Gut Health & The Microbiome

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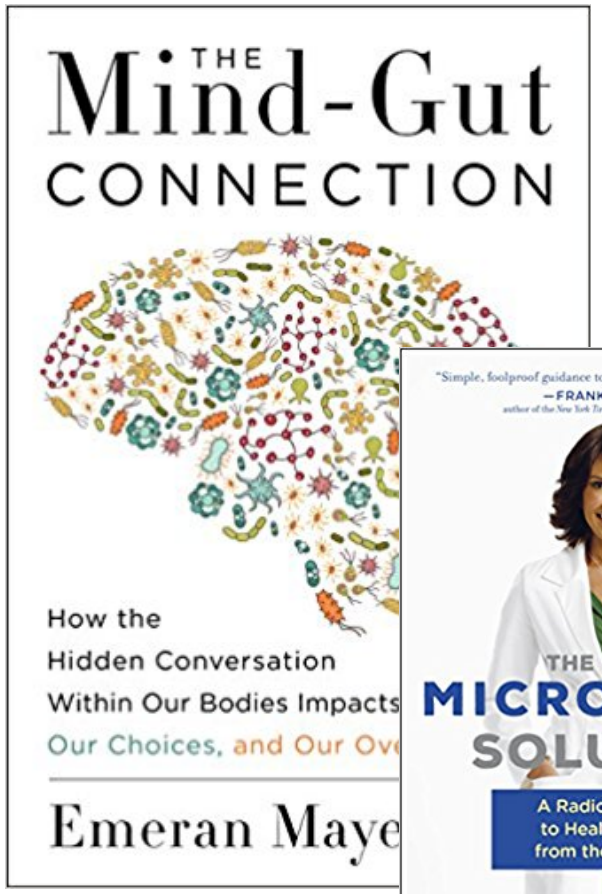
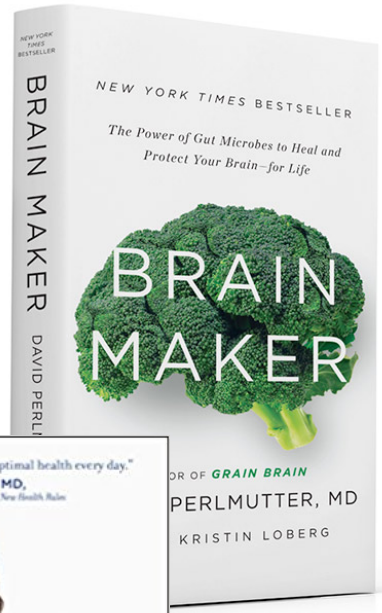
- None

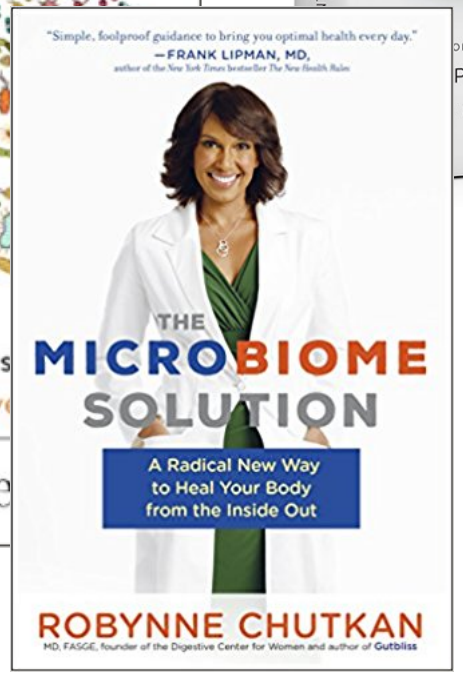
Objectives

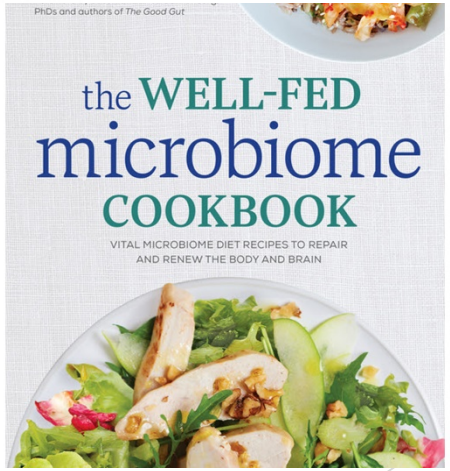
- What is the microbiome?
- Functions of the microbiome
- How can we affect an individual's microbiome?
- The microbiome and it's impact in specific disease states
- Areas for future research

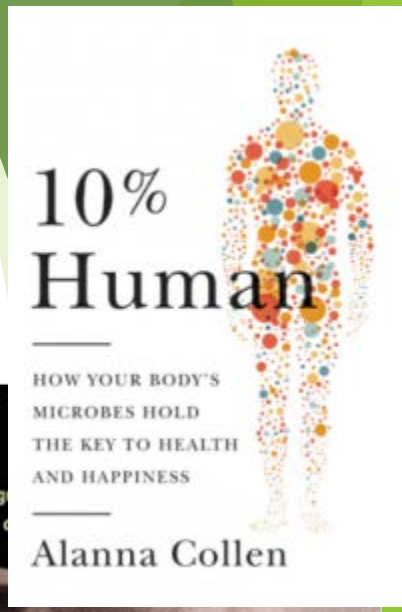
The Microbiome – A Hot Topic!

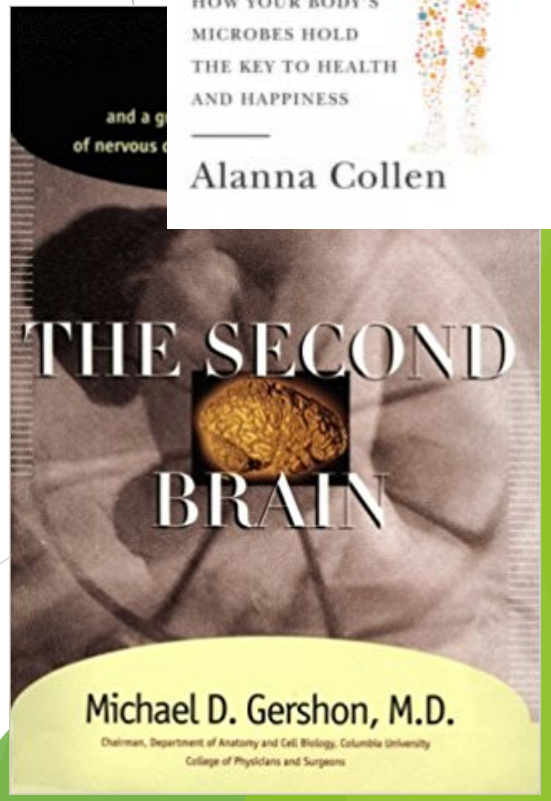






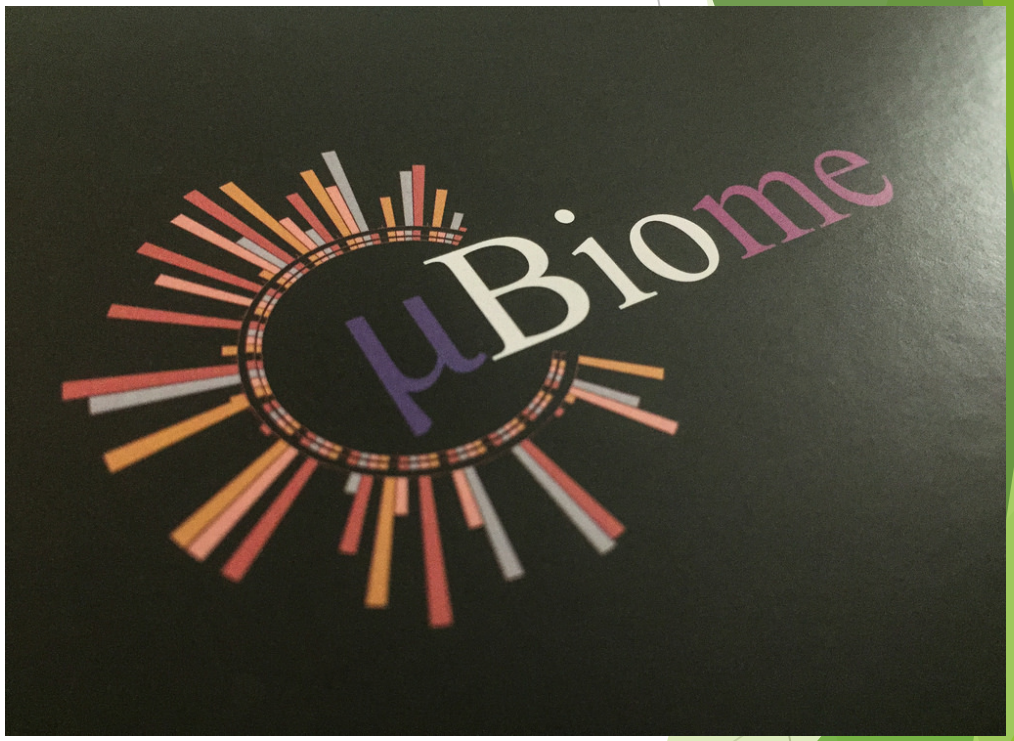






Human Microbiome

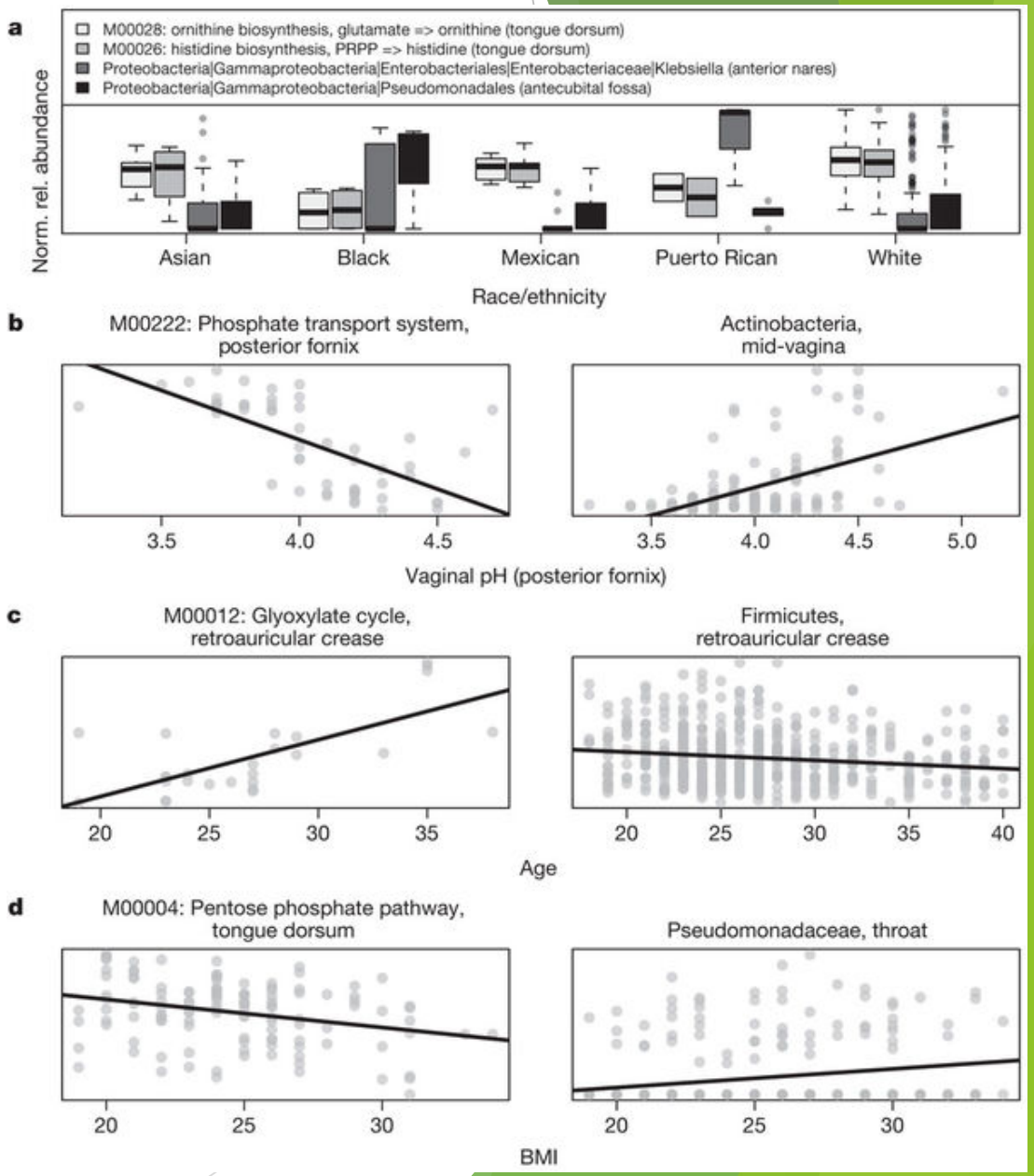
- Microbiome: All microbes that live on humans, contributing 99% of genetic material
- Most are in the GI tract: 10 times as many microorganisms in the GI tract (~100 trillion) than somatic cells in the body
- Mostly bacteria, mostly anaerobic, and majority in the large bowel
- Common genera: *Lactobacillus, Bacteroides, Clostridium, Escherichia, Streptococcus, and Ruminococus*
- Microorganisms affect oxygen levels, digestion/absorption, pH, neurotransmitter levels, and immunological factors
  - Some beneficial
  - Some potentially pathogenic or harmful



1.Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients.* Jan 2015
2. Huttenhower C et al. Structure, function and diversity of the healthy human microbiome. Nature. 2012 3. Tsukumo, DM et al, *Archives of Endocrinology and metabolism. Apr. 2015*

Human Microbiome Project

- Thousands of different microbes inhabit human populations, with high degree of variation between individuals: “unique microbial footprints”
- Microorganisms display patterns of mutualism or competition based on relative abundance at different sites
- Analogous to genetics: certain beneficial bacteria are ubiquitous, while true pathogens are not present at all, and those with modest risk are maintained at low levels in populations
- Correlation with host phenotype (age, gender, BMI, etc)
  - No statistically significant differences in the gut



Huttenhower C et al. Structure, function and diversity of the healthy human microbiome. Nature. 2012

Composition of Gut Flora

- Factors that affect an individual's gut flora
  - How a person is born (Vaginal vs. Cesarean section),
    - Vaginal births result in higher gut bacterial counts at 1 month of age
  - Breast or bottle
    - Higher bifidobacter and lactobacilli in breastfed; more Enterococci and enterobacteria in formula fed
    - Differences generally disappear after introduction of solid foods
  - Use of antibiotics
    - Increase risk for infectious diseases
    - Use in first year of life associated with development of allergies & asthma
  - Diet
  - Hygiene/sanitation
    - Epidemiologic studies between developed and developing countries (higher asthma/allergies with less microbial exposure in developed countries)

1. Gronlund MM et al. *J Pediatr Gastroenterol Nutr.* Jan 1999. 2. Wolowczuk I et al. *Clinical and Developmental Immunology.* Feb 2008. 3. Lin Chong CY et al. Factors Affecting Gastrointestinal Microbiome Development in Neonates. Nutrients. 2018 Mar; 10(3): 274. 4. Vangay P et al. *Cell host & microbe.* May 13 2015. *5.* Azad MB, et al. *Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology.* Apr 2013.

Functions of the Gut Flora

- Role in Digestion/Nutrition
  - Production of vitamin K, B12, biotin, thiamine, and folate (*Bifidobacterium)*
  - Supplying essential nutrients through breakdown of complex carbohydrates (*Bacteroides*)
  - Synthesizing secondary bile acids that help digest fats (*Lactobacillus, Bifidobacterium, Bacteroides)*
- Role in Immune System, Protection, and Inflammation
  - Enzymatic activity promotes healthy mucus barrier lining the gut
  - Promotes lymphatic tissue development and antibody formation
  - Induce protective cytokines, and suppress pro-inflammatory cytokines in gut mucosa
  - Lipopolysaccharides (LPS) in cell wall of gram negative bacteria can cause tissue inflammation

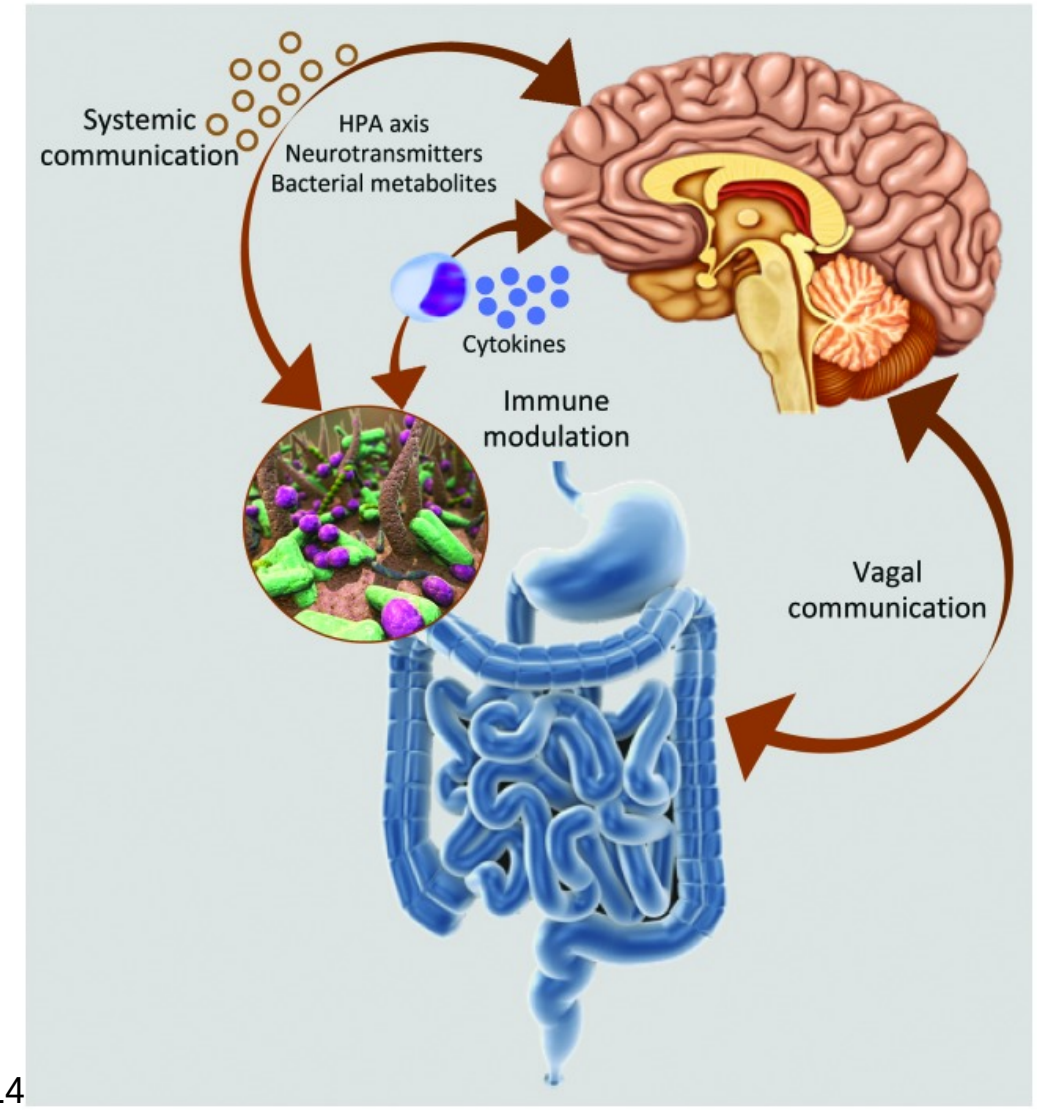
1. Conlon MA, Bird AR. *Nutrients.* Jan 2015. 2. Nicholson JK, et al. *Science.* June 2012. 3. Zhang YJ, et al. *International journal of molecular sciences.* 2015.

Functions of the Gut Flora

- Role in Gut-Brain Axis
  - Bidirectional communication
    - Brain can signal enteric nervous system to speed up or slow down transit time
    - Neurotransmitters generated by bacteria affect CNS via vagal afferent nerves receiving input from the gut
    - Microorganisms affect HPA axis response to stress. Ex) increased cortisol levels in germ-free mice → improved with probiotics
- Modulate pain perception
  - Lactobacillus acidophilus induces expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells, affects pain pathways similar to morphine

1. Tillisch K. *Gut microbes.* May 2014. 2. Cong X, Hender et al. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses.* Oct 2015. 3. Rousseaux C, et al. *Nat Med.* Jan 2007.

Role in Gut-Brain Axis



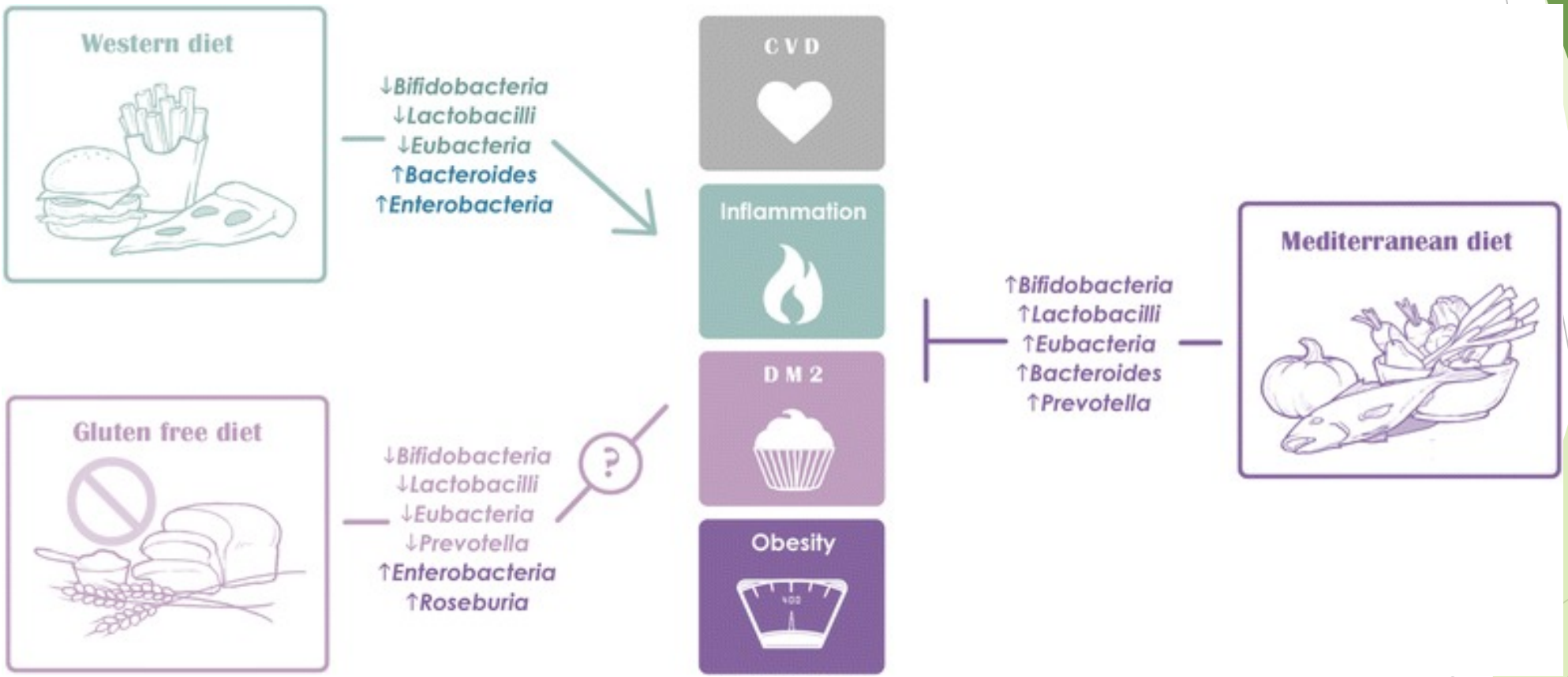
Tillisch K. *Gut microbes.* May 2014

How to Influence the Microbiome

- Diet
  - High Fiber Diets
  - Mediterranean Diet vs. Western Style Diet
  - Elimination diets
- Prebiotics
  - Non-digestible fiber that passes into large intestine, is fermented by microorganisms, and confers health benefits
  - Top Sources: Chicory, Jerusalem Artichoke, raw dandelion green, raw leeks, raw garlic, raw and cooked onions, raw bananas, raw wheat bran, raw asparagus
- Probiotics
  - Healthy bacteria added to diet: lactobacillus, bifidobacterium, saccharomyces, etc
  - Ex: Yogurt, Kefir, Kimchi, Miso, Sauerkraut, Kombucha, Raw Cheese, Apple Cider Vinegar, Natto

1. Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients.* Jan 2015. 2. De Palma G et al. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult humans. Br J Nutr. 2009. 3. Singh RK et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017 Apr 8

How to Influence the Microbiome



Singh RK et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017 Apr 8

Case 1 - JW

- 2-month old infant coming in for well-child
- Birth complicated by maternal chorioamnionitis and unplanned C-section due to fetal bradycardia
- Treated with IV ampicillin and gentamycin for 36 hours until cultures returned negative. Did well and discharged home
- Mother with history of asthma and allergies; father's history unremarkable
- Breast and formula feeding due to poor milk production – mostly formula
- Concern about colic – crying frequently about 3-4 hours per day
- Parents asking about risks/benefits of infant probiotics

Prebiotics and Probiotics for Infants Prevention of Atopic Diseases

- Double-blinded RCT, LGG (lactobacillus) or a placebo was given for 6 months to 132 infant and mother pairs
- The frequency of atopic eczema in the LGG-treated group was 23% versus 46% in the placebo group (RR: 0.51 [95% CI: 0.32–0.84], $P < .01$). NNT = 4.5
- Subsequent studies did not reproduce results, and 2007 Cochrane review concluded insufficient evidence to warrant routine supplementation for prevention

1.Kalliomäki M et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet. 2003;361(9372):1869–1871 2. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev.2007;(4)

Prebiotics and Probiotics for Infants Treatment of Infant Colic

- A systematic review of probiotics as treatment for infant colic
- Five RCTs met criteria
- Analysis showed that infants receiving probiotics had a 2.3-fold greater chance of having a 50% or greater decrease in crying/fussing time compared to controls (P = .01). Probiotic supplementation was not associated with any adverse events

Bird AS et al, Probiotics for the Treatment of Infantile Colic: A Systematic Review, 2016

Prebiotics and Probiotics for Infants Which Products to Choose

- Human breastmilk is rich in prebiotics, and also contains probiotics – a natural synbiotic
- Maternal use of probiotics is unlikely to affect breastmilk probiotic numbers
- All infant formulas are under FDA review and must maintain compliance with manufacturing standards, including those with prebiotics and probiotics
  - All ingredients must be deemed “generally regarded as safe” (GRAS)

1. Thomas DW et al. Clinical Report – Probiotics and Prebiotics in Pediatrics. American Academy of Pediatrics, 2010. 2. Elias J, Are probiotics safe for use during pregnancy and lactation? Can Fam Physician. 2011 Mar;57(3):299-301

Case 1 - JW

- 2-month old infant coming in for well-child
- Birth complicated by maternal chorioamnionitis and unplanned C-section due to fetal bradycardia – treated with IV antibiotics after birth
- Breast and formula feeding due to poor milk production – mostly formula
- Concern about colic – crying frequently about 3-4 hours per day
- **Recommendations**
  - Switch formula to Formula with Probiotics (LGG) and continue breast and formula feeding as they were
  - Over the course of the next 4 months, infant did well and colic improved
  - No new / worsening symptoms

Prebiotics & Probiotics in Infants & Children

- Insufficient evidence to recommend prebiotics or probiotics to otherwise-healthy infants
- Studies are promising for prophylactic use of probiotics during first 6 months in infants at risk for atopic disorders, but further evidence is needed before recommendation for routine use
- Probiotic use in healthy infants and children early in course of infectious diarrhea can reduce duration of symptoms by ~1 day
- Addition of probiotics to infant formulas has not demonstrated harm
- Risks of vaginal seeding to C-section born infants (infection, sepsis in newborn) outweigh potential theoretical benefits

Thomas DW et al. Clinical Report – Probiotics and Prebiotics in Pediatrics. American Academy of Pediatrics, 2010

Case 2 - MT

- 22-year-old female college student coming in for symptoms of bloating, intermittent diarrhea, abdominal pain, and overall discomfort
- Symptoms present most days per week, have been ongoing for about a year. Bowel movements are variable, sometimes normal, sometimes diarrhea 2-3 times per day
- Triggers: Stress (exams, relationships), certain foods (sweets, carbs)
- Alleviating Factors: Symptoms were not as severe over summer vacation
- Otherwise generally healthy; no chronic medical conditions

Case 2 – MT
Irritable Bowel Syndrome (IBS)

- Rome IV Diagnostic Criteria
  - Recurrent abdominal pain at least 1 day per week for the past 3 months, with symptom onset at least 6 months prior to diagnosis
  - PLUS at least 2 of the following:
    - Symptoms related to bowel movements (either better before or after bowel movements)
    - Symptoms associated with change in stool frequency
    - Symptoms associated with change in stool form
  - Subtypes
    - IBS-C, IBS-D, IBS-M, IBS-U
    - Based on Bristol Stool Scale Types

Schmulson MJ, Drossman DA. What is New in Rome IV. J Neurogastroenterol Motil. 2017 Apr; 23(2): 151–163.

Irritable Bowel Syndrome

- Probiotics significantly reduce bloating, pain, flatulence, and fecal urgency symptoms
  - Very few studies on prebiotics and synbiotics
  - Studies are heterogenous, and cannot make conclusion on specific strains or species of probiotics
  - Dosing: At least 20 billion CFU daily, including species of *Lactobacillus* and *Bifidobacterium*
- Dietary Supplements: Fiber
  - Meta-analysis of 14 studies found significant improvement in IBS scores with soluble fiber interventions
  - Improves microbiome diversity
  - Examples in studies: Psyllium, Wheat Bran

1. Didari T et al. *World J Gastroenterol.* Mar 14 2015. 2. Ford AC et al. *Am J Gastroenterol.* Oct 2014. 3. Moayyedi P, et al. *Am J Gastroenterol.* Sept 2014.

Inflammatory Bowel Disease (IBD)

- IBD is associated with dysbiosis
  - Decreased microbiome diversity than controls
  - Cause or effect?
- Probiotics for ulcerative colitis
  - VSL #3 (high dose) effective as primary or adjunct therapy for treatment and to maintain remission
  - 2 capsules daily (225 billion CFU) for 8-12 weeks for induction or long term for maintenance of remission
- Probiotics for Crohn's Disease
  - Studies have been performed, but have not shown effectiveness
- Fecal Microbial Transplant (FMT) (via enema or during endoscopy, colonoscopy)
  - Pilot studies have shown promise, but results are mixed and studies are small
  - Subset of patients may benefit, but more studies needed

1. Hansen JJ, et al. *Current treatment options in gastroenterology.* Mar 2015. 2. Ganji-Arjenaki et al. Probiotics are a good choice in remission of inflammatory bowel diseases: A meta analysis and systematic review. March 2018. 3. Fujiya M, et al. *Clinical journal of gastroenterology.* Feb 2014.

Prebiotics and Probiotics for Diarrhea

- Prevention of Acute Infectious Diarrhea
  - LGG 10^9 reduces risk of nosocomial infections on pediatric wards and reduces acute rotavirus gastroenteritis in childcare settings. However results are mixed and not enough to recommend broad use for prevention
- Treatment of Acute Infectious Diarrhea
  - Several studies demonstrate that probiotic use reduces duration of acute infectious diarrhea, including rotavirus, by approximately 1 day (specifically LGG)
- Prevention of Antibiotic-Associated Diarrhea (AAD)
  - Cochrane Review
    - 23 RCTs of ~4000 children receiving probiotics or placebo with antibiotics
    - Incidence of AAD 8% in probiotics group vs 19% in control groups
    - Recommended further research, but results are promising with few side effects

1. Trivik et al, Use of Probiotics in the Prevention of Nosocomial Infections, 2018. 2. Thomas DW et al. Clinical Report – Probiotics and Prebiotics in Pediatrics. American Academy of Pediatrics, 2010 3. Cochrane Review 2015: Probiotics for the prevention antibiotic-associated diarrhea in children

Case 3 - KT

- KT is a 31-year-old female who has struggled with obesity her whole life. She is otherwise healthy with no significant PMHx.
- BMI = 33
- She comes in for an annual physical and asks about new research on the microbiome, diet, and the use of prebiotics and/or probiotics to help promote weight loss

The Microbiome & Obesity Background

- Role of microbiome and diet in obesity first seen in mice studies
  - Fecal transplants from obese mice into lean, germ-free mice quickly induce obesity despite same (or less) calorie intake. Mechanism related to food processing & absorption affected by microbiome
  - Stress response & cortisol levels reduced if mice are allowed to eat "comfort foods," high fats and sugary drinks
- Obesity and metabolic syndrome has become an epidemic in the US, resulting in more research and attention to ways to combat it
- Obesity is multifactorial process
  - Diet, exercise, genetics, and the microbiome

Borek, Carmia. Gut Microbiome and its Potential Role in Obesity. Journal of Restorative Medicine, Volume 6, Number 1, 1 December 2017, pp. 46-52(7)

The Microbiome & Obesity
Effects of Diet

- Western-style diet high in fat and sugar quickly induces changes to microbiome
  - Increased proportion of Firmicutes, decreased bacteroides
  - Leads to increased breakdown of indigestible polysaccharides and subsequent absorption in the form of monosaccharides & SCFAs → increased triglycerides
- Influence of agricultural revolution
  - Comparing microbiome of children in Europe to children in West Africa. Typical African diet high in non-animal proteins versus western-style diet
  - Higher levels of bacteroides and lower levels of firmicutes in African cohort
  - Theory of co-evolution of microbiome with diet changes
  - As agricultural practices change, there is concern for reduced quality of food products reaching consumers, and subsequent effects on inflammation and the microbiome

Borek, Carmia. Gut Microbiome and its Potential Role in Obesity. Journal of Restorative Medicine, Volume 6, Number 1, 1 December 2017, pp. 46-52(7)

The Microbiome & Obesity
Effects of Diet

- Artificial sweeteners & obesity: saccharine, sucralose, aspartame
  - Artificial sweeteners induce glucose intolerance in mice compared to those fed glucose or sucrose, and cause significant microbiome changes
- Human studies
  - Long-term intake of saccharine in 381 individuals induced weight gain and higher fasting glucose levels
  - Seven individuals consumed FDA maximum of saccharine for 5 days. 4 individuals showed signs of glucose intolerance (responders) and 3 did not (non-responders)
  - Responders developed significant microbiome changes after saccharine consumption, non-responders did not (individualized response)
  - Transporting stool from responders into germ-free mice induced microbiome changes and gluten intolerance

Borek, Carmia. Gut Microbiome and its Potential Role in Obesity. Journal of Restorative Medicine, Volume 6, Number 1, 1 December 2017, pp. 46-52(7)

The Microbiome & Obesity
Effects of Prebiotics, Probiotics, & Synbiotics

- High-quality studies are limited and have shown mixed results
- Small study: 10 healthy volunteers consuming high-fat diet and probiotics (VSL #3) gained less weight than placebo group
- Fecal transplant studies have shown promise in animal models, but limited data in humans, and balanced with danger of introducing pathogens
- Recent meta-analysis only found 4 high-quality studies on probiotics for weight loss, and did not show any statistically-significant differences
- More studies needed

1. Borek, Carmia. Gut Microbiome and its Potential Role in Obesity. Journal of Restorative Medicine, Volume 6, Number 1, 1 December 2017, pp. 46-52(7). 2. Park S, Bae JH. *Nutrition research (New York, N.Y.).* Jul 2015.

Case 3 - KT

- KT is a 31-year-old female who has struggled with obesity her whole life. She is otherwise healthy with no significant PMHx. BMI = 33. She comes in for an annual physical and asks about new research on the microbiome, diet, and the use of prebiotics and/or probiotics to help promote weight loss
- RECOMMENDATIONS:
  - Counsel on importance of diet and food choices and their effect on microbiome and obesity
  - Educate on risks of artificial sweeteners – it is not all about # of calories
  - Recommend Mediterranean-style diet
  - Probiotics are safe intervention, but no strong evidence for weight loss

Case 4 - LM

- LM is a 42-year-old male presenting with new-onset symptoms of situational depression and anxiety
- High stress lifestyle
  - Work: 50-60 hours per week in healthcare administration
  - Father to three young children
  - Taking care of his mother and her deteriorating health
- Diet: No time for regular meals, eats “on-the-go,” many processed foods
- Getting 5-6 hours of sleep at night
- Asking about recommendations to help with irritability and depression, including role of diet and if probiotics would be helpful

Microbiome and Depression & Anxiety

- Mechanisms in which microbiome affects mental health disorders
  - HPA axis and stress response / cortisol levels
  - Production of neurotransmitters: GABA, serotonin, catecholamines
  - Vagal nerve activation
- Preclinical trials
  - Animal studies show that consumption of probiotics prevents stress-induced increases in ACTH, cortisol, adrenaline, and noradrenaline, while also increasing levels of precursors to serotonin
  - Mice receiving probiotics show improved memory and reduced anxiety and depressive-like behaviors
  - Bidirectional association: Fecal transplant from depressed humans into mice induces depressive-like behaviors, but also induction of stress and depressive behaviors results in reduced microbiota diversity

1. Wallace CJ, Malev R. The effects of probiotics on depressive symptoms in humans: a systematic review. Ann Gen Psychiatry. 2017; 16: 14. 2. Winter G et al. Gut microbiome and depression: what we know and what we need to know. Reviews in the Neurosciences 2018-02-05

Microbiome and Depression & Anxiety

- Human Studies
  - Significant differences in microbiota of individuals with MDD versus healthy controls
  - 2017 Systematic Review on Probiotics and effect on mood
    - 10 studies met inclusion criteria. Only 3 studies included individuals with depression or anxiety symptoms. The remaining 7 studies assessed mood changes in healthy adults
    - High degree of variability on strain, dosing, and duration (3 weeks to 6 months) of probiotics
    - Majority of studies found significant improvements in symptoms of depression, anxiety, and fatigue in probiotic groups compared to placebo
    - Largest effects on anxiety symptoms
    - No significant negative side effects

1. Jiang H, et al. *Brain, behavior, and immunity.* Aug 2015. 2. Wallace CJ, Malev R. The effects of probiotics on depressive symptoms in humans: a systematic review. Ann Gen Psychiatry. 2017; 16: 14.

Case 4 - LM

- LM is a 42-year-old male presenting with new-onset symptoms of situational depression and anxiety. High-stress lifestyle and western-style diet, not prioritizing time for meals for healthy food choices
- RECOMMENDATIONS
  - Yes, diet is likely negatively contributing to symptoms. Educate on anti-inflammatory, Mediterranean-style diet
  - Initial studies indicate that probiotics are safe and can help for depression and anxiety symptoms. Unclear what is optimal dose, strain, and duration
  - Recommend a brand that has at least 20 billion CFU (colony forming units), and contain lactobacillus and bifidobacterium (L. casei most studied in the review)
  - This is part of comprehensive management plan, also initiated on SSRI

Other areas of research & promise

- Allergic rhinitis
- Asthma
- ADHD
- Autism
- Chronic fatigue
- Dementia
- Dental diseases
- Diabetes
- Diverticular disease
- Food Allergies and sensitivities
- GERD
- Hypertension
- Hyperlipidemia
- Rheumatoid Arthritis
- Nephrolithiasis
- Nosocomial/ICU infection
- Parkinson's Disease
- Post-op infections
- Upper respiratory infections

Conclusions

- The microbiome and its effects on health is a hot topic both in clinical research as well as popular culture and media
- Complex interplay between human hosts and their microbiomes, and huge diversity within and between individuals
- Early life is particularly important time for development of microbiome
- Affected by diet, lifestyle, illness, and use of antibiotics and probiotics
- Evidence suggests role of microbiome in GI diseases (IBS, IBD), obesity and metabolic syndrome, and mood disorders
- Several other promising areas of research and ongoing trials
- Mediterranean diet most well-studied for effects on health & positive effects on microbiome
  - Foundation: plant-based foods, healthy oils, nuts, whole grains/fiber, poultry and fish
- Pre- pro- and synbiotics are safe interventions, but still more data needed on specifics of when and how to best recommend them
- **Recommendation for type of probiotic: Refrigerated, 20-50 billion CFU, at least 4 strains of bacteria, including lactobacillus and bifidobacterium. Examples include Jarrow and Culturelle**

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