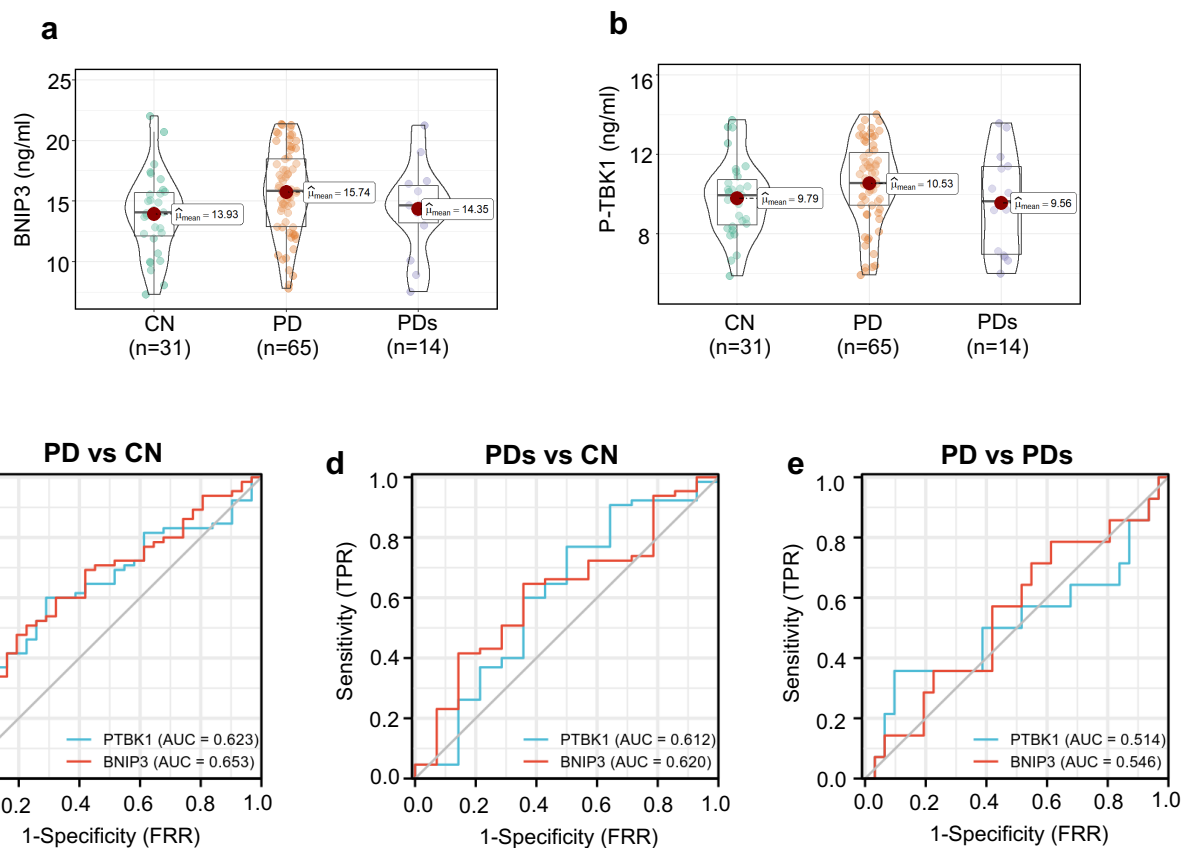
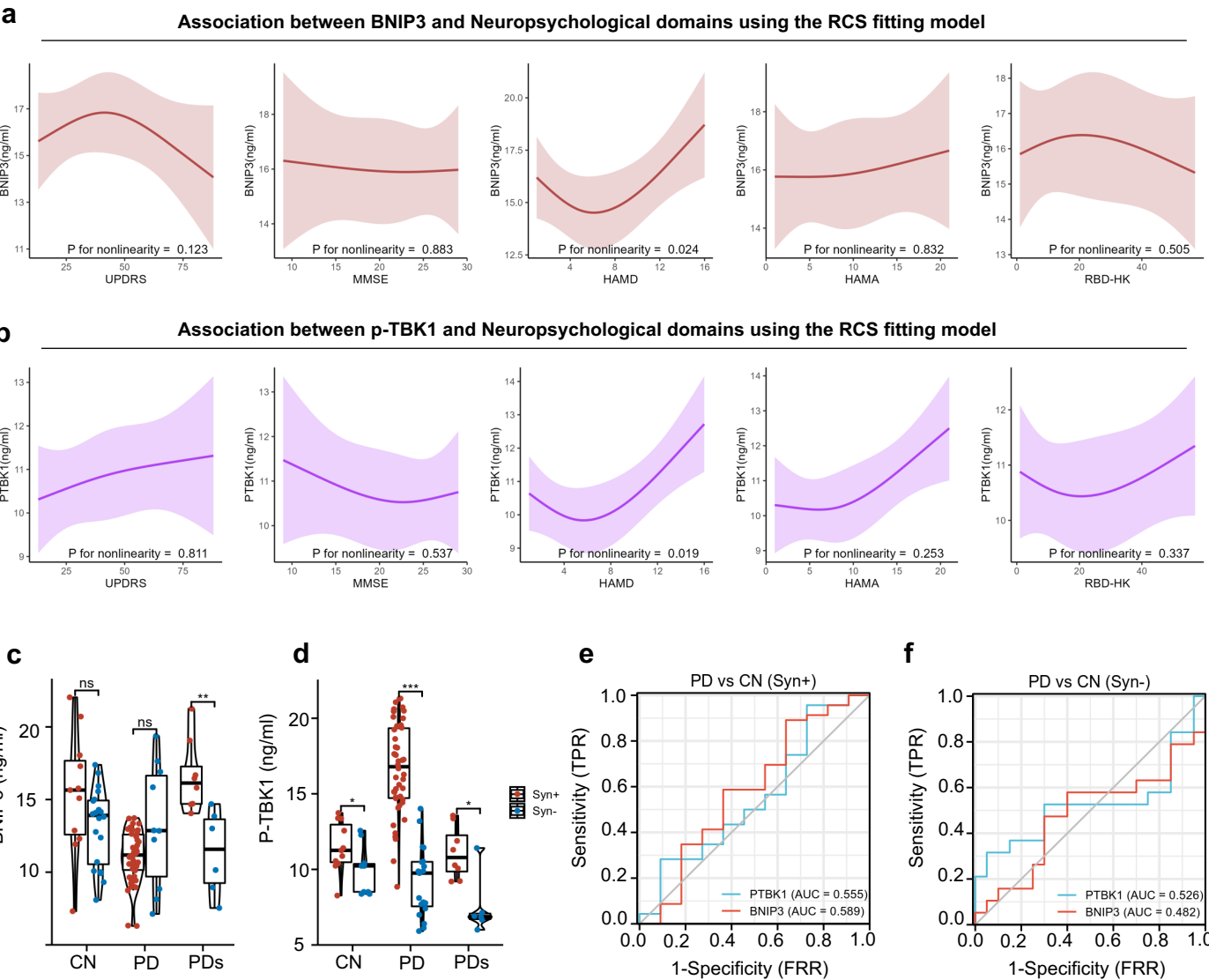


Supplementary documents



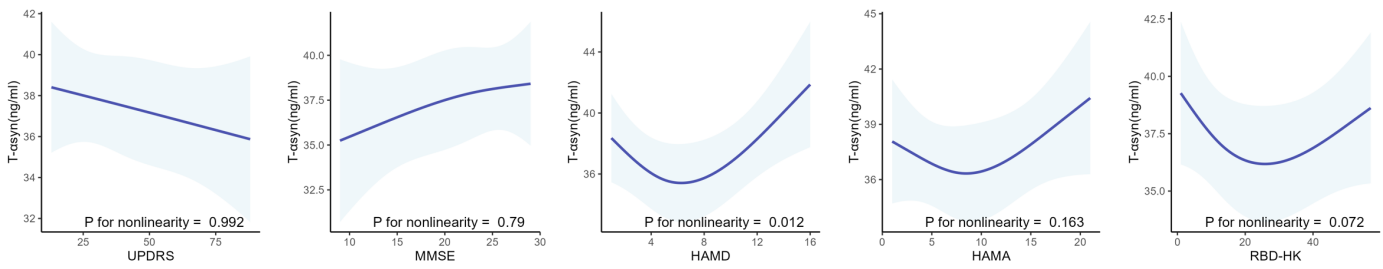
Supple Figure 1



Supple Figure 2

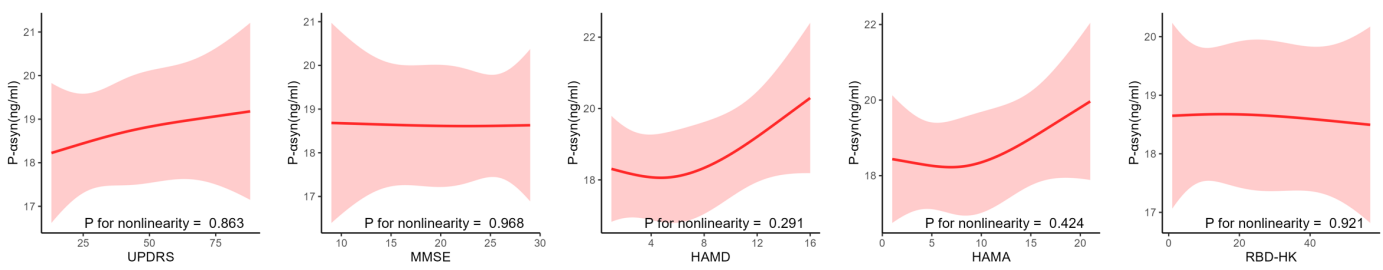
a

Association between T-asyn and Neuropsychological domains using the RCS fitting model



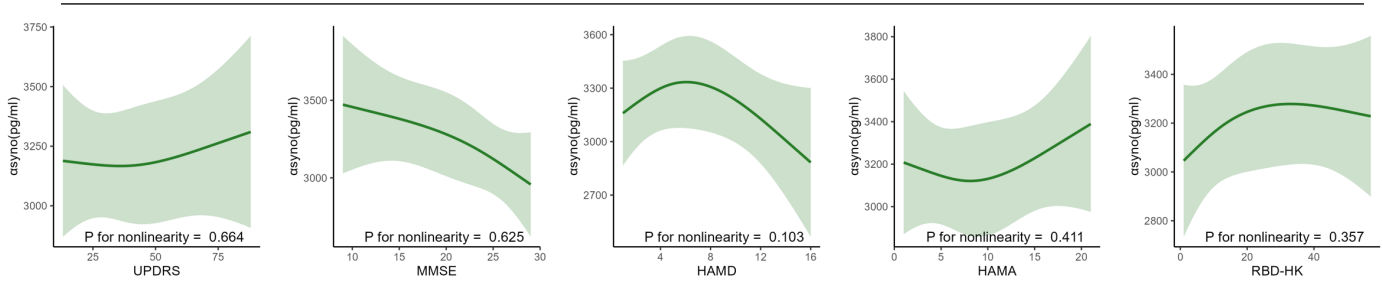
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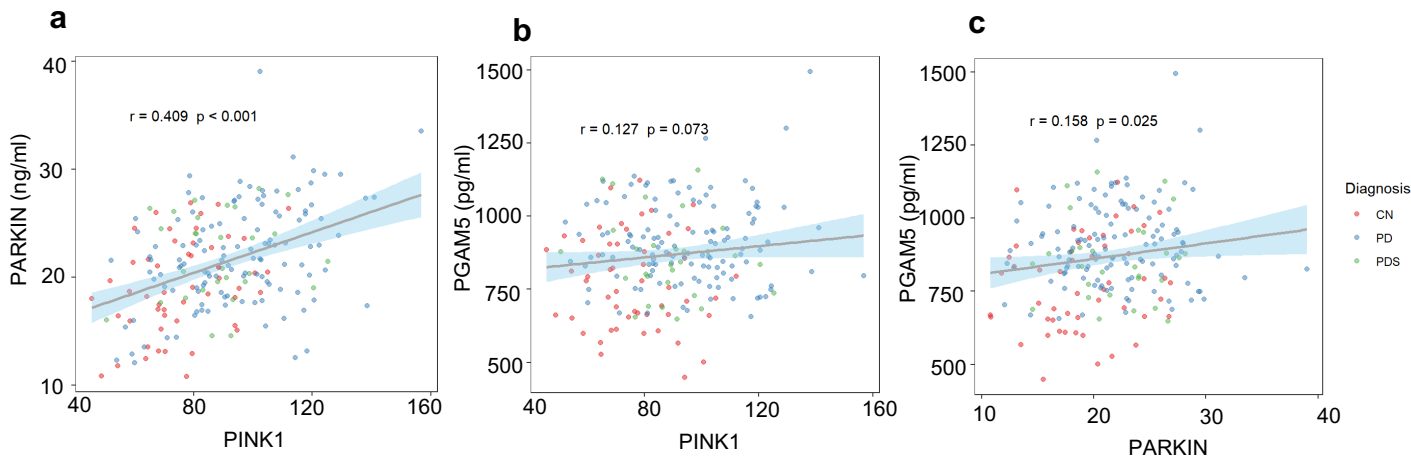
Association between P-asyn and Neuropsychological domains using the RCS fitting model



c

Association between Asy-no and Neuropsychological domains using the RCS fitting model





Supple Figure 4

Supplementary Table 1: Diagnostic performance of different plasma-derived multiple biomarker levels in differentiating PD, PDs, and CN

Features	AUC [95% CI]		
	PD vs CN	PD vs PDs	PDs vs CN
PINK1	0.764 [0.691, 0.836]	0.714 [0.597, 0.830]	0.598 [0.493, 0.703]
PARKIN	0.665 [0.578, 0.752]	0.676 [0.554, 0.797]	0.499 [0.384, 0.614]
PGAM5	0.721 [0.632, 0.810]	0.636 [0.515, 0.757]	0.601 [0.480, 0.722]
BNIP3	0.623 [0.503, 0.743]	0.514 [0.304, 0.723]	0.612 [0.428, 0.796]
P-TBK1	0.653 [0.537, 0.769]	0.546 [0.357, 0.735]	0.620 [0.459, 0.781]
T-asyn	0.735 [0.650, 0.820]	0.721 [0.603, 0.839]	0.528 [0.414, 0.642]
P-asyn	0.669 [0.578, 0.761]	0.644 [0.514, 0.773]	0.525 [0.407, 0.642]
Asy-no	0.737 [0.647, 0.826]	0.726 [0.615, 0.836]	0.564 [0.449, 0.678]
PINK1	0.764 [0.691, 0.836]	0.714 [0.597, 0.830]	0.598 [0.493, 0.703]
MMSE	0.539 [0.442, 0.637]	0.757 [0.639, 0.875]	0.698 [0.590, 0.806]
HAMD	0.700 [0.611, 0.788]	0.758 [0.650, 0.865]	0.532 [0.421, 0.644]
HAMA	0.681 [0.587, 0.775]	0.725 [0.613, 0.837]	0.507 [0.392, 0.622]
RBDQ-HK	0.720 [0.634, 0.805]	0.657 [0.521, 0.793]	0.469 [0.341, 0.597]

Data are presented as AUC [95% CI] (DeLong statistics) in differentiating PD vs CN, PD vs PDs and PDs vs CN; AUC, area under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio; Other abbreviations as in table 1 and table 2.

Supplementary Table 2. Comparisons of the accuracy for combined models in distinguishing PD and CN

Model type	Variables in model	OR [95% CI]	AUC [95% CI]	P-value	AIC
1. MAP-Top3	PINK1	1.055 [1.029, 1.082]	0.842 [0.771, 0.912]	0.324 vs 2	135.7
	PARKIN	1.042 [0.948, 1.146]		0.347 vs 3	
	PGAM5	1.007 [1.004, 1.010]		0.031 vs 4	
2. Bio-Top3	PINK1	1.050 [1.020, 1.080]	0.856 [0.786, 0.926]	0.324 vs 1	128.04
	PGAM5	1.008 [1.005, 1.012]		0.924 vs 3	
	asyno	1.001 [1.000, 1.002]		0.045 vs 4	
3. MAP + Asy-no	PINK1	1.053 [1.020, 1.087]	0.856 [0.785, 0.926]	0.347 vs 1	129.88
	PARKIN	1.008 [1.005, 1.012]		0.924 vs 2	
	PGAM5	0.975 [0.864, 1.101]		0.044 vs 4	
	asyno	1.001 [1.000, 1.002]			
4. MAP + Asy-no + RBDQ-HK	PINK1	1.056 [1.022, 1.092]	0.883 [0.823, 0.942]	0.031 vs 1	123.1
	PARKIN	1.008 [1.004, 1.012]		0.045 vs 2	
	PGAM5	0.952 [0.840, 1.079]		0.044 vs 3	
	asyno	1.001 [1.000, 1.002]			

RBDQ-HK	1.049 [1.010, 1.090]
Results are from logistic regression models using PD vs CN as the outcome. <i>P</i> -values are from the comparison of AUCs (DeLong statistics). Abbreviations: MAP: Mitophagy-associated protein; AIC, Akaike information criterion (lower equals a better model fit); AUC, area under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1 and Table 2.	

Supplementary Table 3: Correlation of different plasma-derived biomarker levels with motor and nonmotor features

r (p)	UPDRS	III	H-Y stage	MMSE	HAMD	HAMA	RBDQ-HK	ADL
ALL								
PINK1	0.247 (0.001)	0.243 (0.001)	0.234 (0.001)	0.025 (0.728)	0.055 (0.437)	0.047 (0.51)	0.054 (0.448)	0.126 (0.074)
PARKIN	0.191 (0.006)	0.133 (0.058)	0.097 (0.171)	0.019 (0.783)	0.08 (0.258)	0.101 (0.152)	0.168 (0.017)	0.197 (0.005)
PGAM5	0.217 (0.002)	0.214 (0.002)	0.108 (0.128)	0.032 (0.65)	0.132 (0.062)	0.167 (0.018)	0.204 (0.004)	0.081 (0.254)
PTBK1	0.072 (0.455)	0.039 (0.689)	0.101 (0.293)	-0.044 (0.648)	0.13 (0.175)	0.16 (0.095)	0.081 (0.4)	0.123 (0.2)
BNIP3	0.057 (0.554)	0.028 (0.772)	0.075 (0.436)	0.042 (0.666)	0.155 (0.107)	0.048 (0.615)	0.017 (0.857)	0.01 (0.916)
T-asyn	0.204 (0.008)	0.195 (0.011)	0.077 (0.319)	-0.004 (0.957)	0.171 (0.027)	0.151 (0.051)	0.093 (0.23)	0.128 (0.097)
P-asyn	0.22 (0.004)	0.201 (0.009)	0.171 (0.026)	-0.109 (0.161)	0.2 (0.009)	0.155 (0.045)	0.135 (0.08)	0.165 (0.032)
asyno	0.295 (0.001)	0.298 (0.001)	0.201 (0.009)	-0.143 (0.065)	0.053 (0.499)	0.12 (0.12)	0.18 (0.019)	0.23 (0.003)
CN								
PINK1	-	-	-	0.06 (0.673)	-0.05 (0.723)	-0.058 (0.684)	0.188 (0.182)	-0.011 (0.938)
PARKIN	-	-	-	0.112 (0.429)	0.109 (0.441)	0.178 (0.207)	0.273 (0.05)	0.113 (0.424)
PGAM5	-	-	-	0.041 (0.772)	-0.152 (0.283)	-0.053 (0.709)	-0.049 (0.73)	0.157 (0.266)
PTBK1	-	-	-	-0.198 (0.286)	0.042 (0.822)	0.015 (0.937)	0.176 (0.345)	0.02 (0.916)
BNIP3	-	-	-	0.094 (0.613)	0.182 (0.327)	-0.027 (0.884)	0.072 (0.698)	0.07 (0.707)
T-asyn	-	-	-	0.08 (0.584)	0.155 (0.289)	0.112 (0.442)	0.19 (0.19)	-0.033 (0.821)
P-asyn	-	-	-	-0.029 (0.841)	0.209 (0.149)	0.149 (0.307)	0.149 (0.308)	-0.03 (0.84)
asyno	-	-	-	0.219 (0.13)	-0.143 (0.328)	-0.036 (0.807)	0.285 (0.047)	0.139 (0.34)
PD								
PINK1	-0.026 (0.775)	-0.048 (0.6)	-0.014 (0.879)	0.057 (0.537)	-0.038 (0.677)	-0.036 (0.696)	-0.114 (0.213)	-0.027 (0.769)
PARKIN	-0.043 (0.636)	-0.144 (0.115)	-0.01 (0.915)	0.169 (0.063)	-0.032 (0.729)	-0.005 (0.955)	0.056 (0.544)	0.052 (0.569)
PGAM5	-0.037 (0.688)	-0.039 (0.671)	-0.04 (0.666)	0.08 (0.386)	0.089 (0.331)	0.089 (0.332)	0.187 (0.04)	-0.091 (0.323)
PTBK1	0.076 (0.548)	0.031 (0.805)	0.049 (0.696)	-0.012 (0.922)	0.241 (0.053)	0.288 (0.02)	0.095 (0.453)	0.12 (0.341)
BNIP3	-0.052 (0.682)	-0.099 (0.435)	-0.131 (0.297)	-0.046 (0.714)	0.175 (0.163)	0.079 (0.531)	-0.066 (0.604)	-0.113 (0.372)
T-asyn	-0.137 (0.197)	-0.171 (0.107)	-0.046 (0.669)	0.095 (0.372)	0.132 (0.214)	0.107 (0.316)	0.027 (0.802)	-0.083 (0.439)
P-asyn	0.069 (0.519)	0.016 (0.883)	-0.019 (0.856)	0.004 (0.973)	0.167 (0.116)	0.14 (0.187)	0.02 (0.853)	0.078 (0.467)
asyno	0.059 (0.581)	0.042 (0.696)	0.073 (0.495)	-0.225 (0.033)	-0.065 (0.543)	0.077 (0.468)	0.05 (0.638)	0.109 (0.307)
PDs								
PINK1	0.101 (0.603)	0.147 (0.446)	0.402 (0.031)	0.087 (0.654)	-0.285 (0.134)	-0.302 (0.111)	-0.059 (0.762)	0.149 (0.439)
PARKIN	0.286 (0.133)	0.192 (0.317)	-0.047 (0.807)	-0.482 (0.008)	-0.006 (0.976)	-0.081 (0.675)	0.143 (0.46)	0.428 (0.021)
PGAM5	0.019 (0.923)	0.012 (0.949)	-0.021 (0.913)	0.027 (0.89)	0.042 (0.829)	0.257 (0.179)	-0.02 (0.919)	0.064 (0.743)

PTBK1	-0.319 (0.266)	-0.4 (0.156)	-0.021 (0.942)	-0.137 (0.64)	-0.325 (0.256)	-0.209 (0.473)	-0.249 (0.391)	0.072 (0.807)
BNIP3	-0.383 (0.177)	-0.404 (0.152)	-0.085 (0.772)	0.301 (0.295)	-0.297 (0.303)	-0.354 (0.214)	-0.109 (0.711)	0.031 (0.916)
T-asyn	-0.046 (0.813)	-0.009 (0.964)	-0.217 (0.259)	-0.089 (0.645)	-0.307 (0.105)	-0.213 (0.268)	-0.405 (0.029)	0.205 (0.287)
P-asyn	-0.053 (0.786)	0.003 (0.987)	0.199 (0.3)	-0.362 (0.054)	-0.141 (0.466)	-0.212 (0.27)	0.094 (0.626)	0.091 (0.64)
asyno	0.066 (0.734)	0.133 (0.491)	0.149 (0.442)	-0.263 (0.168)	0.013 (0.945)	-0.081 (0.677)	-0.078 (0.686)	0.167 (0.387)

Data are expressed as *r* (p value) achieved by Pearson correlation. Abbreviations as in table 1 and table 2.

Supplementary Table 4: *P* value for nonlinearity using RCS models

<i>p</i> for nonlinearity	PINK1	PARKIN	PGAM5	BNIP3	P-TBK1	T-asyn	P-asyn	Asy-no
UPDRS	0.606	0.737	0.101	0.123	0.811	0.992	0.863	0.664
MMSE	0.826	0.004	0.53	0.883	0.537	0.79	0.968	0.625
HAMD	0.228	0.913	0.876	0.024	0.019	0.012	0.291	0.103
HAMA	0.585	0.399	0.435	0.832	0.253	0.163	0.424	0.411
RBDQ-HK	0.460	0.477	0.415	0.505	0.337	0.072	0.921	0.357
ADL	0.170	0.737	0.024	0.230	0.495	0.704	0.469	0.940

Supplementary Table 5: Demographic characteristics and biomarker levels of different α -syn status in Modeling cohort

A-syn status		A-syn (+)			A-syn (-)	
Characteristics	CN (N = 13)	PD (N = 67)	PDs (N = 19)	CN (N = 36)	PD (N = 23)	PDs (N = 10)
Age (years)	67.6 (5.04)	65.2 (7.57)	69.4 (6.91)	63.0 (8.22)	65.7 (8.74)	63.6 (9.31)
Female (%)	7 (53.8%)	33 (49.3%)	5 (26.3%)	22 (61.1%)	8 (34.8%)	4 (40.0%)
Height (cm)	159 (5.67)	160 (7.37)	163 (8.29)	162 (6.89)	163 (8.56)	158 (10.0)
Weight (kg)	60.3 (6.38)	60.6 (8.75)	62.6 (9.77)	62.9 (10.5)	65.0 (12.0)	64.0 (10.2)
BMI	23.9 (2.76)	23.6 (2.72)	23.6 (3.27)	24.0 (3.16)	24.6 (3.58)	26.0 (6.40)
Education (years)	4.23 (3.19)	3.71 (3.43)	5.47 (3.86)	3.83 (4.03)	4.39 (3.37)	3.05 (3.70)
UPDRS	-	42.4 (24.1)	48.8 (24.6)	-	42.0 (17.7)	51.8 (19.3)
I	-	2.78 (2.67)	3.42 (2.09)	-	2.22 (2.45)	3.60 (2.41)
II	-	11.6 (8.18)	14.7 (7.34)	-	11.8 (6.60)	15.4 (6.11)
III	-	25.4 (13.7)	29.1 (17.6)	-	25.4 (12.6)	26.7 (13.4)
IV	-	2.67 (3.47)	1.53 (1.54)	-	2.61 (2.25)	2.10 (2.81)
H-Y	-	2.37 (1.10)	4.76 (7.68)	-	2.43 (1.04)	2.80 (1.25)
MMSE	24.2 (4.62)	21.6 (5.87)	15.6 (7.56)	22.3 (4.62)	22.1 (5.83)	19.1 (5.38)
HAMD	3.31 (2.69)	6.19 (4.47)	5.89 (3.93)	3.36 (3.67)	6.09 (4.48)	8.90 (4.91)
HAMA	5.85 (4.08)	9.16 (6.10)	8.42 (5.70)	5.39 (5.45)	7.57 (4.32)	11.1 (5.53)
RBDQ-HK	8.77 (11.5)	20.1 (20.6)	17.1 (23.2)	6.53 (8.54)	20.6 (19.3)	26.3 (16.8)
ADL	20.8 (1.96)	31.1 (16.7)	41.2 (18.6)	19.8 (3.55)	30.1 (10.2)	35.0 (10.9)
PINK1 (ng/mL)	84.7 (16.2)*	94.1 (16.7)**	91.5 (16.5)	73.6 (14.5)	82.8 (18.8)	82.9 (14.8)
Parkin (ng/mL)	23.0 (3.20)***	22.1 (3.56)	22.8 (3.55)	17.9 (3.91)	20.4 (4.65)	20.2 (4.45)
PGAM5 (pg/mL)	812 (143) *	907 (123)	878 (159)	753 (149)	921 (123)	820 (88.0)
BNIP3 (ng/mL)	15.4 (4.20)	16.6 (3.04)	16.6 (2.45)**	13.1 (2.65)	13.6 (3.87)	11.4 (2.90)
P-TBK1 (ng/mL)	11.5 (1.67)*	11.1 (1.74)***	11.1 (1.72)*	8.87 (1.36)	9.21 (2.34)	7.49 (1.96)

Data are presented as mean (SD) or number (percentage) as appropriate. *p*-values obtained from Mann-Whitney U test for continuous variables or chi-squared test for categorical variables. CN: Control; PD: Parkinson disease; PDs: Parkinsonian syndrome; UPDRS: unified Parkinson's disease rating scale; MMSE: Mini-Mental State Examination; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; RBDQ-HK: REM sleep behavior disorder questionnaire-Hong Kong; ADL: Activity of Daily Living Scale; BMI: Body Mass Index; PINK1: PTEN induced putative kinase 1; P-TBK1: phosphorylated TANK binding kinase 1; PGAM5: phosphoglycerate mutase 5; BNIP3: BCL2 interacting protein 3. *Less participants took the examination of plasma p-TBK1 and BNIP3 (a-Syn+: CN = 11, PD = 46, PDs = 8; a-Syn-: CN = 20, PD = 19, PDs = 6). **P* < 0.05, ***P* < 0.01, ****P* < 0.001, compared to the negative a-Syn status.