Objective—Reactive arthritis may occur from bacterial gastroenteritis. We studied the risk of arthritis after an outbreak of *Escherichia coli* O157:H7 and *Campylobacter* species within a regional drinking water supply to examine the relationship between the severity of acute diarrhea and subsequent symptoms of arthritis.

Methods—Participants with no known history or arthritis before the outbreak participated in a long-term follow-up study. Of the 2299 participants, 788 were asymptomatic during the outbreak, 1034 had moderate symptoms of acute gastroenteritis, and 477 had severe symptoms, which necessitated medical attention. The outcomes of interest were new arthritis by self-report and a new prescription of medication for arthritis during the follow-up period.

Results—After a mean follow-up of 4.5 years after the outbreak, arthritis was reported in 15.7% of participants who had been asymptomatic during the outbreak, and in 17.6% and 21.6% of those who had moderate and severe symptoms of acute gastroenteritis respectively (p for trend =0.009).
Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of arthritis of 1.19 (95% confidence interval [CI] 0.99–1.43) and 1.33 (95% CI 1.07–1.66) respectively. No association was observed between gastroenteritis and the subsequent risk of prescription medication for arthritis (p=0.49).

**Conclusions**—Acute bacterial gastroenteritis necessitating medical attention was associated with a higher risk of arthritic symptoms, but not arthritic medications, up to four years later. The nature and chronicity of these arthritic symptoms requires further study.

**Keywords**
Health survey; Cohort study; *Escherichia coli* O157, *Campylobacter*; Environmental exposure; Arthritis

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**Introduction**

Reactive arthritis is a known consequence of bacterial gastroenteritis. It develops within four weeks of an enteric infection (including *Campylobacter, Salmonella, Shigella*, and *Yersinia*, and to a far lesser extent *E. coli* O157:H7) [1,2] and is usually self-limited. Symptoms primarily involve the musculoskeletal system, and less often the skin, gastrointestinal, ocular, and rarely cardiac symptoms [3,4]. The arthritis ranges in severity and has a predilection for joints of the lower extremity (often knees and ankles), but can also involve small joints and the spine [5–8]. The prevalence of acute ReA following enteric infection has been estimated between 1–7% [9–16], and the incidence following *Campylobacter* enteritis was reported as 7% in a large cohort (n=870) [17]. Symptoms of probable chronic post-*Campylobacter* ReA have been described in 0.7 and 24% of cases [11, 17–20]. Symptoms of chronic ReA may develop in 6% of cases following an infection with *E. coli* [20]. It is undetermined if there is a relationship between the signs and intensity of ReA compared to the initial gastrointestinal infection. While at least one study has reported both more severe and a longer lasting gastrointestinal symptoms in *Campylobacter* patients who reported subsequent joint complications [20], another did not find a clear association between acute gastroenteritis severity and the chronicity of ReA [19]. Thus, the prevalence of chronic ReA, and the factors involved in the development of chronic ReA are currently not well understood. A large bacterial water outbreak occurred in Walkerton, Ontario in the year 2000, and presents a unique opportunity to investigate this study question.

Here we examined the association between acute gastroenteritis during an outbreak of *Campylobacter jejuni* and *Escherichia coli* O157:H7 and participant self-reports of chronic arthritis up to four years after the outbreak.

**Methods**

**Study setting, participants and design**

Detailed methods of this cohort study have been described elsewhere [21–24]. In brief, the municipal water supply in Walkerton, a small rural town in Southwestern Ontario, became contaminated with bacteria, predominantly *E. coli* O157:H7 and *Campylobacter* species, in May 2000. Heavy rainfall had contributed to the surface transport of livestock fecal
contaminants into inadequately chlorinated drinking water, supplied from a shallow well [25]. Over 2300 people became ill with acute gastroenteritis, 27 cases of hemolytic uremic syndrome were identified, and there were 6 deaths [26, 27]. Being the most serious case of water contamination in recent North American history, this event attracted worldwide media attention and sparked public concern about the safety of drinking water [28].

Following this unprecedented event, we initiated a long-term health study. Beginning in February 2002, we annually invited all individuals who either lived in the Walkerton area, or who had consumed municipal water at the time of the outbreak, to attend a study clinic. A total of 4519 participants were enrolled, representing 55% of the town’s population and 82% of those who were acutely ill during the outbreak [population sampling and selection issues summarized in [23]. Participants consented to a review of their medical records and completed annual surveys.

Of the 4519 participants, we excluded those less than 18 years of age at the time of the outbreak (n=1372) because the presence of arthritis described by participants in follow-up could be less reliable in this group, and reactive arthritis after campylobacter is rare in children [29–32]. In addition, we excluded individuals with a history of arthritis prior to the time of the outbreak (n=848). Thus, 2299 adults were included in our analysis.

Defining acute gastroenteritis during the outbreak

We divided the participants into three groups according to the presence and severity of acute gastroenteritis at the time of the outbreak: 1) participants who had been asymptomatic during the outbreak (“none”); 2) those who had had moderate symptoms of acute self-limited gastroenteritis, which could neither be confirmed nor refuted by prior health records because the participant had not sought medical attention (“moderate symptoms”); and 3) those who had had severe symptoms of acute gastroenteritis that necessitated medical attention (“severe symptoms”). This gradient of acute illness was developed and validated elsewhere [24]. Severe symptoms were corroborated by concurrent medical and public health records eliminating potential bias in the recall of severe symptoms of diarrhea. Stool cultures were infrequently performed once the source of the outbreak was known, as the laboratory was overwhelmed at this time. The strains of Campylobacter and E. coli O157:H7 that were isolated also seemed to have a low culture positive rate. Thus outcomes assessed according to positive stool cultures were restricted to a secondary analysis.

Defining arthritis after the outbreak

We summarized results where the primary outcome measurement was participants’ self-reported diagnosis of arthritis by a physician, and the secondary study outcome was the diagnosis of arthritis with a prescription medication. Questions asked if the participant had been told by a doctor or health professional that he/she has arthritis since the outbreak including hip, spine or knee. We tried to reduce subjectivity in response by asking participants about diagnoses made by a health care provider (versus symptoms alone). We also looked at concordance over subsequent years after reporting a positive answer. Of the 1952 participants who were asked in 2 or more study visits if they had received a diagnosis of arthritis, less than 5% (88) reported inconsistent answers across study visits. None of the
participants who were asked in 2 or more study visits if they had a prescription for arthritis medications reported inconsistent answers across study visits.

**Statistical Analysis**

The primary outcome was self-report of new arthritis as told to participants by a doctor or health professional after the outbreak. Differences in baseline characteristics were assessed using analysis of variance (ANOVA) for continuous outcomes and the chi-square test for dichotomous outcomes. We standardized the rates of arthritis and other outcomes for age and sex using regional distributions from Canadian census data. Differences between groups, according to the described categories of acute gastroenteritis, were evaluated by crude and age and sex-adjusted analyses. For standardized rates, the Cochran-Armitage test for trend was used to test the significance of adjusted differences across categories [33, 34].

The crude and adjusted relative risk of arthritis after acute gastroenteritis was calculated in multivariate Poisson regression, along with 95% confidence intervals [35, 36]. Participants with no symptoms at the time of the outbreak served as the reference group. We adjusted for the following known risk factors for arthritis selected a priori, and included them in a multivariate Poisson regression analysis: sex and age (in 1-year increments). To account for potential differences in the access to health care or health surveillance after the outbreak, we also adjusted for the presence of a health assessment in the year before the outbreak. Based on the proportion of individuals in the asymptomatic group, there was at least 80% statistical power to detect a relative risk of at least 1.5 for the diagnosis of arthritis and a relative risk of at least 2.0 for the prescription of arthritis medication.

All analyses were conducted using SAS 8.02 [37]. All participants provided written informed consent and the study was approved by the University of Western Ontario Health Sciences Research Ethics Board.

**Results**

The characteristics of the study participants before and during the outbreak are presented in Table 1. Of the 2299 participants, 788 had no acute symptoms, 1034 had moderate symptoms of gastroenteritis and 477 had severe symptoms. The characteristics of the participants before the outbreak were similar across the 3 groups with the exceptions that persons with severe gastroenteritis were younger in age (42 vs. 45 years old; p<0.0001), and more likely to have smoked tobacco prior to the outbreak (29% vs. 20%; p=0.0002). Compared to those with moderate symptoms, at the time of the outbreak participants with severe symptoms were more likely to describe bloody diarrhea (37% vs. 17%, p<0.0001), prolonged diarrhea (70% vs. 53%, p<0.0001), and fever (47% vs. 31%, p<0.0001) (Table 1). Of those with severe symptoms, 47% visited an emergency room during the outbreak and 6% were admitted to hospital.

Stool cultures were performed in 0.6%, 0.2% and 44% of participants with no symptoms, moderate gastroenteritis and severe gastroenteritis. No positive stool results were identified for participants with no or moderate gastroenteritis. Of the 65 participants with severe
gastroenteritis who had stool cultures performed, 29 (14%) were positive for *E. coli*, 32 (15%) for *Campylobacter* and 4 (2%) for both bacteria.

Participants were followed for a mean of 4.5 (standard deviation 1.0, range 1.7 to 5.4) years after the outbreak. Overall, 84%, 74%, 77% and 71% of the participants returned for annual clinic visits 2, 3, 4, and 5 years after the outbreak.

**Self-Reported Diagnosis of Arthritis**

A total of 454 participants reported arthritis after the outbreak, for an age-sex standardized rate of 17.9% over the 4.5 years of follow-up. The annual rate of reported new arthritis diagnosis one year after the outbreak was 7.0%, while 4.2%, 3.2%, and 3.5%, were identified 2, 3, and 4 years after the outbreak, respectively. Arthritis was reported in 15.7% of the participants who were asymptomatic during the outbreak, in 17.6% of those who had moderate gastroenteritis and in 21.6% of those who had severe gastroenteritis (p for trend 0.009) (Table 2). Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of arthritis of 1.19 (95% confidence interval [CI] 0.99–1.43) and 1.33 (95% CI 1.07–1.66) respectively.

In sensitivity analyses, we decided a priori to conduct a subgroup analysis of those aged <55 years at the time of the outbreak to minimize events due to osteoarthritis and not reactive arthritis. Among individuals less than 55 years of age, 284 reported new onset arthritis. The respective standardized rates of newly reported arthritis were 9.9%, 10.8% and 13.9% among those with no symptoms, moderate symptoms and severe symptoms of gastroenteritis respectively (p for trend 0.06).

When we restricted the analysis to only those with positive stool cultures at the time of the outbreak, arthritis was reported in 26% (17/65) of those with severe gastroenteritis, for an age-sex standardized rate of 23%.

**Prescription Medication for Arthritis**

Among the 2027 participants who were asked if they received prescription medications for arthritis, 193 reported receiving a prescription for an age- and sex-standardized rate of 8.6%. The annual rate of prescription arthritis medication use in year 2 was 3.8%, while 1.9%, and 2.0%, used prescription arthritis medications 3 and 4 years after the outbreak, respectively. The rates were not significantly different among those with no symptoms, moderate gastroenteritis and severe gastroenteritis, 7.7%, 8.2%, and 8.9% respectively (p for trend 0.49). Compared with the asymptomatic participants, those with moderate and severe symptoms had an adjusted relative risk of subsequent prescription for arthritis treatment of 1.17 (95% CI 0.86–1.58) and 1.18 (95% CI 0.82–1.70) respectively. In the subgroup of those aged < 55 at the time of the outbreak, 123 reported receiving prescription medications for arthritis for an age- and sex-standardized rate of 5.4%. The respective rates of newly reported arthritis were 4.8%, 5.5% and 5.5% among those with no symptoms, moderate symptom and severe symptoms of gastroenteritis respectively (p for trend 0.58). When we restricted the analysis to only those with positive stool cultures at the time of the outbreak, the use of prescription medications was reported in 8% (5/58) of those with severe gastroenteritis for an age-sex standardized rate of 6%.
Discussion

Symptoms of acute gastroenteritis during a bacterial outbreak were associated with new onset arthritis over a subsequent 4 years. However, there was no association with the need for prescription medications for arthritis.

The major strength of this study is that as large water-borne infectious outbreaks are extremely rare within Western nations - the willingness of the local community to participate in the study enabled us to obtain detailed information and measurements about their previous and current health. There may never again be an opportunity to systematically study the long-term effects of such a potentially serious widespread outbreak. However, the circumstances surrounding this unique, unexpected catastrophe require the results to be interpreted judiciously.

Both *E. coli* O157 and *Campylobacter* bacteria were present in the contaminated drinking water source, and objective evidence of co-infection was present in some stool cultures. The literature would support that ReA occurs more frequently with *Campylobacter* than *E coli*. We considered gastroenteritis as a single entity attributable to both pathogens. While additional analyses might discern the rate of arthritis according to stool culture results, the small number of routinely collected specimens at the time of the outbreak limited our ability to do so. These strains of gram negative bacteria may not have been particularly arthritogenic, limiting the generalizability of these data to other outbreaks.

Virtually all individuals in the community were exposed but not all were ill. It is theoretically possible that our proposed control group, those who ingested contaminated water but remained well at the time of the outbreak, could also be at higher risk of chronic arthritic sequelae than the general population. In the ReA literature infectious triggers may not be identifiable by the time the patient has presented to a health care professional; however, it is almost certain that patients who go on to develop a prolonged response like chronic ReA, would have at least minor symptoms of initial diarrhea [38–43].

Asymptomatic patients at the time of the outbreak represent a reasonable control group for this study, albeit they have also been exposed. Enrolling a large number of individuals who did not drink contaminated water would represent the ideal control group, but was not practical due to logistical reasons. There may have been cases where the exposure went undetected; however, this situation would bias towards the null.

Our data collection after this unexpected outbreak partly depended on each participant’s ability to recall their health state at the time of the outbreak, which may have been more than two to four years earlier. Recall bias may have been present in this study. Such misclassification of acute gastrointestinal symptoms would minimize any true association between acute gastroenteritis and biologically plausible long-term health sequelae. To further guard against such a bias we established a group with self-reported gastrointestinal symptoms that were confirmed by a medical record and confirmed that the observed association with arthritis remained consistent in all our analyses. Alternatively, some of those who were truly acutely ill during the outbreak may now exaggerate their current symptoms for the purpose of monetary gain, or because they suffer from worse health.
overall, and are more attuned to arthritic symptoms because of stress related to their experience during the outbreak. This would exaggerate any true association between a bacterial gastroenteritis and long-term sequelae. Our questions on self-reported arthritis asked about conditions diagnosed by a primary care physician or health care provider, and had less subjectivity than questions based on symptoms alone.

The cohort was assembled two years after the outbreak. Selection biases (also referred to as participation or response biases) may be influencing these results. However, 1996 and 2001 Canadian Census information, and records from the regional health unit, hospital and Walkerton Health Study confirmed that participants in the Walkerton Health Study are representative of the population of interest.

A high percentage of all groups self-reported arthritis. The questions differed from year to year and the arthritis was not validated, which may have led to over-reporting or misclassification. However, the same degree of misclassification could have occurred in all groups, without any systematic bias.

We are lacking data on the severity, timing, duration and chronicity of the arthritis. Many patients with diarrhea (especially dysentery) could have had contraindications to NSAID prescriptions, and thus, the lack of association with prescription arthritis medications may not be particularly surprising.

This finding supports the hypothesis that either acute or chronic arthritis symptoms occurred in study participants who were exposed to *Campylobacter* or *E. coli* during the contaminated water outbreak. We found similar results when using the same exposure gradient to determine the subsequent risk of hypertension and reduced kidney function [21]. However, those endpoints were more objective and we cannot exclude the possibility that persons who sought medical attention at the time of the water contamination are more likely to report medical conditions such as arthritic symptoms.

One model of the pathogenesis of ReA proposes that bacteria persist in the epithelium, associated lymph nodes, liver and spleen, following invasion of the mucosa [41]. A ‘dose response’ is thus, biologically plausible, i.e. the worse the breakdown of mucosa, the greater the risk of developing ReA. In this model, bacteria and/or their antigens may infiltrate into the joints, causing an inflammatory response and ultimately an arthritic process that may be both driven and supported by CD4+ T-cells. The bacteria and/or antigens may remain in the joints aided by abnormal T helper cell responses.

Studies in the literature have shown that a relationship may exist between the severity of the precipitating gastrointestinal infection and the resulting signs and intensity of ReA. In one study *Campylobacter* patients with self-reported joint pain had both more severe and longer lasting gastrointestinal symptoms than those subjects with no joint pain [20]. Another study found a weak association between gastroenteritis severity and the chronicity of ReA in which 20% of patients with acute gastrointestinal symptoms developed a self-limited ReA (lasting up to one month), but 13% of patients with no gastroenteritis symptoms but positive serology for *Campylobacter* reported longer-term rheumatic problems (presenting 3 to 8 months post-infection) [19].
This study was not designed to determine chronicity of the ReA. A 5-year follow-up of patients with acute post-\textit{Campylobacter} ReA found 5% of the exposed population experience chronic or relapsing arthritic symptoms [19], but the number of participants was small. International data have described the average duration of ReA to be 3 to 5 months, and only 15% of patients develop chronic spondylarthropathy or arthritis [7]. During the years following an acute ReA episode, patients will often report arthralgias, enthesopathy and low back pain [44]. As many as 18% of ReA patients develop chronic arthritis, up to 49% sacroiliitis, and 26% ankylosing spondylitis [44], depending on the time until assessment and the triggering infectious agent.

We conclude that the rates of arthritis that participants reported had been diagnosed by a doctor or health professional was 15.7% in those with no diarrhea, 17.6% in those with moderate symptoms, and 21.6% in those with severe symptoms following a large waterborne outbreak of \textit{Campylobacter} and \textit{E. coli}. This is the largest study to suggest a ‘dose response’ of diarrhea severity and report of subsequent arthritis.

Acknowledgments

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References


Table 1
Baseline characteristics of participants at the time of the outbreak.

<table>
<thead>
<tr>
<th></th>
<th>None n=788</th>
<th>Moderate Symptoms n=1034</th>
<th>Severe Symptoms n=477</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before the outbreak</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Female, %</td>
<td>58</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>Age at time of outbreak, mean (SD), yr</td>
<td>45 (15)</td>
<td>42 (14)</td>
<td>42 (15)</td>
</tr>
<tr>
<td><strong>Health state before outbreak, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>20</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Inflammation of Iris</td>
<td>0.2</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Medical check-up during previous year</td>
<td>69</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>Body mass index in kg/m², mean (SD)</td>
<td>28 (11)</td>
<td>28 (6)</td>
<td>28 (15)</td>
</tr>
<tr>
<td><strong>During the outbreak</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drank from contaminated water source, %</td>
<td>97</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Self-reported symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diarrhea in days, median</td>
<td></td>
<td>4–5</td>
<td>6–7</td>
</tr>
<tr>
<td>≥4 stools per day, lasting ≥3 days, %</td>
<td></td>
<td>53</td>
<td>70</td>
</tr>
<tr>
<td>Bloody diarrhea, %</td>
<td>-</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>Abdominal pain, %</td>
<td>-</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>Fever, %</td>
<td>-</td>
<td>31</td>
<td>47</td>
</tr>
<tr>
<td><strong>Health care utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visited an emergency room, %</td>
<td>-</td>
<td>-</td>
<td>47</td>
</tr>
<tr>
<td>Admitted to hospital, %</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Stool culture performed, %</td>
<td>0.6</td>
<td>0.2</td>
<td>44</td>
</tr>
<tr>
<td>Positive for E. coli O157:H7 only, %</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Positive for Campylobacter only, %</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Positive for both bacteria, %</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

† Positive cultures reported as a percentage of those who had a culture performed.
Table 2

Risk of arthritis over 4.5 years after an outbreak of acute gastroenteritis from bacteria-contaminated drinking water

<table>
<thead>
<tr>
<th>Acute gastroenteritis during the outbreak</th>
<th>% of participants with new self-reported arthritis $^\delta$</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>15.7</td>
<td>Crude $^\dagger$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted $^\ddagger$</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>17.6</td>
<td>1.18 (0.98–1.43)</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>21.6</td>
<td>1.34 (1.07–1.66)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.

$^\delta$ Age- and sex-standardized rates. P for trend=0.009

$^\dagger$ Adjusted for age (1-year increments) (1.03 [1.03 – 1.04]) and male sex (1.26 [1.07–1.49]).

$^\ddagger$ Adjusted for age (1-year increments) (1.03 [1.03 – 1.04]), male sex (1.24 [1.04 – 1.46]), and the absence of a health assessment in the year before the outbreak (1.21 [1.00 – 1.46]).

* Reference group.