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# Gastro-intestinal symptoms in children with autism spectrum disorders

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Running head: GI symptoms in ASD children


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**ABSTRACT**

**Objectives**: To investigate whether parentally-reported gastro-intestinal (GI) symptoms are increased in a population-derived sample of children with autism spectrum disorders (ASD) compared to controls.

**Patients and Methods**: Participants included 132 children with ASD and 81 with special educational needs (SEN) but no ASD, aged 10-14 years plus 82 typically developing (TD) children. Data were collected on GI symptoms, diet, cognitive abilities, and developmental histories.

**Results**: Nearly half (weighted rate 46.5%) of children with ASD had at least one individual lifetime GI symptom compared with 21.8% of TD children and 29.2% of those with SEN. Children with ASD had more past and current GI symptoms than TD or SEN groups although fewer current symptoms were reported in all groups compared with the past. The ASD group had significantly increased past vomiting and diarrhoea compared with the TD group and more abdominal pain than the SEN group. The ASD group had more current constipation (when defined as bowel movement less than three times per week) and soiling than either the TD or SEN groups. No association was found between GI symptoms and intellectual ability, ASD severity, ASD regression or limited or faddy diet.

**Conclusions:** Parents report more GI symptoms in children with ASD than children with either SEN or TD children but the frequency of reported symptoms is greater in the past than currently in all groups.


**Key Words**: autism, autism spectrum disorders, gastro-intestinal symptoms, dietary intake, regression.

An association between gastro-intestinal pathology and autism spectrum disorders (ASD) attracted little attention for many years (Horvath et al. 1999). It was given impetus by the report of ileal-lymphoid-nodular hyperplasia and non-specific colitis in children with regression and ASD (Wakefield et al. 1998) and by the hypothesis of an altered, possibly immature, immune system affecting the gut inflammatory response and repair with resultant impact on the developing brain (Panksepp 1979, Wakefield 2000 & 2002). A gastrointestinal disorder specific to ASD, the 'autistic enterocolitis' proposed by Wakefield et al. (1998), has not been established (Buie et al. 2010) and the paper has since been retracted (Murch et al 2004). No significant difference between lifetime (up to age 20 years) gastro-intestinal disorders (as opposed to symptoms) has been found in ASD compared with age- and gender- matched controls (Ibrahim et al. 2009; Mouridsen et al. 2010). However, an association has been reported between children with language regression in ASD (Valicenti-McDermott et al 2008), a family history of autoimmune disease and gastrointestinal symptoms by Valicenti-McDermott et al (2006) and an association has recently been reported between a functional variant in the promoter of the gene encoding the MET receptor tyrosine kinase (involved in brain development and gut repair) linking co-occurring gastrointestinal (GI) symptoms and autism (Campbell et al. 2009).

The frequency of reported GI symptoms in children with ASD varies from 22% to 70%, depending on the sample, clinical or population-derived; the type, definition and number of symptoms; the method of investigation employed and whether symptoms are current at particular ages or life-time (Levy et al. 2007; Molloy and Manning-Courtney, 2003; Nikolov et al. 2009; Valicenti-McDermott et al. 2006; Wang et al. 2011). The symptoms reported in ASD are most commonly diarrhoea (loose

frequent stools), constipation, and abdominal discomfort/pain (Fombonne and

Chakrabarti 2001; Goodwin et al. 1971; Gorrindo et al. 2012; Horvath et al. 1999;

Molloy and Manning-Courtney 2003; Quigley and Hurley 2000; Valicenti-McDermott

et al. 2006; Pang and Croaker  2011; Wang et al. 2011).

Such GI symptoms are also common in the general population e.g. 28% of 8-10 year

olds experience constipation (de Araujo Sant'Anna et al. 1999, Kokkonen et al.

2004) thus there is a  need for prevalence studies that are prospective, population-

based and use standardized instruments and appropriate controls as advised in the

American Academy of Pediatrics consensus report (Buie 2010) Published studies

that meet these criteria give varied results. Black et al. (2002), in a case-control

analysis matching age and doctor's practice,  found no evidence that children with

ASD were more likely than children without ASD to have had  defined

gastrointestinal disorders prior to the diagnosis of ASD. A history of GI symptoms

was elicited in 70% of children with ASD compared with 28% of children with typical

development (p <.001) and 42% of children with developmental delay (p =.03)

matched for age, sex and ethnicity (Valicenti-McDermott et al. 2006). Smith et al.

(2009) compared a group with ASD with those in special schools and with

mainstream children and similarly found a significant difference between the ASD

and the mainstream school control group in certain GI symptoms (constipation,

diarrhoea, flatulence) and food faddiness but not between the ASD and special

schools group, except for faddiness. In a population cohort, Ibrahim et al. (2009)

found no difference in the lifetime GI symptoms of abdominal bloating, diarrhoea and

gastro-oesophageal reflux and vomiting in those with ASD compared with age- and

gender-matched controls; however, there was increased lifetime constipation and

food selectivity in those with ASD. Two studies have used siblings as controls. A registry-based multiplex family study employing face-to-face interviews with parents (Wang et al. 2011) found increased GI symptoms in those with ASD. Badalyan and Schwartz  (2011) used an on-line survey with families of children with Asperger syndrome and Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS)  and also found significantly higher symptom rates in the probands (odds ratio of 8.3 for frequent constipation and 5.4 for faecal incontinence.

Parental report of GI symptoms was found to be highly concordant with a pediatric gastroenterological evaluation in the study by Gorrindo et al (2012) who compared two groups of children with ASD, one with GI symptoms and one without  and a non-ASD group with GI symptoms.

Food selectivity and altered diet has been implicated in GI symptoms by some groups (Valicenti-McDermott et al.2006; Ibrahim et al. 2009), but not by others (Gorrindo et al. 2012; Levy et al. 2007).Food selectivity is commonly reported as a GI symptom but is, arguably, a symptom of ASD and noted from 15-54 months of age (Emond et al.  2010). Some studies report a positive association between GI symptoms and greater severity of ASD symptoms (Adams et al.  2011; Wang et al. 2011), increased social impairment and lack of expressive language (Gorrindo et al. 2012) and greater severity of other behaviours such as irritability, anxiety, and social withdrawal (Nikolov et al.2009).

Given the lack of consensus on GIS in ASD and given the opportunity of the population-based SNAP study (Baird et al. 2006), this study set out to determine the population-level prevalence of GI symptoms in ASD, including symptoms suggestive of possible enterocolitis (Wakefield 1998), when compared with children with other

developmental disorders but no ASD or typically developing (TD) children. We compared parent-reported past and present GI symptoms in these three groups of similar age children. We assessed whether restricted food intake, severity of ASD, language or intellectual ability or developmental regression were associated with GI symptoms, and screened the ASD group for coeliac disease.


**Methods**

This study received ethical approval from the following Ethics Committees: South Thames (ref MREC 00/1/50); Kent & Medway LREC (ref WK153/8/02), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.


Sample

The sampling methodology of the SNAP study has been described previously (Baird et al. 2006). In brief, within a total population cohort of 56,946 children born between July 1st 1990 and December 31st 1991, all with a current clinical diagnosis of ASD (N=255) or considered 'at risk' by virtue of having a Statement of Special Educational Needs[*] (SEN; N=1,515) were screened using the Social Communication Questionnaire (SCQ) (Rutter et al. 2003). A stratified subsample (by coincidence also N=255) based on SCQ score received a comprehensive diagnostic assessment including standardized clinical observation (Autism Diagnostic Observation Schedule – Generic (ADOS-G); Lord et al. 2000), parent interview assessments of autistic

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[*]A Statement of Special Educational Needs is a legal document issued by the local educational authority when children require significant additional support in school due to any learning and/or behavioural problems.

symptoms (Autism Diagnostic Interview-Revised (ADI-R); Lord et al. 1994), language (BPVS-II) and intelligence (IQ), psychiatric comorbidities (Simonoff et al. 2008) and a medical examination.  All information including ADI-R and ADOS-G was used to derive a clinical consensus diagnosis of ASD (childhood autism and other ASDs; Baird et al. 2006) based on ICD-10 research criteria.  The ASD group was divided into a 'broad ASD' and 'narrow autism' group, the latter defined as meeting autism criteria on the ADI-R, the ADOS-G and clinical consensus ICD-10 childhood autism, and the broad ASD defined as all other cases meeting clinical consensus of any ASD.  Severity of autism was measured in terms of number of ICD-10 symptoms (0-12), ADI-R total scores and calibrated severity scores from the ADOS-G (Gotham et al, 2009).  Regression was defined as in the ADI –R as loss of words or babble with regression of social and play skills. (Baird et al 2008).   Cases not meeting criteria for a diagnosis of ASD were categorized as SEN; these children had special educational needs and a variety of other diagnoses including ADHD, cerebral palsy, language disorders and intellectual disability.

Parental report on GI symptoms was collected at the time of the diagnostic assessment using a questionnaire administered by researcher interview with the parents/carers of the ASD and SEN participants. A questionnaire about diet over 3 days was given to families to complete and return. A blood sample was taken, with consent, from 173 of 255 those in the ASD and SEN groups and a number of analyses performed. In view of the report of the association of autoimmune disorders and autism, (Valicenti-McDermott et al 2008) where there was sufficient blood, a standard diagnostic assay of IgA anti-endomysial antibodies and IgA anti-gliadin antibodies was carried out, in a certified laboratory..

A further 98 typically developing (TD) same age controls (no SEN) were recruited from two mainstream schools within the same geographic area,. Parents were mailed information about the study, a consent form, SCQ and GI symptom questionnaire. The latter was thus completed by post rather than direct interview. An SCQ score of at least 15 was used to screen out possible cases of ASD (Berument et al., 1999).

Measures

A 20-item *GI symptom questionnaire* was constructed both to reflect the presentation of GI symptoms in general paediatric practice and to elicit the presence of possible enterocolitis, symptoms suggestive of an inflammatory condition of the mucosa as suggested by Wakefield et al . (2000 & 2002).. Questions were about current (last three months) and past (prior to the last three months) symptoms. The GI symptoms included: *persistent vomiting* (at least once per day or more than five times in a week)*; stool consistency* (formed, watery or mushy); *abdominal pain* (three or more episodes severe enough to interfere with activity)*, abdominal pain associated with food, bowel movement or sleep*; *constipation* (decreased frequency of bowel movement to less than three times a week in the last three months) and associated symptoms such as *subjective difficulties with bowel movement and harder consistency of stools*; *stool withholding and soiling* (Clayden 2005); *diarrhoea* (loose/watery stools three or more times a day), *weight loss, mouth ulcers, presence of mucus or blood in the stools*. Sub-items of the current and past diarrhoea questions established chronicity (lasting longer than 14 days, with *persistent diarrhoea* being defined as lasting more than 14 days). Five items (*localised*

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*abdominal pain, abdominal pain associated with food consumption, abdominal pain associated with bowel movement, nocturnal abdominal pain* and *watery or mushy stool consistency)* were excluded from the analyses due to a large proportion (>30%) of "do not know" responses across all three groups precluding meaningful analyses.

*Cognitive function* was established using the Wechsler Intelligence Scale for Children-III-UK (WISC) (Wechsler 1992), Raven's Standard Progressive Matrices (SPM) (Raven et al. 1990a) or Coloured Progressive Matrices (Raven et al. 1990b), depending on the child's ability. For children for whom SPM or CPM but not WISC full-scale IQs were available, imputed full-scale IQs were obtained using the regression relationship of full to SPM/CPM IQ within each diagnostic group. The children's verbal abilities were measured by the British Picture Vocabulary Scale-II (BPVS-II: Dunn et al. 1997).

Parents of children with ASD and SEN recorded their child's typical *diet* for three days (including main meals, snacks and drinks over two weekdays and one weekend day), together with the number of different food items habitually eaten, and whether the diet was supplemented in any way or limited by special diet or by faddiness (arbitrary and often unusual likes and dislikes about food) diets as reported by their parents).

Analysis

All analyses were undertaken using Stata 9 (Stata Corporation 2005). Except for the exact number of children with and without GI symptoms, all analyses are weighted to take account of the differences in sampling proportions and the differential response

to the SCQ screening questionnaire associated with a prior local ASD diagnosis, locality and child's sex as well as to completion of the gastro-intestinal questionnaire. Standard errors of simple means and logistic regression contrasts for categorical variables or ordered logistic regression for ordinal variables (current and past GI symptoms counts), Wald test statistics and p-values were calculated using the linearisation version of the robust parameter covariance matrix as implemented by the svy procedures of Stata.

Group differences were examined between the ASD, SEN and TD groups and within the ASD group, between those with and without regression.

GI symptoms were analysed as the following: individual and combined current symptoms  (*persistent vomiting, abdominal pain, recent diarrhoea for more than 14 days, soiling* and *constipation*); individual and combined past symptoms (*persistent vomiting, abdominal pain,  diarrhoea lasting more than 14 days,* and *stool withholding)*; 'possible enterocolitis' (the presence of 2 or more of 4 current GI symptoms*: persistent diarrhoea, weight loss, abdominal pain* or *blood in stool* plus *past persistent diarrhoea* and excluding *current constipation*); lifetime (past and current) symptoms of constipation (current constipation and past stool withholding), abdominal pain, vomiting and diarrhoea (same items reported in the past and currently)  and lifetime GI symptoms but dissimilar in type (any past and current symptoms).   Missing items were pro-rated for the purposes of generating symptom counts.

Within the ASD group, associations between GI symptoms and cognitive functioning, language, severity of autism, regression and dietary habits were tested by regression analyses.

Results

Of the 255 participants from the Special Needs and Autism cohort, 158 met consensus ASD diagnosis and 97 had special educational needs with a variety of other diagnoses (SEN) but did not meet criteria for a diagnosis of ASD.  Of these, 218 (132 ASD, 86 SEN) completed the GI questionnaire; missing data were largely due to time constraints on the day of the assessment. Five SEN cases were subsequently excluded from this analysis on the basis that gastrointestinal problems would likely be integral to their diagnoses of cerebral palsy (3), neuropathic bladder and bowel (1), and spina bifida (1). Regression was reported in 26 children with ASD. There was sufficient blood for IgA anti-endomysial antibodies and IgA anti-gliadin antibodies in 77 (68 with ASD).

Parents of 90 of the 98 TD children completed the GI questionnaire. 8 TD children were excluded from analysis due to SCQ scores of 15 or above. The present report is of the 295 participants who completed the GI questionnaires (132 ASD, 81 SEN, and 82 TD children).

Group characteristics are presented in Table 1. There were no significant IQ or BPVS-II differences between the ASD and SEN groups (adjusted Wald test, $p = .94$). Participants who completed the GI questionnaire did not differ from those who did not in terms of IQ ($p = .10$) , or autism severity as measured by ICD-10 symptom counts ($p = .71$) or ADOS-G severity scores ($p = .10$).

*Lifetime gastro-intestinal (GI) symptoms*

Table 2 shows the weighted mean scores and their 95% confidence intervals (CI) of the current or past GI symptom groups and the weighted rates of individual GI symptoms.

Nearly half (58 out of 128; weighted rate 46.5%) of children with ASD had at least one GI symptom in their lifetime (in the past or currently) compared with 22.9% of typically developed children (adjusted Wald test, $p = .01$) and 25.3% of those with SEN ($p = .02$).


*Current GI symptoms*

Children with ASD had significantly higher rates of reported current GI symptoms than the TD group (mean symptom counts = 0.56 and 0.25 respectively, $p < .001$) and the SEN group (mean SEN symptom count = 0.24, $p < .001$). In particular, higher rates of soiling were reported in the ASD group (18.7%), compared with the TD group (8.5%; adjusted Wald test, $p = .04$ ) and the SEN group (4.7%; $p = .01$). When soiling was removed from the total current GI symptoms, the ASD group continued to show a higher number of current GI symptoms than the TD group ($p<0.001$) and the SEN group ($p < .001$).

The constipation symptom of decreased frequency of bowel movements (less than three times per week), was more commonly reported in the ASD group (16.7%) compared with the SEN group (2.6%; $p = .04$), although comparison with the TD group (4%) did not quite reach statistical significance ($p = .05$). There was no significant difference in rates of constipation across all groups when the criteria for

current constipation  included  harder consistency of stool or difficulty in passing a bowel movement plus decreased frequency of bowel movement (p >.06 for both comparisons).

*Past GI symptoms*

Parents of the ASD group reported significantly more past GI symptoms (mean symptom count = 0.63) than the TD group (mean symptom count = 0.27, $p$ = .02). This difference was composed of increased vomiting and diarrhoea  in the ASD than TD group (14.6% versus 1.2% for vomiting, $p$ = .02; and 16.1% versus 0% for diarrhoea, $p$ < .001 ). Past abdominal pain was reported more frequently in the ASD (21.7%) than the SEN group (6.4%, $p$ = .04) with no significant difference between ASD and TD groups.

*Persistence of GI symptoms over time*

Fewer GI symptoms were reported currently compared to the past in all groups. All groups reported some children who had both past and current GI symptoms with no significant difference found between the groups (11% of TD children, 24% of SEN and 16% of ASD children had at least one past and one current symptom and 0.2% of TD children, 2.9% of SEN and 5.8% of ASD children had at least two past and two current symptoms).

Mouth ulcers were the only symptoms reported in the past and currently in the same individual across all three groups (adjusted Wald tests, $p$ <.001).

Past abdominal pain was associated with current abdominal pain in the ASD group ($p$ = .01), but not the other groups

Four children with ASD had past diarrhoea and current constipation and abdominal pain.

Past stool withholding was not associated with current constipation symptoms or current soiling in any group. There were no significant differences in lifetime constipation, defined as frequency of bowel movement less than three times per week currently (or when hardness and difficulty are included) plus past stool withholding, across the groups although the numbers are small (3 TD, 0 SEN, 6 ASD).

*Gastro-intestinal disorder*

One child, in the SEN group, had GI symptoms that met the enterocolitis definition.

*Association with gender, IQ, verbal ability and ASD severity*

There was no association between gender and current or past GI symptom counts ($p$ = .12 and $p$ = .83) for the sample as a whole, or for the TD group where gender was more balanced (adjusted Wald tests, $p$ >.30). There was no difference in IQ for cases with and without reported GI symptoms in either the SEN group (weighted mean IQs = 68.8 and 73.9, $p$ = .38) or the ASD group (mean IQs = 72.7 and 68.8, $p$ = .53). Within the SEN and the ASD groups, no relationship was found between IQ and current symptoms ($p$ = 0.30 and $p$ = 0.10), or between IQ and past GI symptom counts ($p$ = 0.38 and $p$ = 0.98 for the SEN and ASD groups respectively). There was no significant difference in BPVS-II standard scores between children with and without reported past abdominal pain or constipation.(mean BPVS-II standard scores for those with and without past abdominal pain = 82.9 and 79.3 respectively, $p$ =.53; mean scores for those with and without constipation = 76.3 and 80.0, $p$ =.78). There

were no significant associations between autism severity, in terms of ICD-10 symptom scores, ADI-R totals or ADOS-G severity scores, and current or past GI symptoms (all $p >.09$) in the ASD group.

*Table 2 about here*

*Regression*

There were no differences between ASD children with and without a history of regression for current ($p =.18$) and past ($p = .62$) GI symptom counts.

*Screening for coeliac disease*

One child with ASD of the 68 whose blood was analysed had positive endomysial antibodies (subsequently diagnosed on retest and confirmatory mucosal biopsy as coeliac disease) but had no GI symptoms.

*Diet*

Sufficiently detailed parental information on food selectivity for analysis was available on only 68 children (24 SEN and 44 ASD) who had also completed the GI symptom questionnaire. Those who completed the diet questionnaire did not differ from those who did not in terms of IQ, ICD-10 score, current or past reported GI symptoms (all $p >.32$). A 'limited' diet was defined as less than 10 food items in the diet; two parents reported diets with fewer than 5 food items (one with ASD and the other SEN without ASD). In all, 19 (43.2%) children with ASD were reported to have a limited diet compared to 6 (25.0%) with SEN ($p =.14$). Eleven 11 (25.0%) children

with ASD and 5 without ASD (20.0%) had faddy diets as reported by their parents (*p* =.70). A limited or faddy diet did not account for any of the group differences found in relation to GI symptoms.

*Table 3 about here*

Discussion

In this population-derived group of same age children with ASD, their parents reported at least one lifetime GI symptom (46.5%) compared with TD children within the same age range (21.8%) and with an SEN group (children with special educational needs without ASD ( 29.2%).

These lifetime group differences are composed of a greater number of both past and current symptoms in the ASD group.   There were more past symptoms of diarrhoea and vomiting in ASD ( 14.6% vomiting in ASD versus 1.2% in TD and  16.1% diarrhea in ASD versus 0% in TD), and  past abdominal pain in the ASD group in the SEN group (21.7% compared with 6.4%).  Current group differences are in reported bowel movements of less than three times per week (16.7% in ASD, 4% in TD and 2.6% in SEN)  and soiling  (reported in 19% compared with 8.5% of TD and 5% of SEN groups). Since the symptom of soiling could be due to a variety of causes not all related to GI problems, the lifetime GI symptom comparison was repeated with and without soiling. Significant differences remain between the groups for lifetime reported GI symptoms with more in the ASD group (46%).

Constipation is reported to be one of the commonest GI symptoms in ASD, (Gorrindo et al. 2012), although the frequency reported in previous studies: 8.8% (Taylor et al. 2002), 9.4% (Fombonne and Chakrabarti 2001), and 10.9% in the current study, are not significantly different from the reported 9% in the general paediatric population (Kokkonen et al. 2004). The cumulative incidence of lifetime constipation was found by Ibrahim et al. (2009) to be significantly different between ASD individuals and controls by age 20 years, which is compatible with Pang and Croaker's (2011) findings from a constipation clinic of reported earlier onset and longer history in those with ASD with symptoms and signs similar to slow transit constipation. The issue of the precise diagnosis of childhood constipation is contentious and we chose to use a measure developed in our own institution by Clayden (2005) and informed by ROME III discussions which were contemporaneous with this study (2006) which highlights that frequency of bowel evacuation, difficulty with or distress in defaecation, with or without the presence of harder stools or soiling will identify the majority of children with constipation. Our reported rate of current constipation varies depending on the definition used.  While a decrease in frequency of bowel movement to less than three times per week was reported in 16.7% of ASD cases, which is significantly different from the SEN group and just misses statistical significance from the TD group, only 10.9% with ASD met  criteria for constipation which included  harder consistency of stool and difficulty in passing a bowel movement, a rate of current constipation that is not significantly different between groups.  Stool withholding or a history of retentive behavior is sometimes included in the definition of constipation. The frequency of reporting of this past symptom in the present study was not statistically significantly increased in the ASD group and the number of children who

had a combination of past stool withholding and current constipation (lifetime constipation) is too small in all groups for meaningful comparison.

A frequent parent-reported GI symptom in our study was abdominal pain, both past and current, in both TD and ASD groups, but with persistence over time in the ASD, not in the TD group. The rates of current abdominal pain (8.5% in the TD group) are lower than that of the population based Finnish study (Kokkonen et al. 2004) in which 16% met the Apley criteria of recurrent abdominal pain, although our past rate is comparable.

Past persistent diarrhoea was reported in 16% of the ASD group; with none in the TD group, the SEN group being intermediate (7%). This symptom had largely disappeared by age 11 years in the ASD group but a subgroup (4 children) now had symptoms of constipation (a pattern not found in either the SEN or TD groups).

The intention was to distinguish between GI symptoms due to acute viral illness and other causes including toddler diarrhoea  (chronic non-specific diarrhoea defined as more than 3 loose stools per day for more than 14 days in a child aged between 6 months and 5 years  of age who has no evidence of bowel infection or malabsorption and who is growing normally). However, it is not always easy to do so with certainty in retrospective recall. We may have underestimated viral induced diarrhoea. More persistent chronic non-specific diarrhoea in ASD may be one explanation of the findings. What we can say is that persistent diarrhoea was differentially experienced

in the past across the three groups and had largely disappeared by age 11 years but the cause is unknown.

Past persistent vomiting was reported with similar frequency in both ASD and SEN groups but infrequently in the TD group. This symptom also had substantially but not completely disappeared by age 11 years and there was no significant association between past and current vomiting

Soiling was reported in a striking 19% of those with ASD and 8.5% of the TD group for which we have no explanation. We found no association with past withholding, abdominal pain or diarrhoea or current constipation-however defined- (in contrast to the report of fecal incontinence by Badalyan and Schwartz 2011). Further, more detailed questioning and examination is required to distinguish possible causes.

We found no association between the presence of parent-reported GI symptoms, current or past, and current autism symptom severity (defined by ICD10 symptom score, ADI-R or ADOS score), verbal ability, or intellectual ability.. Nor did we find evidence for an association of GI symptoms in the ASD group with limited dietary intake, consistent with Gorrindo et al. (2012) and  Levy et al. (2007) but at this age, the frequency of limited diet was not significantly different between the ASD and control groups. Consistent with Fombonne and Chakrabati's 2001 study (and in contrast to other studies, Richler et al. 2006; Valicenti-McDermott et al. 2006), we did not find an association between GI symptoms and developmental regression in the ASD group.

We did not find any difference in reported diagnosed GI *disorder* between ASD, SEN and TD groups. The finding of one child with ASD with endomysial antibodies, subsequently confirmed and diagnosed as coeliac disease, is consistent with population prevalence.

One possible explanation of the variation in reported GI symptoms between studies may be difference in definition of GI symptoms eg we find a variation in prevalence depending on number of symptoms beyond frequency required for the diagnosis of constipation; Valicenti-McDermott et al. (2006)'s 'lifetime abnormal stooling;pattern' does not make a clear distinction between current or chronic diarrhoea and toddler diarrhoea; 'change in stool frequency' and 'change in stool consistency' could refer to current or past constipation, or diarrhoea in Richler et al. (2006).

Sample characteristics may also be relevant including the age of the children. We found a difference in GI symptoms with age in that all symptoms but particularly diarrhoea and vomiting, had diminished by 10-11 years. Gorrindo et al (2012) also reported an association between younger age and increased GI symptoms, particularly constipation.

The strengths of our study include the population-based sampling and statistical analyses that uses weights to provide accurate prevalence rates, with appropriate control groups of similar age and intellectual abilities. The GI symptoms have been clearly defined and continuity of symptoms established..

There are several limitations. The SNAP study included all children with a local diagnosis of ASD and screened those with special educational needs which will have identified children with impairment but the whole mainstream population was not screened. Thus it is possible that some children with an ASD diagnosis but without impairment to 10 years of age were missed.

GI symptoms were elicited by parent report and not by a gastroenterologist who was also able to examine the participants and distinguish chronic diarrhoea or soiling, for example, due to constipation with overflow or abdominal pain due to constipation etc. However Gorrindo et al's study shows high concordance between parental and gastroenterologist for the presence of GIS.

A further limitation is that the GI symptoms were elicited by postal questionnaire for the TD group and by face to face interview for the ASD and SEN groups. The effect of this is unknown on the reported rates of symptoms. However, the rates of lifetime GI symptoms in our controls (29.2% in SEN and 21.8% in TD) were similar to those of a Finnish population-based study (Kokkonen et al. 2004) of children aged 10-11 years old (33%), suggesting that our GI questionnaire had reasonable sensitivity and that the method of administering the GI questionnaire is unlikely to have contributed to the results.

There is a male preponderance particularly in the ASD compared to the TD group which may impact on symptom frequency however no sex differences were found within the TD group, and sex was included in the weighting procedure for the SEN and ASD cases. The SEN and TD groups had a small mean age difference from the ASD group which may have had an unknown effect on the results.

We do not have sufficient information about any medications the participants were taking which may have an influence on GI symptoms although medication was not significant in Gorrindo et al. (2012).

Our study supports previous findings that lifetime GI symptoms are more commonly reported in children with ASD compared with TD children and those with other SEN, and are not associated with regression, current dietary habits, IQ or severity of autism. However, in a group aged 10-14 years, many of the symptom differences are past rather than present with the exception of decreased frequency of bowel actions and soiling (which may have several causes including constipation which this study cannot elucidate).

The prevalence of particular GI symptoms may be related to the age of the child at ascertainment of GI symptoms as has been noted by others (Gorrindo et al., 2012). This is a variable that needs to be taken into account in future studies. Symptoms change over time eg the report of persistent diarrhoea in the past but not currently. Some children in all groups have both past and current GI symptoms. Mouth ulcers were consistently present over time within individuals across all groups. We noted two symptom patterns in the ASD group that were not found in the other two groups: one with a persistence of abdominal pain, reported both in the past and currently; the other of past persistent diarrhoea with current constipation and abdominal pain. However before conclusions can be firmly drawn about age related symptoms and patterns of persistence of symptoms, much larger longitudinal population samples are needed with symptoms ascertained at particular ages using agreed criteria.

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**Table 1: Group characteristics (only for the children for whom GI symptom data were available)**

| | TD | SEN controls | All ASD children | Broad ASD | Narrow Autism |
|---|---|---|---|---|---|
| | N=82 | N=81 | N=132 | N=89 | N=43 |
| **Males, females** | 49, 33 | 70, 11 | 117, 15 | 76, 13 | 41, 2 |
| **Age range (years)** | 11.6-12.8 | 10.1-14.2 | 10-13.8 | 10-13.8 | 10.2-13.6 |
| **Mean (SD)** | 12.2 (0.34) | 12.8 (0.93) | 11.6 (0.85) | 11.5 (0.86) | 11.6 (0.86) |
| **IQ** | | | | | |
| **Mean score (SE)** | n/a | 70.61 (2.79) | 70.93 (3.07) | 73.71 (3.82) | 60.43 (2.91) |
| **95% CI** | | 65.1 -76.1 | 64.9-77.0 | 66.1-81.3 | 54.7-66.2 |
| **Regression** | n/a | 2 | 26 | 8 | 18 |
| **ICD-10 score** | | | | | |
| **Mean (SE)** | n/a | 1.7 (0.21)* | 7.3 (0.29)* | 6.4 (0.27) [†] | 10.3 (0.23) [†] |
| **95% CI** | n/a | 1.3-2.1 | 6.7-7.8 | 5.9-7.0 | 9.9-10.8 |
| **ADI-R total score** | | | | | |
| **Mean (SE)** | n/a | 6.0 (0.57)* | 21.0 (0.97)* | 19.8 (1.12) [†] | 26.1 (0.91) [†] |
| **95% CI** | n/a | 4.7-6.9 | 19.1-23.0 | 17-5-22.0 | 24.3-27.9 |
| **ADOS-G severity score** | | | | | |
| **Mean (SE)** | n/a | 2.3 (0.27)* | 5.4 (0.35)* | 4.5 (0.38) [†] | 8.5 (0.27) [†] |
| **95% CI** | n/a | 1.8-2.8 | 4.7-6.0 | 3.8-5.3 | 8.0-9.1 |

| BPVS-II standard score | | | | | |
|---|---|---|---|---|---|
| **Mean (SE)** | n/a | 77.4 (2.43) | 83.0 (2.57) | 85.2 (3.03) | 73.2 (3.67) |
| **95% CI** | n/a | 72.6-82.2 | 77.9-88.0 | 79.2-91.2 | 66.0-80.5 |

Except for the exact numbers of individuals in each group, males and females, children with regression and age, mean scores, their linearised standard errors (LSE) and 95% confidence intervals (CIs) are all weighted.

*p<0.001 (Adjusted Wald Test)

**Table 2: Weighted mean values of composite symptom counts and weighted proportions of endorsed individual GI symptoms across diagnostic groups (N = row counts)**

| Gastro-intestinal Symptoms | TD controls N=82[a] | SEN controls N=81[a] | ASD N=132[a] |
|---|---|---|---|
| **CURRENT GI symptom count (including soiling)** | | | |
| Mean (LSE) | 0.25 (0.07)* | 0.24 (0.08)[†] | 0.56 (.10)*[†] |
| Range | 0-3.67 | 0-3.67 | 0-3.67 |
| 95% Confidence Interval | 0.12-0.38 | 0.08-0.39 | 0.35-0.76 |
| **CURRENT GI symptom count (excluding soiling)** | | | |
| **Mean (LSE)** | 0.17 (0.05)* | 0.19 (0.07)[†] | 0.35 (0.09)*[†] |
| **Range** | 0-2.67 | 0-2.67 | 0-2.67 |
| **95% Confidence Interval** | 0.07-0.27 | 0.04-0.33 | 0.17-0.53 |
| **Individual current symptoms** | *% (N)* | *% (N)* | *% (N)* |
| Persistent vomiting | 0 (0) | 3.5 (3) | 1.3 (2) |
| Abdominal pain | 8.5 (7) | 5.1 (4) | 12.6 (19) |
| Diarrhoea | 0 (0) | 11.0 (3) | 2.7 (3) |
| (Reduced frequency of bowel movement) | 4.0 (3) | 2.6 (2)* | 16.7 (14)* |
| Constipation (3 symptoms[b]) | 3.7 (3) | 1.8 (1) | 10.9 (8) |
| Soiling | 8.5 (7)* | 4.7 (5)[†] | 18.7 (26)*[†] |
| Blood in stools | 0 (0) | 0 (0) | 1.9 (4) |
| Mucus in stools | 0 (0) | 0 (0) | 10.3 (5) |
| Current mouth ulcers | 7.3 (6) | 9.7 (4) | 6.5 (13) |
| **PAST GI symptom count** | | | |
| Mean (LSE) | 0.27 (0.06)* | 0.28 (0.09) | .63 (.11)* |
| Range | 0-4 | 0-4 | 0-4 |
| 95% Confidence Interval | 0.14-0.40 | 0.12-0.45 | 0.51-0.85 |
| **Individual past symptoms** | *% (N)* | *% (N)* | *% (N)* |

| | | | |
|---|---|---|---|
| Persistent vomiting | 1.2 (1)* | 12.5 (7) | 14.6 (18)* |
| Abdominal pain | 16.1 (13) | 6.4 (5)* | 21.7 (26)* |
| Diarrhoea | 0 (0)* † | 6.9 (6) † | 16.1 (18)* |
| Stool withholding | 4.9 (4) | 4.4 (2) | 10.8 (16) |
| Past mouth ulcers | 17.1 (14) | 13.1 (8) | 13.0 (18) |

*, † p<0.05 (Adjusted Wald Test)

[a] Total Ns for weighted cell proportions vary slightly, depending on amount of missing data, largely due to 'do not know' responses on individual items of questionnaire

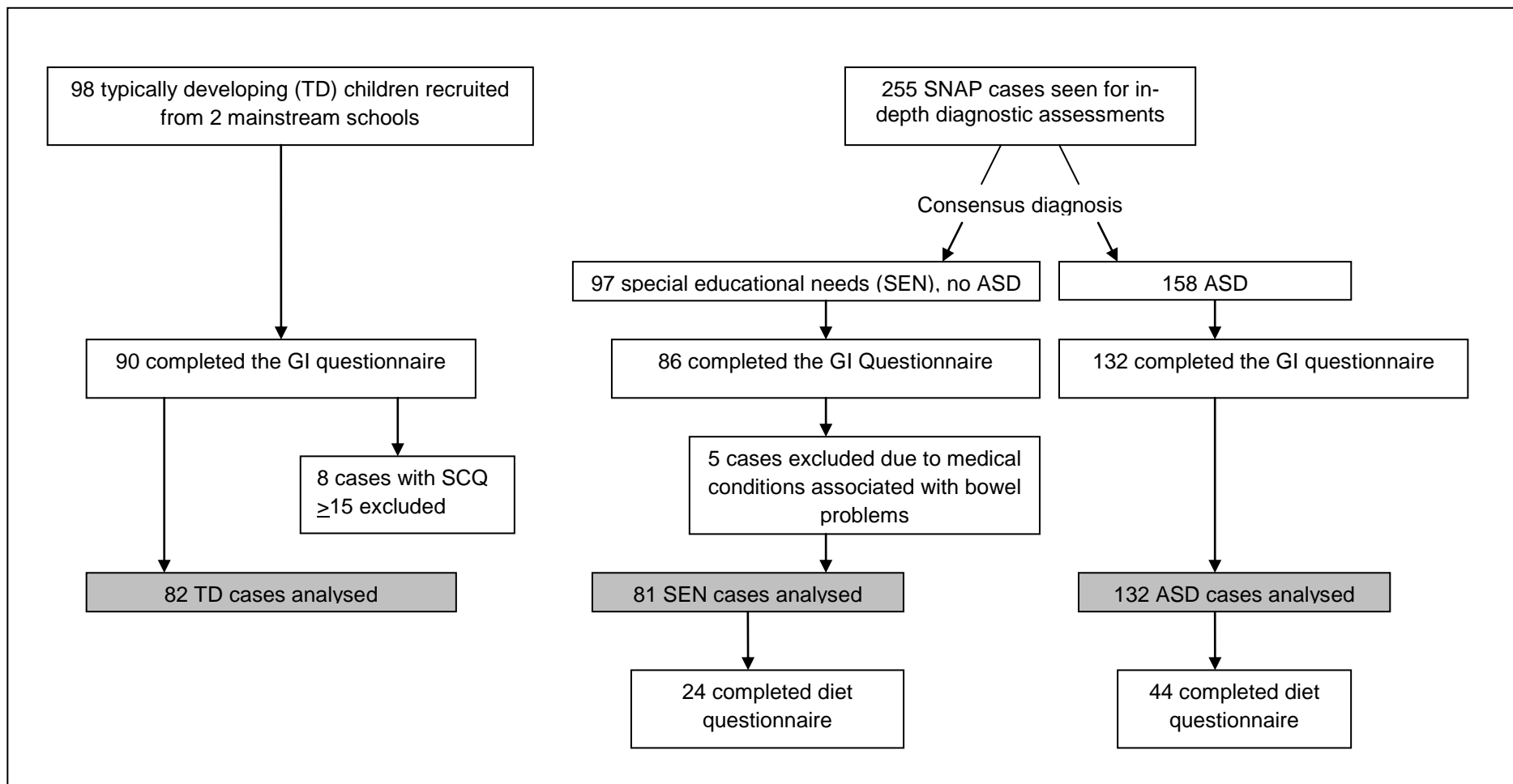[b] Constipation defined as a decrease in frequency of bowel movement, with harder consistency of bowel movement, and difficulty in passing a bowel movement.

Figure 1.  Case ascertainment