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REM Sleep Behavior Disorder and Its Possible Prodromes in General Population

Prevalence, Polysomnography Findings, and Associated Factors

Woo-Jin Lee, MD, PhD, Shin-Hye Baek, MD, Hee-Jin Im, MD, PhD, Seung-Ku Lee, PhD, Jee-Eun Yoon, MD, MMSc, Robert J. Thomas, MD, MMSc, Yun-Kwok Wing, MBChB, FRCPsych, Chol Shin, MD, PhD, and Chang-Ho Yun, MD, PhD

Correspondence
Dr. Yun
ych333@gmail.com
or Dr. Shin
chol-shin@korea.ac.kr

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Abstract

Background and Objectives

To evaluate the prevalence of REM sleep behavior disorder (RBD) and its possible prodromal conditions, isolated dream enactment behavior (DEB) and isolated REM without atonia (RWA), in a general population sample, and the factors associated with diagnosis and symptom frequency.

Methods

From a population-based prospective cohort in Korea, 1,075 participants (age 60.1 ± 7.0 years; range 50–80 years; men 53.7%) completed the RBD screening questionnaire (RBDSQ), a structured telephone interview for the presence and characteristics of repeated DEB, and home polysomnography (PSG). RWA was measured on submentalis EMG, including 30-second epoch-based tonic and phasic activity as well as 3-second mini-epoch–based phasic and any EMG activities. Based on the presence of repeated DEB and any EMG activity of ≥22.3%, we categorized the participants into no RBD, isolated RWA, isolated DEB, and RBD groups.

Results

RBD was diagnosed in 20 participants, isolated RWA in 133 participants, and isolated DEB in 48 participants. Sex and DEB frequency-adjusted prevalence of RBD was 1.4% (95% CI 1.0%–1.8%), isolated RWA was 12.5% (95% CI 11.3%–13.6%), and isolated DEB was 3.4% (95% CI 2.7%–4.1%). Total RBDSQ score was higher in the RBD and isolated DEB groups than in the isolated RWA and no RBD group (median 5 [interquartile range (IQR) 4–6] for RBD, median 4 [IQR 3–6] for isolated DEB, median 2 [IQR 1–3] for isolated RWA, and median 2 [IQR 1–4] for no RBD groups, $p < 0.001$). RBDSQ score of ≥5 had good specificity but poor positive predictive value (PPV) for RBD (specificity 84.1% and PPV 7.7%) and its prodromal conditions (specificity 85.2% and PPV 29.1%). Among the RWA parameters, any EMG activity showed the best association with the RBD and its possible prodromes (area under the curve, 0.917). Three-second mini-epoch–based EMG activity and phasic EMG activity were correlated with the frequency of DEB (standardized Jonckheere-Terpstra statistic [std. J-T static] for trend = 0.488, $p < 0.001$, and std. J-T static = 3.265, $p = 0.001$, respectively).

Discussion

This study provides prevalence estimates of RBD and its possible prodromal conditions based on a structured telephone interview and RWA measurement on PSG from the general population.

From the Department of Neurology (W.-J.L., C.-H.Y.), Seoul National University Bundang Hospital, Seongnam; Department of Neurology (W.-J.L., C.-H.Y.), Seoul National University College of Medicine; Department of Neurology (S.-H.B.), Cheongju Saint Mary's Hospital; Department of Neurology (H.-J.I.), Hallym University Dongtan Sacred Heart Hospital, Hwaseong; Institute of Human Genomic Study (S.-K.L., C.S.), College of Medicine, Korea University, Seoul; Department of Neurology (J.-E.Y.), Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, South Korea; Division of Pulmonary, Critical Care and Sleep Medicine (R.J.T.), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Li Chiu Kong Family Sleep Assessment Unit (Y.K.W.), Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, China; and Biomedical Research Center (C.S.), Korea University Ansan Hospital, South Korea.

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Glossary

ANOVA = analysis of variance; **AUC** = area under the ROC curve; **BDI** = Beck Depression Inventory; **DEB** = dream enacting behavior; **IQR** = interquartile range; **J-T** = Jonckheere-Terpstra; **KoGES** = Korean Genome and Epidemiology Study; **MMSE** = Mini-Mental Status Examination; **NPV** = negative predictive value; **OSA** = obstructive sleep apnea; **PD** = Parkinson disease; **PPV** = positive predictive value; **PSG** = polysomnography; **RBD** = REM sleep behavior disorder; **RBDSQ** = RBD screening questionnaire; **ROC** = receiver operating characteristic; **RWA** = REM without atonia.

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by repeated dream enactment behavior (DEB) associated with loss of muscle atonia during REM.[1-4] RBD is regarded as a prodromal stage for major neurodegenerative diseases, particularly α-synucleinopathies such as Parkinson disease (PD), dementia with Lewy body, and multiple system atrophy.[4-10] A large-sized international cohort reported a 73.5% phenoconversion rate of idiopathic RBD to neurodegenerative diseases after the 12-year follow-up.[11] Given that early diagnosis is fundamental for effective management of neurodegenerative diseases, detection or surveillance of RBD at the level of the general population might provide a key for improving the outcomes of these diseases.[4,9,10]

The prevalence of polysomnography (PSG)–confirmed RBD is suggested at 1.18%–1.34%, based on recent population-based studies.[12-15] The spectrum of RBD is expanding, and the concept of a prodromal state of RBD has been investigated by diverse definitions and terminology.[16-19] Among them, the prodromal state of RBD can be categorized into 2 groups: isolated REM without atonia (RWA), which refers to the condition with RWA values that meet the criteria for RBD diagnosis but without relevant history of DEB, and isolated DEB, the condition with repeated DEB but with subthreshold RWA values.[16,19,20] Extensive discussion has targeted the concept and definition of the prodromal state of RBD,[9,19,21-24] and the International RBD Study group has provided a comprehensive guideline for proper identification and investigative methods for the prodromal state of RBD.[20]

A recent study reported that prodromal RBD, defined by the presence of DEB in the clinical history with subthreshold RWA on PSG, is associated with a 66% phenoconversion rate to full-blown RBD after 8.2 years and a 2.95 times increased risk of developing neurodegenerative disorders.[16] Because the diagnosis of RBD and prodromal RBD requires a clinically relevant history of DEB and RWA measurement on PSG, the prevalence and clinical features of both conditions have not yet been simultaneously established in the general population, and a substantial portion of patients might remain unrecognized. In addition, the efficacy of screening tools of RBD, such as the RBD screening questionnaire (RBDSQ), has not been fully established in the general population,[25-27] and the correlation of the RWA parameters with the phenotypic severity of RBD has not been investigated.[28]

In this study, we aimed to address these issues for the proper detection and surveillance of RBD and its possible prodromal conditions in the general population. First, we measured the prevalence of RBD and its possible prodromal conditions (isolated RWA and isolated DEB) in the general population, based on a clinical interview supplemented with an overnight PSG covering the study population. Second, we compared clinical features, DEB severity, and RWA parameters among RBD, isolated RWA, isolated DEB, and no RBD groups and suggest the diagnostic threshold of RWA parameters or RBDSQ to differentiate RBD spectrum conditions. Third, we evaluated the association between RWA parameters and the frequency of DEB.

Methods

Study Population

This study is a part of an ongoing population-based prospective cohort, the Korean Genome and Epidemiology Study (KoGES)–Ansan.[29] The original cohort was established in Ansan, South Korea, in 2001–2002 and comprised randomly selected 5,012 adults (2,518 men) between the ages of 40 and 69 years. No specific inclusion or exclusion criteria were set for this cohort, but the age and sex distributions were similar among those who were or were not recruited.[29] Participants have been biennially evaluated for sociodemographic characteristics, medical history, lifestyle, sleep-related factors, and a comprehensive battery of laboratory evaluations. For this study, we included 3,030 participants (50.0% men, mean age 59.1 ± 7.2 years, range 50–80 years), who participated in the 2012–2013 evaluation. Among them, the final study population was defined according to the following criteria: (1) performed RBDSQ, (2) were available with adequate clinical information for the determination of presence of DEB through the telephone interview, and (3) had a PSG data adequate for the measurement of RWA. An "adequate" information for the determination of presence of DEB was defined as clear answers for all the questions in the telephone interview which is sufficient for this discrimination. An "adequate" PSG data for the measurement of RWA were defined as (1) without excessive artifacts that might have interfered with scoring of sleep stage and sleep events, (2) sufficient amount of REM sleep (≥30 minutes), (3) without ongoing use of antidepressant or neuroleptics, and (4) stable chin EMG signal for the quantitative assessment of RWA. We performed RBDSQ and PSG in 2012–2013 and clinical interview for DEB in 2013–2014.

Analysis of the Clinical, Lifestyle, Sleep, and Cognitive Function Profiles

Along with demographic information, clinical and lifestyle profiles, including body mass index (kg/m^2), hypertension, diabetes mellitus, and hyperlipidemia, years of education, current status of regular exercise, alcohol consumption, or smoking, were obtained from the biennial survey database of KoGES-Ansan study.[29] Regular exercise was defined as performing sweat-developing intensity of exercise for more than 30 minutes at least once a week. The education level was categorized into low (<12 education year) or high (≥12) group. The presence of stroke, dementia, or PD was determined by the medical history on the structured questionnaires reported by participants and confirmed through the telephone interview performed by neurology specialists. The use of any kind of antidepressant and neuroleptics was documented by reviewing the prescriptions submitted by the participants and confirmed through the telephone interview.

Subjective daytime sleepiness was measured using the Epworth Sleepiness Scale, sleep quality using the Pittsburgh Sleep Quality Index, depressive symptoms using the Beck Depression Inventory (BDI), and cognitive function using the Korean version of the Mini-Mental Status Examination (MMSE) (eMethods, links.lww.com/WNL/D190 for details).[e1-e4]

RBDSQ

RBD was screened by using the RBDSQ, a self-rating questionnaire, validated in a clinic population. The RBDSQ consists of 10 items evaluating the presence of dream content, complex motor behavior during sleep, dream recall, sleep disturbance, and any associated neurologic disorder, with a score range of 0–13, and a score ≥5 is used as a cutoff for a positive result.[25]

Evaluation of DEB

For every participant, DEB was evaluated through a structured telephone interview, performed by 2 neurologists specializing in sleep disorders (S.-H.B., H.-J.I.) (eMethods, links.lww.com/WNL/D190 for details). DEB was regarded "present" when the participant or bedpartners reported abnormal complex or semipurposeful behaviors during sleep, the participant clearly described those behaviors as dream enactments, and the lifetime occurrences were at least twice. Repeated episodes of isolated sleep talking without other motor activity were not regarded as DEB, regardless of the participants' relevant dream recalls. In participants with DEB, the frequency of DEB was evaluated and categorized as follows: <1 night per month, 1–3 nights per month, and ≥1 nights per week, and the onset of the DEB symptom was assessed based on the time when the first DEB symptom occurred, as remembered by the participant or the bedpartner.

Quantitative Analysis of RWA and RBD Definition

The participants underwent unattended home PSG (Embletta X100; Natus Neurology Inc., Middleton, WI) that consisted of EEG (C4-A1), electro-oculography, submentalis EMG, nasal airflow, respiratory effort sensors, modified lead II EKG, and pulse oximetry. The submentalis EMG was acquired with a sampling rate of 200 Hz. Sleep architecture and respiratory events were scored by 2 trained sleep technologists using standard criteria.[30] Details of the methods for PSG recording, sleep staging, and respiratory event scoring are described elsewhere.[e5]

REM sleep was scored using standard criteria.[20,30] However, in participants with excessive RWA, the presence of excessive irregular muscle activity within an epoch but otherwise typical for REM sleep was scored as REM, considering the difficulty in applying the standard REM staging method in such instances.[20,31,32,e6]

The minimum REM sleep duration for RWA measurement was set at 30 minutes. RWA was measured on submentalis EMG by 1 trained sleep technologist (Y.K.) who was blind to other clinical information. The submentalis EMG channel sensitivity was set at 5 μV/mm with a low and high frequency filter of 10 and 70 Hz, respectively. A notch filter was set at 60 Hz. The presence of tonic, phasic, and any EMG activity during REM was visually determined and quantified according to the criteria published in previous studies and recommended as acceptable in the guidelines from the International RBD Study group.[20,32,33] Thirty-second epochs were used to score tonic EMG activity. An epoch was classified as tonic when continuous EMG activity with amplitude of at least 10 μV or ≥2 times higher than the background was present for more than 50% of the analyzable segment.[20,32,33] For the analysis of phasic activity, each 30-second epoch was subdivided into ten three-second mini-epochs. A mini-epoch was considered "phasic" when it contained EMG bursts with an amplitude ≥4 times higher than the background activity and a duration of 0.1–3.0 seconds. The end of phasic activity was defined as a recognizable return of EMG activity to the baseline level for at least 200 milliseconds.[32] A 30-second epoch containing at least 5 (50%) 3-second mini-epochs with a phasic EMG bursts was considered as phasic.[33] A mini-epoch with either tonic or phasic activity was counted as a mini-epoch with any EMG activity.[32,33] Any parts with respiratory event-related artifacts or arousals within the 30-second or 3-second epochs were excluded from the analysis.

Tonic EMG activity (%) and phasic EMG 30-second activity (%) were calculated by dividing the total number of 30-second epochs with each activity by the total number of 30-second epochs during REM sleep. The phasic EMG 3-second activity (%) and any EMG activity (%) were quantified as the percentage of positive mini-epochs to the total number of analyzable 3-second mini-epochs.[32]

On a random sample of 26 PSGs, intrarater (Y.K.) and interrater (Y.K., B.H.S.) agreements were assessed. Intrarater agreement of 2 RWA measurements with a 3-month interval was high (intraclass coefficient for tonic activity, 0.99; phasic, 0.96; and any, 0.99). Inter-rater agreement between 2 technologists was good (for tonic activity, 0.78; phasic, 0.70; and any, 0.75).

Identification of RBD and Its Prodromal Conditions

RBD was defined by the presence of both repeated DEB and any EMG activity exceeding the 90th percentile of normative values on submentalis EMG (>22.3%) in the PSG.[20,31,e7] Participants with any EMG activity of >22.3% but without repeated DEB were assigned to the isolated RWA group, and participants with repeated DEB but any EMG activity of ≤22.3% were assigned to the isolated DEB group.[16,17,20]

Statistical Analyses

Summary data are presented as means ± SD, median (interquartile range [IQR]), or number (percentage). All statistical analyses were performed using R software version 4.0.3 (2021; R team, Vienna, Austria) or SPSS (version 23.0; IBM, Chicago, IL). For group comparisons, analysis of variance (ANOVA), Pearson χ^2, or Kruskal-Wallis test were adopted. The receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated for the RBDSQ and the EMG activity parameters in relation to the "RBD" or "RBD and its prodromes." For RBDSQ, sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPVs) were calculated as the parameters for the diagnostic power. To evaluate the association between the frequency of DEB and the RWA parameters, ANOVA was used along with Jonckheere-Terpstra (J-T) test, a nonparametric, rank-based test for trend. For all analyses, a p value of <0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The study procedures were approved by the Institutional Review Board of the Seoul National University Bundang Hospital and the Korea University Ansan Hospital. Written informed consent was obtained from all study participants.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on request.

Results

Patient Characteristics

Among the initially included 3,030 participants, 166 participants without RBDSQ, 391 with unavailable telephone interview, and 140 with inadequate information for DEB through a telephone interview were sequentially excluded. Among the 2,333 subjects available for RBDSQ and the telephone interview for the presence of DEB, PSG was performed in 1,230 participants. Compared with the participants without PSG, participants who performed PSG were marginally older (60.0 ± 7.0 vs 59.0 ± 7.4 years, $p = 0.001$), had a lower proportion with a history of stroke (0.5% vs 1.3%, $p = 0.041$), less frequent MMSE scores of ≤24 (4.1% vs 6.0%, $p = 0.042$), lower BDI scores ≥14 (11.5% vs 15.2%, $p = 0.009$), and a higher frequency of DEB (6.3% vs 3.4%, $p = 0.001$). Otherwise, clinical, lifestyle, sleep, and cognitive function profiles were similar between the groups with or without PSG (eTable 1, links.lww.com/WNL/D192). Among the 1,230 participants with PSG analysis, 39 with excessive artifacts in the data, 72 with REM sleep duration of <30 minutes, 7 with the use of antidepressant or neuroleptics, and 37 with inadequate submentalis EMG data were sequentially excluded; the remaining 1,075 participants (577 [53.7%] men, 498 [46.3%] women, age 60.1 ± 7.0 years) were included in the final study analyses (Figure 1).

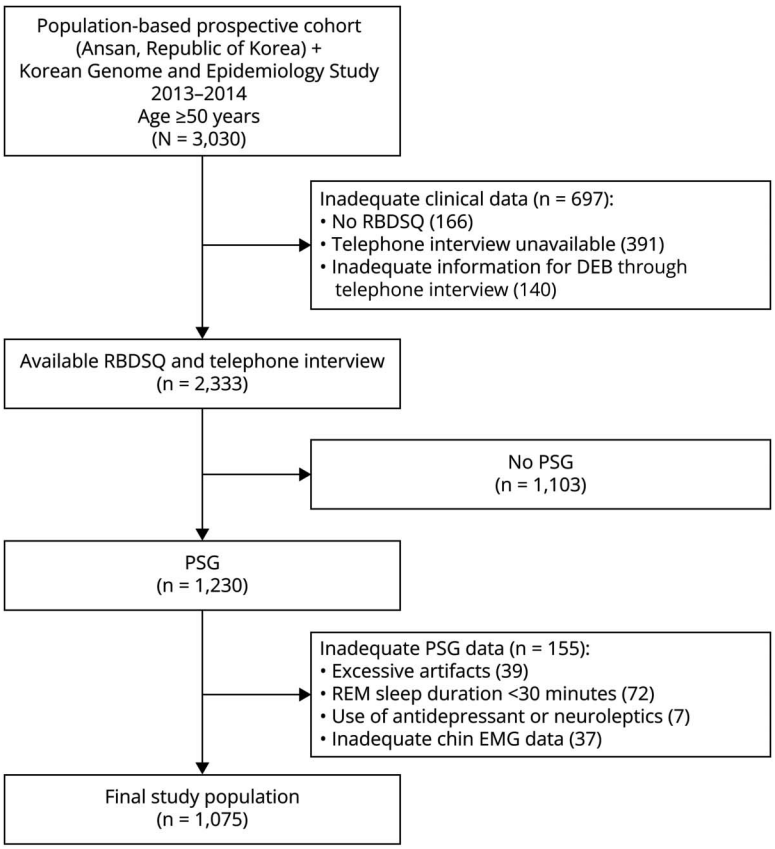
Repeated DEB was identified in 68 (6.3%) participants. Submentalis EMG activity of >22.3% was identified in 153 (14.2%) participants. Among them, 20 (1.9%, 13 [65.0%] men, 7 [35.0%] women) met the criteria for RBD and classified as RBD group, 133 (12.4%, 79 [59.4%] men, 54 [40.6%] women) as isolated RWA group, and 48 (4.5%, 26 [54.2%] men, 22 [45.8%] women) as isolated DEB group. To adjust the frequency of RBD for slight male predominance in the study population and the different DEB frequency between the groups with or without PSG evaluation, the sex-specific frequency of RBD in participants with DEB (13/39 [33.3%] for men and 9/29 [31.0%] for women) in the final study population (N = 1,075) and the sex-specific frequency of DEB in the population available for the telephone interview (N = 2,333) (71/1,266 [5.6%] for men and 43/1,067 [4.0%] for women) were applied to the initial study population from the 2012–2013 KoGES-Ansan evaluation (N = 3,030, men 50.0%). This returned an adjusted prevalence of RBD of 1.4% (95% CI 1.0%–1.8%), isolated RWA of 12.5% (95% CI 11.3%–13.6%), and isolated DEB of 3.4% (95% CI 2.7%–4.1%).

The mean age of DEB onset was 50.7 ± 11.4 years (range 40–74 years) for the RBD group and 50.1 ± 11.3 years (range 14–70 years) for the isolated DEB group. The duration of symptom was 12.9 ± 7.1 years (range 2–24 years) for the RBD group and 12.2 ± 8.5 years (range 0–41 years) for the isolated DEB group. Except for 1 (1.9%) male with PD, no other participants had an established diagnosis of parkinsonism or dementia.

Compared with the no RBD group, the isolated DEB group had a lower frequency of obstructive sleep apnea, defined as apnea-hypopnea index ≥15 per hour. Compared with the isolated DEB group, no RBD and isolated RWA groups had a higher frequency of hypertension, and RBD and isolated RWA groups had a higher frequency metabolic syndrome. Otherwise, there was no difference in clinical, lifestyle, cognitive function, and gross PSG profiles among the groups (Table 1).

For the total participants, the median RBDSQ score was 2 (1–4) and the mean values for phasic EMG 30-second, phasic EMG 3-second, tonic EMG, and any EMG activities were 0.7 ± 3.8, 2.1 ± 3.2, 10.7 ± 10.6, and 6.6 ± 10.3, respectively. Phasic, tonic, and any EMG activities were higher in the RBD group and isolated RWA group compared with the no RBD and isolated DEB groups (all, $p < 0.001$). RBD group

Figure 1 Flowchart Illustrating the Process for Defining the Study Population



DEB = dream enactment behavior; PSG = polysomnography; RBD = REM sleep behavior disorder; RBDSQ = RBD screening questionnaire.

exhibited higher phasic EMG 30-second and phasic EMG 3-second activities compared with the isolated RWA group, while tonic EMG and any EMG activities were similar between the 2 groups. Isolated DEB group exhibited higher EMG activities compared with the no RBD group, while other RWA parameters were similar between the 2 groups (eFigure 1, links.lww.com/WNL/D189).

The frequency of DEB and total RBDSQ score was similar between the RBD and isolated DEB groups, although the frequency of RBDSQ score of ≥5 was the highest in the RBD group, followed by the isolated DEB group and the lowest in the no RBD and the isolated RWA groups (eFigure 2, links.lww.com/WNL/D189).

Association of the RBDSQ and RWA Parameters With the Detection of RBD and Its Possible Prodromal Conditions

In the ROC analyses, the AUC value of RBDSQ for the detection of RBD was 0.855, any EMG activity was 0.937, phasic EMG 3-second activity was 0.768, phasic EMG 30-second activity was 0.719, and tonic EMG activity was 0.862 (Figure 2A). The AUC value of RBDSQ for the detection of RBD and its possible prodromal conditions was 0.576, any EMG activity was 0.917, phasic EMG 3-second activity was 0.662, phasic EMG 30-second activity was 0.609, and tonic EMG activity was 0.872 (Figure 2B).

In the total study population, a RBDSQ score of ≥5 predicted RBD with high specificity 84.1% (887/1,055) and NPV 99.3% (887/893), but with moderate sensitivity 70.0% (14/20) and low PPV 7.7% (14/182) (Figure 3A). For the detection of RBD and its possible prodromal conditions, a RBDSQ score of ≥5 predicted with high specificity 85.2% (745/874) and NPV 83.4% (745/893), but with low sensitivity 26.3% (53/201) and PPV 29.1% (53/182) (Figure 3B). In addition, any EMG activity of ≥6.5% exhibited the highest association with RBD and its possible prodromal conditions, with sensitivity 94.5% (190/201) and NPV 98.0% (539/550), but with moderate specificity 61.7% (539/874) and low PPV 36.2% (190/525) (eFigure 3, links.lww.com/WNL/D189).

In the evaluations for the association between the frequency of DEB and the RWA parameters, subgroups with a higher frequency of DEB were associated with higher EMG activity (standardized J-T static = 0.488, $p < 0.001$) (Figure 4A), phasic EMG 3-second activity (standardized J-T static = 3.265, $p = 0.001$) (Figure 4B), and tonic EMG activity (standardized J-T static = 2.550, $p = 0.011$) (Figure 4C), but

Table 1 Comparison of the Clinical, Sleep, and PSG Profiles Among the Subgroups

	Total (N = 1,075)	Non-RBD (A, N = 874)	Isolated RWA (B, N = 133)	Isolated DEB (C, N = 48)	RBD (D, N = 20)	*p* Value	Post hoc
Clinical profiles							
Age (y)	60.1 ± 7.0	60.1 ± 7.1	60.3 ± 7.0	58.3 ± 6.3	59.9 ± 7.7	0.361	
Age 60 y or older (%)	487 (45.3)	396 (45.3)	66 (49.6)	15 (31.2)	10 (50.0)	0.172	
Sex (men, %)	577 (53.7)	459 (52.5)	79 (59.4)	26 (54.2)	13 (65.0)	0.354	
BMI (kg/m^2)	24.8 ± 2.9	24.7 ± 2.9	25.2 ± 3.1	24.0 ± 2.6	25.1 ± 2.6	0.124	
Education year ≥12 y (%)	233 (21.7)	187 (21.4)	28 (21.1)	9 (19.1)	9 (45.0)	0.158	
Alcohol consumption (%)	499 (46.4)	397 (45.4)	68 (51.1)	22 (45.8)	12 (60.0)	0.389	
Smoking (%)	139 (12.9)	110 (12.6)	24 (18.0)	3 (6.2)	2 (10.0)	0.155	
Regular exercise (%)	512 (47.6)	419 (47.9)	62 (46.6)	22 (45.8)	9 (45.0)	0.977	
Metabolic syndrome (%)	296 (27.5)	232 (26.5)	45 (33.8)	9 (18.8)	10 (50.0)	0.019	D > A, C / B > C
Hypertension (%)	395 (36.7)	323 (37.0)	57 (42.9)	8 (16.7)	7 (35.0)	0.015	A, B > C
Diabetes mellitus (%)	224 (20.8)	190 (21.7)	25 (18.8)	8 (16.7)	1 (5.0)	0.230	
Hyperlipidemia (%)	231 (21.5)	192 (22.0)	24 (18.0)	10 (20.8)	5 (25.0)	0.751	
Parkinson disease (%)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1.000	
Dementia (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	
History of stroke (%)	6 (0.6)	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.709	
MMSE score	28 (26–29)	28 (26–29)	28 (26–29)	28 (27–29)	28 (26–29)	0.777	
MMSE score ≤24 (%)	40 (4.0)	37 (4.2)	3 (2.3)	2 (4.2)	0 (0.0)	0.566	
PSG profiles							
TIB (min)	439.3 ± 73.2	438.7 ± 73.6	447.5 ± 70.0	415.1 ± 66.4	472.1 ± 78.3	0.053	
TST (min)	377.3 ± 74.0	377.1 ± 74.7	381.6 ± 69.2	362.0 ± 76.8	395.4 ± 60.6	0.316	
SL (min)	10.6 ± 21.7	10.8 ± 23.1	9.5 ± 12.5	8.5 ± 9.4	14.1 ± 27.1	0.740	
SE (%)	87.0 ± 28.5	87.1 ± 31.2	85.4 ± 10.3	88.2 ± 8.6	87.4 ± 7.9	0.917	
N1 (%)	8.0 ± 6.0	7.9 ± 6.1	8.3 ± 6.1	7.7 ± 5.7	9.0 ± 4.0	0.748	
N2 (%)	66.6 ± 10.1	66.4 ± 8.9	67.4 ± 16.3	68.3 ± 9.6	65.1 ± 6.0	0.447	
N3 (%)	2.2 ± 4.5	2.4 ± 4.7	1.4 ± 3.4	1.4 ± 3.4	0.9 ± 2.2	0.025	
REM (%)	23.4 ± 6.8	23.2 ± 6.7	24.3 ± 7.8	22.7 ± 6.6	25.0 ± 6.2	0.216	
WASO (min)	51.4 ± 48.6	51.3 ± 50.0	56.8 ± 45.2	40.9 ± 33.9	46.7 ± 32.5	0.268	
AHI (/h)	7.5 ± 9.0	7.5 ± 9.2	8.4 ± 9.4	5.1 ± 5.6	6.1 ± 5.1	0.157	
AHI ≥15 (/h) (%)	152 (14.1)	130 (14.9)	19 (14.3)	2 (4.2)	1 (5.0)	0.127	A > C
Phasic EMG 30-second (%)	0.7 ± 3.8	0.4 ± 2.5	2.5 ± 7.3	0.3 ± 0.7	4.4 ± 9.8	<0.001**	D > B > C, A
Phasic EMG 3-second (%)	2.1 ± 3.2	1.7 ± 1.7	4.1 ± 6.4	2.3 ± 1.8	6.8 ± 9.7	<0.001**	D > B > C, A
Any EMG (%)	10.7 ± 10.6	7.0 ± 5.4	32.4 ± 7.7	9.3 ± 5.1	32.7 ± 8.3	<0.001**	D, B > C > A
Tonic EMG (%)	6.6 ± 10.3	3.2 ± 5.0	27.1 ± 10.9	3.9 ± 4.0	23.6 ± 12.3	<0.001**	D, B > C, A
DEB profiles							
Presence of DEB (%)	68 (6.3)	0 (0.0)	0 (0.0)	48 (100.0)	20 (100.0)	<0.001**	D, C > B, A
DEB frequency (%)						<0.001**	D, C > B, A
No (%)	1,007 (93.7)	874 (100.0)	133 (100.0)	0 (0.0)	0 (0.0)		

Continued

Table 1 Comparison of the Clinical, Sleep, and PSG Profiles Among the Subgroups *(continued)*

	Total (N = 1,075)	Non-RBD (A, N = 874)	Isolated RWA (B, N = 133)	Isolated DEB (C, N = 48)	RBD (D, N = 20)	*p* Value	Post hoc
<1/mo (%)	42 (3.9)	0 (0.0)	0 (0.0)	28 (58.3)	14 (70.0)		
1–3/mo (%)	14 (1.3)	0 (0.0)	0 (0.0)	12 (25.0)	2 (10.0)		
≥1/wk (%)	12 (1.1)	0 (0.0)	0 (0.0)	8 (16.7)	4 (20.0)		
Sleep questionnaires							
RBDSQ score	2 (1–4)	2 (1–4)	2 (1–3)	4 (3–6)	5 (4–6)	<0.001**	D > C > B, A
RBDSQ score ≥5 (%)	182 (16.9)	129 (14.8)	16 (12.0)	23 (47.9)	14 (70.0)	<0.001**	D > C > B, A
RBDSQ_1 (%)	349 (32.5)	278 (31.8)	33 (24.8)	23 (47.9)	15 (75.0)	<0.001**	D > C > B, A
RBDSQ_2 (%)	155 (14.4)	119 (13.6)	18 (13.5)	10 (20.8)	8 (40.0)	0.005**	D > C, B, A
RBDSQ_3 (%)	153 (14.2)	116 (13.3)	20 (15.0)	10 (20.8)	7 (35.0)	0.023*	D > B, A
RBDSQ_4 (%)	381 (35.4)	300 (34.3)	40 (30.1)	27 (56.2)	14 (70.0)	<0.001**	D, C > B, A
RBDSQ_5 (%)	23 (2.1)	11 (1.3)	3 (2.3)	7 (14.6)	2 (10.0)	<0.001**	D, C > B, A
RBDSQ_6A (%)	176 (16.4)	123 (14.1)	16 (12.0)	23 (47.9)	14 (70.0)	<0.001**	D > C > B, A
RBDSQ_ 6B (%)	91 (8.5)	56 (6.4)	8 (6.0)	19 (39.6)	8 (40.0)	<0.001**	D, C > B, A
RBDSQ_6C (%)	46 (4.3)	26 (3.0)	7 (5.3)	11 (22.9)	2 (10.0)	<0.001**	C > D, B, A
RBDSQ_6D (%)	55 (5.1)	38 (4.3)	6 (4.5)	9 (18.8)	2 (10.0)	<0.001**	C > B, A
RBDSQ_7 (%)	434 (40.4)	344 (39.4)	49 (36.8)	29 (60.4)	12 (60.0)	0.006**	C > B, A/D > B
RBDSQ_8 (%)	371 (34.5)	294 (33.6)	42 (31.6)	23 (47.9)	12 (60.0)	0.016**	D > B, A
RBDSQ_9 (%)	301 (28.0)	239 (27.3)	35 (26.3)	18 (37.5)	9 (45.0)	0.146	
RBDSQ_10 (%)	85 (7.9)	65 (7.4)	9 (6.8)	6 (12.5)	5 (25.0)	0.019**	D > B, A
BDI score	6 (3–11)	6 (3–11)	6 (3–12)	6 (2–15)	5.5 (2.5–11)	0.564	
BDI score ≥14 (%)	121 (11.3)	92 (10.5)	19 (14.3)	8 (16.7)	2 (10.0)	0.373	
ESS score	5 (3–7)	5 (3–7)	5 (3–7)	5 (3.5–7)	5 (3.5–7)	0.736	
EDS score ≥11 (%)	75 (7.0)	67 (7.7)	5 (3.8)	2 (4.2)	1 (5.0)	0.326	
PSQI score	3 (2–5)	3 (2–5)	3 (2–4.5)	3 (2–6)	4 (1–5.5)	0.331	
PSQI score ≥5 (%)	339 (31.5)	281 (32.2)	33 (24.8)	18 (37.5)	7 (35.0)	0.280	

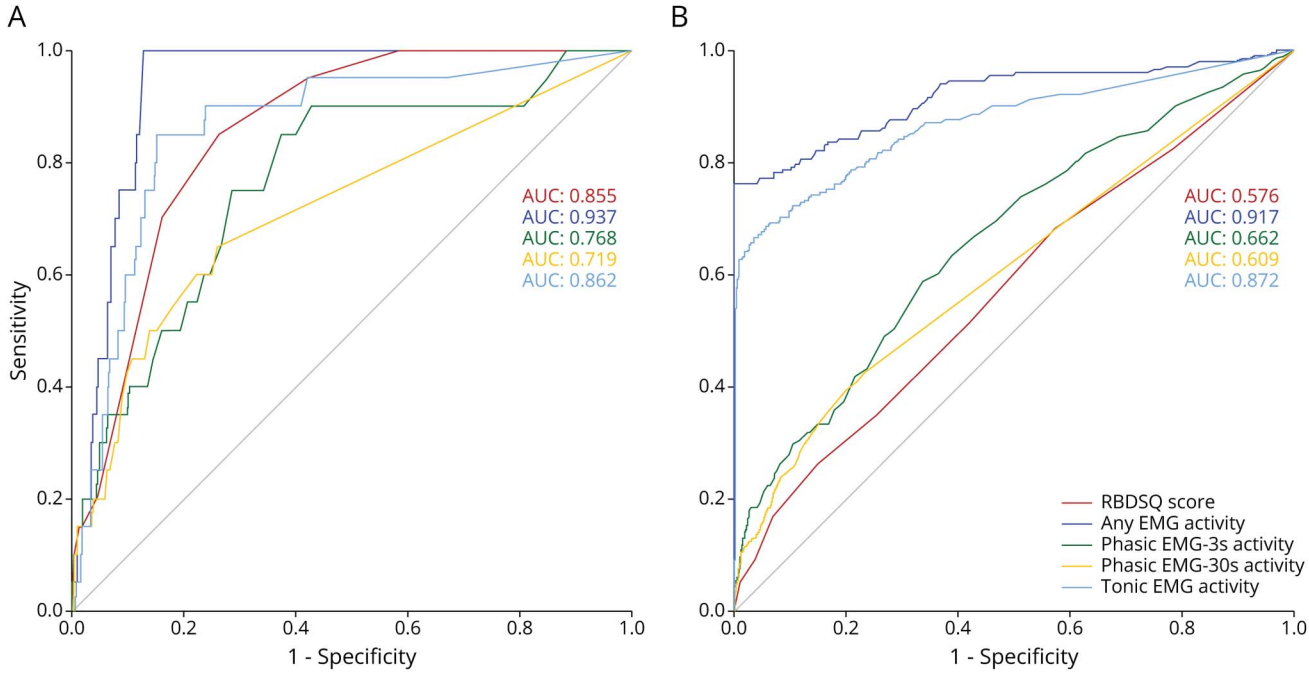
Abbreviations: AHI = apnea-hypopnea index; BDI = Beck Depression Inventory; BMI = body mass index; DEB = dream enacting behavior; ESS = Epworth Sleepiness Scale; IQR = interquartile range; MMSE = Korean version of the Mini-Mental Status Examination; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; RBD = REM sleep behavior disorder; RBDSQ = RBD screening questionnaire; RWA = REM without atonia; SE = sleep efficiency; SL = sleep latency; TIB = time in bed; TST = total sleep time; WASO = wakefulness after sleep onset.
Data are reported as n (%), mean ± SD, or median (IQR).
*$p < 0.05$ and **$p < 0.01$.

not with phasic EMG 30-second activity (standardized J-T static = 1.679, $p = 0.093$) (Figure 4D). In the ANOVA analyses, any EMG activity ($p = 0.009$) and phasic EMG 3-second activity ($p < 0.001$) exhibited significant difference among the subgroups of DEB frequency, while the inter-subgroup differences of phasic EMG 30-second activity ($p = 0.083$) and tonic EMG activity ($p = 0.197$) were not significant. When the study population was categorized into 5 groups according to the RBDSQ scores (score 0, n = 220; score 1, n = 217; score 2, n = 117; score 3, n = 167; score 4, n = 112; and score ≥5, n = 182), the group with higher RBDSQ scores was not associated with the increment of any of the RWA parameters (all, $p > 0.05$, eFigure 4, links.lww.com/WNL/D189).

Discussion

This study provides clinically important findings regarding the detection of RBD and its possible prodromes in a general population. Sex and DEB frequency-adjusted prevalence of RBD was 1.4%, isolated RWA was 12.5%, and isolated DEB was 3.4% in our middle or older aged population. Although the

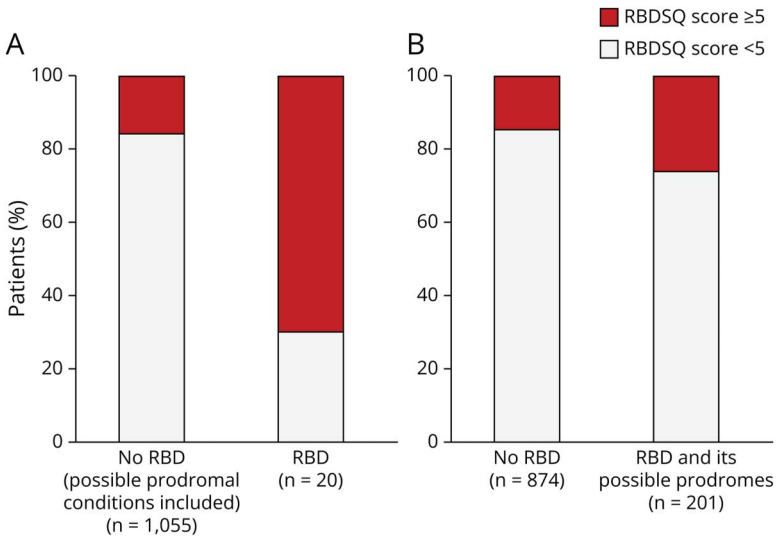
Figure 2 ROC Curves of REM Sleep Behavior Disorder Questionnaire and RWA Parameters for the Detection of RBD and Its Possible Prodromal Conditions



ROC curves for RBD (panel A) and RBD and its possible prodromal conditions (isolated RWA and isolated DEB, panel B). AUC = area under the ROC curve; DEB = dream enactment behavior; RBD = REM sleep behavior disorder; RBDSQ = RBD screening questionnaire; ROC = receiver operating characteristic; RWA = REM without atonia.

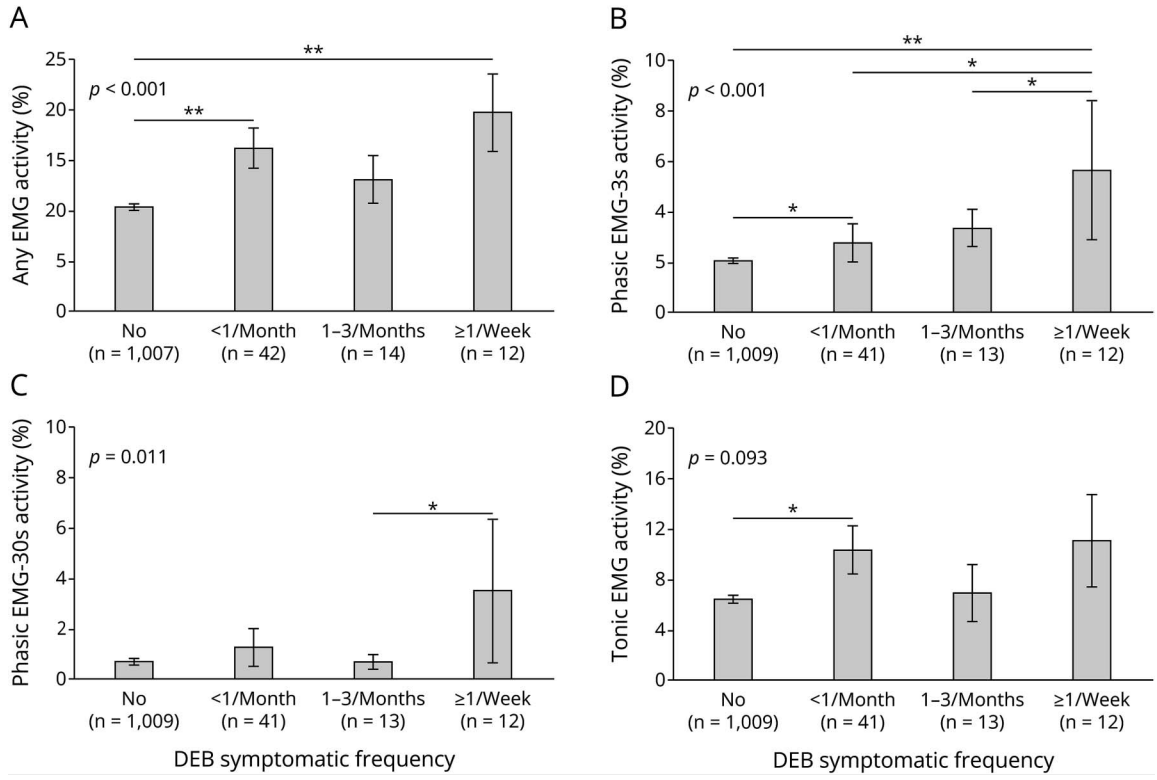
frequency of DEB and the RBDSQ score was similar between RBD and the isolated DEB groups, the frequency of a RBDSQ score ≥5 progressively increased from the no RBD or isolated RWA groups to isolated DEB and RBD groups. EMG activities were higher in the RBD and isolated RWA groups compared with the no RBD and isolated DEB groups. An RBDSQ score of ≥5 yielded high specificity and NPV, but moderate to low sensitivity and PPV for the identification of RBD and its possible prodromal conditions. Any EMG activity and phasic EMG 3-second activity were correlated with the frequency of DEB, while the correlation of phasic EMG 30-second and tonic EMG activity with DEB frequency was not consistent.

Figure 3 Association of RBDSQ Cut-Off Values With the Detection RBD and Its Possible Prodromal Conditions



Association of RBDSQ score of ≥5 with the RBD (panel A) and RBD and its possible prodromal conditions (isolated RWA and isolated DEB, panel B). DEB = dream enactment behavior; RBD = REM sleep behavior disorder; RBDSQ = RBD screening questionnaire; RWA = REM without atonia.

Figure 4 Correlation of the RWA Parameters With the Symptom Frequency of RBD



Association trend of any EMG activity (panel A), phasic EMG 3-second activity (panel B), tonic EMG activity (panel C), and phasic EMG 30-second activity (panel D). ANOVA = analysis of variance; DEB = dream enactment behavior; RBD = REM sleep behavior disorder. *p* Values are derived from Jonckheere-Terpstra tests for trend. Vertical bars indicate standard error. *$p < 0.05$, **$p < 0.01$ from the ANOVA analyses.

Although there are 4 previous population-based studies which have investigated the prevalence of RBD,[12-15] this study is the first to perform a structured telephone interview for confirmation of DEB by sleep medicine specialists followed by a PSG with RWA measurement for the entire study population. A study from Switzerland performed a screening questionnaire and PSG for whole study population, while the REM muscle activity was measured for screening positive participants for RBD.[13] Studies from Japan and Italy performed telephone interviews, to select participants suspected to have RBD had PSG to confirm the diagnosis of RBD.[12,15] Another study from Korea performed PSG evaluation for the whole study population, but the interview was performed for selected participants with RWA in the PSG.[14] Considering the limited sensitivity and PPV of the screening questionnaires in diagnosing RBD from a general population, sleep events other than DEB that could be misinterpreted as DEB,[31,34] and the discrepancy between clinical RBD severity and RWA parameters on PSG, this study might have advantages over the previous studies to provide real-world characteristics of RBD and its possible prodromal conditions in general population, based on a combination of the structured interview for DEB and PSG covering the entire study population.

In this study, the adjusted prevalence of RBD was 1.4%, which is comparable with those reported in previous studies.[12-15] The prevalence of isolated DEB, defined as a confirmed presence of repeated DEB but a subthreshold RWA on PSG, was 3.4%. The prevalence of DEBs in the general population has a wide range from 2.7% to 18.5%, albeit with various assessment tools with varying methodologies.[15] Non-REM parasomnias with dream-like mentation recall, pseudo-RBD,[34,35] or other sleep disorders such as obstructive sleep apnea (OSA) might account for some portion of the participants, although careful exclusion of those conditions was performed through a structured interview. In addition, the frequency of moderate-to-severe OSA was lower in the isolated DEB group, compared with the non-RBD group. This might be explained by the potential protective effect of RBD pathomechanism on OSA during REM.[13,36]

The adjusted prevalence of isolated RWA was 12.5%. Although no population-based surveillance of this prodromal condition has been performed, according to a previous population-based study by Kang et al.,[14] which conducted RWA measurement covering the whole study population, the prevalence of isolated RWA was 5.2% (18/354). Although conducted in a sleep clinic patients, a study by Ferri et al.[19] reported the prevalence of isolated RWA of 13.7%, defined by a REM atonia index of <0.8. The difference in the prevalence of isolated RWA from the previous studies might be due the higher mean values of RWA parameters in this study population, compared with those from the previous

studies.[16,20,32,33] The normative RWA values might vary with the genetic background, the methods to measure RWA, and night-to-night change in RWA. Sleep apnea is also a major cause of muscle tone changes during REM sleep, although our population was not enriched with apnea pathology. Further population-based studies with video PSG evaluation covering the entire population might validate the prevalence of the isolated RWA.

Considering the risk of phenoconversion of prodromal RBD to RBD,[16,17] early detection of the prodromal RBD from general population might be important for the effective planning of strategies to prevent or alleviate neurodegeneration. Although RBDSQ scores showed a high association with the detection of RBD and its prodromal conditions, the sensitivity and PPV of RBDSQ score were low. Considering that the association of any EMG activity of ≥6.5% was also limited, a structured interview followed by PSG confirmation might be the proper method for screening and detection of RBD and its possible prodromes in general population.

In this study, clinical and RWA profiles between the 2 possible prodromal conditions were very different. In addition, the correlation between RWA parameters and DEB frequency were relatively modest. This might be explained by that DEB and RWA might represent different aspects of RBD. In RBD, diminished inhibition of spinal motor neurons because of neurodegeneration in the subcoeruleus nucleus enables input from both brainstem and cerebral cortex to provoke an activation of spinal motor neurons.[37,38] Brainstem, cerebral cortex, and spinal motor neuron networks can have provocative interactions with each other during REM,[39] and DEB might represent the mechanisms involving cortical activation, while RWA represents a downstream activation of the spinal motor neurons.[37] In this regard, 3-second mini-epoch–based parameters, such as any EMG activity and phasic EMG 3-second activity, might better reflect these network activities because of their higher temporal resolution of measurement and exhibit better and more consistent correlation with the frequency of DEB, compared with the 30-second epoch–based parameters.

There are several limitations to be addressed. This study does not include follow-up analysis for the change of RBD symptoms or phenoconversion from possible prodromal RBD to RBD or idiopathic RBD to α-synucleinopathy. Given that the parent cohort of this study is ongoing with biennial surveillance, we are currently planning a 10-year follow-up surveillance covering the entire study population, which might elucidate the longitudinal association of the RWA parameters to the clinical course of participants with RWA with or without clinical DEB.[16,29] However, the relatively high mean age of this study cohort may be a limitation to define the long-term rate and the risk factors of phenoconversion considering average age at onset of PD. The RWA parameters noted might have night-to-night variability and could be affected by sleep-related respiratory events, which might have limited the accuracy of RBD diagnosis based on a single-night PSG evaluation.[40,41] Lack of video PSG, recommended for the proper identification of DEB and exclusion of RBD-mimicking conditions, is another limitation of this study.[20] Although the term "prodromal RBD" was introduced in the previous study by Wing et al.,[16] there remains the possibility of other conditions might be misclassified as true DEB.[34] Nevertheless, we performed structured telephone interview–based identification of repeated DEB, and RWA was carefully identified by excluding those respiratory event-related artifacts or arousals. The term "isolated DEB" defined in this study was not specified in the International RBD Study group guideline. Conversely, the guideline advocates the use of video polysomnography (PSG) for identifying (DEB), defined as motor events that exceed the 90th percentile within a normative distribution. However, considering that the frequency of DEB was less than 1 per month in 70% of patients with definite RBD in this study, defining isolated DEB solely based on a single-night video PSG might result in reduced sensitivity when detecting isolated DEB in the general population. This study did not measure expanded EMG montages such as in the flexor digitorum superficialis or the tibialis anterior and did not include automated measurement such as REM atonia index.[32,39,42] However, mentalis EMG is more practical for home measurements and is the typical EMG acquisition in the clinical sleep laboratory. Slight male predominance in the study population and a higher frequency of DEB in the group with PSG evaluation might have provided a source of selection bias. Although we adjusted for the frequency of DEB, small differences in the factors such as mean age, history of stroke, MMSE score of ≤24, or BDI score of ≥14 between the groups with or without PSG also have affected the prevalence of RBD and its possible prodromes. In addition, the onset of DEB assessed based on the participant's or bedpartner's report might have a possibility of recall bias, which should be interpreted with caution.

To better address outstanding issues, we are planning a 10-year follow-up for the current study population.[29] In addition, advanced tools to screen and detect RBD might enable the population-based regular surveillance of RBD and future phenoconversion. 3D video analyses and advanced actigraphy analysis are promising strategies to overcome the limitation of single-night PSG and improve the efficacy and accuracy of detecting RBD or its prodrome.[43-47] Automated scoring of RWA indices, including flexor digitorum superficialis, can effectively identify participants with RBD and distinguish RBD from other RBD-mimicking conditions during sleep.[47-49] These advanced techniques can be introduced to answer some of the remaining questions.

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Appendix Authors

Name	Location	Contribution
Woo-Jin Lee, MD, PhD	Department of Neurology, Seoul National University Bundang Hospital, Seongnam; Department of Neurology, Seoul National University College of Medicine, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Shin-Hye Baek, MD	Department of Neurology, Cheongju Saint Mary's Hospital, South Korea	Major role in the acquisition of data
Hee-Jin Im, MD, PhD	Department of Neurology, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, South Korea	Major role in the acquisition of data
Seung-Ku Lee, PhD	Institute of Human Genomic Study, College of Medicine, Korea University, Seoul	Drafting/revision of the manuscript for content, including medical writing for content
Jee-Eun Yoon, MD, MMSc	Department of Neurology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, South Korea	Drafting/revision of the manuscript for content, including medical writing for content
Robert J. Thomas, MD, MMSc	Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Yun-Kwok Wing, MBChB, FRCPsych	Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Chol Shin, MD, PhD	Institute of Human Genomic Study, College of Medicine, Korea University, Seoul; Biomedical Research Center, Korea University Ansan Hospital, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Chang-Ho Yun, MD, PhD	Department of Neurology, Seoul National University Bundang Hospital, Seongnam; Department of Neurology, Seoul National University College of Medicine, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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