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ORIGINAL COMMUNICATION

Subjects at risk of Parkinson's disease in health checkup examinees: cross-sectional analysis of baseline data of the NaT-PROBE study

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Abstract

Introduction The present study aimed to survey the prevalence of prodromal symptoms of Parkinson's disease (PD) in Japanese health checkup examinees, for identifying at-risk subjects.

Methods We conducted a questionnaire survey of annual health checkup examinees without neurological symptoms using the following self-reported questionnaires: Japanese version of the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT); Self-administered Odor Question (SAOQ); REM Sleep Behavior Disorder Screening Scale (RBDSQ); Beck Depression Inventory-Second Edition (BDI-II); Epworth Sleepiness Scale (ESS); and Physical Activity Scale for the Elderly (PASE). The presence of prodromal symptoms was determined using the 90th percentile threshold of each questionnaire. Subjects ≥ 50 years of age with ≥ 2 core prodromal symptoms (dysautonomia, hyposmia, and RBD), were classified as at risk.

Results Between March 2017 and March 2018, 4,953 participants sufficiently answered the questionnaires. Among 2,726 subjects ≥ 50 years of age, 155 were classified as at risk. These subjects had worse values of BDI-II (12.0 ± 8.3 vs. 4.4 ± 3.8, $p < 0.001$) and ESS (9.6 ± 5.0 vs. 6.3 ± 3.2, $p < 0.001$), in addition to SCOPA-AUT, SAOQ, and RBDSQ. Male at-risk subjects showed lower values of hemoglobin (14.8 ± 1.3 vs. 15.0 ± 1.1, $p = 0.032$) and low density lipoprotein cholesterol (114.5 ± 30.3 vs. 123.0 ± 28.9, $p = 0.004$) than the examinees reporting no prodromal symptoms.

Conclusion Approximately 6% of the population aged 50 years or older was at risk for PD. Male at-risk subjects had mild hematological and metabolic changes relevant to PD.

Keywords Dementia with Lewy bodies · Risk factors in epidemiology · All movement disorders · Parkinson's disease/parkinsonism

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. In the prodromal phase of PD, various non-motor symptoms, including constipation, hyposmia, REM sleep behavior disorder (RBD), depression, and excessive daytime sleepiness precede the onset of motor deficits by up to 20 years [1, 2]. Because > 50–60% of neurons in the substantia nigra are already lost at the clinical diagnosis of PD [3], earlier detection of individuals at greater risk of developing PD is important.

Various strategies have been initiated in Western countries to identify individuals in the prodromal phase [4–8]. Most have recruited elderly subjects with prodromal features, gene mutations, or a relevant family history. Many risk factors and prodromal markers have been reported [9], but autonomic dysfunction other than constipation has not been comprehensively assessed. Furthermore, most previous studies recruited subjects with specific prodromal symptoms and may not have included the whole spectrum of PD. The Honolulu-Asia Aging Study showed that the risk of developing PD was up to ten times greater in people with ≥ 2 prodromal features than in those without prodromal features

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[10]. In addition, 90.3% of patients with PD had prodromal non-motor symptoms before the clinical diagnosis of PD, and the median number of prodromal symptoms was four in such subjects [11]. Thus, the combination of prodromal markers is important for improving predictive diagnostics.

To identify at-risk subjects for a wide spectrum of PD, we assessed multiple prodromal features using questionnaires in a large Japanese health checkup cohort, and analyzed the epidemiological, anthropometric, and biological characteristics of at-risk individuals.

Methods

Participants

Nagoya-Takayama preclinical/prodromal Lewy body disease study (NaT-PROBE study) is a prospective, longitudinal, multi-center, community-based cohort study coordinated by Nagoya University School of Medicine. From March 2017, we have been conducting a survey of prodromal symptoms in healthy individuals who visited Kumiai Kosei Hospital or Daido Clinic, Japan, for their annual health checkup. The present study shows the cross-sectional analysis of baseline data of the NaT-PROBE study. In Japan, regular medical checkups, which are obligatory for employees, are performed annually according to the Industrial Safety and Health Law. We used health checkup cohorts in Kumiai Kosei Hospital and Daido Clinic to screen for prodromal symptoms in the Japanese community-based population. From March 2017 to March 2018, we sent questionnaires on prodromal symptoms to a total of 12,378 health checkup examinees at the two facilities who were older than 18 years of age. We excluded participants who did not answer the questionnaire completely. Moreover, participants with history of stroke or any neurological disorders, including PD and dementia, were excluded from this study. All participants underwent an anthropometric examination and routine blood test as a part of their health checkup. We analyzed these data together and demographic data.

As a reference, we also evaluated patients with PD or dementia with Lewy bodies (DLB). We enrolled 30 patients with PD who fulfilled the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria [12] and 4 patients with DLB who fulfilled the diagnostic criteria of the third report of the DLB consortium [13]. Patients with history of other neurological disorders were excluded from this study.

Prodromal symptoms

We used the Physical Activity Scale for the Elderly (PASE) [14] to evaluate the amount of physical activity, the Japanese version of the Autonomic Scale for Outcomes in Parkinson's Disease (SCOPA-AUT) [15] to evaluate autonomic dysfunction, the Self-administered Odor Question (SAOQ) [16] to evaluate olfactory dysfunction, the RBD Screening Scale (RBDSQ) [17] to evaluate REM sleep behavior disorder, the Beck Depression Inventory Second Edition (BDI-II) [18] to evaluate depressive symptom, and the Epworth Sleepiness Scale (ESS) [19] to evaluate excessive daytime sleepiness. All scales used in this study were validated for self-administration in Japanese population.

Identification of subjects at risk

To identify subjects at risk for PD, we set the cutoff points of each prodromal score at the 90th percentile value, based on the results of previous studies. For example, the Parkinson's Associated Risk Study (PARS) identified subjects with hyposmia in 13.4% of the general population of ≥ 50 years of age, and the prevalence of constipation and RBD was 23.0% and 43.0%, respectively, in these hyposmic subjects [4]. In addition, the overall prevalence of olfactory impairment in the general population is reported to be 3.8%, but rises to 7.5% at 55–64 years of age, and 13.9% at ≥ 65 years of age [20]. In a previous population-based study in Europe, the prevalence of probable RBD, as assessed by the RBDSQ and RBD-Inventory (RBDI) was 6–9% at ≥ 60 years of age [21]. Taken together, the 90 percentile cutoff values appeared to be appropriate for identifying at-risk subjects using the questionnaires. As such, we classified subjects who were ≥ 50 years of age and who had ≥ 2 abnormal scores in the SCOPA-AUT, SAOQ, and RBDSQ into the at-risk group. We selected these three prodromes, dysautonomia, hyposmia, and RBD, for identifying at-risk subjects, as they are cardinal prodromal symptoms of PD [9, 22]. Subjects who were ≥ 50 years of age who had no prodromal symptoms were classified into the normal group. As sub-analyses, we also used 85th and 95th percentile cutoff values for identifying at-risk groups.

Calculation of the total likelihood ratio for prodromal PD

We calculated the total likelihood ratio (LR) for prodromal PD using the MDS Research Criteria for Prodromal Parkinson's disease issued by Movement Disorder Society in 2015 [22]. The present study only included questionnaires and the results of a medical checkup; thus, we only evaluated limited items of the criteria, including: sex, regular pesticide exposure, occupational solvent exposure, caffeine intake, smoking, familial history of PD, RBD screening by questionnaire, constipation, excessive daytime somnolence, symptomatic hypotension, severe erectile dysfunction, urinary dysfunction, and depression. We defined positive test results as

follows: RBD, RBDSQ ≥ 5; constipation, bowel movements < 3/week; excessive daytime somnolence, ESS ≥ 11; symptomatic hypotension, SCOPA-AUT cardiovascular score ≥ 2; severe erectile dysfunction, SCOPA-AUT erection problem score = 3; urinary dysfunction, SCOPA-AUT urinary score ≥ 5; and depression, BDI-II ≥ 14. We multiplied each item's LR and calculated the total LR for prodromal PD. We used a cutoff score of ≥ 5 for RBDSQ, because a previous study demonstrated that this value showed 88.5% sensitivity and 96.9% specificity in the Japanese population [17]. Regarding the ESS and BDI-II, we used cutoff values of ≥ 11 and ≥ 14, respectively, which were reported to indicate mild sleepiness and mild depression in previous studies [18, 19]. For the SCOPA-AUT cardiovascular and urinary scores, we applied the 90th percentile cutoff values obtained in the present study, because no study has accessed such items in healthy individuals.

Statistics

All data represent the mean ± standard deviation unless otherwise stated. The demographic and clinical scores of the male and female groups were compared using Student's *t* tests or Mann–Whitney *U* tests when appropriate. Fisher's exact test was used to analyze categorical variables between groups, and Bonferroni correction was used to calculate adjusted *p* values for multiple comparisons. For the comparisons among the at-risk, normal, and PD/DLB groups, a parametric one-way ANOVA followed by Tukey's tests or nonparametric Kruskal–Wallis tests followed by Steel–Dwass tests were performed. Spearman's rank correlation was used to determine the relationship between age and the prodromal scores and the relationships between each prodromal score. *P* values of < 0.05 were considered to indicate statistical significance. Correlation coefficients (*r*) were interpreted as follows: > 0.8, very strong; 0.5–0.8, moderately strong; and 0.3–0.5, weak. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Data availability

All data generated in this experiment are summarized in this report. Anonymized individual data will be provided to qualified investigators upon request to the corresponding author.

Results

Participant characteristics

A total of 4,953 of 12,378 (40.0%) participants completed all the questionnaires (Fig. 1). The mean age of the male participants was 2.2 years older than that of the female participants (Table 1). The male participants showed significantly higher rates of smoking, alcohol consumption, and pesticide and organic solvent exposure than the female participants. Among the female participants, the rates of milk and dairy product intake were significantly higher and the frequency of bowel movements was significantly lower in comparison to male participants. The prevalence rates of major health problems such as hypertension, diabetes, hyperlipidemia, hyperuricemia, and depression of the participants were less than those in the survey on lifestyle diseases conducted by the Ministry of Health, Labor and Welfare, Japan [24], or a large-scale epidemiological survey in Japan [25] (Supplemental Table 3).

Prodromal symptom scores

Most scores showed sex differences (Table 2). The PASE scores of the female participants were significantly higher than those of the male participants. The SAOQ and RBDSQ scores of the male participants were significantly worse than those of the female participants. The SCOPA-AUT, BDI-II, and ESS values of the female participants were significantly worse than those of the male participants. Regarding the subscores of SCOPA-AUT, the urinary score of the male participants was worse than that of the female participants, and the gastrointestinal, cardiovascular, and pupillomotor dysfunction scores of the female participants were worse than those of the male participants. None of the scores were correlated with age (Supplemental Fig. 1).

Identification of at-risk group

As all scores showed a non-normal distribution (Fig. 2a–f), we set the cutoff point of each score for identifying the at-risk group at the 90th percentile value. The cutoff value was 10 for SCOPA-AUT, 90.0% for SAOQ, 5 for RBDSQ, 16 for BDI-II, 14 for ESS, and 247 for PASE. Among 2,726 subjects who were ≥ 50 years of age, 155 subjects (5.7%) had ≥ 2 prodromal symptoms, and were classified into the at-risk group (Fig. 2g). On the other hand, among 1653 (60.6%) subjects who were ≥ 50 years of age, all scores were within the 90th percentile, and the subjects were therefore classified into the normal group. The number of subjects in the at-risk group increased to 270 (9.9%) using the 85th percentile

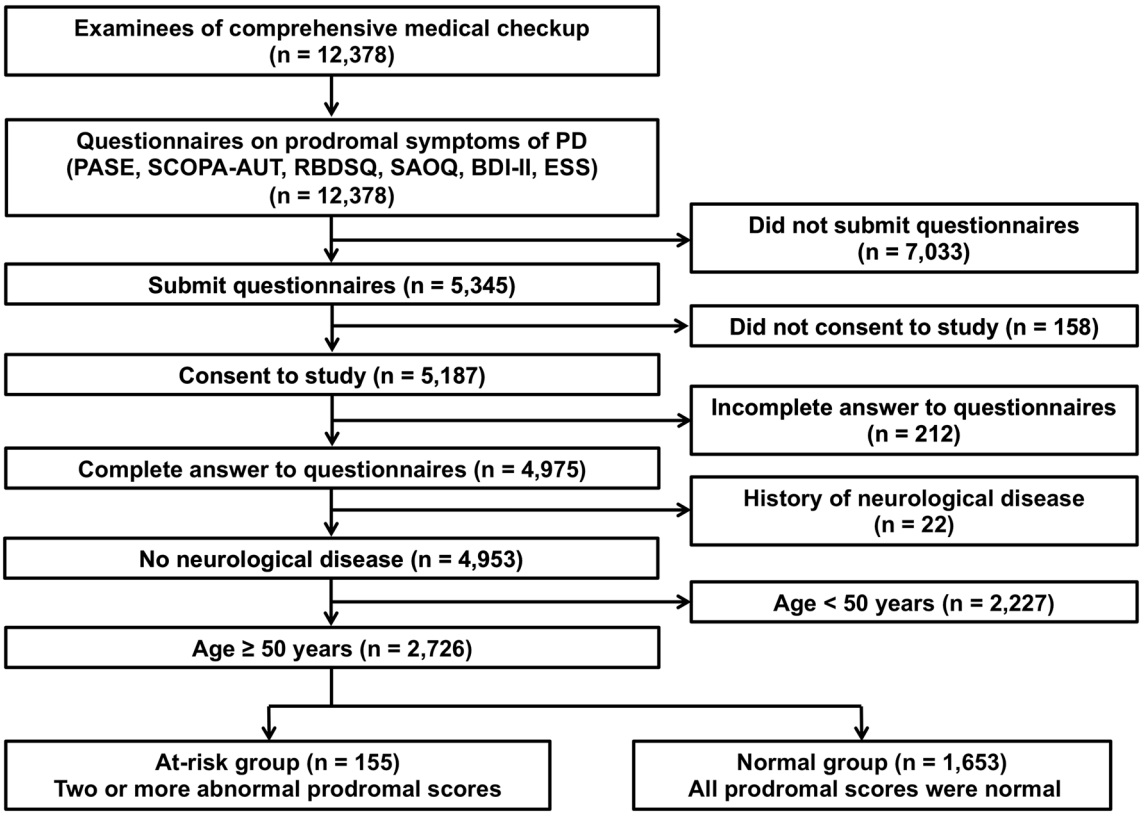


Fig. 1 Participant flowchart of this study. *PASE* Physical Activity Scale for the Elderly, *SCOPA-AUT* the Japanese version of the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms, *SAOQ* Self-administered Odor Question, *RBDSQ* RBD screening scale, *BDI-II* Beck Depression Inventory-Second Edition, *ESS* Epworth Sleepiness Scale

Table 1 Background of the participants

	Total	Male	Female	*p* value[a]
Number	4953	2641	2312	
Age, years	51.1 ± 10.4	52.2 ± 10.6	50.0 ± 10.1	< 0.001[b]
Family history, *n* (%)	212 (4.3)	95 (3.6)	117 (5.1)	0.011[c]
Smoker, *n* (%)	943 (19.0)	764 (28.9)	179 (7.7)	< 0.001[c]
Ex-smoker, *n* (%)	1186 (23.9)	969 (36.7)	217 (9.4)	< 0.001[c]
Never smoker, *n* (%)	2791 (56.3)	891 (33.7)	1900 (82.2)	< 0.001[c]
Alcohol, *n* (%)	2092 (42.2)	1400 (53.0)	692 (29.9)	< 0.001[c]
Caffeine, mg/day	224.5 ± 145.5	225.5 ± 152.4	223.3 ± 137.2	0.599[b]
Milk, *n* (%)	1942 (39.2)	896 (33.9)	1046 (45.2)	< 0.001[c]
Dairy products, *n* (%)	2783 (56.2)	1162 (44.0)	1621 (70.1)	< 0.001[c]
Pesticides, *n* (%)	310 (6.3)	259 (9.8)	51 (2.2)	< 0.001[c]
Organic solvent, *n* (%)	235 (4.7)	203 (7.7)	32 (1.4)	< 0.001[c]
Bowel movements, per week	6.6 ± 3.7	7.3 ± 4.2	5.8 ± 2.8	< 0.001[b]

Data represent the mean ± SD or value (%)

[a]Comparison between males and females

[b]*p* values were determined by Student's *t* test

[c]*p* values were determined by Fisher's exact test

cutoff values, and decreased to 46 (1.7%) using the 95th percentile cutoff values (Supplemental Fig. 3).

Background and prodromal symptoms of the at-risk group

Table 2 Scores of questionnaires on prodromal symptoms

	Total	Male	Female	*p* value[a]
Number	4953	2641	2312	
Age, years	51.1 ± 10.4	52.2 ± 10.6	50.0 ± 10.1	< 0.001[b]
PASE	133.3 ± 82.5	126.4 ± 87.4	141.1 ± 75.7	< 0.001[c]
SCOPA-AUT	5.0 ± 4.2	4.8 ± 4.2	5.2 ± 4.1	< 0.001[c]
Gastrointestinal	1.0 ± 1.4	0.8 ± 1.3	1.2 ± 1.5	< 0.001[c]
Urinary	2.1 ± 2.1	2.3 ± 2.3	1.9 ± 1.9	< 0.001[c]
Cardiovascular	0.4 ± 0.8	0.3 ± 0.7	0.5 ± 0.9	< 0.001[c]
Thermoregulatory	0.9 ± 1.4	0.9 ± 1.3	0.9 ± 1.4	0.128[c]
Pupillomotor	0.3 ± 0.6	0.2 ± 0.5	0.3 ± 0.6	< 0.001[c]
Sexual, male	N/A	0.5 ± 1.1	N/A	N/A
Sexual, female	N/A	N/A	1.0 ± 1.4	N/A
SAOQ, %	96.5 ± 10.6	95.2 ± 12.6	98.0 ± 7.4	< 0.001[c]
RBDSQ	2.1 ± 2.1	2.2 ± 2.2	2.0 ± 1.9	0.002[c]
BDI-II	7.0 ± 6.6	6.3 ± 6.5	7.8 ± 6.7	< 0.001[c]
ESS	8.0 ± 4.4	7.7 ± 4.4	8.2 ± 4.5	< 0.001[c]
LR (range)	1.43 ± 3.11 (0.13–67.54)	1.46 ± 3.24 (0.18–67.54)	1.39 ± 2.95 (0.13–60.36)	0.417[c]

Data represent the mean ± SD or value (%)

PASE Physical Activity Scale for the Elderly, *SCOPA-AUT* the Japanese version of the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms, *SAOQ* Self-administered Odor Question, *RBDSQ* RBD screening scale, *BDI-II* Beck Depression Inventory-Second Edition, *ESS* Epworth Sleepiness Scale, *LR* total likelihood ratio for prodromal Parkinson's disease, *N/A* not applicable

[a]Comparison between males and females

[b]*p* value was determined by Student's *t* test

[c]*p* values were determined by Fisher's exact test

The at-risk group had a higher rate of pesticide exposure in comparison to the normal group (Table 3). The scores of SCOPA-AUT, SAOQ, RBDSQ, BDI-II, ESS, and the total LR for prodromal PD of the at-risk group were significantly worse than those in the normal group (Table 4). In addition, the SCOPA-AUT and RBDSQ scores of the at-risk group were even higher than those in the PD/DLB patient group. All SCOPA-AUT subscores of the at-risk group were significantly worse in comparison to the normal group. The SCOPA-AUT urinary, thermoregulatory, and pupillomotor scores of the at-risk group were significantly worse than those of the PD/DLB patient group. Even with the 85th and 95th percentile cutoff values, the values of SCOPA-AUT, SAOQ, RBDSQ, BDI-II, ESS, and the total LR for prodromal PD of the at-risk group were significantly worse than those in the normal group (Supplemental Tables 1 and 2).

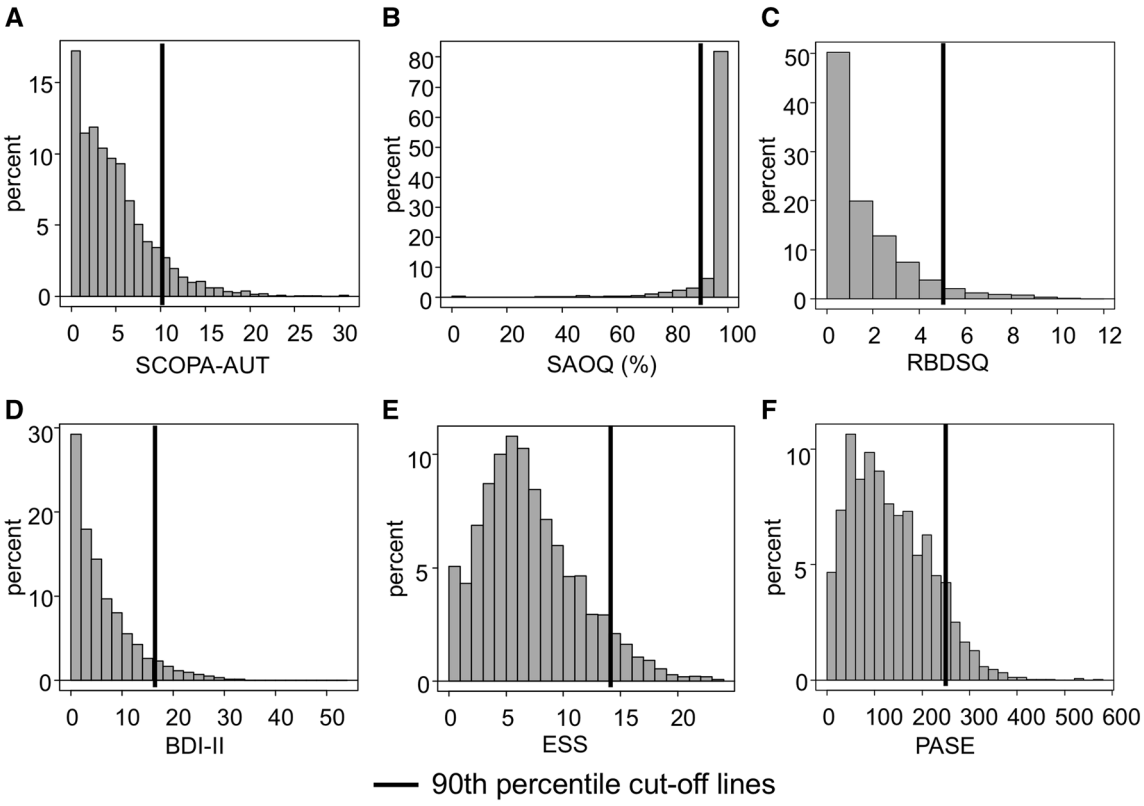
Anthropometric and blood test characteristics of at-risk subjects

The male subjects of the at-risk group showed significantly lower red blood cell (RBC) counts, hemoglobin, hematocrit, total cholesterol (T-Cho), and low density lipoprotein cholesterol (LDL-Cho) levels than the normal group (Table 5). However, the female subjects of the two groups had similar anthropometric results and blood test values. As for uric acid, which is a well-known protective factor for PD, there was no significant difference between the two groups regardless of gender.

Discussion

In the present study, we aimed to identify subjects at risk of developing PD from medical checkup examinees using questionnaires about prodromal symptoms. At-risk subjects accounted for ~ 6% of the Japanese population of ≥ 50 years of age.

Forty percent of the health checkup examinees completed the questionnaires, indicating that our research method showed acceptable generalizability to the general population. Furthermore, the survey was performed in a large community-based population without a selection bias, which further assured the generalizability of our approach. A questionnaire is a simple, non-invasive, and inexpensive method to screen the risk of PD in a large community-based population, and easily assessed by general practitioners. The present study assessed the wide range of prodromal symptoms from all participants who underwent the annual health checkup, to identify subjects at risk for the whole spectrum



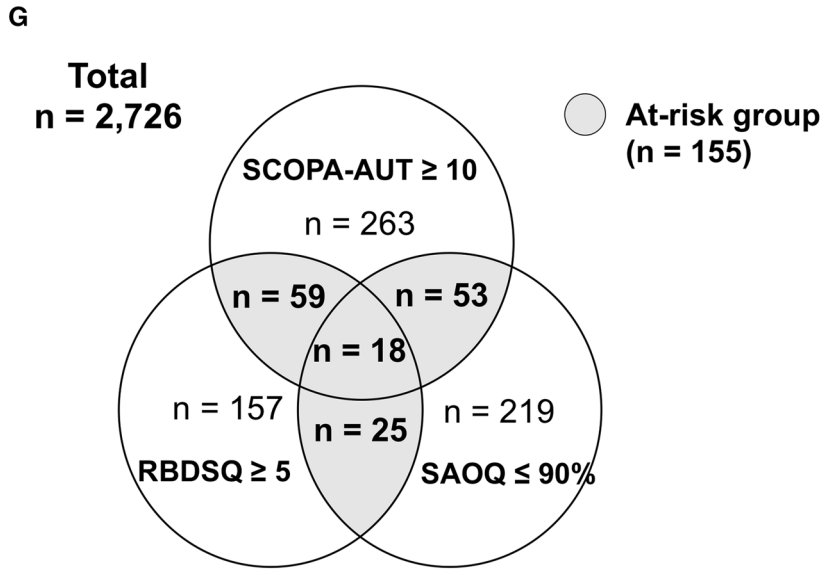


Fig. 2 Histogram and Venn diagram of questionnaires on prodromal symptoms (90th percentile cutoff). **a**–**f** Distribution of the SCOPA-AUT (**a**), SAOQ (**b**), RBDSQ (**c**), BDI-II (**d**), ESS (**e**), and PASE (**f**) values. The vertical lines show the 90th percentile cutoff values: 10 for SCOPA-AUT, 90.0% for SAOQ, 5 for RBDSQ, 16 for BDI-II, 14 for ESS, and 247 for PASE. g The frequency of dysautonomia, hyposmia, and RBD in subjects ≥ 50 years of age. A total of 155 subjects (5.7%) had ≥ 2 prodromal features and were classified into the at-risk group. *PASE* Physical Activity Scale for the Elderly, *SCOPA-AUT* the Japanese version of the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms, *SAOQ* Self-administered Odor Question, *RBDSQ* RBD screening scale, *BDI-II* Beck Depression Inventory-Second Edition, *ESS* Epworth Sleepiness Scale

Table 3 Background of the at-risk group

	Age ≥ 50, total	At-risk group (RG)	Normal group (NG)	PD/DLB patients (PD)	*p* values[a]		
					RG vs. NG	RG vs. PD	NG vs. PD
Number (M:F)	2726 (1531:1195)	155 (113:42)	1653 (900:753)	34 (18:16)			
Age, years	58.8 ± 6.2	61.4 ± 7.1	58.6 ± 6.0	68.9 ± 7.7	< 0.001	< 0.001	< 0.001
Family history, *n* (%)	122 (4.5)	2 (1.3)	84 (5.1)	3 (8.8)	0.087	0.122	0.763
Smoker, *n* (%)	472 (17.3)	27 (17.3)	284 (17.2)	1 (2.9)	1.000	0.097	0.063
Ex-smoker, *n* (%)	766 (28.1)	69 (44.2)	428 (25.9)	11 (32.4)	< 0.001	0.750	1.000
Never smoker, *n* (%)	1472 (54.0)	59 (37.8)	930 (56.3)	22 (64.7)	< 0.001	0.020	1.000
Alcohol, *n* (%)	1180 (43.3)	80 (51.3)	695 (42.0)	14 (41.2)	0.082	0.560	1.000
Caffeine, mg/day	235.8 ± 149.8	243.4 ± 202.3	236.9 ± 147.1	189.4 ± 122.5	0.866	0.129	0.149
Milk, *n* (%)	1121 (41.1)	66 (42.3)	660 (39.9)	13 (38.2)	1.000	1.000	1.000
Dairy products, *n* (%)	1553 (57.0)	82 (52.6)	948 (57.4)	24 (70.6)	0.810	0.160	0.320
Pesticides, *n* (%)	237 (8.7)	22 (14.1)	136 (8.2)	7 (20.6)	0.046	1.000	0.075
Organic solvent, *n* (%)	112 (4.1)	12 (7.7)	63 (3.8)	1 (2.9)	0.092	1.000	1.000
Bowel movements, per week	6.7 ± 3.7	7.3 ± 5.0	6.6 ± 3.2	4.4 ± 2.4	0.023	< 0.001	0.001

PD Parkinson's disease, *DLB* dementia with Lewy bodies

[a]*p* values were determined by Fisher's exact test adjusted by Bonferroni correction or a one-way ANOVA with Tukey's post hoc test

Data represent the mean ± SD or value (%)

Table 4 Scores of questionnaires on prodromal symptoms in the at-risk group

	Age ≥ 50, total	At-risk group (RG)	Normal group (NG)	PD/DLB patients (PD)	*p* values[a]		
					RG vs. NG	RG vs. PD	NG vs. PD
Number (M:F)	2726 (1531:1195)	155 (113:42)	1653 (900:753)	34 (18:16)			
PASE	132.7 ± 82.9	123.1 ± 79.5	133.5 ± 83.0	118.4 ± 80.3	0.314	0.964	0.613
SCOPA-AUT	5.3 ± 4.2	12.5 ± 5.2	3.6 ± 2.5	8.9 ± 6.4	< 0.001	< 0.001	< 0.001
Gastrointestinal	0.9 ± 1.4	2.4 ± 2.1	0.6 ± 0.9	2.5 ± 3.0	< 0.001	0.757	< 0.001
Urinary	2.5 ± 2.3	5.6 ± 3.0	1.9 ± 1.6	3.7 ± 2.8	< 0.001	0.002	< 0.001
Cardiovascular	0.3 ± 1.2	0.9 ± 1.0	0.2 ± 0.5	0.6 ± 0.8	< 0.001	0.275	0.002
Thermoregulatory	0.9 ± 1.3	2.1 ± 1.7	0.6 ± 1.0	1.1 ± 1.4	< 0.001	< 0.001	0.314
Pupillomotor	0.2 ± 0.5	0.7 ± 0.8	0.1 ± 0.4	0.2 ± 0.4	< 0.001	< 0.001	0.945
Sexual, male	0.7 ± 1.3	1.6 ± 2.1	0.5 ± 1.1	1.9 ± 2.2	< 0.001	0.907	0.013
Sexual, female	1.5 ± 1.7	2.7 ± 1.7	1.2 ± 1.5	1.5 ± 2.1	0.008	0.654	0.960
SAOQ, %	96.1 ± 11.9	82.4 ± 19.8	99.5 ± 1.6	72.9 ± 34.3	< 0.001	0.794	< 0.001
RBDSQ	1.9 ± 2.0	5.0 ± 2.7	1.3 ± 1.2	3.8 ± 2.3	< 0.001	0.012	< 0.001
BDI-II	6.6 ± 6.2	12.0 ± 8.3	4.4 ± 3.8	9.3 ± 5.4	< 0.001	0.374	< 0.001
ESS	7.6 ± 4.3	9.6 ± 5.0	6.3 ± 3.2	7.8 ± 3.8	< 0.001	0.229	0.036
LR (range)	1.35 ± 3.00 (0.13–67.54)	6.39 ± 9.64 (0.35–67.54)	0.64 ± 0.69 (0.13–13.37)	N/A	< 0.001[b]	N/A	N/A

PD Parkinson's disease, *DLB* dementia with Lewy bodies, *PASE* Physical Activity Scale for the Elderly, *SCOPA-AUT* the Japanese version of the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms, *SAOQ* Self-administered Odor Question, *RBDSQ* RBD screening scale, *BDI-II* Beck Depression Inventory-Second Edition, *ESS* Epworth Sleepiness Scale, *LR* total likelihood ratio for prodromal Parkinson's disease, *N/A* not applicable

[a]*p* values were determined by Kruskal–Wallis test with Steel–Dwass post-hoc test

[b]*p* value was determined by the Mann–Whitney *U* test

Data represent the mean ± SD

Table 5 Results of the anthropometric and serological examinations

	Males			Females		
	At-risk group	Normal group	*p* value	At-risk group	Normal group	*p* value
Number	113	667		40	746	
Age, years	62.5 ± 7.0	61.5 ± 5.2	0.067	58.7 ± 6.4	58.1 ± 5.7	0.534
Height, cm	167.8 ± 5.8	168.8 ± 6.0	0.092	156.4 ± 5.3	156.2 ± 5.3	0.829
Weight, kg	67.4 ± 10.0	67.8 ± 9.7	0.689	56.4 ± 11.6	54.0 ± 8.5	0.084
BMI, kg/m^2	23.9 ± 3.2	23.8 ± 2.9	0.591	23.1 ± 4.6	22.1 ± 3.2	0.075
Abdominal girth, cm	84.9 ± 9.0	84.5 ± 8.0	0.612	81.5 ± 10.7	78.9 ± 8.8	0.069
Systolic blood pressure, mmHg	120.9 ± 14.8	122.4 ± 14.7	0.313	113.3 ± 15.2	114.1 ± 15.3	0.741
Diastolic blood pressure, mmHg	77.5 ± 9.9	77.5 ± 10.4	0.992	71.5 ± 10.6	71.4 ± 10.5	0.921
WBC, /μL	5005 ± 1303	5324 ± 1398	0.023	4525 ± 1168	4676 ± 1249	0.454
Hemoglobin, g/dL	14.8 ± 1.3	15.0 ± 1.1	0.032	13.4 ± 1.1	13.4 ± 1.0	0.574
RBC, $10^4/\mu L$	466.9 ± 45.7	481.0 ± 37.3	< 0.001	445.1 ± 31.3	445.4 ± 31.9	0.953
MCV, fL	92.9 ± 5.2	91.5 ± 6.7	0.025	89.7 ± 3.9	90.1 ± 4.7	0.586
MCH, pg	31.7 ± 1.9	31.3 ± 1.6	0.009	30.0 ± 1.6	30.2 ± 1.9	0.440
MCHC, %	34.2 ± 0.9	34.1 ± 0.8	0.566	33.4 ± 0.7	33.5 ± 0.8	0.419
Hematocrit, %	43.2 ± 3.5	44.0 ± 2.9	0.010	39.9 ± 3.0	40.1 ± 2.6	0.720
Platelet, $10^4/\mu L$	21.2 ± 5.6	22.2 ± 5.0	0.121	23.5 ± 3.1	23.3 ± 5.1	0.861
Total protein, g/dL	7.07 ± 0.37	7.15 ± 0.37	0.113	7.04 ± 0.37	7.15 ± 0.36	0.534
Uric acid, mg/dL	6.14 ± 1.28	6.11 ± 1.21	0.789	4.80 ± 1.06	4.78 ± 1.05	0.899
Creatinine, mg/dL	0.92 ± 0.32	0.89 ± 0.15	0.217	0.68 ± 0.11	0.66 ± 0.10	0.387
Glucose, mg/dL	102.7 ± 18.3	101.4 ± 22.4	0.548	94.8 ± 19.5	92.0 ± 11.7	0.149
HbA1c, %	5.91 ± 0.68	5.93 ± 0.70	0.868	5.85 ± 0.50	5.74 ± 0.38	0.183
Triglyceride, mg/dL	125.4 ± 84.8	125.6 ± 79.8	0.983	108.3 ± 153.2	92.2 ± 43.3	0.068
T-Cho, mg/dL	198.2 ± 36.1	207.4 ± 32.9	0.007	220.3 ± 34.8	221.7 ± 34.8	0.795
HDL-Cho, mg/dL	57.4 ± 15.2	58.9 ± 14.9	0.341	71.6 ± 17.2	70.6 ± 15.1	0.696
LDL-Cho, mg/dL	114.5 ± 30.3	123.0 ± 28.9	0.004	124.6 ± 30.0	127.6 ± 29.6	0.539
AST, U/L	23.7 ± 6.5	24.2 ± 10.0	0.601	21.6 ± 6.3	21.9 ± 6.6	0.749
ALT, U/L	23.0 ± 11.4	24.6 ± 15.4	0.267	18.7 ± 9.0	19.3 ± 10.0	0.698
γ-GTP, U/L	52.6 ± 55.0	48.6 ± 55.6	0.478	23.0 ± 19.2	26.7 ± 27.1	0.394
ALP, U/L	210.8 ± 53.9	213.2 ± 55.5	0.668	217.8 ± 58.0	221.2 ± 63.9	0.765
T-bil, mg/dL	0.93 ± 0.34	0.96 ± 0.37	0.511	0.80 ± 0.36	0.84 ± 0.31	0.713

BMI body mass index, *WBC* white blood cells, *RBC* red blood cells, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *HbA1c* hemoglobin A1c, *T-Cho* total cholesterol, *HDL-Cho* high density lipoprotein cholesterol, *LDL-Cho* low density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyl transpeptidase, *ALP* alkaline phosphatase, *T-bil* total bilirubin. Data represent the mean ± SD

p values were determined by Student's *t* test

of PD. Moreover, our study also evaluated the anthropometric and blood test results of subjects, presumably providing important information on the biological changes that take place during the prodromal phase of PD.

To identify subjects at risk for PD, we set the cutoff points of each prodromal score at the 90th percentile values. These values matched well with the published normal thresholds. For example, the SCOPA-AUT score was reported to be 10.5 ± 6.6 in patients with PD and 4.0 ± 3.4 in healthy controls in a Chinese population [26]. According to two previous studies in Japan, the normal SAOQ values were reported to be 95.4 ± 5.2 and 95.2 ± 8.6, respectively [16, 27]. The RBDSQ scores of healthy Japanese subjects were 1.6 ± 1.2, and a cutoff score of ≥ 5, which corresponds to the 90th percentile of the population of the present study, showed 88.5% sensitivity and 96.9% specificity [17]. Using the cutoff values of questionnaires related to the core prodromal symptoms, SCOPA-AUT, SAOQ, and RBDSQ, we identified subjects who potentially had prodromal symptoms among the participants of ≥ 50 years of age, because the risk of prodromal PD substantially increases from 50 years of age [22].

In the present study, the prevalence of subjects of ≥ 50 years of age with ≥ 2 prodromal symptoms was 5.7%, which corresponded to the prevalence of PD and DLB,

estimated to be 3–5% in the elderly population [28, 29]. PD and DLB share common prodromal symptoms and neuropathology, and are referred to as Lewy body disease (LBD). It is thus plausible to use a unified strategy to identify individuals with LBD [30].

The at-risk subjects, who were selected based on questionnaires about dysautonomia, hyposmia, and RBD, also had worse scores on other questionnaires about depression and daytime sleepiness. Furthermore, their questionnaire scores were closer to the levels in PD and DLB patients. In comparison to the normal group, the at-risk subjects also had significantly worse scores in all items of the SCOPA-AUT, indicating that they had broad autonomic dysfunction, similar to patients with LBD. Considering the disease modification and neuroprotection, younger-onset (< 60 years of age) PD patients are a better target population [31]. A total of 71 of 155 subjects (45.8%) in our at-risk group were in their 50s, suggesting that the subjects identified in the present study are appropriate targets for prediagnostic research on LBD.

The male subjects in the at-risk group had lower hemoglobin levels in the present study. A previous population-based case–control study showed that young-onset anemia was associated with the future onset of PD [32]. In particular, anemia that started 20–29 years before the onset of PD showed the greatest association with the future risk of PD. Another population-based cohort study in Taiwan showed that subjects with anemia, especially with iron deficiency, were more likely to develop PD than non-anemic subjects [33]. The male subjects in the at-risk group also showed lower T-Cho and LDL-Cho levels than the normal group. A previous population-based longitudinal cohort study showed that among statin-free individuals, higher T-Cho and LDL-Cho levels were only associated with a decreased risk of PD in men [34], in agreement with our results. In addition, PD patients with higher LDL-Cho levels showed slower progression in motor and executive functions [35].

The present study was associated with several limitations. First, this study mostly depended on questionnaires and there were no objective examinations, such as motor and cognitive function tests, smell test, polysomnography (PSG), or imaging studies. Although the total LR for prodromal PD of the at-risk group was significantly higher than that of the normal group, the score of 6.39 ± 9.64 in the at-risk group was not high enough to make a diagnosis of prodromal PD. This is mainly because our study lacks data on subtle motor dysfunction, DAT-SPECT abnormalities, REM without atonia in PSG, and olfactory loss, all of which give extremely high positive LRs and which are crucial to making an accurate diagnosis of prodromal PD. Recently, several studies have reported that the elicitation of subtle subjective and objective motor symptoms before the clinical diagnosis of PD is important to make an early diagnosis of PD [36, 37]. Thus, we are currently performing a detailed analysis of the motor function, PSG, and imaging in our ongoing longitudinal study on the same cohort (UMIN ID: 000030396). Second, the reproducibility of each questionnaire has not been investigated. A questionnaire is an appropriate method for screening large populations, but the answers on the questionnaire are subjective and liable to intra-reporter variance. Third, we only obtained data from two institutes in Japan. Data from other areas, including Asian countries other than Japan, may strengthen the robustness of our results.

In summary, we performed a survey of prodromal symptoms of PD in a large medical checkup cohort in Japan and identified subjects ≥ 50 years of age with ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and RBD. Such at-risk subjects also had worse scores on questionnaires about depression and daytime sleepiness. In addition, all the subscores of SCOPA-AUT were significantly increased in the at-risk subjects, indicating that they had multiple autonomic dysfunctions similar to patients with PD and DLB. Male subjects in the at-risk group showed lower hemoglobin and cholesterol levels, which was consistent with the serum biomarkers of prodromal-phase PD reported in previous studies. The results warrant the performance of a prospective, longitudinal study of our cohort using objective measures, including DAT-SPECT.

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Compliance with ethical standards

Conflicts of interest Drs. Hattori, Tsuboi, Yokoi, Tanaka, Sato, Arahata, Hori, Kawashima, and Washimi report no disclosures.

Ethical standards This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, the Ethics Guidelines for Human Genome/Gene Analysis Research, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government. The study protocol was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine (No. 2016–0328). All participants provided their written informed consent before participation in the study.

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