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Beyond Baseline: Symptom Trajectories and Prognostic Associations of Complementary Therapies in Parkinson's Disease

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Abstract

Background/Objectives: Parkinson's disease (PD) progression is highly heterogeneous, and prognostic biomarkers guiding personalized management remain elusive. Complementary therapies are widely used by people with PD. Their real-world associations with long-term symptom progression remain poorly characterized, and conclusions drawn from observational data depend on the analytic approach used. We examined baseline complementary therapy use in relation to symptom severity and its rate of change using four complementary analytic approaches. Methods: Data came from the Modifiable Variables in Parkinsonism prospective cohort study (2013-present, $n = 2656$ at baseline). Participants reported consistent use of 51 complementary therapies over the prior six months, and the outcome was the Patient-Reported Outcomes in PD (PRO-PD) score. Four approaches were applied: (1) separate regression models for each therapy, (2) a multivariate model including the 24 therapies with ≥100 users, (3) unadjusted smoothed trajectories, and (4) linear mixed-effects models with a Time × therapy interaction. Adjusted models accounted for age, gender, income, and years since diagnosis. Results: Vitamin D (63.1%), vitamin B12 (40.6%), and fish oil (39.5%) were most frequently used. In the full 24-therapy baseline model, low-dose lithium, fish oil, and coenzyme Q10 were associated with lower baseline symptom severity, whereas oral glutathione was borderline ($p = 0.067$) and reached $p = 0.045$ after backward elimination. After false-discovery rate control, baseline use of oral glutathione and coconut oil was associated with slower accumulation of PRO-PD points, and NAC and probiotics with faster accumulation; four further therapies reached unadjusted $p < 0.05$ only. Associations frequently changed across analytic approaches, and several therapies reversed direction between cross-sectional and prognostic analyses. Conclusions: Associations between complementary therapy use and PD symptoms depended strongly on the analytic approach, and cross-sectional associations were a poor guide to later symptom change. Long-term pragmatic follow-up identified over-the-counter therapies associated with slower (oral glutathione, coconut oil) and faster (NAC, probiotics) symptom accumulation. These findings do not establish causation; rather, they illustrate the value of systematically examining longitudinal patient-reported data in identifying biologically plausible patterns that emerge amid the complexity of real-world care and can guide subsequent explanatory research.

Keywords: pragmatic; personalized; nutrition; nutrient; nutraceutical; vitamin; complementary; integrative; prognosis; patient-reported outcomes

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1. Introduction

Parkinson's disease (PD) progression is highly heterogeneous, with substantial variability in symptom severity and rate of decline that is not well explained by age, disease duration, or pharmacologic treatment alone. While dopaminergic therapies remain the cornerstone of symptomatic management, they do not meaningfully alter the underlying disease trajectory, [1] and there are few validated prognostic indicators available to guide personalized, disease-modifying strategies [2]. As a result, many individuals with PD seek complementary and non-pharmacologic interventions in an effort to improve symptoms or slow progression, often in the absence of clear longitudinal evidence to inform these decisions [3–5]. Recently, proposals for adopting complementary and alternative therapies are described along dimensions of biological plausibility, strength of the studies, and patient perception of benefit [6].

Nutraceuticals and other complementary therapies represent a rapidly expanding global industry, yet their use in PD remains under-studied relative to their widespread adoption. Existing research has largely focused on preclinical mechanisms, short-term symptom relief, or isolated supplements studied in controlled settings. Real-world use patterns are far more complex, characterized by concurrent use of multiple supplements, variable duration of exposure, and adoption that is often driven by symptom burden, access to care, and personal beliefs. These features complicate causal inference and limit the generalizability of traditional randomized trials, underscoring the need for pragmatic longitudinal studies capable of capturing real-world exposure and outcomes.

The Modifiable Variables in Parkinsonism (MVP) study was designed as a natural history cohort to evaluate whether lifestyle and behavioral factors, including diet, supplements, exercise, and other non-pharmacologic interventions, are associated with PD outcomes over time. Prior cross-sectional analyses in the MVP cohort demonstrated that the supplements most used by participants were not consistently aligned with those associated with lower symptom burden, highlighting a disconnect between popularity and apparent benefit [7]. However, cross-sectional associations cannot distinguish between therapeutic effects, selection bias, or reverse causation, and do not address whether baseline exposures are associated with subsequent symptom change.

The present study extends this work by evaluating supplement use as a prognostic factor in a longitudinal PD cohort. Using repeated patient-reported outcome assessments and linear mixed-effects modeling, we examined whether consistent use of specific complementary therapies over the six months prior to baseline was associated with differences in subsequent rates of accumulation of PRO-PD points, independent of age, gender, income, and years since diagnosis. By focusing on real-world exposure patterns and longitudinal change, this study aims to identify nutritional and metabolic factors that may be relevant to PD trajectory and to generate hypotheses that can inform future prospective and interventional research.

2. Materials and Methods

2.1. Participants

Participants with self-reported idiopathic PD enrolled in the MVP study (NCT02194816) were included. Baseline data were collected at enrollment, with follow-up assessments approximately every six months. The analysis included participants who completed both the complementary therapy questionnaire and the Patient-Reported Outcomes in PD (PRO-PD) assessment.

2.2. Complementary Therapy Assessment

Participants were asked, "Please mark box if you have taken any of the following consistently over the past 6 months," followed by a checklist of 51 over-the-counter vitamins, herbal supplements, nutraceuticals, and other complementary interventions. "Consistently" was not further defined, so exposure reflects each participant's own judgment of regular use over that period. Each therapy was coded as binary (yes/no). Dose, formulation, frequency, and duration of use were not recorded, and use after baseline was not measured.

2.3. Outcome Measures

The primary outcome was PRO-PD total score, a validated patient-reported measure of Parkinson's disease symptom severity across multiple domains, including motor, non-motor, and quality of life symptoms [8,9]. Higher PRO-PD scores indicate greater symptom burden.

2.4. Statistical Analysis

Four analytic approaches were used, each addressing a different question. All adjusted models included age, gender, income, and years since diagnosis. Behavioral factors such as diet and physical activity were not added because, measured at the same baseline survey as therapy use, they may act as either confounders or mediators, and adjusting for a mediator would remove part of the association of interest [10]. Analyses were conducted in R version 4.2.1 (RStudio 2026.05.0).

- Univariate (cross-sectional) analysis: To replicate previous findings [7], we performed cross-sectional analyses using baseline data. For each supplement, separate linear regression models were fitted with PRO-PD total score as the outcome and supplement use as the primary predictor. Effect estimates (beta coefficients) and 95% confidence intervals were calculated and visualized using forest plots, with supplements ranked by effect size.
- Multivariate Model at Baseline: A multivariate linear regression model was constructed including all supplements with at least 100 baseline users ($n = 24$ supplements). This threshold was selected based on power analysis to ensure adequate statistical power (>80%) to detect small-to-medium effect sizes (Cohen's $f^2 \geq 0.02$) at $\alpha = 0.05$. The multivariate model was adjusted for age, gender, income, and years since diagnosis. Complete case analysis was employed. Manual backward elimination was performed with a p-value to remove >0.1. The reduced model is exploratory. Therapy coefficients in the full multivariate model and after backward elimination were not corrected for multiplicity. Initial and final model fit was evaluated using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Tetrachoric correlations were calculated to examine patterns among the included supplements in the initial model, with clustering analysis used to identify common supplement profiles in the cohort.
- Descriptive longitudinal trajectories. PRO-PD scores were plotted against months since each participant's first questionnaire, not years since diagnosis, among users of commonly used therapies and smoothed using locally weighted scatterplot smoothing (LOESS), without further adjustment.
- Prognostic (longitudinal) analysis. For each therapy with at least 10 baseline users, a linear mixed-effects model was fitted with a Time × therapy interaction and a random intercept, estimated by restricted maximum likelihood (REML). The main effect of therapy estimates the baseline difference between users and non-users, and the interaction estimates the difference in the rate of change. Because therapy use was measured only at baseline, these terms are predictive associations. They describe later PRO-PD change among people who reported use at baseline and are not estimates of treatment

effect. Retention, dose, and adherence during follow-up were not measured. Statistical significance was set at $\alpha = 0.05$ (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). No correction for multiple comparisons was applied to therapy coefficients in the full multivariate baseline model or after backward elimination. Benjamini–Hochberg false-discovery rates were calculated for the 45 univariate tests and for the Time × therapy interactions. Results are exploratory. Time was measured in months from each participant's first questionnaire, not in years since diagnosis. Years since diagnosis was a covariate. The model included a random intercept and no random slope: across all 2330 participants entering the mixed models, the median number of assessments was 2 (IQR 1 to 5), 52.3% contributed at most two assessments (including 942 [40.4%] with a baseline score only), therapy use was measured only at baseline, and adding a random slope (1 + Time|participant) produced near-unidentifiable random-effects covariance and convergence failures in lme4. Under REML, mixed models use all available scores without imputation and provide valid inference under a missing-at-random (MAR) mechanism conditional on observed covariates and observed PRO-PD scores. Baseline PRO-PD was the outcome at time 0, not an additional covariate: the therapy main effect estimates the baseline difference between users and non-users, and adjusting for the time-0 score would instead estimate change conditional on starting severity, which can bias the estimated difference in change when exposure is associated with baseline values and the score is measured with error [11]. The smallest fitted user group had 19 participants, and non-users were included in each model.

3. Results

3.1. Cohort Characteristics

Of 2938 participants with idiopathic PD, 2656 completed a baseline questionnaire on use of complementary therapies (Table 1, Figures 1 and S1). Table 1 counts each participant once, using the first baseline questionnaire; years since diagnosis were recorded for 2555 participants, and a baseline PRO-PD score for 2330 participants. Because time was measured in whole months from each participant's first questionnaire, 59 participants also had a second questionnaire within month 0, yielding 2715 month-0 records. The multivariate models used the 1986 participants with complete data on the PRO-PD, age, gender, income, and years since diagnosis (2039 month-0 records; Tables 2 and S1); restricting these models to each participant's first entry produced nearly identical estimates. The mixed-effects models included all 2330 participants with a baseline PRO-PD score, of whom 1388 contributed at least one later score.

Table 1. Participant characteristics and complementary therapy use at baseline.

(a) Participant Characteristics (N = 2656)			(b) Complementary Therapy Use (N = 2656)		
Characteristic	**n**	**%**	**Complementary Therapy**	**n**	**%**
Baseline age (years), median [IQR]	64.4 [57.3; 70.0]		≥100 users (included in multivariate model)		
Years since diagnosis, median [IQR] (n = 2555)	3.30 [1.31; 6.73]		Vitamin D	1675	63.1%
PRO-PD total score, median [IQR] (n = 2330)	664 [381; 1067]		Vitamin B12	1078	40.6%
Gender			Fish oil	1050	39.5%
Male	1120	43.1%	Vitamin C	852	32.1%
Female	1479	56.9%	CoQ10	799	30.1%
Non-binary	1	<0.1%	Multivitamin/mineral	778	29.3%
Missing	*56*		Probiotics	721	27.1%
Race			Calcium	703	26.5%
Caucasian	2435	93.6%	Turmeric/curcumin	659	24.8%

Table 1. *Cont.*

(a) Participant Characteristics (N = 2656)			(b) Complementary Therapy Use (N = 2656)		
Characteristic	**n**	**%**	**Complementary Therapy**	**n**	**%**
Black	20	0.8%	Melatonin	510	19.2%
Hispanic	49	1.9%	Coconut oil	454	17.1%
Native American	8	0.3%	Homocysteine factors	262	9.9%
Asian/Pacific Islander	40	1.5%	Glutathione, oral	241	9.1%
Other	50	1.9%	NAC	197	7.4%
Missing	*54*		Alpha-lipoic acid	176	6.6%
Continent			DHEA	156	5.9%
North America	1240	78.5%	Estrogen	156	5.9%
South America	7	0.4%	Dance for PD	155	5.8%
Europe	237	15.0%	Marijuana (edible)	149	5.6%
Asia	12	0.8%	Marijuana (inhaled)	143	5.4%
Africa	11	0.7%	Iron (Fe)	142	5.3%
Oceania	73	4.6%	Mucuna	135	5.1%
Missing	*1076*		LSVT	117	4.4%
Household income			Lithium, low dose	110	4.1%
Less than $20,000	133	5.5%	<100 users		
$20,000–40,000	302	12.5%	High-dose B1, oral	99	3.7%
$40,000–60,000	327	13.5%	Resveratrol	96	3.6%
$60,000–80,000	347	14.4%	Ginkgo biloba	85	3.2%
$80,000–100,000	332	13.7%	Quercetin	63	2.4%
$100,000–150,000	464	19.2%	5-MTHF	63	2.4%
More than $150,000	513	21.2%	Glutathione, intranasal	51	1.9%
Missing	*238*		Fava beans	48	1.8%
Highest education			Low-dose naltrexone	44	1.7%
Less than 8th grade	10	0.4%	Lion's mane	44	1.7%
Grades 9-11	24	0.9%	Red light therapy	36	1.4%
High school/GED	251	9.7%	NADH	34	1.3%
Technical school certification	135	5.2%	Inosine	33	1.2%
Associate degree	203	7.8%	NAD+/NR/NMN	25	0.9%
Bachelor's degree	760	29.3%	Tremble Clefs	23	0.9%
Graduate/professional degree	1215	46.8%	Mannitol	23	0.9%
Missing	*58*		Other mushrooms	22	0.8%
			Testosterone, topical	19	0.7%
			IM micronutrients	8	0.3%
			High-dose B1, IM	5	0.2%
			Testosterone, IM	5	0.2%
			IV micronutrients	5	0.2%

IQR, interquartile range; PRO-PD, Patient-Reported Outcomes in Parkinson's Disease; NAC, N-acetyl cysteine; LSVT, Lee Silverman Voice Treatment. Counts are participants, using each participant's first baseline questionnaire. Percentages in panel (a) are calculated among participants with non-missing data for each characteristic (years since diagnosis available for 2555 and baseline PRO-PD for 2330); percentages in panel (b) are calculated among all 2656 participants. The multivariate models include the 1986 participants with complete data on PRO-PD, age, gender, income, and years since diagnosis. Therapy use reflects consistent use over the six months prior to baseline.

The median age at baseline was 64.4 years (IQR 57.3–70.0), and the median time since diagnosis was 3.3 years (IQR 1.3–6.7). Participants were predominantly female (56.9%) and Caucasian (93.6%); among those reporting location, 78.5% lived in North America. The cohort was highly educated (76.0% with a bachelor's degree or higher) and skewed toward higher household income (40.4% reporting more than $100,000 USD annually). The median baseline PRO-PD total score was 664 (IQR 381–1067). In the full multivariate model (Table S1), female gender ($\beta = -46.75$, 95% CI −85.91 to −7.59, $p = 0.019$) and higher income ($\beta = -45.19$ per income category, 95% CI −55.17 to −35.22, $p < 0.001$) were associated with lower symptom severity, while each additional year since diagnosis was associated with greater severity ($\beta = 27.65$, 95% CI 23.71 to 31.59, $p < 0.001$).

3.2. Patterns of Use

The most frequently used interventions were vitamin D (63%), B12 (41%), fish oil (40%) and vitamin C (32%). (Table 1b and Figure 1) These baseline usage patterns reflect real-world adoption among people with PD, independent of efficacy.

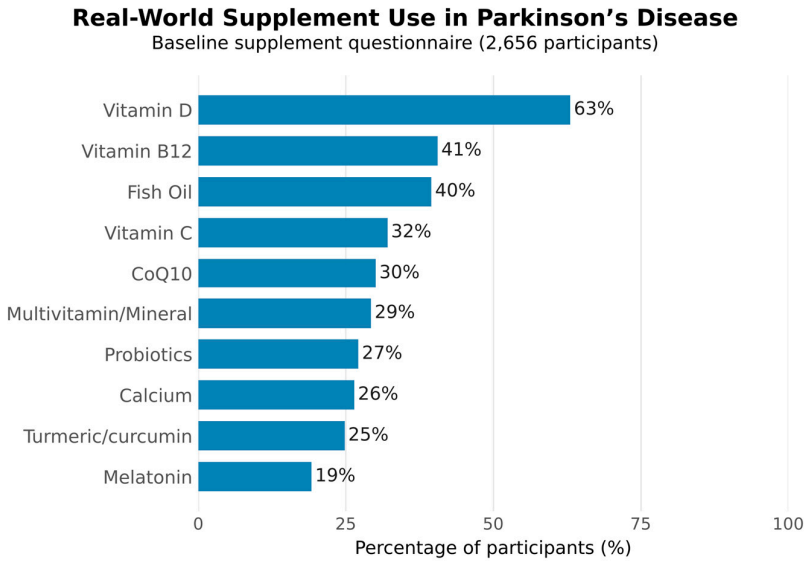


Figure 1. Supplement Use in Parkinson's Disease. Percentage of participants reporting consistent use over the prior six months. (2656 baseline participants).

Table 2. Final multivariate model of complementary therapies and baseline symptom severity.

Characteristic	β	95% CI	*p*-Value
Lithium, low dose	−133.77	−231.78, −35.76	0.007 **
Estrogen	−73.72	−155.89, 8.45	0.079
Glutathione, oral	−73.21	−144.68, −1.74	0.045 *
Fish oil	−65.78	−107.69, −23.86	0.002 **
N-acetyl cysteine (NAC)	−63.88	−136.36, 8.60	0.084
Gender, female (vs. male)	−49.03	−86.95, −11.11	0.011 *
Income (per category)	−45.51	−55.38, −35.63	<0.001 ***
Coenzyme Q10	−44.63	−90.17, 0.91	0.055
Turmeric/curcumin	−41.86	−89.12, 5.40	0.083
Age at baseline (years)	−1.11	−3.13, 0.92	0.283
Years since diagnosis	27.76	23.85, 31.66	<0.001 ***
Multivitamin/mineral	49.20	7.76, 90.65	0.020 *
Vitamin B12	52.41	12.63, 92.18	0.010 *
Melatonin	86.87	40.23, 133.50	<0.001 ***
LSVT speech therapy	91.19	3.08, 179.30	0.043 *
Marijuana (inhaled)	94.17	15.74, 172.61	0.019 *
Iron	99.96	16.21, 183.71	0.019 *
n (participants/records)	1986/2039		
R^2/adjusted R^2	0.183/0.176		
AIC/BIC	30,394/30,501		

The model began with all therapies with ≥100 baseline users (n = 24) and retained 13 after backward elimination ($p > 0.1$). Backward elimination is exploratory, and *p*-values were not corrected for multiplicity. β is the difference in PRO-PD points; negative values indicate fewer symptoms. Shaded rows are non-modifiable covariates, shown for perspective. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. CI, confidence interval; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

3.3. Univariate Analysis

To screen for candidate associations, each therapy was first modeled separately (Figure 2). Of the 45 therapies modeled, 15 were significantly associated with baseline symptom severity. Eleven were associated with fewer symptoms: low-dose lithium, oral glutathione, Ginkgo biloba, Mucuna, N-Acetylcysteine (NAC), coenzyme Q10, estrogen, fish oil, turmeric/curcumin, NAD+/NR/NMN, and IV micronutrients. Among therapies with at least 100 users, the largest estimates were for low-dose lithium and oral glutathione. The estimates for IV micronutrients (n = 5) and NAD/NR/NMN (n = 25) were large but imprecise. Four therapies were associated with greater symptom burden: iron, melatonin, inhaled marijuana, and Lee Silverman Voice Treatment LOUD speech therapy (LSVT) [12].

Across these 45 tests, a Benjamini–Hochberg false-discovery rate below 0.05 was found for oral glutathione, low-dose lithium, fish oil, coenzyme Q10, turmeric/curcumin, and NAC, all associated with fewer symptoms, and for melatonin and iron, both associated with greater symptom burden.

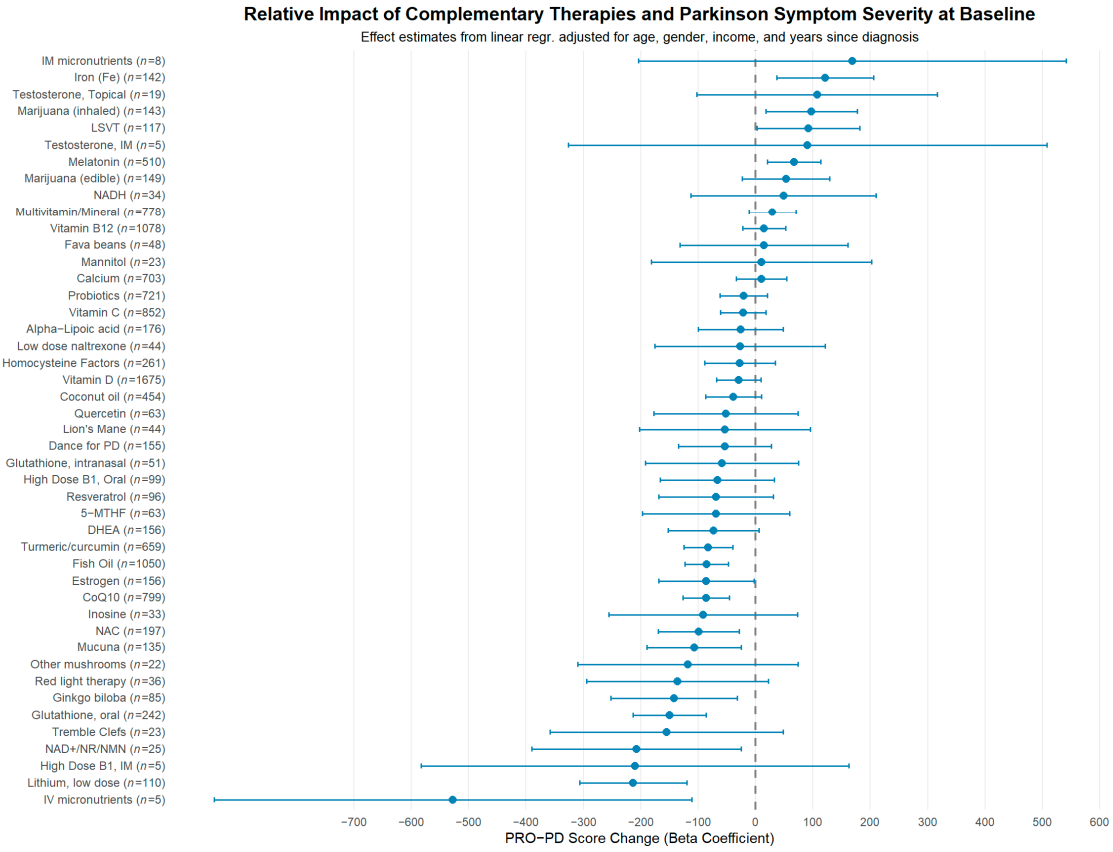


Figure 2. Forest plot for all therapeutic interventions assessed and baseline symptom severity, adjusted for age, gender, income, and years since diagnosis.

These cross-sectional estimates describe who uses what; they are not evidence of benefit or harm. Associations with greater symptom severity, particularly LSVT, likely reflect therapies adopted in response to symptoms, while associations with fewer symptoms may reflect healthier or more engaged individuals choosing particular therapies, known as the healthy-user effect [13]. In addition, each model estimates a therapy in isolation, whereas most participants used several therapies at once.

3.4. Descriptive Longitudinal Trajectories

Figure 3 presents smoothed PRO-PD trajectories for users of the 25 most frequently used therapies. Two features are apparent. First, every trajectory rises: mean symptom burden increased over the observation period for users of every therapy, and no therapy was associated with sustained improvement, consistent with the natural history of a progressive neurodegenerative condition. Second, the trajectories are not parallel. The spread between the most and least favorable curves exceeds 400 PRO-PD points late in follow-up, suggesting meaningful heterogeneity in the rate of symptom accumulation. In these unadjusted curves, users of oral glutathione, low-dose lithium, DHEA, coenzyme Q10, and homocysteine-lowering B vitamins had mean PRO-PD scores below 1000 late in follow-up. The horizontal axis is months from the first questionnaire, not years since diagnosis.

These curves are unadjusted. The groups differ substantially in size, and fewer participants contribute at later times. They are presented as a descriptive overview rather than as estimates of effect; adjusted estimates of the rate of accumulation are reported in Section 3.7.

3.5. Multivariate Analysis

Univariate models estimate each therapy in isolation, but people with PD rarely use therapies in isolation. To account for concurrent use, the 24 therapies with at least 100 baseline users were entered into a single model. Exploratory backward elimination retained 13 therapies. The final model fit better than the full model (AIC 30,394 vs. 30,410 and BIC 30,501 vs. 30,578), with similar explained variance (adjusted R^2 0.176 vs. 0.174). The full prespecified 24-therapy model is provided in Table S1, and the reduced model after backward elimination is shown in Table 2.

In the full 24-therapy model prior to variable selection (Table S1), three therapies were significantly associated with lower baseline symptom severity: low-dose lithium ($\beta = -136.74$, 95% CI −236.29 to −37.19, $p = 0.007$), fish oil ($\beta = -66.45$, 95% CI −109.61 to −23.29, $p = 0.003$), and coenzyme Q10 ($\beta = -46.59$, 95% CI −92.75 to −0.43, $p = 0.048$), whereas oral glutathione showed a similar inverse estimate that did not reach statistical significance ($\beta = -68.43$, 95% CI −141.57 to 4.70, $p = 0.067$). Restricting the analysis to one baseline entry per participant (n = 1986) yielded $\beta = -71.27$ ($p = 0.060$) in the full model and $\beta = -77.03$ ($p = 0.038$) after elimination. After backward elimination (Table 2), which we treat as exploratory, low-dose lithium ($\beta = -133.77$, 95% CI −231.78 to −35.76, $p = 0.007$), oral glutathione ($\beta = -73.21$, 95% CI −144.68 to −1.74, $p = 0.045$), and fish oil ($\beta = -65.78$, 95% CI −107.69 to −23.86, $p = 0.002$) had $p < 0.05$, while coenzyme Q10 was slightly attenuated ($\beta = -44.63$, 95% CI −90.17 to 0.91, $p = 0.055$). These p-values were not corrected for multiplicity, so values near 0.05 should be interpreted cautiously. For scale, each additional year since diagnosis was associated with 27.76 more PRO-PD points. Because these are cross-sectional estimates, this comparison conveys magnitude only.

Four therapies significant in univariate models were attenuated but retained ($p < 0.1$): estrogen, NAC, coenzyme Q10, and turmeric/curcumin, indicating that their univariate estimates were partly carried by co-used therapies. Six therapies were independently associated with greater symptom severity: iron, inhaled marijuana, LSVT, melatonin, vitamin B12, and multivitamin/mineral supplements. Inhaled marijuana, which did not reach significance in the full model ($p = 0.066$), did so in the final model. Among covariates, female gender and higher income were associated with fewer symptoms, and age was not.

3.6. Co-Use of Complementary Therapies

Tetrachoric correlations among the 24 therapies in the full model are shown in Figure 4a, with hierarchical clustering in Figure 4b. The strongest pairings were edible and inhaled marijuana (r = 0.72), alpha-lipoic acid and NAC (r = 0.69), oral glutathione and low-dose lithium (r = 0.66), calcium and vitamin D (r = 0.63), and coenzyme Q10 and oral glutathione (r = 0.61).

Clustering identified one large group of densely co-used therapies, within which oral glutathione and low-dose lithium paired most closely, alongside coenzyme Q10, fish oil, DHEA, the B vitamins, vitamins C and D, turmeric/curcumin, alpha-lipoic acid, NAC, coconut oil, and probiotics. Outside this cluster, co-use was sparse, with three small groupings: edible and inhaled marijuana; iron, calcium, and multivitamin/mineral supplements; and Dance for PD and LSVT. Because NAC and probiotics fall within the same cluster as the therapies most strongly associated with lower severity, their users frequently also use oral glutathione, lithium, and coenzyme Q10. With that amount of co-use, an association

for one therapy may partly reflect the mix of therapies people report, not an effect of that therapy alone.

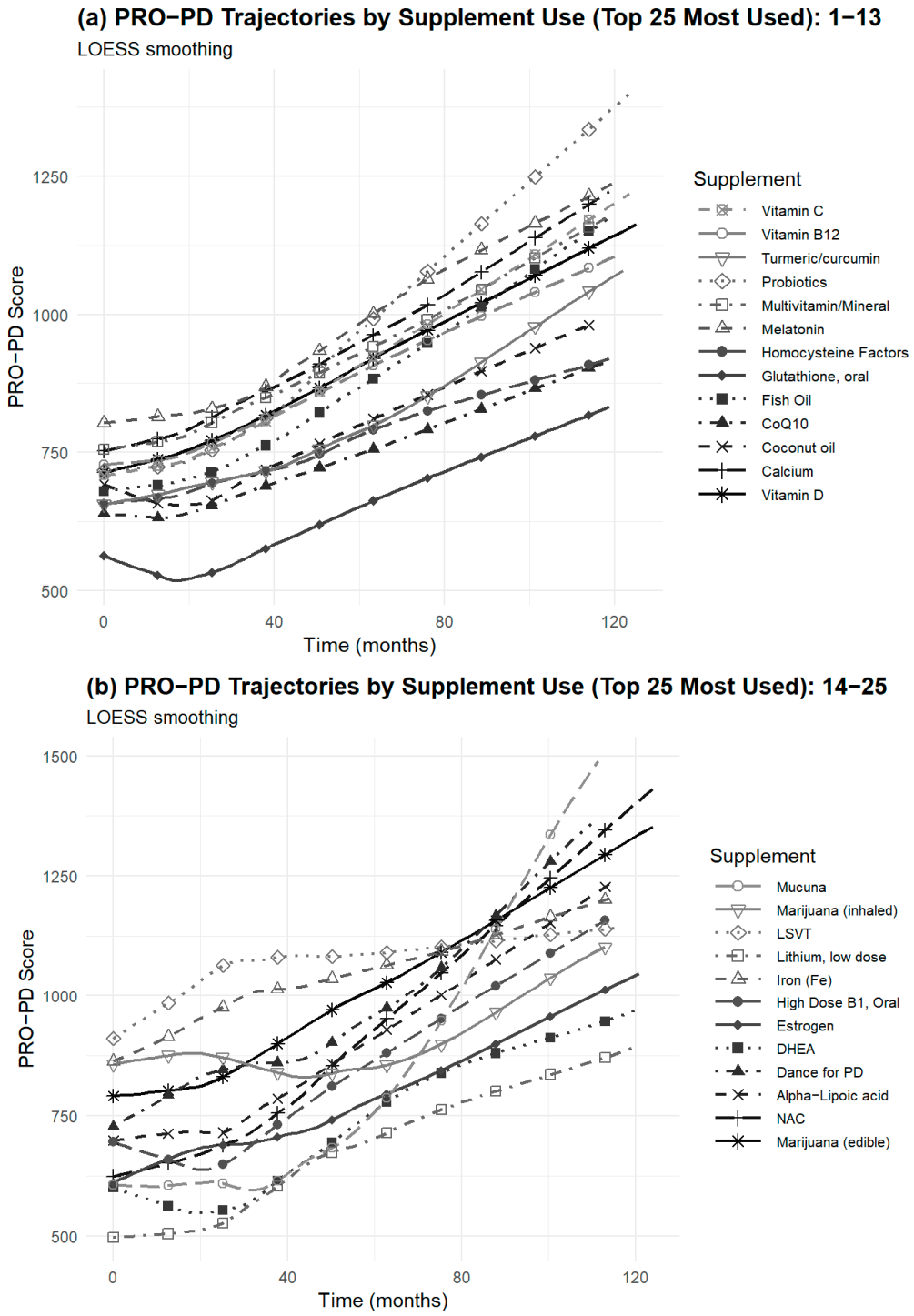
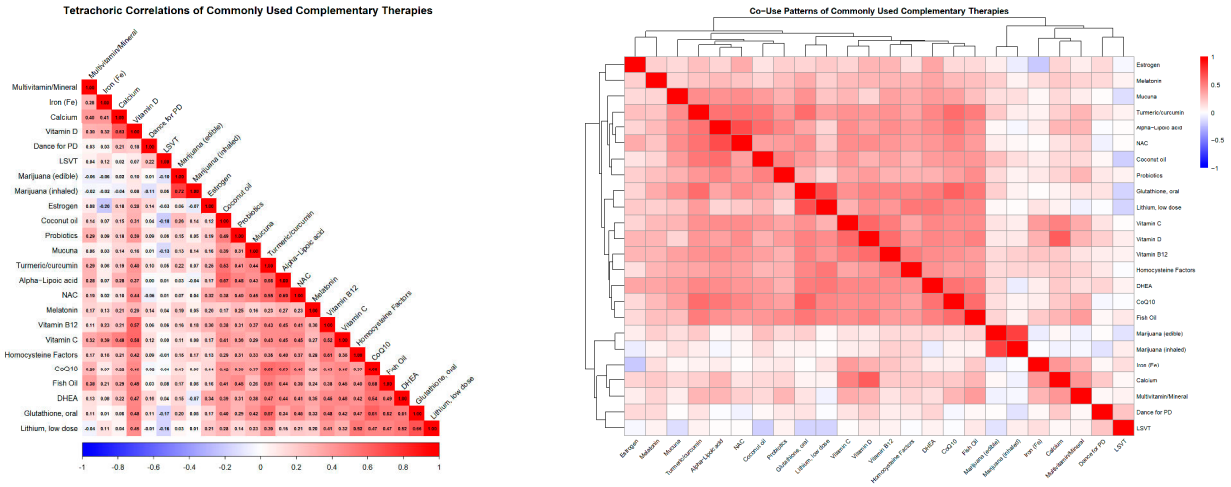


Figure 3. Longitudinal PRO-PD symptom trajectories among users of common therapies. Smoothed trajectories of the PRO-PD score among participants who reported consistent use of one of the 25 most used therapies over the six months before baseline. Curves are unadjusted LOESS smooths. The horizontal axis is months from the first questionnaire. It is unknown whether use continued during follow-up. (**a**) Therapies ranked 1–13 by baseline use. (**b**) Therapies ranked 14–25. PRO-PD: Patient-Reported Outcomes in Parkinson's Disease.



(**a**) (**b**)

Figure 4. Co-use of complementary therapies with ≥100 baseline users. (**a**) Tetrachoric Correlations of Commonly Used Complementary Therapies. (**b**) Co-use patterns of commonly used therapies, with hierarchical clustering.

3.7. Prognostic Analysis

The mixed-effects models estimate both where each group started and how it changed. These baseline estimates can differ from the cross-sectional results in Figure 2 because the mixed models use all 2330 participants with a baseline score and draw on their later scores. Among 2330 participants with a baseline PRO-PD score, 1388 (59.6%) contributed at least one later score, over a median of 42 months (IQR 19 to 68, range 1 to 114), with a median of 5 assessments (IQR 3 to 7, range 2 to 17). Participants with only a baseline score remained in the models and contributed to the baseline difference.

At baseline (Figure 5), greater symptom severity was observed among users of fava beans, inhaled marijuana, intranasal glutathione, LSVT, iron, and multivitamin/mineral supplements, and fewer symptoms among users of low-dose lithium, oral glutathione, coenzyme Q10, fish oil, and vitamin C (all $p < 0.05$, unadjusted).

In the longitudinal models (Figure 6, Table S2), four associations remained after false-discovery rate control (FDR = 0.020 for each). Compared with non-users, baseline users of oral glutathione accumulated about 15 fewer PRO-PD points per year (−1.28 points per month, 95% CI −2.02 to −0.55) and users of coconut oil about 12 fewer (−0.96, 95% CI −1.57 to −0.35), whereas users of NAC accumulated about 16 more (1.35, 95% CI 0.50 to 2.20) and users of probiotics about 9 more (0.74, 95% CI 0.29 to 1.20). Inhaled marijuana, estrogen, homocysteine-lowering B vitamins, and multivitamin/mineral supplements were associated with slower accumulation at $p < 0.05$ but did not survive false-discovery rate control and should be regarded as hypotheses. Estimates for low-dose lithium, DHEA, and other medicinal mushrooms suggested slower accumulation, and those for NAD+/NR/NMN, quercetin, and NADH suggested faster accumulation, but none reached significance. Coefficients, 95% confidence intervals, exact *p*-values, and false-discovery rates for all 41 therapies shown in Figure 6 are reported in Table S2.

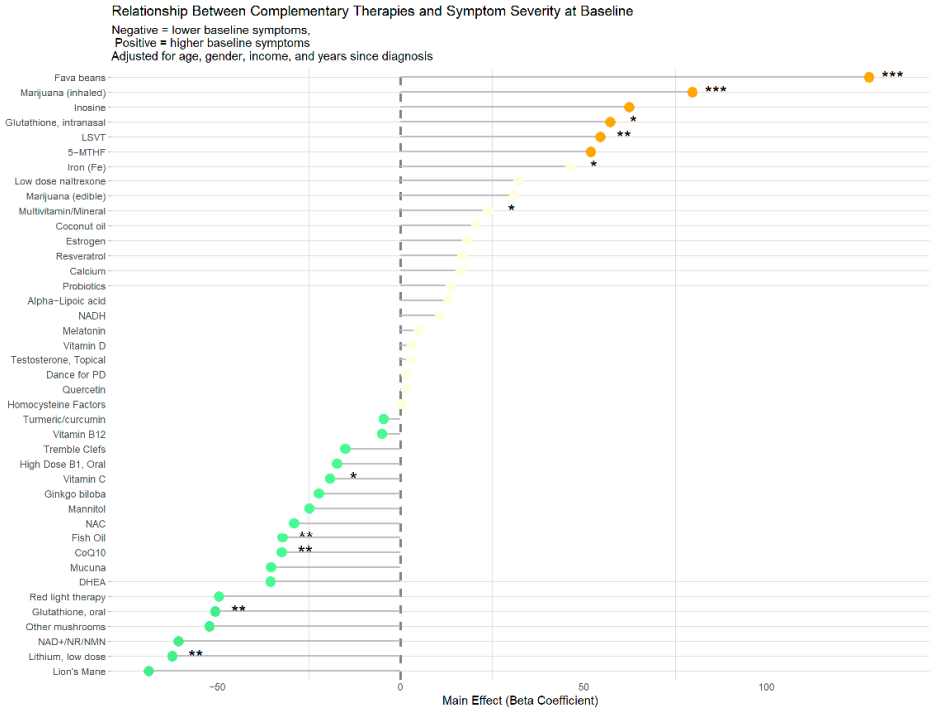


Figure 5. Baseline symptom severity among users of complementary therapies, estimated from longitudinal models. Baseline (intercept) differences in PRO-PD score from linear mixed-effects models. Participants with only a baseline score are included. Estimates are adjusted for age, gender, income, and years since diagnosis. Exposure reflects consistent use over the six months prior to baseline. Positive values indicate greater symptom severity at baseline; negative values indicate fewer symptoms. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Green points indicate a lower baseline PRO-PD score (fewer symptoms), yellow a small increase, and orange a larger increase. Darker shades indicate a larger difference.

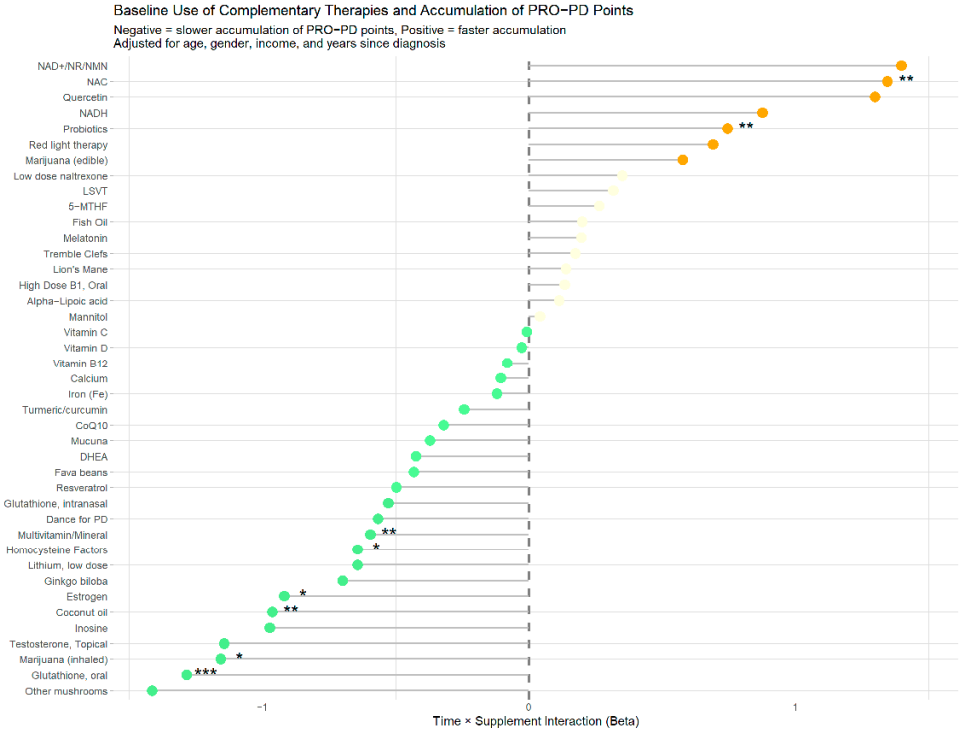


Figure 6. Baseline Use of Complementary Therapies and Accumulation of PRO-PD Points. Time × therapy interaction coefficients (PRO-PD points per month) from linear mixed-effects models,

adjusted for age, gender, income, and years since diagnosis. Negative values indicate slower, and positive values faster, accumulation of PRO-PD points over time compared with non-users. Asterisks show unadjusted *p*-values (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$); coefficients, 95% confidence intervals, exact *p*-values, and false-discovery rates for all 41 therapies are given in Table S2. Green points indicate a lower baseline PRO-PD score (fewer symptoms), yellow a small increase, and orange a larger increase. Darker shades indicate a larger difference.

4. Discussion

The goal of this study was to evaluate whether use of any complementary therapy queried in the MVP study, reported at enrollment, was associated with concurrent symptom severity or with the later rate of PRO-PD accumulation.

The four approaches each ask a different question of the same data. The univariate models ask who uses what; the multivariate model asks which associations survive after accounting for concurrent use. The descriptive trajectories show what happened to users of each therapy over time. The mixed-effects models ask whether baseline use predicts the rate of change. Table 3 summarizes how the answer shifts with the question. It is presented here because such shifts are easy to miss when only one analysis is reported.

Oral glutathione had an inverse estimate in every approach, but the baseline association was not significant in the full multivariate model ($p = 0.067$). The slope result is not a separate replication: it comes from the same people, the same baseline exposure report, and the same PRO-PD score. More often, associations changed with the analytic approach. Coenzyme Q10, estrogen, turmeric/curcumin, and NAC looked protective in univariate models but were attenuated once concurrent use was modeled. These therapies are commonly taken alongside glutathione, lithium, and fish oil (Figure 4), so part of their univariate signal was likely borrowed from those co-used therapies. A coefficient for one therapy is therefore best read as an association with the reported use mix, not as a standalone treatment effect. The opposite also occurred: vitamin B12 and multivitamin/mineral use showed no univariate association but were associated with greater severity after adjustment.

Baseline severity and rate of accumulation also proved to be distinct outcomes. Low-dose lithium and fish oil were consistently associated with fewer symptoms at baseline but did not predict slower accumulation of PRO-PD points. Conversely, probiotics, coconut oil, and homocysteine-lowering B vitamins showed no baseline association but predicted differences in the rate of accumulation. Three therapies reversed direction: inhaled marijuana and multivitamin/mineral users were more symptomatic at baseline yet accumulated PRO-PD points more slowly, while NAC users had fewer symptoms at baseline in univariate models but accumulated PRO-PD points faster. Reversals of this kind can reflect confounding by indication, as therapies adopted in response to symptoms will look harmful cross-sectionally, or regression toward the mean among people who enroll during a period of worse symptoms or selective follow-up, if participants whose symptoms worsened were more likely to stop completing assessments, leaving a slower-progressing group. These explanations cannot be separated with these data, and the reversals should not be read as evidence of benefit or harm without replication. A recent phase 3 trial found that nicotinamide riboside worsened outcomes relative to placebo in early PD [14], consistent in direction with our imprecise prognostic estimate for NAD+ precursors (n = 25; $p = 0.116$) but not with their favorable cross-sectional association.

Some of these findings will be false positives. Roughly 45 therapies were tested in each analysis. A false-discovery rate was calculated for the univariate models and for the Time × therapy interactions, but not for therapy coefficients in the full multivariate baseline model or after backward elimination. The reduced model after variable selection is exploratory, and *p*-values near 0.05 should be interpreted cautiously. About two unadjusted

p-values below 0.05 per set of tests would be expected by chance alone. For this reason, more weight should be given to associations that hold across analyses than to any single estimate. For researchers studying nutritional and lifestyle exposures, the practical lesson is that a cross-sectional association, adjusted or not, says little about disease trajectory, and conclusions about benefit should rest on consistency across analytic approaches and on prospective data.

Table 3. Associations of complementary therapies with symptom severity across analytic approaches.

Therapy	Univariate, Baseline	Multivariate, Baseline	Mixed Model, Baseline	Mixed Model, Rate of Change
Glutathione, oral	Lower ***	Lower * (Table S1: $p = 0.067$)	Lower **	Slower ***
Estrogen	Lower *	Lower ($p = 0.079$)	ns	Slower *
Coconut oil	ns	Not retained	ns	Slower **
Homocysteine factors	ns	Not retained	ns	Slower *
Multivitamin/mineral	ns	Higher *	Higher *	Slower **
Marijuana, inhaled	Higher *	Higher *	Higher ***	Slower *
No difference in rate of accumulation				
Lithium, low dose	Lower ***	Lower **	Lower **	ns
Fish oil	Lower ***	Lower **	Lower **	ns
CoQ10	Lower ***	Lower ($p = 0.055$, Table S1: $p = 0.048$ *)	Lower **	ns
Turmeric/curcumin	Lower ***	Lower ($p = 0.083$)	ns	ns
Mucuna	Lower *	Not retained	ns	ns
Vitamin C	ns	Not retained	Lower *	ns
Vitamin B12	ns	Higher **	ns	ns
Iron	Higher **	Higher *	Higher *	ns
Melatonin	Higher **	Higher ***	ns	ns
LSVT speech therapy	Higher *	Higher *	Higher **	ns
Faster accumulation of PRO-PD points				
NAC	Lower **	Lower ($p = 0.084$)	ns	Faster **
Probiotics	ns	Not retained	ns	Faster **

ns, not statistically significant ($p \geq 0.05$); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Includes therapies with ≥100 baseline users that reached significance in at least one analysis. Univariate: each therapy modeled separately (Figure 2). Multivariate: exploratory final model after backward elimination (Table 2, not corrected for multiplicity), with full-model (Table S1) *p*-values noted where significance differed between models; "Not retained" = removed at $p > 0.1$; *p*-values shown are for terms retained without reaching significance. Mixed model: baseline = intercept difference (Figure 5); rate of change = slope difference (Figure 6). "Lower"/"Higher" refer to symptom severity. All models adjusted for age, gender, income, and years since diagnosis. Shading: green, fewer symptoms or slower accumulation of PRO-PD points; orange, more symptoms or faster accumulation of PRO-PD points; light green, retained but not significant.

4.1. Oral Glutathione

Glutathione is an endogenously produced tripeptide, also obtained from food and available as an encapsulated powder or liposomal oral preparation; PD-specific studies have employed intravenous [15,16] and intranasal [17,18] formulations. Glutathione has been shown to be depleted in the PD substantia nigra [19], and reviews of glutathione biology in PD are available elsewhere [20,21]. Oral glutathione was associated with fewer baseline symptoms in the univariate models, including after false-discovery rate control, and with slower accumulation of PRO-PD points during follow-up (FDR 0.020). In the full baseline model, that association was in the same direction but was not statistically significant ($\beta = -68.43$, $p = 0.067$). It reached $p = 0.045$ only after backward elimination, which we treat as exploratory. The four approaches use the same cohort, exposure measure, and outcome, so agreement among them is not independent replication, and use was recorded only at baseline. We treat the glutathione result as an observational association with reported use. Oral glutathione, low-dose lithium, and coenzyme Q10 are also commonly used together (Figure 4), so its estimate may partly reflect that combination and not glutathione alone. These findings do not establish clinical efficacy. Because the association involved both baseline symptom severity and subsequent accumulation of symptoms, a delayed-start design would be appropriate if oral glutathione were evaluated for disease modification.

Notably, NAC was associated with faster accumulation of PRO-PD points in this cohort and is also being studied as a glutathione precursor in PD [22–26]. A mechanistic account in which prolonged NAC use leads to cysteine accumulation and neuronal injury is speculative [27,28]. The association may instead reflect confounding by indication, co-use, or chance. Figure 7 is a schematic of glutathione metabolism, not a result from this cohort.

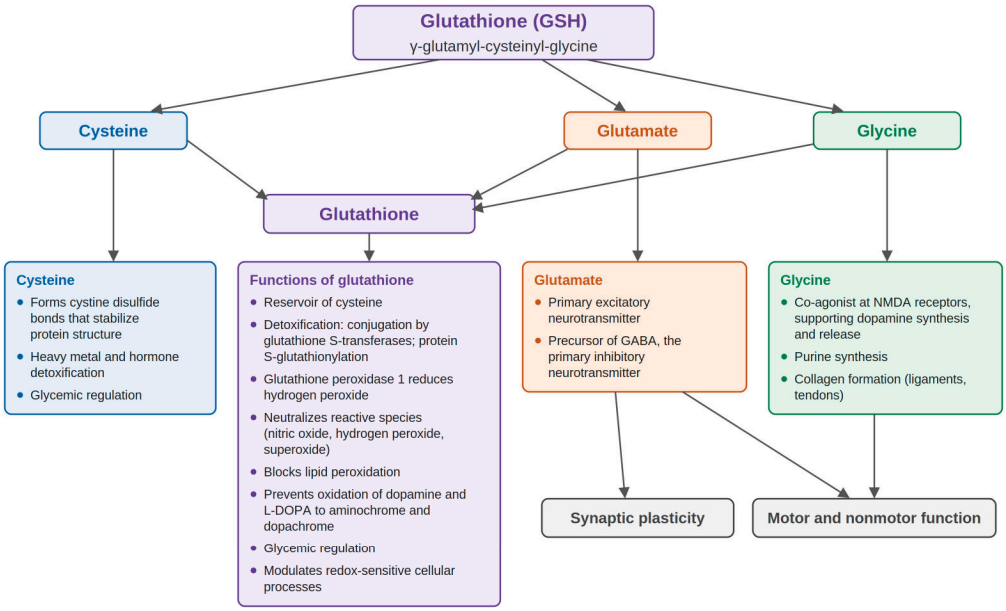


Figure 7. Schematic of glutathione metabolism (not derived from this cohort). Glutathione (GSH; γ-glutamyl-cysteinyl-glycine) is broken down into cysteine, glutamate, and glycine, which can be reassembled into GSH or used independently. Because each amino acid has roles beyond GSH synthesis, supplementing a single precursor is not necessarily equivalent to supplementing GSH. GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate. Adapted *from Glutathione in Parkinson's Disease*, Figure 5 [29]. Colors identify the molecule: purple, glutathione; blue, cysteine; orange, glutamate; green, glycine. Grey boxes are shared downstream outcomes.

4.2. Popularity, Co-Use, and Reverse Causation

The therapies used most often in this cohort were not those associated with the best outcomes. Not every benefit or harm of these therapies is captured here: the outcomes were overall PD symptom severity and its rate of change, and individuals may benefit in other domains, such as probiotics for constipation [30].

The dense co-use cluster centered on oral glutathione and low-dose lithium (Figure 4b) may reflect a highly engaged subgroup adopting strategies linked to better outcomes, or a shared recommendation ecosystem, rather than causal effects. Notably, NAC and probiotics, which were associated with faster accumulation of PRO-PD points, are commonly used by people who also take therapies associated with better outcomes. Individuals using LSVT were less likely than other participants to use Mucuna, coconut oil, oral glutathione, low-dose lithium, and edible cannabis, and Dance for PD participants were more likely to use LSVT.

Irrespective of other therapies used, the most symptomatic participants at baseline were more likely to be using iron, vitamin B12, melatonin, or multivitamin/mineral supplements, or to be participating in LSVT speech therapy. As there is no plausible mechanism by which LSVT would worsen symptoms, reverse causation is the most likely explanation for that association and probably for the others. In contrast, reverse causation is less likely to explain the inverse associations for low-dose lithium, oral glutathione, and fish oil, since lower symptom burden would not be expected to prompt their use. Iron perturbations have been

extensively implicated in PD because the high iron content of dopaminergic neurons is considered a vulnerability, and dopamine is highly susceptible to oxidation [31]. In this cohort, iron use was associated with greater severity in every baseline analysis but not with the rate of accumulation.

4.3. Cannabis

Inhaled and edible cannabis were reported by 143 (5.3%) and 149 (5.5%) participants, respectively, and the co-use analysis suggests cannabis users were not heavy users of supplements, speech therapy, or dance programs. At baseline, inhaled cannabis users were more symptomatic (Figure 2, Table 2), yet in the mixed-effects models their PRO-PD scores accumulated more slowly (Figure 6). The unadjusted trajectories (Figure 3) show greater severity among cannabis users throughout follow-up, so the slower adjusted slope may prove temporary, reflect chance, or reflect regression to the mean as more participants contribute longer follow-up. This design cannot distinguish the effect of cannabis from the characteristics of people who choose it.

4.4. Limitations

This study does not permit causal inference. The longitudinal models give predictive associations between baseline reported therapy use and later PRO-PD change. They do not estimate treatment efficacy. Therapy use was self-reported and measured only at baseline, so retention, dose, formulation, adherence, and later changes in use were not captured. Unmeasured and time-varying confounders, including PD medication, comorbidities, physical activity, diet, and access to healthcare, may influence the associations observed. PRO-PD measures symptoms, which can change with adjustments to dopaminergic medication independently of the underlying disease process; differences in accumulation of PRO-PD points should therefore not be interpreted as differences in neurodegeneration. The cohort was self-selected, highly educated, predominantly Caucasian, and of relatively high income, which limits generalizability. Because the cohort has rolling enrollment, participants with a single assessment include both recently enrolled individuals and those lost to follow-up. Including all 2330 baseline participants in the REML mixed-effects models provides valid fixed-effect slope estimates under missingness at random (MAR) conditional on covariates and observed PRO-PD scores, although unmeasured non-random attrition cannot be excluded in an observational cohort. Models included a random intercept only; if individual rates of change vary, standard errors for the Time × therapy terms may be underestimated. This study on modifiable behaviors is likely to attract a particular cohort of participants, and confounding by the healthy adherer effect should be considered [13]. False-discovery rates are given for the univariate models and the Time × therapy interactions. Therapy coefficients in the full multivariate baseline model and results after backward elimination were not corrected for multiple comparisons. The reduced model is exploratory, and estimates near $p = 0.05$ should be interpreted cautiously. The therapy list continues to expand, and future analyses will include boxing, rock climbing, improvisational theater, and other popular interventions.

5. Conclusions

In a large prospective PD cohort, associations between complementary therapy use and symptom burden changed substantially depending on whether analyses were cross-sectional or prognostic and whether concurrent use was considered. Cross-sectional associations were a poor guide to subsequent rates of PRO-PD score accumulation. Oral glutathione was linked with fewer baseline symptoms in the univariate models, including after false-discovery rate control, and with slower accumulation of PRO-PD points during follow-up

(FDR 0.020). In the full baseline model that included the other common therapies, that association was in the same direction but not significant ($\beta = -68.43$, $p = 0.067$). The $p = 0.045$ after backward elimination is exploratory. The follow-up association is not an independent replication of the baseline finding. These are predictive associations with a patient-reported symptom score among people who reported use at baseline. Retention, dose, and adherence after baseline were not measured, and the results do not show clinical efficacy or disease modification. If oral glutathione is studied in a controlled trial, that work should start from this uncertainty, not from a claim of benefit. More broadly, observational studies of nutritional and lifestyle exposures should examine consistency across analytic approaches before drawing conclusions about benefit or harm.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu18223830/s1, Figure S1: Participant flow; Table S1: Full multivariate model of baseline PRO-PD score including all complementary therapies with at least 100 baseline users (24 therapies), before backward elimination; Table S2: Time × therapy interaction coefficients from the linear mixed-effects models shown in Figure 6.

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Informed Consent Statement: Informed consent was obtained from all participants. The Institutional Review Board of Bastyr University granted a waiver of written informed consent; all participants acknowledged reading a study information sheet before enrolling.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request from qualified researchers, subject to a data use agreement and applicable institutional approval. The data are not publicly available to protect participant privacy.

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