Post-Infectious Irritable Bowel Syndrome

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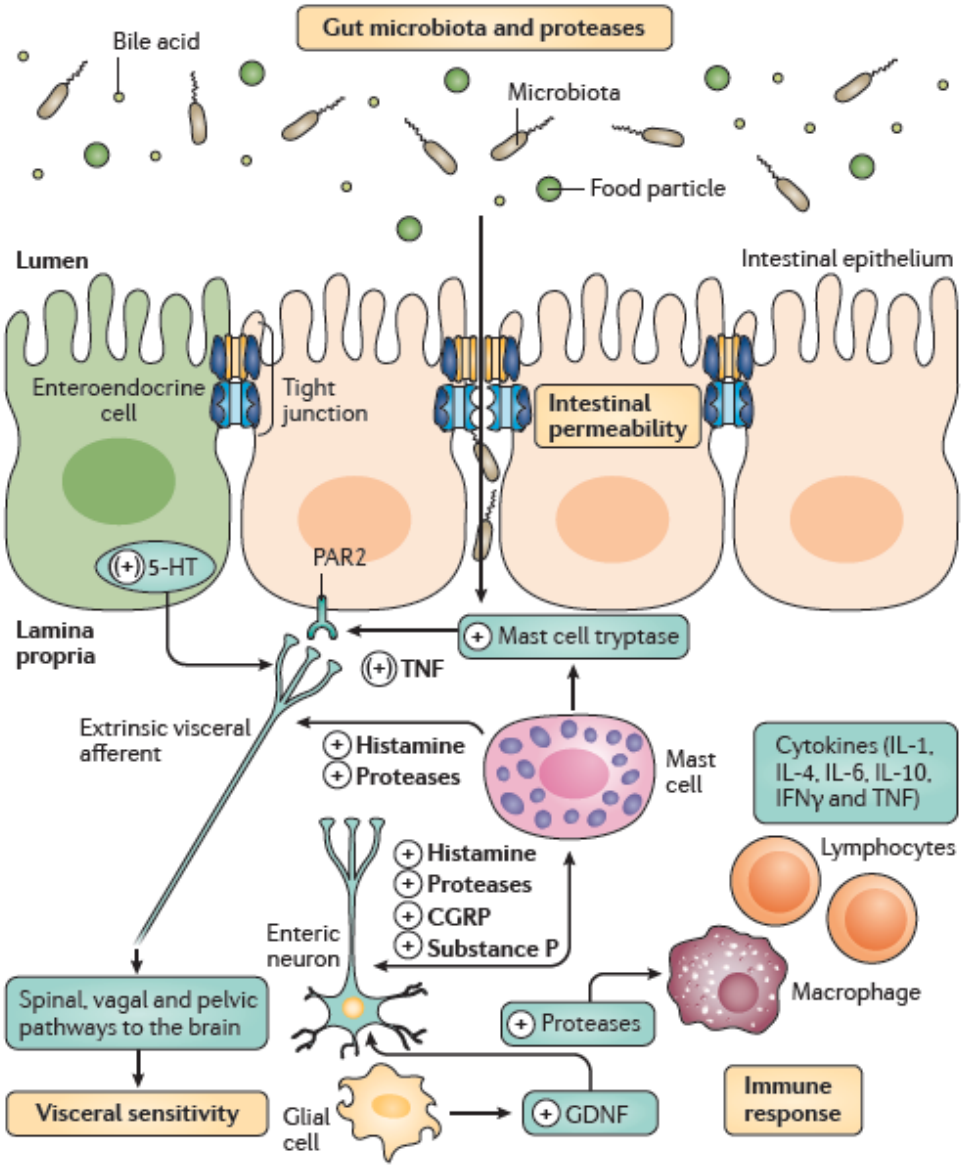
Pathogenesis of IBS



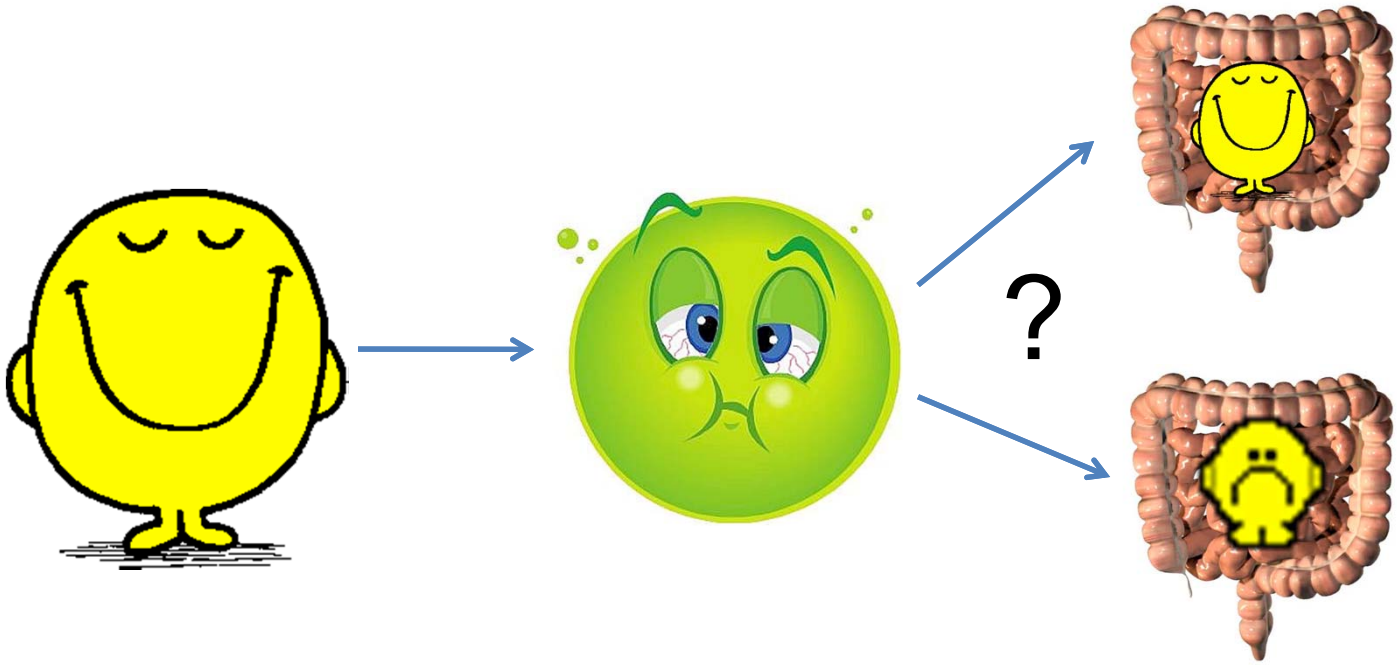
Enck P. Nat Rev Dis Primers 2016;2:16014

Post-Infectious Irritable Bowel Syndrome

- Stewart GT.
  Post-dysenteric colitis.
  BMJ 1950;1:405-9
- Chaudhary NA, Truelove SC.
  The irritable colon syndrome.
  Q J Med 1962;31:3-7-22
- Hunt RH, O'Brien M, Milton-Thompson GJ
  Stress and the enteron.
  J Royal Nav Med Service 1974;69:49-51

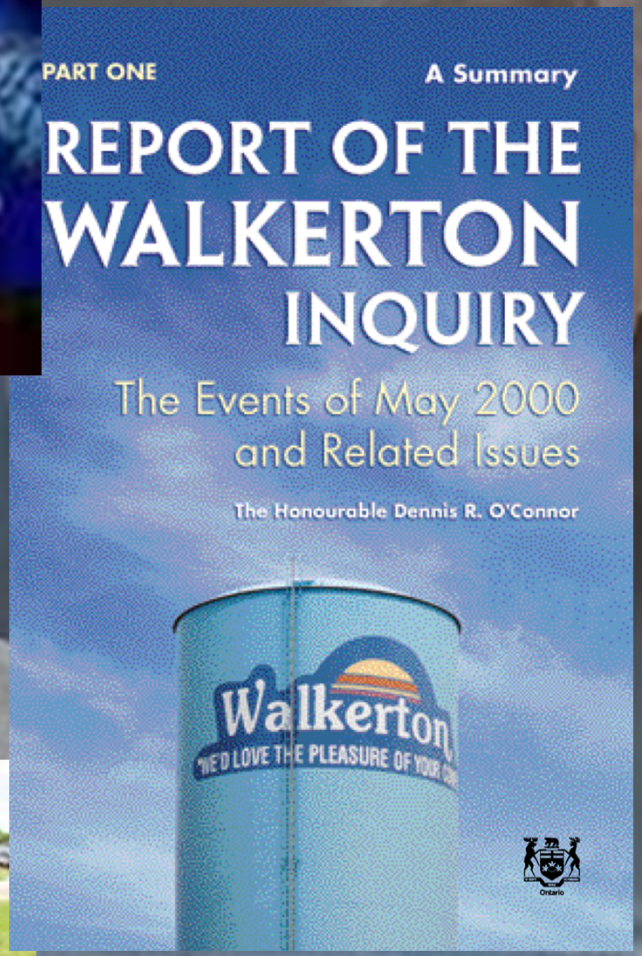
Post-Infectious Irritable Bowel Syndrome

- Altered bowel habit and abdominal discomfort that persist after acute enteric infection despite clearance of the inciting pathogen and recovery from the acute illness



Walkerton, Ontario

- Agricultural community
- Population ~5000
- 180km NW of Toronto
- Groundwater supply: 3 drilled wells with chlorination units



INSIDE WALKERTON

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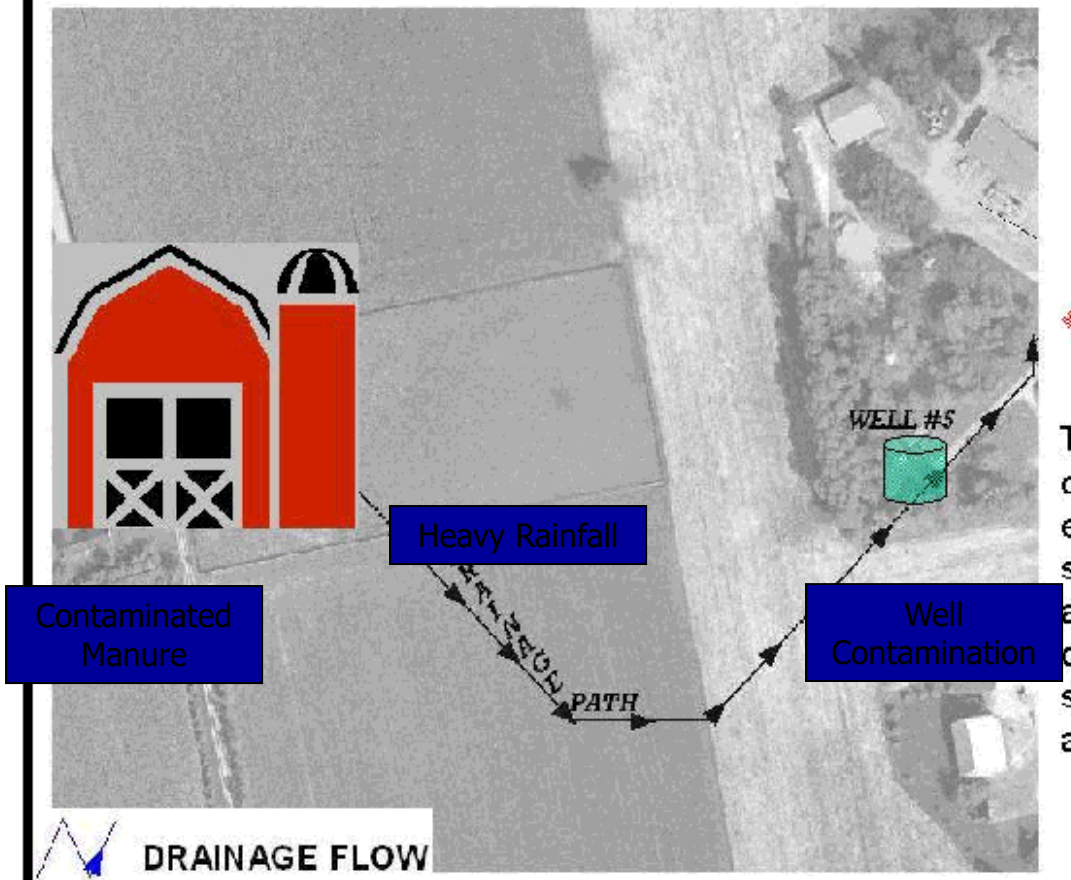
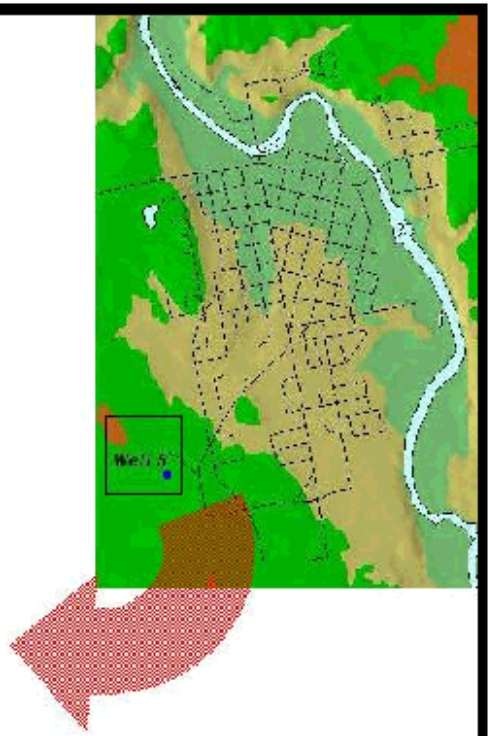
Figure 8: Modelled Farm Drainage Walkerton, Ontario





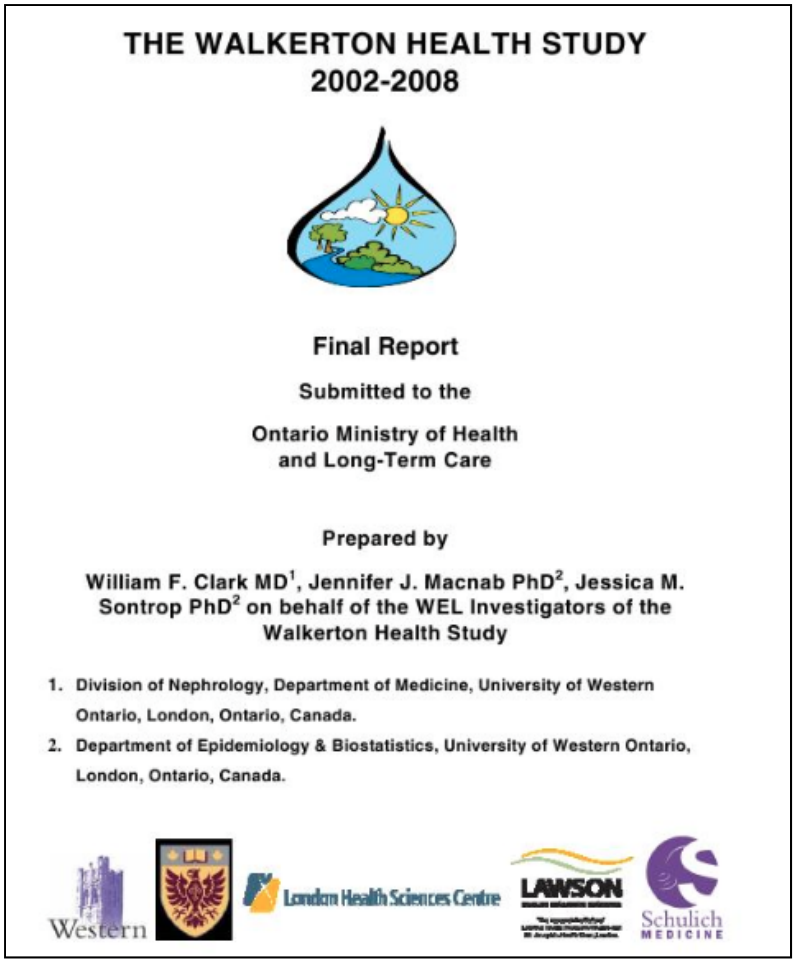
The drainage path was created using a digital elevation model (DEM). It shows surface water run-off, assuming that water flows downward along the steepest slope available. The DEM has a 10 meter spatial resolution.

Walkerton: May 2000

Outcome:	N
Reported cases of acute GE	1346
Affected Walkerton residents	799
Field epidemiology estimate of acute GE	2321
Affected Walkerton residents	1286
Hospitalizations*	65
Documented hemolytic uremic syndrome+	27
Attributable deaths	6

* 55% age 0 to 8 + 52% age 1 to 4

Walkerton Health Study



THE WALKERTON HEALTH STUDY
2002-2008

Final Report

Submitted to the

Ontario Ministry of Health
and Long-Term Care

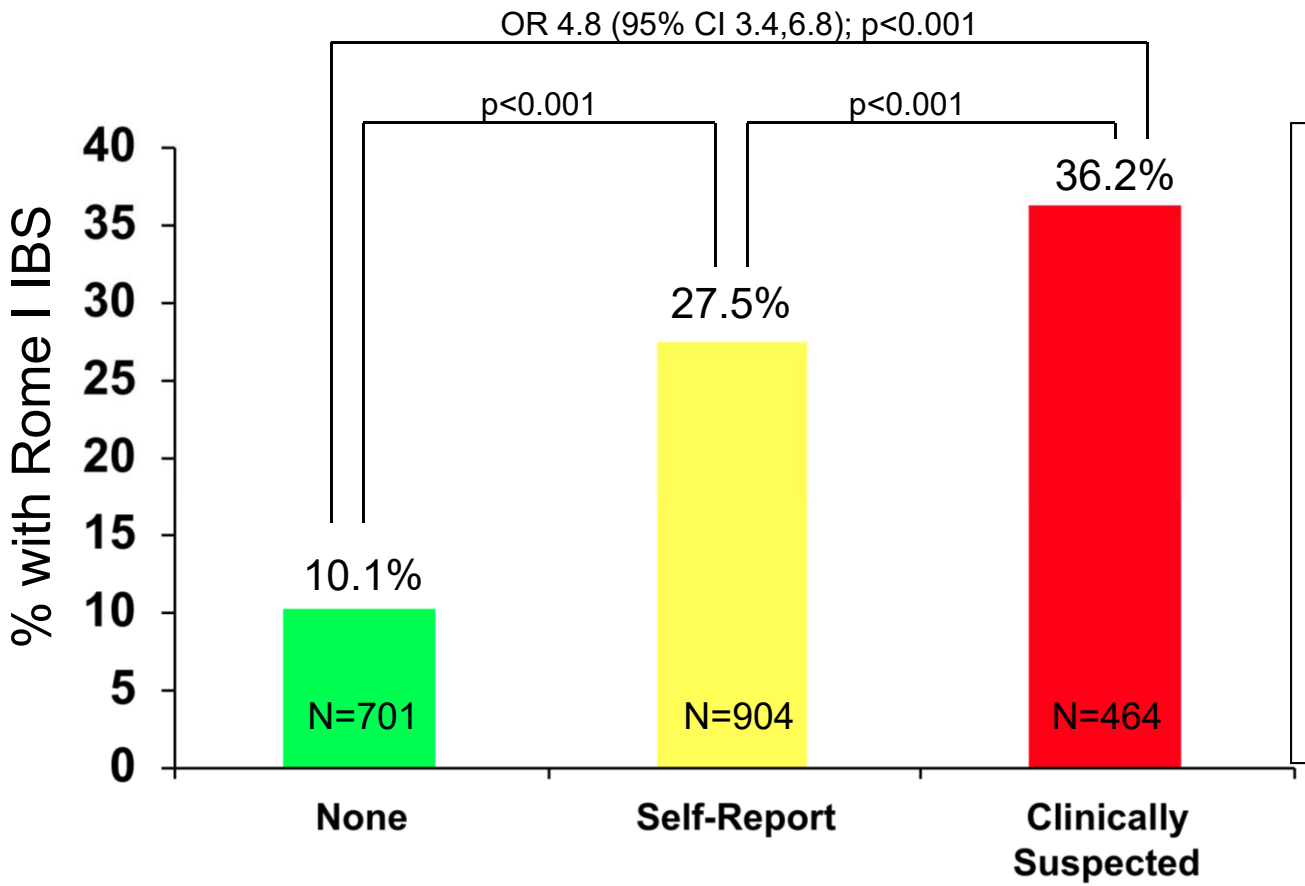
Prepared by

William F. Clark MD[1], Jennifer J. Macnab PhD[2], Jessica M. Sontrop PhD[2] on behalf of the WEL Investigators of the Walkerton Health Study

1. Division of Nephrology, Department of Medicine, University of Western Ontario, London, Ontario, Canada.
2. Department of Epidemiology & Biostatistics, University of Western Ontario, London, Ontario, Canada.

- Funded by Ontario MOH and CCFC
- Multidisciplinary team:
  - Nephrology, ID (UWO)
  - GI (McMaster)
- Mission: study long-term health outcomes and facilitate local access to medical care
- Longitudinal cohort study 2001-2008
- Recruitment through local town hall meetings and advertisements
- In-person annual standardized interviews and assessments
- Total enrolment: N=4561

Incidence of IBS 2 Years After Acute Gastroenteritis in Walkerton Ontario



Study cohort at risk of PI-IBS (N=2069):

Permanent Walkerton adult resident

No prior IBS, IBD, celiac disease

"Self-Reported" GE:

Increased stool frequency in May 2000 (> 3 BM/d for ≥ 3d)

"Clinically Suspected" GE:

Positive stool culture OR

Healthcare contact for acute illness during outbreak OR

Report of acute illness to 2000 public health survey

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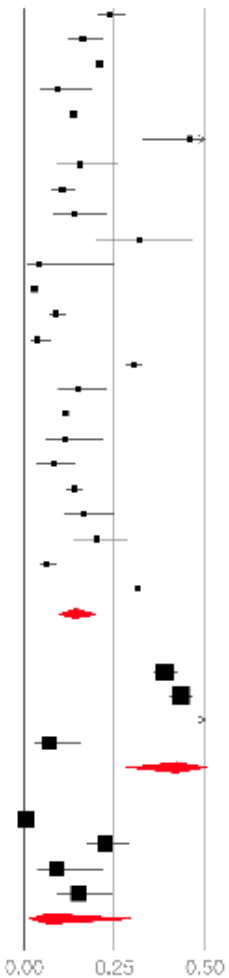
Marshall JK. Gastroenterology 2006;131:445-50

IBS After Infectious Enteritis: Systematic Review and Meta-Analysis

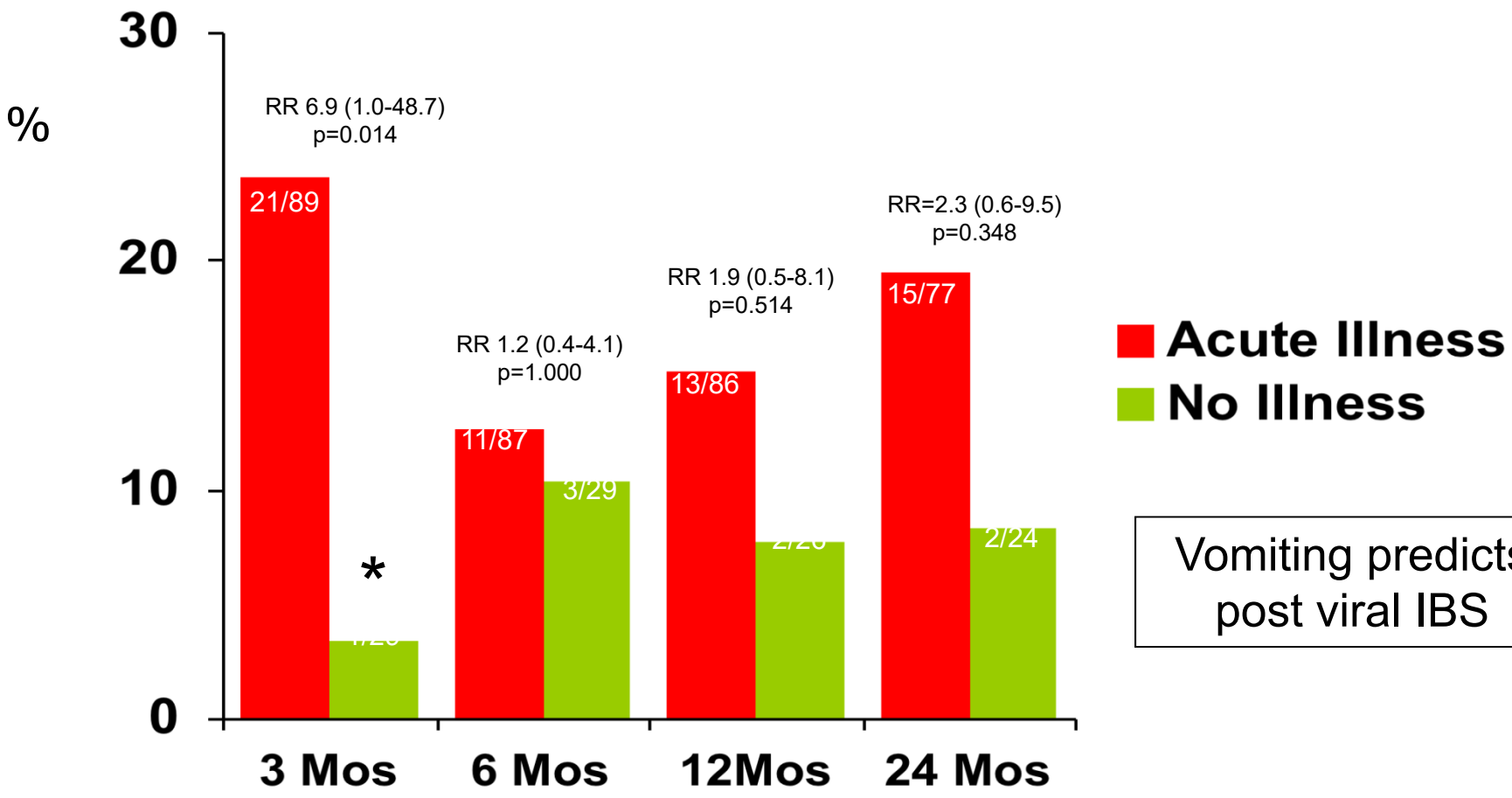
Author, Year	n/N	Event Rate (95% CI)
Bacterial		
Bettes, 2014	101/425	0.238 (0.200-0.280)
Cremon, 2014	33/204	0.162 (0.117-0.219)
Nielsen, 2014	56/268	0.209 (0.164-0.262)
Koh, 2012	6/65	0.092 (0.042-0.191)
Youn, 2012	17/124	0.137 (0.087-0.210)
Schwille Kiuntke, 2011	22/48	0.458 (0.324-0.599)
Lim, 2010	11/71	0.155 (0.088-0.259)
Thabane, 2010	32/305	0.105 (0.075-0.145)
Jung, 2009	12/87	0.138 (0.080-0.227)
Saps, 2008	14/44	0.318 (0.198-0.468)
Piche, 2007	1/23	0.043 (0.006-0.252)
Ruigomez, 2007	167/5894	0.028 (0.024-0.033)
Spence, 2007	49/547	0.090 (0.068-0.117)
Borgaonkar, 2006	7/191	0.037 (0.018-0.075)
Marshall, 2006	417/1368	0.305 (0.281-0.330)
Ji, 2005	15/101	0.149 (0.092-0.232)
Mearin, 2005	31/271	0.114 (0.082-0.158)
Okhuysen, 2004	7/61	0.115 (0.056-0.222)
Wang, 2004	24/295	0.081 (0.055-0.119)
Dunlop, 2003	103/747	0.138 (0.115-0.165)
Parry, 2003	18/108	0.167 (0.108-0.249)
Gwee, 1999	22/109	0.202 (0.137-0.288)
Neal, 1997	23/366	0.063 (0.042-0.093)
McKendrick, 1994	12/38	0.316 (0.189-0.478)
	1200/11760	0.138 (0.094-0.199)
		I²=98%
Protozoal/Parasitic		
Hanevik, 2014	291/748	0.389 (0.355-0.424)
Wensaas, 2012	355/817	0.435 (0.401-0.469)
Hanevik, 2009	66/82	0.805 (0.705-0.877)
Soyturk, 2007	5/72	0.069 (0.029-0.156)
	717/1719	0.419 (0.287-0.565)
		I²=95%
Viral		
Porter, 2012	7/1718	0.004 (0.002-0.009)
Zanini, 2012	40/178	0.225 (0.169-0.292)
Saps, 2009	4/44	0.091 (0.035-0.218)
Marshall, 2007	13/86	0.151 (0.090-0.243)
	64/2026	0.064 (0.011-0.296)
		I²=97%



- 45 studies (N=21,421)
- Follow-up 3 months to 10 years
- Relative risk for IBS if infectious enteritis in last 12 months:
  - 4.2 (95% CI 3.1-5.7)
- Pooled PI-IBS prevalence
  - 10.1% (95% CI 7.2-14.1) at 12 months
  - 14.5% (95% CI 7.7-25.5) > 12 months
- Risk factors for PI-IBS:
  - Female: OR 2.2 (1.6-3.1)
  - Antbiotics: OR 1.7 (1.2-2.4)
  - Anxiety: OR 2.0 (1.3-2.9)
  - Depression: OR 1.5 (1.2-1.9)
  - Somatization: OR 4.1 (2.7-6.0)
  - Neuroticism: OR 3.3 (1.6-6.5)
  - Clinical indicators of enteritis severity

Klem F. Gastroenterology 2017 [in press]

PI-IBS After Viral Gastroenteritis



Vomiting predicts post viral IBS

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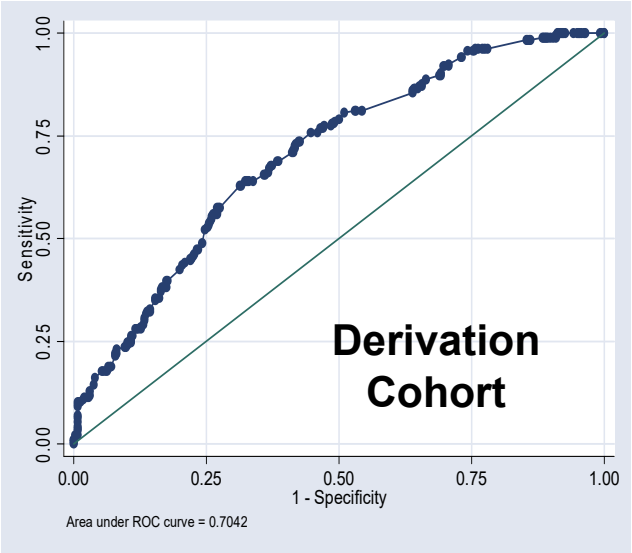
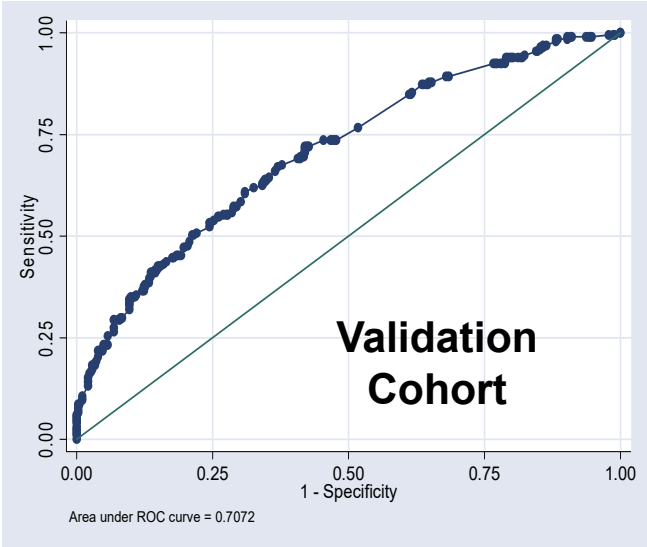
Marshall JK. Clin Gastroenterol Hepatol 2007;5:457-60

A Risk Score for Post-Infectious Irritable Bowel Syndrome





<u>Risk Score Ranges from 0 to 90:</u>

Low (<42) = 10%, Intermediate (43-68) = 35%, High (>69) = 60%

Age under 60 = 6; female =9; duration more than 7 days =7; maximum stool frequency more than 6 =6; bloody stool = 4; abdominal cramps = 32; fever = 5; weight loss over 10 pounds = 8; premorbid anxiety/depression = 1; post infectious anxiety/depression = 10

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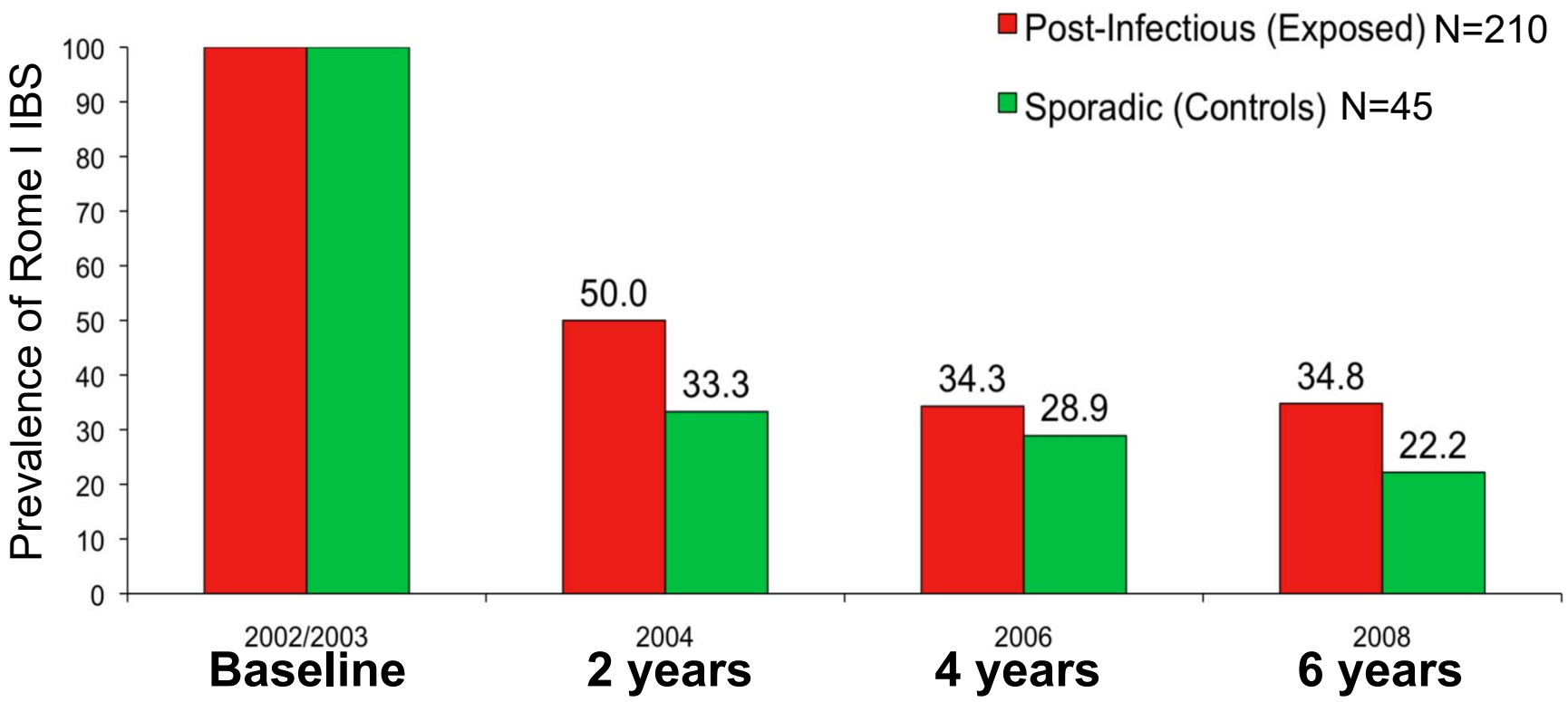
Thabane M, Marshall JK. Am J Gastroenterol 2009;104:2267-74

Persistence of PI-IBS Symptoms

(among subjects with IBS in 2002/2003)



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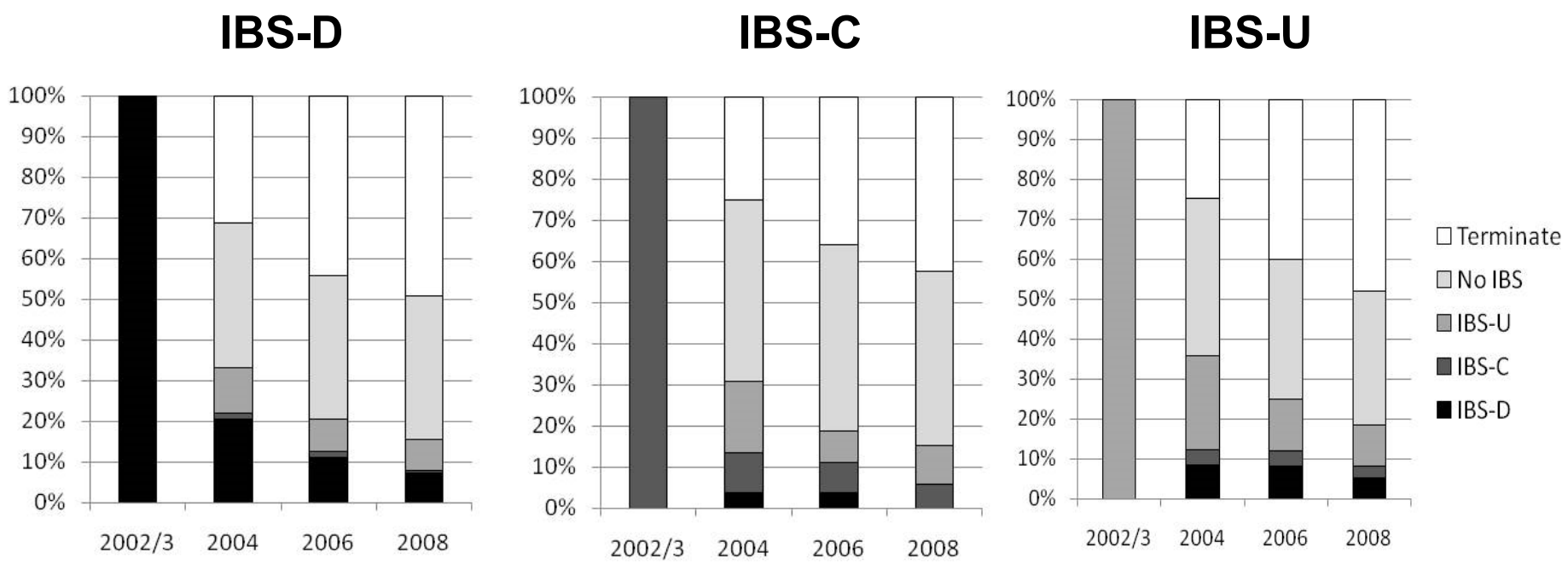
Marshall JK. Gut 2010;59:605-11

Stability of IBS Phenotype



Marshall JK. Gut 2010;59:605-11

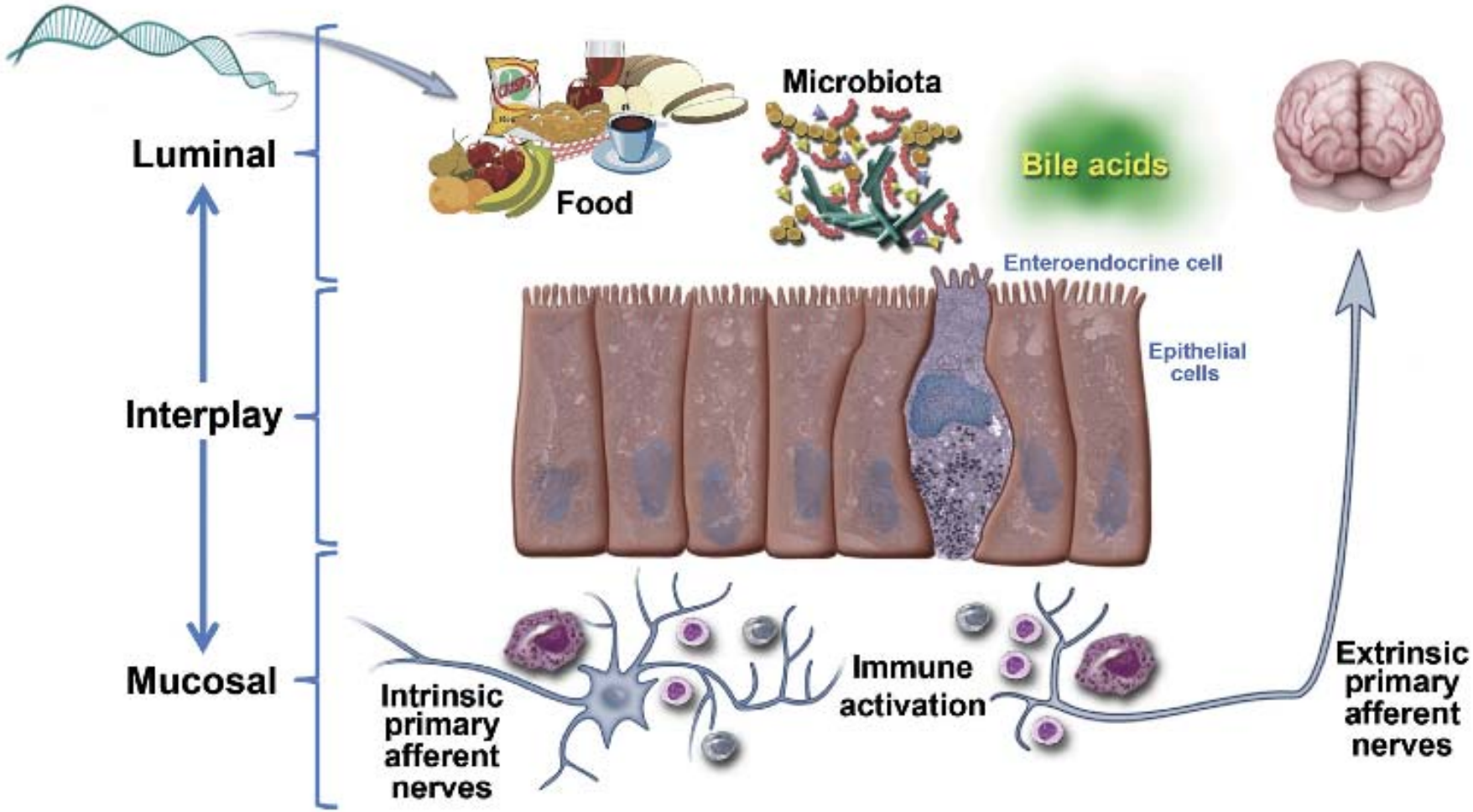
Long-Term Clinical Course of Shigellosis: 10-Year Follow-Up Study

- Prospective cohort study of 2001 Shigella outbreak in Korea
- 124 hospital employees infected by Shigella sonnei due to contaminated cafeteria food
- 105 age- and gender-matched non-infected controls

Survey time (yr)	*Shigella*-exposed group		Control group		Adjusted OR (95% CI)
	Total No.	No. of IBS	Total No.	No. of IBS	
1st	87	12 (13.8%)	89	1 (1.1%)	11.9 (1.49-95.58)
3rd	87	13 (14.9%)	89	4 (4.5%)	3.93 (1.20-12.86)
5th	53	11 (20.8%)	49	6 (12.2%)	1.88 (0.64-5.54)
8th	71	11 (15.4%)	65	6 (9.2%)	1.87 (0.62-5.19)
10th	86	20 (23.3%)	76	15 (19.7%)	1.61 (0.70-3.69)

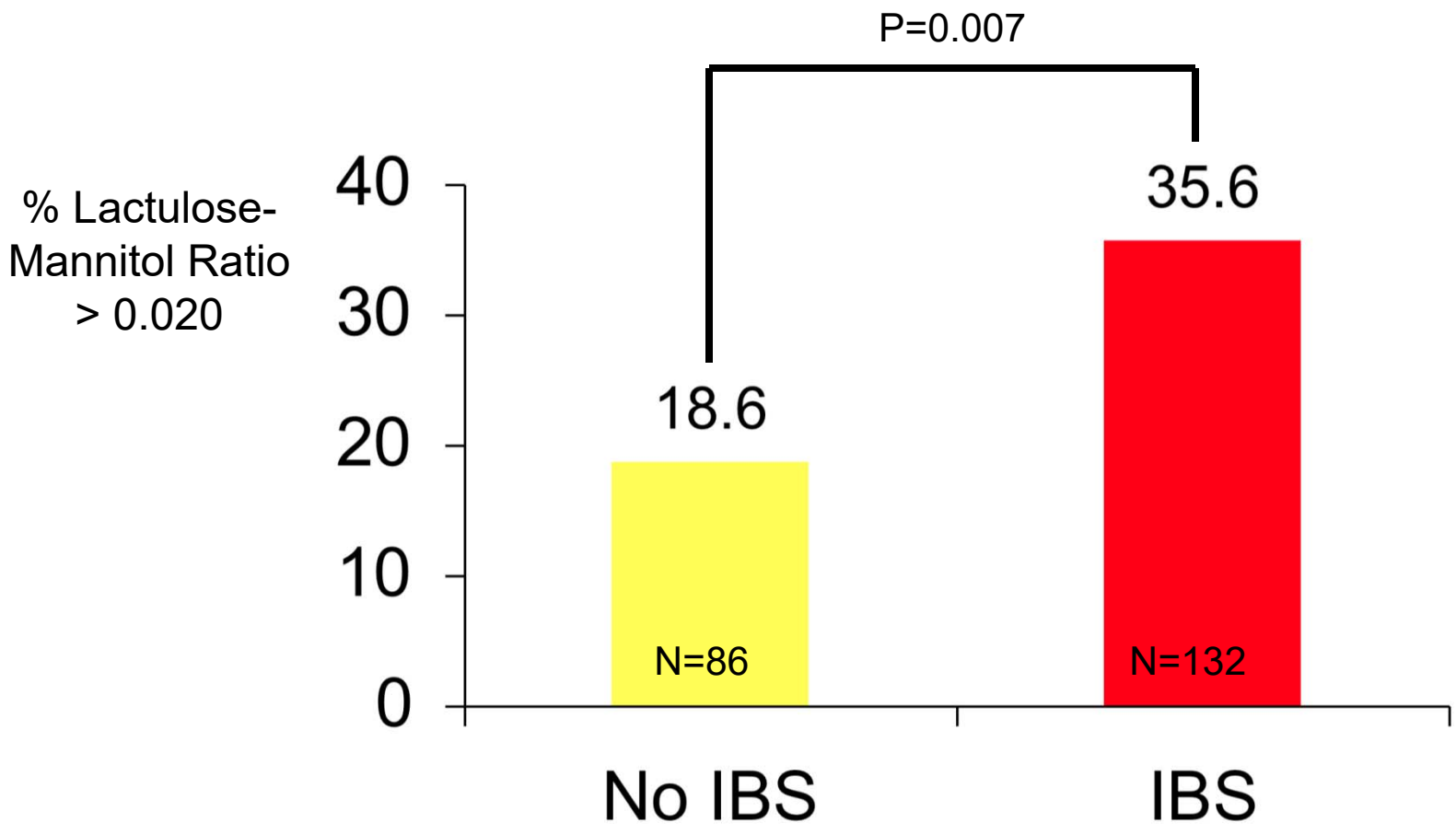
Youn YH. J Neurogastroenterol Motil 2016;22:490-6

Luminal and Mucosal Factors in the Pathogenesis of IBS



Barbara G. Gastroenterology 2016;150:1305-18

Increased Intestinal Permeability with IBS in Walkerton Ontario



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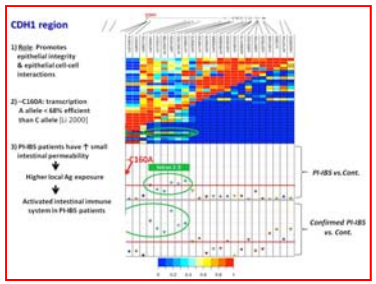
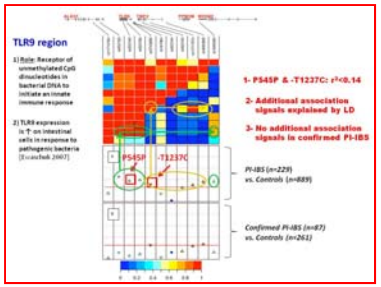
Marshall JK. Aliment Pharmacol Ther 2004;20:1317-22

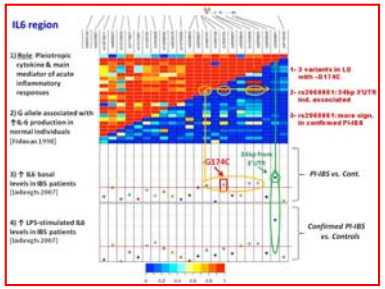
Genetic Associations with PI-IBS

Gene ID	Gene Category	SNP ID	Associated Allele	Frequency Controls	Frequency Cases	Odds Ratio (95% CI)	p value
TLR9	Innate immunity	P545P rs352139	A	41%	48%	1.38 (1.10-1.73)	**0.0059**
TLR9	Innate immunity	-T1237C rs5743836	T	82%	87%	0.69 (0.50-0.95)	**0.025**
IL-6	Innate immunity	-G174C rs1800795	C	39%	44%	1.28 (1.01-1.64)	**0.042**
CDH1	Intestinal epithelial barrier	-C160A rs16260	A	26%	31%	1.26 (0.99-1.61)	**0.035**

IL-6 and CDH1 associations stronger when analysis restricted to subjects with confirmed gastroenteritis exposure







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Villani AC, Marshall JK. Gastroenterology 2010;138:1502-13

Genetic Variants are Independent PI-IBS Risk Factors

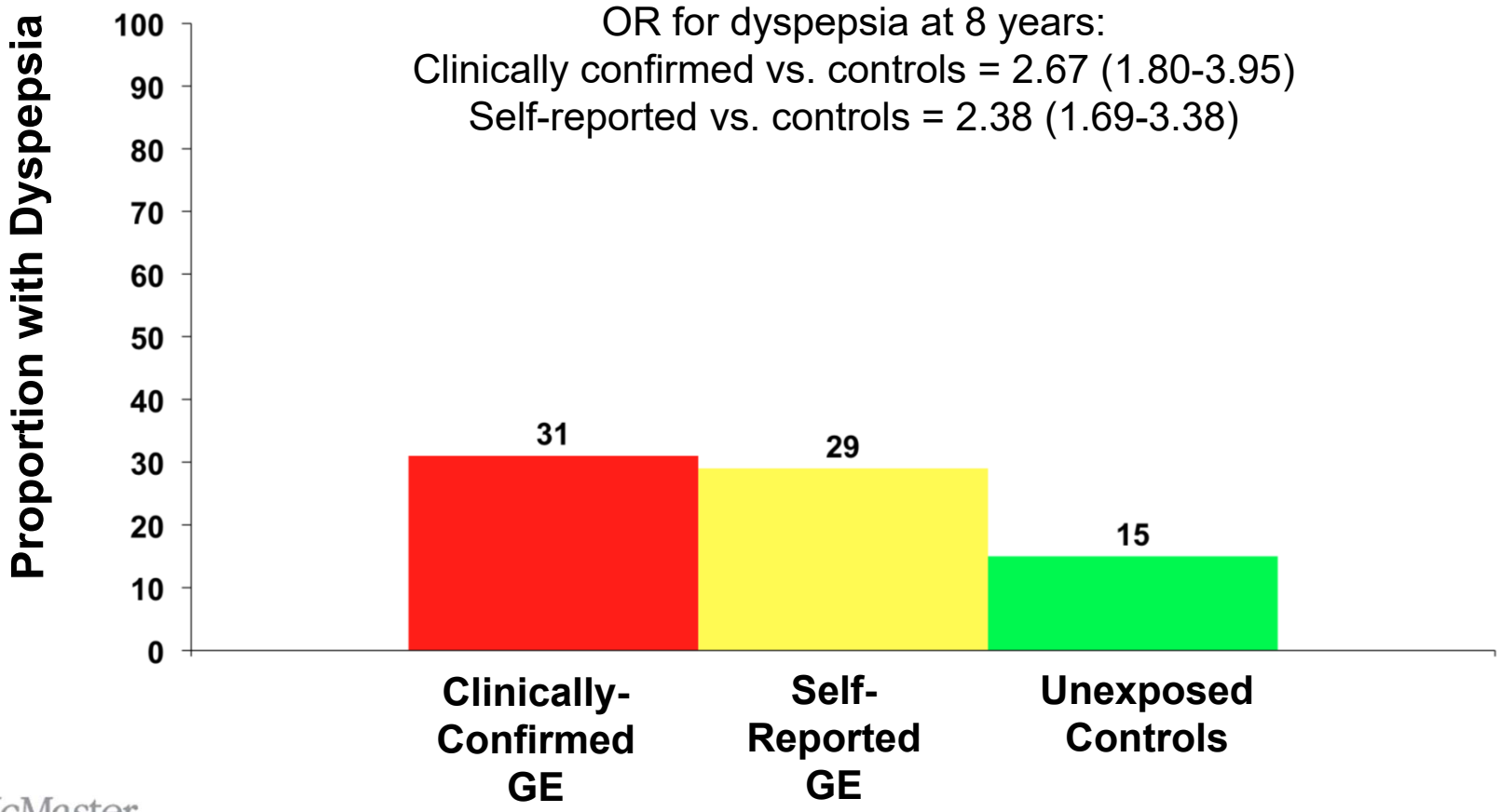
Multiple Logistic Regression Controlling for Clinical Predictors

Variables	Reference	*P* value	Odds ratio (95% confidence interval)
rs5743836:T (*TLR9*)	C	.0168	1.536 (1.080–2.182)
rs2069861:T (*IL6*)	C	.0345	1.509 (1.031–2.209)
rs16260:A (*CDH1*)	C	.0143	1.398 (1.069–1.829)
Age (*y*)		.0159	0.986 (0.975–0.997)
Gender	Female	.0238	1.521 (1.057–2.187)
Features of acute enteric illness			
Duration of diarrhea			
2–3 d	0–1 d	.976	0.987 (0.428–2.275)
4–5 d	0–1 d	.363	1.484 (0.634–3.476)
6–7 d	0–1 d	.626	1.242 (0.519–2.977)
>7 d	0–1 d	.136	1.855 (0.823–4.183)
Bloody stools	No	.00338	1.845 (1.225–2.779)
Abdominal cramps	No	.000745	7.754 (2.258–25.499)
Weight loss (>10 lb)	No	.000921	2.064 (1.345–3.169)

Villani AC, Marshall JK. Gastroenterology 2010;138:1502-13

Prevalence of Dyspepsia at 8 Years Using Rome II Definition

(Short-Form Leeds Dyspepsia Questionnaire)

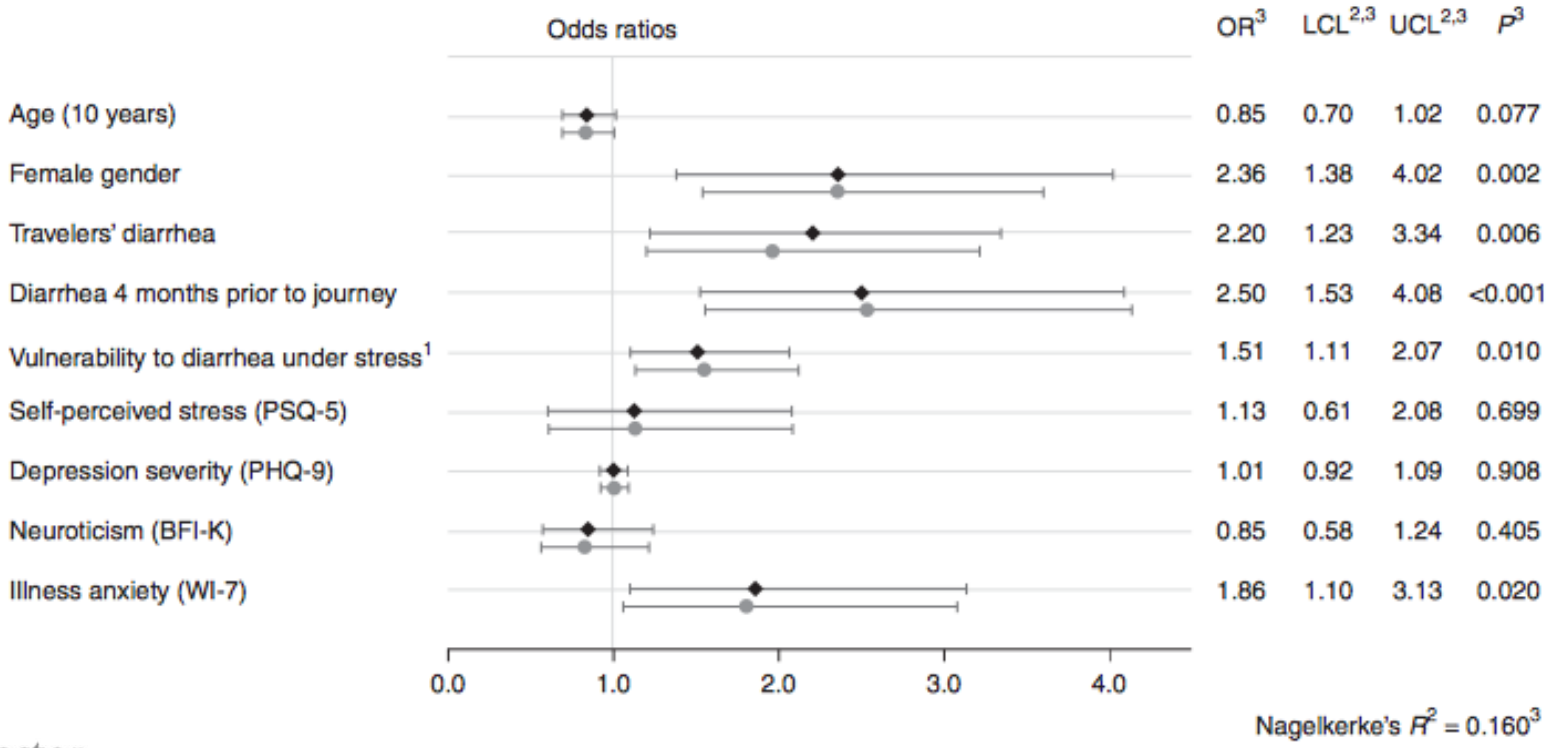


Ford AC, Marshall JK. Gastroenterology 2010;138:1727-36

Post-Infectious IBS After Long-Distance Travel

- Survey of 1190 long-distance travelers, 7 months after journey
  - Traveler's diarrhea (at least moderate) in 43.3%
  - New-onset IBS at 7 months post travel in 7.2% (95% CI 5.8-8.6)

    (10.7% if diarrhea during travel vs. 2.5% if no traveler's diarrhea)



Lowe B. Am J Gastroenterol 2016;111:1320-9

Conclusions

- The Walkerton outbreak was an awful human tragedy
- The contributions of citizens of Walkerton have enhanced understanding of post-infectious IBS
- New insights:
  - Epidemiology and natural history
    - Adult
    - Adolescent
  - Risk factors and risk profiling
  - IBS phenotype stability
  - Risk of IBD
  - Role of intestinal permeability
  - Genetic risk factors

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Study Participants

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Western

McGill

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THANK YOU