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Supplementary Material

Prodromal markers in Parkinson's disease: Limitations in longitudinal studies and lessons learned

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Supplementary Table: Longitudinal Studies of Prodromal Markers in Parkinson's Disease Eligible for Inclusion in the Systematic Review.

Abbreviations: BL, Baseline; CI, Confidence interval; DLB, Dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; FU, Follow-up; HR, Hazard ratio; HC, Healthy control; MMSE, Mini-Mental State Examination; MSA, Multiple system atrophy; OR, Odds ratio; PD, Parkinson's disease; RBD, Rapid-eye-movement behavior disorder; RR, relative risk; ICD, The International Classification of Diseases; SD, standard deviation; SN+, Substantia Nigra hyperechogenicity; TCS, Transcranial sonography; UKBB, United Kingdom Parkinson's Disease Society Brain Bank; UPDRS, Unified Parkinson's Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test.

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Prospective; Clinical cohort	RBD	Video-polysomnography	BL = 174 RBD FU = 168 RBD 22 PD at FU	14 years of FU; Marker duration at BL: about 12 years conversion to PD after 7.5 years (median)				(Iranzo et al., 2014)
Prospective; Clinical cohort	RBD (Additional assessments of: hyposmia, deficits in color vision, quantitative motor tests, antidepressant use, Lifetime depression/ anxiety, personality or autonomic dysfunction)	Polysomnography, UPSIT, Farnsworth-Munsell 100-Hue color test, Timed up-and-go, Purdue pegboard, alternate tap test, UPDRS-III, Tridimensional Personality Questionnaire (TPQ), Autonomic: orthostatic, urinary, erectile, bowel symptoms from the MSA rating scale	BL = 95 RBD FU = 89 RBD (of which 41 developed synucleinopathy: 20 with parkinsonism, 17 PD, 3 MSA; and 21 with dementia (of which 18 had ≥1 cardinal parkinsonism manifestation, 11 met full UKBB criteria for parkinsonism, 3 with abnormal quantitative motor testing, suggesting DLB.	10 years of FU; Marker duration at BL: 9.2 years (mean), Conversion to parkinsonism/ dementia after 3.8 years (mean)	Color vision: HR = 3.1 (1.5–6.3), Olfaction: (MSA excluded): HR = 2.8 (1.3–6.0), Motor testing (2/4 measures): HR = 3.9 (1.9–8.0), Antidepressant use: HR = 0.29 (0.12–0.68) Lifetime depression/anxiety: non-significant TPQ domains: non-significant, Abnormal autonomic (2/4 measures), %: non-significant	(Associations may not be fully PD-specific as patients in part had other synucleinopathies)		(Postuma et al., 2015)
Prospective; Clinical cohort	RBD	Polysomnography	BL = 29 RBD FU = 26 RBD of which 13 developed PD	16 years of FU; From RBD onset to RBD onset to parkinsonism/dementia onset: 14.2 years (mean)		Small sample size; only males; statistical analyses not accounting for (potential) age differences between PD converters and non-converters.		(Schenck et al. 1996)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Prospective; Population-based	Excessive daytime sleepiness	Excessive daytime sleepiness questionnaire	BL = 3,078 HC (after excluding 61 with PD, 215 with dementia and 378 with missing EDS data) FU = 3,078 of which 43 developed PD	Age-adjusted incidence per 10,000 person-years: with EDS: 55.3 (PD diagnosis 7 months and 4.9 years into FU) without EDS: 17.0 (PD diagnosis 2 months to 7.3 years into FU)	OR = 2.8 (1.1-6.4) OR = 3.3 (1.1-6.4) adjusted for sleep-related features	Only males; marker uncertainty (questionnaire/self-report)	HAAS	(Abbott et al., 2005)
Prospective; Population-based	Daytime napping	Self-report	BL / FU = 214,655 (of which 770 PD at FU)	3-4 years of FU (in prediagnostic PD group) Typical sleeping habit over last 12 months.	For ≥1h daytime napping (and ≥7h nighttime sleep): OR = 1.5 (1.2-1.9)	Marker uncertainty (self-report); temporal uncertainty	NIH-AARP Diet and Health Study	(Gao et al., 2011b)
Prospective; Clinical cohort	Hyposmia	Sniffin' Sticks	BL = 30 hyposmics FU = 24 hyposmics (of which 1 PD at FU)	4 years of FU; unknown marker duration of time until conversion		Diagnosis uncertainty (Inclusion of borderline UPDRS-III at BL); small sample size; temporal uncertainty; statistical analyses not accounting for (potential) age differences between PD converters and non-converters.		(Haehner et al., 2007)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Prospective; Clinical cohort	Hyposmia	Sniffin' Sticks	Total BL = 361 Total FU = 354 With clinical examination at FU: BL = 78 with 40 hyposmics, 38 normosmics FU = 74; 5 of 40 hyposmics developed clinical PD, 0 of normosmics	5 years of FU; Motor symptom onset: 15 months (median) after BL				(Ponsen et al., 2010)
Prospective; Population-based	Hyposmia	Brief Smell Identification Test (B-SIT)	BL = 2,267 FU1 = 2,267 FU2 = 1,846 with 35 incident PD at FU1/2	24.6/10,000 person-years; Up to 8 years of FU; Time to diagnosis after BL: 4.0 years (mean)	OR = 5.2 (1.5-25.6); 1. Quartile 4-y-FU	Only males; questionnaire based PD diagnosis	HAAS	(Ross et al., 2008)
Prospective; Population-based	Constipation	Bowel frequency interview	BL = 127,668 BL: ≤1 bowel movements/3d n = 8,016 FU = 558 incident PD cases	HPFS: 6 years of FU; NHS: 24 years of FU	Pooled OR = 3.93 (2.26-6.84) ≤1 bowel movements/3d	PD diagnosed based on medical records; marker uncertainty (self-report, interview); temporal uncertainty	HPFS, NHS	(Gao et al., 2011a)
Prospective; Population-based	Constipation	Bowel frequency interview	BL = 6,860 FU = 6,790 with 96 incident PD at FU	24 years of FU; Time to diagnosis: 12 years (mean); Age-adjusted incidence 18.9/10,000 person-years (1 bowel movement/day); 3.8/10,000 person-years (2/day)	RR = 2.7 (1.3-5.5) < 1 bowel movements/d	Only males; marker uncertainty (self-report, interview)	HAAS	(Abbott et al., 2001)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Nested case-control; Population-based	Constipation	Medical records/medication	BL = 392 FU = 196 incident PD, 196 matched HC	Marker 0–19 years before diagnosis >20 years before diagnosis Enrollment in medical records-linkage system: 38 years (median)	OR = 1.77 (1.04-2.98) (not caused by medication) Marker 0–19 years before diagnosis: OR = 1.96 (1.05-3.65) >20 years before index year: OR = 2.49 (1.24-5.01)	PD diagnosis uncertainty		(Savica et al., 2009)
Prospective; Population-based	Cardiovascular function	Electrocardiogram, carotid ultrasound	BL = 5,828 FU = 5,828 with 154 incident PD at FU	10.4 years (mean) of FU	Electrocardiographic abnormalities: OR = 1.45 (1.02–2.07) carotid stenosis: OR = 2.40 (1.40–4.09)	PD diagnosis and date of PD onset uncertainty; temporal uncertainty	CHS	(Jain et al., 2012)
Nested case-control; Clinical cohort	Cardiovascular function	Cardiac stress testing (CST), electrocardiogram	BL = 54 HC; FU = 36 HC, 18 incident PD Matched HC	10 years of FU PD diagnosis 4.27 years (median) after BL				(Palma et al., 2013)
Nested case-control; Population-based cohort	Cardiovascular function	Cardiac stress testing (CST), electrocardiogram	BL = 60 HC; FU = 40 HC, 20 PD Matched HC	4.64 years (mean) between BL and first motor symptom onset; 1 year between BL and FU (PD diagnosis)	No significant associations			(Yahalom et al., 2014)
Prospective; Population-based	Cognition, rate of cognitive decline	37-MMSE	BL = 2,450 FU= 2,450 with incident 21 PD at FU	3.3 years (median) between BL and FU	No significant associations (after accounting for age and other confounders)	PD diagnosis uncertainty; temporal uncertainty	NEDICES	(Sanchez-Ferro et al., 2013)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Prospective; Population-based	Pain	National Health and Nutrition examination Survey (NHANES)	BL = 33,388 FU = 33,388 with 32 incident PD at FU	3 years (median) between BL and FU; incidence rate of PD per 100,000 person-years: 16 (without pain); 40 (mild pain); 109 (mod./severe pain)	Moderate/severe pain: HR = 2.88 (1.05–7.86). Non-significant when using more stringent PD case definitions (n = 19 PD cases)	PD diagnosis uncertainty; marker uncertainty (questionnaire, self-report)	NHIS	(Lin et al., 2013)
Prospective; Population-based	Vital exhaustion, impaired sleep	Vital Exhaustion Scale	BL = 9,955 FU = 9,955 108 incident PD at FU	14 years (mean) of FU; with No-, 5-year, and 10-year time-lag from pre-motor symptoms	High vs. low vital exhaustion: No-time-lag: HR = 2.50 (1.28-4.89), impaired sleep: HR = 1.49 (0.87-2.56); 5-year time-lag: HR = 1.54 (0.63–3.75) 10-year time-lag: non-significant	PD diagnosis/ date of PD onset unknown at hospitalization	CCHS	(Clark et al., 2013)
Prospective; Population-based	Anxiety	Crown-Crisp phobic anxiety index	BL = 35,815 FU = 35,815 with 189 incident PD at FU	12 years of FU; Person-years of PD incidence for anxiety index 0/1, 2, 3, 4+: 156,520; 62,336; 43,508; 67,136	RR = 1.5 (1.0-2.1)	Only males; PD diagnosis uncertainty; marker uncertainty (questionnaire, self-report)	HPFS	(Weisskopf et al., 2003)
Retrospective; Population-based	Anxiety disorder	ICD (9th revision; Clinical Modification) codes 300, 309.24 and 293.84) or use of anxiolytics (Anatomical Therapeutic Chemical (*ATC*) Classification System code: N05B)	BL = 174,776 FU = 174,776 with 2258 incident PD at FU	5.5 years (mean) of FU; Crude incidence rate of PD per 1 million person-days: No: 5.18 Mild: 6.60 Moderate: 7.08 Severe anxiety: 12.33	Anxiety: Adjusted HR = 1.38 (1.26-1.51)	Retrospective study design; PD diagnosis uncertainty; marker uncertainty (questionnaire, self-report)	Taiwan NHRID system	(Lin et al. 2015)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Prospective; Population-based	Anxiety, pessimistic/depressive personality trait	Minnesota multiphasic personality inventory	BL = 6,822 FU = 5,816 with 156 incident PD at FU	29.2 years (median) of FU; Anxiety 1-3 quartile: 138100 person-years; Anxiety 4th quartile: 43097 person-years	Anxious: HR = 1.63 (95% CI = 1.16-2.27) Pessimistic in men: HR = 1.92 (95% CI = 1.20-3.07) Neuroticism: HR = 1.54 (95% CI = 1.10-2.16)	PD diagnosis uncertainty (parkinsonism; medical records); marker uncertainty (questionnaire, self-report)		(Bower et al., 2010)
Prospective; Clinical cohort	Depression (Major depressive disorder; MDD) (Additional assessment of TCS SN status, cognition, olfaction etc.)	DSM-IV criteria	BL = 57 FU = 46 with 3 incident PD at FU	10 years (median) of FU; Mean ± SD duration of MDD at FU: No PD: 3.9 ± 5.4 PD: 16.0 ± 5.3 years		Diagnosis uncertainty (18% of individuals at BL with UPDRS-III scores >9; but without definite PD diagnosis based on UKBB criteria); statistical analyses not accounting for age differences between PD converters and non-converters.		(Walter et al., 2015)
Nested case-control; Population-based	Depression	ICD-9/10 codes	BL = 562,406 FU = 562,406 with 421,718 matched HC and 140,688 incident PD at FU	6.8 years (median) of FU; Depression HR for PD continuously indicated for 3 months to 25 years after BL.	Within the first year of depression: OR: 3.2 (2.5–4.1); After 15 to 25 years: OR = 1.5 (1.1–2.0)	PD diagnosis uncertainty; marker uncertainty (ICD codes)	NPR Sweden	(Gustafsson et al., 2015)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Nested case-control; Population-based	Depression	Self-reported diagnosis	BL = 280,950 FU = 280,950 with 992 PD incident PD at FU	Depression diagnosed in 5 year intervals (1985-2000), with PD diagnosed after the year 2000.	Depression diagnosed after 2000 OR = 2.0 (1.6-2.4); in 1995–1999: OR = 2.7, 2.0-3.6); in 1985–1994: OR = 1.6 (1.1-2.3); <1985: OR = 1.7 (1.3-2.3).	PD diagnosis uncertainty (self-reported, medical records); marker uncertainty (self-report)	NIH-AARP Diet and Health Study	(Fang et al., 2010)
Retrospective; Population-based	Depression	Medical records/insurance database	BL = 23,180 (4,636 with depression) FU = 23,280 with 163 PD incident PD at FU (match. HC)	10-year FU	HR = 3.24 (2.36-4.44)	Retrospective study design; temporal uncertainty	LHID 2005	(Shen et al., 2013)
Nested case-control; Population-based	Depression	General practice registry	BL = 32,415 FU = 32,415 with 338 incident PD at FU	Medical records from: 1985 to 2000 First depressive episode to PD diagnosis: 10.1 years (mean)	OR = 2.4 (2.1-2.7)	PD diagnosis uncertainty; marker uncertainty (general practice medical records)		(Leentjens et al., 2003)
Case-control; Population-based	Depression, anxiety	Self-reported medical information	BL = 773 FU = 773 with 371 incident PD at FU (sibling controls not included)	Depression/anxiety/medication 2, 5, 10, and 20 years before PD diagnosis	Lifetime depression/anxiety: OR = 1.42 (1.01-2.00); e.g. 5-y-OR = 2.21 (1.21-4.04) in PD males; non-significant for females	Case-control study design; PD diagnosis uncertainty; marker uncertainty (self-report)	UCLA PEG	(Jacob et al., 2010)
Prospective; Population-based	Depression, anxiety	DSM-IV & Health and Life Experiences Questionnaire (HLEQ)	BL = 20,855 FU = 20,855 (with 175 suspected PD; 43 with neurological records)	7.9 years of FU 160,725 person-years	Depression: HR = 2.01 (0.95-4.22); Anxiety: HR = 2.52 (0.78-8.20);MHI-5: HR = 1.28 (0.97-1.68) Neuroticism: HR = 1.33 (0.98-1.79) Extroversion: HR = 1.09 (0.80-1.48)	PD diagnosis uncertainty; marker uncertainty (questionnaire, self-report); temporal uncertainty	EPIC-Norfolk	(Ishihara-Paul et al., 2008)

Study design and sample recruitment	Marker	Assessment	Sample size, number of PD converters, time to conversion	Temporal information e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	Associations of prodromal markers for the conversion of healthy to PD	Limitations	Study acronym	Reference
Prospective; Population-based	Erectile dysfunction	Retrospective questionnaire	BL = 32,616 FU = 32,616 with 200 incident PD	16 years of FU	RR = 3.8 (95% CI = 2.4-6.0)	PD diagnosis uncertainty; marker uncertainty (questionnaire, self-report with possible recall bias); only males; temporal uncertainty	HPFS	(Gao et al., 2007)
Prospective; Population-based	SN+	TCS	BL = 1,847 FU1 = 1,535 FU2 = 1,271 with 21 incident PD at FU2 PRIPS: Drop-out of participants was investigated: higher age, more frequent positive PD history in FU2; sex, SN+ status, no differences compared to FU1	3 and 5 years of FU, respectively.	RR = 20.6 (5.6-98.8)	Temporal uncertainty; analyses not accounting for age differences between PD converters and non-converters.	PRIPS	(Berg et al., 2013a)
Prospective; Population-based	SN+, mild parkinsonian signs, hyposmia, constipation, depression, PD family history	TCS, UPDRS, Sniffin' Sticks, Interview	BL = 1,847 FU1 = 1,535 FU2 = 1,276 with 21 incident PD at FU2	3 and 5 years of FU, respectively.		Marker uncertainty (e.g. constipation self-report), temporal uncertainty (marker duration; time to diagnosis); analyses not accounting for age differences between PD converters and non-converters.	PRIPS	(Lerche et al., 2014)
Prospective; Population-based	Subtle motor impairment, SN+, hyposmia, constipation, depression, PD family history	TCS, 12 Sniffin' Sticks, UDPRS-III	BL = 1,847 FU = 1,535 with 11 incident PD at FU	3 years of FU	Male: RR = 1.8 (0.4-8.5) SN+: RR = 16.8 (3.4-114.9) hyposmia: RR = 6.5 (1.5-31.3) SMI: RR = 4.8 (1.2-20.4) age > 60 y: RR = 3.3 (0.8-16.2) positive family history: RR = 5.4 (1.3-21.4)	Temporal uncertainty; analyses not accounting for age differences between PD converters and non-converters.	PRIPS	(Berg et al., 2013b)

Study design and sample recruitment	Marker	Assessment	Sample size, number of PD converters, time to conversion	Temporal information e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	Associations of prodromal markers for the conversion of healthy to PD	Limitations	Study acronym	Reference
Nested case-control; Population-based	Tremor, balance impairments, constipation, hypotension, erectile dysfunction, urinary dysfunction, dizziness, fatigue, depression, anxiety	Primary care database	BL (e.g. set 5 years before diagnosis) = 30,313 FU: 25,544 matched HC and 4769 incident PD	Marker association calculations for markers 5 and 10 years, respectively before PD diagnosis	5 years before diagnosis: Tremor: RR = 13.70 (7.82–24.31), Balance impairments: RR = 2.19 (1.09–4.16), Constipation: RR = 2.24 (2.04–2.46), Hypotension: RR = 3.23 (1.85–5.52), Erectile dysfunction: RR = 1.30 (1.11–1.51), Urinary dysfunction: RR = 1.96 (1.34–2.80), Dizziness: RR = 1.99, 1·67–2·37), Fatigue: RR = 1.56 (1.27–1.91), Depression: RR = 1.76 (1.41–2.17), Anxiety: RR = 1.41 (1.09–1.79) 10 years before diagnosis: Tremor: RR = 7.59 (1.11–44.83) Constipation RR = 2.01 (1.62–2.49)	PD diagnosis uncertainty; marker uncertainty (primary care medical records)	THIN	(Schrag et al., 2015)
Nested case-control; Population-based	Somatic symptoms, autonomic dysfunction, sleep, depression, dementia, hyposmia	Health care registry	BL= 164 FU = 164 with 86 incident PD at FU (matched HC)	Within 2-years prior to PD diagnosis	Somatic symptoms: OR = 2.45 Constipation: OR = 3.32 Sleep disorders: OR = 6.98	Temporal uncertainty		(Plouvier et al., 2014)
Case-control; Population based	Self-perceived non-motor and early motor signs	Telephone interview	FU = 186 with 93 PD patients (matched HC)	Recalled onset of first prodromal symptoms: 10.2 years (mean); Mean age of onset for each non-motor and motor sign indicated for controls and PD patients.		Case-control study design; marker uncertainty (self-report with possible recall bias)		(Gaenslen et al., 2011)

Study design and sample recruitment	**Marker**	**Assessment**	**Sample size, number of PD converters, time to conversion**	**Temporal information** e.g. Marker duration at baseline, time to conversion after baseline, incidence per person-years	**Associations of prodromal markers for the conversion of healthy to PD**	**Limitations**	**Study acronym**	**Reference**
Case-control; Population based	Various medical symptoms	Hospital/GP records	BL/FU = 60 PD 58 HC	10-years before PD diagnosis; symptom occurrence 10, 6, 4, 3, 2, 1 years before PD		Case-control study design; PD diagnosis uncertainty; marker uncertainty (medical records); small sample size		(Gonera et al., 1997)

Supplementary information: PubMed and MEDLINE search queries

PubMed search strategy (November 2014):

"prodromal" AND "Parkinson's disease" AND "longitudinal"

(Articles written in English)

MEDLINE literature search strategy:

Database: Ovid MEDLINE(R) <1946 to October Week 1 2015>

1 exp Parkinsonian Disorders/ (63479)

2 parkinson*.ti,ab. (77611)

3 1 or 2 (87578)

4 (prediagnostic or prodromal or preclinical or premotor or pre-diagnostic or pre-motor or pre-clinical).ti,ab. (72269)

5 prodromal symptoms/ (551)

6 4 or 5 (72500)

7 3 and 6 (1696)

8 letter/ (923340)

9 editorial/ (375420)

10 news/ (167927)

11 exp historical article/ (345399)

12 Anecdotes as topic/ (4708)

13 comment/ (625819)

14 case report/ (1783962)

15 (letter or comment$).ti. (99622)

16 animals/ not humans/ (4033465)

17 exp Animals, Laboratory/ (766165)

18 exp Animal Experimentation/ (6959)

19 exp Models, Animal/ (454710)

20 exp rodentia/ (2813218)

21 (rat or rats or mouse or mice).ti. (1125197)

22 or/8-21 (8191919)

23 7 not 22 (1220)

24 limit 23 to English language (1144)

The number in brackets indicate the number of hits, i.e. in total 1144 hits for this search query.