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Gastrointestinal Problems in Children with Autism, Developmental Delays or Typical Development

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Abstract

To compare gastrointestinal (GI) problems among children with: (1) autism spectrum disorder (ASD), (2) developmental delay (DD) and (3) typical development (TD), GI symptom frequencies were obtained for 960 children from the CHildhood Autism Risks from Genetics and Environment (CHARGE) study. We also examined scores on five Aberrant Behavior Checklist (ABC) subscales comparing ASD children with high versus low frequency GI symptoms. Compared to TD children, those with ASD [aOR 7.92 (4.89–12.85)] and DD [aOR 4.55 (2.51–8.24)] were more likely to have at least one frequent GI symptom. Restricting to ASD children, those with frequent abdominal pain, gaseousness, diarrhea, constipation or pain on stooling scored worse on irritability, social withdrawal, stereotypy, and hyperactivity compared with children having no

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frequent GI symptoms. Frequent GI problems affect young children with ASD and DD more commonly than those with TD. Maladaptive behaviors correlate with GI problems, suggesting these comorbidities require attention.
Keywords: Gastrointestinal problems, Autism, Developmental delays, Maladaptive behaviors

Introduction

Frequent anecdotal reports of gastrointestinal (GI) problems in children with autism spectrum disorder (ASD) are beginning to be clarified by research efforts examining the issue. The connection between GI problems and autism is not yet resolved, however, and a handful of recent reports provide conflicting findings, where prevalence of GI symptoms ranges from 23 to 70 % (Molloy and Manning- Courtney 2003; Valicenti-McDermott et al. 2006; Ibrahim et al. 2009; Nikolov et al. 2009; Wang et al. 2011; Gorrindo et al. 2012). Variations in prevalence of GI problems in large part may be due to differences across studies including, but not limited to: variations in the criteria used to define a GI problem, the number of different GI symptoms considered, the definition of any particular GI symptom or lack thereof, variations in methodology such as data source (medical chart versus self-report) or time period for reporting (last few months, lifetime, etc.), and study population characteristics such as age and other criteria for participation.

Research using large samples has begun to provide a better understanding of the heterogeneity of GI concerns in children with ASD (Molloy and Manning-Courtney 2003; Valicenti-McDermott et al. 2006; Ibrahim et al. 2009; Nikolov et al. 2009; Wang et al. 2011). However, for comparative purposes, few estimates of GI symptom prevalence are available for children with typical development (TD). Instead, research has focused on GI issues for groups that seem disproportionately affected, namely children with ASD, and more recently, children with developmental disabilities (Schieve et al. 2012). Among the first of these was a study (n = 137) using medical records from a clinic specializing in ASD in a large pediatric medical center serving a 10 county catchment area in the Midwest (Molloy and Manning-Courtney 2003). The study considered solely four GI symptoms and the definitions were relatively restrictive, which may partially explain prevalence of 24 % in this study population. Nikolov and colleagues evaluated GI problems

in a sample (n = 172) of children with pervasive developmental disorders (PDDs) enrolled for one of two randomized clinical trials. They defined a GI problem as one that caused impairment in function, had been brought to the attention of a medical professional and had been or was currently under treatment. They reported 22 % of their sample was positive for GI problems, which were primarily constipation and diarrhea (Nikolov et al. 2009).

A few other studies attempted to not only characterize GI disorders in children with ASD but also make comparisons to other groups of children. Valicenti-McDermott et al. carried out a cross-sectional case–control study (n = 50 in each group) in English and Spanish-speaking families with ASD, TD and DD (Valicenti-McDermott et al. 2006). Children between 1 and 18 years of age were matched for age, gender and ethnicity, and findings indicated a lifetime reported history of 1 or more GI symptoms was higher in cases (ASD 70 %) than both controls (TDs 28 %, DDs 42 %). Another recent case–control population based study (n = 121 cases, n = 242 controls) in Olmstead County, Minnesota, where >95 % of medical care is provided by Olmstead Medical Center/Mayo Clinic, medical charts provided data for GI symptoms from birth to 21 years of age (Ibrahim et al. 2009). Out of the five GI categories compared, only constipation and food selectivity were higher in ASD cases as compared with controls, but potential inclusion of illness episodes in a 21 year period could have skewed results, and 98 % of racial/ethnic makeup was white, raising the issue of generalizability of findings. Finally, in a study using data from the Autism Genetic Resource Exchange (AGRE) where only families with multiple affected members are included, parents reported significantly more GI problems in children with ASD than in their unaffected siblings (42 vs. 12 %; Wang et al. 2011). Furthermore, this was the first study to report that having increased autism severity was associated with higher odds of GI problems.

In light of the existing literature of variable methodologies and findings, our study provides the largest ethnically diverse population-based case–control study to date that compares GI problems for children with clinically confirmed: (1) ASD, (2) DD and (3) TD. It also is the first large population-based sample that examines the relationship of GI symptoms and maladaptive behaviors. Understanding the magnitude of GI problems and their effects on behavior can provide new insight for more effective and appropriate treatment of children who suffer from these problems.

Methods

Study Design and Sample

The CHildhood Autism Risks from Genetics and the Environment (CHARGE) study is an ongoing population based case–control study with participants sampled from three strata: children with (ASD), children with DD but not ASD, and children selected from the general population (Hertz-Picciotto et al. 2006). Recruitment began in April 2003, and a total of 1,513 participants were enrolled in this CHARGE study sample from April 2003 through May 2011. All participating children meet the following criteria: (a) are between the ages of 24 and 60 months, (b) live with at least one biologic parent, (c) have a parent who speaks English or Spanish, (d) were born in California, and (e) reside in one of the catchment areas of a specified list of Regional Centers in California. All subjects were assessed to confirm diagnostic group and parents completed standardized interviews and questionnaires about their children's past history and present behavior and functioning. Diagnosis of ASD was confirmed in all subjects by the Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al. 1993) and the Autism Diagnostic Observation Schedules (ADOS) (Lord et al. 2003). Details have been described previously (Hertz-Picciotto et al. 2006) in which children that met full criteria for autism on both the ADI-R and ADOS were classified as autism (AU), and children that came within two points of meeting criteria for autism on the communications or social domains of the ADI-R and met criteria on ADOS were classified as ASD. Since there was little difference in GI symptoms between the AU and ASD groups, we have combined them, hereafter designated as ASD for comparisons among children with an ASD, DD and TD. All children were assessed with the Mullen Scales of Early Learning (Mullen 1995) and the Vineland Adaptive Behavior Scales (VABS) (Sparrow 1984). Children recruited into the DD or TD group were also screened with the social communication questionnaire (SCQ); children with scores at or above 15 points were referred for assessment of ASD using the ADOS and ADI-R.). We defined DD based on composite scores for Mullen Scales of Early Learning (MSEL) and VABS. A child was classified as DD if he/she did not meet criteria for ASD, scored <70 on either MSEL or VABS *and* scored <77 on the other assessment. Children were classified as TD if their MSEL and

VABS scores were both>70 and they scored<15 on the SCQ. For purposes of this analysis, we excluded participants missing the Gastrointestinal History (GIH) questionnaire (n = 313), siblings of target children (n = 26), participants with an incomplete or pending diagnosis (n = 187), those with evidence of developmental delay on only one of two instruments (n = 24) and those missing data on child's race (n = 3). The final study population therefore consisted of 960 children.

The study was approved by institutional review boards for the State of California and the University of California, Davis and Los Angeles. Informed consent is obtained for all participants prior to data collection.

Measures and Procedures

Prior to clinic visits, participants are mailed several self administered questionnaires including the CHARGE GIH and the Aberrant Behavior Checklist (ABC). Maladaptive behavior was measured using five subscales of the ABC: irritability (15 items), lethargy/social withdrawal (16 items), stereotypy (7 items), hyperactivity (16 items) and inappropriate speech (4 items; Aman and Singh 1994). ABC subscales scores ranged based on the number of items scored using a 4 point Likert scale (0 = Not at all a problem; 1 = Problem slight in degree; 2 = Problem moderately serious; 3 = Problem severe in degree). The GIH includes 10 Likert scale items (0 = never; 1 = rarely; 2 = sometimes; 3 = frequently; 4 = always) for each current gastrointestinal symptom (abdominal pain, gaseousness/ bloating, diarrhea, constipation, pain on stooling, vomiting, sensitivity to foods, difficulty swallowing, blood in stool and blood in vomit). "Current" was defined as the past 3 months. Additionally, the GIH includes four (yes/ no) questions asking about the presence of food allergies, diet restrictions, food dislikes and whether any GI diagnosis has ever been given. Finally, there are open-ended questions asking parents to list: food allergies; reasons for diet/food restrictions; and what GI condition was diagnosed. Other data collected as part of the CHARGE Study protocol include demographics and medications used in the last month. A pediatrician reviewed our list of medications and declared a vast majority of them were known to have some GI side effects, including medications for cold symptoms, allergies, pain relief, and antibiotics. We did not control for medications known to be used in the treatment of GI

symptoms such as anti-diarrheal medications or those used to treat constipation or gastroesophageal reflux disorder (GERD).

Statistical Procedures

Demographic characteristics were examined across groups for ASD, DD and TD using likelihood ratio Chi square tests for categorical variables. We dichotomized the Likert scale items on the GIH into symptoms that occur with 'high' (items ranked either *frequently* or *always*) versus 'low' frequency (items ranked *never*, *rarely* or *sometimes*). We tested for differences in reported frequency of GI symptoms and food allergies, diet restrictions, strong food dislikes, and GI diagnoses using the likelihood ratio Chi square statistic. Odds ratios adjusted for child age, child gender and maternal education, along with 95 % confidence intervals (CI), were calculated for a report of high frequency for at least one GI symptom, and then separately for each individual GI symptom, comparing ASD and DD case groups with TD as the reference. To also control for the possible confounding effect of medications known to have GI side effects, an additional set of analyses was conducted on a smaller sample size (n = 622, due to missing medication data). Within the ASD and DD groups, we used Wilcoxon rank sum test or t-tests to examine differences in scores on the five subscales of the ABC, comparing children with high versus low frequency of GI symptoms.

Responses provided by parents for open-ended GI questions were categorized and tallied by the first author (i.e., reported food allergies, reasons for diet restrictions, and reported GI diagnoses) and categories were reviewed by remaining authors, one of whom is a clinician. All statistical analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population Characteristics

Mothers of children with developmental delay tended to have less formal education than mothers of children with TD or ASD. Roughly half of the study population was white, while approximately one-third

was of Hispanic origin. Reported medication use was higher in children with DD compared to children with TD or ASD (**Table 1**).

Table 1 Characteristics and medication use for cases autism spectrum disorder (ASD), developmental delay (DD) and controls typical development (TD). CHARGE study 2003–2011

	ASD n = 499	Controls TD n = 324	DD n = 137	*p* value[a]
Maternal age		0.29		
Mother's age ≥35 at delivery	27.1 %	22.2 %	25.6 %	
Maternal education				<0.0001
Less than high school	3.8 %	5.3 %	15.3 %	
High school diploma/GED	9.8 %	11.1 %	13.9 %	
Some college/2 year degree	41.7 %	32.4 %	40.2 %	
Bachelor degree	28.5 %	34.6 %	25.6 %	
Graduate or professional degree	16.2 %	16.7 %	5.1 %	
Race/ethnicity (child)				0.02
White	50.5 %	52.5 %	41.6 %	
Hispanic	32.1 %	29.0 %	39.4 %	
Black	2.4 %	1.9 %	5.1 %	
Asian	5.6 %	2.5 % 1	.5 %	
Pacific Islander	0.0 %	0.3 %	0.0 %	
Multi-racial	9.4 %	13.9 %	12.4 %	
Male gender	85.8 %	83.0 %	63.5 %	<0.0001[a]
Child age in years[b]				0.004
2 year olds (24–35 months)	22.4 %	30.6 %	14.6 %	
3 year olds (36–47 months)	36.1 %	36.4 %	38.0 %	
4 year olds (48–59 months)	39.1 %	31.2 %	46.0 %	
5 year olds (60 months ?)	2.4 %	1.9 %	1.5 %	
Regression status (cases only)	44.9 %	na	na	
MSEL[c]				
Mean ± SD	61.5 ± 17.8	106 ±17.	4 53.6 ± 7.1	
Range	49–136	70–149	49–76	
VABS[d]				
Mean ± SD	64.5 ± 12.6	104.5 ± 15	58.9 ± 8.8	
Range	40–150	70–145	33–76	
Medication use	n = 465	n = 315	n = 131	
Ever used any				
conventional treatments?	23.2 %	10.5 %	39.7 %	<0.0001
psychiatric treatments?	1.5 %	0.0 %	3.8 %	0.002
anticonvulsants or benzodiazepines?	3.7 %	0.0 %	13.7 %	<0.0001
CAM treatment?	26.7 %	3.5 %	19.9 %	<0.0001

p values calculated for comparisons across groups using Chi-square test or Fisher's exact test

[a] The TD group was frequency matched to the projected gender distribution of the autism cases, while the DD group was not matched at all

[b] Reflects age at assessment which occurs within a few months after recruitment. All children were recruited between 24 and 60 months of age

[c] Mullen Scales of Early Learning

[d] Vineland Adaptive Behavior Scales

Table 2 Comparison of 'Current' GI symptoms (in the past 3 months) for cases (ASD) and controls (TD and DD). CHARGE study 2003–2011

	ASD n=499 (%)	TD n=324 (%)	DD n=137 (%)	*p* value[a]	AU n=339 (%)	ASD n=160 (%)	*p* value[b]
GI symptoms[b]							
Abdominal pain	5.1	1.6	3.9	0.03	5.9	3.5	0.27
Gaseousness/bloating sensation	11.0	2.0	2.3	<0.0001	11.7	9.6	0.51
Diarrhea	13.0	1.6	6.1	<0.0001	16.1	6.4	0.002
Constipation	15.5	3.5	15.8	<0.0001	16.8	12.5	0.22
Pain on stooling	6.2	1.6	5.5	0.004	7.4	3.4	0.08
Vomiting	2.9	0.3	6.2	0.0006	2.7	3.2	0.76
Sensitivity to foods	31.0	4.5	11.1	<0.0001	32.1	28.9	0.49
Difficulty swallowing	4.2	0.3	4.6	0.0005	4.0	4.6	0.77
Blood in stools	0.4	0.3	0.8	0.62	0.6	0.0	1
Blood in vomit	0.2	0.0	0.0	1	0.0	0.6	0.32
Presence of related issues[c]							
Food allergies Y/N	23.0	11.1	13.5	<0.0001	19.7	20.3	0.88
Food restrictions Y/N	37.4	10.4	21.6	<0.0001	40.2	31.4	0.06
Food dislikes Y/N	63.5	34.0	34.6	<0.0001	63.8	62.9	0.89
GI diagnosis Y/N	7.5	1.9	22.9	<0.0001	7.8	6.9	0.7

Those reporting symptoms occur 'frequently' or 'always' on Likert scale

[a] *p* values calculated for comparisons across groups using Chi-square test or Fisher's exact test

[b] Number of missing data for entire sample for the first ten GI question varies from 29 to 77

[c] Number of missing data for entire sample for the last four questions varies from 19 to 38 (except 'food dislikes' missing = 332)

Comparisons of GI Symptom Reports Across Diagnostic Groups of ASD, DD and TD

Parent report of at least one frequent GI symptom was significantly higher for children with ASD and children with DD, compared to children with TD. Comparison of parent reports suggests that children with either ASD or DD are far more likely to have frequent constipation, diarrhea and difficulty swallowing than children with TD (**Table 2**). Group differences in GI symptoms for children with ASD held up after adjusting for child age, child gender, and maternal education (**Table 3**). Children with ASD were at least three times more likely to experience frequent GI symptoms than children with TD: abdominal pain, pain on stooling, constipation, gaseousness/bloating, diarrhea, sensitivity to foods, as well as vomiting and difficulty swallowing, which were very rare in TD controls. Similarly, reported food allergies, food restrictions, and food dislikes were highest in children with ASD (Table

Table 3 Odds ratio of 'Current' GI symptoms (in the past 3 months) for ASD with typical development (TD) as reference group. CHARGE study 2003–2011

GI symptoms	Unadjusted odds ratio	95 % CI	Adjusted odds ratio[a]	95 % CI	Adjusted odds ratio[b]	95 % CI
ASD versus TD						
Full study population[c] (n = 960)						
Abdominal pain	3.28	(1.23–8.72)	3.26	(1.21–8.78)	na	na
Gaseousness/bloating	6.15	(2.60–14.54)	6.43	(2.71–15.29)	na	na
Diarrhea	9.08	(3.61–22.84)	9.43	(3.73–23.83)	na	na
Constipation	5.02	(2.62–9.62)	5.41	(2.81–10.41)	na	na
Pain on stooling	4.03	(1.54–10.52)	4.20	(1.60–11.03)	na	na
Vomiting	9.08	(1.19–69.38)[e]	9.83	(1.28–75.40)[e]	na	na
Sensitivity to foods	9.51	(5.37–16.83)	9.67	(5.44–17.18)	na	na
Difficulty swallowing	13.29	(1.77–99.53)[e]	12.57	(1.67–94.71)	na	na
Subset with medication data[d] (n = 622)						
Abdominal pain	3.14	(1.11–8.87)	3.01	(1.05–8.64)	2.85	(0.99–8.24)
Gaseousness/bloating	6.13	(2.31–16.25)	6.14	(2.29–16.49)	5.93	(2.20–15.98)
Diarrhea	6.35	(2.16–18.65)	6.09	(2.06–18.03)	6.19	(2.09–18.33)
Constipation	5.76	(2.63–12.62)	6.07	(2.74–13.43)	6.06	(2.74–13.42)
Pain on stooling	2.8	(0.98–7.97)	2.91	(1.01–8.41)	2.84	(0.98–8.21)
Vomiting	7.21	(0.88–59)[e]	7.72	(0.93–64.16)[e]	8.04	(0.97–67)[e]
Sensitivity to foods	8.61	(4.62–16.07)	8.6	(4.58–16.14)	8.57	(4.56–16.09)
Difficulty swallowing	7.23	(0.88–59.20)[e]	6.56	(0.79–54.3)[e]	6.89	(0.83–57.5)[e]

Those reporting symptoms occur 'frequently' or 'always' on Likert scale

[a] Adjusted for child's age, gender, maternal education

[b] Adjusted for child's age, child's gender, maternal education, and medication

[c] TD group n = 324, ASD group n = 499, DD group n = 137

[d] TD group n = 257, ASD group n = 254, DD group n = 111

[e] Wide confidence interval (CI) is a result of only one control having this symptom

2). However, parent report of a GI *diagnosis* was highest in children with DD compared to children with ASD and TD. Moreover, children with DD were at least three times more likely than children with TD to experience frequent sensitivity to foods, pain on stooling, diarrhea, constipation, as well as difficulty swallowing and vomiting.

Analyses using those with parent-report medication data confirm that after adjusting for medications with potential GI side effects, most findings were essentially unchanged: children with ASD are approximately six to eight times more likely to report frequent gaseousness/bloating, constipation, diarrhea and sensitivity to foods regardless of which variables were controlled (Table 3). Similarly, parents of children with DD were five-fold more likely to report constipation, as well as significantly more likely to report difficulty swallowing and vomiting compared to parents of TD children after adjusting for medications

Table 4 Odds ratio of 'Current' GI symptoms (in the past 3 months) for DD with TD as reference group. CHARGE study 2003–2011

GI symptoms	Unadjusted odds ratio	95 % CI	Adjusted odds ratio[a]	95 % CI	Adjusted odds ratio[b]	95 % CI
DD versus TD						
Full study population[c] (n = 960)						
Abdominal pain	2.48	(0.71–8.73)	2.09	(0.56–7.73)	na	na
Gaseousness/bloating	1.19	(0.29–4.86)	1.39	(0.33–5.76)	na	na
Diarrhea	3.97	(1.27–12.36)	4.71	(1.48–15.01)	na	na
Constipation	5.15	(2.41–11.02)	4.77	(2.17–10.46)	na	na
Pain on stooling	3.58	(1.12–11.50)	3.70	(1.11–12.31)	na	na
Vomiting	20.2	(2.5–163.19)[e]	24.00	(2.88–200.24)[e]	na	na
Sensitivity to foods	2.64	(1.22–5.72)	3.14	(1.43–6.92)	na	na
Difficulty swallowing	14.85	(1.77–124.65)[e]	10.42	(1.20–90.27)[e]	na	na
Subset with medication data[d] (n = 622)						
Abdominal pain	1.46	(0.34–6.24)	1.33	(0.30–6.01)	1.19	(0.23–5.45)
Gaseousness/bloating	0.95	(0.18–4.99)	1.08	(0.20–5.85)	0.93	(0.17–5.10)
Diarrhea	2.41	(0.59–9.80)	2.38	(0.56–10.05)	2.51	(0.59–10.64)
Constipation	5.28	(2.18–12.75)	4.92	(1.97–12.32)	4.91	(1.96–12.31)
Pain on stooling	2.53	(0.72–8.94)	3.06	(0.83–11.33)	2.9	(0.78–10.83)
Vomiting	15	(1.78–126.21)[e]	17.83	(2.01–158.34)[e]	20.86	(2.3–189.5)[e]
Sensitivity to foods	1.75	(0.73–4.24)	2.03	(0.82–5.04)	2.01	(0.81–5)
Difficulty swallowing	12.32	(1.42–106.69)[e]	9.36	(1.02–85.77)[e]	12.32	(1.31–115.83)[e]

Those reporting symptoms occur 'frequently' or 'always' on Likert scale

[a] Adjusted for child's age, gender, maternal education

[b] Adjusted for child's age, child's gender, maternal education, and medication

[c] TD group n = 324, ASD group n = 499, DD group n = 137

[d] TD group n = 257, ASD group n = 254, DD group n = 111

[e] Wide confidence interval (CI) is a result of only one control having this symptom

(**Table 4**). The exclusion of those without medication data appears to have resulted in a somewhat lower prevalence of reported diarrhea.

We did not find any meaningful differences between ASD children with DD (n = 114), ASD without DD (n = 377) and DD without ASD (our DD group), beyond what the previous analyses have already described. Specifically, GI symptoms did not significantly differ comparing ASD with DD versus ASD without DD, with the exception of vomiting. Vomiting is a relatively infrequent GI symptom reported, and ASD without DD had higher occurrence than ASD with DD (p = 0.02; Table 1S).

Comparisons by Severity of Autism Spectrum Disorder

Comparisons of AU versus ASD, as originally defined in the CHARGE study, suggest that GI symptoms and related issues are similar between the two groups, with the exception of diarrhea (Table 2). Children with AU have higher reports of diarrhea compared to children with ASD.

Examination of GI Symptoms and ABC Scores

We examined the association between GI symptoms and maladaptive behavior scores for the five subscales of the ABC. In children with ASD, four out of five behavior subscales (irritability, social withdrawal, stereotypy and hyperactivity) on the ABC were significantly higher in children with frequent occurrences of abdominal pain, gaseousness, diarrhea and constipation as compared to children with no frequent GI symptoms (**Table 5**). In addition, two or three of the behavior subscales (irritability, social withdrawal, and stereotypy) on the ABC were significantly higher in children with other frequent GI symptoms (pain on stooling, sensitivity to food, and difficulty swallowing). For children with DD, maladaptive behavior scores for the ABC yielded a pattern of associations only for diarrhea: scores were higher for irritability (GI positive 16.7 SE 4.6, GI negative 8.6 SE 0.9, $p = 0.06$), social withdrawal (GI positive 8.6 SE 2.6, GI negative 4.0 SE 0.5, $p = 0.09$) and hyperactivity subscales (GI positive 22.1 SE 4.8, GI negative 11.0 SE 1.0, $p = 0.02$) in children whose parent reported frequent diarrhea versus infrequent diarrhea (Table 2S).

Open–Ended questions

Descriptive analyses of parental responses to related open ended GI questions indicated the most frequently reported food sensitivity or allergy for all diagnostic groups was dairy/casein (14.6 % ASD, 6.6 % DD and 5.3 % TD). For children with ASD, other commonly reported food allergies or sensitivities included the grains category (including gluten, 7.8 %) and nuts/soy (7 %). The most commonly cited reason for food restrictions in children with ASD was child selectivity (8.6 %) followed by adverse GI symptoms (8.2 %); and for children with DD

Table 5 Comparison of maladaptive behavior scores in GI positive and GI negative children with ASD. CHARGE study 2003–2011

GI symptoms	Irritability				Social withdrawal				Stereotypy				Hyperactivity				Inappropriate speech			
	n	*X*	*SE*	*p*	n	*X*	*SE*	*p*	n	*X*	*SE*	*p*	n	*X*	*SE*	*p*	n	*X*	*SE*	*p*
Abdominal pain																				
GI positive	21	18.9	2.1	0.004	23	15.3	1.8	0.01	23	8.2	1.0	0.001	22	25.3	2.4	0.004	23	3.7	0.6	0.19
GI negative	391	12.6	0.4		390	10.9	0.4		398	4.9	0.2		379	18.1	0.5		400	2.9	0.1	
Gaseousness																				
GI positive	48	18.2	1.3	<0.0001	48	16.1	1.2	<0.0001	49	7.6	0.7	<0.0001	47	24.2	1.6	0.0002	47	3.4	0.4	0.13
GI negative	370	12.2	0.4	372	10.5	0.4	379		4.8	0.2	358		17.8	0.6	381		2.9	0.1		
Diarrhea																				
GI positive	58	16.3	1.2	0.0009	60	15.4	1.0	<0.0001	61	7.1	0.5	<0.0001	56	23.5	1.3	<0.0001	61	2.4	0.3	0.26
GI negative	387	12.3	0.4		389	10.5	0.4		397	4.8	0.2		375	17.7	0.5		394	2.9	0.1	
Constipation																				
GI positive	61	15.9	1.2	0.003	69	13.6	1.0	0.006	70	6.3	0.6	0.03	61	23.1	1.5	0.0006	67	3.3	0.3	0.15
GI negative	384	12.3	0.4		379	10.8	0.4		387	4.9	0.2		372	17.6	0.5		388	2.8	0.1	
Pain on stooling																				
GI positive	28	17.1	2.0	0.03	28	14.8	1.6	0.01	28	7.9	1.0	0.009	27	22.5	2.4	0.1	28	3.3	0.5	0.38
GI negative	404	12.5	0.4		407	10.9	0.4		415	4.9	0.2		393	18.2	0.5		414	2.9	0.1	
Vomiting																				
GI positive	11	18.1	3.7	0.14	14	10.4	2.1	0.79	12	5.4	1.1	0.8	13	24	3.7	0.15	14	5.2	0.9	0.007
GI negative	437	12.7	0.4		438	11.2	0.4		449	5.1	0.2		422	18.2	0.5		445	2.8	0.1	
Sensitivity to foods																				
GI positive	130	14	0.8	0.09	131	12.5	0.7	0.03	133	5.9	0.4	0.01	127	19.1	1.0	0.51	134	2.9	0.2	0.83
GI negative	294	12.4	0.5		296	10.7	0.4		302	4.7	0.2		282	18.2	0.6		298	2.8	0.2	
Difficulty swallowing																				
GI positive	17	18.8	2.8	0.03	18	14.8	2.1	0.06	19	8	1.2	0.01	17	21.8	3.4	0.35	20	5.1	0.8	0.004
GI negative	425	12.6	0.4		427	11	0.4		437	5	0.2		412	18.4	0.5		431	2.7	0.1	
Blood in stools																				
GI positive	1	2	na[a]	0.13	1 8	na[a]	0.72	1	8	na[a]	0.4	1	4	na[a]	0.17	1	0	na[a]	0.22	
GI negative	445	12.9	0.4		449	11.1	0.4		459	5.1	0.2		431	18.5	0.5		455	2.8	0.1	
Blood in vomit																				
GI positive	0	na[a]	na[a]	na[a]	17	na[a]	0.58	1	7	na[a]	0.51	1	32	na[a]	0.2	1	9	na[a]	0.1	
GI negative	446	12.9	0.4		449	11.1	0.4		459	5.1	0.2		431	18.4	0.5	4	55	2.8	0.1	

[a] Cells are suppressed or incomplete due to small numbers

and TD it was adverse GI symptoms (DD 10.2 %, TD 4 %). The most commonly reported GI diagnosis across all groups was gastroesophageal reflux disorder (GERD), although in children with ASD (n = 18), half of these were reported to have resolved. Only 2 cases were reported in the disease category for celiac disease/colitis, 1 in ASD (0.4 %) and 1 in DD (1.5 %), whereas an additional 6 cases in ASD (1.2 %) reported malabsorption, leaky gut or abnormal stool and five children with DD (nearly 4 %) had GI anatomical abnormalities. Five cases of dysbiosis (yeast in stool) were also reported in children with ASD (1 %).

We also examined the types of combinations for children with two or more reported frequent GI symptoms in the last 3 months. In a majority of cases, diarrhea and constipation occur in mutually exclusive groups. For example, in children with ASD, only 9 reported *both* diarrhea and constipation, while 29 reported diarrhea in combination with other symptoms, and 44 reported constipation with other symptoms. In children with DD, only 3 children had *both* diarrhea and constipation, while another 3 reported diarrhea in combination with other GI symptoms, and 8 reported constipation in combination with other GI symptoms.

Discussion

Our findings from the largest population-based case–control study of GI problems in children with ASD and DD confirmed using standardized tests indicate that these symptoms, particularly constipation and diarrhea, affect children with ASD and DD far more often than children with TD. Compared to children with TD, children with ASD and DD were at least three times more likely to experience a higher frequency of most GI symptoms. After adjustment for medications, the odds ratios were changed very little (with the exception of difficulty swallowing in the ASD analysis, reported for only one TD control). Exceedingly strong differences in reported frequency of diarrhea, constipation, gaseousness/bloating and sensitivity to foods were robust across models, with prevalences five to nine-fold higher in ASD. What remains to be understood are the mechanisms or contributing factors that can help explain these differences.

Comparison of our findings to other studies yielded some notable similarities. For example, Valicenti-McDermott et al. in a New York

sample of slightly older children (mean age 7.6 years, SD ± 3.6) reported food selectivity at similar prevalences (ASD 60 %, TD 22 %, and DD 36 %) as food dislikes in our California sample (ASD 63.5 %, TD 34 %, and DD 34.6 %). Abnormal stool patterns (defined as recurrent passage of ≥3 large unformed stools daily for >4 weeks) were reported only slightly more often in cases (ASD 18 %, TD 4 %, DD 2 %); as compared with reports of diarrhea in our sample (ASD 13 %, TD 2 %, DD 6 %).

In contrast to our findings, Ibrahim et al. found that the overall incidence of GI symptoms did not differ between children with autism and gender- and age-matched children with typical development. In the Ibrahim study, information from medical charts covered birth to 21 years of age: constipation; diarrhea; abdominal bloating, discomfort or irritability; gastroesophageal reflux or vomiting; and feeding issues or food selectivity (Ibrahim et al. 2009). However, it was not indicated whether these findings included illnesses such as the flu, which could account for null findings, especially since their study investigated cumulative incidence of GI problems over a long time period. In the CHARGE study, we collected information on GI problems occurring in the last 3 months.

Interestingly, food selectivity for children with ASD is a common thread in several studies (Valicenti-McDermott et al. 2006; Ibrahim et al. 2009). Ibrahim et al. concluded that constipation and food selectivity were attributed to behavioral characteristics of children with ASD such as ritualistic tendencies, need for routine, and insistence on sameness, rather than being indicative of GI pathology. Our results provide some support for these contentions in that children with ASD had not only the highest reports of food dislikes (a proxy for food selectivity), but also the highest odds of reporting GI symptoms not explained by other factors such as the child's age, medication or maternal education. It is plausible that a child with notable food dislikes or selectivity for a variety of reasons such as taste, texture, or temperature, might consume a relatively self-restricting diet that could reduce the variety of foods and nutrients needed to maintain healthy gut function. Only one study to date has examined dietary habits as a possible link between gastrointestinal dysfunction and autism, and findings suggested there was no association (Gorrindo et al. 2012).

To our knowledge, only the Valicenti-McDermott study and ours offer a comprehensive comparison of GI problems in ASD children

versus those having other developmental disorders. One recent study assessed the prevalence of various medical conditions, including one GI symptom, using a nationally representative sample of children ages 3–17 years and found the prevalence of frequent diarrhea/ colitis in the past 12 months was seven times more likely in children with autism [6.8 %, aOR 7.1, 95 % CI (3.9–12.8)] and three times more likely in children with a developmental disability [3 %, aOR 3.5, 95 % CI (2.7–4.5)] than children with typical development (0.9 %; Schieve et al. 2012).

In comparing our findings with others, we note that despite the similarities in the DD groups between Valicenti- McDermott and our study, the two groups are not quite the same. Our CHARGE Study DD group is designated as having a *developmental delay,* regardless of the cause, i.e., it includes those with known chromosomal, genetic or mitochondrial disorders whereas Valicenti- McDermott designates the DD group as children with *developmental disabilities* and they exclude from both the ASD and DD groups, those with "known genetic" syndromes or disorders. In either case, comparisons to children with DD provide information on the specificity of findings in ASD: overall, GI symptoms were more prevalent in both ASD and DD children when comparing with TD children, signifying a lack of specificity in regard to this phenotypic presentation. When we compared subsets within the ASD group, ASD children with DD versus ASD children without DD did not, in the main, differ in their GI symptoms. The one exception was for vomiting, but given that no other symptoms differed and that it was a relatively infrequently reported GI symptom, the finding is likely due to chance.

Our findings in children with ASD demonstrating a consistent relationship between GI symptoms and maladaptive behaviors have perhaps special clinical translational significance, with possible implications for treatment approaches. Similar to the strong and significant relationship we found between GI symptoms and increased measures of irritability, social withdrawal, stereotypy, and hyperactivity, Nikolov et al. observed that children with PDDs and GI problems (all symptoms combined) showed greater symptom severity on measures of irritability and social withdrawal on the ABC, as well as anxiety, and to our knowledge is the only other study addressing GI problems and behavior of children with ASDs (Nikolov et al. 2009). It is plausible that a chronic GI symptom, which can cause pain, discomfort

and anxiety, could contribute to increased irritability and social withdrawal, particularly in someone with deficits in social and communicative skills. Furthermore, for a child with ASD, increased stereotypy and hyperactivity may represent coping mechanisms for an uncomfortable and unpredictable GI condition. A recent report found that behavioral characteristics hypothesized to be expressions of GI problems are common in children with ASD, yet not specific to those with GI problems (Maenner et al. 2012). Therefore the authors suggested that the presence of these behaviors would not be useful on their own for screening or identifying children requiring GI evaluation. However, many ASD children, most especially those who are non-verbal, often do not present with symptoms typically recognized by many primary care physicians or specialists as being GI related, such as self-injurious behavior (SIB) and aggression that may be responses to pain and/or discomfort. Until clinicians and therapists consider a thorough GI history as a possible explanation for adverse behaviors, GI disorders in this population will continue to be over-looked and insufficiently treated. Appropriate treatment of GI symptoms may help alleviate at least some problematic behaviors and improve the quality of life in children with ASD along with their families. A recent consensus report on the evaluation, diagnosis and treatment of GI disorders in children with ASD supports the use of medical investigation for problem behaviors (Statement 7) and provides examples and guidance for clinicians (Buie et al. 2010a).

In children with DD, diarrhea was the only GI symptom associated with measures of maladaptive behaviors, specifically irritability, social withdrawal and hyperactivity. As in ASD, clinicians attending to children with DD should inquire about GI conditions, particularly where behavioral problems or recent changes in behavior have been noted. Larger sample sizes and analyses focused on both idiopathic and specific etiologies of DD should be investigated to understand the role of GI problems in children with DD, and their relationship with a child's behavior.

Comparisons between children with AU and those with ASD yielded very similar GI profiles with the exception of diarrhea. The ten percentage point higher prevalence in those with the more severe diagnosis (AU) might indicate that greater severity induces more co-morbidity or alternatively, that the presence of chronic diarrhea increases symptom severity. Wang and colleagues also reported on autism symptom

severity and odds of having GI problems showing that having "Full Autism" (aOR 14.28, 95 % CI 6.22–32.77) or "Almost Autism" (aOR 5.16, 95 % CI 2.02–13.21) were strongly associated with experiencing GI problems in multiplex families affected with autism compared to unaffected siblings (Wang et al. 2011). Diarrhea was one of the two most reported GI problems in children with ASD.

Dairy and/or casein were cited most often as food allergens among all groups of children. However, it is unclear to what degree these parent-reports reflect true food allergies versus food sensitivities. At least one group of researchers has demonstrated that in children with ASD, it is nonallergic food hypersensitivity to cow's milk protein (CMP), and *not* casein that plays a role in GI symptoms observed in some children with ASD (Jyonouchi et al. 2005). Food allergies are often difficult to diagnose because most intestinal food allergies are cell mediated rather than by immunoglobulin E (IgE) (Buie et al. 2010b). Cell-mediated immunity plays a role in non-allergic food hypersensitivity and reactions take place several hours and even 1–2 days after the intake of the culprit (Jyonouchi et al. 2005). Finally, it is possible that reported food allergens may be neither an allergy or sensitivity, but rather a parent's or child's perception or opinion of a particular food(s).

For children with ASD, parents report *child selectivity* as the primary reason for diet restriction, followed closely by adverse GI symptoms. Although it makes sense for child refusal and adverse GI symptoms to be common reasons for diet restrictions, we would have expected more parents to report food allergy as a reason for imposing a diet restriction considering the number of food allergies or sensitivities reported. Diagnoses of celiac disease were rare, which is interesting given the sizable number reporting a food allergy to grains and/or gluten. A limitation of our study is that these findings are based solely on parent-report rather than medical chart review for diagnostic testing.

Among our study's other limitations is the lack of standardized definitions for GI symptoms. This makes it difficult to make comparisons across studies. Our data was based on parent report, so there will be a level of inherent subjectivity, which on the one hand is a limitation, but for children in this age range, parents are likely best suited to follow and report bowel habits and GI symptoms that may not be reliably recorded in medical records. Furthermore, dietary intake information for the children is also lacking. Diarrhea and constipation are

frequently cited in studies examining GI symptoms in children with autism, but to date, only one has examined the role of diet in GI problems (Gorrindo et al. 2012). To investigate whether diet plays a role in the prevalence of GI problems, future studies should attempt to measure diet quality and quantity of key macronutrients with special attention to fiber, water, and fats, in addition to micronutrients such as iron, zinc, vitamin A, vitamin B12, folate and iodine. One small study suggests that children with ASDs may have inadequate intakes of fiber, calcium, iron, vitamin E and vitamin D (Herndon et al. 2009).

Among the strengths of this analysis are: the CHARGE Study population-based sample, which provided a broader ethnic diversity of cases and controls than previous studies; the large sample size of nearly 1,000 children; and adjustment for confounding from both sociodemographic factors and medications. In addition to demonstrating a much higher incidence of parent-reported frequent diarrhea, gaseousness/bloating, constipation, and food sensitivities in 2–5 years old children with ASD versus their typically developing counterparts, this study identified a strong correlation between deviant behaviors and the presence of GI symptoms in both children with ASD and DD. This underscores the need for clinical medical intervention and attention to GI symptoms in these children. Future work examining GI problems in children with ASD and DD should standardize definitions for GI symptoms and more studies need to incorporate measures of dietary intake and nutritional status.

The variety of GI symptoms evident within a significant portion of the ASD population may be reflective of the heterogeneity of the disorder in general. Further, the neurotransmitter systems that are active in the brain can also be found to function in the gut, which has been referred to as 'the second brain' (de Theije et al. 2011). Thus, it is possible that research into GI symptoms might elucidate aspects of the underlying neurobiological mechanisms associated with the disorder. Investigating the dual role of neurotransmitters active in both the gut and the brain in future studies may advance our understanding of underlying mechanisms important to both.

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Table 1S. Comparison of 'Current' GI symptoms[a] (in the past 3 months) for cases (ASD, with & without DD) and controls (DD). CHARGE study 2003-2011.

	ASD without DD	ASD with DD	DD	*P* value[b]
	n=377	n=114	n=136	
GI symptoms[c]	%	%	%	
Abdominal pain	5.8%	4.7%	4%	0.82
Gaseousness/bloating sensation	9.4%	11.4%	2.4%	0.003
Diarrhea	8.9%	14.4%	6.2%	0.02
Constipation	13.6%	15.5%	15.9%	0.86
Pain on stooling	6.5%	5.6%	5.6%	0.94
Vomiting	5.4%	1.6%	6.2%	0.02
Sensitivity to foods	29.4%	31.6%	11.2%	<0.0001
Difficulty swallowing	5.5%	3.3%	4.7%	0.55
Blood in stools	0.9%	0.3%	0.8%	0.35
Blood in vomit	0.9%	0%	0%	0.19

[a]Those reporting symptoms occur 'frequently' or 'always' on Likert scale

[b]*P* values calculated using chi-square test; Fisher's exact test used where applicable

[c]Number of missing data for entire sample varies from 1-39

Table 2S. Comparison of reported maladaptive behavior scores in GI positive and GI negative children with DD

	Irritability				Social withdrawal				Stereotypy				Hyperactivity				Inappropriate speech			
GI symptoms	n	*X*	*SE*	*P*	n	*X*	*SE*	*P*	n	*X*	*SE*	*P*	n	*X*	*SE*	*P*	n	*X*	*SE*	*P*
Abdominal pain																				
GI positive	5	8.4	3.8	0.98	5	5.4	1.6	0.21	5	2.4	1.5	0.72	5	6.2	2.4	0.34	4	2.5	1	0.27
GI negative	110	9.3	0.9		111	4.1	0.5		114	2.2	0.3		112	12.1	1.1		114	1.6	0.2	
Gaseousness																				
GI positive	3	3.7	0.7	0.43	3	3.7	2.7	0.99	3	3	2.5	0.67	3	4.7	2.7	0.3	3	1	1	0.6
GI negative	112	9.2	0.9		114	4.2	0.5		117	2.2	0.3		115	11.9	1.1		116	1.6	0.2	
Diarrhea																				
GI positive	7	16.7	4.6	0.06	8	8.62	2.6	0.09	8	4.8	1.7	0.11	7	22.1	4.8	0.02	8	2	0.9	0.76
GI negative	110	8.6	0.9		111	4	0.5		114	2	0.3		112	11	1.0		112	1.5	0.2	
Constipation																				
GI positive	20	8.6	2.2	0.58	20	3	0.8	0.25	21	1.6	0.6	0.28	20	10.1	2.5	0.32	21	1.7	0.5	0.79
GI negative	98	9.4	1.0		98	4.6	0.6		101	2.4	0.4		99	12.3	1.2		99	1.6	0.2	
Pain on stooling																				
GI positive	7	10.6	3.9	0.61	7	5.1	1.2	0.21	7	1.1	0.6	0.64	6	14.3	4.6	0.5	7	2.6	0.6	0.07
GI negative	108	9	0.9		109	4.2	0.5		112	2.3	0.3		111	11.7	1.1		111	1.5	0.2	
Vomiting																				
GI positive	7	8.6	2.1	0.53	8	7	2.6	0.25	8	2.8	1.6	0.55	7	11.7	3.1	0.69	7	1.7	0.8	0.78
GI negative	110	9.3	0.9		111	4.1	0.5		114	2.2	0.3		112	11.9	1.1		113	1.5	0.2	
Sensitivity to foods																				
GI positive	12	13.7	3.4	0.23	14	8.9	2.0	0.01	13	4.5	1.2	0.002	13	14.5	3.4	0.51	13	1.6	0.5	0.76
GI negative	101	8.9	0.9		100	3.6	0.5		104	2	0.3		102	11.6	1.1		103	1.6	0.2	
Difficulty swallowing																				
GI positive	6	10.7	5.2	0.8	6	5.5	2.9	0.86	6	3.5	2.2	0.9	6	12	5.8	0.93	6	2.3	1.1	0.43
GI negative	111	9.2	0.9		113	4.2	0.5		116	2.1	0.3		113	11.9	1.1		114	1.5	0.2	
Blood in stools																				
GI positive	1	0	na[a]	0.16	1	0	na[a]	0.25	1	0	na[a]	0.37	1	3	na[a]	0.42	1	1	na[a]	0.88
GI negative	115	9.3	0.9		117	4.3	0.5		120	2.2	0.3		117	12	1.1		118	1.6	0.2	
Blood in vomit																				
GI positive	0	na[a]	na[a]	na[a]	0	na[a]	na[a]	na[a]	0	na[a]	na[a]	na[a]	0	na[a]	na[a]	na[a]	0	na[a]	na[a]	na[a]
GI negative	121	9.5	0.9		122	4.2	0.5		126	2.2	0.3		122	12.1	1.0		124	1.6	0.2	

[a]Cells are incomplete due to small numbers

This table describes the relationship between GI symptoms (measured by the Gastrointestinal History questionnaire) and maladaptive behaviors (measured by the Aberrant Behavior Checklist). Maladaptive behavior was measured using five subscales of the ABC: irritability (15 items), lethargy/social withdrawal (16 items), stereotypy (7 items), hyperactivity (16 items) and inappropriate speech (4 items). ABC subscales scores ranged based on the number of items scored using a 4 point Likert scale (0=Not at all a problem; 1=Problem slight in degree; 2=Problem moderately serious; 3=Problem severe in degree). The GIH includes 10 Likert scale items (0=never; 1=rarely; 2=sometimes; 3=frequently; 4=always) for each current gastrointestinal symptom (abdominal pain, gaseousness/bloating, diarrhea, constipation, pain on stooling, vomiting, sensitivity to foods, difficulty swallowing, blood in stool and blood in vomit). GI positive are those reporting 3 or 4 on the Likert scale; GI negative are those reporting 0-2 on the Likert scale.