Microbiome and nutrition in PD

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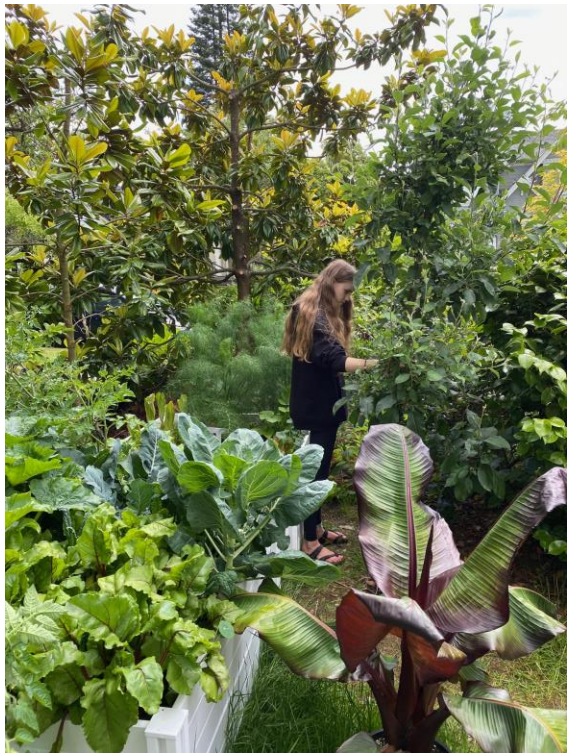
Associate Professor

Marg Meikle Professorship for Parkinson's research

Moving Forward Together Conference

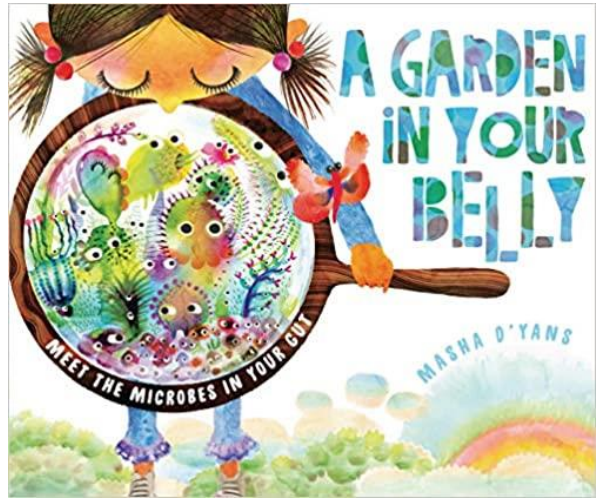
October 2021

Brain Health



Gardening, Nature

Nutrition



Gut microbiome

Masha D’yans, A Garden in your Belly”, 2020

Microbiome

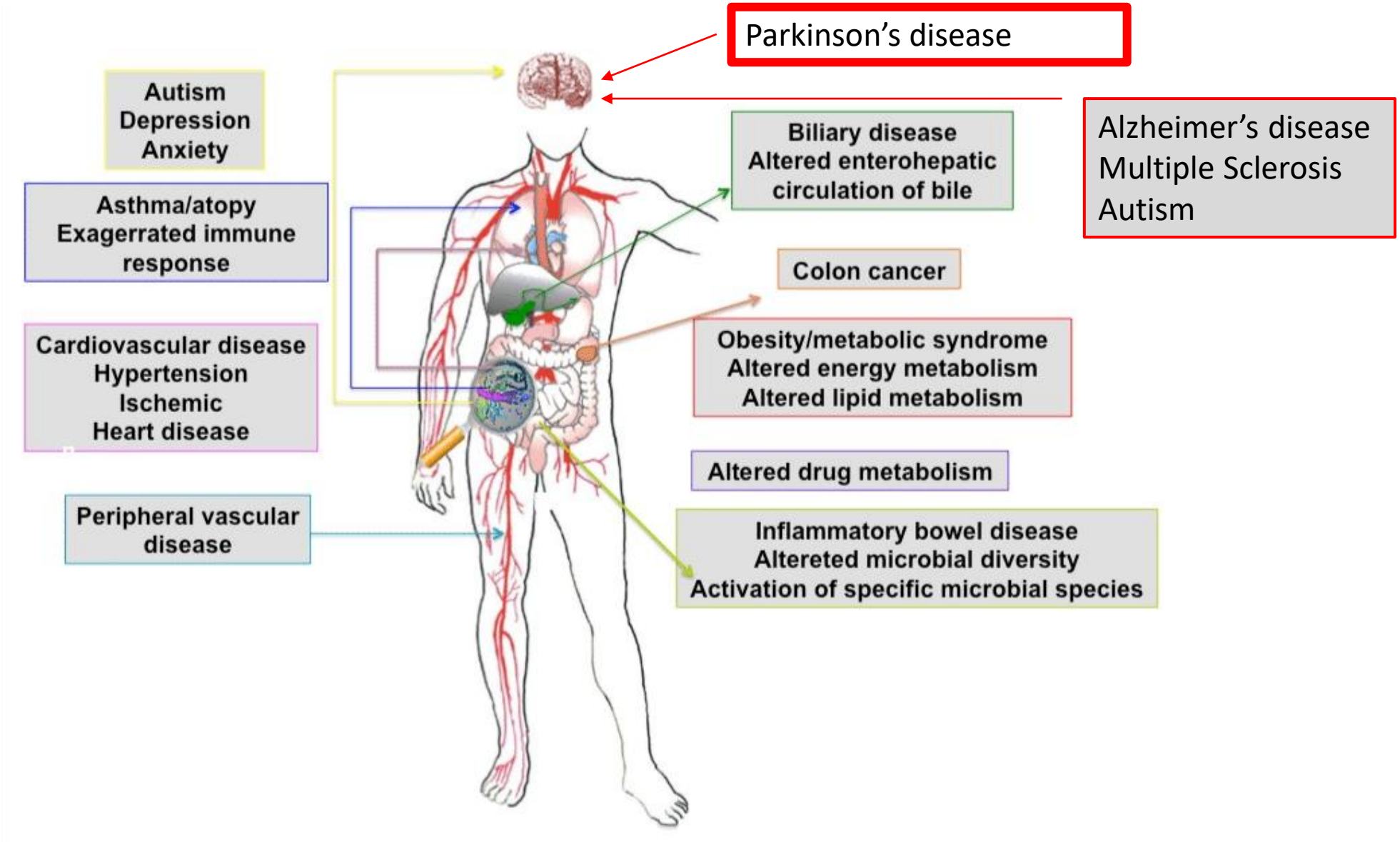
Microbiome and microbiota: an introduction

- **Microbiota:** microbes living in and on us
- Bacteria, viruses, fungi, archaea
- About the same weight as the human brain
- Highest microbial density in the colon

What do the gut microbiota do?

- Defense from pathogens (harmful microbes)
- Breaking down nutrients
- Production of hormones, metabolically active metabolites
- Producing vitamins (e.g. vit K, B12)
- Processing of pesticides, drugs, pollutants
- Influence on gut motility
- Immune system training
- Influence on brain and behaviour

Conditions linked to the gut microbiome



The evolution of Parkinson's disease

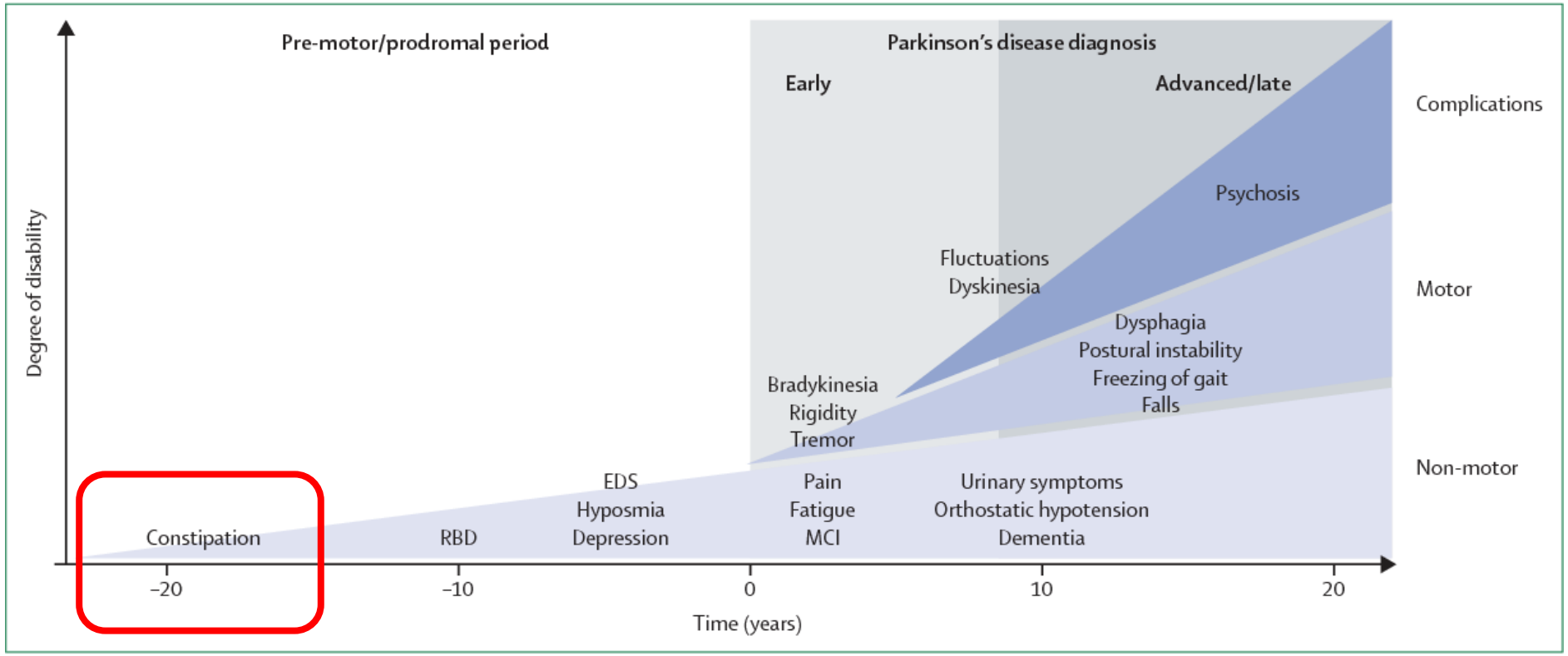


Figure 1: **Clinical symptoms and time course of Parkinson's disease progression**

Kalia, Lang 2015

The evolution of Parkinson's disease

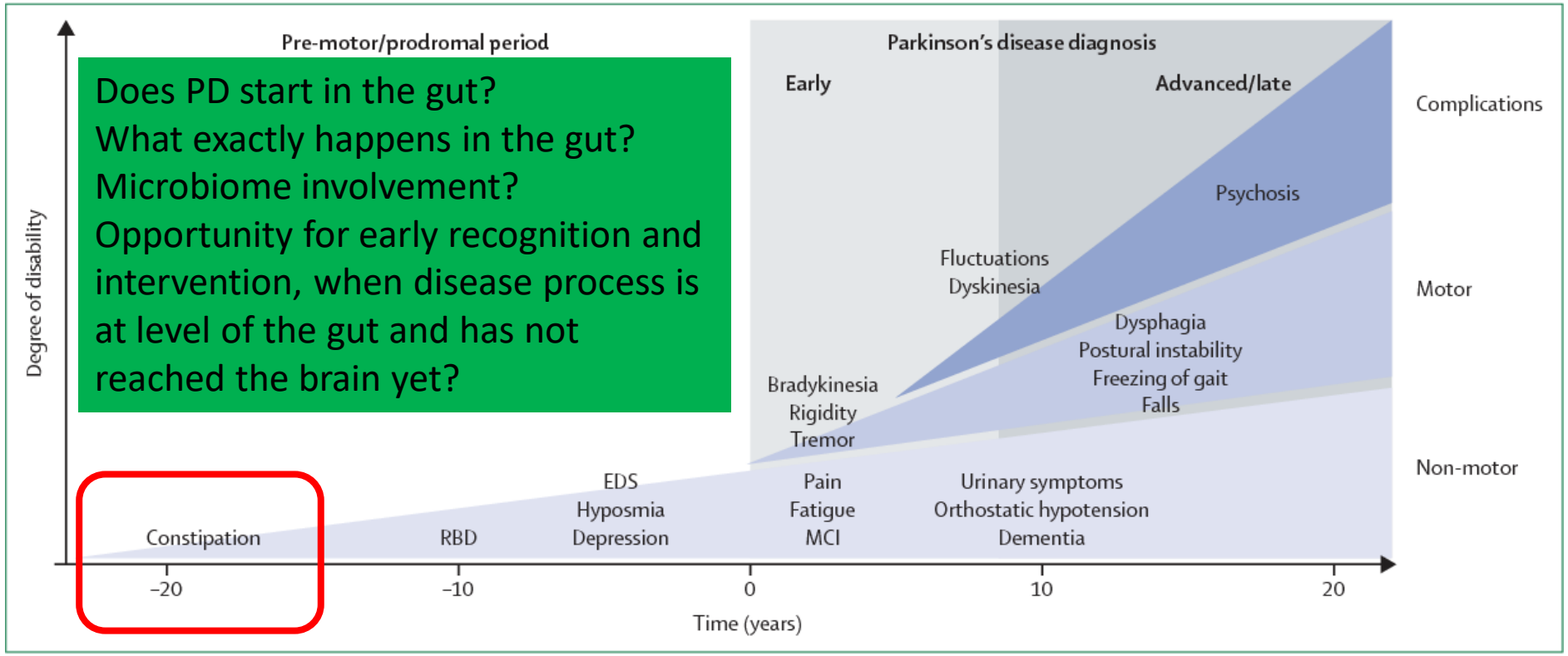


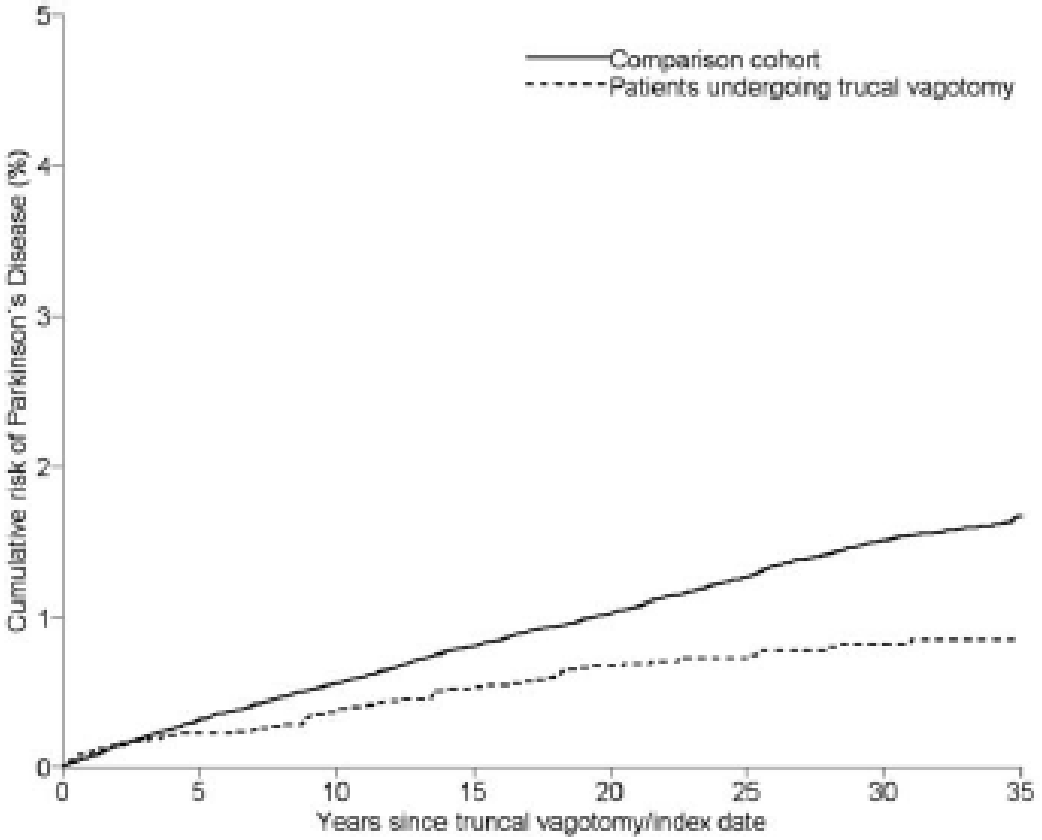
Figure 1: **Clinical symptoms and time course of Parkinson's disease progression**

Kalia, Lang 2015

Hints from the clinic

- Constipation and a poor sense of smell are very early and very frequent symptoms
- The gut and the nose are the internal contact area to the environment and densely populated by microbiota
- Anxiety, depression, fatigue, mild cognitive changes can be early symptoms in PD, all have been associated with the gut microbiome in non-PD individuals

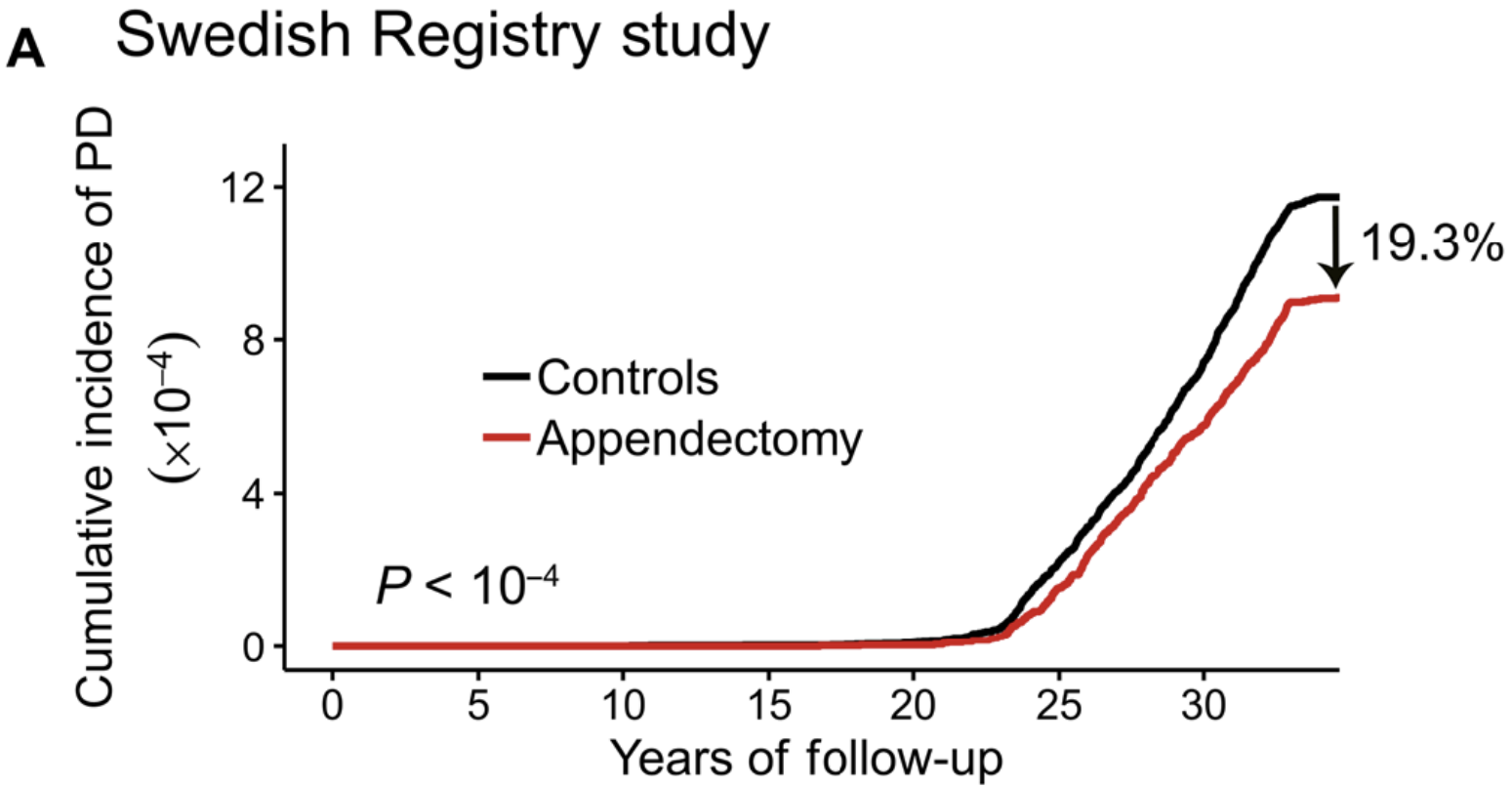
Hints from epidemiology



- Full but not partial vagotomy leads to lower PD risk

Svensson et al., Annals of Neurology, 2015

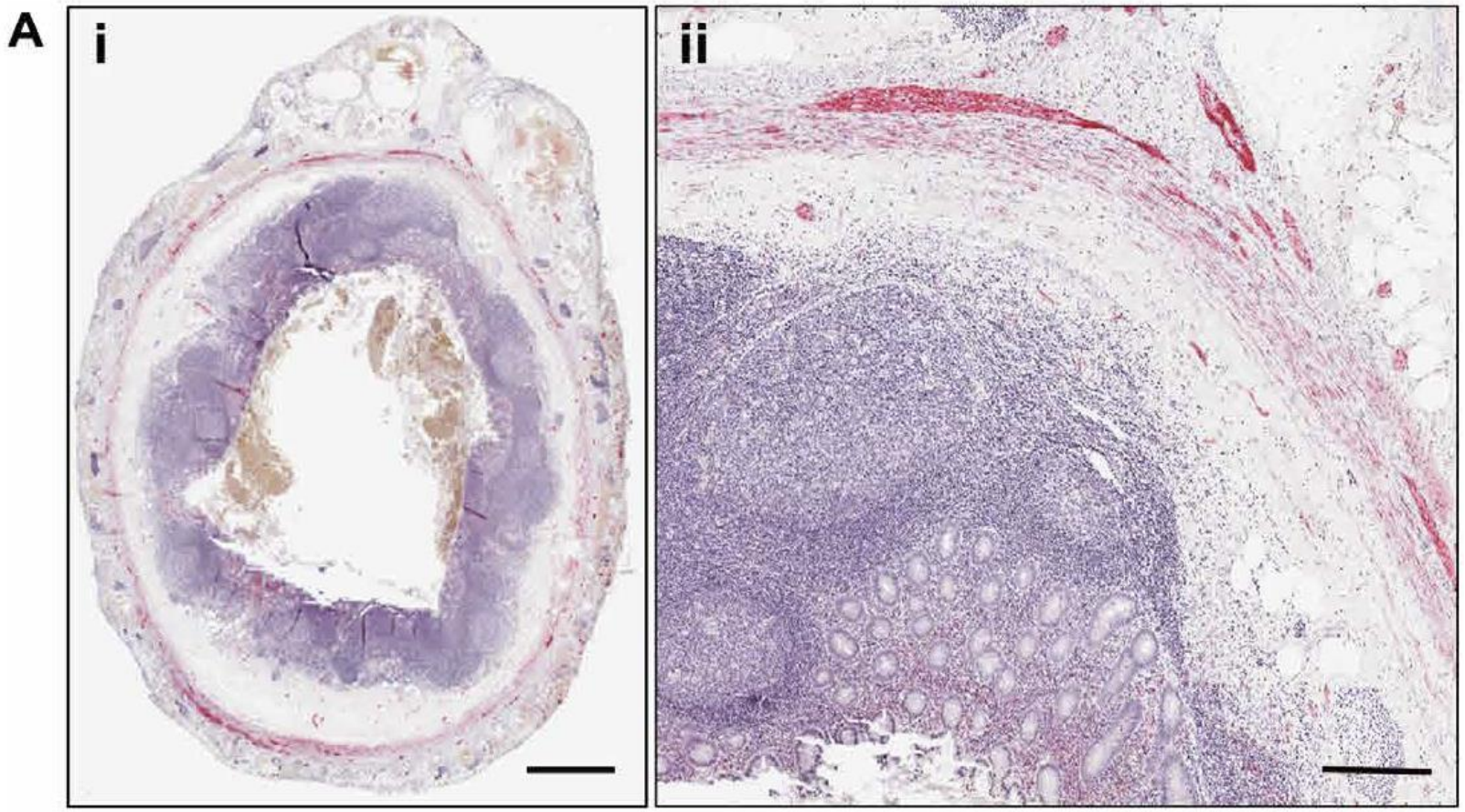
Appendectomy associated with lower risk of PD



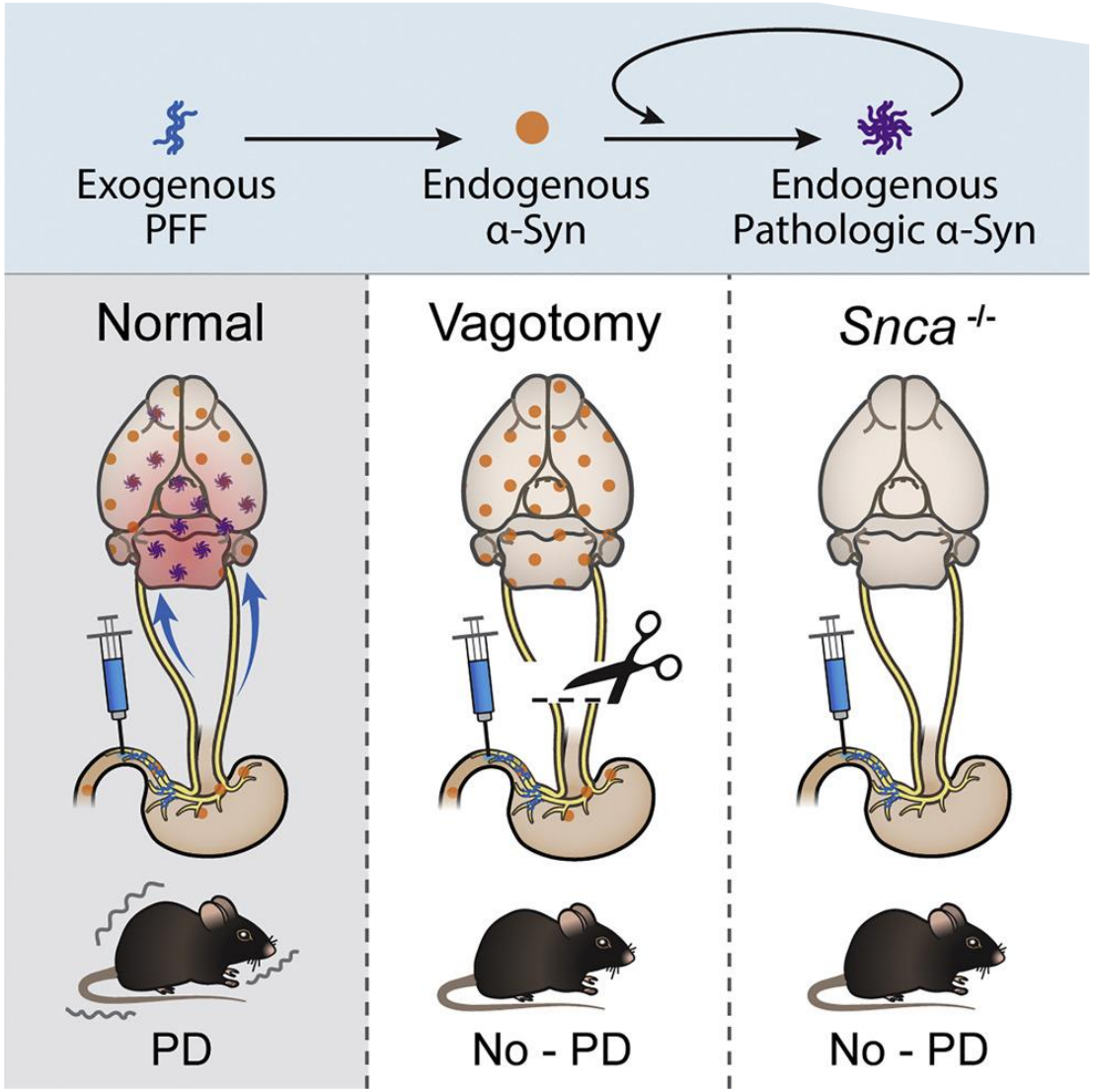
1.7M individuals, with (about 550K) and without (about 1.15M) appendectomy

Killinger et al., 2018, Science Translational Medicine

Alpha-synuclein in the appendix



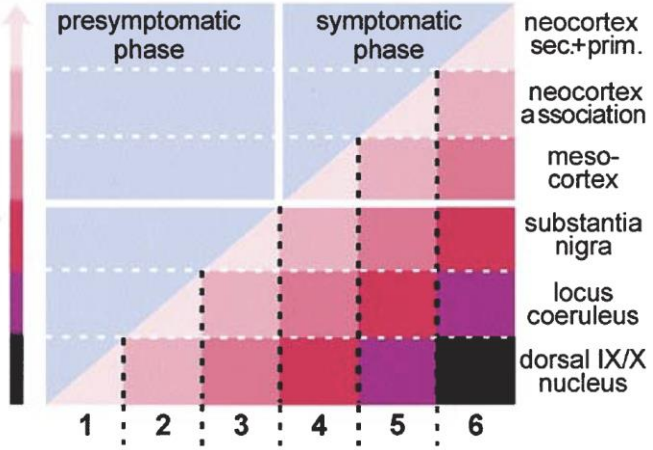
Killinger et al., 2018, Science Translational Medicine

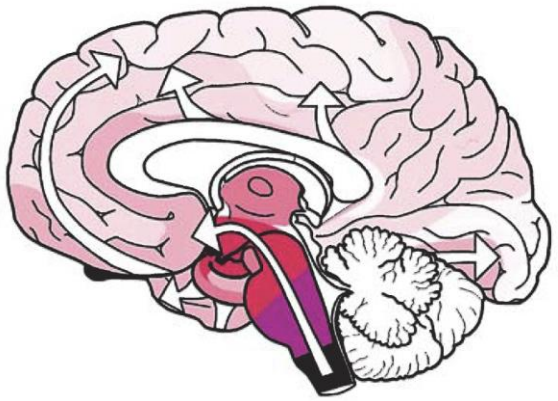


Kim et al., 2019 Neuron

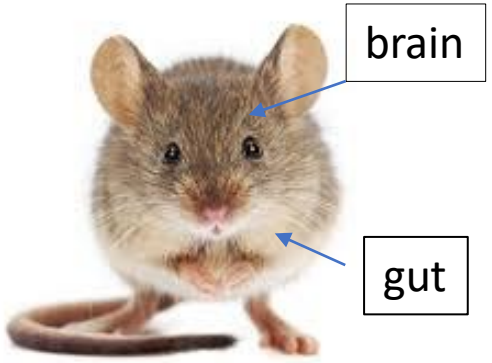
Hints from pathology

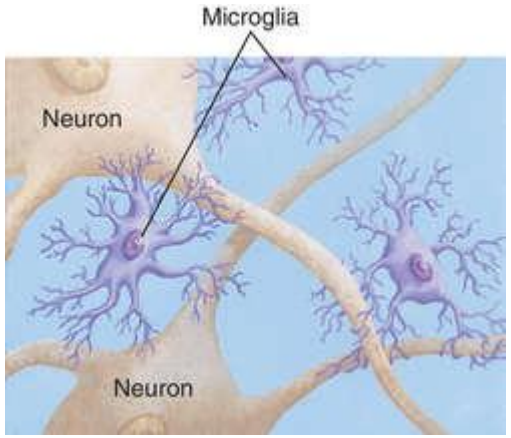
- Mild gut inflammation in PD
- Reduced barrier function and increased E. coli invasion in the gut mucosa (Forsyth et al, 2011)
- Alpha-synuclein deposits can be found before spread to brain (Braak et al., 2003)
- Increased inflammation in PD (blood, CSF, CNS)

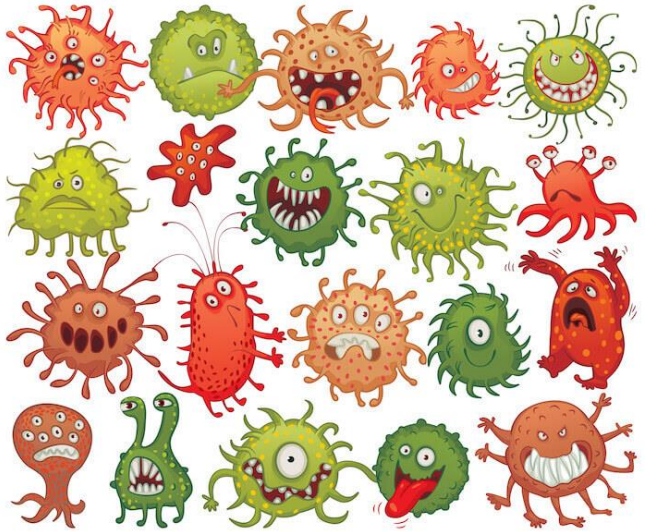




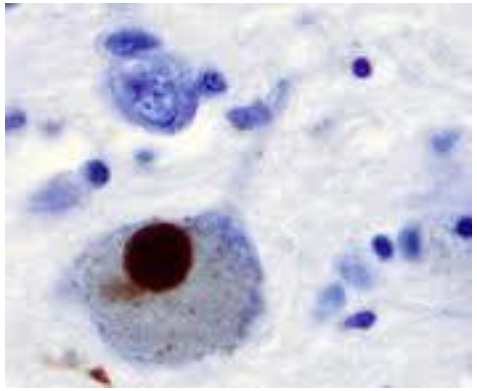
The main players for an elegant experiment







Short chain fatty acids



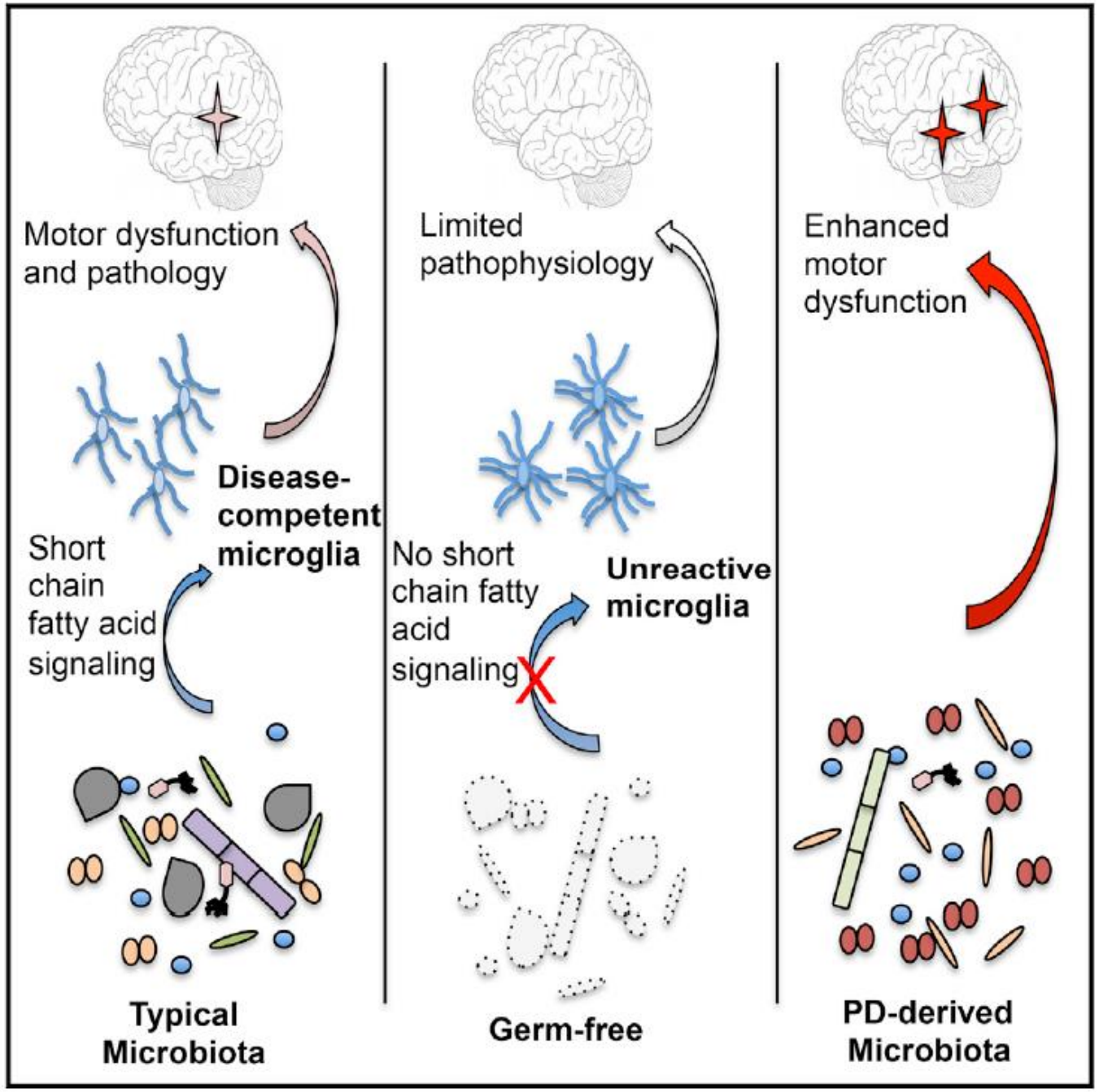
ASO mouse model: A genetically-engineered animal model of PD

- Alpha-synuclein overexpressing (ASO) mice develop signs of Parkinsonism when aging:
  - Motor dysfunction, constipation
  - Increased brain inflammation with increased microglia
  - Alpha-synuclein pathology

- Mice can be reared in completely sterile conditions ("Germ-Free", GF), they do NOT have microbiota living in and on them

Sampson et al, Cell, 2016

ASO mouse model: summary



- Similar findings in models of other brain diseases
- Findings in PD need replication

Sampson et al, Cell, 2016


THEN A MIRACLE OCCURS...
S. Harris
"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

The Vancouver study into the microbiome in PD

- Over 300 participants (individuals living with PD and healthy controls)
- Annual detailed clinical assessments over 5 years
- Fecal, nose, oral samples, blood samples for microbiome analysis
- Metabolomic analysis in blood
- Inflammation markers in blood
- Treatment studies (probiotics)

RESEARCH ARTICLE

Microbiota Composition and Metabolism Are Associated With Gut Function in Parkinson's Disease

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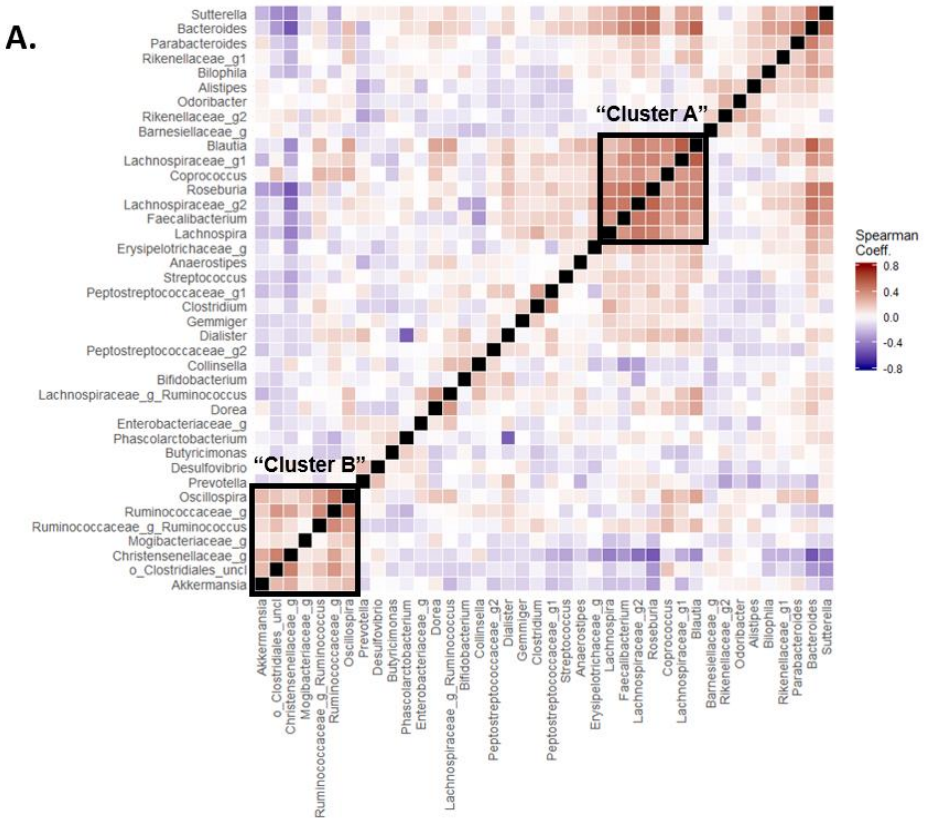
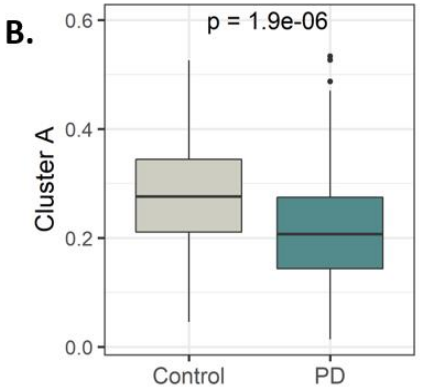
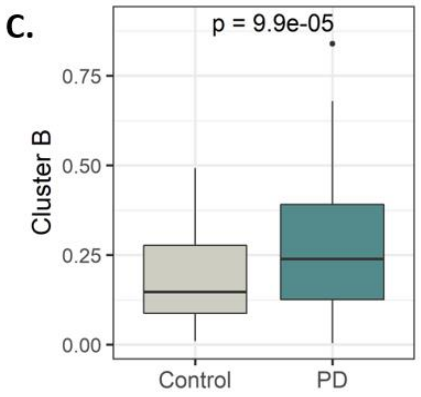
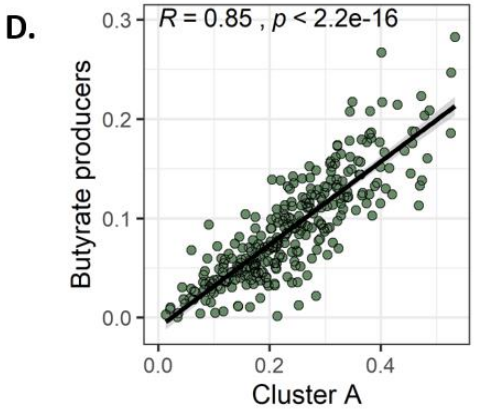
PhD student
Mihai Cirstea

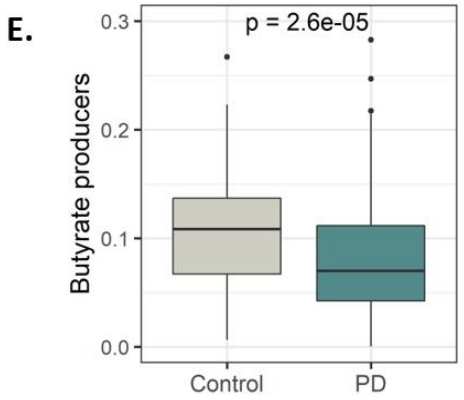
The gut microbiome community is altered in PD and produces less anti-inflammatory substances









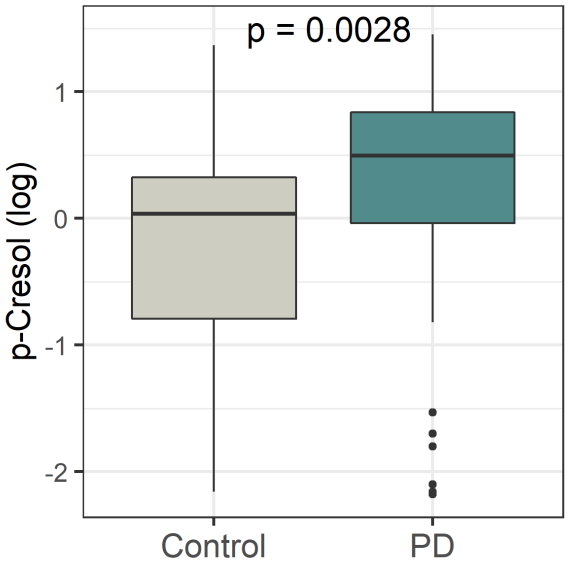


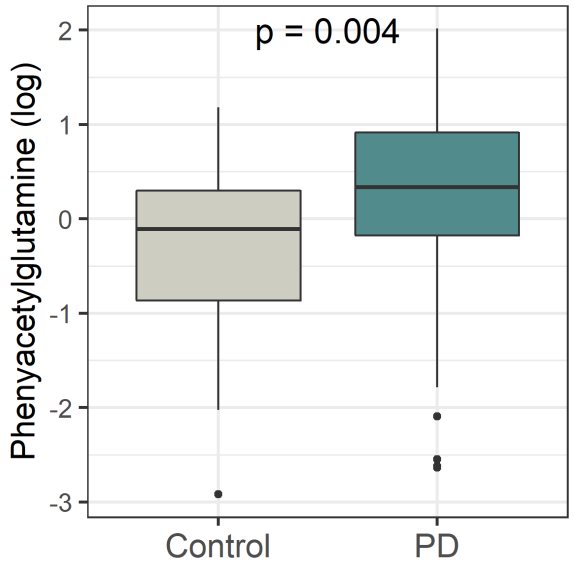
Mihai Cirstea

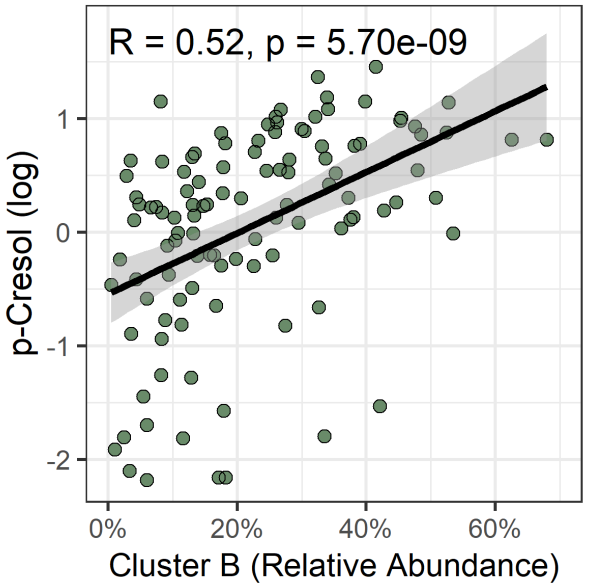
Cirstea et al., Mov Dis, 2020

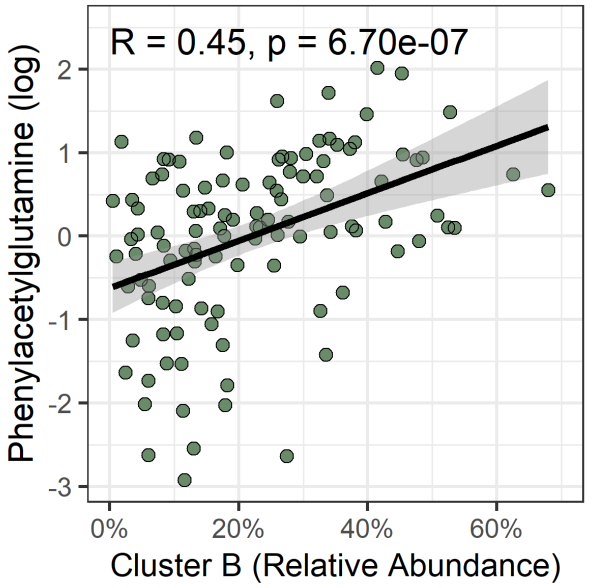
Metabolomics

- Metabolites are the byproducts or end products of metabolism, both by our own bodies and by bacteria
- We measured circulating metabolites in blood samples from patients and controls and were able to detect bacterial metabolites that were altered in PD

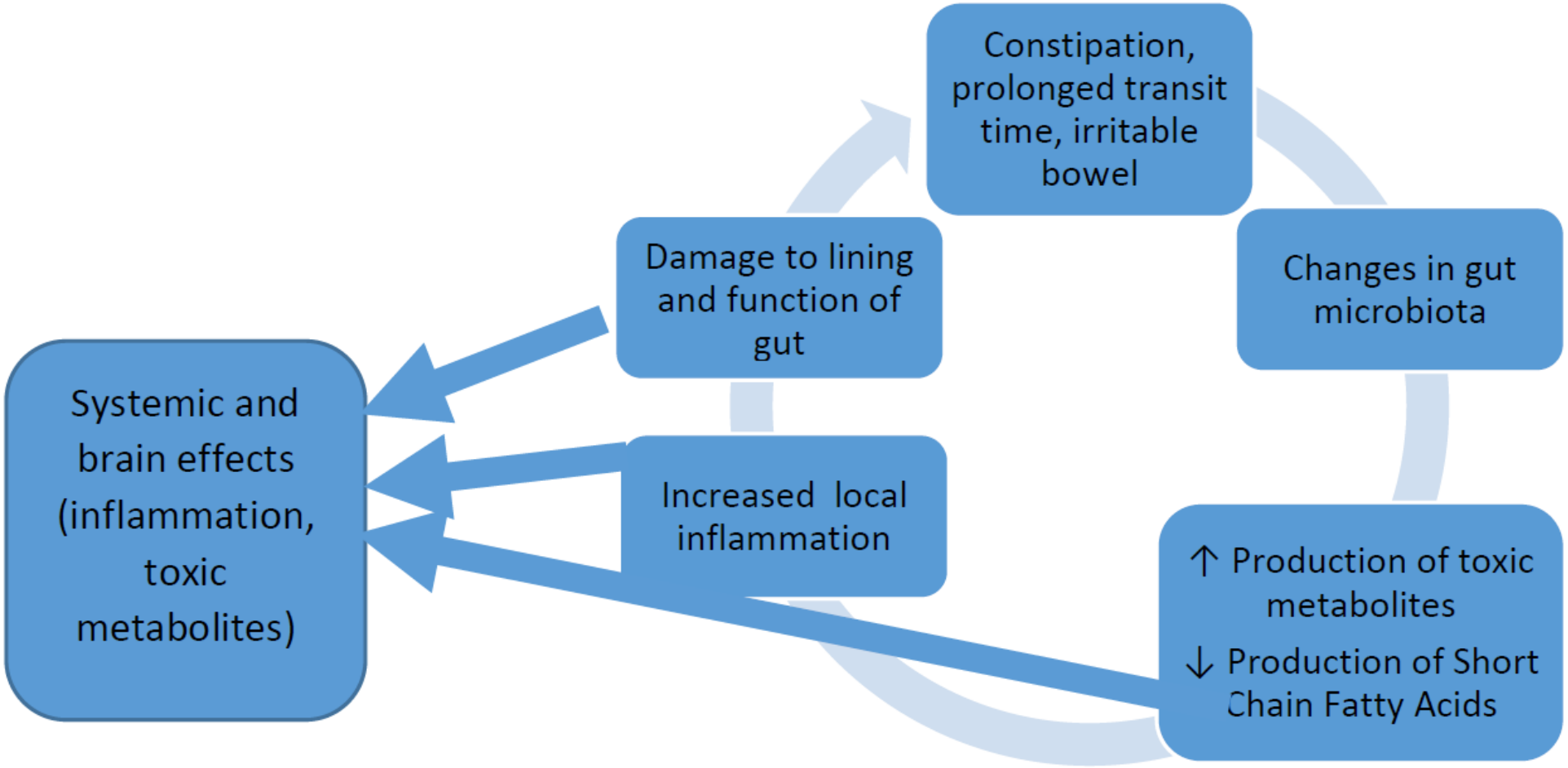






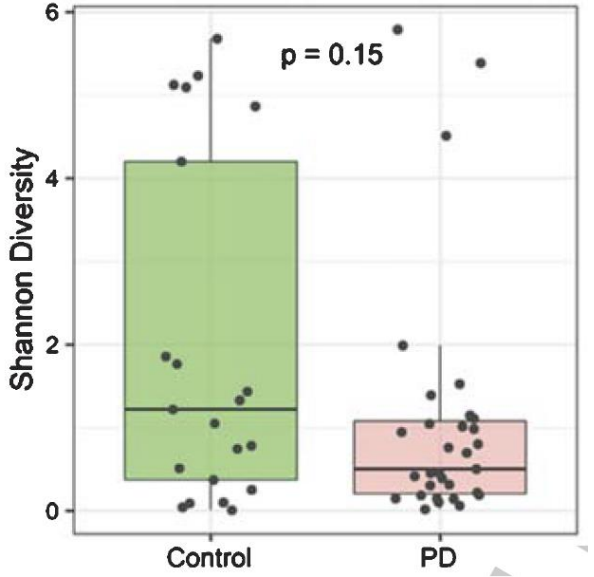


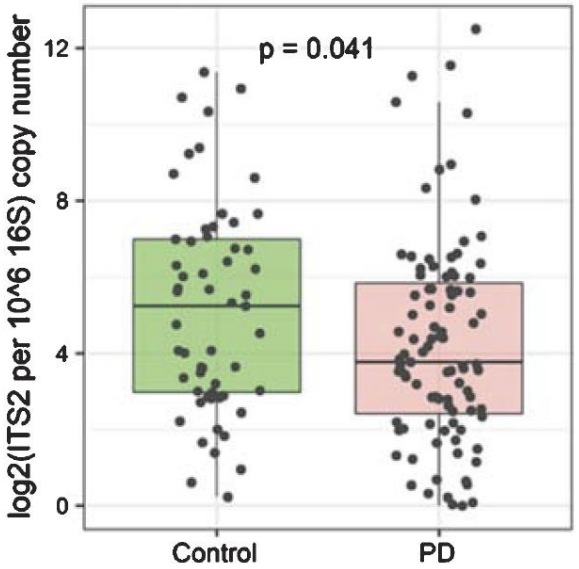
Vicious cycle in Parkinson's



Do fungi play a role in PD?

- Very low fungal load
- No significant difference to healthy controls in specific types of fungi
- Participants with PD trended to have lower fungal diversity than healthy controls and less fungi compared to bacteria than healthy controls
- Gut environment in PD might be more hostile for fungi
- Fungi are unlikely to play a role in PD gut dysbiosis



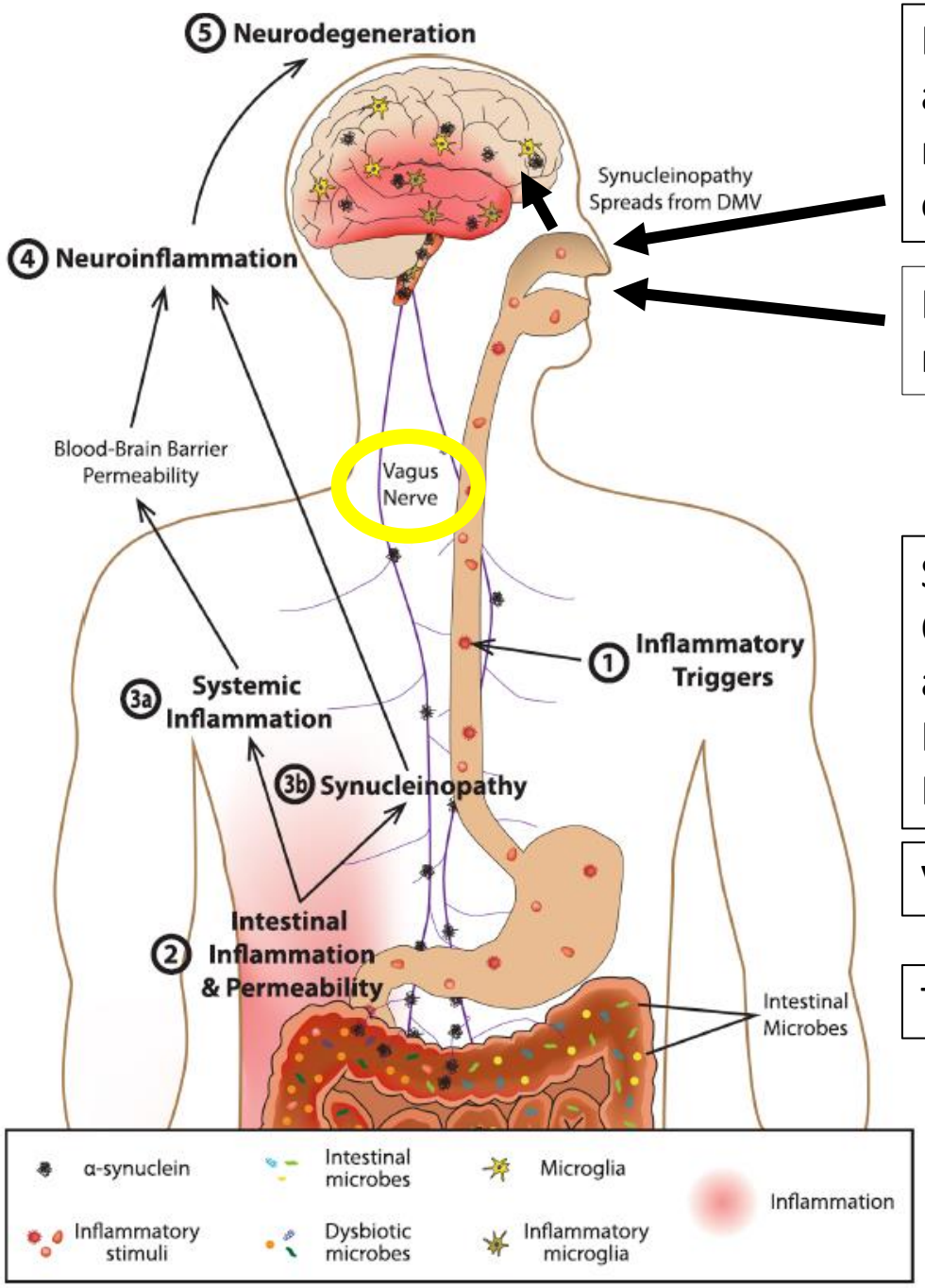


Cirstea et al., J Park Dis, 2020

A summary of microbiome studies in PD

- Over a dozen studies investigating the gut microbiome in PD cross-sectionally
- Gut microbiome profile differs between PD and controls
  - Akkermansia ↑, (Lactobacillaceae ↑, Bifidobacteriaceae ↑, Enterobacteriaceae ↑)
  - Prevotellacea ↓, Faecalibacterium ↓, Roseburia ↓, (Lachnospiraceae ↓)
- Reduced diversity in PD microbiome
- PD microbiome: pro-inflammatory capacity ↑, short chain fatty acid production ↓
- Unclear how much altered gut function such as constipation interacts with gut microbiome changes in PD

Parkinson's and the microbiome – a model of interactions



Loss of sense of smell and early pathology: role of the microbiome of the nose?

Nutrition, toxins, medications

Bacteria? Viruses? Fungi?

Small chain fatty acids? Other metabolically active metabolites? Hormones? Neurotransmitters?

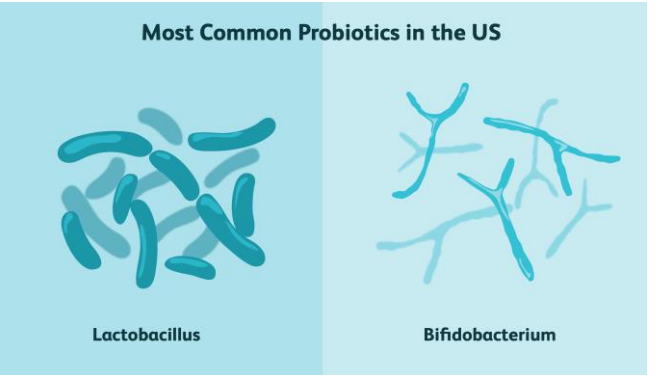
Vitamin production

Constipation

Toxin degradation

Adapted from Houser et Tansey, 2017, NPJparkd

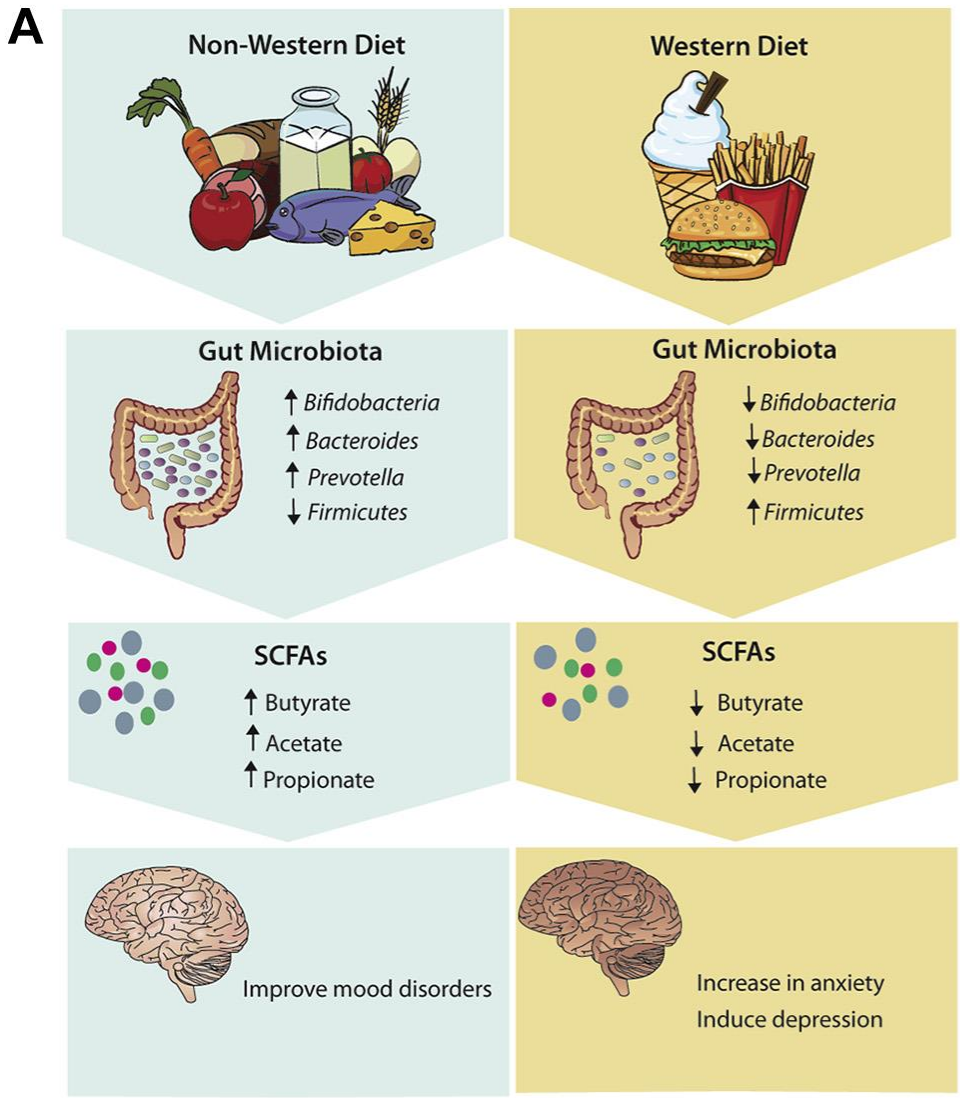
Probiotics

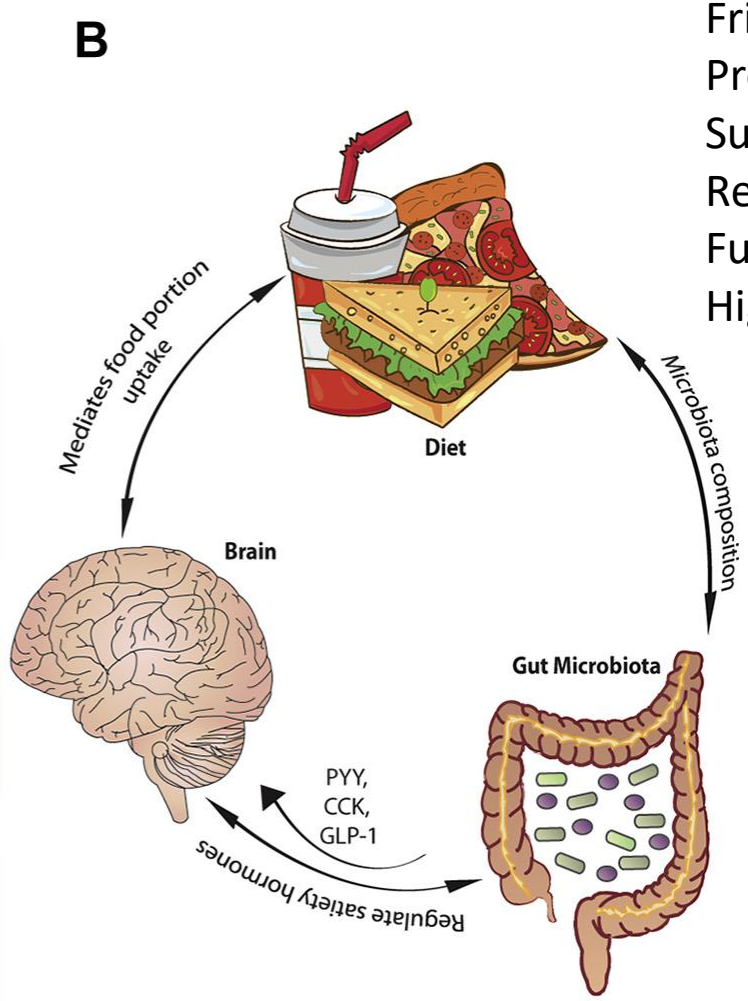


- Current probiotics commercially available are quite similar to each other (mostly various *Bifidobacteria* and *Lactobacilli*)
- Probiotics can improve constipation in PD (Tan et al, 2021, Barichella et al. 2016)
- Probiotics can improve mood, anxiety in non-PD populations
- Ongoing research at our centre into the treatment of anxiety (TAP trial) and soon depression with a multistrain probiotic in PD
  - Contact Petra Uzelman, RN: petra.uzelman@ubc.ca, 604-827-0576
- Aim is to develop more targeted probiotics for PD, alone or in combination with other microbiome-based therapies and nutrition

Nutrition

Diet, gut microbiome and the brain





Western Diet:
Fried foods
Processed foods
Sugar/white flour/sweets
Red meat
Full fat dairy
High salt

Sandhu et al, 2017, Translational Research

Nutrition and prevention of cognitive decline

- Mediterranean diet most studied
- Best evidence for benefits on cognition

- Potentially beneficial nutrients:
  - B vitamins (folate)
  - Flavonoids
  - Vitamin D
  - Polyunsaturated fatty acids
  - High fiber
  - Anti-inflammatory

Scarmeas et al., Lancet Neurology, 2018

Mediterranean –type diets and parkinsonism

- High adherence to healthy, Mediterranean-type eating patterns associated with a reduced risk to develop parkinsonism and symptoms of prodromal Parkinson's disease
- Slower disease progression of Parkinson's disease in healthy eating patterns similar to Mediterranean diet

Maraki et al, Mov Disord., 2019
Molsberry et al., Neurology, 2020
Mischley et al., Oxid Med Cell Longev, 2017
Agarwal et al., J Nutr Health Aging, 2018

The MIND diet, a Mediterranean way to eat

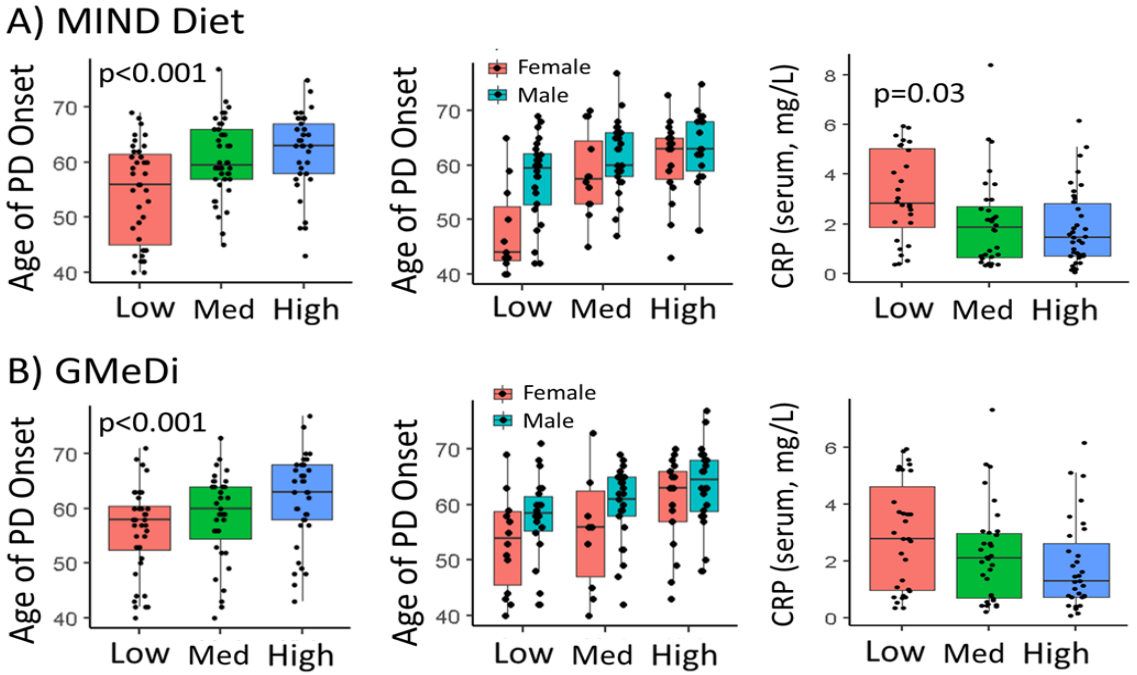
- More: Green leafy and other veggies, seeds, nuts, berries, beans, wholegrains, fish, poultry, olive oil
- Less: red meat, butter, cheese, pastries, sweets, fried or fast (processed) foods

Morris et al., Alzheimers Dement, 2015

Mediterranean-type diets and PD: higher age of onset and less inflammation

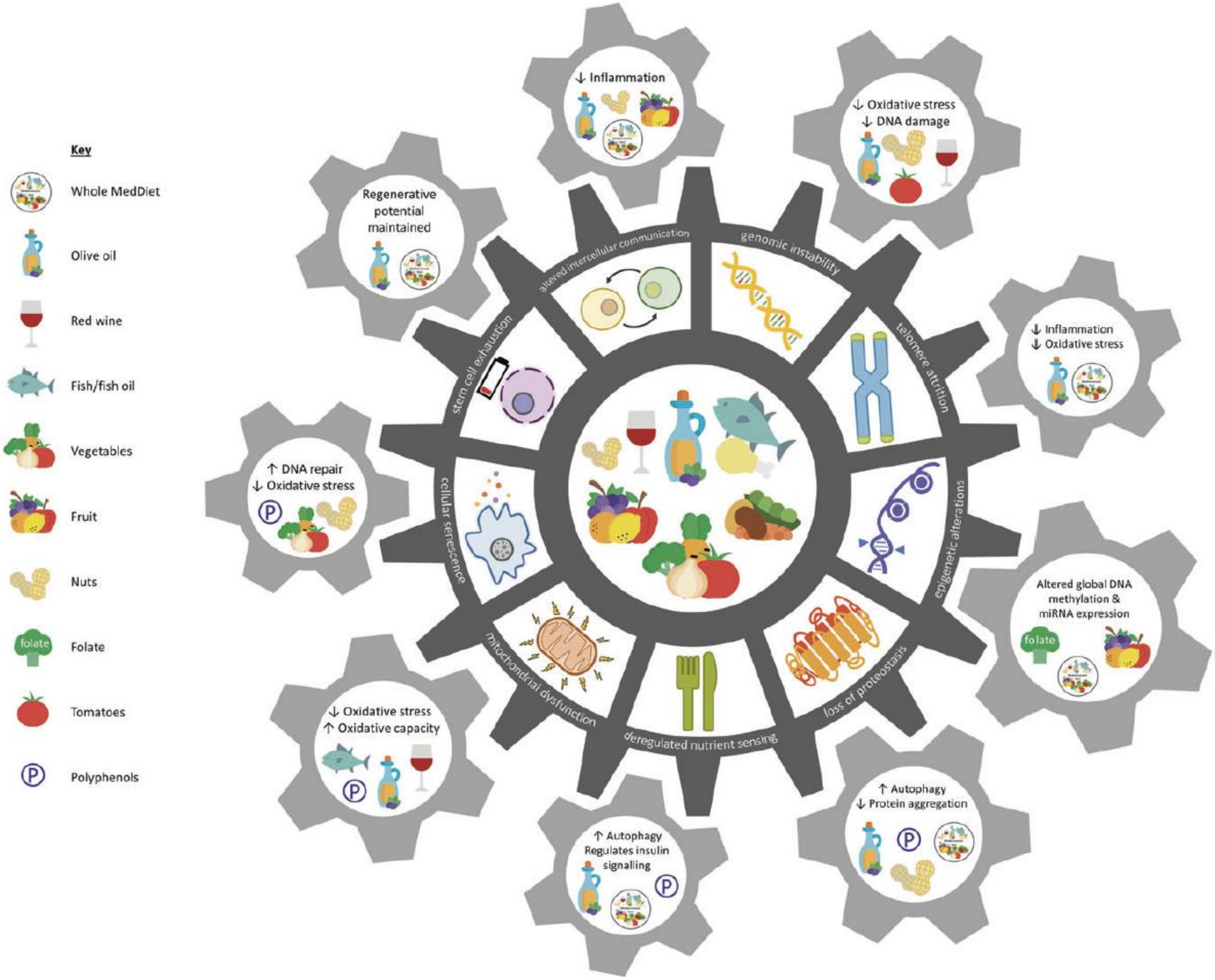
Avril Metcalfe-Roach, PhD student

- Those adhering to a Mediterranean type diet (upper third) have a significantly later onset of Parkinson's than those who are eating a poorer diet (lower third in diet scores)
- Difference for men: age of onset up to 8 years later
- Difference for women: age of onset up to 17 years later
- Less inflammation with better diet



Metcalfe-Roach et al., Jan 2021, Movement Disorders

Mediterranean diet and aging



Shannon et al., Eur J Clin Nutr, 2021

Ketogenic diets

- Low carbohydrate, high fat intake
- Nutritional ketosis: target 0.5 to 4.0 MM of serum beta hydroxybutyrate
- Postulated mechanisms include: improved energy supply for brain cells, improved insulin sensitivity, increased antioxidants, theoretically increased neurotransmitter synthesis, improved brain network stability
- Few published, short-term studies only in Parkinson's
- Important to use mostly plant-derived fats and include fiber in diet, fresh, low carb vegetables, e.g. leafy green vegetables
- Can be challenging to strictly adhere to
- Under guidance of dietitian, medical oversight
- Not known if supplementation, e.g. with medium-chain triglycerides (MCT) or ketone esters or episodic fasting would have same effect in PD
- More research needed!

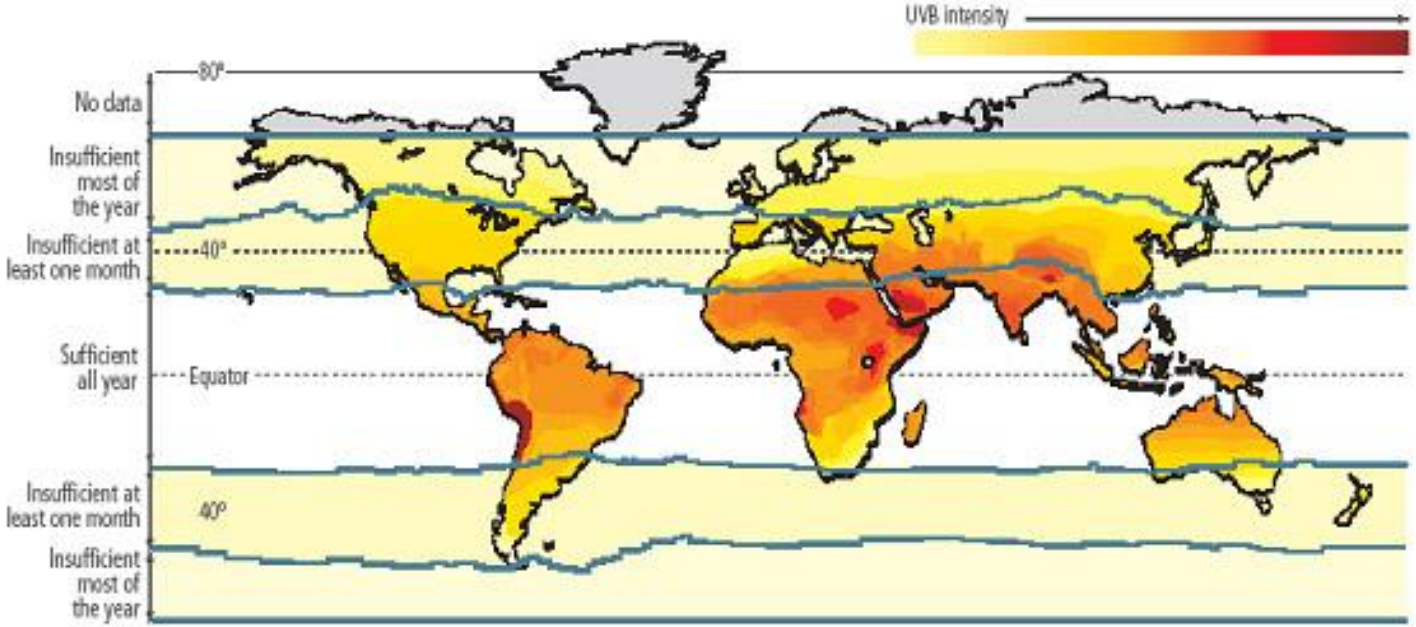
What about supplements?

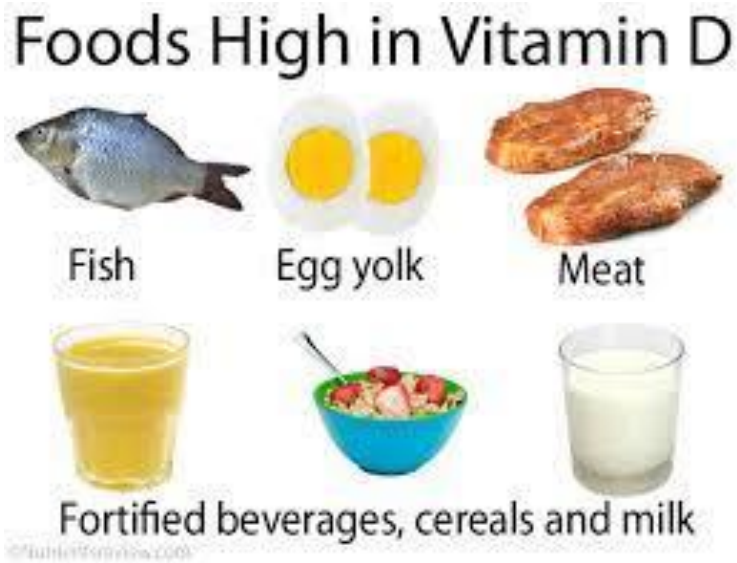
Supplements

- Overall: healthy dietary patterns more beneficial than individual supplements
- Some exceptions where supplements are indicated (e.g. vitamin D)
- Lack of evidence in humans for supplements to slow down progression of PD

Vitamin D

- Important for brain (cognition, mood, energy levels) and bone health
- Canadians are at risk of low vitamin D levels due to Northern location
- Vitamin D is often low in individuals with PD
- Supplementation with 1,000 to 2,000 units per day safe, might need more if deficiency present





Vitamin B12 and other B vitamins

- Low vitamin B12 levels can impact brain, spinal cord, nerves and red blood cell function
- A vegan diet is a risk factor for Vitamin B12 deficiency
- To test levels of vitamin B12 if e.g. cognitive decline, fatigue
- Supplementation if low either as tablet or injection

- Vitamin B6 (pyridoxine) can be low with high dosages of levodopa or duodopa
  - Consult with your medical team

Special considerations in PD

Motor fluctuations

- Levodopa takes long to kick in or is not reliably absorbed: OFF time
- Take levodopa an hour away from protein-containing meals
- Take levodopa with a non-protein containing snack, e.g. cracker, banana, apple sauce etc. to stimulate the stomach to empty contents into small intestine
- **protein re-distribution** can improve OFF times: 80% of protein at dinner time
- Take any iron supplements at least two hours apart from levodopa
- Address constipation!

Constipation

- Early and common issue in PD!
- Ensure sufficient fluid intake (aim for 2 litres per day)
- Fresh fruit, vegetables, leafy green vegetables
- Avoid highly processed foods
- Ensure sufficient fiber intake (30-40 grams per day)
- Fiber also feeds “good” gut bacteria, helps to produce short chain fatty acids which reduce inflammation and improve gut health
- Ongoing use of stool softeners and laxatives often necessary in PD to improve gut health

Weight loss

- Loss of sense of taste and sense of smell common and early in PD
- Loss of appetite and weight common
- Constant moving with dyskinesias can lead to weight loss
- To add extra spices and herbs to food
- Add high-caloric items
- Consult with dietitian

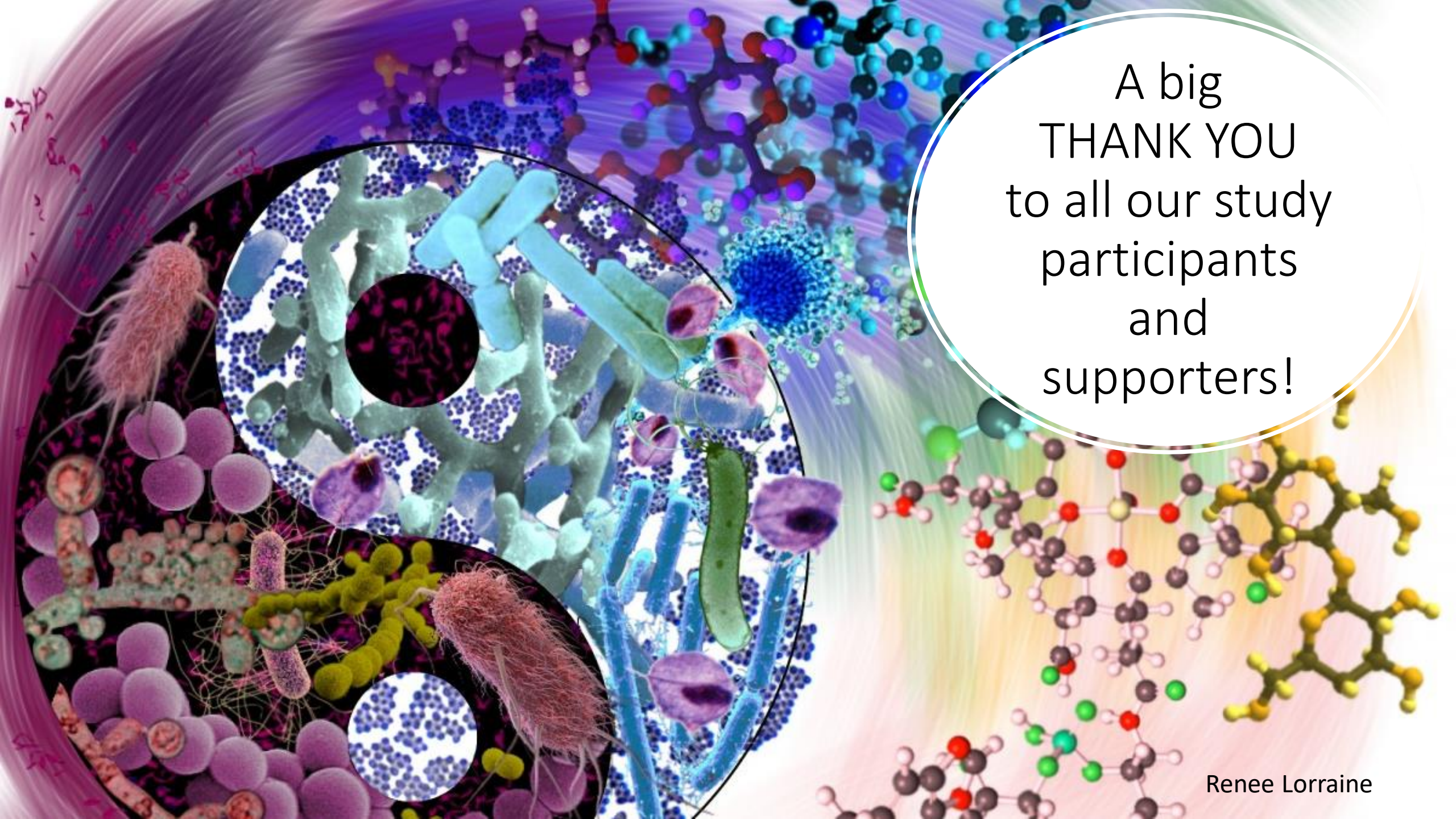
Dietary strategies for low blood pressure on standing – Orthostatic hypotension

- Eat several smaller rather than a few larger meals
- Increase salt intake
- Avoid alcohol
- Have some coffee with meals (before early afternoon, can also help daytime sleepiness)
- Aim for sufficient fluid intake: about 2 litres per day, more in warmer weather or when exercising

Summary

- The gut is closely connected to brain function
- Microbes play a key role in this relationship and especially in Parkinson's disease
- Eating a healthy diet feeds us, our gut microbiome and our brains
- Research opportunities to investigate mechanisms and connections of diet and the microbiome in brain health


Sleep
Nature
Creativity: Music and other arts
Nutrition
Brain health
Learning, cognitive activity
Exercise and movement
BC Brain Wellness Program
Community, relationships
Mindfulness, stress reduction
Addressing risk factors (hypertension, diabetes, obesity, smoking, depression, high alcohol intake)
Hearing


A big
THANK YOU
to all our study
participants
and
supporters!
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- McGill, Montreal: Ron Postuma
- Ottawa: Michael Schlossmacher
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Pacific Parkinson's RESEARCH INSTITUTE

Parkinson Canada

Parkinson Society British Columbia

Weston Family Foundation

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Djavad Mowafaghian CENTRE FOR BRAIN HEALTH

What about gluten?

- Gluten is a protein found in several grains such as wheat, rye, barley
- Gluten has to be avoided by anyone with Celiac's disease
- Parkinson's disease is not known to be related to gluten
- A gluten-free diet can be lower in whole grains yet whole grains are an important part of a healthy diet and provide fibre
- In essence: unless you have gluten-intolerance or Celiac's disease, you should continue to eat gluten-containing foods and whole grains