OneGI

SECOND ANNUAL GI & LIVER *Summit*

Expanding Our Knowledge of the Role of Diet & the Microbiome in IBS

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For a Digestive Peace of Mind, LLC
Medway, MA

Terms to Know

Microbiome Dictionary

Gut microbiota

The microorganisms inhabiting the gastrointestinal tract. The composition of this microbial community is host specific.

Gut microbiome

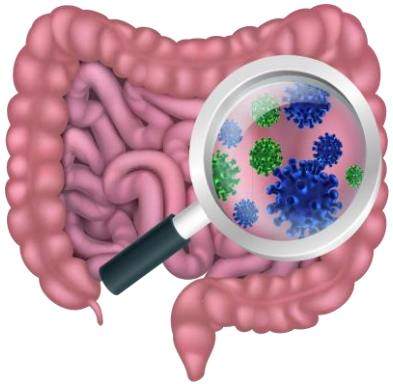
The entire collection of genes found in all of the microbial cells living in the gastrointestinal tract.

Metabolome

The specific metabolites in biological samples (tissues, cells, fluids, or organisms) under normal conditions in comparison with altered states promoted by disease, drug treatment, dietary intervention, or environmental modulation.

https://www.gutmicrobiotaforhealth.com/glossary-index; Klassen A et al. (2017). Metabolomics: Definitions and Significance in Systems Biology. In: Sussulini A. (eds) Metabolomics: From Fundamentals to Clinical Applications. Advances in Experimental Medicine and Biology. Vol 965. Springer, Cham.

Functions of the Gut Microbiome



*What matters more…who is there or **what they are doing**?*

- ✓ Pathogen protection-e.g. competes for nutrients
- ✓ Maintenance of intestinal barrier-protects against increased intestinal permeability
- ✓ Nutrient + drug metabolism
- ✓ Immune modulation
- ✓ Produces and communicates with hormonal products as an endocrine-like organ
- ✓ Impacts brain function via gut-brain axis

- Some examples: microbial produced SCFAs -used as nutrients for colonocytes, neurotransmitter production- potentially impacting mood

Guinane CM, Cotter PD. *Therap Adv Gastroenterol*. 2013;6(4):295-308; Dalton A et al. *Gut Microbes*. 2019;10(5):555-568.

Attributes of a Healthy Gut Microbiome

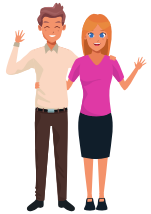
- **Stability**
  - Resist change in the setting of an ecologic stress (resistance) or to return to an equilibrium state following a stress-related perturbation (resilience).
- **Balance** of microbiota
  - Some microbial distributions may increase risk of infection or disease. E.g. antibiotics can put an individual at risk for *Clostridium difficile*.
  - Microbiota can shift with changes in age, diet, geographical location, intake of supplements and drugs
- Microbial **diversity**
  - The lack of sufficient diversity or evenness in a bacterial community structure appears to diminish its ability to withstand perturbation-e.g. obesity + IBD have reduced diversity.

Lifestyle factors can play a role in *positively* impacting these important gut microbiome attributes…

Bäckhed F et al. *Cell Host Microbe*. 2012 Nov 15;12(5):611-22.. PMID: 23159051; Tanaka M, Nakayama J. *Allergol Int*. 2017 Oct;66(4):515-522.





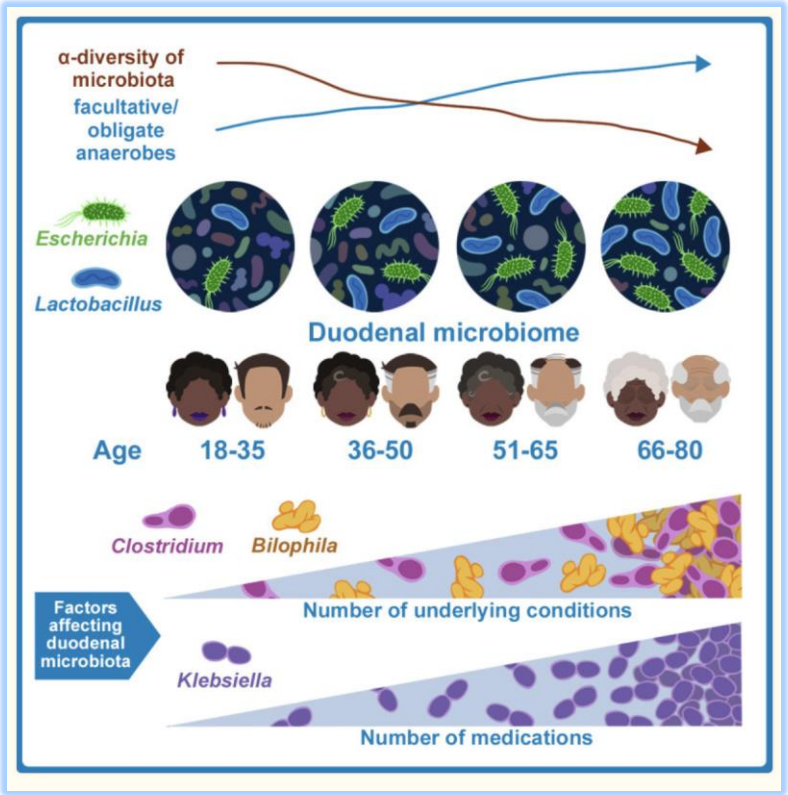



Factors that may impact gut microbiota composition + diversity during life stages

• Gestational health/DM • Diet • Antibiotics • Probiotics + Prebiotics • Bacteria in amniotic fluid • Lifestyle • Hygiene	• Mode of delivery • Birth weight • Environment • Antibiotics • Maternal flora • Hospital flora	• Mode of feeding • Fatty acids in breast milk • Type of formula • Siblings • Pets • Dust/hygiene • Probiotics • Antibiotics	• Diet • Geography • Hygiene • Drugs • Friends • Malnutrition • Allergies • Pets • Pro-Pre-biotics	• Diet • Lifestyle • Antibiotics • Probiotics • Sleep • Pregnancy • Disease • Travel	• Diet • Lifestyle • Age related illnesses • Hospital stays • Hygiene • Menopause • Drugs

Figure adapted from Nagpal R et al. *Nutr Healthy Aging*. 2018;4(4):267-285.

Effects Ageing Process on the Small Bowel Microbiome

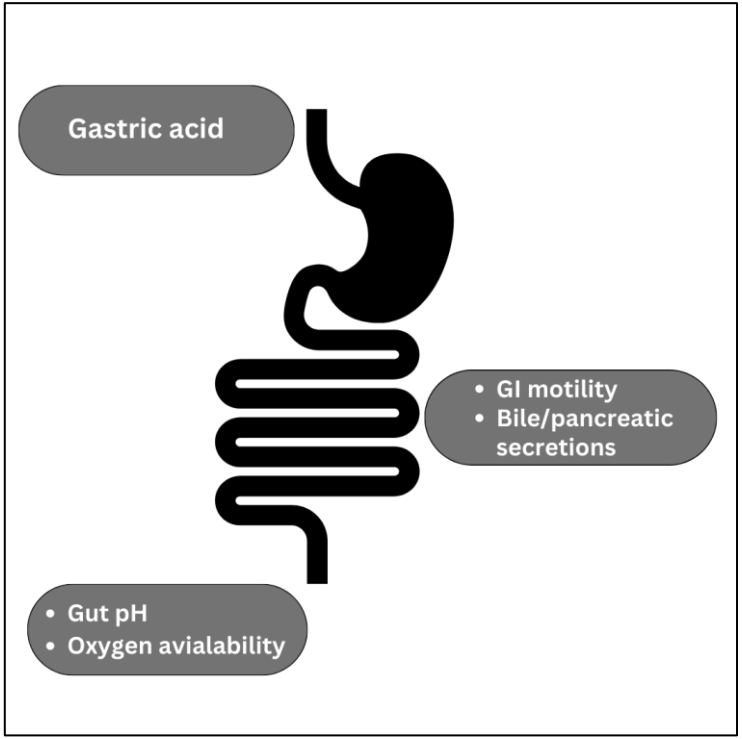


Leite G et al. *Microb Cell*. 2021 Dec 27;9(1):21-23.

Physical Gut Conditions That Impact Gut Microbiome

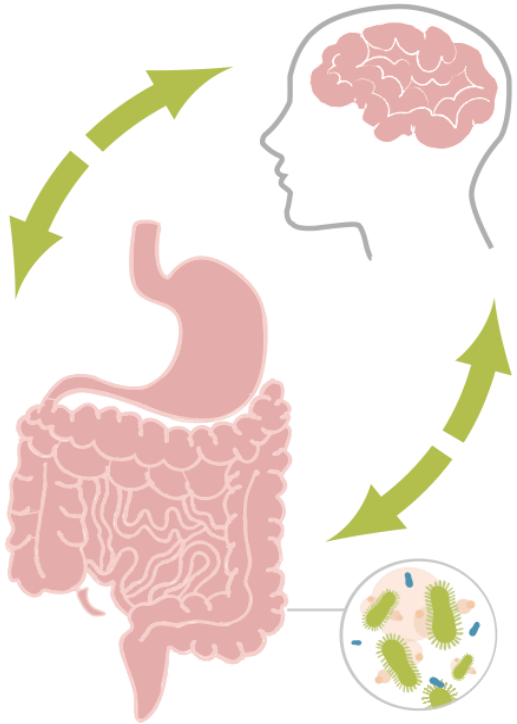
Many factors impact the gut microbiota community:

- Host factors: gender, age, body weight, diet, drug exposure, pathological conditions.
- Adaptability of the gut microbiome
- Physical environmental conditions of the gastrointestinal tract ->



Di Rosa C et al. *Nutrients*. 2023 Mar 28;15(7):1647.

Gut Brain Axis (GBA)



- Gut microbiota regulates neurotransmitters/ brain chemicals such as: serotonin (alters precursors), GABA, dopamine.
- When gut bacteria diversity diminishes, there are systemic consequences, such as GI and psychological distress.

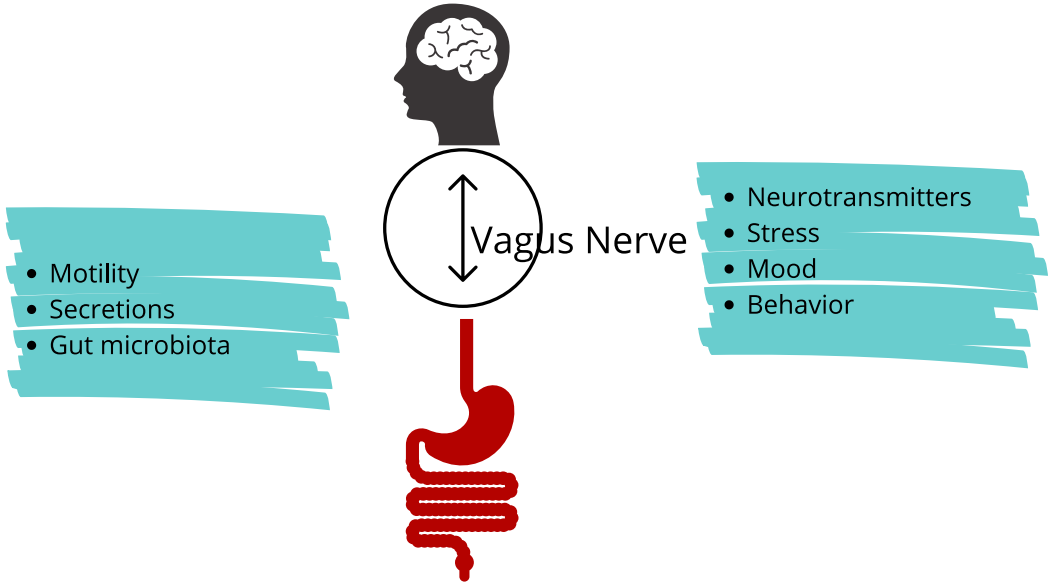
Dinan, TG, Cryan, JF The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol Clin N Am.* 2017;77-89;
Del Toro-Barbosa M et al. *Nutrients*. 2020;12(12):3896. Published 2020 Dec 19; Salminen, S et al. *Nat Rev Gastroenterol Hepatol.* **18,** 649–667 (2021).

The Brain + Gut Connection

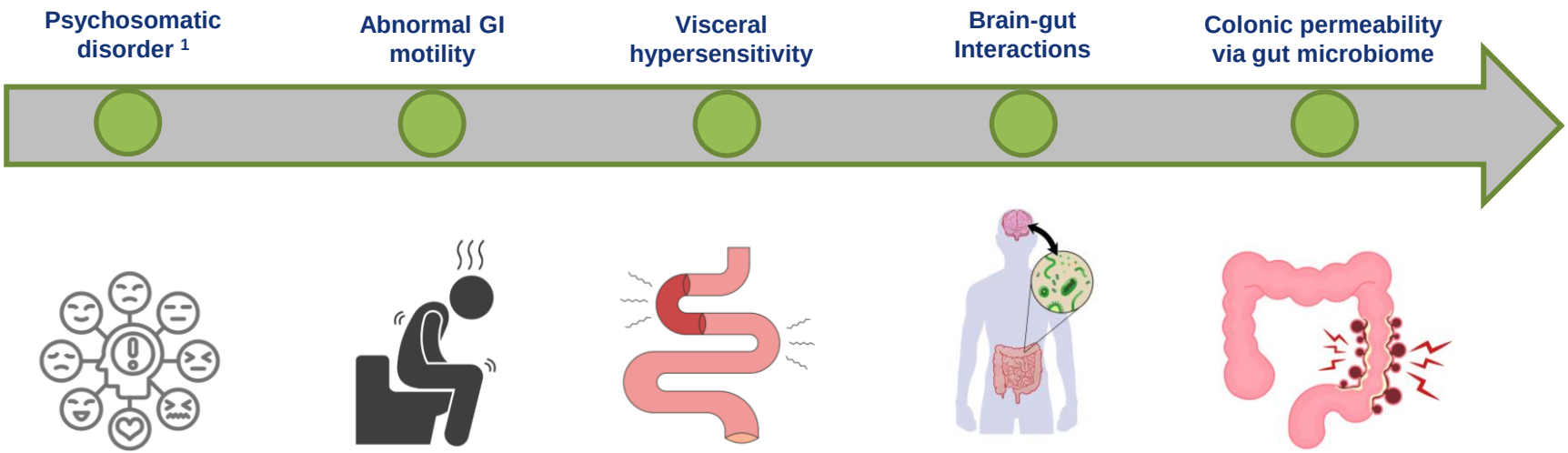
Enteric nervous system + central nervous system highly linked via vagus nerve

Patient example:

Stressful event—induces an emergent trip to the bathroom—or GI symptoms lead to anxiety.

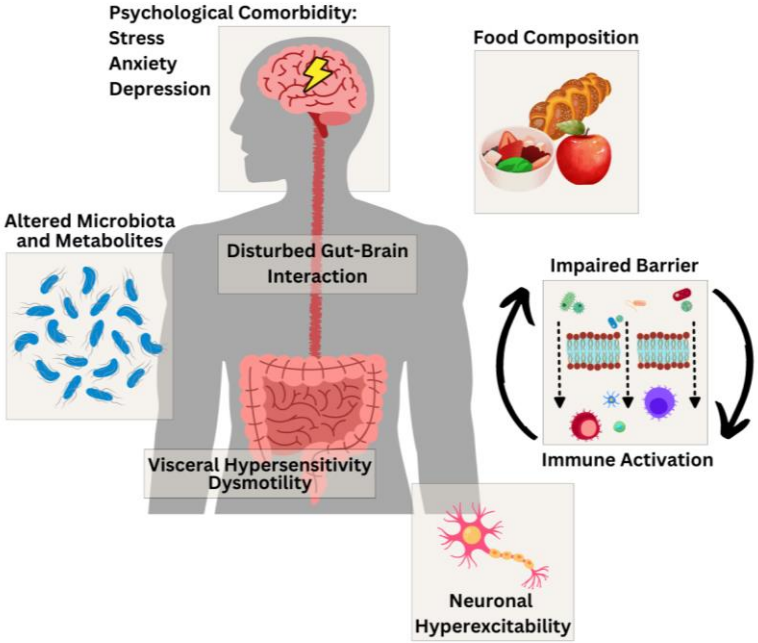


Understanding IBS-a Timeline



1.BROWN PW (1950). "The irritable bowel syndrome". *Rocky Mt Med J*. **47** (5): 343–6.

Complex Interactions That Drive IBS Symptoms

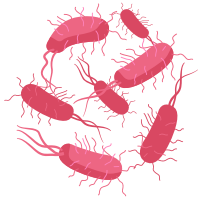


Psychological stress, food components, microbiota and an impaired barrier function may all contribute to immune activation in functional gastrointestinal disorders.

Adapted from Vanuytsel T et al. *Gut*. 2023 Jan 19:gutjnl-2020-320633.

Post-Infectious IBS Model

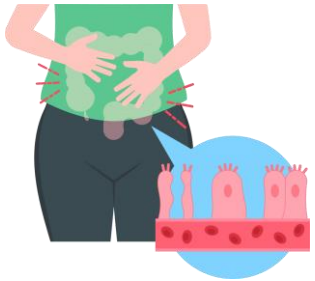
healthy population



food-borne pathogen

acute gastroenteritis

complete recovery



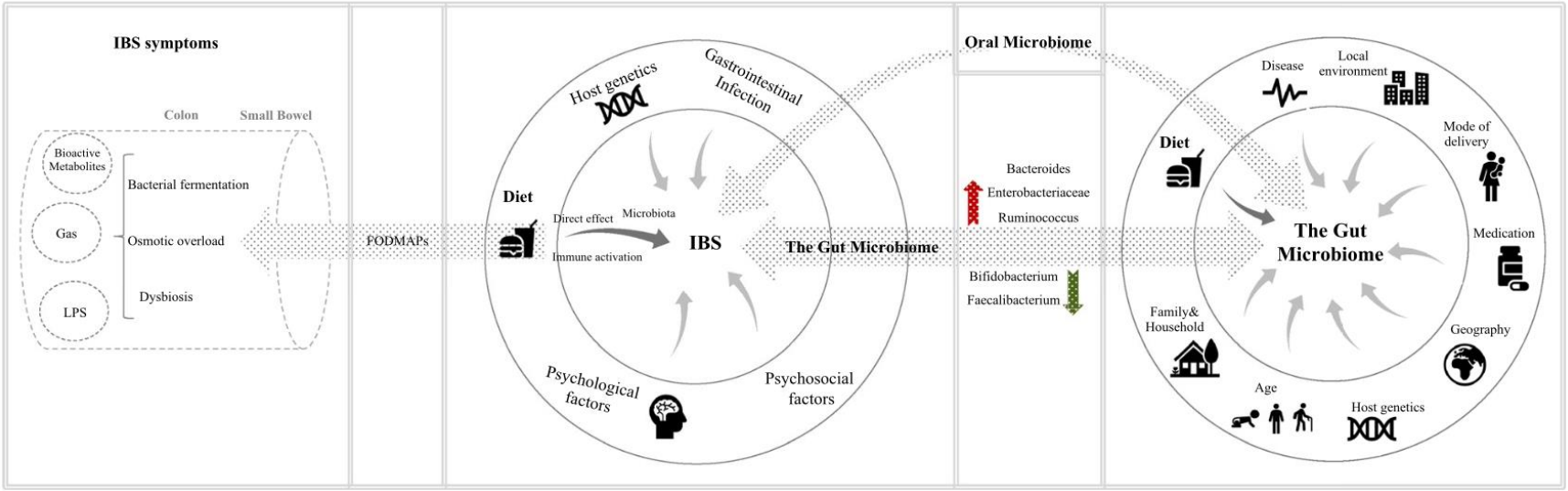
post-infectious IBS

risk factors:

- genetics
- female sex
- severity + duration of illness
- psychological co-morbidities
- younger age

Lupu VV et al. *World J Gastroenterol*. 2023 Jun 7;29(21):3241-3256.

The IBS Microbiome: What Do We Know?

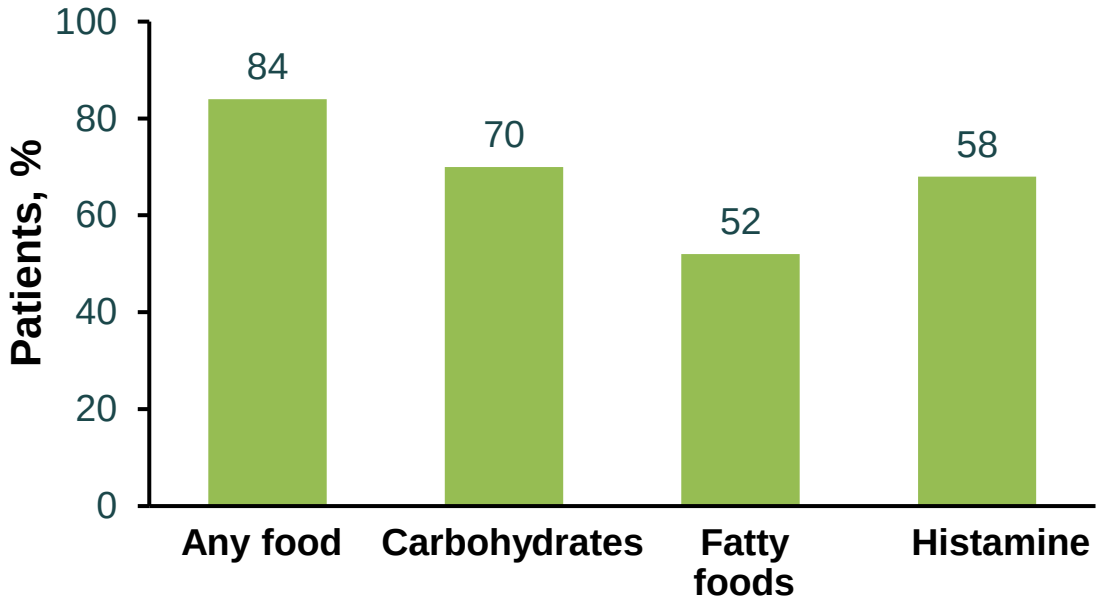


- Diet can change gut microbiota, impact sx. via direct effect of food & immune activation.
- FODMAPs might cause IBS symptoms via microbiome dysbiosis, bacterial fermentation and osmotic overload.
- Oral microbiome may have a potential in diagnosis and patient stratification in IBS.

Ghaffari et al. *Journal of Translational Medicine.* (2022) 20:173.

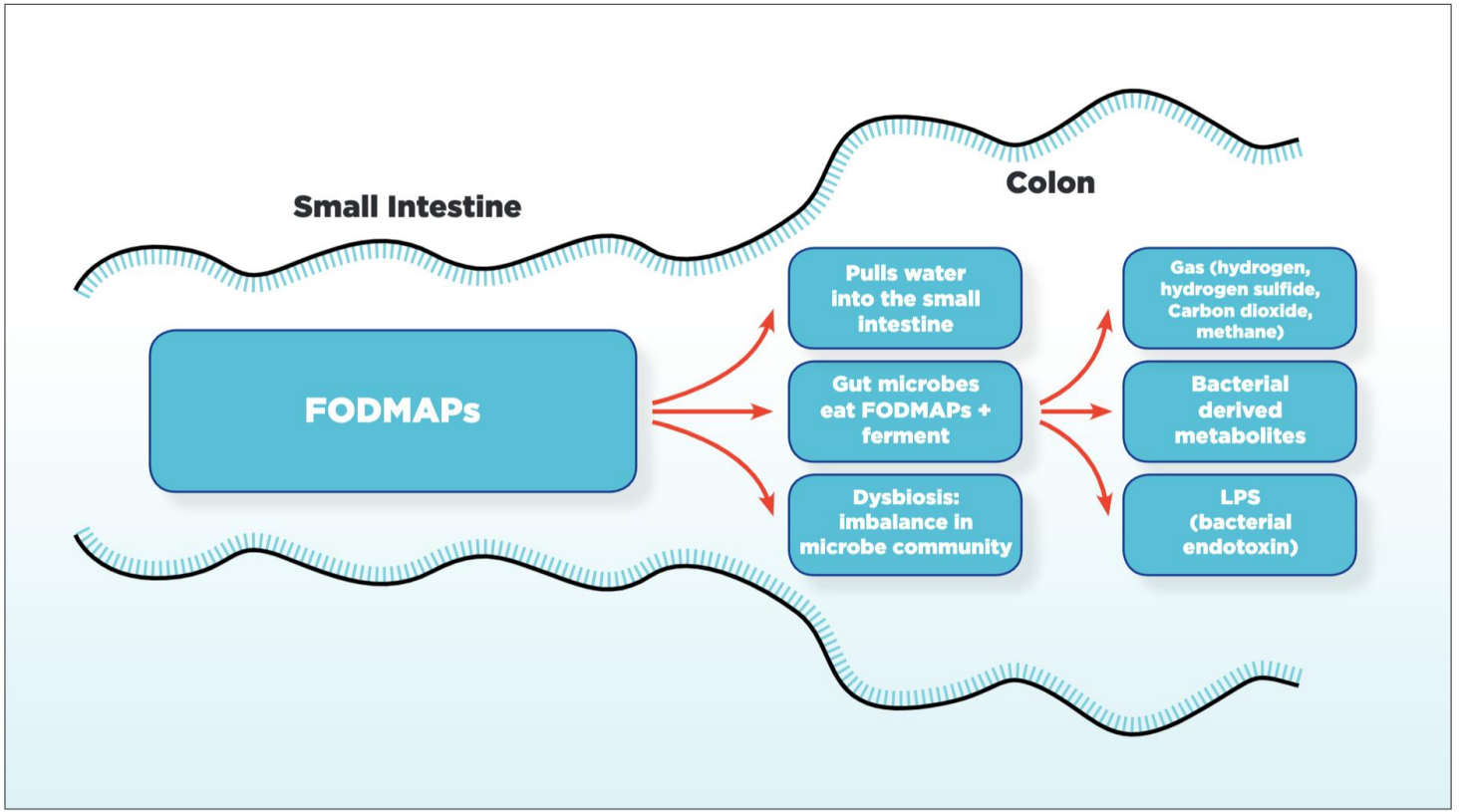
Food and IBS Symptoms

- 197 IBS patients (Rome III)
- Symptom severity correlates with number of food sensitivities

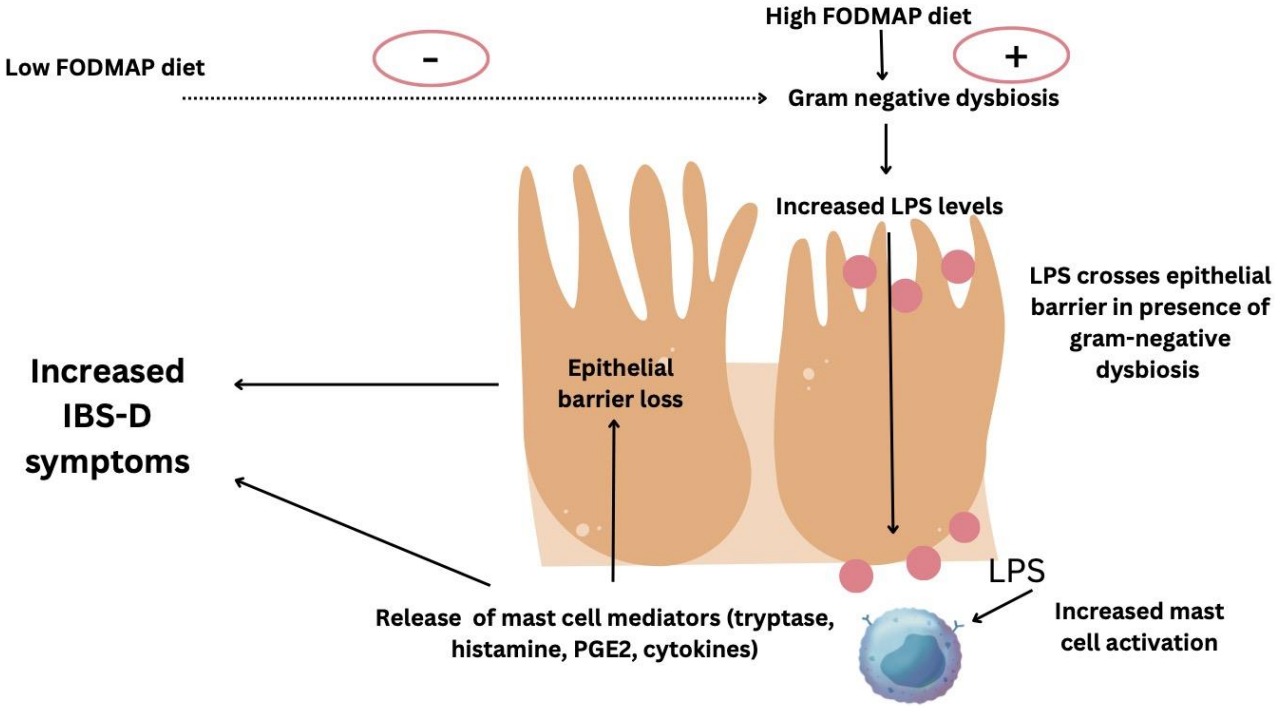


Bohn L et al. *Am J Gastroenterol.* 2013;108:634.

FODMAP and IBS Symptom Generation



FODMAPs, It's Complicated

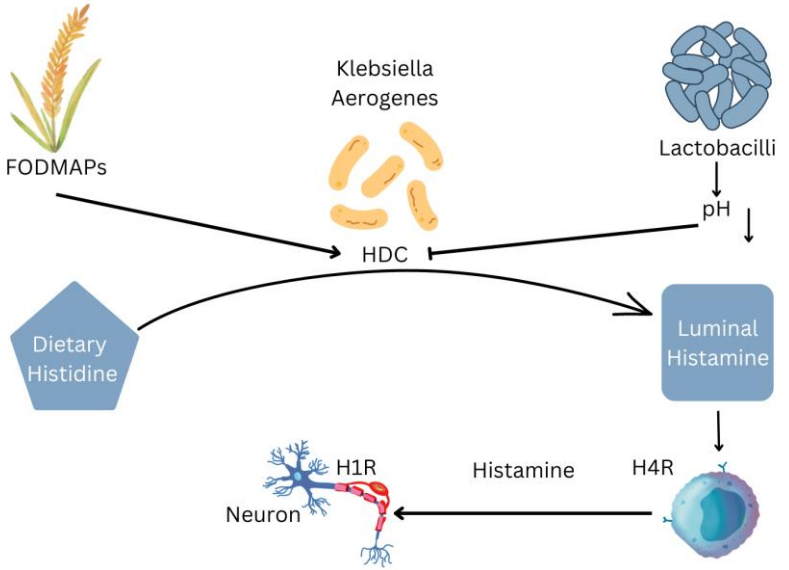


Singh M. et al. *JCI Insight*. 2021;6:e146529; Singh et al. *Am J Gastroenterol.* 2022; 117(6):947-957

Food–Microbiota Interaction in Visceral Hypersensitivity

In rodent model:

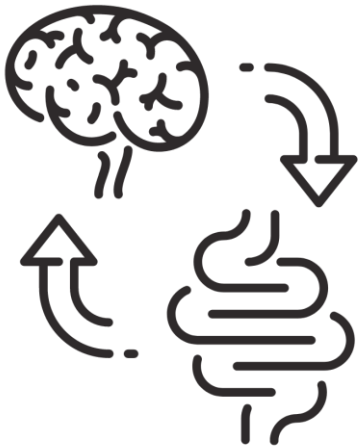
- FODMAPs stimulates high-histamine producing species such as *Klebsiella aerogenes* that are capable in metabol dietary histidine into histamine
- Bacteria-derived histamine can subsequently activate H4R on mast ce contributing to visceral hypersensitivity
- Higher abundance of Lactobacilli may counterbalance this effect—by lowerin luminal pH through production of lactic which reduces histamine production (highly pH dependent).



H1R= histamine 1 receptor
H4R= histamine 4 receptor
HDC=histidine decarboxylase
MC= mast cell
SCFA, short-chain fatty acids

LFD Alters Brain Activity

- RCT-single blinded: LFD n=10 and sham diet n=11 x 6 wks. Assess GI sx and brain responses to emotional tasks in non-constipated IBS (Rome III)
- Results:
  - Post 6-8 weeks post diet, LFD showed >improvement in IBS-SSS, QOL, depression and pain scores
  - LFD significantly reduced brain activities in response to negative stimuli in areas of emotion/cognition processing (No significant changes on sham diet)—suggesting LFD impact on brain-gut interaction.



DDW 2023; Wu PoShan et al. presentation Sa1618L.

Microbiota Subtypes + Response to LFD in IBS

- Metagenomics used to identify taxonomic + functional profiles of stool microbiota from IBS cases + controls (n=56 pairs) on their usual diet.
- Clinical response and microbiota changes were studied in 41 pairs x 4 weeks on a low FODMAP diet.
- IBS cases pre-diet identified 2 distinct microbiota profiles, referred as: **IBS-P (pathogenic-like**) and **IBS-H (health-like)** subtypes.
  - IBS-P microbiomes were enriched in Firmicutes and genes for amino acid and carbohydrate metabolism but depleted in Bacteroidetes species.
  - IBS-H microbiomes were similar to controls.
- On LFD, IBS-H and control -microbiota were unaffected, but the IBS-P signature shifted towards a health-associated microbiome with an increase in Bacteroidetes (p=0.009), a decrease in Firmicutes species (p=0.004) and normalization of primary metabolic genes.
- The clinical response to the low FODMAP diet was greater in IBS-P subjects compared with IBS-H (p=0.02).
- 50% of IBS cases manifested a 'pathogenic' gut microbial signature

Irritable bowel syndrome

OPEN ACCESS

Original research

Two microbiota subtypes identified in irritable bowel syndrome with distinct responses to the low FODMAP diet

Kevin Vervier,[1] Stephen Moss,[2,3] Nitin Kumar,[1] Anne Adoum,[1] Meg Barne,[4] Hilary Browne,[1] Arthur Kaser,[3,5] Christopher J Kiely,[6] B Anne Neville,[1] Nina Powell,[4] Tim Raine,[4,7] Mark D Stares,[1] Ana Zhu,[1] Juan De La Revilla Negro,[2] Trevor D Lawley,[1] Miles Parkes[2,3]

ABSTRACT

Objective Reducing FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) can be clinically beneficial in IBS but the mechanism is incompletely understood. We aimed to detect microbial signatures that might predict response to the low FODMAP diet and assess whether microbiota compositional and functional shifts could provide insights into its mode of action.

Design We used metagenomics to determine high-resolution taxonomic and functional profiles of the stool microbiota from IBS cases and household controls (n=56 pairs) on their usual diet. Clinical response and microbiota changes were studied in 41 pairs after 4 weeks on a low FODMAP diet.

Results Unsupervised analysis of baseline IBS cases pre-diet identified two distinct microbiota profiles, which we refer to as IBS^P (pathogenic-like) and IBS^H (health-like) subtypes. IBS^P microbiomes were enriched in Firmicutes and genes for amino acid and carbohydrate metabolism, but depleted in Bacteroidetes species. IBS^H microbiomes were similar to controls. On the low FODMAP diet, IBS^P and control microbiota were unaffected, but the IBS^P signature shifted towards a health-associated microbiome with an increase in Bacteroidetes (p=0.009), a decrease in Firmicutes species (p=0.004) and normalisation of primary metabolic genes. The clinical response to the low FODMAP diet was greater in IBS^P subjects compared with IBS^H (p=0.02).

Conclusion 50% of IBS cases manifested a 'pathogenic' gut microbial signature. This shifted towards the healthy profile on the low FODMAP diet; and IBS^P cases showed an enhanced clinical responsiveness to the dietary therapy. The effectiveness of FODMAP reduction in IBS^P may result from the alterations in gut microbiota and metabolites produced. Microbiota signatures could be useful as biomarkers to guide IBS treatment; and investigating IBS^P species and metabolic pathways might yield insights regarding IBS pathogenic mechanisms.

SIGNIFICANCE OF THIS STUDY

WHAT IS ALREADY KNOWN ON THIS SUBJECT?

- Patients with IBS often respond to a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet.
- The gut microbiota has been implicated in IBS.
- The microbiota in patients with IBS may change with diet.

WHAT ARE THE NEW FINDINGS?

- We were able to stratify patients with IBS according to their gut microbiota species and metabolic gene signatures.
- We identified a distinct gut microbiota subtype with an enhanced clinical response to a low FODMAP diet compared with other subjects with IBS.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

- The potential development of a microbiota signature as a biomarker to manage IBS cases with a low FODMAP diet recommendation.
- If the bacteria represented in the IBS^P subtype are shown to play a pathogenic role in IBS, perhaps through their metabolic activity, this provides a target for new therapies and an intermediate phenotype by which to assess them.

INTRODUCTION

IBS affects 10%–15% of the population worldwide.[1] It impacts quality of life[2] and incurs significant health economic cost.[3] The pathophysiology of IBS includes changes in visceral nerve sensitivity,[4] intestinal permeability[5] and psychological factors.[6] Several lines of evidence suggest the gut microbiome as a key aetiological factor in IBS. For example, there is a sixfold increased risk of developing IBS following an episode of infective gastroenteritis,[7] probiotics and dietary intervention can reduce the symptoms[8 9] and faecal transplantation has reported efficacy in treating IBS.[10] Recent studies using 16S ribosomal RNA profiles have suggested an altered gut microbiota in IBS subjects compared with controls. Although the findings of earlier studies vary significantly, recent studies more

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-325177).

For numbered affiliations see end of article.

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KV and SM are joint first authors.

TDL and MP are joint senior authors.

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► http://dx.doi.org/10.1136/gutjnl-2021-326284

Check for updates

To cite: Vervier K, Moss S, Kumar N, *et al*. *Gut* 2022;**71**:1821–1830.

Vervier K et al. *Gut.* 2022;**71:**1821-1830.

Changes in Microbiome on LFD-Elimination

Gut microbiota

ORIGINAL ARTICLE

Diets that differ in their FODMAP content alter the colonic luminal microenvironment

Emma P Halmos,[1,2] Claus T Christophersen,[3] Anthony R Bird,[3] Susan J Shepherd,[1] Peter R Gibson,[1,2] Jane G Muir[1,2]

ABSTRACT

Objective A low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) diet reduces symptoms of IBS, but reduction of potential prebiotic and fermentative effects might adversely affect the colonic microenvironment. The effects of a low FODMAP diet with a typical Australian diet on biomarkers of colonic health were compared in a single-blinded, randomised, cross-over trial.

Design Twenty-seven IBS and six healthy subjects were randomly allocated one of two 21-day provided diets, differing only in FODMAP content (mean (95% CI) low 3.05 (1.86 to 4.25) g/day vs Australian 23.7 (16.9 to 30.6) g/day), and then crossed over to the other diet with ≥21-day washout period. Faeces passed over a 5-day run-in on their habitual diet and from day 17 to day 21 of the interventional diets were pooled, and pH, short-chain acid concentrations and bacterial abundance were assessed.

Results Faecal

Significance of this study

What is already known on this subject?

- A diet low in Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols (FODMAPs) reduces GI symptoms in approximately 75% of patients with IBS.
- FODMAPs are fermentable substrates and some have prebiotic effects with putative benefits colonic health.
- A randomised parallel reduction of

not be of asymptomatic populations. should be taken when recommending the low FODMAP diet long-term.

- Liberalising FODMAP restriction to the level of adequate symptom control should be exercised to use the potential health benefits of higher FODMAP intake on the gut microbiota.

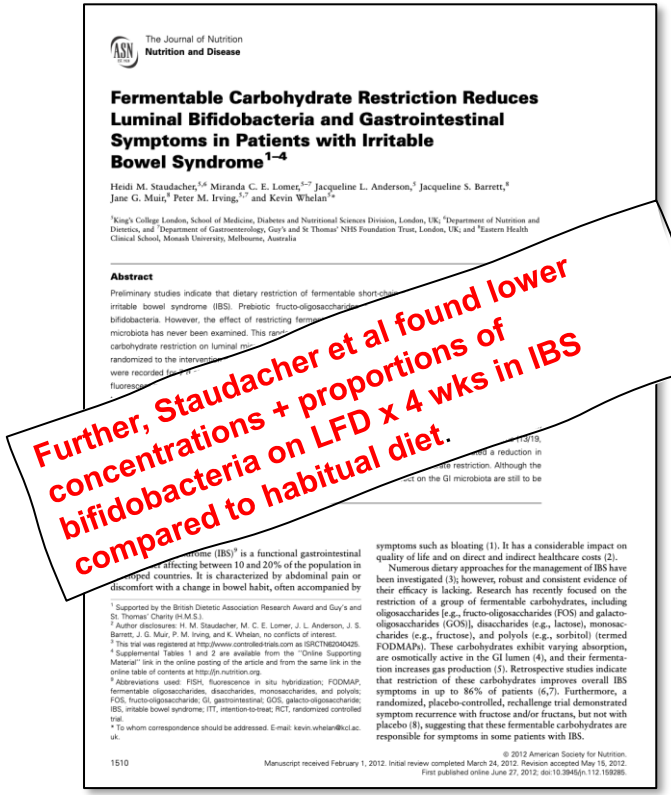
multimodal management include psychological, dietary and pharmacological domains. Dietary therapies are gaining popularity as evidence of efficacy for specific diets have emerged. One strategy is to restrict intake of poorly absorbed short-chain carbohydrates, termed FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols). The evidence-base for efficacy of the low FODMAP diet is building[1–5] with a recent blinded placebo-controlled cross-over study confirming previous studies that about 75% of patients gain clinically significant benefit.[6] The low FODMAP diet is increasingly being applied by health professionals in patients with IBS as first-line therapy.[1 6] Given the high prevalence and chronic nature of IBS, it is possible that many people will restrict intake of FODMAPs over months to years.[2]

To cite: Halmos EP, Christophersen CT, Bird AR, *et al*. *Gut* 2015;**64**:93–100.

BMJ

Halmos EP, *et al*. *Gut* 2015;**64**:93–100. doi:10.1136/gutjnl-2014-307264 93

- **LFD associated with higher fecal pH, similar SCFA, greater microbial diversity, reduced bacterial abundance, compared to "typical Australian diet."**
- **A. muciniphila, Clostridium cluster XIVa >abundance with Australian diet.**



The Journal of Nutrition
Nutrition and Disease

Fermentable Carbohydrate Restriction Reduces Luminal Bifidobacteria and Gastrointestinal Symptoms in Patients with Irritable Bowel Syndrome[1–4]

Heidi M. Staudacher,[5,6] Miranda C. E. Lomer,[5–7] Jacqueline L. Anderson,[5] Jacqueline S. Barrett,[8] Jane G. Muir,[8] Peter M. Irving,[5,7] and Kevin Whelan[5]*

[5]King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, UK; [6]Department of Nutrition and Dietetics, and [7]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK; and [8]Eastern Health Clinical School, Monash University, Melbourne, Australia

Abstract

Preliminary studies indicate that dietary restriction of fermentable short-chain irritable bowel syndrome (IBS). Prebiotic fructo-oligosaccharides bifidobacteria. However, the effect of restricting fermentable microbiota has never been examined. This randomized carbohydrate restriction on luminal microbiota were recorded for 3 wk fluorescence in situ hybridization. Fermentable Carbohydrate Restriction Reduces Luminal Bifidobacteria and Gastrointestinal Symptoms in Patients with Irritable Bowel Syndrome. J Nutr 142: 1510–1518, 2012.

a reduction in restriction. Although the on the GI microbiota are still to be

- **Further, Staudacher et al found lower concentrations + proportions of bifidobacteria on LFD x 4 wks in IBS compared to habitual diet.**

[1] Supported by the British Dietetic Association Research Award and Guy's and St. Thomas' Charity (H.M.S.).
[2] Author disclosures: H. M. Staudacher, M. C. E. Lomer, J. L. Anderson, J. S. Barrett, J. G. Muir, P. M. Irving, and K. Whelan, no conflicts of interest.
[3] This trial was registered at http://www.controlled-trials.com as ISRCTN62040425.
[4] Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[5] Abbreviations used: FISH, fluorescence in situ hybridization; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructo-oligosaccharide; GI, gastrointestinal; GOS, galacto-oligosaccharide; IBS, irritable bowel syndrome; ITT, intention-to-treat; RCT, randomized controlled trial.
* To whom correspondence should be addressed. E-mail: kevin.whelan@kcl.ac.uk.

(IBS)[9] is a functional gastrointestinal affecting between 10 and 20% of the population in developed countries. It is characterized by abdominal pain or discomfort with a change in bowel habit, often accompanied by symptoms such as bloating (1). It has a considerable impact on quality of life and on direct and indirect healthcare costs (2).

Numerous dietary approaches for the management of IBS have been investigated (3); however, robust and consistent evidence of their efficacy is lacking. Research has recently focused on the restriction of a group of fermentable carbohydrates, including oligosaccharides [e.g., fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS)], disaccharides (e.g., lactose), monosaccharides (e.g., fructose), and polyols (e.g., sorbitol) (termed FODMAPs). These carbohydrates exhibit varying absorption, are osmotically active in the GI lumen (4), and their fermentation increases gas production (5). Retrospective studies indicate that restriction of these carbohydrates improves overall IBS symptoms in up to 86% of patients (6,7). Furthermore, a randomized, placebo-controlled, rechallenge trial demonstrated symptom recurrence with fructose and/or fructans, but not with placebo (8), suggesting that these fermentable carbohydrates are responsible for symptoms in some patients with IBS.

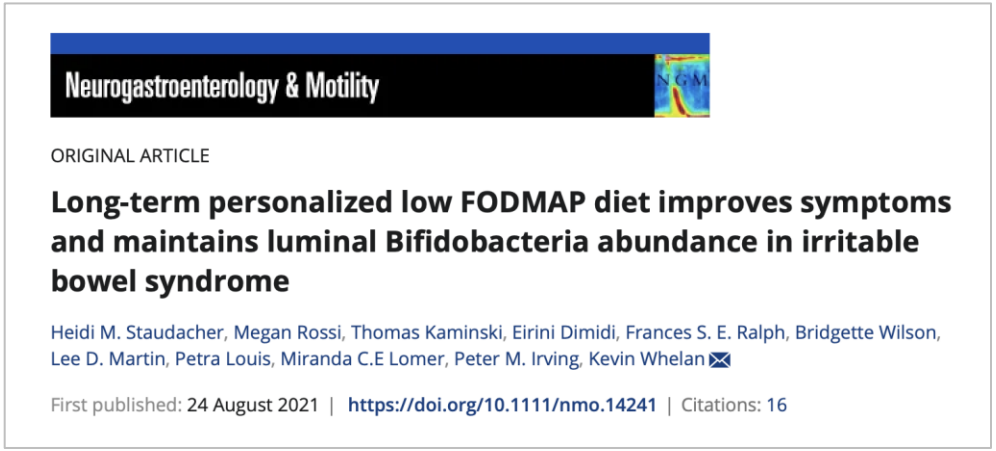
1510

Manuscript received February 1, 2012. Initial review completed March 24, 2012. Revision accepted May 15, 2012. First published online June 27, 2012; doi:10.3945/jn.112.159285.

© 2012 American Society for Nutrition.

Halmos, Emma P et al. *Gut.* vol. 64,1 (2015): 93-100; Staudacher HM et al. *J Nutr*. 2012;142 (8):1510-1518.

Long-Term, Personalized Phase LFD



Neurogastroenterology & Motility

ORIGINAL ARTICLE

Long-term personalized low FODMAP diet improves symptoms and maintains luminal Bifidobacteria abundance in irritable bowel syndrome

Heidi M. Staudacher, Megan Rossi, Thomas Kaminski, Eirini Dimidi, Frances S. E. Ralph, Bridgette Wilson, Lee D. Martin, Petra Louis, Miranda C.E Lomer, Peter M. Irving, Kevin Whelan

First published: 24 August 2021 | https://doi.org/10.1111/nmo.14241 | Citations: 16

- 2/3 patients reported adequate relief of symptoms x 12 months of personalized LFD.
- Personalized LFD did not result in differences from baseline in Bifidobacteria.

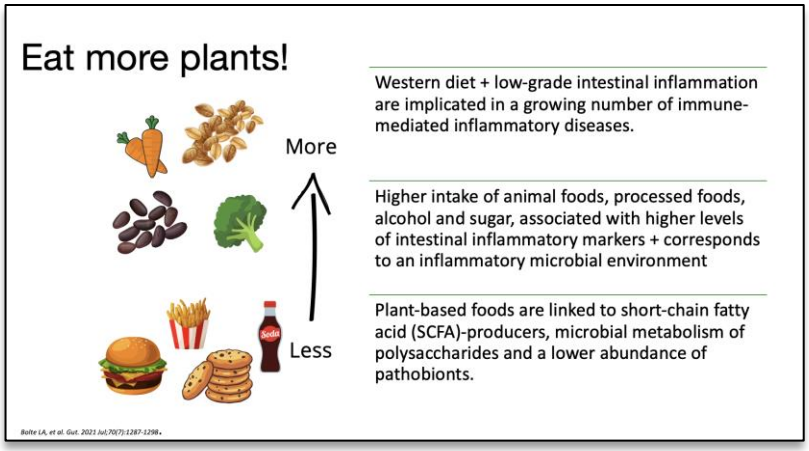
- N=18 on LFD educated on all 3 phase were included in the study.
- Adequate relief of symptoms in (67%) following long-term personalized low FODMAP diet ($p = 0.039$).
- Bifidobacteria abundance was not different between baseline (median 9.29 log10 rRNA genes/g, IQR 1.45) and long term (9.20 log10 rRNA genes/g, 1.41; $p = 0.766$, $q = 0.906$)
  - However, there were lower concentrations of total SCFA, acetate, propionate, and butyrate

Diet for Gut Health—and IBS Symptom Management

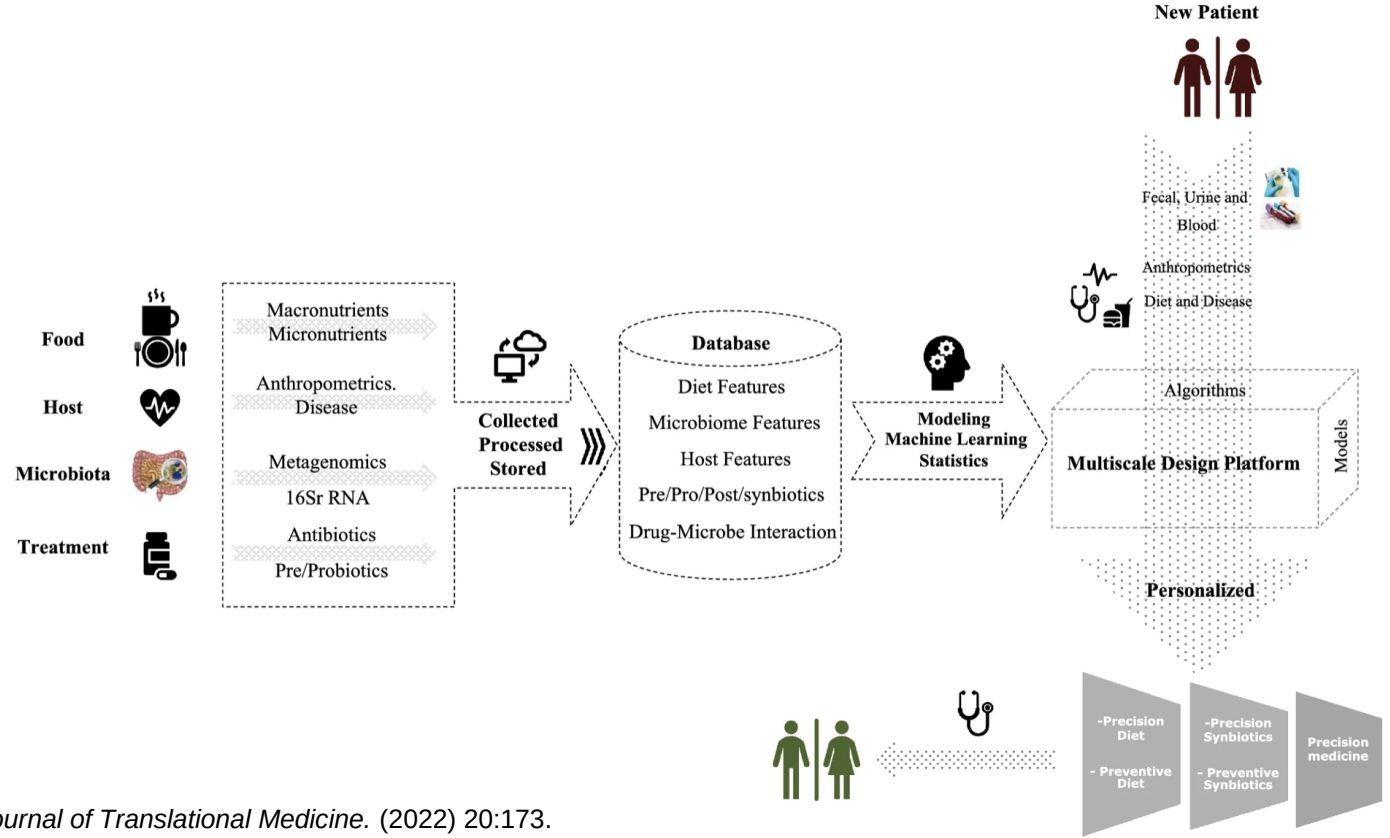
Med and low FODMAP combined?

Food	Beneficial component	Proposed action
Extra-virgin olive oil	Polyphenols	Prebiotic effect, anti-inflammation
Walnuts	Omega-3 fats	Anti-inflammation, shown to increase butyric acid-producing species in healthy individuals.
Fish	Omega-3 fats	Western-type diets with elevate omega 6 vs 3 ratio reaching 20–30:1. *Omega*-3 PUFAs and their bioactive metabolites compete with *omega*-6 PUFAs to promote the resolution of inflammation
Oats	B-glucan	soluble fibers found in abundance in oat grain (free of FODMAPs), prebiotic
Walnuts	Omega-3s	Anti-inflammation, prebiotic
Orange, clementine	Quercetin	Prebiotic, ant-inflammation
Tomatoes	Quercetin	Prebiotic, anti-inflammation
Oregano, rosemary, thyme	Phenolic compounds	Prebiotics
Small amounts chickpeas + lentils (canned)	GOS	Prebiotic effect

Growing data diet in relationship to gut health and beyond



The Future… Precision Nutrition for IBS



Ghaffari et al. *Journal of Translational Medicine.* (2022) 20:173.

Take Away Points

IBS: involves intersecting relationships btw gut microbiome, brain, and diet

- As a complex heterogenous disorder—altered gut microbiome may be more central feature in some compared w/ others
- LFD most evidence-based diet—with a noted complex gut microbial intersection with GI symptoms
- While LFD *elimination* phase alters gut microbiome (e.g. reduced bifidobacteria)—we don't know relevance of this change. Further, expansion to personalization phase appears to have less impact on gut microbiome.
- Like any therapeutic in IBS –tailored recommendations work best, diet is not one size fits all. Precision therapeutics on horizon.