

Supplementary Online Content

Schrag A, Bohlken J, Dammertz L, et al. Widening the spectrum of risk factors, comorbidities, and prodromal features of Parkinson disease. *JAMA Neurol*. Published online November 7, 2022. doi:10.1001/jamaneurol.2022.3902

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

eTable 1. Prodromal Features, Risk Factors, or Comorbidities and Corresponding ICD Codes

Symptoms	ICD-10 codes
Motor dysfunction	
Gait impairment	R26
Neck pain	M54.2
Shoulder pain	M25.51
Stiffness of joints	M25.6
Tremor	G25.0, G25.1, G25.2, R25.1
Psychiatric presentations	
Anxiety	F41.0, F41.1, F41.9
Depression	F32, F33
Memory problems	F06.7, R41.3, R41.8
Impairment of sensory experiences	
Hearing loss	H91.2, H91.9
Anosmia	R43.0
Changes of skin sensation	R20.0, R20.1, R20.2, R20.3
Subjective visual disturbance	H53.1
Non-specific pain	R52.1, R52.2, R52.9
Sleep disorders	
Restless legs syndrome	G25.80, G25.81
Hypersomnia	F51.1 with G47.1
Insomnia	F51.0 with G47.0
Other sleep disorders	F51.2, F51.8, F51.9, G47.2, G47.9
Parasomnia	F51.3, F51.4, F51.5, G47.8
Sleep apnea	G47.3
Skin diseases	
Dermatophytosis	B35
Psoriasis	L40
Seborrheic dermatitis	L21
Autonomic dysfunction and fatigue	
Constipation	K59.0
Dizziness	R42
Fatigue	G93.3
Neurogenic bladder	N31
Orthostasis	I95, R03.1
Sexual dysfunction	F52.0, F52.1, F52.2, F52.8, F52.9
Risk factors and comorbidities	
Risk factors	
Alcohol abuse	F10.1, F10.2
Nicotine abuse	F17.1, F17.2
Traumatic brain injury	S06.0, S06.1, S06.2, S06.3
Metabolic diseases and vascular risk factors	

Diabetes mellitus type 1	E10
Diabetes mellitus type 2	E11
Hypercholesterinemia	E78
Hypertension	I10
Infectious diseases	
Cytomegaloviral disease	B25
Infectious mononucleosis	B27
Gastrointestinal disorders	
Duodenal ulcer	K26
Gastric ulcer	K25
Gastritis	K29
Gastro-oesophageal reflux disease	K21
Gastrojejunal ulcer	K28
Peptic ulcer	K27
Crohn's disease	K50
Ulcerative colitis	K51
Other comorbidities	
Osteoarthritis	M15, M16, M17, M18, M19
Seropositive inflammatory arthritis	M05
Other inflammatory arthritis	M06
Bipolar disorder	F31
Schizophrenia	F20
Epilepsy	G40
Migraine	G43

eTable 2. Odds Ratios and 95% CIs Adjusted for Multiple Comparisons of Prodromal Features, Risk Factors, and Comorbidities in Cases Compared With Controls in the Year Before Index Date and in the Time Periods 2 to 4 Years and 5 to 10 Years Before the Index Date

	Within 1st year before index date	2 to 4 years before index date	5 to 10 years before index date
Symptoms			
Motor dysfunction			
Gait impairment	1.96 (1.88-2.03)	1.64 (1.57-1.71)	1.35 (1.25-1.46)
Neck pain	1.22 (1.16-1.29)	1.16 (1.11-1.21)	1.11 (1.06-1.17)
Shoulder pain	1.26 (1.09-1.46)	1.17 (1.05-1.30)	1.04 (0.91-1.18)
Stiffness of joints	1.42 (1.17-1.73)	1.26 (1.07-1.48)	1.23 (1.01-1.49)
Tremor	14.94 (13.66-16.33)	7.13 (6.53-7.77)	4.49 (3.98-5.06)
Psychiatric presentations			
Anxiety	1.82 (1.71-1.93)	1.66 (1.58-1.75)	1.47 (1.38-1.57)
Depression	2.04 (1.98-2.10)	1.82 (1.77-1.87)	1.57 (1.52-1.62)
Memory problems	1.77 (1.63-1.92)	1.59 (1.46-1.73)	1.49 (1.29-1.71)
Impairment of sensory organs			
Hearing loss	1.17 (1.10-1.24)	1.17 (1.11-1.23)	1.12 (1.05-1.19)
Anosmia	2.45 (1.71-3.51)	2.10 (1.52-2.91)	2.00 (1.35-2.97)
Impairment of skin sensation	1.69 (1.47-1.94)	1.26 (1.13-1.39)	1.21 (1.07-1.37)
Subjective visual disturbance	1.30 (0.86-1.99)	1.22 (0.94-1.58)	1.27 (0.95-1.69)
Non-specific pain	1.53 (1.47-1.58)	1.44 (1.40-1.50)	1.36 (1.29-1.43)
Sleep disorders			
Restless legs syndrome	4.74 (4.41-5.10)	4.24 (3.95-4.55)	3.73 (3.39-4.09)
Hypersomnia	2.64 (1.35-5.18)	2.58 (1.43-4.64)	1.90 (0.84-4.29)
Insomnia	1.49 (1.38-1.61)	1.42 (1.33-1.52)	1.32 (1.21-1.44)
Other sleep disorders	1.46 (1.39-1.54)	1.40 (1.34-1.47)	1.32 (1.25-1.40)
Parasomnia	1.77 (1.49-2.10)	1.53 (1.32-1.77)	1.48 (1.23-1.78)
Sleep apnea	1.47 (1.38-1.55)	1.41 (1.33-1.50)	1.35 (1.26-1.45)
Skin diseases			
Dermatophytosis	1.30 (1.20-1.40)	1.25 (1.18-1.33)	1.19 (1.11-1.27)
Psoriasis	1.11 (1.04-1.20)	1.11 (1.04-1.19)	1.09 (1.01-1.18)
Seborrheic dermatitis	1.42 (1.20-1.67)	1.32 (1.15-1.50)	1.22 (1.04-1.42)
Autonomic dysfunction and fatigue			
Constipation	2.00 (1.88-2.12)	1.86 (1.76-1.96)	1.65 (1.53-1.77)
Dizziness	1.80 (1.74-1.87)	1.56 (1.51-1.61)	1.33 (1.28-1.40)
Fatigue	1.72 (1.61-1.83)	1.38 (1.31-1.45)	1.17 (1.10-1.25)
Neurogenic bladder	1.77 (1.55-2.02)	1.67 (1.47-1.91)	1.56 (1.29-1.88)
Orthostasis	1.47 (1.36-1.60)	1.37 (1.28-1.46)	1.24 (1.14-1.35)
Sexual dysfunction	1.19 (1.08-1.32)	1.21 (1.11-1.31)	1.21 (1.10-1.34)
Risk factors and comorbidities			
Risk factors			
Alcohol abuse	1.32 (1.21-1.44)	1.28 (1.18-1.39)	1.23 (1.11-1.36)
Nicotine abuse	0.93 (0.87-0.99)	0.93 (0.87-0.99)	0.91 (0.84-0.98)
Traumatic brain injury	2.05 (1.55-2.70)	1.44 (1.16-1.79)	1.40 (1.07-1.84)
Metabolic diseases and vascular risk factors			
Diabetes mellitus type 1	1.35 (1.22-1.49)	1.33 (1.22-1.45)	1.30 (1.17-1.45)
Diabetes mellitus type 2	1.25 (1.22-1.29)	1.24 (1.21-1.28)	1.23 (1.19-1.27)
Hypercholesterinaemia	1.09 (1.07-1.12)	1.09 (1.07-1.11)	1.06 (1.04-1.09)
Hypertension	1.24 (1.22-1.26)	1.22 (1.20-1.24)	1.17 (1.15-1.20)
Infectious diseases			
Cytomegaloviral disease	1.07 (0.49-2.34)	1.10 (0.60-2.04)	0.84 (0.42-1.66)

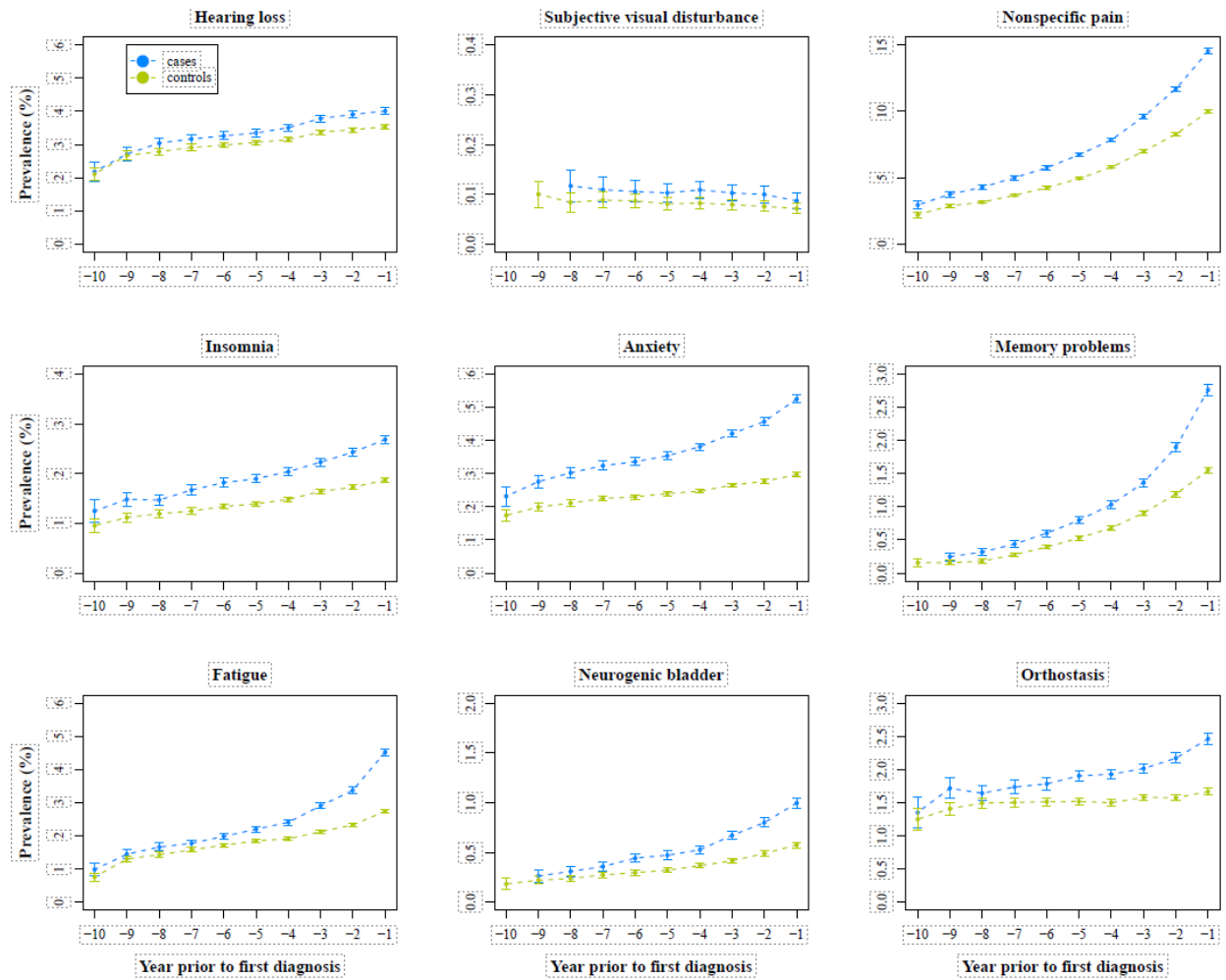
Infectious mononucleosis	1.78 (0.93-3.41)	1.46 (0.87-2.45)	1.53 (0.82-2.85)
Gastrointestinal disorders			
Duodenal ulcer	1.12 (0.97-1.31)	1.13 (0.99-1.29)	1.18 (1.01-1.37)
Gastric ulcer	1.29 (1.14-1.46)	1.25 (1.12-1.39)	1.24 (1.09-1.42)
Gastritis	1.32 (1.27-1.37)	1.27 (1.23-1.32)	1.23 (1.19-1.28)
Gastro-oesophageal reflux disease	1.27 (1.23-1.32)	1.26 (1.22-1.30)	1.24 (1.19-1.29)
Gastrojejunal ulcer	1.32 (0.78-2.22)	1.32 (0.83-2.09)	1.10 (0.62-1.95)
Peptic ulcer	1.43 (0.96-2.15)	1.35 (0.96-1.91)	1.20 (0.80-1.81)
Crohn's disease	1.31 (1.07-1.61)	1.20 (0.98-1.46)	1.15 (0.91-1.45)
Ulcerative colitis	1.26 (1.07-1.47)	1.22 (1.06-1.42)	1.16 (0.97-1.38)
Other comorbidities			
Osteoarthritis	1.20 (1.17-1.23)	1.18 (1.15-1.21)	1.13 (1.09-1.16)
Seropositive inflammatory arthritis	1.21 (0.99-1.48)	1.15 (0.95-1.39)	1.10 (0.86-1.40)
Other inflammatory arthritis	1.19 (1.10-1.29)	1.19 (1.11-1.29)	1.15 (1.05-1.27)
Bipolar disorder	4.09 (3.22-5.21)	3.95 (3.13-4.98)	3.80 (2.82-5.14)
Schizophrenia	4.69 (3.99-5.50)	4.29 (3.68-5.00)	4.00 (3.31-4.85)
Epilepsy	2.44 (2.24-2.65)	2.20 (2.02-2.40)	2.02 (1.81-2.26)
Migraine	1.24 (1.15-1.34)	1.21 (1.13-1.29)	1.17 (1.09-1.27)

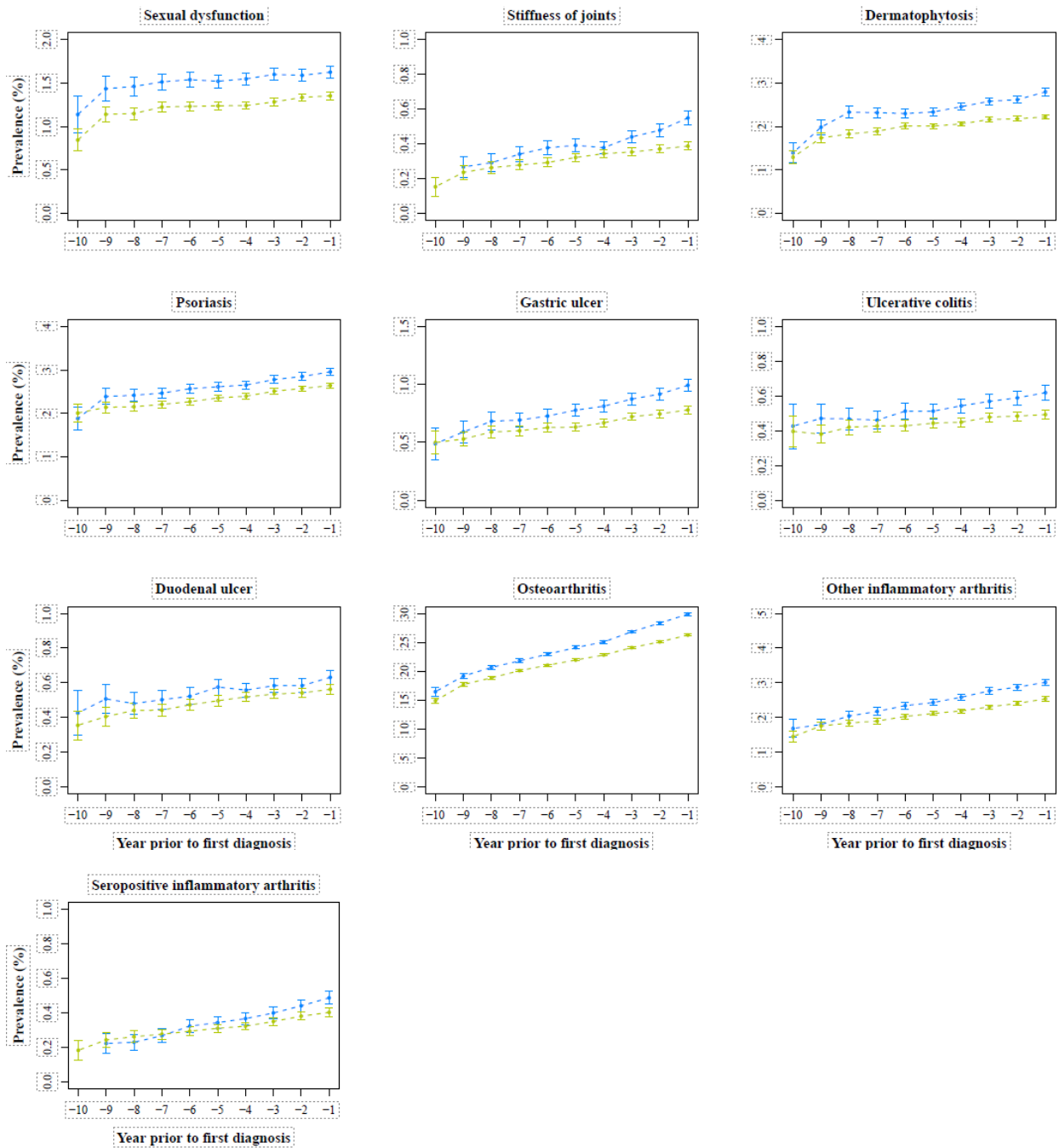
eTable 3. Prodromal Features, Risk Factors, or Comorbidities in Cases and Controls in the Year Before Index Date and in the Time Periods 2 to 4 Years and 5 to 10 Years Before the Index Date

	≤1st year before index date		2 to 4 years before index date		5 to 10 years before index date	
	Cases (n=138,345)	Controls (n=276,690)	Cases (n=138,345)	Controls (n=276,690)	Cases (n=106,957)	Controls (n=213,914)
Symptoms						
Motor dysfunction						
Gait impairment	18274 (13.2%)	19980 (7.2%)	13410 (9.7%)	17007 (6.1%)	3417 (3.2%)	5103 (2.4%)
Neck pain	10139 (7.3%)	16828 (6.1%)	15719 (11.4%)	27626 (10.0%)	11647 (10.9%)	21146 (9.9%)
Shoulder pain	1264 (0.9%)	2004 (0.7%)	2520 (1.8%)	4323 (1.6%)	1537 (1.4%)	2958 (1.4%)
Stiffness of joints	759 (0.5%)	1069 (0.4%)	1033 (0.7%)	1642 (0.6%)	688 (0.6%)	1124 (0.5%)
Tremor	12888 (9.3%)	1890 (0.7%)	7688 (5.6%)	2266 (0.8%)	2933 (2.7%)	1335 (0.6%)
Psychiatric presentations						
Anxiety	7257 (5.2%)	8187 (3.0%)	8823 (6.4%)	10900 (3.9%)	5434 (5.1%)	7498 (3.5%)
Depression	33661 (24.3%)	37696 (13.6%)	36100 (26.1%)	45053 (16.3%)	22589 (21.1%)	31170 (14.6%)
Memory problems	3823 (2.8%)	4369 (1.6%)	3287 (2.4%)	4171 (1.5%)	1135 (1.1%)	1532 (0.7%)
Impairment of sensory organs						
Hearing loss	5542 (4.0%)	9568 (3.5%)	7710 (5.6%)	13295 (4.8%)	5406 (5.1%)	9742 (4.6%)
Anosmia	223 (0.2%)	182 (0.1%)	250 (0.2%)	238 (0.1%)	167 (0.2%)	167 (0.1%)
Change of skin sensation	1291 (0.9%)	1534 (0.6%)	1999 (1.4%)	3193 (1.2%)	1367 (1.3%)	2266 (1.1%)
Subjective visual disturbance	120 (0.1%)	184 (0.1%)	302 (0.2%)	497 (0.2%)	248 (0.2%)	392 (0.2%)
Non-specific pain	20104 (14.5%)	27740 (10.0%)	20171 (14.6%)	29233 (10.6%)	9554 (8.9%)	14398 (6.7%)
Sleep disorders						
Restless legs syndrome	8315 (6.0%)	3682 (1.3%)	7968 (5.8%)	3929 (1.4%)	4147 (3.9%)	2291 (1.1%)
Hypersomnia	66 (0.0%)	50 (0.0%)	85 (0.1%)	66 (0.0%)	38 (0.0%)	40 (0.0%)
Insomnia	3712 (2.7%)	5024 (1.8%)	4977 (3.6%)	7096 (2.6%)	3061 (2.9%)	4670 (2.2%)
Other sleep disorders	7946 (5.7%)	11071 (4.0%)	10790 (7.8%)	15725 (5.7%)	6939 (6.5%)	10696 (5.0%)
Parasomnia	844 (0.6%)	957 (0.3%)	1098 (0.8%)	1440 (0.5%)	666 (0.6%)	900 (0.4%)
Sleep apnea	6831 (4.9%)	9474 (3.4%)	7001 (5.1%)	10062 (3.6%)	4252 (4.0%)	6357 (3.0%)
Skin diseases						
Dermatophytosis	3868 (2.8%)	5995 (2.2%)	6549 (4.7%)	10556 (3.8%)	4696 (4.4%)	7947 (3.7%)
Psoriasis	4087 (3.0%)	7357 (2.7%)	4619 (3.3%)	8345 (3.0%)	3315 (3.1%)	6112 (2.9%)
Seborrheic dermatitis	800 (0.6%)	1132 (0.4%)	1233 (0.9%)	1878 (0.7%)	861 (0.8%)	1418 (0.7%)
Autonomic dysfunction and fatigue						
Constipation	6963 (5.0%)	7158 (2.6%)	9587 (6.9%)	10660 (3.9%)	4766 (4.5%)	5889 (2.8%)
Dizziness	19152 (13.8%)	22629 (8.2%)	22868 (16.5%)	31161 (11.3%)	11711 (10.9%)	18049 (8.4%)
Fatigue	6247 (4.5%)	7423 (2.7%)	8863 (6.4%)	13120 (4.7%)	4732 (4.4%)	8131 (3.8%)
Neurogenic bladder	1376 (1.0%)	1561 (0.6%)	1391 (1.0%)	1669 (0.6%)	658 (0.6%)	848 (0.4%)
Orthostasis	3405 (2.5%)	4665 (1.7%)	4848 (3.5%)	7168 (2.6%)	3130 (2.9%)	5083 (2.4%)

Sexual dysfunction	2248 (1.6%)	3774 (1.4%)	2943 (2.1%)	4891 (1.8%)	2246 (2.1%)	3717 (1.7%)
Risk factors and comorbidities						
Risk factors						
Alcohol abuse	2894 (2.1%)	4392 (1.6%)	3155 (2.3%)	4962 (1.8%)	2037 (1.9%)	3336 (1.6%)
Nicotine abuse	4627 (3.3%)	9917 (3.6%)	5303 (3.8%)	11407 (4.1%)	3471 (3.2%)	7635 (3.6%)
Traumatic brain injury	335 (0.2%)	328 (0.1%)	479 (0.3%)	665 (0.2%)	301 (0.3%)	429 (0.2%)
Metabolic diseases and vascular risk factors						
Diabetes mellitus type 1	2140 (1.5%)	3194 (1.2%)	2885 (2.1%)	4357 (1.6%)	1932 (1.8%)	2977 (1.4%)
Diabetes mellitus type 2	40165 (29.0%)	68098 (24.6%)	40485 (29.3%)	69045 (25.0%)	26716 (25.0%)	45503 (21.3%)
Hypercholesterinemia	59463 (43.0%)	112979 (40.8%)	65653 (47.5%)	125478 (45.3%)	47966 (44.8%)	92783 (43.4%)
Hypertension	93814 (67.8%)	174135 (62.9%)	97145 (70.2%)	182316 (65.9%)	69182 (64.7%)	130454 (61.0%)
Infectious diseases						
Cytomegaloviral disease	32 (0.0%)	60 (0.0%)	53 (0.0%)	96 (0.0%)	39 (0.0%)	93 (0.0%)
Infectious mononucleosis	58 (0.0%)	65 (0.0%)	83 (0.1%)	114 (0.0%)	59 (0.1%)	77 (0.0%)
Gastrointestinal disorders						
Duodenal ulcer	874 (0.6%)	1555 (0.6%)	1136 (0.8%)	2018 (0.7%)	851 (0.8%)	1449 (0.7%)
Gastric ulcer	1372 (1.0%)	2132 (0.8%)	1821 (1.3%)	2932 (1.1%)	1219 (1.1%)	1966 (0.9%)
Gastritis	16013 (11.6%)	24934 (9.0%)	21948 (15.9%)	35694 (12.9%)	15725 (14.7%)	26228 (12.3%)
Gastro-oesophageal reflux disease	20262 (14.6%)	32848 (11.9%)	23307 (16.8%)	38259 (13.8%)	16145 (15.1%)	26796 (12.5%)
Gastrojejunal ulcer	79 (0.1%)	120 (0.0%)	100 (0.1%)	152 (0.1%)	61 (0.1%)	111 (0.1%)
Peptic ulcer	137 (0.1%)	191 (0.1%)	181 (0.1%)	268 (0.1%)	123 (0.1%)	205 (0.1%)
Crohn's disease	500 (0.4%)	764 (0.3%)	526 (0.4%)	879 (0.3%)	370 (0.4%)	646 (0.3%)
Ulcerative colitis	856 (0.6%)	1363 (0.5%)	971 (0.7%)	1590 (0.6%)	646 (0.6%)	1119 (0.5%)
Other comorbidities						
Osteoarthritis	41339 (29.9%)	72653 (26.3%)	46213 (33.4%)	82422 (29.8%)	30589 (28.6%)	56149 (26.2%)
Seropositive inflammatory arthritis	674 (0.5%)	1114 (0.4%)	736 (0.5%)	1279 (0.5%)	443 (0.4%)	806 (0.4%)
Other inflammatory arthritis	4171 (3.0%)	7023 (2.5%)	4690 (3.4%)	7901 (2.9%)	3088 (2.9%)	5372 (2.5%)
Bipolar disorder	862 (0.6%)	423 (0.2%)	912 (0.7%)	464 (0.2%)	535 (0.5%)	282 (0.1%)
Schizophrenia	1678 (1.2%)	723 (0.3%)	1716 (1.2%)	808 (0.3%)	1055 (1.0%)	531 (0.2%)
Epilepsy	4138 (3.0%)	3452 (1.2%)	3849 (2.8%)	3549 (1.3%)	2151 (2.0%)	2148 (1.0%)
Migraine	3744 (2.7%)	6070 (2.2%)	4468 (3.2%)	7439 (2.7%)	3587 (3.4%)	6147 (2.9%)

eFigure. Prevalence of Additional Presentations Associated With PD by Year Before Diagnosis Compared With Controls





Supplementary Figure 1 Prevalence (%) with 95% CI error bars for each year before diagnosis of Parkinson's disease. Part A Hearing Loss, Part B Subjective visual impairment, Part C Non-specific pain, Part D Insomnia, Part E Anxiety, Part F Memory problems, Part G Fatigue, Part H Neurogenic bladder, Orthostasis, Part I Sexual dysfunction, Part J Stiffness of joints, Part K Dermatophytosis, Part L Psoriasis, Gastric ulcer, Part M Ulcerative colitis, Part N Duodenal Ulcer, Part O Osteoarthritis, Part P Other inflammatory arthritis, Part Q Seropositive inflammatory arthritis