An Outbreak of Acute Bacterial Gastroenteritis Is Associated With an Increased Incidence of Irritable Bowel Syndrome in Children

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OBJECTIVES: **Acute bacterial gastroenteritis is associated with subsequent post-infectious irritable bowel syndrome (PI-IBS) in adults. Less is known about this relationship in children. In May 2000, contamination of municipal water by *Escherichia coli* 0157:H7 and *Campylobacter* species caused a large outbreak of acute gastroenteritis in Walkerton, Ontario. We assessed this association among a cohort of children enrolled in the Walkerton Health Study (WHS).**

METHODS: **WHS participants who were under age 16 at the time of the outbreak but who reached age 16 during the 8-year study follow-up were eligible for the pediatric PI-IBS study cohort. Eligibility also required no diagnosis of IBS or inflammatory bowel disease before the outbreak and permanent residency in the Walkerton postal code at the time of the outbreak. Validated criteria were used to classify subjects as having had no gastroenteritis (unexposed controls), self-reported gastroenteritis, or clinically suspected gastroenteritis during the outbreak. From 2002 to 2008, standardized biennial interviews used a modified Bowel Disease Questionnaire to diagnose IBS by Rome I criteria. Risk factors for IBS were identified by logistic regression.**

RESULTS: **In all, 467 subjects were eligible for the pediatric PI-IBS study cohort (47.1% female; mean age 11.6±2.44 years at the time of the outbreak). Of these, 305 were exposed to GE (130 clinically suspected and 175 self-reported) and 162 were unexposed controls. The cumulative incidence of IBS was significantly increased among exposed subjects vs. controls (10.5% vs. 2.5%; odds ratio 4.6, 95% confidence interval (1.6, 13.3)). In an unadjusted risk factor analysis, IBS was associated with a shorter time interval from exposure to assessment of IBS symptoms, female gender, diarrheal illness lasting more than 7 days, weight loss >10 lb, and antibiotic use during the outbreak. In adjusted analyses, both female gender and time interval to assessment of IBS symptoms remained independent predictors of PI-IBS.**

CONCLUSIONS: **Acute bacterial gastroenteritis is associated with subsequent IBS in children as in adults. Risk factors for PI-IBS in children are similar to those identified among adults. Confirmation of these findings in similar cohorts is needed.**

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INTRODUCTION

Childhood functional gastrointestinal disorders, including functional recurrent abdominal pain, irritable bowel syndrome (IBS), and functional dyspepsia, are characterized by chronic and recurrent symptoms without structural or biochemical abnormalities. Since Apley first used the term recurrent abdominal pain to describe a cohort of children with unexplained abdominal pain more than five decades ago (1) numerous studies have reported its

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prevalence in school-aged children to vary between 10 and 17% (2–8). Most of these children also fulfill criteria for IBS (45–65%) (9,10), functional dyspepsia (16%), or functional abdominal pain (7.5%) (9). Population-based studies suggest that children with recurrent abdominal pain may continue to report abdominal pain or symptoms of IBS in adulthood (11).

Though limited, the current understanding of the pathogenesis of functional gastrointestinal disorder assumes a biopsychosocial model, wherein early life experiences and biologic exposures have important functions (12). A link between IBS and acute enteric infection has long been established in adults (13,14). Both prospective and retrospective studies have estimated the incidence of post-infectious (PI)-IBS to range from 5 to 32%. Reported risk factors for PI-IBS have included severity of the acute illness, female gender, and younger age (15–30). The pathogenesis of PI-IBS has been reported to involve persistent intestinal inflammation, altered motility, increased intestinal permeability, and altered serotonergic function (24,31–33). It is hypothesized that exposure to an enteric pathogen disrupts intestinal barrier function, shifts the commensal flora, and triggers a chronic inflammation that sustains IBS symptoms.

Although acute gastroenteritis is common in children (34), the phenomenon of pediatric PI-IBS remains poorly defined. Saps *et al.* (35) reported that 87% of children exposed to acute gastroenteritis developed functional gastrointestinal disorder, but this study is limited by its small sample size, limited documentation of both the acute illness and the assessment of risk factors for PI-IBS, and lack of long-term follow-up into adulthood. This study aims to evaluate the association between childhood exposure to acute gastroenteritis and PI-IBS in early adulthood.

The Walkerton Health Study (WHS) is the largest prospective cohort study of PI-IBS ever undertaken. In May 2000, heavy rainfall washed livestock fecal residue into inadequately chlorinated municipal wells and contaminated the water supply of Walkerton, Ontario with *Escherichia coli 0157:H7*, *Campylobacter* species and other pathogens. The resulting outbreak of acute gastroenteritis affected at least 2,300 local residents with 27 recognized cases of the hemolytic uremic syndrome and seven deaths (36,37). The WHS was initiated 2 years after the outbreak to study the epidemiology and long-term health outcomes of water contamination, and details of its full methodology are published elsewhere. We reported earlier the incidence and prognosis of PI-IBS among adult WHS participants 16 years of age and over and identified risk factors for PI-IBS (23).

This study assesses WHS subjects who enrolled as children and reached age 16 during study follow-up to evaluate the association between childhood exposure to acute gastroenteritis and IBS in adulthood. The study also sought to identify risk factors for PI-IBS in this cohort.

METHODS

Study population

All residents of Walkerton regardless of age were invited to participate in the WHS study. This study identified children who enrolled in 2002 or 2003 for inclusion in the pediatric PI-IBS cohort. Participants were eligible for inclusion in the PI-IBS cohort if they (i) had no diagnosis of IBS or inflammatory bowel disease before the outbreak; (ii) were permanent residents of Walkerton (as identified by postal code) at the time of the outbreak; (iii) were under age 16 at enrollment; and (iv) reached the age of 16 during the study follow-up, at which time they were assessed for IBS. Outcomes for participants aged 16 and older at the time of the outbreak have been reported earlier (23).

Data collection

At study entry, participating children and their parents underwent standardized interviews that included a 20-min structured survey questionnaire. The questionnaire addressed several domains including (i) demographics; (ii) municipal water exposure; (iii) prior medical history; (iv) details of any acute illness experienced during the outbreak; (v) current gastrointestinal symptoms; and (vi) medical history since the outbreak. Every year between 2002 and 2008, WHS study participants were invited for follow-up to assess long-term health outcomes.

All WHS participants were also asked for written consent to link WHS data with ancillary health records, largely to verify self-reported information about premorbid health and acute illness during the outbreak. Consent for access to children's records was sought from parents. These records included (i) individual responses to a survey of 899 Walkerton residents conducted by the local Bruce–Gray–Owen Sound Health Unit once the outbreak was recognized; (ii) regional hospital laboratory data; (iii) pharmacy records; (iv) family physician charts; and (v) Walkerton Hospital medical records. All such data were abstracted by trained research assistants using standardized forms (23).

Definition of exposure

Three operational definitions of exposure to acute gastroenteritis during Walkerton outbreak were developed for previous analyses of adult participants (23): (i) those who reported no acute illness during the outbreak ("controls"); (ii) those who reported an acute illness that could not be substantiated by prior health records ("self-reported" gastroenteritis); and (iii) those with symptoms whose illness was substantiated by review of health records ("clinically suspected" gastroenteritis). Such substantiation could include any of the followings: (i) documented health-care contact for acute gastrointestinal symptoms during the outbreak; (ii) bloody diarrhea in May 2000 reported in health records or in responses to the Bruce–Gray–Owen Sound Health Unit survey; (iii) diarrhea lasting at least 3 days with more than three stools per day reported on the Bruce–Gray–Owen Sound Health Unit survey; or (iv) a documented positive stool culture. In a previous analysis, the ability to confirm gastroenteritis was found to correlate with severity of the acute illness, and with preliminary measures of chronic health outcome (38).

Outcome assessment

The WHS study followed participants biennially for 7 years. Subjects in the pediatric PI-IBS study cohort who reached age

16 between May 2000 and August 2008 were administered a modified version of Talley's Bowel Disease Questionnaire (39). Rome I diagnostic criteria were applied to these responses to identify participants with IBS (40). Given the interval between the outbreak and the final study assessment in 2008, only those subjects whose age was at least 8 years at enrollment would have completed a Bowel Disease Questionnaire by 2008.

Statistical analysis

Cumulative incidence of IBS. The cumulative incidence of IBS was estimated in each cohort stratum as a proportion with 95% confidence interval (CI). The association between acute gastroenteritis (clinically suspected and/or self-reported) using the original definition of exposure and a diagnosis of IBS was tested using χ^2 adjusted for multiple comparisons using Bonferroni correction. Odds ratios (OR) were calculated using controls as the referent group.

Unadjusted logistic regression model: predictors of IBS. Among children who experienced acute gastroenteritis, risk factors for PI-IBS identified in adult studies (16–22,41,42) were evaluated using logistic regression. These risk factors included gender, specific features of illness during outbreak (i.e., duration of diarrhea, peak loose stool frequency, presence of blood stools, abdominal cramp, weight loss >10 lb, and fever), and use of antibiotic during the outbreak. Age was excluded in the model because it confounded with time of assessment. Including age in the model could have created bias as older subjects were assessed for IBS more often and sooner after the episode of gastroenteritis than younger subjects. Accordingly, the time interval from exposure to assessment of IBS symptoms was included.

Weighted logistic regression using propensity scores. A propensity score method was used to address the problem of low number of events relative to the number of predictors. This approach assessed the impact of having clinically suspected or self-reported gastroenteritis on the risk of PI-IBS by adjusting for specific clinical risk factors (i.e., duration of diarrhea, peak loose stool frequency, presence of blood stools, abdominal cramp, weight loss >10 lb, fever, and antibiotic use) (covariates known to confound with exposure) using multivariable logistic regression. These risk factors were collapsed into a single variable, which is the propensity for exposure to a specific group conditional on observed variables.

Weighted logistic regression, using the inverse of propensity scores as weights, was then used to assess whether the time intervals from exposure to assessment of IBS symptoms and gender were predictors of IBS. Propensity scores provide summary measures that control simultaneously for multiple confounders. Propensity score analysis was first introduced by Rosenbaum and Rubin (43) in 1983, to establish a framework for causal inference in observational studies and has since been commonly used in medical research to control for estimation bias and confounding (44–47) and to deal with low event rates relative to the number of risk factors of interest (48). Simulation studies that have compared propensity score method with logistic regression have shown propensity score produced estimates that were less biased, more robust, and more precise than multiple logistic regression when there were seven or fewer events per confounder (48).

All analyses were conducted using STATA version 10 (College Station, TX).

The study protocol received full approval from both the Hamilton Health Sciences/McMaster University Research Ethics Board (Hamilton, ON, Canada) and the University of Western Ontario's Office of Research Ethics (London, ON, Canada).

RESULTS

A total of 1,180 children were enrolled in the WHS study. During the course of the study follow-up, 369 children were terminated (3 deaths, 55 lost to follow-up, and 311 withdrawals). Returning participants and terminates did not differ by gender or exposure to gastroenteritis. However, returning participants were younger than terminates. Data collected before subjects terminated from the study were used in the analysis.

Of the 1,180 children enrolled in the study, 713 (52.1%) were excluded from the study cohort at risk of IBS for one or more of the following reasons: (i) non-permanent residents of the Walkerton postal code during the outbreak ($n=381$); (ii) less than 16 years of age at the time of the final study follow-up and therefore not assessed for IBS ($n=324$); or (iii) diagnosis of IBS or inflammatory bowel disease reported before the outbreak ($n=8$). Among the remaining 467 eligible subjects (**Figure 1**), 220 (47.1%) were female, 305 were exposed to GE in May 2000 (130 clinically suspected and 175 self-reported), and the mean age (s.d.) at the time of outbreak was 11.6 (2.44) years (**Table 1**).

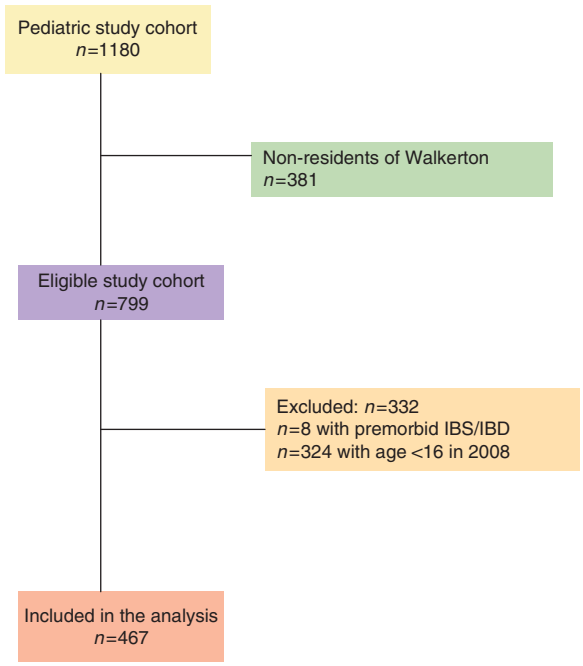

Figure 1. Study flow. IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

Table 1. Demographic and clinical characteristics of eligible study cohort

Characteristics	Clinically suspected (*n*=130)	Self-reported (*n*=175)	Controls *n*=162	Total *n*=467
Mean age (s.d.) in years	11.33 (2.32)	11.79 (2.56)	11.60 (2.41)	11.60 (2.44)
Female gender: *n* (%)	68 (52.3)	68 (38.9)	84 (51.9)	220 (47.1)
Self-reported symptoms during outbreak				
Duration of diarrhea: *n* (%)				
Less than 7 days	74 (56.9)	151 (86.3)	—	225
More than 7 days	56 (43.1)	24 (23.7)	—	80
Maximum loose stools/day: n (%)				
≤6 Loose stools/day	65 (50.0)	127 (72.6)	—	192
>6 Loose stools/day	65 (50.0)	48 (27.4)	—	113
Blood stools: *n* (%)	55 (42.3)	26 (14.8)	—	81
Abdominal cramp: *n* (%)	119 (91.5)	158 (90.1)	—	277
Weight loss >10 lb: *n* (%)	55 (42.3)	31 (17.7)	—	86
Fever: *n* (%)	82 (63.1)	70 (40.0)	—	152
Antibiotic use: *n* (%)	10 (7.7)	5 (2.9)	—	15

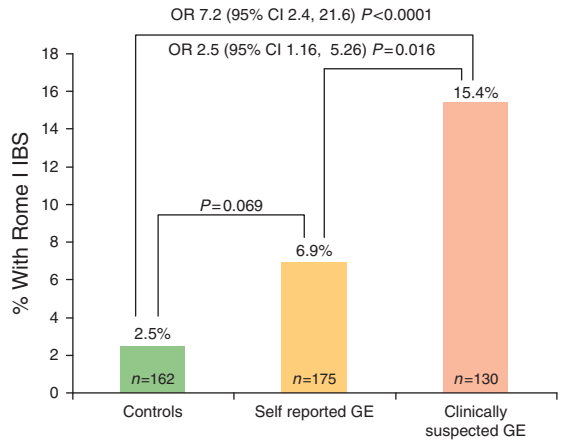

Figure 2. Cumulative incidence of IBS after exposure to acute gastroenteritis from contaminated drinking water during childhood. CI, confidence interval; GE, gastroenteritis; IBS, irritable bowel syndrome; OR, odds ratio.

Table 2. Unadjusted risk factors associated with development of IBS among those exposed to acute gastroenteritis (either self-reported or clinically suspected)

Variable	Odds ratio (95% CI)	*P* value
Time interval to assessment of IBS symptoms (in years)	0.62 (0.47, 0.81)	<0.0001
Female gender	5.21 (2.18, 12.47)	<0.0001
Features of acute enteric illness		
Duration of diarrhea (days)		
>7 days	3.27 (1.55, 6.90)	0.002
Bloody stools	2.06 (0.97, 4.40)	0.061
Weight loss	2.17 (1.03, 4.59)	0.042
Fever	2.07 (0.96, 4.46)	0.063
Antibiotic use	3.40 (1.02, 11.40)	0.047

CI, confidence interval; IBS, irritable bowel syndrome.

Cumulative incidence of IBS

Overall, the cumulative incidence of IBS at any assessment between 2002 and 2008 was significantly increased in subject exposed to GE (self-reported or clinically suspected) compared with controls (10.5% vs. 2.5%; OR 4.63, 95% CI 1.63, 13.33). The OR for IBS after clinically suspected gastroenteritis vs. controls was 7.2 (95% CI 2.4, 21.6; $P<0.001$) (**Figure 2**).

Risk factors for IBS: unadjusted

Among the 305 participants who developed acute gastroenteritis during the outbreak (self-reported GE or clinically suspected), risk factors associated with IBS included female gender (OR 5.21; 95% CI 2.18, 12.47), diarrheal illness lasting more than 7 days (OR 3.27; 95% CI 1.55, 6.90), weight loss >10 lb (OR 2.17; 95% CI 1.03, 4.59), antibiotics use during the outbreak (OR 3.40; 95% CI 1.02, 11.40), and time interval from exposure to first assessment of IBS symptoms (OR 0.62; 95% CI 0.47, 0.81) (**Table 2**). Presence of blood stools and fever during the outbreak showed non-significant trends toward significance.

Propensity score risk adjustment

In weighted multivariate logistic regression analysis, both female gender and time of assessment remained independent predictors of PI-IBS (**Table 3**). Females were roughly six times more likely to develop IBS than their male counterparts (OR 6.30; 95% CI 2.37, 16.75). Furthermore, IBS symptoms were more likely to be

Table 3. Weighted multivariable logistic regression model of predictors of IBS using inverse propensity score[a] as weights

Variable	Odds ratio (95% CI)	*P* value
Time interval to assessment of IBS symptoms	0.63 (0.50, 0.80)	<0.0001
Female gender	6.30 (2.37, 16.75)	<0.0001

CI, confidence interval; IBS, irritable bowel syndrome.
[a]Covariates included in the propensity score model: duration of diarrhea, peak loose stool frequency, presence of blood stools, abdominal cramp, weight loss >10 lb, and fever.

present among subjects who were assessed for IBS closer to the time of infection than among those whose first assessment for IBS was delayed.

DISCUSSION

To our knowledge this is the first prospective study to assess the association between childhood exposure to gastroenteritis and IBS in adulthood. We have shown in this study a greater than four-fold increase in the overall cumulative incidence of IBS among children exposed to acute gastroenteritis (either self-reported or clinically suspected) compared with unexposed controls (10.5% vs. 2.5%; OR 4.63. 95% CI 1.63, 13.33). The risk increases to seven-fold among patients with clinically suspected GE suggesting an exposure gradient effect and a biologic plausibility. Our results are consistent with those reported in adult studies (16–30) and in the only pediatric study of PI-IBS (35).

Unadjusted and adjusted analyses of risk factors for PI-IBS demonstrated the strong influence of female gender on IBS. Female predisposition to PI-IBS has been reported in some PI-IBS studies to be associated with psychological distress (27). We were unable to investigate this confounding effect as only three subjects had reported having depression or anxiety.

Consistent with adult PI-IBS studies, we also observed that the risk of developing IBS increases with the severity of acute gastroenteritis. Participants who developed IBS were likely to have had a longer duration of diarrhea, bloody stools, fever, and weight loss of more than 10 lb during the outbreak. A more severe initial insult may induce more severe mucosal inflammation and neuromuscular dysfunction that take longer to subside (49–53). As with adult PI-IBS, subjects were also more likely to report IBS symptoms if assessed soon after their exposure than if the IBS assessment was delayed. This suggests that symptoms of PI-IBS improve spontaneously over time.

Unadjusted analyses demonstrated an increased risk of IBS among subjects who used antibiotics during the acute infection (OR 3.4; 95% CI 1.02, 11.40). The role of antibiotics in the treatment of acute bacterial dysentery is controversial, as treatment can prolong the acute illness and/or induce antimicrobial resistance (54–57). Although our results might provide an additional reason to avoid antibiotic therapy in the acute phase of infection, they should be interpreted with caution as only 4.9% of children with gastroenteritis reported using antibiotics during the outbreak.

Our study has a number of limitations. First, we did not specifically exclude patients with history of childhood abdominal pain, which may be a precursor to adult IBS (11,58). Second, because Rome I criteria were used to diagnose IBS, IBS symptoms were only assessed in WHS subjects who reached age 16 and hence were unable to assess earlier onset of PI-IBS among younger members of the pediatric cohort. Studies that use pediatric Rome II and Rome III criteria have reported the prevalence of IBS to be as high as 45% among children and adolescents with recurrent abdominal pain (59,60). Our univariate analysis did not identify age as a predictor of PI-IBS, but we cannot determine the effect of exposure to gastroenteritis under age 8. This may be important, given that the prevalence of functional abdominal pain peaks around age 8. Third, the research clinic was not opened until 2 years after the outbreak. As a result, recall of premorbid illness and details of acute illness experienced during the outbreak could have been compromised. Accordingly, WHS responses were linked to local health records and to questionnaires administered by local public health authorities during the outbreak. It is therefore of interest that the relationship between gastroenteritis and IBS was strongest among subjects whose acute illness was substantiated by at least one other source (i.e., clinically suspected).

Our large sample, long-term follow-up, well-defined cohort, and use of propensity scores make this study methodologically advantageous. Propensity score methodology can reduce estimation bias because of differential exposure propensities, control for confounding, and assess more risk factors for small numbers of events. This study confirms a strong association between childhood exposure to acute bacterial dysentery and development of IBS. Consistent with adult studies, female gender and severity of diarrheal illness during outbreak are significant risk factors for PI-IBS. Understanding the relationship between acute gastroenteritis and functional gastrointestinal disorder is important in establishing effective early therapies and defining prognosis. Prospective studies of similar cohorts are needed to validate these findings.

CONFLICT OF INTEREST

Guarantor of the article: John K. Marshall, MD, MSC, FRCPC, AGAF.
Specific author contribution: Study hypothesis and design, statistical methods and analysis, and drafting of the article: Marroon Thabane; study design and hypothesis, provision of clinical expertise, preparation and editing of the article: John K. Marshall; statistical methods and preparation and editing of the article: Noori Akhtar-Danesh; study design and preparation and editing of the article: Marko Simunovic; study design and preparation and editing of the article: Amit X. Garg; study design: William F. Clark; study design: Stephen M. Collins; study design and editing of the article: Marina Salvadori. All authors approved this article.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by abdominal discomfort and altered bowel habits.
- ✓ IBS has a multifactorial etiology.
- ✓ Acute gastroenteritis is an important risk factor for the development of IBS.

WHAT IS NEW HERE

- ✓ Exposure to acute gastroenteritis in childhood is associated with increased risk of IBS in early adulthood.
- ✓ Understanding the relationship between acute gastroenteritis and functional gastrointestinal disorder is important in establishing effective early therapies and defining prognosis.

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