Multivariate prediction of dementia in Parkinson's disease

Supplement

Supplementary Table 1. Association of biological factors with the disease progression rate to dementia (number of years from PD motor onset until PDD)

	Coef.*	95% CI		*P*
Age at onset	-0.37	-0.46	-0.27	7.02×10^{-11}
Sex	-1.85	-4.31	0.61	0.14
APOE	-2.08	-4.44	0.29	0.09
GBA	-5.42	-9.35	-1.49	8.23×10^{-3}
MAPT	-0.73	-2.97	1.52	0.53

*The model is adjusted for site and years of education. Only patients who do not have dementia at the first visit and are known to eventually be diagnosed with dementia are included (n = 97).

Abbreviations: *APOE*, apolipoprotein E gene; CI, confidence interval; *GBA*, glucocerebrosidase gene; *MAPT*, microtubule-associated protein tau gene

Supplementary Table 2. Association of *APOE* ε4 allele, *GBA* status, and *MAPT* haplotype with the cognitive performance in the longitudinal female PUC cohort.

Cognitive tests	Intercept	*APOE*				*GBA*				*MAPT*			
	Random Intercept Std.	**Coef.**	**95% CI**	***P***	P_c	**Coef.**	**95% CI**	***P***	P_c	**Coef.**	**95% CI**	***P***	P_c
Semantic verbal fluency	4.00	-2.45	-3.82 to -1.07	6.88×10^{-4}	6.88×10^{-3}	-2.37	-4.09 to -0.66	8.02×10^{-3}	0.08	0.18	-1.1 to 1.46	0.79	>.99
Phonemic verbal fluency	9.21	-3.48	-6.57 to -0.39	0.03	0.30	-2.74	-6.59 to 1.12	0.17	>.99	0.59	-2.29 to 3.48	0.69	>.99
HVLT-R Total Recall	3.57	-0.56	-1.82 to 0.7	0.39	>.99	-1.21	-2.78 to 0.36	0.14	>.99	0.48	-0.69 to 1.65	0.43	>.99
HVLT-R RDI	0.99	-0.30	-0.69 to 0.1	0.15	>.99	-0.49	-0.98 to 0.01	0.06	0.58	0.38	0.01 to 0.75	0.05	0.49
HVLT-R Delayed Recall	1.84	-0.21	-0.92 to 0.5	0.56	>.99	-0.70	-1.59 to 0.19	0.13	>.99	0.60	-0.06 to 1.27	0.08	0.80
Judgment of Line Orientation	1.51	-0.75	-1.32 to -0.18	0.12	0.11	-0.64	-1.35 to 0.07	0.08	0.83	0.13	-0.39 to 0.66	0.63	>.99
Digit Symbol	8.59	-3.72	-6.56 to -0.87	0.01	0.12	-4.74	-8.29 to -1.19	0.01	0.10	1.05	-1.6 to 3.71	0.44	>.99
Letter Number Sequencing	1.67	-0.43	-1.03 to 0.16	0.16	>.99	-1.14	-1.89 to -0.39	3.49×10^{-3}	0.03	0.21	-0.35 to 0.77	0.47	>.99
TMT B – TMT A	33.27	10.01	-2.83 to 22.87	0.13	>.99	29.03	12.94 to 45.14	6.07×10^{-4}	6.07×10^{-3}	-6.65	-18.71 to 5.27	0.28	>.99
MoCA	2.12	-0.58	-1.38 to 0.21	0.16	>.99	-1.74	-2.73 to -0.75	8.04×10^{-4}	8.04×10^{-3}	0.29	-0.45 to 1.03	0.45	>.99

*Adjusted for age, LEDD, GDS-15, disease duration, site and years of education.

P_c = Bonferroni corrected values

Abbreviations: *APOE*, apolipoprotein E gene; CI, confidence interval; *GBA*, glucocerebrosidase gene; GDS-15, 15-item Geriatric Depression Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; LEDD, levodopa equivalent daily dose; *MAPT*, microtubule-associated protein tau gene; MoCA, Montreal Cognitive Assessment; PUC, Pacific Udall Center; RDI, Recognition Discrimination Index; TMT, Trailmaking Test

Supplementary Table 3. Association of *APOE ε4* allele, *GBA* status, and *MAPT* haplotype with the cognitive performance in the longitudinal male PUC cohort.

Cognitive tests	Intercept	*APOE*				*GBA*				*MAPT*			
	Random Intercept Std.	**Coef.**	**95% CI**	***P***	P_c	**Coef.**	**95% CI**	***P***	P_c	**Coef.**	**95% CI**	***P***	P_c
Semantic verbal fluency	4.05	-0.50	-1.48 to 0.48	0.32	>.99	-1.47	-2.89 to -0.06	0.04	0.42	-0.04	-0.96 to 0.89	0.94	>.99
Phonemic verbal fluency	9.63	-0.58	-2.7 to 1.54	0.59	>.99	-0.93	-3.96 to 2.09	0.55	>.99	-0.40	-2.42 to 1.62	0.70	>.99
HVLT-R Total Recall	3.80	-0.40	-1.3 to 0.49	0.38	>.99	-2.35	-3.64 to -1.07	3.87×10^{-4}	3.87×10^{-3}	0.56	-0.29 to 1.41	0.20	>.99
HVLT-R RDI	1.42	0.14	-0.23 to 0.5	0.46	>.99	-0.62	-1.14 to -0.09	0.02	0.23	-0.01	-0.36 to 0.33	0.93	>.99
HVLT-R Delayed Recall	2.02	-0.05	-0.58 to 0.48	0.86	>.99	-0.61	-1.39 to 0.16	0.12	>.99	0.20	-0.3 to 0.7	0.44	>.99
Judgement of Line Orientation	1.73	-0.29	-0.7 to 0.12	0.17	>.99	-1.27	-1.86 to -0.68	3.49×10^{-5}	3.49×10^{-4}	0.09	-0.3 to 0.48	0.67	>.99
Digit Symbol	9.06	-0.81	-2.83 to 1.22	0.44	>.99	-4.84	-7.74 to -1.94	1.22×10^{-3}	0.01	-0.10	-2.03 to 1.83	0.92	>.99
Letter Number Sequencing	1.76	0.03	-0.39 to 0.45	0.89	>.99	-0.87	-1.48 to -0.26	5.88×10^{-3}	0.06	0.39	-0.02 to 0.79	0.06	0.62
TMT B – TMT A	43.59	2.60	-7.86 to 13.08	0.63	>.99	35.99	20.87 to 51.09	4.35×10^{-6}	4.35×10^{-5}	-9.34	-19.28 to 0.59	0.07	0.68
MoCA	2.71	-0.25	-0.88 to 0.39	0.44	>.99	-1.81	-2.72 to -0.89	1.34×10^{-4}	1.34×10^{-3}	0.14	-0.46 to 0.74	0.65	>.99

*Adjusted for age, LEDD, GDS-15, disease duration, site and years of education.

P_c = Bonferroni corrected values

Abbreviations: *APOE*, apolipoprotein E gene; CI, confidence interval; *GBA*, glucocerebrosidase gene; GDS-15, 15-item Geriatric Depression Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; LEDD, levodopa equivalent daily dose; *MAPT*, microtubule-associated protein tau gene; MoCA, Montreal Cognitive Assessment; PUC, Pacific Udall Center; RDI, Recognition Discrimination Index; TMT, Trailmaking Test

Supplementary Table 4. Neuropsychological measures used for cognitive diagnosis across PUC sites

	Neuropsychological measures	
Cognitive domain	**University of Washington/Oregon Health and Sciences University**	**Stanford University**
Memory	Hopkins Verbal Learning Test-Revised [1] Logical Memory I & II* [2] Brief Visual Memory Test-Revised [4]	Hopkins Verbal Learning Test-Revised [1] Craft Story Recall† [3] Benson Complex Figure recall† [5]
Visuospatial	Judgment of Line Orientation [6] Clock copy [7] Brief Visual Memory Test-Revised copy [4]	Judgment of Line Orientation [6] Clock copy [7] Benson Complex Figure copy† [5]
Language	Boston Naming Test* [8] Shipley Vocabulary [10] Semantic verbal fluency [12]	Multilingual Naming Test† [9] Wechsler Test of Adult Reading [11] Semantic verbal fluency [12]
Executive	Clock Drawing Test [7] Phonemic verbal fluency [12]	Clock Drawing Test [7] Phonemic verbal fluency [12]
Attention/Working Memory	Trailmaking test, parts A & B [12] Letter-Number Sequencing [13] Digit Symbol* [14] Digit Span* [14] Stroop (Golden version)[15]	Trailmaking test, parts A & B [12] Letter-Number Sequencing [13] Digit Symbol* [14] Number Span† Stroop (Victoria version) [12]

* National Alzheimer Coordinating Center Uniform Data Set, version 1
† National Alzheimer Coordinating Center Uniform Data Set, version 2

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[2] D. Wechsler, Wechsler Memory Scale-Revised Manual, The Psychological Corporation, San Antonio, 1987.
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[13] D. Wechsler, WAiS-III® Administration and Scoring Manual, The Psychological Corporation Harcourt Brace & Company, San Antonio, TX, 1997.
[14] D. Wechsler, Wechsler Adult Intelligence Scale-Revised manual, The Psychological Corporation, San Antonio, 1987.
[15] C.J. Golden, Stroop Color and Word Test: A Manual for Clinical and Experimental Uses, Stoelting, Chicago, IL, 1978.

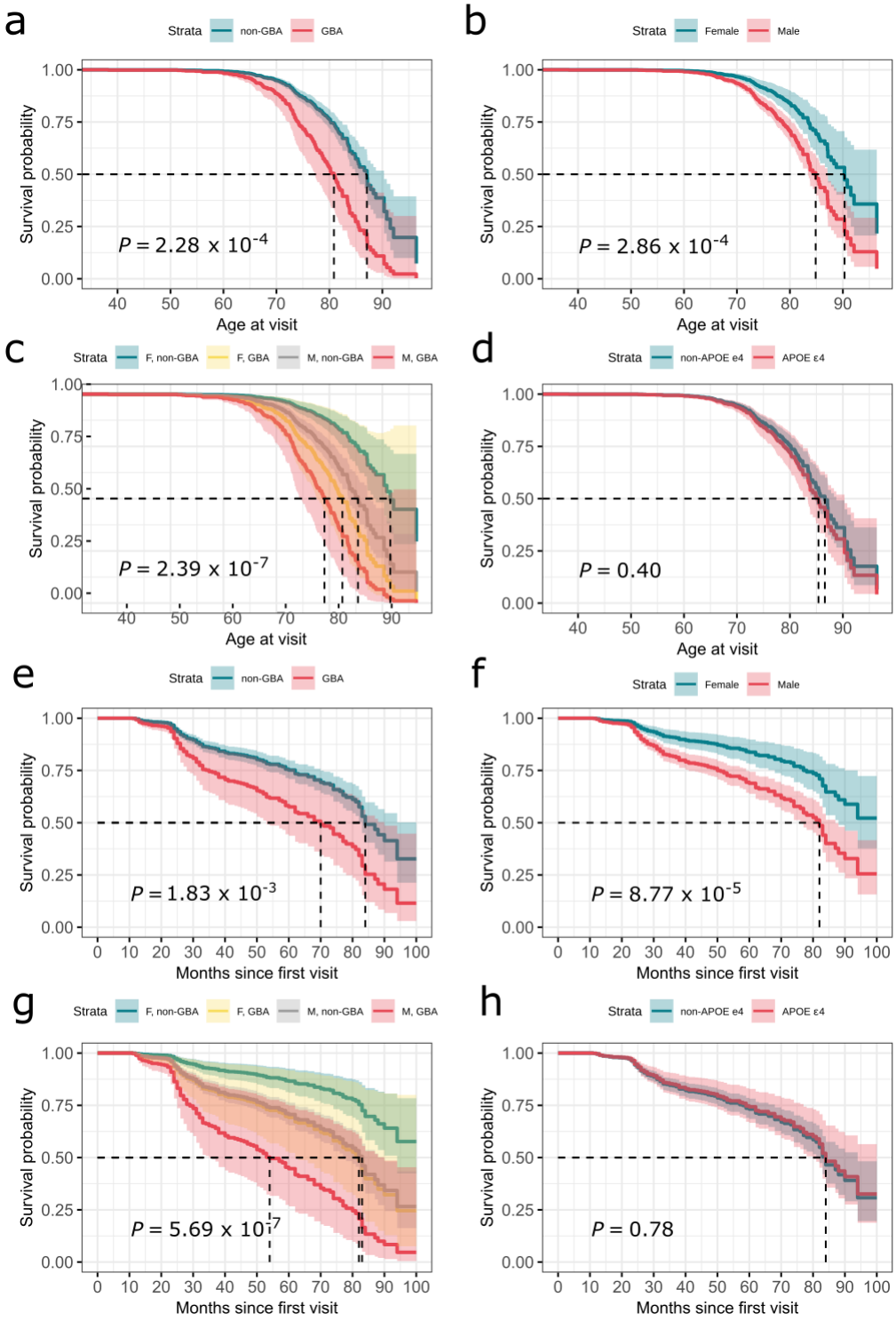
Supplementary Table 5. Baseline characteristics of the Pacific Udall Center cohort by site

	Seattle n = 573	Portland n = 188	Stanford n = 66	Overall *P** pairwise
Age at visit, years				
Mean (sd)	67.8 (9.7)	68.7 (8.4)	68.9 (6.6)	
Range	36.2 – 91.8	41.2 – 90.2	50.7 – 83.4	0.378
Education, years				
Mean (sd)	15.8 (2.5)	15.7 (2.7)	17.2 (2.5)	<0.0001
Range	8 - 20	8 - 20	12 - 20	Stanford>Seattle/Portland
Sex				
n (%) male	373 (65.1%)	159 (84.6%)	35 (53.0%)	<0.0001 Portland>Seattle/Stanford
Disease duration, years				
Mean (sd)	9.2 (6.6)	8.9 (6.5)	8.3 (5.9)	
Range	0 - 43	1 - 33	1 - 30	0.543
PDD				
n (%)	115 (20.1)	42 (22.3)	3 (4.6)	0.005 Portland/Seattle>Stanford
PD-MCI				
n (%)	317 (55.3)	115 (61.2)	27 (40.9)	<0.001 Portland>Seattle/Stanford, Seattle>Stanford
MDS-UPDRS				
Mean (sd)	27.1 (12.8)	30.3 (14.1)	21.0 (10.1)	<0.0001
Range	0 - 87	3 - 72	4 - 64	Portland>Seattle/Stanford, Seattle>Stanford
Modified Hoehn & Yahr				
Median	2	2.5	2	0.0001
Range	(1 – 5)	(1 – 5)	(1 – 4)	Portland>Seattle/Stanford, Seattle>Stanford
GDS-15				
Mean (sd)	6.0 (1.7)	5.9 (1.7)	5.5 (1.5)	
Range	1 - 13	2 - 11	2 - 12	0.076
LEDD				
Mean (sd)	622.3 (526.2)	692.5 (492.7)	377.7 (242.9)	0.0001
Range	0 - 3375	0 - 2876	0 - 1125	Stanford<Seattle/Portland
APOE				
n (%) ε4 allele	126 (22.8%)	45 (23.9%)	11 (16.7%)	0.465
GBA				
n (%) carrier	69 (12.3%)	15 (8.6%)	8 (12.7%)	0.274
MAPT				
n (%) H1 haplotype	174 (33.9%)	50 (32.5%)	-	0.750
MoCA				
Mean (sd)	24.4 (3.8)	23.5 (4.1)	26.2 (3.7)	<0.0001
Range	7 - 30	7 - 30	11 - 30	Stanford>Seattle/Portland, Seattle>Portland

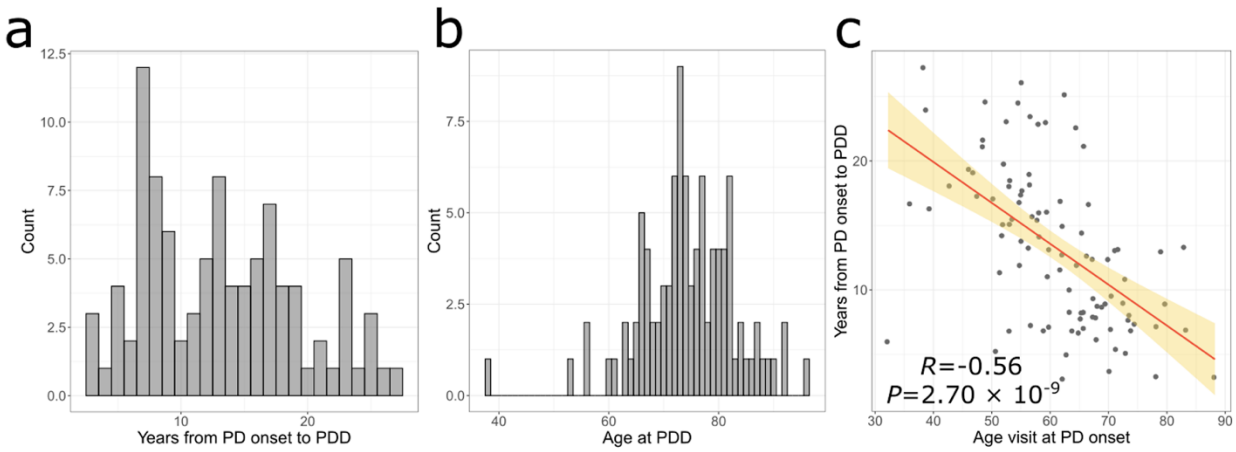
* Overall (pairwise) comparisons based on one-way ANOVA (Scheffe's test) for continuous variables, Kruskal-Wallis (Dunn's test) for ordinal variables, or chi-square for dichotomous variables

† Lower score = better performance

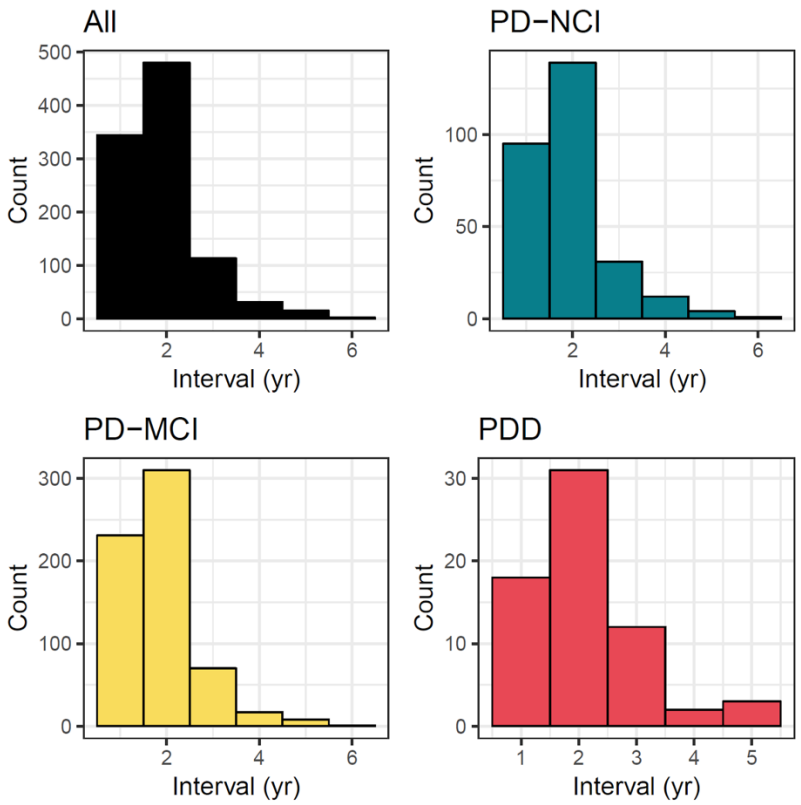
Abbreviations: *APOE*, apolipoprotein E gene; *GBA*, glucocerebrosidase gene; GDS-15, 15-item Geriatric Depression Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; LEDD, levodopa equivalent daily dose; *MAPT*, microtubule-associated protein tau gene; MDS-UPDRS, Unified Parkinson's Disease Rating Scale, Movement Disorders Society revision; MoCA, Montreal Cognitive Assessment; NCI, not cognitively impaired; PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease mild cognitive impairment; RDI, recognition discriminability index; sd, standard deviation



Supplementary Figure 1. Survival analyses indicate significant longitudinal differences between participants of different sex and selected genes. Survival analyses to an endpoint of dementia for participants categorized by GBA mutation (a, e), sex (b, f), combination of both (c, g), and *APOE ε4* allele (d, h) either by the age at their visit or months since their first visit. *P* value obtained from log ratio tests indicated significant effect of sex, *GBA* mutation, and the combination of both.



Supplementary Figure 2. The age at PD onset is a significant factor affecting progression rate to dementia. The distribution of the number of years until a person with PD was diagnosed with PDD (a) and the age at which they were diagnosed with PDD (b). The correlation between age at PD symptom onset to the number of years before they develop PDD (c). The analysis was restricted to patients with more than one time point, did not have dementia in the first visit, and was observed to develop dementia within the data set (n = 97).



Supplementary Figure 3. Distribution of longitudinal visit intervals (in years) in the PUC