Long-term Risk for Hypertension, Renal Impairment and Cardiovascular Disease after Gastroenteritis from Drinking Water Contaminated with *E. coli* O157:H7: Findings from the Walkerton Health Study

Dr. Jessica Sontrop

on behalf of Dr. William Clark and the WEL Investigators
Background: *E.coli* O157:H7

- Since *E.coli* O157:H7 emerged in 1982, outbreaks have been documented worldwide.

- The CDC estimates that *E.coli O157:H7 infections* cause 75,000 gastro-enteric illnesses annually in the US, resulting in over 2000 hospitalizations and 60 deaths.

- Receptors for *E.coli* O157:H7 Shiga toxins reside in the kidney, and exposure can cause both renal and vascular injury resulting in haemolytic uremic syndrome.
The Walkerton Water Contamination Outbreak

• 2,300 cases of gastrointestinal illness
• >750 emergency room visits
• 65 hospital admissions
• 27 cases of hemolytic uremic syndrome
• 7 deaths

Background/Objectives --- Methods --- Results --- Discussion --- Conclusion
Objectives

• To evaluate the long-term risk for hypertension and renal impairment after acute gastroenteritis from drinking water contaminated with *E.coli* O157:H7.

• Self-reported cardiovascular disease was evaluated as a secondary outcome.
Methods

• **Design:** Prospective community-based cohort study with retrospective inception.

• Information was collected annually (2002-2008) via survey, physical examination and laboratory assessment of serum creatinine and urine protein.

Definitions

• **Symptomatic exposure** (*diarrhea-associated gastroenteritis*) was defined as diarrhea lasting >3 days, bloody diarrhea or >3 loose stools/day.
Methods: Definitions

- **Hypertension**: Systolic/diastolic blood pressure \( \geq 140/90 \) mm Hg using annual blood pressure measurements.

- **Structural and/or functional renal impairment**: Microalbuminuria and/or estimated glomerular filtration rate \(< 60 \) mL/min/1.73 m\(^2\).

- **Self-reported, doctor diagnosed CVD** (myocardial infarction, stroke or congestive heart failure)
Methods: Analysis

• **Exclusions:** Participants with evidence of pre-outbreak disease (not mutually exclusive):
  – Gastrointestinal (n=544)
  – Hypertension (n=735)
  – Kidney impairment (n=309)
  – Cardiovascular disease (n=204)
  – Diabetes mellitus (n=235)

• **Final sample size:** 1977
Methods: Analysis

• Hazard ratios (HR) for incident hypertension renal impairment, and cardiovascular disease were estimated using Cox regression models.

• All models controlled for age, sex and health assessment in the year prior to the outbreak.

• Other variables evaluated for confounding included diabetes, obesity, smoking and family history of kidney disease, hypertension, or diabetes.
Results

• 4,561 residents from Walkerton and the surrounding area joined the study between March 2002 and August 2008.

• After exclusions for age<18 and pre-outbreak disease, 1977 adults with at least one assessment were available for analysis.

• Median follow-up time from the outbreak was 7.9 years (interquartile range: 4.9 to 8.0)
# Table 1. Characteristics of Participants in Relation to Self-Reported Symptoms of Diarrhea-Associated Gastroenteritis

<table>
<thead>
<tr>
<th>Characteristics (%)</th>
<th>No illness or mild illness (n=910)</th>
<th>Diarrhea-associated gastroenteritis (n=1067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>58.1</td>
<td>56.0</td>
</tr>
<tr>
<td>Age at study entry (years), mean (SD)</td>
<td>43.1 (15.6)</td>
<td>40.4 (14.4)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>98.5</td>
<td>98.5</td>
</tr>
<tr>
<td>Lived in Walkerton area during outbreak</td>
<td>68.7</td>
<td>69.2</td>
</tr>
<tr>
<td>Exposure related (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drank contaminated water</td>
<td>98.0</td>
<td>99.6</td>
</tr>
<tr>
<td>Self-reported illness of any nature*</td>
<td>25.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>18.9</td>
<td>91.8</td>
</tr>
<tr>
<td>Fever</td>
<td>5.2</td>
<td>41.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 days of diarrhea</td>
<td>0</td>
<td>72.2</td>
</tr>
<tr>
<td>&gt;3 loose stools/day</td>
<td>0</td>
<td>85.3</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>0</td>
<td>29.1</td>
</tr>
<tr>
<td>Stool culture performed†</td>
<td>0.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Positive for <em>Escherichia coli O157:H7</em></td>
<td>1.5</td>
<td>17.6</td>
</tr>
<tr>
<td>Positive for <em>Campylobacter</em></td>
<td>0.8</td>
<td>18.3</td>
</tr>
<tr>
<td>Positive for both bacteria</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Sought help at time of outbreak</td>
<td>8.9</td>
<td>27.6</td>
</tr>
<tr>
<td>Gastroenteritis confirmed from med records‡</td>
<td>4.9</td>
<td>31.2</td>
</tr>
</tbody>
</table>
Results: Hypertension

Study enrolment began in 2002
Table 2. Risk for Hypertension after Exposure to Drinking Water Contaminated with *E. coli* O157:H7: Findings from a Prospective Cohort Study (2002-2008) N=1977

<table>
<thead>
<tr>
<th>Diarrhea-associated gastroenteritis at the time of the outbreak</th>
<th>Incident Hypertension</th>
<th>Age- and Sex-Adjusted</th>
<th>Multivariate-Adjusted&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Years Followed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HR</td>
</tr>
<tr>
<td>No illness or mild illness</td>
<td>294 (32.3%)</td>
<td>7.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea-associated gastroenteritis</td>
<td>403 (37.8%)</td>
<td>7.9</td>
<td>1.43</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, Hazard Ratio. <sup>a</sup>Years followed (median) since outbreak (May 15, 2000). <sup>b</sup>Hazard ratios were estimated using Cox proportional hazard regression adjusted for age (in 1-year increments), sex, obese body mass index at study entry (≥ 30 kg/m²), diabetes, tobacco smoking and family history of hypertension.
Results: Renal Impairment

• Incident renal impairment (either microalbuminuria or eGFR<60) was detected in 572 (28.9%); only 30 (1.5%) had both indicators.

• The age- and sex-adjusted HR for having either indicator was 1.15 (0.97-1.35).

• The age- and sex-adjusted HR for having both indicators was 3.41 (1.51-7.71).

• Controlling for confounders did not change the HRs (<5%) or the statistical significance.
Risk for Cardiovascular Disease after Exposure to Drinking Water Contaminated with \textit{E.coli} O157:H7: Findings from a Prospective Cohort Study (2002-2008). N=1949

<table>
<thead>
<tr>
<th>Diarrhea-associated gastroenteritis at the time of the outbreak</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>Congestive heart failure</th>
<th>Age and Sex-Adjusted HR for CVD$^a$</th>
<th>Multivariate-Adjusted$^b$ HR for CVD$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>No illness or mild illness</td>
<td>6 (0.7%)</td>
<td>5 (0.6%)</td>
<td>2 (0.2%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea-associated gastroenteritis</td>
<td>12 (1.3%)</td>
<td>10 (1.1%)</td>
<td>4 (0.4%)</td>
<td>2.24</td>
<td>1.08-4.65</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, Hazard ratio.$^a$Cardiovascular disease is a composite of self-reported doctor diagnosed myocardial infarction, congestive heart failure and cerebrovascular events. $^b$Hazard ratios were estimated using a Cox proportional hazards model, adjusting for age (in 1-year increments), sex, obese body mass index at study entry ($\geq 30 \text{ kg/m}^2$), tobacco smoking and absence of a medical check-up in the year before the outbreak.
Discussion

Compared to participants who were not ill or only mildly ill during the outbreak, participants who experienced acute diarrhoeal illness were

– 1.3 times more likely to develop hypertension
– 3.4 times more likely to develop both eGFR<60 mL/min/1.73 m² and microalbuminuria, and were
– 2.1 times more likely to report a cardiovascular event such as myocardial infarction, stroke or congestive heart failure
Discussion

Strengths

• Our study represents a rare opportunity to systematically study the long-term sequelae following exposure to bacterially-contaminated water in a single cohort.
• Prospective follow-up using objective, standardized measures.
• Analysis of bias from loss to follow-up.
Discussion

Limitations

• Study enrollment did not begin until two years after the outbreak.
• Potential for recall bias.
• Self-reported exposure and cardiovascular disease.
Conclusion

• These findings underline the need for following up individual cases of food or water poisoning by *E.coli* O157:H7 to prevent or reduce silent progressive vascular injury.

• Annual monitoring of blood pressure and periodic monitoring of microalbuminuria and eGFR may be warranted for individuals who develop diarrhea-associated gastroenteritis after exposure to *E.coli* O157:H7.

• These long-term consequences emphasize the importance of ensuring a safe food and water supply as a cornerstone of public health.
Acknowledgements

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  – WF Clark, JJ Macnab, M Salvadori, L Moist, R Suri, AX Garg

• Sponsors
  – Ministry of Health and Long-term Care

• Walkerton Health Study Participants
  – Major recognition for the success of this seven-year longitudinal study must be directed to the participants. These members of the Walkerton community and surrounding area have freely given of themselves to participate over an extended period of time following a tragic set of circumstances.