



Philadelphia VA PADRECC

*Parkinson's Disease Research,
Education & Clinical Center*



Nutritional Considerations in PD

John E. Duda, MD

Director, Parkinson's Disease Research, Education and
Clinical Center Philadelphia VA Medical Center

Associate Professor of Neurology, Perelman School
of Medicine at the University of Pennsylvania

Disclosure Statement

- ▶ I have no personal financial conflicts of interest
- ▶ I will be discussing numerous off-label indications for the treatment of Parkinson's disease

Why is Nutrition important in PD?

- ▶ GI issues like gastro-intestinal dysmotility, constipation, sialorrhea and dysphagia
- ▶ Nutrition and diet affect the risk of developing PD
- ▶ Nutritional choices can affect PD medications
- ▶ People with PD are often malnourished or losing weight
- ▶ Nutritional choices can affect the symptoms of PD
- ▶ Nutritional choices may affect the progression of PD

Does diet contribute to risk of PD?

- ▶ Analysis of Health Professionals Follow-Up Study and the Nurses' Health Study
- ▶ Over 130,000 subjects! Over 500 PD subjects!
- ▶ Conclusion: Dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and a low intake of saturated fat and a moderate intake of alcohol may protect against PD

Dietary Flavonoids may be part of the reason

- ▶ Same studies, over 20 years f/u and >800 PD
- ▶ Assessed intake of five major sources of flavonoid-rich foods (tea, berry fruits, apples, red wine, and orange/orange juice)
- ▶ In men, after adjusting for multiple confounders, participants in the highest quintile of total flavonoids had a 40% lower PD risk than those in the lowest quintile
- ▶ Also, intakes of anthocyanins and a rich dietary source, berries, were significantly associated with a lower PD risk (HR 0.76 for anthocyanins and 0.77 for berries).

Coffee is protective

- ▶ One of the most consistently identified nutrients associated with PD protection
- ▶ Meta-analysis of over 900,000 subjects
- ▶ Found a 28% reduction in risk of developing PD
- ▶ Maximum benefit reached at approximately 3 cups of coffee daily.

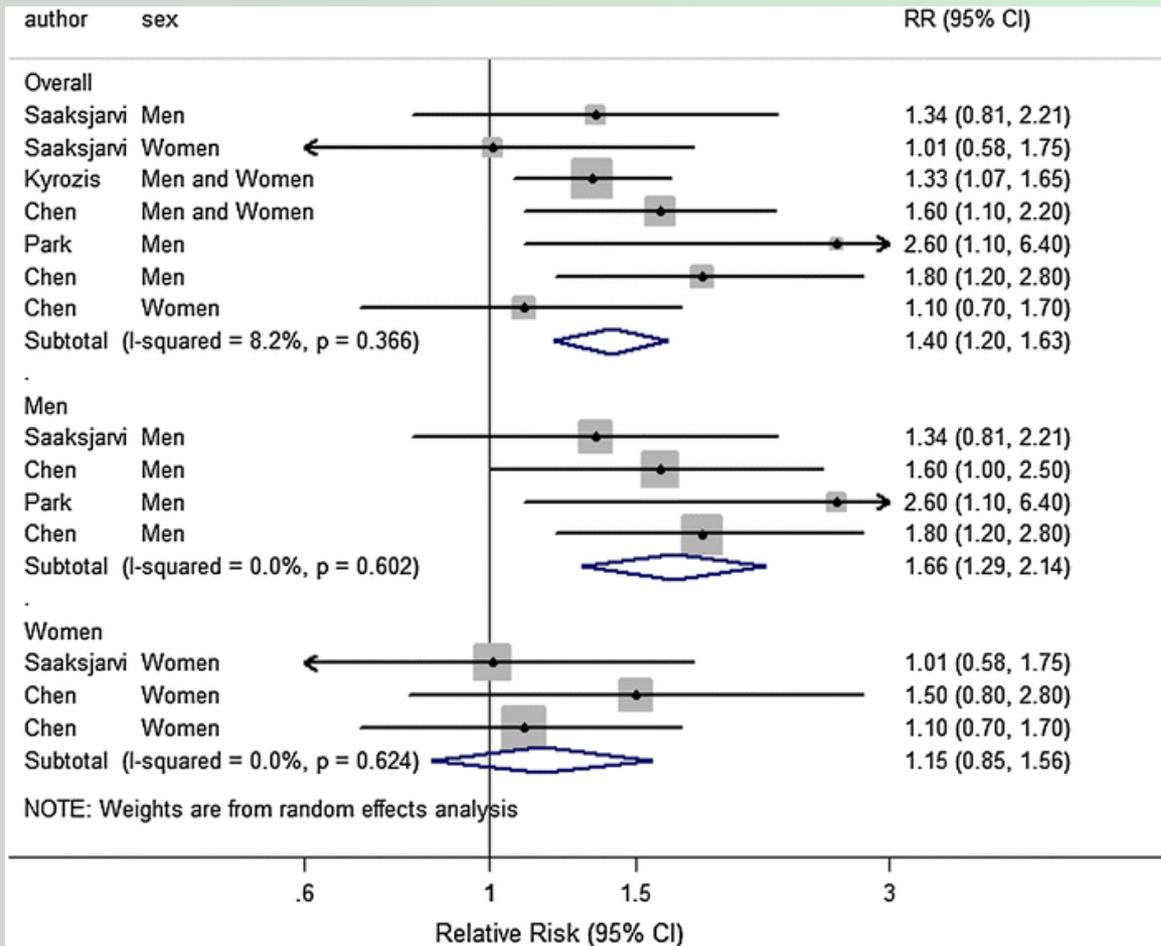


Green & Black Tea are also protective

- ▶ Consumption of 3+ cups/ day of tea delayed motor symptom onset by 7.7 years.



Milk intake and risk of PD in Prospective Studies



PD risk increased by 17% [1.17 (1.06-1.30)] for every 200 g/day increment in milk intake, and 13% [1.13 (0.91-1.40)] for every 10 g/day increment in cheese intake

Dietary Fat intake and PD

Parkinson's disease and dietary fat intake in the FAME Study.

Type of fat	% Energy	Cases		Controls		OR ^a	95% CI	p-trend
		N	%	N	%			
Total	0–34.20	33	37	112	33	1.0	Referent	0.23
	34.21–38.98	31	35	111	33	0.9	0.5 1.6	
	≥38.99	25	28	113	34	0.7	0.4 1.3	
Saturated	0–11.42	33	37	112	33	1.0	Referent	0.56
	11.43–13.41	29	33	112	33	0.8	0.4 1.4	
	≥13.42	27	30	112	33	0.8	0.5 1.5	
MUFA ^b	0–12.84	32	36	112	33	1.0	Referent	0.51
	12.85–14.75	29	33	112	33	0.8	0.5 1.5	
	≥14.76	28	31	112	33	0.8	0.4 1.5	
PUFA ^b	0–6.35	34	38	112	33	1.0	Referent	0.10
	6.36–7.76	33	37	111	33	1.0	0.6 1.7	
	≥7.77	22	25	113	34	0.6	0.3 1.1	
N-6 PUFA ^b	0–5.67	33	37	111	33	1.0	Referent	0.15
	5.68–6.92	33	37	112	33	1.0	0.5 1.7	
	≥6.93	23	26	113	34	0.6	0.3 1.2	
Linoleic acid	0–5.63	33	37	111	33	1.0	Referent	0.12
	5.64–6.87	34	38	112	33	1.0	0.6 1.8	
	≥6.88	22	25	113	34	0.6	0.3 1.1	
N-3 PUFA ^b	0–0.671	45	51	112	33	1.0	Referent	0.006
	0.672–0.846	21	24	112	33	0.4	0.2 0.7	
	≥0.847	23	26	112	33	0.4	0.2 0.8	
α-Linolenic acid	0–0.597	38	43	111	33	1.0	Referent	0.010
	0.598–0.725	34	38	113	34	0.8	0.5 1.4	
	≥0.726	17	19	112	33	0.4	0.2 0.8	

“these findings suggest that a diet high in PUFAs and low in saturated fats might reduce risk of PD”

PD risk and Solanaceae (Nightshade vegetable) Consumption

Vegetable	All Participants, 486 Cases/636 Controls, RR (95% CI) ^c	Ever Used Tobacco, ^b 245 Cases/397 Controls, RR (95% CI) ^c	Never Used Tobacco, 241 Cases/239 Controls, RR (95% CI) ^c
Edible <i>Solanaceae</i> ^a	0.81 (0.67-0.98)	0.81 (0.67-0.98)	0.81 (0.67-0.98)
p_{trend}	0.07	0.07	0.07
Nicotine ^d -weighted p_{trend}	0.004	0.004	0.004
Pepper, 102.1 $\mu\text{g}/\text{kg}$ nicotine ^d	0.43 (0.27-0.70)	0.43 (0.27-0.70)	0.43 (0.27-0.70)
Tomato, 43.8 $\mu\text{g}/\text{kg}$ nicotine ^d	0.83 (0.67-1.02)	0.83 (0.67-1.02)	0.83 (0.67-1.02)
Tomato juice, 29.7 $\mu\text{g}/\text{kg}$ nicotine ^d	0.77 (0.62-0.95)	0.77 (0.62-0.95)	0.77 (0.62-0.95)
Potato, 19.25 $\mu\text{g}/\text{kg}$ nicotine ^d	1.12 (0.93-1.35)	1.12 (0.93-1.35)	1.12 (0.93-1.35)



**What about treatment
considerations?**

Dietary management of motor fluctuations

- ▶ Low protein diet and protein redistribution diets have been tried
- ▶ Meta-analysis in 2010 included 16 studies
- ▶ No support for low protein diet
- ▶ However, over two-thirds of studies reported >80 response rates
- ▶ All studies reported reductions in motor impairment or improvements in fluctuations

Which patients respond best

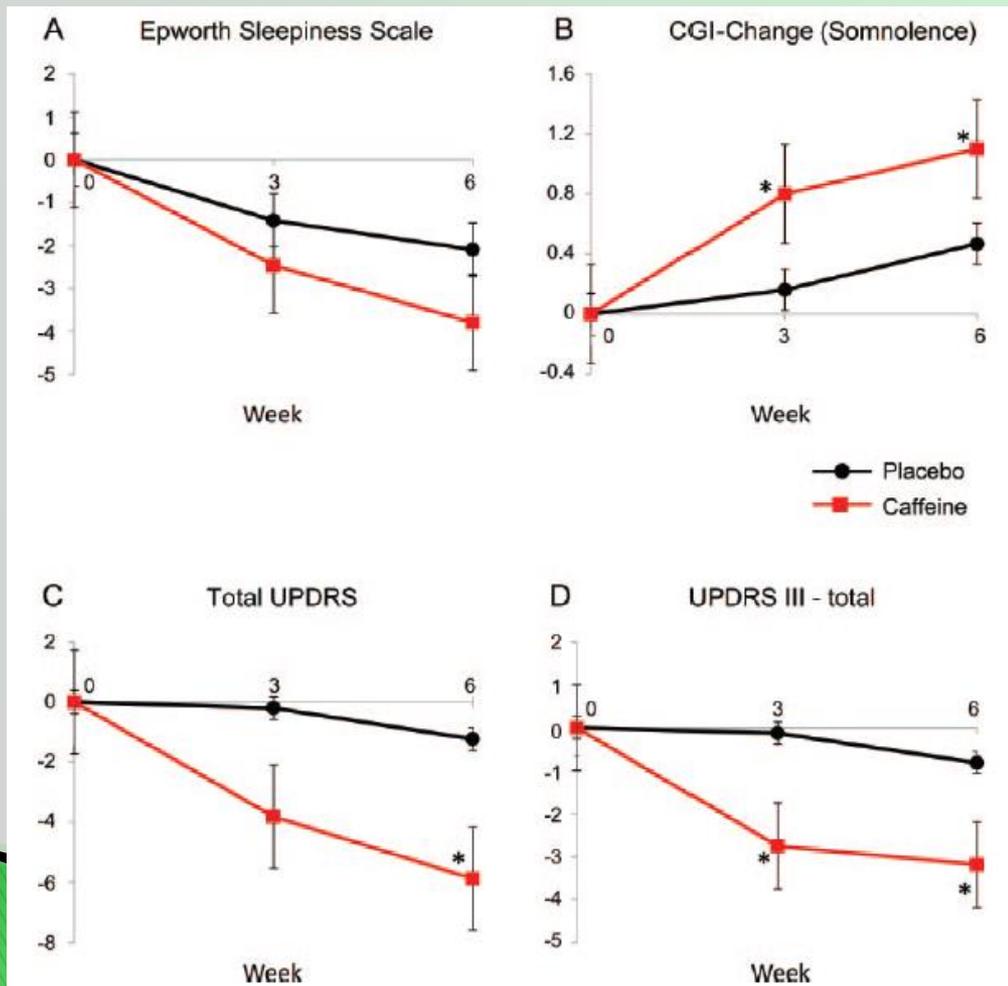
- ▶ Three studies addressed this question

Source (year)	Reference	Feature
Riley et al. (1988)	24	Shorter duration of Parkinson's disease Shorter length of levodopa treatment
Bracco et al. (1991)	26	Shorter duration of fluctuations
Giménez-Roldán et al. (1991)	28	Older age at onset and shorter duration of fluctuations

- ▶ Efficacy and benefits appeared to be higher when started early
- ▶ Long term compliance was possible

Caffeine for the treatment of PD

- ▶ 6-week randomized controlled trial of 100-200mg of caffeine in PD with daytime somnolence



Randomized unblinded trial of plant-based diet in PD

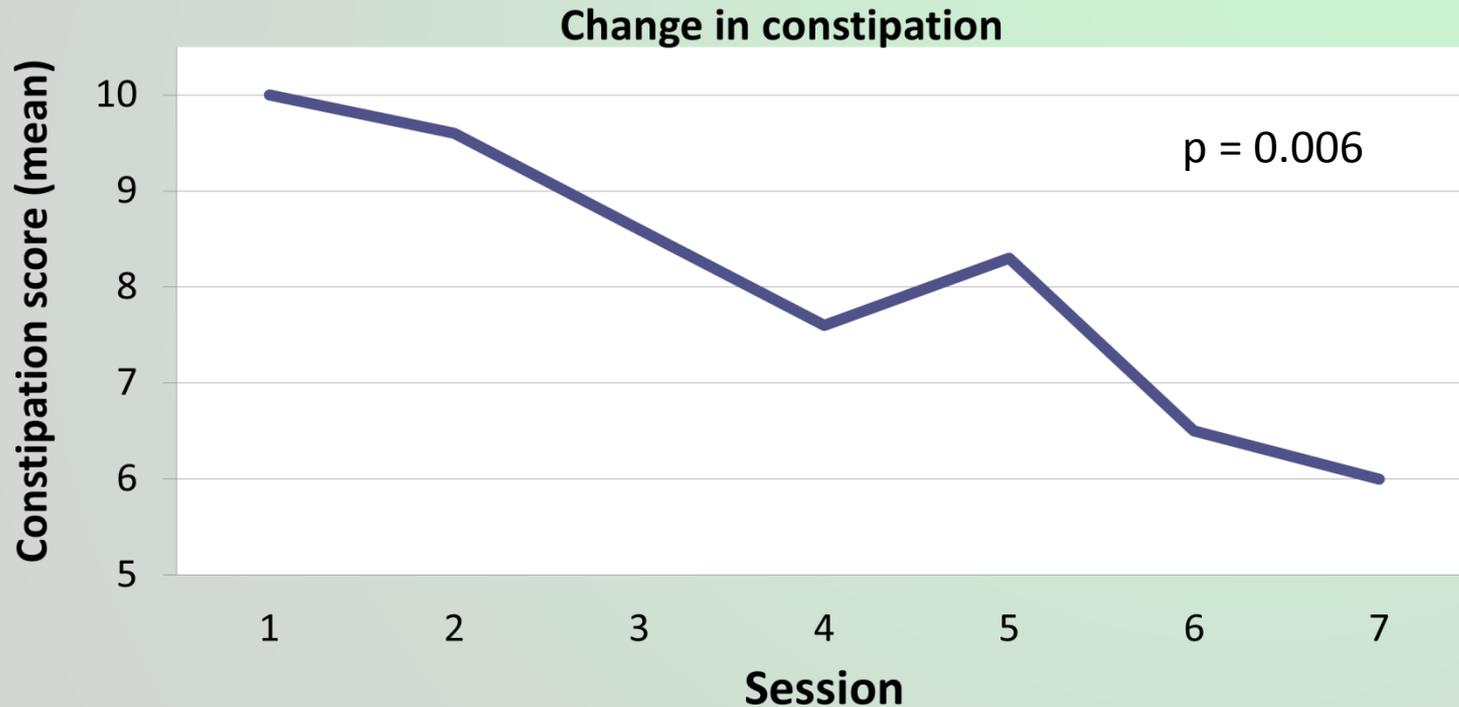
- ▶ Compared the effect of a plant-food menu to an omnivorous menu on motor performance of 25 PD patients, 12 in the intervention group (PDi) and 13 in the control group (PDc).
- ▶ After 4 weeks, the PDi group showed a significant reduction in UPDRS total score (47.67 vs. 74.46, $P = 0.008$) and sub-score III motor performances (25.42 vs. 46.46, $P = 0.001$), and the modified Hoehn and Yahr Staging Scale (1.96 vs. 3.15, $P = 0.005$)

Diet modification trial in Veterans with Parkinson's disease

- ▶ 13 PD patients enrolled in a 14-week dietary intervention studying the feasibility and effects of a plant-based diet in PD.
- ▶ 7 participants completed the study.
- ▶ Participants attended 7 bi-weekly educational seminars and food demos
- ▶ Primary outcome was Constipation Scale score. Secondary outcomes included motor UPDRS, PDQ-39, and diet changes

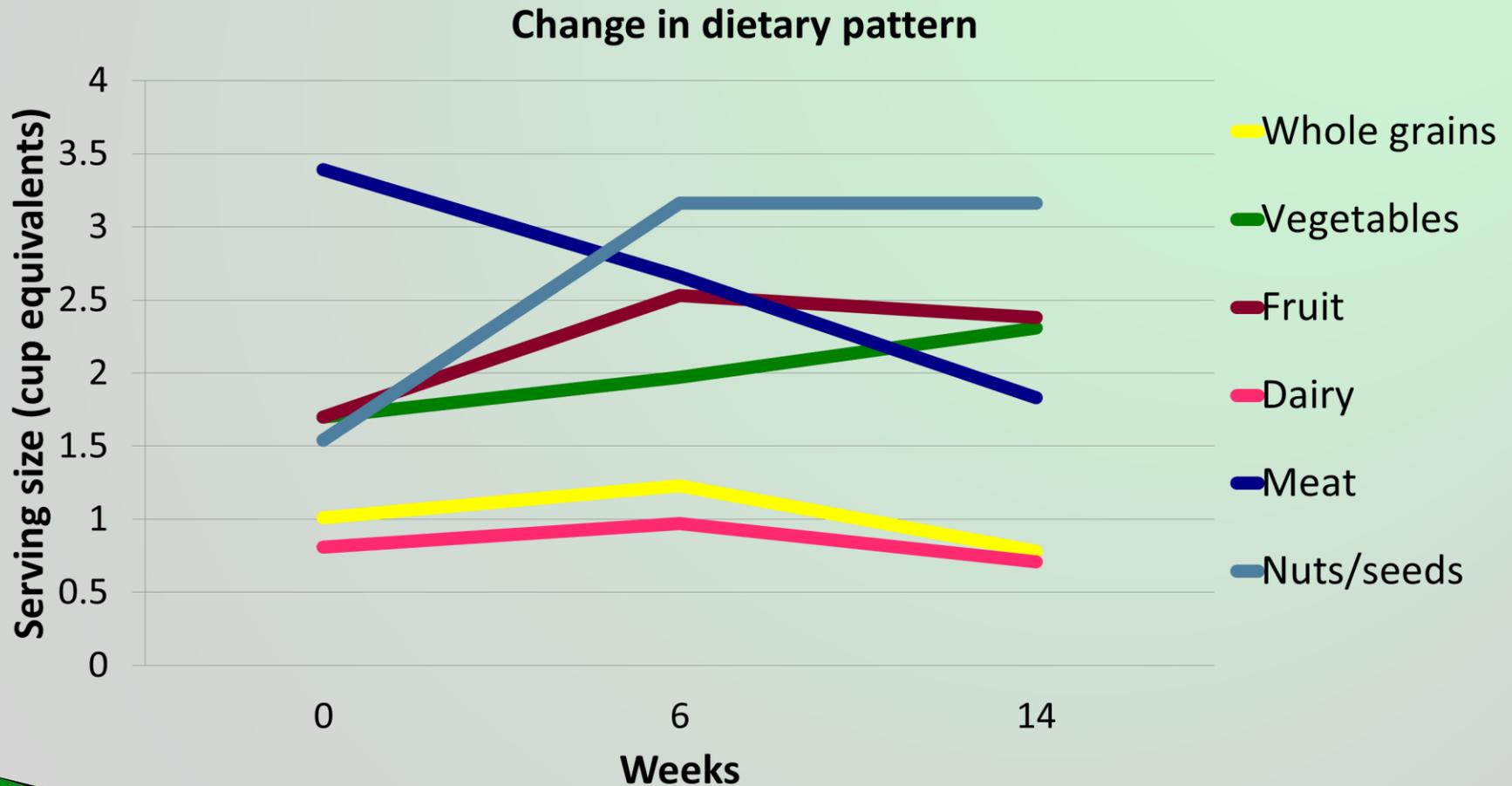
Shital Shah, Heidi Watson, Helen Kane, John Duda in preparation

Constipation Scale scores over time



Constipation was correlated with fiber intake ($r = -0.787$, $p = 0.036$)

Less Meat, More Nuts and Greens



Effect on Symptoms

	UPDRS I		UPDRS II		UPDRS III		UPDRS Total		PDQ-39	
	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
	11.1	7.9	11.9	11.6	22.7	20.7	45.7	40.1	146.1	118.3
p Value	0.121		0.925		0.447		0.263		0.272	

Obviously under-powered, but change in total UPDRS approaching a clinically meaningful difference

		UPDRS I	UPDRS II	UPDRS III	Total UPDRS	PDQ-39
Meat	r	0.458	-0.830	-0.239	-0.484	-0.377
	p	0.302	0.021	0.606	0.271	0.405

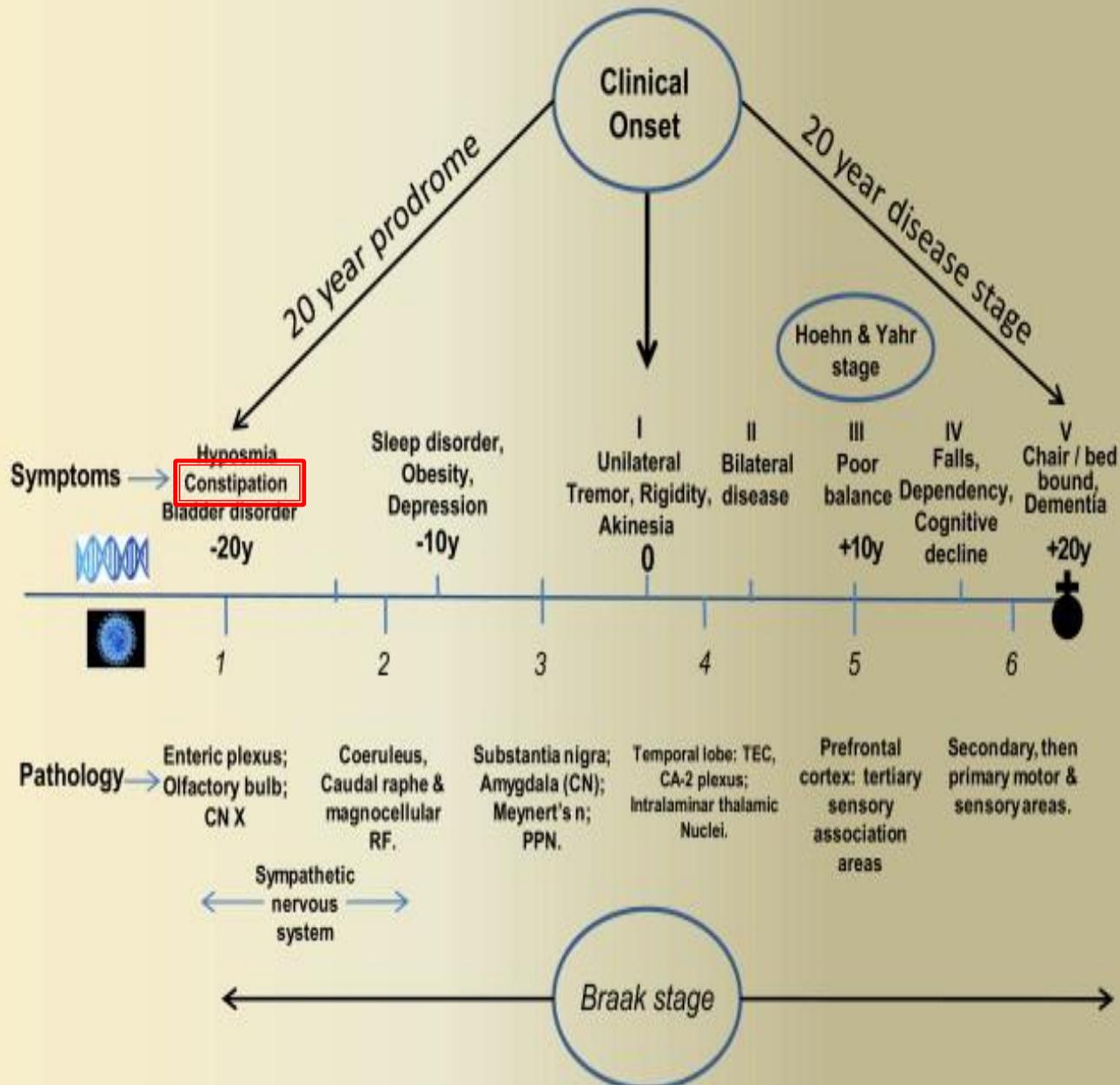
no correlations were seen for whole grains, vegetables, fruit or dairy

Conclusions

- ▶ A significant improvement was seen in constipation with increased dietary fiber consumption.
- ▶ Non-significant improvements were seen in the UPDRS and PDQ-39.
- ▶ Non-significant trends were seen in decreased meat, dairy, sugar, and fat intake and increased nut, vegetable and fiber consumption.
- ▶ This pilot study supports larger and longer studies of nutritional education and modification in the treatment of Parkinson's disease.
- ▶ A sample size of 40 would have allowed us to assess the effects of diet on PD symptoms.

The microbiome and PD

Parkinson's Disease Timeline

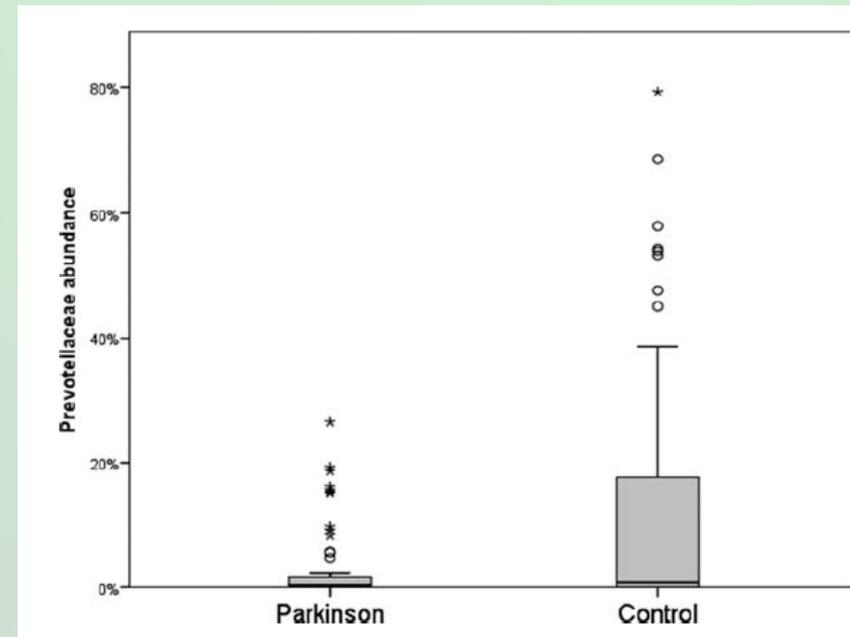


What if constipation was not an early symptom, but a risk factor for PD?

- ▶ Mid-life constipation suggests poor nutritional intake of dietary fiber
- ▶ The longer feces stays in bowels, the more neurotoxins may be absorbed
- ▶ Many pesticides have been shown to be able to cause alpha-synuclein to aggregate
- ▶ Intestinal dysbiosis may lead to inflammation and membrane permeability with absorption of bacterial endotoxins

The gut microbiome is different in PD

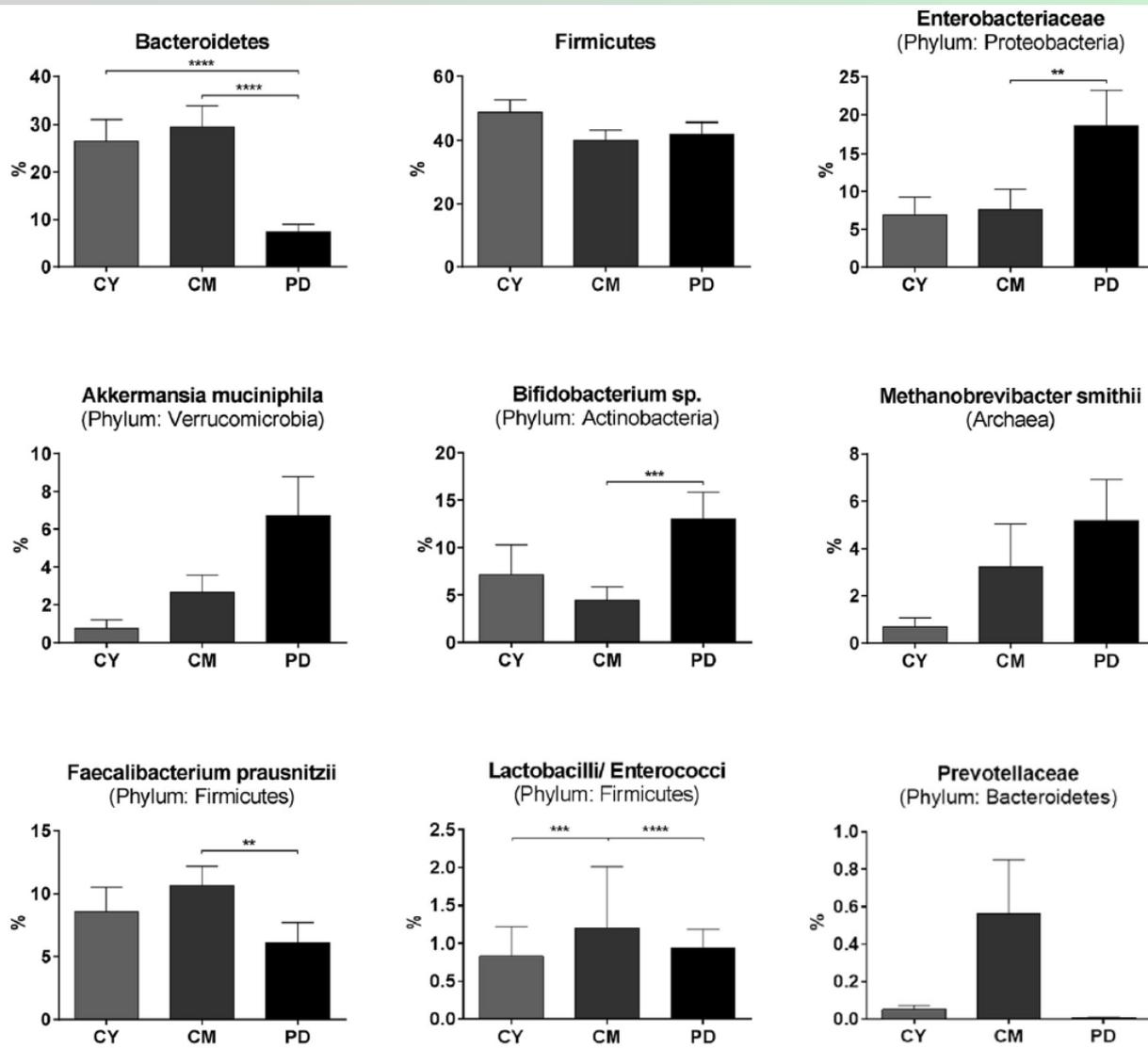
- ▶ 72 PD and 72 controls
- ▶ 16S ribosomal RNA analysis of stool samples
- ▶ Abundance of Enterobacteriaceae was related to the severity of postural instability and gait difficulty
- ▶ 77.6% reduction in abundance of Prevotella in patients with PD
- ▶ Prevotella have been shown to be health-promoting and anti-inflammatory by the production of short chain fatty acid compounds



The gut microbiome is different in PD

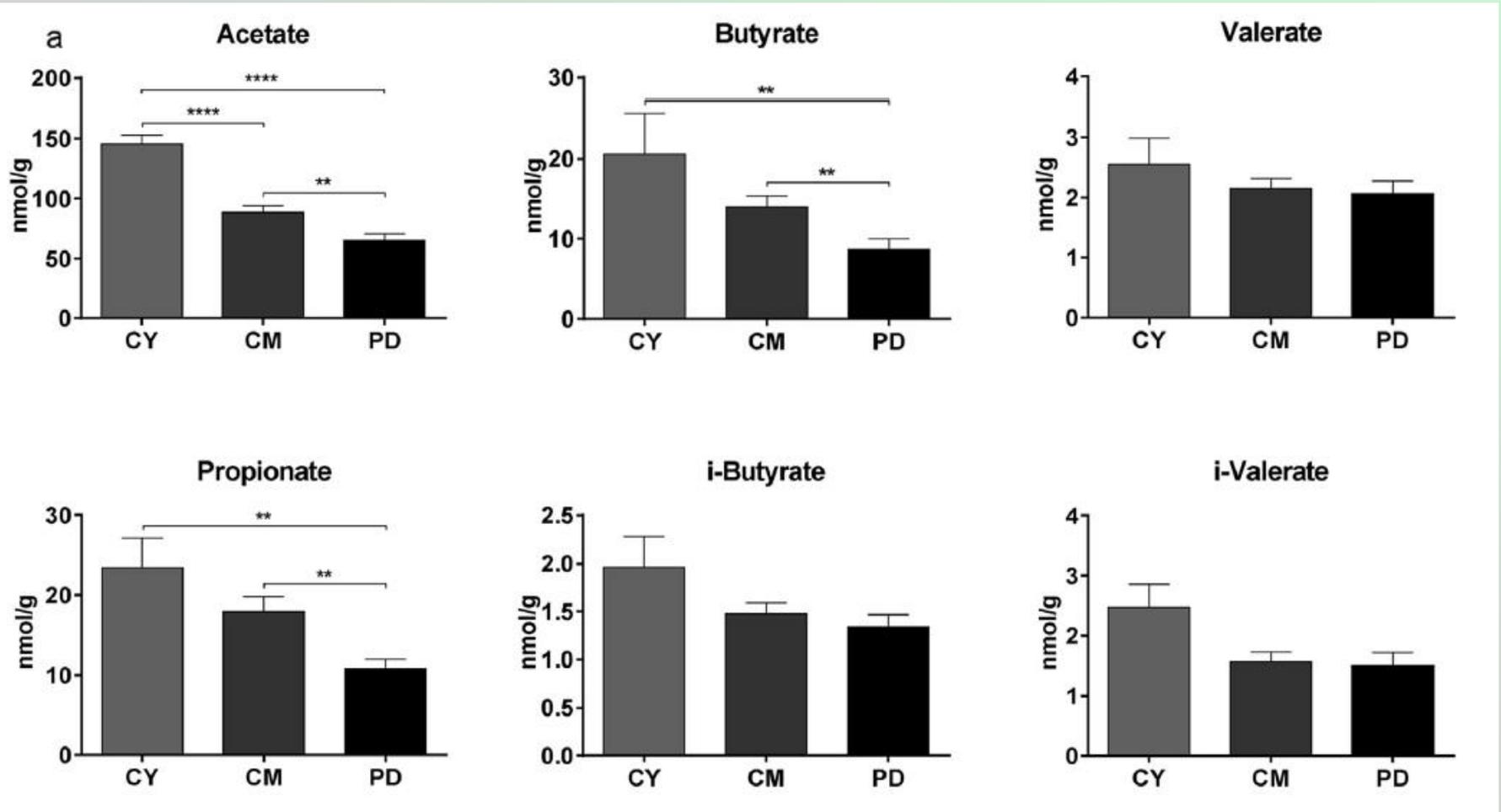
- ▶ Second study with 38 PD samples and 34 controls
- ▶ Assessed sigmoid colonic biopsies and stool
- ▶ Found a non-significant 50% decrease in *Prevotella* in biopsies but no difference in stool
- ▶ SCFA- producing *Blautia*, *Coprococcus*, and *Roseburia* were significantly more abundant in feces of controls than PD patients
- ▶ Bacteria from the genus *Faecalibacterium* were significantly more abundant in the mucosa of controls than PD.
- ▶ Putative, “proinflammatory” Proteobacteria of the genus *Ralstonia* were significantly more abundant in mucosa of PD than controls

Third confirmatory study in PD



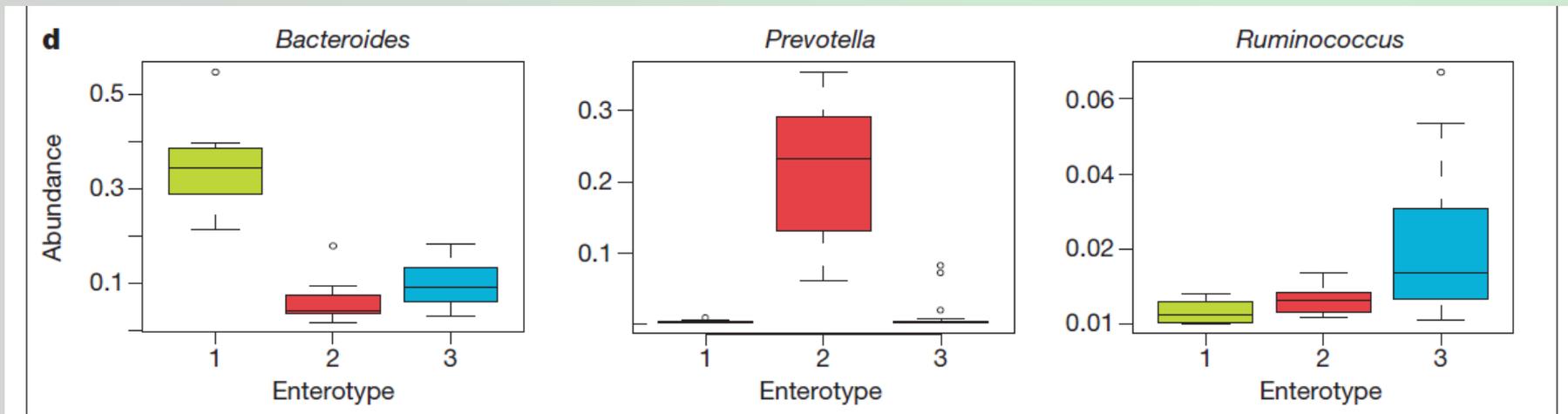
Control Young n=10
 Control old n=34
 PD n=34

Also, short chain fatty acids decreased in PD stool



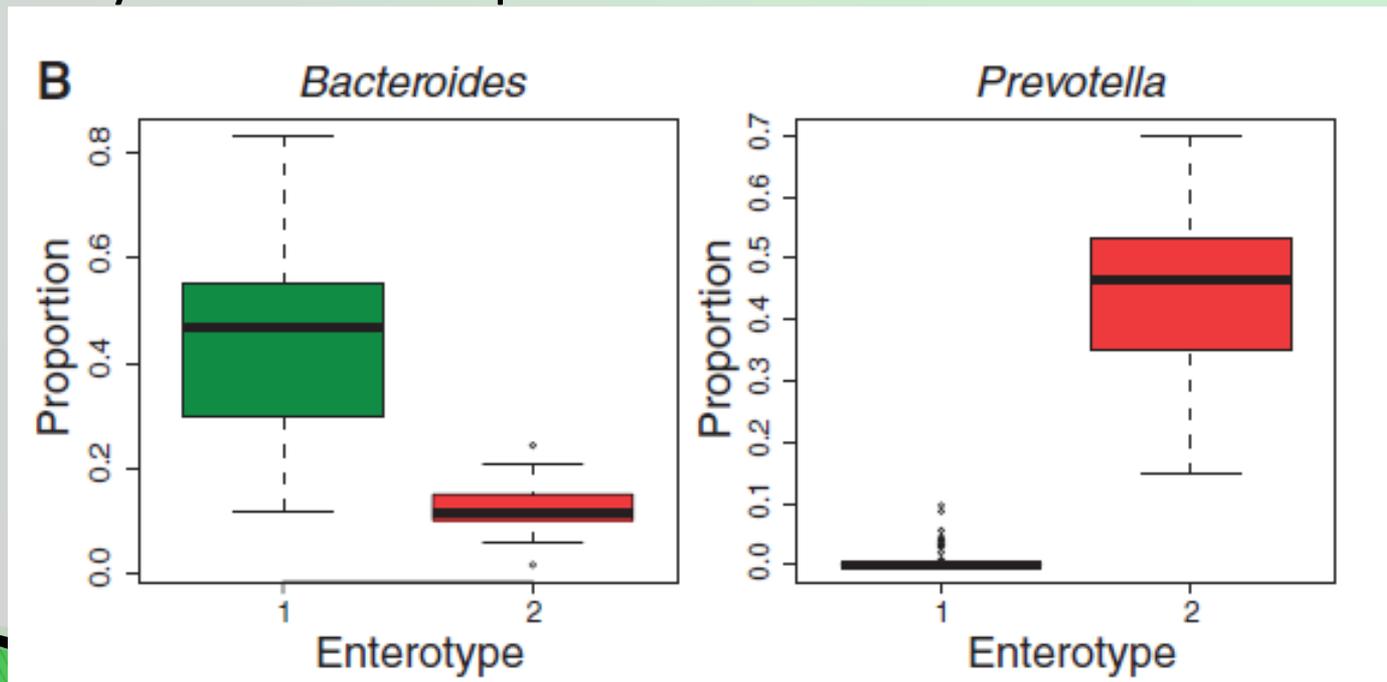
Human gut flora enterotypes

- ▶ 3 distinct enterotypes identified
- ▶ One of the distinguishing factors is prevalence of *Prevotella*



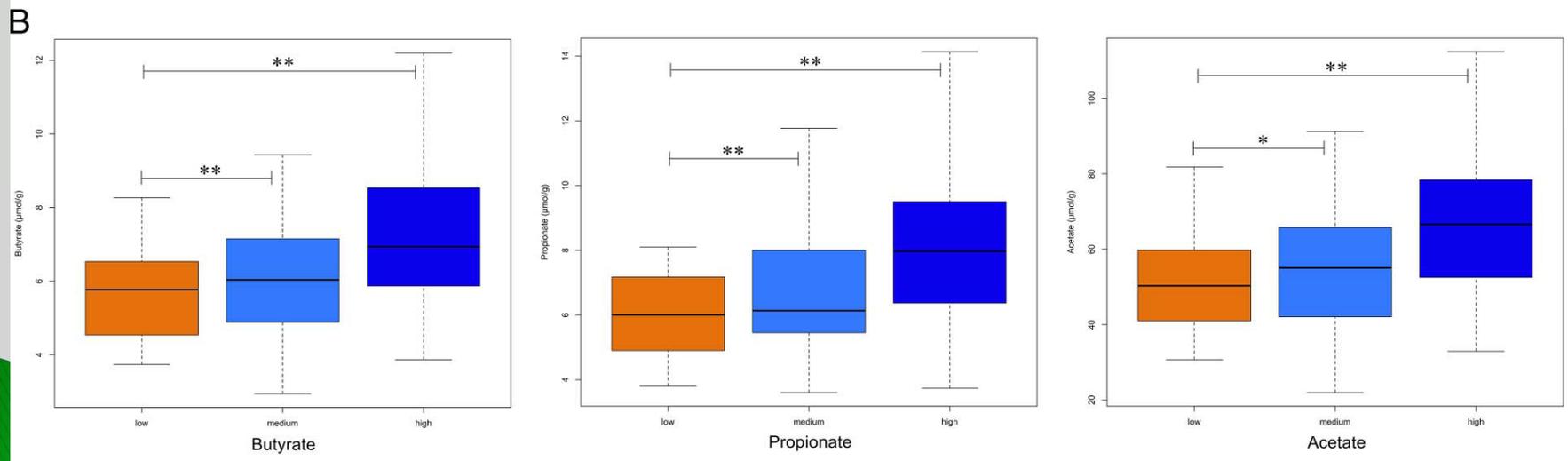
Long term diet patterns are strongly associated with enterotype

- ▶ 100 healthy controls
- ▶ Segregated into two enterotypes
- ▶ Protein and animal fat consumption – Bacteroides
- ▶ Carbohydrate consumption - Prevotella



Adherence to Mediterranean diet increases Prevotella and SCFAs

- ▶ 153 vegan, vegetarian or omnivore Italians
- ▶ The majority of vegans and vegetarians and 30% of omnivores had high Mediterranean diet scores
- ▶ There were significant associations between consumption of vegetable-based diets and increased levels of fecal short-chain fatty acids, Prevotella and some fiber degrading firmicutes, despite overall diet type

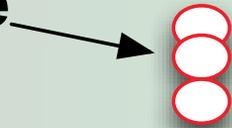


Could plant phytonutrients be neuroprotective in PD?

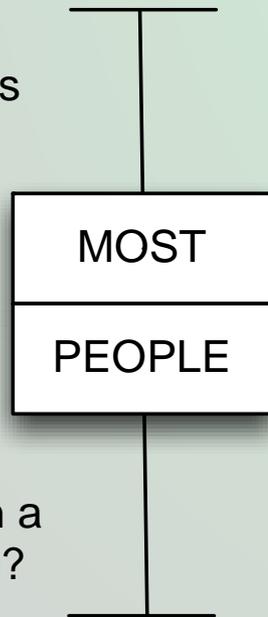
Group	Sub-group	Individual compound or phytonutrient	Major food source
1. Flavonoids	1.1 Flavonols	Kaemferol Quercetin Myricetin	Apples, onions, tomatoes, lettuce, celery, tea, red wines
	1.2 Flavones	Apigenin Luteolin	
	1.3 Flavanols	(+)-Catechin (-)-Epicatechin (-)-Epigallocatechin (-)-Epicatechin gallate Proanthocyanidins	Tea
	1.4 Anthocyanidins	Pelargonidin Cyanidin Delphinidin Peonidin Petunidin Malvidin	Cherries, blueberries
	1.5 Flavanones	Hesperdin Neohesperidin Naringin	Citrus fruits
	1.6 Chalcones & dichalcones	Retrochalcone Isosalipurpuring Phloretin	
	1.7 Isoflavones	Genistein Daidzein Coumestrol	Pulses, eg, soy
2. Carotenoids	2.1 Provitamin A hydrocarbon carotenoids	β -carotene α -carotene	Red to orange pigmented fruits and vegetables,

Thriving with Parkinson's Disease

Who are the
**POSITIVE
DEVIANTS ??**



Can we identify diet, lifestyle, and supplements associated with those doing unusually well?



Are there behavior patterns associated with a more rapid progression?

Study Goals:

Describe lifestyle habits and therapies being used by individuals with PD.

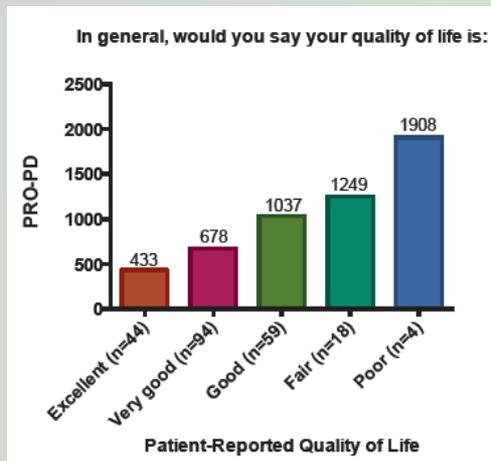
Identify what those who are doing unusually well have in common.

Patient Reported Outcomes in PD (PRO-PD)

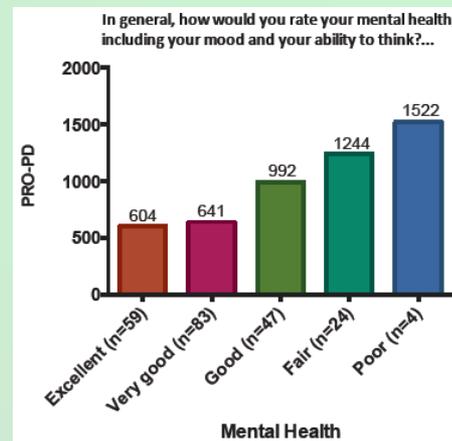
www.propd.org

Falling * must provide value	Never	Occasionally	Daily	<input type="range" value="0"/>	0	reset
Rising from Seated Position * must provide value	With ease	With effort	Unable to rise	<input type="range" value="31"/>	31	reset
Dressing, Eating, & Grooming * must provide value	With ease	With effort	Unable	<input type="range" value="51"/>	51	reset
Motivation/ Initiative * must provide value	Engaged, active	Withdrawn, detached, or isolated		<input type="range" value="23"/>	23	reset
Handwriting or Typing * must provide value	Great; with ease	Slow or small	Completely illegible	<input type="range" value="76"/>	76	reset
Depression (feeling sad, blues) * must provide value	Mentally healthy	Persistent sorrow	Severe	<input type="range" value="18"/>	18	reset

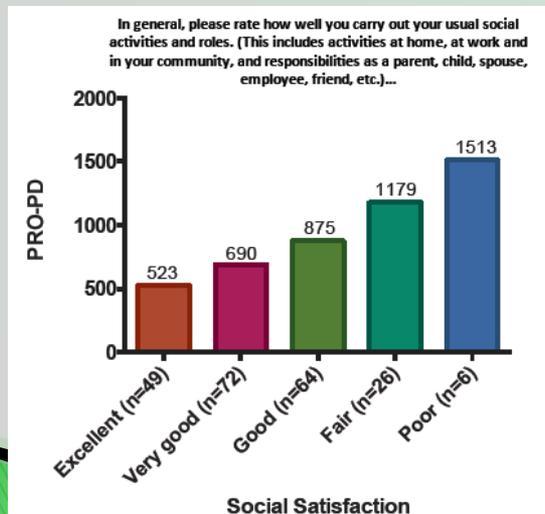
Quality of Life



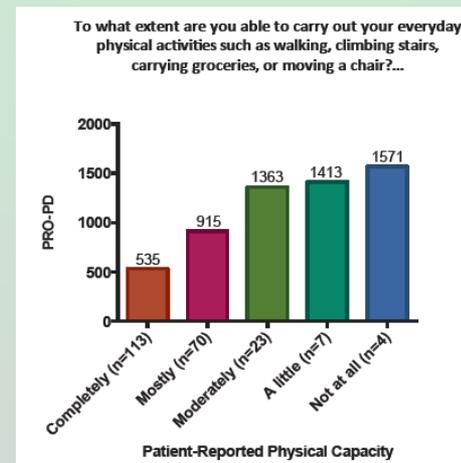
Mental Health



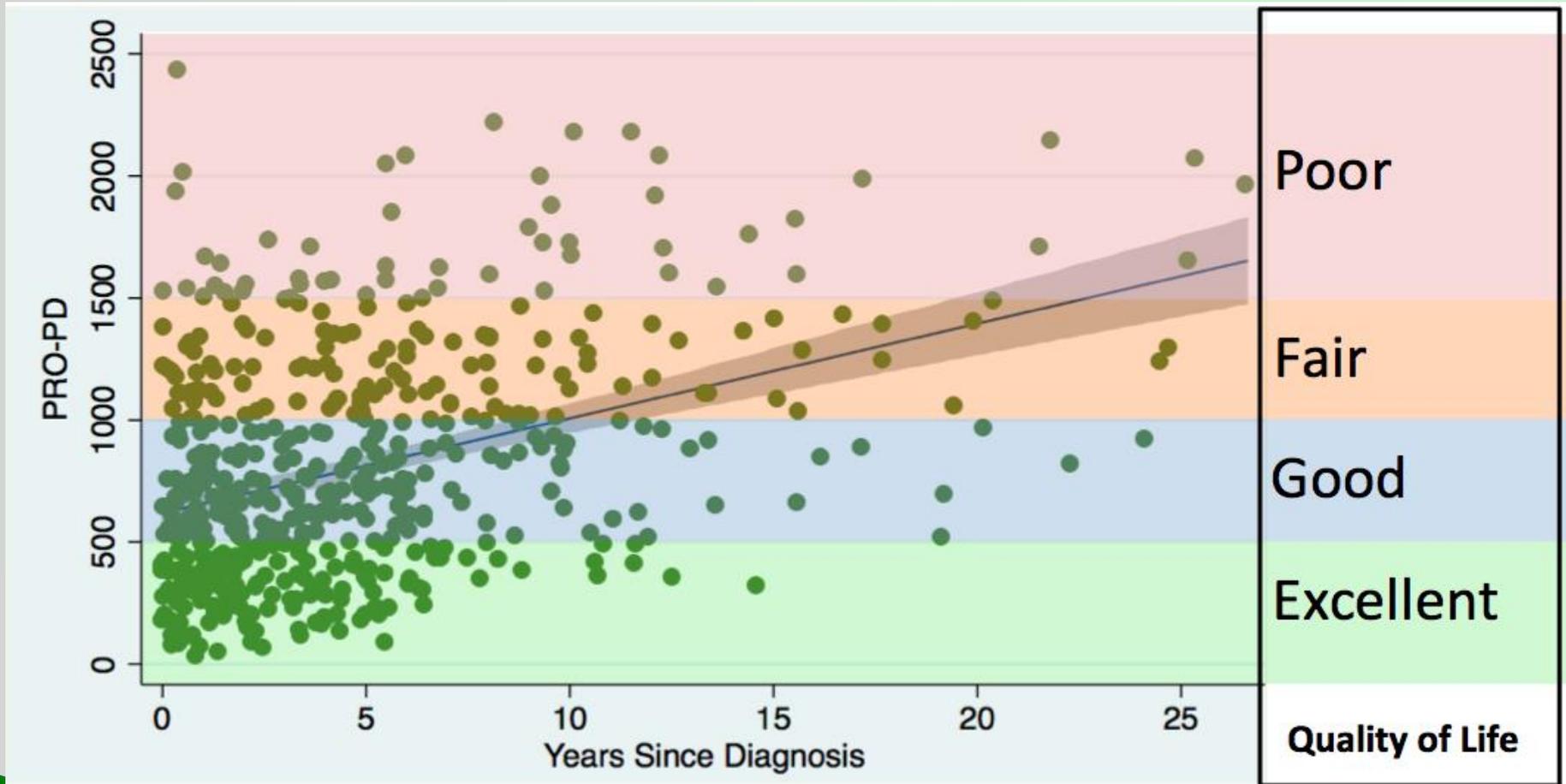
Social Satisfaction



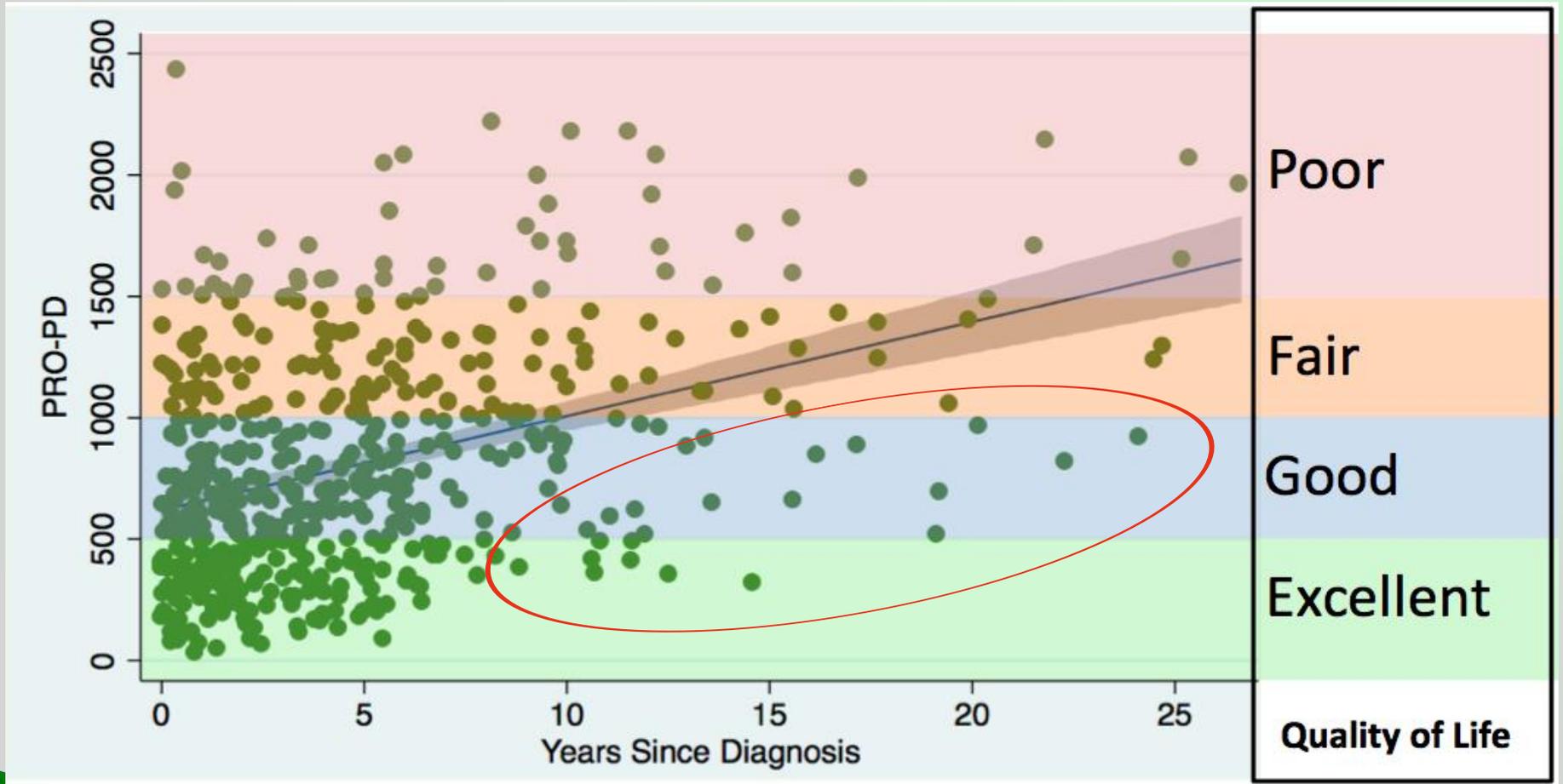
Physical Capacity



PRO-PD & Quality of Life



What are these people doing?



Study Population: 1024 people with PD

Demographics	N=1024
Years Since Diagnosis	5.15 (5.3)
Age, years (SD)	60.7 (9.7)
<u>Gender</u>	
Female	525 (51%)
Male	429 (49%)
<u>Ethnicity</u>	
Caucasian	913 (89%)
Black	8 (1)
Asian/ Pacific Islander	11 (1%)
Hispanic	15 (2%)

Quantifying Dietary Intake

Fresh Fruit - 1 medium, 1/2 cup

- Never
- <1 per month
- 1 per month
- 2-3x month
- 1 per week
- 2-4x week
- 5-6x week
- Once daily
- 2-4x day
- 4-6x day

Improved Outcomes with Food

	Predicted Point Reduction	P	95% CI
<u>Intake Associate with Lower PROPD score</u>		< 0.000	
Fresh Fruit - 1 medium, 1/2 cup	-51	< 0.000	-69.4, -32.7
Fresh Vegetables - 1/2 cup	-48	< 0.000	-64.7, -31.2
Nuts and Seeds - 1/4 cup or 2 Tbsp spread (e.g. peanut butter)	-41	< 0.000	-57.6, -24.4
Olive oil - 1 tsp	-35	< 0.000	-48.5, -20..8
Fish (non-fried) - 4 ounces	-29	0.003	-47.9, -9.5
Wine - 1 med glass, 6 oz	-23	< 0.000	-34.3, -11.2
Eggs - 1 egg	-22	0.018	-39.7, -3.7
Fresh herbs (thyme, basil) - 1 tsp	-22	0.002	-34.9, -8.1
Coconut oil - 1 tsp	-13	0.032	-25.6, -1.1

Worse Outcomes

	Predicted Point Reduction	P	95% CI
<u>Intake Associate with Higher PROPD score</u>		< 0.000	
Fried foods (fries, chicken, etc) - 4 ounces	+20	0.040	0.88, 38.14
Canned Vegetables - 1/2 cup	+20	0.008	5.27, 34.49
Beef - 4 ounces or 1 medium patty	+20	0.027	2.30, 37.70
Diet soda - 12 ounces, 1 can	+21	0.001	8.46, 34.12
Canned Fruit - 1/2 cup	+37	0.000	20.56, 52.88

Interpreting the Data

- ▶ Protective foods cohesive with **Mediterranean diet**.
 - Existing body of literature suggests Mediterranean diet protects against neurodegenerative disease.
 - Mediterranean diet has been associated with improved outcomes in Alzheimer's disease
- ▶ But how does diet compare to other lifestyle modifications?

Exercise

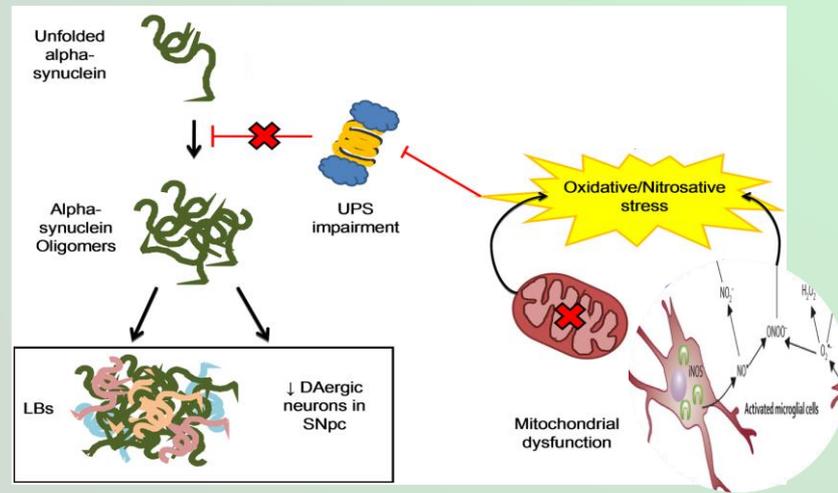
	Predicted Point Reduction	P	95% CI
<u>Day with at least 30 minutes of physical activity</u>			
1	-20	0.833	-203.4, 164.3
2	-65	0.407	-217.9, 88.4
<u>3</u>	-144	0.045	-285.3, -3.5
4	-233	0.001	-373.0, -92.6
5	-252	0.000	-391.6, -112.2
6	-253	0.001	-400.1, -106.7
7	-330	0.000	-469.5, -190.3

Social Health

	Predicted Point Reduction	P	95% CI
Friends	-150	0.000	-212.2, -88.7
Overweight	+152	< 0.000	92.4, 212.3
I am lonely	+323	< 0.000	246.8, 399.6
I am a veteran	+150	< 0.000	66.0, 234.2

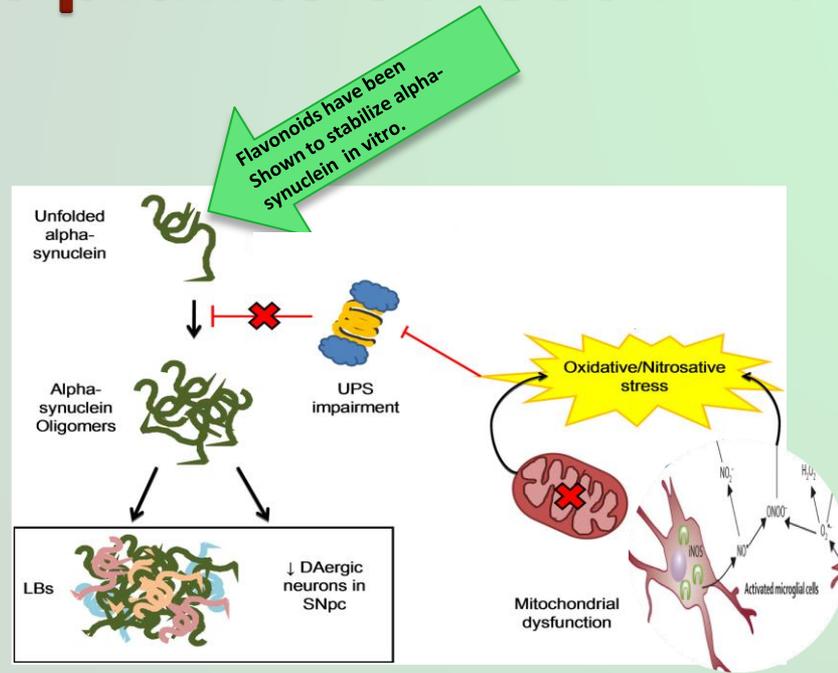
- Pets, church, meditation, vegetarian, seem to not matter so much...
- Loneliness one of the strongest predictors identified

How might plants affect PD?



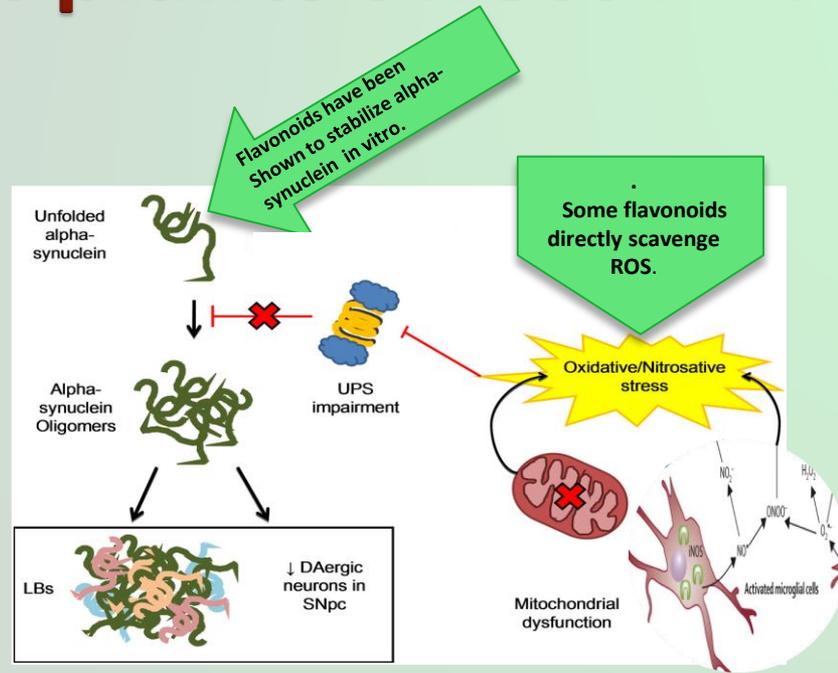
Some of the basic mechanisms thought to be involved in the pathophysiology of PD

How might plants affect PD?



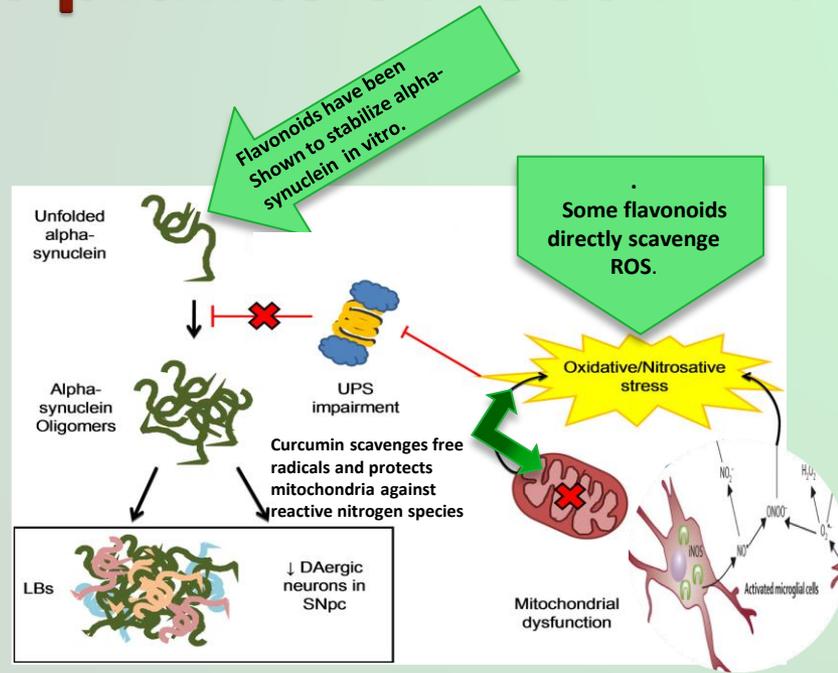
Some flavonoids have been shown to stabilize alpha-synuclein in vitro. *Biochemistry*. 2009;48(34):8206-24.

How might plants affect PD?



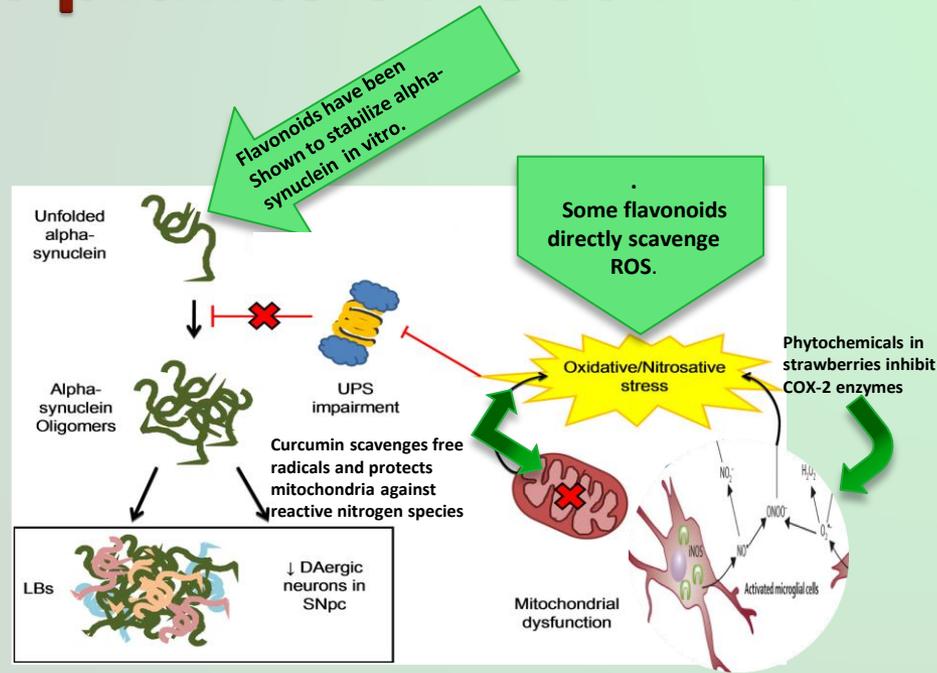
Many phytochemicals have antioxidant properties. Flavonoids, the largest group of phytochemicals, directly scavenge reactive oxygen species. *Nutr Neurosci.* 2012;15(1):1-9.

How might plants affect PD?



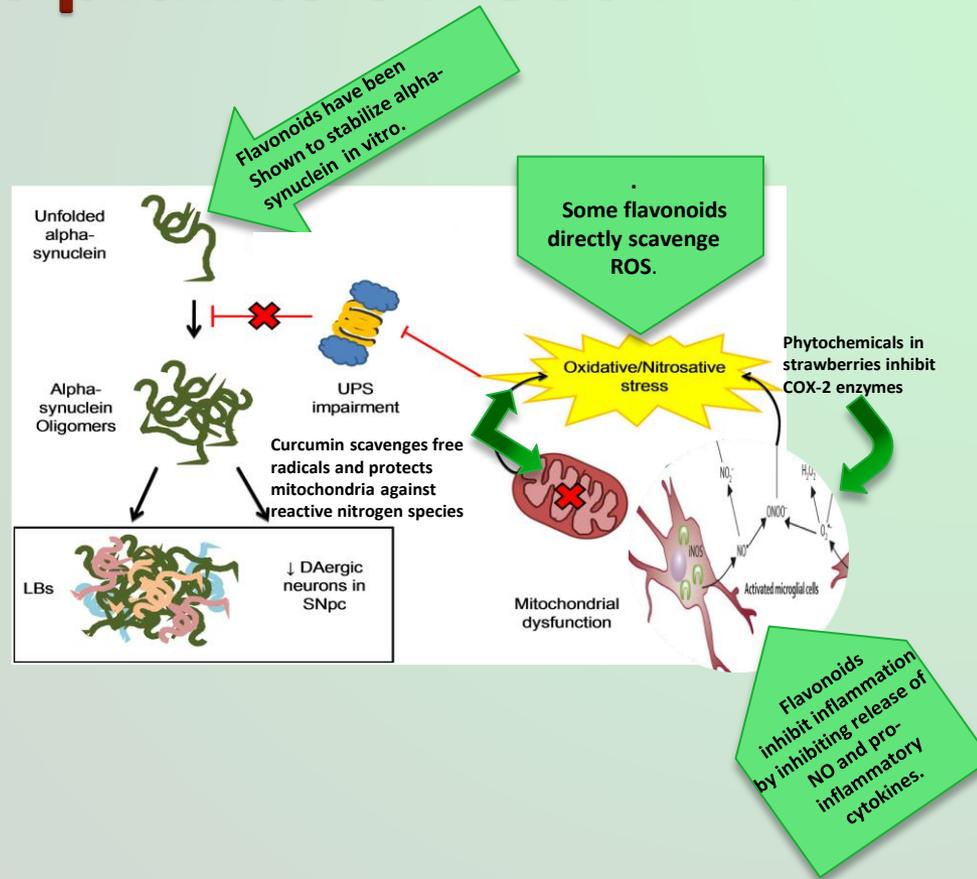
Curcumin, a polyphenol found in turmeric, scavenges free radicals and protects mitochondria against reactive nitrogen species. *Curr Pharm Des.* 2012;18(1):91-9.

How might plants affect PD?



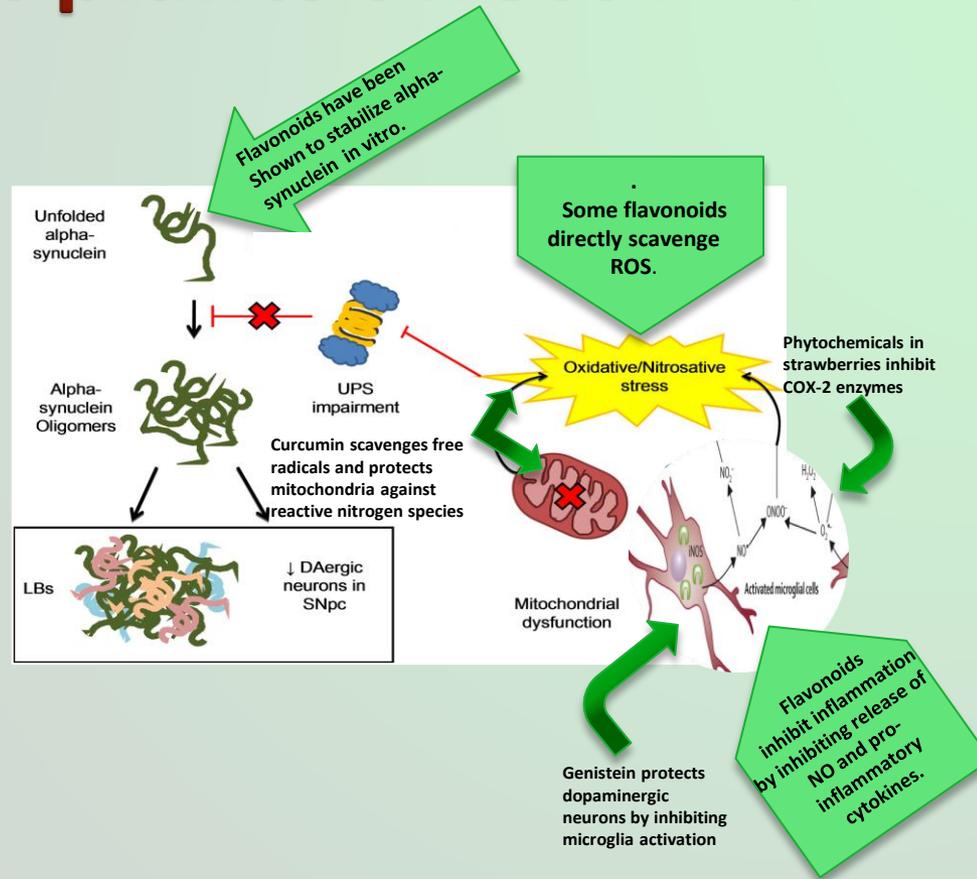
Phytochemicals in strawberries inhibit cyclooxygenase (COX) which is a key enzyme that plays an important role in the conversion of arachidonic acid to various eicosanoids involved in inflammation. Neural Regen Res. 2014;9(16):1557-66

How might plants affect PD?



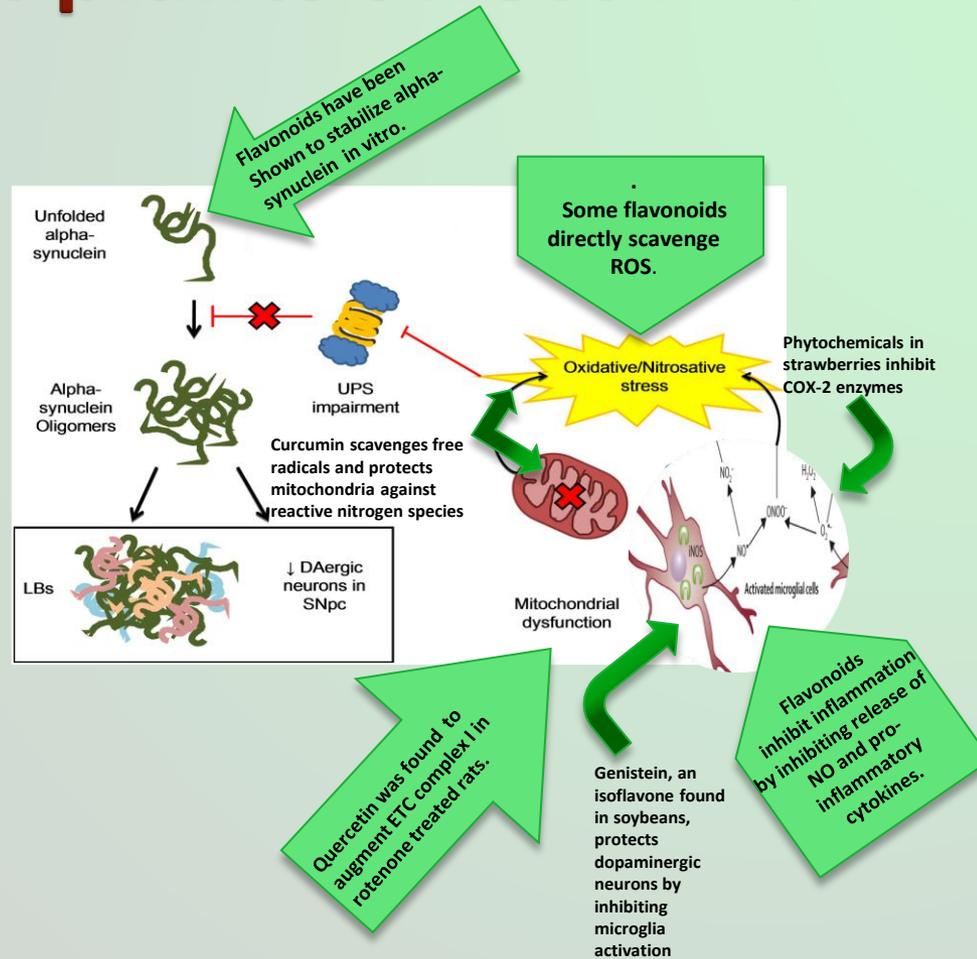
Flavonoids inhibit inflammation by inhibiting release of NO and pro-inflammatory cytokines. Br J Nutr. 2008;99 E Suppl 1:ES60-77.

How might plants affect PD?



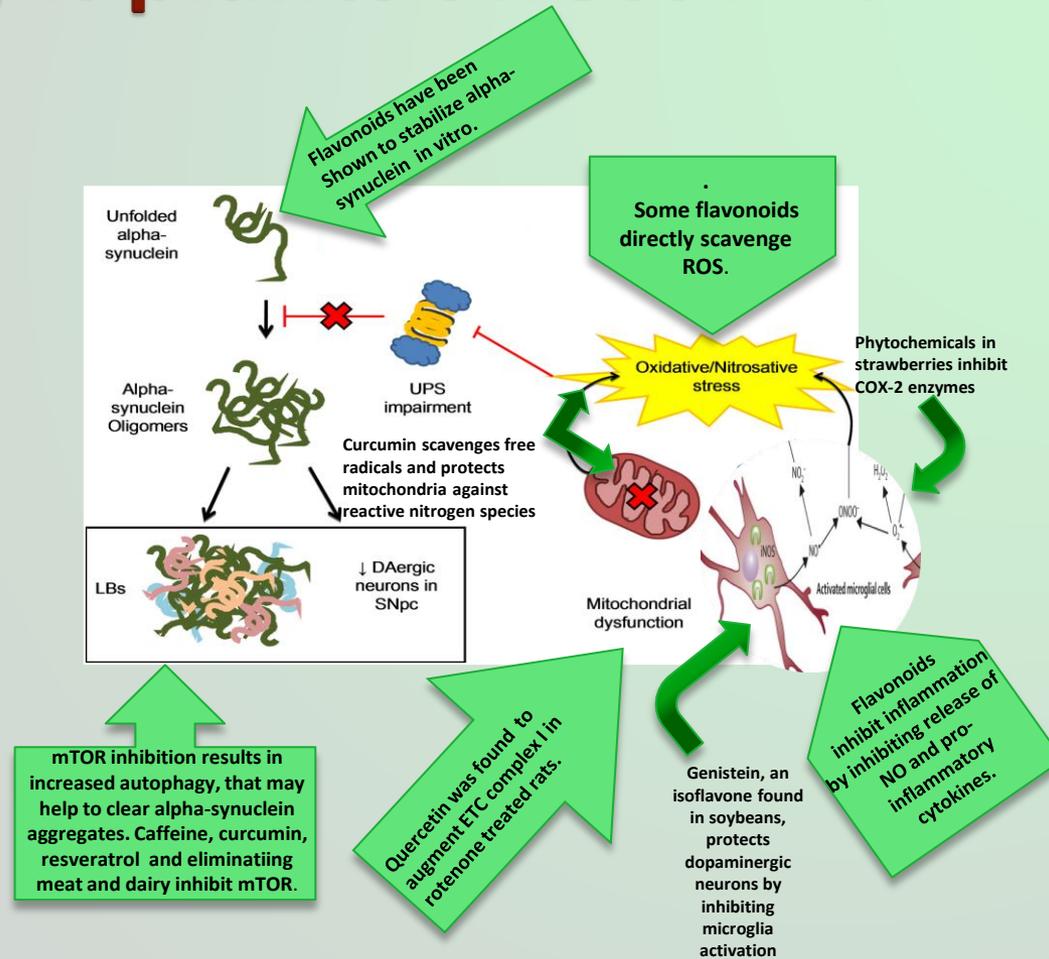
Genistein, an isoflavone found in soybeans, protects dopaminergic neurons by inhibiting microglia activation. *Food Funct.* 2010;1(1):15-31

How might plants affect PD?



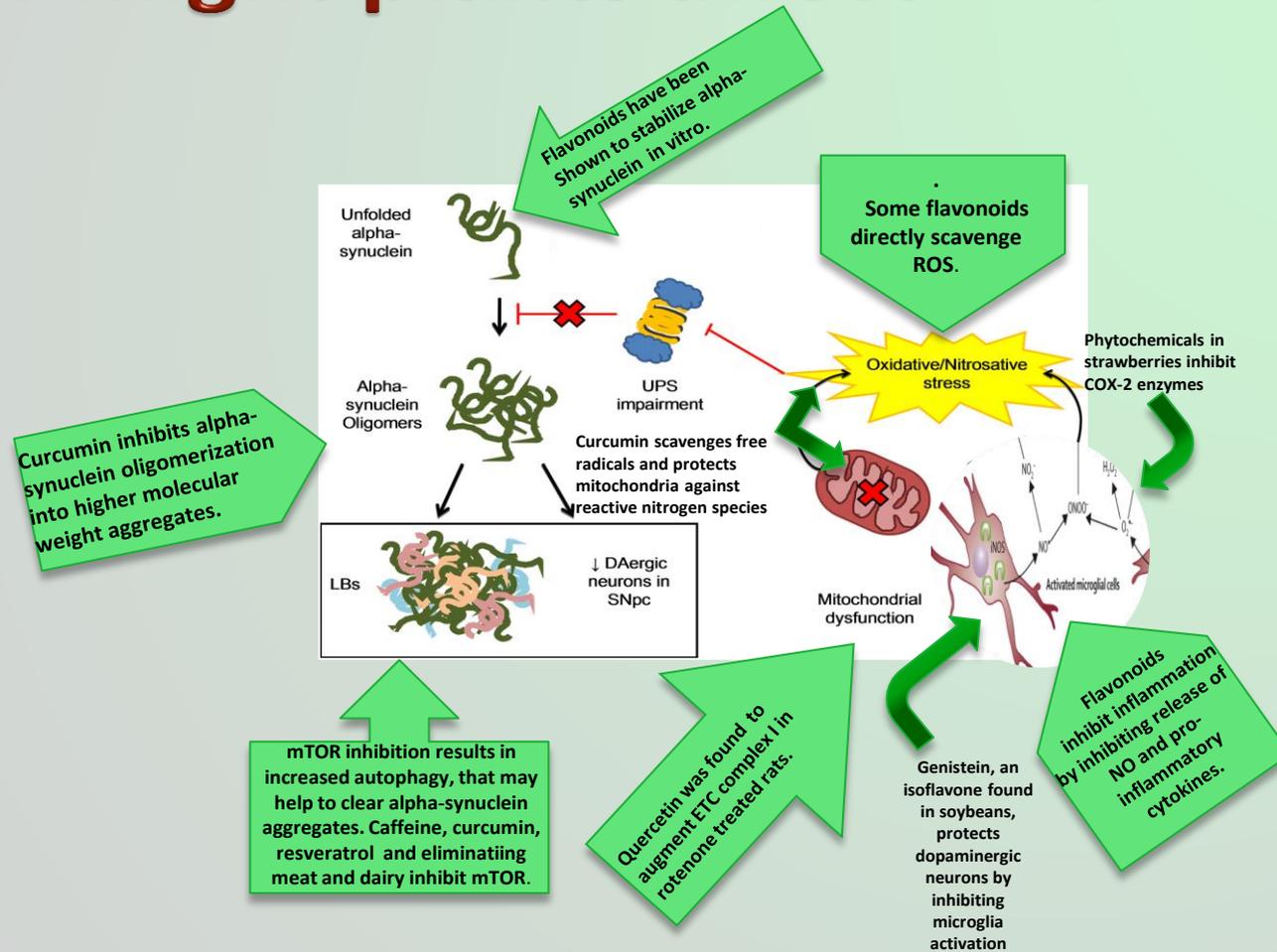
Quercetin, a flavone found in teas, grapes, onions, apples, tomatoes, and berries was found to augment electron transport complex I in rotenone treated rats. *Neuroscience*. 2013;236:136-48.

How might plants affect PD?



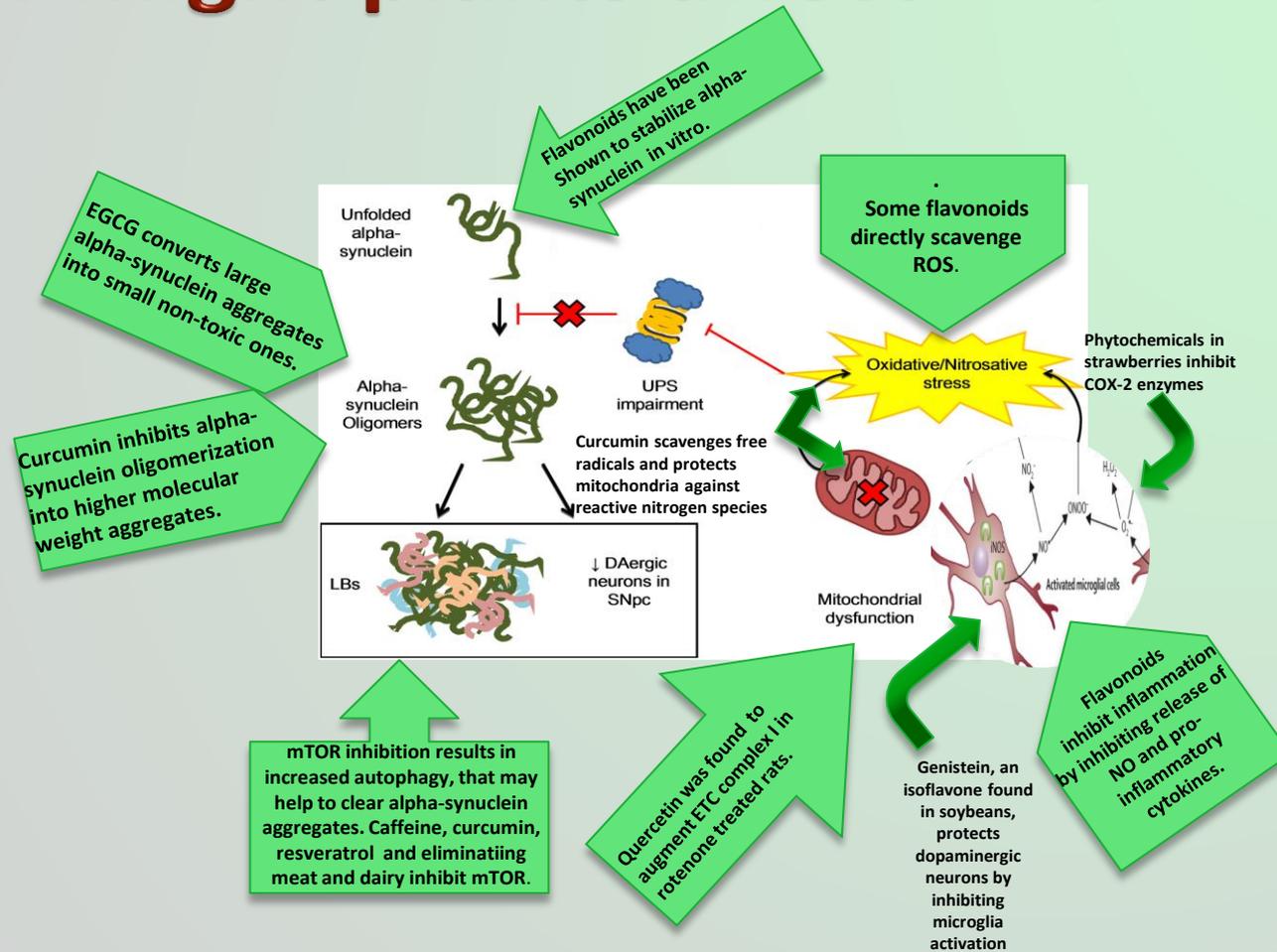
Some phytochemicals inhibit mTOR and induce autophagy which may clear Lewy bodies. Anticancer Agents Med Chem. 2010;10(7):571-81

How might plants affect PD?



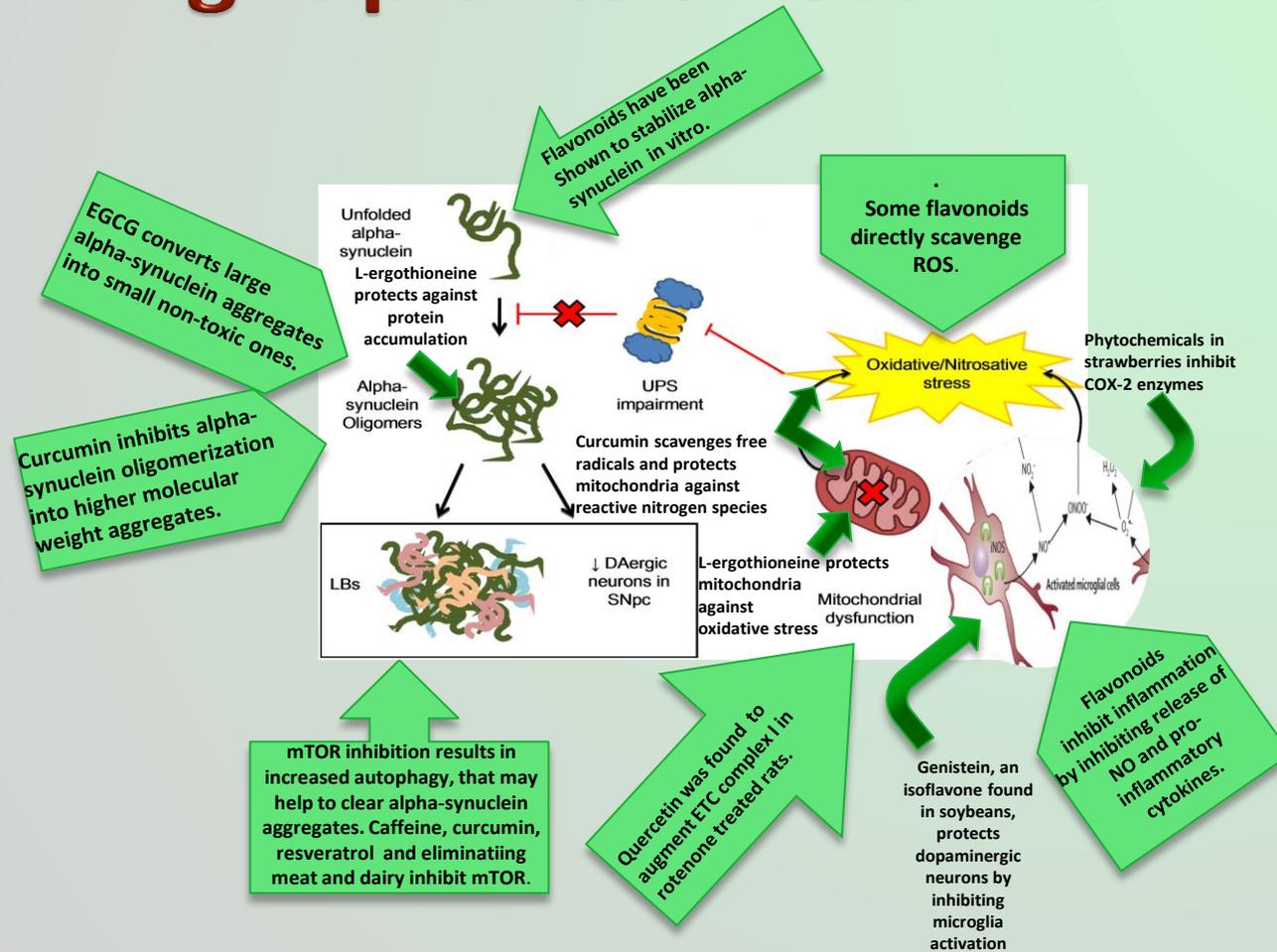
Curcumin has also been shown to inhibit alpha-synuclein oligomerization into higher molecular weight aggregates. Acta Neuropathol 2008;115:479–489

How might plants affect PD?



Epigallocatechin gallate (EGCG), a member of a family of flavanols and most abundant in green tea, inhibits fibril formation of alpha-synuclein, by binding beta-sheet rich aggregates, transforming large alpha-synuclein fibrils into smaller, non-toxic, amorphous protein aggregates that are not toxic to cells. *FEBS Lett.* 2011, 585, 1113–1120.

How might plants affect PD?



L-ergothioneine is an amino-acid, derived from histidine and found in mushrooms. It scavenges ROS, chelates metal cations, and protects against protein aggregation. Recently, it was shown that the metabolomics profiles of PD patients contained lower levels of ergothioneine. Cell Death Differ. 2010;17:1134

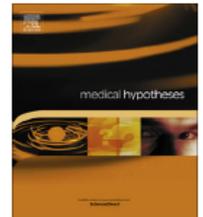
Medical Hypotheses 85 (2015) 1002–1005



Contents lists available at [ScienceDirect](#)

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Dietary modifications in Parkinson's disease: A neuroprotective intervention?

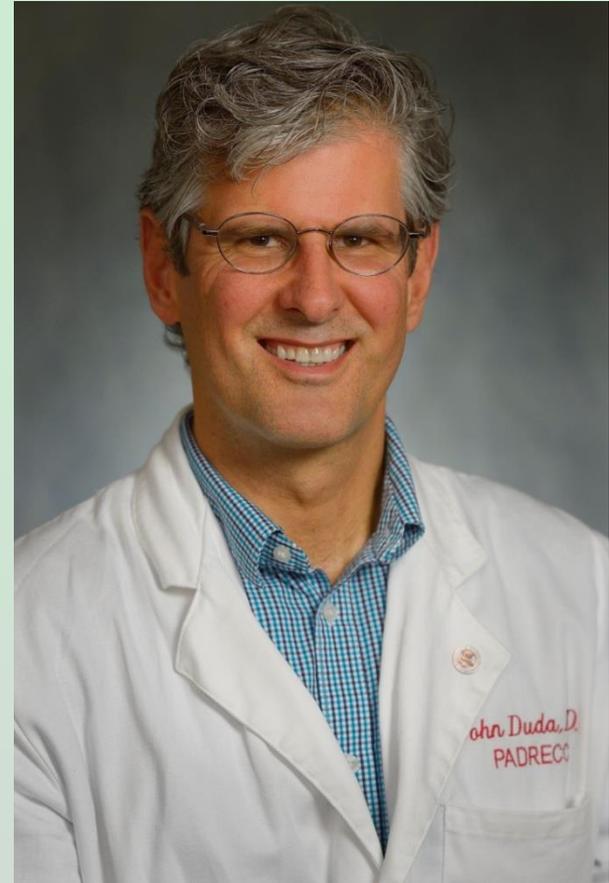
Shital P. Shah^{a,*}, John E. Duda^{a,b}



Side effects of a plant-based diet

- ▶ GI discomfort/flatulence
- ▶ Change bowel movements – less constipation!
- ▶ Medication interactions
 - Warfarin and leafy greens
 - Grapefruit
- ▶ Don't forget:
 - Less heart disease, diabetes, stroke, cancer, depression, dementia, insomnia, hypertension, etc, etc, etc

Before and after giving up dairy!



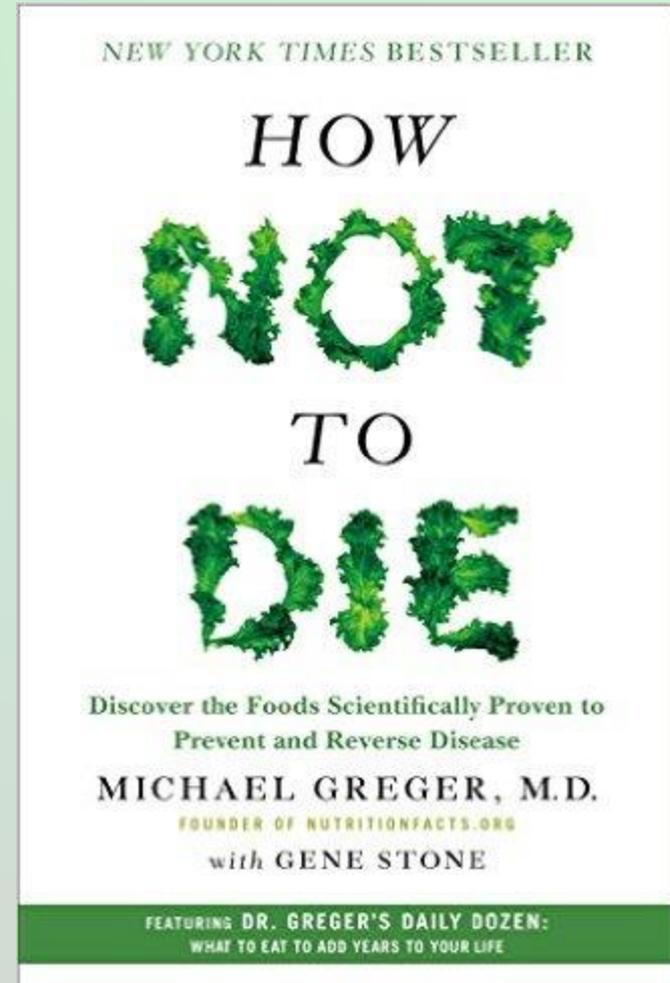
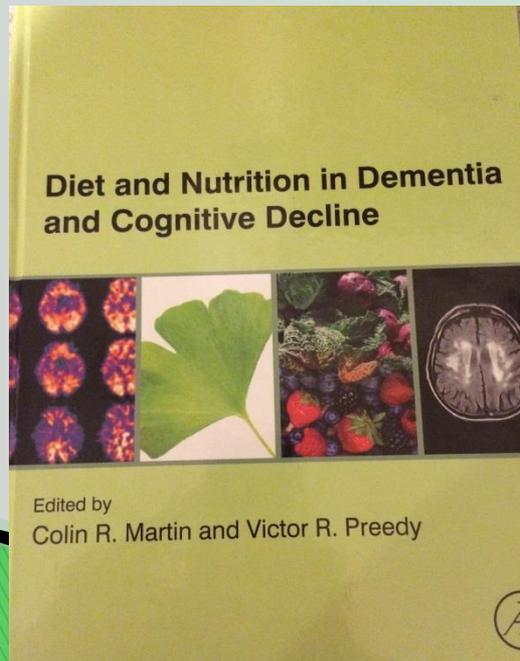
Where to go for more info

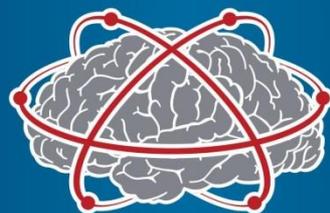
www.nutritionfacts.org

www.pcrm.org

www.ohsheglows.com

www.forksoverknives.com





CONY

**THE 11th WORLD CONGRESS ON
CONTROVERSIES IN NEUROLOGY**

MARCH 23-26, 2017 | ATHENS, GREECE

CONGRESS CHAIRPERSONS

Amos D. Korczyn, Israel

Konstantinos Vadikolias, Greece

www.comtecmed.com/cony | cony@comtecmed.com

**SAVE
THE DATES**