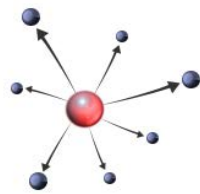

Guideline Supplementary Paper

New Zealand Autism Spectrum Disorder Guideline supplementary paper on gastrointestinal problems in young people with ASD



INSiGHT
Research Ltd

Independent Network of Specialists in Guidelines & Health Technology

With the support of the New Zealand Autism Spectrum Disorder
Living Guideline Group

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Funding and independence

This work was funded by the New Zealand Ministry of Health and sponsored by the New Zealand Ministry of Education.

The work was researched and written by INSIGHT Research Ltd employees or contractors. Appraisal of the evidence, formulation of recommendations and reporting are independent of the Ministries of Health and Education.

Statement of intent

INSIGHT Research produces evidence-based best practice guidelines, health technology assessments and literature reviews to help health care practitioners, policy-makers and consumers make decisions about health care in specific clinical circumstances. The evidence is developed from systematic reviews of international literature and placed within the New Zealand context.

Guidelines, including supplementary papers, are not intended to replace the health practitioner's judgment in each individual case.

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About the evidence review

Purpose

The New Zealand Autism Spectrum Disorder Guideline (the ASD Guideline) [1] was published in April 2008. As part of their commitment to the implementation of the guideline, New Zealand's Ministry of Health and Ministry of Education agreed to establish a Living Guideline process in 2009. This process is where a guideline is regularly updated and refined to reflect new evidence and changing user needs.

Updates within the living guideline process are required when the recommendations in the guideline are no longer considered valid in view of research evidence that has emerged since the guideline's literature searches were conducted. A multidisciplinary team from the Living Guideline Group (LGG) which is responsible for identification of areas for update, consideration of new evidence and reporting on any implications for guideline recommendations.

This supplementary report describes a systematic review which aims to provide an evidence-based summary of research published in or beyond 2004 relating to gastrointestinal problems for children and young people with Autism Spectrum Disorder (ASD) so as to update the evidence considered in the ASD Guideline [1]. Also reported are revised and new recommendations pertinent to the topic developed by the Living Guideline Group following consideration of the reviewed evidence.

The systematic review was undertaken by INSIGHT Research to support the work of the New Zealand Autism Spectrum Disorder Guideline's Living Guideline Group. The methodology followed is consistent with that undertaken for previous supplementary reports of the LGG which were developed and conducted by the New Zealand Guideline Group [2-4].

The systematic review and the entire living guideline process was funded by the Ministry of Health, and sponsored by the Ministry of Education.

Scope of the evidence review

This review aims to systematically update the evidence relating to gastrointestinal (GI) problems in children and young people (aged 18 years or under) with Autism Spectrum Disorder (ASD). The Living Guideline Group have identified this area as worthy of an update and one which could lead to revised or additional recommendations in the ASD Guideline [1].

Some researchers have targeted GI symptomatology as a means of investigating hypotheses about the aetiology of ASD, and as a rationale for employing (unproven) treatments for core symptoms of ASD. These issues are beyond the scope of the

current review update. The reader is referred to the New Zealand ASD Guideline for a comprehensive account of evidence and recommendations relating to treatments, including complementary and alternative dietary interventions.

Because this report is specific to the gastrointestinal problems potentially occurring in young people with ASD, there is a risk that this emphasis might lead health professionals to give pre-eminence to GI assessment over (say) assessment of learning, co-morbid mental health and developmental issues and family functioning, such as the need for respite care. Therefore, this document needs to be read in context of the recommendations in the ASD Guideline [1] regarding the need for all children with ASD to undergo a comprehensive health and developmental assessment.

Definitions

ASD is a group of pervasive developmental disorders that affects communication, social interaction and adaptive behaviour functioning. Subgroups of ASD include Pervasive Developmental Disorders (PDD), classical autism, Asperger syndrome, and Pervasive Developmental Disorders – Not Otherwise Specified (PDD-NOS) (as defined by criteria specified in ICD-10 and DSM-IV diagnostic manuals). There is a diverse range of disability and intellectual function expressed by people with ASD, from severe impairment of a person with classical autism, to a ‘high functioning’ person with Asperger syndrome. A wide range of services and approaches are required to reflect the heterogeneity of the condition.

In this review unless otherwise stated, *gastrointestinal problems* refer to dysfunction that is evident in clinical symptoms, usually chronic, persistent, recurrent, frequent or excessive in nature, which do not have clear anatomic, metabolic, or pathologic process. These problems may include the following:

- chronic constipation
- diarrhoea; faecal incontinence; encopresis (faecal soiling); changes to bowel habit
- vomiting; nausea; gastroesophageal reflux (GER)
- abdominal pain, discomfort, irritability; bloating; flatulence.
- It should be noted that encopresis might be a symptom of constipation. Chronic diarrhoea may be defined as motions occurring several times a day or motions which are of normal or reduced frequency but are abnormally loose.

Target audience

This evidence review and guidance update is intended primarily for the providers of professional health services for New Zealanders with ASD. It is also expected that the recommendations will be accessed by people with ASD and their families.

Treaty of Waitangi

INSIGHT Research acknowledges the importance of the Treaty of Waitangi to New Zealand, and considers the Treaty principles of partnership, participation and protection as central to improving Māori health.

INSIGHT Research's commitment to improving Māori health outcomes means we attempt to identify points in the guideline or evidence review process where Māori health must be considered and addressed. In addition, it is expected that Māori health is considered at all points in the guideline or evidence review in a less explicit manner.

Recommendation development process

The research questions were identified and prioritised by the Living Guideline Group and were used to inform the search of the published evidence. A one day, face-to-face meeting of the Living Guideline Group was held on 29 November 2012, where evidence was reviewed and recommendations were developed.

INSIGHT Research follows specific structured processes for evidence synthesis. Full methodological details are provided in **Appendix 1**. This appendix also includes details of the Living Guideline Group membership and lists the organisations that provided feedback during the consultation period. **Appendix 2** presents a glossary of key epidemiological and topic-specific terms, abbreviations and acronyms. **Appendices 3** and **4** present full evidence tables of included studies.

Summary

Summary of revised and new recommendations

Revised recommendation relevant to gastrointestinal problems in children and young people with ASD

Original Reference	Revised recommendation	Grade
4.6.1	When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders, depression, and gastrointestinal problems.	C

New recommendations relevant to gastrointestinal problems in children and young people with ASD

Reference	New recommendations	Grade
4.1.4a	Gastrointestinal problems, specifically constipation, chronic diarrhoea, altered bowel habits, and encopresis (faecal soiling), are more common in children and young people with ASD compared with typically developing peers.	B
4.1.4b	Children and young people with ASD should have a full evaluation that includes a thorough assessment of gastrointestinal function. Some children, particularly those with social communication difficulties, may have atypical presentations such as increased anxiety, irritability, disordered sleep patterns, and unusual vocalisations and movements.	C

1 Introduction

1.1 Gastrointestinal problems in ASD

Based on initial observations of people with autism spectrum disorder attending specialty clinics [5], researchers have suggested that gastrointestinal (GI) problems may be more common in ASD than in the general population [6]. The GI problems reported have tended to be functional clinical symptoms which are persistent, frequent or excessive in nature, and which do not indicate a clear anatomic, metabolic, or pathologic process. Examples recorded in the literature include the following: constipation; stomach pains, indigestion, gaseousness or bloating; diarrhoea, discoloured, watery stools; reflux or vomiting; night time waking; and unexplained irritability [7].

A multi-disciplinary expert panel forum held in Boston, United States, in 2008 considered the evidence on the prevalence of functional GI problems in ASD [7]. The forum reported a “preponderance of data” consistent with the likelihood of a high prevalence of GI symptoms and disorders associated with ASD. However specific prevalence rates observed for GI symptomatology in ASD populations have been inconsistent [7, 8], ranging from 9% in a study of children pre diagnosis of ASD [9] to over 70% [10]. The lack of consistency appears to relate to wide variations in study methods, including the definitions of GI problems used, measurement tools employed, and sources of study participants. More recently, a UK guideline on recognition, referral and diagnosis of ASD in children and young people included functional gastrointestinal problems as a co-existing condition in ASD [11]. Specific GI symptoms and disorders identified included constipation, altered bowel habit, faecal incontinence or encopresis.

The reasons why some conditions may occur more commonly in people with ASD is not well understood [11]. Whilst GI problems arising in people with ASD may have the same causes as GI problems in people without ASD, some researchers have suggested that people with autism are especially susceptible to gastrointestinal dysfunction. Various theories have been proposed, some controversial, and the area has attracted vigorous debate and investigation over the past decade.

One theory has suggested that people with ASD have “leaky gut syndrome”, where the intestinal lining is inflamed and more porous than usual. Other research has investigated whether people on the autism spectrum may be more prone to viral, bacterial and fungal infections and gastrointestinal parasites. It has also been suggested that people with autism may be exhibiting immune dysregulation, allergies and an inability to digest certain substances, such as gluten or casein. Gastrointestinal problems such as constipation have also been linked to nutritional inadequacies linked to food selectivity, feeding habits, pica, and restricted diets, behaviours commonly observed in children and young people with ASD. Having adverse reactions

to some medications with known side effects including constipation have also been hypothesised to account for increased GI symptomatology in ASD [6, 12].

Some researchers have targeted GI symptomatology as a means to investigating hypotheses about the aetiology of ASD. Investigators have also cited evidence of increased GI dysfunction in children and young people with ASD as a rationale for employing (unproven) dietary/supplement treatments to treat core symptoms of ASD. It is important to note that these issues are beyond the scope of the current review update. The reader is referred to the New Zealand ASD Guideline for a comprehensive account of evidence and recommendations relating to treatments, including complementary and alternative dietary interventions [1].

1.2 Presentation of gastrointestinal symptomatology

A key challenge in recognising and characterising gastrointestinal dysfunction in children and young people with ASD relates to the communication difficulties which are a core feature of autism. Describing intestinal discomfort can be difficult for children and young people in general, but challenges are enhanced for people on the autism spectrum who are non-verbal or minimally verbal [7].

The UK ASD guideline [11] recommended that in the case of recognising GI problems, particular attention be given to information from other sources (including direct observation of the child or young person) and in different settings. It has been observed that the communication difficulties in ASD can lead to unusual presentations of GI problems, including behavioural difficulties [13].

The US expert forum referred to earlier [7] considered presenting signs and symptoms for GI problems in the ASD population as part of its review and development of consensus statements, which have been adopted by the American Academy of Pediatrics. Typical and atypical presentations of underlying GI disorders identified included sleep disturbance; aggressive or self-injurious behaviour; chronic diarrhoea; straining to pass stool, or hard or infrequent stool; flatulence and/or bloating.

Both the recently published UK practice guideline [11] and the US consensus panel's report [7] have been considered as a foundation to the current review, updated by more recent primary research.

1.3 Recommendations relating to GI problems in the NZ ASD Guideline

In the New Zealand ASD Guideline [1], gastrointestinal problems are not currently included in a list of known co-morbidities (see Section 1.3a, p. 57). Gastrointestinal problems are mentioned briefly in Section 2.3.b of the ASD Guideline [1] such that “constipation” is listed among several health issues about which “no reliable evidence

was found". Relevant to this statement, a specific recommendation suggests further research be undertaken on needs of people with ASD with regard to constipation, allergies, medication reactions, menstruation and need for regular exercise (Recommendation 2.3.9).

More generally, in Section 2.3 relating to physical well-being, the guideline recommends that pre-treatment assessments screen for medical conditions (Recommendation 4.1.4) and lists common comorbidities. The assessment of co-morbid conditions, including seizures, attention deficit hyperactivity disorder, anxiety disorders and depression, is also advised when severe behaviours are present (Recommendation 4.6.1). Gastrointestinal problems are not mentioned as a possible co-morbidity with respect to either recommendation.

All three recommendations are presented in **Table 1.1**. The criteria used for grading the recommendations are reproduced in the Appendices (**Table A1.2**).

1.4 Objectives of the current review update

The objective of this review update was to:

- systematically identify, select, appraise and synthesise research evidence published since January 2004 relating to the co-occurrence and presentation of gastrointestinal problems in children and young people with autism spectrum disorder; and to
- consider this evidence as it supplements that of the original ASD Guideline [1] to revise existing recommendations or develop new ones.

Table 1.1: Recommendations relevant to, or that may be modified to address, gastrointestinal problems in children and young people [1]

Original Reference	Original Recommendation	Grade
2.3.9	Research should be undertaken to identify the needs of people with ASD with regard to constipation, allergies, medication reactions, menstruation and exercise.	C
4.1.4	Pre-treatment assessments should gather detailed information on behavioural, emotional and mental health difficulties, address differential diagnosis, screen for medical conditions and address environmental issues.	B
4.6.1	When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders and depression.	C

2 Gastrointestinal problems in children and young people with ASD

This chapter describes the findings of a systematic review update relating to gastrointestinal (GI) problems in children and young people with ASD. It also reports the development of new and revised recommendations by the Living Guideline Group to supplement the ASD Guideline [1] on this topic.

2.1 Scope and methods

Research questions:

The review update's first research question relates to the prevalence of gastrointestinal problems in children and young people with ASD, specifically:

- Question 1: Are gastrointestinal problems more common in children and young people with ASD than those without ASD?

A second question relates to how children and young people with ASD with GI problems present to their health provider:

- Question 2: What gastrointestinal signs or symptoms, typical and atypical, should be investigated in children and young people with ASD?

Sample

Included were children and adolescents aged 1-18 years diagnosed with Autism Spectrum Disorder (ASD) as classified by or consistent with DSM-IV-TR. Children aged under 1 year were excluded as a diagnosis of ASD is difficult to establish at that age. Adults were excluded because gastrointestinal issues vary between children and young people and adults.

Study designs

Methodological designs eligible for inclusion varied for the review questions as described below.

Question 1

Eligible designs were observational studies which compared children and young people with ASD to those without ASD in terms of the prevalence of gastrointestinal problems. Included were prospective cohort studies, retrospective cohort studies and descriptive cross-sectional studies. Case-control studies and case series studies where

cases are defined as people with GI problems were also excluded as these are inappropriate for the study question.

Question 2

The studies appraised for Question 1 were also relevant to Question 2 in describing gastrointestinal signs, symptoms and characteristics arising in children and young people with ASD. The expert forum held in Boston [7] also considered typical and atypical signs of GI dysfunction specifically. To supplement these findings the current review was restricted to observational and descriptive cross-sectional studies of children and adolescents with ASD where they identified *atypical* behavioural signs and symptoms associated with co-occurring GI problems. These included vocal and motor behaviours as well as changes to state of being (such as sleep disturbance or irritability). Case series of people with GI problems alone were excluded.

Identification and selection of studies for inclusion

Search strategies were limited to publications from January 1 2004 onwards to ensure capture of articles published since the search was conducted for the original ASD Guideline [1]. Studies already appraised in the ASD Guideline were excluded from the current review regardless of date of publication.

Sixteen bibliographic, health technology assessment and guideline databases were included in the systematic search. The search was updated on 22-27 August 2012 and identified 886 articles. References of retrieved articles were also cross-checked to identify additional articles.

Selection criteria were applied to abstracts to identify articles for retrieval, and then to retrieved full text articles, to identify included studies. Selection criteria for included and excluded studies are described in **Tables 2.1** and **2.2** respectively.

Critical appraisal of included studies

Included studies were assigned 'levels of evidence' which correspond to an evidence hierarchy [14]. This hierarchy ranks the quality of research designs which are broadly associated with particular methodological strengths and limitations. For the current review, the evidence hierarchy placed systematic reviews of prospective cohort studies as representing the most robust evidence (level 1 evidence), followed by prospective cohort studies (level II), retrospective cohort studies (III.2), and finally cross-sectional studies (level IV).

Within each study design, studies can be conducted with varying degrees of rigour. This was reflected in assessment of methodological quality (including study validity, effect size, precision of results, applicability and generalisability) using design-specific validated instruments (GATE). Quality was coded as either good (+), uncertain (?), or poor (-).

Table 2.1: Inclusion criteria for selection of studies

Characteristic	Criteria
Inclusion criteria	
Publication type	Studies published January 1 2004 or later.
Participant characteristics	Children and adolescents aged 1-18 years diagnosed with Autism Spectrum Disorder (ASD) as classified by or consistent with DSM-IV-TR. Studies that were not restricted to participants within these age ranges, but met any of the following criteria: <ul style="list-style-type: none"> - results reported separately on a subgroup aged 1-18 years - mean age for the sample was no more than 18 years.
Sample size	Sample with ≥ 10 people (per arm, for comparative studies). Exclude studies with $>50\%$ attrition from either arm of trial (unless adequate statistical tests account for missing data).
Study Design	Observational studies including: <ul style="list-style-type: none"> • Prospective cohort studies, retrospective cohort studies, or cross-sectional comparative studies comparing GI problems occurring in children and young people with ASD with those without ASD on (Question 1) • Cross-sectional studies of children and young people with ASD investigating associations between behavioural characteristics and GI problems (Question 2) Systematic studies (systematic reviews and/or meta-analyses) that had a clear and relevant review question, and used at least one electronic bibliographic database.
Exposure	Question 1: Diagnosis of ASD Question 2: To supplement a recent practice guideline on this issue [7], primary studies were restricted to those measuring atypical behavioural presentations of potential GI problems (e.g., including challenging behaviour, sleep disturbance, irritability).
Comparator	Question 1: No diagnosis of ASD Question 2: Absence of behavioural characteristics
Outcome	Prevalence (over lifetime or a specified period) of any functional GI problems (clinical symptoms which are usually chronic, persistent, recurrent, frequent or excessive) across four areas: <ul style="list-style-type: none"> • chronic constipation • diarrhoea; faecal incontinence; encopresis; changes to bowel habit • vomiting; nausea; gastroesophageal reflux (GER) • abdominal pain, discomfort, irritability; bloating; flatulence.

Table 2.2: Exclusion criteria for selection of studies

Exclusion criteria	
Publication type	Non-systematic reviews, correspondence, editorials, expert opinion articles, comments, articles published in abstract form, conference proceedings, or news items. Unpublished data
Attrition	Studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Language	Non-English language articles
Scope	Studies that did not provide separate analyses/syntheses of results relevant to the scope of the review (e.g., with respect to age group and diagnosis). Studies cited in the original ASD Guideline [1].
Study Design	Case-control studies (where cases are people with GI problems) Case series studies (where cases are people with GI problems).
Outcomes	The following conditions were excluded as <i>primary</i> outcomes (though they may be associated with included symptoms): <ul style="list-style-type: none"> • food allergies, food intolerance, and other adverse reactions to foods • food selectivity or feeding issues (e.g., food preferences, fear of new foods, pica) • immunologic dysregulation or dysfunction • intestinal inflammation, inflammatory bowel disease (IBD), colitis, Crohn's disease • metabolic dysfunction • nutritional deficiencies • anatomical abnormalities such as oral-motor problems (e.g., oesophageal achalasia, enterocolitis) and motility disorders (e.g.; Hirschsprung's disease, Achalasia).

For practice guideline recommendations or consensus panel statements, the development process and quality of reporting was assessed using a guidelines appraisal instrument (AGREE II). An overall rating of the guideline is made on a scale ranging from 1 (lowest possible quality) to 7 (highest possible quality). This assessment is in addition to the quality appraisal (using the GATE tool) of any systematic reviews conducted to inform guideline development.

Full details of review methods including search strategies, appraisal of study quality and data extraction are presented in **Appendix 1**.

2.2 Body of evidence

Fourteen studies were appraised in 15 separate evidence tables for the review, with one publication [7] appraised in two separate evidence tables with respect to outcomes relevant to research Questions 1 and 2. The Evidence Tables for included studies for Questions 1 and 2 are presented in **Appendices 3** and **4** respectively. Throughout tables and text, studies are ordered according to the following hierarchy: study type (systematic reviews then primary studies), level of evidence (highest first), year of publication (most recently published first), first author's surname (alphabetical order).

Question 1

Regarding whether there is a greater prevalence of GI problems in children and young people with ASD than those without ASD, 9 studies met selection criteria, including 3 systematic reviews [7, 8, 11] and 6 primary studies [10, 12, 15-18].

Systematic reviews

One essentially narrative review [8] was based on limited though systematic search strategies of a single database. It summarised and critiqued research relating to gastrointestinal symptoms, pathology, nutrition, and dietary treatments for people (particularly children) with ASD. There was no formal appraisal of the methodology of cited papers. Narrative reporting of results was organised by outcome.

The second review [7] informed a meeting of a multidisciplinary panel in Boston in 2008, which generated consensus statements on gastrointestinal aspects of ASD. The literature, based on systematic but quite limited searching, was reviewed prior to the panel meeting by 28 experts distributed across seven working groups each dealing with a specific topic, GI symptoms being the most relevant to the current review. Two members of each working group appraised study quality using a formal checklist (GRADE) and statements (akin to recommendations) were developed by consensus using a systematic method. Included studies were tabulated and narratively synthesised.

The most recently published systematic review [11] was undertaken to inform consensus development of recommendations in a UK guideline on diagnosis and referral for children and young people with ASD. The guideline included consideration of GI problems as a co-occurring condition in this population. Following a rigorous search strategy and tightly controlled selection process, stringent selection criteria were applied and detailed evidence tables provided for included studies.

Primary studies

Six primary studies were appraised relevant to Question 1 [6, 19-22].

Three retrospective cohort studies and three cross-sectional studies compared GI outcomes between children and young people with ASD with those without ASD.

Of the more robustly designed cohort studies, one recruited from a registry of families where at least first degree relatives have ASD [18], accessing medical history through structured interviews with parents. Another accessed inpatient and outpatient records of children with ASD and controls sampled from residents of one county [12]. A third cohort study [10] recruited participants from specialist paediatric and ASD clinics, measuring GI outcomes through standardised instruments. In this study, two comparison groups of matched controls were employed: one of children/adolescents without ASD or any disability, and the other of children/adolescents with developmental disability excluding ASD.

Of the three cross-sectional studies appraised, one assessed GI outcomes by accessing thousands of medical records from four hospitals [15] whereas the other two studies relied on parent recalled responses to a questionnaire or structured interview. Of the latter two studies, one was a moderately large population-based national survey [16], and the other was a small-sampled study of people referred by a specialist ASD clinic [17]. In the latter study, two control groups included students recruited from a mainstream school, and students with developmental or neurological disabilities attending a special school [17]. This UK study was the only one appraised for Question 1 which was conducted outside the United States.

Sample sizes for participants with ASD ranged from small (around n=50) in two studies [10, 17], moderate (n=124-585) for three studies [12, 16, 18] and into the thousands for the multi-site study of medical records [15].

In the four studies where mean age was reported, children with ASD averaged between 6 and 10 years.

ASD diagnosis was confirmed by standardised diagnostic instruments in three studies [10, 17, 18], by review of medical records for two studies [12, 15], and by parental report of diagnosis made by their child's doctor for one study [16].

Outcome indices for gastrointestinal problems varied widely. Different summary measures of general or overall GI symptoms were identified across five of the six appraised primary studies. These included: lifetime prevalence of (any) GI symptom of interest; cumulative incidence of GI symptoms (over a 21 year follow up period); diagnosis of bowel disorder; number of GI symptoms; and rates of stomach/intestinal illness over the last two weeks. Rates of specific GI symptoms recalled over a lifetime or for a specified period were also reported across the four symptom areas of interest. Four studies reported rates of constipation; five reported on diarrhoea, encopresis, bowel movements of abnormal stool patterns; five reported rates of gastroesophageal reflux (GER) or vomiting; and three studies reported on abdominal pain, discomfort or irritability, bloating, or flatulence. Study characteristics are summarised in **Table 2.3**.

Table 2.3: Characteristics and results of included primary studies for Question 1

Reference	Evidence level, design, quality	Sample source	GI outcome assessment	ASD sample	Control group/s	Significant differences in GI problems (ASD vs. control/s groups)	No significant difference in GI problems (ASD vs. control/s groups)
Wang et al [18]	III-2, retrospective cohort; +	national registry of families with multiple members with ASD	parent-recalled medical history via structured interview	n=589 with ASD	n=163 siblings without ASD	Higher lifetime prevalence of GI problems for ASD (42%) vs. non ASD group (12%) Higher lifetime prevalence of: - constipation (20%) - chronic diarrhoea (19%)	No difference in gastroesophageal reflux (GER)
Ibrahim et al [12]	III-2, retrospective cohort; ?	population-based cohort of residents from one county	review of all inpatient and outpatient records	n=124 with ASD	n=248 without ASD	Higher rates for ASD group than control group for cumulative incidence of: - constipation (33.9%)	No differences in cumulative incidence of GI symptoms No difference in cumulative incidence of: - diarrhoea - GER or vomiting - abdominal bloating - discomfort, irritability
Valicenti-McDermott et al [10]	III-2 retrospective cohort; +	referrals from paediatric neurology, developmental & general outpatient paediatric clinics	Parent/child recalled symptom history using structured questionnaire	n=50 with ASD	n=50 without ASD or disability n=50 with other DD	Higher lifetime prevalence of GI problems for ASD group (70%) than neurotypical controls (28%) or other DD controls (36%) Higher rates for ASD group than neurotypical control group: - total GI symptoms over lifetime (35%) - chronic constipation (44%) - bowel movements (M=1.5/day) - abnormal stool pattern (9%) - faecal encopresis (14%) - frequent vomiting (9%) Higher rates for ASD than DD group for: - total number of symptoms (35%) - abnormal stool pattern (9%) - faecal encopresis (14%)	No differences between ASD group and neurotypical control group, in: - GER - frequent abdominal pain. No differences between ASD group and DD control group, in: - chronic constipation - number of bowel movements - GER - frequent abdominal pain.

Table 2.3 continued next page

Table 2.3: Characteristics and results of included primary studies for Question 1 (*continued*)

Reference	Evidence level, design, quality	Sample source	GI outcome assessment	ASD sample	Control group/s	Significant differences in GI problems (ASD vs. control/s groups)	No significant difference in GI problems (ASD vs. control/s groups)
Kohane et al [15]	IV cross-sectional study; quality not determined	electronic medical records from 3 general hospitals, 1 paediatric hospital	review of medical records	Not reported for group aged <18 yrs (<i>but thousands</i>)	Not reported for group aged <18 yrs (<i>but many thousands</i>)	More diagnoses of "bowel disorders" for children with ASD (12%) than those without ASD in hospital sample (5%).	
Schieve et al [16]	IV cross-sectional study; quality not determined	population-based, nationally-representative survey	parent-recalled symptom history using structured interview schedule	n=375 with autism	n=35,775 without DD	Higher rates for autism group than control group without DD: - frequent diarrhoea/colitis over last 12 mths (7%) - stomach/intestinal illness including vomiting or diarrhoea over last 2 wks (12%)	
Smith et al [17]	IV cross-sectional study; quality not determined	register of specialist autism referral clinic; 2 control groups: from 'special' & 'mainstream' schools.	parent response to unvalidated questionnaire	n=51 with ASD	n=112 from mainstream school; n=35 with DD & neurological disabilities	Higher rates for ASD group than mainstream school group: - been diagnosed with a bowel disorder (6%) - constipation (25%) - persistent diarrhoea (8%) - excessive flatulence (24%) - abdominal bloating (14%)	No differences between ASD group and mainstream school group in: - recurrent vomiting - recurrent abdominal pain No differences ASD group and special school group in: - been diagnosed with a bowel disorder - constipation - persistent diarrhoea - recurrent vomiting - excessive flatulence - abdominal bloating - recurrent abdominal pain

Key: +=good quality; ?=uncertain quality; ASD=autism spectrum disorder; DD=developmental disabilities; GER= gastroesophageal reflux; n=sample size; M=mean; mths=months; vs.=versus; wks=weeks

Question 2

Regarding presenting behaviours associated with GI problems, six studies were appraised: one systematic review, also appraised for Question 1 [7], and five primary studies [6, 19-22].

Systematic reviews

The systematic review undertaken to inform the development of recommendations by a multidisciplinary forum held in Boston appraised for Question 1 [7] also considered presenting signs and symptoms for GI problems in people with ASD. Three studies were cited to support the consensus statements relevant to this question: a narrative review [13], a pilot study of an assessment tool in adults with developmental disabilities [23], and a small cross-sectional observational study of the co-occurrence of sick days with behaviour problems in 11 people, 7 of whom had ASD [24]. None of these studies met criteria for inclusion in the current review. This material and expert consensus opinion informed the panel's statements.

Primary studies

Five primary studies met selection criteria for inclusion with respect to Question 2 [6, 19-22]. All were cross-sectional observational studies of children and young people with ASD which compared the signs, symptoms and characteristics of participants with GI problems with those without GI problems.

Mean age was 6-8 years in all studies with the exception of Gorrindo et al [19] where participants' ages averaged 11-12 years. All studies were undertaken in the United States. Of the three modestly sized studies (n=85-172), two recruited from ASD medical clinics [19, 22], and one recruited from two randomised controlled trials of drug treatments [6]. The two large studies involved multi-site recruitment, one included 487 participants recruited from a population-based autism surveillance registry which used medical record data [20], and the other involved 2973 people recruited via 17 autism centres [21].

Measurement of ASD status, medical, psychological, behavioural, and demographic variables were largely taken from interviews, questionnaires, and clinical assessments made at study/clinic enrolment. An exception was a population-based study [20] which relied on medical records. This study identified gastrointestinal problems in only 7% of their samples via this method, whereas ascertainment of GI status using broader methods including parent-report ranged from 23%-59% in the other appraised studies. Ascertainment of GI outcomes based on medical records may be biased toward identifying only significant problems requiring medical intervention and underestimating less severe GI symptoms.

These studies were not eligible for appraisal for Question 1 regarding assessment of prevalence of GI problems. The widely varying range and criteria for GI problems evident across these trials supports the requirement of control groups of people without

ASD applied in the current review. Comparisons between groups applying the same GI-status ascertainment method and definition permits “like for like” comparisons.

Study characteristics are summarised in **Table 2.4**.

2.3 Quality of included studies

Studies were assigned levels of evidence and quality codes according to methods previously described in Section 2.1 above (see also **Appendix A**, section A1.5).

Question 1

There were three included systematic reviews [7, 8, 11]. One [8], although offering useful narrative critique, was essentially a narrative review lacking any formal appraisal; it was rated as being of uncertain quality (?). Another review which informed the expert panel’s consensus recommendations at the Boston forum [7] was coded as being of good quality (+), employing systematic appraisal methods and presenting detailed tables of included studies. The most recently published systematic review, also coded as being of good quality (+), was conducted to inform a UK guideline on diagnosis and referral for children and young people with ASD [11]. The review was based on an extensive search involving multiple databases and explicit selection criteria and identified only two studies relevant to research Question 1. All three reviews included retrospective cohort studies and were ranked at level III.2 in the hierarchy of evidence.

The processes for developing consensus statements by the expert panel in Boston [7] was rated 5/7. The quality of the development and reporting of recommendations for the UK Guideline [11] was coded highly at 6/7.

Of the six primary studies appraised for Question 1, three were retrospective cohort studies ranked III-2 in the hierarchy of evidence [10, 12, 18] and three were cross-sectional studies ranked IV, at the bottom of the evidence hierarchy [15-17]. Of the three cohort studies, two were coded as being of good quality (+) [10, 18], and one was rated as being of uncertain quality (?) [12]. Checklists are unavailable for level IV cross-sectional studies which are regarded as being of low quality due to limitations inherent in their study design.

Table 2.4: Characteristics and results of included primary studies for Question 2

Reference	Evidence level, design	Source of sample	Sample	GI outcome assessment	Behaviours associated with GI problems	Behaviours not associated with GI problems
Maenner et al [20]	IV cross-sectional observational	population-based, autism surveillance register	n=487 children with ASD; all aged 8 years; 7% with GI problems	review of medical records	- sleep abnormalities - abnormal eating habits - argumentative; oppositional, or destructive behaviours	- mood disturbances - tantrums - stereotypic/repetitive behaviours - self-injurious behaviours
Mazurek et al [21]	IV cross-sectional observational	register from multi-site network from 17 autism centres	n=2973 children and young people with ASD; M age=6 years; 25% with chronic GI problems over 3 months	parental report using standardised GI symptom questionnaire	- anxiety - sensory-responsivity	
Gorrindo et al [19]	IV cross-sectional observational	academic hospital ASD clinic, and self-referral	n=85 children and young people with ASD; M age=11-12 years; 47% with GI dysfunction lasting >1 month; 85% with functional constipation	parental report of ongoing GI dysfunction, specific GI symptoms verified by physical examination and questionnaire	- nonverbal - socially impaired	- distinct dietary habits
Nikolov et al [6]	IV cross-sectional observational	enrolled in one of 2 randomised clinical trials	n=172 children and young people with PDD; 88% with autistic disorder; M age=8 years; 23% with GI problems	physical examination, and parent recall through structured interview	- irritability - anxiety - social withdrawal	- measures of adaptive behaviour
Xue et al [22]	IV cross-sectional observational	autism centre (>95% self-referred)	n=160 children with ASD; median age=6 years; 59% with GI dysfunction	review of medical records	- sleep disorders - mood disorders - food intolerance	

Key: ASD=autism spectrum disorder; GI=gastrointestinal; M=mean; N=sample size; PDD=pervasive developmental disorder

Question 2

The literature review undertaken to inform an expert panel appraised for Question 1 [7] also considered presenting signs and symptoms for GI problems. As for Question 1, the review was coded as being of good quality (+) and the development and reporting of consensus statements was rated 5/7. As the review's results relevant to Question 2 appear to be based on cross-sectional studies and expert opinion, it was classified as level IV in the hierarchy of evidence.

All of the 5 included primary studies [6, 19-22] were cross-sectional observational studies which compared the signs, symptoms and characteristics of children and adolescents with ASD who had gastrointestinal problems compared with those who did not.

All primary studies represent level IV evidence in the NHMRC hierarchy (see **Appendix A**, section A.1.5, for further details) for which appropriate appraisal checklists are not available. As level IV evidence these studies are particularly open to biases; care should be taken before generalising findings to different situations.

2.4 Summary of findings

A narrative critique of included studies' individual strengths and limitations is provided in this section. Full details are presented in appendicised Evidence Tables for Question 1 (**Appendix 3**) and for Question 2 (**Appendix 4**).

Question 1

Systematic reviews

Three systematic reviews were included [7, 8, 11].

National Institute for Health and Clinical Excellence (NICE) [11]

The UK guideline [11] was supported by a good quality systematic review. Relevant to functional GI problems, two observational studies met tight inclusion criteria (most studies were excluded from review due to lack of diagnostic confirmation of ASD using specified tools). One observational study reported a 62% prevalence of gastrointestinal symptoms in children and young people with ASD [25] (note that this study included an overlapping sample with another study included in the current review [10]). The other was a retrospective control study [9] from the UK which found that the history of gastrointestinal disorders evident from medical review was the same (9%) for young children around the time of their diagnosis with autism as for matched controls.

Recommendations were developed through consensus expert opinion based on the reviewed evidence. Recommendation 54 detailed common co-existing conditions in

young people with ASD, among which were included specific functional gastrointestinal problems:

“Consider whether the child or young person may have any of the following as a coexisting condition, and if suspected carry out appropriate assessments and referrals: (...)

- Functional problems and disorders (...)

- constipation, altered bowel habit, faecal incontinence or encopresis.”

Buie et al [7]

The multidisciplinary forum held in Boston in 2008 on gastrointestinal aspects of ASD was informed by a literature review [7]. Evidence was largely limited to case reports, observational or descriptive studies, and poorly controlled or uncontrolled studies leading the authors to declare that evidence-based recommendations were not yet possible. The forum panel developed recommendations (presented as statements) based on the literature reviewed and peer-graded by working groups prior to the meeting.

Eleven studies were identified reporting on prevalence of GI abnormalities in people with ASD with rates ranging from 9% to over 70%. Commenting on such inconsistencies, the authors suggested that evidence of significantly high GI symptom reporting (70%) found in studies based in specialist ASD clinics may reflect referral bias. At the other extreme, very low rates of GI symptomatology may relate to timing and measurement issues. For example, a UK medical record review study [9] found only 9% prevalence of a history of GI disorders in very young children at the time of their diagnosis with autism which did not differ from the prevalence of their matched controls. However, this study relied on medical records databases which may be biased toward recording more severe GI diagnoses.

Whilst observing that there is a “preponderance of data” consistent with the likelihood of a high prevalence of GI symptoms and disorders associated with ASD, Buie et al [7] conclude that it is not known with certainty whether prevalence of GI problems is higher in individuals with ASD than in the general population.

Two statements (relevant to the current review) were prepared by expert consensus [7]:

Individuals with ASDs who present with gastrointestinal symptoms warrant a thorough gastrointestinal evaluation, as would be undertaken for individuals without ASDs who have the same symptoms or signs. (Statement 1)

Gastrointestinal conditions that are reported to be common in individuals without ASDs are also encountered in individuals with ASDs. (Statement 2)

Erickson et al [8]

An earlier review published in 2005 [8] found a lack of rigorous data to support there being increased gastrointestinal symptomatology in autistic children, with no

prospective studies. In a methodological critique of the literature, the review noted that research tended to be hindered by samples biased toward including children with severe concurrent GI symptoms, and lacking comparison groups of typically developing children. Other limitations noted included a reliance on retrospective and non-verified reports of outcomes, and varying definitions of outcomes.

The reviewers concluded that there was no evidence to suggest that children with autism were more (or less) predisposed to developing GI symptomatology, or that routine GI testing should occur. Standard evaluation and treatment of GI complaints was advocated for symptomatic children, regardless of their ASD status.

Primary studies

Table 2.3 summarises key findings of the six primary studies appraised relevant to the relative prevalence of GI problems in children and adolescents with ASD and without ASD.

Wang [18]

A population-based retrospective cohort accessed a national (US) registry of children and young people with ASD who come from families where at least two first degree relatives have ASD [18]. Participants were 752 children from 313 families (mean age of 8 years) including 589 with “familial ASD” and 163 unaffected siblings. Diagnosis was confirmed using standardised diagnostic tools. The ASD group were categorised into three “severity” sub-groups based on their diagnostic scores (validated against other diagnostic tools): the most severe were coded as “Full Autism” (69% of the ASD group), 16% classified as “Almost Autism”, and 15% were placed in the least severe category, known as “Spectrum”.

Lifetime prevalence of any gastrointestinal symptoms as well as of specific GI problems were ascertained through parent-recalled medical history during in-home structured interviews with a paediatric neurologist.

The study found that significantly more GI problems were reported for children and young people with ASD than with unaffected siblings (42% vs 12%). The two most common symptoms were constipation (20%) and chronic diarrhoea (19%), with no difference in the prevalence of gastroesophageal reflux found between groups.

The authors employed conditional logistic regression analyses which treated each family as a matched set and allowed within-family comparisons on lifetime prevalence of GI problems whilst controlling for between-family differences (sibling age, gender, current use of medications). Analyses showed that children and young people with ASD had elevated odds of (ever) having a GI problem compared with unaffected children and young people (AOR=7.41, 95% CI=3.63-15.14). Autism symptom severity was also associated with increased odds of having GI problems. The highest odds for having a GI problem (compared with children and young people without ASD) were for those in the most severe symptom (“Autism”) group (14.28, 95% CI=6.22-32.77). Somewhat lower but still significantly increased odds were found for the “Almost

Autism” group (AOR=5.16; 95% CI=2.02-13.2) whilst there was no significant difference in the odds for the least severe symptom “Spectrum” group. Restricting analyses to children aged over 5 years did not alter key findings.

The study used robust statistical analyses and gold-standard confirmation of diagnosis. It was also sufficiently powered to explore sub-group analyses within the ASD group with respect to symptom severity. Limitations included that the sample were accessed through a registry which was under-represented for African-Americans and which tended to include people with a higher educational attainment than in the general population.

The methodology has the important benefit of controlling for inter-family environmental differences in analysis. However the authors acknowledged that conditional logistic regression can only control limited within-family confounders and biases could creep into parental recall of their children’s symptoms. It was hypothesised that parents with a child with ASD may be more attentive to their discomforts or behavioural changes than to those of their typically developing sibling, whose GI problems may be overlooked or minimised, which would exaggerate any differences found. However the opposite hypothesis is also possible such that GI problems may be more apparent in children without the communication and other challenges of ASD. Given the genetic component known to exist for ASD, unaffected children in families multi-affected by ASD may also share some sub-diagnostic autistic traits with their siblings. Such a bias would be expected to lead to an underestimate of GI differences between siblings with ASD and without ASD.

Accepting these limitations, the study suggests that – at least in families with multiple members with ASD - lifetime GI problems are more commonly reported for those with ASD, than without ASD, particularly for those with more severe autistic symptoms. The most common GI problems identified were constipation and chronic diarrhoea.

Ibrahim et al [12]

Computerised inpatient and outpatient medical data were accessed for a population-based cohort of people under age 21 years identified from one US town [12]. From this cohort, data from 124 people with ASD and 248 matched controls without ASD were accessed retrospectively between 1976 and 1997 with median follow up to age of 18.2 years for the ASD group and 18.7 years for controls.

Outcomes were the cumulative incidence (since registration as a patient) of the following 5 gastrointestinal diagnoses: constipation; diarrhoea; abdominal bloating, discomfort, irritability; gastroesophageal reflux (GER) or vomiting; and feeding issues or food selectivity.

No significant differences were found between children and young people with autism and matched controls in cumulative incidence of GI symptoms (77.2% vs 72.2%), or for three of the five symptom groups: diarrhoea; abdominal bloating, discomfort, irritability; or GER or vomiting. However, children and young people with autism were identified as having greater cumulative incidence of constipation than control participants (33.9% vs

17.6%; RR: 1.97 (95% CI: 1.25-3.10), and greater feeding issues/food selectivity (24.5% vs 16.1%; RR: 1.95 (95% CI: 1.18-3.24).

Limitations of the study include its reliance on retrospective analysis of medical chart reports. The sample was 98% white which limits generalisability to other ethnic groups. Recording of any GI symptoms mentioned in inpatient and outpatient records including those which may not have been prolonged, severe, or recurrent, and inclusion of feeding issues, loss of appetite, weight loss and food selectivity as GI problems, would contribute to the high cumulative incidence found for all participants. Overly inclusive ascertainment of GI symptoms may not be sensitive to differences between ASD and control groups in duration, severity, and frequency of recurrence of GI problems.

The frequency of GI symptoms among children and young people with and without ASD was high at over 70%. The authors hypothesise that the increased food selectivity and constipation found in children with ASD may be attributable to behavioural features that define autism or to adverse effects of medical treatment rather than to any autism-specific organic GI pathology.

Valicenti-McDermott et al [10]

A third retrospective cohort study [10] included 150 children and young people (M=7.6 years) across three groups: 50 with ASD, 50 with typical development (TD), and 50 with developmental disabilities excluding ASD (DD). Participants were recruited from paediatric neurology, developmental and general outpatient clinics.

Ascertainment of ASD and DD diagnoses was verified by standardised diagnostic tests. History of GI problems were measured using an adapted standardised instrument (QPGD Rome II) administered to the parent (and/or child).

The study reported a significantly higher lifetime prevalence of at least one GI problem for people with ASD (70%) compared with those with TD (28%). The most common lifetime GI symptom reported was chronic constipation which was also higher for the ASD group (44%) compared with the typically developing group (16%). The ASD group compared with the TD group also had more total GI symptoms, frequent vomiting, abnormal stool patterns, history of bulky stools, chronic constipation, use of laxatives, fecal encopresis, and reporting of a GI consultation. There were no difference for abdominal pain, number of bowel movements, and family history of GI disease.

Higher lifetime prevalence of at least one GI problem was also found for the ASD group (70%) compared with the DD group (36%). However compared with the TD group, few differences were found between the ASD and DD group; these included number of GI symptoms, abnormal stool pattern, and fecal encopresis, all of which were greater for the ASD group.

In multivariate logistic regression analyses adjusting for age, sex, ethnic group and maternal education level, GI symptoms were four times more likely to occur in children with autism than without autism (aOR=3.8; 95% CI: 1.7-11.2). There were no associations between GI symptoms and medication, history of food allergies, or being toilet trained.

The authors concluded that GI symptoms seem to be a common comorbidity of autism. The higher rates of GI symptoms found in their study compared to others may be related to the use of the highly sensitive instrument compared with the reporting of the more severe problems recorded in medical charts in chart review studies. Families of children with ASD may generally be more aware of GI symptoms because of the heavy promotion of dietary interventions from complementary and alternative sources, however it is notable that not all GI symptoms were reported as being higher for the ASD group.

Kohane et al [15]

A recently published cross-sectional study [15] accessed electronic medical records of three general hospitals and one paediatric hospital. Over a 10-year period, data was available from over 3 million entries for people aged under 35 years, including 14,381 with ASD. Only those aged 0-18 years are reported on here (demographic breakdown not reported). Diagnoses for ASD and “bowel disorders” (excluding irritable bowel disorder) were ascertained from ICD-9 codes (the controlled codes used by healthcare providers to bill for their services).

The study reported significantly more bowel disorders in people aged 0-17 years with ASD than without ASD (11.63% vs 5.02%). The authors concluded that certain disease states are significantly over-represented in ASD.

Limitations of the study include that the ICD-9 codes without chart review cannot determine whether diagnosis was established from symptoms or from diagnostic tests. Further, the 112 records of ICD-9 codes relevant to bowel diseases are much broader than functional gastrointestinal symptoms and include diagnoses excluded from this review, in particular, severe conditions requiring medical intervention. The codes in the electronic records are used for billing and may have biases introduced because of this purpose. As the record entries themselves were anonymised and were not mutually exclusive, patients could be entered more than once from different hospitals over the 10 year period data was collected. The authors acknowledge these methodological issues meant that the study can only be exploratory or suggestive in terms of direction of differences rather than producing a valid estimate of prevalence.

The results suggest that bowel disorders appear more prevalent in children and young people with ASD than those without ASD with respect to patient populations of tertiary health centres.

Schieve et al [16]

Also recently published was a cross-sectional observational study [16] of a large representative sample participating in the US-based National Health Interview Survey between 2006 and 2010. From the sample of over 41,000 children and adolescents, four mutually exclusive groups were identified based on diagnostic categories; autism (n=375), and three groups without autism: intellectual disability (ID) (n=2901); attention-deficit/hyperactivity disorder (ADHD) (n=2901); and learning disability (LD)/other developmental delay (n=1905). The referant (comparison) group for analyses were

children and adolescents without developmental disabilities (DD) (n=35,775 children, 49% male).

Diagnostic groups and outcome measures were assessed by in-person interviews with parents using a structured questionnaire. Whether a child had autism was ascertained by asking the parent, “has a doctor told you that your child has autism?” Interviewees were also asked whether the child/young person had had frequent diarrhoea/colitis over the last 12 months, and whether they had had a recent occurrence (within the last 2 weeks) of stomach/intestinal illness that included vomiting or diarrhoea.

Weighted logistic regression models adjusting of sex, age, race/ethnicity, and maternal education found that children and adolescents reported as having autism were seven times more likely to have frequent diarrhoea/colitis over the last 12 months compared to those without a DD (6.8% vs 0.9%; aOR=7.1; 95% CI:3.9-12.8), 70% more likely than children in the ID group, two times more likely than children in the ADHD group, and two times more likely than the LD/other developmental delay groups.

Children and young people with reported autism had over twice the likelihood of having a recent stomach/intestinal illness reported that included vomiting or diarrhoea (12.1% vs 4.9%; aOR=2.6; 95% CI:1.7-3.9).

The strength of this study is that it’s population based and includes a large representative sample. However its central weakness is relying on retrospective parental report of somewhat crudely defined variables without seeking clinical confirmation. Question wording was also problematic. The term “autism” is imprecise and it is not known whether people across the autism spectrum were included in parents’ responses. The inclusion of frequent diarrhoea with colitis conflates two outcomes; whilst colitis may lead to diarrhoea it specifically relates to inflammation of the colon and is not a key included outcome in the current review. The lack of information gathered about the duration of reported recent stomach illnesses means that this measure is not specific to chronic GI problems. And finally, the term “illness” may be understood to refer to a transitory viral condition less relevant to the current review’s outcomes of interest.

Whilst these methodological issues limit the validity of the study’s findings, they are consistent with the suggestion that somewhat non-specific GI problems may be more likely in children and young people with disabilities than without disabilities, particularly for people reported as having autism.

Smith et al [17]

A UK-based cross-sectional observational study considered 51 children and young people (mean age of 10 years) registered with an ASD service which assesses all referrals from hospitals and children’s services within a geographical area. The 51 families had already been enrolled into a urine metabolites study. Two control groups were recruited from local schools: one included typically developing (TD) students (n=112) recruited from a “mainstream school”, and the other included students with developmental and neurological disabilities recruited from “special schools” (n=35).

Control groups were loosely “matched” with the ASD groups only inasmuch as at least one age and sex-matched control were included. Bowel symptoms and dietary habits were measured by parent response to an unvalidated questionnaire devised for the study.

Those in the ASD group were more likely than in the TD group to have reported bowel symptoms including constipation (25% vs 4%); excessive flatulence (24% vs 2%); persistent diarrhoea (8% vs 0%); and abdominal bloating (14% vs 4%). Compared with the TD group, parents of children and young people with ASD were also more likely to have concerns about their child's bowel problems, as indicated by several measures that are likely to be highly correlated. Parents of children and young people with ASD were also more likely to report having concerns about the range of foods their child eats (18% vs 4%); that their child was on a special diet (18% vs 4%); and that they had consulted a dietician (20% vs 4%). There were no significant differences in parent-reported recurrent abdominal pain, recurrent vomiting, blood present in faeces, concerns about child's growth, or seeing a GI specialist.

Like one of the retrospective cohort studies reported earlier [10], this study is notable for including an additional control sample, albeit small, of people with developmental and neurological disabilities. Like those with ASD, children and young people from special schools had high reported rates of constipation (40%), excessive flatulence (20%), diarrhoea (16%), and to have consulted a dietician (48%). Comparing this group to children and young people with ASD identified only one significant difference: parents of children and young people with ASD were more likely to have concerns about the range of foods their child had (35% vs 12%).

Whilst the study found an increase in bowel symptoms in children and young people with autism compared to neurotypical children, the lack of difference with those reported in people with other developmental and neurological problems suggests that increased GI symptomatology may apply to other disabilities and not specifically ASD.

The study had several methodological flaws. The ASD sample were recruited from participants of a separate study involving urine analysis, and represented a poor participation rate of only 37% of the initial sample approached. This sub-sample may also be biased toward families with interest in digestion issues. The sample sizes were relatively small, particularly for those recruited from a special education school, and there was minimal controlling for potentially confounding variables. The small sample prevented sub-group analysis and more sophisticated multivariate techniques such as investigating whether dietary habits were associated with GI problems. Like other studies relying on retrospective parent-reporting of outcomes, there are questions about the validity of reported GI symptoms which were not verified by clinical records or medical assessments. The questionnaire developed for the study included ambiguous and nonspecific questions which were not psychometrically tested and results are therefore difficult to compare with other studies considered in the current review.

Question 2

Systematic reviews

Buie et al [7]

The literature review undertaken to inform the multidisciplinary forum of experts which met in Boston in 2008 [7] considered presenting signs, symptoms and behaviours of people with ASD who went on to be diagnosed with gastrointestinal problems. Related recommendations were primarily informed by consideration of three studies: a narrative review [13], a pilot of an assessment tool in adults with developmental disabilities [23], and a small cross-sectional observation study of the co-occurrence of sick days with behaviour problems [24]. None of these were eligible for inclusion in the current review.

Guided by this evidence and expert opinion based on the collective clinical experience of the forum experts, the authors suggest that the communication impairments characteristic of ASDs may lead to unusual presentations of gastrointestinal disorders compared with people without ASD. Atypical manifestations of GI problems reported include behavioural change, particularly sudden and unexplained change. These are presented in **Table 2.5** (which reproduces Table 2 of the panel review [7]).

The authors suggested that in some cases, problem behaviour may be the primary or only symptom of an underlying gastrointestinal disorder in a person with ASD. As these atypical presentations are frequently attributed to nonmedical causes, the panel argued that they risk going unrecognised (and untreated) as suggestive of GI dysfunction. For example, sleep disturbance may indicate GERD, and aggressive or self-injurious behaviour may indicate constipation, GERD, gastritis, intestinal inflammation.

The panel developed a consensus statement suggesting that caregivers and health care professionals should be alert to the presentation of atypical signs of common gastrointestinal disorders in patients with ASDs.

Table 2.6 presents typical and atypical presentations of possible GI problems and their definitions (adapted from Table 3 of the panel review [7]). In terms of diagnostic evaluation of gastrointestinal symptoms and disorders, the authors found no evidence of pathogenic mechanisms specific to ASDs that warrant a distinct diagnostic approach.

Primary studies

Table 2.4 summarises key findings of the 5 primary studies included in the review relating to signs and symptoms associated with GI problems.

Table 2.5. Atypical behavioural presentations of gastrointestinal problems in ASD [7]

Vocal behaviours	Motor behaviours	Overall change in state of being
<ul style="list-style-type: none"> • frequent clearing of throat, swallowing, tics, etc. • screaming • sobbing “for no reason at all” • sighing, whining • moaning, groaning • delayed echolalia that includes reference to pain or stomach (e.g., child says, “Does your tummy hurt?” echoing what mother may have said to child in the past) • direct verbalizations (e.g., child says “tummy hurts” or says “ouch,” “ow,” “hurts,” or “bad” while pointing to abdomen) 	<ul style="list-style-type: none"> • facial grimacing • gritting teeth • wincing • constant eating/drinking/ swallowing (“grazing” behaviour) • mouthing behaviours: chewing on clothes (shirt sleeve cuff, neck of shirt, etc.), pica • application of pressure to abdomen: leaning abdomen against or over furniture or kitchen sink, pressing hands into abdomen, rubbing abdomen • any unusual posturing, which may appear as individual postures or in various combinations: jaw thrust, neck torsion, arching of back, odd arm positioning, rotational distortions of torso/trunk, sensitivity to being touched in abdominal area/flinching • tapping behaviour: finger tapping on throat • agitation: pacing, jumping up and down • unexplained increase in repetitive behaviours • self-injurious behaviours: biting, hits/slaps face, head-banging, unexplained increase in self-injury • aggression: onset of, or increase in, aggressive behaviour 	<ul style="list-style-type: none"> • sleep disturbances: difficulty getting to sleep, difficulty staying asleep • increased irritability (exaggerated responses to stimulation) • noncompliance with demands that typically elicit an appropriate response (oppositional behaviour).

Maenner et al [20]

The recent cross-sectional observational study published by Maenner et al [20] identified 8-year old children with ASD from 3 sites of a multi-site, population-based, autism surveillance system. Healthcare records permitted ascertainment of documented history of gastrointestinal problems, as well as other demographic, medical and behavioural information. Participants were 487 8-year old children (81% male) with ASD clinically defined from multiple sources, 35 (7%) of whom had GI problems, most commonly constipation and encopresis.

Analyses comparing those children with ASD who had GI problems with those without GI problems found no differences on demographic and diagnostic variables including sex, race and ethnicity, ASD diagnostic classification, or intellectual disability. An exception was an association found between having GI problems and co-occurring cerebral palsy, and with a history of seizures.

Table 2.6. Typical and atypical presentations of GI problems in individuals with ASDs [7]

Symptom	Possible associated GI disorder	Definition
Sleep disturbance	GERD	Parental/provider report
Self-injurious behaviour, tantrums, aggression, oppositional behaviour	Constipation, GERD, gastritis, intestinal inflammation	Parental/provider report
Chronic diarrhoea	Malabsorption, maldigestion	≥3 loose stools daily for >2 wks.
Straining to pass stool, hard or infrequent stool	Constipation	≤2 hard stools per week (Bristol stool score)
Perceived abdominal discomfort: pressing abdomen, holding abdomen and crying, problem behaviours related to meals	Constipation, GERD, intestinal inflammation, malabsorption, maldigestion	
Flatulence and/or bloating	Constipation, lactose intolerance, enteric infection with <i>Giardia</i> or <i>Cryptosporidium</i>	
Any or all of the above	FAP, IBS	FAP: abdominal pain without demonstrable evidence of anatomic, metabolic, infectious, inflammatory, neoplastic, or other pathologic condition
		IBS: FAP associated with alteration in bowel movements

Key: FAP=functional abdominal pain; GERD=gastroesophageal reflux disease; IBS=irritable bowel syndrome

Of documented atypical behaviours hypothesised to be related to GI problems, the following were: sleep abnormalities; abnormal eating habits; and argumentative, oppositional, or destructive behaviours. However these recorded behaviours were not found to be associated with documented GI problems: mood disturbances, tantrums, stereotypic/repetitive behaviours, and self-injurious behaviours.

Also assessed were six control behaviours not generally associated with GI problems, only one of which was found to be associated with GI dysfunction: delayed motor milestones.

Whilst all children with documented GI problems had at least one of the behaviours hypothesised to be associated with them, so did nearly 99% of those people without a history of GI problems in their medical records. This is evident in the low positive predictive value (PPV) for the atypical behaviours considered of only 7.2%. Increasing number of behaviours required to 5 increased PPV to only 9.4% and reduced sensitivity to 80%. And so behaviours such as unusual sleeping habits, unusual eating habits and oppositional behaviour may have limited predictive utility in specifically screening for GI problems.

The finding that control behaviours were generally not associated with GI problems suggests that it is not the case that children with GI problems generally have greater behavioural problems in general. The exception was the incidental and unexpected associations found between GI problems and motor milestones, cerebral palsy, and seizure-like activity, which the authors hypothesise may relate to underlying dysfunction. Given the number of associations investigated it may also be a chance effect.

Limitations of the study include that there was a relatively small sample of 35 children with confirmed GI problems included, which limits statistical power for sub-analyses. Further, many statistical comparisons were conducted without any adjustment to p value to account for the possibility of significant results occurring by chance.

Mazurek et al [21]

Another recently published cross-sectional study [21] included just under 3000 children and adolescents (mean age of 6 years) enrolled with the clinical registry of the Autism Treatment Network (represented by 17 autism treatment and research centers across the US and Canada).

Based on parent-reported indices, 25% of the sample reported having chronic (lasting >3 months) gastrointestinal symptoms (including constipation, abdominal pain, bloating, diarrhoea, and/or nausea). Having any GI symptom was associated with anxiety and of sensory-responsivity (ascertained using validated scales). Additional tests verified these associations for each of the five individual symptoms, with stronger associations observed when a greater number of GI symptoms were reported. Anxiety and sensory-responsivity were themselves highly associated ($r=-0.45$) but each uniquely predicted total number of GI problems in logistic regression analyses, as well as the presence of each GI symptom with the exception of diarrhoea, where there was a trend ($p<0.05$; which did not meet the Bonferroni adjusted p value of $p=0.008$). No associations were evident between chronic GI problems and age, sex, ethnicity, or intellectual functioning, although an association was found with being Caucasian.

Whilst the sample is large and geographically diverse, it was not population-based and may be skewed towards including the more socio-economically advantaged, particularly given that charges are applied by some providers and specialists in the Autism Treatment Network.

The authors hypothesise that anxiety, sensory over-responsivity and GI problems may be inter-related phenomena for children and young people with ASD, with underlying mechanisms. It is unclear why people with ASD who are Caucasian appeared to be more likely to report GI problems. As there was no association observed between ethnicity and GI outcomes, and the finding was not replicated in other appraised studies, it may reflect unknown confounders.

Gorrindo et al [19]

The cross-sectional study by Gorrindo et al [19] included 85 children and adolescents with ASD (mean age of around 11-12 years) recruited largely through a paediatric gastroenterology outpatient clinic. Nearly half ($n=47\%$) the sample had parent-reported gastrointestinal dysfunction (GID) lasting more than one month, as determined by interview with parents at study enrolment. GI dysfunction was associated with lacking expressive language, and being socially impaired.

Gastrointestinal dysfunction was not associated with Body Mass Index (BMI for-age percentile), or with the use of medications with the potential for constipating side effects. GID was also not associated with “distinct dietary habits” as measured by a 7-

day food diary requiring a crude assessment of food intake across 11 broad categories (eg, type of vegetables, type of starch). Amounts of food ingested or food items within the broad categories was not assessed.

Specific GI symptoms were assessed using a standardised instrument (QPGS) and clinical assessment by a paediatric gastroenterologist. A multivariate logistic regression model, adjusted for age and sex, found modestly increased odds for having functional constipation for children and young people with ASD who were: younger (OR 0.81, 95% CI 0.69-0.94, $p < 0.05$); or more socially impaired (OR 1.05, 95% CI 1.01-1.09, $p < 0.05$). Those who were nonverbal were 12 times more likely to have functional constipation (OR 11.98, 95% CI 2.54-56.57, $p < 0.01$), however the wide confidence intervals reflect a lack of precision in this estimate which was based on only 15 non-verbal participants.

With respect to study limitations, source of referral was a university-based paediatric gastroenterology outpatient clinic which may be biased toward including participants with medical concerns, including GID.

Group assignment was also problematic as GID status was determined by parent report at enrollment of GI problems lasting more than one month. However for 19 people, this initial classification was found to conflict with the diagnosis assigned by assessment by a paediatric gastroenterologist and review of the QPGS. As group assignment was not changed to conform with the clinical assessment, some blurring of group allocation may have masked and therefore underestimated differences between the GID and no-GID groups of participants with ASD.

The authors suggest that the strong association found between constipation and language impairment may be mediated by the effect of verbal ability on limited appropriate toileting behaviour. The findings highlight the need for vigilance by caregivers and health professionals to detect and treat latent constipation in children and young people with ASD.

Nikolov et al [6]

The cross-sectional observational study by Nikolov et al [6] included 172 children and young people (M age=8 years) with PDD (88% with ASD) already enrolled in two multi-site randomised clinical pharmacological trials.

Medical history and structured parent interview were used to identify any (current or past) moderate to severe gastrointestinal problems in about a quarter (23%) of the ASD sample; symptoms primarily were constipation and diarrhoea. This outcome was significantly associated with irritability, anxiety, and social withdrawal (eg, listlessness, seeking isolation, staring into space, emotional unresponsiveness).

Gastrointestinal problems were not associated with socio-demographic characteristics, measures of adaptive functioning (including stereotypy, hyperactivity, inappropriate speech, compulsive behaviour), core symptoms of autism (communication, social development, and repetitive behaviour), or intellectual functioning.

The authors reported that recruiting the sample from a medication treatment trial meant that the sample was over-represented by children and young people with hyperactivity and serious problem behaviour (ie, tantrums, aggression, self-injury). These children and young people may have different GI problem profiles to those with fewer behavioural problems. A further limitation was that the GI problems were unspecific and measured without defining the duration for problems, although symptom severity was assessed.

The association of GI symptomatology with several behavioural difficulties (anxiety, irritability and social withdrawal) may reflect interconnected behaviours in children and young people with autism. Whilst it is possible that irritability may be caused by the GI symptoms, participants reporting “current” gastrointestinal problems had lower irritability scores than those reporting past GI problems. The authors suggest that current GI symptoms were not necessarily associated with current irritability.

Xue et al [22]

A retrospective chart review [22] was undertaken of 160 children with ASD recruited from a specialist autism clinic. Their medical and psychiatric history were identified from clinical intake forms completed by caregivers and verified at clinic appointments. Parent-reported symptomatology was confirmed at multiple visits by clinic staff.

Gastrointestinal dysfunction (persisting for more than 6 months) was evident in 59% of the sample, with common symptoms including diarrhoea or unformed stools, constipation, and GERD. GI dysfunction was significantly associated with sleep disorders, mood disorders, and food intolerance. No relationship was observed between prevalence of GI dysfunction and developmental regression, or epilepsy.

The authors concluded that the results suggest a high prevalence of multiple medical and psychiatric co-occurrences. Limitations included that the sample were recruited from a specialist autism clinic which may have biased reported symptoms to those requiring medical attention. A substantial number (n=58) of eligible children were excluded from the original sample due to missing data on their intake forms or missing laboratory reports which may introduce unknown sampling biases. Further, with multiple statistical tests there is the possibility of chance findings and there was no adjustment to p value accepted (Bonferroni’s correction) to account for this.

The authors suggest that it is possible that one medical co-occurrence may be related to another, such that discomfort from GI dysfunction may contribute to night waking, and food intolerance may lead to diarrhoea, bloating or constipation. However the cross-sectional nature of the study precluded a more robust investigation of these issues.

2.5 Limitations and future research directions

Sample recruitment and selection

Several studies included in the review sourced participants with ASD by accessing convenience samples including sub-specialty gastroenterology clinics and developmental paediatric clinics. Larger studies commonly identified children and young people with ASD by chart review of medical records from (often academic) hospitals or sub-specialty clinics. Such approaches can introduce ascertainment biases such that study participants are more likely to have medical complaints requiring clinical treatment [10, 19, 20]. This may result in samples over-represented for more severely affected children and young people with ASD and inflated estimates of GI problems and co-occurring medical conditions than would occur in the general community. Ascertainment from medical records is also biased toward identifying people who visit their doctor regularly. Specifically, children and young people with chronic conditions and comorbidities including those with ASD may be more likely to receive medical care and therefore receive diagnoses of GI problems than their typically developing peers [18].

Methods of recruitment through autism registers, website-based support groups and posters [18, 21] may also be more likely to attract parents who are highly informed, networked, and resourced. Illustrating this point, the registry-sourced study of Wang et al [18] was found to be over-represented by educated, white, middle-class families which are not representative of the general population of children and young people with ASD and their families. Notably the current review did not identify any eligible studies from New Zealand and it is unclear how the data reviewed may apply to the cultural and ethnic heterogeneity of this population.

Finally, some studies included in this review recruited participants from existing studies conducted for research purposes, for example, trialing medications or dietary interventions [6, 17]. These samples may be atypical in a number of ways. They may be more likely to attract volunteers who are interested in the interventions being investigated (e.g., who have GI symptoms or who have tried dietary modifications). Clinical trials, particularly involving pharmacological interventions [6], also tend to have rigid eligibility criteria which excludes coexisting conditions which in turn limits the applicability of study findings to children and young people with ASD more generally [11].

Prospective, multi-centre population-based cohort studies are needed to avoid referral bias and over-estimation of GI symptoms [7]. Such study designs can improve external validity of findings and allow greater generalisability of results to broader populations.

Sample size

Several studies appraised for this review included fewer than 300 people with ASD, making them underpowered to provide accurate estimates of prevalence for co-morbid symptoms [15]. Larger samples allow for the exploration of sub-group differences within samples which reflect the heterogeneity of characteristics across the autism spectrum. For example, the study of families with multiple members affected by ASD [18] had a sample size that permitted comparisons of GI outcomes between children and young people expressing different levels of severity of autistic characteristics. Such approaches allow for the identification of sub-groups of children and young people with ASD who may be particularly prone to having GI problems, which can inform targeted investigation and treatment.

It should be noted that large-sampled studies can sometimes be threatened with other limitations, including less valid measurement of GI outcomes and confirmation of ASD diagnosis (eg, [16]), as these processes are time consuming and resource intensive. Increasing sample size should therefore not be done at the expense of confirmation of diagnostic status and valid measurement of GI outcomes.

Diagnosis of ASD

Varying methods of assessment of ASD diagnosis were employed across studies included in the current review. Whilst diagnosis was required for inclusion in a manner that was classified by or consistent with DSM-IV-TR, many studies did not report confirmation of diagnosis using standardised, psychometrically validated assessment tools such as the ADOS and ADI-R by trained clinicians, as was required by the UK Guideline [11]. The current review was more inclusive in that studies were eligible which may have included participants with autistic symptoms which do not meet current diagnostic criteria [17]. In future research, the use of robust assessment tools and cross-validation with medical records and clinical examinations would give clarity about the diagnostic status of included children and young people.

Definition and measurement of GI outcomes

The studies appraised for the current review reveal a highly variable range of GI symptoms reported and a lack of standardised definitions. Gastrointestinal problems varied with respect to symptom type, severity, frequency, duration, and whether current or past, episodic or “chronic” (which itself can be variously defined as being sustained for more than one month, 3 months, 6 months, etc). There was also variation in what was considered a GI symptom, such as food selectivity and feeding issues [12]. Bowel disorders were sometimes reported as outcomes. Whilst these may include chronic functional GI problems of relevance to the current review, they may also include conditions that are not included [15, 17].

The measurement of GI problems itself is fraught, in part due to the inherently difficult nature of determining and identifying the source of pain or discomfort in any child in general, and particularly in a child on the autism spectrum who has communication challenges and may have limited verbal ability. Some symptoms such as abdominal pain and nausea are not clearly manifested in observable ways and therefore may go under-reported, particularly for less verbal participants.

The way GI symptoms were ascertained also varied across studies in ways likely to impact on findings. Widely varying methods included accessing medical records, standardised medical interview, physician-administered interviews, and parent-completed questionnaires. These methods also varied with respect to whether symptoms were freely reported or prompted in response to questions about specific symptoms or both.

Studies which abstract information from medical records for GI problems are biased toward identifying more severe diagnoses requiring medical attention. Parents may not feel a GI symptom is significant enough to mention in a clinic appointment, the physician may never ask about it, and there may be incomplete documentation of whether it is discussed [18].

In contrast, approaches which rely on parent-reported history of GI issues using structured interviews or questionnaires prompt parents with specific problems rather than relying on free recall. This approach is more likely to be sensitive to a broader range of symptoms than ascertained by chart review [10]. Controlled studies employing the same measurement tool would “even the playing field” in this respect.

There may also be differentially biased parent recall of GI symptoms depending on whether their child has ASD or another developmental, physical or neurological disability. Parents with a child with ASD may be more attentive or even hypervigilant to their discomforts or behavioural changes, especially if they are nonverbal [18]. Attentiveness to GI symptoms may also be heightened given food selectivity and feeding issues common in children and young people with ASD, as well as where attempts have been made to employ dietary restrictions or supplements - strategies widely promoted as alternative (though unproven) behavioural interventions for core ASD symptoms [26]. Nevertheless, GI problems were not reported by parents as being increased indiscriminantly for children and young people with ASD compared with typically developing peers or siblings. Whilst chronic constipation and diarrhoea were commonly reported at higher rates, other GI symptoms such as gastroesophageal reflux and abdominal pain were not [10, 12, 17, 18].

One of the peculiar challenges of prevalence studies in this area are that GI problems tend to be symptom-based “diagnoses of exclusion”. That is, other potential causes need to be ruled out first, meaning that multiple assessments and follow-up laboratory tests and endoscopic procedures may be needed to rule out organic disease [7, 19]. Given this, the authors suggest that future studies provide systematic follow-up evaluations of all participants to confirm original diagnoses of GI problems [19].

Assessing GI symptomatology is likely to need a triangulation of measurements to validate, verify and enrich the breadth of GI symptoms identified. These may include parent-report using free-recall as well as structured, validated instruments such as the QPGS-Rome III (Questionnaire on Pediatric Gastrointestinal Symptoms) [27] in addition to reviewing medical records. The use of standardised criteria for GI symptoms is crucial to permitting valid comparisons between studies, settings, and populations.

Retrospective designs

No studies included in this review were prospective meaning that evaluation of GI outcomes relied on either parental recall of their child's history of GI problems, or retrospective review of medical records. As discussed earlier, parent reports, particularly with respect to lifetime medical history of gastrointestinal symptoms, are open to recall biases. Chart reviews are limited to extracting data as recorded and can suffer from missing data or differential weight given in reporting outcomes (for example, the use of ICD codes can be biased toward conditions that attract a higher payment).

Potential confounders

The current review found evidence of potential confounders or mediators of GI symptomatology with respect to co-occurring conditions. Future studies would be enhanced by requiring medical histories and assessments of physical, neurological, cognitive and adaptive functioning of affected and unaffected children and young people. These would permit investigation of variables identified as possible confounders including those identified by the cross-sectional studies appraised for the current review, such as psychological indices (eg, mood disorders, social withdrawal, sensory responsivity) [6, 19-22], and neuromuscular and genetic conditions (eg, cerebral palsy, seizures and delayed motor milestones) [10, 18, 20].

The ritualistic tendency, insistence on sameness, and feeding abnormalities such as pica that are characteristic of some children and young people with autism may contribute to restricted diets, nutritional deficiencies, and GI side effects. Moreover, many children with autism are actively treated with dietary restrictions (eg, gluten- and casein-free diets), gastrointestinal hormones (eg, intravenous secretin), vitamin and mineral supplements, and systemic antifungal treatments, without evidence of effectiveness for the treatment of the core symptoms of ASD [1, 12, 26, 28]. Such approaches may also introduce nutritional deficiencies and contribute to gastrointestinal symptoms. Medications prescribed in ASD may also be associated with side effects including appetite changes and constipation [12].

Dietary factors and medication use have been considered as possible confounders in several studies investigating prevalence of GI in ASD [10, 18, 19]. Studies appraised in the current review did not find any association between GI problems and medication use [10, 19]. There were mixed results with respect to whether dietary issues were associated with increased GI problems [10, 12, 17, 19, 20, 22]. Given the difficulty of

assessing dietary intake and the imprecision of measures employed in the current study (such as listing food groups eaten from over 7 days), this is an area requiring further investigation.

Lack of matched control group

The majority of studies conducted in this review lacked an appropriate control group or one of a reasonable size. Some researchers have recommended including control groups of typically developing children and young people matched for known confounders (Erickson et al, 2005). Commonly matched variables include age and sex, but others such as maternal education and ethnicity have been matched in control groups [10, 16]. Where sample sizes permit, multivariate logistic regression analyses allow statistical adjustment for several known confounders. In one study included in the current review, conditional logistic regression analyses were used to analyse families (of affected and unaffected siblings) as a matched set and to investigate within-family comparisons whilst controlling for between family effects [18]. This approach has the advantage of removing known and unknown confounders that are common within a family, although findings from multiple affected families may not generalise to all families where ASD is represented.

In order to investigate whether any increased frequency of GI symptoms is specific to ASD, some studies appraised in the current review included a comparison group of children and young people unaffected by ASD but affected with other developmental or neurological disorders [10, 17]. These studies are important in determining whether any increased prevalence of GI problems found in people with ASD are specific to this family of conditions or are shared by other disabilities. Whilst this may be the case, careful consideration needs to be taken of co-occurring biases, such as the possibility that parents of children with disability in general may be more aware of or attentive to the gastrointestinal habits of their children. There may also be confounding factors (eg, medication use, dietary restrictions, heightened anxiety) contributing to increased GI symptoms that may be more common among people with disability generally compared to people without any disability.

In conclusion, the research field needs large, prospective, population-based studies using validated diagnostic tools and outcome measures and including appropriate unrelated control groups [7, 18]. New Zealand-based research studies are also needed to investigate cultural and ethnic factors that may impact on the findings.

2.6 Summary, synthesis and conclusions

Overview

This systematic review updates evidence for the New Zealand Autism Spectrum Disorder Guideline [1] with respect to the prevalence and presenting signs of

gastrointestinal problems in children and adolescents with ASD. Following a comprehensive database search and reference checking of primary studies and systematic reviews published since 2004, 14 met selection criteria for inclusion, including two reported within the context of practice guidelines.

Are GI problems more common in young people with ASD?

Prevalence of (any) GI problems

With respect to whether GI problems are more common in children and adolescents with ASD than those without ASD (research question 1), three systematic reviews, three retrospective cohort studies, and three cross-sectional studies were appraised. No prospective studies were identified and study methods varied widely across the primary studies considered.

Limitations to study designs introduced biases to determining the prevalence of GI outcomes, and led to the wide variations evident in the current review. Major sources of variation between studies which impact on prevalence estimates include:

- how the diagnosis of ASD in sample participants was made and confirmed
- how the sample and control group members were identified and recruited
- how gastrointestinal problems were defined
- how gastrointestinal problems were assessed.

Given the diversity of study methods represented in the evidence base to date, it is not possible to obtain valid prevalence estimates for lifetime prevalence of (any) GI problems, or of having a specific GI symptom. However despite these methodological variations, some consistency was observed across studies with respect to whether GI problems were significantly more prevalent in children and young people with ASD than in those without ASD.

Higher lifetime prevalence of (any) GI problems was observed for children and adolescents with ASD than in those without ASD in two, good quality, retrospective cohort studies [10, 18]. One was the robustly controlled study of Wang et al [18] recruiting from a registry of families with two or more first degree relatives with ASD. The study had a good sample size for this field (n=589 with ASD), used gold-standard confirmation of diagnosis, and ascertained GI outcomes through in-home interviews with a paediatric neurologist. Conditional logistic regression analyses controlling for between family differences found that siblings with ASD had seven times the adjusted odds of reported lifetime prevalence of at least one GI problem than their unaffected siblings. Odds of having GI problems increased with the severity of ASD symptoms.

The other good quality cohort study reporting on lifetime prevalence by Valicenti-McDermott et al [10] also found a greater total number of lifetime GI symptoms for those with ASD. Prevalence rates for any GI outcome were higher (70%) compared

with Wang et al's [18] study (42%). The difference may relate to an ascertainment bias in the former study such that people with ASD were recruited from sub-specialty paediatric neurology and developmental clinics which may be over-represented for problems requiring medical intervention [18].

In addition to these two cohort studies, two cross-sectional studies reported a greater number of bowel disorders diagnosed in people with ASD than without ASD [15, 17], and another reported more stomach/intestinal illnesses for the ASD group [16].

The only exception relating to global measures of GI problems was a population-based cohort study rated as being of uncertain quality [12]. This study found very high (over 70%) cumulative incidence of GI problems during followup (to median age of 18-19 years) in both people with ASD and those without ASD, with no difference between these groups. The high rate of GI problems found may relate to them being identified by broad record review of any symptoms or diseases reported in inpatient and outpatient records, including developmental check or "well-child" visits, regardless of their duration, severity or frequency. Unlike other studies appraised for the current review, feeding issues including lactose intolerance, loss of appetite, or loss of weight were also counted as reflecting GI problems. Such overly inclusive ascertainment of GI symptoms may not be sensitive to differences in duration, severity, and frequency of recurrence of GI problems between ASD and control groups.

Prevalence of specific GI symptoms

With respect to prevalence of specific GI symptoms, constipation was consistently found to be more prevalent in children and young people with ASD than in those without ASD, based on four primary studies [10, 12, 17, 18]. Chronic or frequent diarrhoea, number of bowel movements, abnormal stool patterns, and fecal encopresis were more prevalent for participants with ASD than without across four studies, including the two good quality cohort studies [10, 15, 16, 18]. The exception was the population-based cohort study which found no difference in overall cumulative incidence of GI symptoms [12].

No difference was found in prevalence of vomiting or gastroesophageal reflux (GER) between ASD and control groups in four studies, including all three of the retrospective cohort studies [10, 12, 17, 18]. One of these studies was the only included study to measure lifetime prevalence of frequent vomiting. This good quality retrospective cohort study found higher prevalence recalled for children with ASD than without ASD [10].

Abdominal pain, bloating, discomfort or irritability was not found to vary in two retrospective cohort studies [10, 12]. A small sampled cross-sectional study employing an unvalidated questionnaire found no group difference in abdominal pain or but higher reporting of abdominal bloating and excessive flatulence in the ASD group compared with those attending a mainstream school [17].

In the good quality study of siblings in multiple-affected families, a "dose response" effect was evident such that gastrointestinal problems were increased relative to autism

symptom severity [18]. Compared with children and young people without ASD, those in the most severe symptom ASD group were 14 times more likely to have a GI problem, those in the moderate symptom ASD group were five times more likely to have a GI problem, whilst there was no significant difference in the odds for the lowest symptom severity ASD group. Similarly in a cross-sectional observational study [19], nonverbal children and young people with ASD were 12 times more likely to have functional constipation compared with the normally developing group, though this was based on only 15 non-verbal participants.

Conclusion

Despite methodological limitations, the evidence base gathered across several studies, involving hundreds of people with ASD, across a wide range of settings, and using a range of outcome measures are broadly consistent with the conclusion that GI problems are more common in children and young people with ASD compared with typically developing peers. Specifically, people with ASD appear to be more prone to gastrointestinal problems including constipation, frequent diarrhoea, altered bowel habits, and fecal encopresis.

These results are consistent with the findings of the expert forum held in Boston in 2008 [7] and of the high quality UK Guideline on recognition, referral and diagnosis of ASD in young people [11]. The UK Guideline recommended that *functional gastrointestinal problems should be considered as a potentially coexisting condition, with the more common symptoms including constipation, altered bowel habit, fecal incontinence or encopresis.*

How may GI problems present in a young person with ASD?

With respect to research Question 2 regarding the presenting signs, typical and atypical, of GI problems in children and adolescents with ASD than those without ASD, one systematic review, and six cross-sectional studies were appraised.

Behavioural changes

This question was investigated by the expert forum held in Boston in 2008 and informed by a systematic review appraised in the current report [7]. The expert panel's report suggested that GI problems may present in unusual ways in people with ASD compared with people without ASD. These atypical presentations relate to behavioural change, particularly sudden and unusual change, across a range of domains including vocal, motor, and state of being. Detailed illustrative examples are provided across these areas (see **Table 2.5**), and possible GI diagnoses are suggested for specific typical and atypical symptoms (see **Table 2.6**).

Whilst the panel's review identified very limited published evidence, the descriptive advice on how GI problems may manifest themselves in the young individual with ASD was informed by multi-disciplinary experts based on their collective professional

judgement and experience. Indeed, an expert consensus process is arguably the most appropriate way to answer this research question in a detailed and descriptive way, and the guideline process was graded as being reasonably robust. The information offers a useful guide for clinicians and caregivers to be alert to the possibility of gastrointestinal dysfunction.

To supplement the work of the expert forum, the current review identified five cross-sectional studies that investigated atypical behaviours (and other factors) that may be associated with GI problems. It should be noted that these studies do not re-create a clinic appointment where presenting behaviours are measured at the same time as GI problems. Given these and other limitations described in the individual study appraisals, these cross-sectional studies are best considered with respect to whether they support the consensus advice offered by the expert panel [7]. They also provide insights into potential confounders in the relationship between ASD status and GI dysfunction considered for research Question 1.

Sleep abnormalities, irritability, and problem behaviour

In the cross-sectional studies appraised in the current review, GI problems were found to be associated with sleep abnormalities in two studies [20, 22] and with irritability in one study [6]. The recently published population-based study by Maenner et al [20], considered indices of problem behaviour with mixed results. A history of GI problems was found to be associated with argumentative, oppositional, or destructive behaviours, but not with tantrums, or with self-injurious behaviours [20]. These findings are broadly consistent with the appraised expert forum's descriptions of atypical presentations of GI problems presented in **Table 2.5**.

The Maenner et al study [20] is notable for its attempt to investigate associations between GI problems and related behaviours as documented by the expert forum [7]. Based on review of medical records, the study found that whilst all children with documented GI problems had at least one of the behaviours hypothesised to be associated with them, so did nearly 99% of those people without a history of GI problems, suggesting they have limited predictive utility in specifically screening for GI problems [20]. This interpretation should be considered with caution however as the study included only 35 children with GI problems. Moreover, the association of variables relied on chart review of medical histories which may reflect GI symptoms and problem behaviours which did not occur at the same time. As discussed earlier, such investigations may poorly represent GI symptoms that manifest as co-occurring presenting behaviours in a clinic appointment. This study, and other cross-sectional studies appraised for the current review, are also limited in capturing broad brush-strokes of behaviours rather than the detailed and specific examples detailed in the expert forum's consensus report [7], such as "leaning abdomen against or over furniture or kitchen sink". The descriptive details of such signs have not been proposed (or should necessarily be investigated) as screening tools *per se*, but rather as advice based on consensus expert opinion about clinical best practice in this area.

Why behavioural changes may indicate GI symptoms?

It is difficult to ascertain specifically how one condition may be related to another, whether sleep difficulties, irritability and aggressive behaviour may be a manifestation of underlying GI discomfort as suggested by Buie et al's expert panel [7], or whether discomfort from GI dysfunction itself may contribute to night waking, irritability and aggression, or both. It is also possible that co-occurring conditions may arise from a common pathogenesis, or as symptoms from a common disorder [22] such as anxiety (which was associated with GI problems in two studies appraised in the current review [6, 21]). The complex inter-relationship of variables is exemplified by reported association between GI problems and sensory over-responsivity [21]. This finding is interesting in light of the ASD Guideline's [1] report that sensory processing impairments in ASD may be expressed as sensory over-sensitivities to sound, lights, smell or touch, being "often anxious", and having stomach aches (Section 2.3; p. 79-80). Investigating these associations and what they signify is an area of continuing research and debate.

Clinical implications

Gastrointestinal problems as a co-existing condition in ASD

It is not known with certainty whether the generally higher prevalence of GI symptoms reported for children and young people with ASD is due to their being more biologically predisposed to these problems than people in the general population, or to other co-occurring environmental factors (such as dietary intake), or to emotional state (such as anxiety). It is also not clear whether GI problems are more prevalent for people on the autism spectrum than those with other disabilities, altered eating habits and/or communication issues. Nor is it known why gastrointestinal problems may present as specific vocal, motor or change of state behaviours. These issues are the subject of ongoing research and debate.

The clinical implications of the review's findings remain regardless of the uncertainty surrounding these issues. That is, that clinicians and parents should be alert to the possibility that children and young people with ASD may be experiencing distressing and uncomfortable gastrointestinal problems, particularly constipation and diarrhoea, as a co-existing condition. The UK's clinical guideline on recognition, referral and diagnosis of ASD in children and young people advocates the importance of identifying co-existing conditions in ASD as a means of understanding of the individual's profile of strengths and weaknesses, and to inform overall treatment plans [11].

Atypical presentation of gastrointestinal problems in ASD

Based primarily on consensus expert opinion, it appears that gastrointestinal problems may not present in typical ways. GI problems may be manifested in a range of behavioural changes, particularly where sudden and unexplained, and expressed in unusual vocalisations, movements, and changed state of being, such as through

increased irritability and disordered sleep patterns [7]. As challenging behaviour may signify comorbidities other than GI problems, care needs to be taken in interpreting and investigating behavioural changes. However where gastrointestinal problems are suspected, clinicians and caregivers should seek appropriate evaluation, referral and treatment [11, 18].

2.7 Recommendation development

The Living Guideline Group were tasked with considering the systematically updated evidence on gastrointestinal problems reported above in terms of its implications for the ASD Guideline [1]. Specifically, whether the new evidence required revisions of (potentially relevant) existing recommendations as well as the development of any new recommendations. Both text of recommendations and their graded “strength of evidence” (see Appendix 1, **Table A1.2**) were considered at an all day face-to-face meeting. The LGG’s decisions for recommendation development and grading are presented below. Revised or new recommendations are accompanied by a brief rationale which highlights any particular issues that the LGG took into account while formulating the recommendations.

Unchanged recommendations

Two recommendation from the original ASD Guideline [1] relevant to the current review update were considered as requiring no change in view of the updated evidence. These recommendations were:

- **Recommendation 2.3.9:** “Research should be undertaken to identify the needs of people with ASD with regard to constipation, allergies, medication reactions, menstruation and exercise.” GRADE C.
- **Recommendation 4.1.4:** “Pre-treatment assessments should gather detailed information on behavioural, emotional and mental health difficulties, address differential diagnosis, screen for medical conditions and address environmental issues.” GRADE C.

Revised recommendations

One recommendation in the ASD Guideline [1] was revised by the Living Guideline Group. The final wording and grades for this recommendation is presented in **Table 2.7**.

- **Original Recommendation 4.6.1:** “When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders and depression.” GRADE C

- **Revised Recommendation 4.6.1:** “When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders, depression, and gastrointestinal problems.” GRADE C

Rationale: Challenging behaviour may be the primary or sole symptom of gastrointestinal problems. This evidence is based on consensus expert opinion and cross-sectional studies.

New recommendations

Two new recommendations were developed by the LGG (see **Table 2.8**).

- **New Recommendation 4.1.4a:** Gastrointestinal problems, specifically constipation, chronic diarrhoea, altered bowel habits, and encopresis (faecal soiling), are more common in children and young people with ASD compared with typically developing peers. GRADE: B

Rationale: There was a consistent trend observed across studies indicating that gastrointestinal problems were significantly more prevalent in children and young people with ASD than in those without ASD. However, a grade of B was given to reflect the limitations of the evidence. Limitations to study designs introduce biases to determining the prevalence of GI outcomes in individuals with ASD and without ASD, and lead to the wide variations evident in the current review. Major sources of variation between studies which impacted on prevalence estimates include:

- how the diagnosis of ASD in sample participants was made and confirmed
- how the sample and control group members were identified and recruited
- how gastrointestinal problems were defined
- how gastrointestinal problems were assessed.

- **New Recommendation 4.1.4b:** Children and young people with ASD should have a full evaluation that includes a thorough assessment of gastrointestinal function. Some children, particularly those with social communication difficulties, may have atypical presentations such as increased anxiety, irritability, disordered sleep patterns, and unusual vocalisations and movements. GRADE C

Rationale: A thorough assessment of GI function would often consist of a dietary history, history of bowel function, relevant family history, physical examination of the abdomen, and, where indicated by symptoms or signs of disorder, further investigations or specialist consultation. This evidence is based on consensus expert opinion and cross-sectional studies. Recognition and evaluation of gastrointestinal

problems in children and young people with ASD can be more challenging due to the communication difficulties characteristic of ASD.

Table 2.7: Revised recommendation from the ASD Guideline relevant to gastrointestinal problems in children and young people with ASD.

Original Reference	Revised Recommendation	Grade
4.6.1	<ul style="list-style-type: none"> When challenging behaviours are evident, people with ASD need to be assessed for co-morbid conditions such as seizures, ADHD, anxiety disorders, depression, and gastrointestinal problems. 	C

Reference	New recommendations	Grade
4.1.4a	<ul style="list-style-type: none"> Gastrointestinal problems, specifically constipation, chronic diarrhoea, altered bowel habits, and encopresis (faecal soiling), are more common in children and young people with ASD compared with their typically developing peers. 	B
4.1.4b	<ul style="list-style-type: none"> Children and young people with ASD should have a full evaluation that includes a thorough assessment of gastrointestinal function. Some children, particularly those with social communication difficulties, may have atypical presentations such as increased anxiety, irritability, disordered sleep patterns, and unusual vocalisations and movements. 	C

Table 2.8: New recommendations relevant to gastrointestinal problems in children and young people with ASD.

Appendix 1: Methods

This appendix describes the living guideline update process and includes details on:

- the living guideline group (LGG) team
- review scope and research questions
- review methodology
- recommendation development processes.

A1.1 Contributors

Living Guideline Group members

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Declarations of competing interest

None

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We also acknowledge the helpful contribution of Tracy Merlin, Managing Director, Adelaide Health Technology Assessment (AHTA), who was consulted with respect to the application of the NHMRC hierarchy of evidence to the current review.

A1.2 Review scope

The current review updates evidence on gastrointestinal problems in children and young people with ASD for the ASD Guideline [1].

The original searching for the ASD Guideline [1] was performed in July 2004. Papers published after the completion of searching and in some cases before the search dates were suggested by members of all workstreams and incorporated in the text and evidence tables, where appropriate.

In the current update, the search was limited to articles published in the English language on or beyond January 1 2004. Given the overlap in search periods in 2004, and the inclusion of papers outside the date range in the original Guideline, papers identified in the current search strategy which were already appraised in the original ASD Guideline [1] were excluded.

Publications were considered where relevant to people aged 18 years or under.

A1.3 Research questions

The Living Guideline Group identified gastrointestinal problems in children and young people with ASD as a priority topic to update. The lead researcher prepared the research questions in the PECO format (which identifies the Patient, Exposure, Comparison, and Outcomes of interest) to ensure effective and focused searches and reviews could be undertaken. The primary research questions are below.

RESEARCH QUESTION 1: Are gastrointestinal problems more common in children and young people with ASD than those without ASD?

It has been suggested that gastrointestinal problems may be missed in children and young people with ASD either due to social and communication issues or because the symptoms may present atypically with behavioural change or problem behaviours (eg, sleep disturbance, increased aggression or stimming, or abnormal posturing).

RESEARCH QUESTION 2: What gastrointestinal symptoms, typical and atypical, should be investigated in children and young people with ASD?

A1.4 Search strategy

Search strategies were limited to publications from January 1 2004 onwards. Database searches were conducted on 28 March 2012 and updated 22-27 August, 2012.

The INSIGHT Research lead researcher set the inclusion and exclusion criteria for the review in consultation with the Ministry of Health. Systematic database searching was designed and conducted by the INSIGHT Research information specialist. Full search strategies are available upon request.

Search databases

Bibliographic, health technology assessment and guideline databases were included in the search strategy, listed below.

- Medline & PreMedline
- Cochrane Database of Systematic Reviews
- Controlled Trials Register
- DARE
- NHS EED
- HTA Database
- PsychInfo

- Embase
- AMED
- CINAHL
- Australian New Zealand Reference Centre
- Index New Zealand
- Web of Science (ISI Web of Knowledge) (citation searching)
- PubMed (last 60 days)
- National Guideline Clearing House
- GIN International Guideline Library

Cross-checking of references from retrieved studies was conducted to identify additional references.

A1.5 Appraisal of studies

For this review, a single researcher performed study selection, critical appraisal and synthesis. The following steps were followed in appraising the evidence.

Assigning a level of evidence

Following the completion of searches, retrieved studies meeting the selection criteria were assigned a 'level of evidence'. The level of evidence indicates how well the study eliminates bias based on its design. INSIGHT Research uses a published evidence hierarchy, designed by the National Health and Medical Research Council of Australia (NHMRC) [14]. These describe research designs which are broadly associated with particular methodological strengths and limitations so as to rank them in terms of quality, from I (systematic reviews of level II studies) to IV (case series).

For intervention studies where an intervention can be allocated experimentally, randomised controlled trials are considered the most robust way of determining a true association. However, for exposures which are observed and cannot be manipulated such as ASD status, a different hierarchy of evidence applies where observational studies are the most appropriate study design (see **Table A1.1**). This hierarchy is commonly used for aetiological research questions (eg, does exposure to asbestos cause lung cancer), however the association being investigated does not need to be causal or investigated as a causal relationship¹.

¹ Tracy Merlin, Managing Director, Adelaide Health Technology Assessment (AHTA), who contributed to the revision of the NHMRC hierarchy of evidence [14]

In the hierarchy of evidence employed, systematic reviews which included level II studies are ranked as level I evidence whereas systematic reviews of lower order evidence rank at the same level.

Prospective cohort studies are considered the most robust primary study design (level II evidence) in this review. For these designs, study participants are identified by exposures of interest (eg, ASD status) from a well-described starting point to see what outcomes (GI problems) occur. Retrospective cohort studies are graded as level III-2 evidence; these follow the same design as for prospective cohort studies except that outcomes that have occurred since the starting point are identified *historically* (eg, from medical records).

“All or none” studies (III-1) are where an association appears absolute; that is, every person being exposed develops the outcome, and every person not exposed does not develop the outcome. As this is known not to be the case for GI problems and ASD, this study design is not applicable in the current review.

Case-control studies (III-3) and case series studies (level IV) where case status is defined based on presence or absence of GI problems were excluded as they do not permit comparative analyses by ASD status, and are therefore inappropriate for the research questions considered in the current review. Whilst some follow-up studies in the review were reported as being case-control studies, they were appraised as being retrospective cohort studies where they defined cases as having ASD rather than GI problems².

Cross-sectional studies provide descriptive information about exposures and outcomes (including chronic conditions) which are assessed at the same time. These are considered as providing level IV evidence. For Question 1, cross-sectional studies were included where they compared GI problems arising in children and young people with ASD with those in people without ASD. For Question 2, cross-sectional studies were included where they described the co-occurrence of GI problems with behavioural characteristics in a sample of children and young people with ASD.

Table A1.1: Levels of evidence for investigating associations [14]

Level	Association
I	A systematic review of level II studies
II	A prospective cohort study
III-1	All or none (not applicable)
III-2	A retrospective cohort study
III-3	A case-control study (not applicable)
IV	A cross-sectional (comparative) study or case series (not applicable)

² A common source of confusion when describing a study population is to refer to patients with a disease as “cases” and a comparison group without the disease as “controls.” A study that compares case patients with control participants might be unwittingly labeled as a case-control study, even if it was a cohort study that contrasted the follow-up of people with a particular disease with a group without that disease [29].

Appraising the quality of included studies

Appraisal of primary and secondary studies

Studies were appraised using adapted versions of the GATE (Graphic Appraisal Tool for Epidemiology) Frame tools (designed by the University of Auckland's School of Population Health) appropriate to study design (including systematic reviews, randomised controlled trials, cohort studies, case-control studies, and qualitative studies). The adapted GATE has been validated by the New Zealand Guidelines Group (NZGG).

In brief, the GATE checklists are comprised of slightly different criteria depending on the study design but all broadly address each part of the PECO framework. The case is slightly different for systematic reviews and meta-analyses where additional criteria are included to assess the appropriateness of combining and analysing multiple studies. In general however, the checklists help the researcher to assess study quality in three main areas:

- study validity (steps made to minimise bias)
- study results (size of effect and precision)
- study relevance (applicability and generalisability).

For each checklist item, the reviewer codes whether the criterion for quality has been met (+), is unmet (x) or, where there is not enough information to make a judgement, is unknown (?). Reviewers then assign the same quality codes to each of three summary sections which assess the accuracy, relevance and applicability of the findings. Here, the reviewer indicates whether the study has any major flaws that could affect the validity of the findings and whether the study is relevant to clinical practice. The three summary sections include:

1. internal validity – potential sources of bias
2. precision of results
3. applicability of results/external validity – relevance to key questions and clinical practice.

Finally, reviewers assign an overall assessment of quality for the study as a whole based on a consideration of all checklist criteria; codes used are:

- + good
- x not ok, poor
- ? unclear

Codes for each of the three summary domains, and an overall study quality code are presented in the evidence tables for each study (**Appendices 3 and 4**).

There are no critical appraisal checklists for cross-sectional observational studies investigating non-causal associations. In such cases, narrative critique of individual

studies and their limitations in the evidence tables and in the review text deals with individual study's strengths and weaknesses.

Appraisal of guidelines

Where practice guideline recommendations or consensus panel statements were identified, the development process and quality of reporting was appraised using the Appraisal of Guidelines for Research and Evaluation Instrument - version II (AGREE II).³ The AGREE II is a valid and reliable instrument comprising 23 items organised into 6 quality domains that are rated on an ordinal scale ranging from 1 (strongly disagree) to 7 (strongly agree). The 6 domains include: scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence. Taking into account the ratings across the domains, an overall rating of the guideline is made on a scale ranging from 1 (lowest possible quality) to 7 (highest possible quality). Only the overall score is reported for guidelines or expert consensus reports in the current review.

Whilst the AGREE II assesses the overall quality of an existing guideline, the individual systematic review/s relating to specific topics contained within that guideline are also appraised using the GATE tool for systematic reviews as described above.

Completing evidence tables

Evidence tables (**Appendices 3 and 4**) present the key characteristics of each of the appraised studies including sample characteristics, methodology, results, the level of evidence, and the summary codes of study quality and/or guideline quality where applicable.

A1.6 Preparing recommendations

Developing recommendations

A one-day face-to-face meeting was held on 29 November 2012 where the LGG considered the findings of the current systematic review and developed new recommendations or revised those of the original ASD Guideline [1]. Using their collective professional judgement and experience, the LGG discussed the body of evidence with respect to the research questions and the applicability of the evidence within New Zealand.

Developing recommendations involves consideration of the whole evidence base for each of the research questions. The quality and consistency of the evidence and the clinical implications of the evidence within a New Zealand context is weighed up by all the LGG members. The recommendations were agreed by consensus during the meeting.

³ Available from www.agreetrust.org.

Grading recommendations

Each recommendation is assigned a grade to indicate the overall ‘strength of the evidence’ upon which it is based. Strength of the body of evidence is determined by three domains [30]:

- quality (the extent to which bias was minimised as determined by study design and the conduct of the study)
- quantity (magnitude of effect, numbers of studies, sample size or power)
- consistency (the extent to which similar findings are reported).

It should be noted that systematic reviews and meta analyses (secondary studies) considered drawing on publications over an overlapping timeframe could report on (some of) the same studies. For this reason it is important to be aware that the results from secondary studies should not be summated as independent sources of evidence as this would misrepresent the quantity of studies and give shared primary studies undue weight.

The grades of recommendations used by the Living Guideline Group, and also used in the original ASD Guideline [1] are presented in **Table A1.2**.

Table A1.2: Guide to grading recommendations [1]

Recommendations	Grade
The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)	B
The recommendation is supported by international expert opinion	C
The evidence is insufficient, evidence is lacking, of poor quality or opinions conflicting, the balance of benefits and harms cannot be determined	I

Note: Grades indicate the strength of the supporting evidence rather than the importance of the evidence.

Good practice point	Grade
Where no evidence is available, best practice recommendations are made based on the experience of the Living Guideline Group or feedback from consultation within New Zealand.	✓

Note: Good practice points are the opinion of the Living Guideline Group, or developed from feedback from consultation within New Zealand where no evidence is available.

A1.7 Consultation

Seeking comments from stakeholders is vital for peer-review and quality assurance processes in developing the report. In a focused consultation eight key stakeholder organisations/individuals were approached for feedback on a late draft of the report. Particular attention was sought regarding the relevance of the report to New Zealand services and needs, clarity and ease of use of the report, and implementability of the revised or new recommendations.

Responses were received from seven organisations, one of which (the Royal New Zealand College of General Practitioners) declined to provide formal feedback as they considered the report's conclusions to be uncontroversial. The remaining six respondents providing feedback included: Altogether Autism, Autism New Zealand, New Zealand Dieticians Association, New Zealand Nurses Organisation, and the Paediatric Society of New Zealand.

Feedback was largely very positive, with three respondents not suggesting any changes were needed, and one suggesting some minor sub-editing. Two suggestions from two respondents were more noteworthy.

The lead researcher collated feedback and drafted revisions for the LGG to consider. Amendments were finalised by group consensus. Suggestions identified in the consultation led to minor improvements to the final report including additional text to clarify a recommendation and the scope of the Guideline. INSIGHT Research and the LGG are grateful to those individuals and organisations who participated in the consultation process.

Appendix 2: Abbreviations and glossary

A2.1 Abbreviations and acronyms

Miscellaneous Terms

ADHD	attention-deficit/hyperactivity disorder
aOR	adjusted Odds Ratio
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
CI	confidence interval
DD	developmental disabilities
FAP	functional abdominal pain
FC	functional constipation
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GID	gastrointestinal dysfunction
hrs	hours
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICD	International Classification of Diseases
ID	intellectual disability
INSIGHT Research	Independent Network of Specialists in Guidelines & Health Technology Research
LD	learning disability
LGG	Living Guideline Group
Mth/s	month/s
M	mean
N (or n)	number (usually, sample size)
NA	not applicable
NHMRC	National Health and Medical Research Council (Australia)
NICE	National Institute for Health and Clinical Excellence (UK)
NIH	National Institute of Health (US)
NIMH	National Institute of Mental Health (US)
NZ	New Zealand
NZGG	New Zealand Guidelines Group
OR	odds ratio
PDD	Pervasive Developmental Disorder
PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
PECO	Patient, Exposure, Comparison, Outcome
PPV	positive predictive value
p/wk	per week
RCT	Randomised controlled trial
RR	Relative Risk
RUPP	Research Units on Pediatric Psychopharmacology
SD	Standard deviation

SR	Systematic review
TD	Typically developing
UK	United Kingdom
US	United States of America
vs	versus
wk/s	week/s

Tests, scales and measures

ADI-R	Autism Diagnostic Interview-revised
ADOS-G	Autism Diagnostic Observation Schedule-Generic
BMI	Body Mass Index
CARS	Childhood Autism Rating Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders - IV (text revision)
GATE	Graphic Appraisal Tool for Epidemiology
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
SRS	Social Responsiveness Scale
QPGD-II	Questionnaire on Pediatric Gastrointestinal Disorders-Rome II Version
QPGS-III	Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version

Databases

AMED	Allied and Complementary Medicine
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DARE	Database of Abstracts of Reviews of Effects
Embase	Excerpta Medica Database
GIN	Guidelines International Network
HTA Database	Health Technology Assessment Database
Medline	Medical Literature Analysis and Retrieval System Online
NHS EED	National Health Service Economic Evaluation Database
PsycINFO	Psychology Information Database

A2.2 Glossary

Epidemiological and statistical terms

All or one study	All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
Bias	Bias is a systematic deviation of a measurement from the 'true' value leading to either an over- or under-estimation of the treatment effect. Bias can originate from many different sources, such as allocation of patients, measurement, interpretation, publication and review of data.
Bonferroni's correction	In statistics, the Bonferroni correction is a method used to counteract the problem of multiple comparisons increasing the likelihood of chance effects being interpreted as significant. The correction increases the p value accepted as denoting a statistically significant difference or effect.
Case series	Case series are collections of individual case reports, which may occur within a fairly short period of time. Cases consist of either only the exposed people with the outcomes, or people with the outcome regardless of the exposure. In neither of these examples can the risk for the outcome be determined.
Case-control study	Patients with a certain outcome or disease and an appropriate group of controls without the outcome or disease are selected (usually with careful consideration of appropriate choice of controls, matching, etc.) and then information is obtained on whether the subjects have been exposed to the factor under investigation.
Coexisting condition	One that exists at the same time as another condition in the same individual.
Cohort study	Subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed in different degrees, to a risk factor or factors hypothesised to influence the probability of occurrence of a given disease or other outcome. Subjects are followed from a well-described starting point to determine whether the outcome/disease occurs (either retrospectively, or prospectively). The control group of people not exposed to the risk factor can be identified within the population-based cohort, and be matched by confounders known to be associated with the outcome (e.g., age, sex), or can be obtained from an historical cohort. Studies usually involve the observation of a large population, for a prolonged period (years).
Comorbid condition	One that exists at the same time as another condition in the same individual. The two conditions are usually independent of each other. For example a child who has autism might also develop leukaemia. That the child has autism complicates treating the leukaemia, but the two conditions are independent of each other.

Co-morbidities	Conditions which occur in association with another condition (e.g., ASD) more commonly than in the general population
Cross-sectional study	A study that examines the relationship between exposures (e.g., risk factor) and outcomes (e.g., disease) as they exist in a defined population, at a particular time.
Cumulative incidence	Cumulative incidence is a measure of disease/outcome frequency during a specified period of time.
Dose response	The relationship between the amount (dose) of an exposure and the resulting changes in body function or health (response).
Effectiveness	A measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population.
Generalisability	Applicability of the results to other populations.
Incidence	The number of new events (new cases of a disease) in a defined population, within a specified period of time.
Level of evidence	A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.
Matched controls	Matching is a method used to ensure that two study groups are similar with regards to "nuisance" factors that might distort or confound a relationship that is being studied.
Mean	Calculated by adding all the individual values in the group and dividing by the number of values in the group.
Observational studies	Also known as epidemiological studies. These are usually undertaken by investigators who are not involved in the clinical care of the patients being studied, and who are not using the technology under investigation.
Positive predictive value	The probability that a person with a positive test result has, or will develop, the tested for condition/disease.
Power	The probability that a statistical test or study will detect a defined pattern in data and declare the extent of the pattern as showing statistical significance.
Prevalence	A measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some time period.
Quality of evidence	Degree to which bias has been prevented through the design and conduct of research from which evidence is derived.
Randomised controlled trial (RCT)	An epidemiological experiment in which subjects in a population are randomly allocated into groups to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The groups are compared prospectively.
Relative Risk (RR)	Relative risk measures the magnitude of an association between an exposed and non-exposed group. It describes the likelihood of developing disease/outcome in an exposed group compared to a non-exposed group. Relative risk is calculated using cumulative incidence data to measure the probability of developing disease.
Secondary study	An analysis or synthesis of research data reported elsewhere, including systematic reviews, meta analyses and guidelines.
Selection bias	Error due to systematic differences in characteristics between those who are selected for inclusion in a study and those who are not (or between those compared within a study and those who are not).

Strength of evidence	The strength of evidence for an intervention effect includes the level (type of studies), quality (how well the studies were designed and performed to eliminate bias) and statistical precision (P-value and confidence interval).
Systematic review (SR)	A literature review reporting a systematic method to search for, identify and appraise a number of independent studies.
Odds Ratio (OR)	Defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group, or to a database estimate of that ratio. An odds ratio estimates the probability of a disease/outcome given exposure to a specific factor by measuring the probability of exposure given the presence of disease.

Topic specific terms

colitis	inflammation of the colon
encopresis	is the voluntary or involuntary passage of stools in a child who has been toilet trained (typically over the age 4 years), which causes the soiling of clothes
enuresis	the involuntary passing of urine
echolalia	frequent repetition of set words and phrases
functional abdominal pain	abdominal pain without demonstrable evidence of anatomic, metabolic, infectious, inflammatory, neoplastic, or other pathologic condition
irritable bowel syndrome (IBS)	functional abdominal pain associated with alteration in bowel movements
pica	the persistent craving and compulsive eating of nonfood substance

Appendix 3: Evidence Tables of included studies for Question 1

Studies are ordered using the following hierarchy: study type (systematic reviews then primary studies), level of evidence (highest first), year of publication (most recently published first), first author's surname (alphabetical order).

Systematic reviews

National Institute of Health and Clinical Effectiveness (NICE), 2011 [11]					
Country, study type, aims	Review scope	Participants and search method	Inclusion and exclusion criteria	Results	Conclusions
<p>Country: UK Study type: systematic review of varied study designs informing guideline recommendations Evidence level: III-3 (systematic review includes level III-3 primary studies).</p>	<p>Review scope: recognition, referral and diagnosis of ASD in children and young people. Relevant to the current review: What are the common coexisting conditions that should be considered as part of assessment? Functional gastrointestinal problems reviewed as a potential comorbidity.</p>	<p>Participants: individuals with ASD Search method: extensive search involving multiple databases. Search terms available. Appraisal: Formal (checklist) appraisal not permitted for observational uncontrolled studies. Recommendations were developed by consensus by the guideline development team of experts.</p>	<p>Inclusion: none stated, but all included studies relate to children and young people with ASD Exclusion: conference abstracts, theses, unpublished trials.</p>	<p>Only results pertinent to "gastrointestinal symptoms" relevant to the current review reported here.</p> <ul style="list-style-type: none"> - Two studies: an uncontrolled observational study and a retrospective control study. - Consensus expert opinion developed recommendations based on the reviewed evidence. <p>Key findings:</p> <ul style="list-style-type: none"> - The prevalence of GI problems in people with or who were to be diagnosed with autism was 9%, which did not differ from that of matched controls who did not have ASD [9]. - The prevalence of GI problems in people with ASD was 62% [25]. <p>Limitations of evidence base</p> <ul style="list-style-type: none"> - Methodological limitations included lack of an appropriate control group. 	<p>Author's conclusions: The following relevant recommendation was developed: <i>"Consider whether the child or young person may have any of the following as a coexisting condition, and if suspected carry out appropriate assessments and referrals: (...)</i> <i>- Functional problems and disorders (...)</i> <i>- constipation, altered bowel habit, faecal incontinence or encopresis.</i></p> <p>Reviewer's comments: Systematic, extensive search, narrative appraisal (due to low evidence level of study designs identified), detailed evidence tables available, consensus expert development of recommendations. Source of funding: NICE</p>
Study quality: Internal validity: + Precision: ? Applicability: +					Overall Score: +
Quality of guideline recommendation/statement development and reporting:					Overall Score: 6/7

Key: ASD= autism spectrum disorder; GI=gastrointestinal; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NICE= National Institute of Health and Clinical Excellence; UK= United Kingdom

Buie et al, 2010 [7]					
Country, study type, aims	Review scope	Participants and search method	Inclusion and exclusion criteria	Results	Conclusions
<p>Country: US</p> <p>Study type: systematic review of varied study designs informing expert consensus statements</p> <p>Evidence level: III-2 (systematic review includes level III-2 studies).</p>	<p>Review scope: evaluation, diagnosis and treatment of gastrointestinal disorders of people with ASD, relevant to seven topics considered by separate working groups, including "gastrointestinal symptoms".</p>	<p>Participants: individuals with ASD</p> <p>Search method: searched MEDLINE. Search terms provided. Additional publications identified by working group members.</p> <p>Appraisal: two experts from each working group reviewed each relevant paper applying a modified GRADE system to rate the type and quality of evidence. Final grading was determined by consensus by the full working group.</p> <p>Recommendations were developed by forum participants through nominal group technique.</p>	<p>Inclusion: none stated, but all included studies relate to children and young people with ASD</p> <p>Exclusion: none stated</p>	<p>Only results pertinent to "gastrointestinal symptoms" relevant to the current review reported here.</p> <ul style="list-style-type: none"> - 11 studies identified and key details presented in a table (Table 4). - Because of the "absence, in general, of high-quality clinical research data", evidence-based recommendations were deemed not yet possible. - Consensus expert opinion developed recommendations based on the reviewed evidence. <p>Key findings:</p> <ul style="list-style-type: none"> - The prevalence of GI abnormalities in people with ASD is "incompletely understood", with <i>reported</i> prevalence ranging from 9% to 91%. - Inconsistent reports. - Much data consistent with the likelihood of a high prevalence of GI symptoms and disorders associated with ASDs. However, whether prevalence of GI problems is higher in individuals with ASD than in the general population is not known with certainty. <p>Limitations of evidence base</p> <ul style="list-style-type: none"> - Methodological limitations included lack of an appropriate (non-related) control group. - Sample sources may lead to referral bias. 	<p>Author's conclusions:</p> <ul style="list-style-type: none"> - Individuals with ASDs who present with gastrointestinal symptoms warrant a thorough gastrointestinal evaluation. - All of the common gastrointestinal conditions encountered by individuals with typical neurologic development are also present in individuals with ASDs. - Whether prevalence of GI problems is higher in individuals with ASD than without is not known with certainty. <p>Reviewer's comments: Systematic but limited search, checklist-guided appraisal but grading not reported for individual studies.</p> <p>Source of funding: Autism Forum paid honoraria to all panel participants. Two authors have received funding from various pharmaceutical companies, and one is Chair of a laboratory that generates revenue from genetic laboratory testing.</p>
Study quality: Internal validity: + Precision: ? Applicability: +					Overall Score: +
Quality of guideline recommendation/statement development and reporting					Overall Score: 5/7

Key: ASD= autism spectrum disorder; GI=gastrointestinal; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; US= United States of America

Erickson et al, 2005 [8]					
Country, study type, aims	Review scope	Participants and search method	Inclusion and exclusion criteria	Results	Conclusions
<p>Country: US</p> <p>Study type: systematic review of varied study designs</p> <p>Evidence level: III.2 (systematic review includes level III-2 studies).</p>	<p>Review scope: critically analyse literature as it applies to all aspects of gastrointestinal factors in autism, including discussion of symptoms, pathology, nutrition, and treatment.</p>	<p>Participants: people with ASD (age not specified)</p> <p>Search method: searched MEDLINE from 1963. Citation searching of retrieved papers. Search terms provided.</p> <p>Appraisal: narrative summary, no checklists.</p>	<p>Inclusion: pertaining to GI symptoms and autism</p> <p>Exclusion: none stated</p>	<p>Only results pertinent to current review reported here. 73 papers identified, though most relate to issues out of scope for current review.</p> <p>Key findings:</p> <ul style="list-style-type: none"> - there is a lack of published rigorous data to support increased gastrointestinal symptomatology in autistic children - no prospective and little retrospective data employing a control group - data not put in context with typically developing children; i.e., GI symptoms can be common in children without autism. <p>Limitations of evidence base:</p> <ul style="list-style-type: none"> - retrospective designs - lack of control group of children without ASD - variation in definition of symptoms - sampling bias in recruiting participants presenting with GI symptomatology. 	<p>Author's conclusions: no evidence that specific GI abnormalities exist (for children with ASD). No support for the routine role of specialised GI testing in the <i>asymptomatic</i> autistic child. Standard evaluation and treatment of GI complaints should be followed.</p> <p>Reviewer's comments: Narrative review with systematic but limited search. Narrative methodological critique with no formal critical appraisal using checklists. Thorough consideration of methodological limitations.</p> <p>Source of funding: research fellowships, career awards, government research grants.</p>
<p>Study quality: Internal validity: ? Precision: ? Applicability: ?</p>					<p>Overall Score: ?</p>

Key: ASD= autism spectrum disorder; GI=gastrointestinal; US= United States of America

Primary studies

Wang et al, 2011 [18]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: US Study type: population-based retrospective cohort Evidence level: III.2</p>	<p>Setting: national registry of children and young people with ASD from families with multiple affected members recruited through website, autism-related meetings, and posters in clinics and schools.</p> <p>Participants: 752 children and young people from 313 multiply affected (by ASD) families (M age=8.4 years) - 589 with ASD (78% male) (three severity sub-groups: 69% with Full Autism, 16% with Almost Autism, and 15% with Spectrum classified using ADOS and ADI-R). - 163 unaffected siblings (46% male).</p>	<p>Inclusion: member of family where at least 2 family members are on the autism spectrum as confirmed using the ADOS, ADI-R and expert clinical judgement.</p> <p>Exclusion: people with previously diagnosed neurogenetic disorders, those with missing data.</p> <p>Follow up: retrospectively reported outcomes over lifetime.</p>	<p>Parent-recalled medical history via in-home structured interviews with a paediatric neurologist.</p> <p>Exposure: diagnosis of ASD using ADOS and ADI-R</p> <p>Comparison: unaffected siblings</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> - ever had GI problems? (lifetime prevalence) - what type of GI problems? (lifetime prevalence): - gastroesophageal reflux (GER), - peptic ulcer disease, - irritable bowel disease, - chronic diarrhoea, - constipation, - unknown GI problem, - other GI problem. 	<p>Parents reported more GI problems in their children with ASD than with unaffected siblings (42% vs 12%, $p < 0.001$). Most common symptoms were constipation (20%) and chronic diarrhoea (19%). GER did not differ.</p> <p>In conditional logistic regression analyses adjusting for between-family differences (sibling age, gender, current use of medications), affected children and young people had higher odds of having a GI problem vs unaffected children and young people (AOR=7.41, 95% CI=3.63-15.14). Odds significantly elevated for the full Autism group (14.28, 95% CI=6.22-32.77) and Almost Autism group (AOR=5.16; 95% CI=2.02-13.2), but not Spectrum group.</p> <p>Restricting analyses to people aged > 5 years did not alter key findings.</p> <p>Limitations</p> <p>Conditional logistic regression can't control within-family confounders. Parents with a child with ASD may be more attentive to their discomforts and may overlook GI symptoms in unaffected sibling. Sample had few African-Americans and biased toward higher educated.</p>	<p>Author's conclusions: Parents report significantly more GI problems in children and young people with familial ASD than in their unaffected children. Autism symptom severity is associated with increased odds of having GI problems. Claim this as the first study with sample large enough to permit investigating more homogenous subgroups. Study has important implications for clinicians and parents of children and young people with ASD to be cognizant of the discomforts that these individuals may experience and to provide proper work-up and treatment.</p> <p>Reviewer's comments: Sample tends to be white, educated. Control siblings not independent from children and young people with ASD. Thorough assessment of ASD diagnoses. Convergent validity of severity factor using additional cognitive and adaptive functioning scales. Power calculation performed. Sophisticated use of conditional logistic regression analyses treated each family as a matched set and allowed within-family comparisons whilst controlling for between family effects.</p> <p>Source of funding: Autism Genetic Resource Exchange (AGRE) and Autism Speaks.</p>
Study quality: Internal validity: ? Precision: + Applicability: +					Overall Score: +

Key: ADOS=Autism Diagnostic Observation Scale; ADI-R=Autism Diagnostic Inventory-revised; aOR=adjusted Odds Ratio; ASD= autism spectrum disorder; CI=confidence interval; GI=gastrointestinal; GER=gastroesophageal reflux; US=United States

Ibrahim et al, 2009 [12]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: US Study type: retrospective cohort study Evidence level: III-2</p>	<p>Setting: Sample drawn from a population-based cohort of residents of Olmsted County, Minnesota, aged 0-20 years between 1976-1997. Through the Rochester Epidemiology Project, all inpatient and outpatient diagnoses (and accompanying symptoms) are indexed for computerised retrieval. Includes well-child visits, developmental, psychiatric, neurological and psychological assessments.</p> <p>Participants: 363 children and young people (76% male)</p> <ul style="list-style-type: none"> - 124 with ASD (identified from a previous study) - 248 (matched controls) without ASD. <p>Mean age at diagnosis of autism was 6.1 years, mean age at last follow-up was 17.4 years (ASD group) and 16 years (controls).</p>	<p>Inclusion: children and young people aged 1-20 years with autism (cases) Exclusion: none reported Follow-up: median of 18.2 years (ASD group) and 18.7 years (controls).</p>	<p>All medical diagnoses <21 years are indexed for computerised retrieval.</p> <p>Exposure: ascertainment (of autism diagnosis) based on complete review of medical and school records.</p> <p>Comparison: 2 controls per person with ASD, matched for age, gender, year of registration as a patient, and duration of follow-up.</p> <p>Outcome measures: Cumulative incidence of any and each of the following 5 gastrointestinal diagnoses:</p> <ul style="list-style-type: none"> - constipation - diarrhoea - abdominal bloating, discomfort, irritability - gastroesophageal reflux (GER) or vomiting - feeding issues or food selectivity. 	<p>Results relating to review question reported here: No significant differences between children and young people with autism and matched controls in cumulative incidence of GI symptoms (77.2% vs 72.2%), or for the following individual GI outcomes:</p> <ul style="list-style-type: none"> - diarrhoea (50.3% vs 41.1%) - abdominal bloating, discomfort, irritability (44.9% vs 41.3%) - GER or vomiting (25.3% vs 16.9%) <p>Children and young people with autism were identified as having greater cumulative incidence of constipation than control participants (33.9% vs 17.6%; RR: 1.97 (95% CI: 1.25-3.10), and feeding issues/food selectivity (24.5% vs 16.1%; RR: 1.95 (95% CI: 1.18-3.24).</p> <p>Limitations Retrospective study, however authors suggest that scrutiny was high. Sample was 98% white which limits generalisability. Study did not assess duration, severity, and recurrence of GI symptoms.</p>	<p>Author's conclusions: Frequency of GI symptoms among children and young people with and without ASD was high. The ritualistic tendency, need for routine, and insistence on sameness that are characteristics of children with autism may lead these children to choose stereotyped diets. Adverse effects of treatment may also contribute to appetite changes and constipation. Suggest that the increased food selectivity and constipation may be attributable to behavioural features that define autism or to adverse effects of medical treatment rather than to an underlying autism-specific organic GI pathology.</p> <p>Reviewer's comments: As the GI symptoms are common generally in children and young people, lifetime cumulative incidence may not be sensitive to differences between groups in severity, extent and frequency of GI symptoms.</p> <p>Source of funding: a grant from the David and Elaine Dana family and the National Institutes of Health (NIH).</p>
Study quality: Internal validity: ? Precision: + Applicability: ?					Overall Score: ?

Key: ASD= autism spectrum disorder; CI=confidence interval; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders – 4th edition; GER=gastroesophageal reflux; GI=gastrointestinal; NIH=National Institute of Health; RR: relative risk; US=United States; vs=versus

Valicenti-McDermott et al, 2006 [10]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: US Study type: retrospective cohort (matched control) study Evidence level: III.2</p>	<p>Setting: Children and young people from ASD or developmental disabilities (DD) referred by paediatric neurology and developmental programmes, children and young people with typical development (TD) recruited from general outpatient paediatric clinic. Participants: 150 children and young people (74% male; M age=7.6 years) - 50 with ASD (ASD group) - 50 (matched controls) with TD - 50 (matched controls) with other (DD)</p>	<p>Inclusion: children and young people aged 1-18 years with clinician diagnosed ASD (ASD group) or other developmental disability (DD group). Children and young people living with their families. Exclusion: children and young people with known genetic syndromes including trisomy 21, tuberous sclerosis, Rett disorder, and static or, progressive neurological conditions, and non-ambulatory patients. For typically developing children and young people, excluded if repeated a school year, been referred to for developmental evaluation. For both control groups, CARS scores of 20 or less. Follow-up: lifetime GI problems reported retrospectively.</p>	<p>Structured interviews with parents/children including Clinical Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders. Exposure: diagnosis of ASD using DSM-IV and CARS schedules. Comparison: two control groups matched for age, sex and ethnicity - children and young people with typical development - children and young people with other (DD) using DSM-IV criteria. Outcome measures: QPGD Rome II adapted to identify lifetime GI and feeding problems, current and in the past, and frequency. GI symptoms included frequent vomiting, history of GER, frequent abdominal pain, no. bowel movements per day, abnormal stool pattern, chronic constipation, use of laxatives or enemas, faecal encopresis, visits to gastroenterologist, family history of GI disease.</p>	<p>Results relating to review Question 1 reported here: Lifetime prevalence of GI problems was 70% for people with ASD compared with 28% of those with typical development ($p<0.001$); and 36% with other DD ($p<0.023$). Most common symptom was constipation (44% in ASD vs 16% in TD group). Significant difference between ASD only and TD group in all GI symptoms except GER, abdominal pain, number of bowel movements, and family history of GI disease. Only significant differences between ASD group and DD group were total number of symptoms, abnormal stool pattern, and faecal encopresis. In multivariate logistic regression analyses adjusting for age, sex, ethnic group and maternal education level, GI symptoms were associated with autism (aOR=3.8; 95% CI: 1.7-11.2). No associations found between GI symptoms and medication, history of food allergies, or being toilet trained. Limitations QPGD Rome II may yield higher reported GI problems than physician surveys or chart reviews. Reliance on family-reported symptoms and lack of specimens may introduce recall biases.</p>	<p>Author's conclusions: GI symptoms seem to be a common comorbidity of autism. Suggest that families of children and young people with ASD may be more aware of nutritional treatments and therefore may report more GI symptoms, however not all symptoms were reported as higher. Reviewer's comments: Study strength was that the samples of people with ASD or DD were not drawn from gastroenterology clinics where GI outcomes would be expected to be higher. Source of funding: Empire Research Fellowship for Clinical Investigation of New York State and the Albert Einstein College of Medicine Clinical Research Training Program Pilot Funding, and National Institute of Health (NIH) grants.</p>
Study quality: Internal validity: + Precision: + Applicability: ?					Overall Score: +

Key: aOR=adjusted odds ratio; ASD= autism spectrum disorder; CARS= Childhood Autism Rating Scale; CI=confidence interval; DD=developmental disabilities; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders – 4th edition; GER=gastroesophageal reflux; GI=gastrointestinal; IBD=irritable bowel disease; QPGD(Rome II)=Questionnaire for Pediatric Gastrointestinal Disorders; NIH=National Institute of Health; TD=typical development; US=United States

Kohane et al, 2012 [15]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: US</p> <p>Study type: population-based, cross-sectional study</p> <p>Evidence level: IV</p>	<p>Setting: accessed distributed query system across electronic medical records from 3 general hospitals and 1 paediatric hospital from 2001 - 2010.</p> <p>Participants: (up to)* 2,393,778 people/entries (under 35 years) including 14,381 with ASD. Mean age not reported; 70% male.</p> <p>* Records from each hospital/clinic source not mutually exclusive.</p>	<p>Inclusion: 0-35 years, only analyses with 0-18 years reported here.</p>	<p>Accessed electronic health care record datasets where ICD-9 codes are used to record diagnoses.</p> <p>Exposure: ASD including autistic disorder, Asperger's syndrome and other pervasive developmental disorders identified with ICD-9 codes.</p> <p>Comparison: absence of ICD-9 codes for ASD diagnosis</p> <p>Outcome measures: "bowel disorders" according to 112 ICD-9 codes, excluding those for inflammatory bowel disease (IBD).</p>	<p>Over the study period, more bowel disorders in people aged 0-17 years with ASD than those patients without ASD in hospital sample (11.63% vs 5.02%).</p> <p>Limitations</p> <p>The ICD-9 codes without chart review cannot determine whether diagnosis was established from symptoms or diagnostic tests. Acknowledged that study can only be exploratory or suggestive.</p>	<p>Author's conclusions: The comorbidities of ASD encompass disease states that are significantly over-represented in ASD with respect to patient populations of tertiary health centres.</p> <p>Reviewer's comments: records of bowel diseases are much broader than functional gastrointestinal symptoms and include some diagnoses excluded from this review.</p> <p>Source of funding: CTSA award from National Institute of Health (NIH)/National Centre for Research Resources (NCRR); i2b2 National Centre for Biomedical Computing, and the Conte Centre for Computational System Genomics of Neuropsychiatric Phenotypes.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ASD= autism spectrum disorder; IBD= inflammatory bowel disease; ICD=International Classification of Diseases; NIH=National Institute of Health; US=United States of America; vs=versus

Schieve et al, 2012 [16]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: US</p> <p>Study type: cross-sectional observational study</p> <p>Evidence level: IV</p>	<p>Setting: nationally representative sample from 2006-2010 National Health Interview Surveys with and without developmental disabilities (DD). Response rate >70%.</p> <p>Participants: 41,244 children and young people (3-17 years, from 4 mutually exclusive disability groups:</p> <ul style="list-style-type: none"> - n=375 with autism (78% male) - n=2901 with intellectual disability (ID) without autism - n=2901 with attention-deficit/hyperactivity disorder (ADHD) without autism - n=1955 with learning disability (LD) or other developmental delay without autism, ID or ADHD. <p>Compared with: n=35,775 children and young people without DD (49% male)</p>	<p>Inclusion: 3-17 years with and without selected mutually exclusive behavioural and learning DDs.</p> <p>Exclusion: people who are institutionalised or in the armed forces do not participate in the survey.</p>	<p>Structured interview with parent or guardian.</p> <p>Exposure: diagnosis of autism (answering yes to "has a doctor told you that your child has autism?")</p> <p>Comparison: without diagnosis of autism or any developmental disabilities</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> - frequent diarrhoea/colitis over the last 12 months - recent occurrence (last 2 weeks) of stomach/intestinal illness that included vomiting or diarrhoea. 	<p>Only results pertinent to Question 1 reported here.</p> <p>Weighted logistic regression models adjusting of sex, age, race/ethnicity, and maternal education found that children and adolescents with autism, compared to without DD, had higher odds of having:</p> <ul style="list-style-type: none"> - frequent diarrhoea/colitis over the last 12 months (6.8% vs 0.9%; aOR=7.1; 95% CI:3.9-12.8) - recent stomach/intestinal illness that included vomiting or diarrhoea (12.1% vs 4.9%; aOR=2.6; 95% CI:1.7-3.9). <p>Limitations</p> <p>Diagnoses of autism and medical co-occurrences by self-report (of whether a doctor has made this diagnosis). Not clear whether this includes diagnoses across the autism spectrum.</p>	<p>Author's conclusions: Children and young people with autism were 70% more likely to have frequent diarrhoea/colitis over the last 12 months than those in the ID group, two times more likely than those in the ADHD group and LD/other developmental delay groups, and seven times more likely than children and young people without DDs (extrapolated from data, statistics not reported). Findings inform ongoing debate (regarding whether prevalence of GI problems is higher in people with autism).</p> <p>Reviewer's comments: Study measures of developmental and medical diagnoses by parent self-report. Open to recall biases.</p> <p>Source of funding: National Center on Birth Defects and Developmental Disabilities, Centre for Disease Control and Prevention.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: aOR=adjusted odds ratio; ADHD=attention-deficit/hyperactivity disorder; ASD= autism spectrum disorder; CI=confidence interval; DD=developmental disabilities; GI=gastrointestinal; ID=intellectual disability; LD=learning disability; US=United States, vs=versus

Smith et al, 2009 [17]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions, quality issues
<p>Country: UK Study type: cross-sectional study Evidence level: IV</p>	<p>Setting: Children and young people with ASD registered with the York Autism Spectrum Disorders Forum, which assesses all referrals in the district. The sample were recruited from participants of another study into urine metabolites</p> <p>Children in control groups recruited from "Special" and "Mainstream" schools in response to a leaflet.</p> <p>Participants: 198 children and young people; gender distribution not reported.</p> <ul style="list-style-type: none"> - 51 with ASD; M age=9.7 years - 112 (matched controls) from mainstream school; M age=10.0 years - 35 (matched controls) with developmental and neurological disabilities from special school; M age=12.6 years. 	<p>Inclusion: children and young people with ASD (age range not specified) as consistent with ICD-10 criteria.</p> <p>Exclusion: any known metabolic disorder, and for non-autistic group, any previous assessment for ASD.</p>	<p>Exposure: ASD diagnosis based on ADI-R and (for 72% of children and young people) ADOS-G, or independent validation of meeting ICD-10 criteria.</p> <p>Comparison: "at least one" age and sex matched control from both control groups.</p> <p>Outcome measures: Developed a questionnaire to record common bowel symptoms and changes in bowel habit.</p>	<p>Children and young people with ASD were more likely than those from mainstream school to have (at $p<0.001$):</p> <ul style="list-style-type: none"> - constipation (25% vs 4%) - excessive flatulence (24% vs 2%) - parents concerned about bowel issues (35% vs 4%) - seen a doctor re concern re bowel disorder (27% vs 4%). <p>And to have (at $p<0.05$):</p> <ul style="list-style-type: none"> - persistent diarrhoea (8% vs 0%) - abdominal bloating (14% vs 4%) - been diagnosed with a bowel disorder (3 with ASD with constipation: 6% vs 0%) <p>Children and young people with ASD were also more likely to:</p> <ul style="list-style-type: none"> - be on a special diet (18% vs 4%) - have parents concerned about range of foods eaten (18% vs 4%) - have consulted a dietician (20% vs 4%) - have received bowel problem "treatment" (24% vs 5%). <p>There were no significant differences in parent-reported recurrent abdominal pain, recurrent vomiting, blood present in faeces, concerns about child's growth, or seeing a GI specialist.</p> <p>Children and young people with ASD more likely than those with developmental and neurological disabilities to have concerns about range of foods (35% vs 12%, $p<0.001$), but did not differ on any other variable.</p> <p>Children and young people from special schools had high reported rates of constipation (40%), excessive flatulence (20%), diarrhoea (16%), and seeing a dietician (48%).</p> <p>Limitations</p> <p>Used unvalidated retrospective parent reports. Participation rate of 37% of families initially approached for another study. No participation rate reported for the matched control groups. Questionnaire not psychometrically tested and poorly worded; e.g., "does he/she have constipation". No adjustment to p value for multiple tests.</p>	<p>Author's conclusions: The study found an increase in bowel symptoms in children and young people with autism, however it would appear that this is not specifically associated with autism as bowel symptoms were reported in similar frequency to a comparison group of children and young people with other developmental and neurological problems.</p> <p>Reviewer's comments: Sample recruitment could bias towards families with GI concerns, and participation rate was low as it depended on involvement in a separate study on urine metabolites. Small sample sizes. Lacked multivariate analyses. Relied on retrospective parental report using an unvalidated questionnaire with ambiguous and nonspecific questions.</p> <p>Source of funding: not reported</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADI-R=Autism Diagnostic Interview-revised; ADOS-G=Autism Diagnostic Observation Schedule-Generic; ASD= autism spectrum disorder; CI=confidence interval; GER=gastroesophageal reflux; GI=gastrointestinal; ICD-10=International Classification of Diseases-version 10; UK=United Kingdom; vs=versus

Appendix 4: Evidence Tables of included studies for Question 2

Tables present studies are grouped using the following hierarchy: study type (systematic reviews then primary studies), level of evidence (highest first), year of publication (most recently published first), first author's surname (alphabetical order).

Systematic reviews

Buie et al, 2010 [7]					
Country, study type, aims	Review scope	Participants and search method	Inclusion and exclusion criteria	Results	Conclusions
<p>Country: US Study type: systematic review of varied study designs Evidence level: IV (systematic review based on IV evidence and international consensus expert opinion).</p>	<p>Review scope: evaluation, diagnosis and treatment of gastrointestinal disorders of people with ASD, relevant to seven topics considered by separate working groups, including "gastrointestinal symptoms".</p>	<p>Participants: individuals with ASD. Search method: searched MEDLINE. Search terms provided. Additional publications identified by working group members. Appraisal: 2 experts reviewed each relevant paper applying a modified GRADE system to rate the type and quality of evidence. Final grading determined by group consensus. Recommendations developed by forum through nominal group technique.</p>	<p>Inclusion: none stated, but all included studies relate to children and young people with ASD Exclusion: none stated</p>	<p>Only results pertinent to Question 2 reported here.</p> <ul style="list-style-type: none"> - 3 studies cited: a narrative review [13], a pilot of an assessment tool in adults with developmental disabilities [23], and a small cross-sectional observation study of the co-occurrence of sick days with behaviour problems [24]. - Consensus expert opinion developed statements based on reviewed evidence. <p>Key findings:</p> <ul style="list-style-type: none"> - in ASD, GI conditions can present typically or atypically, including behavioural change and/or problem behaviours such as self-injury, aggression - vocal behaviour, motor behaviours, and overall change in state of being (e.g., sleep disturbance or irritability) may be manifestations of abdominal pain or discomfort in persons with ASD (paper's Table 2) - presentations associated with specific gastrointestinal problems reported (paper's table 3) - no evidence of pathogenic mechanisms specific to ASDs that warrant a distinct diagnostic approach. 	<p>Author's conclusions:</p> <ul style="list-style-type: none"> - The communication impairments may lead to unusual presentations of gastrointestinal disorders, including sleep disturbance and problem behaviours. - Caregivers and health care professionals should be alert to the presentation of atypical signs of common GI disorders in patients with ASDs. <p>Reviewer's comments: Systematic but limited search, checklist-guided appraisal but not for individual studies.</p> <p>Source of funding: Autism Forum paid honoraria to panel participants, 2 authors received funding from pharmaceutical companies, and one is Chair of a genetic testing laboratory.</p>
Study quality: Internal validity: + Precision: ? Applicability: +					Overall Score: +
Quality of guideline recommendation/statement development and reporting					Overall Score: 5/7

Key: ASD= autism spectrum disorder; GI=gastrointestinal; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; US= United States of America.

Primary studies

Maenner et al, 2012 [20]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions
<p>Country: US</p> <p>Study type: Population-based cross-sectional observational study</p> <p>Evidence level: IV</p>	<p>Setting: identified from three sites (Alabama, Pennsylvania, Wisconsin) from the Autism and Developmental Disorders Monitoring (ADDM) Network (multi-site, population-based, autism surveillance system where records from healthcare sources were available).</p> <p>Participants: 487 children aged 8 years; 397 (81%) male) with ASD.</p>	<p>Inclusion: children who were 8 years old in 2006 who met the ADDM's definition for ASD (clinically defined by DSM-IV-TR from multiple sources) whose records contained a medical record from their doctor.</p> <p>Exclusion: none reported</p>	<p>Exposure: Standardised clinical scales measured in the ADDM dataset included abnormalities in sleeping; stereotyped and repetitive motor mannerisms; self-injurious behaviours; abnormal eating habits; abnormalities in mood or affect; argumentative; oppositional, defiant, or destructive behaviours; aggression; temper tantrums.</p> <p>Also assessed 6 control behaviours not generally associated with GI problems: oblivious to other children; lack of imaginative play; lack of or excessive fear; insistence on sameness; delayed motor milestones; and abnormal cognitive development.</p> <p>Comparison: absence of the above signs, symptoms, characteristics</p> <p>Outcomes: Documented history of GI problems (from ADDM data set) defined as constipation, abdominal pain, diarrhoea, encopresis, gastrointestinal reflux disease (GERD), gastritis, abdominal bloating, disaccharidase deficiencies, inflammation of the GI tract, abnormalities of the enteric nervous system, functional abdominal pain, irritable bowel syndrome, flatulence, Celiac disease.</p>	<p>35 (7%) of children had documented history of GI problems, most commonly constipation and encopresis.</p> <p>Children with diagnosed GI problems were more likely to have co-occurring cerebral palsy ($p<0.01$) and seizure-like activity ($p<0.01$), but did not differ in terms of sex, race and ethnicity, ASD classification, or intellectual disability.</p> <p>Of behaviours hypothesised to be related to GI problems, the following were:</p> <ul style="list-style-type: none"> - sleep abnormalities ($p<0.01$) - abnormal eating habits $p<0.05$ - argumentative; oppositional, or destructive behaviours ($p<0.05$) <p>and the following were not related to GI problems:</p> <ul style="list-style-type: none"> - mood disturbances - tantrums - stereotypic/repetitive behaviours - self-injurious behaviours. <p>Of the 6 control behaviours, 1 associated: - delayed motor milestones ($p<0.01$).</p> <p>Nearly all children with ASD (with and without GI problems) had at least one of the behaviour problems hypothesised to be related to GI distress; PPV=7.2%, sensitivity 100%. Increasing number of behaviours to 5 increased PPV to 9.4% and reduced sensitivity to 80%.</p>	<p>Author's conclusions: Unusual sleeping or eating habits and oppositional behaviour were significantly associated with GI problems. However nearly all children had at least one of these behaviours, regardless of whether they had documented GI problems, and so behaviours have limited predictive utility in screening for GI problems.</p> <p>Not the case that children with GI problems generally have greater behavioural problems in general.</p> <p>The incidental association between motor milestones, cerebral palsy and seizure-like activity with GI problems may relate to underlying dysfunction.</p> <p>Reviewer's comments: Relatively small sample with confirmed GI problems. No adjustment to p value to account for multiple tests.</p> <p>Use of medical records likely to be accurate in identifying GI dysfunction requiring medical attention, but likely to under-identify less severe and less persistent GI problems. However population-based sampling makes results more representative of general ASD population.</p> <p>Source of funding: grants from Autism Science Foundation, Centers for Disease Control and Prevention.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADDM=Autism and Developmental Disorders Monitoring; ASD=autism spectrum disorder; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders - IV (text revision); PPV=positive predictive value; US= United States of America

Mazurek et al, 2012 [21]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions
<p>Country: US Study type: Cross-sectional observational study Evidence level: IV</p>	<p>Setting: enrolled in the clinical registry of the Autism Treatment Network (ATM), a multi-site network of 17 autism centres across US and Canada. Participants: 2973 children and adolescents; mean age=6 years, 2505 (84%) male) with ASD, 84% were Caucasian.</p>	<p>Inclusion: children and young people aged 2 to 17 years with clinically diagnosed ASD (with ADOS) required to meet DSM-IV-TR criteria and have a confirmed diagnosis of an ASD. Exclusion: none reported</p>	<p>Exposure: Parent-report for: Sensory Over-Responsivity (SOR) (a subset from the Short Sensory Profile); Anxiety using the DSM-Oriented Problems T-score from the Child Behavior Checklist (CBCL); Intellectual functioning. Comparison: absence of the above signs, symptoms, characteristics Outcomes: GI Symptom Inventory Questionnaire assessed presence, duration and nature of five chronic GI complaints over the last 3 months: defined as constipation, abdominal pain, bloating, diarrhoea, and/or nausea.</p>	<p>733 (25%) of sample experienced at least one type of chronic GI problem, most commonly constipation (12% of sample). Chronic GI problems associated with - anxiety (p<0.0001) - sensory-responsivity (p<0.0001) - being Caucasian (p<0.0001). Note these effects existed for each of the 5 GI symptoms investigated, and effects increased by number of GI problems. No association between chronic GI problem and: - age - sex - ethnicity - intellectual functioning. In logistic regression analyses anxiety and sensory over-responsivity independently contributed to predicting total number of chronic GI problems. And also predicted each of the 5 GI symptoms with the exception of diarrhoea, where there was a trend (p<0.05 but not meeting the adjusted p value of p=0.008). Anxiety and sensory-responsivity were themselves highly associated (r=-0.45, p<0.0001).</p>	<p>Author's conclusions: Results indicate that anxiety, sensory over-responsivity and GI problems are possibly inter-related phenomena for children and young people with ASD, and may have underlying mechanisms. Causal direction of relationship between the three variables not known. Reviewer's comments: Bonferroni correction applied leading to an adjusted alpha level of p=0.008. Sample is large, geographically diverse but not population-based. Relied on parent-report. Source of funding: Autism Speaks funds ATM. Other support comes from a formal cooperative agreement between the Massachusetts General Hospital and US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Research Program.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADOS=Autism Diagnostic Observation Schedule; ATM=Autism Treatment Network; ASD=autism spectrum disorder; CBCL= Child Behavior Checklist ; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders - IV (text revision); PPV=positive predictive value; SOR: Sensory Over-Responsivity; US= United States of America

Gorrindo et al, 2011 [19]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions
<p>Country: US Study type: Cross-sectional observational study Evidence level: IV</p>	<p>Setting: children and young people with ASD recruited at Vanderbilt University's hospital ASD medical clinic, and self-referral. Children and young people with gastrointestinal dysfunction (GID) only recruited through paediatric gastroenterology outpatient clinic.</p> <p>Participants: 121 children and young people (mean age 11-12 years; 91 (75% male) recruited into 3 groups: n= 40 with ASD co-occurring with GID (ASD-GID) n=45 with ASD without GID (ASD only) n=36 with GID without ASD (GID only) Note: GID group only used to illustrate that types of GID were similar for people with ASD and without.</p>	<p>Inclusion: 5-18 years, meeting ASD criteria on ADOS (in ASD groups), and GI symptoms lasting more than one month (in GID groups, as determined by structured interview with parent at enrolment)</p> <p>Exclusion: severe sensory or motor impairment, neurodevelopmental disorders of known aetiology (e.g., Fragile X Syndrome), <36 wk or >42 week gestation, birth weight < 2500 grams.</p>	<p>Exposure: Standardised clinical scales including expressive language (ADOS) A parent report instrument, the Social Responsiveness Scale (SRS). Medication use noted for medications with potential GI side effects in greater than 10% of patients. Diet was assessed by a food diary where presence of absence of 11 broad food categories documented (volumes not measured) over 7 days.</p> <p>Comparison: absence of the above signs, symptoms, characteristics</p> <p>Outcomes: Assignment to GID groups done based on initial parental report of ongoing GID. Type of gastrointestinal dysfunction then assessed by paediatric gastroenterologist and involved medical history, GI symptoms review by parent-completed Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS), and physical examination. Laboratory test and endoscopic procedures pursued at physician's discretion to identify organic disease but data was not used to alter group assignment or diagnoses of specific GIDs.</p>	<p>47% of children and young people in ASD had GI, 85% of whom had functional constipation.</p> <p>In the 2 groups of children and young people with ASD, GI dysfunction was associated with being:</p> <ul style="list-style-type: none"> - nonverbal ($p<0.01$) - socially impaired (on SRS) ($p=0.001$) and GI was not associated with - distinct dietary habits (distribution of food over 11 categories) - BMI (body mass index)-for-age - use of medications with potential for constipating side effects. <p>In multivariate logistic regression model adjusted for age and sex, increased odds for functional constipation for children and young people with ASD who were:</p> <ul style="list-style-type: none"> - younger (OR 0.81, 95% CI 0.69-0.94, $p<0.05$) - more socially impaired (OR 1.05, 95% CI 1.01-1.09, $p<0.05$) - nonverbal (OR 11.98, 95% CI 2.54-56.57, $p<0.01$) <p>but was <i>not</i> associated with:</p> <ul style="list-style-type: none"> - BMI-for-age percentile - use of medications with potential for constipating side effects. <p>Parental report of "any GID" was highly concordant (92%) with clinical diagnosis.</p>	<p>Author's conclusions: the strong association between constipation and language impairment highlights the need for health-care providers to detect and treat latent constipation in children and young people with ASD. Lack of expressive language may contribute to constipation by limiting appropriate toileting behaviour.</p> <p>Reviewer's comments: GID diagnoses were based on assessment at enrolment. However 19 children and young people assigned to ASD only group by parental report were then found to have functional GIDs by the QPGS but not reassigned.</p> <ul style="list-style-type: none"> - Food categories do not consider amount of food ingested or selectivity within categories. - Referral source may be biased toward children and young people seeking specialist GI intervention. - Confidence interval very large for relationship between functional constipation and being nonverbal, reflecting low precision. Only 15 participants were non-verbal. <p>Source of funding: Vanderbilt University from National Institutes of Health (NIH), Marino Autism Research Institute, Pediatric Clinical Research Center and the Vanderbilt Autism Treatment Network Site, a program funded by Autism Speaks.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADOS=Autism Diagnostic Observation Schedule; ASD=autism spectrum disorder; BMI=Body Mass Index; CI=confidence interval; FC=functional constipation; GID=gastrointestinal dysfunction; NIH=National Institutes of Health, OR=odds ratio; QPGS=Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III; SRS=Social Responsiveness Scale; US= United States of America; wk=week

Nikolov et al, 2009 [6]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions
<p>Country: US Study type: Cross-sectional observational study Evidence level: IV</p>	<p>Setting: children and young people enrolled in 2 multi-site randomised clinical trials undertaken by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network Participants: 172 children and young people with PDDs (88% ASD, 8% PDD-NOS, 4% AS) (n=145/84% male; M age=8.3 years (range 5-17).</p>	<p>Inclusion: Diagnosis of PDD (according to ADI-R criteria), needed to be medication free. Exclusion: not reported but recruited for treatment trial using medication and over-represented with children and young people with PDD accompanied by hyperactivity and serious problem behaviour (tantrums, aggression, self-injury),</p>	<p>Measurement of GI and other clinical characteristics based on complete medical history, physical examination by health professional, and systematic interview with primary caregiver using structured questionnaire. Standardised clinical scales used to assess intellectual functioning, adaptive behaviour, irritability, obsessive-compulsive behaviour, and anxiety. Exposure: Baseline signs, symptoms, characteristics Comparison: absence of the above signs, symptoms, characteristics Outcomes: gastrointestinal problems defined as causing impairment in function, been brought to attention of medical professional, has received treatment. Could be past, current or chronic problem rated as mild, moderate or severe by structured questionnaire. Note: p value adjusted to 0.01 to account for multiple tests and reduce likelihood of chance findings (Bonferroni's adjustment).</p>	<p>39 (23%) with moderate to severe gastrointestinal problems, primarily constipation and diarrhoea. GI problems were associated with: - irritability (p=0.01) - anxiety (p=0.01) - social withdrawal (P=0.01) GI problems were NOT associated with: - demographic characteristics (sex, age, weight, ethnicity, rate of placement in special education classes, whether in two parent families). - various aspects of adaptive functioning (including stereotypy, hyperactivity, inappropriate speech, compulsive behaviour) - core symptoms of autism (communication, social development, and repetitive behaviour) - intellectual functioning. Trend (toward adjusted significance) of GI negative people were twice as likely to show positive response to treatment than GI positive people (p<0.05). Limitations GI problems measured by screening questionnaire and medical history dependent on parental recall, which cannot confirm timeframes.</p>	<p>Author's conclusions: Based on data, it may be that anxiety, irritability social withdrawal and GI problems could be interconnected in children and young people with autism, but more study is needed to support this speculation. Reviewer's comments: GI problems measured by retrospective recall of parents without attention to whether timeframe of problems. Sample ascertained without reference to GI symptomatology and therefore avoided selection bias. Used a convenience sample from trials over-represented by children and young people with co-occurring maladaptive behaviours including hyperactivity and serious problem behaviour. These children and young people may have different GI problem profiles. Source of funding: Trials funded by National Institute of Medical Health (NIMH).</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADI-R=Autism Diagnostic Interview-revised; AS=Asperger Syndrome; ASD= autism spectrum disorder; GI=gastrointestinal; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NIMH=National Institute of Medical Health; PDD=pervasive development disorder; PDD-NOS= Pervasive Developmental Disorder – Not Otherwise Specified ; RUPP=Research Units on Pediatric Psychopharmacology; US= United States of America.

Xue et al, 2008 [22]					
Country, study type, aims	Participants	Inclusion and exclusion criteria	Exposure, comparison and outcome measures	Results	Conclusions
<p>Country: US</p> <p>Study type: cross-sectional observational study (retrospective chart review)</p> <p>Evidence level: IV</p>	<p>Setting: People with autism who presented consecutively to The Autism Center New Jersey between 1999 and 2003 (>95% referred by their parents).</p> <p>Participants: 160 (of 218) children and young people with ASD (n=131/82% male; median age=6 years)</p>	<p>Inclusion: children and young people (2-18 years) with confirmed diagnosis of ASD (according to DSM-IV, ADI-R, ADOS-generic, or CARS criteria)</p> <p>Exclusion: missing data, diagnosis of Down syndrome, fragile X syndrome, premature birth, birth asphyxia, cerebral palsy, Rett syndrome, disintegrative disorders, or having chromosomal abnormalities.</p>	<p>Measures based on retrospective chart review from clinic visits and intake forms completed by caregivers and verified in clinic.</p> <p>Exposure: Presenting medical and psychiatric co-occurrences (diagnosis, duration, frequency of symptoms)</p> <p>Comparison: absence of the above signs, symptoms, characteristics</p> <p>Outcomes: diagnosed gastrointestinal symptomatology including any of diarrhoea, unformed stools, constipation, GERD, or bloating, persisting for more than 6 months.</p>	<p>Gastrointestinal dysfunction was evidence for 59% (n=94) of the sample, 38% had history of diarrhoea or unformed stools, 28% constipation, and 19% GERD.</p> <p>GI dysfunction (n=94, 59% of children and young people attending clinic) was associated with:</p> <ul style="list-style-type: none"> - sleep disorders (p<0.05) - mood disorders (p<0.01) - food intolerance (P=0.001) <p>Gastrointestinal dysfunction NOT significantly associated with:</p> <ul style="list-style-type: none"> - developmental regression - epilepsy. 	<p>Author's conclusions: There is a high prevalence of multiple medical and psychiatric co-occurrences. Recognition of concurrent disorders may inform therapeutic strategy.</p> <p>Reviewer's comments: Measures of medical history open to recall biases from caregivers, although history was verified over several clinic visits. Missing data (n=58) from intake forms or unavailable laboratory reports may introduce unknown sampling biases. Diagnosis of mood disorders is challenging and likely to be under-reported. With multiple tests possibility of chance findings (no adjustment to p value accepted).</p> <p>Source of funding: none reported.</p>
Study quality: formal appraisal checklist not available for this study design					

Key: ADI-R=Autism Diagnostic Interview-revised; ADOS=Autism Diagnostic Observation Schedule-Generic; ASD=autism spectrum disorder; CARS=Childhood Autism Rating Scale; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders – 4th edition; GI=gastrointestinal; GERD=gastrointestinal reflux disorder; GRADE=Grading of Recommendations Assessment, Development, and Evaluation; US=United States of America

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Studies included for appraisal in the current review are identified by an asterix (*)

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