



Connecting the dots: Norovirus, Gut Microbiota and Post-infectious IBS

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Joint Graduate Seminar

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5th December, 2017

Outline

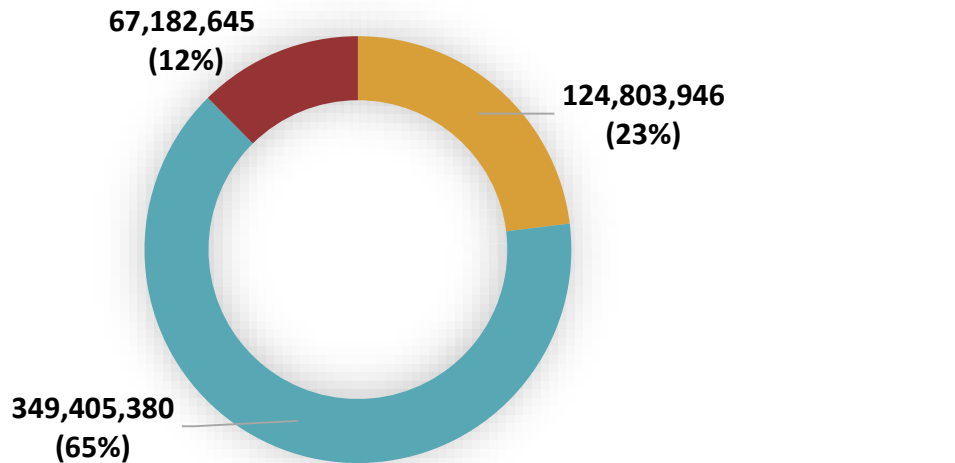
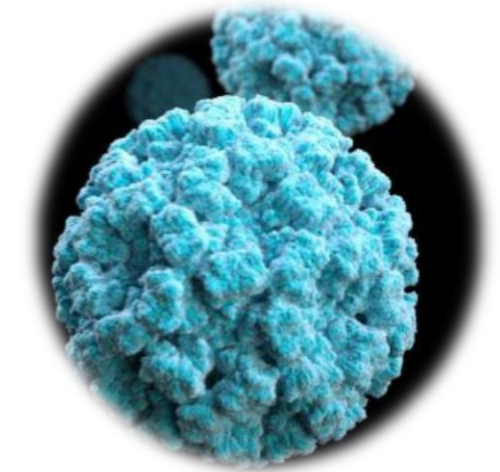
1. Background information on norovirus and post-infectious irritable bowel syndrome (PI-IBS)
2. Linkage with gut microbiota
3. Proposed mechanism
4. Observation based on literature review
5. Future work



1.1

Norovirus

- The leading cause of viral acute gastroenteritis
(18% in norovirus metanalysis)



■ Viruses (Norovirus)

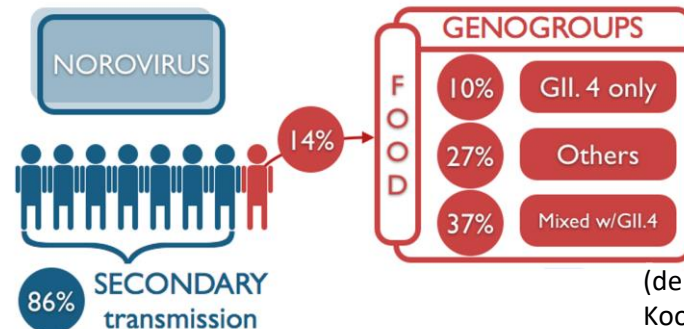
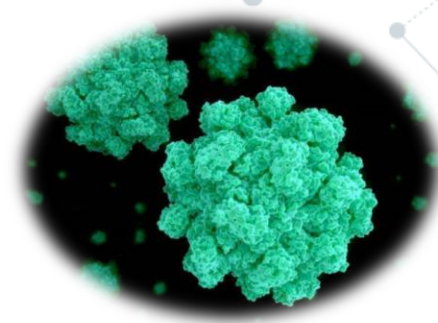
■ Protozoa (Giardia etc)

■ Bacteria (including E. coli, Shigella etc)

(Ahmed *et al.*, Lancet ID, 2014;
Havelaar *et al.*, PLOS Medicine, 2010)

What are noroviruses?

- A member of the *Caliciviridae* family
- Faecal-oral route and affect all age groups
- Low infectious dose, 12-48 hours incubation period and self-limiting
- Bind to histo-blood group antigens (HBGAs) as functional receptors/co-receptors on host cells
- No licensed vaccine available



(de Graaf, van Beek and Koopmans, Nature Reviews Microbiology, 2016)

A light gray network diagram with nodes and connecting lines is visible in the top-left and bottom-right corners of the slide.

1.2

Post-infectious Irritable Bowel Syndrome



What is Post-infectious IBS?

- **IBS**

→ gastrointestinal tract disorder, characterised by abdominal discomfort and chronically disturbed bowel habit

- **PI-IBS**

→ *de novo* development of IBS after acute gastroenteritis, despite the clearance of the inciting pathogen

→ involved persistent subclinical inflammation, changes in intestinal permeability and alteration of gut microbiota

What is IBS?

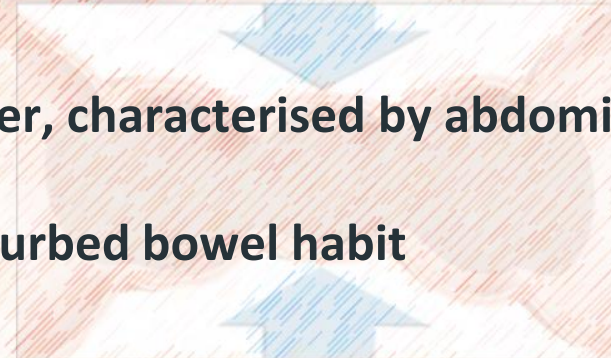
Intestinal bowel syndrome (IBS) is a functional disorder characterised by chronic abdominal pain or discomfort, often associated with altered bowel habits, and no identifiable organic cause. The diagnosis is based on the Rome criteria, which require the presence of abdominal pain or discomfort, at least some days per month, for at least three months, with two or more of the following symptoms: change in stool frequency, change in stool form (appearance), and change in stool sensation (urgency or incomplete evacuation).

Possible Causes of IBS

The exact cause of IBS is unclear, but it is thought to be a multifactorial disorder involving a combination of genetic, environmental, and psychological factors. It is often associated with a history of acute gastroenteritis, which may lead to post-infectious IBS. Other factors that may contribute to the development of IBS include stress, anxiety, and changes in the gut microbiota.

Colon Spasm (External)

Colon spasm (external) is a condition characterised by abdominal pain and discomfort, often associated with altered bowel habits. It is thought to be caused by a spasm of the smooth muscle of the colon, which may be triggered by stress, anxiety, or changes in the gut microbiota.



Colon Spasm (Internal)

Symptoms

Patients report abdominal cramps and pain, and may experience a sense of urgency, diarrhoea, or constipation. Symptoms are often associated with changes in bowel habits, such as diarrhoea, constipation, or alternating diarrhoea and constipation. Other symptoms may include bloating, excessive mucus in stool, and a feeling of incomplete evacuation.

• Bloating

• Excessive mucus in stool

• Passage of mucus with a bowel movement

• Feeling that the bowel is not completely empty

System Overview of IBS

Psychological Distress

Symptoms & Disease

Sensitivity Spasm

Stressors & Triggers

Symptom Management

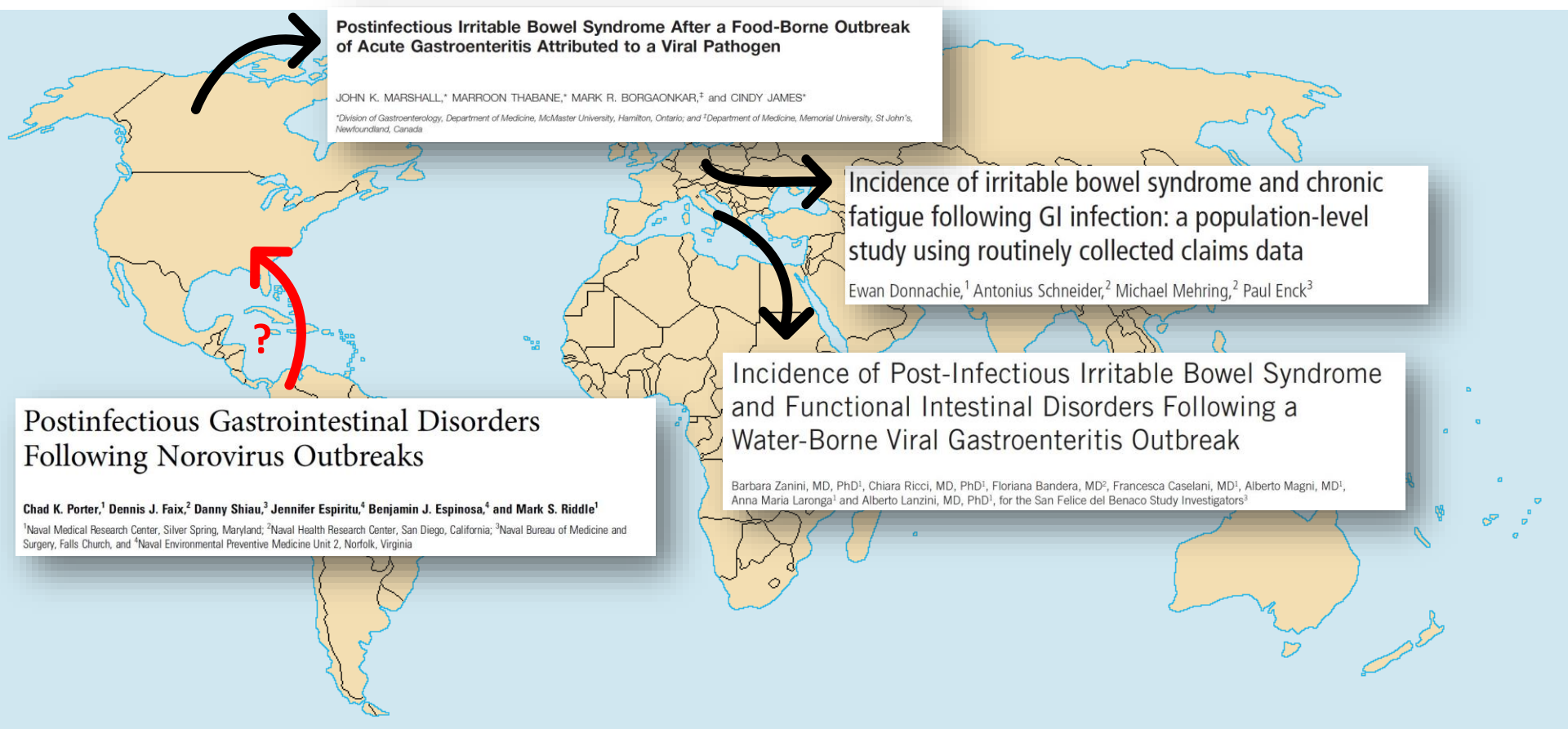
• Evaluate your diet to see if there are foods that appear to trigger IBS symptoms.

A background pattern of a network diagram with various nodes and connections. The nodes are represented by circles of different sizes and colors (grey, white, blue), and they are interconnected by thin lines of varying thickness and style (solid, dashed).

BUT

How are they related to each other?

Epidemiological evidence



Postinfectious Irritable Bowel Syndrome After a Food-Borne Outbreak of Acute Gastroenteritis Attributed to a Viral Pathogen

JOHN K. MARSHALL,^{*} MARROON THABANE,^{*} MARK R. BORGAONKAR,[‡] and CINDY JAMES^{*}

^{*}Division of Gastroenterology, Department of Medicine, McMaster University, Hamilton, Ontario; and [‡]Department of Medicine, Memorial University, St John's, Newfoundland, Canada

Incidence of irritable bowel syndrome and chronic fatigue following GI infection: a population-level study using routinely collected claims data

Ewan Donnachie,¹ Antonius Schneider,² Michael Mehring,² Paul Enck³

Incidence of Post-Infectious Irritable Bowel Syndrome and Functional Intestinal Disorders Following a Water-Borne Viral Gastroenteritis Outbreak

Barbara Zanini, MD, PhD¹, Chiara Ricci, MD, PhD¹, Floriana Bandera, MD², Francesca Caselani, MD¹, Alberto Magni, MD¹, Anna Maria Laronga¹ and Alberto Lanzini, MD, PhD¹, for the San Felice del Benaco Study Investigators³

Postinfectious Gastrointestinal Disorders Following Norovirus Outbreaks

Chad K. Porter,¹ Dennis J. Faix,² Danny Shiau,³ Jennifer Espiritu,⁴ Benjamin J. Espinosa,⁴ and Mark S. Riddle¹

¹Naval Medical Research Center, Silver Spring, Maryland; ²Naval Health Research Center, San Diego, California; ³Naval Bureau of Medicine and Surgery, Falls Church, and ⁴Naval Environmental Preventive Medicine Unit 2, Norfolk, Virginia

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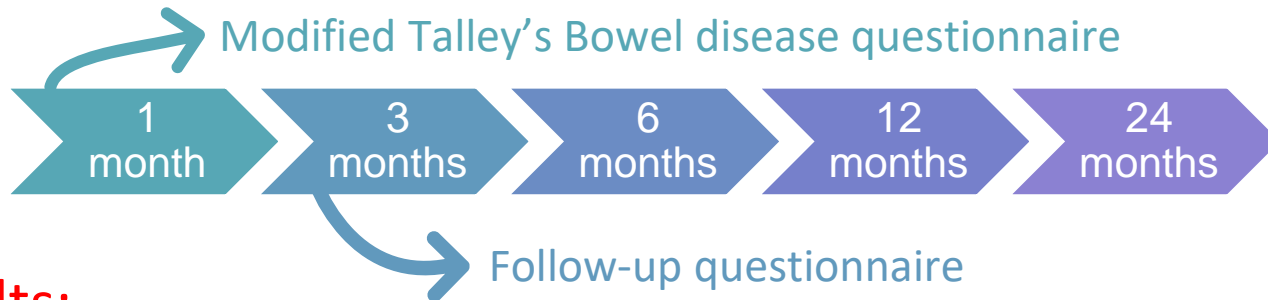
Epidemiological evidence- Canada

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Methods:



Results:

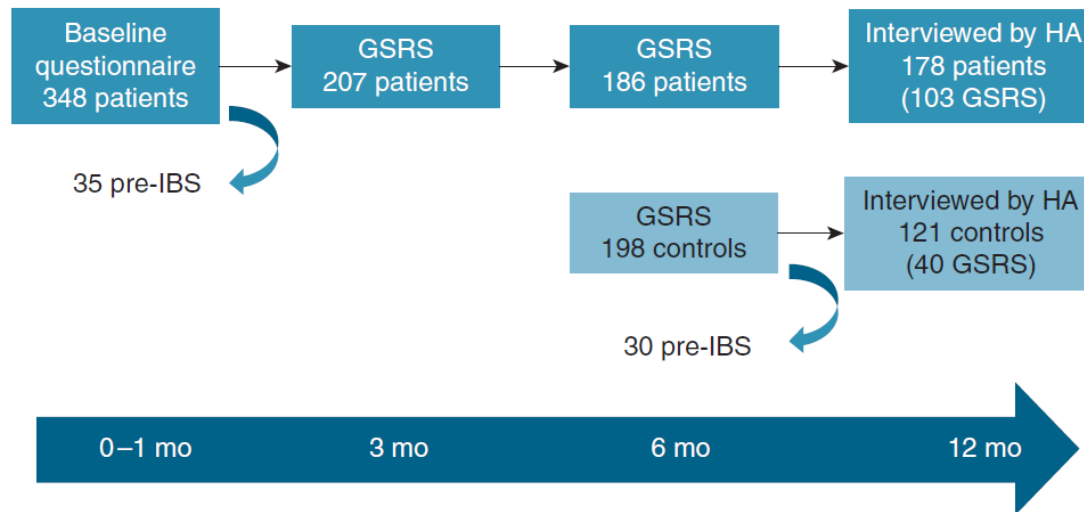
Time point	All subjects	Cases exposed to gastroenteritis	Unexposed controls	P value	OR (95% CI)
3 Mo	22/118 (18.6)	21/89 (23.6)	1/29 (3.4)	.014	6.9 (1.0–48.7)
6 Mo	14/116 (12.1)	11/87 (12.5)	3/29 (10.3)	1.000	1.2 (0.4–4.1)
12 Mo	15/112 (13.4)	13/86 (15.1)	2/26 (7.8)	.514	1.9 (0.5–8.15)
24 Mo	17/101 (19.0)	15/77 (19.5)	2/24 (8.3)	.348	2.3 (0.6–9.5)

Mo, months.

Epidemiological evidence- Italy

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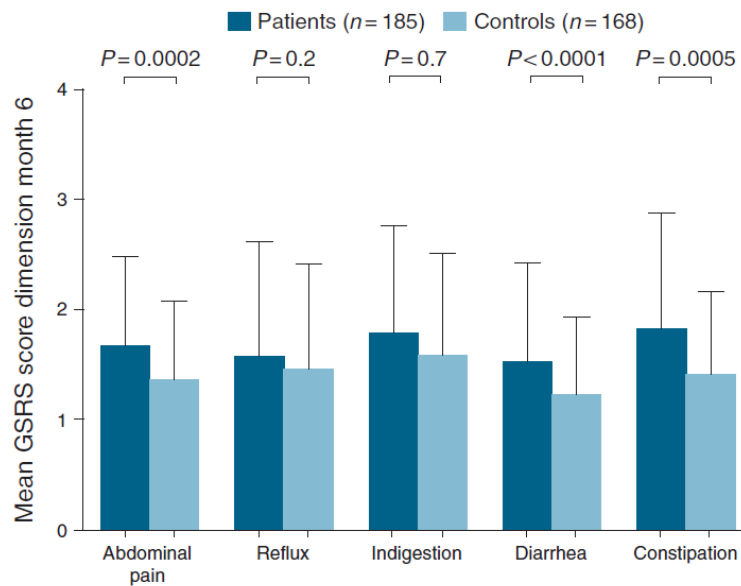


Epidemiological evidence- Italy

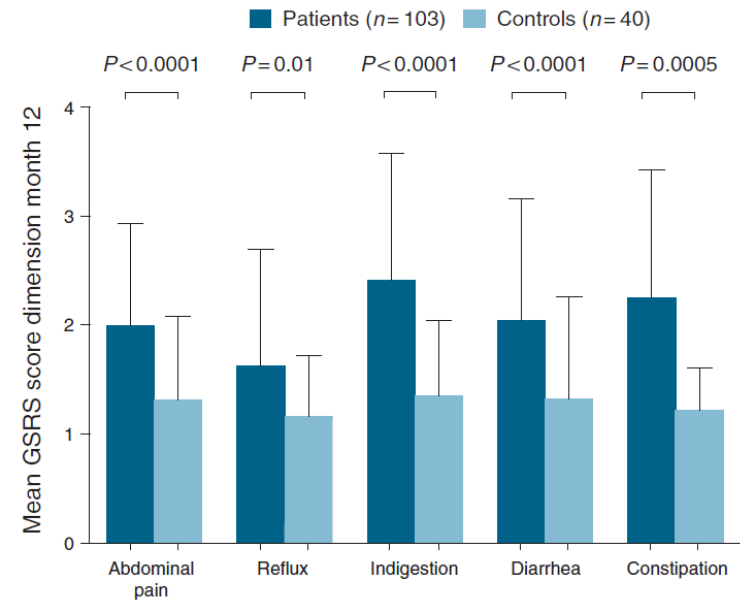
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Month 6



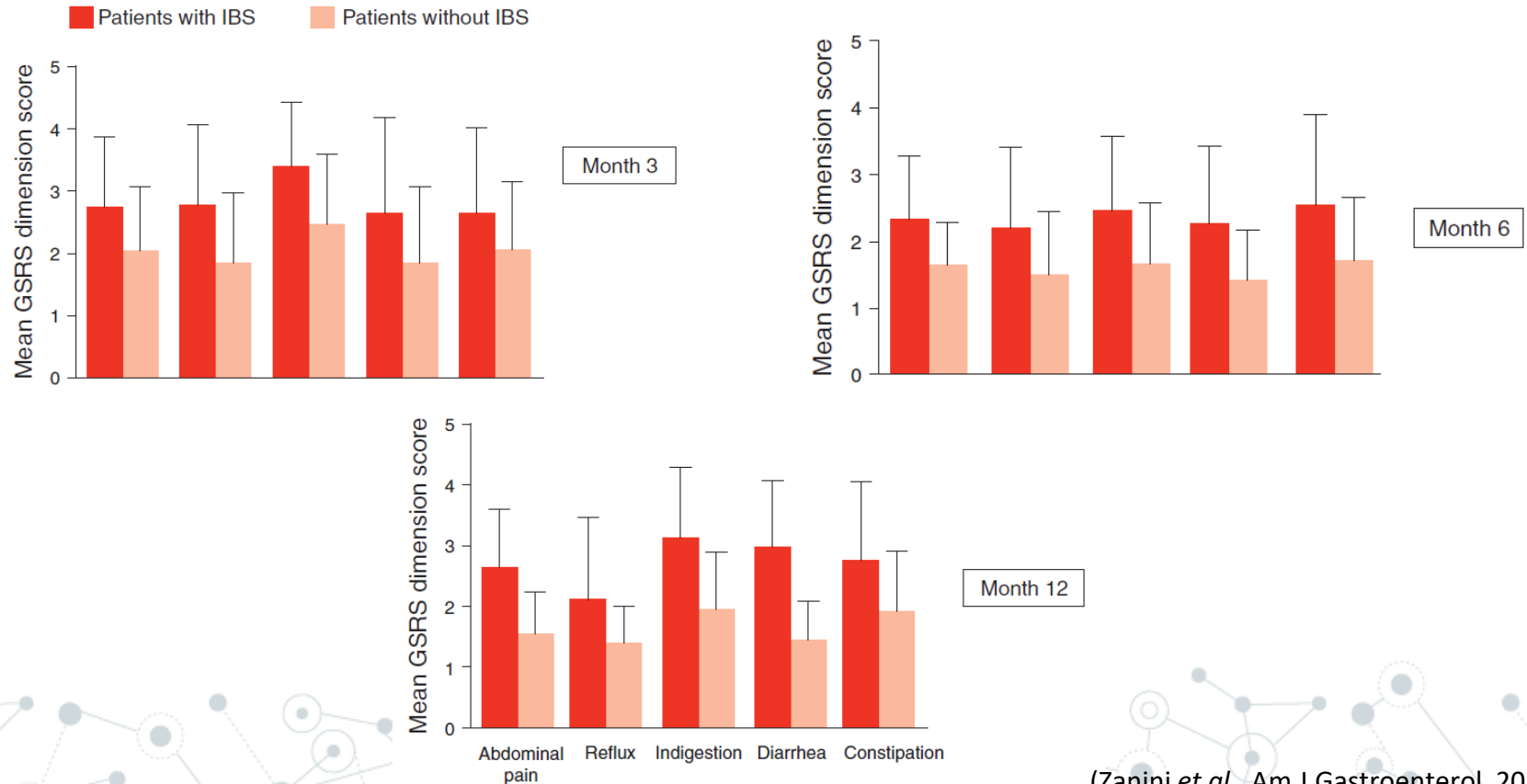
Month 12



Epidemiological evidence- Italy

Incidence of Post-Infectious Irritable Bowel Syndrome and Functional Intestinal Disorders Following a Water-Borne Viral Gastroenteritis Outbreak

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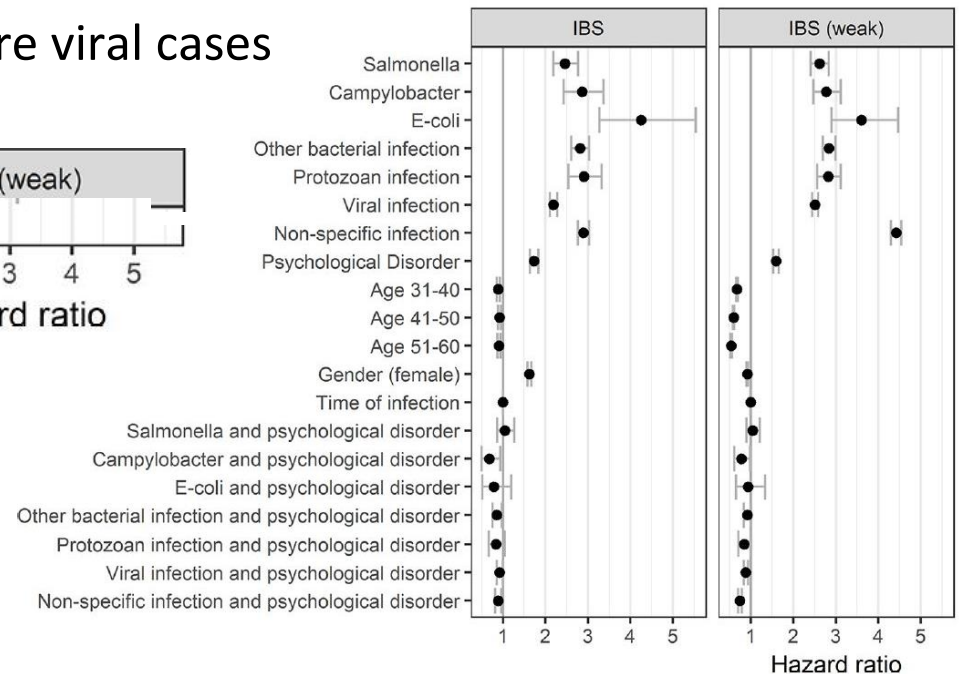
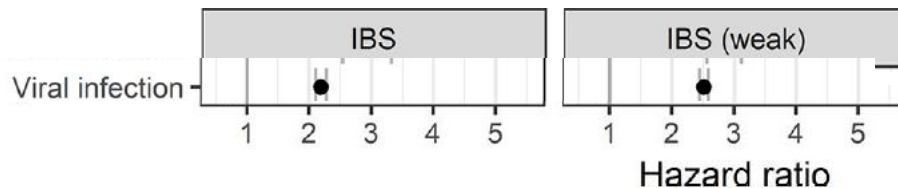


Epidemiological evidence- Germany

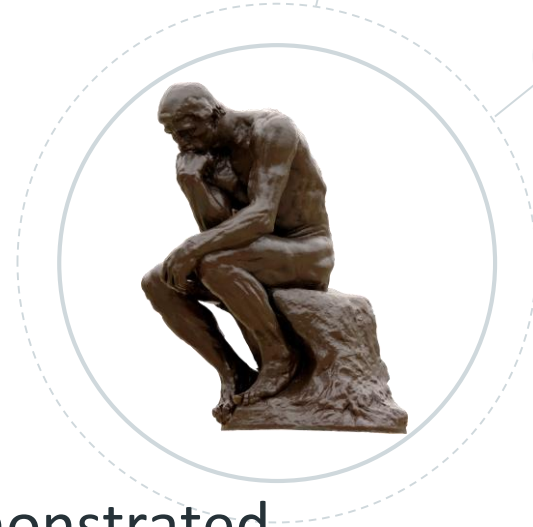
Incidence of irritable bowel syndrome and chronic fatigue following GI infection: a population-level study using routinely collected claims data

Ewan Donnachie,¹ Antonius Schneider,² Michael Mehring,² Paul Enck³

- Followed-up **508,287** patients up to 5 years after first episode of GI infection **305,697** were viral cases



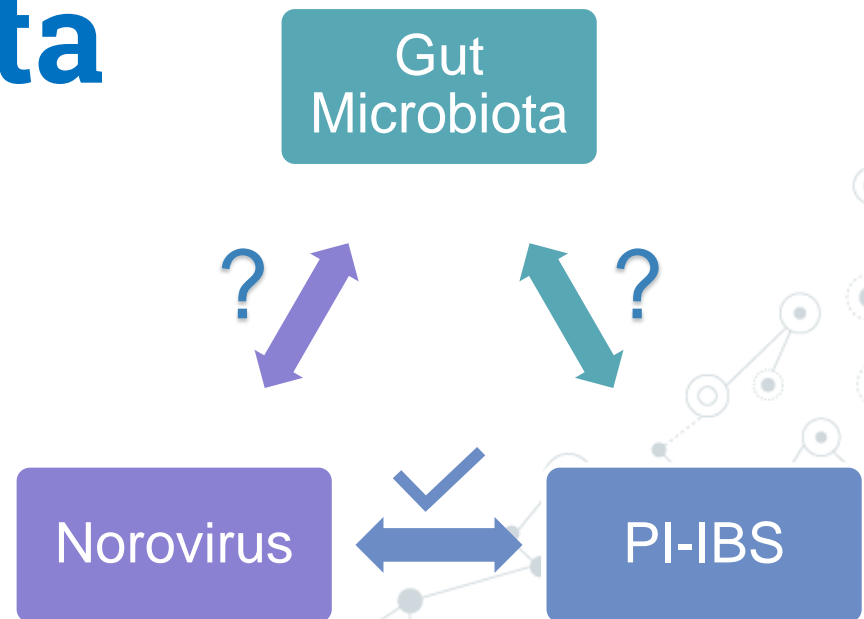
So...



All the three researches demonstrated that PI-IBS **frequently occurs** after acute viral gastroenteritis

2.

Linkage with gut microbiota



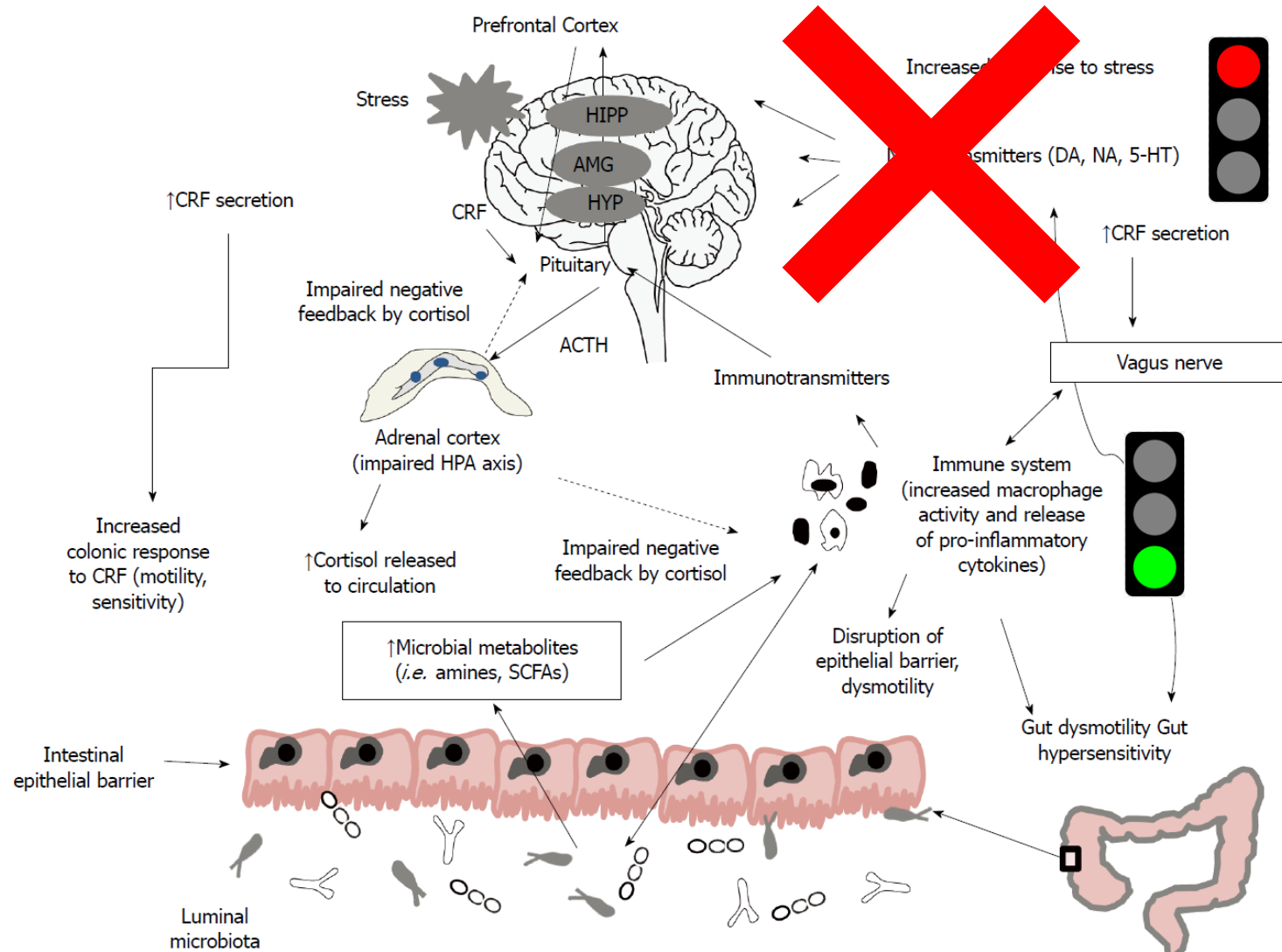
Gut microbiota

- Complex living ecosystem (✓ bacteria, viruses, archaea and eukaryotes) 🖐️ 10-fold of human cells
- Highly dynamic between individuals and is dependent on environmental factors
- ~~Mutualistic~~ relationship under healthy condition
- **However** → changes in numbers and composition
→ lead to appearance of a spectrum of diseases (e.g. Obesity, IBD etc)

MICROBIAL CELLS
~100 TRILLION
(~70-90%)

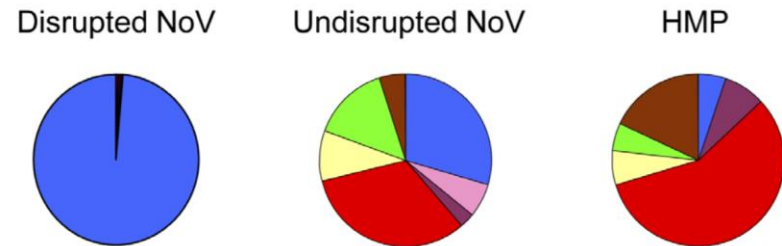
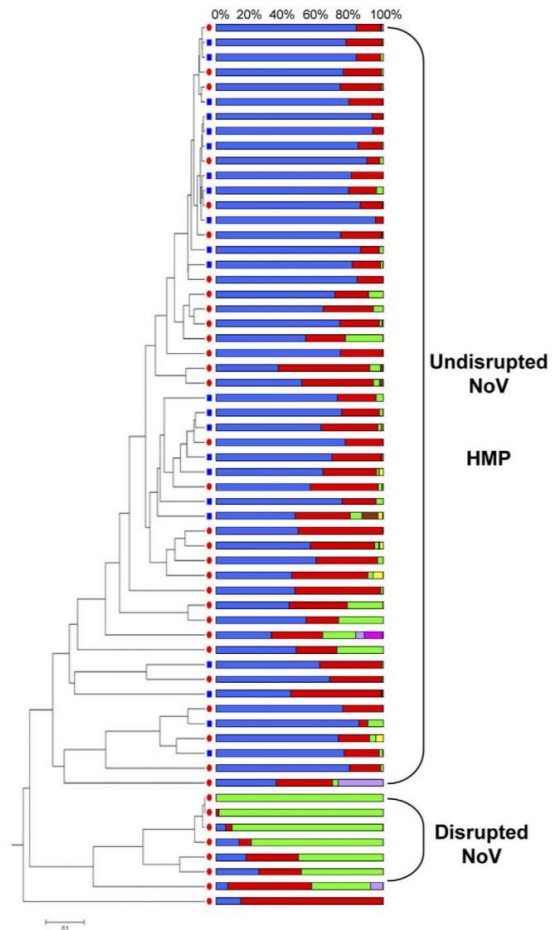
HUMAN CELLS
~30 TRILLION

Gut microbiota and IBS



Gut microbiota and norovirus

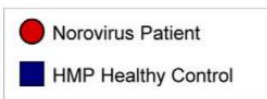
- Gut microbiota's diversity was highly disrupted after norovirus infection
- Significant increase in proteobacteria community (e.g. *E.coli*)
 → increase incidence in mucosal inflammation development



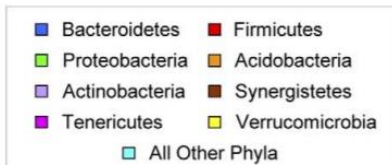
Family level assignments within Proteobacteria
 Mean proportion of bacteria per treatment group

Family	Disrupted NoV	Undisrupted NoV	HMP
<i>Enterobacteriaceae</i>	98.65 % ±1.89	29.36 % ±35.29	5.64 % ±19.11
<i>Pasteurellaceae</i>	0.52 % ±1.22	2.72 % ±8.06	8.46 % ±21.99
<i>Pseudomonadaceae</i>	0.14 % ±0.32	6.52 % ±21.35	0.00 % ±0.00
<i>Alcaligenaceae</i>	0.56 % ±1.18	32.63 % ±36.04	56.08 % ±41.98
<i>Neisseriaceae</i>	0.03 % ±0.04	9.44 % ±24.28	6.99 % ±21.72
<i>Desulfovibrionaceae</i>	0.04 % ±0.06	14.40 % ±26.40	5.60 % ±11.65
All Other Families	0.05 % ±0.07	4.93 % ±11.86	17.24 % ±26.97

Sample ID Chart



Phylum Classification Color Chart



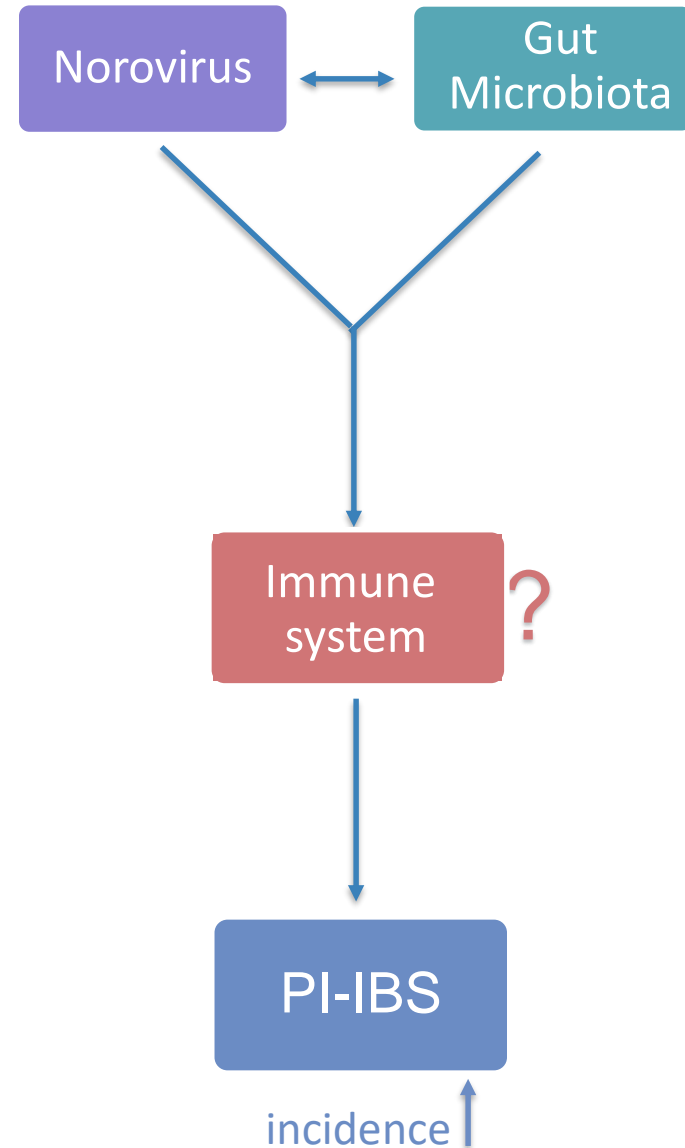
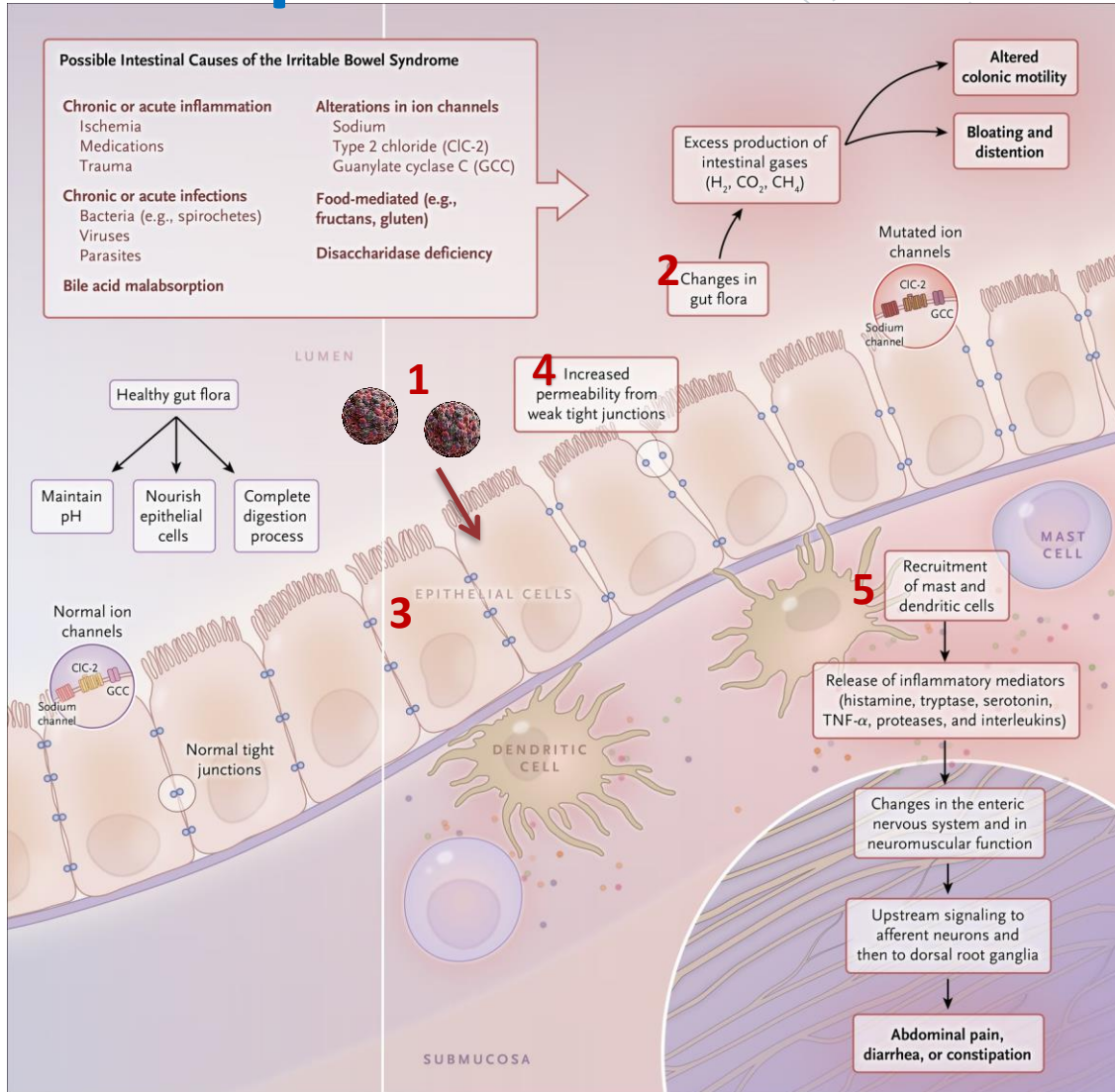
A decorative network diagram in the top-left corner, featuring a complex web of interconnected nodes and lines. The nodes are represented by small circles, some of which are larger and have a double-circle outline, while others are smaller and solid. The lines connecting them are thin and light gray, creating a dense, organic structure.

3.

Connecting the dots

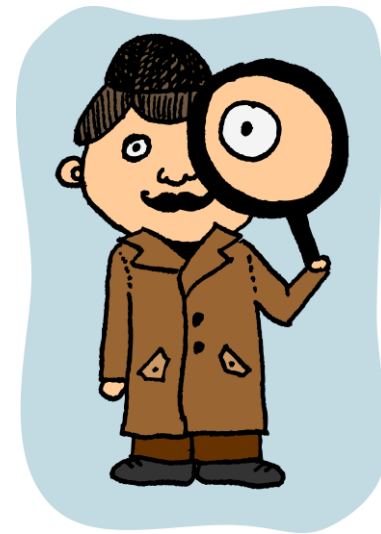
A decorative network diagram in the bottom-right corner, mirroring the style of the top-left diagram. It consists of a network of nodes and connecting lines, with some nodes highlighted by larger, double-outlined circles.

Proposed mechanism



4.

Observation based on literature review



Observation

- An inverse proportion relationship between gastroenteritis occur time and PI-IBS development



Restoration of gut microbiota balance?

- Severity of gastroenteritis could be a chronic consequence of an acute mucosal injury



Less severity would lead to fewer long term sequelae? + further reduce the long term risk of PI-IBS development?



5. **Future work**





- Porter *et al*, show that there is no significant increase in incidence of PI-IBS after AGE by measuring the inflammatory signal
- To evaluate long term sequelae of norovirus infection (is it really self-limiting?)
- To establish association studies → should also collect patient's stool for microbiota analysis during longitudinal studies
- For norovirus vaccine studies
 - may need to consider the prevention of the potential outcomes
 - or is there any possibility of secondary benefits (e.g. alleviate PI-IBS) towards the general public?



Any questions?

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