

# A gradient of acute gastroenteritis was characterized, to assess risk of long-term health sequelae after drinking bacterial-contaminated water

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## Abstract

**Objective:** A municipal water system became contaminated with *Escherichia coli* O157:H7 and *Campylobacter* spp. Beginning 2 years after an outbreak, all residents from the region were invited to participate in a cohort study assessing the risk of long-term sequelae. We aimed to develop a method to grade the accuracy and severity of self-reported acute symptoms.

**Study Design and Setting:** We corroborated participant survey responses with health records at the time of the outbreak. Of the 4,135 participants, 1,388 were asymptomatic during the outbreak, 1,752 had symptoms of acute self-limited gastroenteritis that could neither be confirmed nor refuted by prior health records, and 995 had symptoms that necessitated medical attention (and thus were confirmed by prior health records).

**Results:** The gradient related to the severity of acute symptoms. Compared to those with unconfirmed gastroenteritis, participants with confirmed gastroenteritis were more likely to describe fever, bloody diarrhea, and prolonged diarrhea (all  $P < .03$ ). The gradient also correlated with long-term plausible outcomes, including chronic gastrointestinal symptoms, chronic symptoms of arthritis or depression, and the avoidance of municipal water ingestion after the outbreak ( $P$  for trend consistently  $< .03$ ). Conversely, for the outcome of chronic tinnitus, an association was neither expected nor observed ( $P$  for trend =  $.26$ ).

**Conclusion:** We successfully characterized a gradient to be used in future primary analyses assessing the risk of long-term health sequelae after an outbreak. © 2006 Elsevier Inc. All rights reserved.

**Keywords:** Health survey; Cohort study; *Escherichia coli* O157; *Campylobacter*; Environmental exposure; Risk factors; Gastroenteritis; Bias

## 1. Introduction

Walkerton is a small rural town located in one of Ontario's prime agricultural areas. In May 2000, municipal water in Walkerton became contaminated with bacterial

pathogens *Escherichia coli* O157:H7 and *Campylobacter* spp. At the time of the outbreak, heavy rainfall contributed to the transport of livestock fecal contaminants into inadequately chlorinated drinking water, supplied from a shallow well [1,2]. Many individuals were either primarily or secondarily exposed to the bacteria, including permanent residents of Walkerton, commuters employed in the town, and visitors from neighboring communities. This outbreak produced an estimated 2,300 cases of acute gastrointestinal illness, > 750 emergency room visits, 65 hospital admissions, 27 recognized cases of hemolytic uremic syndrome, and 7 deaths [3]. The most serious case of water contamination in recent Canadian history, this event attracted worldwide media attention and sparked public concerns about the quality of drinking water [4].

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Initial medical care of course focused on the acute management of infected persons, but attention has now shifted toward long-term health sequelae. Previous biological and observational studies suggest that survivors of campylobacter gastroenteritis and severe *E. coli* O157:H7 infection may have poorer long-term health, regardless of whether they initially experienced overt hemolytic uremic syndrome. Beginning 2 years after the outbreak, all residents from the region were invited to participate in a large cohort study assessing the risk of long-term sequelae—the Walkerton Health Study. Individuals were eligible for study participation if they lived in the Walkerton area or had consumed municipal water in May 2000, whether or not they had developed an acute illness. The Walkerton Health Study provides a unique opportunity to characterize new and existing epidemiological associations between acute bacterial gastroenteritis and chronic diseases, including postinfectious irritable bowel syndrome, arthritis, hypertension, renal disease, and diabetes mellitus [5–11]. Additionally, any psychosocial sequelae of this stressful environmental disaster, as well as health care utilization after the outbreak, may be better characterized [12,13].

In observational studies, causality is inferred if an exposure is associated with specific outcomes supported by biological rationale [14]. The strength of association between exposure and outcome also requires consideration: stronger associations (i.e., larger relative risks) are more likely to indicate causality, although it is recognized that small relative risks do not imply lack of causality and may be important if the disease is common (i.e., the population attributable risk is high). Lastly, if the risk of the disease in question increases with the amount of exposure (termed biologic gradient, or dose response), this is considered superior evidence of causality [14].

To guide inferences of causality, we aimed to characterize a gradient of acute gastroenteritis at the time of the outbreak. It would have been ideal to enroll participants and elicit their symptoms immediately after the outbreak, but this proved unrealistic for a number of reasons. First, time was required to prepare the study protocol, obtain financial support, submit an application for ethical review, and develop local facilities and procedures. In addition, the community was not affiliated with an academic health center, and for months after the outbreak the public inquiry was the focus of attention. Accordingly, 2 years elapsed before the first participant was enrolled in the Walkerton Health Study and could be asked about symptoms of acute gastroenteritis experienced during the outbreak.

The accuracy of symptom recall is further limited by availability of government financial compensation for those who suffered acute enteric illness. Misclassification of truly asymptomatic individuals as ill could dilute any apparent relationship between acute gastrointestinal illness and chronic health outcomes. Alternatively, those with long-term health problems could exaggerate their recall of initial

symptoms, thus amplifying any association between that outcome and bacterial gastroenteritis.

Biased recall was empirically demonstrated in 405 health study participants who were questioned about acute symptoms by public health officials just after the outbreak [3], and again by Walkerton Health Study personnel 2 years later (Table 1). As many as 27% of participants recalled acute symptoms that they had denied just after the outbreak. We therefore elected not to categorize acute gastroenteritis solely by self-reported bloody diarrhea, frequency or duration of diarrhea, fever, vomiting, or abdominal pain.

Positive stool cultures for known enteric pathogens would provide the best confirmation of acute enteric illness. However, once the outbreak source and causative organisms were identified, local citizens were advised not to submit stool samples, in part because local health services were overwhelmed. Even so, stool cultures can lack sensitivity, and negative results do not exclude infection in the setting of acute symptoms during a large outbreak. We considered the use of serological testing for *E. coli* O157:H7 and campylobacter gastroenteritis during the outbreak, but such assays are not commercially available. (Some assays exist as research tools, they have not been approved for clinical use and antibodies might not persist 2 years after the outbreak.) Serology might also have proven unreliable in a rural population with considerable previous exposure to farm flora [15–17].

Given these concerns, we aimed to characterize a gradient of acute gastroenteritis using prior health records to confirm recalled gastrointestinal symptoms at the time of the outbreak. We divided participants into three groups: no history of gastroenteritis, a history of gastroenteritis that could be neither confirmed nor refuted by health records at the time of the outbreak because the individual did not seek medical attention (classed as unconfirmed gastroenteritis), and gastroenteritis that necessitated medical attention and thus was confirmed by a prior medical record (confirmed gastroenteritis).

We examined demographic and acute outbreak characteristics of children and adult study participants grouped

Table 1  
Self-reported symptoms recalled 2 years after the outbreak, compared with original responses

Questions Posed*	Response unchanged, %	Response changed, %		$\kappa$
		Absence of symptom previously present	Presence of symptom previously absent	
Were you ill?	73	1	26	.49
Did you have a fever?	81	4	15	.40
Did you have abdominal pain?	71	2	27	.46
Did you have bloody diarrhea?	91	1	8	.59

\* These questions were posed to 405 study participants by public health officials just after the outbreak, and again by Walkerton Health Study personnel 2 years later.

by these levels. Although this gradient was initially characterized by diagnostic certainty, we expected that it would also parallel the severity of acute illness, as those who were most ill would be most likely to have sought health care, with subsequent documented health care utilization. To test this hypothesis, we compared the prevalence of self-reported fever, abdominal pain, bloody diarrhea, and prolonged diarrhea in each of the three groups. We also believed the gradient would correlate with long-term plausible outcomes. Thus, we compared long-term health outcomes among the three groups. We expected that the group with confirmed gastroenteritis would demonstrate the highest incidence of long-term sequelae.

## 2. Methods

### 2.1. Participants in the Walkerton Health Study

As of November 2004, 4.5 years after the original outbreak, 4,496 individuals had contacted the clinic and enrolled in the study. These participants represent a convenience sample from the town of Walkerton (total population of 4,845), the greater municipality of Brockton, and visitors to the area, with the cohort being formed 2–4 years after the outbreak (88% of the sample enrolled in the second year, 8% in the third year, and 4% in the fourth year). We have previously used Canadian Census data and external data sources to assess study representativeness and potential selection biases among study participants [18]. These data confirm that 55% of the town's population and 82% of those who were acutely ill during the outbreak are participants in the study, and the sample is demographically similar to the population of interest.

When we compared initial participants to those persons recruited later after substantial additional recruitment efforts, the latter were more likely to be free of symptoms at the time of the outbreak ( $P < .01$ ), but are otherwise similar in terms of age, sex, the use of medical care resources, and underlying health state predating the outbreak. The risk of renal sequelae in those with acute gastroenteritis did not significantly differ between initial and late study recruits. Informative censoring attributable to loss of participant follow-up due to acute fatalities is not a concern, given that the proportion of the town's population who died during the outbreak was 0.14%. Thus, based on these data, selective participation biases are unlikely to threaten the generalization of results to the entire community affected by this outbreak. The study sample is appropriate to provide reasonably unbiased estimates of the associated risk between acute bacterial gastroenteritis and long-term health sequelae.

### 2.2. Data collection methods

We asked each participant to attend an annual clinic visit 2, 3, and 4 years after the initial outbreak, to complete a standard questionnaire and physical examination, and to provide blood and urine specimens. Survey items were

guided by the U.S. Third National Health and Nutrition Examination Survey (NHANES III) [19]. Health information for younger children (20% of study participants) was obtained from their parents. As already noted, participant health information predating the outbreak, as well as symptoms during the time of the outbreak, were self-reported, and elicited  $\geq 2$  years after the initial outbreak. Thus, we corroborated a self-reported history of acute gastroenteritis with health records from the time of the outbreak, obtained from multiple sources. Self-reported symptoms were confirmed if there was evidence of symptomatic gastroenteritis in at least one prior medical record.

### 2.3. Historical health record linkages

At study enrollment, consent was obtained to review medical records to confirm information on past health and acute illness during the outbreak. Historical medical data included those obtained by a formal investigation at the time of the outbreak by the Regional Health Unit; physician, pharmacy, and hospital charts; and local laboratory data from the last 10 years.

A formal investigation conducted at the time of the outbreak by the Regional Health Unit compiled information for all individuals who were acutely ill by the following criteria: (i) persons who contacted the Regional Health Unit directly, (ii) those with laboratory stool cultures positive for *E. coli* O157:H7 or *Campylobacter* spp., and (iii) persons who visited an emergency room or were admitted to any of the three local hospitals in Owen Sound, Walkerton, and Hanover, Ontario, for diarrhea, bloody diarrhea, abdominal cramping, vomiting, or fever [3]. The Ministry of Health advised all provincial health units to investigate any potential cases in their area. Such individuals were then interviewed by the Regional Health Unit to determine if they met criteria for acute gastroenteritis. The Regional Health Unit also conducted a cross-sectional study survey of a random sample of 367 households and 899 individuals within the postal code of Walkerton [3]. These databases were linked to Walkerton Health Study data.

We downloaded data directly from the regional hospital laboratory computer system, which contained renal function and glucose results up to 10 years predating the outbreak, as well as laboratory tests and stool cultures performed during the outbreak.

For ~90% of study participants ( $n = 4,069$ ), trained research assistants used standardized forms to abstract relevant health information from family physician and hospital charts from the periods predating and during the outbreak. The reliability of abstraction was good, but not formally quantified, for 25 charts performed in triplicate.

### 2.4. Preliminary long-term outcomes used to test gastroenteritis gradient

To test the reliability of the gastroenteritis gradient, we assessed the association between each grade and five

preliminary outcomes. Four of these represented plausible sequelae of an acute gastroenteritis. The fifth represented a distracter, tinnitus, where an association was not expected.

Acute bacterial dysentery can lead to postinfectious irritable bowel syndrome [5,7,20] and reactive arthropathy [9,21]. We asked participants the following screening question for chronic gastrointestinal symptoms: “Over the last year, have you regularly had problems with abdominal pain or discomfort, constipation, or diarrhea on average 4 or more days a month?” Symptoms of chronic arthritis were elicited by the following question: “Since the outbreak, have you been told by a doctor that you have arthritis of the back, hip or knees?”

Within the community, there was substantial emotional stress following this environmental disaster. It was hypothesized that those most severely affected by the outbreak would be under the most duress, and might have the largest concerns pertaining to their long-term health [22]. Mental health was assessed by the following screening question: “Since the outbreak, have you been told for the first time by a doctor or health care professional that you developed depression, anxiety disorder, panic disorder or posttraumatic stress disorder?”

Those most severely affected from the outbreak would be predicted to be the most reluctant to drink from the same municipal water source, despite governmental efforts to ensure the safety of their drinking water after the outbreak. Two years after the outbreak we asked, “Since the water outbreak, have you been drinking Walkerton municipal tap water?”

Given evidence of biased recall (Table 1) due to ongoing claims for financial compensation, we were concerned that some, but certainly not all, individuals who reported being ill could be more likely to respond yes to any posed question about long-term sequelae [23]. There is no biological reason to suspect acute bacterial gastroenteritis would predispose to chronic tinnitus. Thus, we chose this as a needed distracting outcome and asked, “Over the last 2 years, have you experienced a ringing or buzzing in your ears lasting more than 3 days?”

### 2.5. Statistical analysis

Chi-square tests or Cochran–Armitage chi-square tests for trend were used to assess for differences between groups of the gradient [24,25]. Relative risks for long-term sequelae after acute gastroenteritis and their 95% confidence intervals (95% CI) were calculated [26,27], with participants with no symptoms at the time of the outbreak as the referent group. Those with chronic gastrointestinal conditions predating the outbreak (irritable bowel syndrome, celiac disease, inflammatory bowel disease) ( $n = 291$ ), those exposed to contaminated water while in utero ( $n = 46$ ), and those who developed hemolytic uremic syndrome during the outbreak ( $n = 24$ ) were excluded, leaving 4,135 participants for the analyses reported here. In addition,

participants with a history of arthritis ( $n = 761$ ) or mental disorder ( $n = 443$ ) predating the outbreak were excluded from analyses that assessed the outcomes of arthritis or mental disorder, respectively. All analyses were performed using SAS 8.02 software (SAS Institute, Cary, NC). All participants provided written informed consent, and the study was approved by the University of Western Ontario Research Ethics Board.

### 3. Results

Preoutbreak and outbreak characteristics of children and adults grouped according to the gradient of gastroenteritis are presented in Tables 2–5. More than 98% of participants reported drinking from the contaminated municipal water source; the others are possible secondary contacts. Of the 4,135 participants, 1,388 (34%) reported no symptoms at the time of the outbreak, 1,752 (42%) had unconfirmed gastroenteritis, and 995 (24%) had gastroenteritis confirmed. Among the latter, symptoms were confirmed by the Regional Health Unit (85%), emergency rooms (55%), inpatient hospital records (5%), or physician office records (29%). (Note that sources of confirmation are not mutually exclusive.) In those with confirmed gastroenteritis, 390 (39%) described bloody diarrhea and 506 (51%) submitted a stool culture, of which 102 (20%) were positive only for *E. coli* O157:H7, 70 (14%) were positive only for *Campylobacter* spp., and 16 (3%) were positive for both.

Demographics, health status, and family history of participants prior to the outbreak were similar across the gastroenteritis gradient, with a few exceptions. Children 4 years and younger were frequently seen in an emergency room; this age group is thus overrepresented in the group with confirmed gastroenteritis. In addition, permanent residents of Walkerton were more likely to have confirmed gastroenteritis than were individuals who visited the town during the outbreak. Compared to those with no symptoms, adult participants with either unconfirmed or confirmed gastroenteritis were more likely to have a history of smoking or of gallstones (each  $P < .01$ ).

Compared to participants with unconfirmed gastroenteritis, participants with confirmed gastroenteritis were more likely to describe a history of fever (54% vs. 35%,  $P < .001$ ), bloody diarrhea (39% vs. 17%,  $P < .0001$ ), or prolonged diarrhea (median 6–7 days vs. 4–5 days,  $P < .0001$ ) at the time of the outbreak. Similarly, they were more likely to meet criteria for acute diarrhea as defined by  $\geq 4$  stools per day lasting  $> 3$  days (71% vs. 52%,  $P < .0001$ ).

The dose response of associations between the gradient of acute gastroenteritis and long-term health outcomes among participating adults is presented in Table 6. The average follow-up time since the outbreak for included participants was 3.7 years (range 1.7 to 4.4). Compared to

Table 2  
Child characteristics before the outbreak, grouped according to history of gastroenteritis after drinking bacteria-contaminated municipal water

Characteristic	History of acute gastroenteritis		
	None	Unconfirmed symptoms	Symptoms confirmed by prior health records
Sample size	<i>n</i> = 324	<i>n</i> = 319	<i>n</i> = 354
Demographics, %			
Caucasian	99	98	99
Female	54	48	50
Age at time of outbreak			
≤4 years	21	24	40
5–14 years	77	74	59
15–17 years	3	2	1
Residence in Walkerton	59	61	95
Residence in Brockton municipality	95	94	99
Health status predating outbreak, %			
General medical check-up in year prior to outbreak	45	51	64
Lab results predating outbreak, %			
Urine dipstick protein performed	28	24	31
≥1 random urine dipstick protein ≥ 0.3 g/L <sup>a</sup>	9	12	9
Serum creatinine performed	5	7	5
≥1 estimated GFR < 60 mL/min per 1.73 m <sup>2</sup> <sup>b</sup>	0	0	0
Family history predating outbreak, %			
Diabetes mellitus	3	3	5
Hypertension	21	15	15

Participants were classified as children based on age when responses were given at last follow-up.

Abbreviation: GFR, glomerular filtration rate as estimated by the Schwartz formula.

<sup>a</sup> Percentage based on participants with a random urine protein prior to the outbreak (28% of all participants on average of 2.7 years prior).

<sup>b</sup> Percentage based on participants with a serum creatinine prior to the outbreak (6% of all participants on average 2.7 years prior).

adults with no symptoms at the time of the outbreak, the risk of chronic gastrointestinal symptoms was 1.9 (95% CI = 1.7–2.2) in those with unconfirmed gastroenteritis, and increased to 2.4 (95% CI = 2.2–2.7) in those with confirmed gastroenteritis. Similar graded associations were evident for other biologically plausible outcomes—specifically, chronic symptoms of arthritis or depression, and avoidance of consumption of municipal water after the outbreak (*P* for trend < .03 for all three variables). Conversely, for the outcome of chronic tinnitus, an association was neither expected nor observed (*P* for trend = .26).

#### 4. Discussion

The Walkerton Health Study was designed to identify whether persons with symptomatic *E. coli* O157:H7 or campylobacter gastroenteritis are at increased risk of long-

Table 3  
Child symptoms and health care utilization during the outbreak, grouped according to history of gastroenteritis after drinking bacteria-contaminated water

	History of acute gastroenteritis		
	None	Unconfirmed symptoms	Symptoms confirmed by prior health records
Sample size	<i>n</i> = 324	<i>n</i> = 319	<i>n</i> = 354
Recalled, self-reported symptoms, %			
Drank from contaminated municipal water source	98	99	98
Duration of diarrhea			
1 day	—	7	2
2–3 days	—	29	15
4–5 days	—	20	22
6–7 days	—	21	17
>1 week	—	23	44
Diarrhea of ≥4 stools per day lasting ≥3 days	—	51	73
Bloody diarrhea	—	18	40
Abdominal pain	—	85	88
Fever	—	46	69
Another person in household ill	63	89	96
Documented health care utilization, %			
Spoke to or visited physician in clinic	—	—	26
Visited emergency room	—	—	69
Admitted to hospital	—	—	3
Stool culture performed <sup>a</sup>	1 <sup>b</sup>	3 <sup>b</sup>	64
Positive for <i>E. coli</i> O157:H7 only	—	—	29
Positive for <i>Campylobacter</i> spp. only	—	—	11
Positive for both bacteria	—	—	5
Regional Health Unit record of illness	—	—	92

Sixteen child participants (1.6%) demonstrated inconsistent data, given that they reported a history of no symptoms at the time of the outbreak but prior health records documented the presence of an acute gastroenteritis. Here such participants were classified as having had a confirmed gastroenteritis.

—, Not present in any participant.

<sup>a</sup> Positive cultures reported as a percentage of those who had a culture performed.

<sup>b</sup> Stool cultures were negative.

term adverse health outcomes. It uses the strongest feasible epidemiologic design, a cohort analytic study. For the purpose of screening, prognosis and, in this case, potential compensation, it is imperative that any true association between acute infection and long-term sequelae be characterized accurately. The biological rationale, strength of association, dose–response relationship, and specificity of association can all be used to infer causality [14]. By applying these criteria, the risk of falsely assigning causality to an exposure is reduced.

Here, we organized participants into three distinct levels of acute gastroenteritis based on symptom recall and medical record confirmation. Given that participants with

Table 4

Adult characteristics before the outbreak, grouped according to history of acute gastroenteritis after drinking bacteria-contaminated municipal water

	History of acute gastroenteritis		
	None	Unconfirmed by prior symptoms	Symptoms confirmed health records
	<i>n</i> = 1,064	<i>n</i> = 1,433	<i>n</i> = 641
<b>Demographics, %</b>			
Caucasian	99	99	99
Female	57	55	60
<b>Age at time of outbreak</b>			
14–19 years	12	13	12
20–24 year	4	7	6
25–54 years	52	55	57
55–64 years	16	14	12
65–74 years	12	8	8
≥75 years	5	3	4
Residence in Walkerton	65	61	93
Residence in Brockton Municipality	95	94	98
<b>Health status predating outbreak, %</b>			
Diabetes mellitus	6	7	9
Hypertension	26	24	29
Smoking	20	27	27
Elevated cholesterol	15	13	13
Gallstones	7	8	10
General medical check-up in year prior to outbreak	67	64	71
<b>Lab results predating outbreak, %</b>			
Urine dipstick protein performed	63	58	69
≥1 random urine dipstick protein ≥ 0.3 g/L <sup>a</sup>	9	11	13
Serum creatinine performed	40	40	50
≥1 estimated GFR < 60 mL/min per 1.73m <sup>2</sup> <sup>b</sup>	7	5	8
<b>Family history predating outbreak, %</b>			
Diabetes mellitus	25	26	26
Hypertension	41	41	41

Participants were classified as adults based on age when responses were given at last follow-up.

**Abbreviation:** GFR, glomerular filtration rate as estimated by the MDRD formula using calibrated serum creatinine.

<sup>a</sup> Percentage based on participants with a random urine protein prior to the outbreak (62% of all participants on average of 2.7 years prior).

<sup>b</sup> Percentage based on participants with a serum creatinine prior to the outbreak (42% of all participants on average 2.4 years prior).

confirmed gastroenteritis were more likely to report that they had fever, prolonged diarrhea, and bloody diarrhea, this gradient reflects the severity of acute symptoms during the outbreak. We assessed the strength of association between the gradient of acute gastroenteritis and five preliminary long-term outcomes. For the four plausible outcomes, there was a clear dose–response relationship along the gradient of acute gastroenteritis. Conversely, for the distracting outcome, an association was neither expected nor observed. Taken together, these results establish the utility of the gradient for future primary analyses assessing the risk of long-

Table 5

Adult symptoms and health care utilization during the outbreak, grouped according to a history of acute gastroenteritis after drinking bacteria-contaminated water

Variables	History of acute gastroenteritis		
	None	Unconfirmed by prior symptoms	Symptoms confirmed health records
	<i>n</i> = 1,064	<i>n</i> = 1,433	<i>n</i> = 641
<b>Sample size</b>			
Recalled, self-reported symptoms, %			
Drank from contaminated municipal water source	98	100	100
<b>Duration of diarrhea</b>			
1 day	—	9	4
2–3 days	—	32	16
4–5 days	—	17	18
6–7 days	—	15	17
> 1 week	—	27	44
Diarrhea of ≥4 stools per day lasting ≥3 days	—	52	70
Bloody diarrhea	—	17	39
Abdominal pain	—	87	91
Fever	—	33	48
Another person in household ill	52	93	86
<b>Documented health care utilization, %</b>			
Spoke to or visited physician in clinic	—	—	31
Visited emergency room	—	—	48
Admitted to hospital	—	—	5
Stool culture performed <sup>a</sup>	0.4 <sup>b</sup>	0.2 <sup>b</sup>	43
Positive for <i>E. coli</i> O157:H7 only	—	—	13
Positive for <i>Campylobacter</i> spp. only	—	—	16
Positive for both bacteria	—	—	1
Regional health unit record of illness	—	—	82

Twenty-six adult participants (0.8%) demonstrated inconsistent data, given that they reported a history of no symptoms at the time of the outbreak but prior health records documented the presence of an acute gastroenteritis. Here such participants were classified as having had a confirmed gastroenteritis.

—, Not present in any participant.

<sup>a</sup> Positive cultures reported as a percentage of those who had a culture performed.

<sup>b</sup> Stool cultures were negative.

term health sequelae after acute gastroenteritis during the outbreak [28].

Limitations of this exposure gradient and framework to assess long-term health risks should be appreciated. Both *E. coli* O157:H7 and *Campylobacter* spp. bacteria were present in the contaminated drinking water source, and objective evidence of coinfection was present in some stool cultures. In theory, some participants may have been ill selectively from only one of the bacteria, and may not be at risk for long-term sequelae specific to the alternative organism. In the future, better markers of illness during an outbreak (e.g., using serological or molecular techniques) may be available to attribute health outcomes to individual

Table 6  
Among participating adults, outcomes 2–4 years after acute bacterial gastroenteritis

Variables	History of acute gastroenteritis			P for trend
	None	Unconfirmed symptoms	Symptoms confirmed by prior health records	
Sample size	<i>n</i> = 1,064	<i>n</i> = 1,433	<i>n</i> = 641	
Outcomes supported by rationale				
Chronic GI symptoms, %	27	53	66	<.0001
Chronic GI symptoms, RR (95% CI)	1.0 <sup>a</sup>	1.9 (1.7–2.2)	2.4 (2.2–2.7)	
New arthritis dx, %	10	12	14	.026
New arthritis dx, RR (95% CI)	1.0 <sup>a</sup>	1.2 (0.9–1.6)	1.4 (1.0–2.0)	
New psychiatric dx, %	8	10	15	<.0001
New psychiatric dx, RR (95% CI)	1.0 <sup>a</sup>	1.4 (1.0–1.8)	2.0 (1.5–2.7)	
Refuses to drink municipal water after outbreak, %	42	54	59	<.0001
Not drinking municipal water, RR (95% CI)	1.0 <sup>a</sup>	1.3 (1.2–1.5)	1.5 (1.3–1.7)	
Distracting outcome				
Chronic tinnitus, %	10	11	11	.26
Chronic tinnitus, RR (95% CI)	1.0 <sup>a</sup>	1.2 (0.9–1.5)	1.2 (0.9–1.6)	

Abbreviations: CI, confidence interval; dx, diagnosis; GI, gastrointestinal; RR, relative risk.

<sup>a</sup> Referent.

pathogens. The proposed gastroenteritis gradient would be strengthened by addition of an internal referent group who did not drink bacterial contaminated water. Unfortunately, few individuals without a history of tainted water ingestion have participated in the study (<1%). The costs of establishing a research clinic in a comparison community to recruit such individuals would have proven prohibitive. Thus, the internal referent control group used in the gastroenteritis gradient drew on those who drank from the contaminated water source but remained well at the time of the outbreak. In theory, some members of this referent group could have remained asymptomatic despite ingesting pathogenic bacteria or other toxins in the water supply, which would bias against finding a risk of chronic sequelae after acute gastroenteritis. Future comparisons with external data sources that describe expected rates of disease in rural Ontario will help to verify our results.

A large number of study participants had no detailed health assessment before an unpredictable event like an outbreak. Thus, it could be argued that a group of participants with undiagnosed clinical or subclinical diseases are more likely to develop acute symptoms from pathogenic bacteria. This could partially account for associations between acute gastroenteritis and chronic sequelae. It is reassuring, however, that baseline health conditions predating the outbreak were similar across the three groups of the gradient, suggesting baseline comorbidity was not associated with increased susceptibility to infection during the outbreak. Future analyses that assess relevant outcomes in children would also guard against this source of bias, because children are unlikely to have substantial undetected health conditions associated with long-term sequelae. Moreover, primary analyses assessing the risk of long-term sequelae after gastroenteritis can be adjusted for other measured prognostic factors, to assess how these covariates attenuate any observed associations.

In conclusion, we successfully characterized participants into three distinct levels of acute gastrointestinal illness. Using this gradient, future epidemiological analysis can provide a unique opportunity to better characterize the risk of long-term sequelae following this unfortunate catastrophe.

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