

Autism Spectrum Disorder (ASD) is defined as a neurodevelopmental disorder, characterized by the association of abnormalities in social interaction, in communication and restricted or repetitive thought and behavior patterns [1]. This particularly severe and long-lasting condition affects 1 % of the population worldwide, with a 30% prevalence increase over the last decade [2]. ASD not only places a severe emotional strain on families but is an economic burden as well. The absence of diagnostic biomarkers, its heterogeneous clinical manifestations and the high rates of comorbidity including intellectual disabilities, psychiatric and neurological disorders make identification of etiological risk factors considerably harder. To date, ASD is a highly heritable condition but current genetic studies explain only a small proportion of this heritability and generally involve multiple genes, each with a small effect. It has actually been estimated that the heritability of ASD is between 50% and 80% [3,4] leaving a substantial

proportion of contribution to the non-heritable risk factors of ASD risk [5]. In the past years, possible gene environment interactions have been hypothesized to play a role in ASD through epigenetic underpinning mechanisms [6]. Epigenetics modulates gene expression by histone acetylation, DNA methylation, chromatin remodelling or micro RNAs mediated inhibition, without affecting DNA sequences [7], and is influenced by environmental factors. However its exact underpinning mechanisms in ASD pathophysiology are not identified so far [8]. All this, has enhanced an increased interest to assess the extent to which environmental factors and life style habits are associated with increased risk of ASD, its clinical phenotype and the severity of the core symptoms of ASD [9]. Amongst these non-genetic factors, we believe it of importance to further explore the role of nutrition and diet in ASD. The potential importance of prenatal diet in the aetiopathology of neurodevelopmental disorders including ASD and the high prevalence in children with ASD of dietary behaviour disorders (including food

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selectivity and food intolerance) linked to autistic traits lead to consider nutrition and diet as cornerstones in ASD etiology [10]. In addition, the daily exposure of dietary intakes combined to the fact that diet is a highly modifiable factor-offering therefore the possibility to implement primary and secondary prevention strategies with no or limited side effects- reinforce the urgency to understand how and when, which dietary factors impacts ASD risk and ASD clinical trajectories. However the multi-facetted aspect of diet makes it a complex exposure in relation to ASD outcomes, ranging from understanding the metabolic and biological role of nutrients in processes leading to ASD development, to the understanding of the social, cultural and clinical underpinnings of dietary behaviour and their association with ASD trajectories. Here we propose a short overview of these aspects and, based on the study-based knowledge, some suggestions for future research directions of nutritional epidemiology in the field of ASD.

■ Prenatal maternal dietary exposure and risk of ASD

Maternal diet is essential for fetal neurodevelopment [11-13]. Studies carried out both in animal models and humans

showed associations between maternal nutrient deprivation and the development of various neuropsychiatric disorders in offspring including Attention deficit and Hyperactivity Disorder [14], schizophrenia [15], as well as anxiety and depression [16]. Nutritional deficiencies are particularly common during pregnancy due to increased metabolic demands imposed by a growing placenta, fetus and maternal tissues [17] and have been shown to influence brain development in terms of structure and function [18]. Given that ASD results from early brain development alterations and aberrant neural connectivity [19], the possibility that maternal nutrition influences ASD risk is therefore biologically possible.

Epidemiological studies assessing the association between prenatal diet and risk of ASD in offspring examined, whether deficiencies or excess in specific nutrients/foods were associated with an increased risk of ASD in offspring using mainly observational and case-control studies. Table 1 summarizes hypothesis and potential mechanisms underlying the association between these specific nutrients and ASD.

A majority of studies investigated the potential etiological role of folate status in the development

**Table 1: Summary of nutrients/foods for which observational studies assessed association between their level/intake during gestational period and the risk of ASD in offspring.**

Nutrients or foods whose deficiency has been hypothesized to increase the risk of ASD	
	Main underlying mechanisms
<b>Folic acid</b>	A maternal deficiency of methyl donors - such as folates and other nutrients involved in homocysteine - on DNA hypomethylation in the brains can induce a modification in gene expression controlling the fetal brain development and sustains the plausible importance of prenatal folate status on the risk of developing ASD [20,21].
<b>Vitamin D</b>	Vitamin D's properties to reduce neuroglial activation and neuroinflammation (by its role in up-regulating production of anti-oxidant) to contribute to DNA repair genes, and to induce T regulatory cells may have a role in reducing autoimmune conditions [22]. All of this process could therefore contribute to link vitamin D to ASD risk [23].
<b>PUFA, Omega 3/Omega 6, proxies of PUFA: fish oil, fish intakes and seafood</b>	PUFAs (Omega 3 and 6) play an important role in various neurodevelopmental processes. The links associating PUFAs with ASD[24] involve the myelination process [25], synapse formation [26], BDNF expression levels [27] and the GABAergic transmission [28].
<b>Iron deficiencies</b>	Iron is crucial to early neurodevelopment. In the brain, iron contributes to neurotransmitter production, myelination, and immune function dysregulation- three pathways involved in ASD [29].
Nutrients or foods for whose high intakes has been hypothesized to increase the risk of ASD	
	Main underlying mechanisms
<b>Foods containing methanol (aspartame and processed fruit juice)</b>	Congenital malformation and behavioral abnormalities were observed in children of women exposed to methanol [30] According to the Centers for Disease Control and Prevention "methanol may cause birth defects of the central nervous system in humans" [31], however the exact mechanism by which methanol induced neurological damage and might be related to ASD development remains unclear [31].
<b>Fat products (high fat diet)</b>	Maternal obesity and high fat diet (HFD) are hypothesized to impact neural development and the regulation of offspring behavior [16]. High fat consumption during pregnancy has been associated with activation of many of the same inflammatory cytokines that are found to be elevated during gestation in mothers of children with ASD [10,16,32,33]. Maternal HFD consumption might also impact offspring neural development indirectly by modifying maternal behavior toward the infant, which has also been shown to induce changes in neural pathways critical in regulating behavior (though serotonergic [34], dopaminergic [35], and melanocortineric pathways [36]).

of ASD but the findings have been mixed [5,20,37-39]. The heterogeneity in methods estimating the levels of folates (retrospective self-report data versus blood measure, lack of information on duration, dose or exposition windows, background nutritional contexts of the countries), the quality and precision of ASD diagnosis as well as other methods limitations including study design, accounting for other nutrients involved in homocysteine pathway, the adjustment for potential confounders and presence of moderators such as carrying specific gene variants might contribute to explain the lack of consistent evidence linking prenatal folate to ASD risk. Other lines of studies examined whether prenatal PUFA were associated with ASD risk. [24,39,40] Some focused on PUFA  $\Omega 3$  and PUFA  $\Omega 6$  [40] others on the ratio of  $\Omega 3$  on  $\Omega 6$  [24], while two other studies considered proxy measures of PUFA by examining intakes of fish oil supplement or fish /seafood intakes [39,40]. Here again, the mixed findings reported might be attributable to the heterogeneity of the exposures. Despite growing evidence linking ASD with gestational iron [5,29] or vitamin D deficiencies [41,42], maternal diet with excess of high fat [43], and food rich in methanol (mainly aspartame and processed fruit juice) [31] and xenobiotics dietary exposition [44], firm conclusions on the association between levels in these nutritional compounds during pregnancy in relation to ASD risk cannot be formulated given the too small number of observational studies for each compound, and, therefore requires further investigation.

Beyond the methodological limitations mentioned above, further explanations can be proposed as they may have contributed to inconsistencies in the evidence of a role of prenatal nutrients on ASD. First, although a potential beneficial effect of some nutrients exposure during pregnancy on the ASD development may exist, the effect of single nutrients may be too small to be detected [45]. Indeed, as people are not eating individual nutrients or individual foods, but meals which consist of complex combinations of nutrients which interact with one another [45], it appears that focusing on individual nutrients or food may provide an incomplete understanding of the relationship between diet and multi-etiological diseases such as ASD.

Accordingly, based on hypothesis that epigenetics mechanisms in intrauterine environment are associated with offspring health status, a recent

systematic review of randomized case control studies showed that supplementing maternal diet with micronutrients does not affect the DNA methylation patterns in neonates [46]. However this study highlights possible strong interactions of maternal diet supplementation with body mass index -that partly reflects overall diet quality and quantity-and with smoking habits -that have been showed to be associated with dietary behaviours.

To conclude, more emphasis needs to be given to the influence of overall diet assessed through dietary patterns on ASD as it offers the possibility to assess the cumulative and synergistic effects of nutrients. While this overall diet approach has been implemented for more than a decade in the field of depression, contributing to the evidence of the importance of nutrition and diet in depression prevention [47], it is urgent to export it in the field of ASD.

#### ■ Feeding disorders, putative physiological pathways, and their clinical implications in ASD children

Feeding disorders are frequently reported in children with ASD. Even if its prevalence estimation varies highly across studies (from 13 to 89 %) [48, 49], a fivefold increase of the feeding disorders has been reported in children with ASD compared to those without [50]. Food selectivity is the most frequent feeding disorder [51] and encompasses all form of food refusal such as having a restricted repertoire of foods or a frequent intake of a single type of food defined as a function of their nutritional components or their sensory characteristics [52]. In ASD, food selectivity often involves (i) strong preferences for carbohydrates, snacks, and/or processed foods while rejecting fruits and vegetables [53,54]; and (ii) particular attention to texture and taste [55]. While sensory sensitivity [48,56,57] as well as repetitive and ritualistic behaviours [58]—two common ASD traits—have been proposed to explain the food selectivity in ASD children [48,56,57], the extent to which food selectivity influenced ASD clinical symptoms, their severity and their long-term trajectories remains to be further examined [55]. Despite the lack of well-phenotype prospective cohorts allowing investigating the complex diet-ASD outcomes associations, several mechanistic-based arguments support the importance of food selectivity on ASD clinical symptoms. Some involved mitochondrial dysfunctions whose higher prevalence has been described in ASD

population compared to general population [59,60], but a majority involved the micro biome gut brain axis [61,62] as illustrated in **Figure 1**.

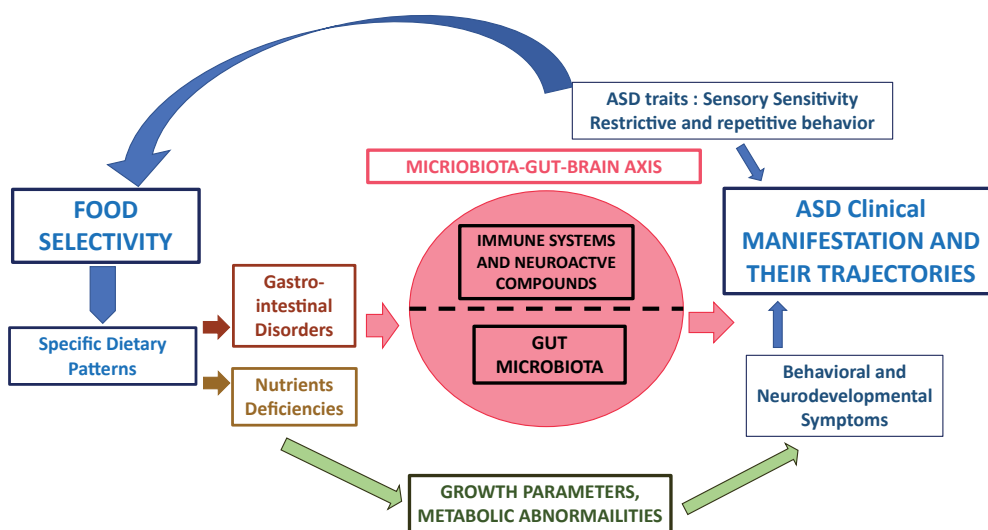
Indeed, several lines of studies suggested that food selectivity has been described to contribute to gastrointestinal disorders[50]-a prominent symptoms in ASD children [63,64], whose occurrence has been correlated to ASD severity [64]. While gastrointestinal tract regulates the homeostasis of its gut microbiota [10], a strong association between -gut microbiota imbalance-named intestinal dysbiosis - and gastrointestinal disorders has been evidence on one side, and, on the other side, this intestinal dysbiosis has been described as a “*fundamental mechanism linking ASD to the gut*” [61,65]. Indeed it allows metabolites product by certain microbiota to cross the gut barrier leading to gut inflammation and to affect the neurodevelopment and brain function though neuroinflammation process [66]. Regarding ASD specifically, it has been shown that neuroactive compounds produced by some microbiota can (i) influence neurotransmitters regulation and oxytocin expression level [67,68] (ii) activate enteric neuron and affect brain function via the vagus nerve with a bidirectional dimension and (iii) activate the gut immune cells leading to a release of pro-inflammatory cytokines involved in ASD [61,69]. While intestinal dysbiosis has been evidenced by many studies in ASD children [61], gastro-intestinal permeability and inflammation is also suspected to be involved in ASD [70]. Children diet can influence the intestinal dysbiosis, in particular intakes of carbohydrates

whose digestion is disrupted in ASD [71]. In addition microbiota is partially inherited from the mother [72]. At birth, gut microbiota is very poor. Its composition and diversity increase will depend on the birth delivery mode (vaginal birth or Caesarean section) [72], the infant term at birth [73], and also the infant alimentation mode (breast or artificial milk) [74]. It is usually admitted that microbiota is established at about 3 old.

However, studies assessing the link between food selectivity, gastrointestinal disorders, children intestinal dysbiosis, and their related effect on intestinal permeability and intestinal inflammation and maternal factors influencing post-natal microbiota composition, has never been explored in an observational framework, neither in regards to the clinical features and developmental trajectories of ASD children.

Beyond the fact that food selectivity can be a significant stress factor for families with a negative impact on quality of life [55], food selectivity and the associated dietary patterns lead to higher risks of nutritional deficiencies (including calcium, protein, vitamin D, vitamin A and vitamin B12 in ASD children[50,51,75,76] placing these children at risk for growth (bone development) [77] metabolic and neuro-developmental disorders [55] which might have deleterious impact on ASD symptoms trajectories.

This exciting field of research linking diet and nutrition to ASD has led parents and pediatricians to settle dietary interventions based on food restrictions (such gluten free casein free



**Figure 1:** Hypothesis linking food selectivity to ASD outcomes.

diet, ketogenic diet) as well as supplementation of nutrients and pro-/prebiotics targeting the microbiome-gut brain axis. Despite the little evidence supporting the effectiveness of most of these intervention [78], their use are increasingly widespread. However some authors have called attention to the possibility that some of these intervention may actually increase some nutrient deficiencies (such as calcium in dairy restricted diet) or mask an even greater risk of compromised dietary status (after a vitamin supplementation) [50].

Given the complex and multi-etiological nature of ASD, and its highly heterogeneous phenotype, a better understanding is needed on the long-term effect of dietary manipulation on nutritional and metabolic status on one hand, and, on the second hand, on biological processes and ASD outcomes trajectories.

## CONCLUSION

In conclusion, to face the challenge of primary and secondary prevention of ASD based on intervention on diet, more knowledge is needed on maternal nutrition during pregnancy and ASD development in offspring and the impact

of food disorders in children with ASD on their clinical trajectories. The accumulating evidence of the involvement of the microbiome-gut-brain axis in ASD etiology, combined with the fact that 50% of the microbial changes can be attributed to diet, strongly support enhanced holistic nutritional epidemiology research programs in the field on ASD. In addition, the key role of gene-environment interactions in ASD through epigenetics mechanisms [6], that are highly influenced by environmental factors such as nutrition [79], reinforce the need to set up research programs based on well-phenotype prospective cohorts. Those programs are required to further understand the links between food dietary behaviours (disorders and patterns) and (i) long term nutritional status, (ii) the composition and function of gut microbiota, (iii) neuroinflammation and stress oxidative processes [80], (iv) the better understanding of epigenetics mechanisms and (v) the clinical symptoms of ASD, their comorbidities and their trajectories. This approach is essential to target the setting up of efficient personalized dietary interventions to prevent ASD and its severity and to allow transition from an empirical ASD clinical medicine to an exact medical science.

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