NHDA 2017

May 11, 2017

Mary Beth Augustine, RDN, CDN, FAND

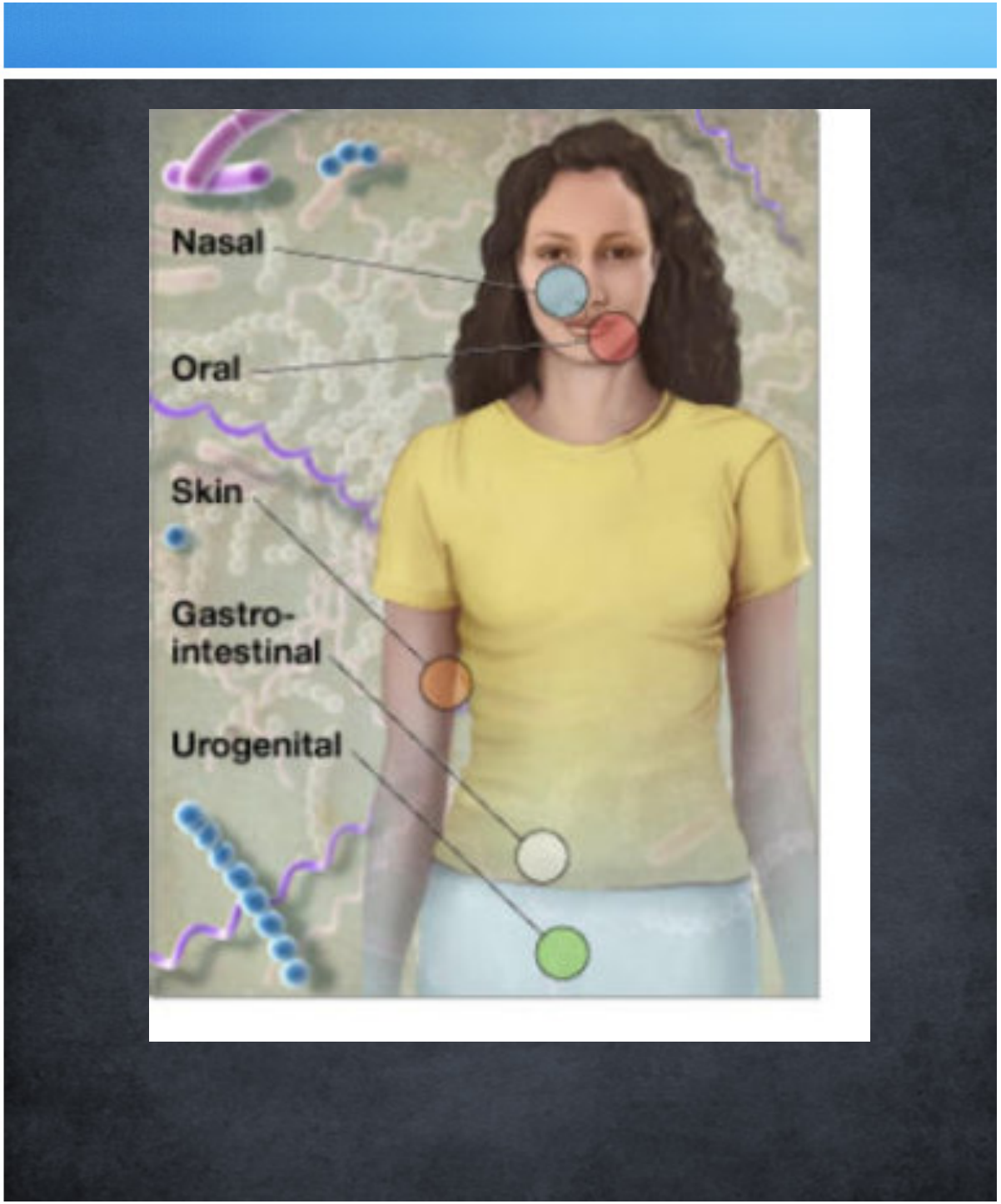
Microbiome Nutrition for the RDN

Microbiome Glossary

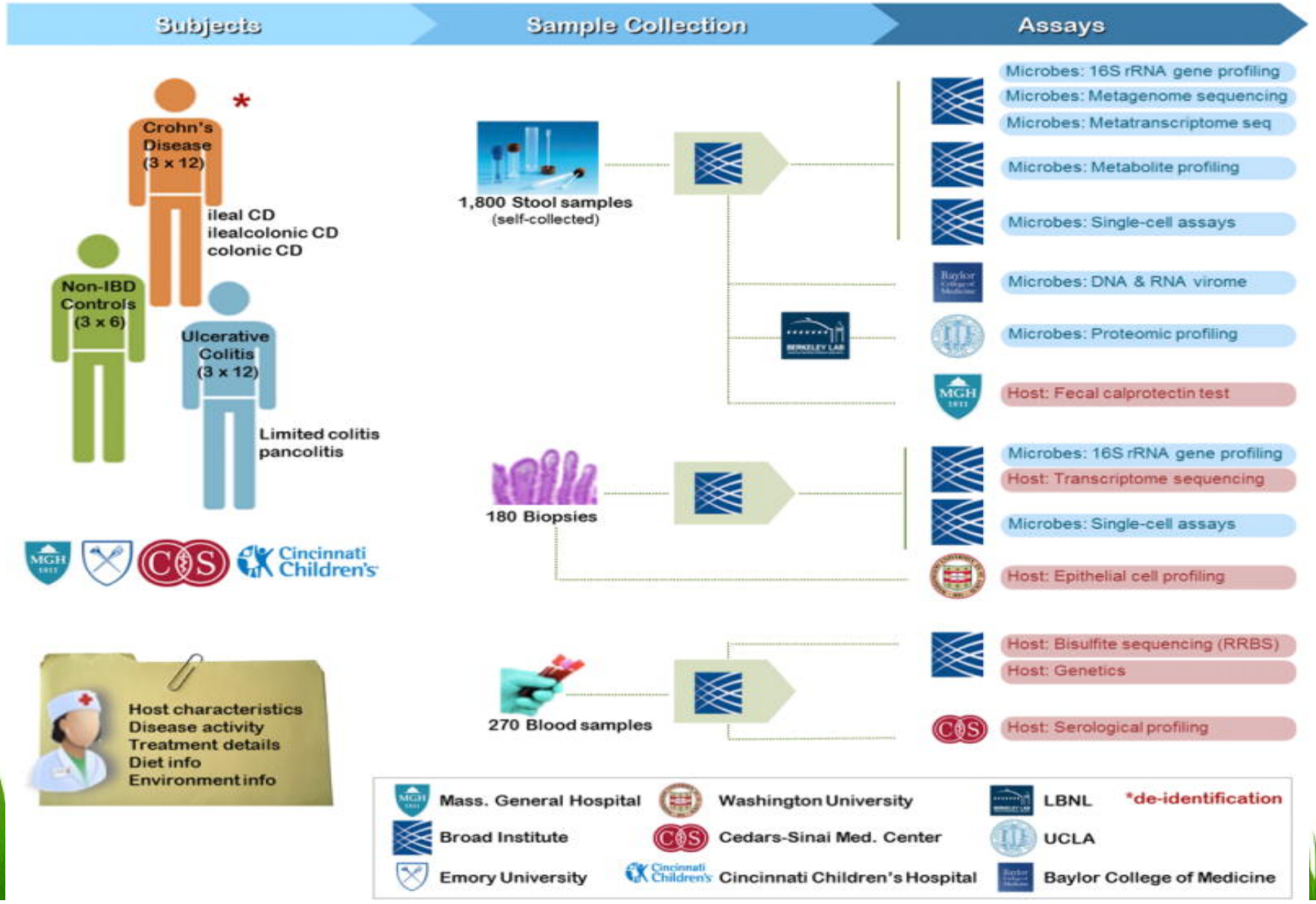
- **Microbes**: single-cell microorganisms- includes bacteria, archaea, fungi, protists (algae, amoebas, slime molds, and protozoa), and viruses
  - 100 trillion cells in our bodies
  - 10-fold # of human cells
  - 100-fold # of human genes
  - Majority reside in gut, profoundly influence nutrition and physiology, and are crucial for human life
- **Microbiome**: The aggregate genomes and genes found in the members of a microbiota; includes bacteria, viruses, fungi, and archaea
- **Microbiota**: A microbial community; commonly referred to according the the habitat that it occupies- e.g., the gut microbiota
- **Phylotype**: a group of microbes
- **Metagenomics**: study of collective genomes of a microbial community

NIH Human Microbiome Project

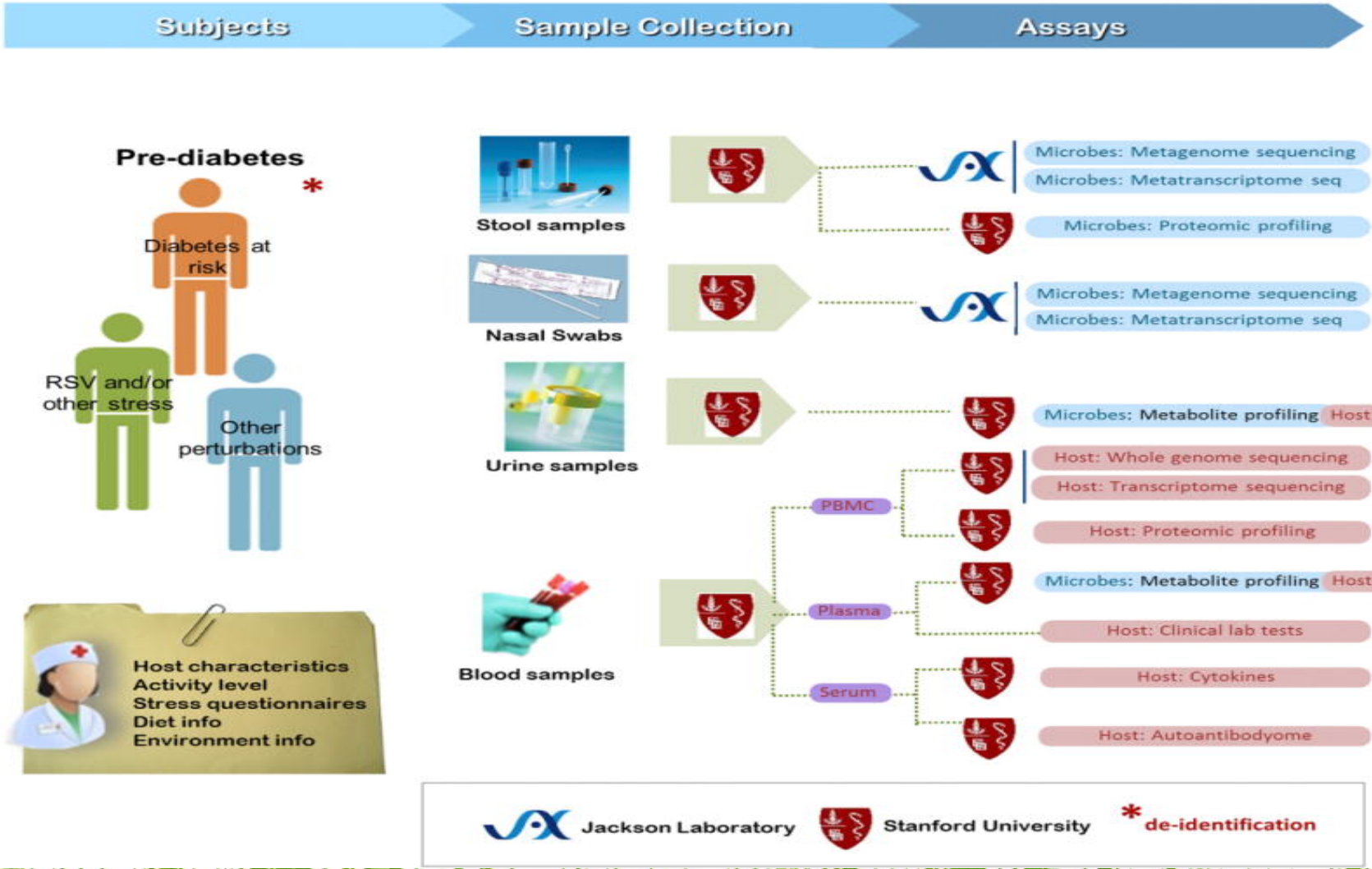
- **Samples collected from 15 body sites in men and 18 body sites in women**
- Analyzing microbial DNA and conducting metagenomic sequencing to study metabolic capabilities encoded in microbe genes
- **Calculated that >10,000 microbial species occupy the human ecosystem!**



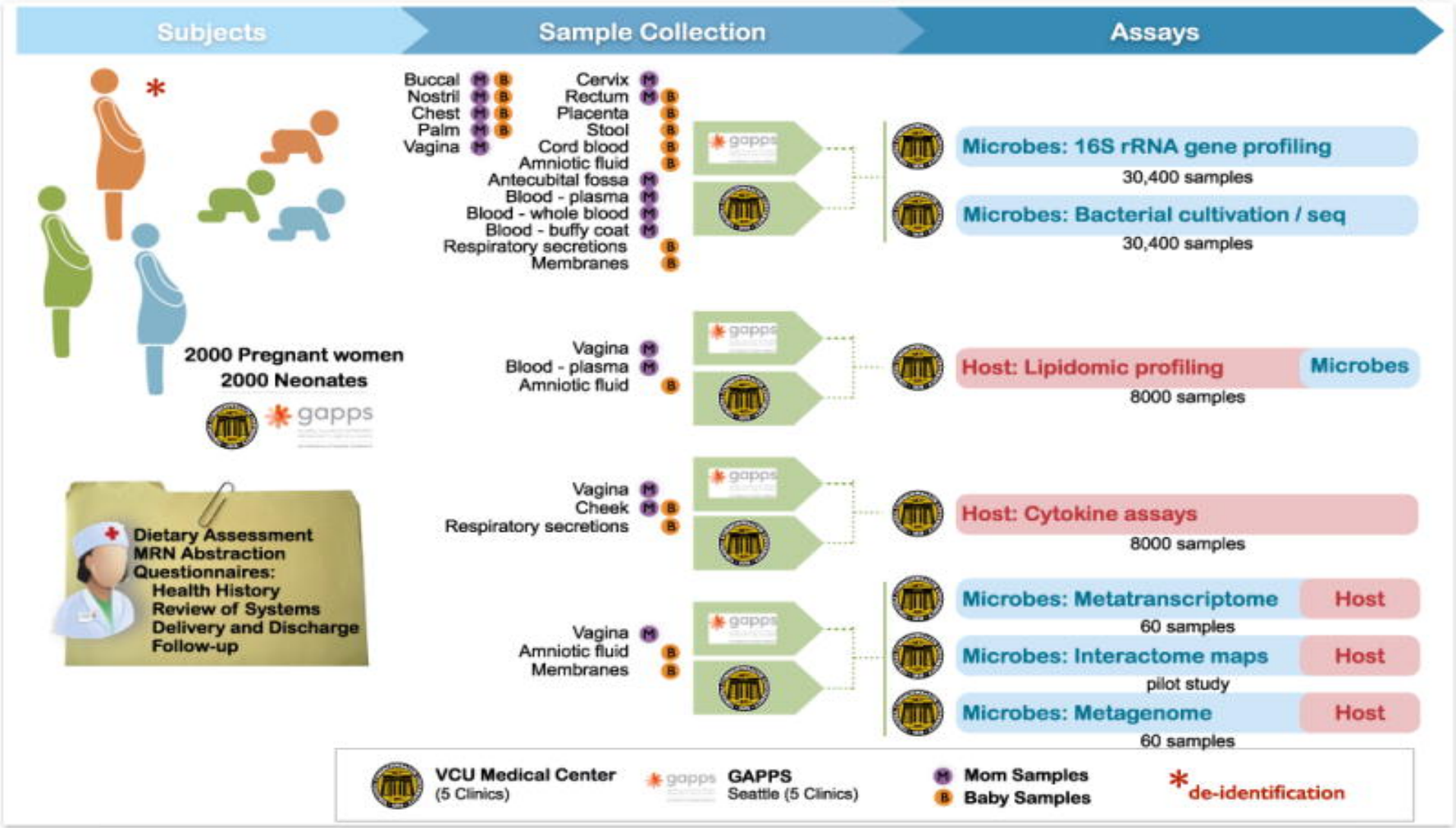
Human Microbiome Project– Characterizing the Gut Microbial System for Diagnosis and Therapy in IBD

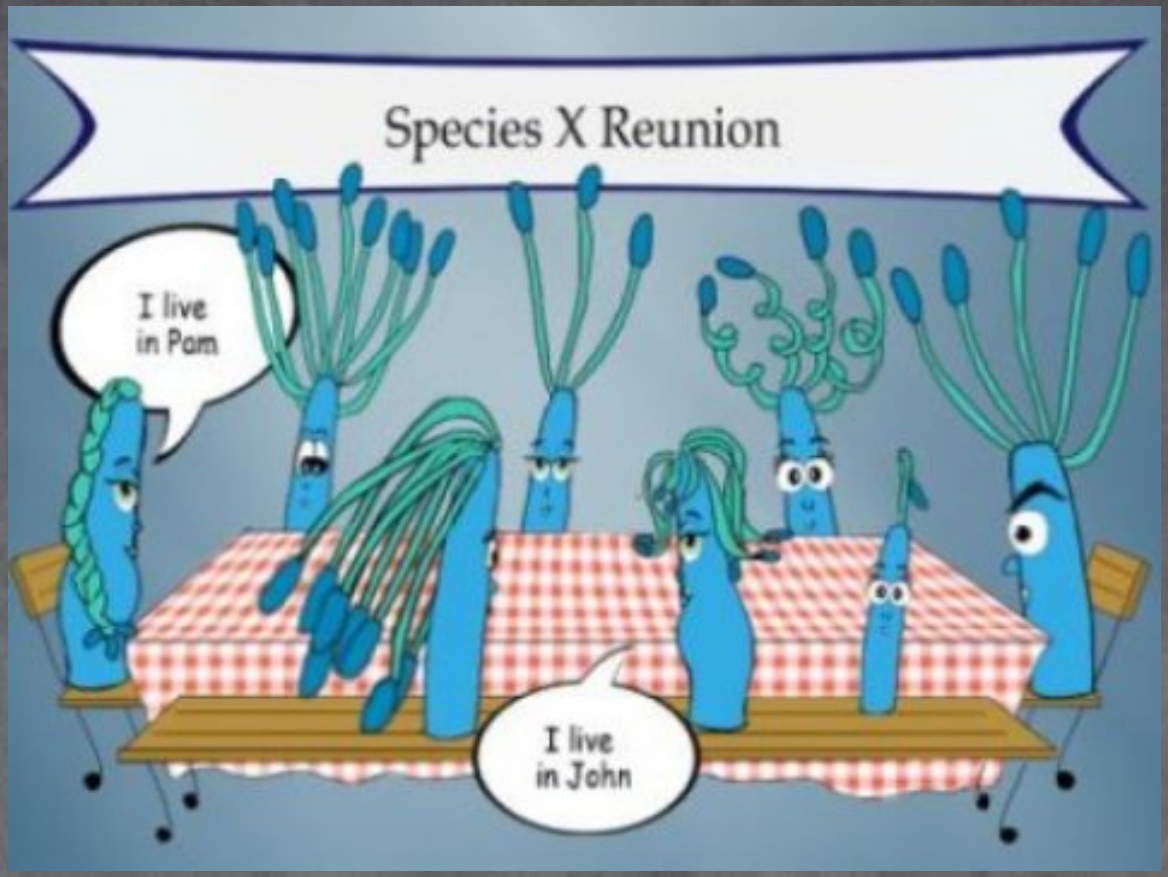


Human Microbiome Project-- Microbiome and Host Changes During Respiratory and Other Stress Conditions in Individuals at High Risk for T2DM



Human Microbiome Project – Integrative Multi-Omic Analysis of the Vaginal and Related Microbiomes in Pregnancy

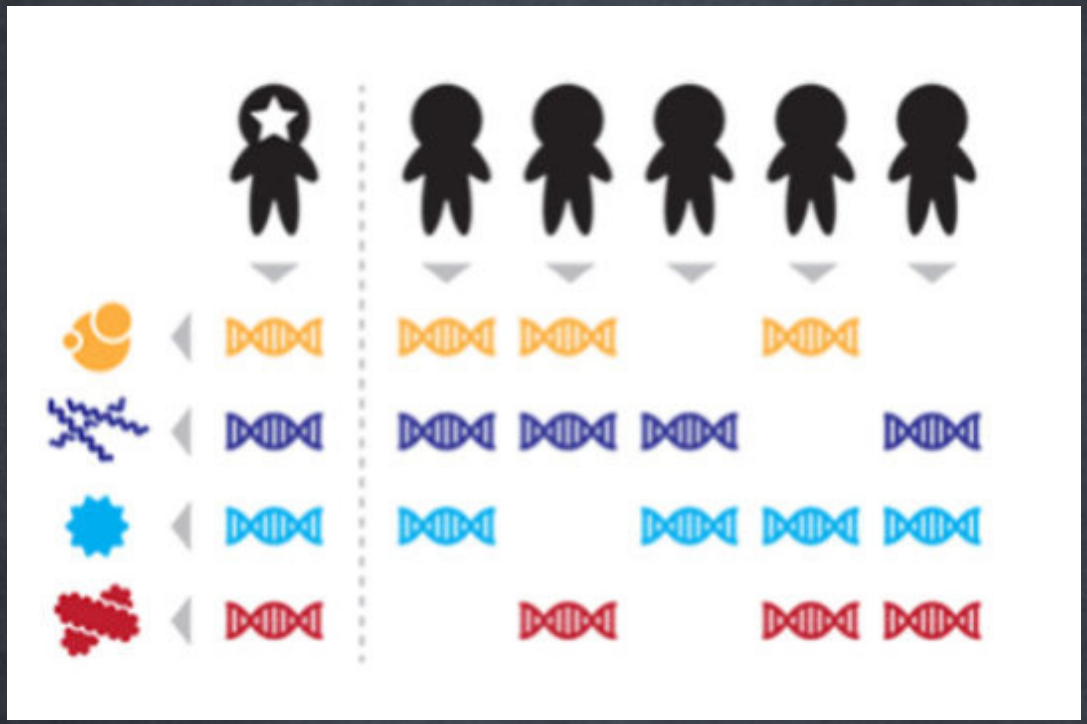




Microbiota Give New Meaning to the Terms *Host* and *Hostess*…

Microbiome ‘Fingerprints’

- **Personal microbiomes contain enough distinguishing features to identify an individual**



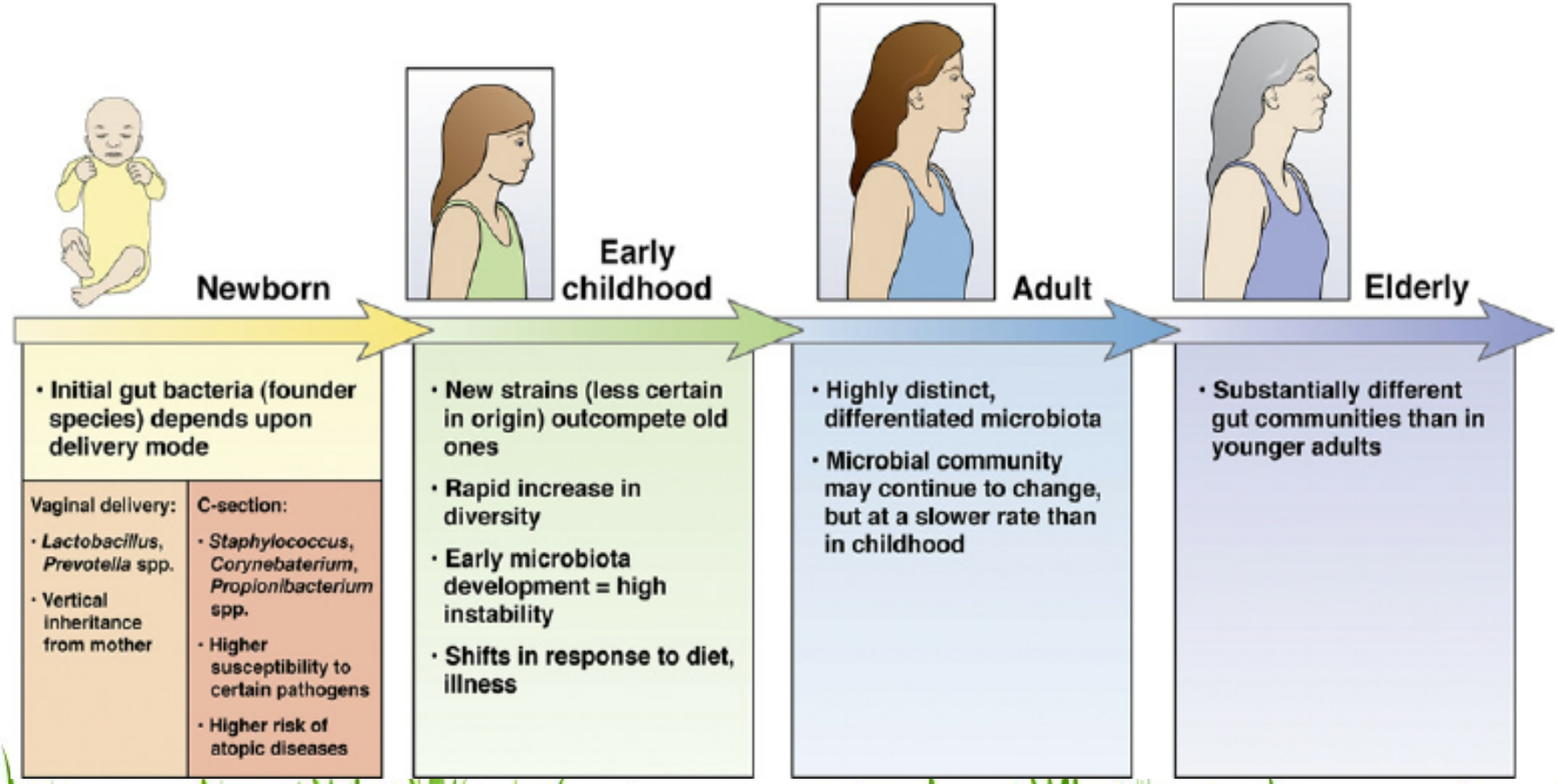
Franzosa et al. (2015). *PNAS,* doi:10.1073/pnas.1423854112

Human 'Microbial Cloud'

- Humans emit 10^6 biological particles per hour
- Airborne release, direct contact with surfaces, and dust facilitate acquisition and exchange of microbes
- Study of skin, oral, and gut microbiome of cohabitating humans resemble each other- and even their companion animals!
- Adults share more microbial taxa with their dogs than they do with other dogs!

Meadow et al. (2015), Humans differ in their personal microbial cloud. DOI 10.7717/peerj.1258

Lifecycle Microbiome
More 'Transient State' in Early Life
More 'Steady State' in Adulthood



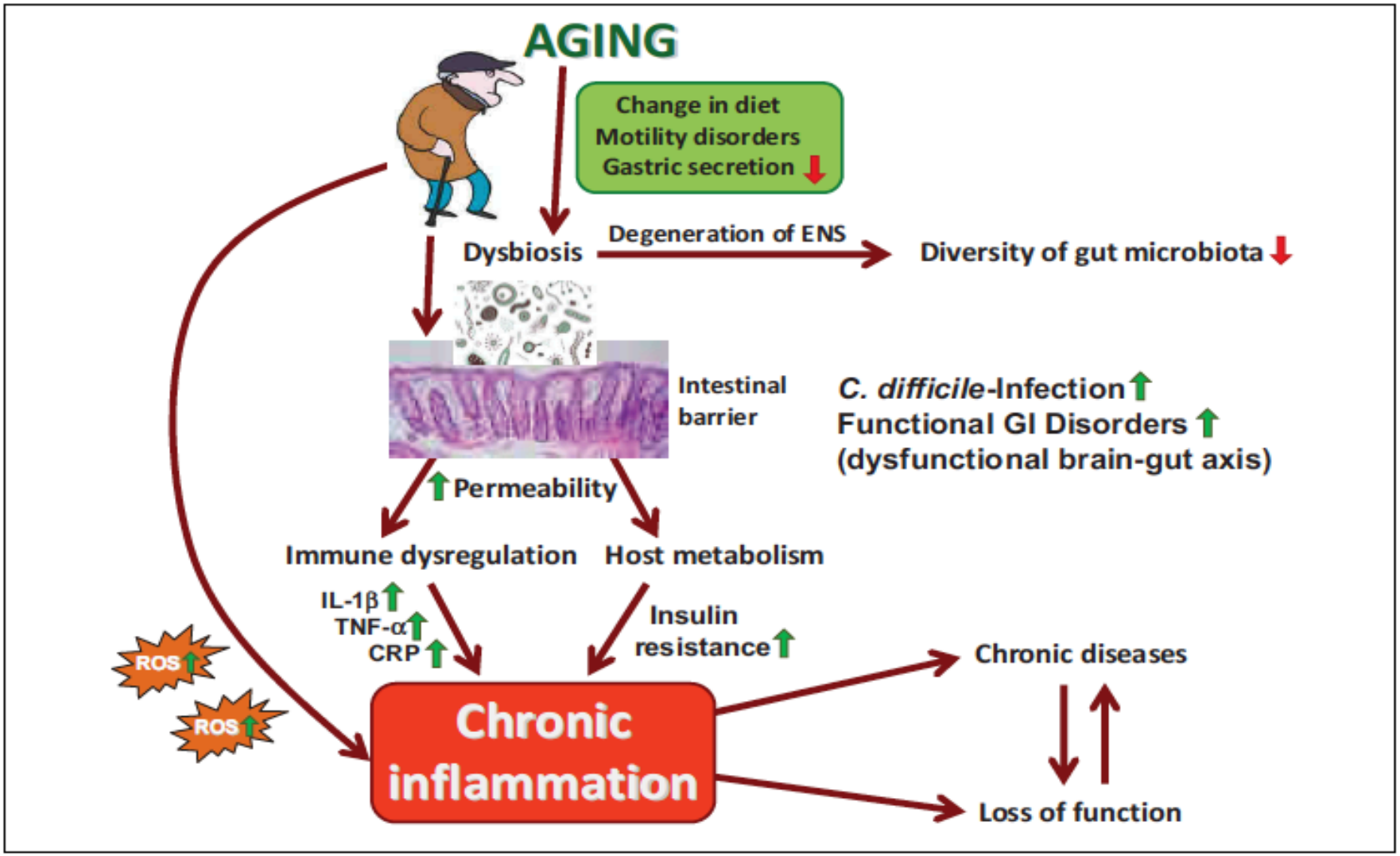


Fig. 3. Impact of aging on gut microbiota, pathology of gastrointestinal tract and various clinical consequences leading to dysbiosis causing chronic inflammation resulting from impairment of mucosal barrier, generation of reactive oxygen metabolites (ROS), proinflammatory mediators, the decrease in diversity of gut microbiota, increased risk of *Clostridium difficile* infection (CDI) and functional gastrointestinal disorders (FGID).

Adult Gut Microbiome
Short Term Diet Changes = 'Transient State'
Long Term Diet Changes = New 'Steady State'

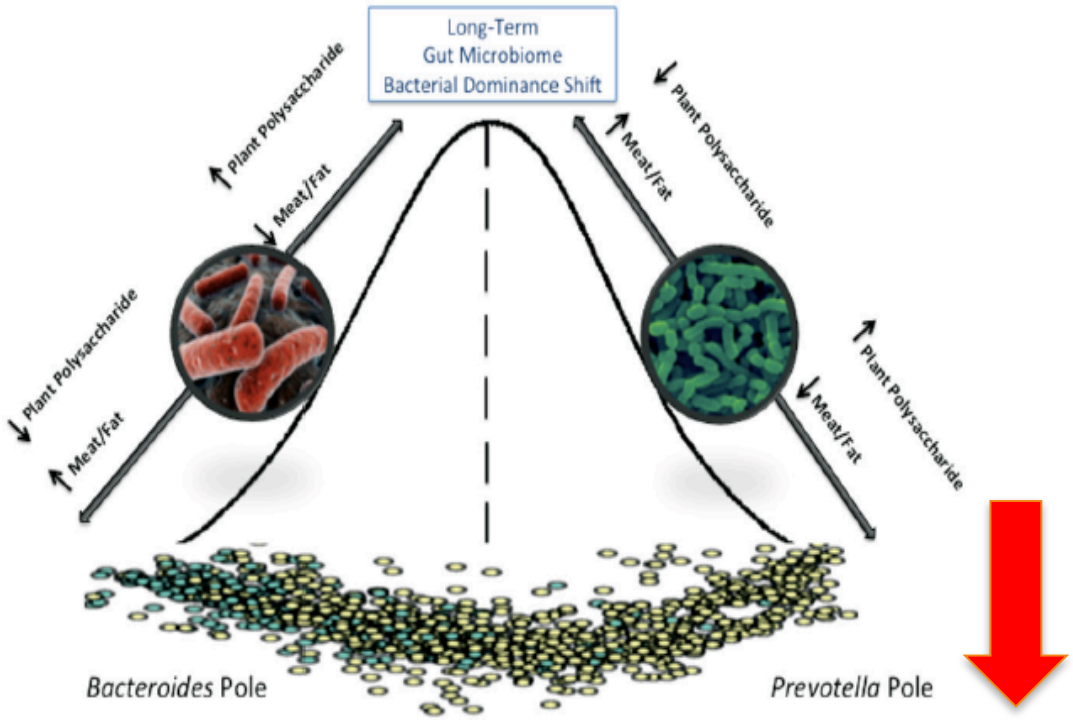


FIGURE 2 | The adult gut microbiome is characterized as existing in a steady state that requires a major disturbance to permanently alter that state. Short-term diet interventions may transiently alter the gut microbiome community structure, but long-term diet changes are required to shift to a new steady-state.

Each Body Surface Has Own Microbiome

- Every surface of the human body has a unique, specific, very complex microbiome- mouth, hair, eyes, nose, ears, vagina, lungs, gut, skin
- Each microbiome has distinct functions
- The gut microbiome has been described as an *organ within an organ*, a *super organ*, and a *potent bioreactor* which controls numerous metabolic functions- many of which remain unrecognized

Eye Microbiota Changes with Contact Lenses

- Associated with microbial keratitis and inflammatory eye conditions
- Wearing contact lenses changes eye microbiota to more similar to that of skin microbiota
- Further research is needed to determine effect on ocular infections and diseases

American Society for Microbiology. March/April 2016. 7(2): e00198-16.

Salivary Microbiome in Health and Disease

DNA RESEARCH

DNA Res. 2014 Feb; 21(1): 15–25.
Published online 2013 Sep 7. doi: 10.1093/dnares/dst037
PMCID: PMC3925391

Dysbiosis of Salivary Microbiota in Inflammatory Bowel Disease and Its Association With Oral Immunological Biomarkers

Heba S. Said,[1] Wataru Suda,[1] Shigeki Nakagome,[2] Hiroshi Chinen,[3] Kenshiro Oshima,[1] Sangwan Kim,[1] Ryosuke Kimura,[4] Atsushi Iraha,[3] Hajime Ishida,[4] Jiro Fujita,[5] Shuhei Mano,[2] Hidetoshi Morita,[6] Taeko Dohi,[7] Hiroki Oota,[8] and Masahira Hattori[1,*]

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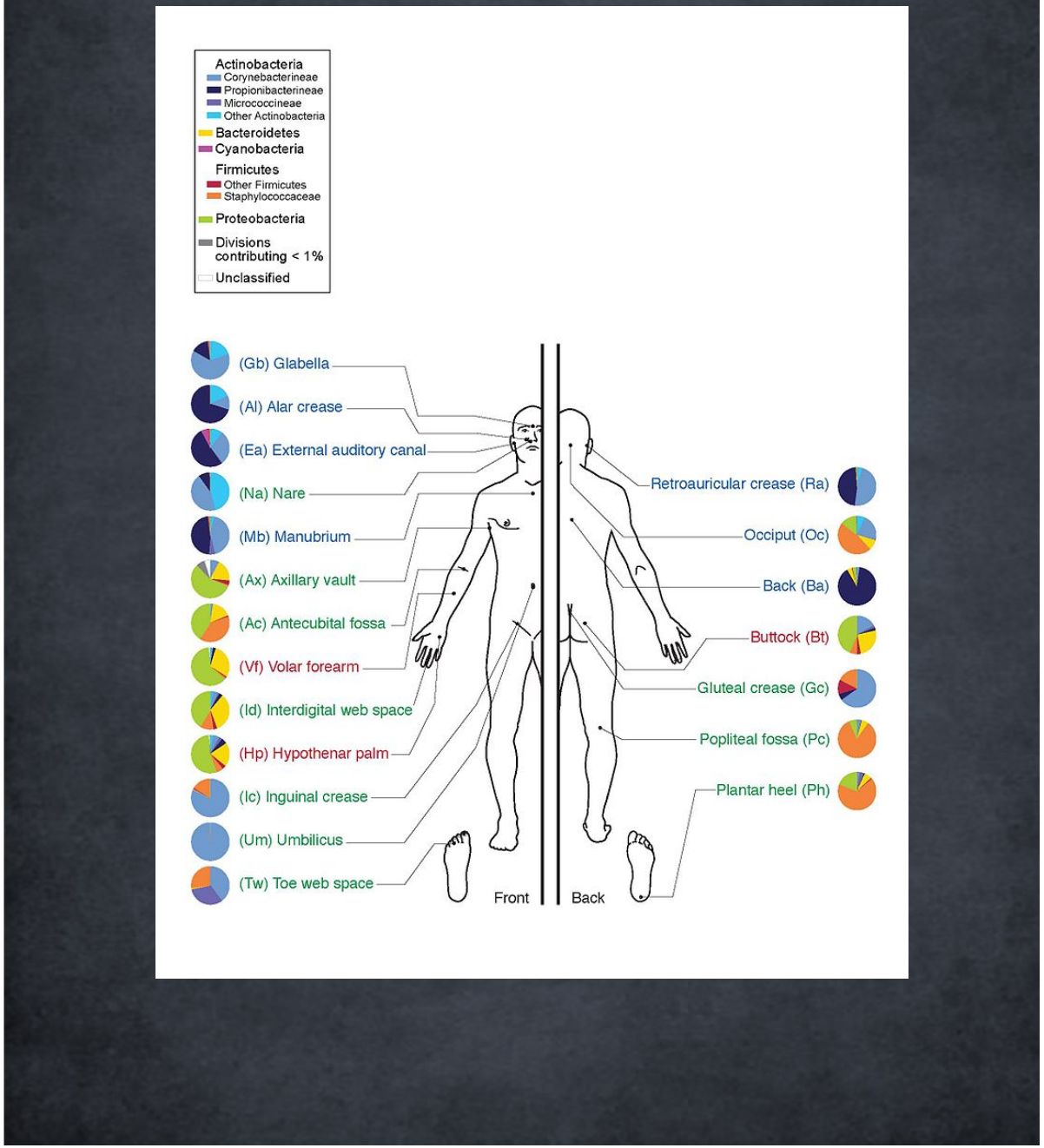
Abstract

Go to:

Analysis of microbiota in various biological and environmental samples under a variety of conditions has recently become more practical due to remarkable advances in next-generation sequencing. Changes leading to specific biological states including some of the more complex diseases can now be characterized with relative ease. It is known that gut microbiota is involved in the pathogenesis of inflammatory bowel disease (IBD), mainly Crohn's disease and ulcerative colitis, exhibiting symptoms in the gastrointestinal tract. Recent studies also showed increased frequency of oral manifestations among IBD patients, indicating aberrations in the oral microbiota. Based on these observations, we analyzed the composition of salivary microbiota of 35 IBD patients by 454 pyrosequencing of the bacterial 16S rRNA gene and compared it with that of 24 healthy controls (HCs). The results showed that Bacteroidetes was significantly increased with a concurrent decrease in Proteobacteria in the salivary microbiota of IBD patients. The dominant genera, *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, *Veillonella*, and *Gemella*, were found to largely contribute to dysbiosis (dysbacteriosis) observed in the salivary microbiota of IBD patients. Analysis of immunological biomarkers in the saliva of IBD patients showed elevated levels of many inflammatory cytokines and immunoglobulin A, and a lower lysozyme level. A strong correlation was shown between lysozyme and IL-1β levels and the relative abundance of *Streptococcus*, *Prevotella*, *Haemophilus* and *Veillonella*. Our data demonstrate that dysbiosis of salivary microbiota is associated with inflammatory responses in IBD patients, suggesting that it is possibly linked to dysbiosis of their gut microbiota.

Skin Microbiome

- Skin has myriad bacteria, fungi and viruses linked to health and disease
- Great differences in individuals
- Great differences in anatomical region of skin
- Critical barrier function for immunity
- Dysfunctional epidermal barrier involved in antigen-driven skin disease, allergic disease, and psoriasis



Gut Microbiome- Functions of Microbiota

- Preserve mucosal barrier function (aka permeability)
- Modulate intestinal immunity
- Maturation of gut-associated lymphatic tissue (GALT)
- Secretion of IgA and antimicrobial peptides
- Trophic and developmental functions on intestinal mucosa
- Bile acid metabolism
- Eiccosanoid synthesis
- Steroid hormone synthesis
- Potent 'bioreactor' of indigestible food substances- converting by fermentation to SCFA, nutrients, antioxidants, vitamins, and productions of thousands of unique substances- many of which remain unrecognized

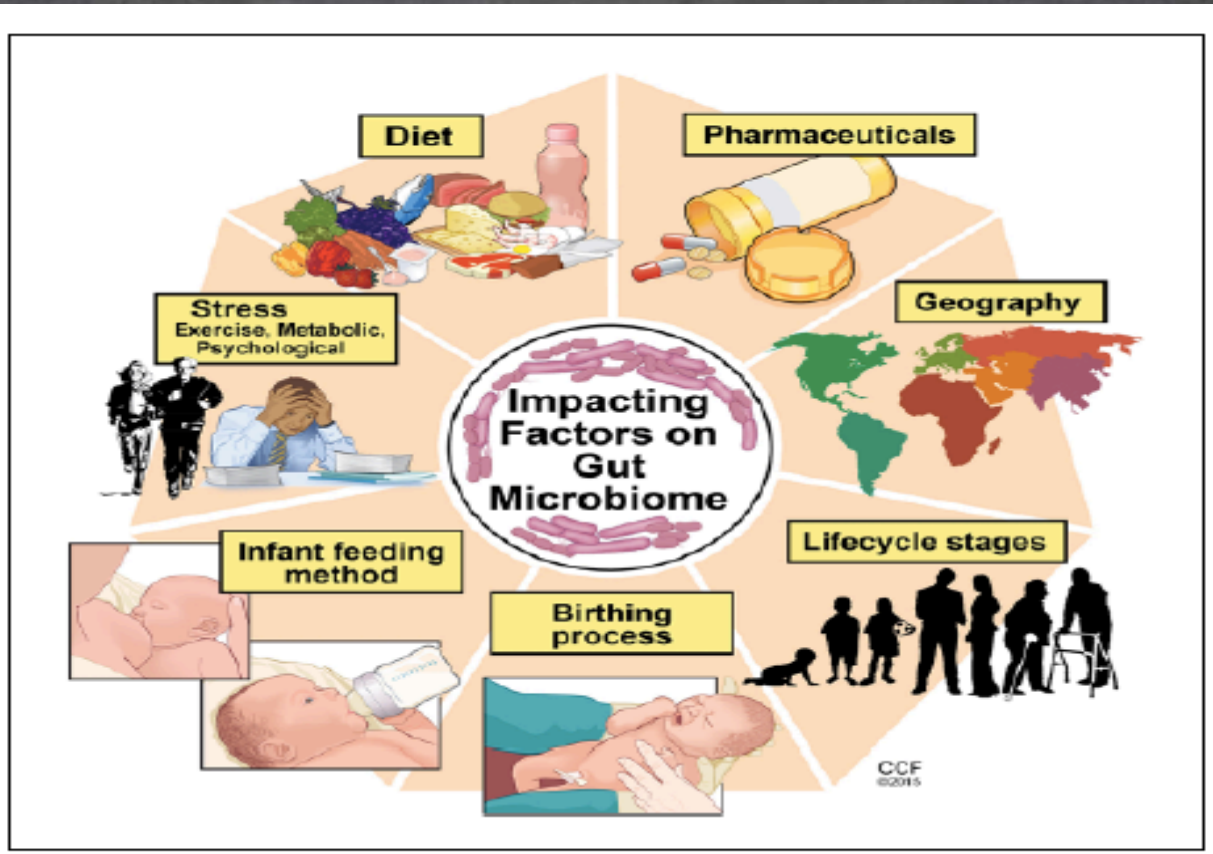


Figure 2. Factors affecting gut microbiome. Illustration by David Schumick, BS, CMI. Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2015. All rights reserved. CCF, Cleveland Clinic Foundation.

Factors Affecting Gut Microbiome

How Important is Diet to the Microbiome?

- "Of all the environmental factors studied to date, diet has the largest known impact on the gut microbiota in healthy as well as sick humans."

Bengmark, S. (2013). Processed foods, dysbiosis, systemic inflammation, and poor health. *Current Nutrition and Food Science*, 9, 113-143.

Diet-Microbiome Pathways and Disease Risk

Figure 3

Possible Relevance to Disease:	Acceleration of Coronary Vascular Disease?	Reduce disease activity in IBD?
Diet:	Choline*	Fiber (Glycans)*
Intestinal Microbiome Enzymatic Function:	Choline-TMA Lyases*	Fermentative enzymes in the production of propionate and butyrate*
Bacterial Metabolite:	TMA	Short Chain Fatty Acids*
Host Cellular Targeting:	Hepatic Conversion of TMA to TMAO	Activation of GPCRs*
Physiologic Impact on Host:	Alteration of cholesterol transport?	Augmentation of Tregs, restoration of mucosal immune tolerance

Table 2 **Indications for associations between the microbiota and health aberrations, provided as an alphabetical listing of the aberrations suggested to be associated with the intestinal microbiota, along with support for such an association.**

Disease or aberration	Type of support	Reference*
Alzheimer's disease	Microbiota in a mouse model of Alzheimer's disease	Karri et al. 2010[103]
Atherosclerosis	Analysis of plaques in humans	Koren et al. 2011[104]
Autistic spectrum disorders	Analysis of mucosa in children with autism spectrum disorders	Williams et al. 2011[105]
Chronic fatigue syndrome	Cultured microbiota in patients with chronic fatigue syndrome	Sheedy et al. 2009[106]
Colic babies	Longitudinal analysis of colic babies cohort	de Weerth et al. 2012 unpublished data
Cardiovascular disease	Cardiovascular-diseased mice and microbial metabolism	Wang et al. 2011[48]
Depression and anxiety	Probiotic intervention in stressed mice	Bravo et al. 2011[34]
Frailty	Analysis of elderly and high frailty scores	van Tongeren et al. 2005[107]
Graft-vs-host disease	Review of human data on graft-vs-host disease	Murphy et al. 2011[108]
Multiple sclerosis	Involvement of microbiota in mice with multiple sclerosis	Berer et al. 2011[109]
Nonalcoholic fatty liver disease	Effect of choline depletion in humans	Spencer et al. 2011[101]
Parkinson's disease	Role of enteric nervous system and review of Parkinson's disease development	Braak et al. 2003[110]
Rheumatoid arthritis	Microbiota as predisposing factor in rheumatoid arthritis	Scher and Abramson 2011[111]
Retrovirus infection	Mouse retrovirus infection relies on microbiota	Kane et al. 2011[112]
Poliovirus infection	Mouse microbiota promotes poliovirus infection	Kuss et al. 2011[113]

* The most recent single reference is given.

Microbiome: Ancestral vs. Modern Western Diet

- Microbiome differences between indigenous tribes, rural, and urban/industrialized individuals- Venezuelan Amazon, rural Malawi, African Burkina Faso, Hadza hunter-gatherers in Tanzania
- Paleo ancestors consumed fresh greens, young leaves, flowers, ripe and unripe fruits, fresh and dried seeds, roots, tubers, piths, bark, and insects (same diet as wild chimps today!)
- Asian, Middle Eastern, and African diets still still contain many foods preserved and prepared through traditional methods
- Modern Western diet- 50% refined carbohydrates cooked at high temperature- rice, bread pasta, potato, other tubers; 30% animal products and refined oils; **only 20% of foods similar to ancestors**
  - Decreased cooking with wood fire
  - Decreased preservation of meat and fish with wood smoke
  - Increased canning and refrigeration
  - Increased sterilization techniques and 'controlled fermentation'

Bengmark, S. (2013). Processed foods, dysbiosis, systemic inflammation, and poor health. *Current Nutrition and Food Science*, 9, 113-143.

Western Versus Prudent Diet Study

- 1 month crossover study
- On Western diet 71% increase in plasma endotoxin
- On Prudent diet 31% decrease in plasma endotoxin

Pendyala, et al. (2012). A high fat diet is associated with endotoxemia that arises from the gut. *Gastroenterology*, 142: 1100-1.

‘Bacterial Penetration Cycle’ Hypothesis

- Hypothesis that dietary components may be able to cause a *localized acquired bacterial clearance defect*
- Leading to *bacterial adhesion and penetration* and subsequent inflammation in the gut

Increased Intestinal Permeability- a.k.a. 'Leaky Gut'

- Stress
- NSAIDs and other medications
- Alcohol
- Toxic exposures
- Food antigens
- Wheat proteins- gluten/gliadin and amylase trypsin inhibitors (ATIs)
- Inflammation
- Malnutrition
- Low fiber diet
- High intake processed foods
- Emulsifying agents
- Artificial sweeteners

Leaky Gut, Bacterial Translocation, & Dysbiosis

- Leakage over the membrane of various tissues of damaging
  - Microbial toxins
  - Endotoxins
  - Food-derived proteotoxins
  - Advanced glycation endpoints (AGEs)
  - Advanced lipoxidation endpoints (ALEs)
  - Bacterial debris and whole dead or live bacteria

Bengmark, S. (2013). Processed foods, dysbiosis, systemic inflammation, and poor health. *Current Nutrition and Food Science*, 9, 113-143.

Dysbiosis, Leaky Barriers & Disease: Beyond Leaky Gut

- **Leaky oral cavity**: gingivitis, periodontitis, and gingival bleeding bleeding associated with increased CVD risk; salivary enzymes include lysozomal enzymes for destroying bacteria cell walls
- **Leaky skin**: drug delivery effective and reliable; translocation of chemicals and microbes with intact skin through hair follicles; burn patients sepsis and multi-organ system failure via skin
- **Leaky airways**: endothelial gaps leak plasma and inflammatory mediator compounds, accompanied by leukocyte influx; microbiota studies in airway disease of asthma, CF, COPD, ventilated infants

Dysbiosis, Leaky Barriers & Disease: Beyond Leaky Gut

- **Leaky placenta**: recent studies reveal pathogens in amniotic cavity from the mother's oral cavity, gut or other sites, which contributes to preterm labor and birth; umbilical cord blood of healthy neonates found to have bacterial species; chorioamnioniontitis inflammatory condition due to microbial invasion
- **Leaky vagina/female reproductive tract (FRT)**: FRT evolved with unique immune mechanisms to protect against potential pathogenic bacterial and viral STDs, allogeneic spermatazoa, and immunologically developing fetus; vaginal infections
- **Leaky blood brain barrier (BBB**): microvascular endothelium tight junctions between BBB, CSF, and CNS; dysruption of these barriers results in neurodegenerative disease, sepsis, encephalopathies

Alcohol Induces Endotoxemia, Dysbiosis, Leaky Gut, and Gut Inflammation

Biomolecules. 2015 Dec; 5(4): 2573–2588.
Published online 2015 Oct 15. doi: 10.3390/biom5042573
PMCID: PMC4693248

Alcohol and the Intestine

Sheena Patel,[1,†*] Rama Behara,[1,†*] Garth R. Swanson,[1,†] Christopher B. Forsyth,[1,2,†] Robin M. Voigt,[1,†] and Ali Keshavarzian[1,3,4,5,†]

Natalia Osna, Academic Editor and Kusum Kharbanda, Academic Editor

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Abstract

Go to:

Alcohol abuse is a significant contributor to the global burden of disease and can lead to tissue damage and organ dysfunction in a subset of alcoholics. However, a subset of alcoholics without any of these predisposing factors can develop alcohol-mediated organ injury. The gastrointestinal tract (GI) could be an important source of inflammation in alcohol-mediated organ damage. The purpose of review was to evaluate mechanisms of alcohol-induced endotoxemia (including dysbiosis and gut leakiness), and highlight the predisposing factors for alcohol-induced dysbiosis and gut leakiness to endotoxins. Barriers, including immunologic, physical, and biochemical can regulate the passage of toxins into the portal and systemic circulation. In addition, a host of environmental interactions including those influenced by circadian rhythms can impact alcohol-induced organ pathology. There appears to be a role for therapeutic measures to mitigate alcohol-induced organ damage by normalizing intestinal dysbiosis and/or improving intestinal barrier integrity. Ultimately, the inflammatory process that drives progression into organ damage from alcohol appears to be multifactorial. Understanding the role of the intestine in the pathogenesis of alcoholic liver disease can pose further avenues for pathogenic and treatment approaches.

Keywords: alcohol, dysbiosis, endotoxemia, gut leakiness

Alcohol, Circadian Rhythms, and Melatonin Abnormalities Impact Leaky Gut

Alcohol. 2015 Jun;49(4):389-98. doi: 10.1016/j.alcohol.2014.07.021. Epub 2014 Nov 14.

Circadian rhythms, alcohol and gut interactions.

Forsyth CB[1], Voigt RM[2], Burgess HJ[3], Swanson GR[2], Keshavarzian A[4].

⊕ **Author information**

Abstract

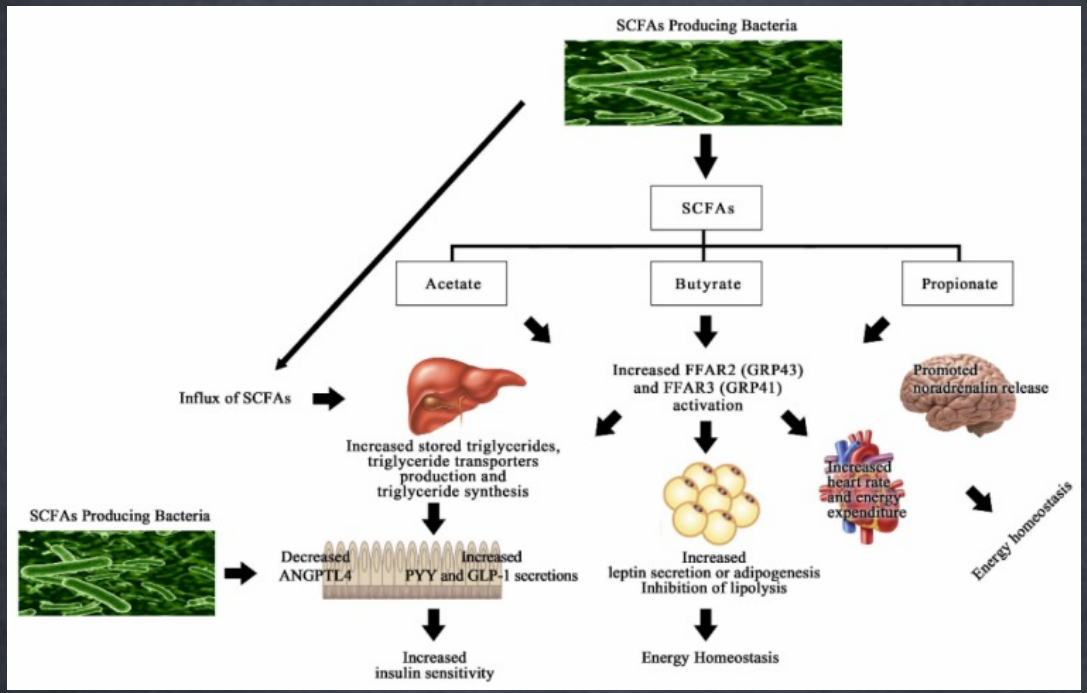
The circadian clock establishes rhythms throughout the body with an approximately 24 hour period that affect expression of hundreds of genes. Epidemiological data reveal chronic circadian misalignment, common in our society, significantly increases the risk for a myriad of diseases, including cardiovascular disease, diabetes, cancer, infertility and gastrointestinal disease. Disruption of intestinal barrier function, also known as gut leakiness, is especially important in alcoholic liver disease (ALD). Several studies have shown that alcohol causes ALD in only a 20-30% subset of alcoholics. Thus, a better understanding is needed of why only a subset of alcoholics develops ALD. Compelling evidence shows that increased gut leakiness to microbial products and especially LPS play a critical role in the pathogenesis of ALD. Clock and other circadian clock genes have been shown to regulate lipid transport, motility and other gut functions. We hypothesized that one possible mechanism for alcohol-induced intestinal hyperpermeability is through disruption of central or peripheral (intestinal) circadian regulation. In support of this hypothesis, our recent data shows that disruption of circadian rhythms makes the gut more susceptible to injury. Our in vitro data show that alcohol stimulates increased Clock and Per2 circadian clock proteins and that siRNA knockdown of these proteins prevents alcohol-induced permeability. We also show that intestinal Cyp2e1-mediated oxidative stress is required for alcohol-induced upregulation of Clock and Per2 and intestinal hyperpermeability. Our mouse model of chronic alcohol feeding shows that circadian disruption through genetics (in Clock(Δ19) mice) or environmental disruption by weekly 12h phase shifting results in gut leakiness alone and exacerbates alcohol-induced gut leakiness and liver pathology. Our data in human alcoholics show they exhibit abnormal melatonin profiles characteristic of circadian disruption. Taken together our data support circadian mechanisms for alcohol-induced gut leakiness that could provide new therapeutic targets for ALD.

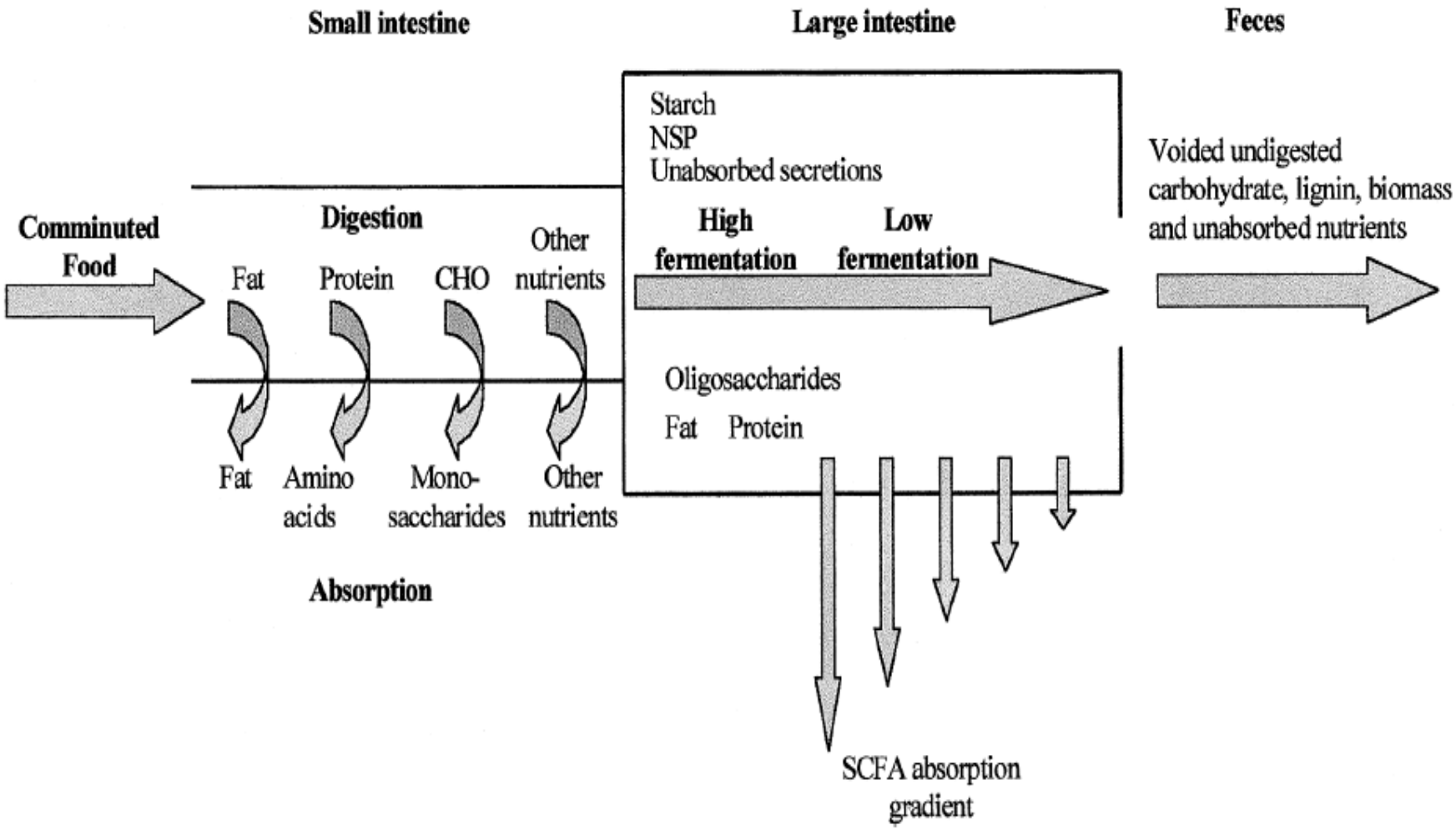
Leaky gut = new target for ALD

KEYWORDS: Alcohol; Circadian rhythms; Cyp2e1; Dysbiosis; Intestinal permeability; Per2

Short Chain Fatty Acids (SFCA)

- Microbes liberate SCFA from indigestible dietary fibers
- SCFA are an important energy source for intestinal mucosa
- SCFA are critical for modulating immune responses and tumorigenesis in the gut
- SCFA play a role in leptin secretion, adipogenesis, and inhibition of lipolysis
- Butyrate is the most abundant SCFA in the gut




Small intestine
Large intestine
Feces
Starch
NSP
Unabsorbed secretions
Voided undigested carbohydrate, lignin, biomass and unabsorbed nutrients
Comminuted Food
Digestion
Fat
Protein
CHO
Other nutrients
High fermentation
Low fermentation
Oligosaccharides
Fat
Protein
Fat
Amino acids
Mono-saccharides
Other nutrients
Absorption
SCFA absorption gradient

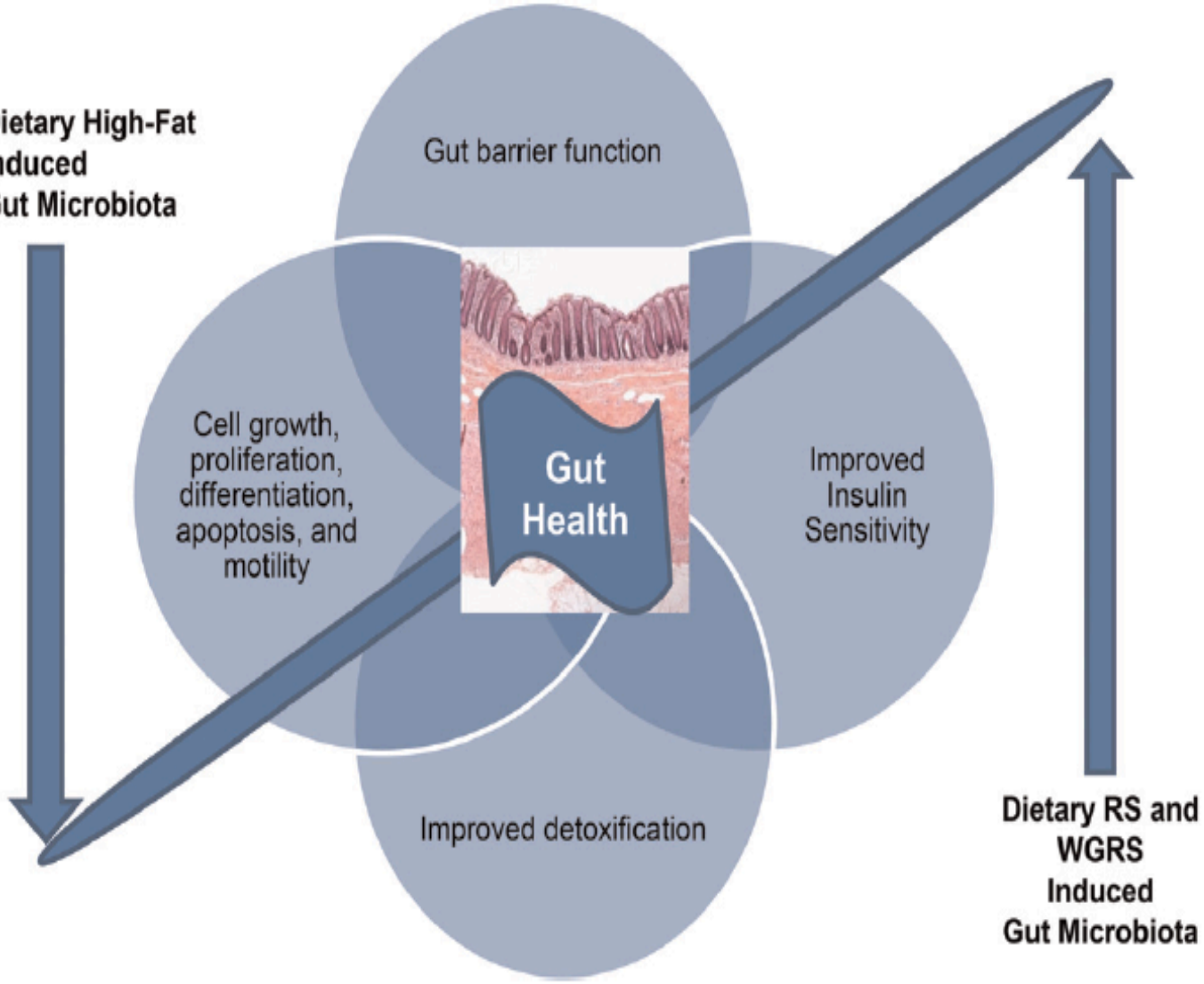


FIGURE 1 A schematic summary of the beneficial gut health effects of a microbiota in response to the feeding of a high-fat diet vs. a gut microbiota in response to the feeding of RS or a whole-grain RS product. The former reduces and the latter increases beneficial health effects. RS, resistant starch; WGRS, whole-grain resistant starch.

Impact of Nutrient Fibers on Nutrient Management and Detoxification Organs: Gut, Liver, and Kidneys

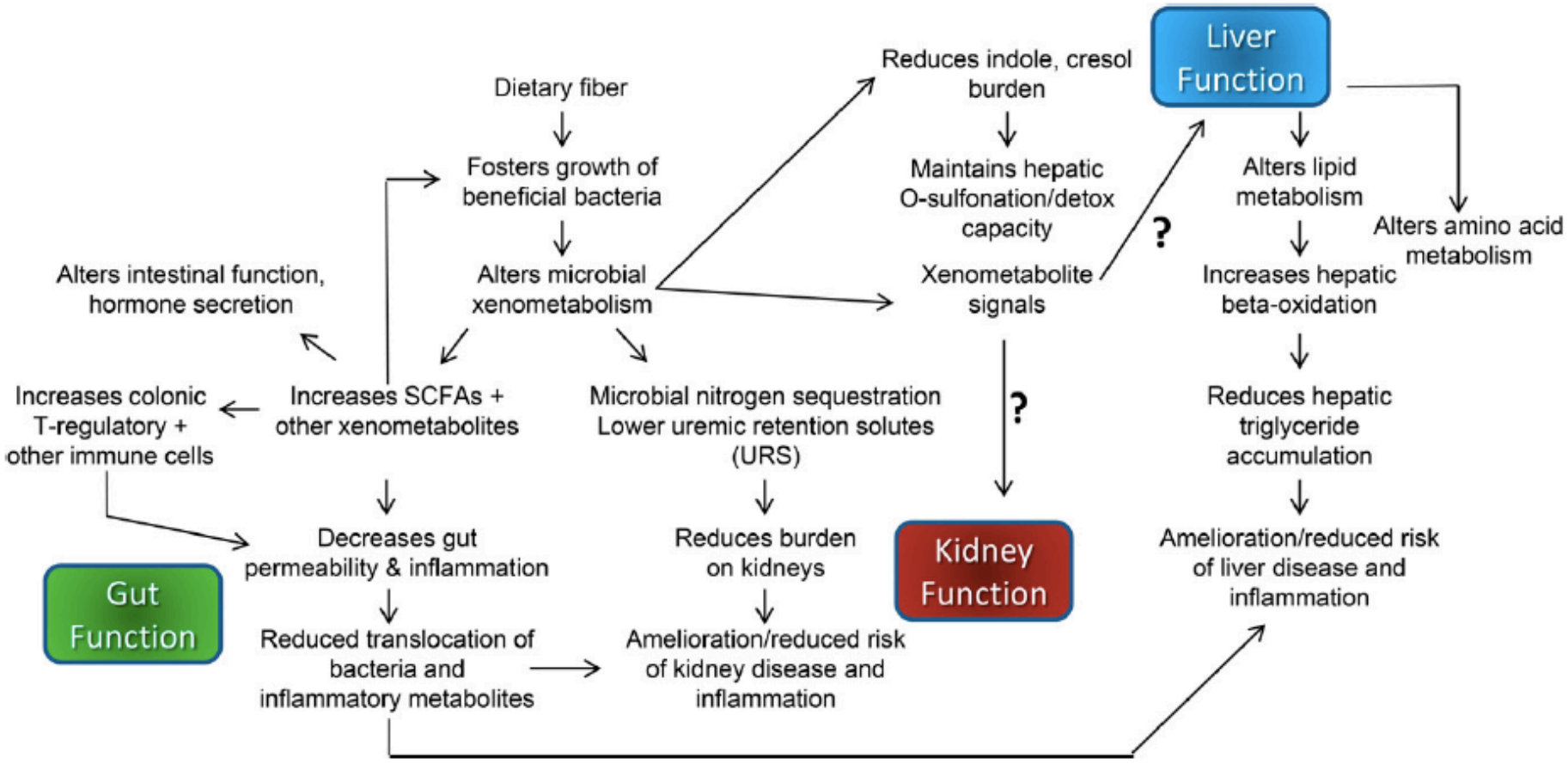


FIGURE 1 Schematic overview of the major mechanisms by which dietary fiber affects gut, liver, and kidneys.

Kieffer et al., 2016 Advances in Nutrition


I DON'T EAT STARCH
IT'S RESISTANT STARCH

Iron, Magnesium, and Fiber Gaps, Oh My!

- Iron deficient rats show significantly lower levels of butyrate and proprionate and changes in dominant microbial species
- Mg+ is involved in > 300 biochemical processes, including microbial multiplication; mice deprived of Mg+ for just 2 days reveal significant reduction in gut bifidobacteria
- **Fiber gap is associated with decreased microbial diversity and number**

Global Dietary Diversity, Agricultural Diversity, Soil Diversity, and Microbial Diversity

- Compelling evidence for decreased gut microbial diversity with industrialization is seen in comparisons of gut microbiota of individuals living in
  - South America
  - New Guinea
  - Africa
  - Europe
  - Japan (*Japanese gene coding for porphyanase enzyme likely transferred from seaweed microbes!*)
  - USA (*In African Americans, change to a traditional South African diet with 55g fiber/d improved colon cancer markers in 2 weeks! (O'Keefe et al., 2015))*

Deehan & Waters. (May 2016). The fiber gap and the disappearing gut microbiome: Implications for human nutrition. *Trends in Endocrinology and Metabolism,* 27(5), 239-241.

IT'S ALL ABOUT THE MATERNAL AND PEDIATRIC BUGS

Obesity Influences Maternal Bacterial Load and Bacterial Diversity in Pregnancy

Pediatr Res. 2015 Jan;77(1-2):196-204. doi: 10.1038/pr.2014.169. Epub 2014 Oct 14.

Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk.

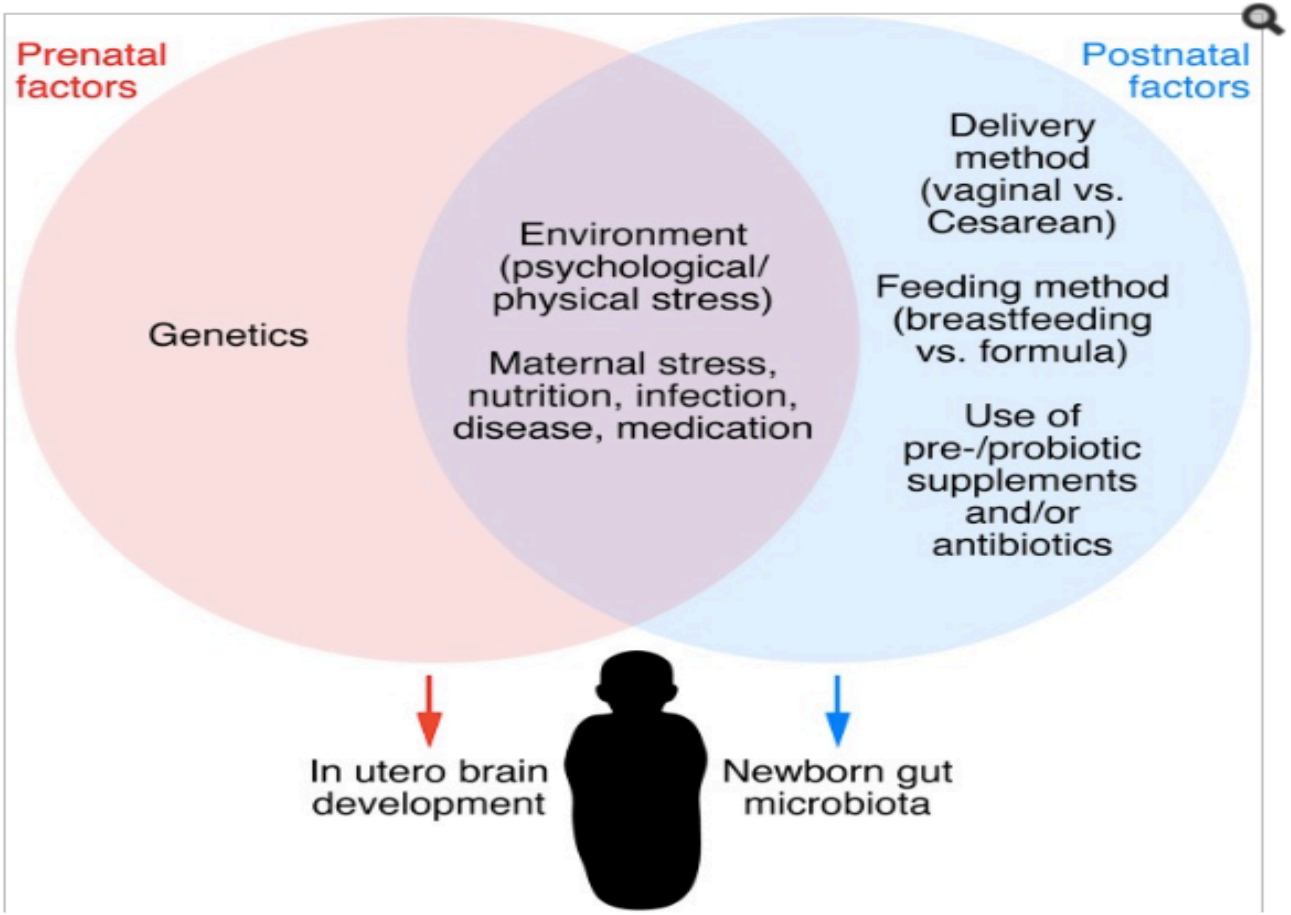
Gohir W[1], Ratcliffe EM[2], Sloboda DM[3].

Author information

Abstract

Chronic disease risk is inextricably linked to our early-life environment, where maternal, fetal, and childhood factors predict disease risk later in life. Currently, maternal obesity is a key predictor of childhood obesity and metabolic complications in adulthood. Although the mechanisms are unclear, new and emerging evidence points to our microbiome, where the bacterial composition of the gut modulates the weight gain and altered metabolism that drives obesity. Over the course of pregnancy, maternal bacterial load increases, and gut bacterial diversity changes and is influenced by pre-pregnancy- and pregnancy-related obesity. Alterations in the bacterial composition of the mother have been shown to affect the development and function of the gastrointestinal tract of her offspring. How these microbial shifts influence the maternal-fetal-infant relationship is a topic of hot debate. This paper will review the evidence linking nutrition, maternal obesity, the maternal gut microbiome, and fetal gut development, bringing together clinical observations in humans and experimental data from targeted animal models.

PMID: 25314580 [PubMed - indexed for MEDLINE]

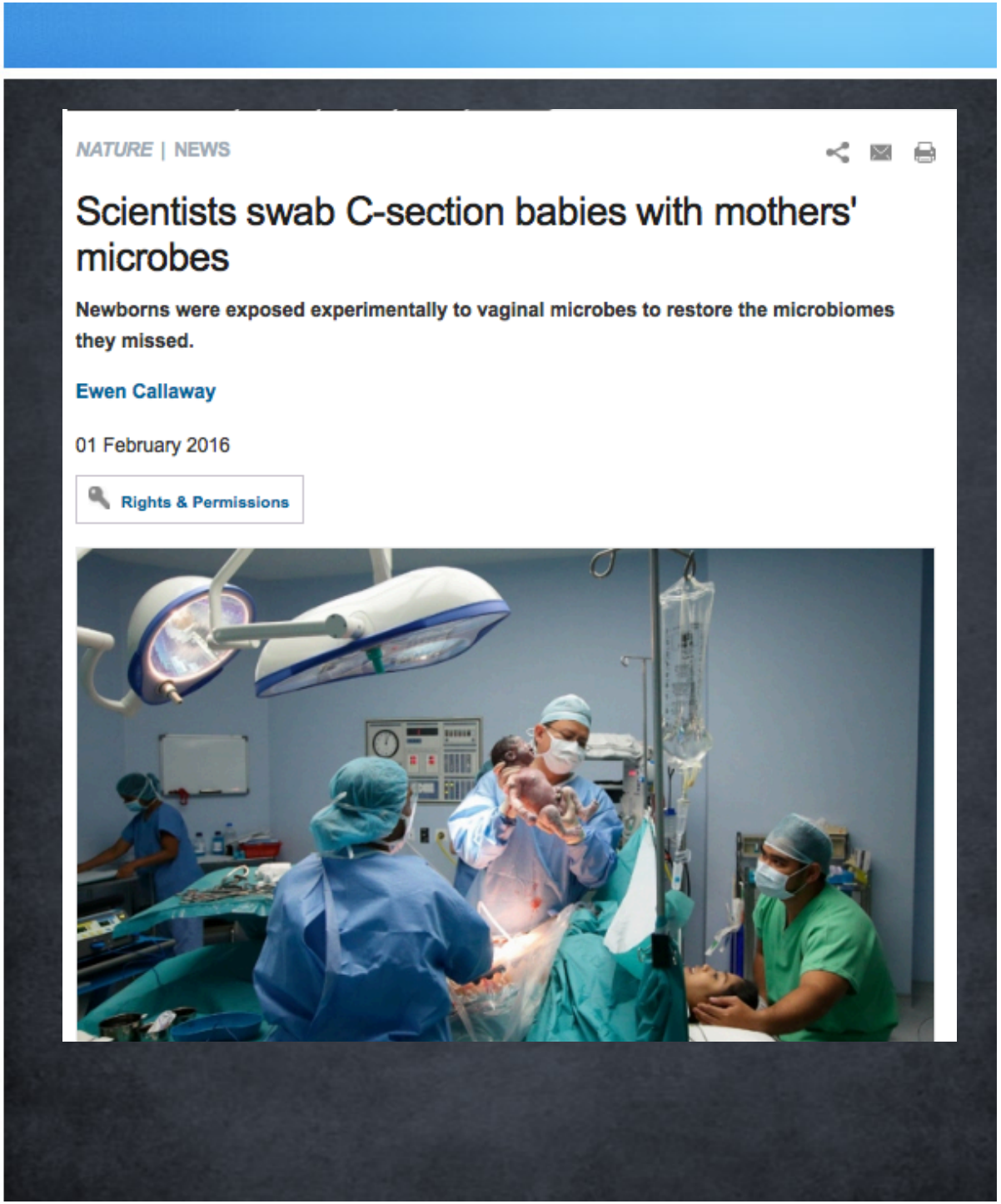


Influences on the gut microbiota/brain axis in the perinatal period.

Multiple factors affecting the maternal gut microbiota can influence brain development in utero via microbial m
strongly influenced by the maternal vaginal or skin-derived microbiota (depending on the mode of delivery) dur
Trends in Molecular Medicine (139).

‘Microbial Bath’

- Just before C-section mother’s vaginal microbes collected with sterile gauze
- Swabbed all over infant’s bodies within 2 minutes of birth
- Follow-up at 1, 3, and 5 years old will explore differences in body composition, asthma and allergies



NATURE | NEWS

Scientists swab C-section babies with mothers' microbes

Newborns were exposed experimentally to vaginal microbes to restore the microbiomes they missed.

Ewen Callaway

01 February 2016

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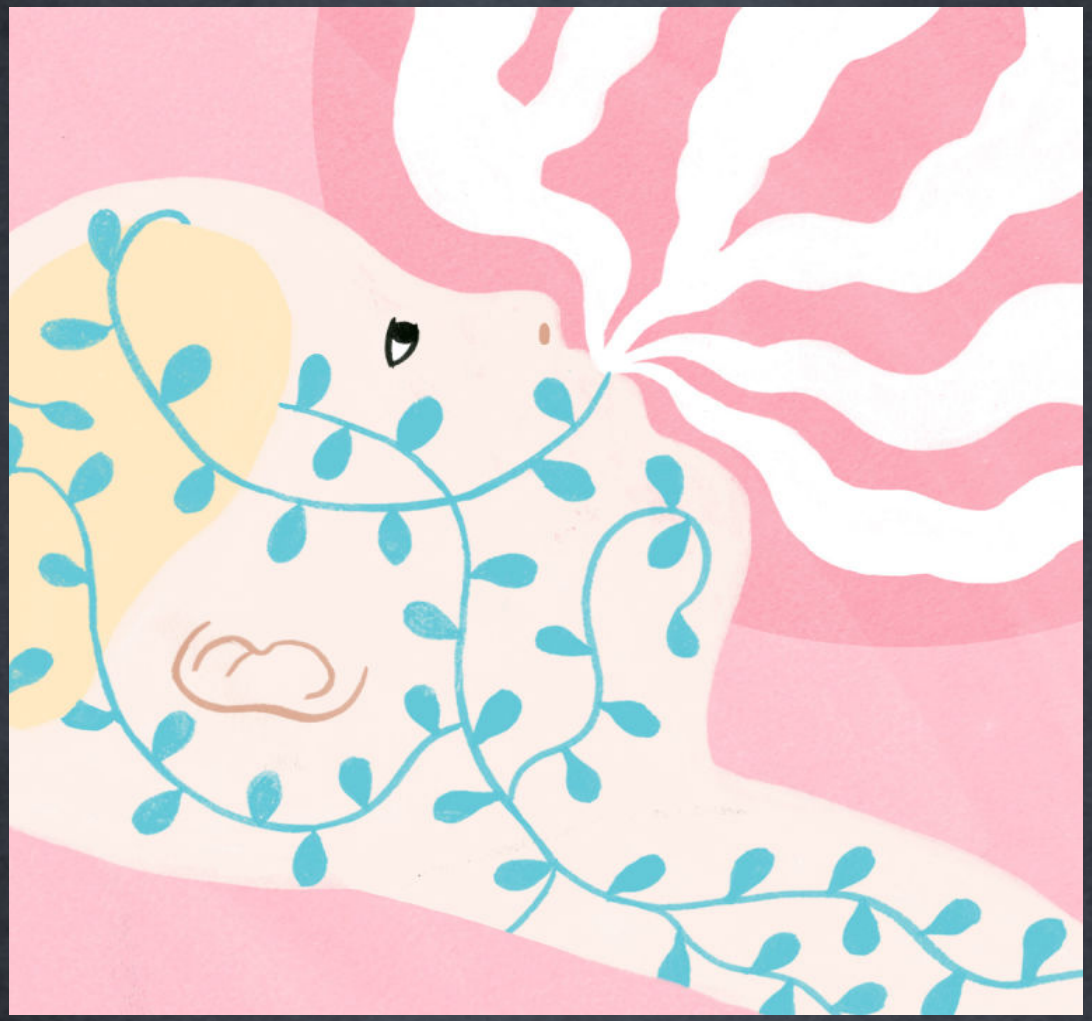
Breastfeeding the Microbiome

- Human breast milk rich in human milk oligosaccharides (HMOs)
- More than 200 HMOs identified
- 3rd most plentiful ingredient in human milk after lactose and fats
- HMOs can't be digested in stomach or SI- HMOs pass through to large intestine/colon!
- Are HMOs food for babies, or food for microbes?
- B-infantis bacteria uses HMOs to produce SCFA, adhesive proteins to decrease gut permeability, and antiinflammatory molecules
- Human breast milk has 5 x > HMOs vs. bovine milk



The New Yorker July 22, 2016

‘Microbiome Plasticity’ in Infant Feeding

frontiers in
CELLULAR AND INFECTION MICROBIOLOGY

ORIGINAL RESEARCH ARTICLE
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Milk- and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome

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The development of the infant intestinal microbiome in response to dietary and other exposures may shape long-term metabolic and immune function. We examined differences in the community structure and function of the intestinal microbiome between four feeding groups, exclusively breastfed infants before introduction of solid foods (EBF), non-exclusively breastfed infants before introduction of solid foods (non-EBF), EBF infants after introduction of solid foods (EBF+S), and non-EBF infants after introduction of solid foods (non-EBF+S), and tested whether out-of-home daycare attendance was associated with differences in relative abundance of gut bacteria. Bacterial 16S rRNA amplicon sequencing was performed on 49 stool samples collected longitudinally from a cohort of 9 infants (5 male, 4 female). PICRUSt metabolic inference analysis was used to identify metabolic impacts of feeding practices on the infant gut microbiome. Sequencing data identified significant differences across groups defined by feeding and daycare attendance. Non-EBF and daycare-attending infants had higher diversity and species richness than EBF and non-daycare attending infants. The gut microbiome of EBF infants showed increased proportions of *Bifidobacterium* and lower abundance of Bacteroidetes and Clostridiales than non-EBF infants. PICRUSt analysis indicated that introduction of solid foods had a marginal impact on the microbiome of EBF infants (24 enzymes overrepresented in EBF+S infants). In contrast, over 200 bacterial gene categories were overrepresented in non-EBF+S compared to non-EBF infants including several bacterial methyl-accepting chemotaxis proteins (MCP) involved in signal transduction. The identified differences between EBF and non-EBF infants suggest that breast milk may provide the gut microbiome with a greater plasticity (despite having a lower phylogenetic diversity) that eases the transition into solid foods.

Keywords: infant gut microbiome, breastfeeding, metagenomics, daycare, feeding transitions

Infant and Toddler Microbiome
By 3 Y.O. Toddler's Microbiomes Similar to Adult's

FIGURE 1 | Representation of the infant gut microbiome development from birth to 3 years of age. By 3 years old, toddler's microbiomes are similar to that in adults and long-term dietary patterns are beginning to establish.

Maternal Obesity Is Associated with Alterations in the Gut Microbiome in Toddlers

Jeffrey D. Galley[1], Michael Bailey[1,2]*, Claire Kamp Dush[3], Sarah Schoppe-Sullivan[3], Lisa M. Christian[2,4,5,6]

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Abstract

Children born to obese mothers are at increased risk for obesity, but the mechanisms behind this association are not fully delineated. A novel possible pathway linking maternal and child weight is the transmission of obesogenic microbes from mother to child. The current study examined whether maternal obesity was associated with differences in the composition of the gut microbiome in children in early life. Fecal samples from children 18–27 months of age (n = 77) were analyzed by pyro-tag 16S sequencing. Significant effects of maternal obesity on the composition of the gut microbiome of offspring were observed among dyads of higher socioeconomic status (SES). In the higher SES group (n = 47), children of obese (BMI≥30) versus non-obese mothers clustered on a principle coordinate analysis (PCoA) and exhibited greater homogeneity in the composition of their gut microbiomes as well as greater alpha diversity as indicated by the Shannon Diversity Index, and measures of richness and evenness. Also in the higher SES group, children born to obese versus non-obese mothers had differences in abundances of *Faecalibacterium* spp., *Eubacterium* spp., *Oscillibacter* spp., and *Blautia* spp. Prior studies have linked some of these bacterial groups to differences in weight and diet. This study provides novel evidence that maternal obesity is associated with differences in the gut microbiome in children in early life, particularly among those of higher SES. Among obese adults, the relative contribution of genetic versus behavioral factors may differ based on SES. Consequently, the extent to which maternal obesity confers measureable changes to the gut microbiome of offspring may differ based on the etiology of maternal obesity. Continued research is needed to examine this question as well as the relevance of the observed differences in gut microbiome composition for weight trajectory over the life course.

Citation: Galley JD, Bailey M, Kamp Dush C, Schoppe-Sullivan S, Christian LM (2014) Maternal Obesity Is Associated with Alterations in the Gut Microbiome in Toddlers. PLoS ONE 9(11): e113026. doi:10.1371/journal.pone.0113026

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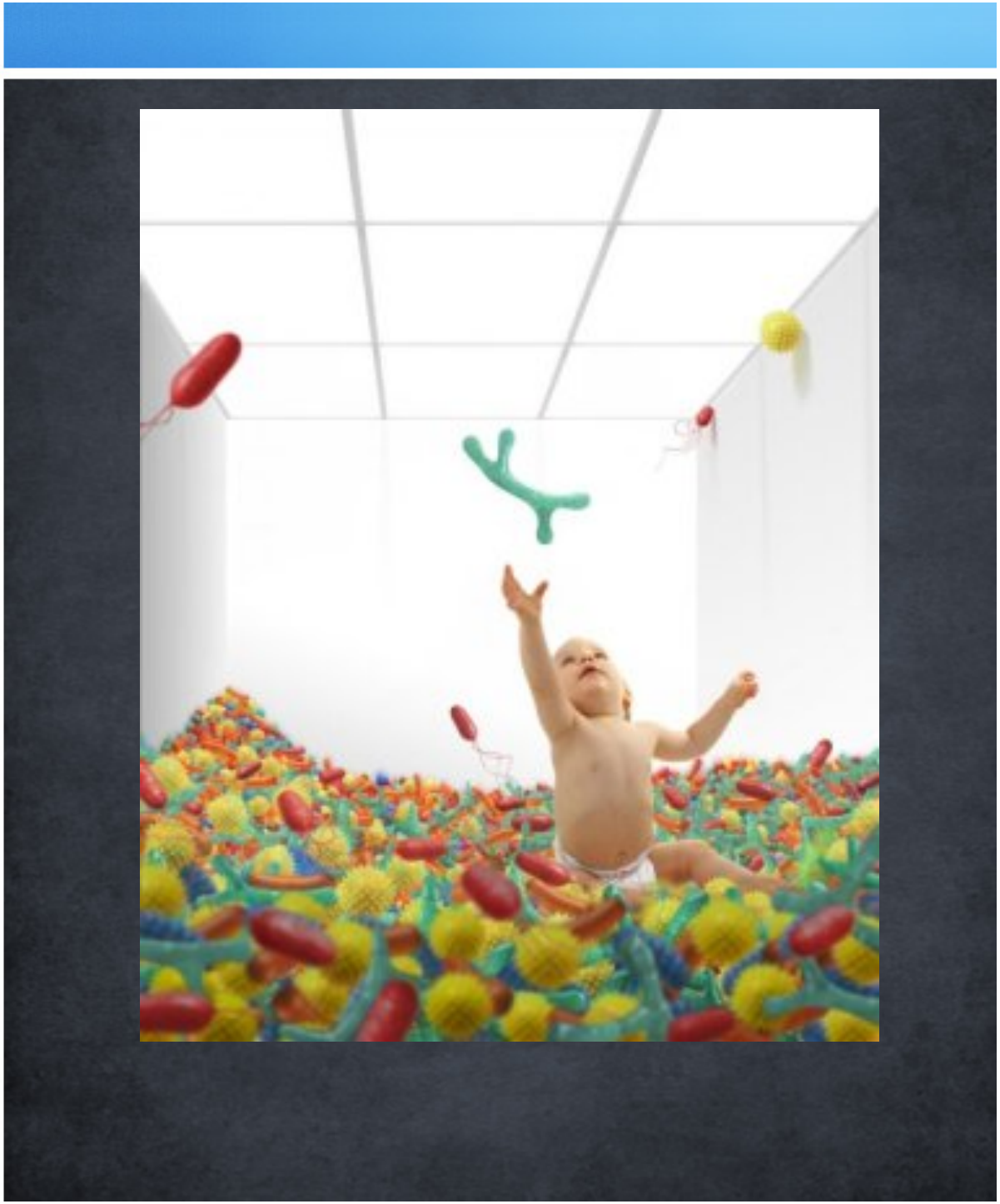
Infant/Toddler Gut Microbiome and Autoimmunity

- Bacteria samples of infants birth to age 3 in three countries
- Lab tests and questionnaires on infant feeding, diet, allergies, infections, and family history
- Evidence supports hygiene hypothesis and variations in e-coli and bacteroides-derived LPS signaling



Vatanen et al. *Cell*, 2016. doi:10.1016/j.cell.2016.04.007

Role of Gut Microbiome in Pathogenesis and Prevention of Type I DM

- A leaky gut has been implicated in type 1 DM, where altered microbiota and disruptions in the immune system promote **autoimmune islet cell destruction.**

Guiden, Wong, & Wen. 2015. The gut microbiota and Type I diabetes. Clinical Immunology, 159(2): 143-153

‘Microbial Mood’- Temperament in Toddlers

Brain Behav Immun. 2015 Mar;45:118-27. doi: 10.1016/j.bbi.2014.10.018. Epub 2014 Nov 10.

Gut microbiome composition is associated with temperament during early childhood.

Christian LM[1], Galley JD[2], Hade EM[3], Schoppe-Sullivan S[4], Kamp Dush C[4], Bailey MT[2].

Author information

Abstract

BACKGROUND: Understanding the dynamics of the gut-brain axis has clinical implications for physical and mental health conditions, including obesity and anxiety. As such disorders have early life antecedents, it is of value to determine if associations between the gut microbiome and behavior are present in early life in humans.

METHODS: We used next generation pyrosequencing to examine associations between the community structure of the gut microbiome and maternal ratings of child temperament in 77 children at 18-27months of age. It was hypothesized that children would differ in their gut microbial structure, as indicated by measures of alpha and beta diversity, based on their temperamental characteristics.

RESULTS: Among both boys and girls, greater Surgency/Extraversion was associated greater phylogenetic diversity. In addition, among boys only, subscales loading on this composite scale were associated with differences in phylogenetic diversity, the Shannon Diversity index (SDI), beta diversity, and differences in abundances of Dialister, Rikenellaceae, Ruminococcaceae, and Parabacteroides. In girls only, higher Effortful Control was associated with a lower SDI score and differences in both beta diversity and Rikenellaceae were observed in relation to Fear. Some differences in dietary patterns were observed in relation to temperament, but these did not account for the observed differences in the microbiome.

CONCLUSIONS: Differences in gut microbiome composition, including alpha diversity, beta diversity, and abundances of specific bacterial species, were observed in association with temperament in toddlers. This study was cross-sectional and observational and, therefore, does not permit determination of the causal direction of effects. However, if bidirectional brain-gut relationships are present in humans in early life, this may represent an opportunity for intervention relevant to physical as well as mental health disorders.

KEYWORDS: Childhood; Children; Early life; Gut microbiome; Gut–brain axis; Human; Mood; Stress; Temperament

Childhood Undernutrition- ‘Microbial Immaturity’

Cultivating Healthy Growth and Nutrition through the Gut Microbiota

Sathish Subramanian,[1,2] Laura Blanton,[1,2] Steven A. Frese,[3] Mark Charbonneau,[1,2] David A. Mills,[3] and Jeffrey I. Gordon[1,2,*]

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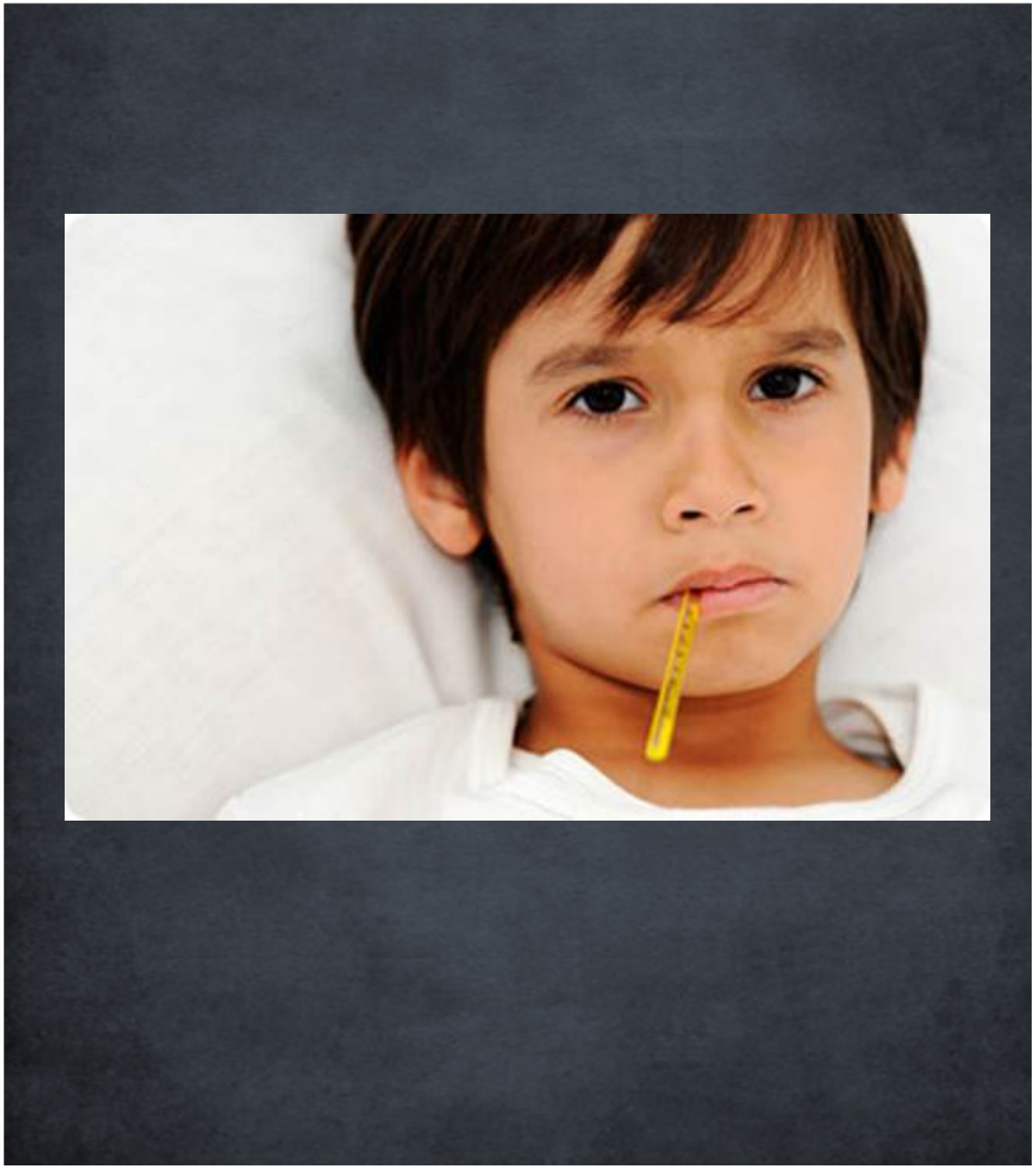
Abstract

Go to:

Microbiota assembly is perturbed in children with undernutrition, resulting in persistent microbiota immaturity that is not rescued by current nutritional interventions. Evidence is accumulating that this immaturity is causally related to the pathogenesis of undernutrition and its lingering sequelae. Preclinical models in which human gut communities are replicated in gnotobiotic mice have provided an opportunity to identify and predict the effects of different dietary ingredients on microbiota structure, expressed functions, and host biology. This capacity sets the stage for proof-of-concept tests designed to deliberately shape the developmental trajectory and configurations of microbiota in children representing different geographies, cultural traditions, and states of health. Developing these capabilities for microbial stewardship is timely given the global health burden of childhood undernutrition, the effects of changing eating practices brought about by globalization, and the realization that affordable nutritious foods need to be developed to enhance our capacity to cultivate healthier microbiota in populations at risk for poor nutrition.

Nasal Microbiome

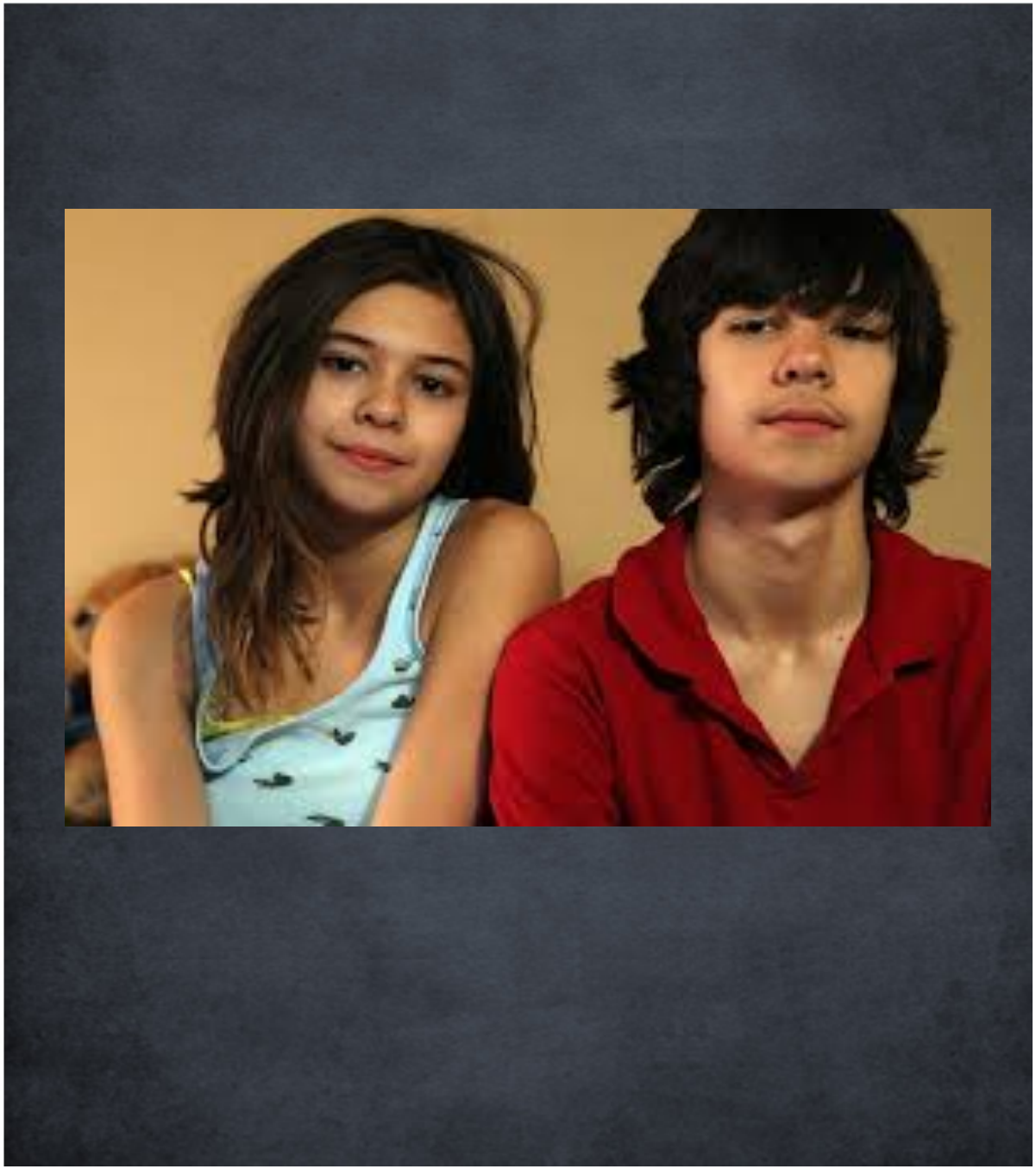
- A study of children with unexplained fevers compared nasal microbiome samples
- Feverish children had 5x more viral DNA, and viral DNA from a wider range of species vs. kids without fever
- Rapid tests for viral loads may help avoid inappropriate antibiotic treatment that harms the healthy microbiome



Nurture Trumps Nature in Oral Bacteria of Twins

- A long term study of identical and fraternal twins found oral microbiota is driven more by environmental factors than heritability
- Salivary microbiome changed the most during adolescence
- Hormones or lifestyle changes at this age may play a role

Stahringer et al. Genome Research, 2012.



Microbiota of Very Low Birth Weight Neonates

Gut Microbes. 2014 May-Jun;5(3):304-12. doi: 10.4161/gmic.28849.

The development of gut microbiota in critically ill extremely low birth weight infants assessed with 16S rRNA gene based sequencing.

Drell T[1], Lutsar I[2], Stšepetova J[2], Parm U[2], Metsvaht T[3], Ilmoja ML[4], Simm J[5], Sepp E[2].

Author information

Abstract

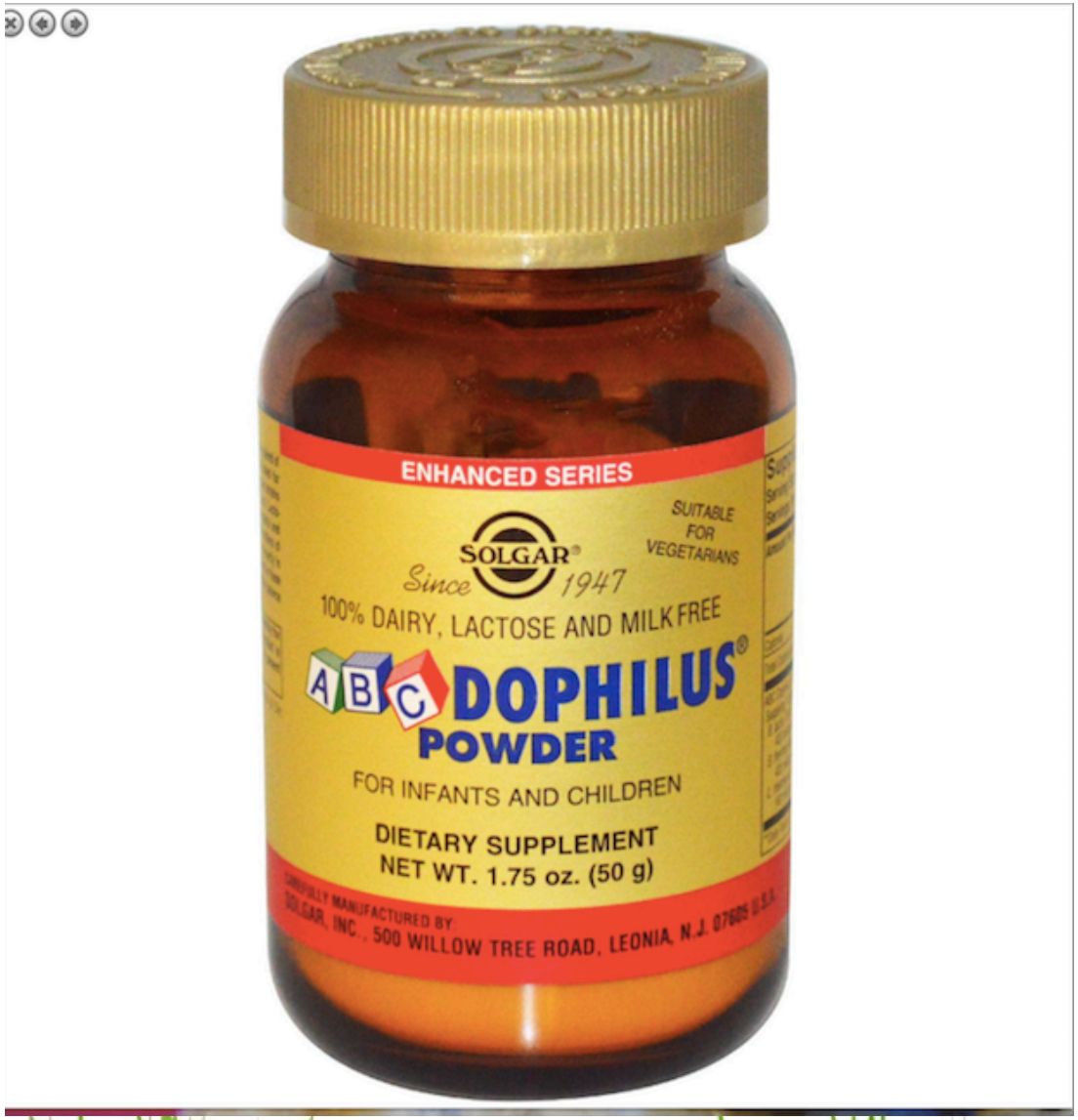
OBJECTIVE: An increasing number of studies that are using high-throughput molecular methods are rapidly extending our knowledge of gut microbial colonization in preterm infants whose immaturity and requirement for extensive treatment may result in altered colonization process. We aimed to describe the profile of gut microbiota in 50 extremely low birth weight (<1200 g) critically ill infants at three different time points during the first two months of life by using 16S rRNA gene specific sequencing.

PATIENTS AND METHODS: Stool samples were collected at the age of one week, one month and two months. Bacterial community profiling was done using universal amplification of 16S rRNA gene and 454 pyrosequencing.

RESULTS: The diversity of gut microbiota in preterm neonates in the first week of life was low but increased significantly over two months. The gut microbiota was dominated by facultative anaerobic bacteria (Staphylococcus spp. and Enterobacteriaceae) and lacked colonization with bacteria known to provide resistance against pathogens (Bacteroides, Bifidobacterium, and Lactobacillus) throughout the study. Colonization of Escherichia coli and uncultured Veillionella was positively correlated with maturity. Infants born to mothers with chorioamnionitis had significantly higher bacterial diversity than those without.

CONCLUSIONS: High prevalence and abundance of potentially pathogenic Enterobacteriaceae and Staphylococcaceae with low prevalence and abundance of colonization resistance providing taxa bifidobacteria, Bacteroides and lactobacilli may lead to high infection risk via microbial translocation from the gut. Additionally, our data suggest that maternal chorioamnionitis may have an effect on the diversity of infants' gut microbiota; however, the mechanisms involved remain to be elucidated.

KEYWORDS: 16S rRNA gene sequencing; extremely low birth weight; gut microbiota; microbiome profiling; preterm neonates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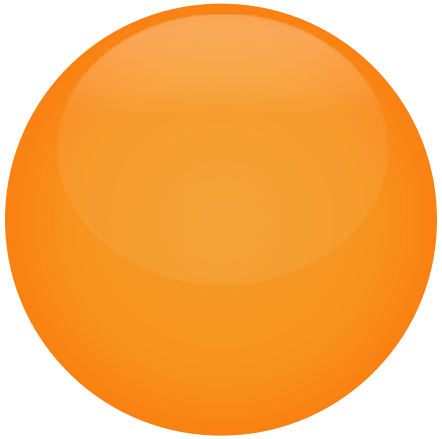
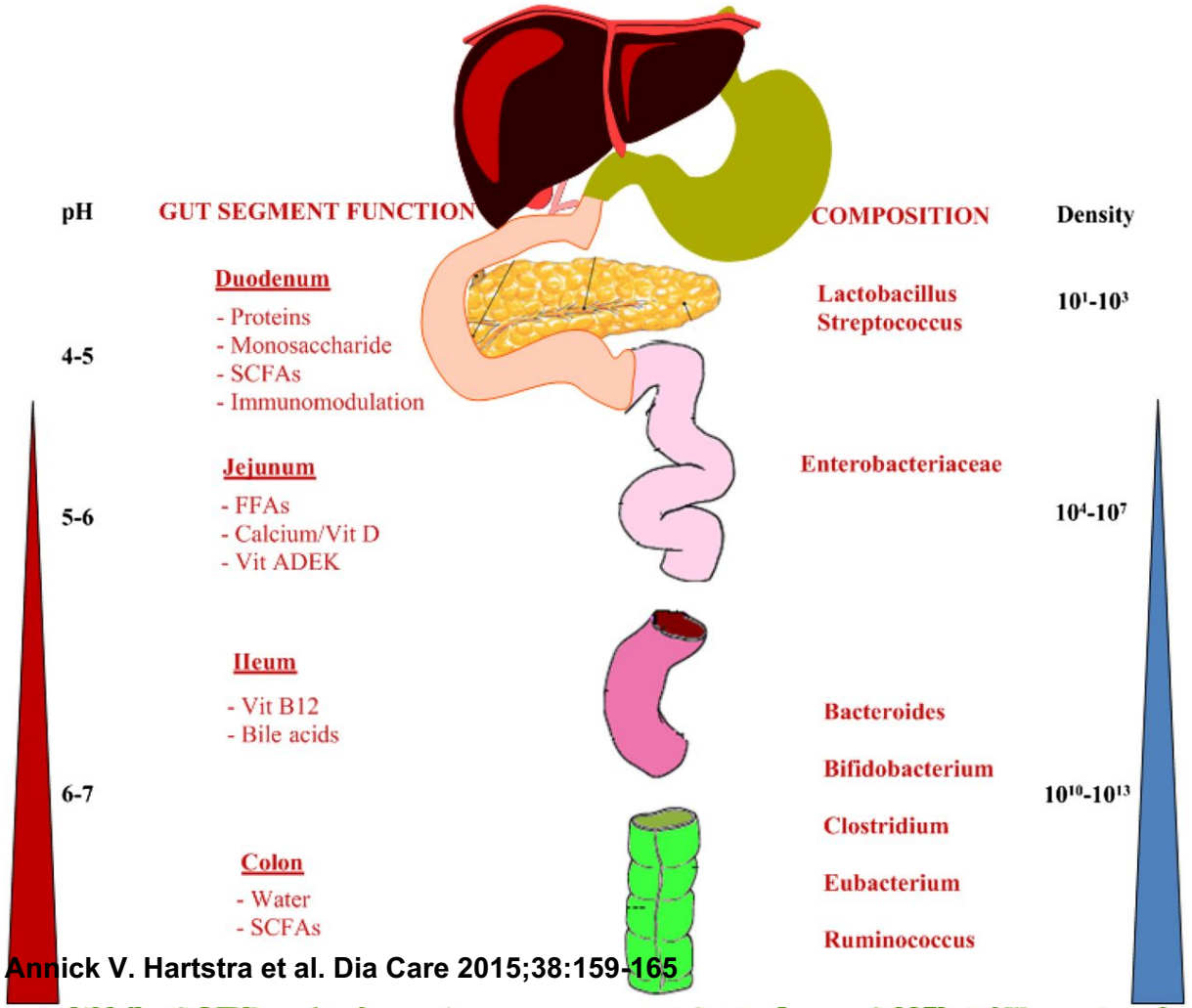


MICROBIOME IN GASTROINTESTINAL DISEASE

Functions of Small and Large Intestine in Relation to Microbial Density



Annick V. Hartstra et al. Dia Care 2015;38:159-165

American Diabetes Association.

Table 1 **Intestinal microbiota-associated diseases, syndromes, or other aberrations, with summaries of multiple studies that support an association between the microbiota and the indicated aberration.**

Aberration	Most relevant observations and potential correlation	References
Crohn's disease	Diversity decrease – reduced *F. prausnitzii*	Kaser et al. 2010[51]; Sokol et al. 2009[52]; Willing et al. 2010[53]
Ulcerative colitis	Diversity decrease – reduced *A. muciniphila*	Png et al. 2010[54]; Kaser et al. 2010[51]; Lepage et al. 2011[55]
Irritable bowel syndrome	Global signatures – increased *Dorea* and *Ruminococcus*	Salonen et al. 2010[36]; Saulnier et al. 2011[56]; Rajilić-Stojanović et al. 2011[13]
Clostridium difficile infection	Strong diversity decrease – presence of *C. difficile*	Grehan et al. 2010[57]; Khoruts et al. 2010[58]
Colorectal cancer	Variation in *Bacteroides* spp. – increased fusobacteria	Sobhani et al. 2011[59]; Wang et al. 2012[60]; Marchesi et al. 2011[61]
Allergy/atopy	Altered diversity – specific signatures	Stsepetova et al. 2007[62]; Bisgaard et al. 2011[63]; Storrø et al. 2011[64]
Celiac disease	Altered composition, notably in small intestine	Nistal et al. 2012[65]; Di Cagno et al. 2011[66]; Kalliomäki et al. 2012[67]
Type 1 diabetes	Signature differences	Vaarela 2011[68]; Giongo et al. 2011[69]; Brown et al. 2011[70]
Type 2 diabetes	Signature differences	Larssen et al. 2010[71]; Wu et al. 2010[72]; Kootte et al. 2012[73]
Obesity	Specific bacterial ratios (*Bacteroidetes*/*Firmicutes*)	Ley et al. 2006[74]; Turnbaugh et al. 2009[10]; Musso et al. 2011[75]

Simple Carbs Associated with Prevotella Bacteria, Protein and Animal Fats with Bacteroides Bacteria

Anaerobe. 2013 Dec;24:117-20. doi: 10.1016/j.anaerobe.2013.03.011. Epub 2013 Mar 30.

Diet, the human gut microbiota, and IBD.

Wu GD[1], Bushmanc FD, Lewis JD.

⊕ Author information

Abstract

The human gut contains a vast number of microorganisms known collectively as the "gut microbiota". Despite its importance in maintaining the health of the host, growing evidence suggests the gut microbiota may also be an important factor in the pathogenesis of various diseases, a number of which have shown a rapid increase in incidence over the past few decades. Factors including age, genetics, and diet may influence microbiota composition. We used diet inventories and 16S rDNA sequencing to characterize fecal samples from 98 individuals. Fecal communities clustered into previously described enterotypes distinguished primarily by levels of Bacteroides and Prevotella. Enterotypes were associated with long-term diets, particularly protein and animal fat (Bacteroides) vs. simple carbohydrates (Prevotella). Although the distinction of enterotypes as either discrete clusters or a continuum will require additional investigation, numerous studies have demonstrated the co-exclusion of the closely related Prevotellaceae and Bacteroides genera in the gut microbiota of healthy human subjects where Prevotella appears to be a discriminatory taxon for residence in more agrarian societies. Ultimately, the impact of diet on the human gut microbiota may be an important environmental factor involved in the pathogenesis of disease states that show a rapidly increasing incidence in industrialized nations such as the inflammatory bowel diseases (IBD).

KEYWORDS: Diet; Genomics; Gut; Human; Microbiota

PMID: 23548695 [PubMed - indexed for MEDLINE]

Bacteria Associated with IBD

Potentially Harmful	Potentially Protective
Adherent–invasive Escherichia coli • ↑in mucosa of ileal CD (also post-operative recurrence)[77], colonic CD and UC[80] *Fusobacterium*[26] • ↑in active UC pouchitis[94] • *Fusobacterium varium*: ↑in UC (adherence and invasion of colonic epithelial cells, increasing IL-8 and TNF-α secretion)[98] • *Fusobacterium nucleatum*: ↑in mucosa of IBD adults[99] and newly diagnosed CD children (with prognostic implication)[21] *Campylobacter concisus* • ↑in pediatric CD[52,58], adult CD[86] and UC[86,87] *Desulfovibrio* • Associated with less sulphated mucin and correlated with mucosal inflammation in UC[100] *Klebsiella* • Associated with CD[101] *Enterohepatic Helicobacter* • ↑in mucosa in UC and CD[102] *Ruminococcus gnavus*: controversial • ↑in faeces in CD (mucolytic properties)[65] • ↓ in mucosa of newly diagnosed CD children[21] *Clostridium difficile* • ↑risk of colonization/infection in IBD[103] • IBD children at diagnosis: significantly↑prevalence[104] • IBD children: 10 fold more common vs. celiac disease; correlated with IBD severity[105] *Veillonella* • ↑in mucosa of newly diagnosed CD children[21] and associated with worse clinical outcome[42] • ↑in post-surgical recurrence in CD[92] *Cytmegalovirus* • Reactivation associated with worse outcome in IBD colitis[106] *Mycobacterium avium subspecies paratuberculosis* • Proposed link with CD in the past, but doubtful lately[11]	*Fecalibacterium prausnitzii* • ↓ in ileal mucosa in newly diagnosed pediatric CD[21] and in faeces in adult CD[45,65,68], active IBD[64] and adult UC[107] • ↓ in ileal mucosa in post-operative recurrence of CD[62] • ↓ in mucosa of healthy siblings of CD patients[66] • ↓ levels associated with relapse after infliximab withdrawal in CD[97] *Clostridium clusters IV and XIVa*[26] • ↓ in ileal mucosa in CD[61] and in faeces in active CD and UC[64] • *Roseburia*: ↓ in mucosa of adult CD and UC[65] and of newly diagnosed CD children[21] • *Roseburia hominis*: ↓ in faeces in UC[107] *Some Bacteroides species*[26] • ↓ in mucosa in adult CD and UC[63], active UC pouchitis[96] and newly diagnosed pediatric CD[21,42,50] and UC[51] • *Odoribacter* (SCFAs production): ↓ in mucosa in pancolonic UC and ileal CD[45] *Bifidobacterium*[26] • ↓ in CD (newly diagnosed children, in mucosa)[21] and UC (in mucosa[60] and faeces[64]) • *BF. Adolescentis*:↓ in faecal samples in CD[65] *Anaerostipes* (butyrate production) • ↓ in current or former smokers[26,45] *Dorea, Butyricicoccus, Coriobacteriaceae* • ↓ in patients receiving antibiotics[26,45]

Figure 2. Bacteria associated with inflammatory bowel disease (IBD): data from human studies.[11,21,26,42,45,50-52,58,60-62,64-66,68,77,80,86-87,92,94,96-107] ↑, abundance increased; ↓, abundance decreased; *BF*, *Bifidobacterium;* CD, Crohn's disease; IL-8, interleukin 8; SCFAs, short-chain fatty acids; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.

Diet Influences Gut Microbiota in IBD

Curr Opin Gastroenterol. 2012 Jul;28(4):314-20. doi: 10.1097/MOG.0b013e328354586f.

Food and the gut microbiota in inflammatory bowel diseases: a critical connection.

Albenberg LG[1], Lewis JD, Wu GD.

⊕ Author information

Abstract

PURPOSE OF REVIEW: The inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract apparently due to an abnormal immune response to environmental factors in genetically susceptible hosts. The composition of the gut microbiota is thought to be a critical environmental factor in IBD, and recent evidence suggests a connection between diet and the intestinal bacteria. In this review, we describe the current evidence regarding the impact of diet on the gut microbiome and how this may be relevant to the pathogenesis of IBD.

RECENT FINDINGS: Novel culture-independent DNA sequencing technology has revolutionized the approach to the characterization of intestinal bacterial communities. Recent studies have demonstrated an association between the diet and the human microbiome. Because the development of a 'dysbiotic' microbiota is thought to be involved in the pathogenesis of IBD, diet is being investigated as an important etiologic factor.

SUMMARY: The recent studies highlighting the impact of diet on the gut microbiome provide a strong rationale for further investigation of the link between diet, the gut microbiome, and the development of IBD. Such studies may provide novel information about disease pathogenesis as well as identify new therapeutic alternatives for patients suffering from IBD.

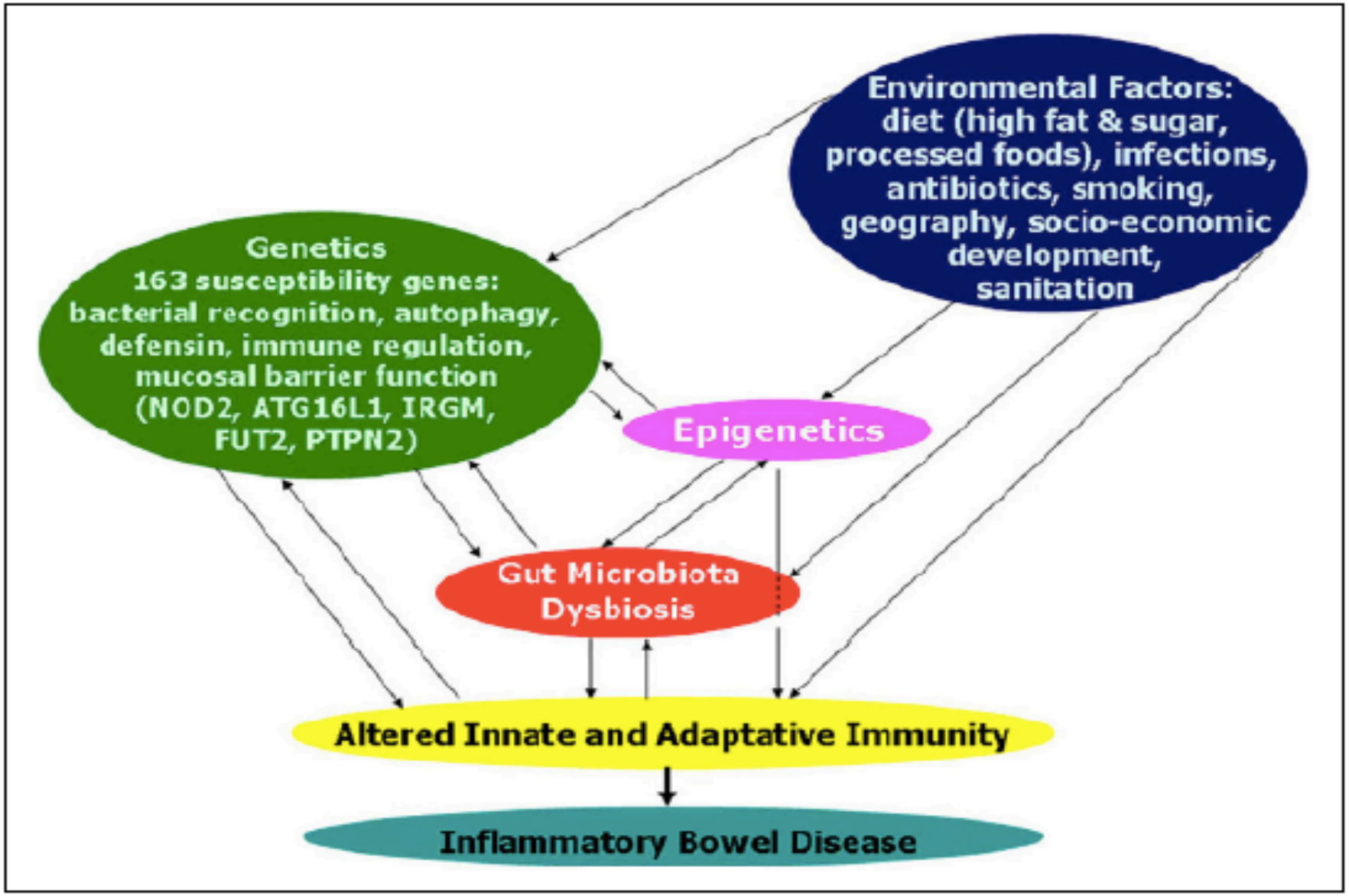


Figure 1. Complex interactions in the pathogenesis of inflammatory bowel disease.

Microbiota May Activate Innate Immunity and Inflammation in Celiac Disease

Dig Dis Sci. 2016 Jan 2. [Epub ahead of print]

Gut Microbiota and Celiac Disease.

Marasco G[1], Di Biase AR[2], Schiumerini R[3], Eusebi LH[4], Iughetti L[5], Ravaioli F[6], Scaioli E[7], Colecchia A[8], Festi D[9].

⊕ Author information

Abstract

Recent evidence regarding celiac disease has increasingly shown the role of innate immunity in triggering the immune response by stimulating the adaptive immune response and by mucosal damage. The interaction between the gut microbiota and the mucosal wall is mediated by the same receptors which can activate innate immunity. Thus, changes in gut microbiota may lead to activation of this inflammatory pathway. This paper is a review of the current knowledge regarding the relationship between celiac disease and gut microbiota. In fact, patients with celiac disease have a reduction in beneficial species and an increase in those potentially pathogenic as compared to healthy subjects. This dysbiosis is reduced, but might still remain, after a gluten-free diet. Thus, gut microbiota could play a significant role in the pathogenesis of celiac disease, as described by studies which link dysbiosis with the inflammatory milieu in celiac patients. The use of probiotics seems to reduce the inflammatory response and restore a normal proportion of beneficial bacteria in the gastrointestinal tract. Additional evidence is needed in order to better understand the role of gut microbiota in the pathogenesis of celiac disease, and the clinical impact and therapeutic use of probiotics in this setting.

KEYWORDS: Celiac disease; Dysbiosis; Gluten-free diet; Gut microbiota; Probiotic

Oats Reduce Leaky Gut in ALD Rat Studies

J Pharmacol Exp Ther. 2001 Nov;299(2):442-8.

Preventing gut leakiness by oats supplementation ameliorates alcohol-induced liver damage in rats.

Keshavarzian A[1], Choudhary S, Holmes EW, Yong S, Banan A, Jakate S, Fields JZ.

⊕ Author information

Abstract

Only 30% of alcoholics develop liver disease (ALD) suggesting that additional factors are needed. Endotoxin is one such factor, but its etiology is unclear. Since the gut is the main source of endotoxin, we sought to determine whether an increase in intestinal permeability (leaky gut) is required for alcohol-induced endotoxemia and liver injury and whether the gut leakiness is preventable. For 10 weeks, rats received by gavage increasing alcohol doses (to 8 g/kg/day) and either oats (10 g/kg) or chow b.i.d. Intestinal permeability was then assessed by urinary excretion of lactulose and mannitol. Liver injury was evaluated histologically, biochemically (liver fat content), and by serum aminotransferase. Alcohol caused gut leakiness that was associated with both endotoxemia and liver injury. Oats prevented these changes. We conclude that chronic gavage of alcohol in rats is a simple experimental model that mimics key aspects of ALD, including endotoxemia and liver injury, and can be useful to study possible mechanisms of endotoxemia in ALD. Since preventing the gut leakiness by oats also prevented the endotoxemia and ameliorated liver damage in rat, our results suggest that alcohol-induced gut leakiness 1) may cause alcohol-induced endotoxemia and liver injury and 2) may be the critical cofactor in the 30% of alcoholics who develop ALD. Further studies are needed to determine whether ALD in humans can be prevented by preventing alcohol-induced gut leakiness, studies that should lead to the development of useful therapeutic agents for the prevention of ALD.

Lactobacillus GG Reduces Leaky Gut in ALD

Alcohol. 2009 Mar;43(2):163-72. doi: 10.1016/j.alcohol.2008.12.009.

Lactobacillus GG treatment ameliorates alcohol-induced intestinal oxidative stress, gut leakiness, and liver injury in a rat model of alcoholic steatohepatitis.

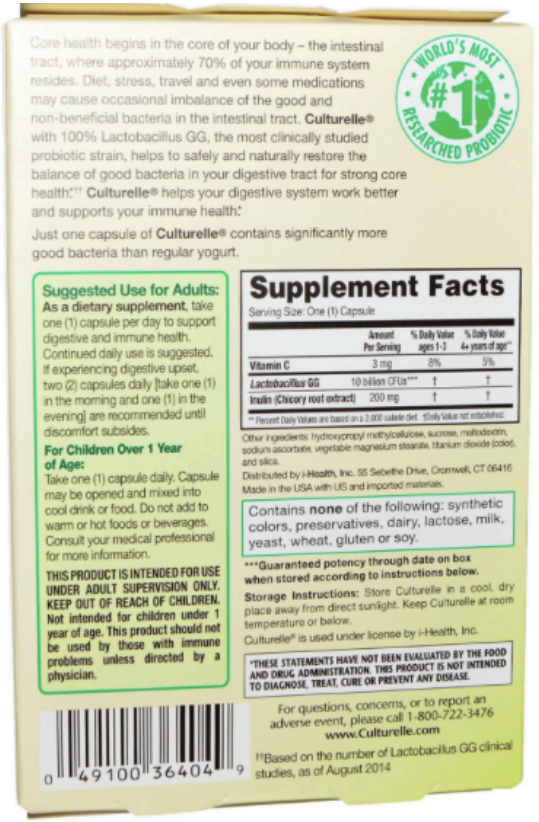
Forsyth CB[1], Farhadi A, Jakate SM, Tang Y, Shaikh M, Keshavarzian A.

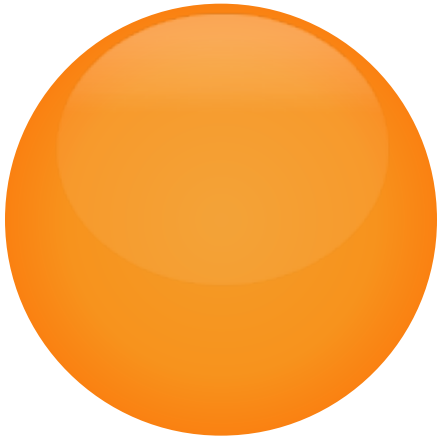
⊕ Author information

Abstract

Because only 30% of alcoholics develop alcoholic liver disease (ALD), a factor other than heavy alcohol consumption must be involved in the development of alcohol-induced liver injury. Animal and human studies suggest that bacterial products, such as endotoxins, are the second key co-factors, and oxidant-mediated gut leakiness is one of the sources of endotoxemia. Probiotics have been used to prevent and treat diseases associated with gut-derived bacterial products and disorders associated with gut leakiness. Indeed, "probiotic"Lactobacillus rhamnosus has been successfully used to treat alcohol-induced liver injury in rats. However, the mechanism of action involved in the potential beneficial effects of L. rhamnosus in alcohol liver injury is not known. We hypothesized that probiotics could preserve normal barrier function in an animal model of ALD by preventing alcohol-induced oxidative stress and thus prevent the development of hyperpermeability and subsequent alcoholic steatohepatitis (ASH). Male Sprague-Dawley rats were gavaged with alcohol twice daily (8 gm/kg) for 10 weeks. In addition, alcoholic rats were also treated with once daily gavage of either 2.5 x 10(7) live L. rhamnosus Gorbach-Goldin (LGG) or vehicle (V). Intestinal permeability (baseline and at 10 weeks) was determined using a sugar bolus and GC analysis of urinary sugars. Intestinal and liver tissues were analyzed for markers of oxidative stress and inflammation. In addition, livers were assessed histologically for severity of ASH and total fat (steatosis). Alcohol+LGG (ALC+LGG)-fed rats had significantly (P< or =.05) less severe ASH than ALC+V-fed rats. L. rhamnosus Gorbach-Goldin also reduced alcohol-induced gut leakiness and significantly blunted alcohol-induced oxidative stress and inflammation in both intestine and the liver. L. rhamnosus Gorbach-Goldin probiotic gavage significantly ameliorated ASH in rats. This improvement was associated with reduced markers of intestinal and liver oxidative stress and inflammation and preserved gut barrier function. Our study provides a scientific rationale to test probiotics for treatment and/or prevention of alcoholic liver disease in man.

Lactobacillus GG

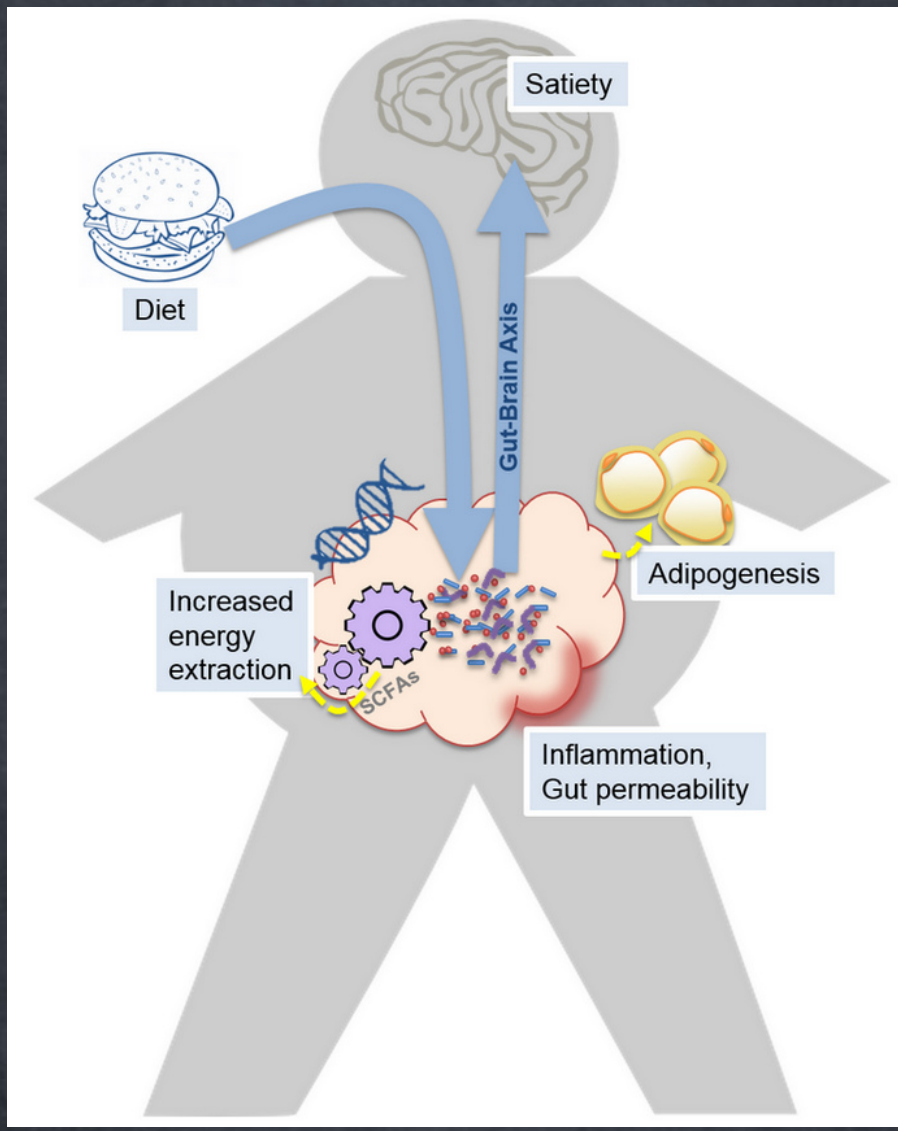




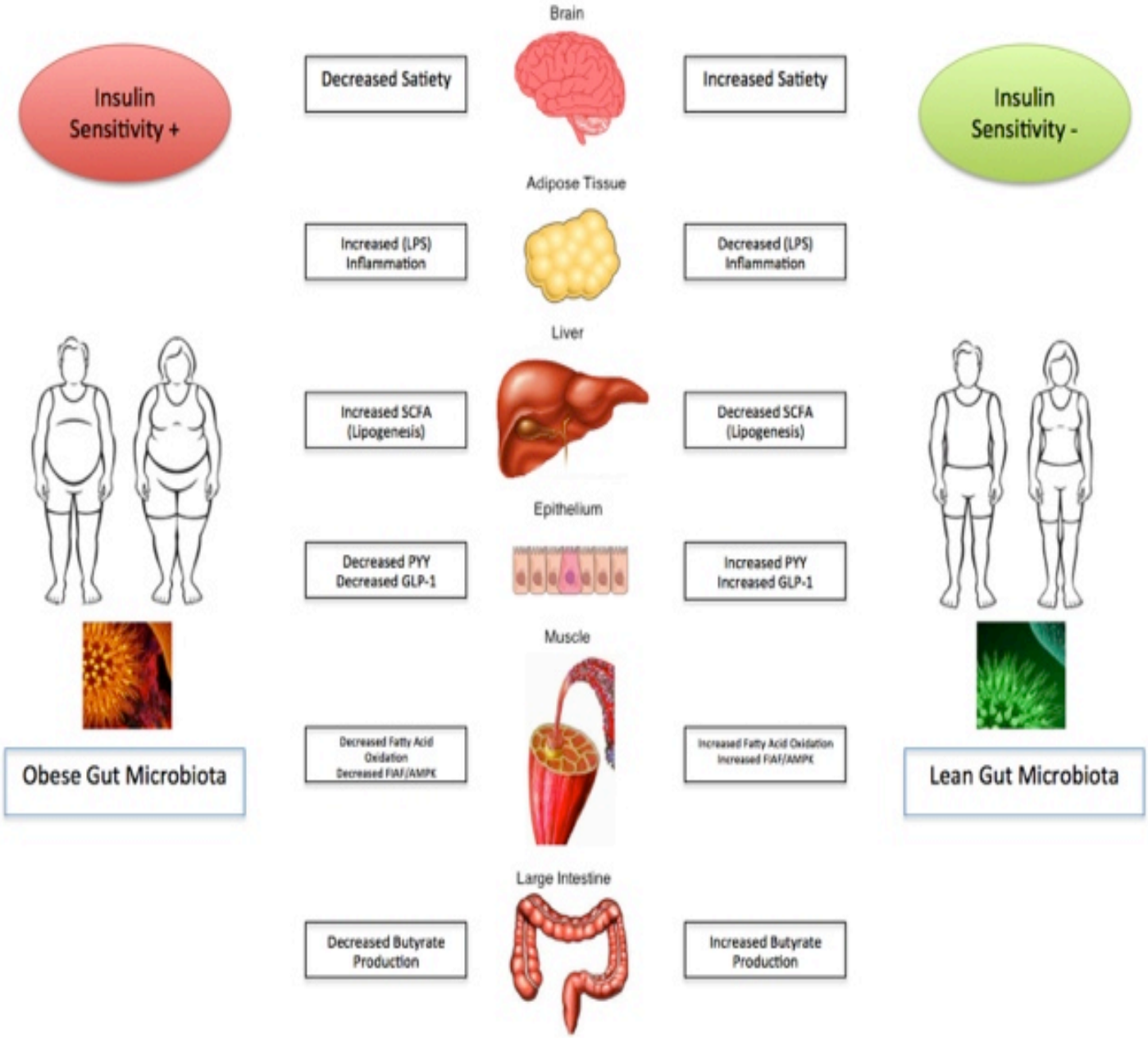
MICROBIOME AND OBESITY

Obesogenic Microbiome

- Diet influences microbiome
- Brain gut axis signaling influences satiety (De Vadder *et al.*, 2014)
- Increased permeability allows excess nutrient absorption and weight gain (Moran & Shanahan, 2014)
- Obesogenic microbiome more efficient at extracting energy from food (Turnbaugh et al., 2006)
- Adipogenesis control linked to gut bacteria through endocannabinoid system Muccioli *et al.*, 2010)



Discovery Medicine. (2015). 19(103): 81-8.


Insulin Sensitivity +
Decreased Satiety
Brain
Increased Satiety
Insulin Sensitivity -
Adipose Tissue
Increased (LPS) Inflammation
Decreased (LPS) Inflammation
Liver
Increased SCFA (Lipogenesis)
Decreased SCFA (Lipogenesis)
Epithelium
Decreased PYY Decreased GLP-1
Increased PYY Increased GLP-1
Muscle
Decreased Fatty Acid Oxidation Decreased FIAF/AMPK
Increased Fatty Acid Oxidation Increased FIAF/AMPK
Large Intestine
Decreased Butyrate Production
Increased Butyrate Production
Obese Gut Microbiota
Lean Gut Microbiota

Probiotics and Prebiotics
Mechanisms Supporting Use In Obesity

- Reduce intestinal permeability
- Inhibit bacteria translocation
- Improve insulin sensitivity
- Decrease inflammation
- Decrease endotoxemia

Fecal Microbial Transplant (FMT), Obesity, and BMI of FMT Donors

Therapeutic Potential of Fecal Microbiota Transplantation

Loek P. Smits, Kristien E.C. Bouter, Willem M. de Vos, Thomas J. Borody, Max Nieuwdorp
Robert F. Schwabe and John W. Wiley, Section Editors

Altmetric 25

DOI: http://dx.doi.org/10.1053/j.gastro.2013.08.058

Article Info

Abstract | Full Text | Images | References

There has been growing interest in the use of fecal microbiota for the treatment of patients with chronic gastrointestinal infections and inflammatory bowel diseases. Lately, there has also been interest in its therapeutic potential for cardiometabolic, autoimmune, and other extraintestinal conditions that were not previously considered to be associated with the intestinal microbiota. Although it is not clear if changes in the microbiota cause these conditions, we review the most current and best methods for performing fecal microbiota transplantation and summarize clinical observations that have implicated the intestinal microbiota in various diseases. We also discuss case reports of fecal microbiota transplantations for different disorders, including *Clostridium difficile* infection, irritable bowel syndrome, inflammatory bowel diseases, insulin resistance, multiple sclerosis, and idiopathic thrombocytopenic purpura. There has been increasing focus on the interaction between the intestinal microbiome, obesity, and cardiometabolic diseases, and we explore these relationships and the potential roles of different microbial strains. We might someday be able to mine for intestinal bacterial strains that can be used in the diagnosis or treatment of these diseases.

Keywords:
Gutmicrobiota, Human Disease, Fecal Transplantation, Therapy

Weight Gain After Fecal Microbiota Transplantation

Neha Alang[1] and Colleen R. Kelly[2]
+ Author Affiliations

Correspondence: Neha Alang, MBBS, Internal Medicine, Newport Hospital, 11 Friendship St, Newport, RI 02840 (nalang@lifespan.org)

(See the Editorial Commentary by Weil et al at doi 10.1093/ofid/ofv005)

Received November 24, 2014.
Accepted November 28, 2014.

Abstract

Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor. This case may stimulate further studies on the mechanisms of the nutritional-neural-microbiota axis and reports of outcomes in patients who have used nonideal donors for FMT.

MICROBIOME AND CARDIOVASCULAR DISEASE (CVD)

How What's in Your Gut Can Affect Your Heart Health

Mediterranean diet, or a diet focused on plants can help you reduce your risk

March 24, 2016 / By Heart & Vascular Team

Rethinking Diet and Lipid Levels

"Our studies suggest the gut microbiome plays an important role in variation in BMI and lipids independent of age, gender, and host genetics".

Circulation Research

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ORIGINAL RESEARCH

The Gut Microbiome Contributes to a Substantial Proportion of the Variation in Blood Lipids

Jingyaun Fu, Marc Jan Bonder, María Carmen Cenit, Ettje Tigchelaar, Astrid Maatman, Jackie A.M. Dekens, Eelke Brandsma, Joanna Marczynska, Floris Imhann, Rinse K. Weersma, Lude Franke, Tiffany W. Poon, Ramnik J. Xavier, Dirk Gevers, Marten H. Hofker, Cisca Wijmenga, Alexandra Zhernakova

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DOI https://doi.org/10.1161/CIRCRESAHA.115.306807
Circulation Research. 2015;CIRCRESAHA.115.306807
Originally published September 10, 2015

Article Supplemental Materials Info & Metrics

Abstract

Rationale: Evidence suggests the gut microbiome is involved in the development of cardiovascular disease (CVD), with the host-microbe interaction regulating immune and metabolic pathways. However, there was no firm evidence for associations between microbiota and metabolic risk factors for CVD from large-scale studies in humans. In particular, there was no strong evidence for association between CVD and aberrant blood lipid levels

Objective: To identify intestinal bacteria taxa, whose proportions correlate with body mass index (BMI) and lipid levels, and to determine whether lipid variance can be explained by microbiota relative to age, gender and host genetics.

Methods and Results: We studied 893 subjects from the LifeLines-DEEP population cohort. After correcting for age and gender, we identified 34 bacterial taxa associated to

Current Issue

Circulation Research
April 28, 2017, Volume 120, Issue 9

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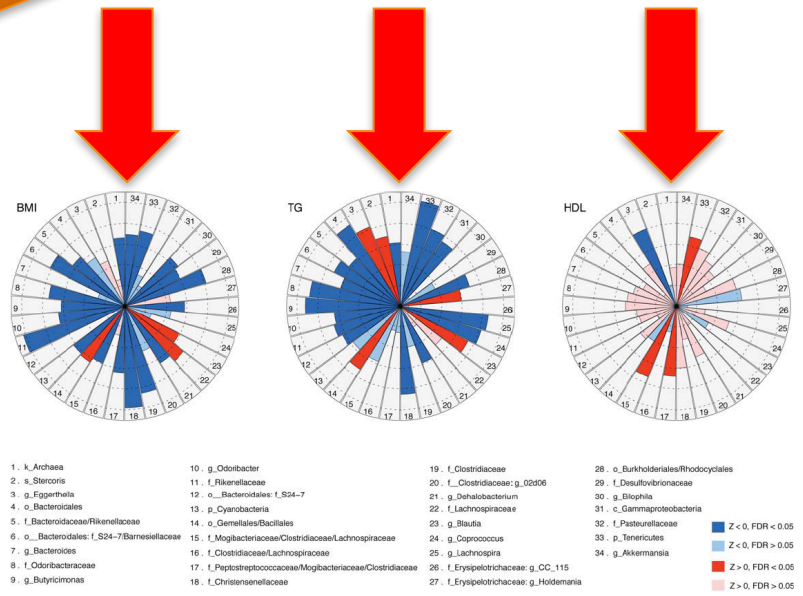

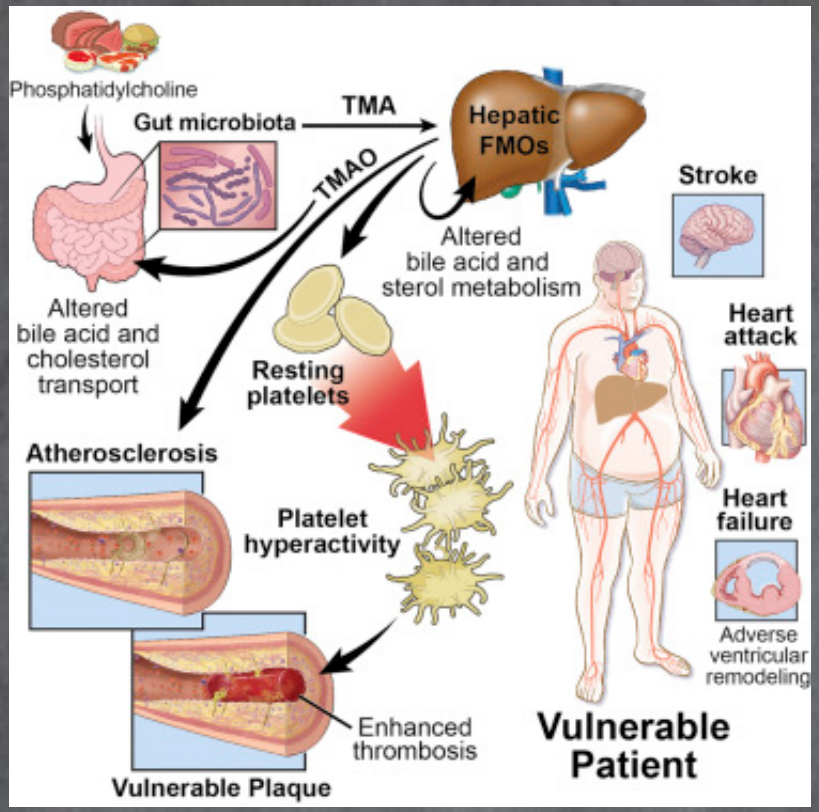

Gut TMAO Increases Clotting and Heart Disease Risk

Cell

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Cell All cell.com

Explore Online Now Current Issue Archive Journal Information For Authors

< Previous Article

Volume 165, Issue 1, p111–124, 24 March 2016

Article

Switch to Standard View

Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk

Weifei Zhu[7], Jill C. Gregory[7], Elin Org, Jennifer A. Buffa, Nilaksh Gupta, Zeneng Wang, Lin Li, Xiaoming Fu, Yuping Wu, Margarete Mehrabian, R. Balfour Sartor, Thomas M. McIntyre, Roy L. Silverstein, W.H. Wilson Tang, Joseph A. DiDonato, J. Mark Brown, Aldons J. Lusis, Stanley L. Hazen

[7] Co-first author

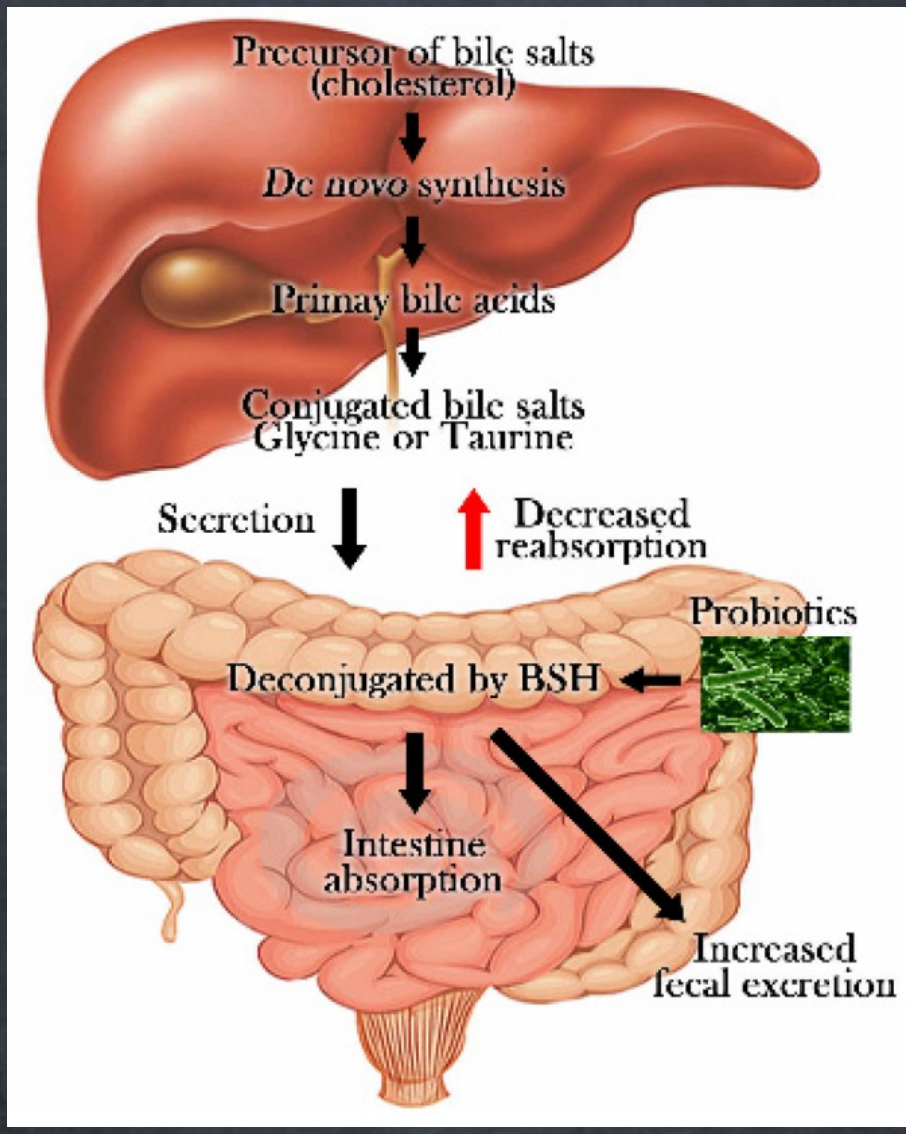
DOI: http://dx.doi.org/10.1016/j.cell.2016.02.011 | CrossMark

Microbiota and Cardiovascular Disease (CVD)

- Microbial metabolism of dietary phosphatidylcholine into the proatherosclerotic metabolite trimethylamine-*N*-oxide (TMAO)
- TMAO levels are associated with increased risk for CVD and cardiac events
- Vegan diets are associated with low TMAO levels
- Omnivorous and carnivorous diets are associated with higher TMAO levels
- TMAO is associated with toxic products of sulfate-reducing bacteria, such as hydrogen sulfide, which is toxic for colon cells and inhibits phagocytosis, bactericide, and butyrate utilization

Probiotics- Proposed Mechanisms for Lowering Cholesterol

- Deconjugation of bile via bile salt hydrolase activity
- Binding of cholesterol to probiotic cellular surface and incorporation into bacteria cell membrane
- Production of SCFAs from oligosaccharides
- Co-precipitation of cholesterol with deconjugated bile
- Cholesterol conversion to coprostanol



Ishimwe et al. (2015) *Molecular Nutrition and Food Research,* 58(1), 94-105.

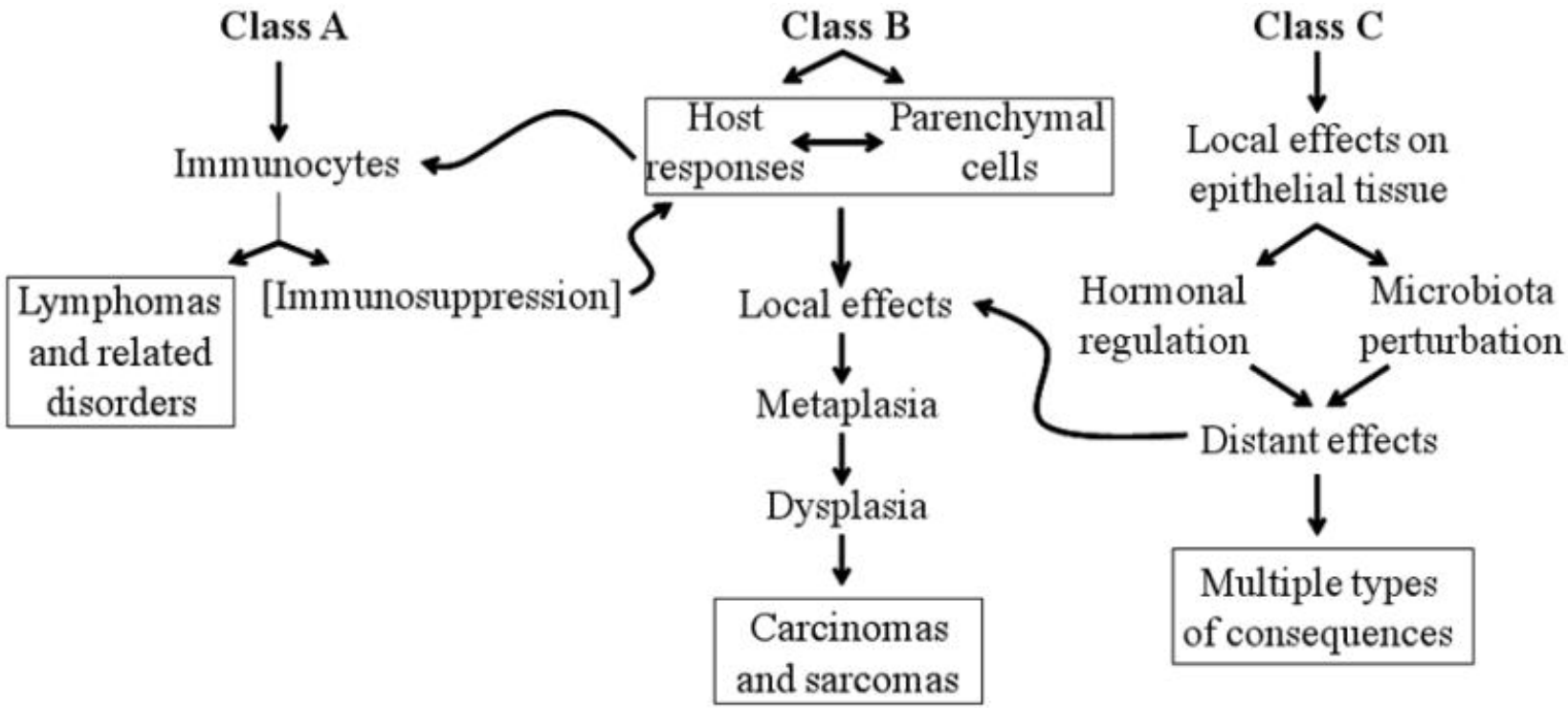
MICROBIOME AND MALIGNANCY

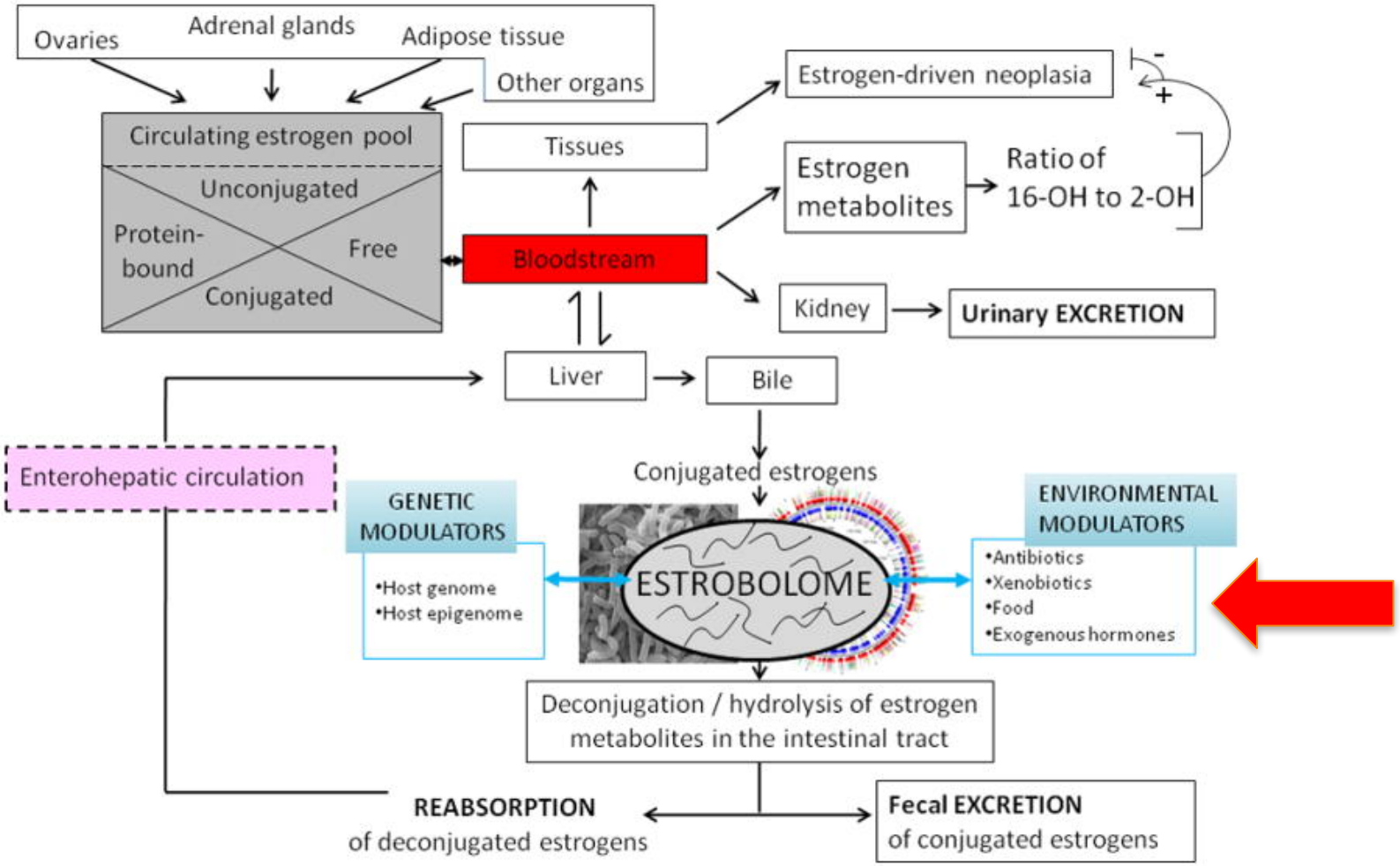
Understanding Microbe-Induced Cancers

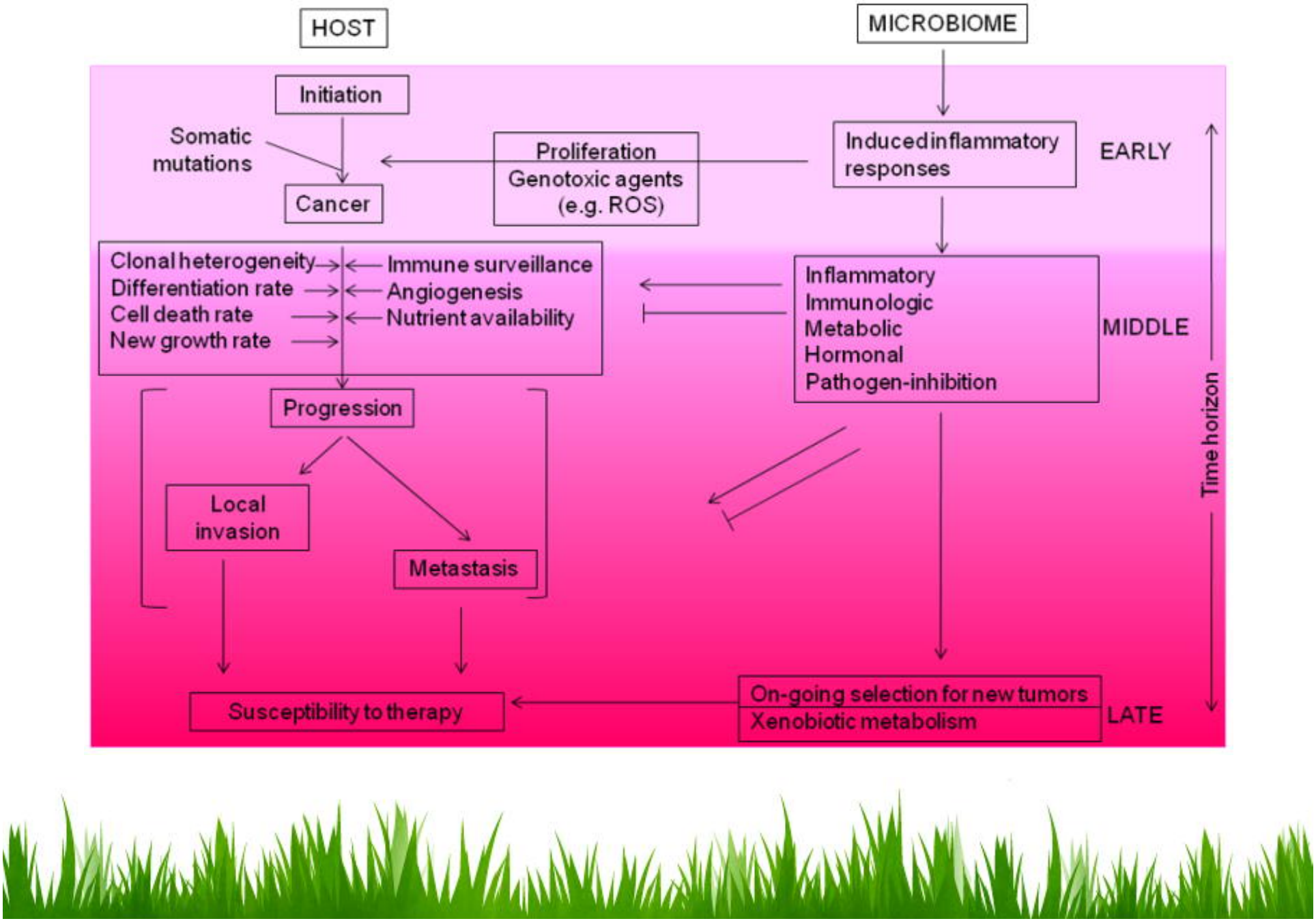
Table 1

Classification of microbe-induced human malignancies

Microbe(s)	Examples of malignancies by class		
	A	B	C
EBV	Lymphoma		
HTLV-1	ATL		
HHV-8	1	Kaposi's sarcoma	
HIV	Lymphoma	Kaposi's sarcoma	
Hepatitis B		Hepatocellular carcinoma	
Hepatitis C	Lymphoma	Hepatocellular carcinoma	
H. pylori	MALT gastric lymphoma	Gastric adenocarcinoma	[Esophageal adenocarcinoma]*
HPV		Anogenital carcinomas, oropharyngeal carcinoma	
Schistosomal species		Bladder cancer	
Liver flukes		Cholangiocarcinoma	
Hypothesized scenarios: microbiome			[Breast, endometrial carcinomas]
ΔMicrobiome†			[Testicular adenocarcinoma]
Microbiome		Colon adenocarcinoma	


Class A
Class B
Class C
Immunocytes
Host responses
Parenchymal cells
Local effects on epithelial tissue
Lymphomas and related disorders
[Immunosuppression]
Local effects
Hormonal regulation
Microbiota perturbation
Metaplasia
Distant effects
Dysplasia
Multiple types of consequences
Carcinomas and sarcomas


Ovaries
Adrenal glands
Adipose tissue
Other organs
Circulating estrogen pool
Unconjugated
Protein-bound
Free
Conjugated
Tissues
Bloodstream
Estrogen-driven neoplasia
Estrogen metabolites
Ratio of 16-OH to 2-OH
Kidney
Urinary EXCRETION
Liver
Bile
Enterohepatic circulation
Conjugated estrogens
GENETIC MODULATORS
•Host genome
•Host epigenome
ESTROBOLOME
ENVIRONMENTAL MODULATORS
•Antibiotics
•Xenobiotics
•Food
•Exogenous hormones
Deconjugation / hydrolysis of estrogen metabolites in the intestinal tract
REABSORPTION
of deconjugated estrogens
Fecal EXCRETION
of conjugated estrogens


HOST
MICROBIOME
Initiation
Somatic mutations
Cancer
Proliferation
Genotoxic agents (e.g. ROS)
Induced inflammatory responses
EARLY
Clonal heterogeneity
Differentiation rate
Cell death rate
New growth rate
Immune surveillance
Angiogenesis
Nutrient availability
Inflammatory
Immunologic
Metabolic
Hormonal
Pathogen-inhibition
MIDDLE
Progression
Local invasion
Metastasis
Time horizon
Susceptibility to therapy
On-going selection for new tumors
Xenobiotic metabolism
LATE

GUT-BRAIN AXIS

Role of the Microbiome in Brain, Stress, Psychiatric, & Sleep Disorders

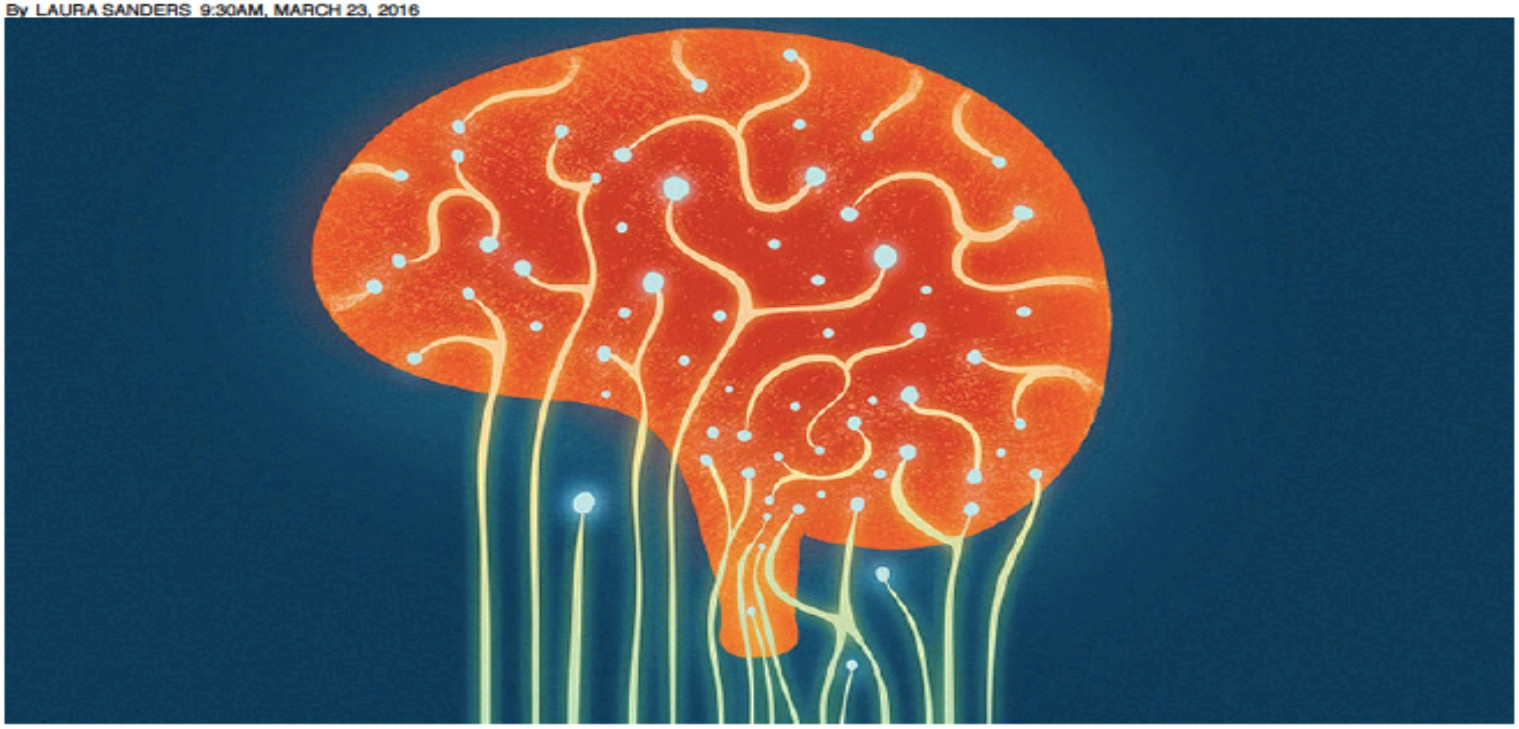
ScienceNews
MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC

Feature: Health,Mental Health

Microbes can play games with the mind

The bacteria in our guts may help decide who gets anxiety and depression

By LAURA SANDERS 9:30AM, MARCH 23, 2016



GUT FEELINGS Through several lines of communication, gut bacteria and the brain affect each other.

Tang Yau Hoong

Magazine issue: Vol. 189, No. 7, April 2, 2016, p. 23

frontiers
in Cellular Neuroscience

REVIEW
published: 14 October 2015
doi: 10.3389/fncel.2015.00392

Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders

John R. Kelly[1,2], Paul J. Kennedy[1], John F. Cryan[1
Gerard Clarke[1,2]* and Niall P. Hyland[1,4]

[1] Laboratory of Neurogastroenterology, APC Microbiome Inst
Psychiatry and Neurobehavioural Science, University Colleg
Neuroscience, University College Cork, Cork, Ireland, [4] Depa
Cork, Cork, Ireland

Mounting evidence suggests the gut microbiome modulates brain development, function and behavior by immune, endocrine, and neural pathways of the brain-gut microbiome axis

The emerging links between our gut microbi
are regarded as a paradigm shift in neuroscien
understanding the pathophysiology of stress-relate
treatment. Thus the gut microbiome and its influence on h
to be a critical node within the brain-gut axis. Mounting prec
suggests that the gut microbiota can modulate brain development, func
by immune, endocrine and neural pathways of the brain-gut-microbi ed
mechanistic insights explaining these specific interactions are currentl ped.
However, the concept that a "leaky gut" may facilitate communic en the
microbiota and these key signaling pathways has gained traction. intestinal
permeability may underpin the chronic low-grade inflammation ob n disorders
such as depression and the gut microbiome plays a critical role in ting intestinal
permeability. In this review we will discuss the possible role played b e gut microbiota
in maintaining intestinal barrier function and the CNS consequenc when it becomes
disrupted. We will draw on both clinical and preclinical evidence to support this concept
as well as the key features of the gut microbiota which are necessary for normal intestinal
barrier function.

Keywords: gut microbiota, intestinal barrier, gut-brain axis, depression, probiotics, psychobiotics

OPEN ACCESS

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Published: 14 October 2015

The Gut Microbiome

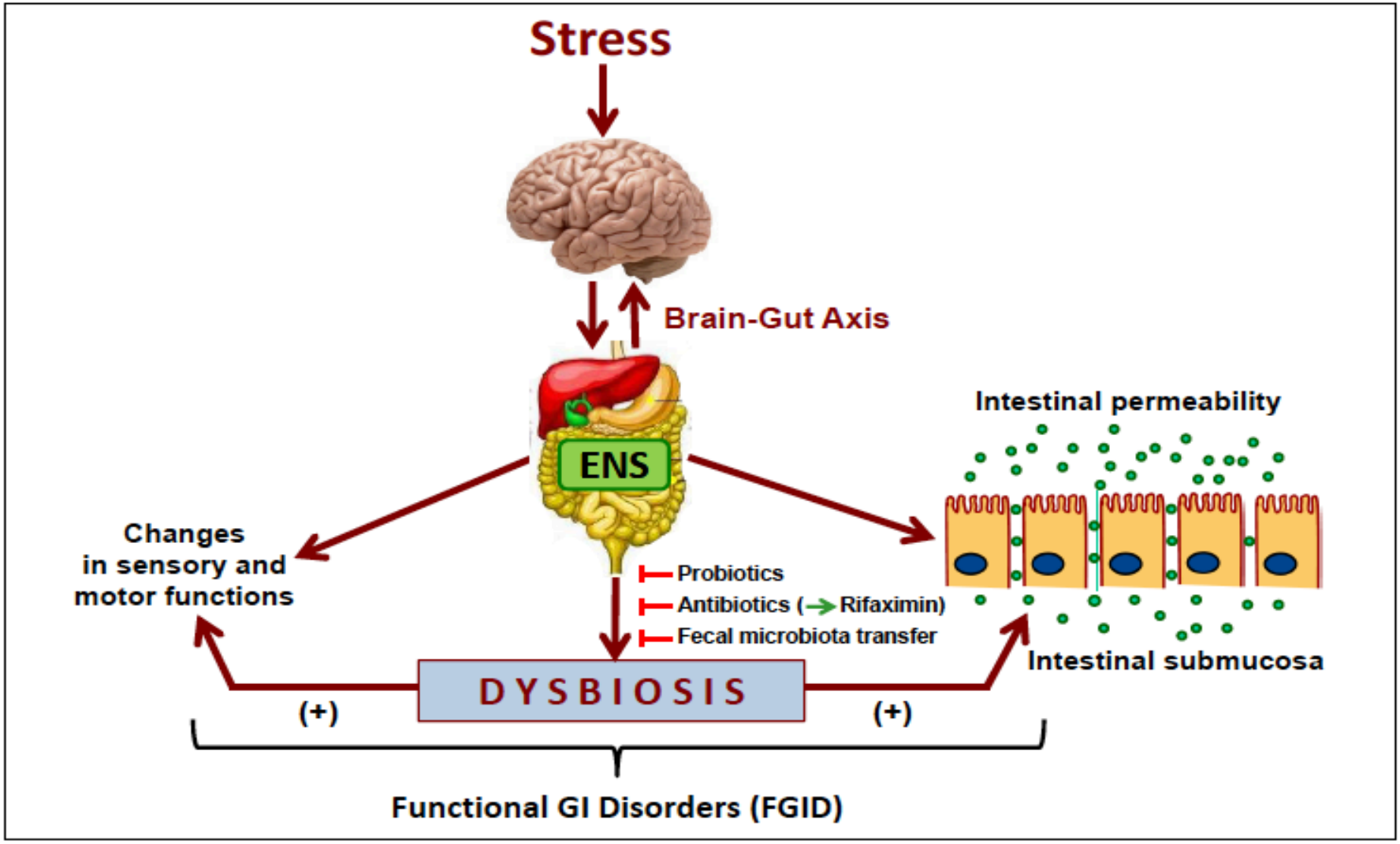

Fig. 5. The proposed mechanism of stress acting *via* brain-gut axis affecting the enteric nervous system (ENS) and gut microbiota that may lead to dysbiosis, increased intestinal permeability and functional gastrointestinal disorders (FGID). The importance of probiotics, transfer of fecal microbiota from healthy donor and modern therapy with antibiotics such as rifaximin to counteract dysbiosis and restore the hypersensitive and pain sensory signals from the gut and alterations in motility of lower bowel.

Bacteria that make brain chemicals

Type of bacteria	Neural messengers
Bacillus	Dopamine, norepinephrine
Bifido-bacterium	Gamma-aminobutyric acid (GABA)
Enterococcus	Serotonin
Escherichia	Norepinephrine, serotonin
Lactobacillus	Acetylcholine, GABA
Streptococcus	Serotonin

Source: T.G. Dinan et al/J. Psych. Res. *2015*

Gut Bacteria
Eat Brain Chemicals

GABA major inhibitory NT

Low levels of GABA associated with depression

GABA ***producing*** bacteria identified

GABA ***consuming*** bacteria identified

Research team found fewer GABA producers in cohort of depressed individuals

ASM Microbe 2016 Meeting

Ann Epidemiol. 2016 Mar 8. pii: S1047-2797(16)30062-X. doi: 10.1016/j.annepidem.2016.02.008. [Epub ahead of print]

Brain-gut-microbiota axis: challenges for translation in psychiatry.

Kelly JR[1], Clarke G[1], Cryan JF[2], Dinan TG[3].

⊕ Author information

Abstract

PURPOSE: The accruing data linking the gut microbiome to the development and function of the central nervous system has been proposed as a paradigm shift in neuroscience. The gut microbiota can communicate with the brain via neuroimmune, neuroendocrine, and neural pathways comprising the brain-gut-microbiota axis. Dysfunctional neuroimmune pathways are implicated in stress-related psychiatric disorders.

METHODS: Using depression as our primary example, we review both the preclinical and clinical evidence supporting the possible role played by the gut microbiota in stress-related psychiatric disorders. We consider how this can inform future treatment strategies and outline the challenges and necessary studies for moving the field forward.

RESULTS: The role played by the gut microbiota has not been fully elucidated in psychiatric populations. Although tempting to speculate that psychiatric patients may benefit from therapeutic modulation of the brain-gut-microbiota axis, the translational applications of the results obtained in rodent studies have yet to be demonstrated.

CONCLUSIONS: Evidence of altered gut microbiota composition and function in psychiatric patients is limited and cannot be regarded as proven. Moreover the efficacy of targeting the gut microbiota has not yet been established, and needs further investigation.

KEYWORDS: Brain-gut axis; Depression; Gut microbiota; Inflammation; Psychobiotics

Psychobiotics- New Frontier Psychiatry?

- Study of B-longum strain for 4 weeks followed by matching placebo capsule for 4 weeks in 22 men
- Measured cortisol output, standardized stress and neuropsychological scales, resting EEG
- Results: reduction in cortisol, less perceived stress and anxiety, subtle improvement on visual memory task, and altered EEG output

Society for Neuroscience 2015 Annual Meeting

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Neuropsychiatric Disease and Treatment

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Neuropsychiatr Dis Treat. 2015; 11: 715–723.
Published online 2015 Mar 16. doi: 10.2147/NDT.S61997
PMCID: PMC4370913

Psychobiotics and the gut–brain axis: in the pursuit of happiness

Linghong Zhou[1] and Jane A Foster[1,2]

Author information ▶ Copyright and License information ▶

Abstract Go to:

The human intestine houses an astounding number and species of microorganisms, estimated at more than 10^{14} gut microbiota and composed of over a thousand species. An individual's profile of microbiota is continually influenced by a variety of factors including but not limited to genetics, age, sex, diet, and lifestyle. Although each person's microbial profile is distinct, the relative abundance and distribution of bacterial species is similar among healthy individuals, aiding in the maintenance of one's overall health. Consequently, the ability of gut microbiota to bidirectionally communicate with the brain, known as the gut–brain axis, in the modulation of human health is at the forefront of current research. At a basic level, the gut microbiota interacts with the human host in a mutualistic relationship – the host intestine provides the bacteria with an environment to grow and the bacterium aids in governing homeostasis within the host. Therefore, it is reasonable to think that the lack of healthy gut microbiota may also lead to a deterioration of these relationships and ultimately disease. Indeed, a dysfunction in the gut–brain axis has been

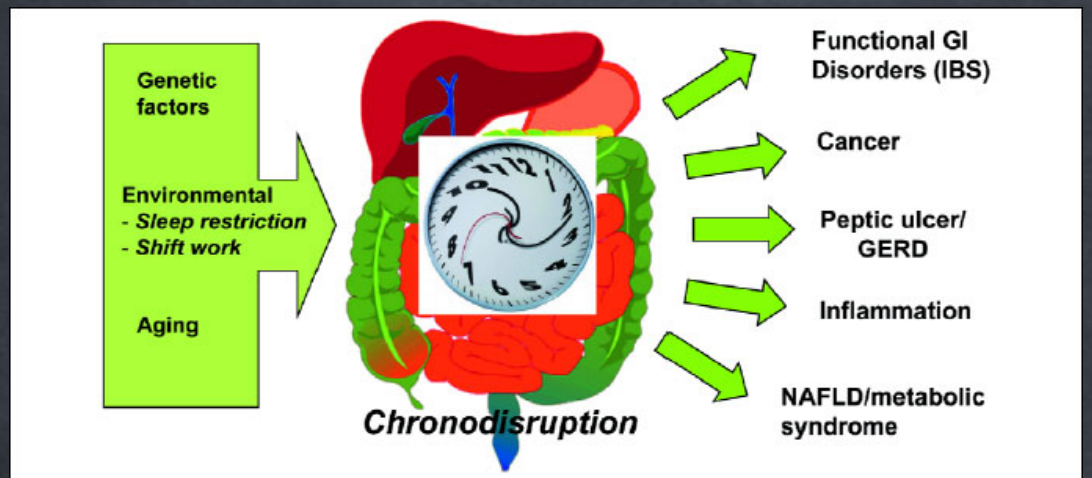
Fecal Microbiota Transplant: New Bacteria, New Behavior

- **‘Melancholic microbes’**
- Rats that got FMT from depressed humans show signs of depression and anxiety. Rats that got FMT from humans without depression showed no change in behavior.
- Floods in Walkerton Canada contaminated town’s water supply with e-coli and campylobacter in 2000. Many fell ill. Years later spike in depression among townspeople attributed to infections.

Science News, April 2, 2016. p. 23.

Microbes Need Sleep, Too? Gut Clock, Sleep, Light-Dark Cycles, and the Microbiome

- Microbiome circadian rhythmicity and ‘chronodisruption’ being studied
- Altered microbial communities and dysbiosis seen in shift workers and jet-lagged individuals
- Interaction with light-dark cycle and high fat, high sugar diet in animal studies
- High fat diet in obstructed sleep apnea (OSA) worsened OSA hypertension and altered gut microbiota, including decreasing SCFA butyrate in animal studies



Gut microbes affect brain injury after stroke

Published: Tuesday 29 March 2016

Adapted Media Release

Altering the gut microbiota of mice can reduce brain damage after a **stroke**, reports a new study published online in *Nature Medicine*. These findings highlight a previously unrecognized link between the intestine and the brain.

Communities of microbes - the microbiome - colonize the gut and other barrier surfaces in the body early in life, and they have a pronounced influence on the development of the immune system and on metabolic processes. Alterations in the microbiome have been identified in several diseases, including inflammatory bowel disease, **obesity** and **asthma**, and they influence disease outcome.

Josef Anrather and colleagues used a mouse model of stroke to show that microbes in the gut regulate the development of pro-inflammatory immune cells, which migrate from the intestine to the brain after a stroke is induced. The authors treated mice with **antibiotics**, and found that this shifted the balance of pro- and anti-inflammatory immune cell types in the gut, increasing the number of anti-inflammatory, regulatory T (Treg) cells present. These microbial shifts ultimately reduce the number of pro-inflammatory cells that travel to the brain after stroke, which results in reduced brain damage. The transferal of microbes from mice treated with antibiotics to untreated mice provided similar protection from brain damage after stroke. The authors conclude that the subset of immune cells identified in the study and the cells' migration to the brain could potentially be targeted therapeutically to affect stroke outcomes, if this specific link between the intestine and the brain is also found in humans.

THE MICROBIOME & REPRODUCTIVE HEALTH

The Vaginal Microbiome

Clin Lab Med. 2014 Dec; 34(4): 747–761.
Published online 2014 Sep 15. doi: 10.1016/j.cll.2014.08.006

The Changing Landscape of the Vaginal Microbiome

Bernice Huang,[1] Jennifer M. Fettweis,[1] J. Paul Brooks,[2] Kimberly K. Jefferson,[1] and Gregory A. Buck[1]

Author information ► Article notes ► Copyright and License information ►

Introduction

Go to:

The microbiome influences humans in many still underappreciated respects, including but not limited to development and growth, immunity, metabolism and even behavior[1,2]. Most bacterial communities exist in mutualistic relationships with the healthy human host, and it is clear that our microbiota evolved in concert with our genome, the product of which is a true human-microbial symbiosis. However, it is also clear that microbial dysbiosis can result in disease, and the outgrowth of opportunistic pathogens can threaten the health and life of the human host. Fueled in part by the *Human Microbiome Project* (HMP) of the National Institutes of Health (NIH), and similar efforts by other groups worldwide[3–5], large-scale efforts have been made to define the "normal" microbiome of healthy individuals across multiple body sites. Facilitated by the advent of next-generation sequencing, a major success of the first phase of these efforts has been the wealth of data generated, which collectively has revealed the previously poorly recognized complexity and dynamic nature of the human microbiome and its stunning impacts on human health and well-being. To further explore the functional role of the microbiome in human health and disease, the NIH has launched HMP2, now termed the *integrative* HMP or iHMP, a second phase of study that mandates a more in depth 'multi-omic' approach to explore host-bacterial interactions and community dynamics in the context of human health and disease.

Colonizing the transfer catheter tip with lactobacillus at time of embryo transfer!

Semin Reprod Med. 2014 Jan;32(1):35-42. doi: 10.1055/s-0033-1361821. Epub 2014 Jan 3.

Potential influence of the microbiome on infertility and assisted reproductive technology.

Sirota I[1], Zarek SM[2], Segars JH[2].

Author information

Abstract

Although an altered vaginal microbiota has been demonstrated to affect parturition, its role in assisted reproductive technologies is uncertain. Nevertheless, the effect of known pathogens such as Mycoplasma tuberculosis, Chlamydia trachomatis, and Neisseria gonorrhoeae is clear, causing subclinical changes thought to be risk factors in subfertility. The Human Microbiome Project (HMP) has allowed for metagenomic studies to aid in characterizing normal vaginal flora. Recent findings from the HMP demonstrate that many different species of Lactobacillus are present in the vaginal tract, with a few that predominate. Studies that characterize the vaginal microbiome in assisted reproductive technology support the hypothesis that colonizing the transfer-catheter tip with Lactobacillus crispatus at the time of embryo transfer may increase the rates of implantation and live birth rate while decreasing the rate of infection. In addition, there is some evidence that a progesterone-resistant endometrium might increase the risk of an abnormal vaginal microbiome.

Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

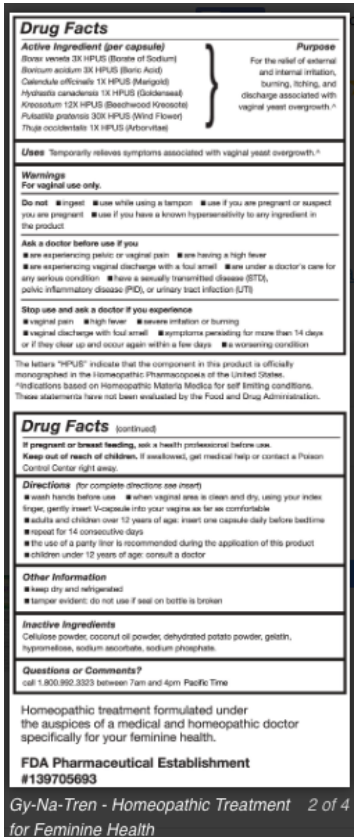
PMID: 24390919 [PubMed - indexed for MEDLINE] PMCID: PMC4137456 Free PMC Article

Dietary Supplements for Vaginal Health

Dietary Supplements for Vaginal Health

Dietary Supplements for Vaginal Health

**Vaginal Suppository- Drug, Not Dietary Supplement*



Drug Facts

Active Ingredient (per capsule) — **Purpose**

Borax venata 3X HPUS (Borate of Sodium)
Borricum acidum 3X HPUS (Boric Acid)
Calendula officinalis 1X HPUS (Marigold)
Hydrastis canadensis 1X HPUS (Goldenseal)
Kreosotum 12X HPUS (Beechwood Kreosote)
Pulsatilla pratensis 30X HPUS (Wind Flower)
Thuja occidentalis 1X HPUS (Arborvitae)

For the relief of external and internal irritation, burning, itching, and discharge associated with vaginal yeast overgrowth.^

Uses Temporarily relieves symptoms associated with vaginal yeast overgrowth.^

Warnings
For vaginal use only.

Do not ■ ingest ■ use while using a tampon ■ use if you are pregnant or suspect you are pregnant ■ use if you have a known hypersensitivity to any ingredient in the product

Ask a doctor before use if you
■ are experiencing pelvic or vaginal pain ■ are having a high fever ■ are experiencing vaginal discharge with a foul smell ■ are under a doctor's care for any serious condition ■ have a sexually transmitted disease (STD), pelvic inflammatory disease (PID), or urinary tract infection (UTI)

Stop use and ask a doctor if you experience
■ vaginal pain ■ high fever ■ severe irritation or burning ■ vaginal discharge with foul smell ■ symptoms persisting for more than 14 days or if they clear up and occur again within a few days ■ a worsening condition

The letters "HPUS" indicate that the component in this product is officially monographed in the Homeopathic Pharmacopoeia of the United States.
^Indications based on Homeopathic Materia Medica for self limiting conditions. These statements have not been evaluated by the Food and Drug Administration.

Drug Facts (continued)

If pregnant or breast feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions (for complete directions see insert)
■ wash hands before use ■ when vaginal area is clean and dry, using your index finger, gently insert V-capsule into your vagina as far as comfortable ■ adults and children over 12 years of age: insert one capsule daily before bedtime ■ repeat for 14 consecutive days ■ the use of a panty liner is recommended during the application of this product ■ children under 12 years of age: consult a doctor

Other Information
■ keep dry and refrigerated ■ tamper evident: do not use if seal on bottle is broken

Inactive Ingredients
Cellulose powder, coconut oil powder, dehydrated potato powder, gelatin, hypromellose, sodium ascorbate, sodium phosphate.

Questions or Comments?
call 1.800.992.3323 between 7am and 4pm Pacific Time

Homeopathic treatment formulated under the auspices of a medical and homeopathic doctor specifically for your feminine health.

FDA Pharmaceutical Establishment #139705693

Gy-Na-Tren - Homeopathic Treatment for Feminine Health 2 of 4

Dietary Supplements for Vaginal Health
**Vaginal Suppository- Drug, Not Dietary Supplement*

DAIRY FREE & GLUTEN FREE

Suggested Use: Take one oral probiotic capsule daily (purple label bottle), just before a light meal.

Potency & Purity
Each capsule supplies a minimum of 5 billion cfu of live, active *L. acidophilus*, beneficial probiotic bacteria **NAS super strain**. Potency guaranteed through expiration date, if kept **dry** and **refrigerated**.

FOR COMPLETE DIRECTIONS SEE INSERT.

Oral Capsule
GY-NA-TREN®
PROBIOTIC SUPPLEMENT
Supports vaginal and urinary health*

Supplement Facts
Serving Size: 1 Capsule

Amount per Serving		%DV
Vitamin C 2 mg		4%
Lactobacillus acidophilus Super Strain NAS	5 billion cfu	†

†Daily Value (DV) not established.

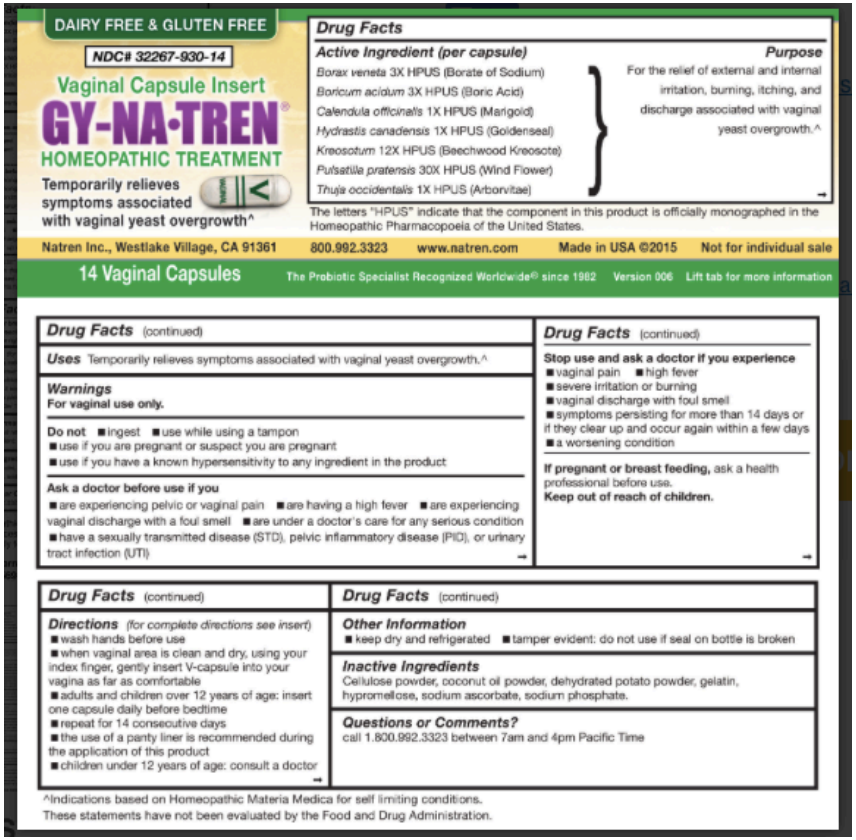
Other Ingredients: Cellulose powder, dehydrated potato powder, organic garbanzo bean (chick-pea) extract, vegetable capsule (hypromellose), and L-leucine.

Contains no preservatives or artificial colors and flavors.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

800.992.3323 www.natren.com Natren Inc., Westlake Village, CA 91361

The Probiotic Specialist Recognized Worldwide® since 1982 14 Oral Capsules Not for individual sale Version 005



DAIRY FREE & GLUTEN FREE

NDC# 32267-930-14

Vaginal Capsule Insert
GY-NA-TREN®
HOMEOPATHIC TREATMENT

Temporarily relieves symptoms associated with vaginal yeast overgrowth^

Drug Facts

Active Ingredient (per capsule)	Purpose
Borax veneta 3X HPUS (Borate of Sodium)	For the relief of external and internal irritation, burning, itching, and discharge associated with vaginal yeast overgrowth.^
Boricum acidum 3X HPUS (Boric Acid)	
Calendula officinalis 1X HPUS (Marigold)	
Hydrastis canadensis 1X HPUS (Goldenseal)	
Kreosotum 12X HPUS (Beechwood Kreosote)	
Pulsatilla pratensis 30X HPUS (Wind Flower)	
Thuja occidentalis 1X HPUS (Arborvitae)	

The letters "HPUS" indicate that the component in this product is officially monographed in the Homeopathic Pharmacopoeia of the United States.

Natren Inc., Westlake Village, CA 91361 800.992.3323 www.natren.com Made in USA ©2015 Not for individual sale

14 Vaginal Capsules The Probiotic Specialist Recognized Worldwide® since 1982 Version 006 Lift tab for more information

Drug Facts (continued)

Uses Temporarily relieves symptoms associated with vaginal yeast overgrowth.^

Warnings
For vaginal use only.

Do not ■ ingest ■ use while using a tampon
■ use if you are pregnant or suspect you are pregnant
■ use if you have a known hypersensitivity to any ingredient in the product

Ask a doctor before use if you
■ are experiencing pelvic or vaginal pain ■ are having a high fever ■ are experiencing vaginal discharge with a foul smell ■ are under a doctor's care for any serious condition ■ have a sexually transmitted disease (STD), pelvic inflammatory disease (PID), or urinary tract infection (UTI)

Drug Facts (continued)

Stop use and ask a doctor if you experience
■ vaginal pain ■ high fever
■ severe irritation or burning
■ vaginal discharge with foul smell
■ symptoms persisting for more than 14 days or if they clear up and occur again within a few days
■ a worsening condition

If pregnant or breast feeding, ask a health professional before use.
Keep out of reach of children.

Drug Facts (continued)

Directions *(for complete directions see insert)*
■ wash hands before use
■ when vaginal area is clean and dry, using your index finger, gently insert V-capsule into your vagina as far as comfortable
■ adults and children over 12 years of age: insert one capsule daily before bedtime
■ repeat for 14 consecutive days
■ the use of a panty liner is recommended during the application of this product
■ children under 12 years of age: consult a doctor

Drug Facts (continued)

Other Information
■ keep dry and refrigerated ■ tamper evident: do not use if seal on bottle is broken

Inactive Ingredients
Cellulose powder, coconut oil powder, dehydrated potato powder, gelatin, hypromellose, sodium ascorbate, sodium phosphate.

Questions or Comments?
call 1.800.992.3323 between 7am and 4pm Pacific Time

^Indications based on Homeopathic Materia Medica for self limiting conditions.
These statements have not been evaluated by the Food and Drug Administration.

ROLE OF DIET IN THE MICROBIOME

What's An RDN to Do?

Two Key Questions About Microbiome Practice Applications

1. **Can we *predict* disease by monitoring changes in the microbiome?** If standardized measures for microbial species existed and could link variations to the onset of disease, could this information be used in the same way changes in blood pressure are used to measure cardiovascular disease risk? Although detailed knowledge of microbiome composition and its functional significance may be out of reach, can surrogate markers of microbiome health and disease risk be defined and validated?
2. **Can we *prevent* disease by manipulating the microbiome (molecular gene targeting)?** If the presence of specific communities of microbes could be linked with healthy outcomes, could probiotics, prebiotics, dietary interventions, narrow-spectrum antibiotics, and fecal microbiome transplantation (FMT) be used as an intervention in the same way micronutrients prevent deficiency-related disease?

Recommendations for Healthy Microbiome

1. Restrict foods rich in IGF-1 such as dairy and insulinotrophic foods
2. Restrict highly inflammatory fructose (<25g/d)
3. Restrict milk powder, butter, and cheese high in SFA, hormones, and IGF-1, and high fat meat
4. Restrict foods heated above 100 degrees Celsius high in AGE's ALE's
5. Restrict chemical and pharmaceutical exposure
6. Restrict exposure to microbe-derived endotoxin in aged meats
7. Minimize intake of proteotoxin-rice foods such as casein, gluten, and zein (corn)
8. Increase dramatically fresh and raw greens, seeds, fresh spices and vegetables
9. Increase antioxidant-rich, high fiber, low-calorie 'ancient' grains not manipulated by industry
10. Supplement vitamin D and omega-3 (as needed)

Bengmark, S. (2013). Processed foods, dysbiosis, systemic inflammation, and poor health. *Current Nutrition and Food Science*, 9, 113-143.

Avoid
Negative Effect on Gut Microbiome

- *Western diet*
- High calories (↓diversity)
- Frequent snacking (↓diversity)
- Sugar sweetened soda (↓diversity)
- High fat milk (↓diversity)
- High dietary carbohydrates (↓diversity)
- Low dietary diversity
- Fast food
- High intake of alcohol (U-shaped curve)
- Red and processed meats
- Animal fat
- Excess omega-6's and long chain fatty acids
- Emulsifiers
- Gums
- Maltodextrin
- Simple sugars
- Artificial sweeteners (*gut motility and microbiome)
- Metformin
- PPIs

Science, April 29, 2016. 352(6285), 565-569;
British Jrnl Nutr (2015), 113, S1-S5

JNM
J Neurogastroenterol Motil, Vol. 22 No. 2 April, 2016
pISSN: 2093-0879 eISSN: 2093-0887
http://dx.doi.org/10.5056/jnm15206
Journal of Neurogastroenterology and Motility

Review

Artificial Sweeteners: A Systematic Review and Primer for Gastroenterologists

A 'must read'!

Marisa Spencer,[1] Amit Gupta,[2] Lauren Van Dam,[1] Carol Shannon,[3] Stacy Menees,[1] and William D Chey[1]*

Departments of [1]Gastroenterology and [2]Medicine, University of Michigan, Ann Arbor, Michigan, USA; and [3]Taubman Health Sciences Library, University of Michigan, Ann Arbor, Michigan, USA

Artificial sweeteners (AS) are ubiquitous in food and beverage products, yet little is known about their effects on the gastrointestinal (GI) tract, and whether they play a role in the development of GI symptoms, especially in patients with irritable bowel syndrome. Utilizing the PubMed and Embase databases, we conducted a search for articles on individual AS and each of these terms: fermentation, absorption, and GI tract. Standard protocols for a systematic review were followed. At the end of our search, we found a total of 617 eligible papers, 26 of which were included. Overall, there is limited medical literature available on this topic. The 2 main areas on which there is data to suggest that AS affect the GI tract include motility and the gut microbiome, though human data is lacking, and most of the currently available data is derived from in vivo studies. The effect on motility is mainly indirect via increased incretin secretion, though the clinical relevance of this finding is unknown as the downstream effect on motility was not studied. The specific effects of AS on the microbiome have been conflicting and the available studies have been heterogeneous in terms of the population studied and both the AS and doses evaluated. Further research is needed to assess whether AS could be a potential cause of GI symptoms. This is especially pertinent in patients with irritable bowel syndrome, a population in whom dietary interventions are routinely utilized as a management strategy.

(J Neurogastroenterol Motil 2016;22:168-180)

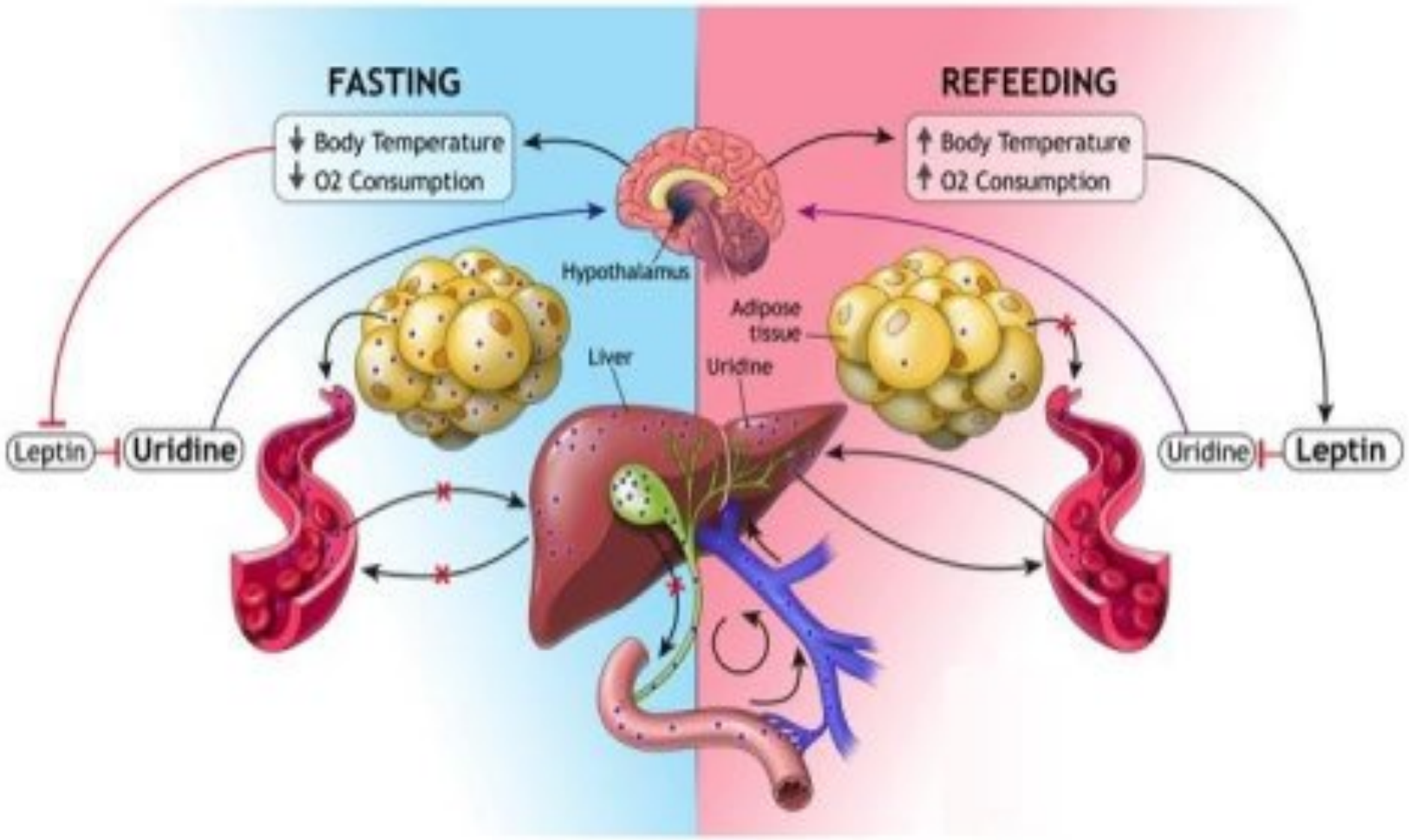
Key Words
Gastrointestinal tract; Irritable bowel syndrome; Microbiota; Motility; Sweetening agents

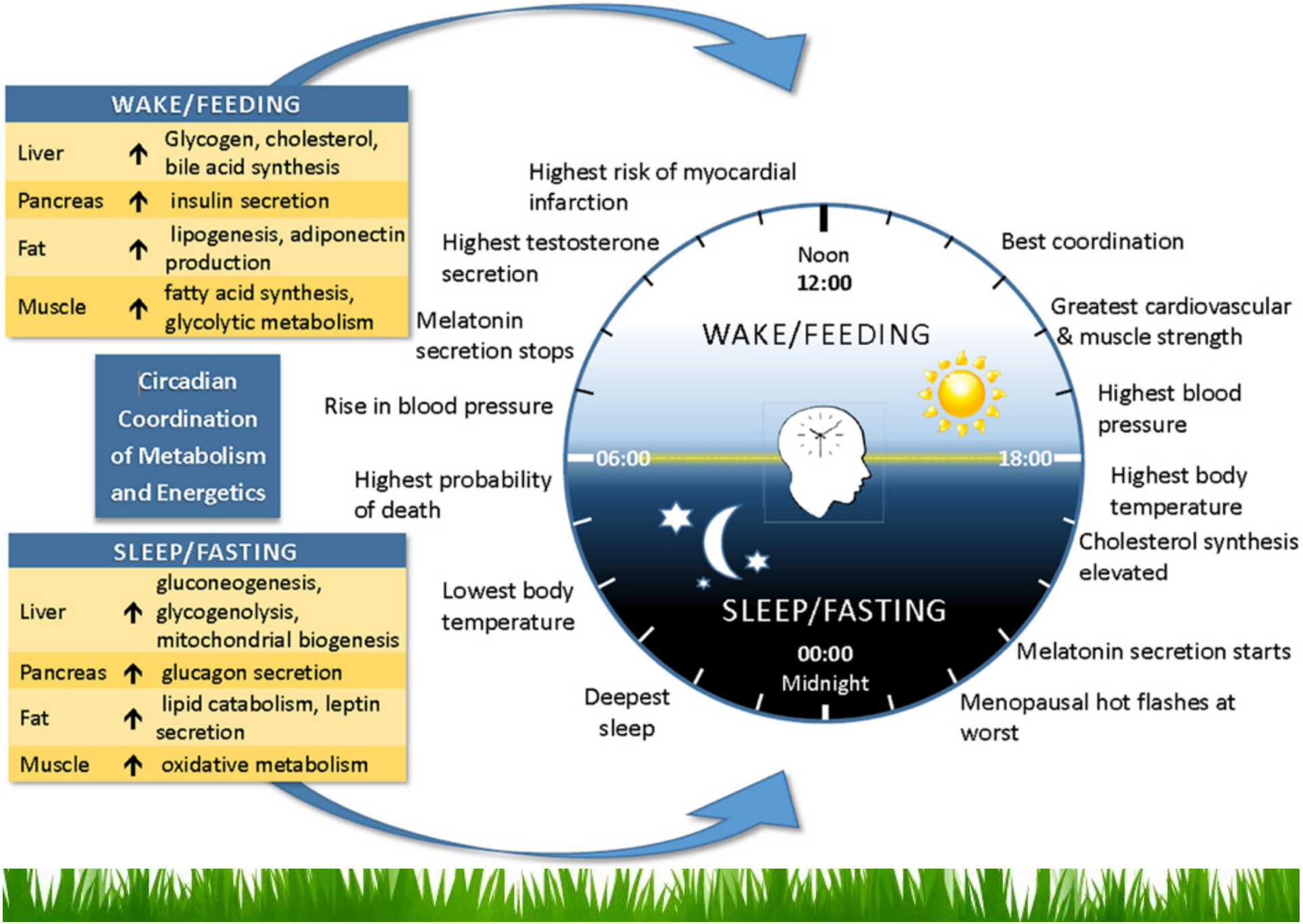
Recommend
Positive Effect on Gut Microbiome

- Breastfeeding
- Plant based diet
- **High dietary diversity**
- High vegetable/fruit intake
- Fiber
- Resistant starch
- Fermented foods
- Omega-3s

- Leafy greens
- Seaweeds
- Coffee (↑diversity)
- Tea (↑diversity)
- Red wine (↑diversity)
- Chocolate (↑diversity)
- Buttermilk (↑diversity)
- Intermittent fasting
- Longer nighttime fasting duration and circadian alignment

***Science,* April 29, 2016. 352(6285), 565-569;**
***British Jrnl Nutr,* (2015), 113, S1-S5**


FASTING
Body Temperature
O2 Consumption
Hypothalamus
Liver
Leptin
Uridine
REFEEDING
Body Temperature
O2 Consumption
Adipose tissue
Uridine
Uridine
Leptin


WAKE/FEEDING
Liver ↑ Glycogen, cholesterol, bile acid synthesis
Pancreas ↑ insulin secretion
Fat ↑ lipogenesis, adiponectin production
Muscle ↑ fatty acid synthesis, glycolytic metabolism
Circadian Coordination of Metabolism and Energetics
SLEEP/FASTING
Liver ↑ gluconeogenesis, glycogenolysis, mitochondrial biogenesis
Pancreas ↑ glucagon secretion
Fat ↑ lipid catabolism, leptin secretion
Muscle ↑ oxidative metabolism
Highest risk of myocardial infarction
Highest testosterone secretion
Melatonin secretion stops
Rise in blood pressure
Highest probability of death
Lowest body temperature
Deepest sleep
Noon
12:00
WAKE/FEEDING
06:00
18:00
SLEEP/FASTING
00:00
Midnight
Best coordination
Greatest cardiovascular & muscle strength
Highest blood pressure
Highest body temperature
Cholesterol synthesis elevated
Melatonin secretion starts
Menopausal hot flashes at worst

Use of Low FODMAP Diet in IBS and SIBO

- While a low FODMAP diet may decrease symptoms of IBS, it should not be used long term
- Low FODMAP diet long term can have a negative effect of the microbiome
- Gut fermentation is a good thing in the right amounts! Treat SIBO, then reintroduce high FODMAP carbs!

Feeding the Microbiome: Fermented Foods

- Yogurt, kefir, and buttermilk
- Cultured coconut milk and coconut water
- Sauerkraut
- Pickles and pickled beets, radish, garlic, and cucumbers
- Kimchi
- Fermented meat, fish and eggs
- Miso, natto, tempeh, and soy sauce
- Kvass
- Lassi
- Beer
- Kombucha

Closing the Fiber Gap with Supplements

- Grain, nut, seed, legume, and vegetable-based whole food fiber supplements
- Arabinoxylan
- Beta-glucan
- Cellulose
- Inulin/oligosaccharides
- Galactooligosaccharide/xylooligosaccharide
- Polydextrose
- Soluble corn fiber
- Alginate
- Pectin (apple, citrus)
- Gums (arabic, acacia, guar)

Trends in Endocrinology & Metabolism, May 2016, Vol 27, No 5

Resistant Starch Trial of Raw Unmodified Potato Starch to Increase Gut Butyrate

- Day 1- 12g raw potato starch mixed in cold water
- Day 2- 12g raw potato starch mixed in cold water twice daily (total 24g/day)
- Day 3- 24g raw potato starch mixed in cold water twice times daily (total 48g/day)
- Days 4-10 24g raw potato starch mixed in cold water twice times daily (total 48g/day)

** Bob's Red Mill brand used in study;*

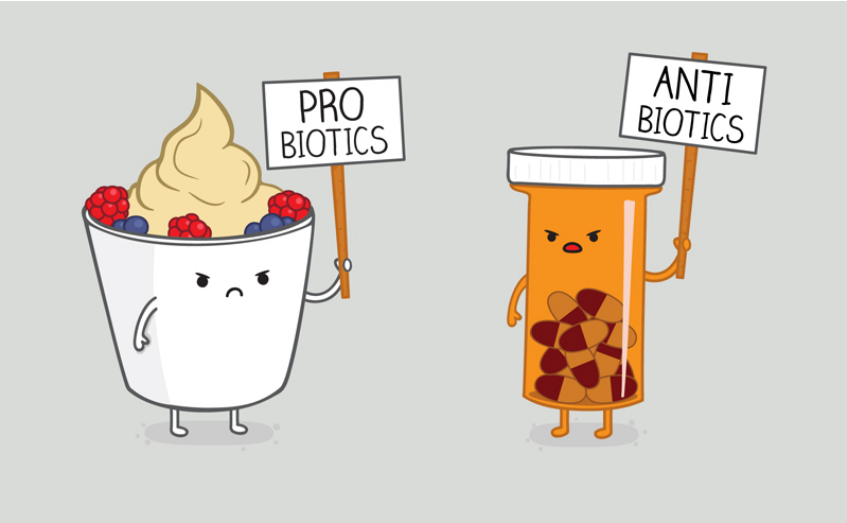
** Raw potato starch is ~50% resistant starch by weight*

Venkataraman et al. Microbiome (2016) 4:33 DOI 10.1186/s40168-016-0178-x

Optimizing the Microbiome with Optimal Digestion

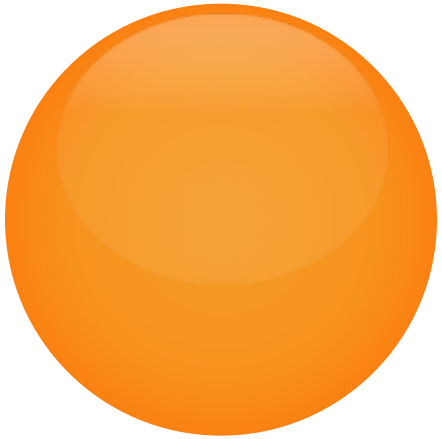
- **Complete** mastication
- Salivary enzymes (amylase, lysozyme, lingual lipase)
- HCl and pepsin
- Cholecystokinin and bile acids
- Pancreatic and brush border enzymes
- Parasympathetic tone (controls peristalsis)
- Intact intestinal barrier

Probiotics, Prebiotics, & Symbiotics- An Emerging Science



Prebiotics: Three Criteria

1. Resistance to gastric acidity, hydrolysis by enzymes, and gastrointestinal absorption
2. Fermentation by intestinal microflora
3. Selective stimulation of the growth and/or activity of beneficial intestinal bacteria
   - **Prebiotics that fulfill these criteria:** fructooligosaccharides, galactooligosaccharides, lactulose, non-digestible large polysaccharides (inulin, resistant starches, cellulose, hemicellulose, pectins, and gums), some oligosaccharides that escape digestion, and unabsorbed sugars and alcohols.

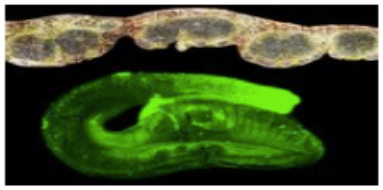


MICROBIOME RESOURCES

Subscribe to Health News for Latest Research!

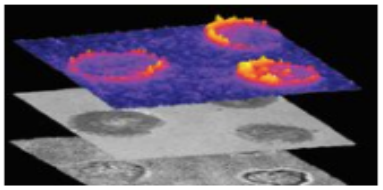
- ‘The Daily News’ (Academy Knowledge Center)
- Medical News Today
- Medline Plus
- Science Daily
- NIH Human Microbiome Project

Health & Medicine News *May 6, 2016*



Surprise: Intestinal Worms Boost Immune System

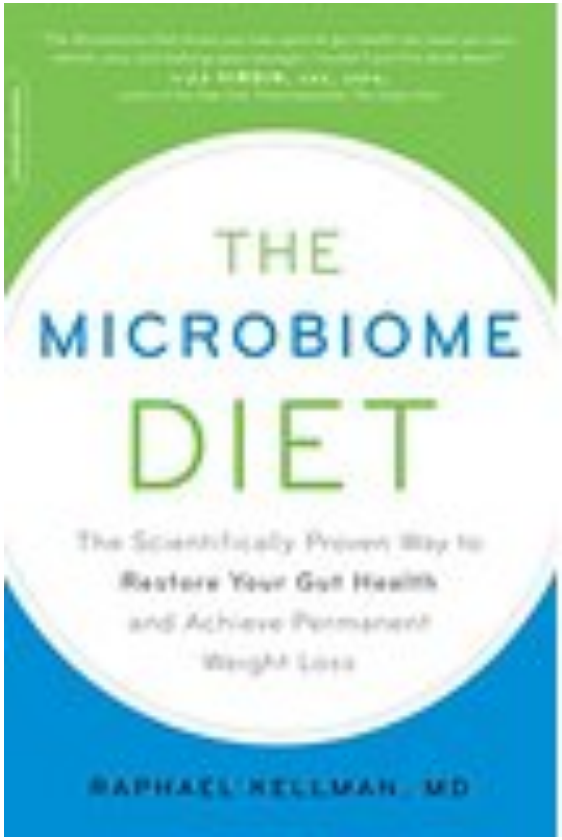
Meat Consumption Raises Mortality Rates: Study

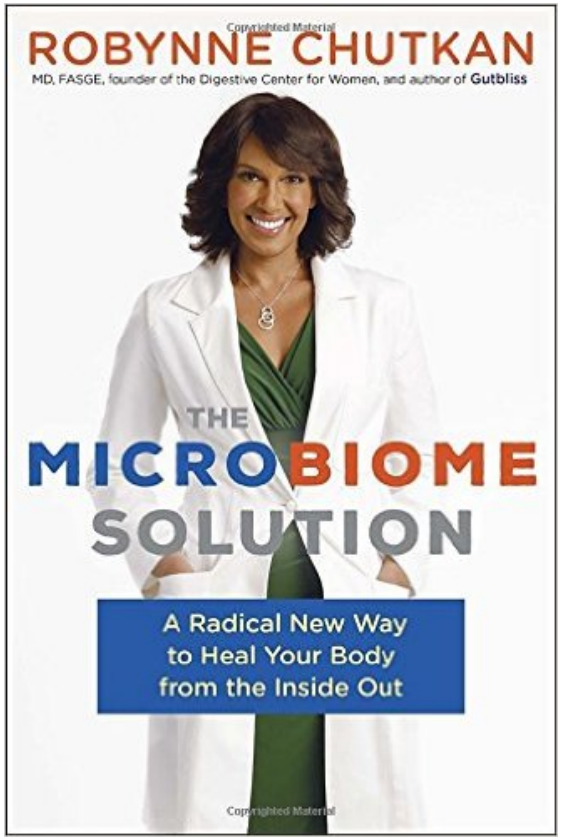


T Cells Use 'Handshakes,' Sort Friend from Foes

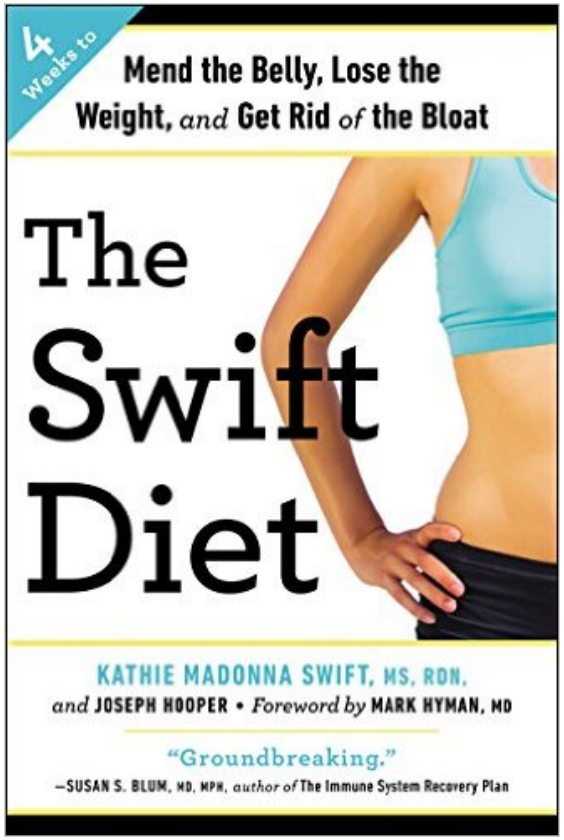
Breast Milk Improves Gut Microbiome, Later Health

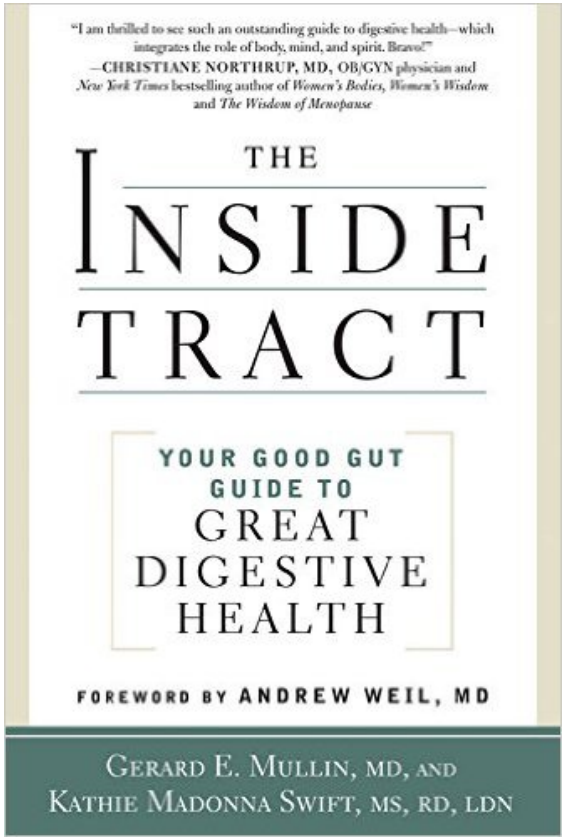
Consumer Resources





Consumer Resources





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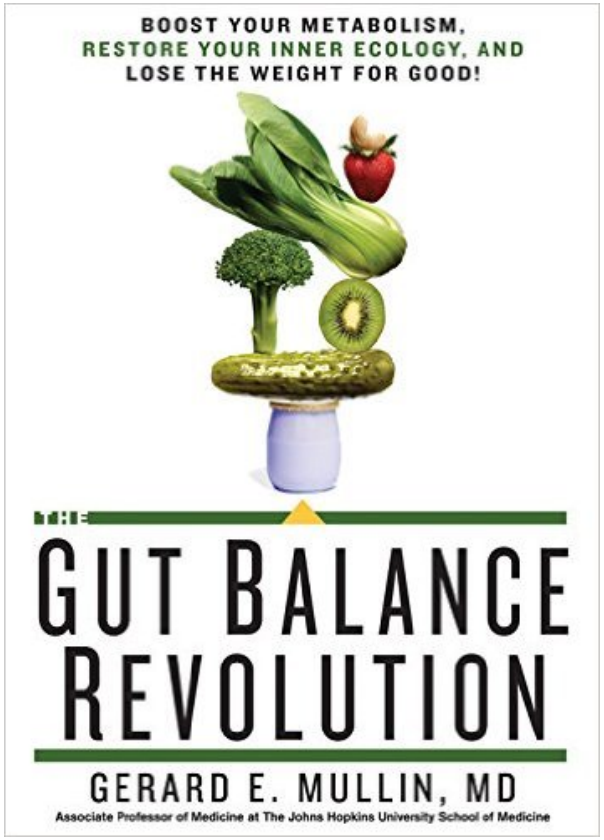

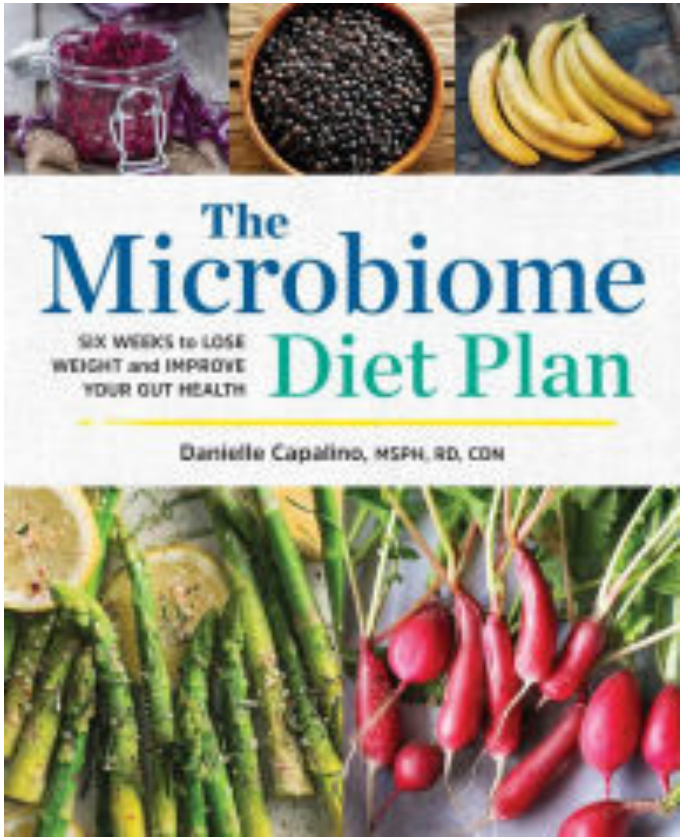

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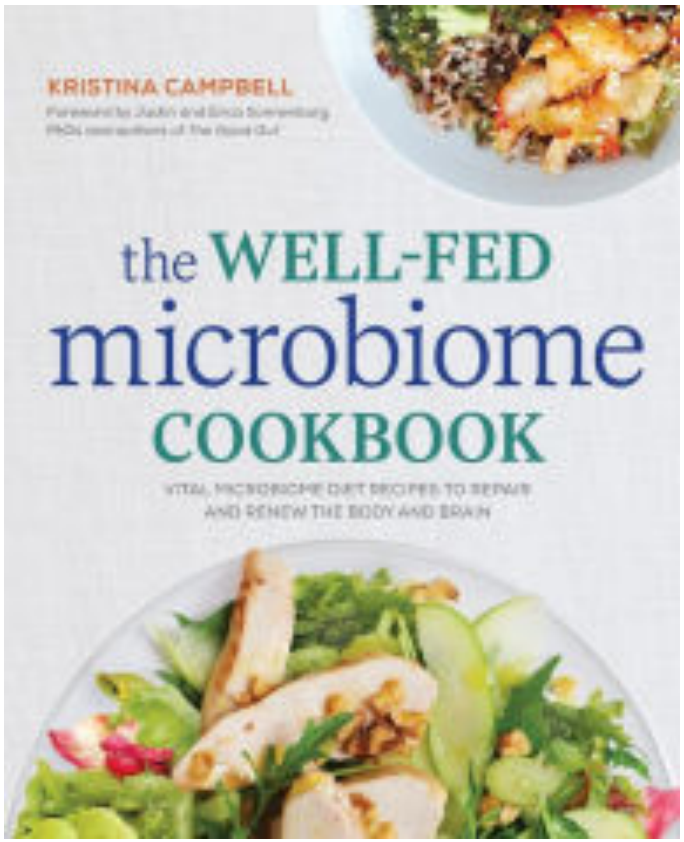

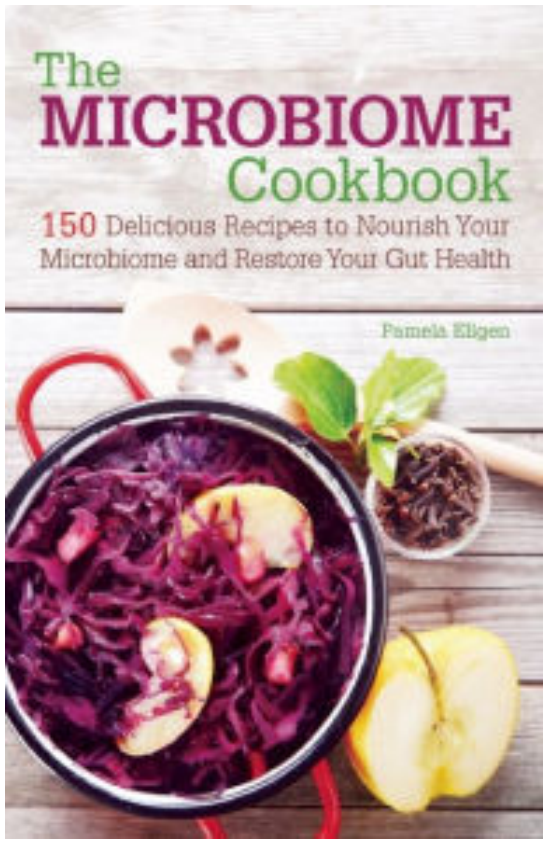

Got A Question?

Ask Me!
DelegateDIFM@gmail.com