

Parkinson's, Diet and the Gut-Brain Connection

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Disclosures

- Speaker is an employee within Medical Affairs & Research at Abbott Nutrition
- This program is not intended for individual medical advice or continuing education credits for any healthcare professional

Objectives

1. Learn how the gut microbiome is altered in Parkinson's
2. Discuss the role of the gut-brain axis on Parkinson's disease
3. Review how diet may impact on Parkinson's symptoms and gut health

My Background in Parkinson's Disease

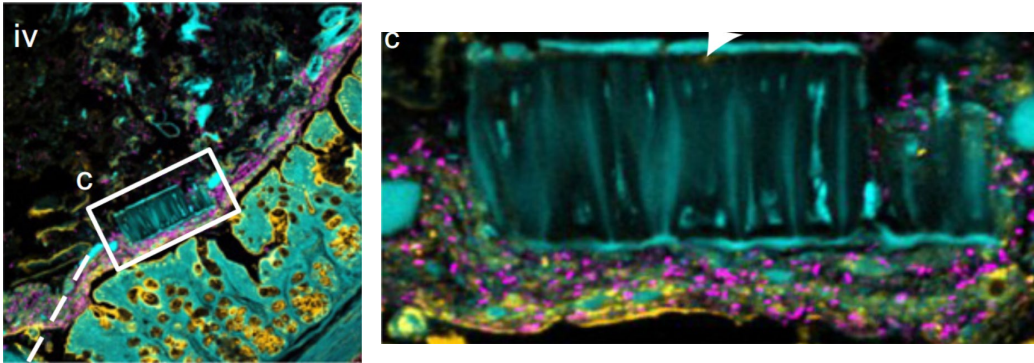


Let me know whether you are a:

- Person with Parkinson's/Caregiver
- Physician
- Advanced Practice Provider (PA, NP)
- Nurse
- Dietitian
- Rehab Provider (PT, OT, SLP)
- Researcher
- Other

Parkinson's, Diet and the Gut-Brain Connection

GUT MICROBIOME AND THE GUT-BRAIN AXIS



Mark Welch JL, et al. *Proc Natl Acad Sci USA* 2017;114(43):E9105-E9114.

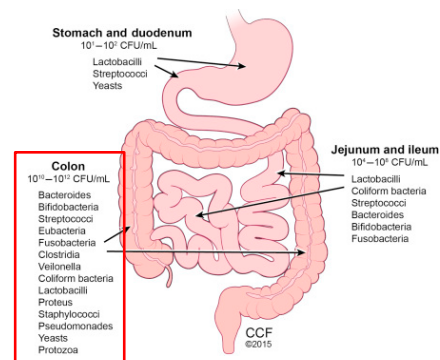
Microbiome Overview

Microbiome = the totality of microorganisms and their collective genetic material present in the intestinal tract

- **Gut Microbiota** = the microorganisms of the intestinal tract (i.e., bacteria, viruses, fungi, and protists)

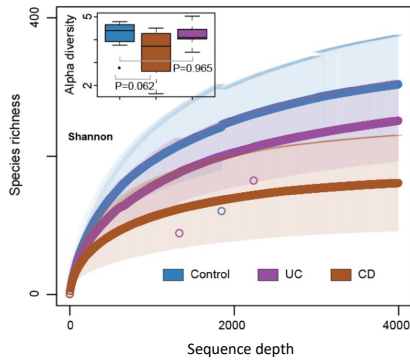
Greatest density and diversity located in the colon

- Up to 10^{12} CFU/ml

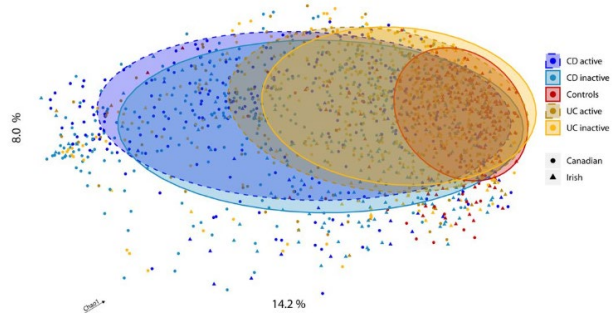


Morgan XC & Huttenhower C. *PLoS Comput Biol.* 2012;8(12):e1002808.

What is a “healthy” gut microbiome?



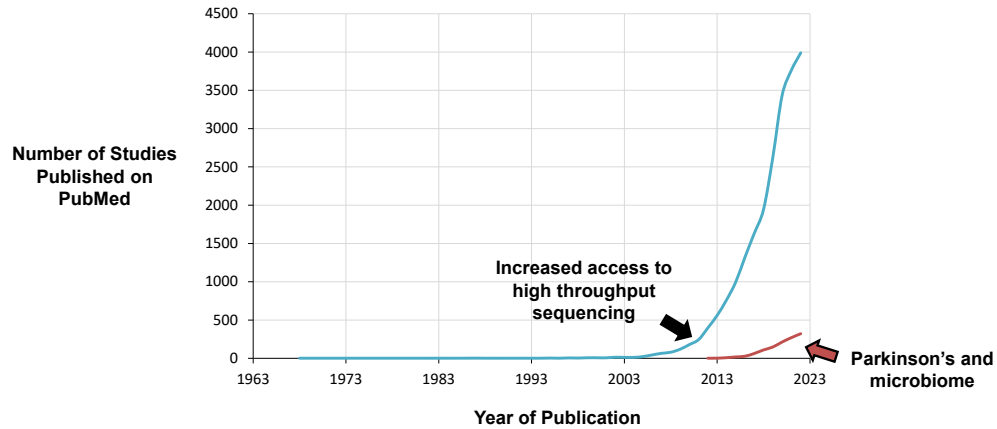
Alam MT, et al. *Gut Pathog.* 2020;12:1.



Clooney AG, et al. *Gut.* 2021;70(3):499-510.



Interest in diet and the microbiome are growing exponentially.



Alpha-synuclein pathology has been documented across the GI tract in PwP¹

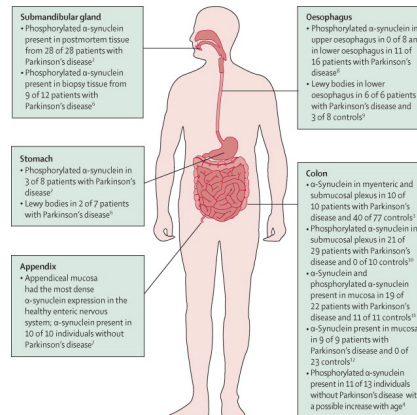
Parkinson's Pathophysiology

Progressive loss of **dopamine neurons** of the substantia nigra pars compacta of the midbrain²

- Estimated 60-70% loss at presentation of motor symptoms (motor stage)

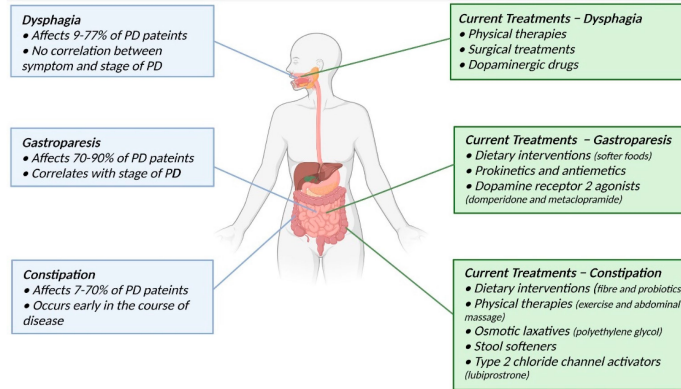
Accumulation of Lewy bodies (aggregated **alpha-synuclein**) are found in the neurons of PwP³

- May trigger loss of neurons (e.g., dopaminergic)
- Also found in other neurodegenerative diseases



PwP: People with Parkinson's
 1. Fasano A, et al. *Lancet Neurol.* 2015;14(6):625-39.
 2. Mhyre TR, et al. *Subcell Biochem.* 2012;65:389-455.
 3. Calabresi P, et al. *Cell Death Dis.* 2023;14(3):176.

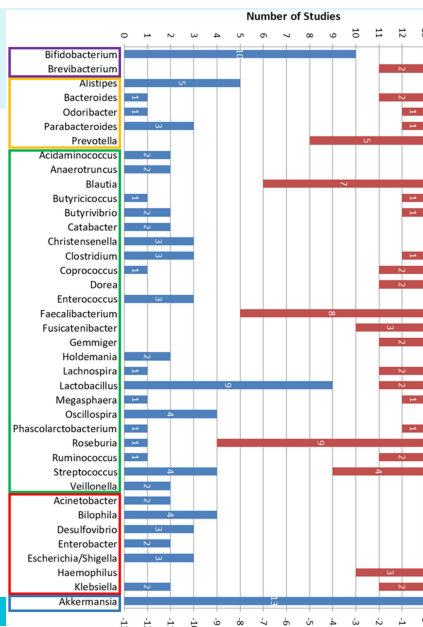
Gastrointestinal dysfunction is common in Parkinson's disease



Han MN, et al. *J Pers Med*. 2022;12(2):144.

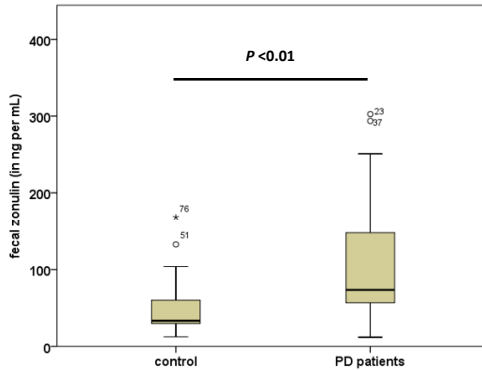
Differences in Microbiota Profiles Across Studies

■ PD > HC
■ PD < HC

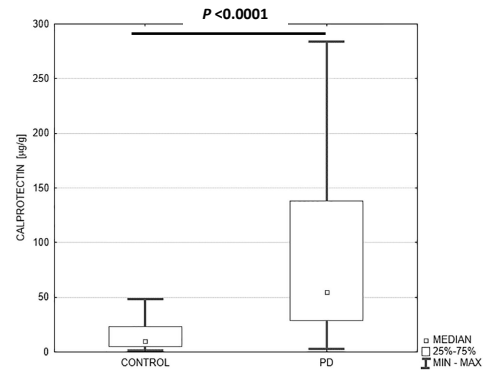


PD: Parkinson's disease
HC: Healthy control
Li Z et al. *CNS Neurosci Ther*. 2023;29(1):140-157.

Markers for intestinal permeability and inflammation are elevated in Parkinson's compared to controls



Schwartz A, et al. *Parkinsonism Relat Disord.* 2018;50:104-107.



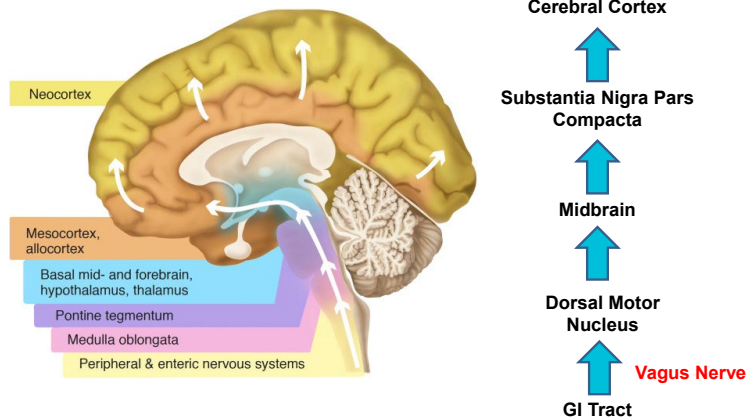
Mulak A, et al. *Front Neurosci.* 2019;13:992.

“Braak To The Future”



Braak's Hypothesis (2003)

Postulated **alpha-synuclein** pathology can spread *from* the gastrointestinal (GI) tract via the vagus nerve → ventral midbrain



Braak H, et al. *Neurobiol Aging.* 2003;24(2):197-211
 Visanji N, et al. *Acta Neuropathol Commun.* 2013;1:2.

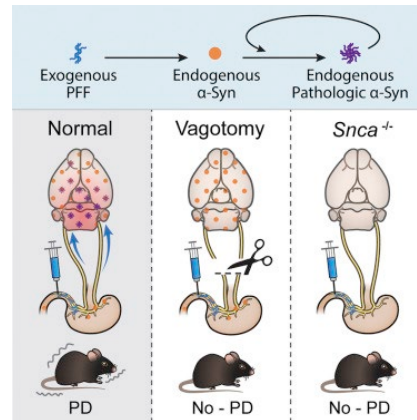
Recent preclinical models suggest a gut-to-brain spread via the vagus nerve

Exogenous preformed fibrils (PFF) of alpha-synuclein were injected into the GI tract of mice

–Measured amount of pathologic α -syn accumulation in the brain

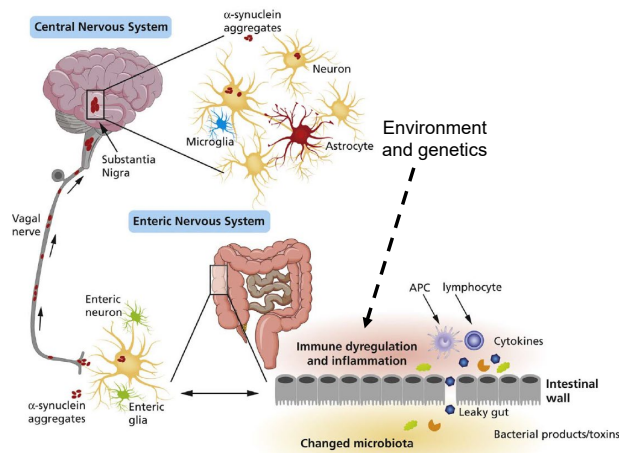
Mice with intact vagal nerves accumulated pathologic alpha-synuclein in the brain (including Substantia nigra) and developed Parkinson's symptoms





Parkinson's-like pathology and symptoms required endogenous alpha-synuclein



Kim S, et al. Neuron. 2019;103(4):627-641.e7

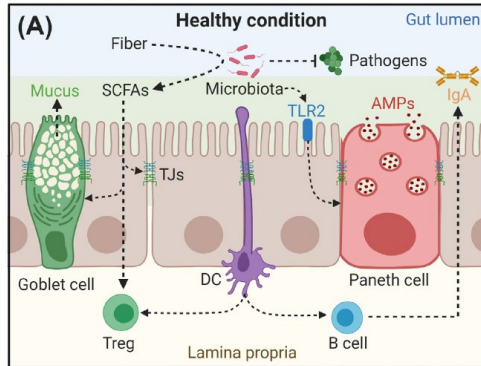
Braak's Hypothesis and the Gut-Brain Axis



-  Beneficial microbes and SCFAs
-  Proinflammatory cytokines
-  LPS, zonulin and calprotectin
-  Intestinal permeability

Perez-Pardo P, et al. Eur J Pharmacol 2017
Houser MC, et al. Mov Disord 2018
Tansey MG, et al. Nat Rev Immunol 2022

Inflammation and barrier integrity are important for gastrointestinal health



Martel J, et al. *Trends Endocrinol Metab.* 2022;33(4):247-265.

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Short-Chain Fatty Acids (SCFA): Butyrate

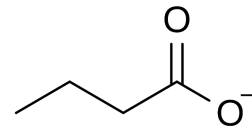


Major energy source for colonocytes

Least abundant SCFA produced by intestinal microbes through fiber fermentation

Butyrate-producing microbes frequently rely on cross-feeding off others

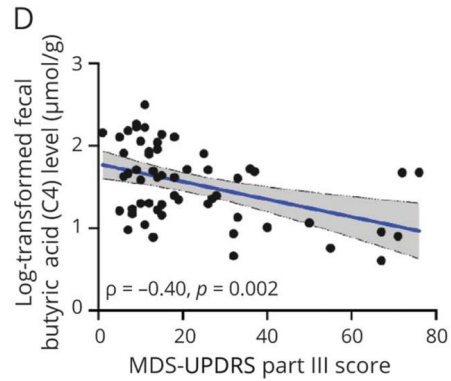
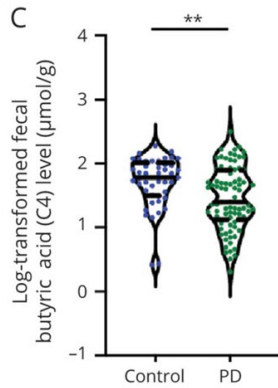
Influence immune function and gene transcription (primarily anti-inflammatory effects)



Fu X, et al. *Crit Rev Food Sci Nutr.* 2019;59(sup1):S130-S152

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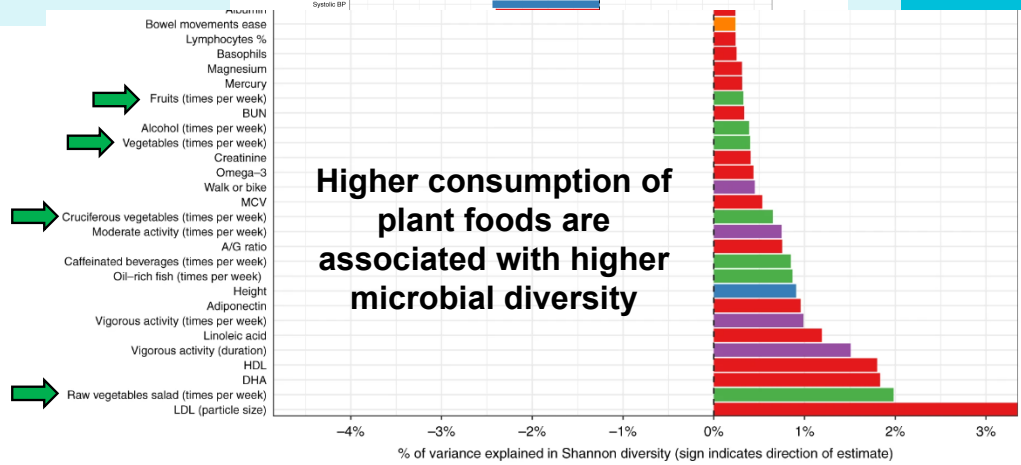
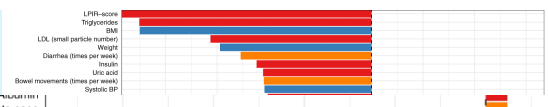
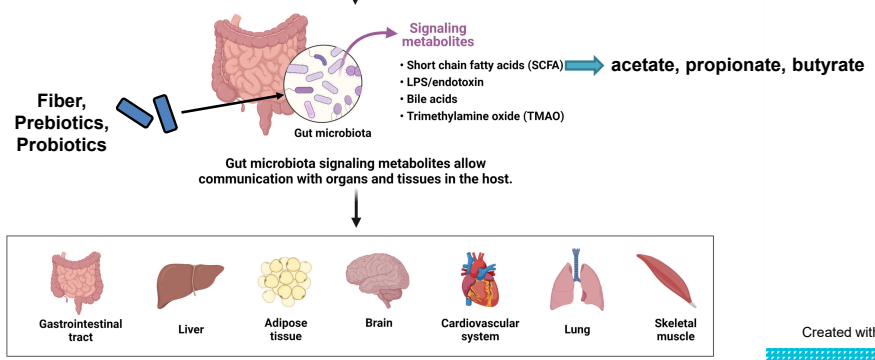
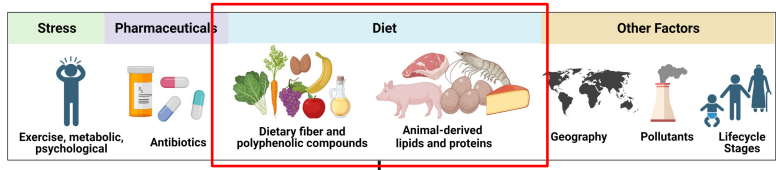
Fecal butyrate is lower in Parkinson's and correlated with motor severity scores.



Chen S.J. et al. *Neurology*. 2022;98(8):e848-e858.

Parkinson's, Diet and the Gut-Brain Connection

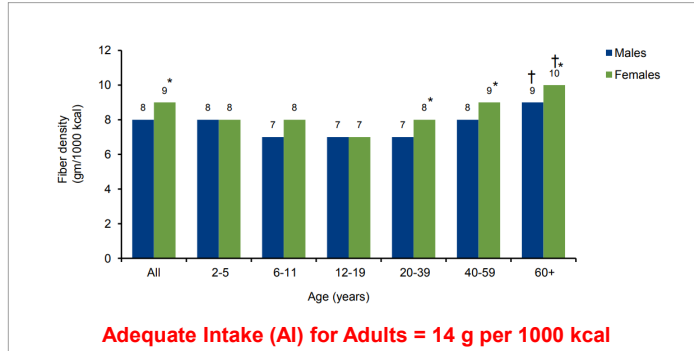
DIETARY INTERVENTIONS TO MODULATE THE MICROBIOME



Higher consumption of plant foods are associated with higher microbial diversity

Dietary Fiber: Frequently Under Consumed in the US

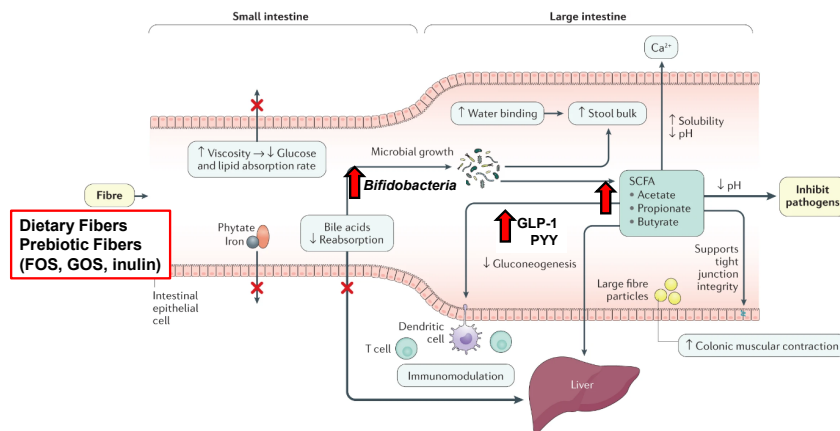
Figure 2. Fiber density (gm/1000 kcal) of U.S. population, WWEIA, NHANES 2009-2010



*Significantly different from males (p<0.001)
 †Within gender, intake of males and females 60+ years significantly higher than other age groups combined, p<0.001
 SOURCE: What We Eat in America, NHANES 2009-2010, day 1, individuals 2+ years

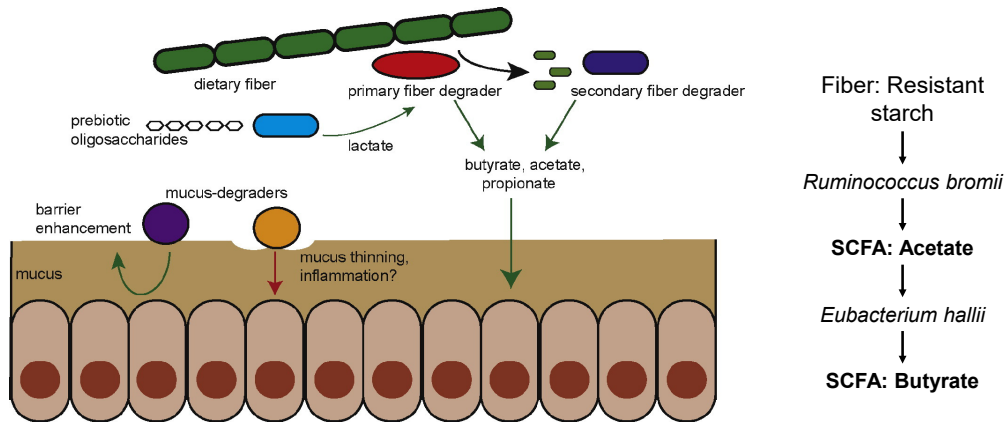
Hoy MK & Goldman JD. 2014. In: FSRG Dietary Data Briefs [Internet]. Beltsville (MD): United States Department of Agriculture (USDA); 2010-. Dietary Data Brief No. 12. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK589559/>

The Many Functions of Fibers



Gill SK, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):101-116.

Fermentation of Non-Digestible Carbohydrates and Cross Feeding



Cockburn DW et al. J Mol Biol 2016;428(16):3230-3252.

Prebiotic Fibers

Prebiotic Definition: a substrate that is *selectively utilized by host microorganisms conferring a health benefit*

– Not all fibers meet this definition!

Naturally-Containing Prebiotic Foods:

- Bananas
- Onions
- Garlic
- Chicory root
- Artichokes
- Beans



Prebiotics can be made and added to food products:

- Galactooligosaccharides (GOS)
- Fructooligosaccharides (FOS)
- Oligofructose (OF)
- Chicory root
- Inulin

Gibson GR, et al. Nat Rev Gastroenterol Hepatol. 2017;14(8):491-502.

Recommended to consume 3-5 g/day prebiotic fibers (ISAPP)

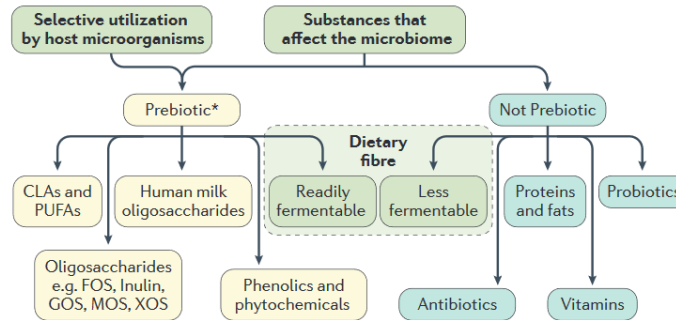
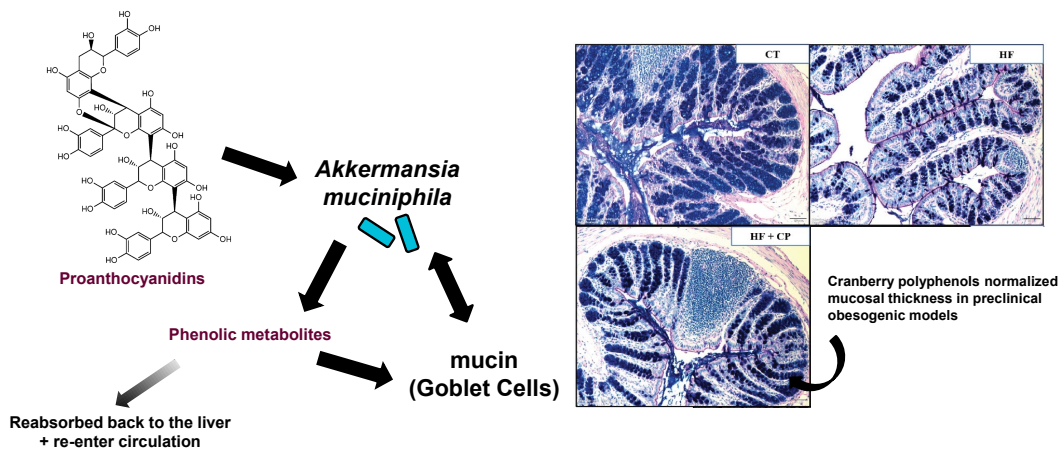


Figure 1 | Distinguishing what is considered a prebiotic with the proposed definition.

ISAPP: International Scientific Association for Probiotics and Prebiotics
 Gibson GR, et al. *Nat Rev Gastroenterol Hepatol.* 2017;14(8):491-502.

Prebiotics – not just fibers!



Probiotics



Probiotic Definition¹: Live microorganisms that, when administered in adequate amounts, *confer a health benefit on the host*

– Benefits are species/strain specific!

Probiotic vs. Fermented Foods:

- Evidence for a health benefit not required for fermented foods²
- Examples of fermented foods → yogurt, kefir, kimchi, cheese, some breads, etc.

Synbiotic³ → combination of probiotic + prebiotic

No general recommendation exists for consumption of probiotics.

1. Hill C, et al. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506-14.
 2. Marco ML et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(3):196-208
 3. Swanson KS, et al. *Nat Rev Gastroenterol Hepatol.* 2020;17(11):687-701.

Clinical Guide to Probiotics in the US



AEProbio Clinical Guide to Probiotic Products Available in USA
 Applications, Dosage Forms and Clinical Evidence to Date - 2021 Edition

Introduction Adult Health Womens Health Pediatric Health Functional Foods References About

PROBIOTIC APPLICATIONS IN ADULT HEALTH

Show 30 entries

Brand Name	Probiotic Strain	Applications (Level of Recommendation)	Dosage Form	CFU/Dose	No of Doses/Day
ActiVast	B. animalis lactis CNCM I-2404	C - Constipation (I) IBS - Irritable bowel syndrome (I)	Ferm. milk lq	18/serving	1-3 servings
Align	B. longum 35624	IBS - Irritable bowel syndrome (I)	Capsules	18/capsule	1 capsule
Align Chewables	B. longum 35624	IBS - Irritable bowel syndrome (I)	Tablet	18/tablet	1 tablet
Align Extra Strength	B. longum 35624	IBS - Irritable bowel syndrome (I)	Capsules	58/capsule	1 capsule
Align Gut Health & Immunity Support	B. animalis subsp. lactis BB-126	C - Constipation (II)	Capsule	18/capsule	1 capsule
Bio-K-8 BiomePRO	L. acidophilus CL 1285 L. casei LBC30R L. thermosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) C/DAD - Clostridium difficile associated diarrhea - Prevention (I) IBS - Irritable bowel syndrome (I)	Capsule	900/capsule	1-2 capsules
Bio-K-8 BiomePRO drinkable probiotic	L. acidophilus CL 1285 L. casei LBC30R L. thermosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) C/DAD - Clostridium difficile associated diarrhea - Prevention (I)	Ferm. rice lq	1000/bottle	0.5-1 bottle
Bio-K-8 drinkable probiotics	L. acidophilus CL 1285 L. casei LBC30R L. thermosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) C/DAD - Clostridium difficile associated diarrhea - Prevention (I)	Ferm. soy lq Ferm. rice lq Ferm. milk lq Ferm. gna lq	500/bottle 500/bottle 500/bottle 500/bottle	1 bottle 1 bottle 1 bottle 1 bottle
Bio-Kutti	Bacillus subtilis FXNB 21™ B. bifidum FXNB 23™ B. brevis FXNB 25™ B. infantis FXNB 27™ B. longum FXNB 30™ L. acidophilus FXNB 35™ L. delbrueckii sp. longum FXNB 39™ L. casei FXNB 37™ L. plantarum FXNB 47™ L. thermosus FXNB 54™ L. tetraevus FXNB 61™ L. salivarius FXNB 57™ L. lactis subsp. lactis FXNB 63™	IBS - Irritable bowel syndrome (I) MP - Migraine prevention (reduction of frequency and severity) (I)	Capsule	28/capsule	4 capsule

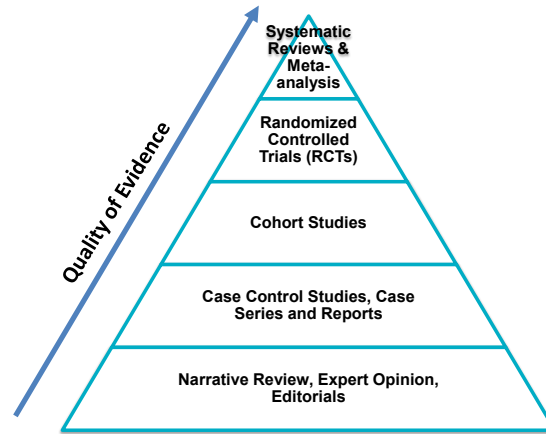
http://www.usprobioticguide.com/?utm_source=intro_pg&utm_medium=civ&utm_campaign=USA_CHART

Research on Diets for Parkinson's: Not There Yet, But Getting Closer

Majority of research has focused on identifying *risk factors* for Parkinson's

Trials on supplements hasn't shown strong results in humans (unless you have a clinical deficiency)

Single food components vs. dietary patterns

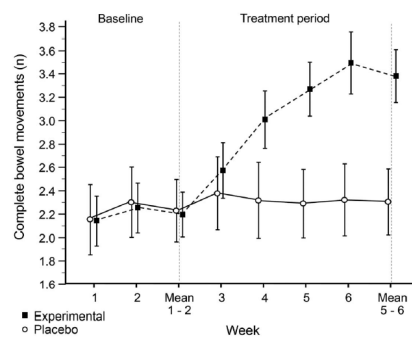


A synbiotic drink increased number of complete bowel movements in PwP after 6 weeks

	Fermented milk containing probiotics and prebiotic fiber (125 g)	Placebo (pasteurized fermented milk) (125 g)
Energy, kcal	75	77
Proteins, g	2.8	3.5
Carbohydrates, g	12.6	13.4
Fats, g	0.9	1.1
Fiber, g	7.8	0.26
Fructooligosaccharides, g	2.4	—
Calcium, mg	104	131
Phosphorus, mg	81	105
Probiotics,* CFU	250 × 10 ⁹	—

Abbreviation: CFU = colony-forming unit.
Interventions shelf life: 37 days (to be stored between 0°C and 4°C).
*Including the following strains: *Streptococcus salivarius* subsp. *thermophilus*, *Enterococcus faecium*, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Bifidobacterium* (*breve* and *animalis* subsp. *lactis*).

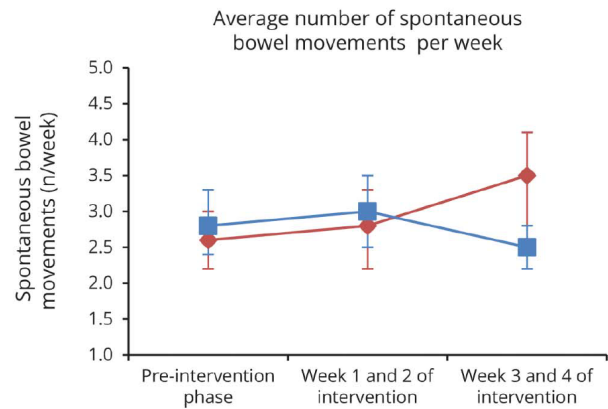
Figure 2 Complete bowel movements during the study



Mean number of weekly complete bowel movements according to intervention.

Barichella M, et al. *Neurology*. 2016;87(12):1274-80.

A multi-strain probiotic increased spontaneous bowel movements after 4 weeks in PwP



Tan AH, et al. *Neurology*. 2021;96(5):e772-e782.

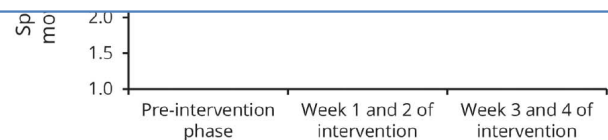
A multi-strain probiotic increased spontaneous bowel movements after 4 weeks in PwP



Average number of spontaneous bowel movements per week

Average fiber intake at baseline was ~30 grams per day!

Did not find improvements in stool consistency or constipation-related quality of life



Tan AH, et al. *Neurology*. 2021;96(5):e772-e782.

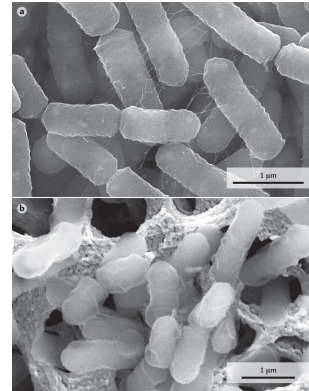
A New Era? Postbiotics and Purified SCFAs

Postbiotic: preparation of inanimate microorganisms and/or their components that confers a health benefit on the host (ISAPP Consensus Statement 2021)

- Some evidence for efficacy in *H.pylori* infections, IBS, COPD
- Safety?

Purified SCFA (acetate, butyrate, propionate):

- FDA GRAS status
- Some evidence in humans for efficacy in IBD and radiation proctitis
- Delivery route?



***Lactobacillus rhamnosus* GG**
A) active B) inactivated

SCFA: Short-chain fatty acids
Salminen S, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(9):649-667.

What about the Mediterranean diet?

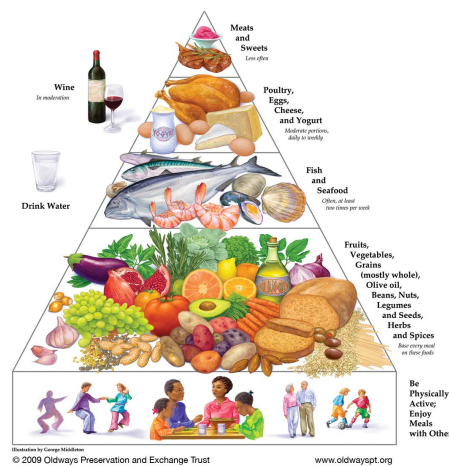


Image source: <https://oldwayspt.org/traditional-diets/mediterranean-diet>

Health Benefits of the Mediterranean Diet



Antioxidants from plant foods

"Scavengers" that help prevent or slow damage to our body's cells



Omega-3 fats from fish/seafood

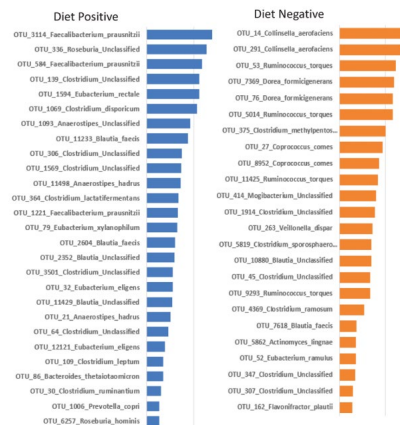
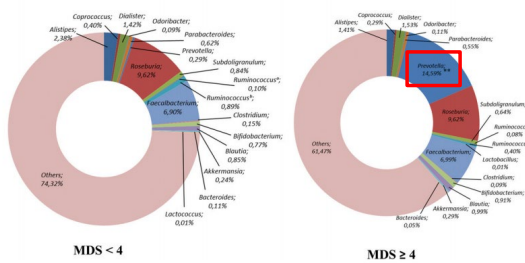
Essential dietary fat that may influence brain health/function



Dietary fiber from plant foods

Non-digestible carbohydrate that can influence our gut health and immune function

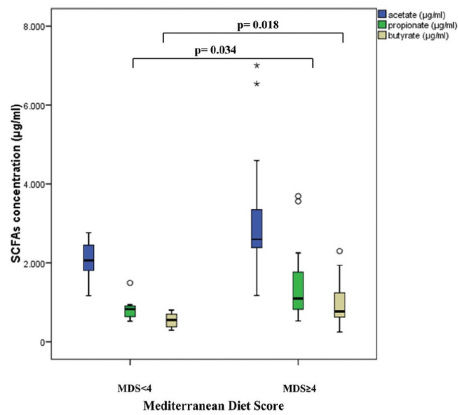
Mediterranean diet is associated with higher abundance of commensal microbes



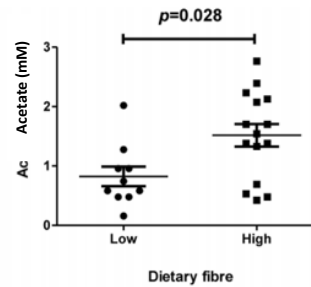
n=31 (23F, 8M)
Gutierrez-Diaz I, et al. *Food Funct.* 2016;7(5):2347-56.

NU-AGE Cohort (n=612)
Ghosh TS et al. *Gut.* 2020;69(7):1218-1228.

Mediterranean diet and dietary fiber are associated with higher SCFA concentrations



n=31 (23F, 8M)
Gutierrez-Diaz I, et al. *Food Funct.* 2016;7(5):2347-56.



n=27 (16F, 11M)
Garcia-Mantrana I, et al. *Front Microbiol.* 2018;9:890.

Mediterranean diet may slow age-related cognitive decline (PREDIMED Trial)



334 volunteers

- Average age ~65 years

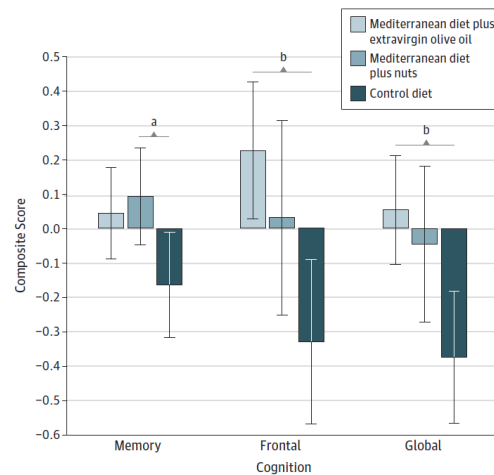
High risk for heart disease

Assigned to either:

- Mediterranean diet + EVOO
- Mediterranean diet + Nuts
- Control (low-fat) diet

Followed for ~4 years

EVOO: Extra virgin olive oil
2015 Valls-Pedret et al. *JAMA Intern Med.*



Mediterranean diet is associated with lower risk of Parkinson's and prodromal symptoms

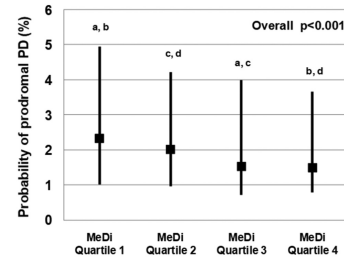
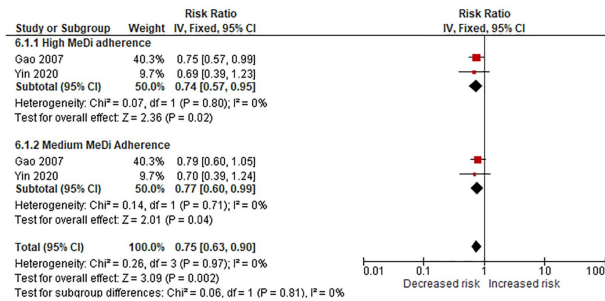


FIG. 2. Probability of Prodromal Parkinson's Disease (PD) according to the International Parkinson and Movement Disorders Society's research criteria, in older people by quartiles of the Mediterranean Diet score (MeDi). Values are medians (Q1, Q3). P-value from a Kruskal-Wallis test is shown. Values sharing the same superscript letter are statistically significantly different from each other, according to post-hoc Mann-Whitney rank tests (Bonferroni corrected for multiple comparisons). MeDi score ranges: Quartile 1: 17-30, Quartile 2: 31-33, Quartile 3: 34-36, Quartile 4: 37-46.

Solch RJ, et al. *J Neurol Sci.* 2022;434:120166.

Maraki MI, et al. *Mov Disord.* 2019;34(1):48-57.

RESEARCH ARTICLE

Intake of Flavonoids and Flavonoid-Rich Foods and Mortality Risk Among Individuals With Parkinson Disease

A Prospective Cohort Study

Xinyuan Zhang, BS, Samantha A. Molsberry, PhD, Tian-Shin Yeh, MD, PhD, Aedin Cassidy, PhD, Michael A. Schwarzschild, MD, PhD, Alberto Ascherio, MD, DrPH, and Xiang Gao, MD, PhD
Neurology® 2022;98:e1064-e1076. doi:10.1212/WNL.0000000000013275

Correspondence
 Dr. Gao
 xxg14@psu.edu

Flavonoids → plant-derived polyphenolic molecules that are rapidly metabolized and can cross the blood brain barrier

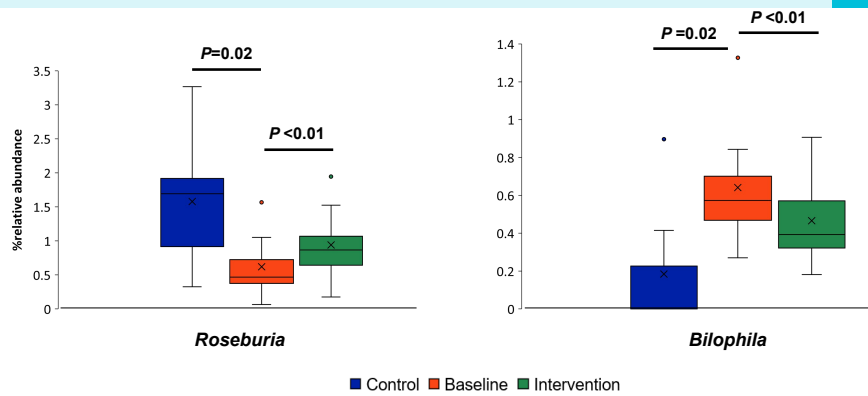
- Found naturally in fruits, vegetables, tea and red wine
- May reduce inflammation and atherosclerosis

Studied 1,251 people who were newly diagnosed with PD **over 34 years**

Found people with ↑ flavonoid intakes = ↓ risk of death in PD

PD: Parkinson's disease
 Zhang X, et al. *Neurology.* 2022;98(10):e1064-e1076.

Relative abundance of two genera identified to be different in PwP and altered after a 5-week MediDiet



Relative abundance (%) in two genera for spouses (n=8, control) and people with PD (n=8) at week 0 and MediDiet week 5 determined by stool 16s rRNA sequencing. Values within boxes represent interquartile range (25th to 75th percentiles) with a median line (50th percentile) and mean shown as "X". Whiskers represent minimum/maximum values and outliers are shown. Paired t-tests or nonparametric equivalent were used for case-control and intervention comparisons.

PwP: People with Parkinson's
MediDiet: Mediterranean diet
Rusch C et al. *Front Neurol* 2021;12:794640.

Diet and the Gut-Brain Axis in Parkinson's

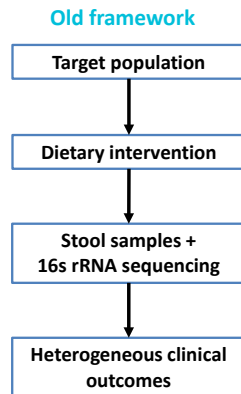
Consume a diet rich in plant foods (e.g., MediDiet)

Dietary fiber intake (25-30 g/day)

Increase production of beneficial microbes and their byproducts (SCFAs)

Modulate inflammation and brain health (??)

Leveraging Diet and Microbiome for Precision Nutrition in Parkinson's disease



Kolodziejczyk AA, et al. *Nat Rev Microbiol.* 2019 Dec;17(12):742-753.

Summary



1. The gut microbiome and the gut-brain axis are implicated in people with Parkinson's disease
2. Diet (dietary fiber, pre- and probiotics and Mediterranean diet) can shape microbial diversity and metabolic capabilities of the gut microbiome
3. Microbial response and the gut-brain axis is host specific – precision nutrition with AI has the potential to differentiate responders to diet



Questions?

Thank you!