Diet & the Microbiome

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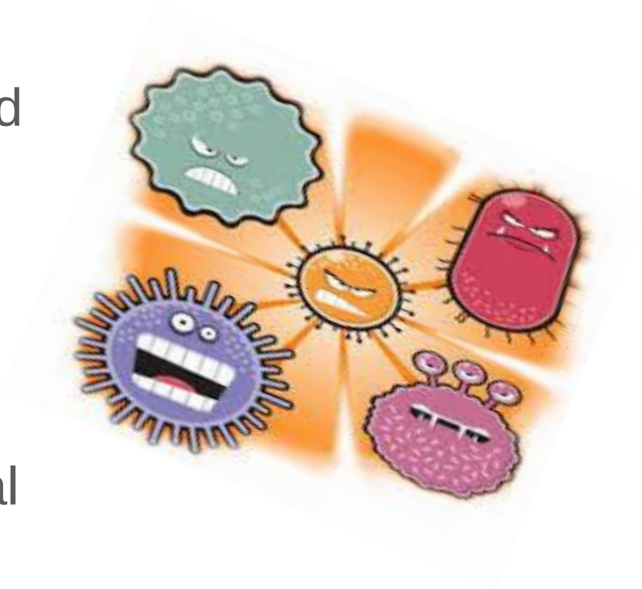
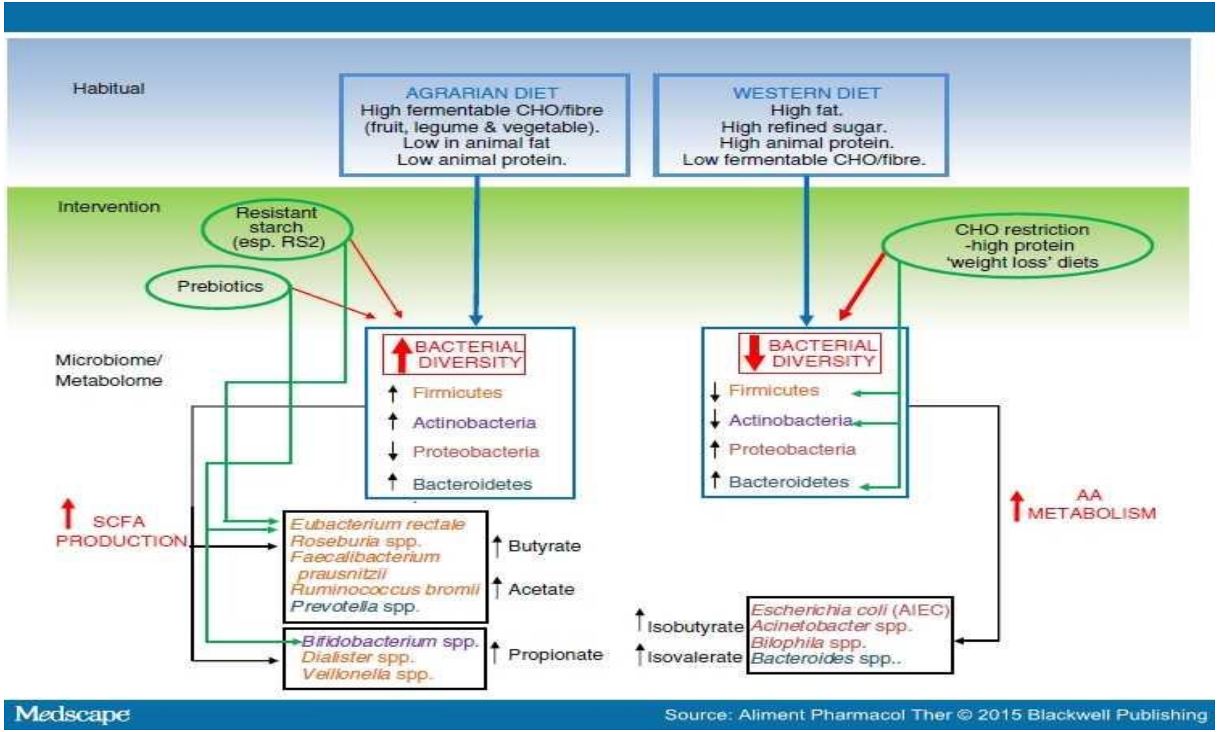
Diet & Gut Microbiome

- Gut ecosystem is complex & contingent upon multiple factors----Diet being ONE of them.
- Plant based fiber (& undigested protein, fat and carbs) influences composition and metabolic activity of microbiome (SCFA, metabolites)
- Agrarian diets high in fruit/legume fiber associated with increase in microbial diversity
- Western diet associated w/ decrease beneficial Firmucutes & increase Proteobacteria (including enteric pathogens)



Agrarian vs. Western Diet



Diet only part of picture

- Wu et al. Eval of gut microbiota comp, plasma metabolome btw vegans and omnivores in urban Western environment.
  - Changes in bacterial community were only modest; However, the diet differences correlated with large variations in metabolome.
- Production of gut derived metabolites from diet is limited by the composition of the gut microbiota.
- Diet plays a role in microbiota but may be constrained by other factors; Gut microbiota likely differs in globally distinct populations.

Wu, GD, et al Gut 2016;65:63-72.

Global Variations

- Japanese frequently noted to have microbiota capable of degrading seaweed but absent in N. Americans

- 30% Western population are equol producers vs. 60% Asians (equol:a soy-based gut microbiota metabolite)

Food & Microbial Interactions

Colonic microbiota is largely driven by efficient breakdown of complex indigestible carbs while the sm. intestine is shaped by capacity for the fast import and conversion of small carbs.

Machesi, JR *Gut*. 2016;65(2):330-339

Food Is Complicated & Has Changed Rapidly

- Westernized diet: sugar, additives, low in fiber, high in fat, animal protein
- Fats: man-made fats: partially hydrogenated fats; fattier meats due to feeding and farming practices
- Fiber intake: reduced
- Food additives: emulsifiers (carboxymethylcellulose Polysorbate 80), HFCS, artificial sweeteners
- Many chronic Western diseases have inflammatory component; Bacterial metabolites likely play a role. e.g. LPS bacterial endotoxin linked w/ systemic inflammation.

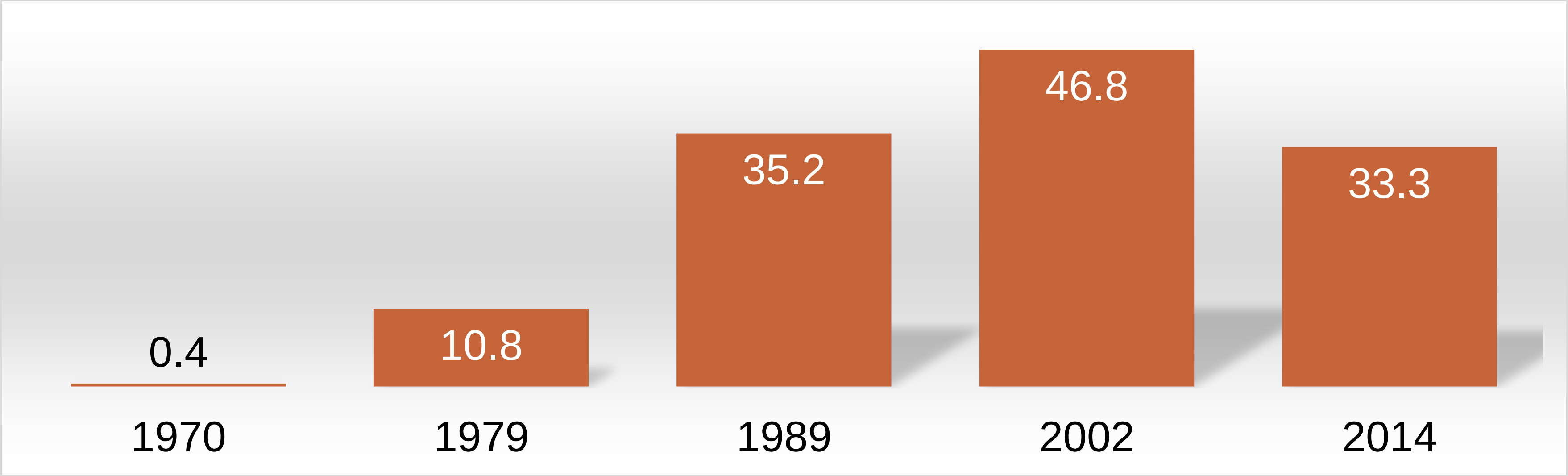
Djuric, Z *Transl Res*. 2016

HFCS Intake in US

- USDA food consumption tables (1967 to 2000) showed the consumption of HFCS increased > 1000% between 1970 and 1990, far exceeding the changes in intake of any other food or food group.
- The consumption of total fructose increased by nearly 30% between 1970 and 2000, largely due to the increased use of HFCS.
- 1 in 3 malabsorb fructose: ? Effect of large dose on gut microbiome.

Bray, G Am J Clin Nutrition 2004

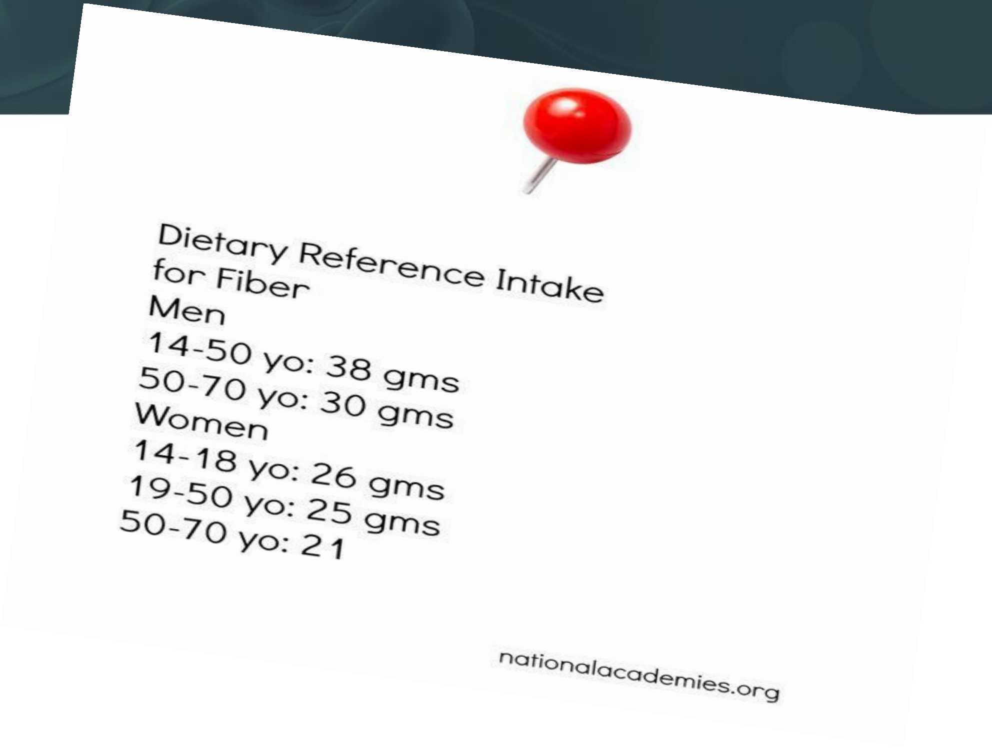
U.S. Per Capita g HFCS Consumed/Daily



Excerpted from US Department of Agriculture, Economic Research Service. Sugars and Sweeteners Yearbook 2015. Table 52—High Fructose Corn Syrup: Estimated number of per capital calories consumed daily, by calendar year. http://www.ers.usda.gov/data-products/sugar-and-sweeteners-yearbook-tables.aspx. Accessed 10/18/2105.

Fiber

Usual intake of dietary fiber in the United States is only 15 g/day.


Dietary Reference Intake for Fiber

Men

14-50 yo: 38 gms

50-70 yo: 30 gms

Women

14-18 yo: 26 gms

19-50 yo: 25 gms

50-70 yo: 21

nationalacademies.org

Slavin JL. Position of the American Dietetic Association: health implica- tions of dietary fiber. *J Am Diet Assoc* 2008;108:1716–31; nationalacademies.org

Fiber: Umbrella Term

- **Fiber subtypes** classified dependent on chain length, solubility, fermentability, viscosity, gel forming
- Plant based foods often contain a mix of fiber subtypes
- Fiber subtypes provide range of selective growth of gut microbes. A fiber that gels limits fermentation as the 3-dimentional structure of the cross-linked gel limits access to the bacteria.

McRorie, J. and Fahey, G. (2015) Chapter 8: Fiber Supplements and Clinically Meaningful Health Benefits: Identifying the Physiochemical Characteristics of Fiber that Drive Specific Physiologic Effects, in the CRC Handbook on Dietary Supplements in Health Promotion, CRC Press.

Fiber: Short Chain

- **Soluble highly fermentable oligosaccharides**; DP 2-10
- **Sources:** FOS, GOS; (FODMAP fibers) Legumes; nuts and seeds, wheat, rye, onions, garlic, artichoke
- **Laxation:** weak laxative effect.
- **Transit time:** does not hasten transit time.
- **Balance of bacteria:** selective growth of certain microbiota, e.g., Bifidobactia
- **SCFA:** very rapidly fermented in terminal ileum and proximal colon
- **Gas production:** high

Eswaran, S. *Am J Gastroenterol*. 2013 May;108(5):718-27

Fiber: Long Chain

- **Soluble highly fermentable fiber**
- **Sources:** RS, pectin, guar gum, wheat dextrin and inulin: DP>10, unripe banana, millet, oats, cooked and cooled pasta, potato & rice, legumes
- **Laxation:** Mild laxative effect
- **Transit time:** Does not hasten gut transit. Can slow absorption from the small intestine.
- **Balance of bacteria:** Increases overall bacterial species but not selective for bifidobacteria
- **SCFA:** Rapidly fermented in proximal colon to produce SCFA. RS is excellent substrate for the production of the *SCFA butyrate*.
- **Gas production:** moderate

Eswaran, S. *Am J Gastroenterol*. 2013 May;108(5):718-27

Fiber Long Chain

- **Intermediate soluble fermentable** fiber
- **Source:** oats
- **Laxation:** good laxative effect
- **Transit time:** does hasten transit time.
- **Balance of bacteria:** increases overall bacterial species but little evidence for selective growth
- **SCFA:** moderately fermented along length of colon to produce SCFA.
- **Gas production:** moderate

Eswaran, S. *Am J Gastroenterol*. 2013 May;108(5):718-27

Fiber Long Chain/Insoluble

- **Insoluble slowly fermentable fiber**
- **Sources:** Some vegetables and fruit; Wheat bran, Wholegrain cereal, rye, whole-meal pasta, brown rice, quinoa, flax seed.
- **Laxation:** good laxative effect
- **Transit time:** does hasten transit time
- **SCFA:** Balance of bacteria: increases overall bacterial species but little evidence for selective growth SCFA; slowly fermented to produce SCFA along the length of the colon.
- **Gas production:** moderate-high

Eswaran, S. *Am J Gastroenterol*. 2013 May;108(5):718-27

Fiber-Insoluble; Non-Fermenting

- **Insoluble, non-fermentable ‘fiber’**
  (e.g. cellulose and methylcellulose)
- **Sources:** Some high fiber grains and cereals; skins of fruit and vegetables
- **Laxation:** good laxative effect
- **Transit time:** does hasten transit time
- **SCFA:** poorly fermented; no evidence for selective growth
- **Gas production:** low

Eswaran, S. *Am J Gastroenterol*. 2013 May;108(5):718-27

RS: Key Points

- Soluble & highly fermentable
- Intake varies widely globally; 30-40 g in developing countries and 3-8 grams in developed
- Shown to increase butyrate: but response individual
- May offer protective effect in presence of high protein diet
- RS: 4 types (ripe banana, cooked and cooled potato & rice, oats etc)

Aryana, K F1000Research (2015), 4, 139;Simpson, H Aliment Pharmacol Ther. 2015;42(2):158-179.

Resistant Starch

- A number of *in vivo* animal studies have demonstrated that RS has significant prebiotic effect. *J Nutr* 2012; 142: 832–40; J Animal Sci 1997, J Appl Microbiol 2002;93:390-7
- RS-rich diets have been shown to have a protective effect, attributed to observed increased SCFA concentrations, significantly lowering the level of colonocyte DNA damage when compared to animals fed Western style (moderate fat and protein, low RS)

RS

- 20 healthy young adults- dietary supplementation with resistant starch (unmodified potato starch-resistant starch (RS) type 2).
- RS supplementation increased fecal butyrate concentrations in this cohort but responses varied widely between individuals. Higher butyrate in those w/ abundance of the butyrogenic microbes
- Dynamics of both starch-degrading and butyrogenic bacteria may explain much of observed variation

Venkataraman, A *Microbiome*. 2016 Jun 29;4(1):33

Protein

- In GI tract, dietary and endogenous protein are hydrolyzed by host and bacteria-derived proteases and peptidases
- Not all AA absorbed in small intestine. About 6–18 g protein reaches the large intestine daily, the majority from the diet and a small proportion from endogenous origins.
- Higher rate of bacterial protein fermentation has been r/t high pH & low carbohydrate availability in colon; As carb becomes depleted in colon—protein or amino acids inline for fermentation.

Cumming, JH Appl Bacteriol 1991; 70: 443–59.
Neis, EPJG, Nutrients 2015,7, 2930-2946; CK Yao Aliment Pharmacol Ther. 2016

Protein

- Protein metabolic end products linked w/mucosal inflammation & may modulate the enteric nervous system & intestinal motility (ammonia, N-nitroso compounds, amines and phenolic and indolic compounds, branched chain fatty acids)
- Microbial metabolism of AA can give rise to biogenic amines: e.g. histamine
- Histamine has potent immuno-regulatory effects

Windey, K, De Preter V, Verbeke, K Relevance of protein fermentation to gut health. Mol Nutr Food Res 2012;56:184-96.

High Protein, Mod Carb Diet

- 17 obese men wt. maintenance diet x 7 days followed by high protein/ mod carb diet (HPMC): 139 g protein/181 g carb & high protein/ low carb (HPLC): 137 g protein/22 g carb: crossover study
- Fecal samples analyzed for phenolic metabolites, SCFA and nitrogenous compounds
- Compared to maintenance diet: both high protein diets resulted in branch chained fatty acids, phenylacetic acid & N-nitroso compounds; the HPLC also reduced butyrate in fecal samples.
- ? Impact long-term for colonic health

Russell, WR *Am J Clin Nutr*;2011;93:1062-72

Protein/RS Diet

- Rats fed cellulose, potato fiber or potato RS w/ diet of 12% casein for 2 wks; then similar diet w/ 25% cooked beef x 6 wks.
- After 8 wks-cecal-colonic microbial composition, fermentation end products, colon structure & colonocyte DNA damage analyzed

Fiber & RS on Biomarkers of Colonic Health W/ Protein Rich Diet

- Colonic Bifidobacterium & Lactobaccillus were higher in potato fiber and potato resistant starch diet vs. cellulose.
- Phenol and p-cresol concentrations were lower in cecum & colon of rats fed potato fiber
- Increase in goblet cells per crypt; longer crypt in colon of rats fed potato fiber and potato RS diet.
- Showing benefit of adding fermentable fiber.

Paturi, GJ Food Sci 2012;77(10):H216-23.

Fat

- Mice: High fat diet induces inflammation via increasing LPS-plasma and fecal endotoxin levels and resulting in dysregulation of the gut microbiota: increasing Firmucutes to Bacteriodes ratio.
- HFD reduced expression of tight junction associated proteins claudin-1 & occludin in the colon >intestinal permeability

Kyung, AK, et al PLoS One 2012;7(10)

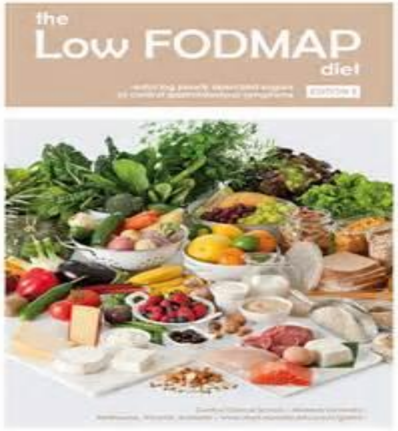
Fat

- HFD associated with GI motility disorders
- HFD-fed mice reduced numbers of enteric neurons w/ delay in transit; HFD: higher firmicutes and E. coli and lower bacteroidetes compared to regular diet fed mice.
- Supplemented with oligofructose protected against neuron loss and improved intestinal transit time as well as reduction in endotoxin.

Anitha, M et al *Cell Mol Gastroenterol Hepatol* 2016;2(3):328-339

Low FODMAP Diet

- A nutritional approach to manage symptoms of IBS.
- Diet involves reduction of commonly malabsorbed & rapidly fermentable short chain carbohydrates
- 3 phase diet approach: eliminate, challenge, integrate to personal tolerance
- LFD: manages symptoms in ~70 % of those w/ IBS.



Halmos, EP *Gastroenterology*. 2014 Jan;146(1):67-75

FODMAPs & IBS

Please check question mark. May be missing character

IBS symptoms are triggered ***due to response of the enteric nervous system*** *to the luminal distention, likely due to:*

- ✓ Nature of gut flora
- ✓ Dysmotility impacting fluid and gas clearance
- ✓ Visceral hypersensitivity
- ✓ ? Mast cell degranulation
- ✓ Bacterial metabolites as by-product of fermentation of FODMAPs may likely play a role.

FODMAP Microbiome Biomarkers & Response to the Low-FODMAP Diet

- 33 children w/ IBS
- Less abdominal pain occurred during the low FODMAP diet vs. typical US childhood diet
- Responders enriched at baseline in taxa with known *greater saccharolytic metabolic capacity*
  - e.g. Bacteroides, Ruminococcaceae, Faecalibacterium prausnitzii
- Responders enriched at baseline for *3 Kyoto Encyclopedia of Genes and Genomes orthologues*
  - two relate to carbohydrate metabolism

Chumpitazi et al. *Aliment Pharmacol Ther* 2015; 42: 418–427

Low FODMAP and the Metabolome

- Single bind study: 40 Rome III criteria: 20 low FODMAP vs. 20 High FODMAP x 3 wks.
- Metabolome evaluated : lactulose breath testing and metabolic profiling
- 37 completed study: lactulose breath test showed some decrease in H_2 production on LFD; **Metabolite profiling showed eightfold decrease in histamine in LFD**, hydroxybenzoic acid and azeliac acid (has anti-inflammatory properties) increased on LFD; LFD increased Actinobacteria richness & diversity

Gut 2016;0:1-11McIntosh, K et al

LFD & Metabolome

Do FODMAPs modulate visceral sensitivity due to changes in gut microbiome and gut permeability?

- N=12 ; 6 IBS and 6 HC
- Fecal samples obtained before & after LFD
- Fecal LPS was 2 fold higher in IBS-D patients compared to HC
- 4 week treatment of LFD resulted in significant improvement of IBS symptoms and normalized fecal LPS to level similar of HC

DDW 2016 Zhou, SY et al; U. Michigan

Visceral Hypersensitivity

- In separate study, fecal supernatant from IBS-D patients and HC were administered intra-colonically to naïve rats & visceral hypersensitivity to colonic distention was evaluated 3 hours later.
- Behavioral pain studies showed fecal supernatant from IBS-D patients given in colon caused a 3-4 increase in visceral motor response to colonic distention while no visceral motor response occurred in rats receiving fecal supernatant from HC.

DDW 2016 Zhou, SY et al; U. Michigan

Gut Microbiome Changes in 4 Weeks

- A randomized controlled trial demonstrated a reduction in concentration and proportion of luminal bifidobacteria after 4 wk of FODMAP restriction.

- Finding: Low FODMAP was effective in managing IBS symptoms, but the implications of its effect on the GI microbiota are still to be determined.

Staudacher et al *J Nutr*. 2012

Low FODMAPs and Microbiome

- 27 IBS & 6 healthy subjects were randomly put on 21-day diets, differing only in FODMAP content: low ~3.05 g/day vs typical Australian diet ~23.7 g/day.
- Then crossed over to the other diet with ≥21-day washout period. Feces 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 fatty acid concentrations and bacterial abundance and diversity were assessed.
- Fecal indices were similar in IBS and healthy subjects during habitual diets.

Halmos, E et al. *Gut*. 2015

Gut Microbiome Change

- The low FODMAP diet was associated with higher fecal pH (7.37 (7.23 to 7.51) vs 7.16 (7.02 to 7.30); p=0.001), similar short-chain fatty acid concentrations, greater microbial diversity and reduced total bacterial compared with the Australian diet.
- The typical Australian diet increased relative abundance for butyrate-producing Clostridium cluster XIVa and mucus-associated Akkermansia muciniphila, and **reduced unfavorable mucus consuming** Ruminococcus torques.
- Long term implication of these changes are unknown!

Gut. 2014 Jul 12.

IBD, Low FODMAP & Gut Microbiome

- Impact of low FODMAP compared with typical Australian diet x 21 days on gut microbiome, calprotectin levels & symptoms.
- N=8; Australian diet resulted in > butyrate producing Clostridium cluster XIVa and mucus associated Akkermansia mucinophila and lower for Ruminoccus torques compared to low FODMAP diet.
- The diets had no effects on calprotectin, but symptoms doubled in severity with the Australian diet.

Halmos, E *Clin Transl Gastroenterol* 2016

Future

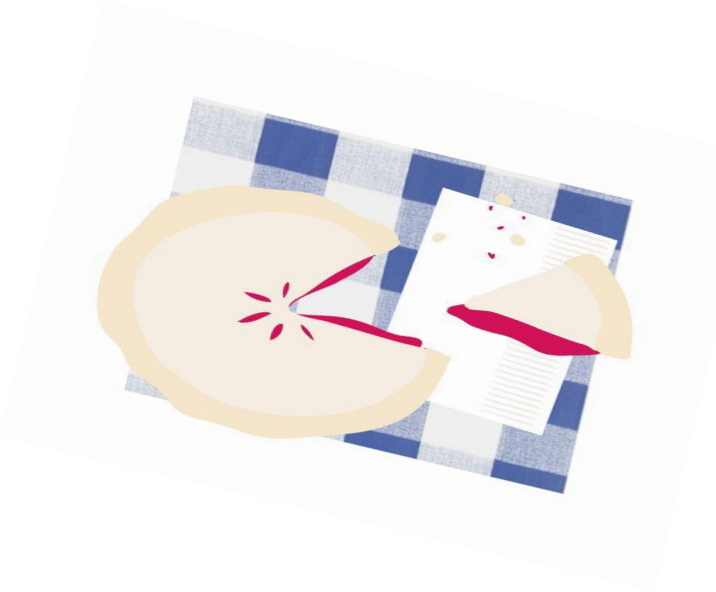
- Functional foods on the horizon (conventional foods that contain bioactive components)
  - Ex: Synthesized food ingredients such as *indigestible oligosaccharides* that provide a health benefit, or serve as precursors to compounds that provide a health benefit
- Development of prebiotics to produce desirable microbial metabolites should take in consideration the composition & function of the individual's gut microbiota
- ? Use metabolomics to guide individual nutritional therapy

Concept #1

- Our food environment has changed rapidly & its impact on our gut microbiome/metabolome is complicated!
- Fiber is not 'just fiber' –comes in many shapes and forms and impacting microbiome differently. Different types of fiber offer different benefits (laxation, fermentation effects) and nature of gut microbes may dictate tolerance: trial and error. Lack of fiber may increase pH allowing pathogenic flora to proliferate.
- The macronutrient balance to our plate & what we digest need to be factored into health plan: High protein, low carb diets may have long term impact on colonic health due to toxic metabolites/colonic inflammation potential. (Paleo, SCD & low FODMAP combo diet, ketogenic)

Concept #2

- How food impacts our microbiota is likely driven by other factors beyond diet.
- Who is there? What they are capable of degrading? What metabolites they produce?
- Diet is “a piece of the pie”



Concept #3

- Low FODMAP diet shown to manage symptoms in 70% of those with IBS
- FODMAPs rapidly ferment and have osmotic effects contributing to luminal distention
- Low FODMAP diet reduces beneficial probiotic microbiota & increases fecal pH. Long term impact unknown.
- Metabolome research w/ low FODMAP diet revealing interesting reduction in LPS and histamine. Low FODMAP story still evolving.

Big Picture QOL: What's the Goal?

"I was on the low-carbohydrate diet for a week and lost three inches off my smile."