REM Sleep Behavior Disorder and Its Possible Prodromes in General Population: Prevalence, Polysomnography Findings, and Associated Factors

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ABSTRACT

Objective: 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 subjects (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. REM without atonia (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 subjects into no RBD, isolated RWA, isolated DEB, and RBD groups.

Results: RBD was diagnosed in 20, isolated RWA in 133 subjects, and isolated DEB in 48 subjects. Sex and DEB frequency-adjusted prevalence of RBD was 1.4% (95% confidence interval [CI] 1.0–1.8%), isolated RWA 12.5% (95% CI 11.3–13.6%), and isolated DEB 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). 3-second mini-epoch based any 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).

Conclusions: 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.
INTRODUCTION

Rapid-eye movement (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’s disease, 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 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-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 two 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 polysomnography (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 has not yet been simultaneously established in the general population, and a substantial portion of patients might remain unrecognized. Additionally, the efficacy of screening tools of RBD, such as the RBD screening questionnaire (RBDSQ), has not been fully established in the general population, and the correlation of the RWA parameters with the phenotypic severity of RBD has not been investigated.

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.

MATERIALS AND METHODS

Study population

This study is a part of an ongoing population-based prospective cohort, the Korean Genome and Epidemiology Study (KoGES)-Ansan. 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. Participants have been biennially evaluated for socio-demographic characteristics, medical history, lifestyle, sleep-related factors, and a comprehensive battery of laboratory evaluations. For this study, we included 3,030 subjects (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 via 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 was 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/M²), 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. Regular exercise was defined as performing sweat-developing intensity of exercise for more than 30 minutes at least once a week. Education level was categorized into low (<12 education-year) or high (≥12) group. The presence of stroke, dementia, or Parkinson’s disease was determined by the medical
history on the structured questionnaires reported by participants and confirmed through the telephone interview performed by neurology specialists. 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 (ESS), sleep quality using the Pittsburgh Sleep Quality Index (PSQI), depressive symptoms using the Beck Depression Inventory (BDI), and cognitive function using the Mini-Mental Status Examination-Korean version (K-MMSE) (eMethods for details).\textsuperscript{e1,e2,e3,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 $\geq 5$ is used as a cutoff for a positive result.\textsuperscript{25}

**Evaluation of DEB**

For every subject, DEB was evaluated through a structured telephone interview, performed by two neurologists specializing in sleep disorders (S.B., H.I.) (eMethods for details). DEB was regarded “present” when the subject or bedpartners reported abnormal complex or semi-purposeful behaviors during sleep, the subject 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 subjects’ relevant dream recalls. In subjects with DEB, the frequency of DEB was evaluated and categorized as follows: $<1$ night/month, 1–3 nights/month, and $\geq 1$ nights/week, and the
onset of the DEB symptom was assessed based on the time when the first DEB symptom occurred, as remembered by the subject or the bedpartner.

**Quantitative Analysis of RWA and RBD definition**

The subjects underwent unattended home PSG (Embletta X100, Natus Neurology Inc., USA) 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 two trained sleep technologists using standard criteria. Details of the methods for PSG recording, sleep staging, and respiratory event scoring are described elsewhere.

REM sleep was scored using standard criteria. However, in subjects 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.

The minimum REM sleep duration for RWA measurement was set at 30-minutes. RWA was measured on submentalis EMG by one 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 Hz and 70 Hz, respectively. A notch filter was set at 60Hz. 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. Thirty-second (30s) 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.
analysis of phasic activity, each 30s epoch was subdivided into ten three-second (3s) 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. A 30s epoch containing at least 5 (50%) 3s mini-epochs with a phasic EMG bursts was considered as phasic. A mini-epoch with either tonic or phasic activity was counted as a mini-epoch with any EMG activity. Any parts with respiratory event-related artifacts or arousals within the 30s or 3s epochs were excluded from the analysis.

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

On a random sample of 26 PSGs, intra-rater (Y.K.) and inter-rater (Y.K., B.S.) agreement were assessed. Intra-rater agreement of two RWA measurements with a 3-month interval was high (intra-class coefficient for tonic activity, 0.99; phasic, 0.96; and any, 0.99). Inter-rater agreement between two technologists was good (for tonic activity, 0.78; phasic, 0.70; and any, 0.75).
Identification of RBD 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\textsuperscript{20, 31, e7}. Subjects with any EMG activity of >22.3% but without repeated DEB were assigned to the isolated RWA group and subjects with repeated DEB but any EMG activity of ≤22.3% were assigned to the isolated DEB group.\textsuperscript{16, 17, 20}

Statistical analysis

Summary data are presented as means ± standard deviation, 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, USA). For group comparisons, analysis of variance (ANOVA), Pearson’s chi-square, or Kruskal-Wallis test were adopted. The 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 (NPV) 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 non-parametric, 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 datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

RESULTS

Patient characteristics

Among the initially included 3,030 subjects, 166 subjects without RBDSQ, 391 with unavailable telephone interview, and 140 with inadequate information for DEB via 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 subjects. Compared to the subjects without PSG, subjects 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). Among the 1,230 subjects with PSG analysis, 39 with excessive artifacts in the data, 72 with REM sleep duration of < 30 min, 7 with use of antidepressant or neuroleptics, and 37 with inadequate submentalis EMG data were sequentially excluded; the remaining 1,075 subjects (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%) subjects. Submentalis any EMG activity of >22.3% was identified in 153 (14.2%) subjects. 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 subjects 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) was 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% confidence interval [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 RBD 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 one (1.9%) male with Parkinson’s disease, no other subjects had an established diagnosis of parkinsonism or dementia.

Compared to the no RBD group, isolated DEB group had a lower frequency of obstructive sleep apnea, defined as apnea-hypopnea index ≥ 15/hour. Compared to the isolated DEB group, no RBD and isolated RWA groups had a higher frequency of hypertension, and RBD and isolated RWA 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-30s, phasic EMG-3s, 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 to the no RBD and isolated DEB groups (all, \(P<0.001\)). RBD group exhibited higher phasic EMG-30s and phasic EMG-3s activities compared to the isolated RWA group, while tonic EMG and any EMG activities were similar between the two groups. Isolated DEB group exhibited higher any EMG activities compared to the no RBD group, while other RWA parameters were similar between the two groups (eFigure 1).

The frequency of DEB and total RBDSQ score were similar between the RBD and isolated DEB groups, although the frequency of RBDSQ score of \(\geq 5\) 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).

**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-3s activity was 0.768, phasic EMG-30s 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 576, any EMG activity was 0.917, phasic EMG-3s activity was 0.662, phasic EMG-30s activity was 0.609, and tonic EMG activity was 0.872 (Figure 2B).

In the total study population, a RBDSQ score of \(\geq 5\) 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 detection of RBD and its possible prodromal conditions, a RBDSQ score of \(\geq 5\) 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). Additionally, an 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) (Figure 3).

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 any EMG activity (standardized J-T static=0.488, P<0.001) (Figure 4A), phasic EMG-3s 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 not with phasic EMG-30s 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-3s activity (P<0.001) exhibited significant difference among the subgroups of DEB frequency, while the inter-subgroup difference of phasic EMG-30s activity (P=0.083) and tonic EMG activity (P=0.197) were not significant. When the study population was categorized into five 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, Figure 4).

**DISCUSSION**

The current 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%, of isolated RWA was 12.5%, and of isolated DEB was 3.4% in our middle or older aged population. Although the frequency of DEB and the RBDSQ score were similar
between RBD and the isolated DEB groups, the frequency of a RBDSQ score \( \geq 5 \)
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 to the no
RBD and isolated DEB groups. An RBDSQ score of \( \geq 5 \) provided high specificity and NPV,
but moderate or low sensitivity and PPV, for detection of RBD, or of RBD and its possible
prodromal conditions. Any EMG activity and phasic EMG-3s activity were correlated with
the frequency of DEB, while the correlation of phasic EMG-30s and tonic EMG activity with
DEB frequency were not consistent.

Although there are four 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 subjects for RBD.\(^{13}\) Studies from Japan and from Italy
performed telephone interviews, to select subjects who then 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 subjects 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 those reported in previous studies.\textsuperscript{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.\textsuperscript{15} Non-REM parasomnias with dream-like mentation recall, pseudo-RBD,\textsuperscript{35, 36} or other sleep disorders such as OSA might account for some portion of the subjects, although careful exclusion of those conditions were performed by structured interview. Additionally, the frequency of moderate-to-severe OSA was lower in the group isolated DEB group, compared to the non-RBD group. This might be explained by the potential protective effect of RBD pathomechanism on OSA during REM.\textsuperscript{13, 37}

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., which conducted RWA measurement covering the whole study population, the prevalence of isolated RWA was 5.2% (18/354).\textsuperscript{14} Although conducted in a sleep clinic patients, a study by Ferri et al. reported the prevalence of isolated RWA of 13.7%, defined by a REM atonia index of <0.8.\textsuperscript{19} 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 to those from the previous studies.\textsuperscript{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 in 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,\textsuperscript{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 was low. Considering that the association of any EMG activity of $\geq 6.5\%$ 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 two possible prodromal conditions were very different. Additionally, 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 due to neurodegeneration in the subcoeruleus nucleus enables input from both brainstem and cerebral cortex to provoke an activation of spinal motor neurons.\textsuperscript{38, 39} Brainstem, cerebral cortex, and spinal motor neuron networks can have provocative interactions with each other during REM,\textsuperscript{43} and DEB might represent the mechanisms involving cortical activation, while RWA represent a downstream activation of the spinal motor neurons.\textsuperscript{38} In this regard, 3s mini-epoch based parameters, such as any EMG activity and phasic EMG-3s activity, might better reflect these network activities due to their higher temporal resolution of measurement, and exhibit better and more consistent correlation with the frequency of DEB, compared to the 30-s epoch based parameters.

There are several limitations to be addressed. The current 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 $\alpha$-synucleinopathy. Given that the parent
cohort of the current study is ongoing with biennial surveillance, we are currently planning a ten-year follow-up surveillance covering the entire study population, which might elucidate the longitudinal association of the RWA parameters to the clinical course of subjects with RWA with or without clinical DEB.\textsuperscript{16, 29} However, the relatively high mean age of the current study cohort may be a limitation to define the long-term rate and the risk factors of phenoconversion considering average age of onset of Parkinson’s disease. 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.\textsuperscript{40, 41} Lack of video PSG, recommended for the proper identification of DEB and exclusion of RBD-mimicking conditions, is another limitation of the current study.\textsuperscript{20} Although the term ‘prodromal RBD’ was introduced in the prior study by Wing et al.,\textsuperscript{16} there remains the possibility of other conditions might be misclassified as true DEB.\textsuperscript{36} Nevertheless, we performed structured telephone interview-based identification of repeated DEB, and REM without atonia was carefully identified by excluding those respiratory event-related artifacts or arousals. The term ‘isolated DEB’ defined in the current study was not specified in the International RBD Study group guideline. Instead, the guideline recommended video PSG based detection of DEB, defined as motor events exceeding the 90th percentile of normative. However, considering that the frequency of DEB was less than 1/month in 70% of patients with definite RBD in the current 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. The current 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.\textsuperscript{32, 42, 43} 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. Additionally, the onset of DEB assessed based on the subject’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 ten-year follow-up for the current study population. In this follow-up study, home PSG including multi-night recording with simultaneous video monitoring is planned. Additionally, 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. Automated scoring of RWA indices including flexor digitorum superficialis can effectively identify subjects with RBD and distinguish RBD from other RBD mimicking conditions during sleep. These advanced techniques can be introduced to answer some of the remaining questions.

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FIGURE LEGENDS

Figure 1. A flow chart illustrating the process for defining the study population

RBD: REM sleep behavior disorder, RBDSQ: RBD screening questionnaire, DEB: dream-enactment behavior, PSG: polysomnography, and EMG: electromyography
Figure 2. Receiver operating characteristic (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, RBD: REM sleep behavior disorder, DEB: dream-enactment behavior, RWA: REM without atonia, RBDSQ: RBD screening questionnaire, and EMG: electromyography.
Figure 3. Association of RBDSQ cutoff 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). RBD: REM sleep behavior disorder, RWA: REM without atonia, DEB: dream-enactment behavior, and RBDSQ: RBD screening questionnaire
Figure 4. Correlation of the RWA parameters with the symptom frequency of RBD

Association trend of any EMG activity (panel A), phasic EMG-3s activity (panel B), tonic EMG activity (panel C), and phasic EMG-30s activity (panel D). RBD: REM sleep behavior disorder, DEB: dream-enactment behavior, and EMG: electromyography. P values are derived from Jonckheere-Terpstra tests for trend. Vertical bars indicate standard error. *P<0.05, **P<0.01 from the analysis of variance (ANOVA) analyses.
Table 1. Comparison of the clinical, sleep, and PSG profiles among the subgroups

<table>
<thead>
<tr>
<th>Clinical profiles</th>
<th>Total (N=1075)</th>
<th>Non-RBD (A, N=874)</th>
<th>Isolated RWA (B, N=133)</th>
<th>Isolated DEB (C, N=48)</th>
<th>RBD (D, N=20)</th>
<th>P</th>
<th>Post Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>60.1±7.0</td>
<td>60.1±7.1</td>
<td>60.3±7.0</td>
<td>58.3±6.3</td>
<td>59.9±7.7</td>
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<tr>
<td>Age ≥ 60 years (%)</td>
<td>487 (45.3%)</td>
<td>396 (45.3%)</td>
<td>15 (31.2%)</td>
<td>13 (65.0%)</td>
<td>10 (50.0%)</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td><strong>Sex (men, %)</strong></td>
<td>577 (53.7%)</td>
<td>459 (52.5%)</td>
<td>79 (59.4%)</td>
<td>26 (54.2%)</td>
<td>13 (65.0%)</td>
<td>0.354</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.8±2.9</td>
<td>24.7±2.9</td>
<td>25.2±3.1</td>
<td>24.0±2.6</td>
<td>25.1±2.6</td>
<td>0.124</td>
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<tr>
<td>Education-year ≥ 12 years (%)</td>
<td>233 (21.7%)</td>
<td>187 (21.4%)</td>
<td>28 (21.1%)</td>
<td>9 (19.1%)</td>
<td>9 (45.0%)</td>
<td>0.158</td>
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<td><strong>Alcohol consumption (%)</strong></td>
<td>499 (46.4%)</td>
<td>397 (45.4%)</td>
<td>68 (51.1%)</td>
<td>22 (45.8%)</td>
<td>12 (60.0%)</td>
<td>0.389</td>
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<td>Smoking (%)</td>
<td>139 (12.9%)</td>
<td>110 (12.6%)</td>
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<td>3 (6.2%)</td>
<td>2 (10.0%)</td>
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<td>Metabolic syndrome (%)</td>
<td>296 (27.5%)</td>
<td>232 (26.5%)</td>
<td>45 (33.8%)</td>
<td>9 (18.8%)</td>
<td>10 (50.0%)</td>
<td>0.019</td>
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<td>Hypertension (%)</td>
<td>395 (36.7%)</td>
<td>323 (37.0%)</td>
<td>57 (42.9%)</td>
<td>8 (16.7%)</td>
<td>7 (35.0%)</td>
<td>0.015</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>224 (20.8%)</td>
<td>190 (21.7%)</td>
<td>25 (18.8%)</td>
<td>8 (16.7%)</td>
<td>1 (5.0%)</td>
<td>0.230</td>
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<tr>
<td>Hyperlipidemia (%)</td>
<td>231 (21.5%)</td>
<td>192 (22.0%)</td>
<td>24 (18.0%)</td>
<td>10 (20.8%)</td>
<td>5 (25.0%)</td>
<td>0.751</td>
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<td>Parkinson’s disease (%)</td>
<td>1 (0.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (5.0%)</td>
<td>1.000</td>
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</tr>
<tr>
<td>Dementia (%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>6 (0.6%)</td>
<td>6 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.709</td>
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</tr>
<tr>
<td>MMSE score ≤24 (%)</td>
<td>40 (4.0%)</td>
<td>37 (4.2%)</td>
<td>3 (2.3%)</td>
<td>2 (4.2%)</td>
<td>0 (0.0%)</td>
<td>0.566</td>
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</tr>
</tbody>
</table>

**PSG profiles**

<p>| TIB (minutes)   | 439.3±73.2 | 438.7±73.6 | 447.5±70.0 | 415.1±66.4 | 472.1±78.3 | 0.053 |        |
| TST (minutes)   | 377.3±74.0 | 377.1±74.7 | 381.6±69.2 | 362.0±76.8 | 395.4±60.6 | 0.316 |        |
| SL (minutes)    | 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 |        |</p>
<table>
<thead>
<tr>
<th>WASO (minutes)</th>
<th>51.4±48.6</th>
<th>51.3±50.0</th>
<th>56.8±45.2</th>
<th>40.9±33.9</th>
<th>46.7±32.5</th>
<th>0.268</th>
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<td>AHI (/h)</td>
<td>7.5±9.0</td>
<td>7.5±9.2</td>
<td>8.4±9.4</td>
<td>5.1±5.6</td>
<td>6.1±5.1</td>
<td>0.157</td>
</tr>
<tr>
<td>AHI ≥ 15 (/h) (%)</td>
<td>152 (14.1%)</td>
<td>130 (14.9%)</td>
<td>19 (14.3%)</td>
<td>2 (4.2%)</td>
<td>1 (5.0%)</td>
<td>0.127</td>
</tr>
<tr>
<td>Phasic EMG-30s (%)</td>
<td>0.7±3.8</td>
<td>0.4±2.5</td>
<td>2.5±7.3</td>
<td>0.3±0.7</td>
<td>4.4±9.8</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Phasic EMG-3s (%)</td>
<td>2.1±3.2</td>
<td>1.7±1.7</td>
<td>4.1±6.4</td>
<td>2.3±1.8</td>
<td>6.8±9.7</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Any EMG (%)</td>
<td>10.7±10.6</td>
<td>7.0±5.4</td>
<td>32.4±7.7</td>
<td>9.3±5.1</td>
<td>32.7±8.3</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Tonic EMG (%)</td>
<td>6.6±10.3</td>
<td>3.2±5.0</td>
<td>27.1±10.9</td>
<td>3.9±4.0</td>
<td>23.6±12.3</td>
<td>&lt;0.001**</td>
</tr>
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### DEB profiles

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<tr>
<th>Presence of DEB (%)</th>
<th>68 (6.3%)</th>
<th>0 (0.0%)</th>
<th>0 (0.0%)</th>
<th>48 (100.0%)</th>
<th>20 (100.0%)</th>
<th>&lt;0.001**</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEB frequency (%)</td>
<td>1007 (93.7%)</td>
<td>874 (100.0%)</td>
<td>133 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001**</td>
</tr>
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</table>

#### Sleep questionnaires

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</thead>
<tbody>
<tr>
<td>RBDSQ ≥5 (%)</td>
<td>182 (16.9%)</td>
<td>129 (14.8%)</td>
<td>16 (12.0%)</td>
<td>23 (47.9%)</td>
<td>14 (70.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_1 (%)</td>
<td>349 (32.5%)</td>
<td>278 (31.8%)</td>
<td>33 (24.8%)</td>
<td>23 (47.9%)</td>
<td>15 (75.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_2 (%)</td>
<td>155 (14.4%)</td>
<td>119 (13.6%)</td>
<td>18 (13.5%)</td>
<td>10 (20.8%)</td>
<td>8 (40.0%)</td>
<td>0.005**</td>
</tr>
<tr>
<td>RBDSQ_3 (%)</td>
<td>153 (14.2%)</td>
<td>116 (13.3%)</td>
<td>20 (15.0%)</td>
<td>10 (20.8%)</td>
<td>7 (35.0%)</td>
<td>0.023*</td>
</tr>
<tr>
<td>RBDSQ_4 (%)</td>
<td>381 (35.4%)</td>
<td>300 (34.3%)</td>
<td>40 (30.1%)</td>
<td>27 (56.2%)</td>
<td>14 (70.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_5 (%)</td>
<td>23 (2.1%)</td>
<td>11 (1.3%)</td>
<td>3 (2.3%)</td>
<td>7 (14.6%)</td>
<td>2 (10.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_6A (%)</td>
<td>176 (16.4%)</td>
<td>123 (14.1%)</td>
<td>16 (12.0%)</td>
<td>23 (47.9%)</td>
<td>14 (70.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_6B (%)</td>
<td>91 (8.5%)</td>
<td>56 (6.4%)</td>
<td>8 (6.0%)</td>
<td>19 (39.6%)</td>
<td>8 (40.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_6C (%)</td>
<td>46 (4.3%)</td>
<td>26 (3.0%)</td>
<td>7 (5.3%)</td>
<td>11 (22.9%)</td>
<td>2 (10.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_6D (%)</td>
<td>55 (5.1%)</td>
<td>38 (4.3%)</td>
<td>6 (4.5%)</td>
<td>9 (18.8%)</td>
<td>2 (10.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_7 (%)</td>
<td>434 (40.4%)</td>
<td>344 (39.4%)</td>
<td>49 (36.8%)</td>
<td>29 (60.4%)</td>
<td>12 (60.0%)</td>
<td>0.006**</td>
</tr>
<tr>
<td>RBDSQ_8 (%)</td>
<td>371 (34.5%)</td>
<td>294 (33.6%)</td>
<td>42 (31.6%)</td>
<td>23 (47.9%)</td>
<td>12 (60.0%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>RBDSQ_9 (%)</td>
<td>301 (28.0%)</td>
<td>239 (27.3%)</td>
<td>35 (26.3%)</td>
<td>18 (37.5%)</td>
<td>9 (45.0%)</td>
<td>0.146</td>
</tr>
<tr>
<td>RBDSQ_10 (%)</td>
<td>85 (7.9%)</td>
<td>65 (7.4%)</td>
<td>9 (6.8%)</td>
<td>6 (12.5%)</td>
<td>5 (25.0%)</td>
<td>0.019**</td>
</tr>
<tr>
<td>BDI score ≥ 14 (%)</td>
<td>121 (11.3%)</td>
<td>92 (10.5%)</td>
<td>19 (14.3%)</td>
<td>8 (16.7%)</td>
<td>2 (10.0%)</td>
<td>0.373</td>
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</table>

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<td>EDS score ≥ 11 (%)</td>
<td>75 (7.0%)</td>
<td>67 (7.7%)</td>
<td>5 (3.8%)</td>
<td>2 (4.2%)</td>
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<td>0.326</td>
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<tr>
<td>PSQI score ≥ 5 (%)</td>
<td>339 (31.5%)</td>
<td>281 (32.2%)</td>
<td>33 (24.8%)</td>
<td>18 (37.5%)</td>
<td>7 (35.0%)</td>
<td>0.280</td>
</tr>
</tbody>
</table>

Data are reported as a number (percentage), mean±standard deviation, or median [interquartile range, IQR]. RBD: REM sleep behavior disorder, BMI: body mass index, MMSE: Korean version of the mini-mental status examination, PSG: polysomnography, TIB: time in bed, TST: total sleep time, SL: sleep latency, SE: sleep efficiency, WASO: wakefulness after sleep onset, AHI: apnea-hypopnea index, EMG: electromyography, RWA: REM without atonia, DEB: dream enacting behavior, RBDSQ: RBD screening questionnaire, BDI: Beck depression inventory, ESS: Epworth sleepiness scale, and PSQI: Pittsburgh Sleep Quality Index. *P<0.05 and **P<0.01.
# REM Sleep Behavior Disorder and Its Possible Prodromes in General Population: Prevalence, Polysomnography Findings, and Associated Factors

Woo-Jin Lee, Shin-Hye Baek, Hee-Jin Im, et al.

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