# Gastrointestinal Symptoms in Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder that presents with restrictive, repetitive patterns of behavior, interests, and activities, and/or deficits in communication and social interactions, which typically manifest within the first three years of life. Individuals with ASD frequently have comorbidities and they are at greater risk of experiencing co-occurring gastrointestinal (GI) symptoms, including constipation, diarrhea, and abdominal pain.

Keywords: autism spectrum disorders ; gastrointestinal symptoms ; comorbidity ; regression ; language and communication ; severity ; challenging behavior ; psychopathology ; sleep problems ; sensory issues ; autism symptoms

## 1. Introduction

### 1.1. Gastrointestinal Symptoms in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that presents with restrictive, repetitive patterns of behavior, interests, and activities, and/or deficits in communication and social interactions, which typically manifest within the first three years of life [1]. Individuals with ASD frequently have comorbidities [2] and they are at greater risk of experiencing co-occurring gastrointestinal (GI) symptoms, including constipation, diarrhea, and abdominal pain [3]. GIS are experienced by between 9 and 91% of children with ASD, and individuals with GIS have a lower quality of life compared to that of those with no GIS [4]. GIS can cause pain and distress and individuals who have little to no communication skills and may not be able to tell their caregivers that they are in pain [5]. Abdominal pain may also act as a trigger for challenging behavior [6]. Challenging behaviors are more frequent in children with ASD who also experience abdominal pain, diarrhea, and constipation. Additionally, individuals with ASD with GIS can be more irritable, withdrawn, or hyperactive compared to those without GIS [7][8]. Abdominal pain and constipation have also been found to predict challenging behavior, the presence of diarrhea predicts tantrum behavior, and nausea predicts worrying/depression and avoidant behavior [9]. In addition, children with sleep abnormalities are more likely to have GI problems than those who have good sleep quality [10]. Chronic GI problems have also been associated with higher levels of sensory over-responsivity [11].

There is growing evidence that GI disorders can arise due to genetic and environmental risk factors for ASD [12][13]. However, the etiology of GIS in ASD remains poorly understood [14]. A detailed understanding of the nature of GIS and how they are associated with co-occurring conditions is required to facilitate the diagnosis of ASD and the treatment of GIS [15].

A literature review by Mannion and Leader examined twenty-eight studies that focused on the relationship between GIS and developmental regression, language, ASD severity, challenging behavior, comorbid psychopathology, sleep problems, and sensory issues [4]. The term regression, in relation to ASD, refers to the loss of previously used or developed skills such as motor, social, and/or language skills [16]. Mannion and Leader [4] identified in 2014 that contradictory evidence existed about the prevalence of GIS in relation to language regression, communication, and ASD severity. For example, children with ASD who present with language regression experience more GIS than those without language regression [17] and yet, a history of regression is not significantly associated with current and past GIS [18][19]. In relation to communication, Gorrindo et al. [20] found that younger, more socially impaired, and nonverbal children have an increased likelihood of constipation. In contrast, Chandler et al. [18] and Williams et al. [21] found no difference between the verbal ability of children with and without GIS. Similar contradictions are evident regarding whether the presence and frequency of GIS are associated with ASD symptom severity. Some studies found that GIS are related to the severity of ASD [22], whereas other research found current or previous GIS have no significant association with ASD severity [18]. To address these contradictions, Mannion and Leader [4] argued that more rigorously designed studies were needed to identify the

risk factors of GI disorders, atypical presentations of GI disorders in ASD, and subpopulations within ASD that experience GIS.

## 2. The Prevalence and the Nature of GIS

Studies vary regarding the proportion of children with ASD in samples reported to experience at least one GIS. The prevalence of GIS in autistic samples has been reported to be 30–37.4% [23][24] and 82.4% in the previous three months [25]. Whereas Khalil et al. [26] reported that all their autistic sample ($n$ = 58) had at least one GIS. In contrast, a large epidemiological study involving $n$ = 1244 children with ASD found GIS were reported for 43.1% of children with ASD, aged 2–5 years.

The studies in this entry found that children with ASD are significantly more likely to experience GIS than control groups and children with typical development (TD) [8][27][28]. Chaidex et al. [8] found children with ASD were at least three times more likely to experience a higher frequency of most GIS than children with TD. This finding was supported by a large prospective study that examined GIS frequency in ASD ($n$ = 195) in comparison to TD ($n$ = 4095) and children with other developmental disabilities (DD) ($n$ = 4636) [28]. In this conducted research, mothers were twice as likely to report GIS in children with ASD than in those with DD and TD. Children with ASD aged 6–18 months were more likely than those with TD to report constipation (adjusted odds ratio (aOR), 2.7; 95%CI, 1.9–3.8; $p < 0.001$) and food allergy/intolerance (aOR, 1.7; 95%CI, 1.1–2.6; $p = 0.01$). Parents of children with ASD aged 18–36 months were more likely to report diarrhea (aOR, 2.3; 95%CI, 1.5–3.6; $p < 0.001$), constipation (aOR, 1.6; 95%CI, 1.2–2.3; $p < 0.01$), and food allergy/intolerance (aOR, 2.0; 95%CI, 1.3–3.1; $p < 0.01$).

There is contradictory evidence regarding whether the prevalence of GIS differs according to gender. Several studies have reported no significant differences in gender, for children with and without GIS [29][30][31]. However, other studies have reported gender differences in the frequency of GIS. Babinska et al. [27] found GIS more common in girls with ASD than in boys (97.1% to 87.6% 2 = 13.57, $p = 0.009$), and 70.6% of girls and 44.5% of boys experienced GIS several times weekly or every day. Mazefsky et al. [32] also found that a significantly higher proportion of females than males had GIS, $p < 0.05$.

The evidence suggests that the prevalence of symptoms is not associated with the age of children with ASD. No difference in the prevalence of GIS was noted after adjusting for age [8][14], and younger and older children had similar rates of four common types of GIS (p's > 0.05) [14]. Furthermore, GIS persist over time for individuals as they increase in age [27]. Bresnahan et al. [28] found GIS that existed between the ages of 6 to 18 months were also present between 18 and 36 months. Change in GIS over time has also been examined to assess whether comorbid symptoms persist or change and to determine if a relationship exists between family medical history, history of autoimmune diseases, and child comorbid conditions [33]. This follow-up study was conducted two years after the initial research took place in 2013. The original study had involved $n$ = 89 children and adolescents, and the follow-up included $n$ = 56 of the original children. Results of the follow-up indicated that GIS continued in 84.4% of participants. However, there was a significant difference between overeating at baseline and at two-year follow-up when overeating had become more severe. The majority of participants (92.9%) presented with a family history of autoimmune disease which was most commonly osteoarthritis, psoriasis, and hypothyroidism. They also reported a relationship between thyroid disorders and GIS.

The type of GIS experienced by children with ASD can be divided into those that affect the upper and lower GI tract, and more generalized GI discomfort/pain. The evidence regarding the prevalence of GIS affecting the upper GI tract reveals that reflux was found in 5.5% of participants [34], but in half of a sample of children with ASD ($n$ = 18) who had experienced reflux, this symptom had resolved in children aged 25–98 months [8]. Nausea was reported in 23.2% [14] and 27.9% [25] of the samples. Whereas vomiting was reported in between 4.2% and 11.4% of the samples [34][31]. Symptoms affecting the lower GI tract include constipation, diarrhea, and pain on stooling. Constipation occurred in 22.1–24.1% of children with ASD in some samples [34][29] and 47.1–65% in other samples [14][27][25][31]. Pain on stooling affected between 7.4% and 29.5% of two samples of children with ASD [29][31]. The prevalence of diarrhea symptoms ranged between 10.6% and 29.7% [14][26][34] and 40.4–64.7% [25][31]. Khalil et al. [26] also noted that 86.2% of their sample experienced offensive stools. Symptoms of discomfort and pain throughout the GI tract were described as stomachache and/or abdominal pain and bloating. These symptoms were reported to affect between 22.9% and53.7% [14][25][31] and 24.3–44.3% [34][31], respectively. Chaidex et al. [8] investigated how GIS are combined in individuals. They reported that when individuals experienced one or more symptoms, diarrhea and constipation did not tend to be experienced in the same individuals. Only nine children with ASD were reported to have both diarrhea and constipation in the previous three months. In contrast, constipation co-occurred with other GIS in the same children, and 29 children had diarrhea in combination with other GIS.

Several studies have reported the number of GIS types experienced by individual children with ASD. Ferguson et al. [14] found that the number of GIS ranged from one to four, with an average number of 1.66 (SD = 0.880). In other studies, the number of individuals with two symptoms ranged from 8.3T to 22.1% [25][34]; three symptoms 3–22.1% [25][34]; four or more symptoms 2.6–22% [25][34]. GIS were experienced several times a week or daily by 47.6% of children with ASD [27]. Neuhaus et al. [34] found severe abdominal pain in 5.1% of their autistic sample, whereas Prosperi et al. [29] reported that 25.8% experienced at least one severe GIS.

## 3. GIS and ASD Severity

Several studies have found that ASD severity is unrelated to GIS [35][26][32][31]. Khalil et al. [26] found a positive but not significant relationship between GIS and ASD severity. Jiang et al. [35] also found no association between small samples of age and gender-matched groups of children with ASD aged 17–37 months, with ($n$ = 28) and without GIS ($n$ = 28). However, Yang et al. [24] found that children with and without GIS had significantly different levels of social interaction and stereotyped behaviors.

Further evidence of the relationship between GIS and ASD symptoms and the existence of a gut–immune–brain axis was provided by studies that have investigated differences in the gut microbiota composition of children with ASD and the presence of GIS. Rose et al. [36] investigated differences in biological signatures in terms of immune dysfunction and microbiota composition in a sample of children with ASD ($n$ = 102) aged from 3 to 12 years old. The results showed the microbiota composition of the children with GIS differed from that of those without GIS and they produced increased levels of mucosa-relevant cytokines. Rose et al. concluded that this suggested that chronic gut inflammation plays a part in ASD pathogenesis. Tomova et al. [37] also provided evidence that the gut microbiota plays a role in ASD. They identified changes in the fecal microbiota in children with ASD to determine its role in the development of GI disorders and other manifestations of ASD. The fecal microflora of a small sample of children with ASD ($n$ = 10), siblings ($n$ = 9), and healthy children ($n$ = 10) was investigated, and parental questionnaires were used to collect data on GIS. The fecal microbiota of the children with ASD showed a significant decrease of the Bacteroidetes/Firmicutes ratio, and an elevated amount of Lactobacillus spp. Results also showed a trend in the incidence of elevated *Desulfovibrio* spp. in children with ASD. In addition, there was a very strong association of the amount of *Desulfovibrio* spp. with the severity of ASD according to the Autism Diagnostic Interview (ADI) restricted/repetitive behavior subscale score [38]. The participants demonstrated a strong positive correlation of ASD severity with the severity of GI dysfunction. Supplementing the diet with probiotics normalized the Bacteroidetes/Firmicutes ratio, *Desulfovibrio* spp., and the amount of Bifidobacterium spp. in feces of children with ASD. Shaahan et al. [39] also evaluated the efficacy and tolerability of a probiotic in children with ASD ($n$ = 30; 5–9 years; mean age (84.77 ± 16.37 months)). In this small trial with no placebo group, assessors were unblinded, and participants were receiving behavioral therapy. Children with ASD were gender/age-matched with healthy controls who were relatives. Three probiotic strains of Lactobacillus acidophilus were administered for 12 weeks. After the treatment period, there were significant improvements in GIS with reductions in constipation (42.5%), diarrhea (37.5%), abdominal pain (60%), flatulence (57%), and improved stool consistency (16.6%). There were also significant improvements in ASD severity concerning speech and language communication, sociability, sensory cognitive awareness, health physical behavior.

Long-term improvements on GIS and ASD symptoms have also been found following interventions designed to normalize gut microbiota using microbiota transfer therapy (MTT). Kang et al. [40] investigated the safety and tolerability of MTT and its effects on microbiota, GIS, and other ASD-related symptoms. The study involved participants with ASD ($n$ = 18) aged 7 to 17 years. Treatment involved a two-week antibiotic, a bowel cleanse, and then an extended fecal microbiota transplant (FMT). The results indicated an 80% reduction of GIS at the end of treatment, with improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. These improvements persisted for eight weeks after treatment. Clinical assessments demonstrated that the behavioral symptoms of ASD improved significantly and that these remained improved at eight weeks follow-up. Kang et al. [41] report that these improvements were maintained two years after the treatment phase was completed. Grimaldi et al. [42] conducted a small double-blind placebo RCT that examined multiple interventions. Participants were randomly assigned for six weeks to a prebiotic and exclusion diet ($n$ = 12) or a placebo and exclusion diet, or a prebiotic and unrestricted diet ($n$ = 18). Those taking the prebiotic and exclusion diet had significantly lower abdominal pain ($p < 0.05$), bowel movements ($p < 0.001$), a significant increase of Lachnospiraceae family, significant changes in fecal and urine metabolites, and reduced antisocial behavior. Furthermore, the exclusion diet and prebiotic group had a higher abundance of B. Longum. Grimaldi et al. suggested that a synergistic effect on behavior resulted from the combination of prebiotic and casein/gluten-free exclusion diet.

There is some evidence that suggests the relationship between GIS and ASD severity may be impacted by the presence or absence of developmental delay, and which GIS is being examined. Chaidex et al. [8] compared children with ASD who

were with and without developmental delay. They found that GIS did not significantly differ between groups regarding total GIS. However, there was a higher occurrence of vomiting in children with ASD without developmental delay, whereas vomiting was infrequently reported in children with ASD with developmental delay. In contrast, children with more severe ASD symptoms had 10% more frequent diarrhea (16.1% vs. 6.4% $p = 0.002$) than those with fewer ASD symptoms.

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