BUGS AT THE DINNER TABLE:
Role of the Gut Microbiome in Obesity & Metabolic Syndrome

NIKHIL PAI, MD FAAP FRCPC
Assistant Professor, Department of Pediatrics, Division of Pediatric Gastroenterology & Nutrition
Medical Lead, Complex Nutrition Service, McMaster Children's Hospital
Associate Faculty, Farncombe Digestive Health Research Institute
McMaster University

McMaster Children's Hospital
McMaster University
FARNCOMBE
Farncombe Family Digestive Health Research Institute

Disclosures

- Advisory Board: Janssen, Ferring, Abbvie
- Research Materials: Rebiotix

Objectives for Today's Talk

INTRODUCTION: Understanding the literature

1. Review the relationship between the intestinal microbiome and obesity
2. Discuss evidence supporting the role of the microbiome in T2DM
3. Describe interactions between the intestinal microbiome in NAFLD

CONCLUSION: Microbial therapeutics and the future

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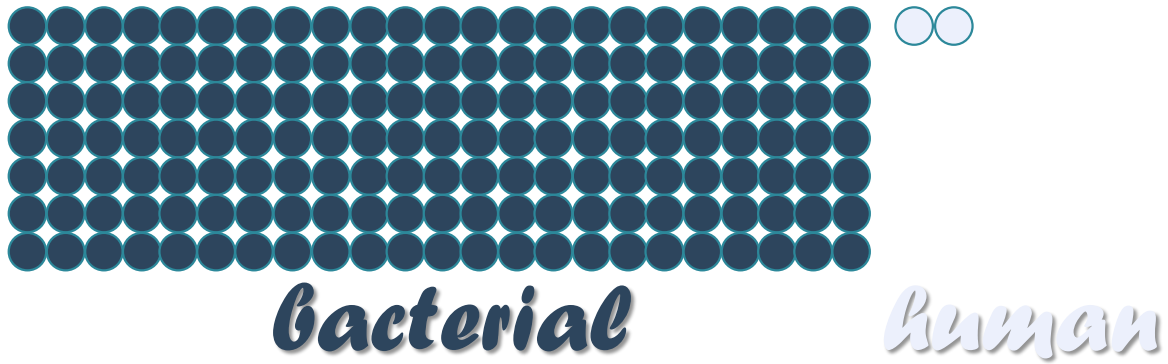
Microbiome refers to the collective genetic material of all nonhuman cells in the body

- Microbiota = bacterial, viral, fungal cells in the body
- Microbiome = genes within these cells
- 150x more microbial genes than human genome
- Relevance across disease states

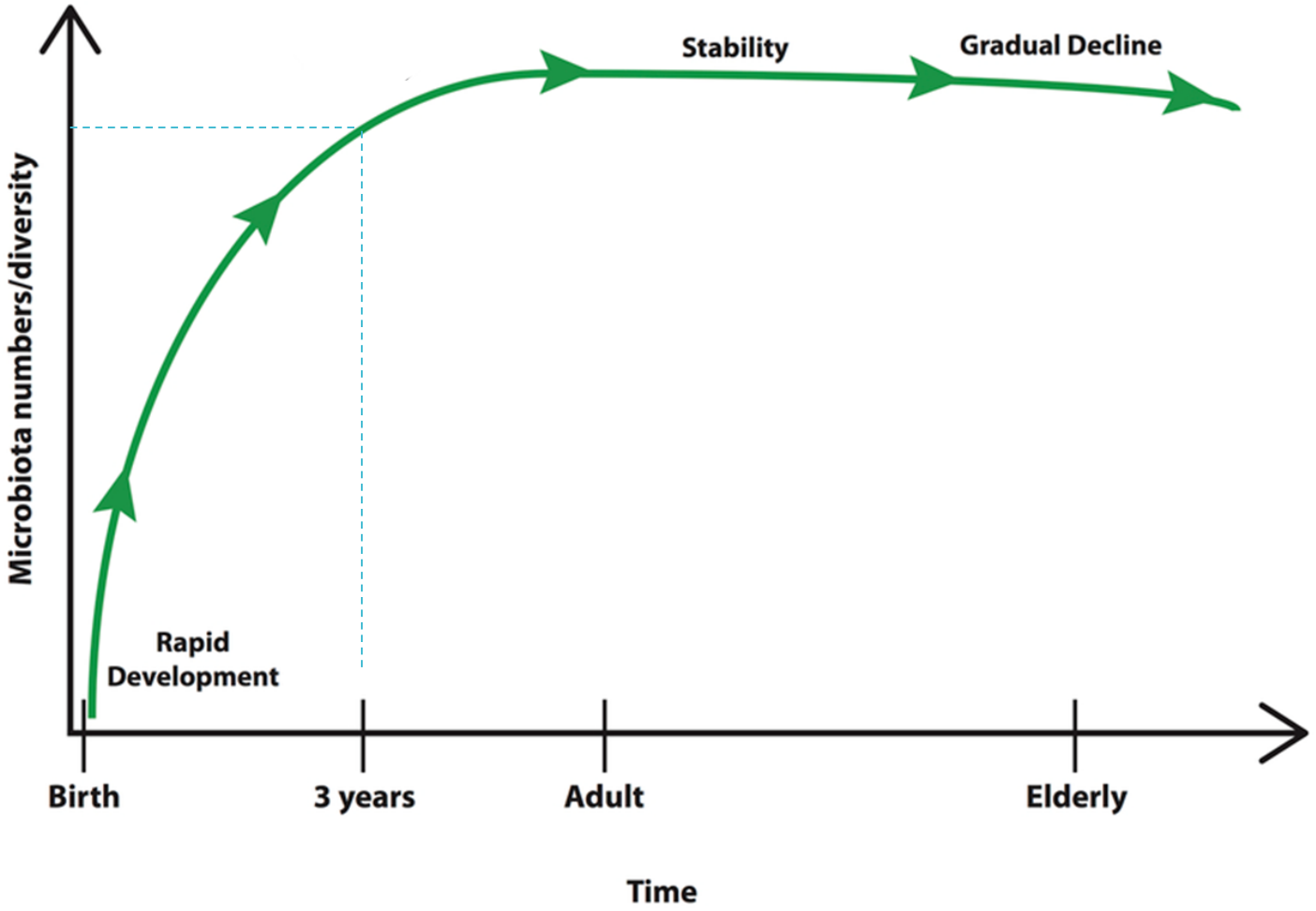


Qin J, Li R, Raes J et al. A human gut microbial gene catalog established by metagenomic sequencing. Nature 2010; 464: 59–65.

- protection against pathogenic bacterial blooms
- maintenance of gut barrier

Intestinal microbiota has multiple intestinal, and endocrine functions

Qin J, Li R, Raes J et al. A human gut microbial gene catalog established by metagenomic sequencing. Nature 2010; 464: 59–65.



Early life influences greatest impact on long-term microbial structure and function

Colonization with maternal microbes during delivery

Breastfeeding

Breastmilk

Limited heritability
(monozygotic / dizygotic twin studies)

Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222–227.

Literature is plagued by misattribution of *association* with *causation*

- Many confounders
- Dietary influences most significant: obesity, T2DM literature

- Germ-free animal models provide best evidence for causal roles
- Similar experimental designs lacking in humans

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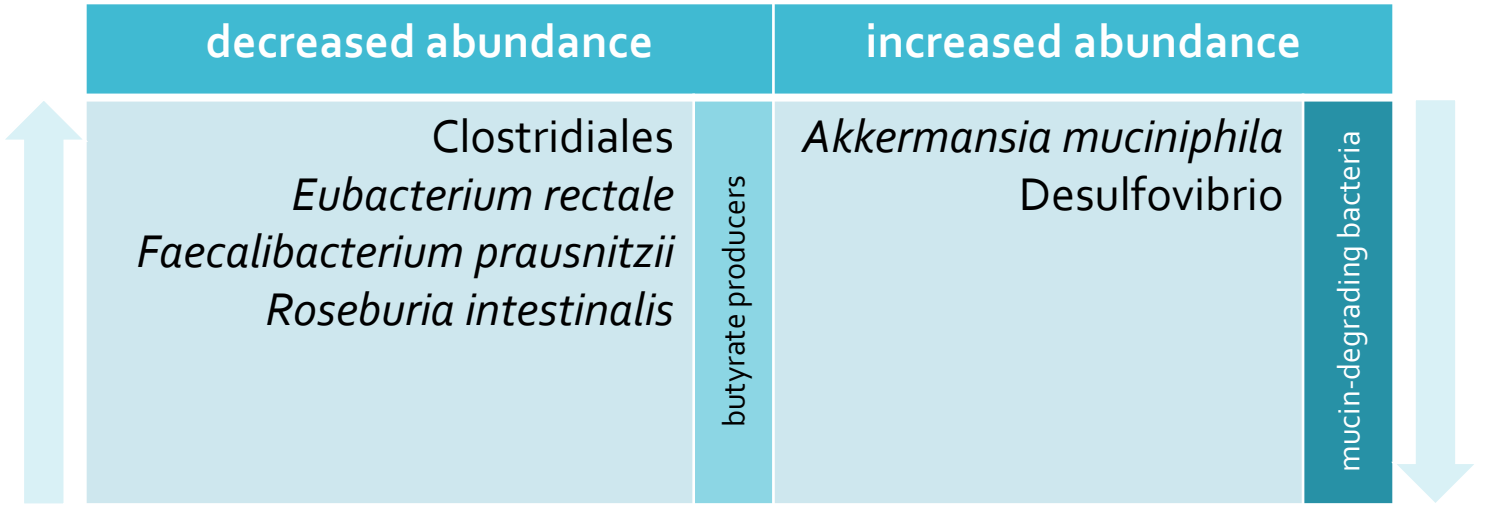
Differences in microbial communities between lean and obese individuals

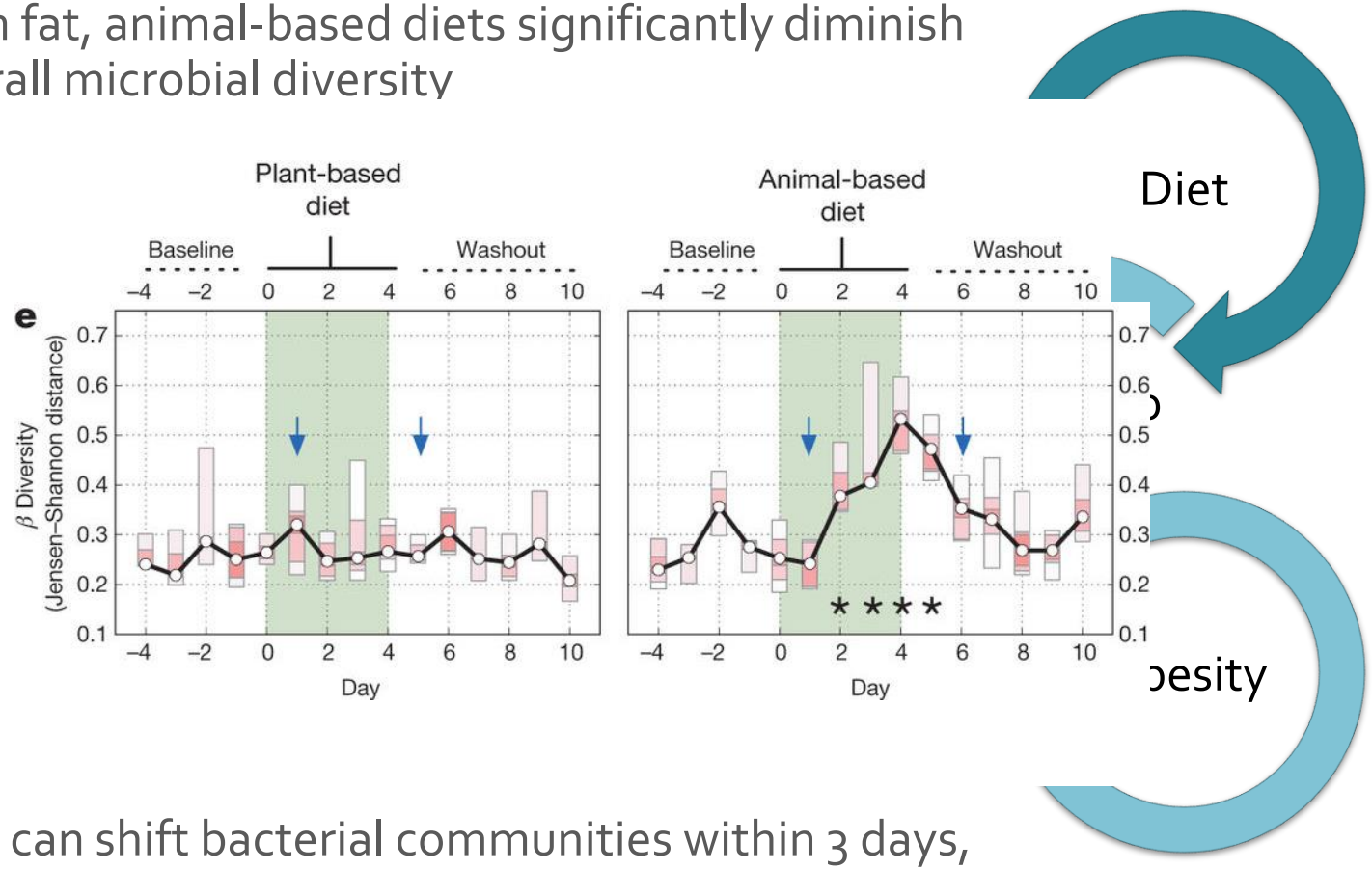


- Broadly: reduced bacterial diversity in obesity
- Animal studies: reduced diversity correlates with ↑BMI, adiposity, dyslipidemia, inflammation

Finucane MM, Sharpton TJ, Laurent TJ, et al. A taxonomic signature of obesity in the microbiome? Getting to the guts of the matter. PLOS ONE 2014; 9:e84689.

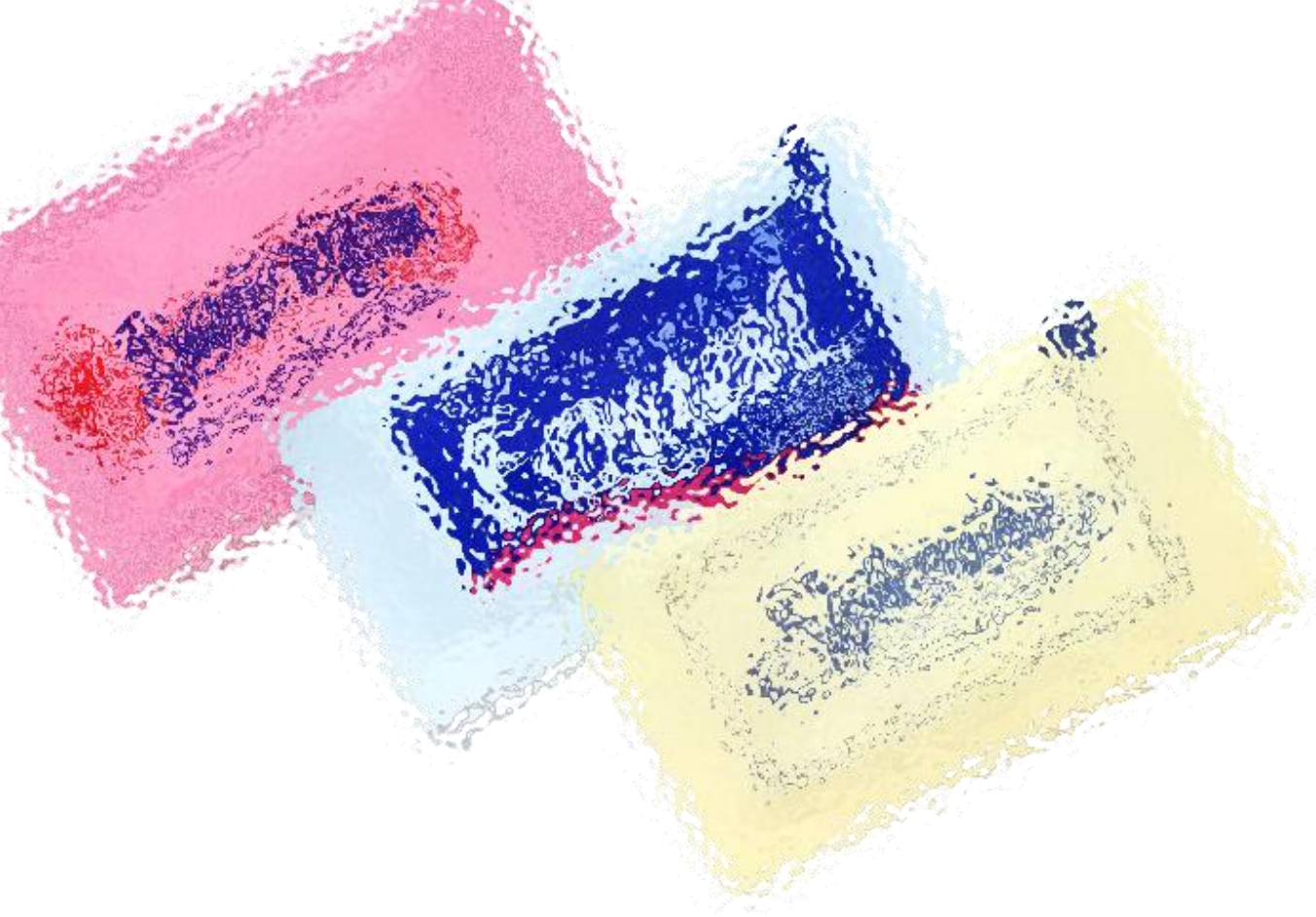
Microbiota strongly influenced by diet

- High fat, animal-based diets significantly diminish overall microbial diversity



- Diet can shift bacterial communities within 3 days, long before clinical phenotype emerges

David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559-63.

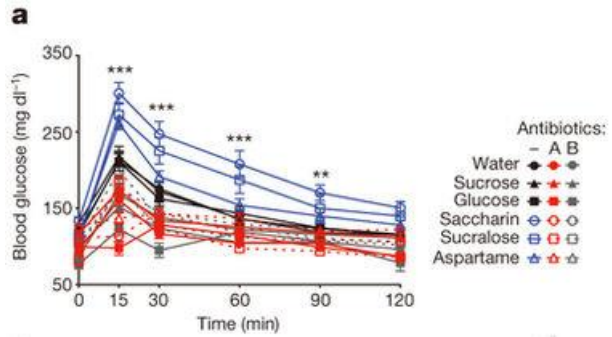


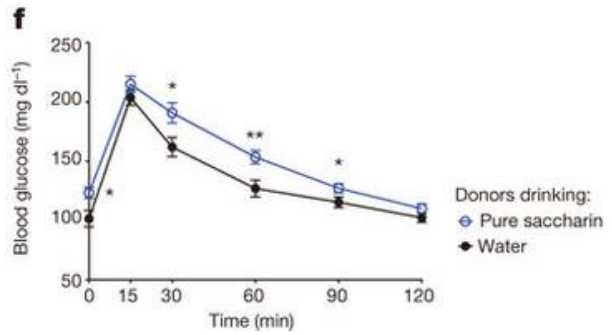
“Association of artificial sweeteners and T2DM risk”

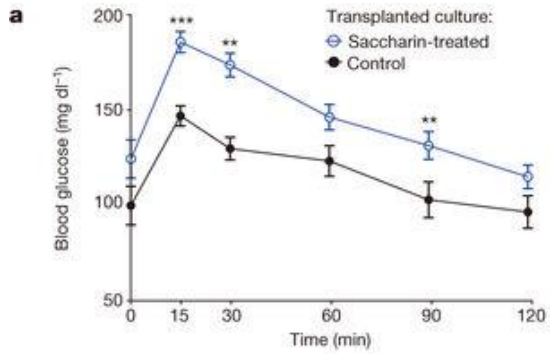
Schulze MB, Manson JE, Ludwig DS, et al. (2004) Sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 292, 927–934.

Artificial sweeteners associated with altered microbial composition

1. n=20 mice, non-artificial sweetener (NAS) added to normal chow diet → glucose intolerance
2. n=15 mice, receiving NAS diet given **oral antibiotics** → **no glucose intolerance**
3. n=12 germ-free mice received **fecal transplant** from NAS-fed animals → **glucose intolerance** in recipients
4. n=12 germ-free mice received **fecal transplant** from **healthy donor stool** incubated in **NAS cell culture** → **glucose intolerance** in recipients







Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014;514(7521):181-6.

Cardiovascular risks associated with red meat intake linked to microbiota metabolism

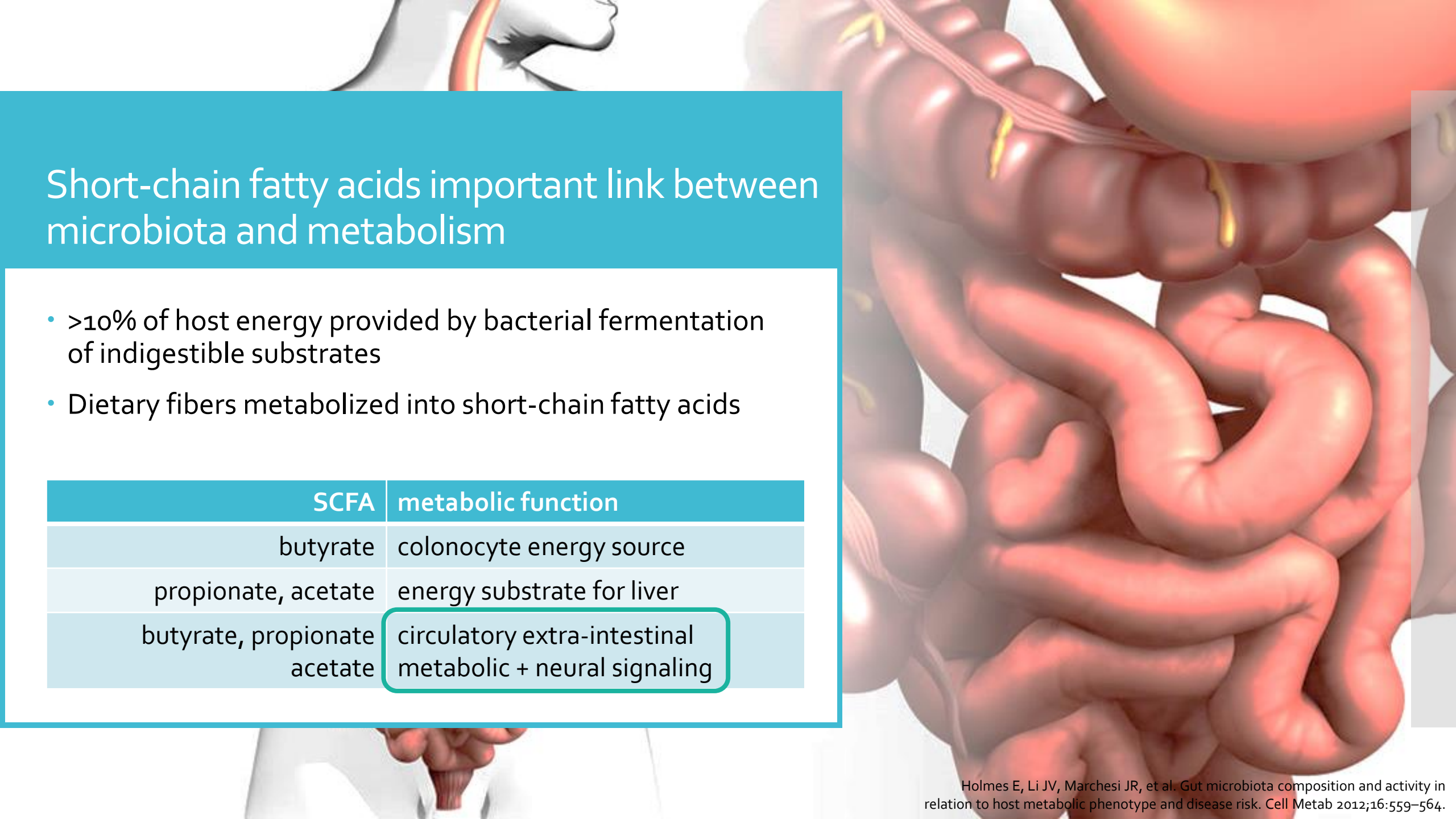
- Red meat (+carnitine, +choline) metabolized by gut microbiota to trimethylamine (TMA)
- TMA synthesized by hepatic FMO_3 to TMAO
- Strong correlation between [TMAO] with CAD incidence
- 2016 Cell: TMAO enhances platelet aggregation, thrombosis

Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013; 19:576–585.
Tang WH, Hazen SL. Microbiome, trimethylamine N-oxide, and cardiometabolic disease. Transl Res 2017; 179:108–115.
Zhu W, Gregory Jill C, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell 2016;165:111–124.

Short-chain fatty acids important link between microbiota and metabolism

- >10% of host energy provided by bacterial fermentation of indigestible substrates
- Dietary fibers metabolized into short-chain fatty acids

SCFA	metabolic function
butyrate	colonocyte energy source
propionate, acetate	energy substrate for liver
butyrate, propionate acetate	circulatory extra-intestinal metabolic + neural signaling



Holmes E, Li JV, Marchesi JR, et al. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab 2012;16:559–564.

Microbially derived SCFA affects central sympathetic pathways

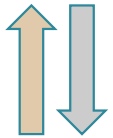
- Acetate affects CNS via vagal nerve afferents
- Animal studies have demonstrated possible weight-reduction effects in animals receiving supplementation
- Mixed results in recent literature

De Vadder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014; 156:84–96.

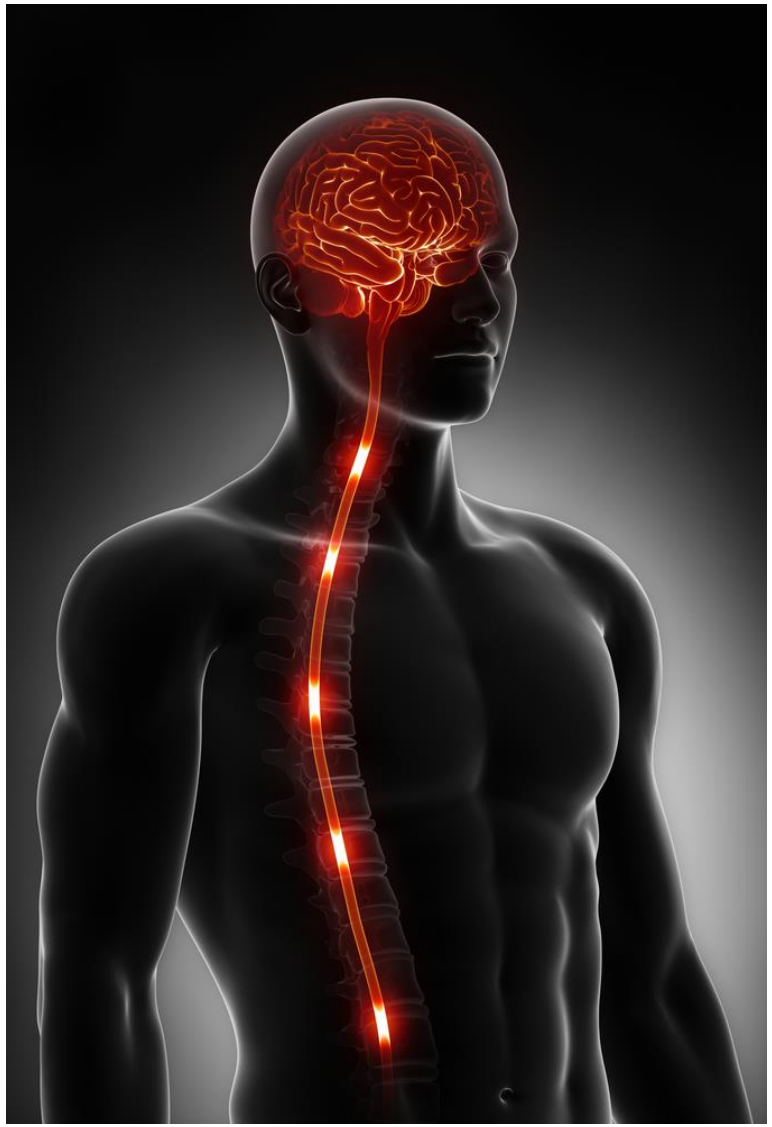
Influence on central appetite regulation

- Microbiota can influence hypothalamic signaling

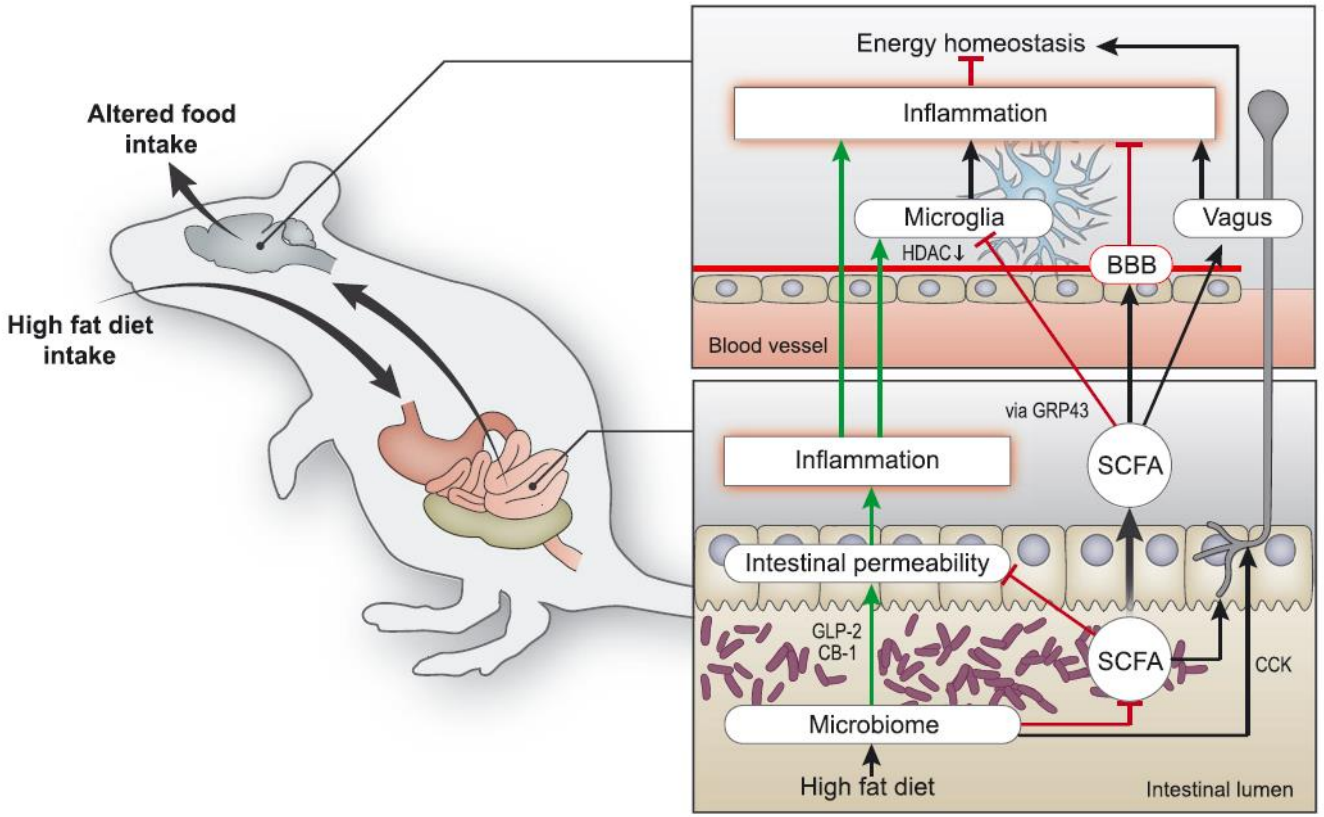
- Hypothalamic gene expression varies with microbial composition
- *Roseburia, Lactobacillus spp.*



Anorectic: POMC, DNF, and CRF
Orexigenic: AgRP, PYY



Schéle E, Grahnemo L, Anesten F, Hallenń A, Bakhed F, Jansson JO. The gut microbiota reduces leptin sensitivity and the expression of the obesity-suppressing neuropeptides proglucagon (Gcg) and brain-derived neurotrophic factor (Bdnf) in the central nervous system. Endocrinology 2013; 154: 3643–3651.



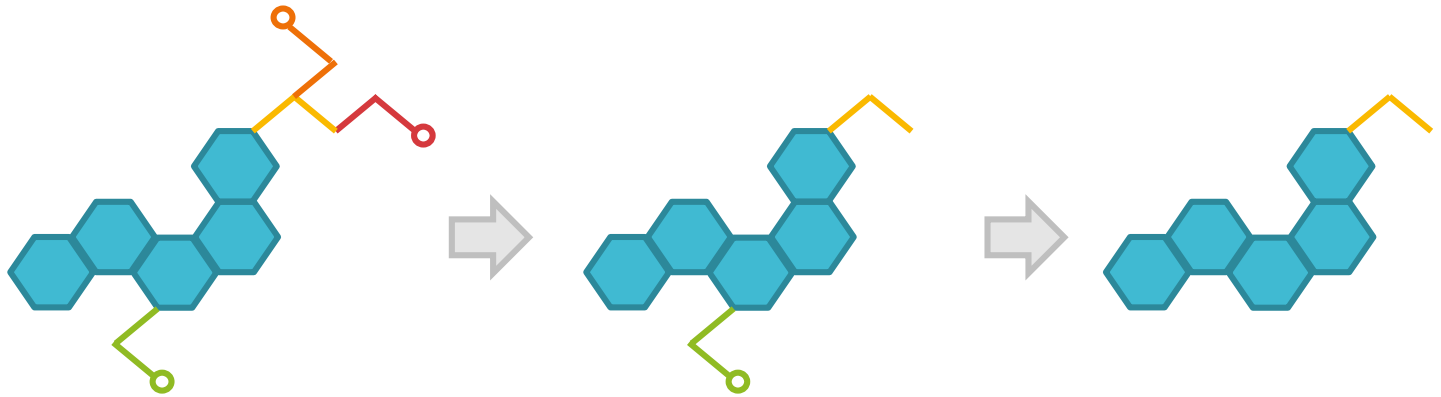
- Microglia influenced by intestinal bacteria
- GF mice have poorly developed microglia
- Antibiotics given to non-GF mice rapidly affects microglial permeability
- Recolonization with fecal transplant corrects this within six weeks
- Dynamic, rapid process of microbiota influencing blood brain barrier and CNS

Microbiota affects CNS pathways by altering blood brain barrier permeability

Erny D, Hrabě de Angelis AL, Jaitin D et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci 2015; 18: 965–977.

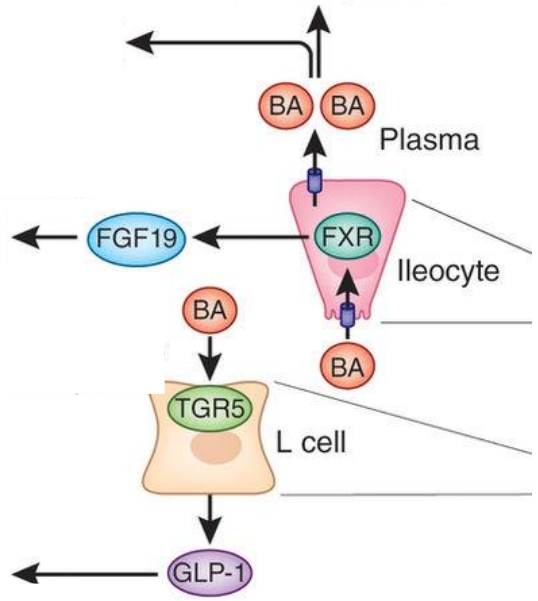
Physiologic functions of endogenous, host-produced metabolites also affected

- Example: intestinal bile acids
- Produced by body and metabolized by bacteria to 2˚ bile acids
- Further dehydroxylated by non-pathogenic *Clostridia spp.* in colon



Microbially metabolized bile acids have major effects on host metabolism

- Bile acids activate FXR receptor in ileum and liver
- TGR5 in intestinal L-cells
- Significantly higher ligand potential of dehydroxylated bile acids (microbiota) for FXR/TGR5



Kuipers F, Bloks VW, Groen AK. Beyond intestinal soap–bile acids in metabolic control. Nat Rev Endocrinol 2014; 10:488–498.
Kuipers F, Groen AK. FXR: the key to benefits in bariatric surgery?. Nat Med. 2014;20(4):337-8.

Bariatric surgery further suggests role for microbiota in obesity

- Roux-en-Y gastric bypass: most effective longterm interventions to induce weight loss
- Decreased caloric intake unlikely to explain rapid metabolic and appetite suppression effects alone

- Series of experiments in surgical mouse models:
  a) Vertical sleeve gastrectomy performed in FXR knock-out mice: no weight loss
  b) Surgical diversion of biliary flow from duodenum to ileum: weight loss + metabolic improvements
  c) Fecal transfers from RYGB mice to non-operative obese mice: weight loss + metabolic improvements

BARIATRICS → GUT MICROBIOTA → ↓OBESITY / METABOLIC SYNDROME

Liou AP, Paziuk M, Luevano J-M Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. 2013; 5:1–23.
Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature 2014;509:183–188.
Flynn CR, Albaugh VL, Cai S, et al. Bile diversion to the distal small intestine has comparable metabolic benefits to bariatric surgery. Nat Commun 2015;6:7715.
Buchwald H, Oien DM. Metabolic/Bariatric Surgery Worldwide 2008. Obes Surg 2009;19:1605–1611.

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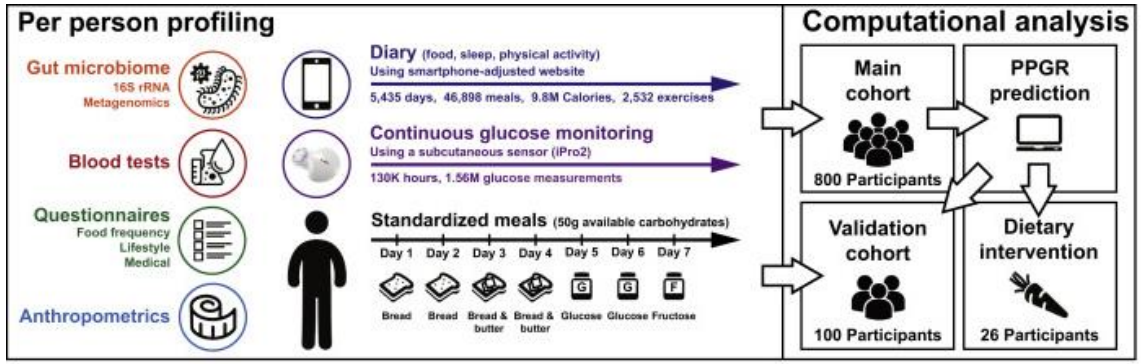
Landmark 2015 Cell paper: diabetes management through personalized microbiota manipulation

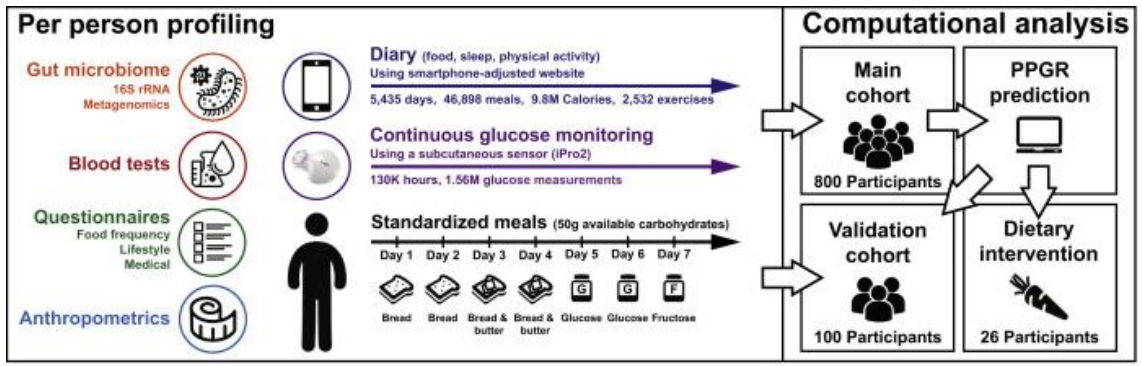
- Israeli team led by Eran Elinav and Eran Segal
- Stool samples, post-prandial glucose response of **800** T2DM patients fed **46,000** meals over **5,400** days



Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell 2015; 163:1079–1094.
Levy M, Thaiss Christoph A, Zeevi D, et al. Microbiotamodulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. Cell 2015;163:1428–1443.
Griffin NW, Ahern PP, Cheng J, et al. Prior Dietary Practices and Connections to a Human Gut Microbial Metacommunity Alter Responses to Diet Interventions. Cell Host Microbe 2017;21:84–96.
Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 2016;352:565–569.

Landmark 2015 Cell paper: diabetes management through personalized microbiota manipulation

- Computational prediction rule developed:
  foods + microbiome + blood glucose + interindividual variability
- Validated against 100 T2DM participants
- Microbiome-guided nutritional counselling performed better than dietitian-guided counselling for predicting blood glucose response



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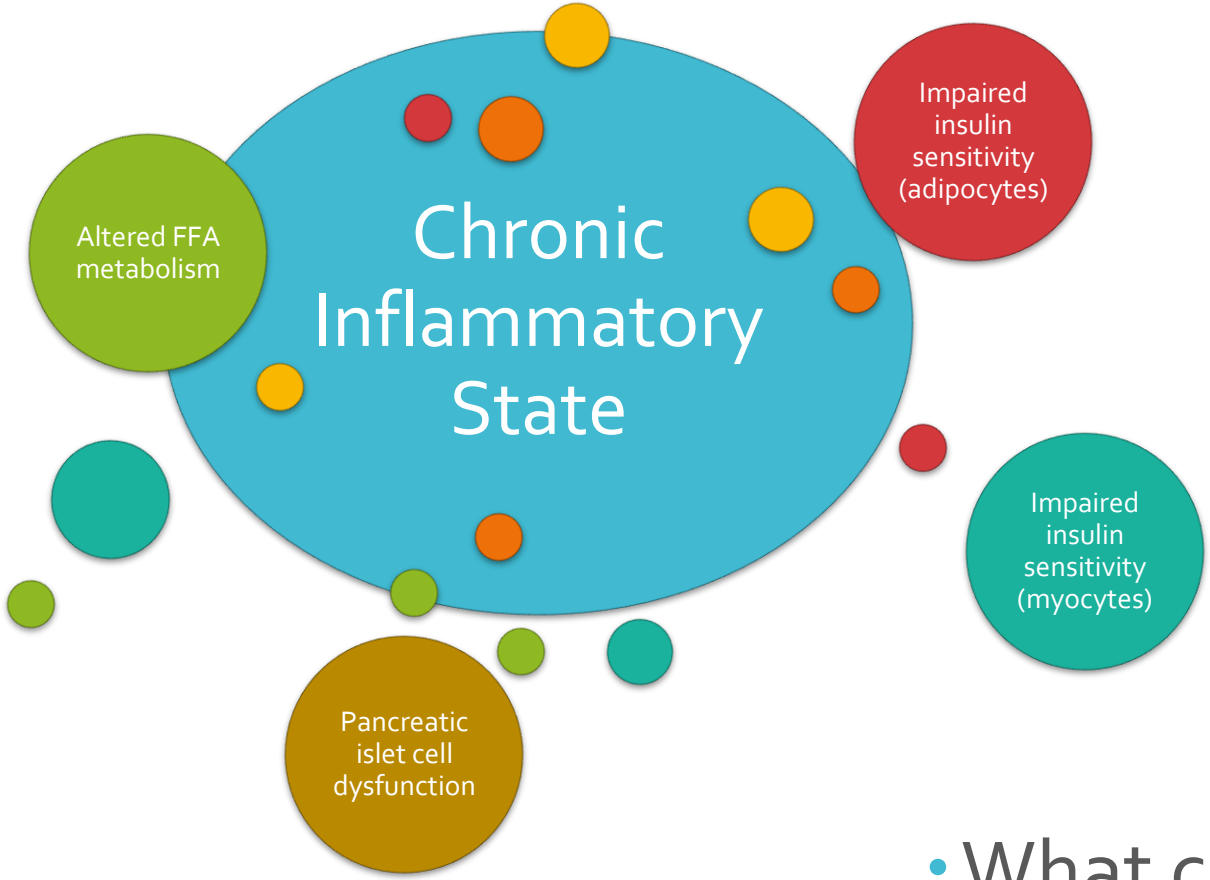
Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 2016;352:565–569.

- Heterogeneous patient responses to routine nutritional counselling
- Differences in microbial composition may underlie post-prandial glucose response

Insulin resistant in Type 2 Diabetes characterized by low-grade systemic inflammation

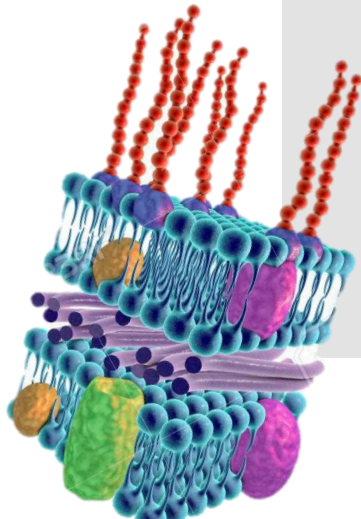


- What causes the inflammation?

Hotamisligil G, Shargill N, Spiegelman B. Adipose expression of tumor necrosis factor-alpha: direct role in obesity linked insulin resistance. Science 1993;259:87–91.
Donath MY. Targeting inflammation in the treatment of type 2 diabetes. Diabetes Obes Metab 2013;15:193–196.

Microbial dysbiosis may be the inciting factor for low-grade chronic inflammation

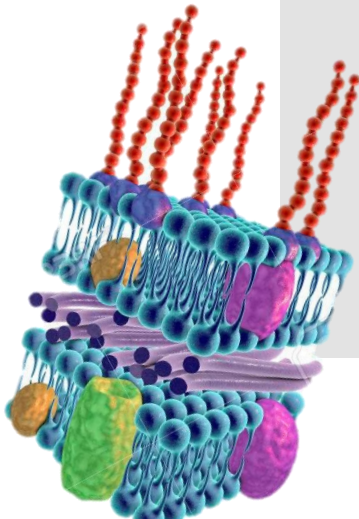
- 2007, Diabetes: Patrice Cani described *metabolic endotoxemia*
- Mice fed high-fat diets found to develop obesity, insulin resistance, diabetes + systemic inflammation



Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56:1761–1772.

Microbial dysbiosis may be the inciting factor for low-grade chronic inflammation

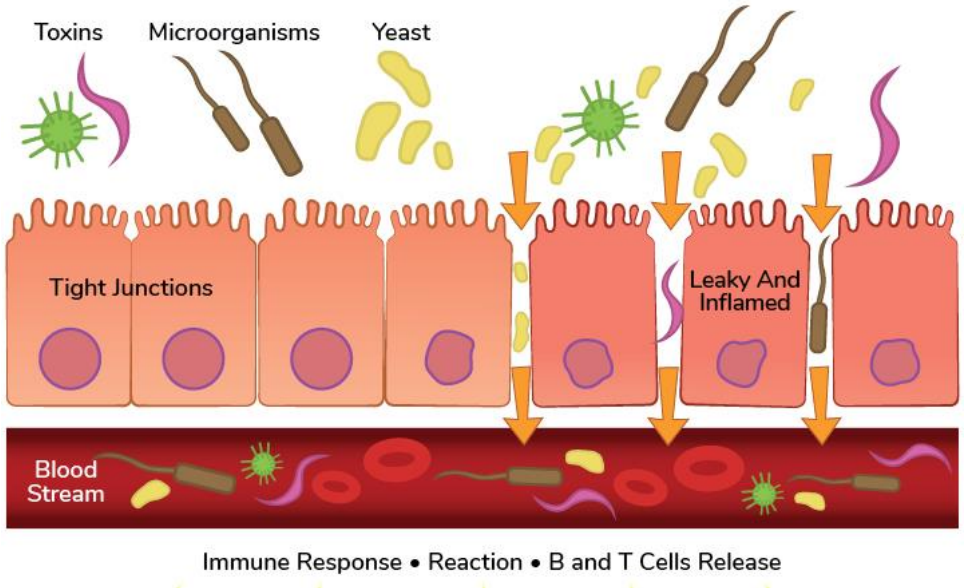
- Gram-negative bacterial lipopolysaccharide (LPL)
- Transmembrane TLR receptors sense intestinal bacterial LPL
- Triggers inflammatory cytokine pathway



Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56:1761–1772.

Bacterial LPL also may directly enter circulation through leaky gut membranes

- High [LPL] in in portal vein, plasma of T2DM patients
- Intestinal permeability increased between epithelial cells
- 2015 JD Schertzer (McMaster University): certain bacterial strains disrupt localization of tight-junction proteins



Denou E, Lolmède K, Garidou L, et al. Defective NOD2 peptidoglycan sensing promotes diet-induced inflammation, dysbiosis, and insulin resistance. EMBO Molec Med 2015;7:259–274.

Microbially derived short-chain fatty acids may have a protective effect against T2DM

- High fiber diets beneficial in T2DM management
- Possible microbial basis

- Bacterially produced SCFA stimulate liver/muscle protein kinases (AMPK)
- AMPK activates PPAR receptors →
  - improved glucose uptake
  - oxidation of free-fatty acids
  - increased energy expenditure

den Besten G, Lange K, Havinga R, et al. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. Am J Physiol Gastrointest Liver Physiol 2013;305:G900–G910.
Zhang X, Zheng X & Yuan Y. Treatment of insulin resistance: straight from the gut. Drug Discov 2016;21 1284-1290.

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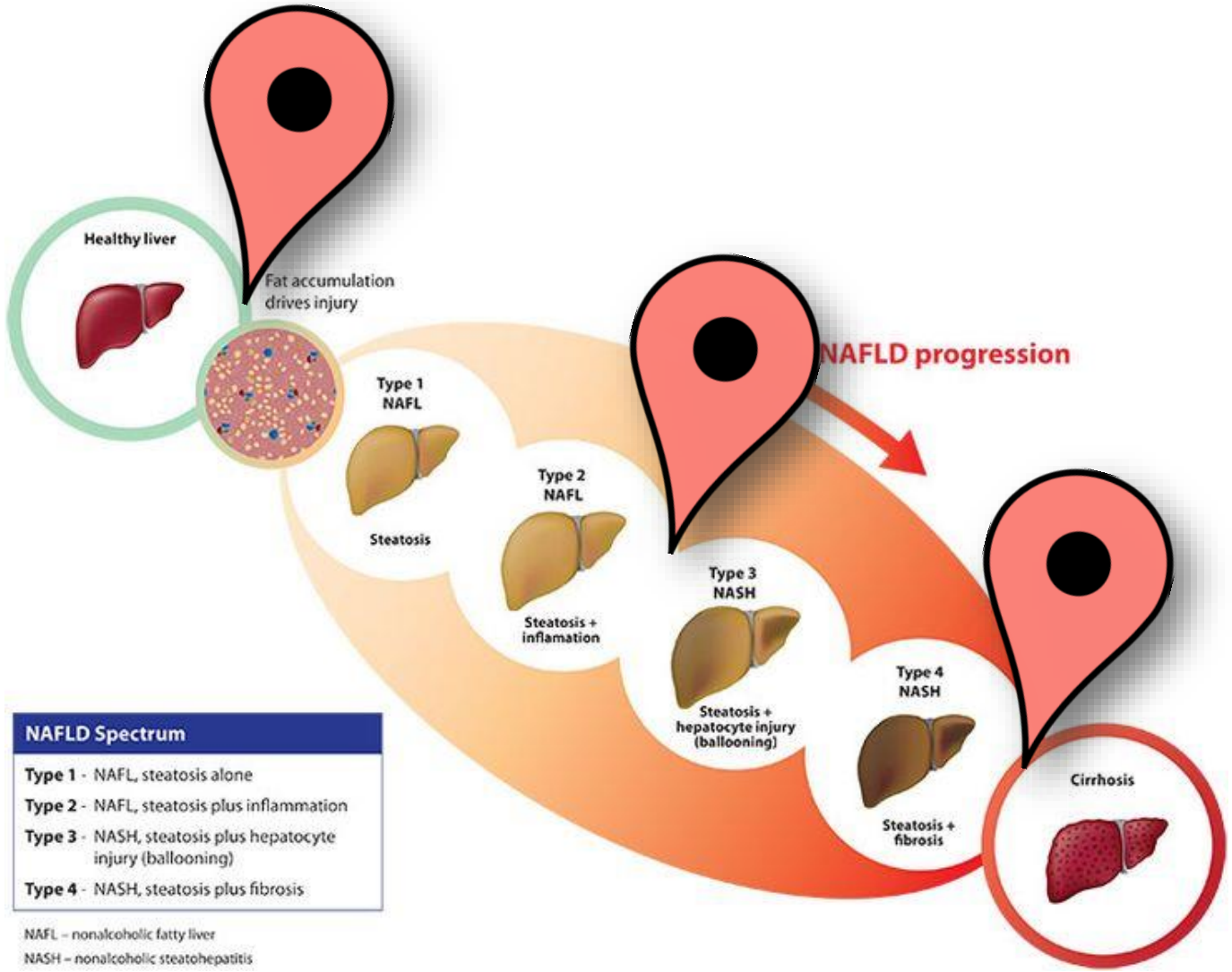


Progression of NAFLD to cirrhosis is much less linear than the picture suggests

30% NAFL develop NASH

30% NASH develop cirrhosis

Calzadilla Bertot L, Adams LA. The Natural Course of Non-Alcoholic Fatty Liver Disease. Int J Mol Sci. 2016;17(5)

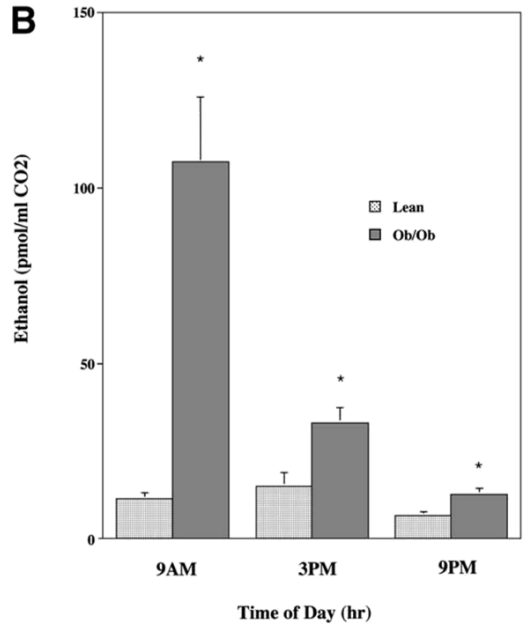
Microbially derived ethanol may have direct hepatotoxic effects

- Microbiome composition of NAFLD and non-NAFLD obese patients differ in abundance of multiple species
- *Enterobacteriaceae* higher compared to healthy controls
- Major metabolite of *Enterobacteriaceae* is ethanol

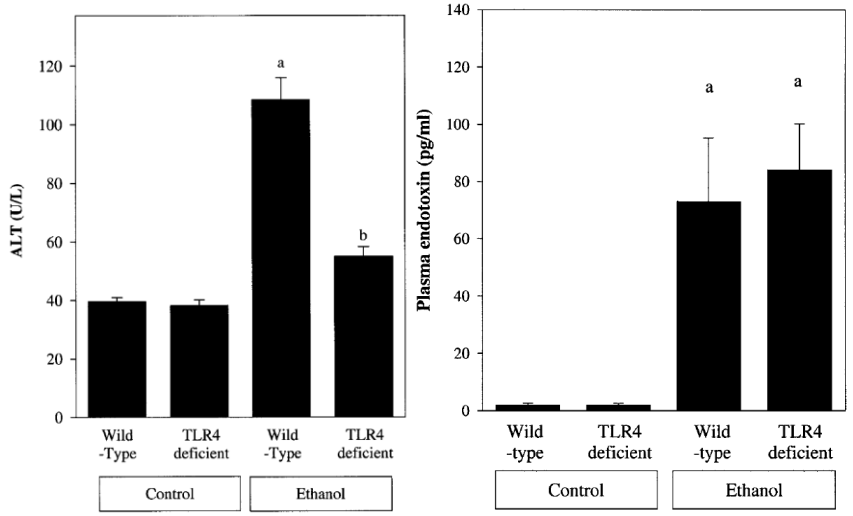
Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. Gastroenterology 2000;119:1340–1347.

Microbially derived ethanol may have direct hepatotoxic effects

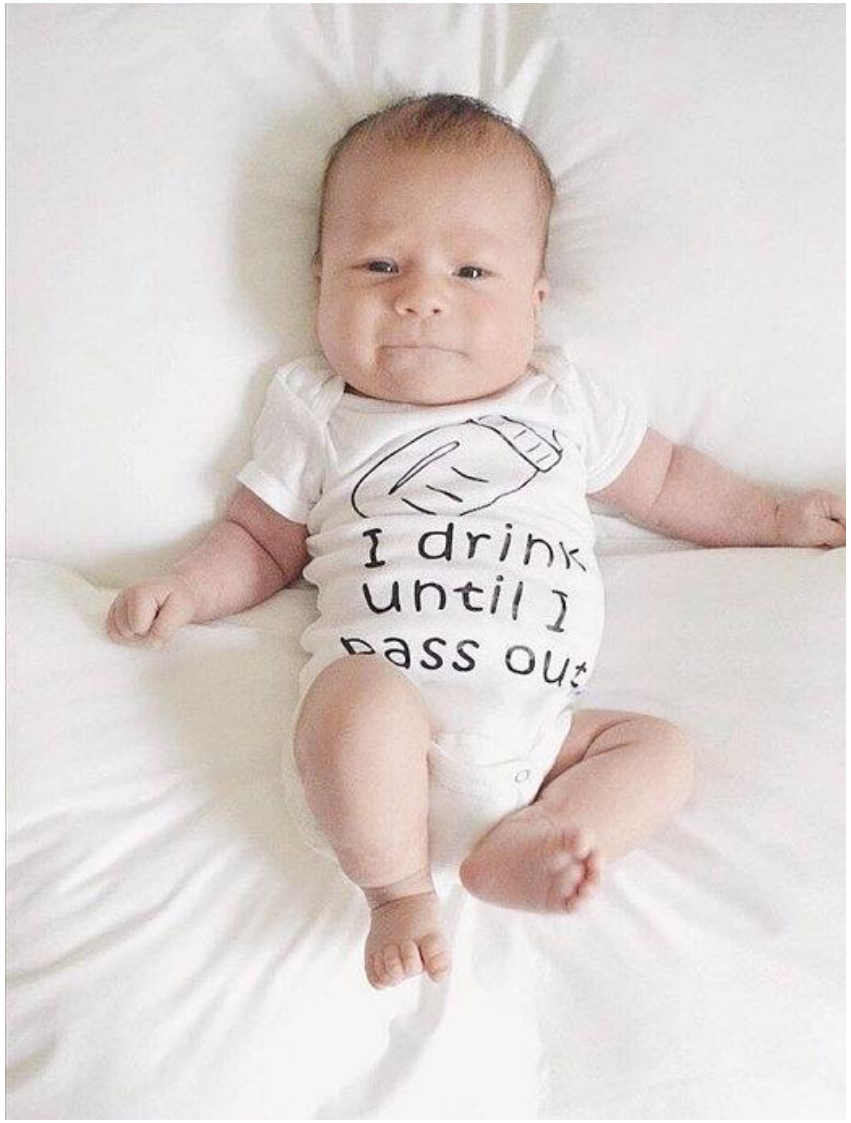
- Obese animals higher blood concentrations of ethanol vs lean animals
- Ethanol produced *de novo* produces ROS → liver inflammation



- Rats fed nonabsorbable antibiotics less-severe liver inflammation after ethanol administration
- $TLR4^{-/-}$ mice no liver inflammation after ethanol administration

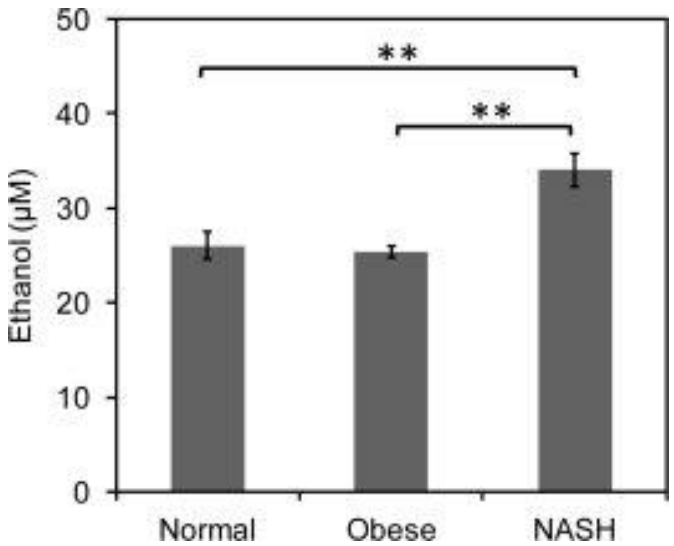


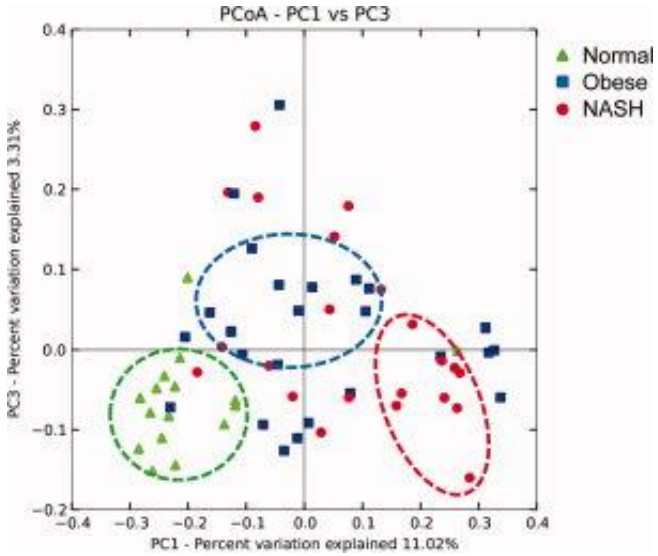
Adachi Y, Moore LE, Bradford BU, et al. Antibiotics prevent liver injury in rats following long-term exposure to ethanol. Gastroenterology 1995;108:218–224.
Uesugi T, Froh M, Arteel GE, et al. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. Hepatology 2001;34:101–108.



Pediatric data also suggests microbial ethanol hepatotoxicity in NAFLD/NASH

- n=75, mean age 14.4
- 3 groups: healthy controls + obesity + NASH





Zhu L, Baker SS, Gill C, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013;57:601–9.

Small bowel bacterial overgrowth more common in NAFLD

SIBO: disorder of abnormally high bacterial abundance in small intestine

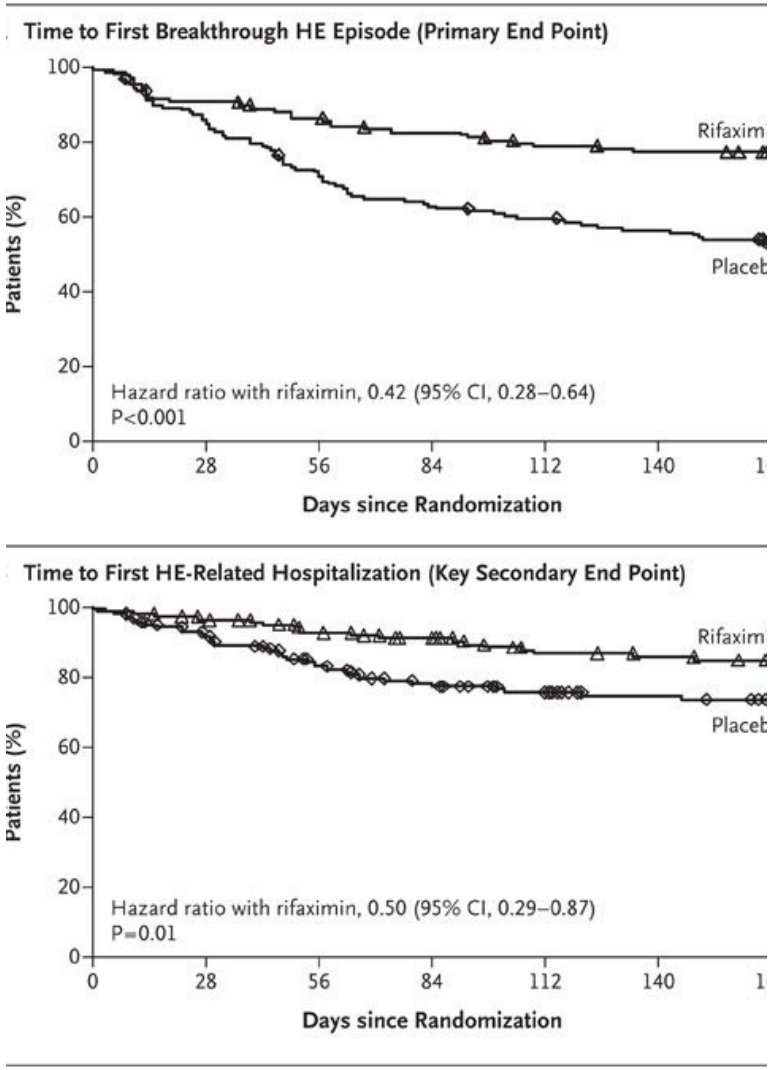
Patients with obesity, NAFLD have higher bacterial load versus healthy controls

SIBO correlates with degree of steatosis, inflammation and fibrosis

Bauer TM, Schwacha H, Steinbrückner B, et al. Small intestinal bacterial overgrowth in human cirrhosis is associated with systemic endotoxemia. Am J Gastroenterol. 2002;97(9):2364-70.

Treatment of small bowel bacterial overgrowth results in significant improvement in patients with cirrhosis

- Rifaximin: nonabsorbable antibiotic for hepatic encephalopathy
- Reduction of luminal bacteria, reduction of NH_3 production
- Clinical trials ongoing to determine if Rifaximin may affect natural history of liver disease pre-cirrhosis



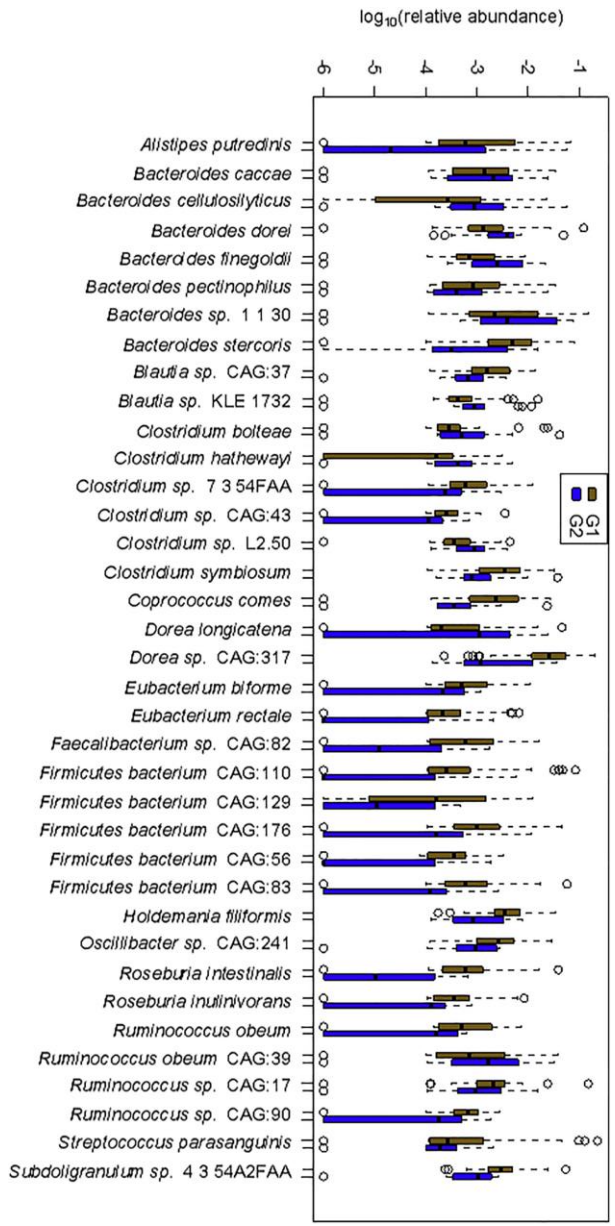
Sidhu SS, Goyal O, Mishra BP, et al. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). Am J Gastroenterol 2011;106:307–316.
Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071-81.

Therapeutic bile-acid therapy effective at reducing bacterial overgrowth, inflammation

- Supplemental bile acids may reverse cirrhosis in rats
- Obeticholic acid, FXR agonist
- Multicenter RCT of obeticholic acid in NASH (n=283)
  - Reduced inflammatory activity
  - Reduced fibrosis
  - Improved NAFLD Activity Scores
- Phase 2 clinical trials

Fickert P, Fuchsbichler A, Moustafa T, et al. FXR critically determines the fibrotic response in mice but is expressed to a low extent in human hepatic stellate cells and periductal myofibroblasts. Am J Pathol 2009;175:2392–2405.

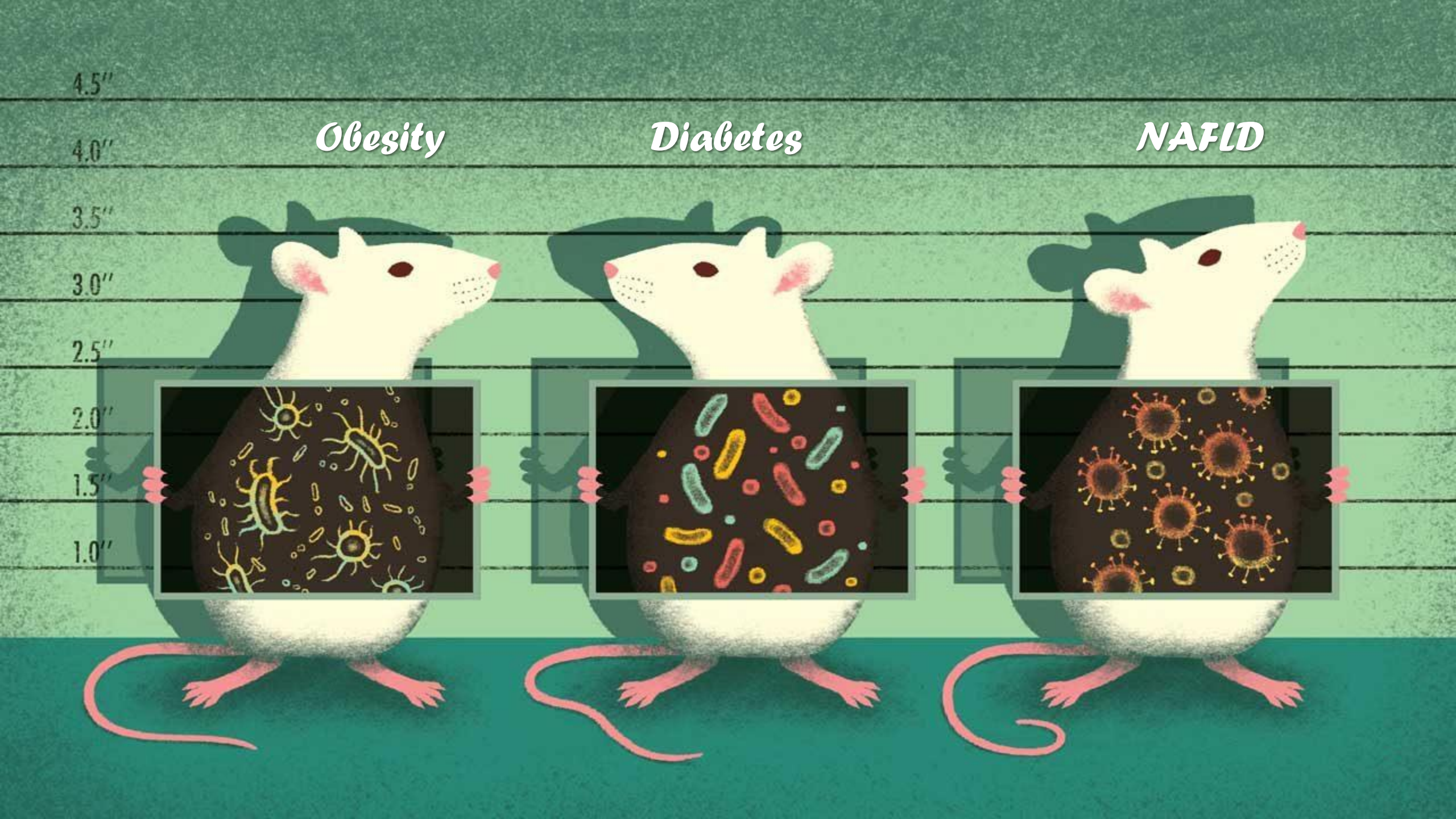
Microbial signatures may offer noninvasive biomarkers for NAFLD staging



- Liver biopsy high-risk in cirrhosis
- 37 gut microbial species predicted Stage 0-2 fibrosis vs. Stage 3-4 fibrosis
- AUROC 0.936

- Stool samples alternative to liver biopsy for detection of advanced fibrosis

Thomas H. NAFLD: A gut microbiome signature for advanced fibrosis diagnosis in NAFLD. Nat Rev Gastroenterol Hepatol. 2017;14(7):388.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Obesity
Diabetes
NAFLD

Objectives

INTRODUCTION: Understanding the literature

1. Review the relationship between the intestinal microbiome and obesity
2. Discuss evidence supporting the role of the microbiome in T2DM
3. Describe interactions between the intestinal microbiome in NAFLD

CONCLUSION: Microbial therapeutics and the future

As clinicians… how can we apply this to our patients?

Microbiota based therapies are a hot area of research

Wang Z, Roberts Adam B, Buffa Jennifer A, et al. Nonlethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 2015; 163:1585–1595.
Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7.

Microbiota based therapies are a hot area of research: TMAO & atherosclerosis

- Targeted inhibition of gut microbial trimethylamine production for atherosclerosis prevention
- Structural analogue of precursor choline (DMB)
- *In vitro* testing on human stool significantly reduces TMA production
- Human trials lacking

Wang Z, Roberts Adam B, Buffa Jennifer A, et al. Nonlethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 2015; 163:1585–1595.
Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7.

Fecal transplant for T2DM

- Fecal microbiota transplant assessed in 1 RCT for T2DM
- N=38, autologous vs. healthy donor FMT
- Improvement in insulin sensitivity after 6 weeks
  - No sustained effect at 12 weeks

Wang Z, Roberts Adam B, Buffa Jennifer A, et al. Nonlethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 2015; 163:1585–1595.
Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7.

Fecal transplant for obesity

- No human studies yet
- 6 clinical trials registered: Boston, Helsinki, Tel Aviv, Hong Kong +
- Dr. Michael Silverman (ID): London, Ontario
- Dr. Johane Allard (GI): Toronto, Ontario

Wang Z, Roberts Adam B, Buffa Jennifer A, et al. Nonlethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 2015; 163:1585–1595.
Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7.

Probiotics have little defined role

- A topic unto itself…
- Have not shown any (generalizable) benefit
- Significant placebo effect
- Low risk

Wang Z, Roberts Adam B, Buffa Jennifer A, et al. Nonlethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 2015; 163:1585–1595.
Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–916.e7.

The last 5 years have shown an exponential increase in microbiome literature. Next 5 years?

- Estimate: ~1700 patients per cohort study to assess obesity/microbiome relationship where one variable is controlled
- NIH Funded: Human Microbiome Project
- Future studies may establish sub-classifications of metabolic syndrome

ie. T2DM driven by bacterial composition vs. T2DM where microbiota does not have role in pathophysiology

Falony G, Joossens M, Vieira-Silva S, et al. Population level analysis of gut microbiome variation. Science 2016; 352:560–564.

Conclusions

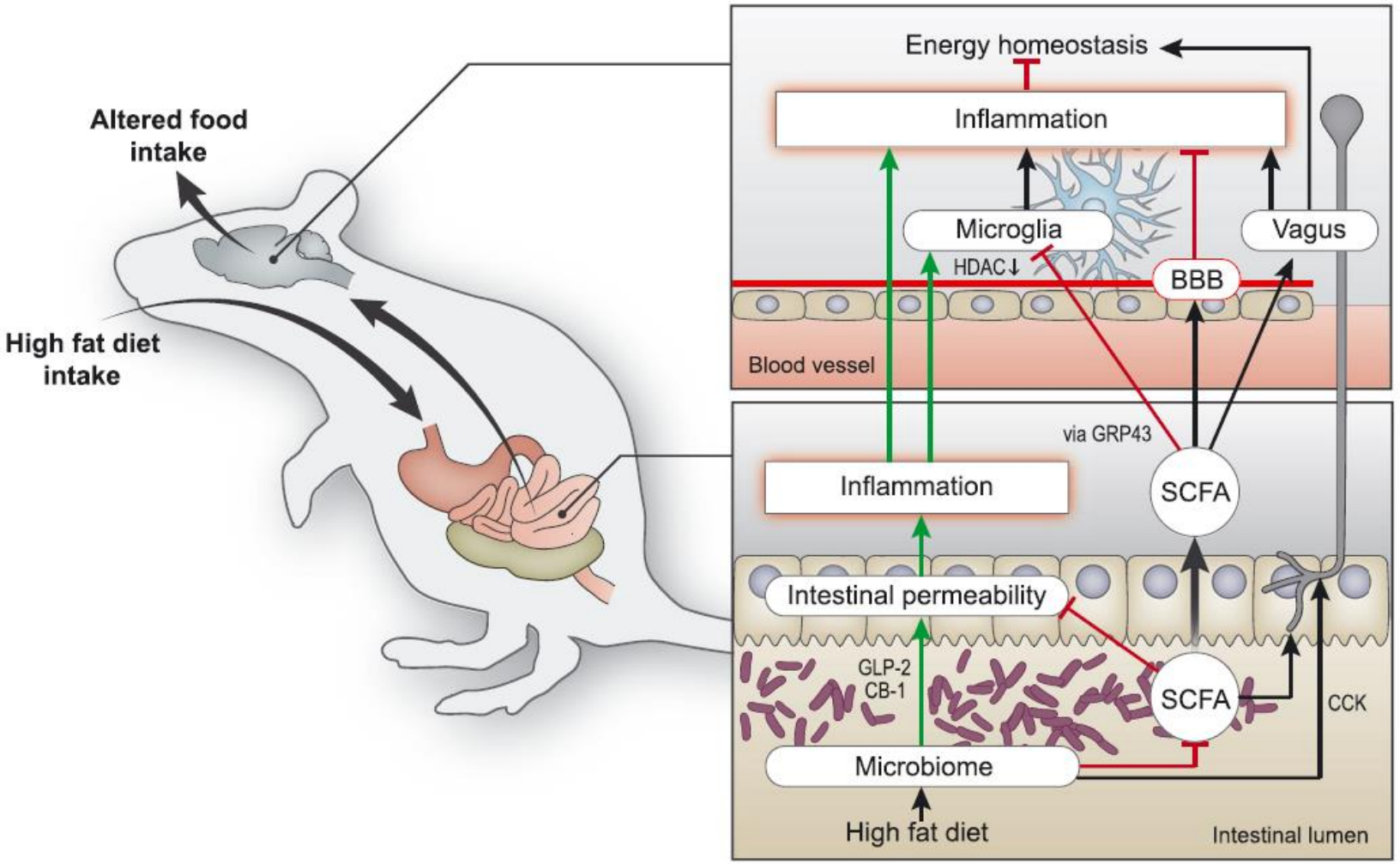
Microbiota influences obesity:	• dietary influences on microbiome • influence on central hypothalamic function
Microbiota influences T2DM through:	• LPS • SCFA regulate glycemic control
Microbiota influences NAFLD through:	• microbial ethanol production • SIBO

pain@mcmaster.ca
Nikhil Pai, MD FAAP FRCPC
DIVISION OF PEDIATRIC GASTROENTEROLOGY & NUTRITION
ASSISTANT PROFESSOR OF PEDIATRICS, MCMASTER CHILDREN'S HOSPITAL

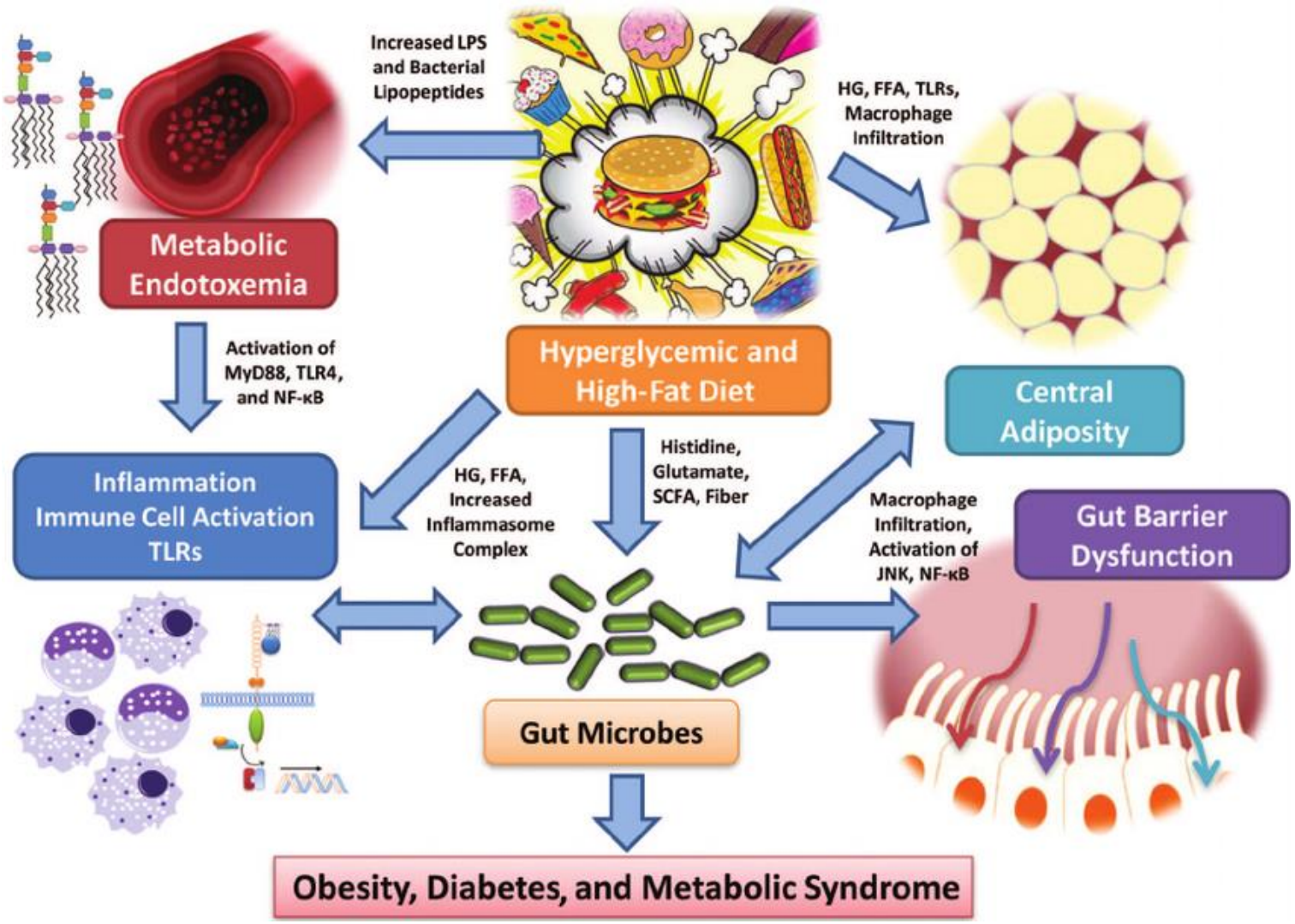
APPENDIX

The proposed mechanisms of how microbiota influences energy homeostasis during high-fat diet feeding. During high-fat diet feeding, microbiota increases intestinal permeability via mechanisms involving GLP-1 and CB1, leading to systemic inflammation. Systemic inflammation induces central inflammation via humoral, cellular (microglia) or neural (not shown) pathways, impairing energy homeostasis and increasing food intake. Short-chain fatty acid, of which the production is decreased during diet-induced obesity, promotes colonic integrity, blood–brain barrier integrity and induces a neuroprotective and anti-inflammatory state in microglia by inhibiting (HDAC, histone deacetylase) via the G-protein coupled receptor 43. Moreover, both microbiota and short-chain fatty acid interact with vagal afferent nerves, communicating with the hypothalamus about inflammation and energy homeostasis, although its influence is unclear. Red lines depict negative connections; green lines depict positive connections, and black lines depict unknown connections (CB1, cannabinoid receptor 1; CCK, cholecystokinin; GPR43, G protein-coupled receptor 43).

Mulders RJ, De git KCG, Schéle E, Dickson SL, Sanz Y, Adan RAH. Microbiota in obesity: interactions with enteroendocrine, immune and central nervous systems. Obes Rev. 2018

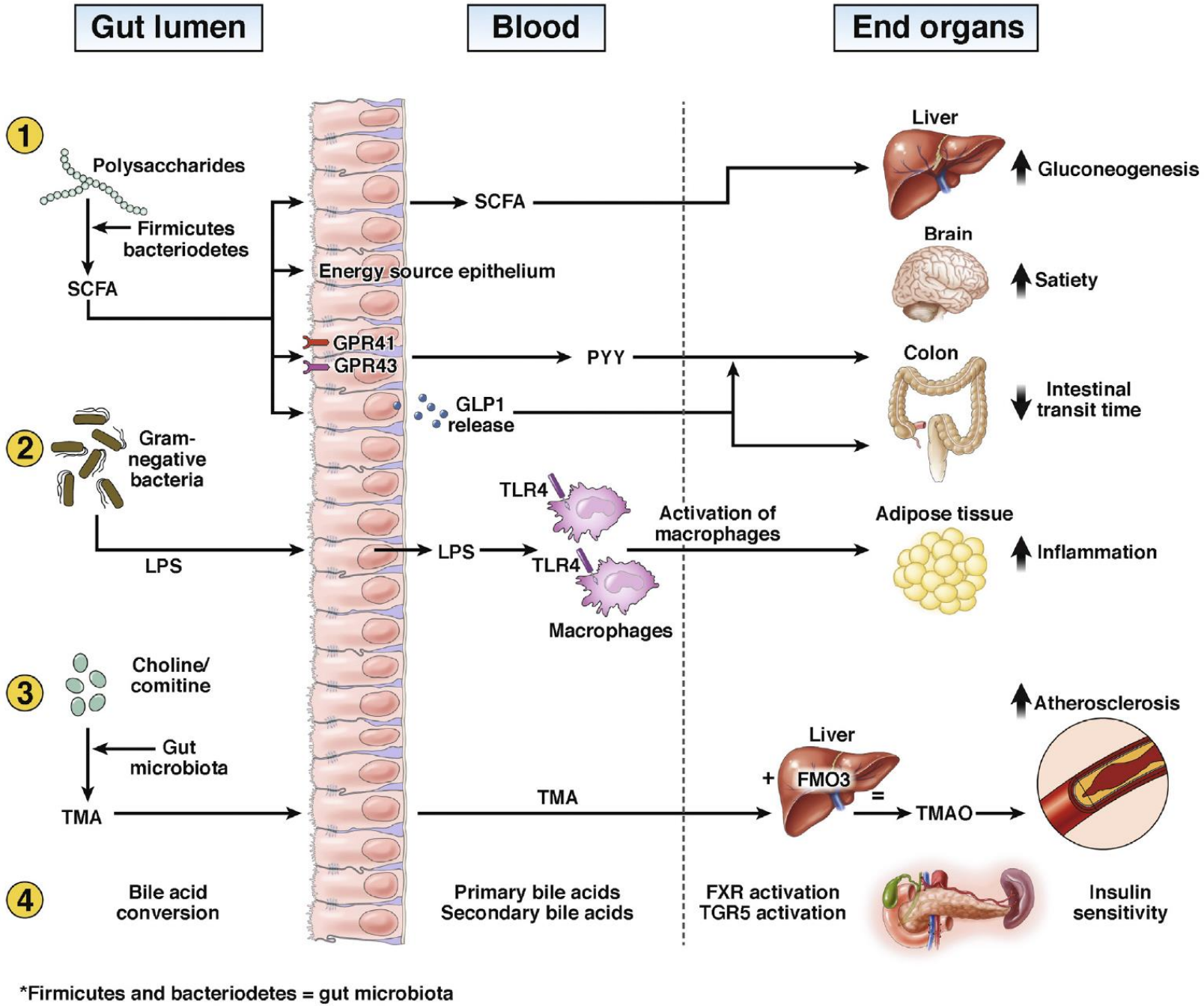


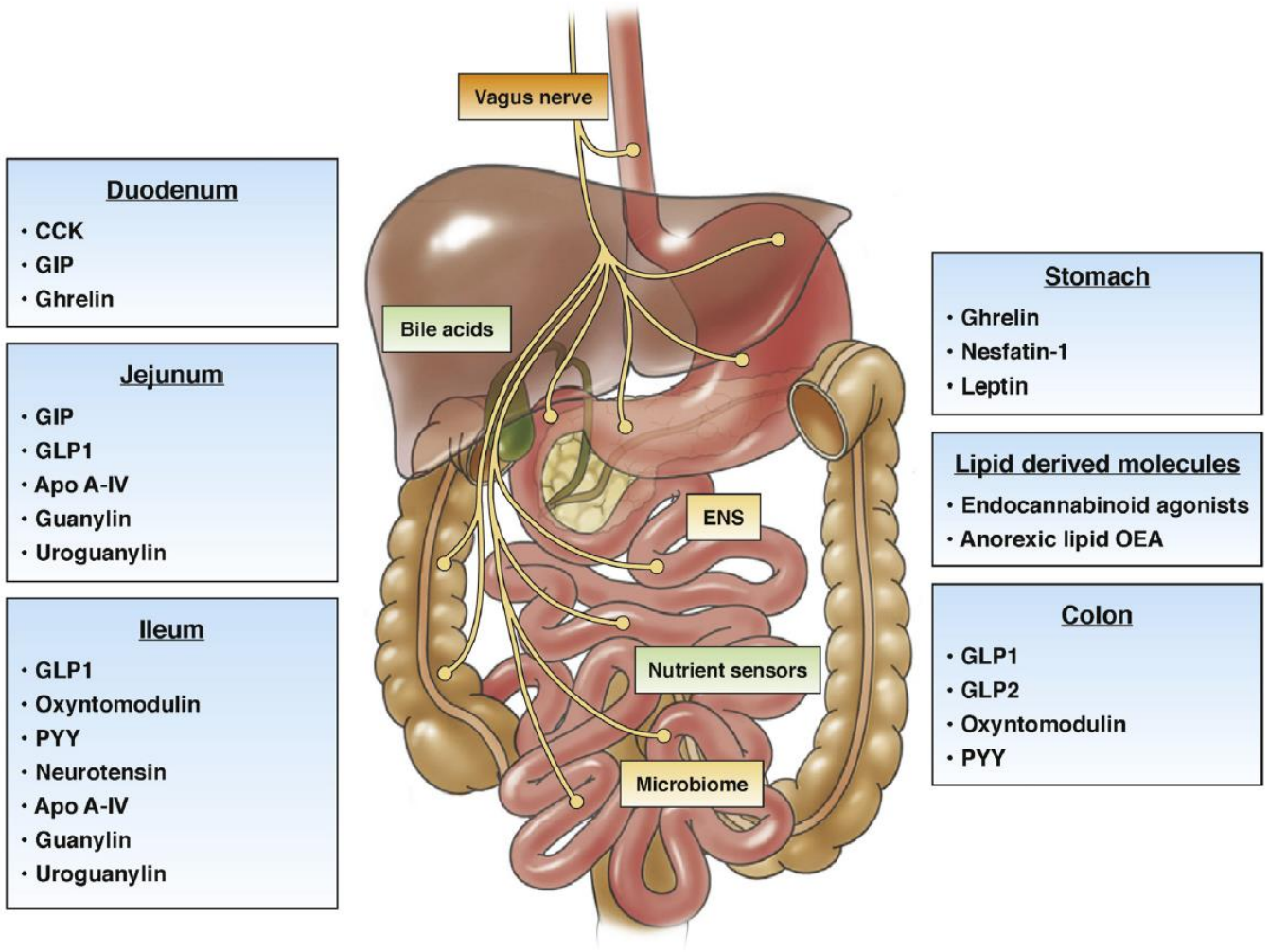
Interactions between the intestinal microbiota and T2DM.



Schematic overview of functions attributed to intestinal bacterial strains. SCFA, short chain fatty acids; GPR41, G-protein coupled receptor 41; GPR43, G-protein coupled receptor 43; GLP1, glucagon like protein 1; PYY, peptideYY; LPS, lipopolysaccharide; TLR4, Toll like receptor 4; TMA, trimethylamine; FMO3, flavin-containing monooxygenase; TMAO, trimethylamine-N-oxide; FXR, farnesoid X receptor TGR5 transmembrane G protein-coupled receptor.

Bouter KE, Van raalte DH, Groen AK, Nieuwdorp M. Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. Gastroenterology. 2017;152(7):1671-1678.





Several signals arising from the GI tract are able to regulate energy homeostasis and body weight. These comprise GI peptides/hormones, which are secreted by different discrete enteroendocrine cell populations distributed along the entire GI tract from the stomach to the distal colonic mucosa and include the orexigenic hormone ghrelin and anorexigenic hormones (CCK, GLP-1, OXM PYY, nesfatin-1, and leptin); intestinal epitheliumderived signals, such as ApoA-IV, guanylin, and uroguanylin; anorexigenic and orexigenic lipid-derived molecules (oleoyethanolamide [OEA] and endocannabinoid); and nutrient metabolites produced by gut microbiota (acetate, butyrate, and propionate). The ENS interacts with the autonomic nervous system, EEC products and is able to directly sense absorbed nutrients. In turn, the ENS finetunes the function of EECs. Vagal afferent firing is influenced by a wide-range of gut peptides, gut-derived lipid mediators, shifts in gut microbiota, gut inflammation, and leptin.

Monteiro MP, Batterham RL. The Importance of the Gastrointestinal Tract in Controlling Food Intake and Regulating Energy Balance. Gastroenterology. 2017;152(7):1707-1717.e2.