Modern Life at a Crossroad: The intersection of diet, the gut microbiome, inflammation, and cancer.

James D. Lewis, MD, MSCE
Division of Gastroenterology, Department of Medicine
Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine at the University of Pennsylvania

Weill Cornell
Medicine-Qatar

DISCLOSURE STATEMENT

Speaker:

James Lewis, MD, MSCE

- Has served as a consultant and received research funding from Nestle Health Science
- Will not be discussing the off-label or investigational use of products

Weill Cornell Medicine-Qatar

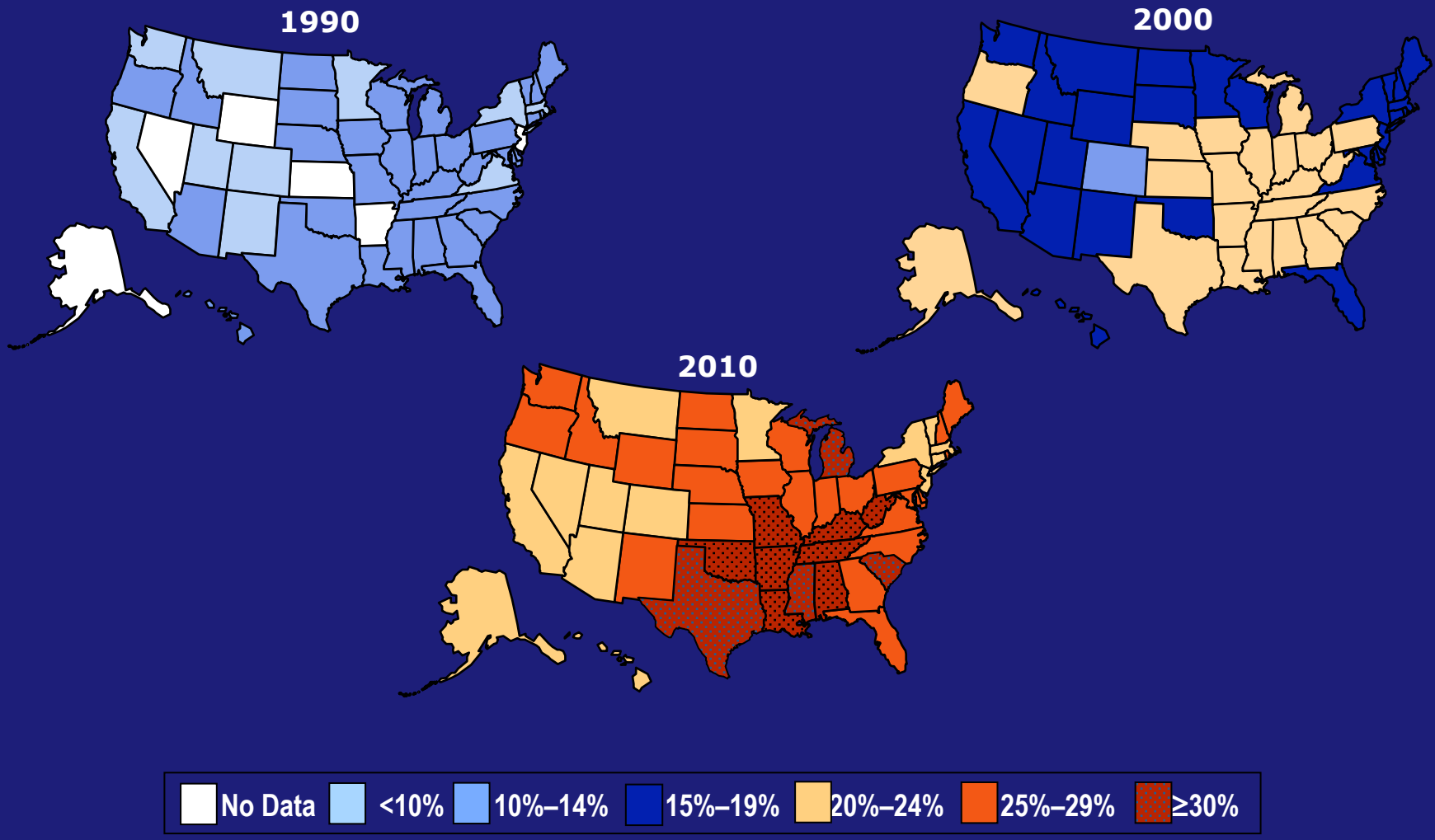
We Love to Eat!

What have you eaten in the last 24 hours that might be detrimental to your health?

What have you eaten in the last 24 hours that might be beneficial to your health?

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



Prevalence of DM in US

- DM
  - 26.9% (10.9 million) among >65 yrs in 2010
- Pre-DM
  - 35% among > 20 yrs
  - 50% among > 65 yrs

http://diabetes.niddk.nih.gov/dm/pubs/statistics/

BMJ Open

Prevalence and determinants of metabolic syndrome in Qatar: results from a National Health Survey

Mohamed Hamad Al-Thani,[1] Al Anoud Mohammed Al-Thani,[1] Sohaila Cheema,[2] Javaid Sheikh,[3] Ravinder Mamtani,[2] Albert B Lowenfels,[4] Walaa Fattah Al-Chetachi,[1] Badria Ali Almalki,[1] Shamseldin Ali Hassan Khalifa,[1] Ahmad Omar Haj Bakri,[1] Patrick Maisonneuve[5]

Obesity

	N	(95% CI) All age groups
Men		
Mean waist circumference	1021	100 cm (98 to 102)
Proportion with waist ≥94 cm*	686	63.4% (58.7% to 68.2%)
Proportion with waist ≥102 cm†,‡	480	45.4% (40.1% to 50.8%)
Women		
Mean waist circumference	1314	90 cm (88 to 92)
Proportion with waist ≥80 cm*	985	68.5% (64.3% to 72.7%)
Proportion with waist ≥88 cm†	775	51.3% (47.3% to 55.3%)
Proportion with waist ≥94 cm‡	607	38.7% (34.7% to 42.7%)

Metabolic Syndrome

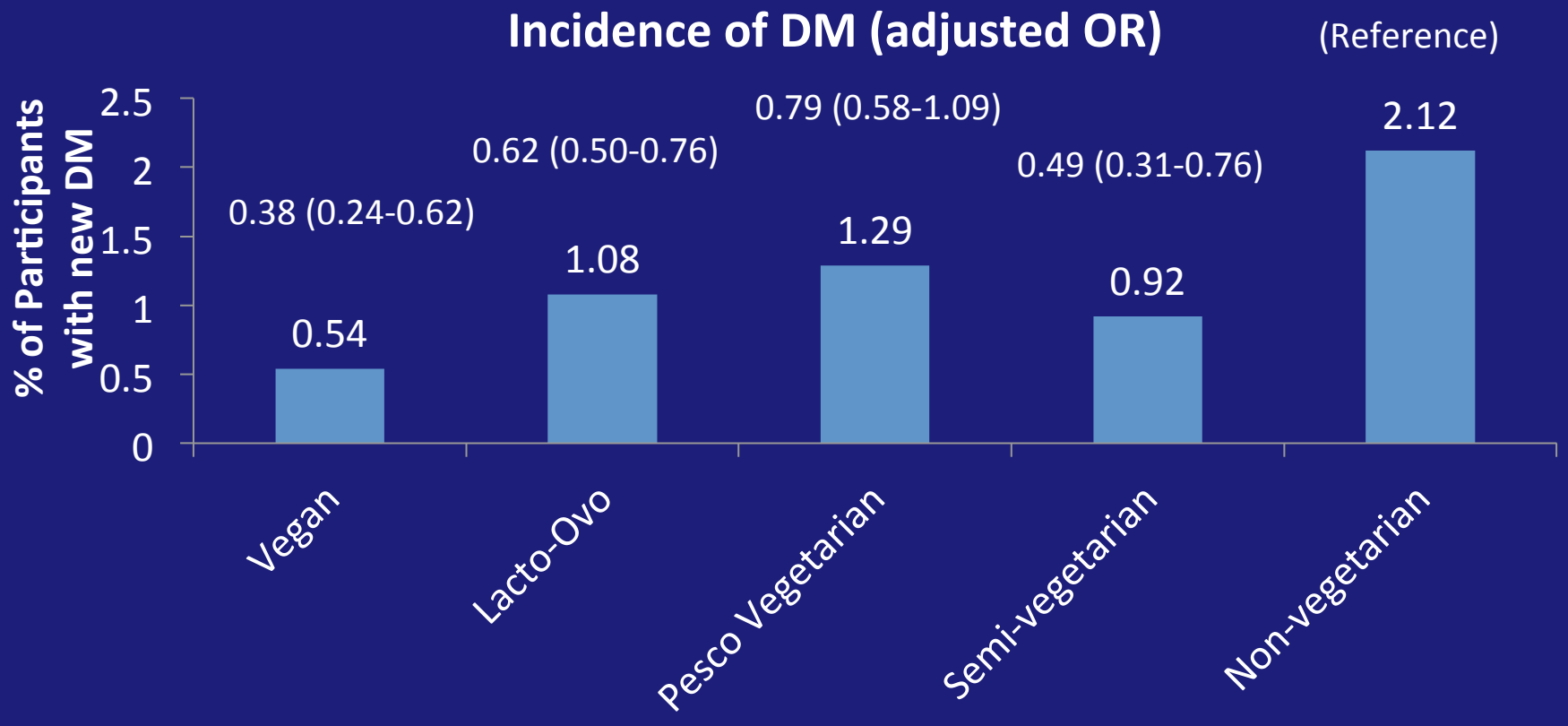
	N exposed/ N available	% (95% CI) All age groups
Both sexes (n=2496)		
Metabolic syndrome (≥3 risk factors)*	430/1373	27.7% (24.5% to 30.9%)
Raised fasting blood glucose†	374/1470	22.5% (19.0% to 26.0%)
Raised BP‡	1107/2432	42.7% (40.0% to 45.4%)
Raised triglycerides§	270/1518	16.4% (13.7% to 19.0%)
Reduced HDL cholesterol¶	676/1526	45.5% (41.3% to 49.8%)
Abdominal obesity**	1302/2356	50.6% (47.7% to 53.6%)

Vegan - Vegetarian Diets and Risk of Diabetes

- Adventist Health Study 2
  - Prospective cohort study launched in 2002
  - 53,536 with baseline FFQ and follow-up data (2 years later)
  - 616 diagnosed with diabetes by 2007
  - Incidence lower in vegans and vegetarians than in omnivores after adjusting for potential confounders

Tonstad S. Nutr. Metab. Cardiovasc. Dis. 2013;23:292–299

Vegan - Vegetarian Diets and Risk of Diabetes

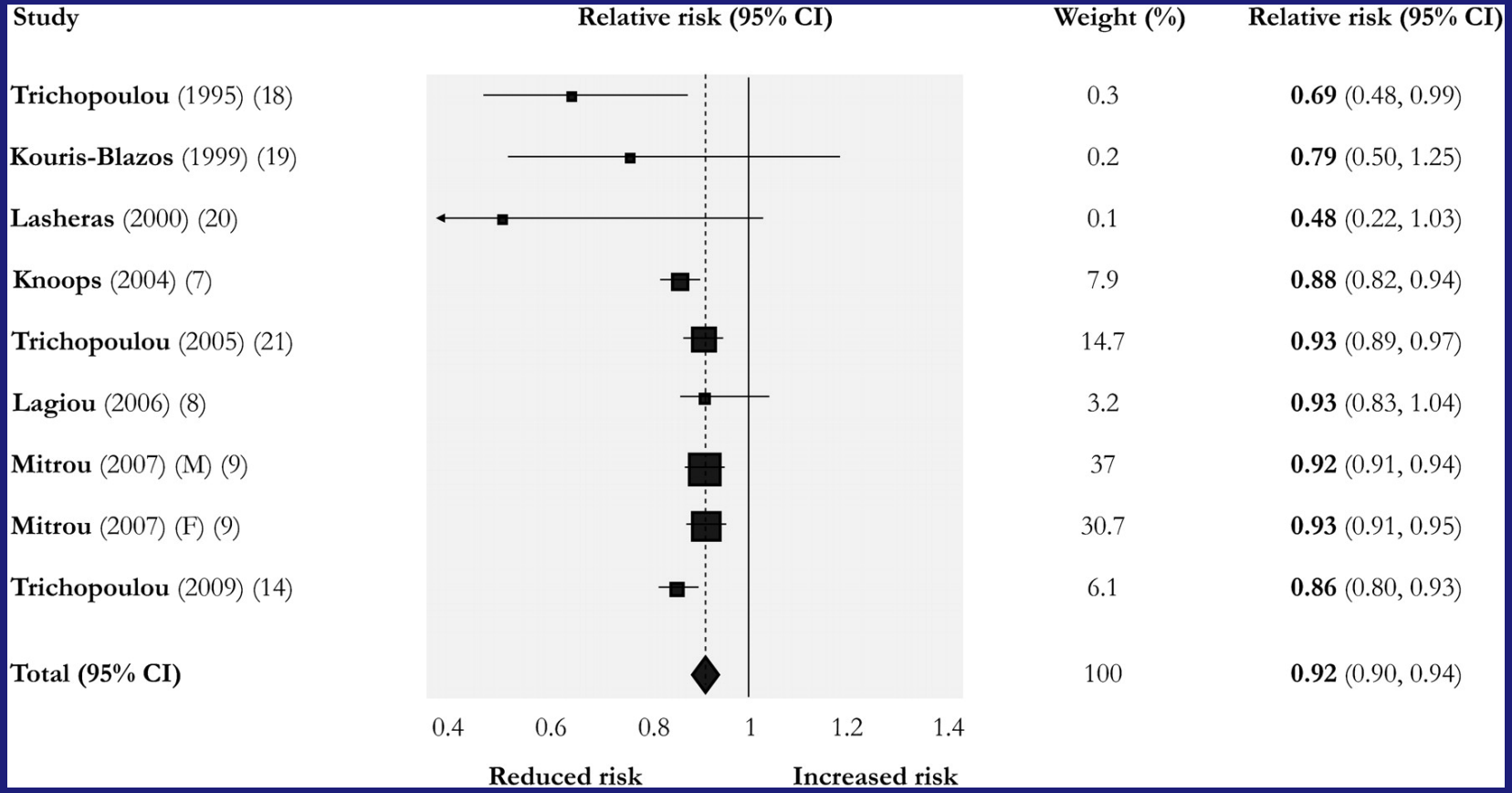


Tonstad S. Nutr. Metab. Cardiovasc. Dis. 2013;23:292–299

Mediterranean Diet

- Olive oil as the main source of fats
- High consumption of fruit, vegetables, legumes, and complex carbohydrates
- Moderate consumption of fish and poultry
- Limited consumption of red and processed meats, dairy, and sweats
- Low-to-moderate amount of red wine during meals

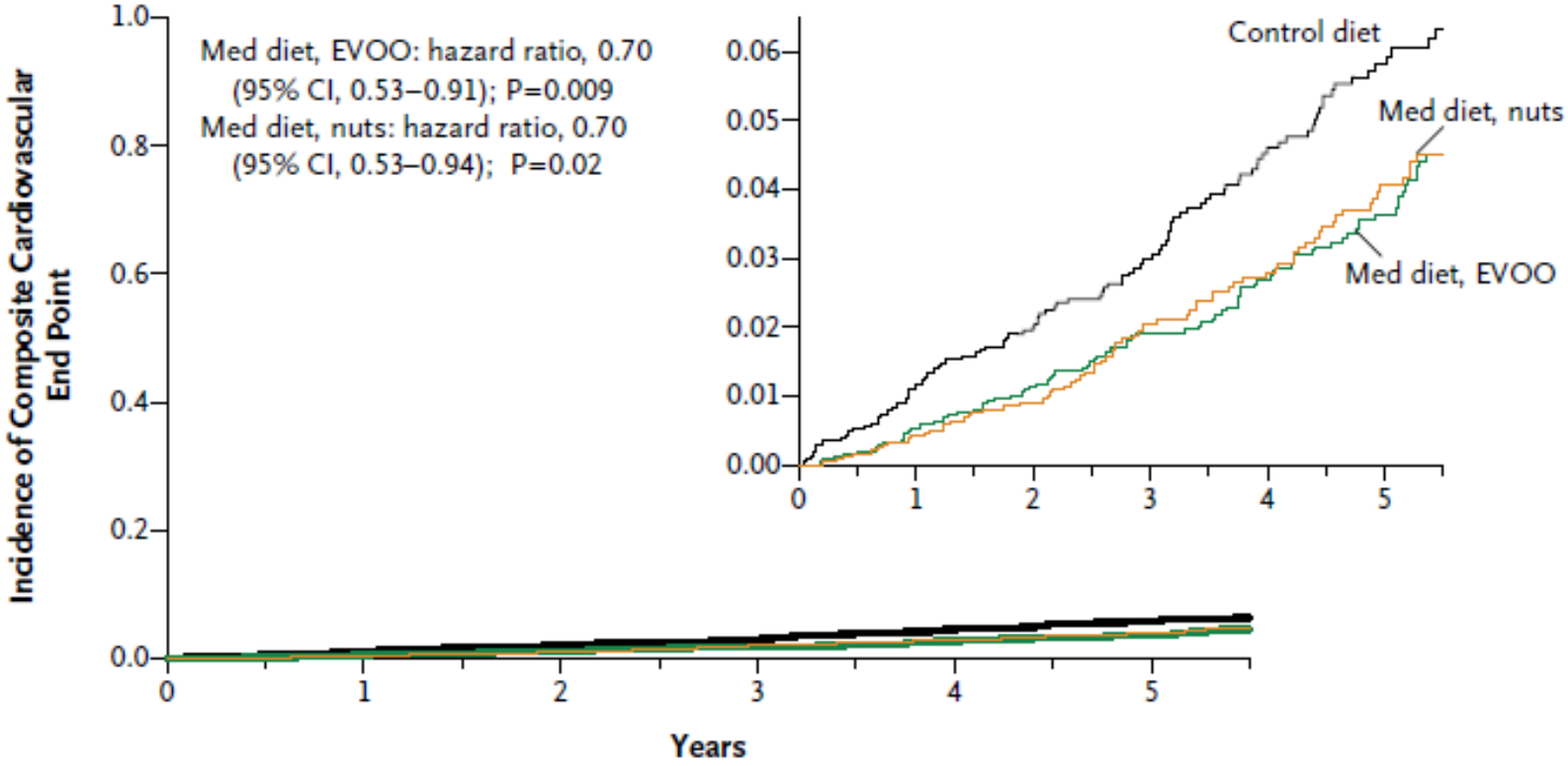
Association between a 2-point increase of adherence score to the Mediterranean diet and the risk of all-cause mortality



Sofi F et al. Am J Clin Nutr 2010;92:1189-1196

RCT of Mediteranean Diet for Primary Prevention of MACE

A **Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)**



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Estruch R. **N Engl J Med 2013;368:1279-90**

Meta-Analysis of Mediterranean Diet and Health Outcomes

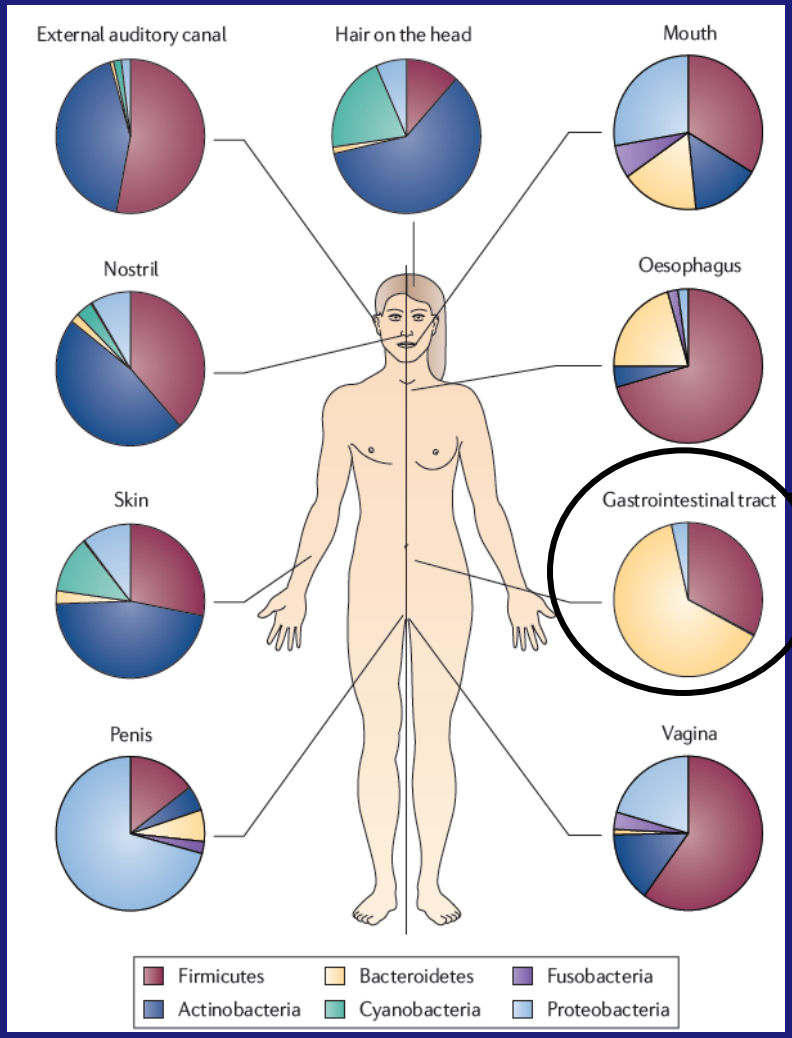
	Pooled RR	95% CI
Overall mortality	0.92	0.90 – 0.94
Cardiovascular mortality and incidence	0.90	0.87 – 0.93
Cancer mortality and incidence	0.94	0.92 – 0.96
Neurodegenerative disease	0.87	0.81 – 0.94

Sofi F et al. Am J Clin Nutr 2010;92:1189-1196

What is the Link Between CV Disease, Cancer, and Mediterranean Diet?

What is the Link Between CV Disease, Cancer, and Mediterranean Diet?

The Human Microbiome



Nat. Rev. Micro. 2011;9:279-290

Comprised of Bacteria, Viruses, others (Archaea, Eukaryotes)

- **Distinctive microbiomes at each body site (gut, lung, skin, mucosa etc.)**

The Gut Microbiota

- **Human gut is home to ~ 100 trillion bacterial cells**
- **Density of 10^{11} to 10^{12} per gram in the colon**
- **Estimated 10^{3}/mL of aspirate in jejunum**
- **Increasing concentration as approach cecum**
- **Genome size of microbiota at least 100-fold greater than human**
- **Large numbers species present, most uncultured**

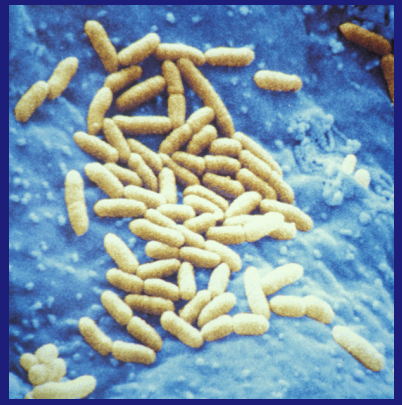
Host-Microbial Mutualism the Gut

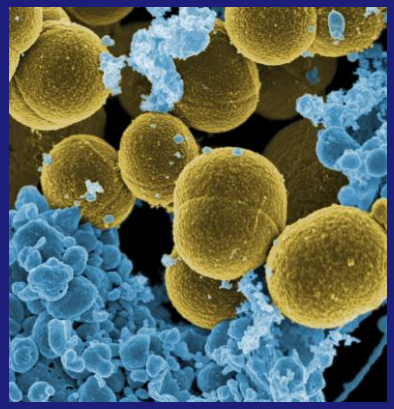
Host benefits to bacteria

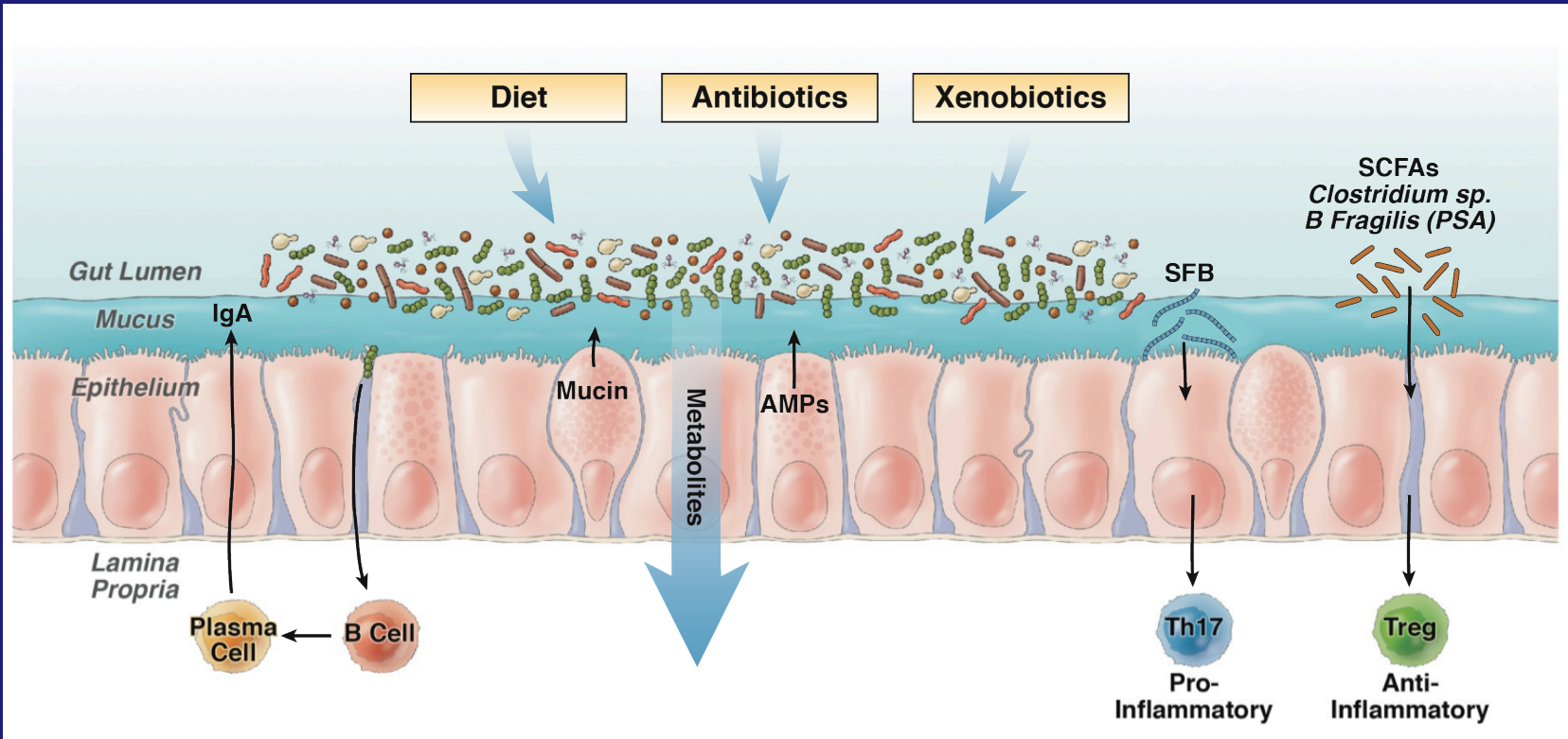
- Provides a unique niche
- Intestinal mucus provides a source of nutrition

Bacteria benefits the host

- Fermentation of indigestible carbohydrates and the production of SCFAs
- Biotransformation of conjugated bile acids
- Urease activity participates in nitrogen balance
- Synthesis of certain vitamins
- Metabolize drugs
- Education of the mucosal immune system





Diabetes: Type 1 DM (MyD88-dependent in NOD Mice); Type 2 DM (TLR4 and TLR5 KOs)

Atherosclerosis: Oral, gut and plaque microbiota; Microbial metabolism of choline to TMA

Asthma: Sanitized environment

Colon Cancer: Enterotoxigenic *Bacteroides fragilis and Fusobacterium*

Inflammatory Bowel Disease: Dysbiosis

Key Questions

- How does diet affect the gut microbiota in the absence of disease?
- Does the gut microbiota cause non-infectious disease?
- Can nutrition be a therapy for diseases associated with alteration of the gut microbiota?

COMBO - Cross-Sectional Study of Diet and Stool Microbiome

- Is there an association between overall composition of diet and composition of the gut microbiome?

- Are individual nutrients associated with overall gut microbiome composition?

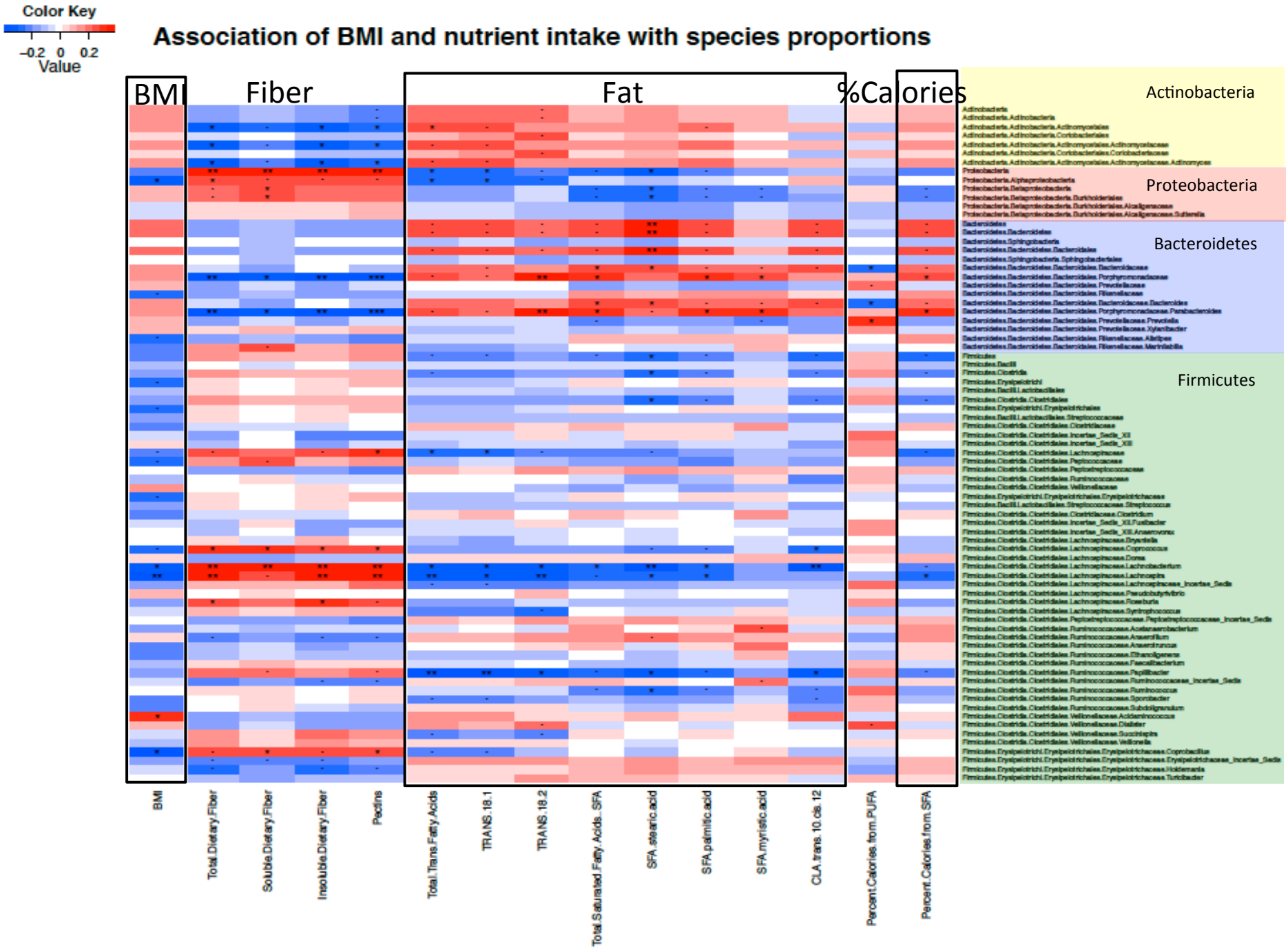
Microbial, Dietary, and Clinical Assessment

- Microbiome – 16s rRNA phylogenetics; 18s for microeukaryotes
- Usual diet - Standardized food frequency questionnaires
- Recent diet – Three 24 hour diet recalls within week prior to provision of the stool sample
- Demographics – Subject interviews and questionnaires

COMBO

Are individual demographic factors associated with overall gut microbiome composition?

Variable	No. subject	Distance based test (unweighted)	Distance based test (weighted)
Sex(M,F)	**F:55 M:44**	**0.035**	**0.0333**
Race(Black,White)	**ASI:7 BLK:25 WHT:66**	**0.0242**	**0.1075**
BMI (continuous)	**99**	**0.0039**	**0.0314**
Children <=3 years old in the household (Y,N)	**N:69 Y:8**	**0.1018**	**0.0276**
Pets(Y,N)	**N:60 Y:39**	**0.0925**	**0.0665**


Color Key
−0.2 0 0.2
Value
Association of BMI and nutrient intake with species proportions
BMI
Fiber
Fat
%Calories
Actinobacteria
Proteobacteria
Bacteroidetes
Firmicutes
BMI
Total.Dietary.Fiber
Soluble.Dietary.Fiber
Insoluble.Dietary.Fiber
Pectins
Total.Trans.Fatty.Acids
TRANS.18.1
TRANS.18.2
Total.Saturated.Fatty.Acids..SFA
SFA.stearic.acid
SFA.palmitic.acid
SFA.myristic.acid
CLA.trans.10.cis.12
Percent.Calories.from.PUFA
Percent.Calories.from.SFA

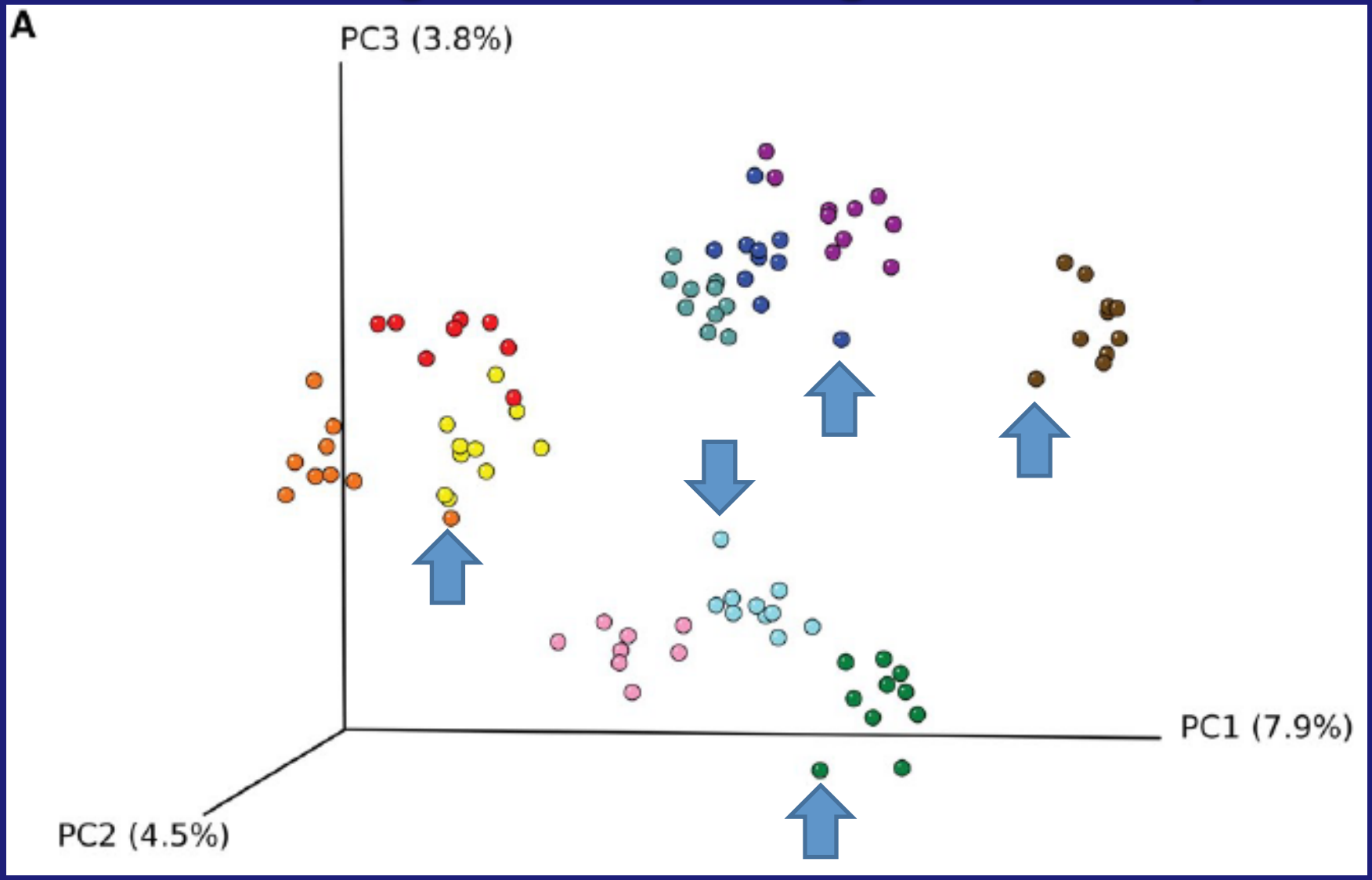
CaFE Study: Controlled Feeding Experiment

- Does short term dietary fat or fiber alter the composition of the human gut microbiome and switch Enterotypes?
- What is the time course over which a diet alters the composition of the human gut microbiome?
- Will a standardized diet reduce microbiome intersubject variability?

CaFE Study - Controlled Feeding Experiment

- 10 Healthy volunteers
- Randomized to high fat vs. low fat diet
- 10 day inpatient stay with same meals each day
- Caloric intake adjusted to maintain current weight
- Daily stool sample collection
- Sitz marker study to assess time to clearance of residual stool

Day 1 is Different But Within Individual Clustering Remains Strong Over 10 Days



Wu GD. Science 2011

Summary

- Promising findings for diet as therapy
  - Major nutrient categories (Fat, Fiber & Vegetables, Protein, and Carbohydrates) cluster independently with relative proportions of bacterial taxa where “Fat” and “Fiber” as well as “Amino Acids” and “Carbohydrates” are inversely related.

- Less promising findings for diet as therapy
  - Although there are rapid changes in the gut microbiome composition seen within 24 hours of dietary intervention. But short-term diet **does not** reduce intersubject variability in gut microbiome composition

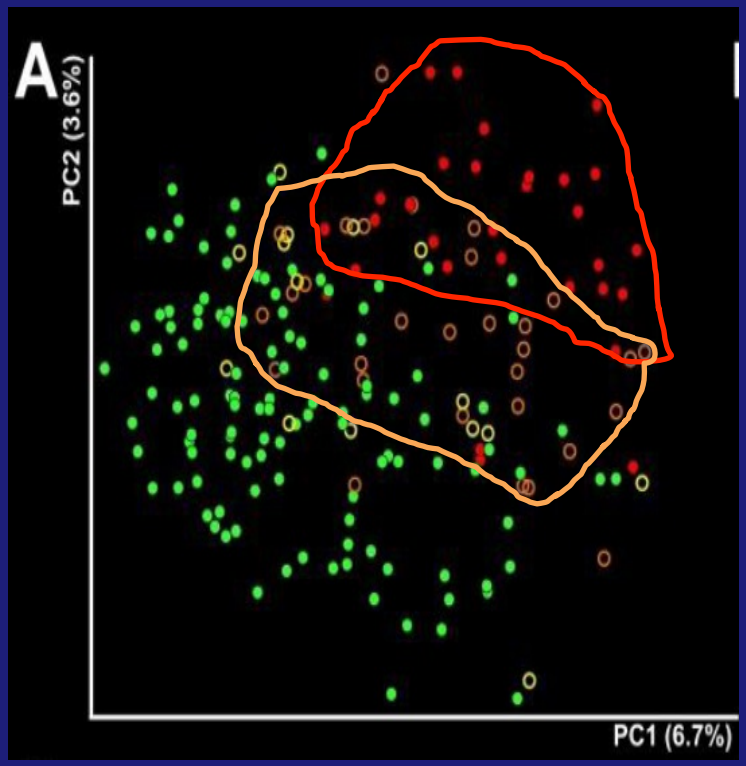
How long does it take for diet to change the gut microbiome?

- Cross-sectional study of elderly
  - Ambulatory
  - Short term nursing home
  - Long term nursing home
- Decreased dietary diversity among nursing home residents
- Decreased dietary diversity correlated with decreased microbiota diversity

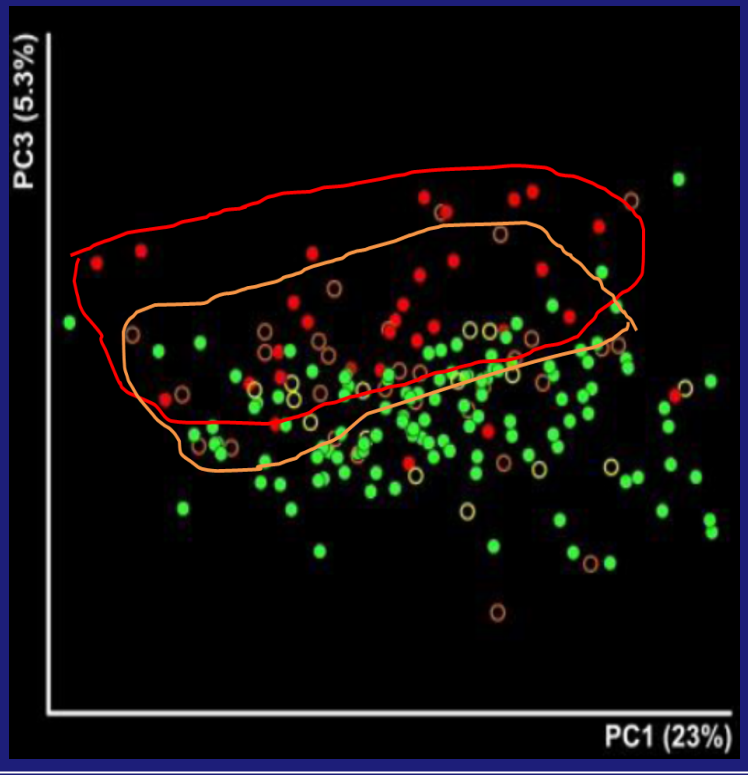
Claeson MJ. Nature 2012. doi: 10.1038

How long does it take for diet to change the gut microbiome?

UNWEIGHTED

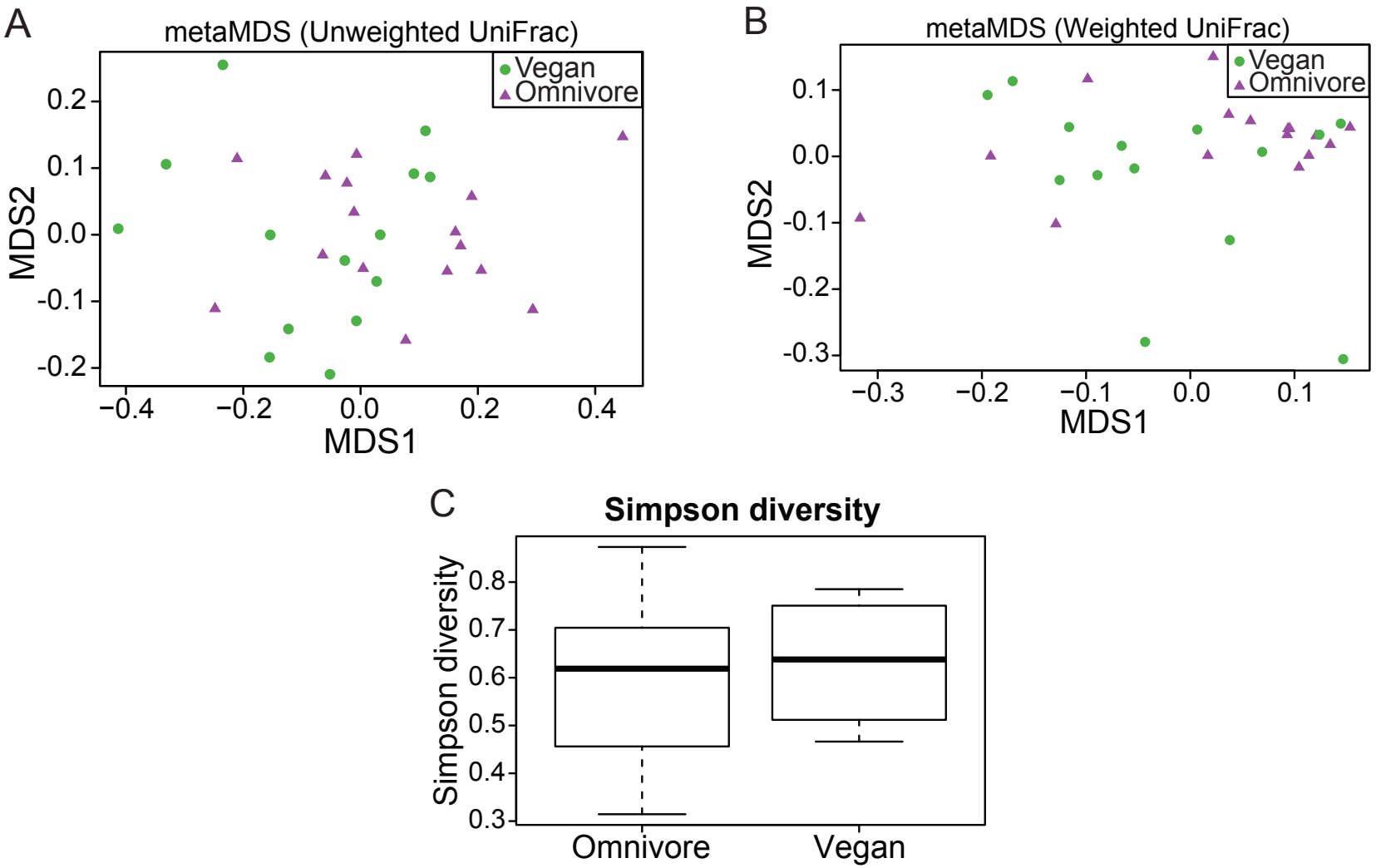


WEIGHTED



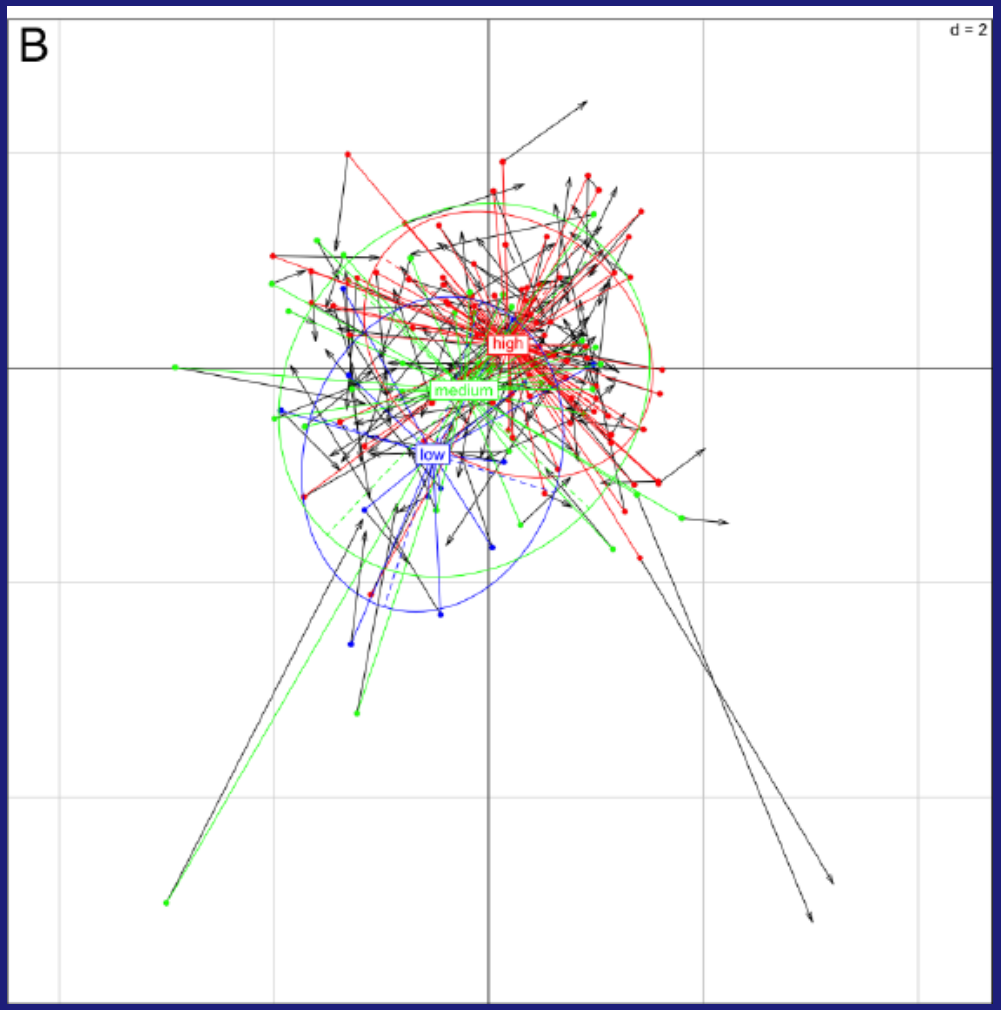
Orange – 6 weeks to 12 months of long term care
Red – long term care >12 months

COMBO 2 – Vegans and Omnivores Have Relatively Similar Microbiota



Wu GD et al. Gut. 2014 Nov 26. pii: gutjnl-2014-308209. doi: 10.1136/gutjnl-2014-308209.

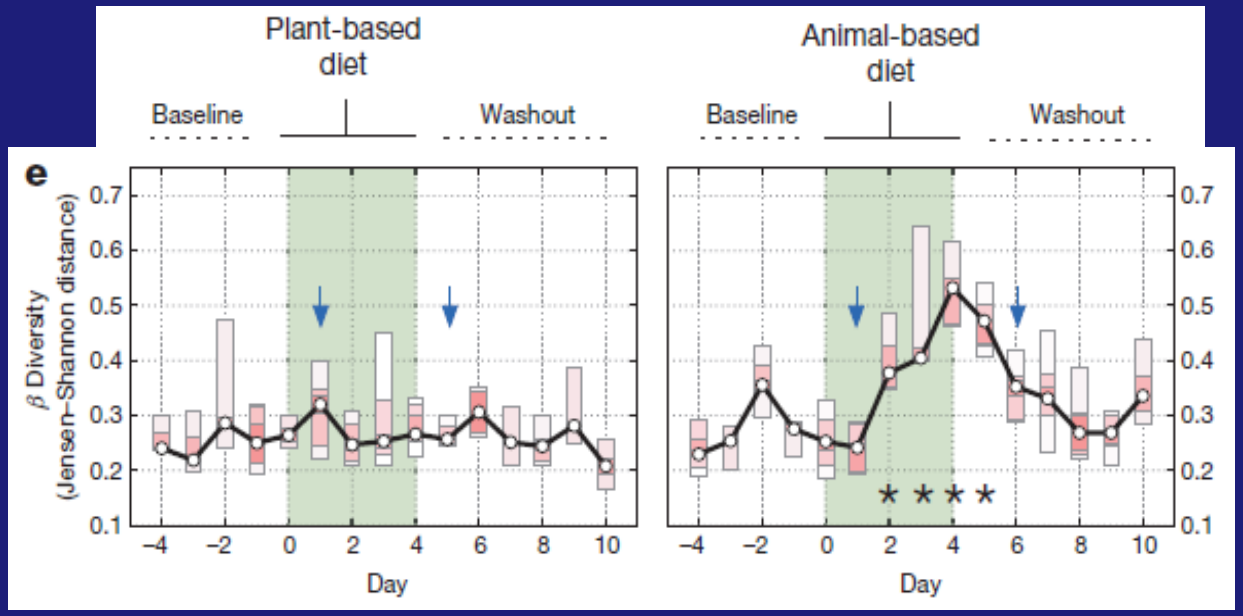
Adherence to Mediterranean Style Diet and Composition of Microbiota



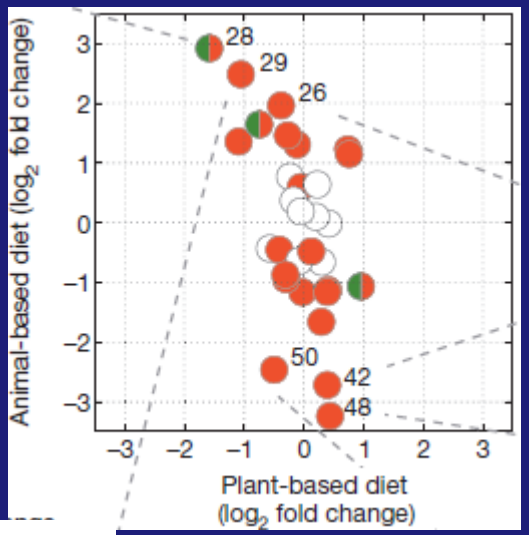
F De Filippis. Gut 2015

Rapid Changes with Extreme Diets Driven by Exclusion of Plant Products

Change in Community Structure from Baseline



Change in Abundance of Bacterial Clusters

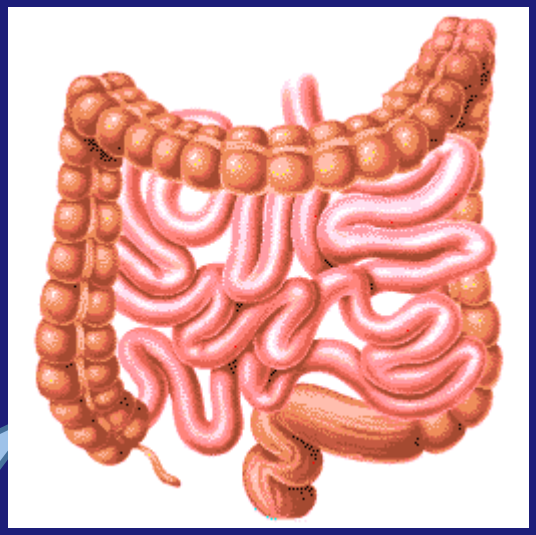


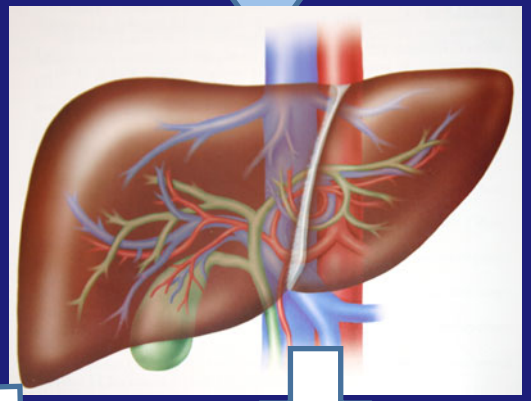
Diet rapidly and reproducibly alters the human gut microbiome

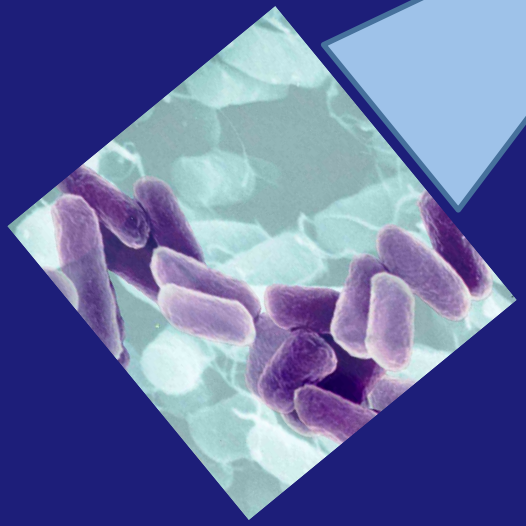
Lawrence A. David[1,2]†, Corinne F. Maurice[1], Rachel N. Carmody[1], David B. Gootenberg[1], Julie E. Button[1], Benjamin E. Wolfe[1], Alisha V. Ling[3], A. Sloan Devlin[4], Yug Varma[4], Michael A. Fischbach[4], Sudha B. Biddinger[3], Rachel J. Dutton[1] & Peter J. Turnbaugh[1]

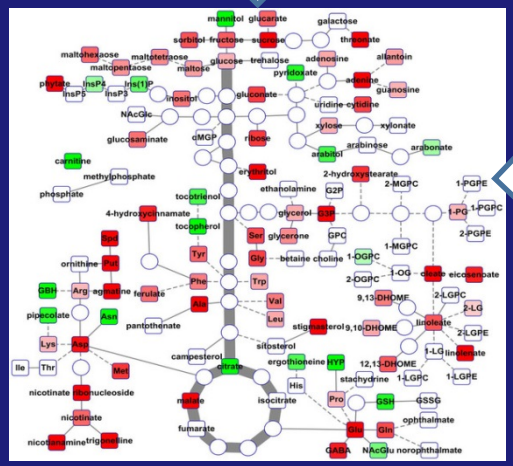
doi:10.1038/nature12820

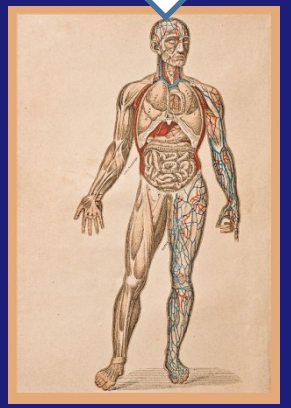
What the Microbiota Do May Be More Important Than Who Is There



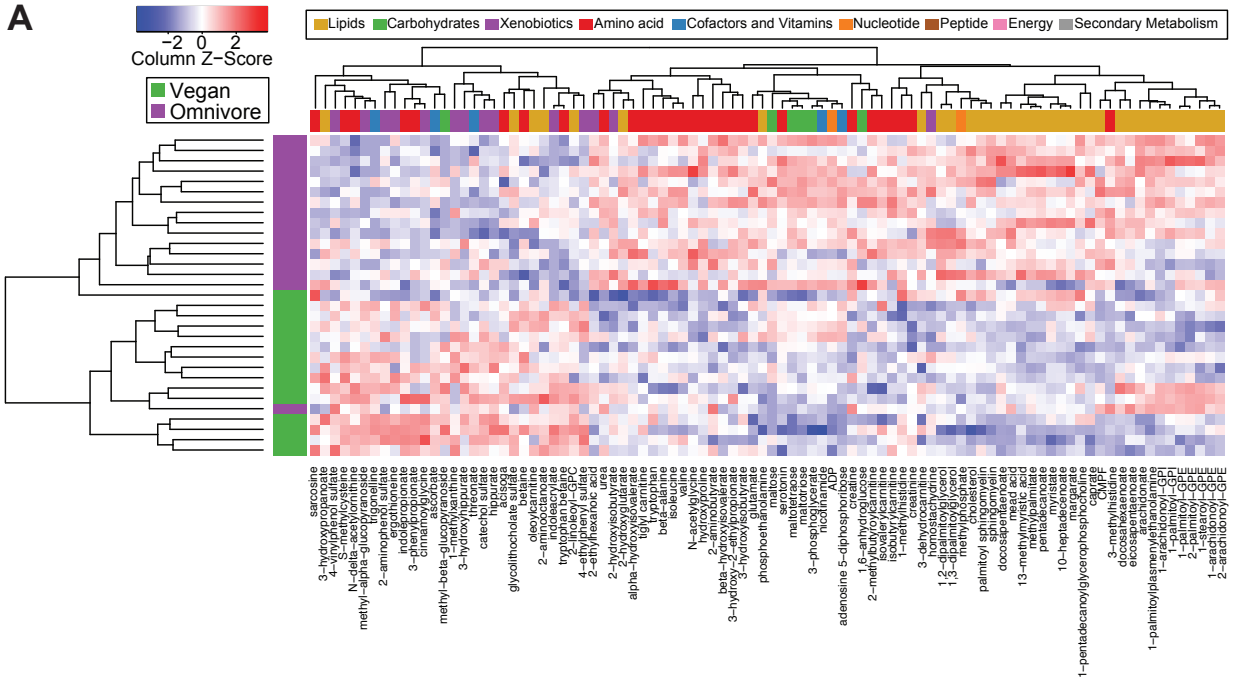


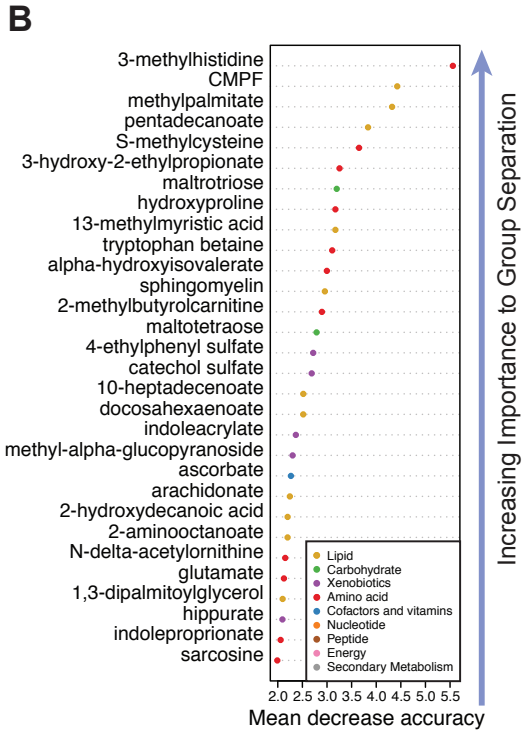


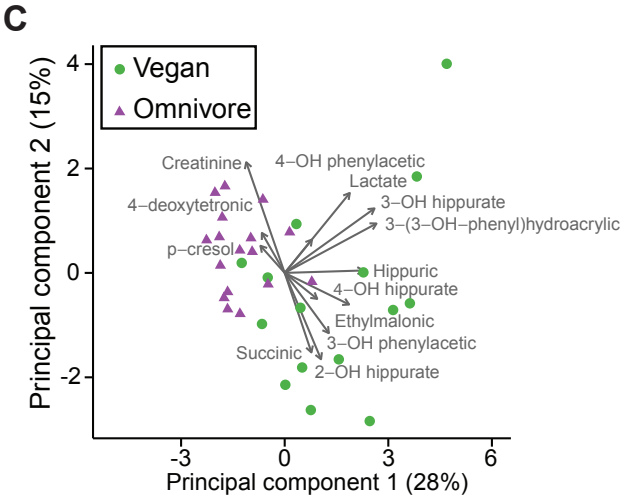




The Plasma and Urinary Metabolome of Omnivores vs. Vegans



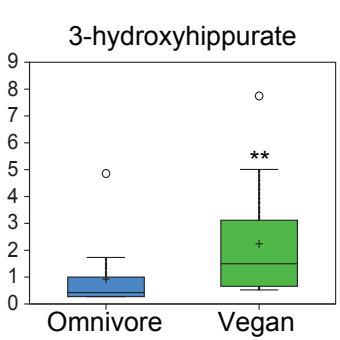


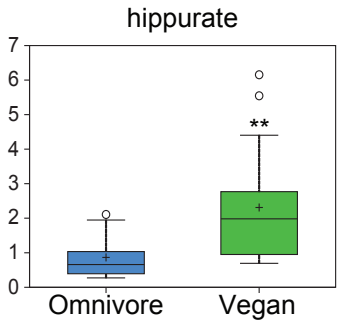


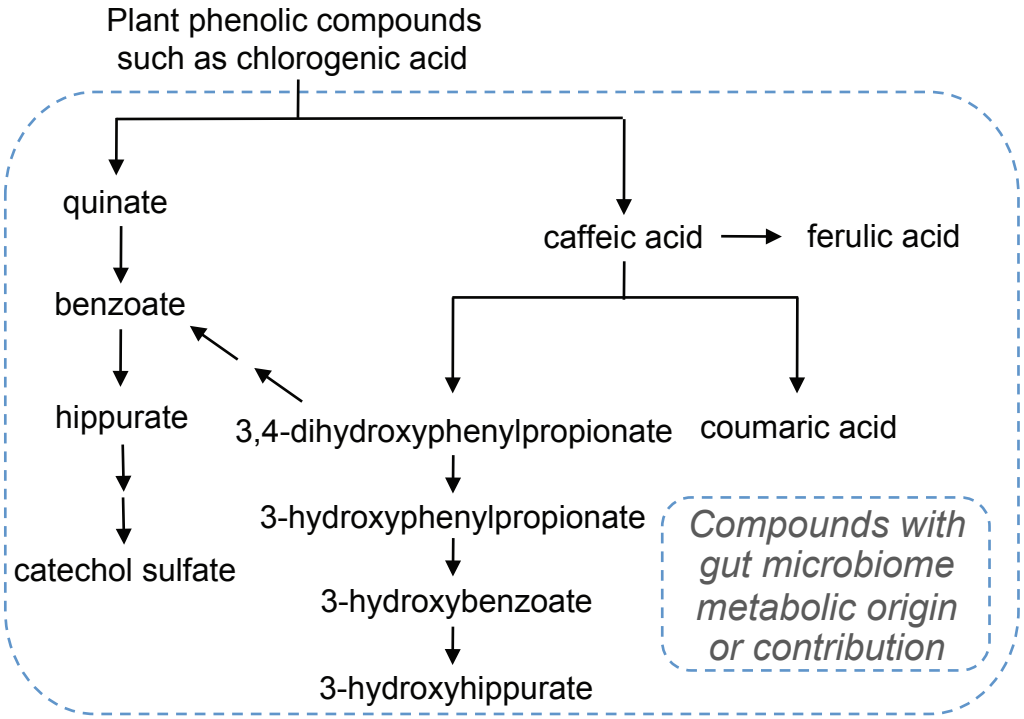
Both diet and both the plasma/ urinary metabolome were dramatically different where gut microbiota metabolites contributed more greatly to the plasma metabolome of vegans than omnivores

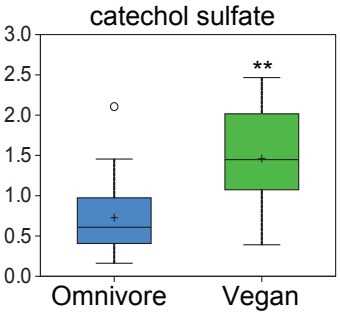
Wu GD. Gut. 2014 Nov 26. pii: gutjnl-2014-308209. doi: 10.1136/gutjnl-2014-308209.

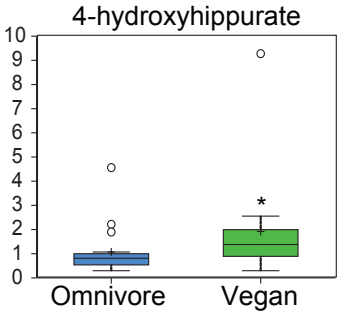
Dietary Plant Products and the Plasma Metabolome

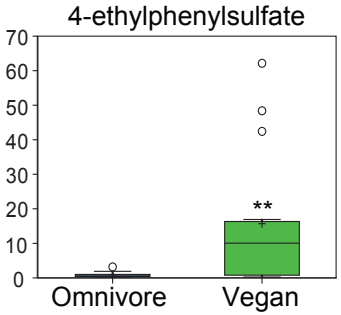


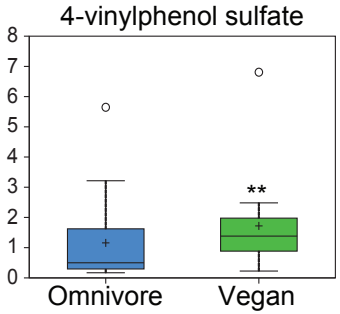












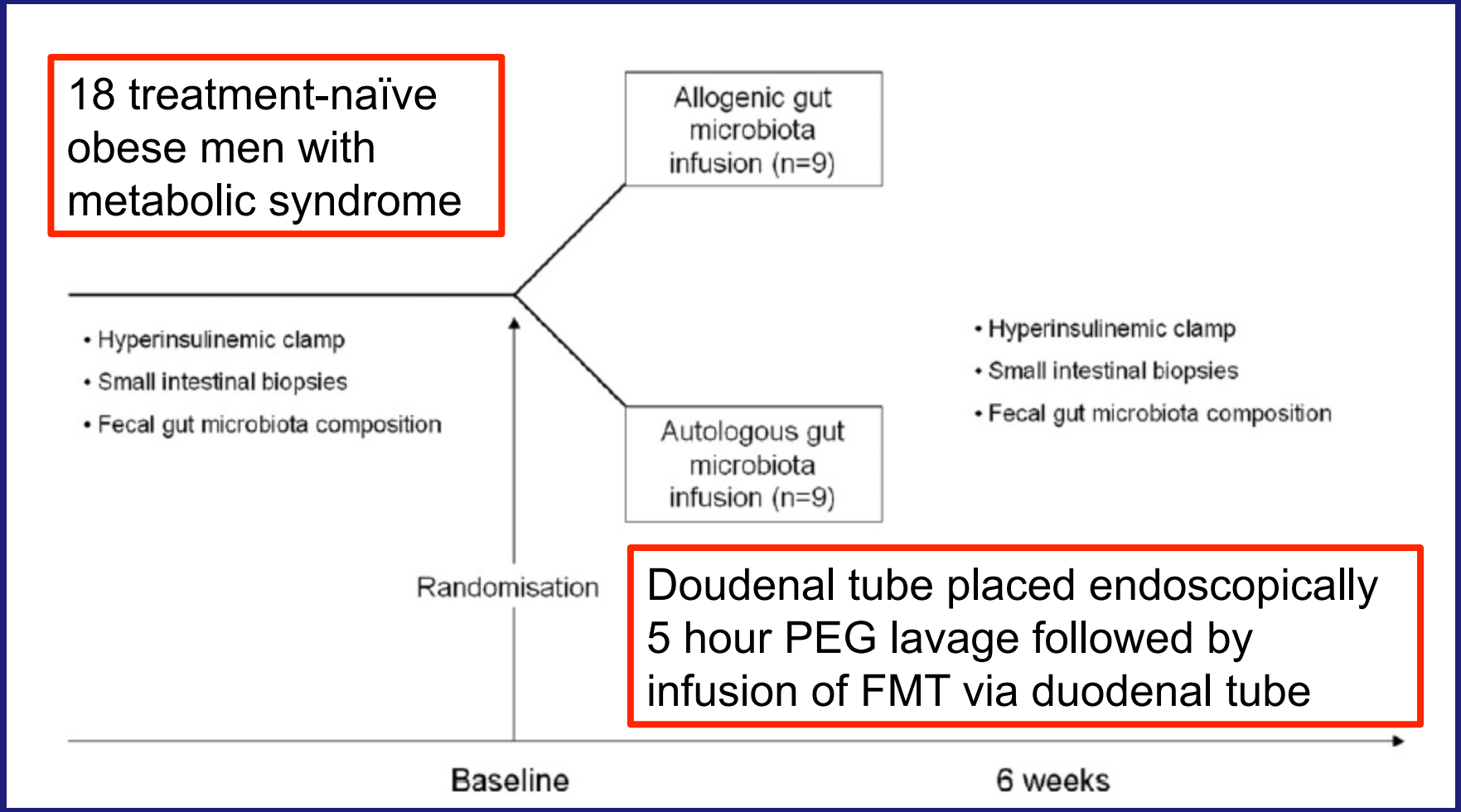
Wu GD. Gut. 2014 Nov 26. pii: gutjnl-2014-308209. doi: 10.1136/gutjnl-2014-308209.

Summary

- Dietary patterns are associated with the composition of the gut microbiota
  - Exclusion of plant products leads to rapid and more extreme changes in the composition of the gut microbiota
  - Modest dietary changes have much smaller effects
- The microbiota interacts with diet to impact the gut, plasma and urinary metabolome
  - Rate limiting effects of production can be either the precursor (food) or generator (microbes)

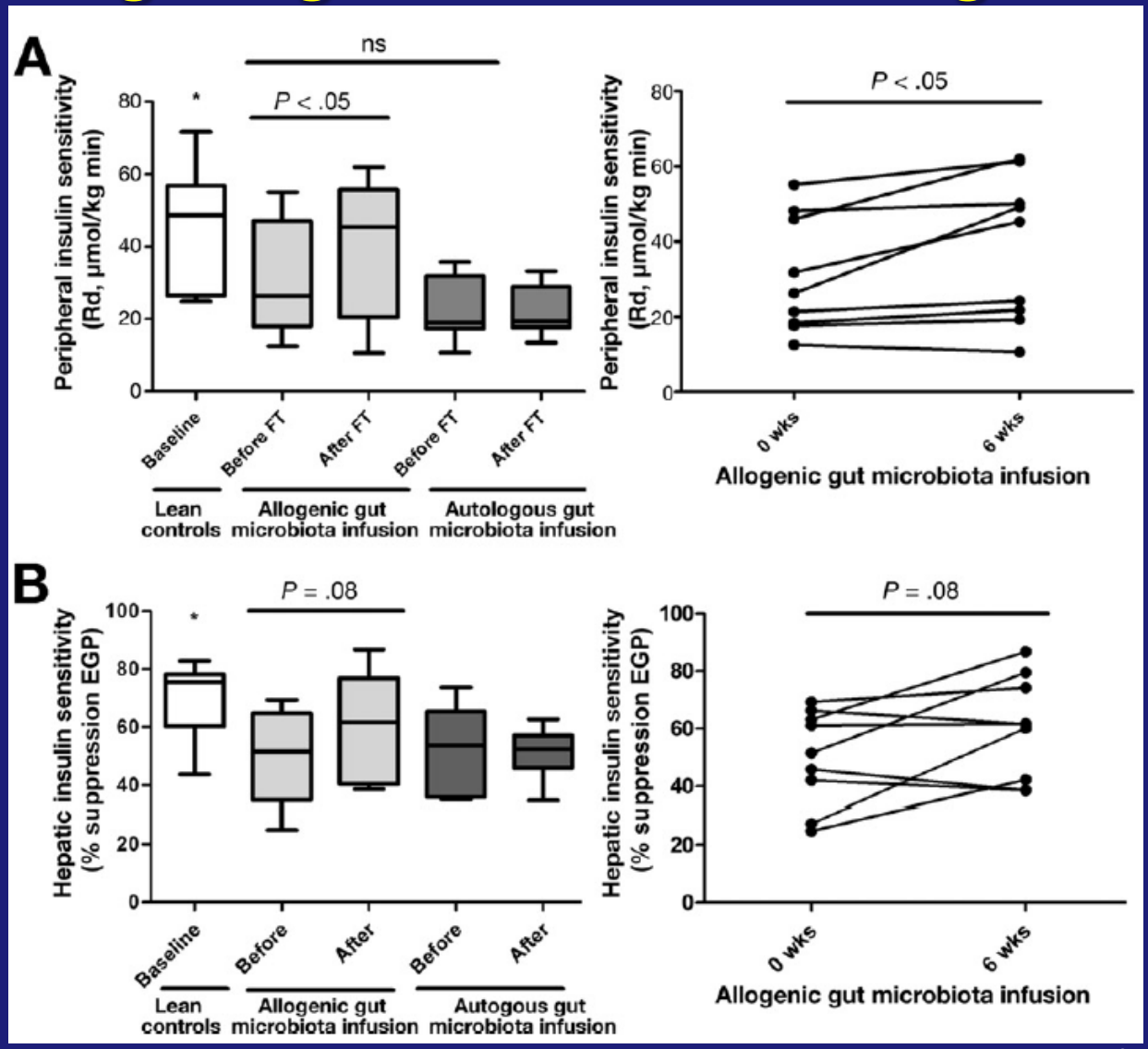
What is the Link Between CV Disease, Cancer, and Mediterranean Diet?

Altering Small Bowel Microbiota Increases Insulin Sensitivity



Vrieze A. Gastroenterol 2012;143:913-6

Increase in Peripheral Insulin Sensitivity Following Allogenic but not Autologous FMT



Vrieze A. Gastroenterol 2012;143:913-6

Altered Composition of SB Microbiota Following FMT via Duodenal Infusion

Supplementary Table 4. Gut Microbiota in Small Intestinal Biopsy Specimens

Phylum level	Bacterial group	Fold-change after/before allogenic infusion	Fold-change after/before autologous infusion
Proteobacteria	*E coli* et rel.[a]	0.58	2.21
Actinobacteria	*Corynebacterium* spp.[a]	0.87	1.34
Proteobacteria	*A faecalis* et rel.[a]	1.18	0.97
Bacteroidetes	*Prevotella ruminicola* et rel.	0.99	1.01
Firmicutes	*Streptococcus bovis* et rel.	0.89	1.23
Firmicutes	*Lachnobacterium bovis* et rel.	0.63	0.98
Firmicutes	*E hallii* et rel.	1.09	0.61

NOTE. Seven groups of small intestinal gut microbiota were changed within the allogenic lean donor gut microbiota treatment group after 6 weeks. Moreover, a total of 3 different gut microbiota were identified between allogenic and autologous treatment groups ([a]$P < .05$; for description of statistical models see the Supplementary Materials and Methods section).

Vrieze A. Gastroenterol 2012;143:913-6

Altered Composition of Fecal Microbiota Following FMT via Duodenal Infusion

Supplementary Table 3. Gut Microbiota in Fecal Samples

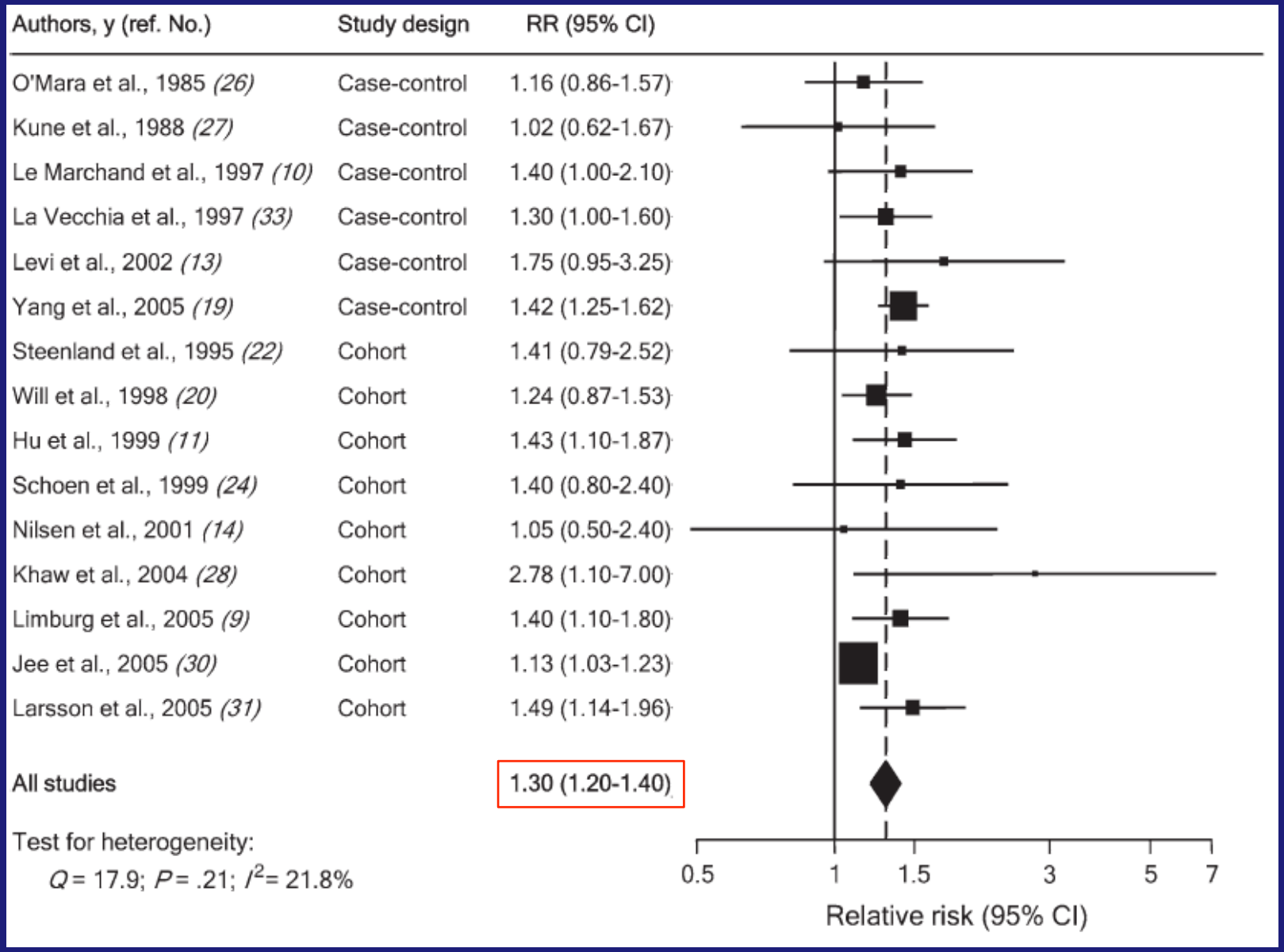
Phylum level	Bacterial taxa	Fold-change after/before allogenic infusion	*q value after/before allogenic infusion*	Fold-change after/before autologous infusion	*q value after/before autologous infusion*
Firmicutes	*Dorea formicigenerans* et rel.[a]	1.92	*0.02*	1.4	*0.26*
Firmicutes	*Ruminococcus gnavus* et rel.	1.74	*0.02*	1.22	*0.33*
Firmicutes	*Clostridium sphenoides* et rel.[a]	1.95	*0.02*	1.29	*0.32*
Firmicutes	*Clostridium symbiosum* et rel.	1.71	*0.05*	1.45	*0.18*
Firmicutes	*Coprobacillus catenaformis* et rel.[a]	1.65	*0.02*	1.18	*0.33*
Firmicutes	*Clostridium ramosum* et rel.	1.51	*0.02*	1.13	*0.3*
Firmicutes	*Aneurinibacillus*	1.26	*0.04*	1.1	*0.33*
Firmicutes	*Ruminococcus lactaris* et rel.[a]	2.47	*0.02*	1.47	*0.3*
Firmicutes	*Clostridium nexile* et rel.[a]	2.09	*0.03*	1.38	*0.32*
Firmicutes	*Anaerotruncus colihominis* et rel.	1.49	*0.01*	1.14	*0.31*
Firmicutes	*Eubacterium siraeum* et rel.	1.56	*0.02*	1.00	*0.6*
Firmicutes	*Sporobacter termitidis* et rel.	1.39	*0.05*	1.31	*0.18*
Proteobacteria	*O formigenes* et rel.[a]	1.70	*0.02*	1.27	*0.24*
Firmicutes	*Ruminococcus callidus* et rel.	1.63	*0.02*	1.15	*0.42*
Firmicutes	*Ruminococcus bromii* et rel.	2.49	*0.02*	1.65	*0.2*
Firmicutes	*R intestinalis* et rel.	2.45	*0.05*	1.22	*0.52*

NOTE. Significant changes in 16 fecal gut microbiota within the allogenic lean donor gut microbiota treatment group after 6 weeks are shown, whereas no significant change was seen after autologous gut microbiota treatment. Moreover, a total of 6 different gut microbiota were identified between allogenic and autologous treatment groups ([a]$P < .05$; for description of statistical models see the Supplementary Materials and Methods section).

Vrieze A. Gastroenterol 2012;143:913-6

What is the Link Between CV Disease, Cancer, and Mediterranean Diet?

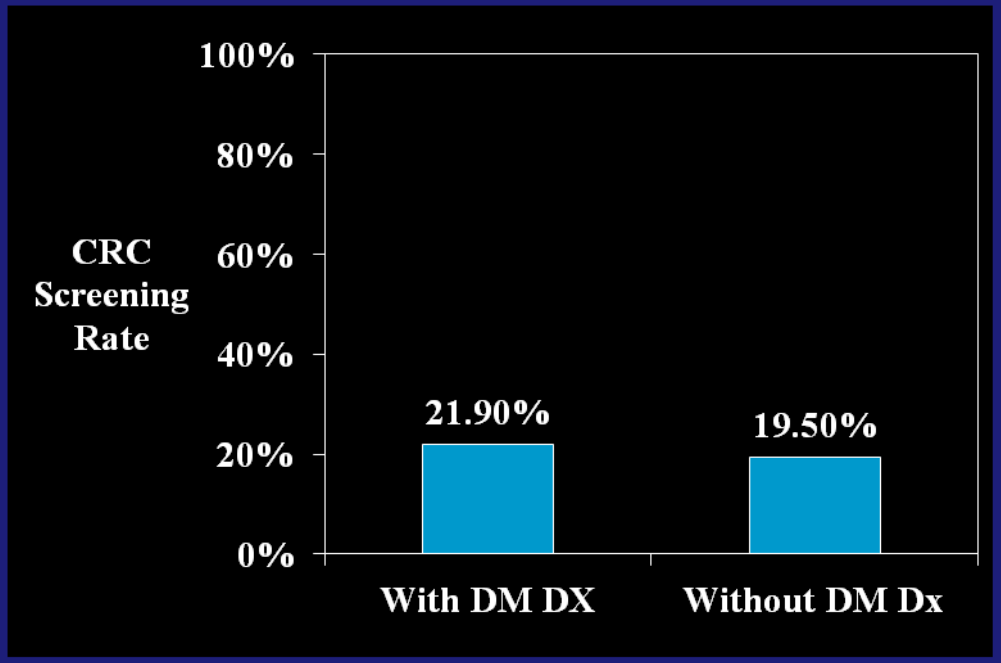
DM and CRC Risk



JNCI 2005;97:1679-87

Detection Bias?

- The Behavioral Risk Factor Surveillance System data (1993, 1995,1997)



Bell RA, et al. Prev Med 2001;32:163-167

Detection Bias?

Crude and multivariable adjusted ORs and 95% CIs

Type II DM OR (95%CI)	DM Dx prior to Index	DM Dx 1yr prior to Index	DM Dx 2yrs prior to Index	DM Dx 3yrs prior to Index
Crude	1.43 (1.27-1.62)	1.39 (1.22-1.59)	1.34 (1.16-1.55)	1.34 (1.14-1.57)
Adjusted*	1.38 (1.22-1.56)	1.33 (1.16-1.52)	1.28 (1.10-1.49)	1.28 (1.09-1.50)

***Adjusted for sex, cholecystectomy, BMI, smoking, NSAID/aspirin use**

Yang et al. Clinical Gastroenterology & Hepatology 2005;3:587-94

Control of DM Seems Less Important

Table 3. Longitudinal analysis comparing mean yearly average HbA1c levels among case groups with any adenoma or advanced adenoma versus controls without any adenoma

	Study 1: Adenoma anywhere in the colon			Study 2: Distal adenoma		
	No adenoma	Advanced adenoma	Any adenoma	No adenoma	Advanced adenoma	Any Adenoma
N	2,952	478	1,296	8,862	289	951
Mean estimate[a] (SE), %	8.20 (0.026)	8.28 (0.057)	8.26 (0.036)	8.32 (0.016)	8.42 (0.079)	8.37 (0.044)
Difference in mean estimates[b] (95% CI, *P*), %	Reference	0.07 (−0.04 to 0.19, $P = 0.24$)	0.06 (−0.02 to 0.14, $P = 0.16$)	Reference	0.09 (−0.06 to 0.25, $P = 0.24$)	0.05 (−0.04 to 0.14, $P = 0.25$)

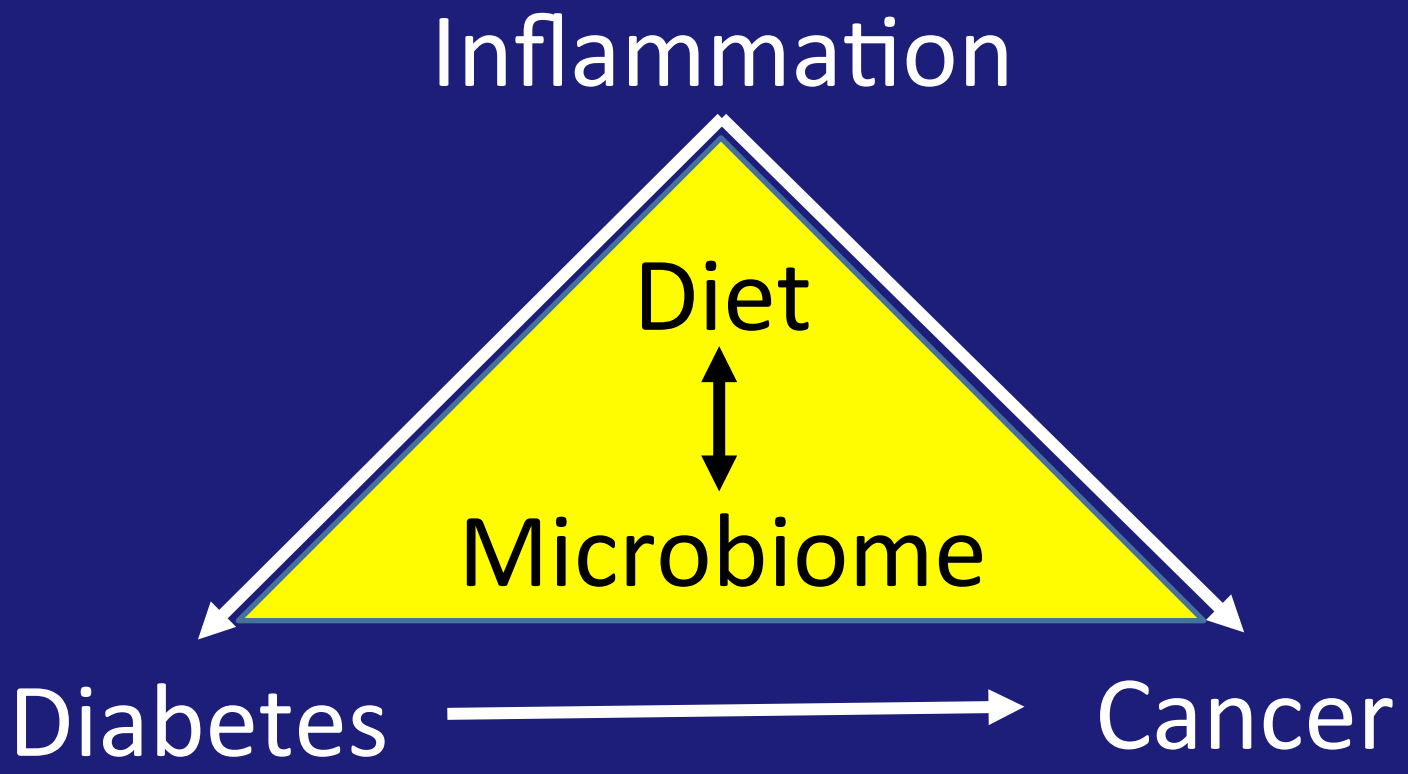
Abbreviation: SE, standard error.

[a]Least-squares means adjusted for sex, age, ethnicity, BMI, income status, duration of diabetes, NSAID use, aspirin use, statin use, and acid-suppressive medication use.

[b]Based on longitudinal analysis adjusted for sex, age, ethnicity, BMI, income status, duration of diabetes, NSAID use, aspirin use, statin use, and acid-suppressive medication use.

Yang YX. *Cancer Epidemiol Biomarkers Prev* 2010;19:3027-3036

What is the Link Between CV Disease, Cancer, and Mediterranean Diet?



Anti-inflammatory Drugs Associated with Lower CRC Risk

Nested case-control study in THIN
N=21,185; 7080 cases with CRC
Chronic use defined as receipt of a prescription in each of the 60-day intervals between 1 and 360 days prior to diagnosis

Exposure (Chronic Use)	Adjusted OR
Aspirin	0.77 (0.67-0.88)
NSAIDs	0.54 (0.44-0.67
Cox-2 inhibitor	0.58 (0.28-1.17

Lewis JD. Pharmacoepidemiol Drug Saf 2007:16:393-401

Anti-inflammatory Diet Associated with Reduced CRC Risk

- Dietary Inflammatory Index
  - Based on correlation of dietary components with inflammatory biomarkers
    - Markers = IL-1β, IL-4, IL-6, IL-10, TNFα, and CRP
    - 45 specific foods and nutrients
      - Saturated fat and trans-fats among the most pro-inflammatory
      - Fiber among the most anti-inflammatory
  - In the WHI FFQ, 32 of the 45 original DII

Shivappa N. Public Health Nutr 17:1689–1696

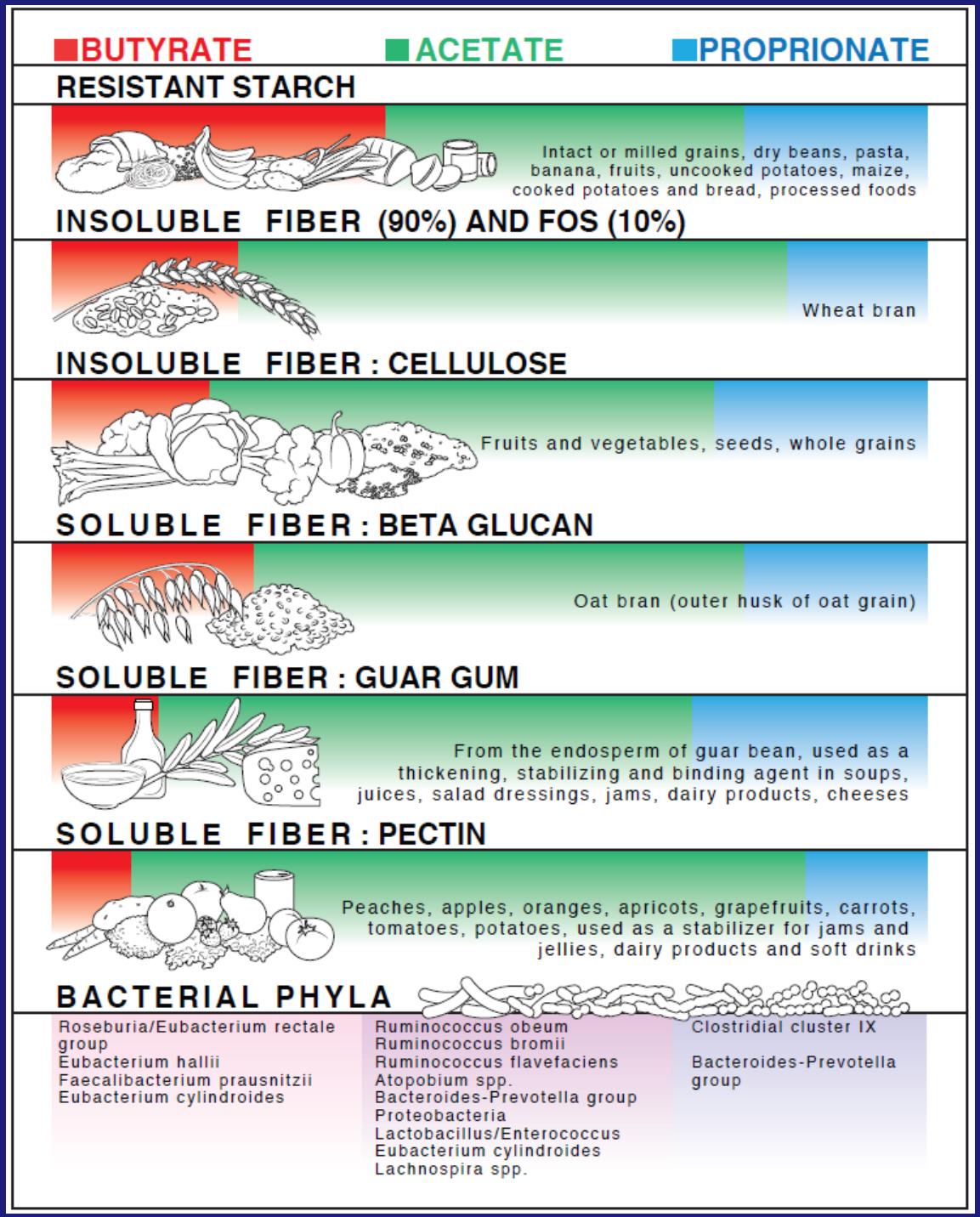
Anti-inflammatory Diet Associated with Reduced CRC Risk - WHI

	Q1 (−7.055, <−3.136) (healthiest)	Q2 (−3.136, < −1.995)	Q3 (−1.995, < −0.300)	Q4 (−0.300, <1.953)	Q5 (1.953, 5.636) (least healthy)	p_{trend}
	Referent	HR (95 % CI)[a]	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	
Age-adjusted model	1.00	1.10 (0.96, 1.26)	1.06 (0.93, 1.22)	1.11 (0.97, 1.27)	1.38 (1.21, 1.57)*	<0.0001
Multivariable-adjusted model[b]	1.00	1.05 (0.91, 1.21)	0.98 (0.84, 1.13)	1.02 (0.88, 1.19)	1.22 (1.05, 1.43)*	0.02
Colorectal cancer cases, 1,920	365 (19.0 %)	388 (20.2 %)	359 (18.7 %)	373 (19.4 %)	435 (22.7 %)	

Tabung FK. Cancer Causes Control. 2015:26: 399–408

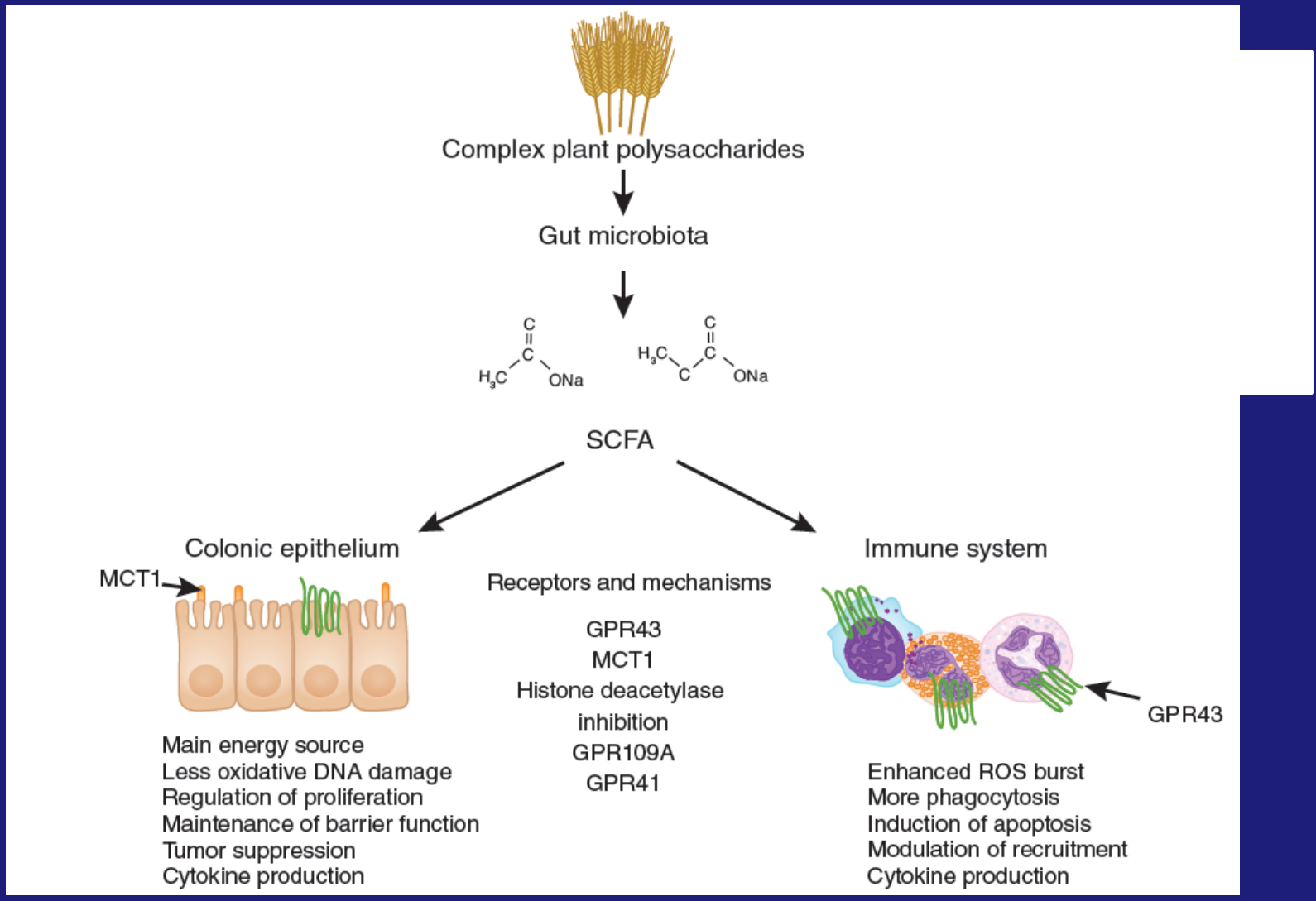
Dietary Fiber

- Nondigestible polysacharides, oligosacharides, lignen, and resistant starch
- Major source of SCFAs in the gut
- Variable fermentation patterns



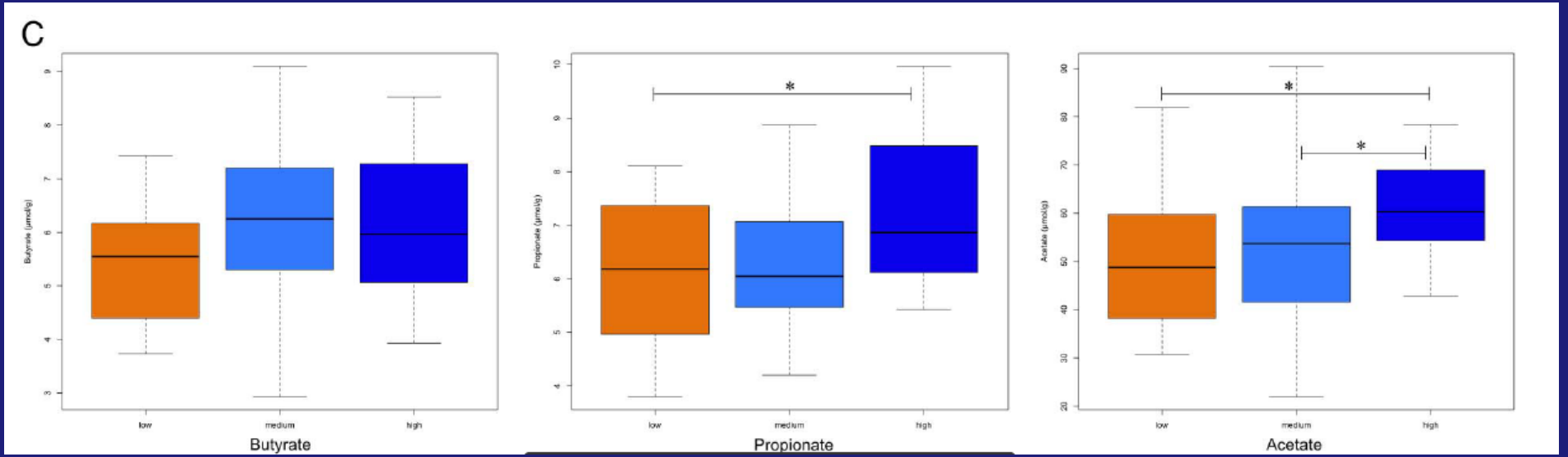
Lewis JD. Gastoenterology 2016

SCFA Production Depends on the Gut Microbiome



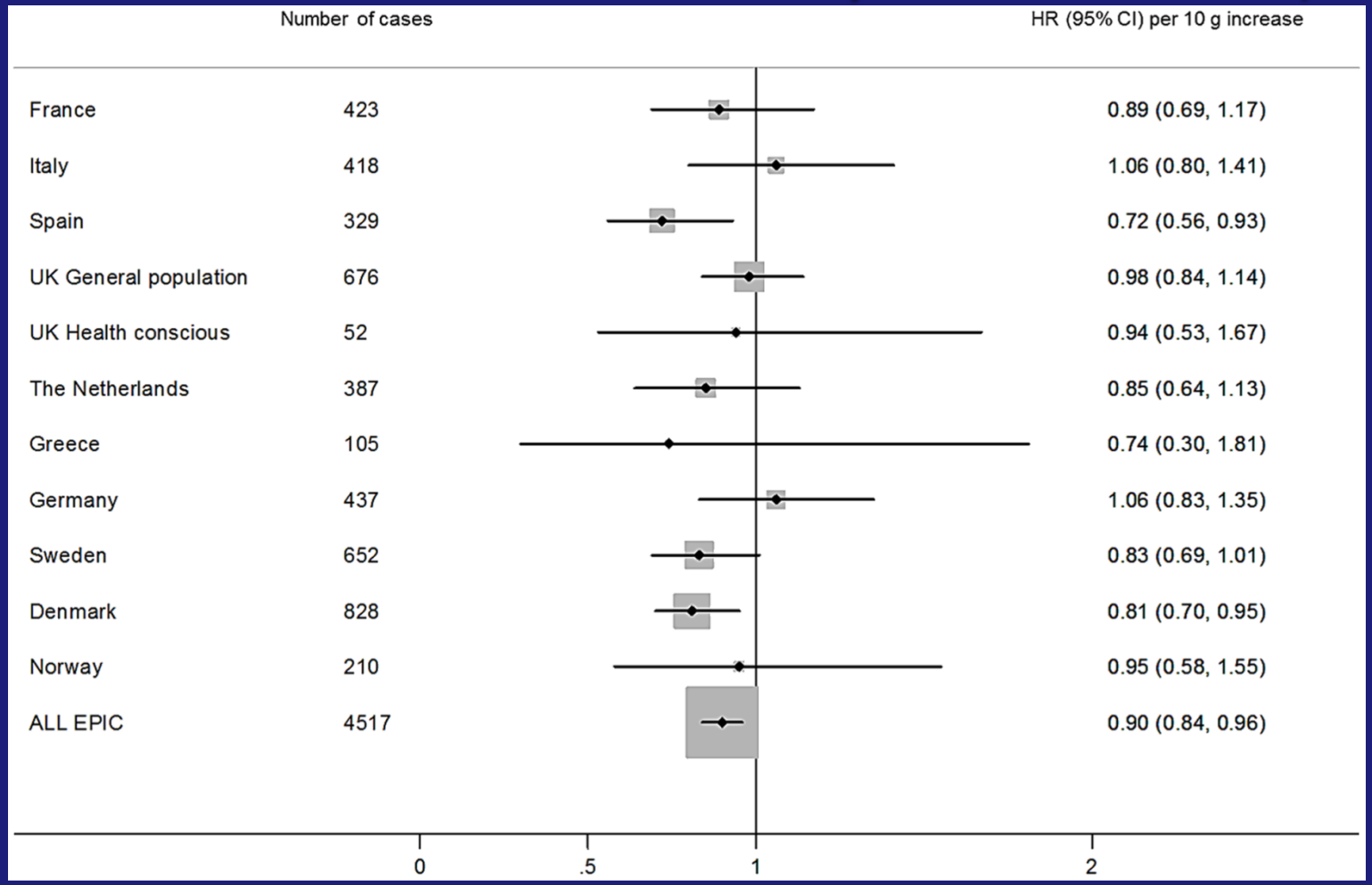
Maslowski KM. Nat Immunol 2011;12:5-9.

Adherence to MSD and Fecal SCFAs



F De Filippis. Gut 2015

HR for CRC in EPIC Cohort (per 10 g/day increase in total dietary fiber intake)



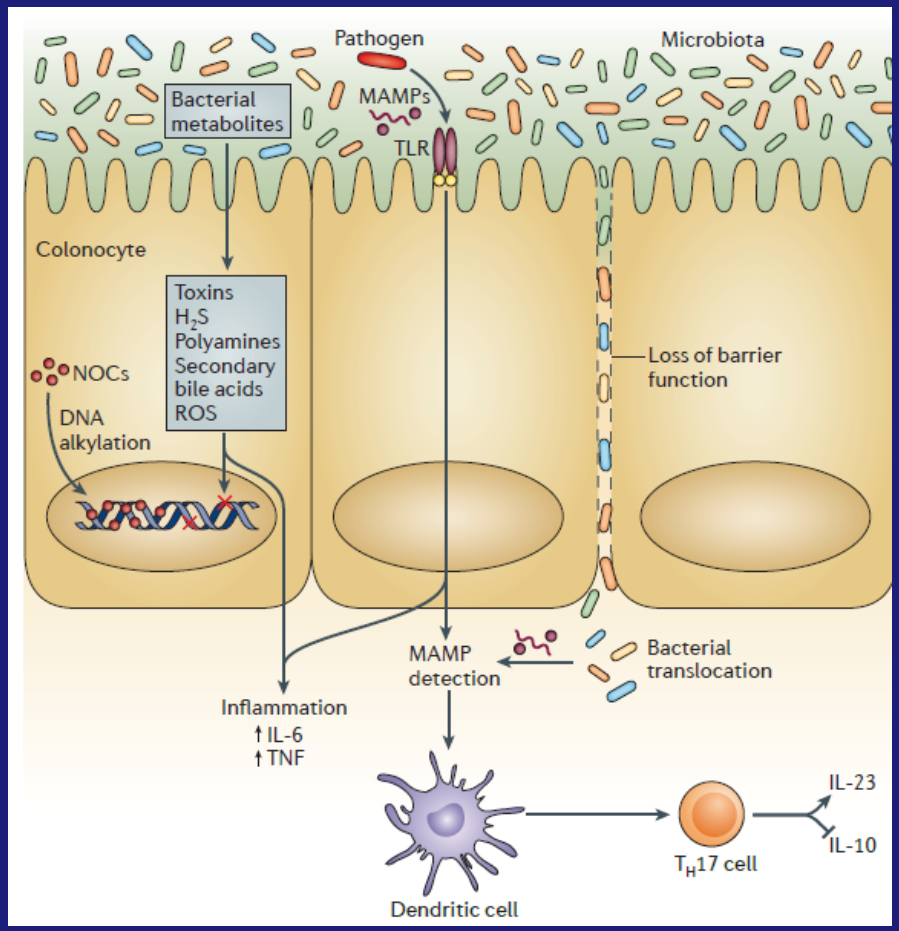
Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, et al. (2012) Dietary Fibre Intake and Risks of Cancers of the Colon and Rectum in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLOS ONE 7(6): e39361. doi:10.1371/journal.pone.0039361

Other Dietary Components Proposed to Reduce Risk of CRC

- Folic acid
  - -0.190 on Dietary Inflammatory Index
  - Pooled RR for CRC (highest vs. lowest quintile of intake) 0.92 (95% CI 0.84-1.00)
- Magnesium
  - -0.484 on Dietary Inflammatory Index
  - Pooled RR for CRC (highest vs. lowest quintile of intake) 0.89 (95% CI 0.79-1.00)

Chen GC. European Journal of Clinical Nutrition. 66(11):1182-6, 2012
Kim DH. Cancer Causes & Control. 21(11):1919-30, 2010
Shivappa N. Public Health Nutr 17:1689–1696

How Diet & Microbiome May Increase Risk of Cancer



Dietary and enviromental compounds	Microbial products	Known effect on host
Non-digestible carbohydrates	SCFAs	• Microbiota modulation • Cellular differentiation; apoptosis • Inflammation
Phytochemicals	Phenolic acids; isothiocyanates	• Xenobiotic detoxification • Microbiota modulation • Cellular differentiation; apoptosis • Inflammation
Protein	NOCs; ammonia	• ROS production; genotoxicity
	Polyamines	• Inflammation • ROS production; genotoxicity
	Hydrogen sulphide	• Inflammation • ROS production; genotoxicity
Fat → Bile acids	Taurine	• Microbiota modulation
	Secondary bile acids	• Microbiota modulation • Cellular differentiation; apoptosis • ROS production; genotoxicity
Xenobiotics	Carcinogens	• ROS production; genotoxicity
Ethanol	Acetaldehyde	• ROS production; genotoxicity

Louis P. Nature Reviews Microbiol 2014

JAMA Oncology | Original Investigation

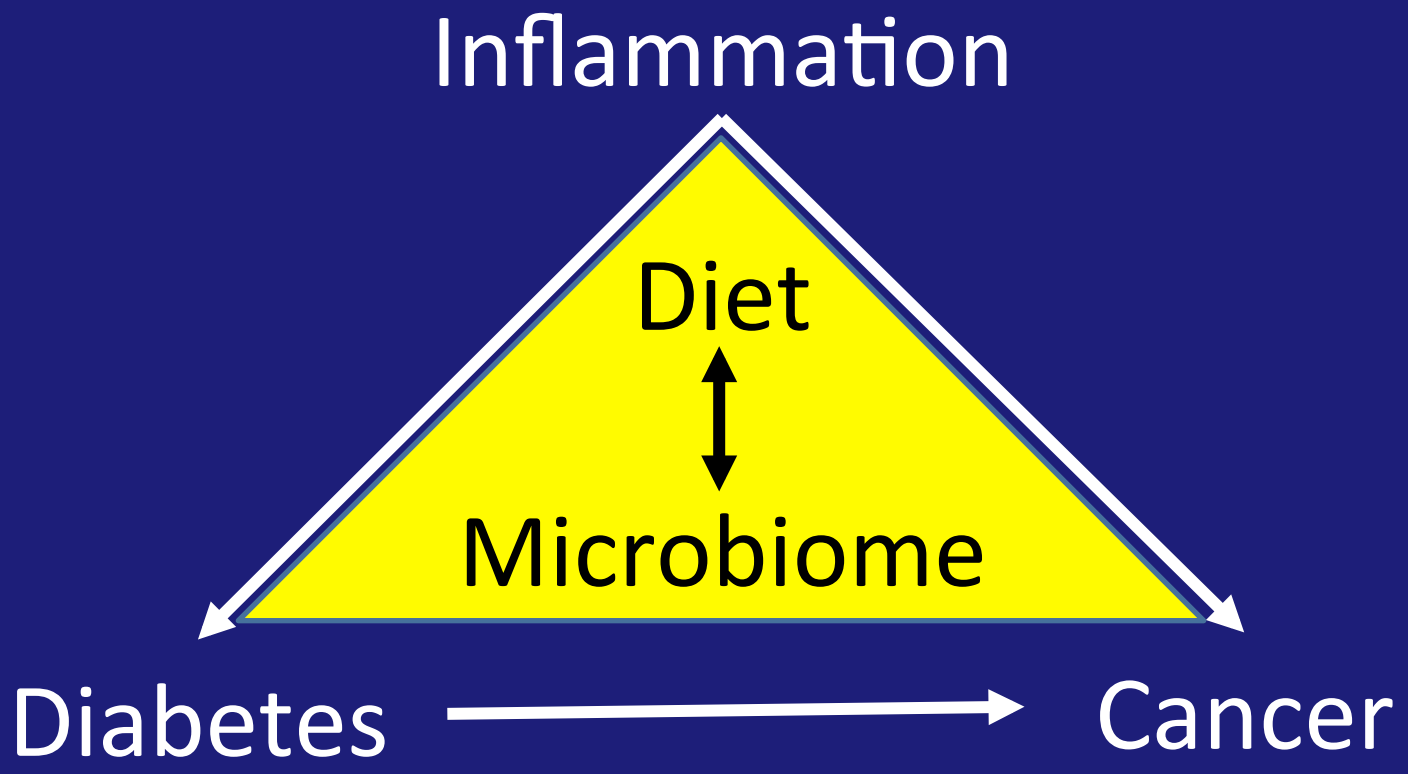
Association of Dietary Patterns With Risk of Colorectal Cancer Subtypes Classified by *Fusobacterium Nucleatum* in Tumor Tissue

Quartiles Based on Prudent Dietary Pattern Score

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P trend
Overall CRC	Ref	0.95 (0.80-1.14)	0.95 (0.79-1.14)	0.85 (0.69-1.03)	0.08
F nucleatum positive CRC	Ref	0.56 (0.34-0.92)	0.70 (0.44-1.10)	0.43 (0.25-0.72)	0.003
F nucleatum negtive CRC	Ref	1.04 (0.86-1.26)	1.00 (0.83-1.22)	0.95 (0.77-1.17)	0.47

Health Professionals Follow-up Study (1986-2012) and the Nurses' Health Study (1980-2012).

What is the Link Between CV Disease, Cancer, and Mediterranean Diet?



Gastroenterology & Hepatology Clinical Research Program

James D. Lewis, MD, MSCE – Director
Yu-Xiao Yang, MD, MSCE – Associate Director

<u>Faculty</u>

Kimberly Forde, MD, MS	Liver disease
David Goldberg, MD, MSCE	
Vincent LoRe, MD, MSCE	
Ronac Mamtani, MD, MSCE	Cancer
Chyke Doubani, MD, MPH	
Shivan Mehta, MD, MSHP	
Meenakshi Bewtra, MD, PHD	IBD
Frank Scott, MD, MSCE	

"Penn Intestinal Microbiome Project Group"

Patient/subject recruitment and phenotyping, dietary assessment, sample collection and processing

Robert Baldassano, MD (CHOP)

*James D. Lewis, MD (Penn)

*Gary D. Wu, MD (Penn)

Gary L. Lichtenstein, MD (Penn)

Charlene Compher, PhD, RD (Penn)

Anthony Otley, MD (Dalhousie)

Anne Griffiths, MD (Toronto)

*Co-Principal Investigators

DNA sequencing, data analysis, and mathematical modeling

*Frederic D. Bushman, PhD (Penn)

Hongzhe Li, PhD (Penn)

Kyle Bittinger, PhD (CHOP)

Microbiology

Mark Goulian, PhD (Penn)

Metabolomics

Michael Bennett, PhD (CHOP)

Marc Yudkoff, MD (CHOP)

Clary Clish, PhD, Ramnik Xavier, MD, and Jonathan Braun, MD-PhD

Biological Oxymetry

Sergei Vinogradov, PhD (Penn)

Jun Chen, Sam Minot, Serena Dollive, Eric Chen, Christian Hoffmann, Ying-Yu Chen, Kyle Bittinger, Jennifer Hwang, Erin Gilroy, Kernika Gupta, Lisa Nessel, Lindsey Albenberg, Judith Kelsen, Colleen Judge, Christel Chehoud, David Shen, Rohini Sinha, David Metz, Tatiana Esipova, Susan Parrott, Elliot Friedman, **Josie Ni**, Sarah Smith, Lillian Chau, Erica Panfen, Andrew Lin, Sarah Smith, Jack Jiang

The Joint Penn-CHOP Center for Digestive, Liver, and Pancreatic Medicine

Center for Molecular Studies in Digestive and Liver Diseases (P30 DK050306)

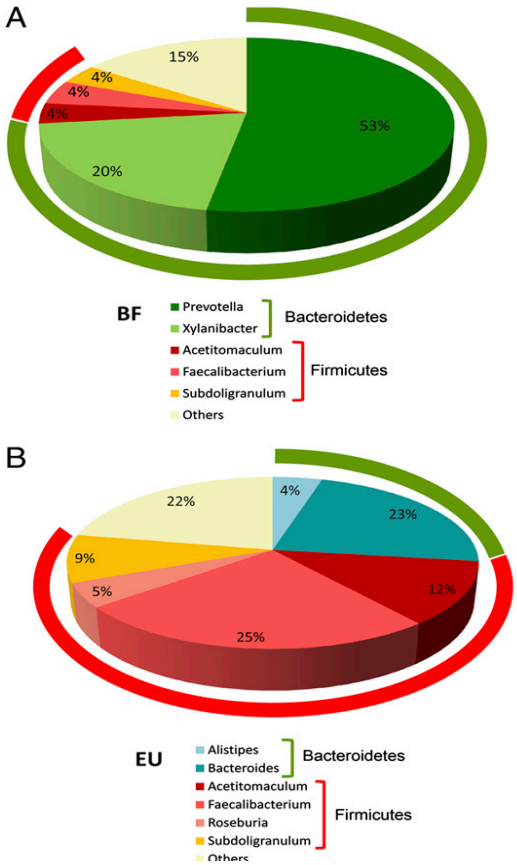
Back-Up Slides

Table S3. Dietary intake of macronutrients and fecal short chain fatty acid levels in vegan-omnivore and CAFE study subjects as well as in two previously published studies comparing these parameters in residents of agrarian vs. Western societies.

PNAS 2010;107:14691–14696

Study	Diet	Energy (kcal) †	Pro (g) †	Fat (g) †	Carb (g) †	Starch (g) †	Fiber (g) †	Sugars (g) †	Acetate (μM/g) #	Propionate (μM/g) #	Butyrate (μM/g) #
Vegan-Omnivore	Vegan (N=11)	2100.9 (555.9)	79.1 (22.9)	63.8 (20.5)	296.9 (98.3)	154.4 (67.0)	35.3* (18.3)	79.6 (27.5)	43.9 (4.7)	15.6 (3.0)	14.0 (2.3)
	Omnivore (N=16)	2156.6 (727.0)	89.1 (33.0)	86.3 (39.1)	246.5 (81.2)	125.2 (53.5)	17.5 (8.1)	87.8 (50.0)	56.3 (5.3)	19.3 (2.4)	13.7 (1.4)
CAFE	High Fiber Low Fat (N=5)	2511.9 (579.9)	113.1 (25.2)	37.0* (8.7)	456.5* (105.5)	96.0 (24.3)	48.7* (10.7)	285.3* (64.5)	56.5 (12.0)	18.5 (2.3)	9.13 (2.8)
	Low Fiber High Fat (N=5)	2227.7 (443.7)	144.4 (29.2)	94.8 (19.6)	205.6 (38.8)	72.5 (13.0)	21.5 (4.0)	103.1 (20.7)	54.2 (11.5)	22.1 (4.4)	14.2 (4.7)
Ou (Ou et al., 2013)	Native African (N=18)	1669* (160)	58* (4)	38* (3)	282 (28)	n/a	17 (2)	n/a	71.1* (11.9)	26.9* (5.6)	16.7* (3.3)
	African American (N=17)	2650 (230)	94 (9)	114 (11)	312 (27)	n/a	20 (1.5)	n/a	26.3 (3.0)	7.9 (1.2)	8.5 (2.2)
DeFilippo (De Filippo et al., 2010)	Burkina Faso, age 2-6 y (N=11)	996.1	40.2	31.3	148.7	134.4	14.3	0	34.7 (4.4)	22.9* (7.3)	9.3* (1.9)
	Italy, age 2-6 years (N=11)	1512.7	66.7	73.9	137.6	119.2	8.4	10	20.9 (2.7)	6.2 (1.2)	2.5 (0.5)

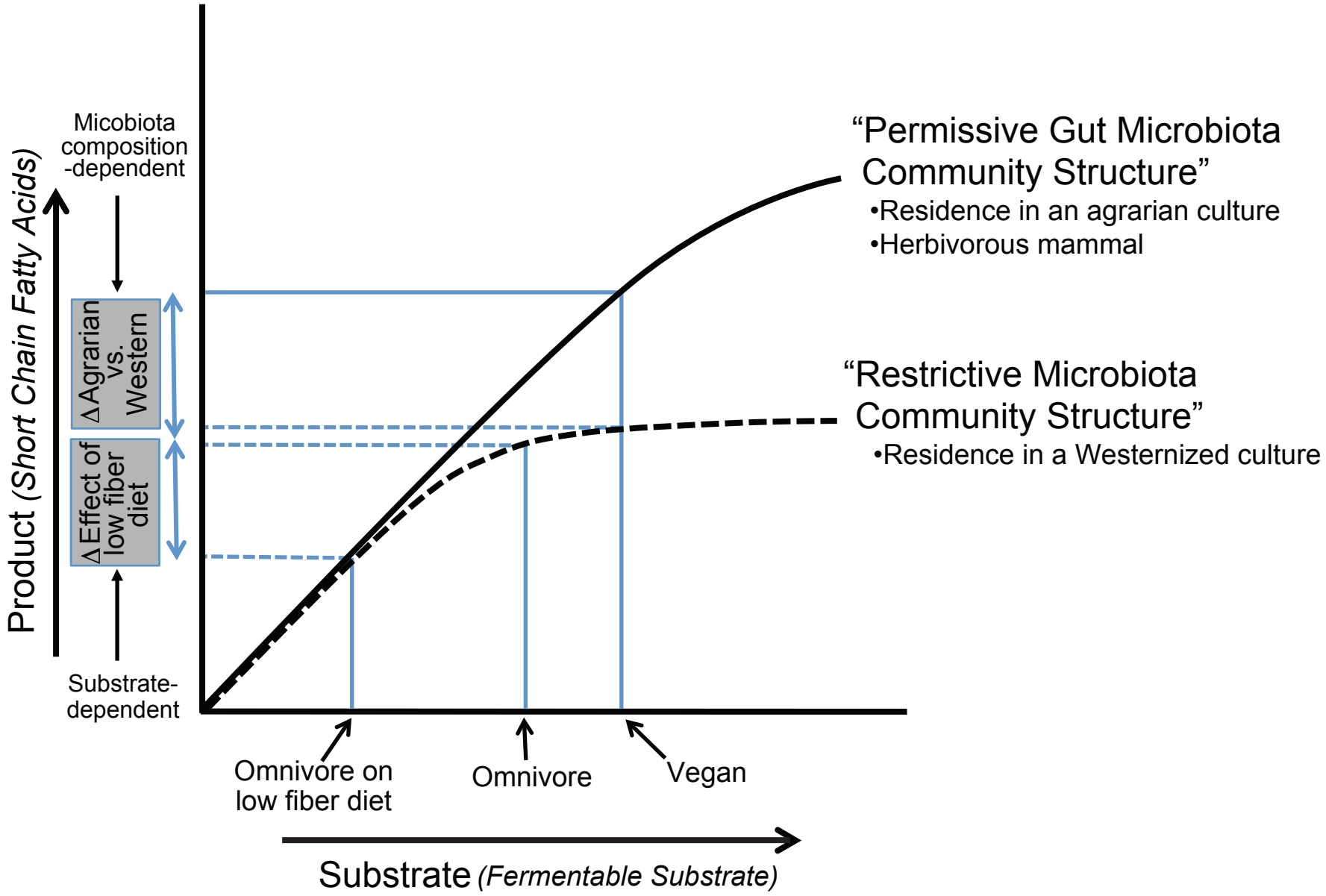
† Average daily consumption and standard deviation
# Mean and standard error of mean
*P<0.01, Vegans vs. Omnivores; High Fiber Low Fat vs. Low Fiber High Fat in Café; Native African vs. African American in Ou; Burkina Faso vs. Italy in De Filippo



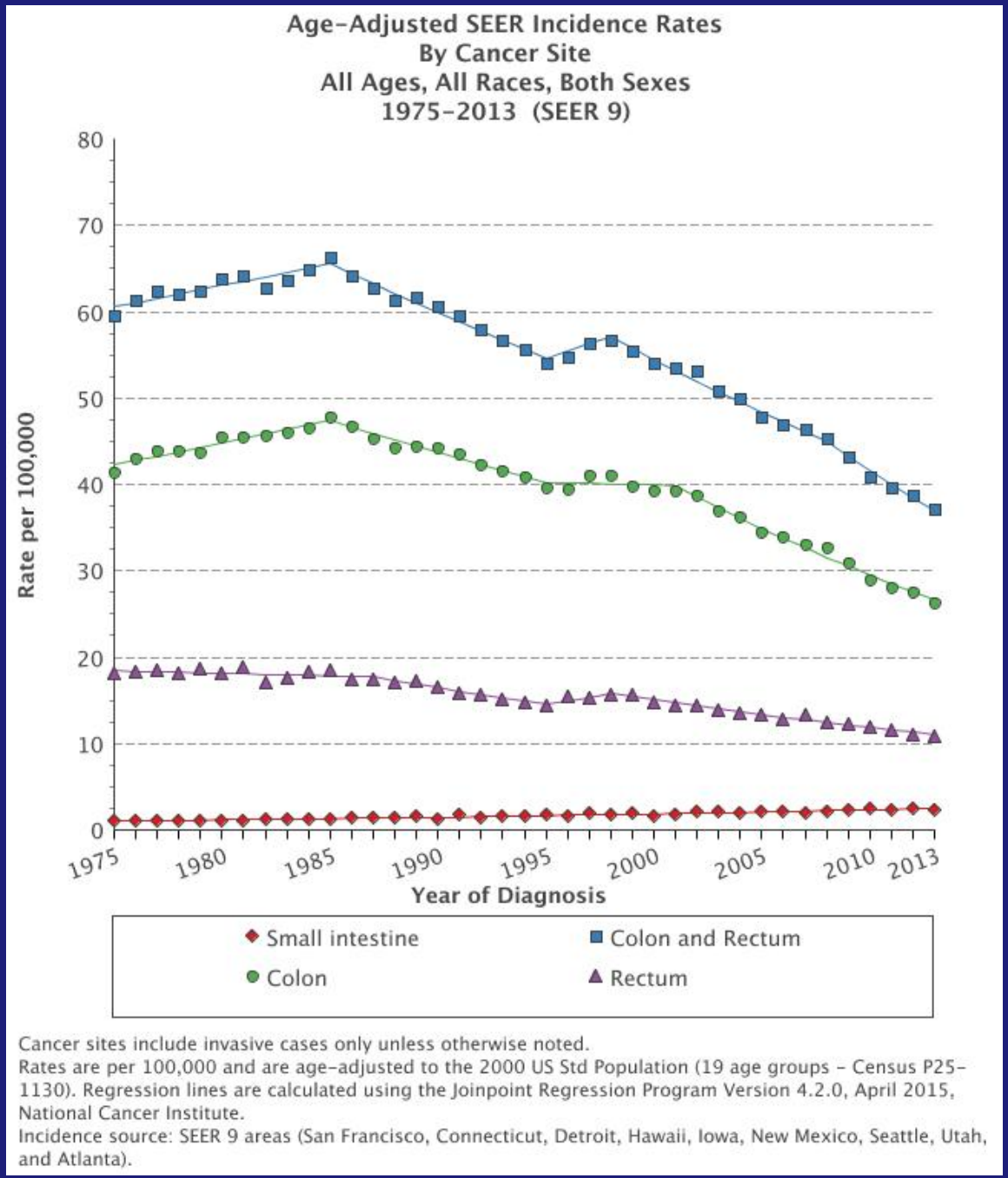
Wu GD. Gut. 2014 Nov 26. pii: gutjnl-2014-308209. doi: 10.1136/gutjnl-2014-308209.

- Supplementation of diets with fermentable substrates in omnivores residing in industrialized nations does not generally lead to an increase in fecal SCFA levels.

- Removal of fermentable substrates from the diet of omnivores residing in industrialized nations leads to a significant reduction in fecal SCFAs (Lawrence et al. Nature 2013, Duncan et al. 2007).



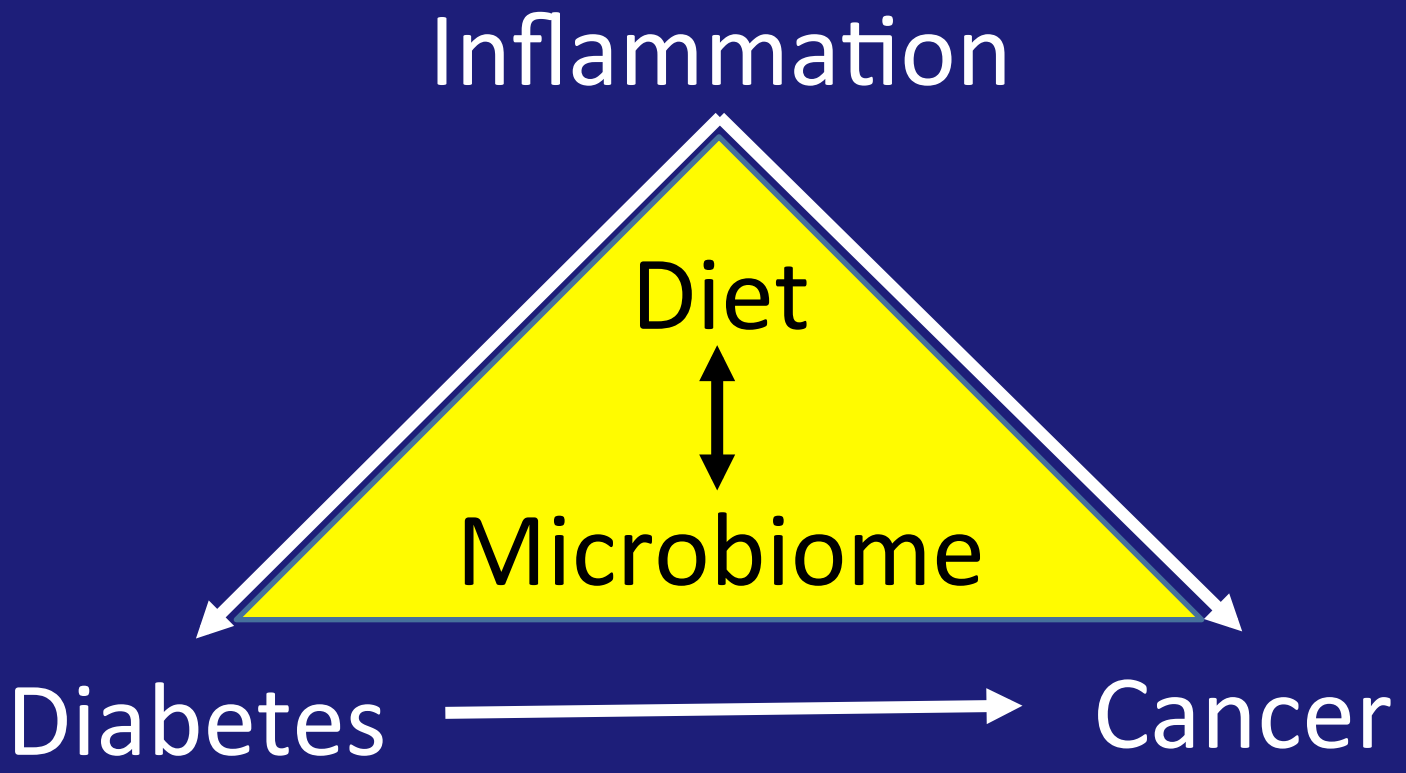
Wu GD. Gut. 2014 Nov 26. pii: gutjnl-2014-308209. doi: 10.1136/gutjnl-2014-308209.



All trends with $p<0.001$ (Spearman)

Why is the incidence of cancer so much higher in the colon and rectum than in the small bowel despite the small bowel being much larger?

Complex Relation Between Diet, Inflammation and Cancer



COMBO Analytic Pipeline

Is there an association between overall composition of the diet and composition of the gut microbiome?

Analytic Method: Summarize microbiome data using UniFrac distance matrices as principle coordinates and summarizing the diet data using a nutrient data matrix (Singular Value Decomposition-SVD) to produce several principle components.

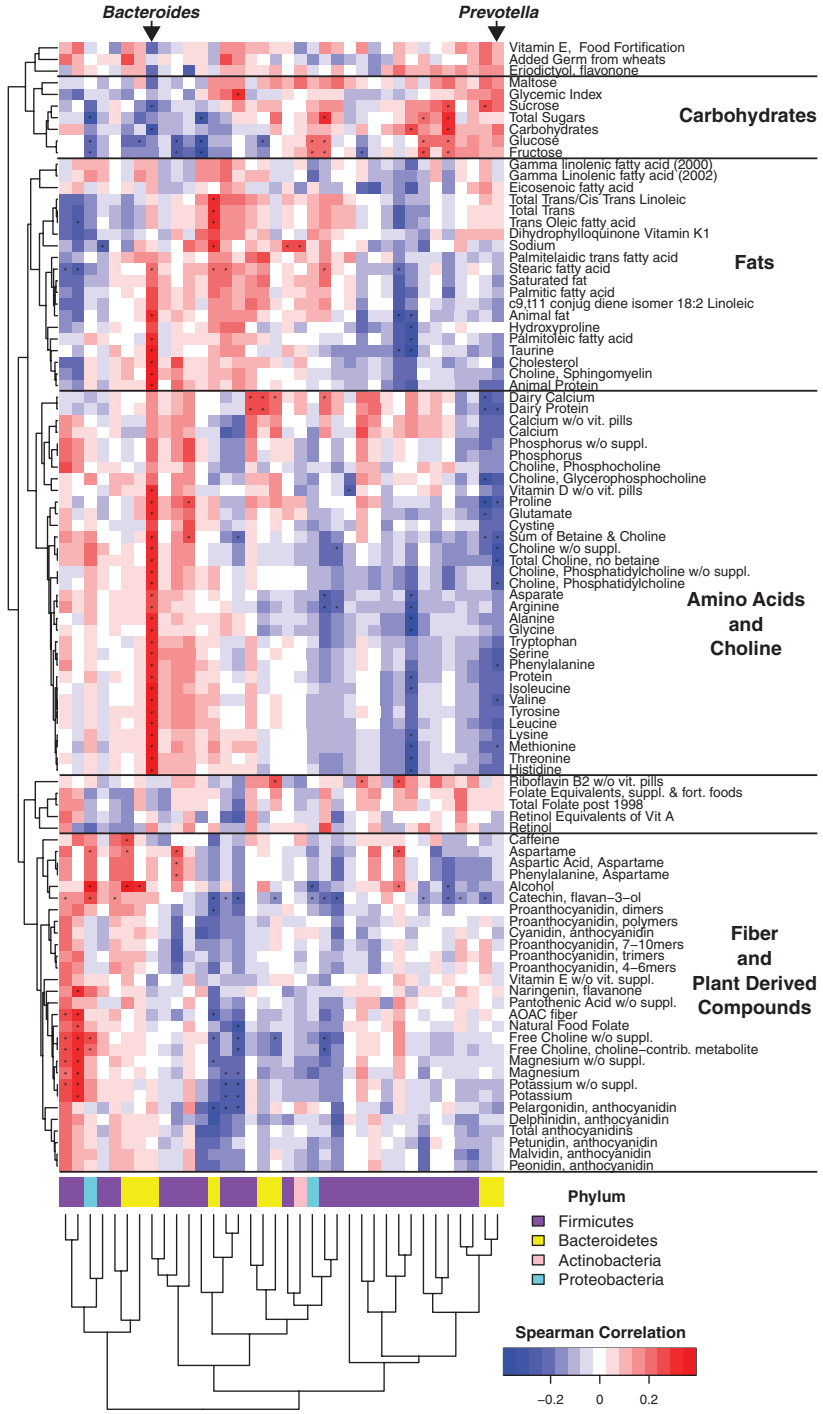
The Result:

	P Value (Weighted)	P Value (Unweighted)
Recall (PC1)	0.075	0.021
FFQ (PC2)	0.016	0.053

COMBO

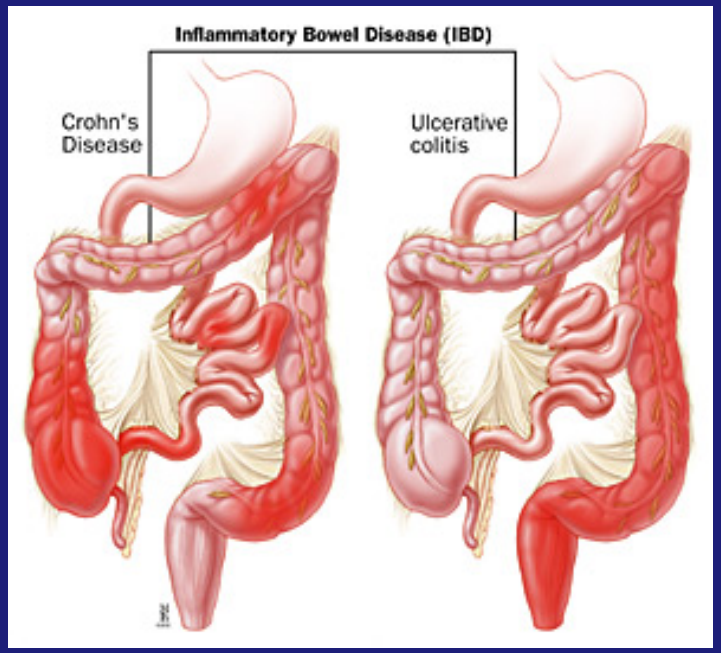
Are nutrients associated with specific bacterial taxa?

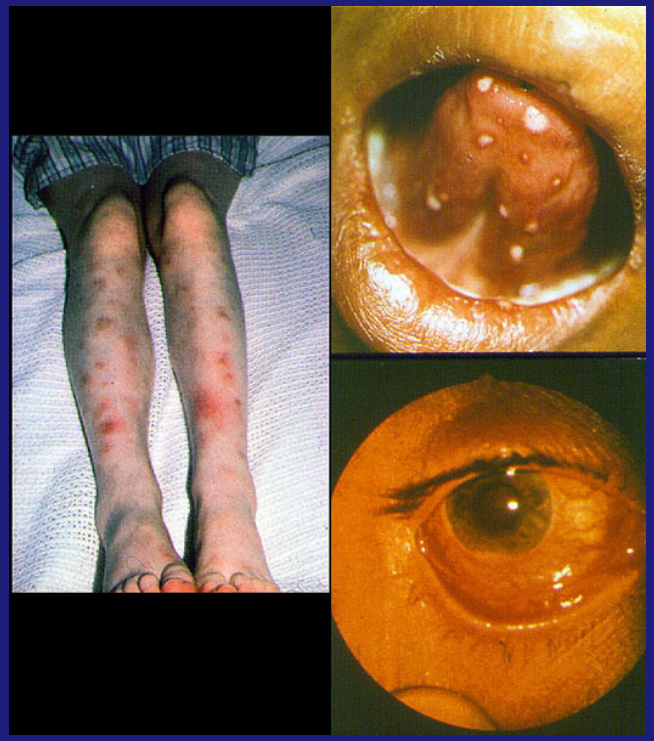
Analytic Method: Calculation of Spearman Correlation Coefficient using nutrient and taxanomic abundance.

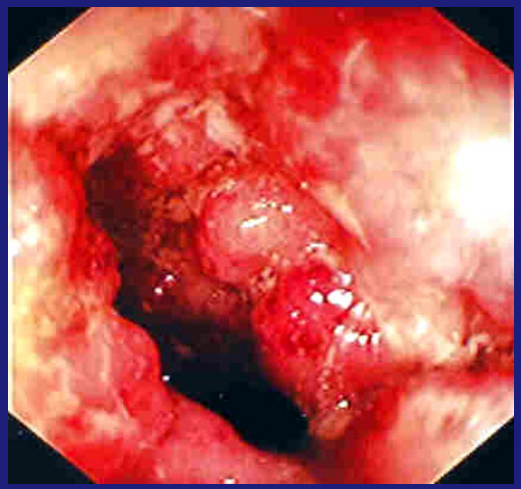


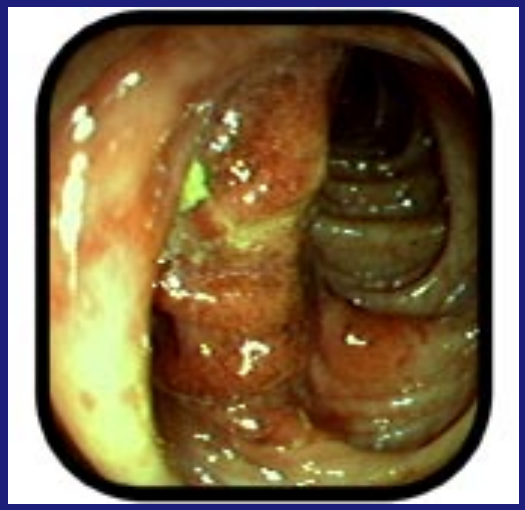
Science. 2011 Oct 7;334(6052):105-8

Inflammatory Bowel Disease (IBD) Afflicts Approximately 1-1.5 Million People in the U.S. Alone



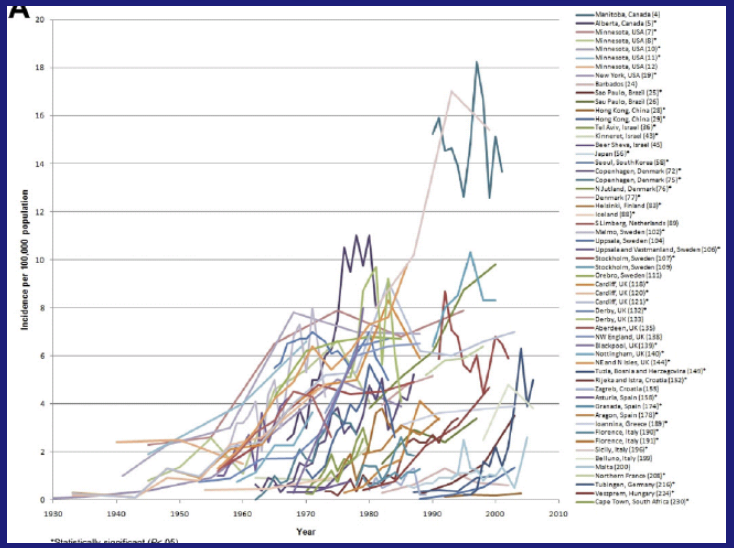




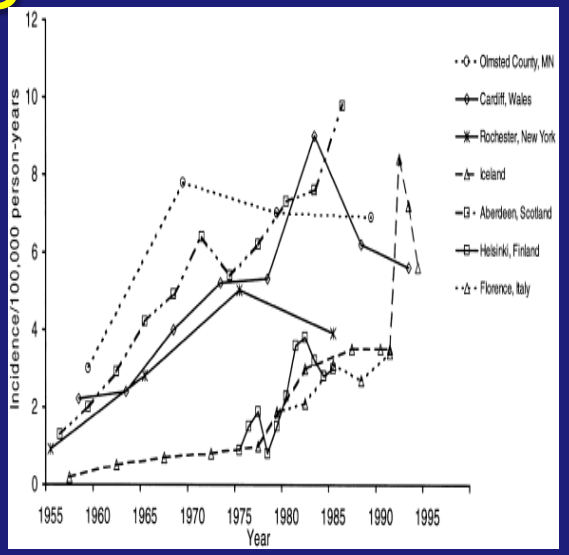


Incidence of IBD Increasing Worldwide

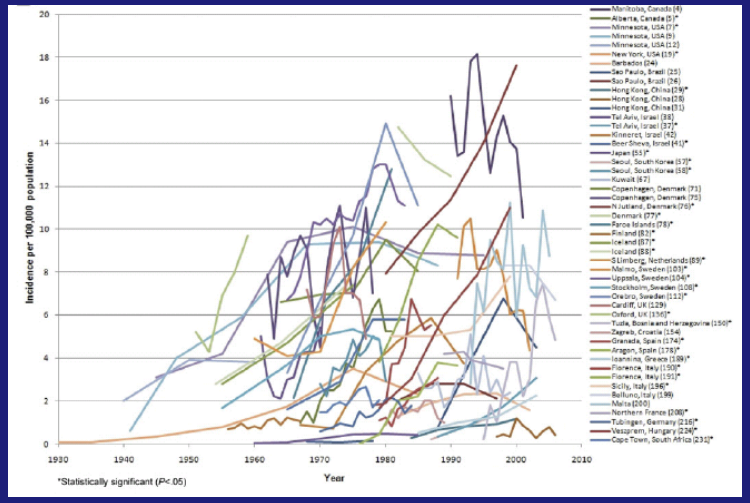
CD



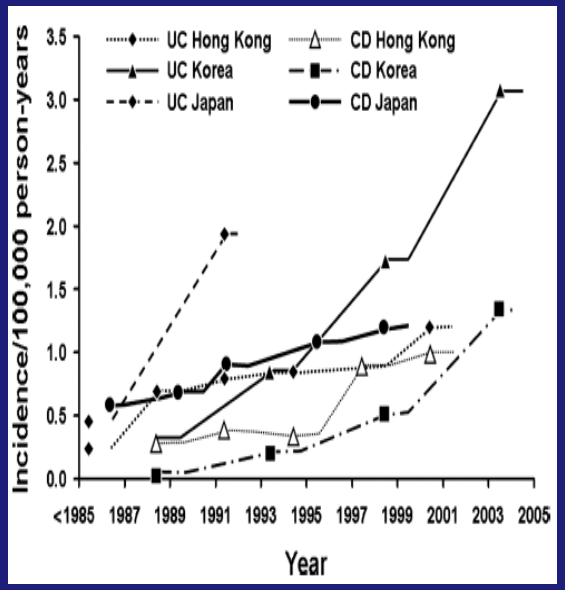
NA & Europe (70s-80s)



UC



Asia (2000s)

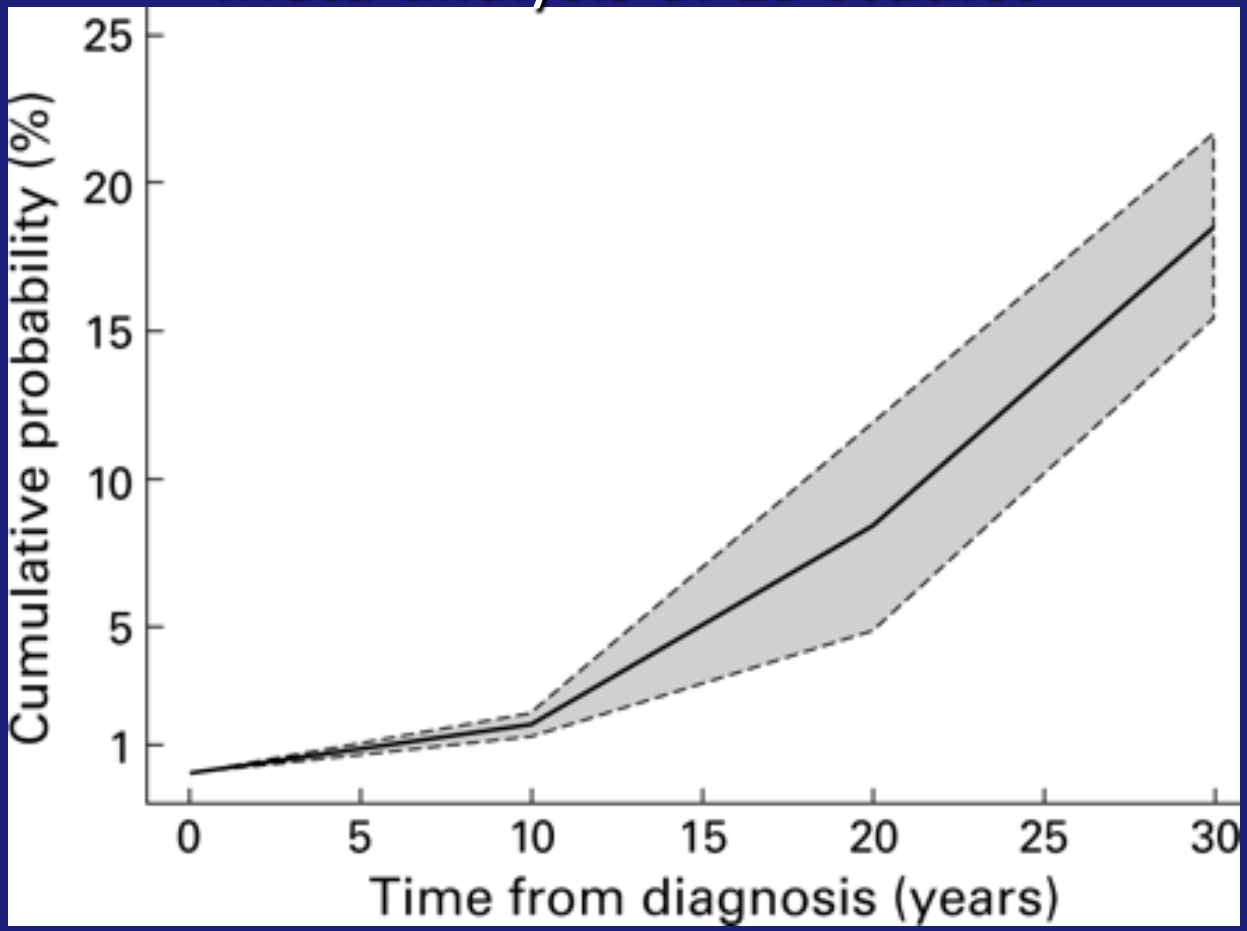


Molodecky MA. Gastroenterology 2012;142:46-54

Loftus EV. Gastroenterology 2004;126:1504

Cumulative Incidence CRC in UC

Meta-analysis of 19 studies



Total Colitis Cumulative Risk

10 years - 2.1%

20 years - 8.5%

30 years - 17.8%

Eaden at a. Gut 2001;48(4):526-35

Chronic Inflammation - Culprit?

- 68 patients with neoplasia detected during surveillance
- 136 controls matched on age at onset, duration of colitis, extent of colitis, and sex
- Univariate
  - Endoscopic inflammation OR=5.33 (2.0-14.2)
  - Histologic inflammation OR=6.98 (2.4-20.2)
- Multivariable
  - Histologic inflammation OR=5.40 (1.8-16.0)

Rutter M, et al. Gastroenterology 2004:126:451-9