Supplemental Online Content

Zheng Z, Lv J, Rong S, Sun T, Chen L. Physical frailty, genetic predisposition, and incident parkinson disease. *JAMA Neurol*. Published online March 13, 2023. doi:10.1001/jamaneurol.2023.0183

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Disease Definitions in UK Biobank Study

	ICD-9	ICD-10	Self-reported fields
Parkinson's Disease	332.0, 332.1, 333.0	G20, G21, G21.0, G21.1, G21.2, G21.3, G21.4, G21.8, G21.9, G22, G23.0, G23.1, G23.2, G23.3, G23.8, G23.9, G25.9, G26, G90.3	20002 (1262)
Dementia	290.2, 290.3, 290.4, 291.2, 294.1, 331.0, 331.1, 331.2, 331.5	A81.0, F00, F00.0, F00.1, F00.2, F00.9, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G30, G30.0, G30.1, G30.8, G30.9, G31.0, G31.1, G31.8, I67.3	20002 (1263)

Variable definitions constructed using ICD-9, ICD-10 codes, and self-reported data fields with choice-, disease- or procedure-specific codes between brackets are shown.

Abbreviations: ICD, International Classification of Diseases.

eTable 2. Frailty Definition and Cut-off Points in UK Biobank Study

Individuals components	Criteria	Field IDs
Weight loss	Self-reported: “Compared with one year ago, has your weight changed?” Response: yes, lost weight = 1; other = 0; Do not know/Prefer not to answer = missing data.	2306
Exhaustion	Self-reported: “Over the past two weeks, how often have you felt tired or had little energy?” Response: more than half the days or nearly every day = 1; other = 0; Do not know/Prefer not to answer = missing data.	2080
Low physical activity	Quintiles of sex- and age-specific levels of total MET minutes per week derived from IPAQ. The lowest 20% of total MET minutes per week = 1; other = 0; No response/ Prefer not to answer = missing data.	31, 21022, 22037, 22038, 22039
Slow gait speed	Self-reported: “How would you describe your usual walking pace?” Response: slow = 1; other = 0; Do not know/Prefer not to answer = missing data.	924
Low grip strength	Measured grip strength expressed in kg by sex- and BMI- adjusted cut-off points. Cut-off points: <u>Men</u> If BMI ≤24.0 kg/m^2 & grip strength ≤29 kg If BMI 24.1 to 26.0 kg/m^2 & grip strength ≤30 kg If BMI 26.1 to 28.0 kg/m^2 & grip strength ≤30 kg If BMI >28.0 kg/m^2 & grip strength ≤32 kg <u>Women</u> If BMI ≤23.0 kg/m^2 & grip strength ≤17 kg If BMI 23.1 to 26.0 kg/m^2 & grip strength ≤17.3 kg	31, 21001, 46, 47

	If BMI 26.1 to 29.0 kg/m^2 & grip strength ≤18 kg If BMI >29.0 kg/m^2 & grip strength ≤21 kg If data on BMI or grip strength is not available = missing data.	

Abbreviations: BMI, body mass index; MET, metabolic equivalent of energy; IPAQ, International Physical Activity Questionnaire.

eTable 3. Information of 44 SNPs for PD in UK Biobank

SNP	Effect allele/ alternate allele	EAF in 1000 Genomes	*P*-value	OR
rs10797576	T/C	0.137	1.76×10^{-10}	1.13
rs10906923	C/A	0.306	2.37×10^{-8}	0.93
rs11060180	G/A	0.45	3.08×10^{-11}	0.91
rs11158026	T/C	0.307	2.88×10^{-10}	0.91
rs11343	T/G	0.454	1.46×10^{-9}	1.07
rs115185635	C/G	0.036	2.2×10^{-8}	1.79
rs11724635	C/A	0.437	4.26×10^{-17}	0.89
rs117896735	A/G	0.012	1.21×10^{-11}	1.77
rs12456492	G/A	0.332	2.15×10^{-11}	1.10
rs12497850	G/T	0.347	6.8×10^{-8}	0.93
rs12637471	A/G	0.219	5.38×10^{-22}	0.84
rs13294100	T/G	0.371	1.99×10^{-12}	0.91
rs14235	A/G	0.397	3.63×10^{-12}	1.10
rs143918452	G/A	0.996	2.25×10^{-7}	0.68
rs1474055	C/T	0.881	7.11×10^{-16}	0.82
rs1555399	T/A	0.544	5.7×10^{-16}	1.15
rs17649553	T/C	0.232	6.11×10^{-49}	0.77
rs199347	G/A	0.368	5.62×10^{-14}	0.9
rs2280104	T/C	0.367	9.06×10^{-7}	1.06
rs2414739	G/A	0.292	3.59×10^{-12}	0.9
rs2694528	C/A	0.115	1.69×10^{-11}	1.15
rs2740594	A/G	0.753	9.54×10^{-11}	1.10
rs329648	T/C	0.327	8.05×10^{-12}	1.11
rs34043159	C/T	0.352	3.83×10^{-8}	1.07
rs34311866	C/T	0.199	6×10^{-41}	1.26
rs353116	T/C	0.385	9.73×10^{-7}	0.94
rs356182	G/A	0.375	1.85×10^{-82}	1.34
rs35749011	G/A	0.976	6.1×10^{-23}	0.57
rs3793947	A/G	0.463	2.59×10^{-8}	0.91
rs4073221	G/T	0.132	3.02×10^{-9}	1.11
rs4653767	C/T	0.315	2.4×10^{-10}	0.92
rs4784227	T/C	0.265	8.29×10^{-8}	1.08
rs591323	A/G	0.293	3.17×10^{-8}	0.91
rs601999	C/T	0.699	8.03×10^{-9}	0.93
rs62120679	T/C	0.324	2.52×10^{-9}	1.14
rs6430538	T/C	0.488	3.35×10^{-19}	0.88
rs6812193	T/C	0.398	1.85×10^{-11}	0.91
rs76904798	T/C	0.132	4.86×10^{-14}	1.16

rs78738012	C/T	0.106	2.11×10^{-9}	1.14
rs8005172	T/C	0.424	1.2×10^{-9}	1.08
rs8118008	A/G	0.596	2.32×10^{-8}	1.11
rs823118	C/T	0.467	1.96×10^{-16}	0.89
rs9275326	T/C	0.114	5.81×10^{-13}	0.80
rs9468199	A/G	0.172	3.44×10^{-13}	1.12

Abbreviations: EAF, effect allele frequency; SNP, single nucleotide polymorphism; OR, odds ratio.

eTable 4. Association between PD-PRS and Incident PD

	Low PRS	Intermediate PRS	High PRS
Case/person-years	486/1286269	591/1287125	839/1287027
Incident cases per 100,000 person-years	37.8	45.9	65.2
Hazard ratio (95% CI)*	1.00 (reference)	1.22 (1.08-1.37)	1.72 (1.54-1.93)

*Model adjusted for genotyping array and the first 10 principal components of ancestry.

Abbreviations: CI: confidence interval; PRS, polygenic risk score.

eTable 5. Definition and List of Long-Term Morbidities

	Morbidity grouping*	Conditions included	Code
1	Hypertension	Hypertension	1065
		Essential hypertension	1072
2	Coronary heart disease	Heart attack/MI	1075
		Angina	1074
3	Diabetes	Diabetic nephropathy	1607
		Diabetic neuropathy/ulcers	1468
		Diabetes	1220
		Type 1 diabetes	1222
		Type 2 diabetes	1223
		Diabetic eye disease	1276
4	Stroke/TIA	Stroke	1081
		TIA	1082
		Subarachnoid haemorrhage	1086
		Brain haemorrhage	1491
		Ischaemic stroke	1583
5	Atrial fibrillation	Atrial fibrillation	1471
6	Heart failure	Cardiomyopathy	1079
		Hypertrophic cardiomyopathy	1588
		Heart failure/pulmonary oedema	1076
7	Peripheral vascular disease	Peripheral vascular disease	1067
		Leg claudication/intermittent claudication	1087
8	COPD	COPD/Chronic obstructive pulmonary disease	1112
		Emphysema/Chronic bronchitis	1113
		Emphysema	1472
9	Asthma	Asthma	1111
10	Bronchiectasis	Bronchiectasis	1114
11	Cancer*	“yes”/”no” to “have you ever had cancer?”	
12	Dyspepsia	Gastro-oesophageal reflux (GORD)	1138
		Oesophagitis/Barrett’s oesophagus	1139
		Gastric stomach ulcers	1142
		Gastric erosions/gastritis	1143
		Duodenal ulcer	1457
		Dyspepsia/indigestion	1510
		Hiatus hernia	1474
		Helicobacter pylori	1442
13	Diverticular disease	Diverticular disease/diverticulitis	1458

14	Irritable bowel syndrome	Irritable bowel syndrome	1154
15	Chronic liver disease	Oesophageal varices	1141
		Non infective hepatitis	1157
		Liver failure/cirrhosis	1158
		Primary biliary cirrhosis	1506
16	Inflammatory bowel disease	Inflammatory bowel disease	1461
		Crohn’s disease	1462
		Ulcerative colitis	1463
17	Constipation	Constipation	1599
18	Viral hepatitis	Hepatitis B	1579
		Hepatitis C	1580
		Hepatitis D	1581
19	Depression	Depression	1286
		Postnatal depression	1531
20	Anxiety	Anxiety/panic attacks	1287
		Nervous breakdown	1288
		Post-traumatic stress disorder	1469
		Obsessive compulsive disorder	1615
		Stress	1614
		Insomnia	1616
		Psychological/psychiatric problem	1243
21	Schizophrenia/Bipolar affective disorder	Scizophrenia	1289
	Bipolar	Mania	1291
		Bipolar disorder	1291
		Manic depression	1291
22	Connective tissue diseases	Myositis/myopathy	1322
		Systemic lupus erythematosus/SLE	1381
		Connective tissue disorder	1373
		Sjogren’s syndrome.sicca syndrome	1382
		Dermatopolymyositis	1383
		Scloeroderma/systemic sclerosis	1384
		Rheumatoid arthritis	1464
		Psoriatic arthropathy	1477
		Dermatomyositis	1480
		Polymyositis	1481
		Polymyalgia rheumatica	1377
23	Painful conditions	Back pain	1534

		Joint pain	1537
		Headaches (not migraine)	1436
		Sciatica	1476
		Plantar fasciitis	1540
		Carpal tunnel syndrome	1541
		Fibromyalgia	1542
		Arthritis	1538
		Shingles	1573
		Disc problem	1532
		Prolapsed disc/slipped disc	1312
		Spine arthritis/spondylitis	1311
		Ankylosing spondylitis	1313
		Back problem	1294
		Osteoarthritis	1465
		Gout	1466
		Cervical spondylosis	1478
		Trigeminal neuralgia	1523
		Disc degeneration	1533
		Trapped nerve/compressed nerve	1257
24	Osteoporosis	Osteoporosis	1309
25	Thyroid disorders	Thyroid problem (not cancer	1224
		Hyperthroidism/thyrotoxicosis	1225
		Hypothyroidism/myxoedema	1226
		Grave’s disease	1522
		Thyroid goitre	1610
		Thyroititis	1428
26	Alcohol problems	Alcohol dependency	1408
		Alcoholic liver disease/alcoholic cirrhosis	1604
27	Chronic kidney disease	Polycystic kidney	1427
		Diabetic nephropathy	1607
		Renal/kidney failure	1192
		Renal failure requiring dialysis	1193
		Renal failure not requiring dialysis	1194
		Kidney nephropathy	1519
		Immunoglobulin A (IgA) nephropathy	1520
28	Prostate disorders	Prostate problem (not cancer)	1207
		Enlarged prostate	1396
		Benign prostatic hypertrophy	1516

29	Glaucoma	Glaucoma	1277
30	Epilepsy	Epilepsy	1264
31	Dementia	Dementia/Alzheimer/cognitive impairment	1263
32	Psoriasis or eczema	Eczema/dermatitis	1452
		Psoriasis	1453
33	Migraine	Migraine	1265
34	Chronic sinusitis	Chronic sinusitis	1416
35	Anorexia or bulimia	Anorexia, bulimia/other eating disorder	1470
36	Parkinson’s disease	Parkinson’s disease	1262
37	Multiple sclerosis	Multiple sclerosis	1261
38	Chronic fatigue syndrome	Chronic fatigue syndrome	1482
39	Endometriosis	Endometriosis	1402
40	Meniere disease	Meniere disease	1421
41	Pernicious anaemia	Pernicious anaemia	1331
42	Polycystic ovaries	Polycystic ovaries	1350

*Self-report lifetime diagnosis by doctor recorded by nurse-led interview (UK Biobank data field ID: 20002), except cancer diagnosis which was reported by touch-screen questionnaire. The list of disease groupings was based on Barnett et al (2012). In the present study, we did not include patients with Parkinson’s disease (code 1262) and dementia (code 1263) at baseline.

eTable 6. Risk of incident PD according to genetic risk and frailty phenotype

	Low PRS	Intermediate PRS	High PRS
Non-frailty	1.00 (reference)	1.25 (1.04-1.51)	2.04 (1.72-2.41)
Pre-frailty	1.45 (1.20-1.75)	1.75 (1.46-2.09)	2.21 (1.86-2.63)
Frailty	2.25 (1.56-3.25)	2.55 (1.81-3.59)	3.22 (2.35-4.41)

Model adjusted for age, sex, Townsend deprivation index, assessment centers, alcohol consumption, smoking status, BMI, the number of long-term morbidities, genotyping array, and the first 10 principal components of ancestry.

eTable 7. Stratified Analysis for the Association between Physical Frailty and Incidence of PD

	N	Non-frailty	Pre-frailty	Frailty	*P* for interaction
Age					
<60 years	185860	1 (ref.)	1.37 (1.13-1.67)	2.11 (1.38-3.21)	0.07
≥60 years	129138	1 (ref.)	1.25 (1.12-1.39)	1.86 (1.48-2.33)	
Sex					
Male	154739	1 (ref.)	1.32 (1.18-1.48)	2.03 (1.58-2.60)	0.24
Female	160259	1 (ref.)	1.14 (0.96-1.36)	1.60 (1.15-2.23)	
Townsend deprivation index					
Above median value (high deprivation)	157489	1 (ref.)	1.35 (1.18-1.55)	1.95 (1.51-2.52)	0.10
Below median value (low deprivation)	157509	1 (ref.)	1.18 (1.03-1.35)	1.76 (1.27-2.44)	
The number of long-term conditions					
None	111690	1 (ref.)	1.14 (0.94-1.39)	0.55 (0.14-2.22)	0.02
One	105031	1 (ref.)	1.26 (1.07-1.50)	1.82 (1.11-3.00)	
Two or more	113196	1 (ref.)	1.37 (1.18-1.58)	2.24 (1.78-2.81)	

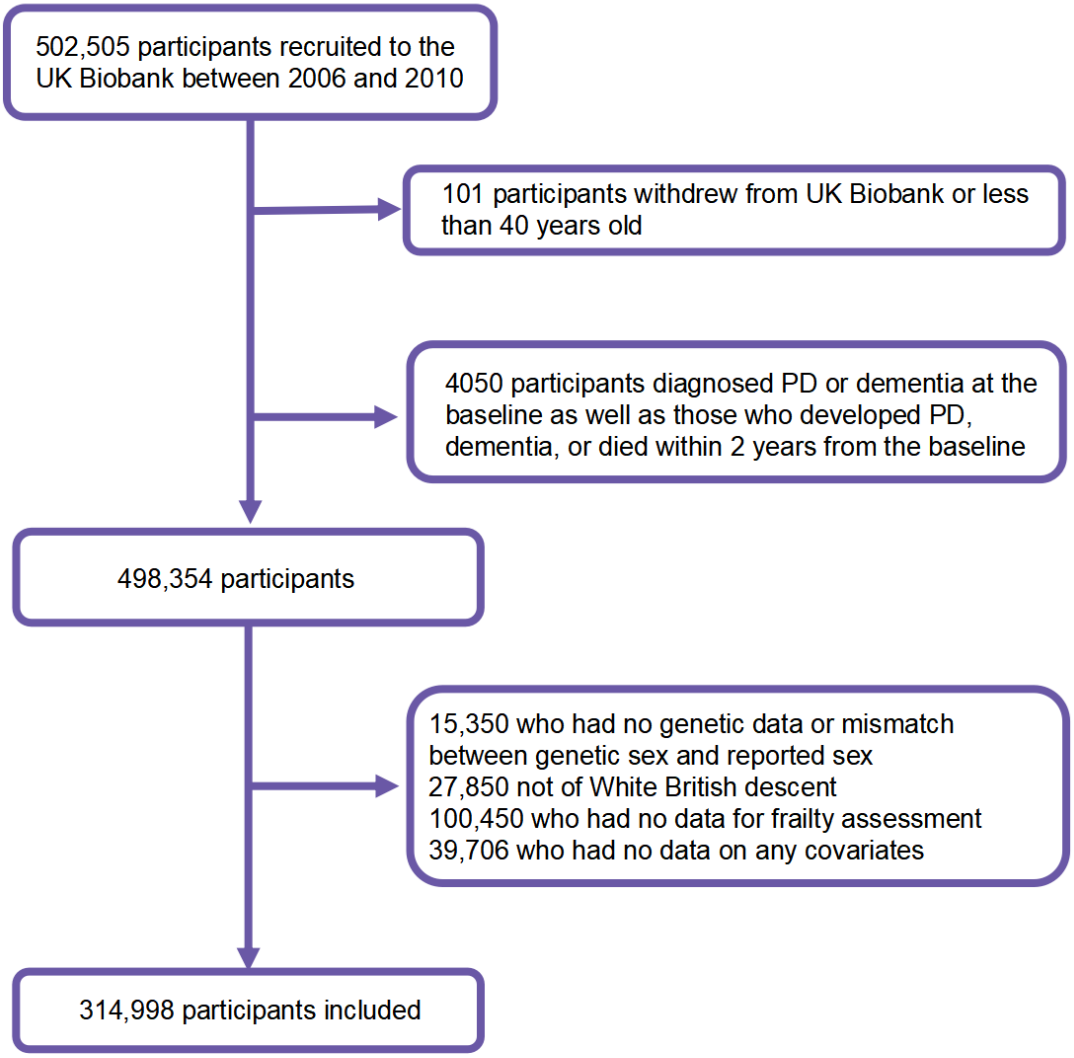
Model adjusted for age (continuous) and sex (male, female), Townsend deprivation index (in quintiles), assessment centers (22 categories), alcohol consumption (daily or most daily, 3 or 4 times a week, 1or 2 times a week, 1 to 3 times a week, or never or special occasions only), smoking status (never, former, or current), BMI (continuous), the number of long-term morbidities (0, 1, 2, 3, 4, or ≥5), PD-PRS, genotyping array, and the first 10 principal components of ancestry.

eTable 8. Association of Frailty and PD Using Fine & Gray Models for Competing Risk

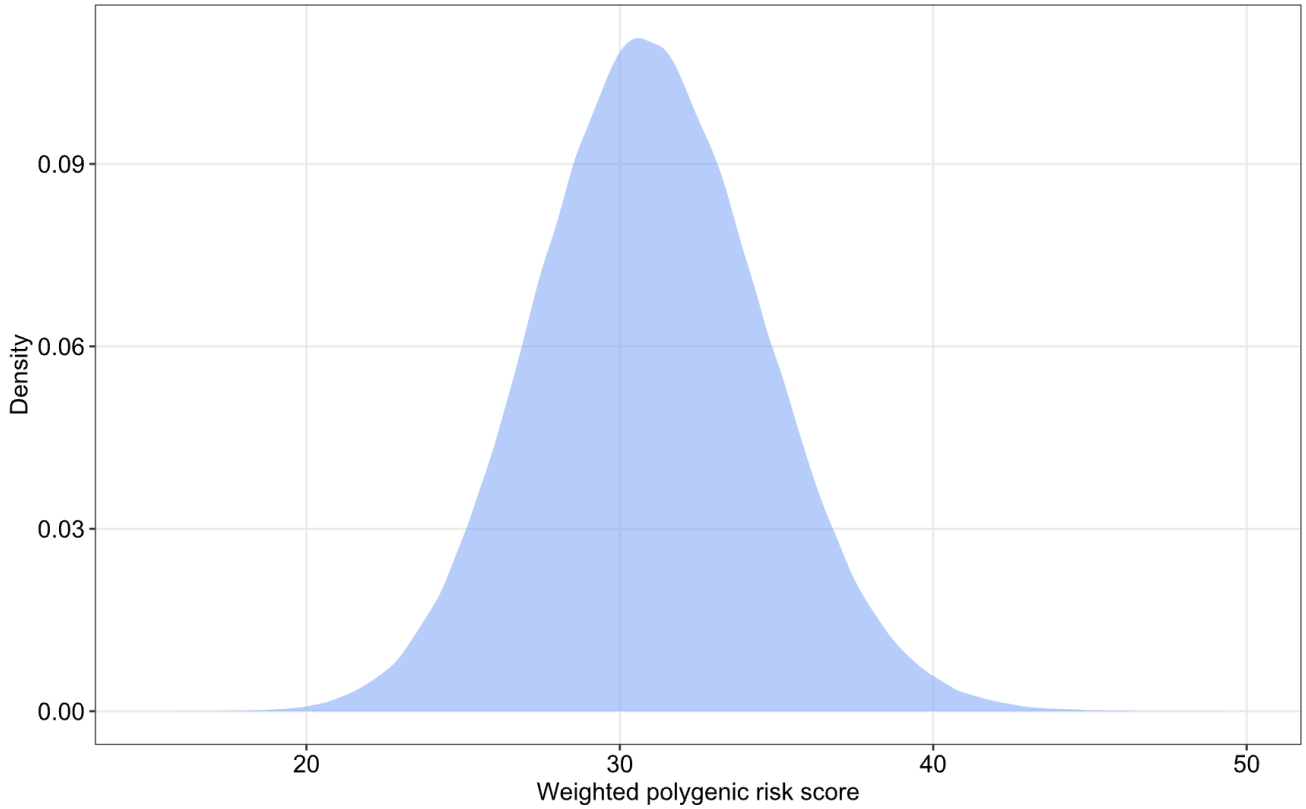
Frailty phenotypes	Non-frailty	Pre-frailty	Frailty	Per score increment
Hazard ratio (95% CI)	1.00 (ref.)	1.24 (1.13-1.37)	1.73 (1.42-2.11)	1.18 (1.12-1.24)

Model adjusted for age (continuous) and sex (male, female), Townsend deprivation index (in quintiles), assessment centers (22 categories), alcohol consumption (daily or most daily, 3 or 4 times a week, 1or 2 times a week, 1 to 3 times a week, or never or special occasions only), smoking status (never, former, or current), BMI (continuous), the number of long-term morbidities (0, 1, 2, 3, 4, or ≥5), PD-PRS, genotyping array, and the first 10 principal components of ancestry.

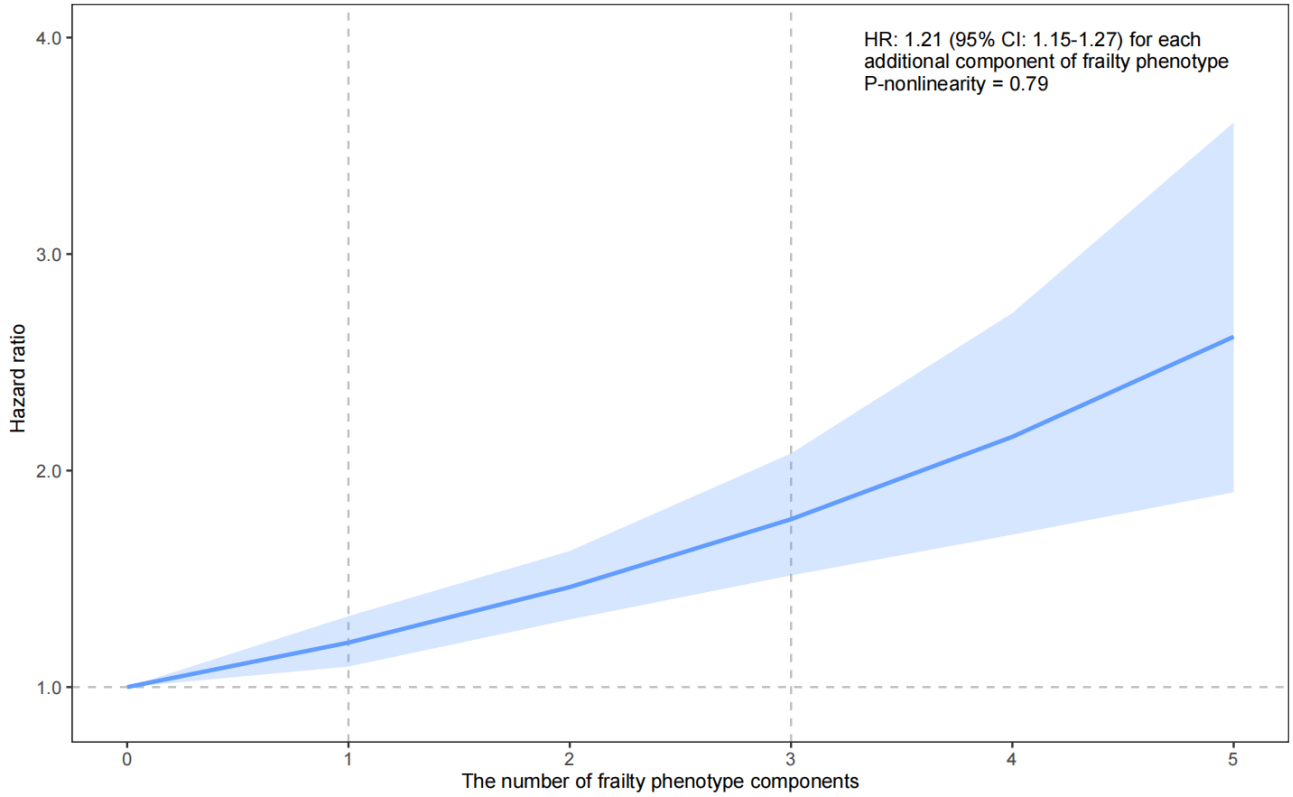
eFigure 1. Flow Chart



eFigure 2. The Curve of Density Distribution and Weighted Polygenic Risk Score



eFigure 3. The Accumulation of Frailty Phenotype Components and Risk of PD



Model adjusted for age (continuous) and sex (male, female), Townsend deprivation index (in quintiles), assessment centers (22 categories), alcohol consumption (daily or most daily, 3 or 4 times a week, 1 or 2 times a week, 1 to 3 times a week, or never or special occasions only), smoking status (never, former, or current), BMI (continuous), the number of long-term morbidities (0, 1, 2, 3, 4, or ≥5), PD-PRS, genotyping array, and the first 10 principal components of ancestry.