Diet and Microbiome Influences on Breast Cancer Risk

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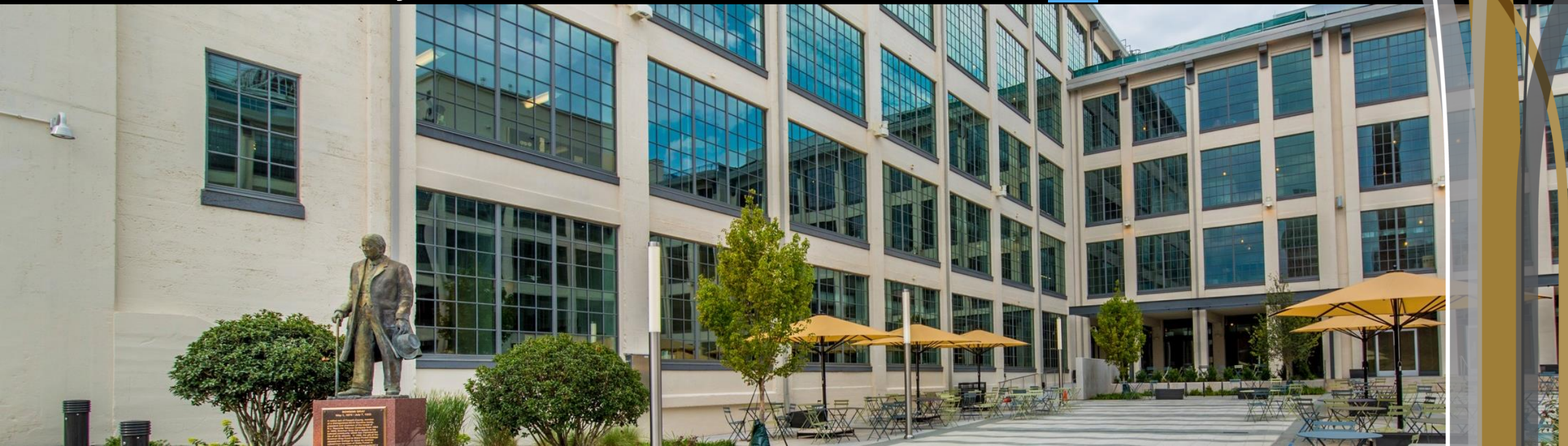
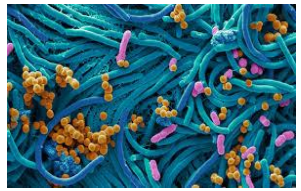
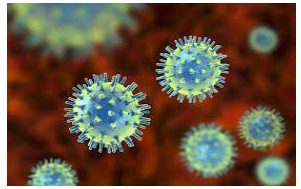
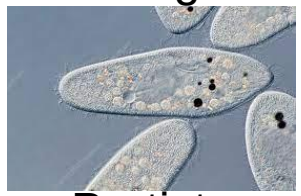


Microbiome

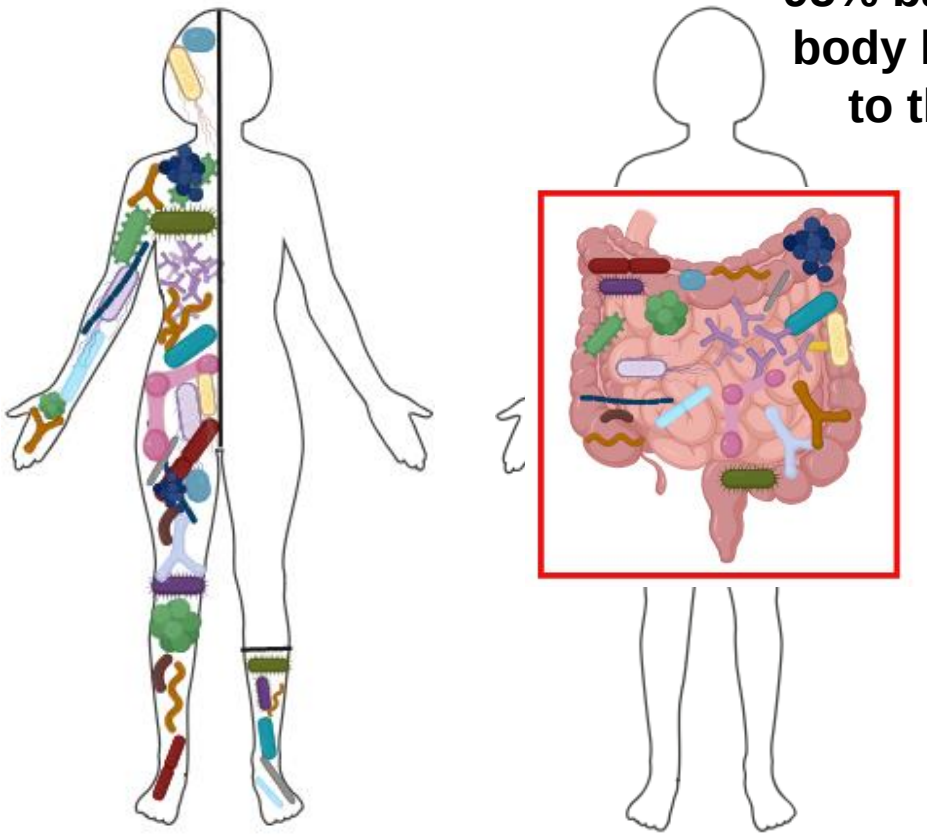

Bacteria


Viruses


Fungi

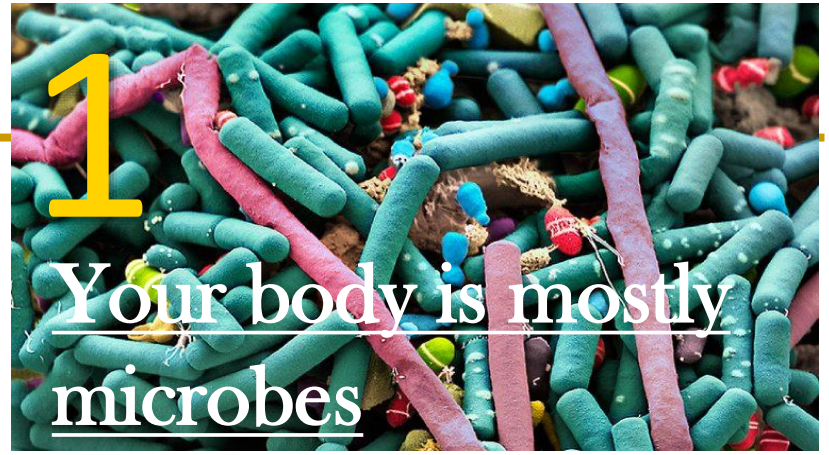

Protists

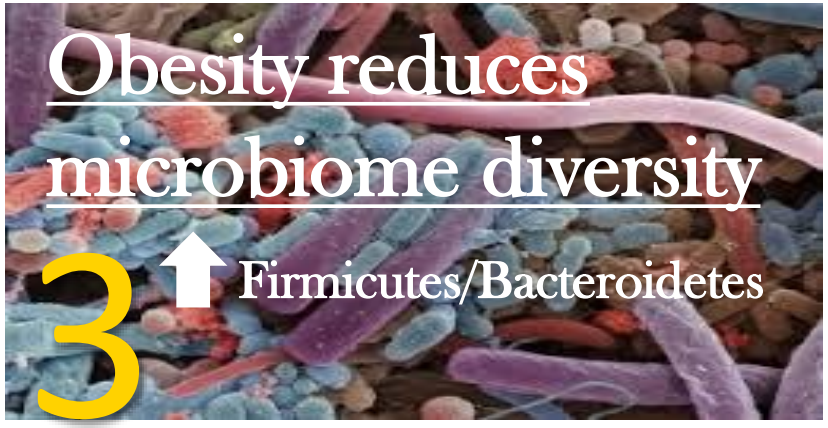

Phages



95% bacteria in body localized to the gut

39 trillion bacteria cells: 30 trillion human cells
Our body is only 43% human!

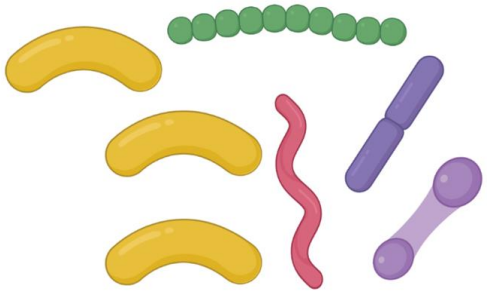




Good to know microbiome terms and explanations

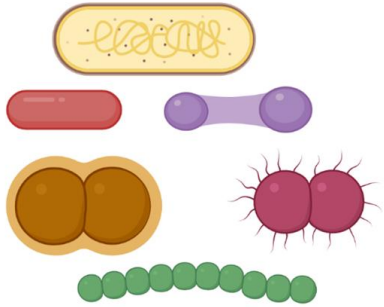
Alpha-diversity: richness measure/total number of different microbes in a sample

Sample 1



5 different types of bacteria

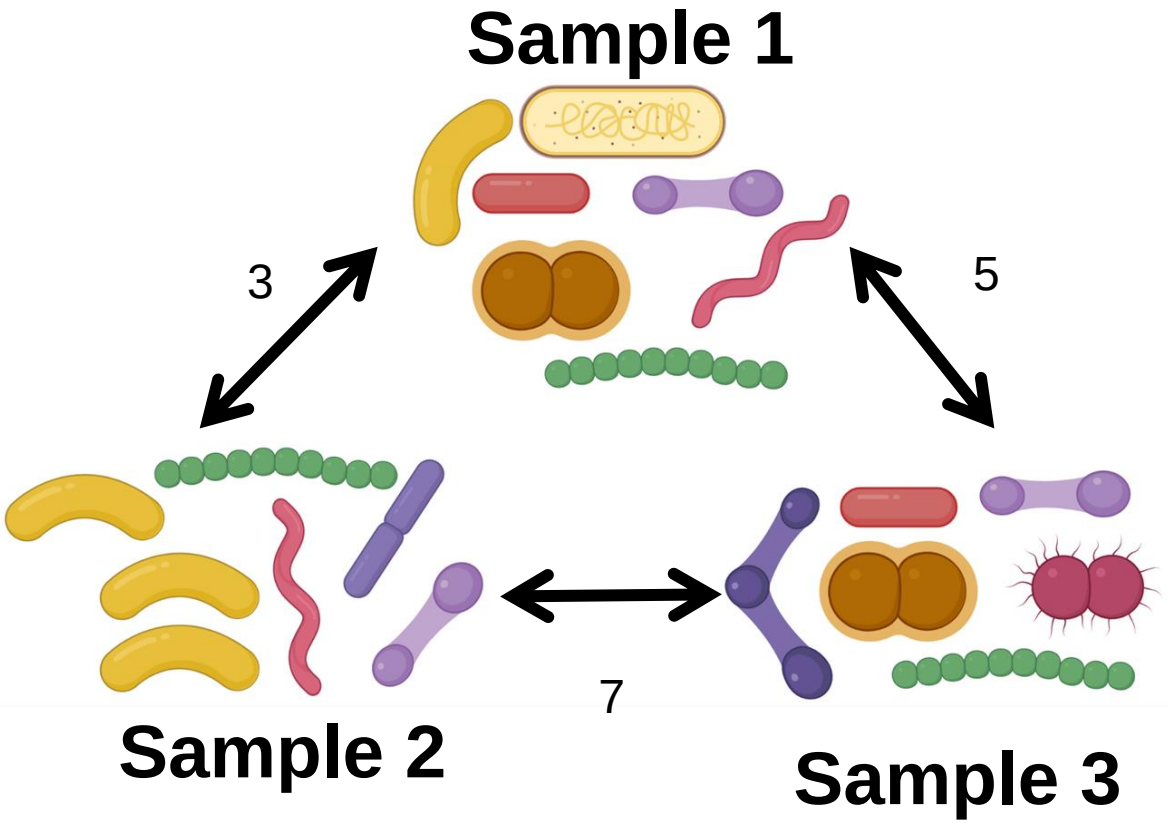
Sample 2



6 different types of bacteria

Sample 2 has a higher α-diversity

Beta-diversity: difference in communities of microbes



Samples 2+3 are the most different from each other and have a higher β-diversity

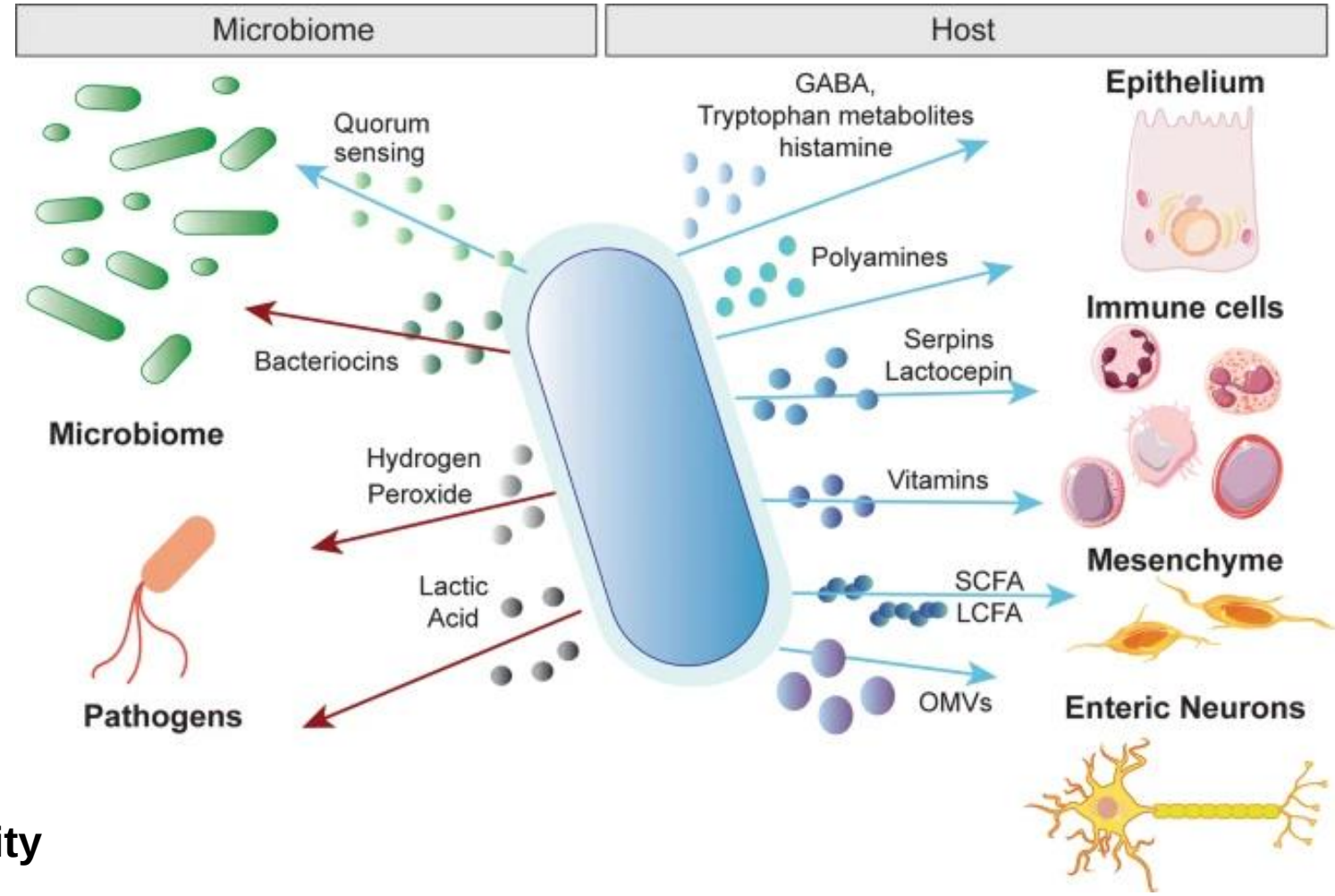
Functions of a healthy gut bacterial microbiome

Internal microbiome control

Protection from pathogens & infections

Prevention of allergies

Improved gut motility



Modulation of central nervous system

Immune system development

Synthesis of vitamins

Insulin/glucose homeostasis

Ruan et. al., 2020

What shifts your gut bacterial microbiome?

Consumption of a high saturated fat diet increases Firmicutes phyla

Mediterranean diet consumption associated with increased Bacteroidetes phyla

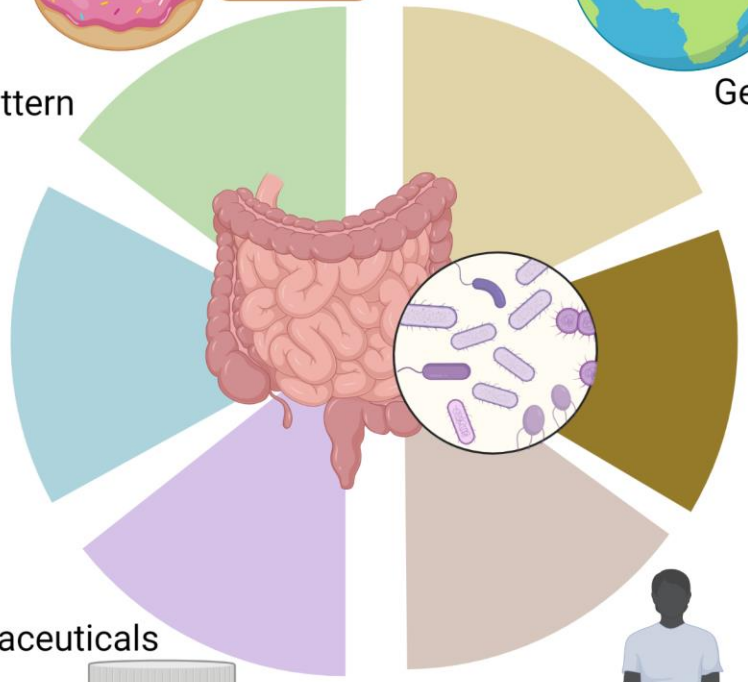
Dietary pattern

Urbanization associated with decreases in gut diversity

Geography

Moderate exercise increases gut diversity

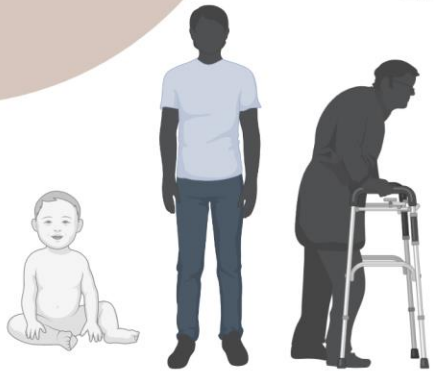
Exercise



Early-life factors

Pharmaceuticals

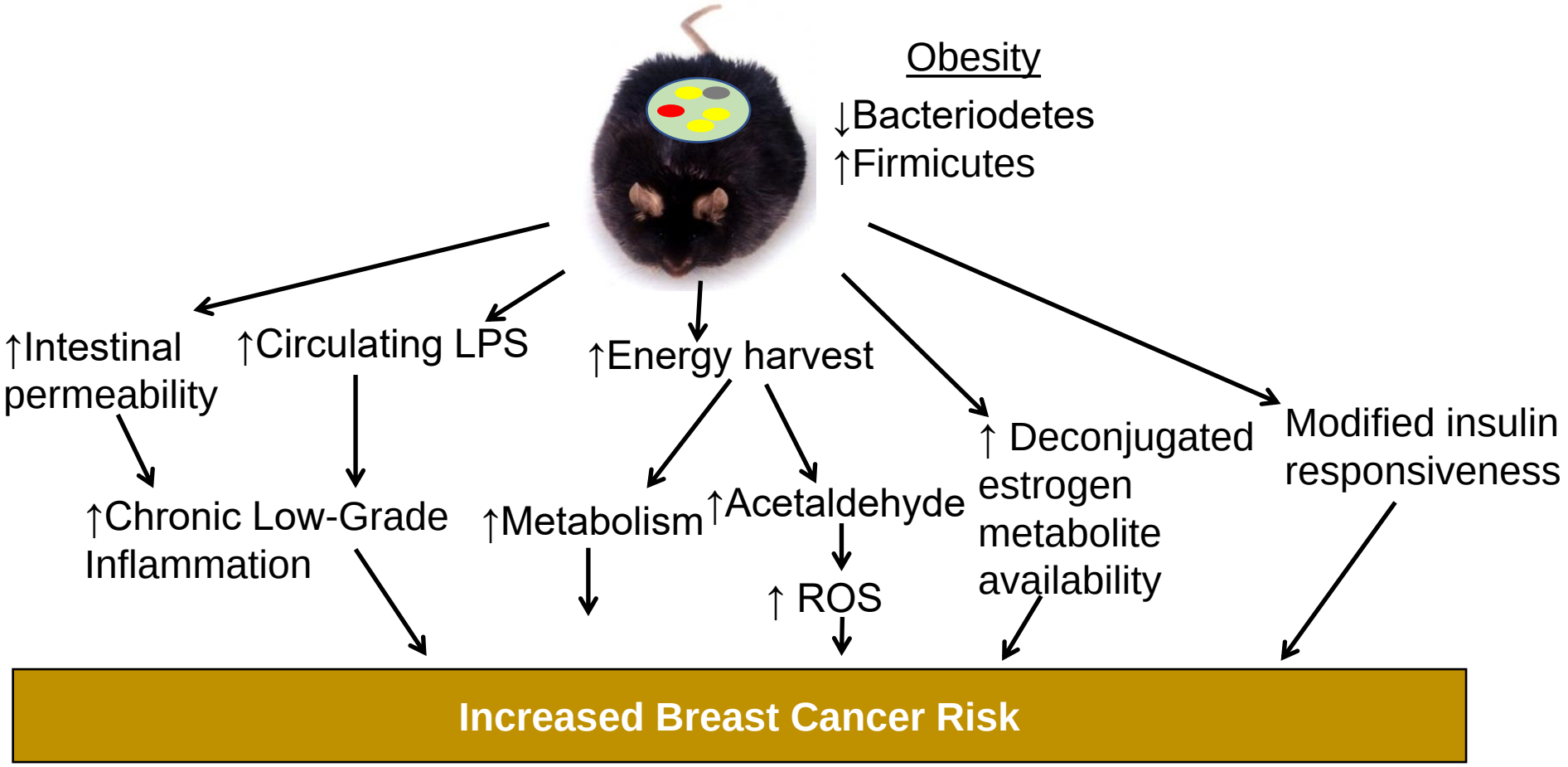
Commonly used drugs such as proton pump inhibitors, metformin, selective serotonin reuptake inhibitors and laxatives influence gut microbiome composition.



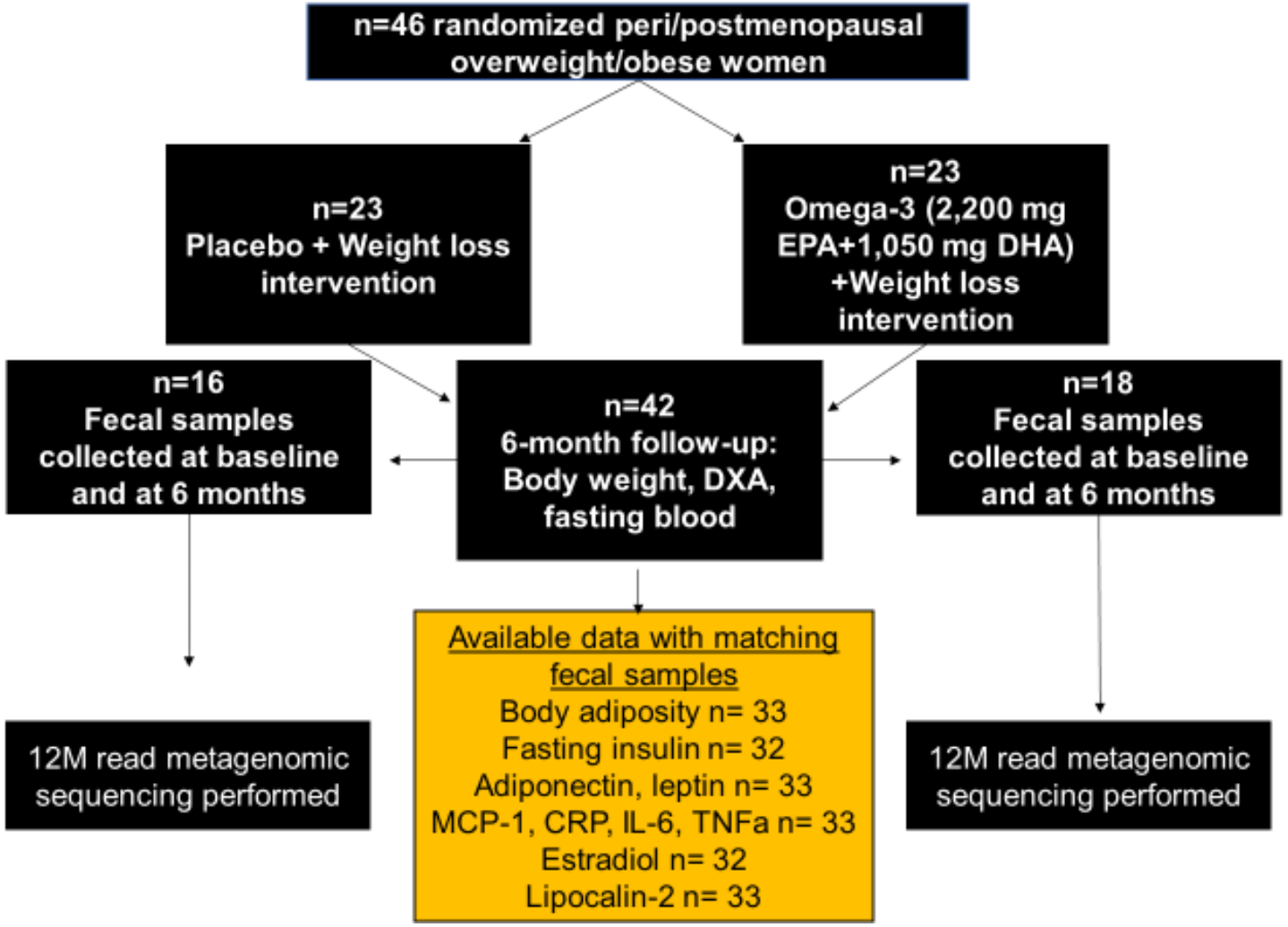
Lifecycle stage

Firmicutes and Proteobacteria phyla increases in elderly populations

How the gut microbiome composition may affect breast cancer risk



Exploring the gut microbiome for breast cancer prevention

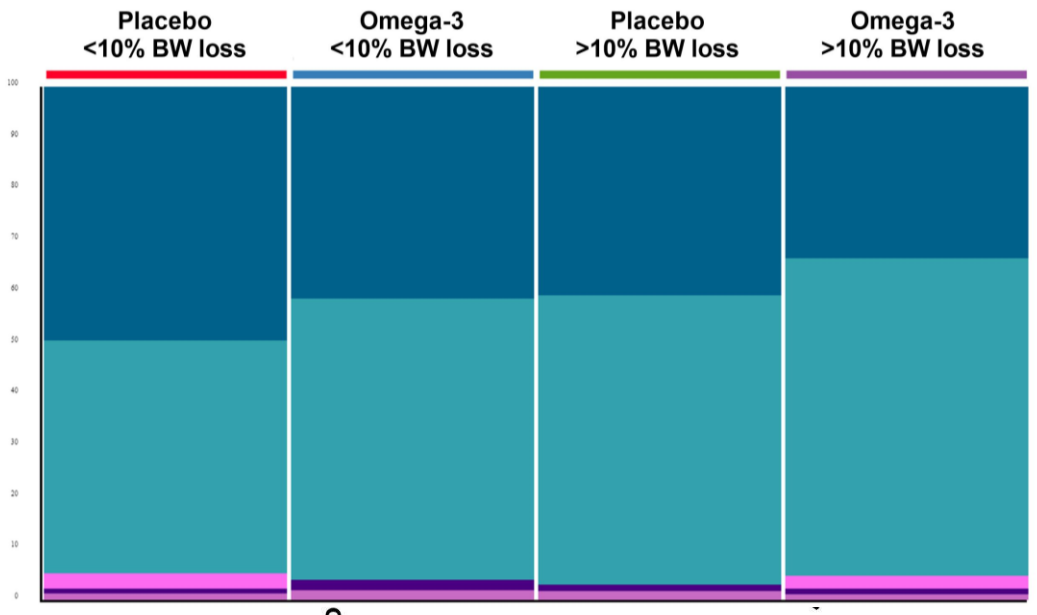


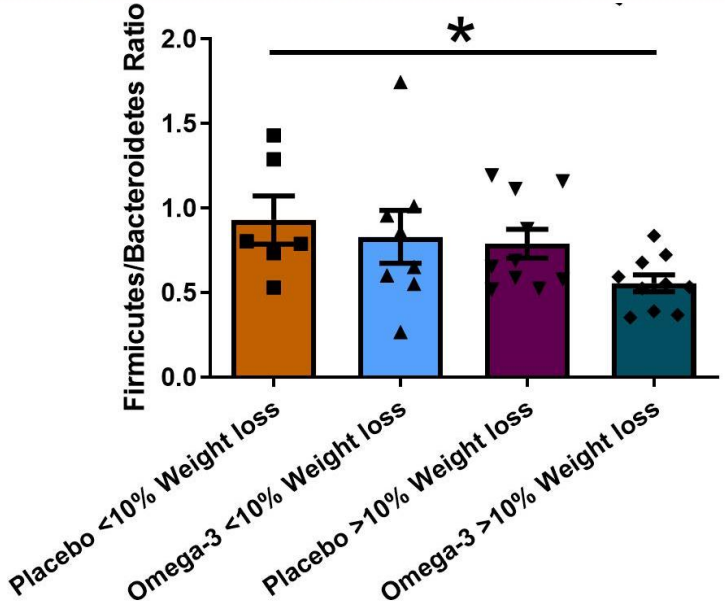
	Placebo n=16	Omega-3 PUFA n=18
Age, years	52.7 ± 5.7 (45-63)	51.8 ± 7.0 (43-64)
BMI baseline, kg/m^2	31.7 ± 3.3 (28-40)	32.2 ± 3.6 (28-42)
% Body fat composition	46.5 ± 4.5 (37.4-54.9)	48.0 ± 3.2 (42.2-51.7)
10-year Tyrer-Cuzick model, % risk	12.0 ± 8.5 (6.2-37)	9.1 ± 4.8 (1.9-19)

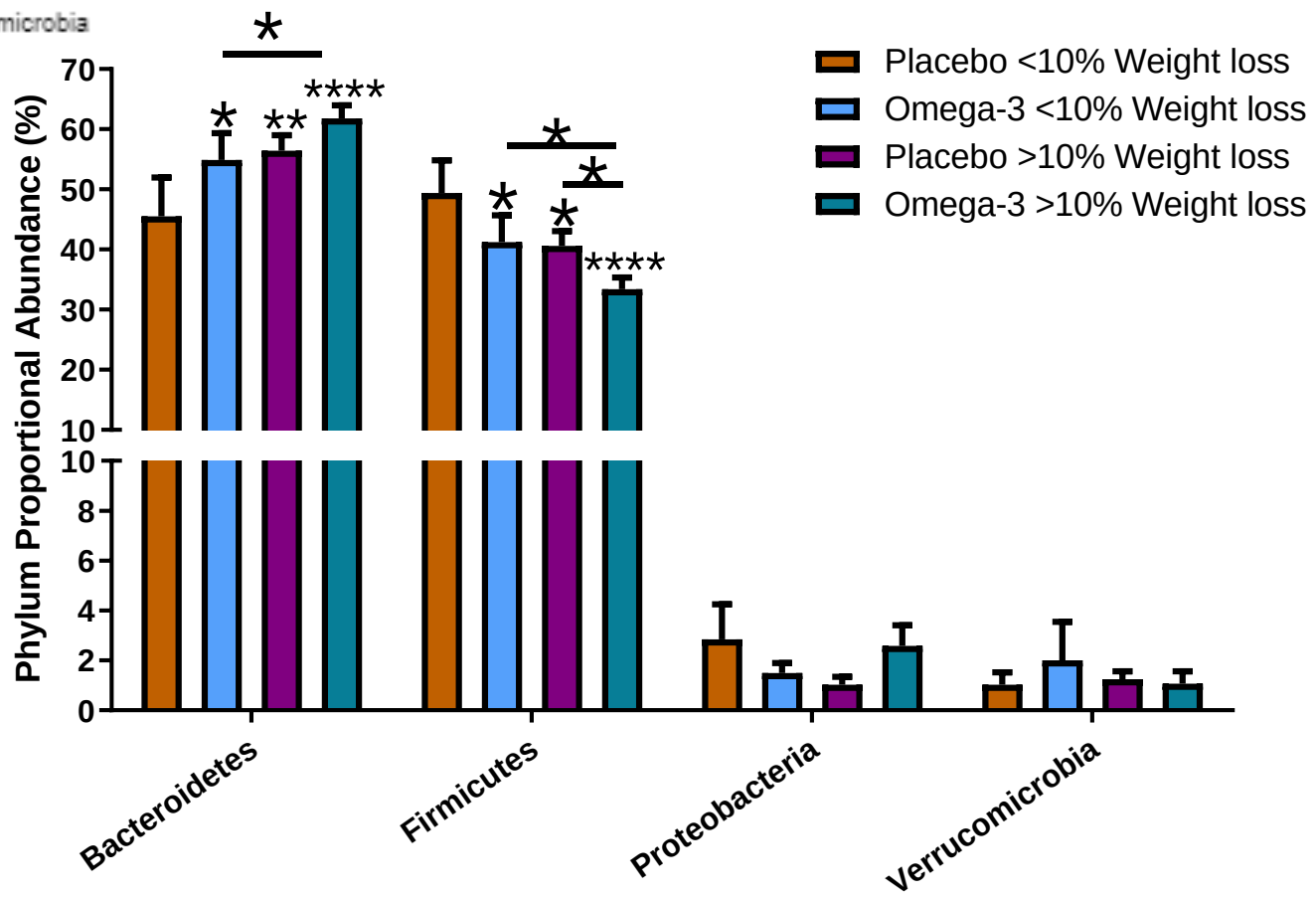
No significant differences between groups at baseline in patients with collected fecal samples

Fabian et. al., *Prevent Cancer Research* 2021

Weight loss and omega-3 supplementation interactions on the phyla level microbiota abundances



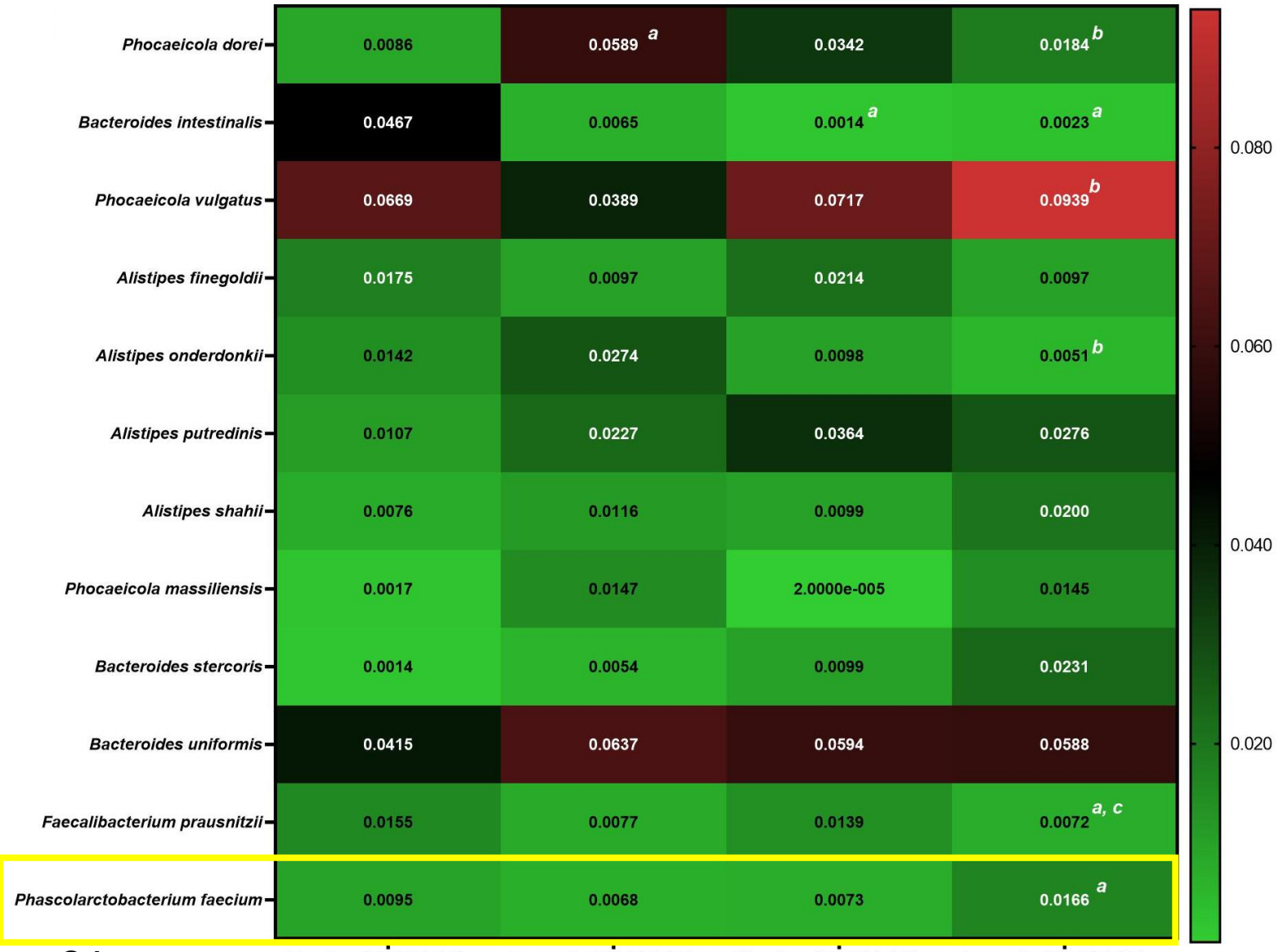




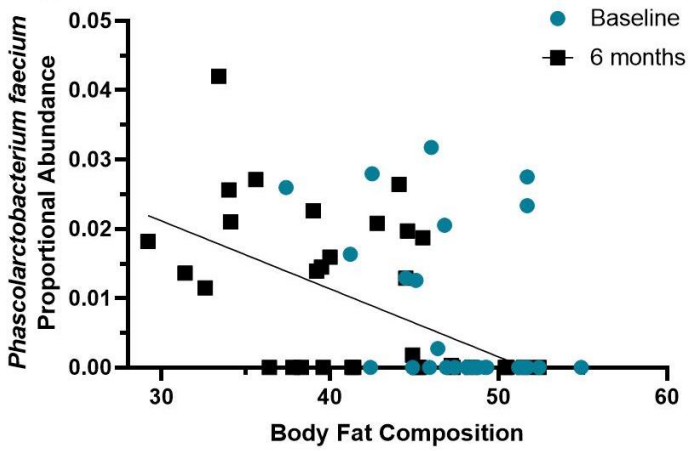
n=7-10; *p<0.05

Cook et. al., unpublished data

Weight loss and omega-3 supplementation interactions on select microbiota species

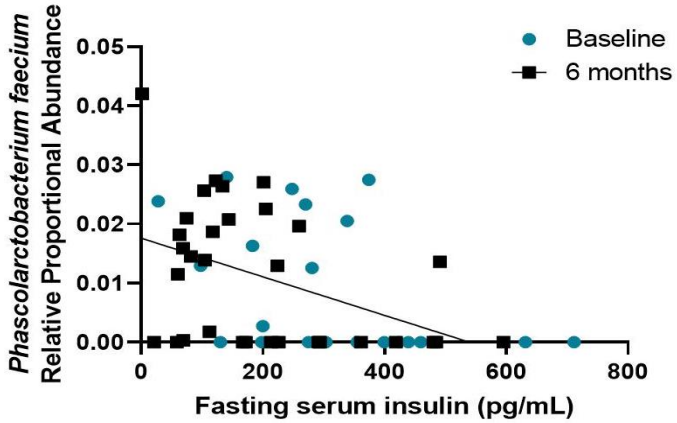


n=34



Pearson correlations:

	Baseline	Endpoint	Combined
r =	-0.38	-0.52	-0.45
p =	0.06	0.002	0.0004

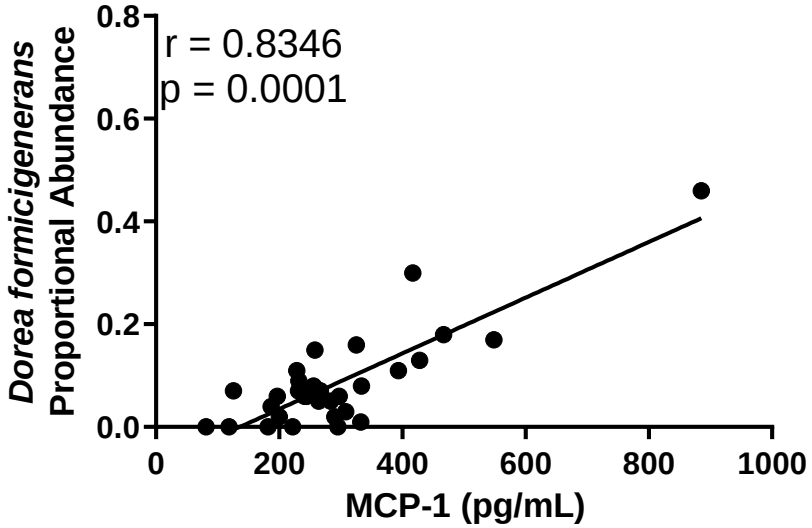


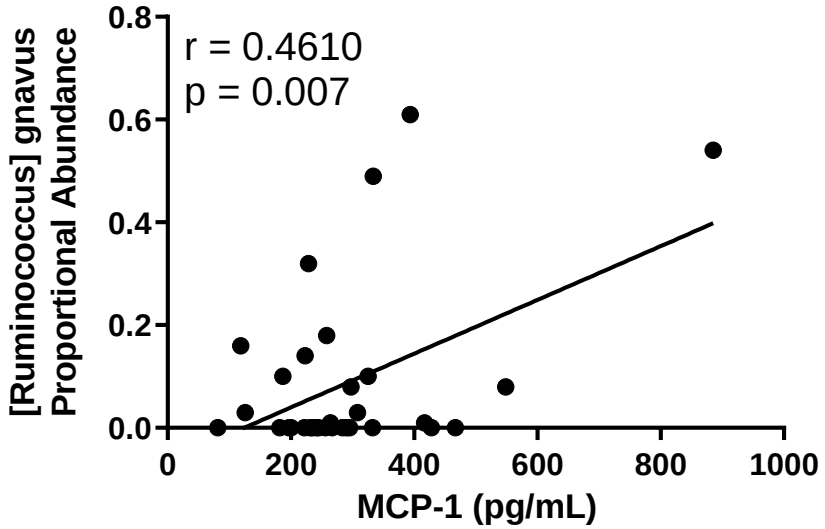
Pearson correlations:

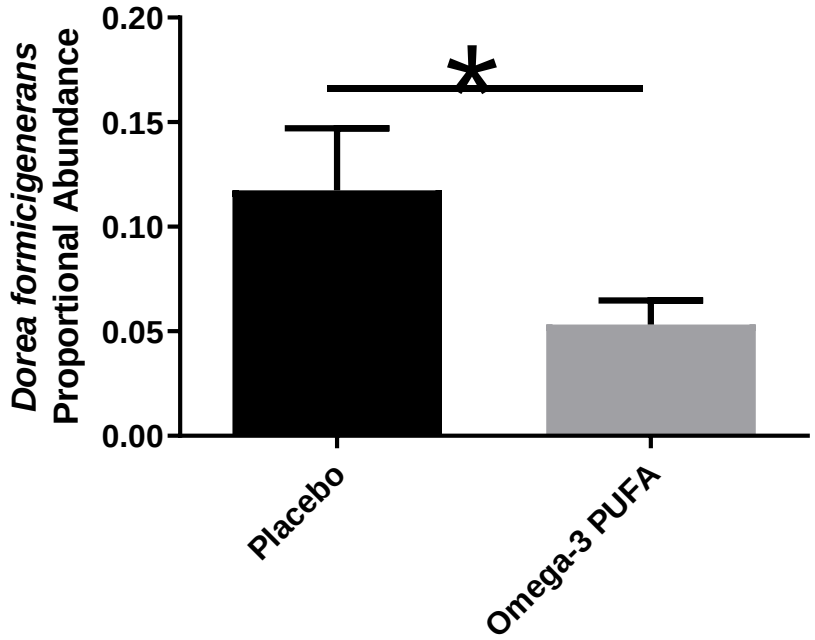
	Baseline	Endpoint	Combined
r =	-0.384	-0.428	-0.422
p =	0.070	0.014	0.0013

Cook et. al., unpublished data

Omega-3 PUFA supplements modulates inflammation associated microbes







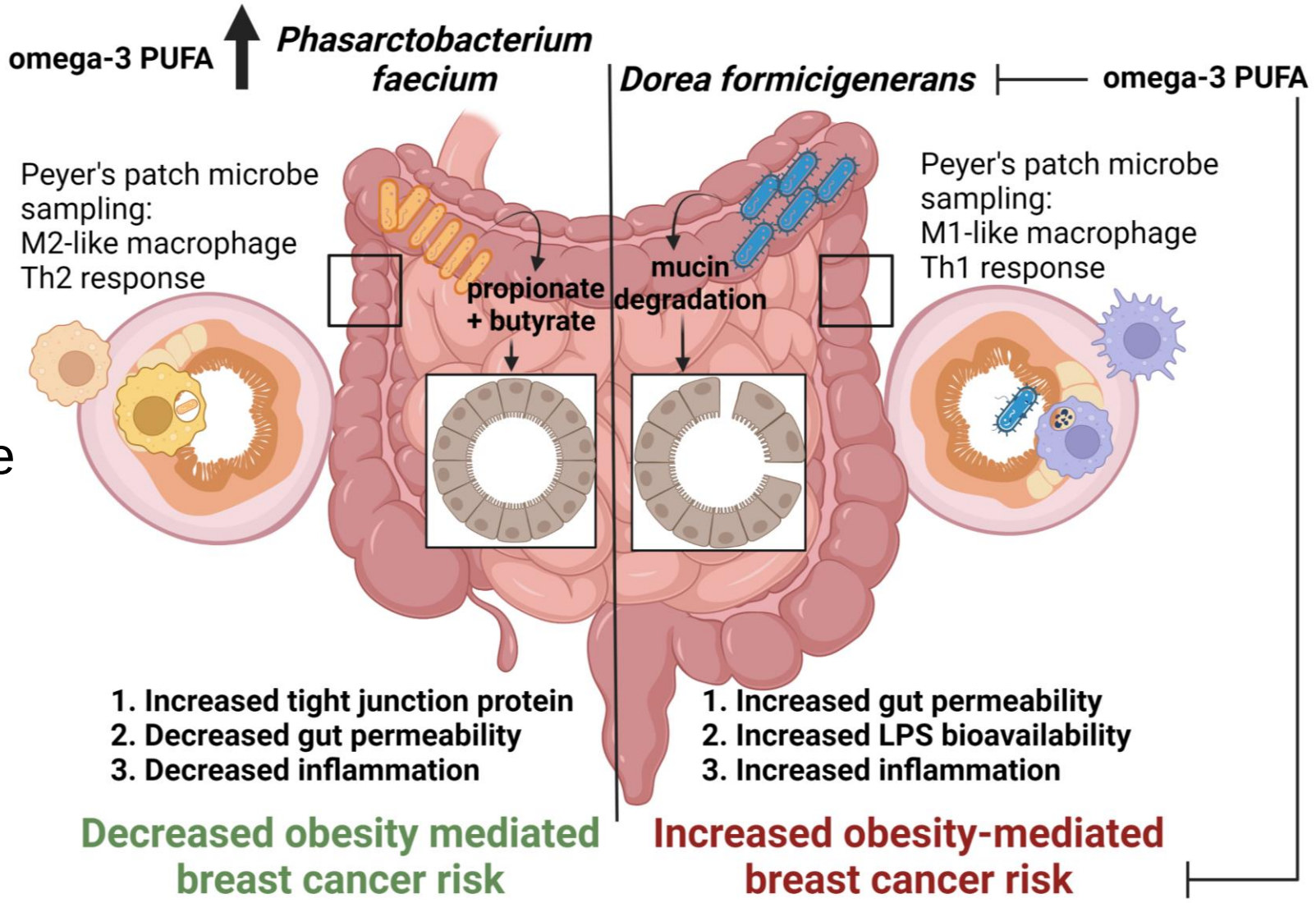
Previous European cohort (n=53) showed a positive correlation between gut *D. formicigenerans* and circulating C-reactive protein in obese postmenopausal women (Brahe et. al., *Nutrition and Diabetes* 2015

n=16-18; *p<0.05

Cook et. al., unpublished data

Snap-shot summary

- Omega-3 PUFA regardless of weight loss reduces inflammation-associated *D. formicigenerans*
- Omega-3 PUFA and >10% weight loss interact to significantly decrease Firmicute phyla proportional abundance compared with all other groups
- Omega-3 PUFA and >10% weight loss interact to increase metabolic health associated microbe *P. faecium*



The breast microbiome and cancer

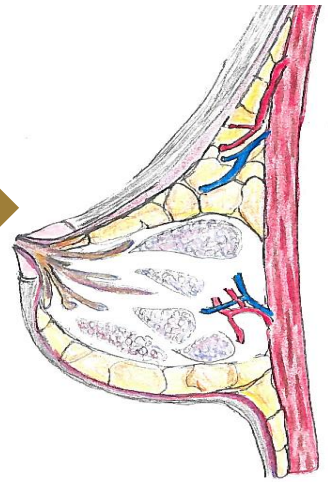
- **Microbiota of human breast tissue**. Urbaniak et al, 2014

Microbiota Genus	Canadian breast tissue (% of microbiota population)	Irish breast tissue (% of microbiota population)
Bacillus	11.4%	<2%
Acinetobacter	10%	<2%
Enterobacteriaceae	8.3%	30.8%
Pseudomonas	6.5%	5.3%
Staphylococcus	6.5%	12.7%
Propionibacterium	5.8%	10.1%
Prevotella	5%	<2%
Listeria	<2%	12.1%

- **The microbiota of breast tissue and its association with breast cancer.** Urbaniak et al, 2016
  - Increased Staphylococcus in breast tissue from women with BC when compared with healthy controls

- **The microbiome of aseptically collected human breast tissue in benign and malignant disease.** Hieken et al, 2016
  - Decreased Lactobacillus in breast tissue from women with malignant BC

Since diet is main determinant of the gut microbiome, can what you eat modify you breast microbiome?



10-fold increase in MG *Lactobacillus* (genus) proportional abundance

Newman *et al. Microbiome* (2021) 9:100
https://doi.org/10.1186/s40168-021-01069-y

Microbiome

RESEARCH Open Access

Diet, obesity, and the gut microbiome as determinants modulating metabolic outcomes in a non-human primate model

Tiffany M. Newman[1], Carol A. Shively[2], Thomas C. Register[2], Susan E. Appt[2], Hariom Yadav[3,4], Rita R. Colwell[5], Brian Fanelli[5], Manoj Dadlani[5], Karlis Graubics[5], Uyen Thao Nguyen[6], Sivapriya Ramamoorthy[6], Beth Uberseder[2], Kenysha Y. J. Clear[7], Adam S. Wilson[7], Kimberly D. Reeves[4], Mark C. Chappell[7], Janet A. Tooze[8,9] and Katherine L. Cook[1,7,8,10*]

Cell Reports
Article

Consumption of Mediterranean versus Western Diet Leads to Distinct Mammary Gland Microbiome Populations

Carol A. Shively,[1] Thomas C. Register,[1] Susan E. Appt,[1,3] Thomas B. Clarkson,[1,6] Beth Uberseder,[1] Kenysha Y.J. Clear, Adam S. Wilson,[2] Akiko Chiba,[2,3] Janet A. Tooze,[4] and Katherine L. Cook[2,3,5,7,*]

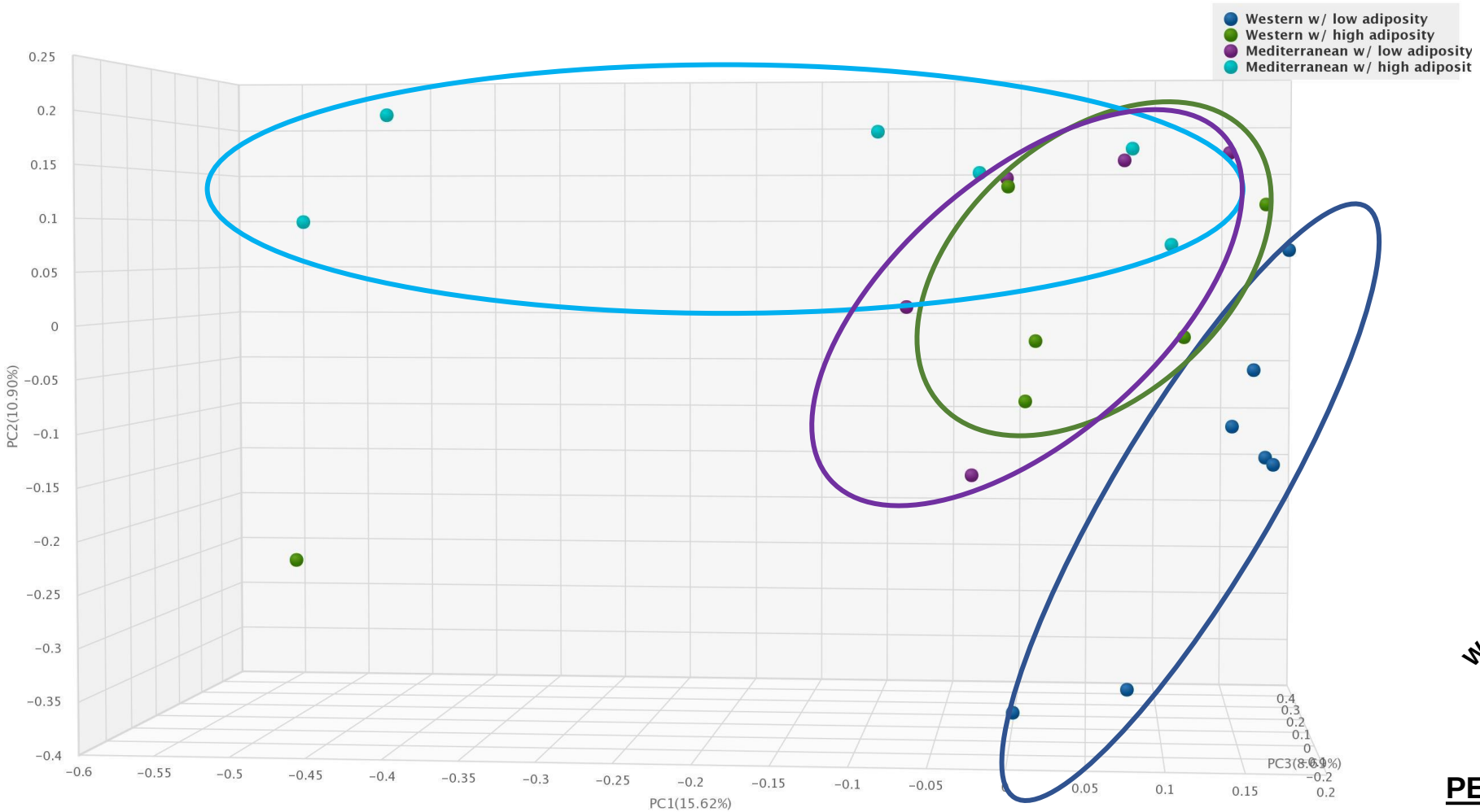
Detangling obesity and diet using NHP cohort

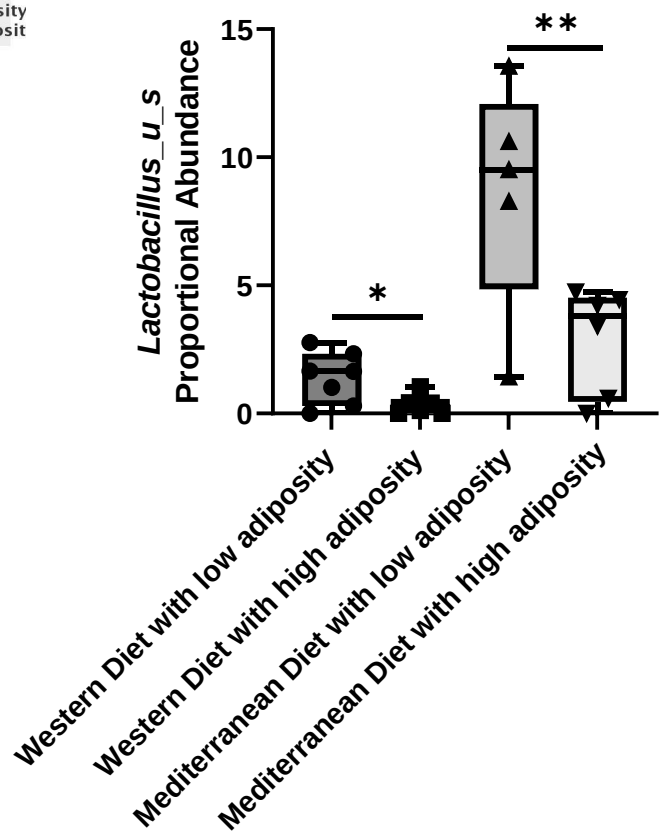
Table 1. Metabolic Parameters by Body Weight Group. Values represent mean ± standard deviation.

	Mediterranean-Lean (n=7)	Mediterranean-Heavy (n=7)	Western-Lean (n=7)	Western-Heavy (n=8)
BW (kg)	2.5±0.2	4.1±1.0	2.7±0.2	4.9±1.2
BMI (kg/m^2)	36.7±4.2	48.2±6.9	39.7±4.5	60.2±10.4
Body Fat Composition (%)	8.4±2.0	23.4±9.0	11.7±4.3	39.1±10.5
Insulin AUC	1721±335	6456±5703	3431±4043	10526±8427
TPC (mg/dL)	133.4±29.4	163.7±48.0	159.5±33.1	149.9±28.5
HDL-C	48.6±8.6	66.7±29.8	78.4±40.6	72.1±17.2
TPC/HDL-C ratio	2.78±0.50	2.62±0.46	2.38±0.95	2.13±0.16
Cortisol	36.5±4.2	29.3±5.6	33.7±8.8	41.1±5.7

Cook et. al., unpublished data

Diet and adiposity interact to shift NHP breast microbiome





n=5-7; *p<0.05; **p<0.01

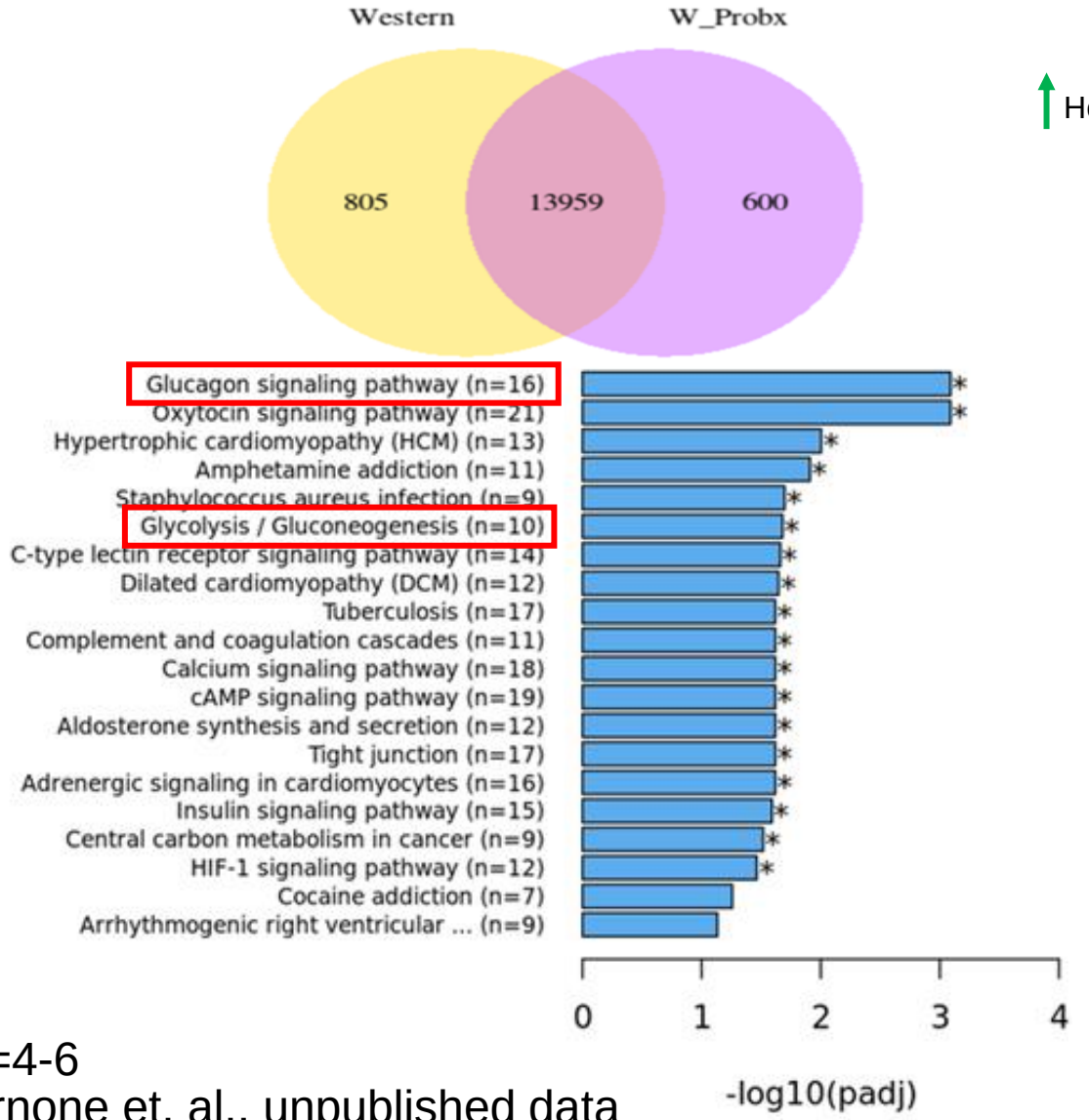
Cook et. al., unpublished data

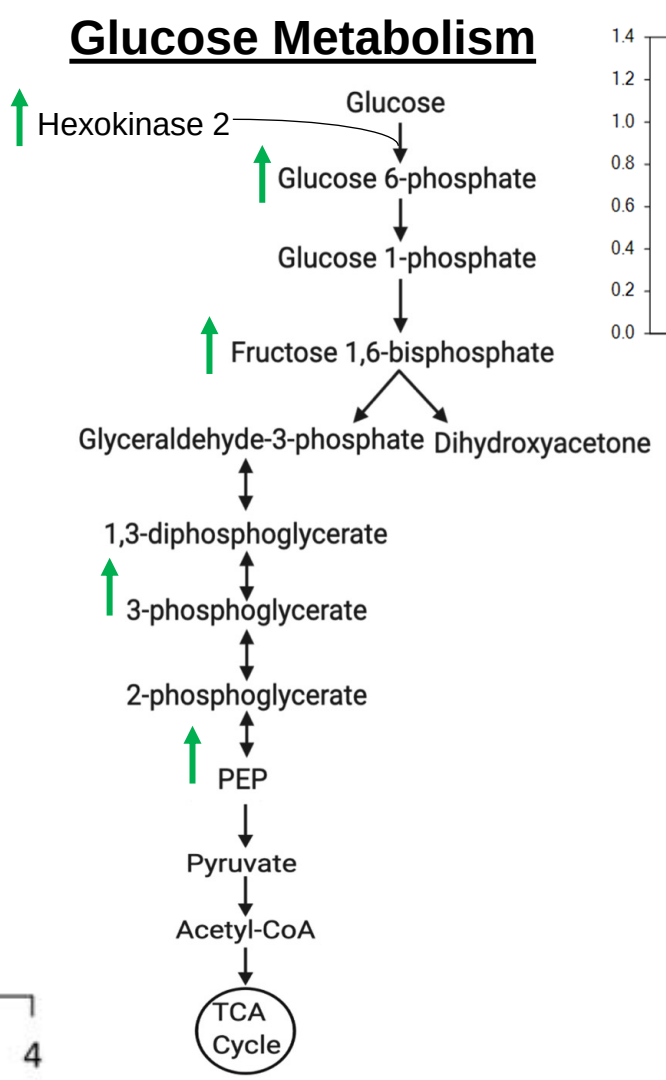
PERMANOVA Analysis

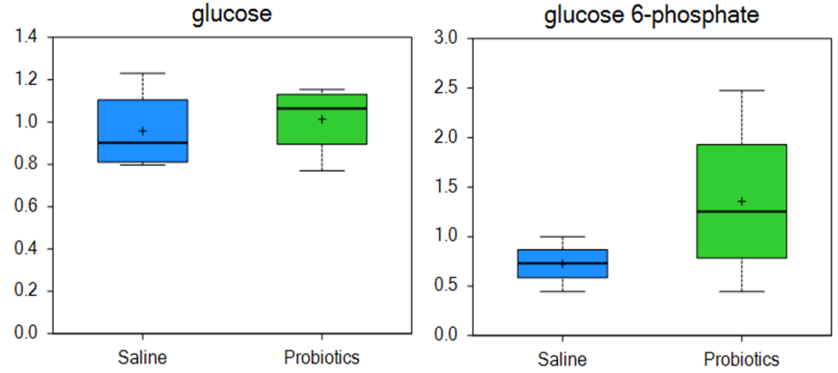
Western + low adiposity vs Western + high adiposity p=0.006

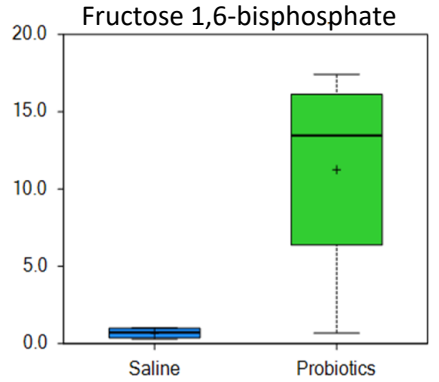
Western + low adiposity vs Mediterranean + low adiposity p=0.013

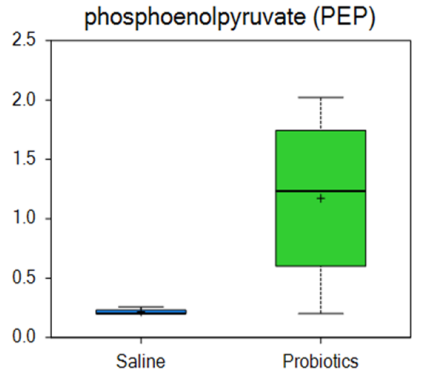
Elevating mammary gland *Lactobacillus* modifies tissue metabolism









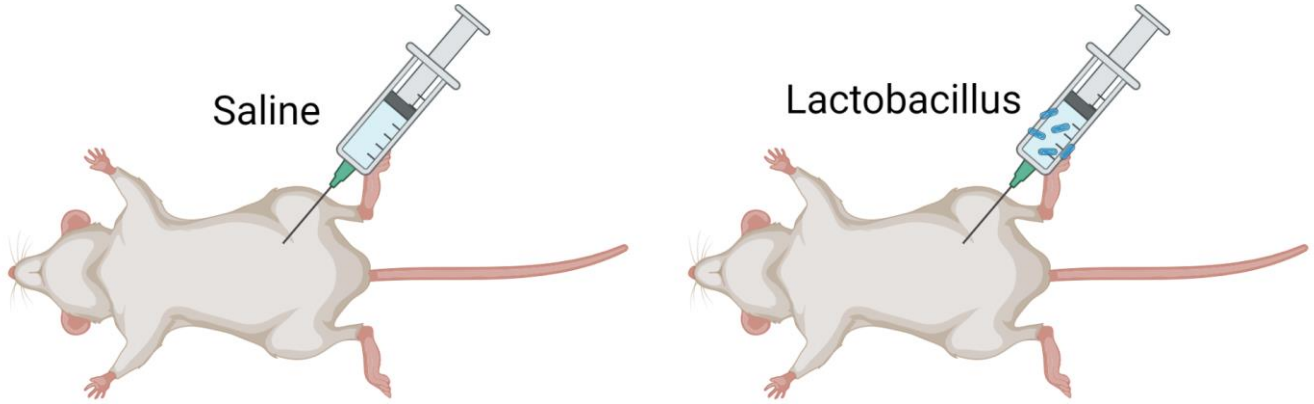


n=4-6

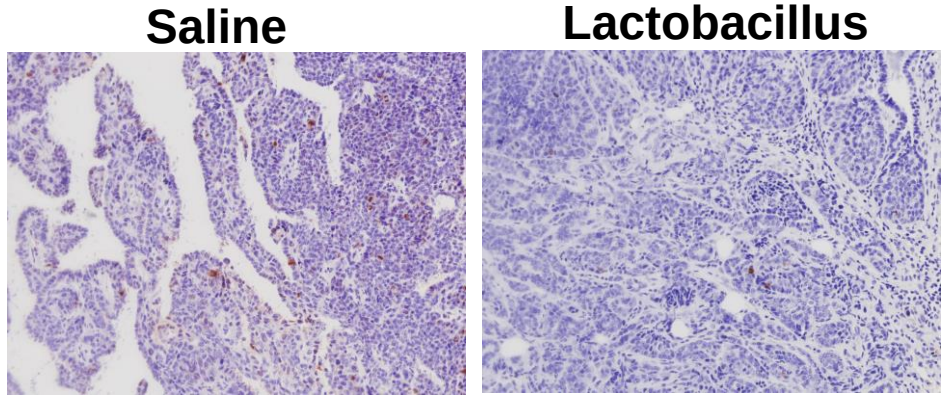
Arnone et. al., unpublished data

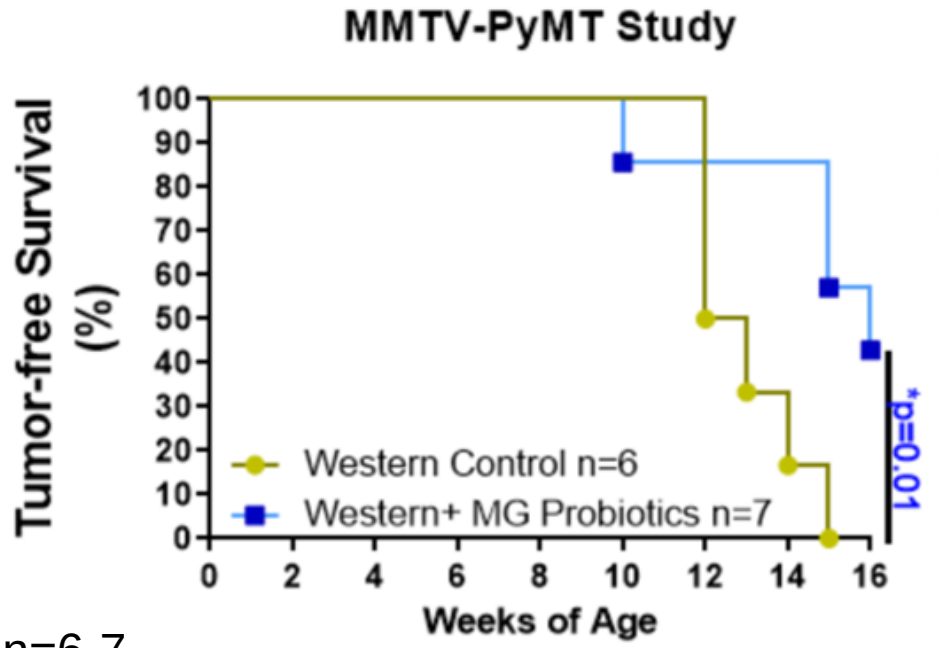
Mammary gland *Lactobacillus* reduces tumorigenesis

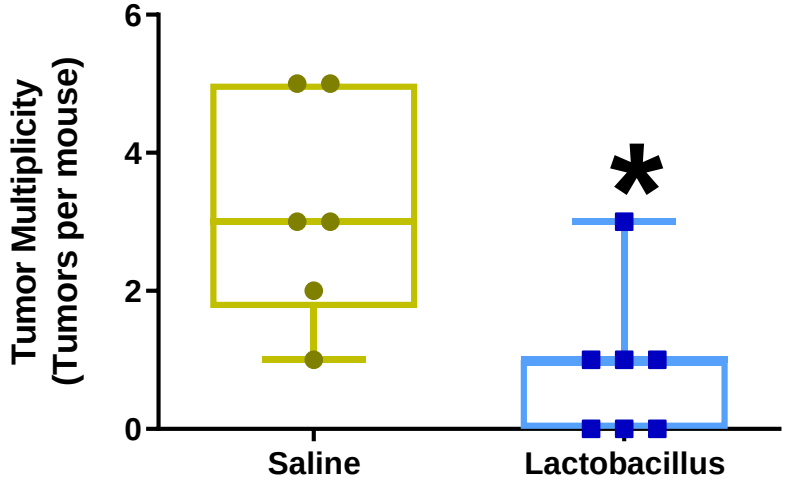
MMTV-PyMT Mammary Carcinogenesis Model

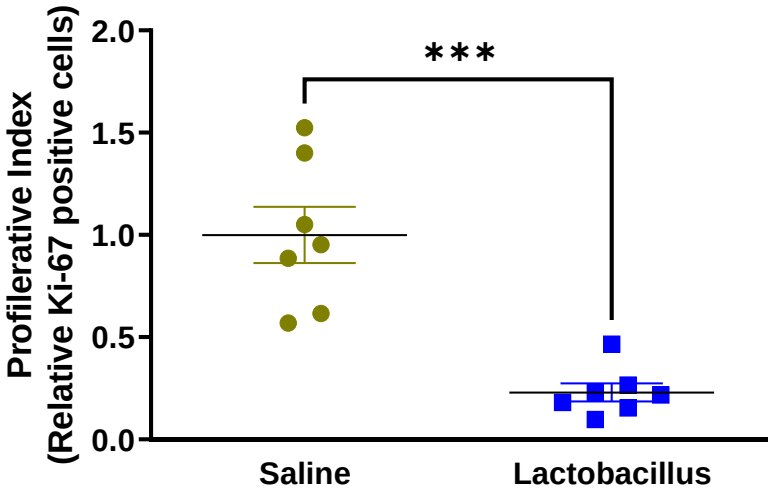


Ki67 Tumor Proliferation









n=6-7

Arnone et. al., unpublished data

Conclusions

- We have identified several pro-health associated species (such as *P. faecium*) that may be a potential novel probiotic to reduce metabolic breast cancer risk factors.
- Diet and adiposity interact to influence the breast tissue microbiome.
- Lower body fat composition was associated with increased breast *Lactobacillus* populations in NHP cohort regardless of dietary pattern.
- Mammary gland *Lactobacillus* enhances normal tissue glucose metabolism.
- Mammary gland *Lactobacillus* prevents breast tumorigenesis and decreased tumor proliferation in a MMTV-PyMT murine model.
- Both the gut and breast microbiome may be a modifiable target for breast cancer prevention.

Thank you!

Thank you to all the patients that participate in clinical trials and donate their samples!

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Questions?