# Modifiable Variables in Parkinsonism (MVP) Study: Summary of Study Findings

2013-2023

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For more information about the study, please visit: <u>www.MVP-Study.com</u>

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## MODIFIABLE VARIABLES IN PARKINSONISM (MVP) STUDY 10 YEAR REPORT

## **1. INTRODUCTION**

#### A. Why this study needs to be done

Parkinson's disease (PD) was first described in 1817, and the conventional perspective is that the condition is irreversible, progressive, and no strategies for disease modification exist. Despite this, we know there is a tremendous amount of diversity in symptoms and rate of progression. Since only  $\sim 12\%$  of people with parkinsonism are carrying a PD-related gene, it is reasonable to conclude that non-genetic variables are influencing PD progression.

For decades, there has been a small, but growing, body of literature suggesting environmental factors increase or decrease a person's risk of being diagnosed with PD. Variables identified to be related to PD risk include diet, physical activity level, pesticide exposure, well water and even post-traumatic stress disorder; while these data may be useful for PD prevention, the topic of prevention is of little use to people who have already been diagnosed.

#### **B.** Positive Deviance Model

In the 1960's, the term "positive deviance" was introduced by nutrition researchers studying malnutrition in children from poverty-stricken regions. Researchers identified the existence of healthy children in these communities and worked to identify *why* some kids in these regions were doing better than others.

The positive deviance model is best used when there is a persistent problem within a community, when some people in that community are clearly doing better than others, when resources are limited, when behavior is suspected to play a critical role in outcomes, when there may be more than one contributing factor, when traditional interventions have failed or plateaued, when rapid, sustainable, and scalable solutions are needed, and when the community is open to exploring unconventional solutions.

The **Modifiable Variables in Parkinsonism (MVP) Study** is the first attempt to apply the positive deviance model to neurodegeneration.

PI: LK Mischley

#### 2. METHODS

#### A. Ethics approval

This study has been approved by the Bastyr University Institutional Review Board (IRB) since its inception in 2013. All study subjects confirmed they had read the Participant Information Sheet, that they understood their rights as a study participant, and consented to be in this research project.

#### **B.** Recruitment

Recruitment efforts have included postcards, flyers, advertisements on social media, and lectures both in person and online.

To date, more than 3500 individuals have enrolled in the MVP Study.

#### **Under-represented cohorts:**

- Other forms of parkinsonism: MSA, PSP, LBD, CBD, etc.
- People who were diagnosed more than 10 years ago
- People from diverse ethnic backgrounds
- People with prodromal parkinsonism (early possible signs & symptoms, presence of PD genes, etc.)

#### C. Data management

During the first year of the MVP Study, study participants were allowed to skip any question they did not want to answer. Unfortunately, if a person does not rate the severity of one of their symptoms on the PRO-PD scale, it is impossible to obtain a cumulative score. For the first 971 responses, there were an average 15 skipped responses for each symptom, ranging from 10 missed (hallucinations) to 40 (memory). From our angle, it is impossible to determine whether the participant accidentally skipped those variables or chose not to answer them.

To improve data integrity moving forward, IRB approval was obtained to make a response to all symptoms mandatory, which is essential for the cumulative score. Now, when a participant attempts to complete the PRO-PD the tab must be toggled/ touched so that the system will-ensure that none of the critical variables are skipped.

Over the past 10 years, we have published portions of these data and presented them at conferences around the world. In the fall of 2024, the de-identified dataset was given to two PhD-level statisticians; the figures, tables, and results that follow are a combination of the data output generated by these statisticians and previously published data from the MVP Study. Based on the date of analysis and the data cleaning methods used, the number of participants in each analysis varies.

## 3. COHORT SIZE

## A. Enrollment over time

Except for 2019 (COVID-related study disruption), more than 200 participants have enrolled annually since 2014.



Prior to COVID, the MVP-Study used to send a survey to each participant on a 6month schedule based on when each individual enrolled. Because we were not allowed on campus to access the files necessary to maintain this system, we switched the schedule to send everyone the survey at the same time each year.

Due to staffing issues, only one survey was sent out in 2024.

In addition to making efforts to recruit more individuals to join the study, maintaining participation in those who have already submitted a baseline is essential for data integrity. The longer a person participates, the greater the value of these data for understanding progression.

## **B.** Continued Participation



### Approximately 600 people have provided at least 3 responses. One person has provided 18 responses over the past 10 years!

	PD	Parkinsonism	MSA	PSP	CBD	DLB	Picks	ΟΡϹΑ	other	No Diagnosis but believed increased risk
1	2766	188	11	12	4	2	1	6	42	10
2	1818	108	7	6	2	1	1	3	19	2
3	1469	81	4	2	2	1	0	0	16	1
4	1183	60	3	1	2	1	0	0	12	0
5	941	40	3	1	2	0	0	0	7	0
6	748	34	1	1	2	0	0	0	7	0
7	574	24	0	1	1	0	0	0	6	0
8	422	16	0	1	0	0	0	0	5	0
9	326	9	0	0	0	0	0	0	5	0
10	261	6	0	0	0	0	0	0	3	0
11	201	2	0	0	0	0	0	0	1	0
12	138	2	0	0	0	0	0	0	0	0
13	95	1	0	0	0	0	0	0	0	0
14	63	1	0	0	0	0	0	0	0	0
15	44	0	0	0	0	0	0	0	0	0
16	23	0	0	0	0	0	0	0	0	0
17	14	0	0	0	0	0	0	0	0	0
18	1	0	0	0	0	0	0	0	0	0

Cumulative Number of Times Participants Answered Survey by Diagnosis

## C. Types of Parkinsonism

It is scientifically honest to tell you that we are still unclear what Parkinson's is and how to define it. Over time, we have learned that the field of parkinsonism is complex and that where and how proteins aggregate in the brain can have profoundly different consequences in terms of how the patient manifests symptoms.

What commonly happens is that people are given a presumptive diagnosis of probable PD, but as the disease progresses and symptoms become more severe, it can become clear that the patient has a form of parkinsonism other than idiopathic PD. On autopsy, the distinction is often messy, with many individuals having evidence of pathology in areas beyond what is expected based on their diagnosis and symptoms.

Because idiopathic PD, the type most of you have, is the most common established cause of parkinsonism, the other forms of parkinsonism are often neglected by researchers and industry. In fact, we've found that journal editors are unlikely to publish data that isn't restricted to PD only, again leaving the other forms of parkinsonism under-represented.

	Total	PD	Parkins onism	MSA	PSP	DLB	CBD	Other
N	3255	2766	188	11	12	2	4	59
Male	52.6%	54.0%	56.9%	54.5%	50%	100%	75%	54.2%
Female	41.1%	40.5%	38.8%	45.5%	33.3%	0%	25%	33.9%
Other (incl n/a's)	6.2%	5.5%	4.3%	0%	16.7%	0%	0%	11.9%
Mean years Since Diagnosis (N=3019)	4.86 (5.94)	4.94 (6.08)	3.88 (3.93)	3.98 (3.47)	5.25 (3.69)	1.66 (2.07)	7.42 (12.47)	4.29 (6.34)
Mean Propd	766.6 (472.2)	752.4 (457.6)	880.5 (543.8	1455.5 (353.3)	1333.8 (474.4)	1050.0 (247.5)	1090.7 934.6	1040.2 (739.9)

#### Demographic statistics by Diagnosis at Baseline

Approximately 85% of the study participants enrolled to date have idiopathic PD, commonly referred to simply as "Parkinson's disease" and "PD." To date, only 4-12 individuals with each of the following Parkinson-plus syndromes have enrolled: **multiple system atrophy (MSA), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB) and corticobasal degeneration (CBD)** have enrolled.



Stage	Total	PD	Parkinso nism	MSA	PSP	DLB	CBD	Other
N	3255	2766	188	11	12	2	4	59
1-sided symptoms only	53.8%	55.2%	39.8%	10.0%	8.3%	0%	25%	40.0%
Both sides affected, balance stable	17.4%	17.7%	18.8%	0%	0%	50.0%	25.0%	6.7%
Mild to moderate disability, balance affected	23.9%	22.8%	36.5%	50.0%	75.0%	0%	50.0%	17.8%
Severe disability, able to walk and stand without help	2.7%	2.7%	2.2%	10.0%	8.3%	0%	0%	11.1%
Confinement to bed or wheelchair unless aided	0.4%	0.2%	0.6%	30.0%	8.3%	0%	0%	2.2%
Don't know	1.7%	1.3%	2.2%	0%	0%	50.0%	0%	22.2%

#### Stage by Diagnosis at Baseline

## **Prodromal Parkinsonism= No Diagnosis but increased risk**

By the time a person is diagnosed with Parkinson's, the current thinking is that the disease has been underway for a decade or two. Initially, the disorder begins without any perceptible symptoms at all, and then eventually many people start to develop nonspecific symptoms, such as constipation, loss of smell, fatigue, erectile dysfunction, anxiety, etc. While these symptoms can often be attributed to parkinsonism in hindsight, there are many other reasons that a person might develop these symptoms, meaning that the presence of these symptoms alone is insufficient to identify individuals at increased risk of PD. Thus, our goal is to identify individuals with some of these early symptoms and enroll them in this study to see if we can improve our ability to identify people with PD early and decrease their risk of diagnosis.

The "prodromal" cohort was added in 2023 and the MVP Study. Currently, there are only 10 people enrolled in this group and we need thousands to make these data useful.

If you know of individuals who meet any of these criteria who might be interested in participating, please refer them to www.MVP-Study.com.

<u>Cı</u>	riteria for Increased Risk for MVP Study Participation
-	Positive SYN-ONE skin biopsy
-	Positive Parkinson-related gene (LRRK-2, GBA, etc.)
-	Positive canine test
-	REM Sleep Behavior Disorder (acting out dreams)
-	HRV less than 30 (monthly average)
-	Hyposmia (poor sense of smell)
-	Abnormal DAT Scan
-	Irritable Bowel Syndrome (IBS)
-	Inflammatory Bowel Disease (IBD), including
	Ulcerative Colitis or Crohn's Disease
-	Chronic constipation
-	Other
<u> </u>	

## D. How Long Does It Take to Be Diagnosed?

Individuals can have symptoms for year before they are finally diagnosed with PD. The figure on the left shows the number of years that study participants report being symptomatic. The figure on the right shows how many years since diagnosis. As expected, people have symptoms long before diagnosis.



By enrolling more individuals in the Prodromal cohort, we hope to give more attention to these early symptoms, so that people may get to a diagnosis sooner.

## E. Demographics of Study Participants



#### Age

Age is centered on ~65. Is skewed slightly to the left, which means more people under the age of 65 have enrolled in this study than people over 65.

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#### **Income Categories (US Dollars)**

The study team has done an excellent job recruiting study participants across income categories. That said, according to the Census Bureau, the median income is  $\sim$  \$80,610, which means the individuals participating in this study are generally in a higher income bracket than the general US population.



#### **Education Level**

As is common across diseases, people with greater levels of education are more likely to enroll in clinical trials. A disproportionate number of participants in the MVP-Study have graduate level education.



## Race & Ethnicity

Most study participants identify as Caucasian. While we need and appreciate enrollment of white people, it is critical that we increase enrollment, and thus representation, of individuals across all races and ethnicities.

#### **Marital Status**

This is a highly coupled cohort! Less than 500 of the 3500 people in this study are single.

## **Global Representation**

To date, participants from 57 unique countries have participated in this survey. (Different journals and rules apply as to whether we are all allowed to publish data collected from individuals living in countries where we don't have an ethics board approving this study.)

The four countries with the greatest response rate are all English-speaking. Thus, these results are likely skewed to represent these cultures.

## Until there is greater MVP Study participation globally, we do not know whether the findings reported here are globally generalizable.

Efforts should be made to reproduce this type of study in native languages or translate this study, and expand questions to include culturally relevant foods, practices, etc.



	Number of MVD
Country	Study Participants
United States	6996
United Kingdom	696
Canada	619
Australia	377
New Zealand	110
Spain	56
Ireland	41
Germany	36
Norway	35
Netherlands	34
Italy	30
France	27
Switzerland	27
Israel	27
Portugal	19
South Africa	19
Argentina	16
Denmark	15
Venezuela	12
Sweden	8
India	8
Pakistan	8
Ecuador	7
Croatia	6
Costa Rica	6
Dominican Republic	6
Azerbaijan	6
Trinidad and Tobago	5
Thailand	5
Singapore	5
Afghanistan	5
Kenya	4
Iceland	4
Brazil	4
Belgium	3
Mexico	3
Austria	3
Greece	3
Macedonia	3
runisia	2
Egypt	2
Poland	2
	2
Saudi Arabia	2
Chile	2
Finialiu	2

## F. Measuring Symptom Severity

The question about "PD Stage" is based on the historical outcome measure, the Hoehn and Yahr (HY). We asked individuals to estimate their HY score. While this is only an *estimated* HY score, most of the study participants are HY stage 1-3.

Historical Hoehn & Yahr
Stage 1.0: Unilateral involvement only.
Stage 1.5: Unilateral and axial involvement.
Stage 2.0: Bilateral involvement without impairment of balance.
Stage 2.5: Mild bilateral involvement with recovery on retropulsion (pull) test.
Stage 3.0: Mild to moderate bilateral involvement, some postural instability but physically independent.
Stage 4.0: Severe disability, still able to walk and to stand unassisted.
Stage 5.0: Wheelchair bound or bedridden unless aided.

Of note, during a clinical exam, a trained provider can usually elicit symptoms on the other side (e.g. finger tapping with one had can help identify rigidity on the other side). Thus, while "1-sided symptoms" are the most common self-reported

response among study participants, if this study were to include an objective evaluation by a trained provider, it is likely a large proportion of people in the "1sided" group would meet criteria for "both sides affected."





On average, over the past 6 months, do you think your condition has improved, been stable, or gotten worse?

This figure shows how study participants responded during their baseline study visit.

## F. Measuring Symptom Severity

Symptom severity, in this study, is measured by the **Patient Reported Outcomes** in **Parkinson's Disease (PRO-PD)** scale. The scale was designed by Dr. Mischley to meet the needs of this study, as well as to give patients a sense of control. The scale consists of 33 symptoms of Parkinson's, each on a slider bar, with left (0), representing health and far right (100) representing that the symptom is severely debilitating, on average, over the past week.

While the scale is logical, because of its novelty, when it was implemented as the

primary outcome measure for this study it was not a validated measure, e.g. the wrong symptoms could have been chosen. Fortunately, the PRO-PD scale has since been validated by an independent group of researchers in Sweden.



## **PRO-PD** Validation

Dr. Mischley gave the researchers permission to use the PRO-PD free of charge in the West Sweden Parkinson Objective Measurement Registry Study. Taking advantage of the social healthcare system, every fourth patient was selected from a list of patients with a PD diagnosis, arrange by birth date, which resulted in a random 25% of patients in the Region Västra Götaland (population: 1.5m). These individuals were then invited to participate. 286 patients participated in the study.

In the Swedish cohort, there was a median 71-point increase in PRO-PD score per year.

The researchers determined a **119-point change in PRO-PD score was the Minimally Clinically Important Change.** In other words, when the PRO-PD score was considered alongside other assessment tools, a 119-point change was required for patients to perceive the change.

The authors concluded, "**PRO-PD was found reliable and valid for monitoring** symptoms in a representative sample of outpatients with PD."



## G. PRO-PD Baseline Scores & Progression Over Time

In general, most of the people who have enrolled in this study were diagnosed less than 10 years ago and a disproportionate number of participants have relatively mild symptoms. *The study aims to recruit more highly symptomatic people*.

This figure shows the average Parkinson symptom severity, as measured by the PRO-PD, according to study timepoint, e.g. 0 baseline, 6: 6 months. It is evident that a lot of participants complete their baseline survey and do not complete subsequent surveys. *The study aims to improve long-term participation in this study*.

Shortage of enrolled participants diagnosed more than 10 y ago

Below is a linear model of PRO-PD. Each of the dots is a person with PD and the straight blue line running through the center represents the estimated average symptom severity in this cohort over time. The dark bars that run vertically represent study participation in response to the email we send out every 6 months.

Overall smoothed PRO-PD evolution for n=3450

## **Parkinson Symptom Fluctuation Over Time**

It is well known that the symptoms of Parkinson's fluctuate, over hours, days, and weeks. Here, these data suggest symptom severity fluctuates over years. This means that outcome measures and assessment tools that rely on a single point in time have limited utility, given the underlying fluctuations. (This is true for all "clinical snapshots" your physician may do as well as cross-sectional studies, whether using the MDS-UPDRS or PRO-PD.)

The graph is a sample of 45 participants out of 3000+, to demonstrate that while some people remain quite stable or even improve, others fluctuate notably over

months and years. These fluctuations may or may not have anything to do with Parkinson's – many of the symptoms of Parkinson's are non-specific; if someone were to get in a car accident, their pain, fatigue, and sleep scores are likely to be higher for a little while. Again, this is an excellent example of why we need large numbers of individuals to join the study to drown out some of this background noise.

Statistically, we have ways of smoothing out these fluctuations to provide estimates for everyone's average rate of progression, despite the fluctuations. Notice the tremendous diversity in *slope* – while most people's scores increase over time, you'll see there are people reporting fewer symptoms (downward slope) over time.





10 13

14

16

20 22

24

27 35

36

38

40

43

This is another version of the figure above, showing a sample of individuals' slope (rate) of change over time. This figure demonstrates:

- The tremendous diversity between individual patients.
- The lack of representation among participants who have been diagnosed more than 10 years ago.
- The importance of study participants continued long-term participation in the study.



When studying disease progression, the two variables that matter most are **symptoms** and **time**. All study participants have given us their symptom severity score (PRO-PD) at least once, which IS helpful, but the ability of this study to accurately represent your decisions on symptoms requires that you continue to tell us, over time, how and what you're doing. *Your continued participation in this study is integral to the success of this project*.

## H. Progression by Sex



In this cohort, thus far, it appears that women are accumulating symptoms at a slower rate than men.

It is possible that this discrepancy between male and female progression is simply due to chance, and other groups might have different results. It's also possible that these data are an accurate representation of the

community, and that the discrepancy is related to biology (e.g. hormones) or lifestyle (e.g. healthier mindset, behavior, decisions).

In 2022, we added additional questions related to women's health to better understand these data. We now ask about years of menstruation, pregnancies, use of hormones, etc. *Over the next few years, one of the goals of this study will be to better understand details related to biological sex and PD severity and progression*.



2024 Analysis by Magdelena Murawska, one of our statisticians, who is looking continuously at people in the study over time suggests that women may be accumulating symptoms at a slightly higher rate, but we don't know whether this is statistically or clinically significant. As we follow more participants over time, we'll be able to further describe these differences.

## I. Change in Individual Symptoms Over Time

These figures show the actual change in individual symptom severity over time following diagnosis. **This is our first look at our longitudinal data**, made possible by people who have repeatedly responded to surveys over time. Previously, we've only been able to take a snapshot of a point in time and try to piece together the 'story of progression.' Here, we follow people over time and describe the average change in symptoms during in the first 7 years following diagnosis for the people in this cohort.



Smoothed symptoms score evolution for n=3450

## I. Change in Individual Symptoms Over Time

The figures that follow are the same as the figure above, but displayed by individual symptom to make it easier to see changes in different symptoms over time.





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PRO-PD: Correlation with QOL and established measures

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Table 2. PRO-PD se	verity by sympton	m and years since dia	ignosis				
PRO-PD Scores Follo	wing PD Diagnos	iis					
PD Symptom	Number (%) reporting symptom (N = 1029)	0–5 years after diagnosis Mean (SD) (n = 642)	5–10 years after diagnosis Mean (SD) (n = 227)	10–15 years after diagnosis Mean (SD) ( $n = 85$ )	15 + years after diagnosis Mean (SD) ( $n =$ 77)	Estimated yearly increase Mean (95% CI)	P-value
Fatigue	92%	33.1 (24.3)	40.0 (23.1)	50.5 (25.1)	47.4 (24.6)	1.19 (0.91, 1.48)	<0.000
Handwriting	91%	32.4 (24.2)	44.8 (25.5)	55.3 (27.0)	51.0 (29.3)	1.61 (1.31, 1.91)	<0.000
Daytime sleepiness	89%	27.9 (23.3)	36.0 (22.5)	45.9 (25.8)	43.1 (24.7)	1.18 (0.9, 1.46)	<0.000
Slowness	88%	25.9 (21.8)	34.6 (20.4)	46.6 (21.9)	41.9 (23.1)	1.3 (1.04, 1.56)	<0.000
Tremor	88%	26.4 (20.9)	30.4 (21.5)	28.5 (23.4)	29.4 (26.4)	0.23 (-0.04, 0.49)	0.089
Muscle cramps	88%	27.2 (24.0)	35.4 (25.4)	45.2 (26.8)	35.7 (26.5)	0.98 (0.68, 1.27)	<0.000
Memory/ forgetfulness	88%	27.5 (21.0)	32.7 (21.8)	37.4 (20.8)	34.6 (23.2)	0.58 (0.33, 0.84)	<0.000
Sense of balance	86%	21.0 (19.6)	28.8 (19.8)	40.9 (23.2)	43.3 (26.5)	1.51 (1.26, 1.76)	<0.000
Sense of smell	85%	45.2 (32.8)	49.3 (32.0)	55.2 (29.8)	53.2 (32.9)	0.72 (0.33, 1.10)	<0.000
Sexual dysfunction	82%	33.2 (30.3)	40.8 (30.7)	47.8 (29.7)	46.8 (30.8)	1.01 (0.65, 1.38)	<0.000
Urinary functions	82%	25.9 (24.7)	37.4 (26.7)	44.3 (26.3)	45.0 (30.4)	1.52 (1.21, 1.83)	<0.000
Stooped posture	82%	21.8 (18.7)	30.4 (21.3)	36.8 (22.9)	35.8 (20.7)	1.09 (0.85, 1.32)	<0.000
Walking	82%	18.8 (18.0)	27.1 (20.0)	40.3 (21.4)	33.6 (22.4)	1.24 (1.01, 1.47)	<0.000
Anxiety	79%	22.1 (22.9)	24.4 (22.9)	37.5 (27.3)	28.5 (25.4)	0.74 (0.46, 1.02)	<0.000
Insomnia	77%	26.2 (26.1)	31.5 (27.3)	46.5 (28.0)	32.9 (26.4)	1.01 (0.69, 1.33)	<0.000
Motivation and Initiative	77%	23.4 (22.8)	27.1 (23.0)	34.0 (23.5)	32.7 (24.3)	0.61 (0.33, 0.88)	<0.000
Speech	77%	18.2 (18.6)	29.2 (21.9)	40.1 (24.5)	32.5 (23.3)	1.32 (1.08, 1.57)	<0.000
Rising from seated	76%	18.4 (18.9)	25.9 (19.2)	36.5 (21.1)	33.9 (22.8)	1.1 (0.86, 1.33)	<0.000
Dressing, grooming, eating	73%	14.8 (16.7)	23.3 (18.4)	32.8 (21.4)	28.6 (20.5)	1.15 (0.94, 1.36)	<0.000
Constipation	73%	20.3 (21.8)	27.4 (24.2)	31.2 (22.5)	31.6 (25.4)	0.85 (0.58, 1.12)	<0.000
Depression	73%	17.4 (19.4)	20.6 (21.7)	26.0 (22.0)	21.5 (20.7)	0.38 (0.13, 0.62)	0.002
Loss of interest	71%	19.2 (21.6)	22.5 (22.7)	28.5 (23.2)	27.5 (25.1)	0.56 (0.3, 0.83)	<0.000
Comprehension	69%	16.0 (18.6)	21.5 (20.2)	24.9 (21.2)	25.2 (21.4)	0.66 (0.43, 0.89)	<0.000
Sleep behavior disorder	65%	19.3 (24.2)	27.7 (26.5)	34.3 (27.2)	35.8 (26.1)	1.26 (0.96, 1.56)	<0.000
Drooling	65%	16.7 (20.5)	26.7 (23.9)	34.6 (24.8)	31.4 (24.8)	1.17 (0.91, 1.43)	<0.000
Restless legs	64%	18.7 (24.3)	24.7 (25.6)	31.3 (26.1)	27.8 (26.4)	0.79 (0.49, 1.08)	<0.000
Dizzy on standing	64%	14.6 (19.7)	19.5 (20.9)	23.7 (24.7)	24.5 (23.8)	0.6 (0.35, 0.85)	<0.000
Visual disturbance	58%	12.3 (17.9)	21.5 (23.7)	30.8 (26.8)	22.5 (23.2)	1.01 (0.75, 1.26)	<0.000
Falling	55%	11.0 (17.1)	18.0 (21.9)	30.1 (24.0)	29.2 (28.3)	1.35 (1.12, 1.59)	<0.000
Dyskinesia	47%	8.8 (16.7)	22.5 (23.0)	33.2 (27.0)	30.7 (25.7)	1.73 (1.49, 1.97)	<0.000
Freezing	47%	9.4 (16.1)	16.6 (20.5)	26.5 (24.3)	26.9 (26.8)	1.14 (0.92, 1.37)	<0.000
Nausea	43%	9.6 (17.0)	12.6 (18.9)	15.7 (20.2)	10.5 (15.0)	0.19 (-0.03, 0.4)	0.084
Hallucinations	31%	4.6 (10.2)	10.1 (16.1)	15.3 (19.6)	14.2 (21.4)	0.73 (0.56, 0.89)	<0.000

In 2017, we published a study using the results from the MVP-Study, combined with data from two other research projects to look at how individual symptoms change over time. What we learned was **tremor** (and nausea) are the only symptoms on the PRO-PD that don't get statistically worse over time.

Mischley LK, Lau RC, Weiss NS. Use of a self-rating scale of the nature and severity of symptoms in Parkinson's Disease (PRO-PD): Correlation with quality of life and existing scales of disease severity. NPJ Parkinsons Dis. 2017



#### Longitudinal Data (Following the Same People Over Time)

This figure represents longitudinal data related to a few hundred people who provided at least 6 datapoints, allowing for granular descriptions of change over time. (This figure suggests that there is an initial period of progression, followed by a few years of relative stability between years 4-8 (approximately), followed again by a progression of symptoms.

Most of the other analysis are cross-sectional, i.e. looking at a slice of the data.

## Non-Motor Subset of the PRO-PD – PRO-PD<sub>nm</sub>

K. Ray Chaudhuri is the creator of the Non-Motor Symptom Scale (NMSS) and is universally recognized as the curator of the non-motor concept in PD. At a conference in San Diego in 2015, Dr. Chaudhuri and I went over the list of symptoms I had chosen for the PRO-PD scale, and he selected the ones that he thought should be included in the non-motor subset. [Personal communication, KR Chaudhuri, 2015] That list has been used to define the non-motor PRO-PD subset.

**Non-Motor Symptoms:** constipation, lack of motivation, depression, loss of interest, anxiety, fatigue, daytime sleepiness, temperature dysregulation, orthostatic hypotension, visual disturbances, insomnia, REM sleep behavior disorder, muscle pain, drooling, memory impairment, comprehension disability, hyposmia, sexual dysfunction, urinary dysfunction, hallucinations.

## Contribution of non-motor symptoms to overall PRO-PD scores

Non-motor symptoms (PRO-PDnm) make up more than half of the total PRO-PD score.



The PRO-PD*non-motor* subset correlates well with the NMSS scale Dr. Chaudhuri created, speaking to consistency, thus lending validation to both scales.



Mischley, L.K., Lau, R.C. & Weiss, N.S. Use of a self-rating scale of the nature and severity of symptoms in Parkinson's Disease (PRO-PD): Correlation with quality of life and existing scales of disease severity. *npj Parkinson's Disease* **3**, 20 (2017).

#### PI: LK Mischley

How Symptoms are Rated	Please rate the severity of your symptoms over the past 7 days, on average. The more severe and debilitating the symptom, slide right. If you're not having that symptom, slide to the left.							
	Slowness * must provide value	Move with ease Severe slowness						
If a person gave		resel						
themselves a score	Constipation (incomplete bowel emptying) * must provide value	Healthy, daily Require Severe bowel medication constipation movements						
of 5 or more (out of		read						
100), we coded	Walking	I move freely						
them as having that	* must provide value	with ease Unable to move						
symptom. Below is		resel						
a table describing	Freezing * must provide value	None Severe, debilitating						
how common each								
of the symptoms are								

## Free scores available at www.PROPD.org

## Frequency that Patients with Parkinson's Report the Symptoms

Percent of Patients Reporting Symptom	Symptoms
80-85%	Fatigue, Impaired Handwriting, Hyposmia
70-80%	Memory impairment, Muscle pain, Daytime sleepiness, Slowness, Tremor, Sexual impairment, Balance, Urinary dysfunction, Stooped posture
60-70%	Lack of motivation, Insomnia, Difficulty walking, Anxiety, Difficulty rising, Impaired speech
50-60%	Constipation, Difficulty dressing, Depression, Withdrawn, Acting out dreams, Comprehension, Restless legs, Drooling
40-50%	Dizzy on standing, Visual disturbance, Falls
30-40%	Dyskinesia, Freezing
<30%	Nausea, Hallucinations

## J. Relationship Between Individual Symptoms on the PRO-PD Scale

We asked two different statisticians to show us the relationship between each of the symptoms on the PRO-PD scale.

These heat maps use color coding to describe the correlation between symptoms. For instance, **balance and falls** are highly correlated, as are **medication side effects and dyskinesia**, as well as **lack of interest (apathy) and lack of motivation**.



## J. Relationship Between Individual Symptoms on the PRO-PD Scale



Correlation Matrix of All PD Symptoms

#### Modifiable Variables in Parkinsonism Study Summary Report 2024

## K. Quality of Life



## K. Quality of Life Higher PRO-PD Scores are Associated with Lower Quality of Life



## **Determining Categories of Quality of Life**

Once the computer generates a PRO-PD score, people want a point of reference to know what those scores mean. We asked people how they rated their quality of life, and this box plot shows how PRO-PD symptoms change as quality-of-life changes.



#### Modifiable Variables in Parkinsonism Study Summary Report 2024



## Count of 6 Month Progression Status by Age



## K. Quality of Life

## **Setting Standards**

A precise numerical value where "Excellent" quality of life becomes "Good" does not exist. The concept is logical, but true numerical representation is only an imprecise estimate. Depending on the date we download the data, and the cleaning and imputation methods used, different statisticians come up with slightly different cutoff numbers.





Score	Quality of Life
0-500	Excellent
500-1000	Good
1000-1500	Fair
1500+	Poor

For the sake of simplicity, "Very good" and "Good" have been merged into a "Good" category. This PRO-PD-Quality of Life (QoL) legend was created by combing PRO-PD scores with response to Question 1 on the PROMIS Quality of Life Global question.

Published: Mischley LK, Lau RC, Bennett RD. Role of Diet and Nutritional Supplements in Parkinson's Disease Progression. Oxid Med Cell Longev. 2017.<sup>7</sup>



FIGURE 1: The PRO-PD score is the sum of 33 motor, mood, and other nonmotor symptoms common in PD. Higher scores represent either more symptoms or greater symptom severity of a few symptoms. Lower PRO-PD scores correlate with better social, emotional, and physical quality of life [7].

#### PI: LK Mischley

## K. Quality of Life

## **Different Aspects**

The PROMIS Quality of Life scale was developed by the National Institutes of Health to standardize how we communicate about quality of life across diseases, cultures, and ages. A tremendous amount of work went into developing the wording of the questions and their cross-cultural applicability. Using the PROMIS Global questions, we compared participants' answers to their PRO-PD scores.

## **Mental Health**

In general, how would you rate your mental health, including your mood and your ability to think?

## Social Health

In general, please rate how well you carry out your social activities and roles. (This includes activities at home, at work, and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.) ...

## **Patient-Reported Physical Capacity**

To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?



## L. Describing the Behaviors of Participants Across PRO-PD Scores

After the initial ~ 1000 participants joined the study, our Bastyr University team took our first look at behaviors associated with different rates of progression [Mischley et al, 2017]. In addition to the food people consumed we also found some behaviors that were strongly correlated with Parkinson symptom severity.

Of all the variables we tracked, these are the ones most strongly associated with Parkinson symptom severity, as measured by PRO-PD scores.



## Can 'situation modification' be turned into a therapeutic intervention?

If a weekly box of healthy groceries showed up on the doorstep of individuals in financial need, would their Parkinson symptoms improve? Can we involve people in community-based, stress-reduction programs and see symptom reduction? If a person loses weight, via dietary modification, exercise, and/ or GLP-1 medications, might that translate to symptom reduction?

## WE ARE LOOKING FOR FUNDING TO FIND OUT



#### M. Social Health and Parkinson Symptom Severity

A few years later we decided to look a little more closely at loneliness. [Subramanian I, et al. 2020] In this cross-sectional analysis (slice of data) of 1527 people with PD, it didn't look like lonely people progressed at a faster rate, but their symptoms were consistently rated more severely.

## Loneliness ~ $\uparrow$ 55% PRO-PD Lots of friends ~ $\downarrow$ 21% PRO-PD

"Individuals who reported being lonely experienced a 55% greater symptom severity than those who were not lonely (P < 0.01). Individuals who documented having a lot of friends had 21% fewer symptoms than those with few or no friends (P < 0.01)."



PD to evaluate whether social isolation is associated with PD symptom severity and quality of life. Only individuals reporting a diagnosis of idiopathic PD were included in this analysis. The primary outcome measures were the Patient-Reported Outcomes in PD (PRO-PD) and questions from PROMIS Global related to social health. PRO-PD scores increased as social performance and social satisfaction scores diminished. Individuals who reported being lonely experienced a 55% greater symptom severity than those who were not lonely (P < 0.01). Individuals who documented having a lot of friends had 21% fewer symptoms than those with few or no friends (P < 0.01). Social isolation was associated with greater patient-reported PD severity and lower quality of life, although it is unclear whether this is the cause and/or a consequence of the disease. In essence, the Parkinson pandemic and the pandemic of social isolation have been further compounded by the recent COVID-19 pandemic. The results emphasize the need to keep PWP socially connected and prevent loneliness in this time of social distancing. Proactive use of virtual modalities for support groups and social prescribing should be explored.

npj Parkinson's Disease (2020)6:28; https://doi.org/10.1038/s41531-020-00128-9

#### Modifiable Variables in Parkinsonism Study Summary Report 2024



In the study, not only were we able to demonstrate that symptoms were worse in the individuals that felt lonely; by turning the PRO-PD into a radar chart and organizing symptoms by domain we are able to see which symptoms are more strongly associated with loneliness. In a radar chart like this, the larger the size, the greater the symptom severity. The dark blue center represents the total symptom burden of people who said they were not lonely, and the line represents symptom severity of lonely people. As you can see, lonely people reported greater symptom severity for all 33 symptoms. The greatest discrepancies in symptom severity scores between lonely and not lonely people were in social withdrawal/loss of interest, motivation/ initiative, depression, and anxiety.

Subramanian I, Farahnik J, Mischley LK. Synergy of pandemics-social isolation is associated with worsened Parkinson severity and quality of life. NPJ Parkinsons Dis. 2020 PI: LK Mischley

## Gratitude and Parkinson Symptom Severity

Using a validated scale designed to measure a person's sense of gratitude, we plotted individual symptoms from the PRO-PD scale in the respondents with **high amounts of gratitude** versus **lack of gratitude**. Almost all the symptoms measured are rated a bit higher in people with the lowest gratitude scores.



## Averaged symptoms at baseline per each gratitude group

## Being Single is a Risk Factor for Lower Quality of Life

Among people who identify their quality of life as "Poor," there is a 50/50 change they are single or partnered. As quality of life improves, it is less and less likely the cohort is single. In fact, only 9% of people with an "Excellent" quality of life identify as being singe.



As reported quality of life increased, the likelihood that a person was single continued to decrease.

A future goal of this study will be to better understand which components of partnership offer the greatest therapeutic value. For people who prefer to be single, is there a way to access the benefit of partnership without a partner?

While some people might benefit from a finding a partnership, the goal will be to increase the number of single people with an excellent quality of life.

Subramanian I, Farahnik J, Mischley LK. Synergy of pandemics-social isolation is associated with worsened Parkinson severity and quality of life. NPJ Parkinsons Dis. 2020
# "I have a lot of friends."

In this chart we categorized people by their quality of life, ranging from "Poor" to "Excellent."

Across different quality of life categories, we described the how people rated their tremor severity, their loneliness, and their friendship status. **Tremor had little impact on quality of life, whereas loneliness and friendships were highly correlated.** [Subramanian I, et al 2020]



Fig. 2 Loneliness and friendships predict quality of life in PD. According to patients, loneliness and friendships were a better predictor of quality of life than tremor severity score.

According to these data, which reflects Parkinson symptom severity as measured by the PRO-PD, **being lonely was worse for individuals than 7 days per week of exercise was good for them!** [Subramanian I, et al 2020]



Fig. 4 Modifiable lifestyle variables and impact on patient-reported outcomes in PD (PRO-PD) score. Error bars indicate one standard deviation. Regression analysis adjusted for age, gender, income, and years since diagnosis.

# EXERCISING WITH FRIENDS SHOULD BE STUDIED AS A THERAPUETIC INTERVENTION

Subramanian I, et al. presented a poster at the International Movement Disorders Congress attempting to further describe the components of loneliness relevant to this population. Using the validated UCLA loneliness questionnaire scores and PRO-PD scores using the survey administered during the COVID-19 restrictions.

# **UCLA Loneliness Questions:**



For all the questions on the UCLA Loneliness Scale, greater symptom severity was associated with greater loneliness.

The question most strongly correlated with PD severity was "Do you feel left out?" People who reported feeling left out "Often" were more than twice as symptomatic as people who reported "Never" feeling left out.

In the poster we suggested providers might be able to use this single question as a screening test for loneliness.

# N. Physical Activity

We ask individuals in the survey, "On how many of the past 7 days have you done at least 30 minutes of physical activity?" Of note, for this question, we left it up to each individual to define what 'physical activity' means to them. Using this ill-defined approach, we can see a clear trend – the more days per week



individuals reported getting physical activity, the fewer symptoms they reported.

After adjusting for age, gender, income, and years since diagnosis, people who reported exercising every day of the past week scored an average 301 points lower than people who reported physical activity 6 of the past 7 days (they were 292 points lower than people who don't exercise at all.)

Notice how for the bottom two groups – those that only exercise 1 or 2 days per week – have black lines that cross the center. Even though the 1-or-2-days-per-week exercisers were generally less symptomatic than non-exercisers (green bar goes to the right), the impact was mild enough that it wasn't statistically significant. In other words, a minimum of 3 days per week of physical activity was required to see an association with fewer symptoms over time.

We did this analysis of type of exercise before the pandemic and before the relatively recent popularity of Rock Steady Boxing, so at the time of analysis only 10 people in our study were participating in RSB – thus, these data should be considered outdated. We have expanded the types of exercise we are



asking about and added sections to further clarify whether and how much exercise intensity and duration influence outcomes.

PI: LK Mischley



These figures come from a poster we presented at the 2016 World Parkinson Congress. **People doing yoga were more likely to report improvement over the past 6 months than runners or daily exercisers.** 

PRO-PD Score



#### **Types of Exercise Being Reported**

#### Examples of responses:

B.I.G. Activity, weekly cardio/yoga class
Backpacking
Badminton
Badminton
Badminton, Boxing
Badminton, racket ball badminton, table tennis, pilates, strength, cardio
Balance
Balance, Boxing for Parkinson's, Songshine
Balance and Bones balance and streach daily, weight machines 2 to 3 times per week
Balance and strength
balance and strengthening
balance and stretch program, smovey rings
balance and weights
Balance class
Balance class
balance class at local park district
Balance class Tue, Thu, Fri (45 minutes each)
balance class, SAIL fitness class
balance ex./big & loud ex.
balance execises for Parkinson's
BALANCE EXERCISES
Balance exercises
balance exercises & seated exerr via U Tube
Balance exercises and walking with Wii
balance exercises from physical therapist
Balance exercises from PT
Balance exercising and elliptical
balance specific exercise
Balance training
Balance, fitness training w/ instructor
Balance, fitness training w/ instructor
Barbells
Barre
Barre method, Pilates, snowshoeing
Baseball

basic housework - had injured ankle in Feb, not fully returned to previous activity level Basketbal (not the game, just practicing shotsl; horseback riding basketball basketball Basketball (x2), indoor soccer (x1), nordic skiing (x2) basketball, golf, ping pong basketball, efx basketball, home construction, soccer Basketball, ice hockey, nordic skiing basketball, juggling weighted balls basketball, soccer Basketball, soccer, ice hockey, rowing machine basketball, soccer, rowing machine Basketball, volleyball, Nordic skiing, telemark skiing Batting tennis ball around Beamer, vibration Becky Farley balance/big movements Becky Farley balance/big movements Becky Farley BIG program Bedridden- leg exercises and weights for upper body. (former weight lifter) Better 5, claire@roguept.com Better Bones & Balance Better Every Day BGF Boot Camp, water Zumba, AMT elliptical machine BIG BIG BIG BIG and Tai Chi Big / loud therapy big and loud Big and Loud Big and Loud (Parkinsons exercises) working in yard and shop, 3 days a week walk and lift weights at gym

Baseball and basketball and mowing

baseball, basketball

Big and Loud exercise routine Big and Loud program Big and Loud, Parkinson's Voice Project, **PWR Moves** Big and Loud, Stationary bike big bag, kickboxing, weight training, cardio drumming Big bootcamp **BIG Exercise Class** BIG exercise learned at therapy BIG exercise program BIG exercise program, strength training **BIG** exercises **BIG** exercises **BIG exercises and POWER exercises** BIG exercises for pd BIG exercises with PT BIG Exercises, free weights Big exercises, weight training, arm exercycle BIG for PD Big moves big gains. Boxing. **BIG** physical therapy **BIG Program BIG Program** BIG program for Parkinson's BIG program for PD patients BIG PT and weight lifting IN REHAB Big therapy BIG therapy program BIG training packet = continue exercises **BIG Zoom exercise class** BIG, range of motion Bike bike, weighjt lifting Biking biking Power up **bIKING ON A THEAPIC BIKE Bio-kinetics** BIOKINETICIST Boat maintenance, fishing, physical work around house bocce, ping pong, badminton

Body Balance, Fit Over 50s, RPM/Spin, Personal Training Body Building Strength training Body Project (cardio and resistance) body pump body sculpting with handweights, step. stretching, light zumba, core strengthening Body weight exercises pull-ups pushups squats body weight interval training body weight resistance training Body weight trainingt body-building, wt. lifting Bodybuilding Boogie Bounce, Qigong boogie bounce, Qigong, pilates **Booster Program** booster tribe sarah king boot camp Boot camp Boot camp (YMCA) Boot camp total body conditioning Boot Camp x1, cardio x2, pilates x1, boxing x2 Boot Camp, 65+ Exercise -strength, agility, balance Boot camp, Treadmill, Parkinson's strength training Boot Camp; Yardwork, PWR Exercises, West Coast Dance Boot Camp; Yardwork, PWR Exercises, West Coast Dance bootcamp Bootcamp Bouncebackexercise.com Bowflex MaxTrainer, Weight lifting Bowl Bowl, see a biokineticist and workout at gym. Bowling Bowls; resistance training box Box circuit training Box-fit at a koala gym Boxercise

boxercise class, agua balance class, forever Boxing (not Rock Steady) active class Boxing (not Rock Steady), gym Boxercise, neuroheroes Boxing (not Rock Steady), YMCA PD Boxercise, PD Power, Boxing & agility training Boxercise, PD Power, walking boxing a bag, light weight training Boxfit, Body Combat, weights Boxing and a muscle fitness program Boxfit, body combat, weights Boxing and Boorcamp Boxfit, Combat & Tone boxing and skiing boxiingboxing boxing and stretching Boxing Boxing at home Boxing Boxing at home weights sit-ups Boxing boxing at home with a punching bag Boxing Boxing but not Rock Steady, Spinning, TRX Boxing boxing but was stopped due to Covid19, now 2 x week online aerobics, hope to do online Boxing boxing soon Boxing boxing class for PWP Boxing Boxing for Parkinson's; weight training; Boxing walking Boxing Boxing for PD Boxing Boxing golf weights Boxing Boxing lessons Boxing boxing training Boxing boxing training Boxing boxing training boxing training for PD, Zumba Gold for PD, Boxing resistance training Boxing Boxing training, cardio workouts, strength Boxing training Boxing training, strength training, Mirror Boxing cardiio, stretching, toning Boxing boxing training, zumba Boxing Boxing Training; Resistance Training; Boxing Flexibility Training Boxing Boxing training; weight training Boxing boxing weights TREADMILL Boxing Boxing, but not at Rock Steady Boxing Boxing, circuit training, high intensity Boxing Boxing, circuit training, weights, gym work Boxing (at home), workout (at home) boxing, gardening Boxing (Home) boxing, golf Boxing (Individual) Boxing, group classes boxing (not at rock steady) PWR moves, brain Boxing, gym and PD Boxing, gym Boxing (not Rock Steady) Boxing, high intensity, circuit training

boxing, HIIT Boxing, Kim Brooks PD exercise Boxing, not Rock Steady Boxing, Olympic weight lifting, Qi gong, other exercises Boxing, Olympic weightlifting, qi gung, acupuncture boxing, optimizing, physical therapy Boxing, pad workout from Brian Grant Foundation Boxing, pd boot camp Boxing, PD Warrior in gym Boxing, rowing machine, yardwork Boxing, standard; gym aerobic & weight lifting Boxing, Stretching boxing, table tennis Boxing, Tennis Boxing, tennis Boxing, tennis Boxing, TREADMILL, WEIGHTS boxing, weight strength boxing, weight training Boxing, weights Boxing, weights Boxing, Weights Boxing, weights & strengthening exercises



Boxing, weights, body weight training, circuits boxing; cardio HIIT & cardio cognitive class, strength training Boxing; circuit training, PWR! Moves boxing; NIA, weight training Boxing; physical therapy using Pilates and core align; PWR! Exercises boxing; PWRMoves level 2; fitness workout boxing/ PD warriors/LGBTbig Boxing/weight training personal trainer Boxingphysical therapy Brain Wave Singers, PD Exercise group, Brazillian Jiu-Jitsu build a shelf, take apart a bed Building and putting up a tunnel house - up and down to the ground to pick things up and gardening - lots of it!

building shed

**Burst Training** 

bycicle like machine, leg presses

#### **Analysis of Exercise Data**

We have recently submitted a manuscript on exercise and PRO-PD scores over time. Because so many people have taken the time to describe their exercise(s) of choice, we now have a rich body of data that can be used to further explore whether starting or stopping some of these activities might impact symptoms.

Parties interested in analyzing subsets of this dataset should apply here:

https://redcap.link/c49s8ht4

#### **O.** Supplements and Nutraceuticals

These are generally considered over-the-counter concentrated sources of nutrients designed to promote health and reduce nutritional deficiencies. Depending on the country, oversight is more or less limited. In the United States product contents have been shown to vary from label claims. Said another way, people may think they are taking a supplement, but the pills don't always contain what the label says, making it hard to study. On top of quality control concerns, products vary by production methods, storage, shipping, delivery method, and dose. Twice over the

past 10 years we have attempted to formally evaluate whether self-reported supplement use was associated with better or worse outcomes over time.

> Hindawi Oxidative Medicine and Cellular Longevity Volume 2017, Article ID 6405278, 9 pages https://doi.org/10.1155/2017/6405278

#### Supplements Associated with Better & Worse Outcomes in 2017 Analysis

Nutraceutical Used	Associated Change
Consistently Over Past	in PRO-PD Score
6+ Months	Assocated with Use
Coenzyme Q10	-70
Fish oil	-70
Melatonin	139
Iron	146

#### **Research Article**

# Role of Diet and Nutritional Supplements in Parkinson's Disease Progression

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*Objectives.* The goal of this study is to describe modifiable lifestyle variables associated with reduced rate of Parkinson's disease (PD) progression. *Methods.* The patient-reported outcomes in PD (PRO-PD) were used as the primary outcome measure, and a food frequency questionnaire (FFQ) was used to assess dietary intake. In this cross-sectional analysis, regression analysis was performed on baseline data to identify the nutritional and pharmacological interventions associated with the rate of PD progression. All analyses were adjusted for age, gender, and years since diagnosis. *Results.* 1053 individuals with self-reported idiopathic PD were available for analysis. Foods associated with the reduced rate of PD progression included fresh vegetables, fresh fruit, nuts and seeds, nonfried fish, olive oil, wine, coconut oil, fresh herbs, and spices (P < 0.05). Foods associated with more rapid PD progression include canned fruits and vegetables, diet and nondiet soda, fried foods, beef, ice cream, yogurt, and cheese (P < 0.05). Nutritional supplements coenzyme Q10 and fish oil were associated with reduced PD progression (P = 0.026 and P = 0.019, resp.), and iron supplementation was associated with the rate of PD progression. These are the first data to provide evidence that targeted nutrition is associated with the rate of PD progression.

#### Oxidative Medicine and Cellular Longevity

TABLE 3: Logistic regression model of nutritional supplements and PD progression. Predicted PD severity score, as measured by the PRO-PD, based on the positive report of consistently using of supplements over the previous 6 months. \*Adjusted for years since diagnosis, age, and gender. \*\*Adjusted for years since diagnosis, age, gender, and income.

Association between dietary supplements & risk of Parkinson's disease progression					
Nutritional supplement	n	Mean change in PRO-PD score (SE)*	<i>P</i> value (95% CI)*	Mean change in PRO-PD score (SE)**	<i>P</i> value (95% CI)**
Inosine	13	-181.1 (125.6)	0.15 (-427.5 to 65.3)	-107.1 (122.9)	0.384 (-348.4 to 134.2)
Glutathione, oral	43	-126.1 (69)	0.068 (-261.6 to 9.3)	-126.7 (70)	0.07 (-263.9 to 10.5)
DHEA	47	-87.6 (70.8)	0.216 (-226.6 to 51.4)	-72.2 (70.9)	0.309 (-211.3 to 67)
Lithium, low dose	21	-84.9 (100.2)	0.397 (-281.6 to 111.8)	-118.9 (100.4)	0.237 (-315.9 to 78.1)
Low-dose naltrexone	14	-76.1 (120.9)	0.529 (-313.4 to 161.2)	-87.8 (118)	0.457 (-319.3 to 143.8)
CoQ10	286	-70.4 (31.5)	0.026 (-132.2 to -8.6)	-46.6 (31.6)	0.141 (-108.7 to 15.4)
Fish oil	376	-69.5 (29.5)	0.019 (-127.4 to -11.6)	-57.7 (29.6)	0.052 (-115.7 to 0.4)
Quercetin	21	-50.7 (105.9)	0.632 (-258.5 to 157.1)	-60.5 (106.4)	0.569 (-269.3 to 148.2)
Turmeric/curcumin	197	-47.3 (35.6)	0.186 (-117.3 to 22.8)	-49.5 (35.9)	0.168 (-120 to 20.9)
Gingko biloba	30	-47.2 (83.2)	0.57 (-210.5 to 116)	-61.1 (81.2)	0452 (-220.5 to 98.2)
Coconut oil	190	-35.8 (36.4)	0.324 (-107.2 to 35.5)	-52.7 (36.4)	0.147 (-124.1 to 18.6)
Resveratrol	43	-28.5 (70.7)	0.687 (-167.3 to 110.3)	-18.7 (72.7)	0.797 (-161.4 to 124)
Vitamin D	623	-26.1 (29)	0.368 (-83 to 30.8)	-3.6 (29.2)	0.902 (-60.9 to 53.7)
Alpha-lipoic acid	79	-19.1 (53.4)	0.72 (-123.9 to 85.7)	0.05 (54.4)	0.999 (-106.7 to 106.7)
5-Methyltetrahydrofolate (5-MTHF)	27	-17.1 (91.4)	0.852 (-196.4 to 162.2)	-25.1 (95.6)	0.793 (-212.7 to 162.5)
Probiotics	249	-12.3 (32.7)	0.708 (-76.5 to 52)	-12.4 (32.9)	0.706 (-77 to 52)
NADH	14	-9.7 (120.8)	0.936 (-246.7 to 227.3)	-25.2 (122.6)	0.837 (-265.7 to 215.4)
Multivitamin/mineral	342	-7.8 (30.2)	0.795 (-67.1 to 51.4)	9.9 (30.3)	0.744 (-49.6 to 69.5)
Calcium	324	-6.2 (32.2)	0.847 (-69.4 to 57)	12.5 (32.6)	0.701 (-51.4 to 76.4)
B6, B12, folic acid, betaine combination	88	3.4 (49.7)	0.946 (-94.2 to 101)	11.1 (48.9)	0.82 (-84.9 to 107.1)
Vitamin C	327	4.2 (30.6)	0.891 (-55.9 to 64.3)	-3.8 (31)	0.902 (-64.6 to 56.9)
N-Acetyl cysteine (NAC)	59	12.8 (60.1)	0.831 (-105 to 130.7)	26.9 (60.8)	0.658 (-92.4 to 146.1)
Vitamin B12 (methyl-B12/cyano-B12)	353	26.7 (29.8)	0.37 (-31.8 to 85.3)	43 (29.8)	0.15 (-15.6 to 101.6)
Rubidium	2	34.2 (306)	0.911 (-566.4 to 634.7)	93.1 (298.5)	0.755 (-492.7 to 678.8)
Estrogen	51	40 (67.4)	0.553 (-92.2 to 172.3)	15.2 (69.6)	0.827 (-121.4 to 151.8)
Glutathione, intranasal	24	62.9 (95.5)	0.51 (-124.5 to 250.4)	55.6 (93.2)	0.551 (-127.3 to 238.5)
Mucuna	33	67 (81.7)	0.412 (-93.3 to 227.2)	21.8 (80)	0.785 (-135.1 to 178.6)
Fava beans	17	122 (109)	0.263 (-92 to 336)	87.8 (110.1)	0.425 (-128.2 to 303.8)
Melatonin	148	139.3 (40.5)	0.001 (59.8 to 218.8)	134.8 (40.2)	0.001 (56 to 213.6)
Iron (Fe)	57	146.4 (63.9)	0.022 (21 to 271.9)	179.7 (64.3)	0.005 (53.6 to 305.9)

## Nutraceuticals and Parkinson Progression, Updated Data - 2023





#### Communication Parkinson Symptom Severity and Use of Nutraceuticals

Laurie K. Mischley <sup>1,2,\*</sup>, Joshua Farahnik <sup>2</sup>, Ludwig Mantay <sup>2</sup>, Jamie Punzi <sup>2</sup>, Kayla Szampruch <sup>2</sup>, Tyrice Ferguson <sup>2</sup> and Devon J. Fox <sup>1</sup>

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Abstract: Background: It is estimated that half of the individuals with Parkinson's disease (PD) use some form of over-the-counter vitamin, herbal supplement or nutraceutical. The goal of this study was to survey individuals with PD about their use of the nutraceuticals and evaluate the association of the nutraceutical with the severity of symptoms. Methods: Participants with self-reported idiopathic PD within the 2021 cohort (n = 1084) were included in a cross-sectional study to assess association of nutraceuticals with symptom severity via linear regression analysis. PD severity was measured using the patient-reported outcomes in PD, and supplement use reflected self-reported consistent use over the previous six months. All regression analyses adjusted for age, gender, income and years since diagnosis. The use of the term progression refers to PRO-PD scores adjusted for years since diagnosis. Results: The most frequently used supplements were vitamin D (71%), B12 (44%), vitamin C (38%) and fish oil (38%). None of the supplements being used were associated with statistically significant worse outcomes. Nutraceuticals associated with improved outcomes were Ginkgo biloba (GB), NAD+ or its precursors, 5-methyltetrahydrofolate, glutathione, mucuna, CoQ10, low dose lithium, curcumin, homocysteine factors, DHEA, coconut oil, vitamin C, and omega-3 fatty acids (fish oil). Conclusions: These data suggest that in a real-world setting, some over-the-counter supplements are associated with fewer patient-reported symptoms. Supplements with significant associations with fewer symptoms have biological plausibility and future clinical trials should be explored.



#### Most Used Supplements among People with Parkinson's



Note: The list of supplements being used is different than the next list of supplements associated with reduced rate of progression.

Figure 1. Ten most used supplements in this sample cohort with percentage of cohort using the supplement.

#### Supplements Taken Consistently Over the Past Six Months & PRO-PD Score

Of the 1000+ participants who responded to the survey, the 19 people reporting consistent use of Gingko biloba scored, on average, -357 PRO-PD points better than people not taking Gingko. These 19 people are likely to be taking other supplements, eating foods, doing activities, etc. that might explain their great score rather than the Gingko; or maybe the Gingko is so effective that it only takes 19 people for us to be able to measure an impact! Over time,



Figure 2. Relative impact on PRO-PD scores with 95% confidence intervals by linear regression adjusted for age, gender, income and years since diagnosis.

more Gingko takers will join the MVP Study and if this trend continues, intervention trials could provide a useful source of information.

**This is not a shopping list.** Talk to a healthcare provider *trained in nutritional medicine* about the pros and cons of any supplements you are considering.

Mischley, L.K.; Farahnik, J.; Mantay, L.; Punzi, J.; Szampruch, K.; Ferguson, T.; Fox, D.J. Parkinson Symptom Severity and Use of Nutraceuticals. *Nutrients* 2023, *15*, 802.

## Melatonin, Sleep, and Parkinson Progression

Melatonin is a commonly used supplement as a sleep aid in people with PD. In our 2017 publication, use of melatonin was associated with worse Parkinson symptoms. We reasoned most of the people taking melatonin were more likely to have a problem with sleep, and impaired sleep is associated with worse PD



outcomes, we reconsidered the melatonin data with respect to insomnia scores. Among people who are bad sleepers, those taking melatonin reported accumulating fewer total Parkinson symptoms over time. [Mischley et al, 2017]

# **Melatonin: Risk or Protection in Parkinson's Disease**

Michael A Rak ND MS, Paul Nicolai ND, Laurie K Mischley ND PhD MPH

A 2016 World Parkinson Congress poster presentation attempted to describe what we were seeing: Among the1024 participants with PD, 13.48% reported using melatonin. Melatonin users had a worse overall PRO-PD score compared to individuals who did not use melatonin, although the significance of this association diminished after adjusting for insomnia. Insomnia was worse among those taking melatonin than those not taking melatonin. 94% of subjects taking melatonin reported symptoms of daytime sleepiness vs 88% of those not taking melatonin. Reported daytime sleepiness was worse among subjects taking melatonin than those not, although this did not reach statistical significance.



7

## P. Pharmaceuticals

We have been collecting data on use of pharmaceutical, or prescription, medications for the duration of this project, but have yet to publish the analysis.

In 2017 poster at the International Movement Disorder Society meeting, both nutraceutical and pharmaceutical medicines were analyzed alongside one another. **Rasagiline was the only pharmaceutical medication associated with statistically significantly fewer PRO-PD symptoms over time.** 



**The Roles of Diet, Exercise, & Supplements in Parkinson's Disease Progression** Laurie K Mischley ND PhD MPH, Richard C Lau MPH



Demographics	N=1024
Age, years (SD)	60.7 (37.5%)
Years Since Diagnosis (SD)	6.7 (5.6%)
<u>Gender</u> Female Male	525 (51.3%) 429 (41.9%)
<u>Ethnicity</u> Caucasian Black Hispanic Native American Asian/Pacific Islander Other	913 (89.2%) 8 (0.8%) 15 (1.5%) 2 (0.2%) 11 (1.1%) 10 (1.0%)
<u>Types of Parkinsonism</u> Idiopathic PD Other Parkinsonism	946 (92.4%) 78 (7.6%)

**Supplements & Pharmaceuticals** 

Supplement/ Pharmaceutical	Estimated Impact on PRO-PD Score	P-value
Oral glutathione	-187.2	0.038
Rasagiline (Azilect)	-158.8	0.021
Coenzyme Q10	-90.8	0.011
Melatonin*	+94.4	0.045
*after considering poor sleep		0.406
Iron	+184	0.006

#### Social Health

	PRO-PD Est Impact	P-value
I have a lot of friends.	-150	<0.000
I am overweight.	+152	<0.000
I am lonely.	+323	<0.000

These data suggest that in a realworld setting, using the PRO-PD as an outcome measure, **people using rasagiline reported fewer symptoms over time**, adjusting for age, gender, income, and years since diagnosis.

# **Study Participants**

#### Levodopa Reduces Parkinson Symptoms Using PRO-PD

We looked at people who joined the MVP Study prior to initiating levodopa, and

then looked at their scores in the six months following initiation of dopamine replacement (100 mg levodopa 3x/day). In these 439 individuals, not a single symptom worsened and there statistically significant improvements in 15 of the 33 symptoms measured. Notably, there were statistically significant increases in nonmotor symptoms after starting levodopa, including anxiety, muscle pain, sleep, and apathy. (The hand-drawn blue line shows which symptoms met statistical significance for improvement.)

Unpublished data. C Weaver, J Farahnik, L Mischley 2021 \*We forgot to include **slowness** in the analysis, so must redo it!



Patient-Reported Change in PD Symptoms

# SYMPTOMS THAT IMPROVED AFTER STARTING DOPAMINE, ACCORDING TO PATIENTS

#### On average, over the past week, please rate the severity of your symptoms:

Symptom	Achors on the Slider Bar
Anxiety	None Severe
Muscle cramping, pain, or aching	None Severe
Insomnia	Not a problemSevere problem
Motivation/ Initiative	Engaged, active Withdrawn, detached, or isolated
Loss of Interest	Active, engaged Severely withdrawn
Balance	Sturdy, steady Occasional falls Lose balance spontaneously
Daytime Sleepiness	None Severe
Fatigue	None Severe
Tremor	None Slight & infrequently present Severe, debilitating
<b>REM Sleep Behavior Disorder</b>	NoneYelling, kicking, interferes with sleep
Depression (feeling sad, blues)	Mentally healthy Severe
Handwriting or Typing	Great; with ease Slow or small Completely illegible
Restless Leg Syndrome	None Severe
Speech	Normal Sometimes asked to repeat statements Not understandable most of the time
Dressing, Eating, & Grooming	With ease With effort Unable

C Weaver , J Farahnik, L Mischley 2021

# Q. Deep Brain Stimulation Surgery (DBS)

These slides are from a presentation given by LK Mischley at the Basal Ganglia Coterie in 2021, comparing Parkinson symptoms before and after DBS. There was an improvement in tremor, sleep, and dyskinesia following the procedure, and a worsening of selfrated sexual function and comprehension, defined by frequent confusion, in these 48 participants. Future research will include a larger cohort and describe results based on the type of DBS.



#### SHORT- AND LONG-TERM SYMPTOM EXACERBATION NEEDS MORE ATTENTION



Greater attention to

patient-reported outcomes following DBS is a priority in the upcoming years.

#### STATISTICALLY SIGNIFICANTLY WORSE SYMPTOMS FOLLOWING DBS

Symptom	Achors on the Slider Bar	
Sexual Dysfunction		
(loss of libido, erectile dysfunction, difficulty with orgasm)	Healthy   Severe	
Balance	Sturdy, steady   Occasional falls   Lose balance spontaneously	
Speech	Normal   Sometimes asked to repeat statements   Not understandable most of the time	
Loss of Interest	Active, engaged   Severely withdrawn	
Drooling	None   Nighttime only   Severe	
Stooped posture	Stand tall   Rounded shoulders   Severely stooped	

# Q. Food

Identifying dietary habits common to the "positive deviants" has always been a priority of the MVP Study. Over time, in response to the data, your questions, and our improved understanding, we have added foods over the years. Thus, we have thousands of responses about vegetable intake, but only hundreds of responses for quinoa. As more participants enroll and the food lists are expanded, our ability to describe the details is improved. Fluctuating numbers of respondents each year, from slightly different populations means the data changes based on timing of the intake and the angle from which we ask the question.

## PUBLISHED DATA

In 2017 we published our first paper from this study that included both food and food-related behaviors. The behaviors associated with the lowest PRO-PD scores (fewest symptoms) were routinely preparing meals for others, cooking most of your own meals, buying food locally, e.g. farmer's markets, co-ops, and trying to eat organic grown food. The behaviors associated with the worst PRO-PD scores were having difficulty affording groceries, especially healthy food, being overweight, and drinking from plastic bottles.



# Q. Food: Behaviors

While all of the items below were statistically significant when we adjusted for age, gender, income, and years since diagnosis, it was still only a point in time and we didn't really know what questions to ask, or what they mean.

## • I routinely cook for myself and others

To do this, one must be highly functional – physically to get to the store, cognitively to organize the meal, energy must be good enough to stand at counter, motor symptoms good enough for chopping, speed good enough that a 20 min dish doesn't take 2 hours, etc. A person with a high PRO-PD score would not be expected to be cooking for themselves and others, in which case this variable is a *consequence* of the PRO-PD score.

Is it possible that cooking for others and ourselves could be *causative?* Inviting friends over for a shared meal has the potential to be therapeutic. Taking responsibility for what you feed yourself, from buying groceries and thoughtful use of ingredients does reduce exposure to preservatives, pesticides, fried foods, and other neurotoxic insults common in the food supply.

- I try to eat organically grown food when possible
- I buy food from local farmers (co-op, farmer's markets)

These variables were included in the MVP Study since day one based on a growing body of epidemiological and biologically plausible evidence that we are being exposed to neurotoxic insults via the food supply. It would be convenient to interpret this to mean buying from your local organic farmer results in measurable benefits (*it might mean that*), or it may mean there is something about the type of people who [are informed/educated/financially stable enough to] seek out locally grown, pesticide-free produce.

Mischley LK, Lau RC, Bennett RD. Role of Diet and Nutritional Supplements in Parkinson's Disease Progression. Oxid Med Cell Longev. 2017;2017:6405278. PI: LK Mischley

# Q. Food: Behaviors

# • I am overweight

Given the well-established association between obesity and a sedentary lifestyle and poor diet, things also shown here to be associated with Parkinson symptom severity, it is not a surprise that obesity is associated with worse outcomes. Adipose tissue can serve as a reservoir for fat-soluble toxicants and is a source of inflammatory chemicals, supporting the biological plausibility of the association. People who identify as overweight should work with their trainer, coach, physician, therapists, dietician, etc. to develop a plan for healthy weight management.

# Drinking from plastic bottles

The University of Washington, where I completed my MPH Epidemiology training, has an incredibly strong Department of Environmental & Occupational Medicine. I was fortunate enough to take courses from their program and learn about the neurodevelopmental consequences associated with exposure to phthalates and polychlorinated biphenyls (PCBs) commonly found in plastic, presumably via the mechanism of endocrine disruption. The question was incorporated into the original survey questionnaire based on the animal model and epidemiological research being done in other conditions.

As this is a cross-sectional analysis, we cannot determine whether people doing poorly drink out of more plastic bottles, or whether drinking out of plastic bottles leads to worse symptoms. Until further data is available, individuals, including their undiagnosed family members, are encouraged to minimize use of plastics and instead drink try to drink from glass cups, stainless steel water bottles, and ceramic mugs.

#### Q. Food Intake and Parkinson Symptom Severity

From the same first publication in 2017, this is the list of foods and PRO-PD outcomes. The more negative the "Mean change" number, the fewer symptoms reported among frequent consumers of that food. Alternatively, the higher the number, the more symptoms associated with consumption of that food.

#### **Baseline Associations Between Food Frequency and PRO-PD Score**

4

#### Oxidative Medicine and Cellular Longevity

 $T_{ABLE 2}: Multiple linear regression model of dietary intake and PD progression. Predicted PD severity score, as measured by the PRO-PD, per unit increase in food intake frequency, intake measured on a 10-point scale: never, <1/month, 1/month, 2-3×/month, 1/week, 2-4×/week, 5-6×/week, 1/day, 2-4×/day, 5-6×/day. *Adjusted for years since diagnosis, age, and gender. **Adjusted for years since diagnosis, age, gender, and income.$ 

Association between dietary practices and Parkinson's disease progression						
Food item (serving size) Mean change i PRO-PD score (S		P value (95% CI)*	Mean change in PRO-PD score (SE)**	P value (95% CI)**		
Fresh vegetables (1/2 cup)	-53.2 (7.9)	<0.000 (-68.7 to -37.6)	-48.9 (8.3)	<0.000 (-64.7 to -33.1)		
Fresh fruit (1/2 cup)	-44.1 (8.5)	<0.000 (-60.7 to -27.5)	-40.7 (8.6)	<0.000 (-57.5 to -23.9)		
Nuts (1/4 cup or 2 tbsp spread)	-38.5 (7.5)	<0.000 (-53.2 to -23.7)	-33.2 (7.6)	<0.000 (-48.1 to -18.4)		
Fish (4 oz)	-37.1 (8.9)	<0.000 (-54.6 to -19.5)	-29.5 (9.1)	0.001 (-47.3 to -11.6)		
Olive oil (1 tsp)	-34.1 (6.8)	<0.000 (-47.4 to -20.8)	-31.4 (6.8)	<0.000 (-44.7 to -18.1)		
Wine (6 oz)	-23.6 (5.3)	<0.000 (-34.1 to -13.1)	-14.6 (5.6)	0.009 (-25.5 to -3.7)		
Turkey (4 oz)	-20.2 (18.7)	0.281 (-57.1 to 16.7)	-10.8 (19.2)	0.573 (-48.7 to 27)		
Coconut oil (1 tsp)	-18.6 (5.5)	0.001 (-29.3 to -7.8)	-20.2 (5.5)	<0.000 (-31 to -9.4)		
Fresh herbs (1 tsp)	-14.9 (6.4)	0.02 (-27.4 to -2.4)	-8.9 (6.5)	0.169 (-21.7 to 3.8)		
Spices (1/4 tsp)	-14.2 (6.4)	0.027 (-26.7 to -1.6)	-13.4 (6.4)	0.037 (-26 to -0.8)		
Eggs (1 egg)	-9.5 (8.2)	0.251 (-25.6 to 6.7)	-9.7 (8.3)	0.241 (-26 to 6.5)		
Bread (1 slice)	-7.7 (6.8)	0.26 (-21.2 to 5.7)	-6.9 (6.9)	0.314 (-20.4 to 6.6)		
Beans (1/2 cup)	-6.3 (8.6)	0.466 (-23.3 to 10.7)	-5.4 (8.8)	0.54 (-22.6 to 11.8)		
Butter (1 tsp)	-4 (5.9)	0.494 (-15.6 to 7.5)	-3.8 (6)	0.522 (-15.5 to 7.9)		
Oatmeal (1 cup)	-3.2 (6.5)	0.624 (-15.9 to 9.5)	-4.4 (6.6)	0.501 (-17.3 to 8.5)		
Liquor (1 oz)	-2.8 (7.7)	0.717 (-17.8 to 12.3)	3.6 (7.7)	0.47 (-11.5 to 18.7)		
Green tea (1 cup)	-2.3 (5.7)	0.68 (-13.5 to 8.8)	1.6 (5.7)	0.779 (-9.6 to 12.7)		
Juice (8 oz)	-2.3 (5.8)	0.687 (-13.8 to 9.1)	-1.4 (5.9)	0.811 (-12.9 to 10.1)		
Frozen fruit (1/2 cup)	-1.9 (6.1)	0.757 (-13.8 to 10)	-2.2 (6.1)	0.714 (-14.1 to 9.7)		
Cream (1/4 cup)	-0.5 (7.4)	0.942 (-15.2 to 14.1)	-0.3 (7.4)	0.971 (-14.7 to 14.2)		
Coffee (8 oz)	-0.1 (4.4)	0.983 (-8.8 to 8.6)	4.3 (4.5)	0.342 (-4.5 to 13.1)		
Soy (3 oz)	0.4 (7.9)	0.962 (-15.2 to 16)	2.3 (8)	0.77 (-13.4 to 18.1)		
Safflower oil (1 tsp)	0.7 (6.9)	0.922 (-12.8 to 14.2)	6.8 (6.9)	0.325 (-6.8 to 20.5)		
Beer (12 oz)	1.1 (7.6)	0.88 (-13.7 to 16)	2 (7.5)	0.789 (-12.8 to 16.8)		
Chicken (4 oz)	3.3 (9.7)	0.34 (-15.6 to 22.3)	13.4 (9.8)	0.171 (-5.8 to 32.5)		
Milk (1 cup) (mammalian, for example, cow)	5.8 (4.8)	0.226 (-3.6 to 15.2)	5.1 (4.8)	0.291 (-4.4 to 14.5)		
Pork (4 oz)	6.1 (8.6)	0.482 (-10.8 to 22.9)	7 (8.7)	0.42 (-10 to 24)		
Black tea (1 cup)	8.6 (5.6)	0.121 (-2.3 to 19.5)	8.4 (5.6)	0.131 (-2.5 to 19.3)		
Eat food from a can	9.6 (8.1)	0.234 (-6.2 to 25.4)	6.1 (8.1)	0.449 (-9.7 to 22)		
Pasta (1 cup)	10.1 (9.3)	0.28 (-8.2 to 28.4)	9.2 (9.4)	0.326 (-9.2 to 27.6)		
Frozen vegetables (1/2 cup)	11 (6.9)	0.11 (-2.5 to 24.4)	10.3 (6.9)	0.137 (-3.3 to 23.9)		
Cheese (1 slice, 1/2 oz, 1 tbsp)	11.7 (6.9)	0.091 (-1.9 to 25.3)	15.5 (6.9)	0.026 (1.9 to 29.1)		
Yogurt (3/4 cup)	13.5 (7.5)	0.073 (-1.3 to 28.3)	15.2 (7.6)	0.046 (0.2 to 30.1)		
Ice cream (1/2 cup)	13.8 (7.4)	0.064 (-0.8 to 28.3)	18.3 (7.5)	0.015 (3.6 to 32.9)		
Soda (12 oz)	15.4 (7.8)	0.049 (0.03 to 30.7)	15.2 (7.9)	0.054 (-0.3 to 30.6)		
Beef (4 oz)	16.2 (8.3)	0.051 (-0.1 to 32.4)	21.8 (8.3)	0.009 (5.5 to 38.1)		
Fried food (4 oz)	19.5 (8.8)	0.027 (2.2 to 36.8)	23 (8.9)	0.009 (5.6 to 40.4)		
Canned vegetables (1/2 cup)	19.9 (7)	0.005 (6.1 to 33.6)	18.3 (7)	0.009 (4.5 to 32.1)		
Diet soda (12 oz)	20.7 (6.1)	0.001 (8.7 to 32.8)	23.6 (6.1)	<0.000 (11.6 to 35.6)		
Canned fruit (1/2 cup)	36.1 (7.9)	<0.000 (20.5 to 51.6)	32 (7.9)	<0.000 (16.5 to 47.6)		

This was our first formal look at the data and became the basis of what has since been referred to as the "PRO Diet", as it is based on PROs in PD.

This is problematic in that the food included/ excluded change based on the type of analysis done, and changes year to year.

Mischley LK, Lau RC, Bennett RD. Role of Diet and Nutritional Supplements in Parkinson's Disease Progression. Oxid Med Cell Longev. 2017; 2017:6405278.

Using the same methods described in the manuscript above and an updated, larger dataset, we have identified several modifiable variables associated with accumulation (or lack) of symptoms over time have been identified.



# Q. Food: Frequency and Fast vs. Slow Slope of Progression

MetLife donated the time of one of their statisticians to analyze some de-identified data for us. Caleb Weaver looked at the  $\sim 300$  people who had – at that time – given us 6+ datapoints over the study period and assigned each of them a slope. He took the top 20% and the bottom 20% and is showing us here how often each group reports eating each type of food.







# Q. Food:

# Using MVP Study Data to Study Other Diets

Standardized scales exist to answer the question, "How Mediterranean is your diet?" This allows researchers to determine whether people with the greatest adherence to a diet (note: *not a food*) have better outcomes. Using these validated scales, both MIND and MEDI scores were associated with fewer patient-reported symptoms over time. **Each MIND point was twice as strong as a MEDI point in reducing symptom severity.** Future dietary intervention trials should consider the MIND diet as a therapeutic strategy for improving long-term PD outcomes.

The greater one's adherence to the MIND diet, the fewer non-motor symptoms they had, with **MIND adherence associated with less constipation, apathy**, **depression, anxiety, insomnia, muscle pain, sexual, urinary, and cognitive dysfunction.** 



# Q. Food:

# What's the Difference Between the Diets?

The circle on the left represents the composition of the Mediterranean diet, as defined by researchers. The circle on the right is the MIND diet. The overlapping portion shows how they both encourage nuts, fish, and vegetables and avoidance of red meat and pork.

The Medi diet encourages "Sofrito", and the MIND diet encourages "Poultry" – both of these, as individual variables, were associated with *worse* PRO-PD outcomes. In other words, the diets would have been better for PD scores had they not included Sofrito and Poultry, which were individually associated with worse PRO-PD scores.

The box in the center represents the portions of each diet that were statistically associated with better (green) or worse (red) PRO-PD outcomes



Fox DJ, Park SJ, Mischley LK. Comparison of Associations between MIND and Mediterranean Diet Scores with Patient-Reported Outcomes in Parkinson's Disease. Nutrients. 2022 Dec 6;14(23):5185.

# **Q. Food: The Difference Between the Diets**

Despite the debate over dairy and poultry, the overlap between popular diets is reassuring. For each diet, foods in green are encouraged, foods in red are discouraged.

Similarities and Differences Beween Popular Parkinson Diets					
	PRO	MIND	Medi	Keto	
Vegetables		green leafy			
Nuts & Seeds					
Seafood, Fish					
Olive oil					
Fruit		berries			
Wine					
Legumes					
Coconut oil					
Green tea					
Fresh herbs					
Spices					
Buy organic					
Cook at home					
Whole Grains					
Egg					
Dairy			low-fat	high-fat	
Poultry					
Canned fruit, Canned vegetables					
Chicken					
Drinking from plastic bottles					
Sweets & Pastries					
Pasta					
Refined Grains					
Pork					
Red meat					
Fried food					
Soda / Carbonated beverages					

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## Q. Food: Patterns

Diets are complex and no single food is eaten in isolation and because people who eat beef also tend to eat pork and chicken, it's difficult to tell whether any one, all three, or something else about meat-eaters are the culprit. One of our statisticians, Devon Fox, produced a figure of describing the correlation between different foods. The darker the blue shading, the more those foods went together (e.g. people eating a lot of Fresh Vegetables are also eating a lot of Fresh Fruit), and the red shading demonstrates aversion (e.g. people who eat Coconut Oil rarely eat Bread and Pasta).



Figure S1: Correlation plot between all significant items (adjusted for demographics without Holm-Bonferroni correction) which showed no items with correlation values between -0.6 < x > 0.6.

#### Q. Food: Food and Specific Symptoms

#### Highest Food Frequency Column: Absolute Value

Statistician Matthew Kollada explored the dataset to see if any of the foods were associated with specific symptoms. The numerical values show the relative impact of the association but doesn't describe the direction. The graph below shows the direction of the association, with dark blue being inversely correlated with PRO-PD severity (e.g. high fish, nuts, beans, tend to have lower PRO-PD scores).

winefreq	4.221067
cfruitfreq	4.114400
nutfreq	3.435737
sodafreq	3.429104
icecrfrq	3.418787
fvegfreq	3.271050
friedfreq	3.002632
redwineffq	2.720050
quinoafreq	2.715687
dietsodafreq	2.663413
cvegfreq	2.651148
fishfreq	2.623300
frvegfreq	2.589084
buttrfreq	2.464724
juicefreq	2.423328



PI: LK Mischley

	propd	winefreq	0.195888
O. Food:	balance	cfruitfreq	0.187341 0.184712
	rising	cfruitfreq	0.183893
Highest Correlation Pair: Absolute Value	dressing walk fatigue	cfruitfreq winefreq winefreq	0.180439 0.172034 0.171974
This analysis attempts to describe the food(s) most	propd handwriting	icecrfrq guinoafreg	0.170106 0.167154
highly correlated with Parkinson symptoms.	motivation falls	fvegfreq cfruitfreq	0.166368 0.164066
Total PRO-PD was associated with wine (good) and	stoop walk ballucipations	winefreq cfruitfreq	0.162574 0.162459
ice cream (bad).	nactucinations	recrirq	0.102057

Wine was particularly associated with total PRO-PD scores, gait, fatigue, and stooped posture.

**Canned fruit** was associated with worse balance, rising from a seated position, dressing/eating/ grooming, more frequent falls, and gait impairment.

Ice cream was associated with total PRO-PD score and more frequent hallucinations.

Fresh vegetables were associated with greater motivation (less apathy) scores.

Quinoa was associated with better handwriting.

#### **Highest Correlation Pair Absolute values**



#### Q. Food: Associated with PRO-PD Severity



#### Food and Parkinson Symptoms Severity

This is a cross-sectional analysis of 2000+ participants' baseline data. The regression model adjusted for age, gender, income, and years since diagnosis.

Foods highlighted green are statistically significantly associated with fewer symptoms over time, and the foods highlighted red are associated with more symptoms over time.

The larger the Impact, the greater that food is associated with Parkinson symptom severity.

	Baseline (n =	2022 survey	
	2228)	event (n = 873)	
Gender	N (%)	N (%)	
Male	937 (42.1)	343 (39.3)	
Female	1275 (57.2)	518 (59.3)	
Other/NA	16 (0.7)	12 (1.4)	
Age			
Mean (SD)	63.3 (9.30)	67.3 (8.75)	
Median [Min, Max]	64.0 [23.0, 99.0]	68 [23, 91]	
Income			
<\$20,000	118 (5.3)	40 (4.6)	
\$20-40,000	264 (11.8)	78 (8.9)	
\$40-60,000	288 (12.9)	100 (11.5)	
\$60-80,000	297 (13.3)	116 (13.3)	
\$80-100,000	294 (13.2)	105 (12.0)	
\$100-150,000	385 (17.3)	158 (18.1)	
>\$150,000	440 (19.7)	191 (21.9)	
NA	142 (6.4)	85 (9.7)	
Education			
< High school	29 (1.3)	5 (0.5)	
High School Diploma/GED	220 (9.9)	72 (8.2)	
Technical School	117 (5.3)	44 (5.0)	
Certification			
Associate degree	176 (7.9)	60 (6.9)	
Bachelor's Degree	646 (29.0)	253 (29)	
Graduate/Professional	1023 (45.9)	422 (48.3)	
Degree			
Years since Diagnosis			
Mean (SD)	4.76 (4.86)	8.46 (5.56)	
Median [Min, Max]	3.30 [0, 43.4]	7.70 [0, 38.8]	
PRO-PD score			
Mean (SD)	760 (461)	836 (502)	
Median [Min, Max]	665 [ 29.0, 2430]	749 [30.0, 2660]	
Missing	272 (12.2)	44 (5.0)	
Table 1: demographics and desc	criptive statistics of b	aseline and 2022	
cohort			

	Baseline Only (2013-2022)			
	n	impact (SE)	p-value	R^2
Herbs & Spices				
Spices-1/4 teaspoon	1789	-5.31 (4.43)	0.2	0.146
Fresh Herbs-1 tsp	1781	-11.1 (4.13)	0.007	0.147
Vegetables & Fruits	1012		1.000	2.4.12
Frozen Vegetables	1789	16.1 (4.56)	<0.001*	0.149
Frozen Fruit	1787	-3.53 (4.26)	0.4	0.145
Fresh Vegetables	1785	-23.7 (6.38)	<0.001*	0.151
Nute Seeds Beans	1/0/	-29.9 (0.00)	<b>NO.001</b>	0.156
Roops	1773	-10 8 (5 32)	0.04	0.146
Sov - 3 ounces	1778	-8.92 (5.41)	0.1	0.142
Nuts/Seeds-1/4 cup	1788	-25.6 (4.90)	<0.001*	0.156
Oils		2010 (1100)		0.100
Fried foods-4 ounces	1774	34.7 (6.01)	<0.001	0.161
Plant-based oils	1776	5.43 (4.40)	0.2	0.145
Olive oil	1782	-9.5 (4.39)	0.03	0.149
Coconut oil	1769	-16.3 (3.91)	<0.001*	0.155
Grains				
Millet	14	70.1 (64.5)	0.3	0.119
White rice	200	18.8 (22.6)	0.4	0.162
Pasta-1 cup	1788	15.9 (6.24)	0.01	0.147
Bread-1 slice	1768	9.20 (4.52)	0.04	0.145
Oats	196	5.79 (16.2)	0.7	0.138
Oatmeal - 1 cup	1778	-2.77 (4.28)	0.5	0.142
Barley	1807	-2.64 (57.1)	0.9	0.179
Brown rice	732	-8.55 (20.1)	0.7	0.165
Quinoa	249	-18.7 (22.0)	0.4	0.196
Farro	74	-61.4 (54.5)	0.3	0.0118
Buckwheat	46	-76.5 (42.4)	0.08	0.268
	1707	24 2 (4 70)	-0.0041	0.400
Rutter 1 ten	1787	31.2 (4.76)	<0.001*	0.163
Chaese 1/2 oz	1781	19.5 (3.91)	<0.001*	0.150
Vogurt-3/4 cup	1457	14.8 (4.42)	<0.001*	0.132
Milk(cows)-1 cup	1785	12.6 (3.47)	<0.001*	0.148
Cream-1/4 cup	1781	8.82 (5.26)	0.09	0.145
Meat & Eggs			0.00	22.5.0
Beef	1791	28.3 (5.31)	<0.001*	0.157
Chicken	1795	18.7 (5.47)	<0.001*	0.149
Pork	1786	18.0 (5.69)	0.002	0.152
Turkey	1274	2.71 (7.88)	0.7	0.121
Fish	1783	-26.5 (5.88)	<0.001*	0.153
Eggs	1788	-4.38 (4.99)	0.4	0.146
Alcoho			24	
Wine-6 oz	1786	-21.5 (3.87)	<0.001*	0.161
Red wine-6oz	217	-9.21 (11)	0.4	0.126
White wine-6oz	215	2.71 (14.49)	0.9	0.121
Beer-12 ounce	1779	-4.27 (5.4)	0.4	0.143
Liquor-1 oz	1772	5.35 (5.56)	0.3	0.143
Canned (1/2 cup)				
Canned Beans	68	53.9 (30.67)	0.08	0.228
Canned Fruit	1782	43.5 (6.18)	<0.001*	0.168
Canned Vegetables	1788	26.0 (4.95)	<0.001*	0.156
Canned food (general)	1780	14.0 (5.42)	<0.001	0.147
	67	-18.4 (29.4)	0.5	0.191
Beverages	1775		-0.0011	0.400
Diet soda - 12 ounces	1775	30.3 (4.79)	<0.001*	0.163
Non-diet soda - 12 ounces	1778	26.8 (6.11)	<0.001*	0.155
luice - 8 oz	1795	9.01 (4.06)	0.001-	0.157
Coffee - 8 oz/1 oz espresso	1785	0.99 (3.54)	0.03	0.144
Black tea - 1 cup	1774	0.29 (3.04)	0.0	0.144
Green tea -1 cup	1778	-10.6 (3.99)	<0.001	0.146
Canned Coconut milk	68	-57.6 (43.9)	0.2	0.213

# Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS

Univariate analyses are often the first step in data analysis for several reasons, especially when working with complex datasets. Univariate analysis provides the "raw" effect of each food frequency variable on PRO-PD scores without adjustments for confounding factors. Univariate analysis provides **a clear understanding of the distribution** of each variable (e.g., mean, median, variance, skewness, kurtosis). This is critical for identifying whether certain foods or PRO-PD scores have normal, skewed, or bimodal distributions.

In terms of **variable selection**, univariate analysis can filter out variables with no apparent relationship to PRO-PD scores, reducing the complexity of multivariate models. Including only variables with some evidence of association in univariate analyses helps **avoid overfitting** when building multivariate models.

The Free Learning Platform for Better Future provides a great metaphor for understanding **univariate analysis**.

While valuable, univariate analyses **do not account for confounding** variables (e.g., age, gender, income, years since diagnosis) and **can overestimate or misrepresent the importance** of variables that may lose significance in multivariate models.

# What is Univariate, Bivariate, and multivariate Analysis in Data Visualisation?

#### Why should anyone learn this analysis?

Imagine you're in your kitchen and about to bake a cake. Learning about univariate, bivariate, and multivariate analysis in data visualization is like learning different ways to work with ingredients.

- **Univariate Analysis** is like examining each ingredient separately. Before you start, closely examine the flour, sugar, eggs, and cocoa powder one by one. You want to know their characteristics-how much flour you have, how sweet the sugar is, and so on. This helps you understand what each ingredient brings to the cake.
- **Bivariate Analysis** is when you start pairing up ingredients to see how they interact. You might mix flour and sugar to understand their sweetness or combine eggs and cocoa powder to see how they affect the cake's colour and texture. It's about understanding how two ingredients work together.
- Multivariate Analysis takes it a step further. Now, you're not just looking at pairs of ingredients but considering the entire recipe. You're thinking about how flour, sugar, eggs, cocoa powder, and other ingredients combine to make the final cake. It's about understanding the complex relationships between all the ingredients.

Just as a chef needs to understand how different ingredients work together to create a delicious dish, a data analyst or scientist needs to understand these analysis techniques to make sense of data effectively. Univariate, bivariate, and multivariate analysis help you "taste" your data, so to speak, and discover its unique flavours and complexities.

https://www.javatpoint.com/what-is-univariate-bivariate-and-multivariate-analysis-in-data-visualisation

# Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS

#### Fresh/ Frozen/Canned Vegetables, Pork, Beef, Chicken

The most beneficial food was fresh vegetables, at least one serving daily.



Chicken and beef were associated with worse outcomes, with highest intakes associated with worst outcomes.

Infrequent **pork** consumption was associated with worse outcomes, but more frequent consumption was not (seemingly not dose-dependent), contrary to our prior findings.

# **Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS**

## Milk, Cheese, Ice Cream, Canned Fruit



Milk and cheese (even 2-3 servings per month) were associated with worse outcomes; the highest intakes were associated with most severe symptoms.

Ice cream 5-6 servings per week was associated with greater symptom severity.

**Canned fruit** was associated with greater symptom severity, in a dose dependent manner. The more frequently people ate canned fruit, the greater their symptom severity.

#### Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS



#### Soda/ Diet Soda, Fried Food, Eggs, Fish, Bread

**Fried food** associated with worse outcomes, in a **dose-dependent** manner. Adverse association detectable with one serving per week.

**Eggs** were associated with worse outcomes, contrary to what we've previously seen in adjusted data.

4-6 slices of **bread** per day was associated with worse outcomes.

## Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS

#### Pasta, Olive/ Coconut oil, Green/Black tea, Fresh herbs, Coffee, Beer, Wine



Wine is consistently associated with lower PRO-PD scores, with the highest category "2-4 glasses per day" associated with fewer symptoms than "once daily," which was lower than weekly or monthly consumption. A dose-response relationship lends weight to a causal role.

Unlike prior analyses of this dataset, **beer** was associated with fewer symptoms. An estimated 2-3 beers per month was associated with reduction in symptoms, but 5-6 per week was even better.

Frequent use of **olive oil and coconut oil** wer associated with fewer symptoms. **Fresh herbs** were consistently protective, across doses.

**Green tea** (2-4x/day) was associated with better outcomes, but **black tea** (5-6x week) was associated with worse outcomes. Since this is the same plant, differently processed, further studies should investigate the effects of roasting, etc.

Pasta was strongly associated with worse outcomes, in a dose-dependent manner.

**Coffee** was surprisingly associated with worse Parkinson outcomes, is a dosedependent fashion. This is surprising given the large body of literature suggesting coffee is associated with reduced incidence of PD diagnosis, but here is suggests coffee intake after diagnosis is associated with worse outcomes.
### Example of How We Can Use AI to Aid Research

### 常 Perplexity

#### Differences Between Green and Black Tea in Relation to Neurodegeneration

Green tea and black tea, both derived from the *Camellia sinensis* plant, exhibit distinct biochemical properties that may influence neurodegenerative processes such as Parkinson's disease (PD). The primary differences lie in their processing methods, chemical composition, and potential neuroprotective effects.

#### Processing and Chemical Composition

- Green Tea: This tea undergoes minimal oxidation during processing. The leaves are
  quickly steamed or pan-fired to prevent oxidation, preserving high levels of catechins,
  particularly epigallocatechin gallate (EGCG). These catechins are potent antioxidants
  that contribute to green tea's neuroprotective properties 1 2.
- Black Tea: In contrast, black tea is fully oxidized, which alters its chemical profile. While it contains some beneficial compounds, including theaflavins and thearubigins formed during oxidation, its catechin content is significantly lower than that of green tea. This difference in composition may affect their respective impacts on health and disease progression 3.

#### Neuroprotective Effects of Green Tea

Research has consistently indicated that green tea consumption is associated with a reduced risk of PD and may slow its progression. Key findings include:

- Antioxidant Properties: Studies demonstrate that regular consumption of green tea can enhance antioxidant status and reduce oxidative stress markers in PD patients. Increased activities of antioxidant enzymes like catalase and superoxide dismutase were observed alongside decreased levels of lipid peroxidation 1 2.
- Neuroprotective Mechanisms: EGCG has been shown to inhibit the aggregation of alpha-synuclein, a protein implicated in PD pathology. This inhibition may protect dopaminergic neurons from toxicity associated with PD 2 2 . Additionally, green tea polyphenols modulate microglial activation and inflammatory responses, further contributing to their protective effects against neurodegeneration 2 7.
- Clinical Implications: Epidemiological studies suggest that higher intake of green tea correlates with slower progression to dementia and depression in PD patients. This protective role is thought to stem from both direct neuroprotective effects and improvements in overall brain health 2 (2).

### Potential Risks Associated with Black Tea

Conversely, black tea has been linked to an increased risk of PD progression in some studies:

- Oxidative Stress: The compounds formed during the oxidation process may have less favorable effects on oxidative stress compared to the catechins in green tea. Some research indicates that black tea may not provide the same level of neuroprotection and could potentially exacerbate neurodegenerative processes 3
- Caffeine Content: While both teas contain caffeine, the effects of caffeine on neurodegeneration are complex. Some studies suggest that caffeine may have protective effects against PD; however, the overall impact of black tea's caffeine content combined with its other constituents remains less clear compared to the benefits attributed to green tea ③.

The discrepancy between green and black tea led me down a research rabbit hole, beginning with the AI tools only recently available to us.

Perplexity is an AI-powered conversational search engine designed to provide direct answers to user queries by synthesizing information from various online sources.

I asked Perplexity to describe possible reasons for the discrepancy between green and black tea with respect to neurodegeneration and this is the output I received within seconds. Such tools are likely to reduce barriers to information access, expand perspective, and speed up information access, all of which facilitate ideas and propel research.

To be clear, we do *not* yet know whether drinking green tea and avoiding black tea is associated with fewer symptoms over time, as a therapeutic intervention and we are even less certain that these AI-generated ideas regarding possible mechanisms of action are the reason for the benefit, if the benefit exists. These are unadjusted, cross-sectional results and they may change in multi-variate models.

## Q. Food: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS

Infrequent **soy products** (2-3 servings per month) were associated with fewer symptoms.





### Q. COMBINED RESULTS OF UNIVARIATE (UNADJUSTED) ANALYSIS

**Foods Associated with More Symptoms:** Fried food, canned fruit and canned vegetables, soda/diet soda, chicken, beef, pork, eggs, bread, pasta, coffee, dairy products (yogurt, cheese, milk, ice cream), black tea, and frozen vegetables.

**Foods Associated with Fewer Symptoms:** Fresh vegetables, Olive and coconut oil, wine and beer, green tea, fish, fresh herbs and occasional turkey (2-4 times per week).

**Unadjusted Univariate Analysis:** Doesn't take income, age, sex, or years since diagnosis into account, or any other variables. *These are likely to change once we start taking other things into consideration!* 

Food	Strength of	Dose-Dependent	Consistent		
	Association				
Fried food	****	Y	Y		
Canned Fruit	****	Y	Y		
Canned vegetables	*/***	Y	Y		
Soda, Diet Soda	***	Y	Y		
Chicken	*/***	Y	Y		
Beef	*/***	Y	Y		
Pork	**	Ν	Y		
Eggs	***	Y	Y		
Bread	***	Y	Y		
Pasta	***	Y	Y		
Coffee	**/ ***	Y	Y		
Yogurt	**	Ν	Y		
Cheese	**	Y	Y		
Milk	**	Y	Y		
Ice cream	**	Y	Y		
Black tea	**	Ν	Ν		
Frozen vegetables	*	Ν	Y		
Soy		Ν	Ν		
Fresh vegetables	***	Ν	Y		
Turkey, 2-4x/week	**				
Olive oil	*/**	Y	Y		
Coconut oil	**		Y		
Wine	* / **	Y	Y		
Beer (max 5-6/week)	**	Y	Y		
Green tea	*		Y		
Fish	*		Y		
Fresh herbs	*		Y		

# **R. Food Behavior: Associated with PRO-PD Severity: UNIVARIATE ANALYSIS**

There is a section on the MVP Study that is comprised of a series of True/ False statements. Here, we show how answering **True** to the following statements is associated with overall Parkinson symptom severity, as measured by the PRO-PD.

**Poverty**, expressed here as inability to afford healthy food and groceries, is strongly associated with greater symptom severity. While pervasive, relevant, and congruent with findings in other disorders, the role of financial health in Parkinson symptom severity has received very little attention.

Consistent with our findings from prior analyses, people who identify as **overweight** also report greater symptom severity. Whether this is related to perception or metabolism cannot be determined from this analysis; whether weight loss improves outcomes should be the consideration of future research endeavors.



### S. Available Data

Over the years we have modified and expanded the data collected. We are trying to balance consistency with changing trends, discerning details without overburdening participants, and dropping variables that are wasting your time and incorporating new ones based on new understanding and recent analyses.

We intend to continue this project, with enhancements to data collected, more diversity in enrollments, and continued collaborations with researchers across universities and continents.

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Number of Study Participants	48	558	648	761	1019	1000	573	1118	1169	1074	794	200
Demographics	48	558	648	761	1019	1000	573	1118	1169	1074	794	200
Diagnostic information												
Symptom severity												
.PRO-PD												
.Estimated Hoehn & Yahr												
Supplements												
Pharmaceuticals												
Biometric data												
Heart Rate Variability (HRV)												
Body Mass Index (BMI)	12	68	95	113	178	221	139	288	339	382	537	183
Have you lost weight recently without trying?	NA	521	176									
How much weight have you lost?	NA	99	26									
Sleep												
.Pittsburg Sleep Quality Index	NA	518	173									
Sleep score												
Physical activity												
Champs												
Activity- Days per week	45	526	622	723	983	951	554	1053	1116	1014	572	182
Type of exercise	48	558	648	761	1019	1000	573	1118	1169	1074	794	200
.exercise intensity	NA	2	NA	1	NA	1	NA	954	1100	988	567	178
Quality of Life												
.Global	48	548	635	746	1007	982	564	1066	1122	1037	761	185
.Sexual	NA	212	82									
Satisfaction with Life	NA	527	178									
Posttraumatic Grwoth Inventory	NA	465	161									
Stigma	NA	496	159									
Gratitude	NA	496	160									
Music												
Interoception (MAIA)	NA	514	172									

# T. FUTURE DIRECTIONS

The next round of analyses will include multivariate models, which take multiple other things into consideration, such as age, income, and years since diagnosis. As we gain clarity about the symptoms that are most likely to be associated with progression in the refined analyses, we'll develop a way to weight different foods for the purposes of teaching and scoring.



**Packaging & Delivery of Lifestyle Modification** 



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If you know of others with a diagnosis of any form of parkinsonism, or a possible prodromal stage of parkinsonism, please invite them to participate: <u>www.MVP-Study.com</u>