The Role of the Gut Microbiome in Weight Modulation and Management

Arnab Ray, MD
Ochsner Clinic Foundation
Gastroenterology Section Head

Disclosure

None.

Objectives

- Case Presentation
- Microbiome Basics and Key Players
- Clinical Trials
- Conclusions

Case Presentation

- 76 year old female suffered a dog bite, treated with ciprofloxacin
- Subsequently developed C. diff infection, treated with flagyl and vancomycin for recurrent infection
- Subsequent recurrence led to hospitalization treated with IV flagyl and vancomycin

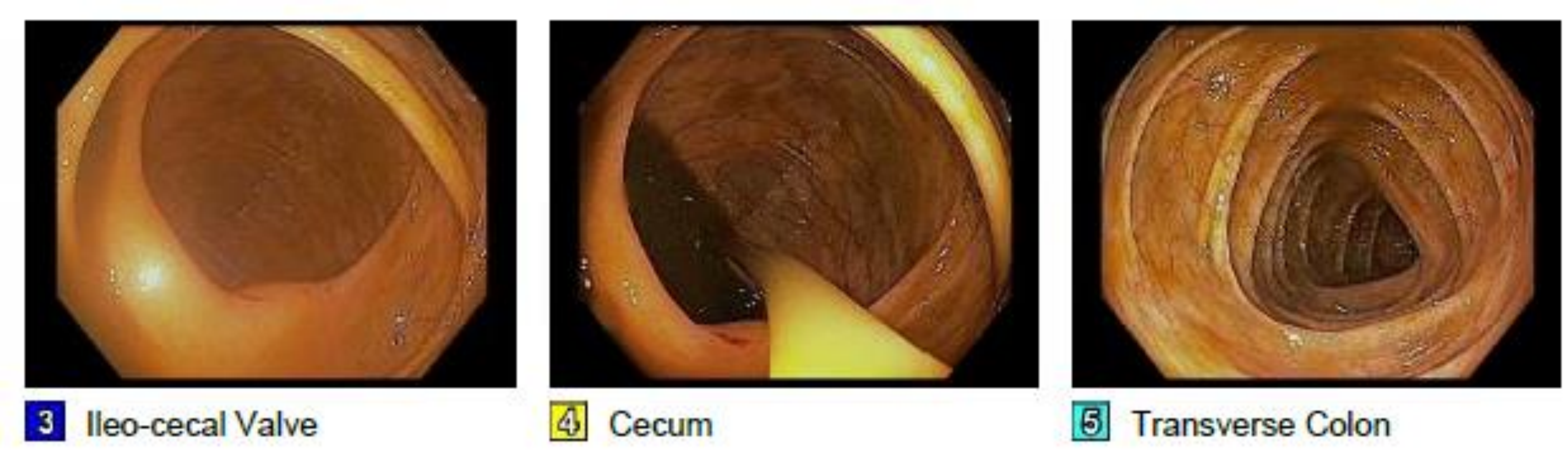
Case Presentation

- Past Surgical history:
  - Cholecystectomy, appendectomy, hysterectomy
- No living children, no spouse, no siblings

Case Presentation

- 7/2013 - GI service consulted for fecal transplantation request
    - No close relatives available as stool donor so tandem donor sought
        - Elderly gentleman with mild obesity offered to “donate”

FMT in Action



FMT Selfie!

Case Presentation

- 8/2013 - Successful FMT, C. diff resolved
  - Weight 133 lbs
- 2/2014 - Maintenance of C. diff resolution
- 12/2015
  - Weight 155 lbs

Case Presentation

- 10/2016 - Trial of low carb diet, Mediterranean diet
    - Weight 145 lbs
    - Complains of extreme discomfort from central adiposity, worsening arthritis

Case Presentation

- 4/2017
  - Requests repeat FMT
    - Repeat testing for C. diff negative
  - Requests plastic surgery consultation
  - Requests second opinion plastic surgery consultation

Case Presentation

- 8/2017
  - Complains of severe headaches and likely giant cell arteritis
  - New diagnosis of Polymyalgia Rheumatica requiring prednisone and further weight gain

HEALTH

Fecal transplants may up risk of obesity onset

Fecal microbiota transplantation can be effective for recurrent *Clostridium difficile* infection, but new-onset obesity could follow transplant of stool from an overweight donor, a new study finds

February 13, 2015

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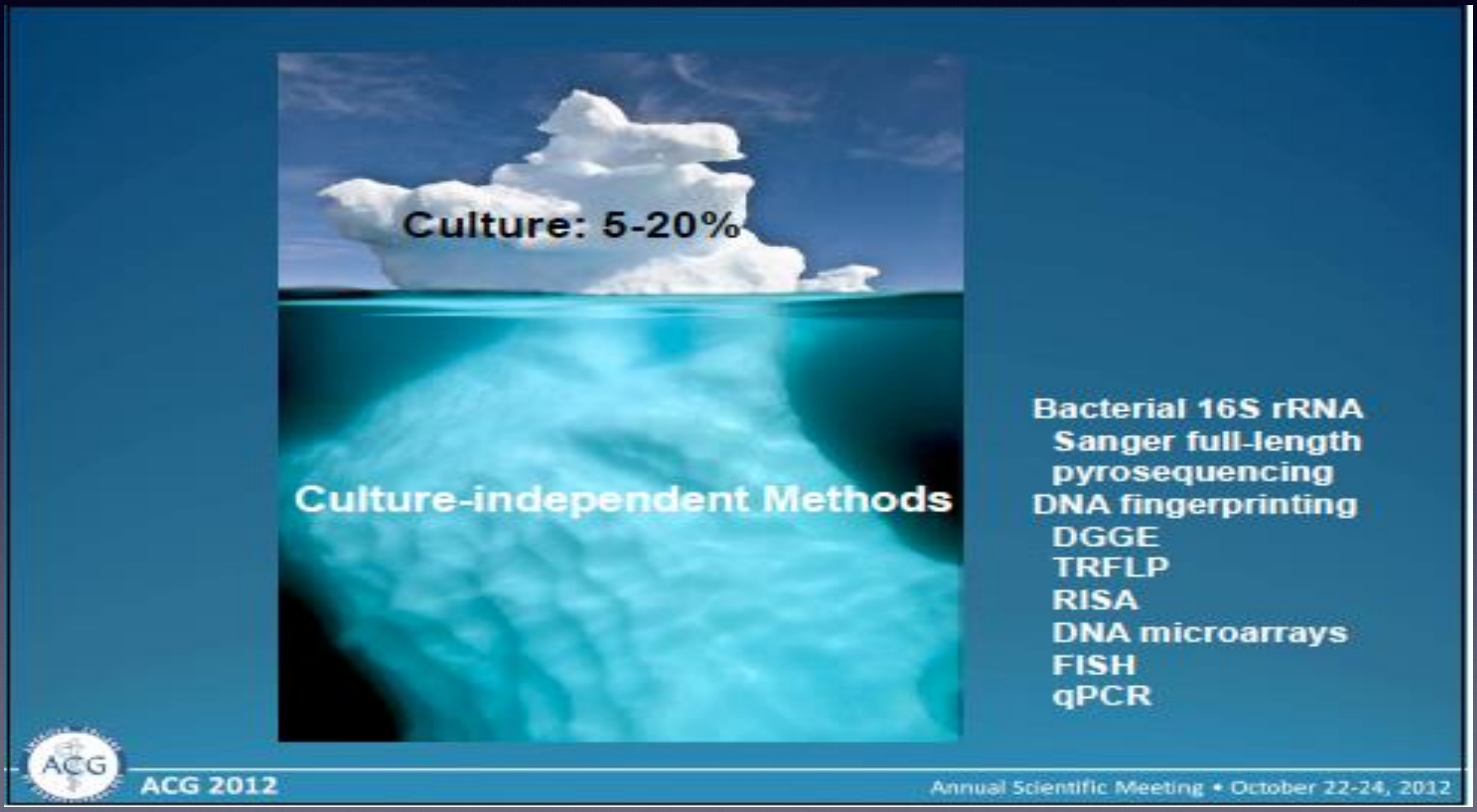
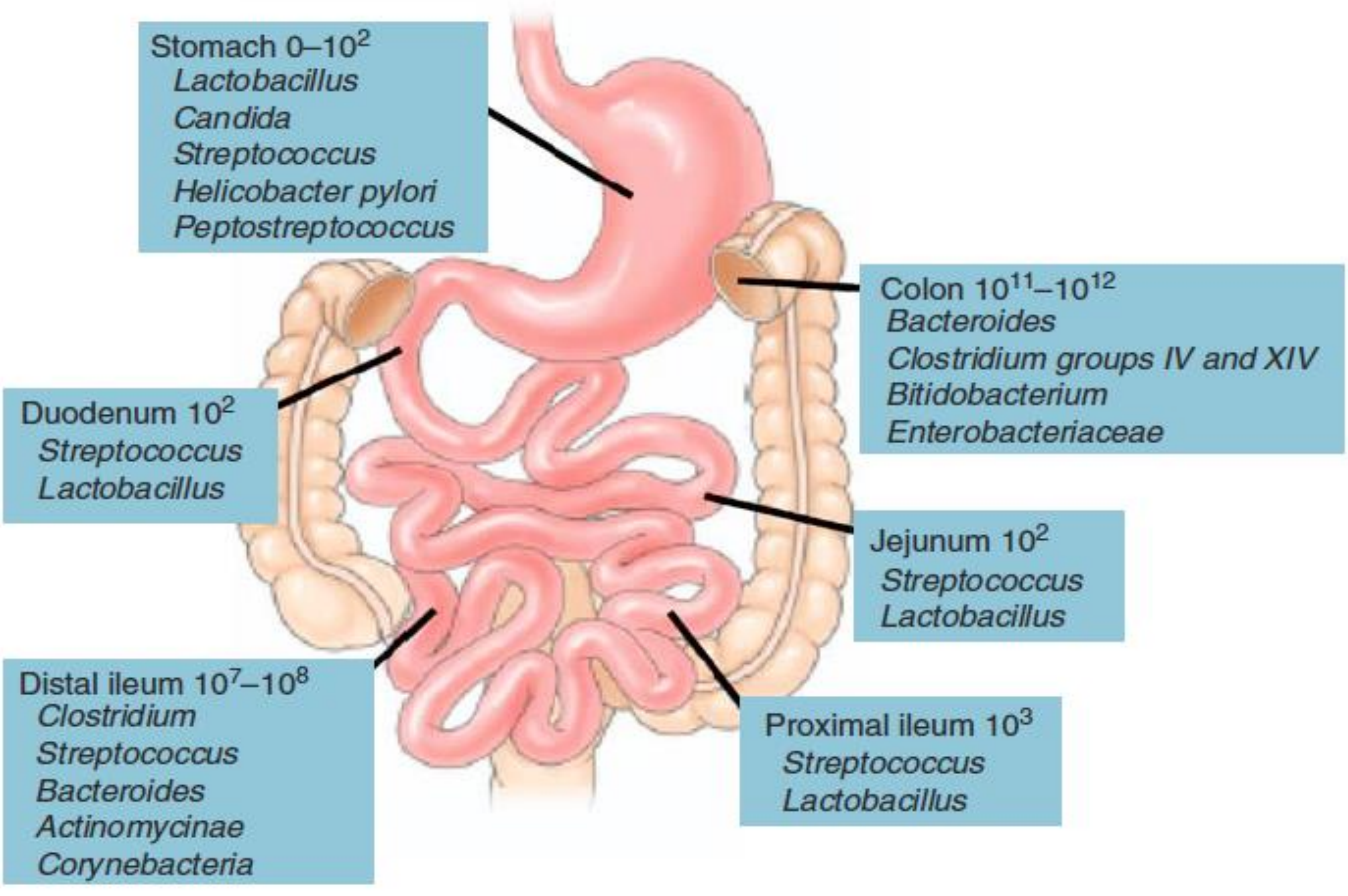
Microbiome Basics

- Vertical Heterogeneity
- Horizontal Heterogeneity
- Predominant phyla
- Enterotypes
- Ratios

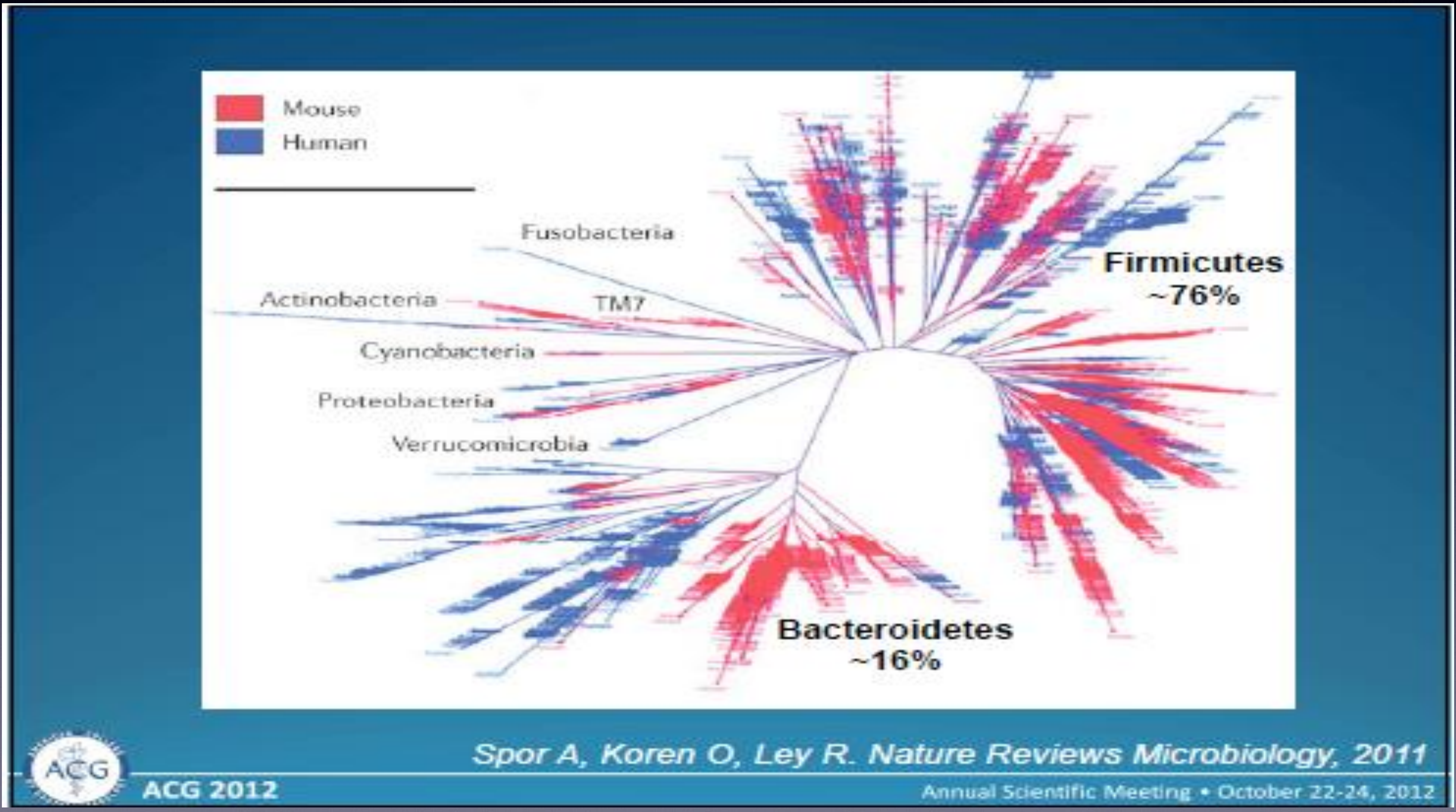
Understanding the Human Microbiota



Vertical Heterogeneity



Colonic Microbiota



Human Microbiota

- 2 predominant phyla
  - Firmicutes 76%
  - Bacteroidetes 16%
- 4,000 species and 10^{14} bacterial cells
- Bacteria comprise 60% of dry weight of feces

PHYLA	GENUS
Firmicutes	Ruminococcus Clostridium Streptococcus Enterococcus Lactobacillus
Bacteroidetes	Bacteroides Prevotella
Actinobacteria	Bifidobacterium
Proteobacteria	Desulfovibrio Escherichia Helicobacter

F/B Ratio

- Firmicutes = Fat
- Bacteroidetes = Be Skinny
- Increased F/B ratio associated with obesity and insulin resistance
- Not all studies show correlation between BMI and F/B Ratio

F/B Ratio

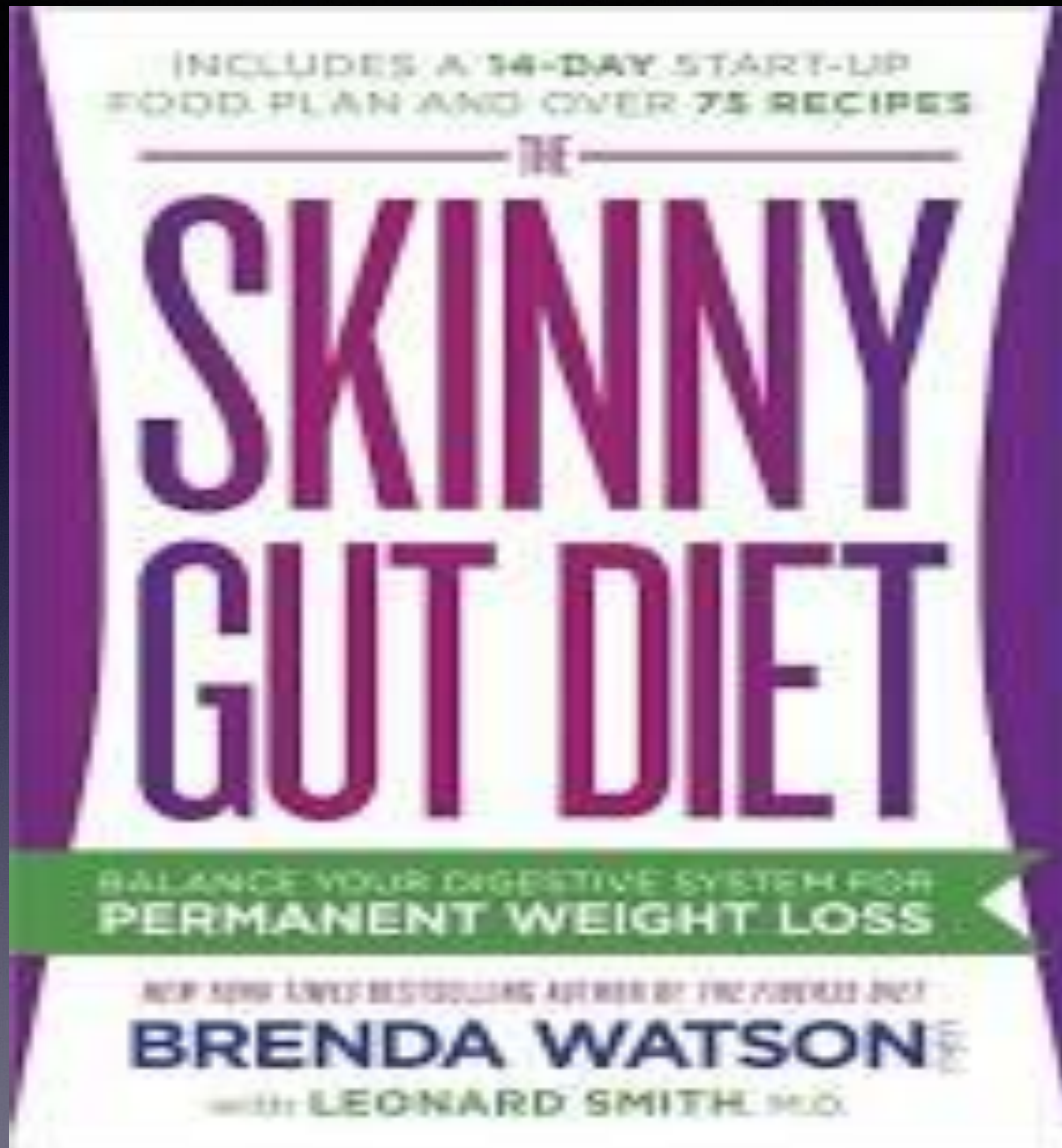
- Dr. Jeffrey Gordon at Washington University
  - Overweight individuals consumed weight loss diet x 1 year
  - At beginning of study F/B ratio higher than normal controls
  - Maintenance of weight loss correlated with normalization of ratio

F/B Ratio [2]

- Transfer of gut microbes from conventionally raised genetically obese mice into gnotobiotic mice led to them becoming obese
- Obese mice had 50% reduction in abundance of Bacteroidetes and proportional increase in Firmicutes

F/B Ratio

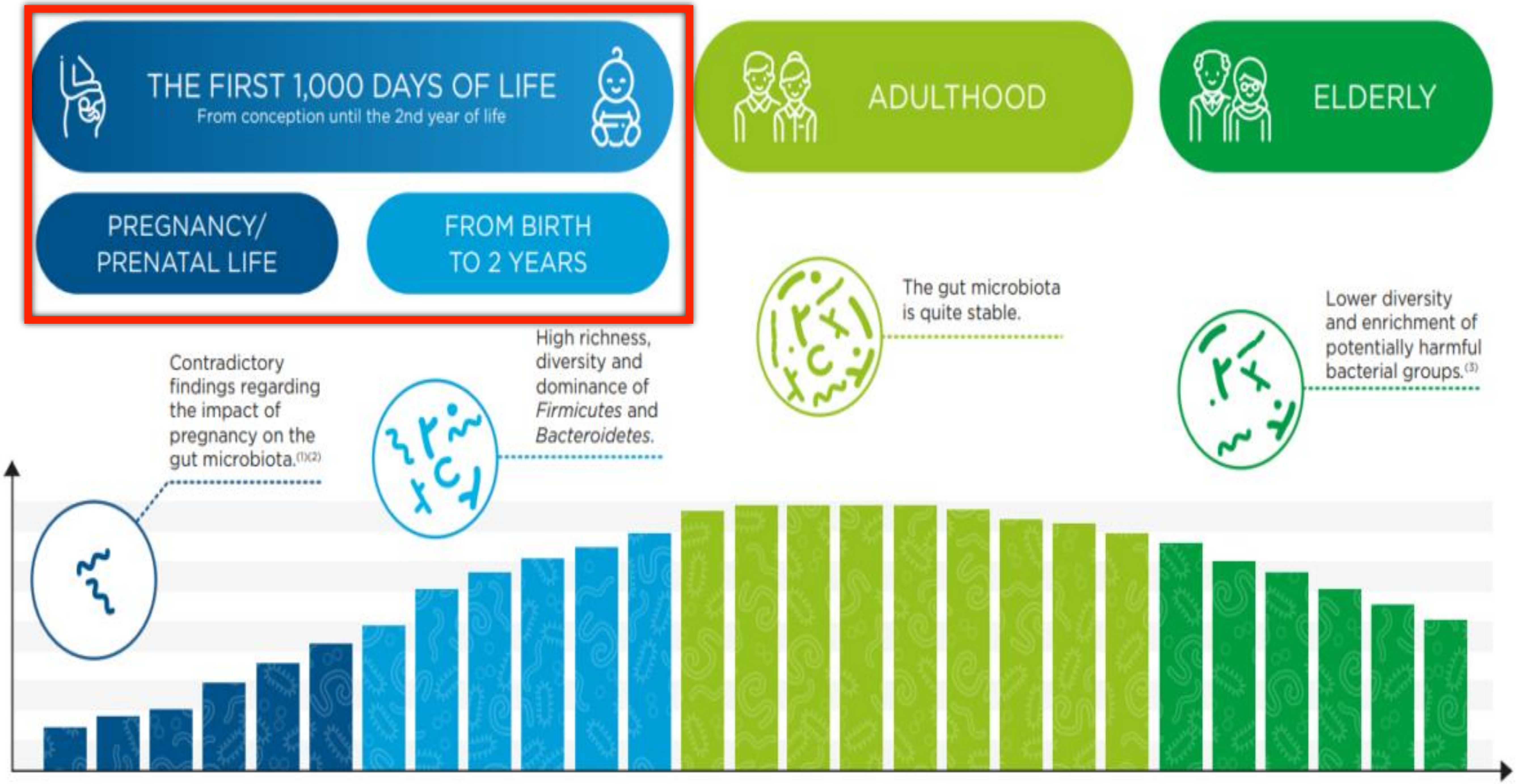
- Duncan et al did not confirm F/B ratio, however did show a diet dependent reduction in Firmicutes from obese individuals on a low carb diet
  - Amount of SCFA produced seemed to have a better correlation with weight loss


INCLUDES A 14-DAY START-UP
FOOD PLAN AND OVER 75 RECIPES
THE
SKINNY
GUT DIET
BALANCE YOUR DIGESTIVE SYSTEM FOR
PERMANENT WEIGHT LOSS
BRENDA WATSON
LEONARD SMITH

Skinny Gut Diet

- Rule 1 eat more healthy fats
- Rule 2 eat living foods every day
- Rule 3 eat protein at every meal and snack to eliminate cravings

Horizontal Heterogeneity



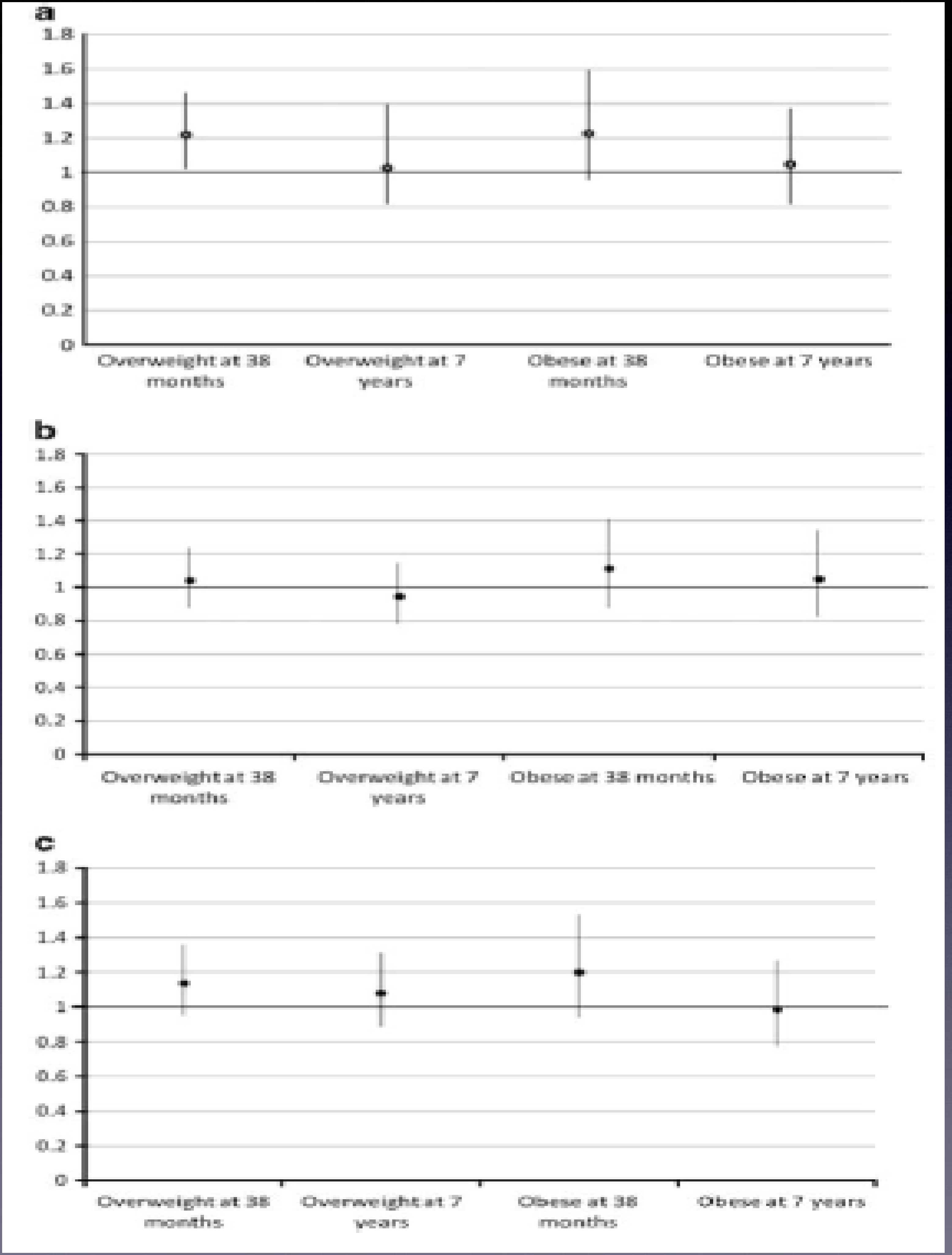
ALSPAC Study

- 14,500 Pregnant women in Avon, England
- Longitudinal Cohort Study
- Survey inquiry of antibiotic usage given to babies at 6, 15, 24 months
  - 1/3 at 6 months
  - 3/4 at 24 months
- Control for maternal and baby weight, bottle fed, breast fed

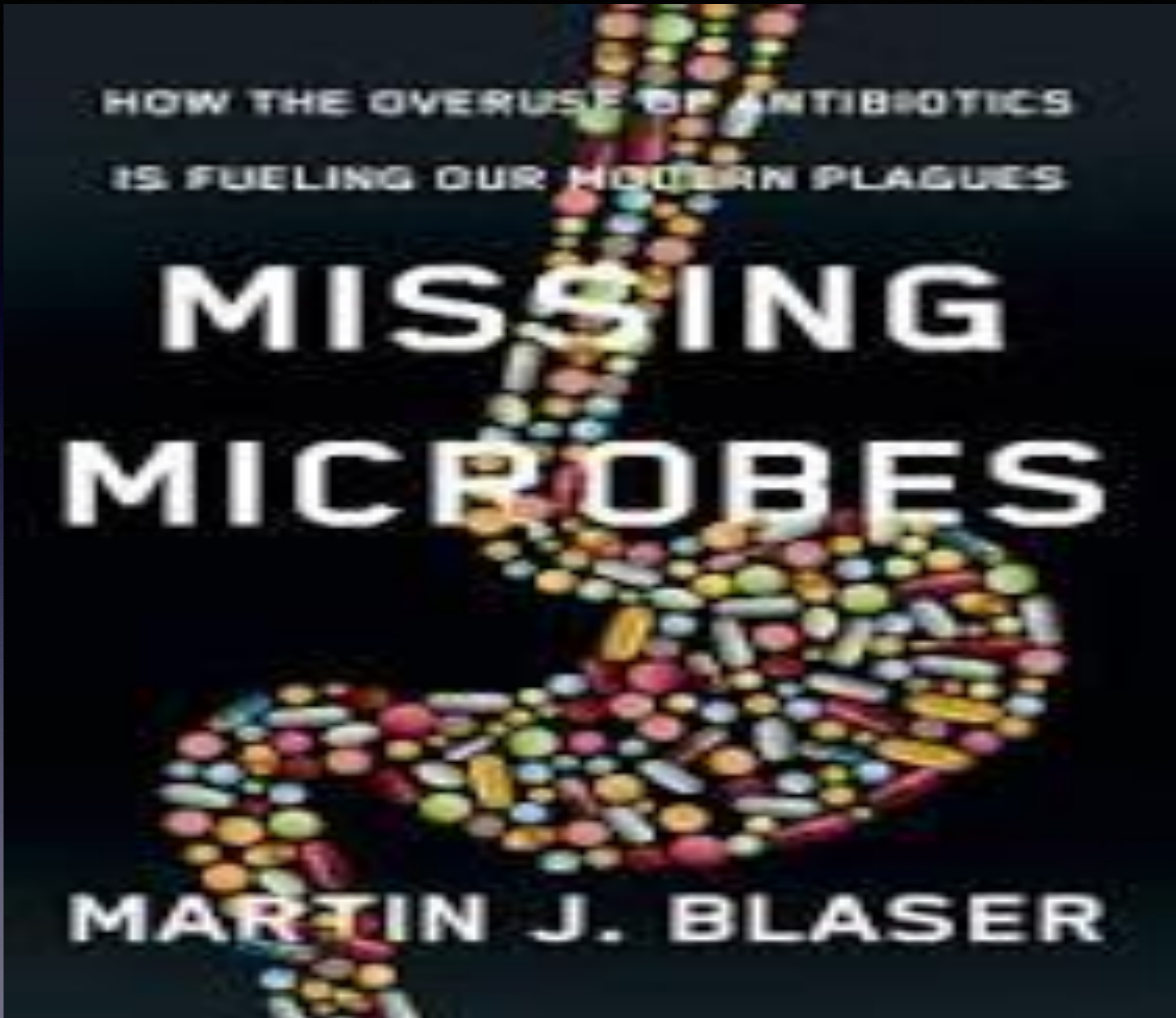
Abx < 6 months

Abx 6-14 months

Abx 15-23 months



Int J Obes (Lond). 2013 January ; 37(1): 16–23. doi:10.1038/ij


HOW THE OVERUSE OF ANTIBIOTICS
IS FUELING OUR MODERN PLAGUES
MISSING
MICROBES
MARTIN J. BLASER


I'm Lovin' it!
"Funny and outrageous"
"Two thumbs up!"
SUPER SIZE
ME
A Film of Epic Portions

Microbial Diversity [1]

- Danish study of 292 obese and non obese individuals
- Separated into 2 groups based on microbial genes
- Lowest bacterial counts had more abdominal fat, insulin resistance, high insulin, increased TG, decreased HDL, increased hsCRP

Enterotypes [3]

- Prevotella
  - Carbohydrates, Resistant starches, Fibers
  - Agrarian
- Bacteroides
  - High fat, low fiber
  - Western
- Ruminococcus

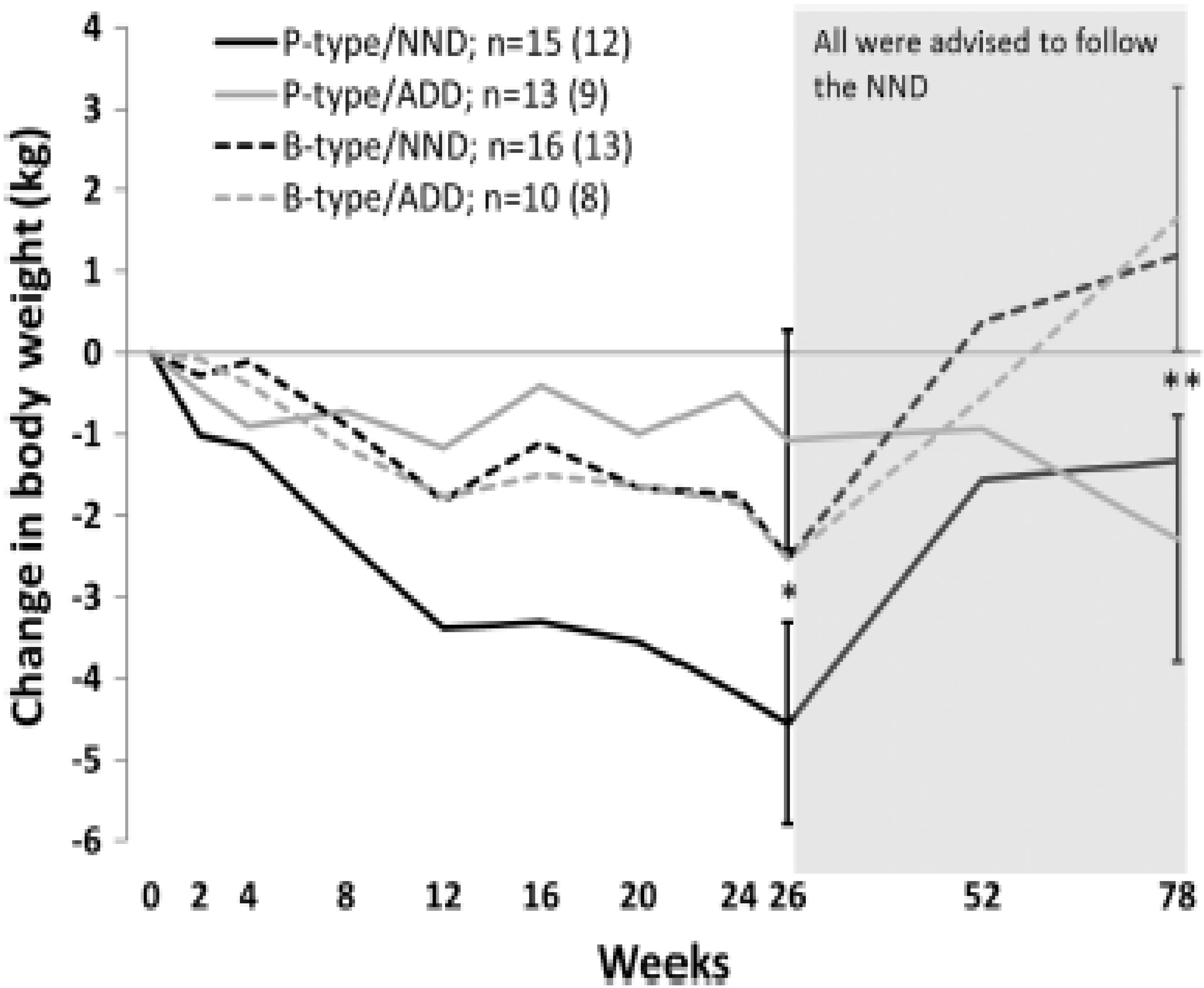
Enterotypes

	Prevotella enterotype	*Bacteroides* enterotype
Habitual diet	• Associated with a diet high in fiber and resistant starch	• Associated with a diet high in fats and low in fiber
Enzymatic capacity	• Hydrolases effective in degradation of plant fibers	• Enzymes specialized in degradation of animal carbohydrates and proteins.
Prevalence	• Increased prevalence in developing countries	• Increased prevalence in industrialized countries
Enterotype stability		• May have increased susceptibility to decreased microbial richness and load
	• Enterotypes remain unchanged on dietary interventions, even on high-fiber diets	

Bifidobacteria-type

A Bacteroides sub-type with high abundance of bifidobacteria is prevalent in Japan, and is promoted by Acarbose treatment resulting in improved bile acid metabolism and metabolic improvements

Enterotypes



Specific Players

- Akkermansia muciniphila
  - Verrucomicrobia
  - Loves mucus
  - People with obesity have lower levels
- Bilophila
  - Proteobacteria
  - Loves bile (meat and fat)
  - People with obesity have higher levels

Specific Players

- Roseburia and F. prausnitzii
  - Major butyrate producing bacteria
  - Diet with high levels of non digestible carbohydrates stimulate growth
  - Inversely proportional to obesity

Hormone Basics [4]

- Ghrelin - “hunger hormone”
  - Possibly decreased by prebiotics
- Leptin - “feed me”
  - Positive correlation with bifidobacteria and Lactobacillus
- Both decrease after gastric bypass

Hormone Basics

- Glucagon like peptide (GLP) 1
  - Produced in ileum/colon and pancreatic alpha cells
  - Decreased in obesity/DM2
  - Feeding rats with prebiotic oligofructose leads to increased GLP 1
- Peptide YY

Bariatric Surgery Hormonal Effects [5]

Fig. 1. Common bariatric surgical procedures [19].

a: Roux-en-Y gastric bypass; b: adjustable gastric banding; c: sleeve gastrectomy; d: biliopancreatic diversion with duodenal switch.

Table 3. A summary of the changes in key hormones related to energy balance and weight loss for each of the established surgical procedures and for intentional dietary behavioral weight loss [26]

	RYGB	LSG	LAGB	BPD	Behavioral weight loss
Leptin	▼	▼	▼	▼	▼
Insulin	▼	▼	▼	▼	▼
Adiponectin	▲	▲	▲	▲	▲
Glucagon	▲	?	—	?	▼
Ghrelin	▲, ▼, —	▼	▲, —	▲, —	▲
GLP-1	▲	▲	—	?	—
PYY	▲	▲	?	▲	—

▲: a substantial number of studies indicate an increase; ▼: a substantial number of studies indicate a decrease; —: a substantial number of studies found no change; ?: too few data.

RYGB: Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy; LAGB: Laparoscopic adjustable gastric banding; BPD: Biliopancreatic diversion

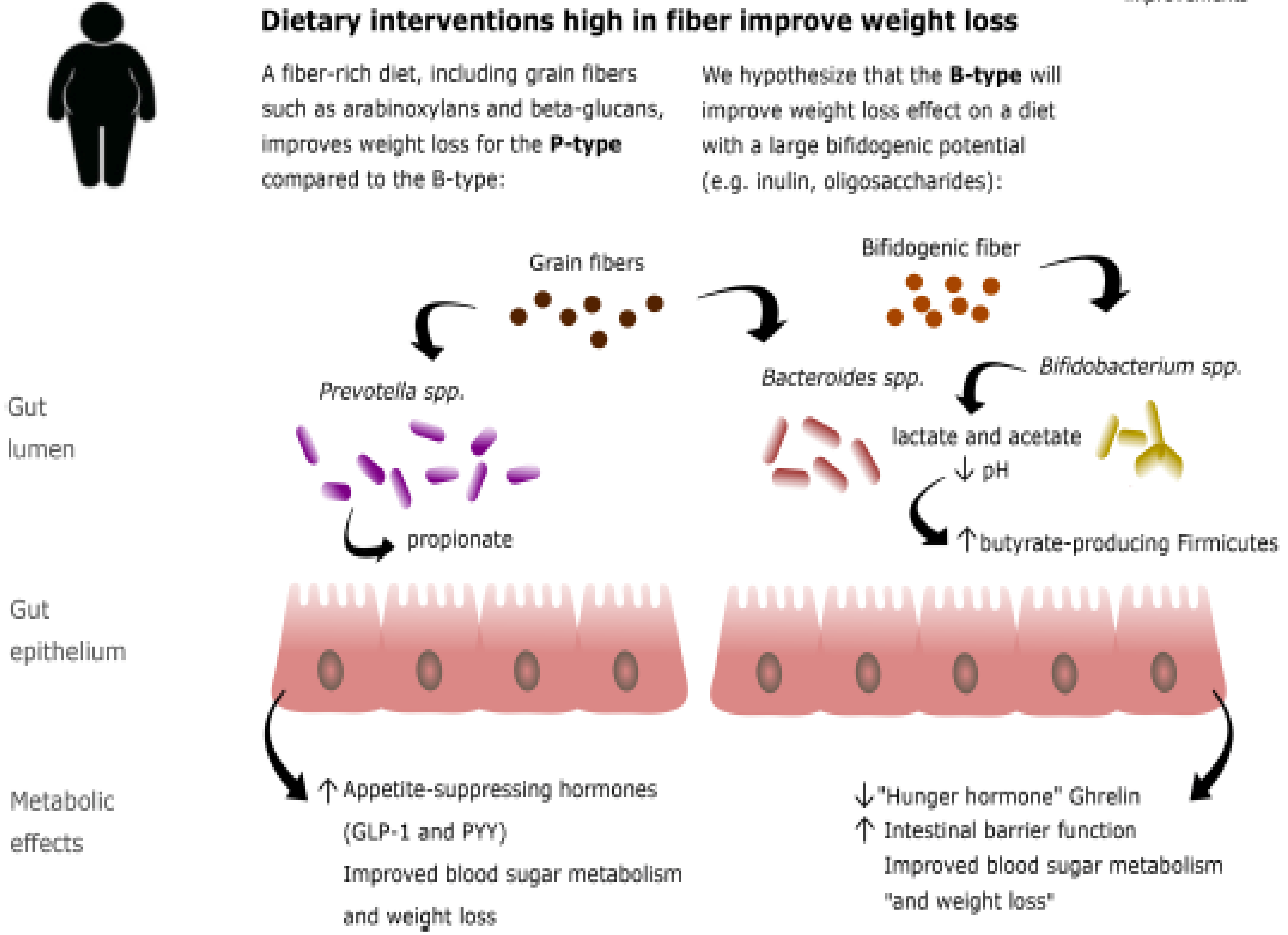


FIGURE 2 Enterotype differences and proposed weight loss mechanisms. Summary of the essential differences between the 2 enterotypes, their proposed responses to different dietary fibers in the gut lumen, and how their response via production of short-chain fatty acids (e.g., propionate) may affect metabolic parameters (e.g., appetite-regulating hormones) and body weight. B-type, *Bacteroides* enterotype; GLP-1, glucagon-like peptide 1; P-type, *Prevotella* enterotype; PYY, peptide YY.

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- Conclusions


OF MICE AND MEN

Mouse Studies

- 4 pairs of discordant human twins (2 lean, 2 obese)
  - Stool given to gnotobiotic mice, similar diet
  - Mice getting obese stool become obese
  - Lean mice have increased bacteroides

Mouse Studies

- If you give mice antibiotics (continuous or pulsed), they get fatter
  - Gain 10-15% more weight, 30-60% more fat
  - After stopping antibiotics and restoring microbial diversity, they remain fat

GASTROENTEROLOGY 2012;143:913–916

BRIEF REPORT

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome

ANNE VRIEZE,* ELS VAN NOOD,* FRITS HOLLEMAN,* JARKKO SALOJÄRVI,‡ RUUD S. KOOTTE,§ JOEP F. W. M. BARTELSMAN,‖ GEESJE M. DALLINGA-THIE,§ MARIETTE T. ACKERMANS,¶ MIREILLE J. SERLIE,# RAISH OOZEER,** MURIEL DERRIEN,** ANNE DRUESNE,** JOHAN E. T. VAN HYLCKAMA VLIEG,** VINCENT W. BLOKS,‡‡ ALBERT K. GROEN,‡‡ HANS G. H. J. HEILIG,§§ ERWIN G. ZOETENDAL,§§ ERIK S. STROES,§ WILLEM M. DE VOS,‡,§§ JOOST B. L. HOEKSTRA,* and MAX NIEUWDORP*,§

*Department of Internal Medicine, §Department of Vascular Medicine and Experimental Vascular Medicine, ‖Department of Gastroenterology, ¶Department of Clinical Chemistry, Laboratory of Endocrinology, #Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands; ‡Department of Basic Veterinary Medicine, University of Helsinki, Helsinki, Finland; **Danone Research, Center Daniel Carasso, Palaiseau, France; ‡‡Center for Liver, Digestive, and Metabolic Diseases, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; §§Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands

Landmark Study 2010

- 18 Male subjects with metabolic syndrome
- 9 received FMT from lean donors, 9 from their own feces
    - Administered via naso-duodenal tubes
- Marked reduction in fasting TG and improvement in insulin sensitivity

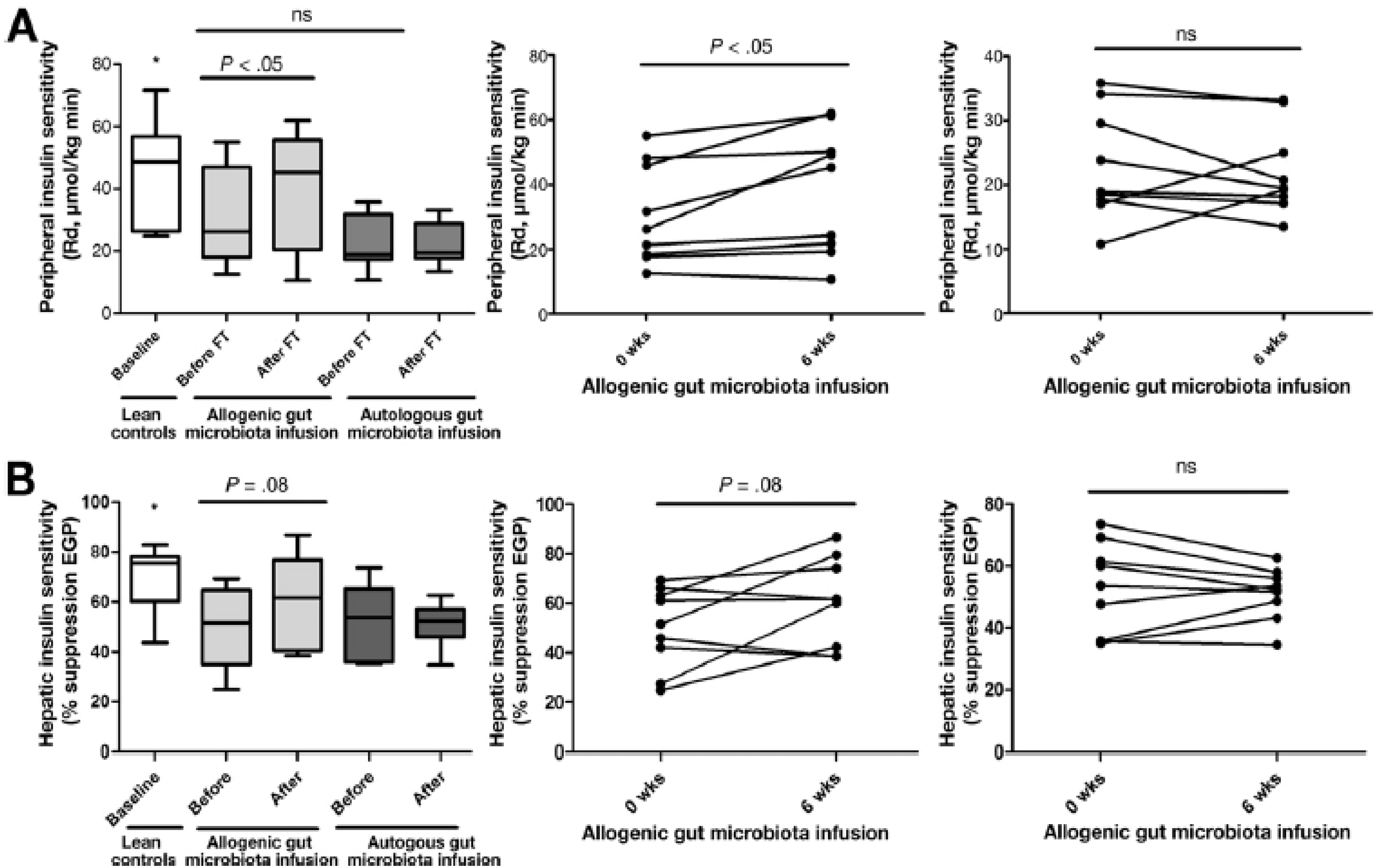


Figure 1. Box plots and individual changes between baseline and after 6 weeks for (*A*) peripheral and (*B*) hepatic insulin sensitivity. **P* < .05 lean controls vs obese subjects (Mann–Whitney test).

Can FMT make you fat?

Clinical Gastroenterology and Hepatology 2018;16:1351–1353

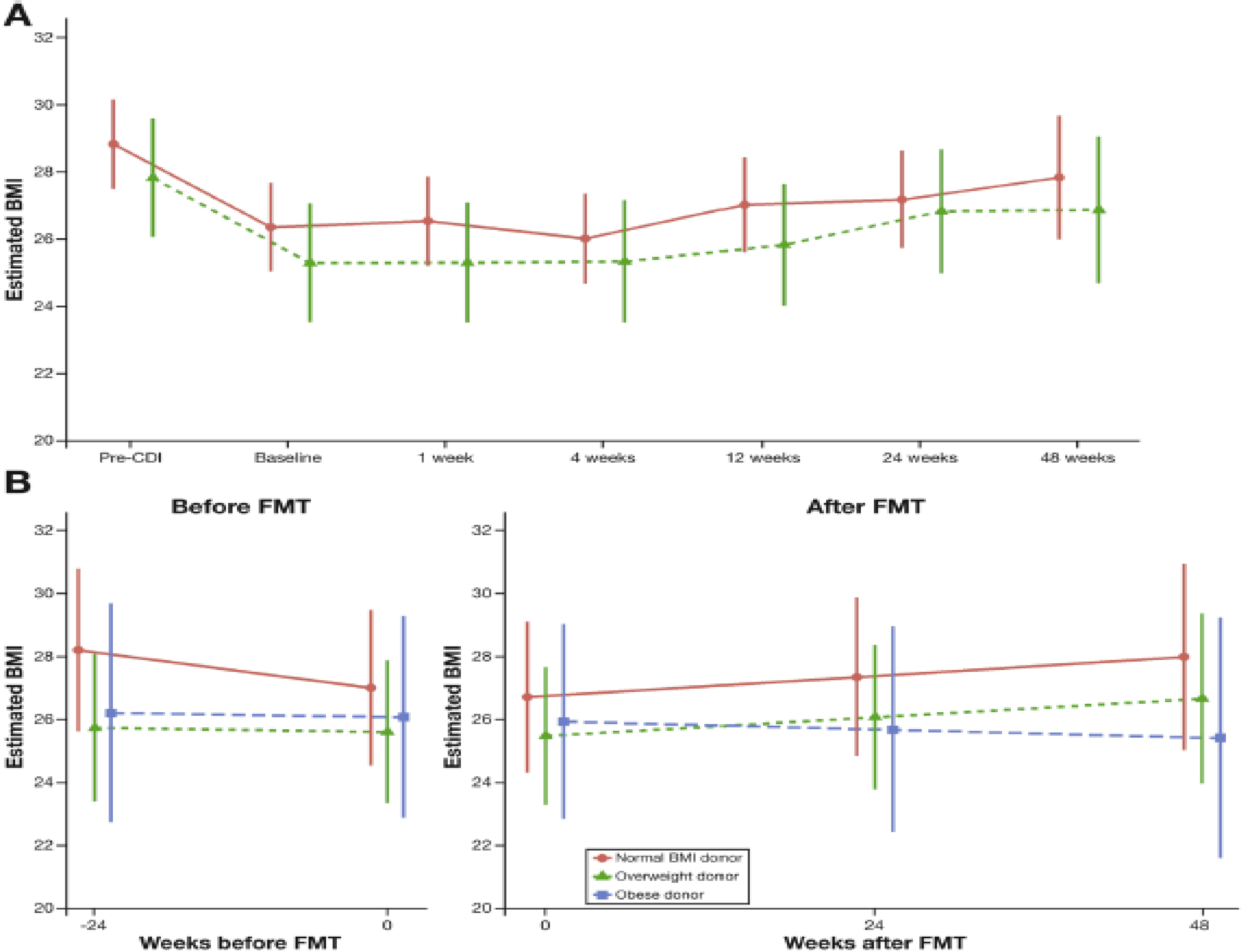
RESEARCH CORRESPONDENCE

Stool Donor Body Mass Index Does Not Affect Recipient Weight After a Single Fecal Microbiota Transplantation for *Clostridium difficile* Infection

Monika Fischer,[*] Dina Kao,[‡] Zain Kassam,[§] Justin Smith,[‡] Thomas Louie,[||] Brian Sipe,[¶] Michelle Torbeck,[*] Huiping Xu,[#] Fangqian Ouyang,[#] Dariush Mozaffarian,[**] and Jessica R. Allegretti[‡‡,§§]

Can FMT make you fat?

- Data aggregated from a RCT and observational study assessing FMT in CDI
  - RCT
    - FMT randomized from single capsule or via colonoscopy
  - Observational cohort had FMT by colonoscopy and BMI data 6 months before up to 1 year after FMT


A
Estimated BMI
32
30
28
26
24
22
20
Pre-CDI
Baseline
1 week
4 weeks
12 weeks
24 weeks
48 weeks
B
Before FMT
After FMT
Weeks before FMT
-24
0
Weeks after FMT
0
24
48
Normal BMI donor
Overweight donor
Obese donor

Can FMT make you fat?

- Patients regained weight lost from CDI, but returned to pre CDI weight and did not exceed it
- No statistically significant differences in recipient BMI based on donor BMI after single FMT

Can FMT make you skinny?

Clinical Gastroenterology and Hepatology 2020;18:855–863

Effects of Fecal Microbiota Transplantation With Oral Capsules in Obese Patients

Check for updates

Jessica R. Allegretti,* Zain Kassam,‡ Benjamin H. Mullish,§ Austin Chiang,‖ Madeline Carrellas,* Jonathan Hurtado,* Julian R. Marchesi,§ Julie A. K. McDonald,§ Alexandros Pechlivanis,§ Grace F. Barker,§ Jesús Miguéns Blanco,§ Isabel Garcia-Perez,§ Wing Fei Wong,¶ Ylaine Gerardin,‡ Michael Silverstein,‡ Kevin Kennedy,# and Christopher Thompson*

**Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Finch Therapeutics Group, Somerville, Massachusetts; §Division of Integrative Systems Medicine and Digestive Disease, Faculty of Medicine, Imperial College London, London, United Kingdom; ‖Division of Gastroenterology, Jefferson University, Philadelphia, Pennsylvania; ¶Openbiome, Cambridge, Massachusetts; #Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts*

Can FMT make you skinny?

- Double blind placebo controlled trial of 22 obese patients
  - No diagnosis of DM, NASH, or metabolic syndrome
- Randomized to FMT capsules
  - 30 @ week 4 then 12 @ week 8
  - Derived from donor: BMI 17.5

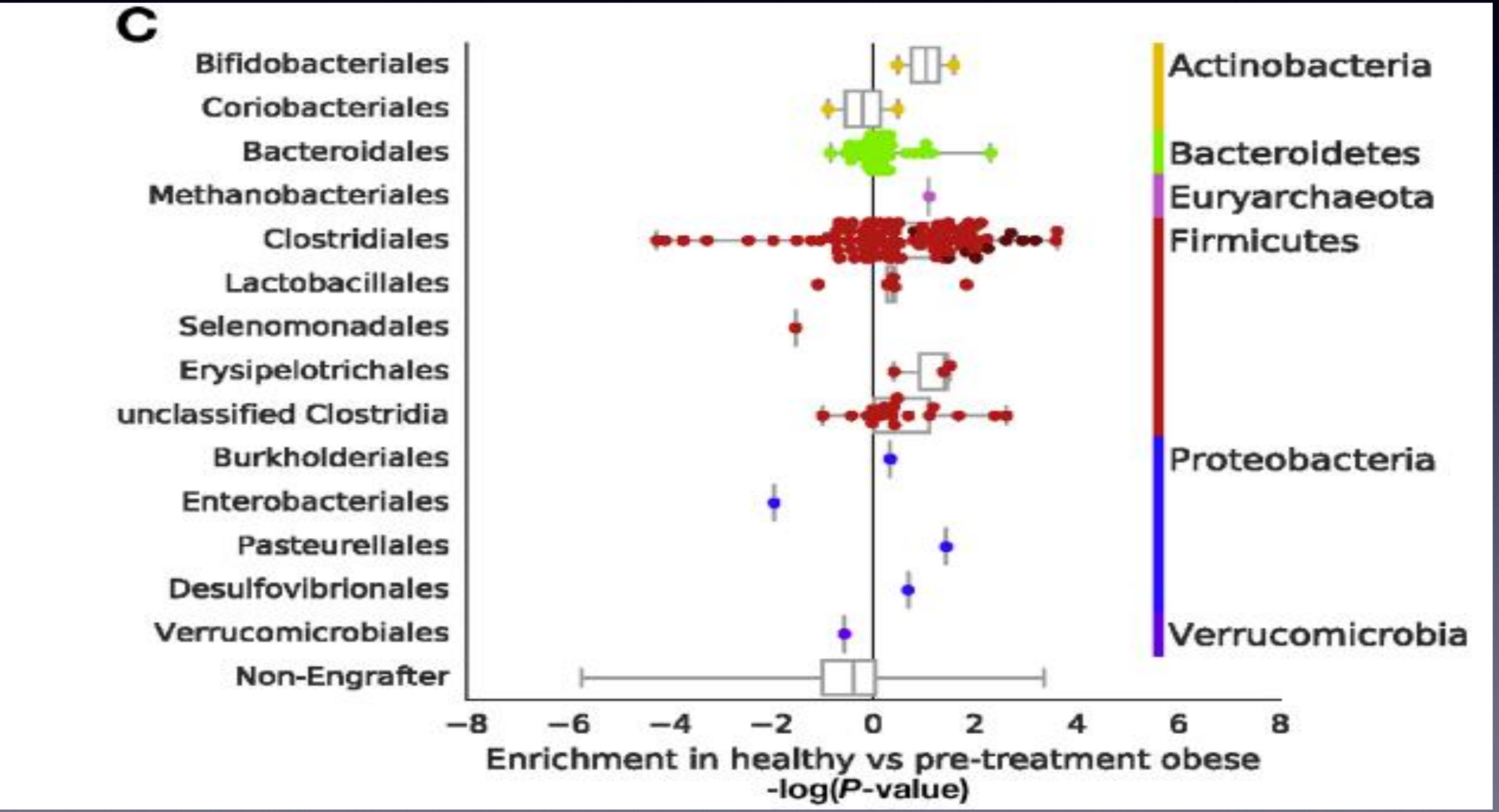
Can FMT make you skinny?

- Primary endpoints
  - Safety
- Secondary outcome
  - Area under Curve of GLP-1
  - BMI changes
  - Microbial changes
  - Bile acid pool changes

Can FMT make you skinny?

- Results
  - Safe - no adverse events
  - No significant change in BMI at week 26
  - No increase in AUC of GLP-1 in either group at week 12

Can FMT make you skinny?



Can FMT make you skinny?

RESEARCH ARTICLE

Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial

Elaine W. Yu[1,2*], Liu Gao[1], Petr Stastka[1], Michael C. Cheney[1], Jasmin Mahabamunuge[3], Mariam Torres Soto[3], Christopher B. Ford[4], Jessica A. Bryant[4], Matthew R. Henn[4], Elizabeth L. Hohmann[2,3]

1 Endocrine Unit, Division of Endocrinology and Metabolism, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 2 Harvard Medical School, Boston, Massachusetts, United States of America, 3 Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 4 Seres Therapeutics, Cambridge, Massachusetts, United States of America

Can FMT make you skinny?

- 12 week double blind RPCT pilot: 2016-2018
- Weekly oral FMT capsules x 6 weeks to 24 adults
    - 71% female
    - BMI 38 in FMT group/41 placebo group

Can FMT make you skinny?

- Primary outcome - change in insulin sensitivity at 6 weeks measured
- Secondary outcomes - HbA1c, body weight, absorptimetry

Table 2. Metabolic parameters in FMT and placebo groups throughout the 12-week study.

Characteristic	Placebo group			FMT group			Difference between FMT and placebo groups in change from baseline (95% CI)	
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks	Baseline to 6 weeks	Baseline to 12 weeks
Weight (kg)	111 ± 20	111 ± 20	111 ± 19	110 ± 26	114 ± 26	111 ± 27	−0.2 (−2.4, 2.0)	0.2 (−2.0, 2.4)
Lean mass (kg)	58 ± 12	58 ± 12	58 ± 11	60 ± 15	62 ± 15	61 ± 16	−0.4 (−2.1, 1.4)	−0.1 (−1.9, 1.6)
Fat mass (kg)	53 ± 10	53 ± 10	52 ± 10	49 ± 13	51 ± 14	50 ± 14	1.1 (−0.7, 3.0)	1.2 (−0.6, 3.0)
VAT volume (cm^3)	998 ± 319	991 ± 285	976 ± 308	1048 ± 368	1107 ± 423	982 ± 358	19 (−76, 115)	−52 (−147, 42)
Fasting glucose (mmol/l)	4.8 ± 0.4	4.8 ± 0.4	5.1 ± 0.6	5.0 ± 0.7	4.8 ± 0.7	5.1 ± 0.6	0.02 (−0.3, 0.4)	−0.1 (−0.4, 0.3)
HbA1c (%)	5.5 ± 0.3	5.5 ± 0.3	5.5 ± 0.3	5.6 ± 0.2	5.5 ± 0.4	5.4 ± 0.4	−0.1 (−0.2, 0.1)	**−0.1 (−0.3, −0.01)**
HOMA-IR	3.5 ± 1.9	3.4 ± 1.3	4.8 ± 1.7	3.5 ± 1.4	3.9 ± 1.4	4.7 ± 2.0	0.3 (−0.6, 1.3)	−0.02 (−0.9, 0.9)
Total cholesterol (mmol/l)	5.1 ± 0.6	5.1 ± 1.1	5.2 ± 0.7	5.5 ± 0.6	5.2 ± 0.8	5.2 ± 1.0	−0.3 (−0.8, 0.2)	−0.3 (−0.8, 0.2)
HDL (mmol/l)	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	1.3 ± 0.3	0.04 (−0.1, 0.2)	0.08 (−0.1, 0.2)
LDL (mmol/l)	3.3 ± 0.6	3.3 ± 1.2	3.2 ± 0.7	3.3 ± 0.8	3.0 ± 0.9	2.9 ± 0.9	−0.2 (−0.6, 0.2)	−0.2 (−0.6, 0.2)
Triglycerides (mmol/l)	1.3 [1.1, 1.8]	1.2 [1.1, 2.0]	1.4 [1.0, 2.7]	1.7 [1.1, 2.2]	1.9 [1.2, 2.3]	1.5 [1.3, 2.1]	−0.4 (−1.4, 0.5)	−0.8 (−1.7, 0.1)
CRP (mg/l)	3.5 [2.3, 7.3]	3.0 [1.7, 5.0]	4.6 [2.5, 6.8]	2.9 [1.7, 5.6]	3.5 [1.9, 5.0]	2.9 [2.0, 4.1]	**1.8 (0.3, 3.3)**	−0.1 (−1.6, 1.3)
REE (kcal/day)*	1,503 ± 218	1,536 ± 241	n/a	1,588 ± 305	1,705 ± 351	n/a	8.4 (−97, 114)	n/a
Caloric intake (kcal/day)	1,939 ± 463	2,006 ± 693	1,689 ± 760	2,121 ± 729	2,236 ± 949	2,331 ± 822	−50 (−603, 502)	389 (−155, 932)

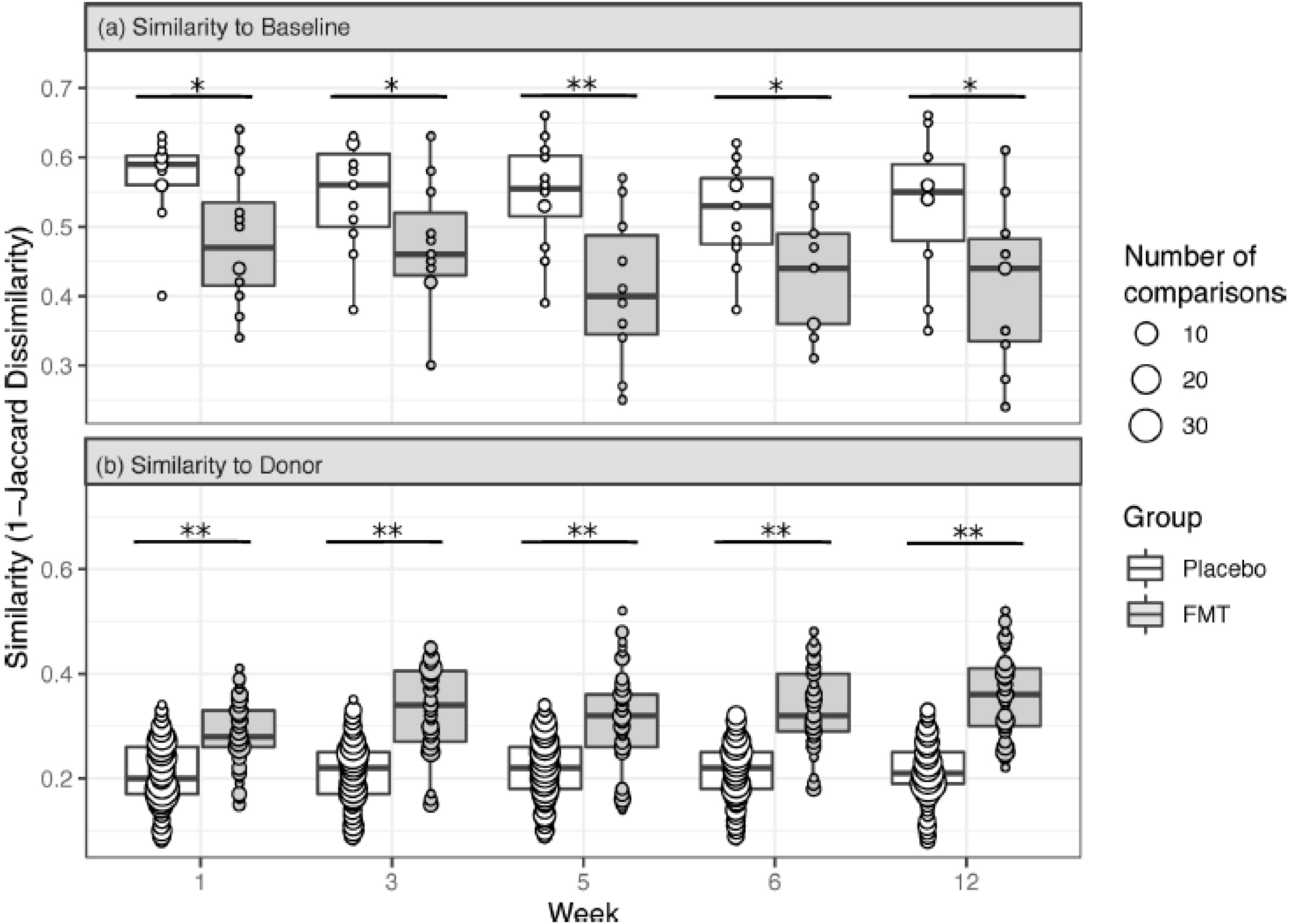


Fig 4. Beta diversity boxplots displaying microbiome compositional similarity of each participant to their respective baseline or triplicate donor preps. Microbiome similarity to baseline (a) and to donor (b) is compared between fecal microbiota transplantation (FMT) and placebo

FMT Trial Limitations

- Small sample size
- Lack of pretreatment antibiotics
  - We are not gnotobiotic
  - FMT is not BMT
- Lack of dietary controls/standardization
- Need for more time

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Case Presentation

- 9/18 - Diagnosed with Myelodysplastic Syndrome
- Attempt at bowel lavage followed by probiotics
- 11/18 - Passed away

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Conclusions

- Watch out for antibiotics early in life
- Fiber is good!
  - Aim for a Prevotella enterotype
- Microbial diversity is key
- No magic pill….yet

Schitt$ Creek

References

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