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SCIENTIFIC INVESTIGATIONS

Prevalence of isolated RBD in the city of Catania, Italy: a population-based study

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Study Objectives: Few studies have analyzed the prevalence of isolated rapid eye movement sleep behavior disorder (RBD) giving different estimates. Aim of the study was to estimate the prevalence of isolated RBD in the city of Catania.

Methods: A 3-stage design was adopted. Participants attending the offices of general practitioners in the city of Catania were screened with the RBD Single Question Screen questionnaire (Stage I). Positive participants were interviewed by phone and, if suspected of RBD, were invited for clinical examination by a movement disorders specialist and a sleep specialist (Stage II). After the clinical examination, patients diagnosed as probable isolated RBD (pRBD) were invited to undergo a video polysomnography (Stage III) to confirm the diagnosis of definite RBD.

Results: A total of 1,524 participants were screened. Of these, 220 (14.4%) screened positive. One hundred forty-three of them were further screened by phone, of whom 75 were suspected RBD. Thirty-six patients were diagnosed as pRBD, giving a prevalence of 2.36% (95% confidence interval, 1.71–3.25). Twelve pRBD agreed to a video polysomnography and, of these, 4 were diagnosed as definite RBD, giving a prevalence of 0.26% (95% confidence interval, 0.07–0.67). Prevalence adjusted by nonparticipants was 3.48% (95% confidence interval, 2.67–4.52) and 1.18% (95% confidence interval, 0.45–1.37) for pRBD and definite RBD, respectively.

Conclusions: Prevalence of both pRBD and definite RBD in Italy is comparable to the estimates reported in literature, confirming that isolated RBD has a low prevalence in the general population.

Keywords: REM sleep behavior disorder, epidemiology, population-based study, polysomnography

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Prevalence studies of isolated rapid eye movement sleep behavior disorder (RBD) are difficult to perform. In Italy, prevalence of isolated RBD has been studied using only the clinical confirmation.

Study Impact: This is the first RBD prevalence study conducted in Italy that employed video polysomnography using a population-based 3-stage design allowing to calculate estimates for both probable and definite RBD. This study also discusses the reasons behind the differences in prevalence rates across different studies and the challenges in epidemiological research on RBD.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a condition characterized by the presence of abnormal behaviors in the sleep phase, such as sudden movements and vocalizations caused by a dream enactment behavior.[1] Definite diagnosis can be made only with a video polysomnographic recording (VPSG) showing the lack of atonia during rapid eye movement sleep and the presence of abnormal behaviors, according to the current diagnostic criteria.[2]

Isolated RBD could be considered as an alpha-synucleinopathy in its earliest stages, conferring a high risk to convert to either Parkinson disease (PD), dementia with Lewy bodies, or multiple system atrophy.[3] Indeed, it represents the most specific risk factor for the development of PD being the strongest prodromal marker in the diagnosis of "Prodromal PD"[4] and is part of the core criteria for the dementia with Lewy bodies diagnosis.[5] For this reason, it is of paramount importance to study the prevalence of the disease in the general population. Nonetheless, data about prevalence of isolated RBD are scarce, with few population-based studies often reporting estimates that differ significantly depending on the diagnostic process employed.[6,7]

According to a recent a recent meta-analysis, to date 5 studies have evaluated the prevalence of isolated definite RBD (dRBD) (confirmed by VPSG), resulting in a pooled prevalence of dRBD of 0.68% (95% confidence interval [CI], 0.38–1.05) while the pooled prevalence of probable RBD (pRBD, not confirmed by VPSG), based on 14 studies, was 5.65% (95% CI, 4.29–7.18).[8] In Italy, only 2 studies have been conducted on the prevalence of pRBD.[7,9]

Aim of the current study is to assess the prevalence of both probable and definite isolated RBD in the city of Catania using a population-based 3-stage design.

METHODS

Study population and study design

The study has been conducted in the municipality of Catania, Italy (population: 314,555 inhabitants; Istituto Nazionale di Statistica, ISTAT 2016) from April 2016 to November 2017.

For the first stage (screening phase–Stage I) a sample of general practitioners (GPs) working in the study area was randomly selected from the provincial roster of the Italian Society of General Medicine to participate in the study. Before conducting the survey, several meetings were carried out with the selected GPs to explain the aim of the survey. GPs were given posters to be displayed in their waiting rooms explaining what is RBD.

Seven trained medical students visited each of the GPs' offices at least 3 times a week. Participants aged 40 years and above attended by the GPs were interviewed face-to-face by the students who administered the RBD Single Question Screen questionnaire. The RBD Single Question Screen is a screening questionnaire with 94% sensitivity and 87% specificity validated in Italian language[10] and consists of the following question: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?"

At the second stage (Stage II), participants positive at the screening phase underwent a structured phone interview carried out by a board-certified sleep specialist (LG) to confirm the suspicion of isolated RBD. When the suspicion was confirmed, patients were invited to undergo a clinical evaluation at the neurology clinic of the AOU Policlinico–Vittorio Emanuele of Catania. A board-certified sleep specialist (LG) and a movement disorders expert (CEC) confirmed the presence of pRBD, based on a standardized semistructured interview to exclude other sleep disorders and to evaluate the presence of other neurological disorders, including parkinsonisms. When available, bed partners were contacted to provide information on the sleep behaviors. For all the enrolled patients at Stage II, the presence of extrapyramidal symptoms has been evaluated using the Unified Parkinson's Disease Rating Scale III.[11] To exclude patients with dementia at this stage, cognition and activities of daily living were assessed with the Unified Parkinson's Disease Rating Scale sections I and II. Subjects with a suspected cognitive impairment underwent an extensive neuropsychological evaluation. The second stage allowed us to reach the diagnosis of isolated pRBD.

Patients considered as pRBD at second stage were invited to undergo a VPSG to confirm the presence of RBD (Stage III). Patients with a VPSG-confirmed RBD were diagnosed as isolated dRBD according to the current diagnostic criteria.[2] In the case of patients with a highly suggestive clinical history and presence of VPSG clinical events, but not satisfying the rapid eye movement sleep without atonia (RSWA) cut-off criteria for the diagnosis of RBD, a diagnosis of provisional RBD (provRBD) was proposed.[2] The study has been conducted in accordance with the Standards of Reporting of Neurological Disorders guidelines.[12]

Polysomnographic recordings

VPSG was recorded for at least 1 night for each participant. The VPSG recording was carried out using a minimum of 8 electroencephalography channels (placed according to the international 10-20 system), 2 electrocardiographic derivations, submentalis muscle, the bilateral flexor digitorum superficialis muscle, and the bilateral anterior tibialis muscle electrodes, electrooculogram, nasal thermistor, snore monitor, chest and abdominal movements, pulse rate, and oximetry (Micromed SpA, Mogliano Veneto, Italy).

The VPSG recordings were scored by 2 investigators (LG, CEC) according to the American Academy of Sleep Medicine criteria[13] and, in case of disagreement, the conclusions were sorted out by discussion. RSWA was visually scored.[13] RBD was defined according to the *International Classification of Sleep Disorders*, third edition.[2] The presence of periodic limb movements during sleep and sleep apneas was also recorded.[13] We considered pathological a periodic limb movements during sleep index > 15 events/h and an apnea-hypopnea index > 5 events/h.[2]

Sample size calculation

Sample size calculation was based on a previous described prevalence of 0.74%[14] in a European country with similar population characteristics to southern Italy. Thus, considering the population of the city of Catania in 2016, a 0.5 precision interval, and 95% CIs, a minimum number of 1,122 participants was calculated. Moreover, to account for an estimated proportion of 20% of nonparticipants, minimum sample size was increased to 1,346.

Statistical analysis

Demographic, clinical, and instrumental data were double entered in an ad hoc created database. Before analysis, a range and consistency check has been conducted on the variables considered for the study. Missing data were identified and cross-referenced with the original documents. Qualitative variables have been described as frequencies, while quantitative variables as means and standard deviations. Differences of demographic and clinical qualitative data were analyzed with the chi-squared test and quantitative data with the *t*-test. When not normally distributed, appropriate nonparametric test was used. Data have been analyzed with STATA 16.0 software. Lifetime prevalence and the 95% CI were calculated for isolated pRBD and dRBD. Moreover, the combined prevalence of provRBD and dRBD were calculated. For pRBD, age and sex specific prevalences were also measured. Prevalence estimates considering only the population ≥ 50 years and ≥ 60 years were also calculated. Prevalence rates for both isolated pRBD and dRBD were adjusted, projecting the obtained rates to the nonparticipants (both at Stage I and Stage II).

Ethics

The study was approved by the Ethical Committee of the AOU Policlinico-Vittorio Emanuele. All the patients were given a paper briefly explaining the reasons of the study containing a written informed consent model to be signed.

RESULTS

Stage I: screening phase

In the offices of 22 GPs who participated in the study, a total of 1,524 participants (642 [42.1%] men; mean age 62.2 ± 11.7 years)

were screened. Of these, 220 (14.4%) were positive at the screening questionnaire (mean age 63.8 ± 11.6; 119 [54.1%] men). Flowchart of the participants at each of the study stages is reported in **Figure 1**. Participants who screened positive were older (P = .03) and with a higher prevalence of men (P < .001). Demographic characteristics of the entire sample are reported in **Table 1**.

Stage II: prevalence of isolated pRBD

Of the 220 who screened positive, 10 (4.5%) were excluded because they were either deceased (n = 6) or did not meet inclusion criteria (3 had a neurodegenerative disease and 1 a demyelinating disease). Sixty-seven (31.9%) of the 210 screened positive did not participate at Stage II (29 [43.2%] could not be traced and 38 [56.7%] refused to participate in the study). Finally, 143 participants were further evaluated, leading to a participation rate at Stage II of 68.1% (**Figure 1**). Compared to nonparticipants, those who have been evaluated were younger (mean age 61.9 ± 11.4 years vs 66.3 ± 11.0 years; P = .01) and with a higher educational level (high school graduated 23.8% vs 10.5%; P = .02).

Sixty-eight of the 143 (47.5%) screened positive were excluded because the suspicion of RBD was not confirmed at the phone interview. Out of the 75 suspected RBD, 73 were in-person evaluated at the neurologic clinic while 2 were unable to come to the hospital and the diagnosis of pRBD was confirmed just by an accurate phone interview.

Of the 75 suspected RBD, 53 (70.7%) had a bed partner who shared information on the nocturnal behaviors of the patients. Thirty-nine (52%) were excluded, because 7 (18.0%) had a suspicion of non-rapid eye movement parasomnia, 6 (15.4%) of restless legs syndrome, 10 (25.6%) of insomnia, 6 (15.4%) of obstructive sleep apnea, while 3 (7.7%) presented with other alternative diagnoses, such as posttraumatic stress disorder, epileptic seizures, and laryngospasm, and 4 (10.2%) had sleep complaints of uncertain clinical significance. An additional 3 patients (7.7%) were excluded because they presented with other associated disorders, thus leading to a diagnosis of secondary RBD (2 PD and 1 dementia with Lewy bodies).

Finally, 36 patients (20 men [55.6%]; mean age 62.5 ± 10.8 years) fulfilled the diagnosis of isolated pRBD, giving a prevalence of 2.36% (95% CI, 1.71–3.25); a similar prevalence of 2.45% (95% CI, 1.73–3.46) was obtained for the population aged ≥ 50 years, and 2.53% (95% CI, 1.66–3.84) for those aged ≥ 60 years. Prevalence was higher among men (3.10%; 95% CI, 2.01–4.74) than women (1.82%; 95% CI, 1.12–2.93) and steeply increased with age starting from 1.91% (95% CI, 0.82–4.40) in the population aged 40–49 years to reach a peak of 3.38% (95% CI, 1.98–5.70) in the group aged 60–69 years and to slowly decline soon after (**Table 2**). Baseline characteristics of pRBD are reported in **Table 3**.

Stage III: prevalence of isolated dRBD

Out of the 36 patients with pRBD, only 12 (33.3%) agreed to spend a night in the clinic to undergo a VPSG. The 24 (66.7%) pRBD who refused the VPSG were slightly older (65.8 ± 9.4 years vs 56.4 ± 11.3 years; P = .01), but apart from age, no significant differences were found. Considering the 12 patients who underwent VPSG, 4 (33.3%) were diagnosed as isolated dRBD, while 5 (41.7%) were diagnosed as provRBD, reaching a confirmation rate of 75% (**Figure 1**). For the other 3 patients, diagnoses of obstructive sleep apnea, restless legs syndrome, and fragmented sleep were made. Among the dRBD cases, 2 also presented with a periodic limb movements during sleep index > 15 events/h, while 1 showed an apnea-hypopnea index higher than 5 events/h. Sleep comorbidities for provRBD were periodic limb movements during sleep in 2 and sleep apnea in 1. Participants with provRBD were slightly younger compared to those with dRBD (**Table 3**).

Considering the 4 patients with isolated dRBD, the prevalence was 0.26% (95% CI, 0.07–0.67) with a slightly higher prevalence among men (0.31% [95% CI, 0.04–1.0] vs 0.23% [95% CI, 0.006–0.8]). Prevalence of dRBD was slightly higher both in the population aged ≥ 50 years (0.31% [95% CI, 0.12–0.81]) and in the population aged ≥ 60 years (0.36% [95% CI, 0.12–1.06]). Prevalence reached 0.59% (95% CI, 0.27–1.12) when provRBD cases were also considered. Clinical, demographic, and polysomnographic characteristics of patients with dRBD and provRBD are reported in **Table 3**.

Adjusted prevalence of isolated pRBD and dRBD

When prevalence rates obtained for participants were applied to nonparticipants, prevalence of pRBD was 3.48% (95% CI, 2.67–4.52) while prevalence of dRBD was 1.18% (95% CI, 0.45–1.37). Considering both, dRBD and provRBD prevalence adjusted by nonparticipants was 2.62% (95% CI, 1.93–3.55).

DISCUSSION

Compared to other neurologic diseases, there is still a paucity of information on the epidemiology of RBD. According to a recent meta-analysis, the pooled prevalence of dRBD is 0.68% and 5.65% for pRBD.[8] However, prevalence estimates vary widely across the studies due to the different methodological approaches, study designs, diagnostic criteria, screening questionnaires adopted, age structure of the selected populations, and participation rate.[8]

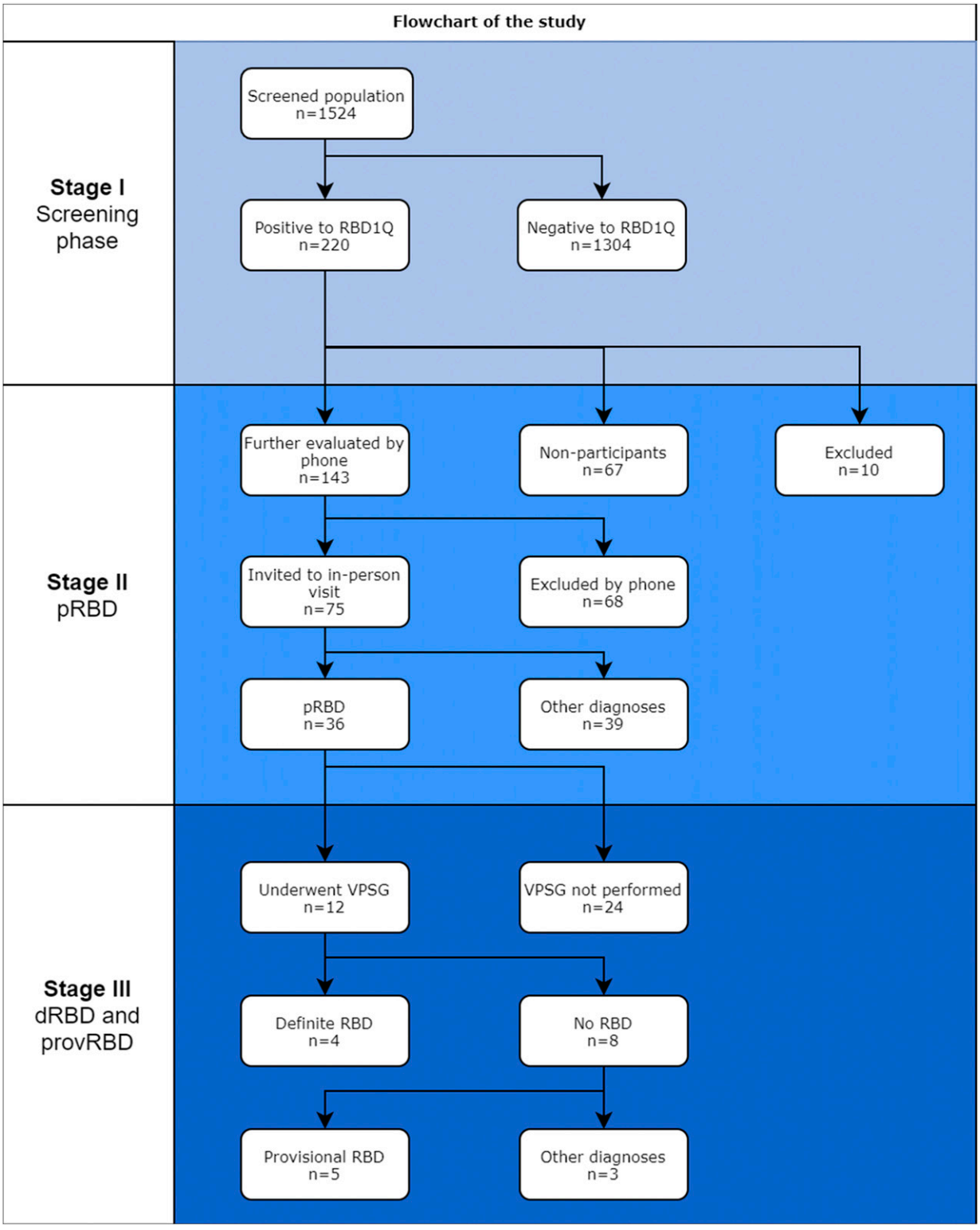
In our study, using a 3-stage design we found a prevalence of isolated pRBD of 2.36% and 0.26% for dRBD that rose to 0.59% when patients with provRBD were considered. Our prevalence estimates are lower than those reported in the meta-analysis on isolated RBD, albeit within the observed range for both dRBD and pRBD diagnosis.[8] Nonetheless, they get closer to those reported in literature when adjusted by the participation rate.

Prevalence of isolated pRBD: stage II

In our study, at stage II, we found a prevalence of pRBD of 2.36%. However, 30.5% of the screened population did not participate at the second stage, and when prevalence rate was adjusted projecting the observed rate to the nonparticipants, an adjusted prevalence rate of 3.48% was obtained.

To date, 14 studies have evaluated the prevalence of pRBD and rates reported ranges from 0.6% to 13.6%.[8] Although our prevalence is in the range of those reported in literature it is lower than the average pooled prevalence (5.65%). However, the majority of these studies adopted a 1-stage design, thus

Figure 1—Flowchart of the study.



dRBD = definite rapid eye movement sleep behavior disorder, pRBD = probable RBD, provRBD = provisional RBD, RBD = rapid eye movement sleep behavior disorder, RBD1Q = rapid eye movement sleep behavior disorder single-question screen, VPSG = video polysomnography.

Table 1—Characteristics of the screened sample.

	Total (n = 1,524)	Negative RBD1Q (n = 1,304)	Positive RBD1Q (n = 220)	*P*
Age, y (mean ± SD)	62.2 ± 11.7	61.9 ± 11.7	63.8 ± 11.6	**.03**
Sex (male), n (%)	642 (42.1)	523 (40.1)	119 (54.1)	**< .001**
Marital status, n (%)				.225
Not married	141 (9.3)	122 (9.4)	19 (8.6)	
Married	1,111 (72.9)	958 (73.5)	153 (69.6)	
Widow	138 (9.1)	110 (8.4)	28 (12.7)	
Other	134 (8.8)	114 (8.7)	20 (9.1)	
Educational level, n (%)				.086
Primary school	380 (24.9)	324 (24.9)	56 (25.5)	
Secondary school	544 (35.7)	461 (35.4)	83 (37.7)	
High school	370 (24.3)	327 (25.1)	43 (19.6)	
University	137 (9.0)	120 (9.2)	17 (7.7)	
Other	93 (6.1)	72 (5.5)	21 (9.6)	
Occupation, n (%)				**.021**
Unemployed	121 (7.9)	100 (7.7)	21 (9.6)	
Employee	255 (16.7)	218 (16.7)	37 (16.8)	
Housewife	442 (29.0)	400 (30.7)	42 (19.1)	
Professional	87 (5.7)	72 (5.5)	15 (6.8)	
Retired	515 (33.8)	428 (32.8)	87 (39.6)	
Other	104 (6.8)	86 (6.6)	18 (8.2)	
Familial history of Parkinson disease, n (%)	51 (3.4)	39 (3.0)	12 (5.5)	.06

Significant *P* values are in bold. RBD1Q = rapid eye movement sleep behavior disorder single-question screen, SD = standard deviation.

Table 2—Age- and sex-specific prevalence of pRBD.

Age Classes, y	Men			Women			All		
	Sample	Cases	Prevalence (95% CI)	Sample	Cases	Prevalence (95% CI)	Sample	Cases	Prevalence (95% CI)
40–49	93	2	2.15% (0.60–7.50)	168	3	1.78% (0.61–5.11)	261	5	1.91% (0.82–4.40)
50–59	146	5	3.42% (1.47–7.76)	262	5	1.91% (0.82–4.38)	408	10	2.45% (1.33–4.45)
60–69	177	5	2.82% (1.21–6.44)	207	8	3.86% (1.97–7.43)	384	13	3.38% (1.98–5.70)
70–79	165	6	3.63% (1.67–7.70)	200	0	0	365	6	1.64% (0.75–3.53)
80–89	61	2	3.27% (0.90–11.19)	42	0	0	103	2	1.94% (0.53–6.80)
90–99	3	0	0	0	0	0	3	0	0
Total	645	20	3.10% (2.01–4.74)	879	16	1.82% (1.12–2.93)	1,524	36	2.36% (1.71–3.25)

CI = confidence interval, pRBD = probable rapid eye movement sleep behavior disorder.

the diagnosis of pRBD was not confirmed through a clinical interview but was only based on the screening questionnaires. Comparison with these studies is, in general, difficult, because 1-stage studies tend to overestimate the prevalence of RBD (pooled prevalence 6.40%),[8] that in this case depends on the sensitivity and specificity of the adopted questionnaires. Indeed, sensitivity and specificity of RBD screening questionnaires depend on the studied population,[15] clinical setting,[16] and might not be consistent across repeated evaluations.[17] Except for the Mayo Sleep Questionnaire,[18] the majority of these tools have been validated in just a hospital setting. Nonetheless, it is well known that hospital validations tend to overestimate both

Table 3—Clinical and demographic characteristics of patients with pRBD, dRBD, and provRBD.

	pRBD (n = 36)	dRBD (n = 4)	provRBD (n = 5)
Age, y (mean ± SD)	62.5 ± 10.8	65.2 ± 12.5	52.5 ± 8.5
Age, y (median and range)	63 (42–86)	64 (52–81)	54 (42–62)
Sex (men), n (%)	20 (55.6)	2 (50)	2 (40)
UPDRS-III	5.7 ± 5.1	4.5 ± 4.5	4 ± 2.3
Sleep macrostructure			
Total sleep time, min (mean ± SD)	—	323.7 ± 71.9	314.2 ± 114.2
Sleep latency, min (mean ± SD)	—	34 ± 19.2	7.4 ± 7.3
Sleep efficiency, % (mean ± SD)	—	77 ± 7.2	83.8 ± 8.6
Wake after sleep onset, min (mean ± SD)	—	84 ± 23.3	59.2 ± 30.3
N1 sleep, % (mean ± SD)	—	8 ± 4.3	2.6 ± 3.2
N2 sleep, % (mean ± SD)	—	52 ± 11.0	52 ± 9.9
N3 sleep, % (mean ± SD)	—	24.8 ± 7.4	24.6 ± 12.5
REM sleep, % (mean ± SD)	—	16.3 ± 3.4	19.2 ± 7.5

dRBD = definite rapid eye movement sleep behavior disorder, pRBD = probable RBD, provRBD = provisional RBD, REM = rapid eye movement, SD = standard deviation, UPDRS-III = Unified Parkinson's Disease Rating Scale-III.

sensitivity and specificity levels.[19] Furthermore, the 1-stage design does not allow for exclusion of the presence of secondary RBD, such as RBD associated with alpha-synucleinopathies.

Only 2 studies adopted a 2-stage design in which participants who screened positive were confirmed by a clinical evaluation (Stage II).[7,20] Prevalence rates reported in these latter studies were on average lower with respect to the 1-stage studies (pooled prevalence 2.1%)[8] and closer to our estimates.

To the best of our knowledge only 2 small studies involving about 400 participants aged 60 years and above evaluated the prevalence of pRBD in Italy.[7,9] In particular a 2-stage study was carried out in the Trentino-Alto Adige region[7] and reported a prevalence of 4.6%, while a 1-stage survey focused on the mild parkinsonian signs was carried out in the Emilia Romagna region[9] and reported a prevalence of 4.3%. These estimates are higher with respect to the rate reported in our study (2.36%), but close if we consider the adjusted rate (3.48%). The participation rate at Stage II (68.1%) in our study could, in fact, in part explain such a difference, but we strongly believe that the confirmation of the pRBD at Stage II by an expert on sleep disorders has played an important role in lowering the number of false positives. As a matter of fact, only 16.4% of those screened positive at Stage I were confirmed at Stage II. In agreement with other studies, prevalence of pRBD was higher among men.[20–22]

Prevalence of isolated dRBD: stage III

Our study is the first VPSG-based study on the prevalence of isolated RBD in Italy. Prevalence of isolated dRBD in our study was 0.26% but reached 0.59% when provRBD were also considered. These rates are close to those reported in literature.[8] Only 5 studies aimed to determine the prevalence of isolated dRBD have been carried out, reporting rates ranging from 0.29% to 1.15% (pooled 0.68%),[8] and of these, 3 adopted a similar 3-stage design and reported on average a low prevalence rate ranging from 0.29% to 0.74%.[14,23,24]

In particular, our prevalence for dRBD (0.26%) is lower than that reported by a European 3-stage study performed in Spain[14] where prevalence of dRBD was 0.74%. However, the participation rate in our study at both stage II (68.1%) and Stage III (33.3%) was lower than that reported in the Spanish study. Indeed, when adjusting for the nonparticipants, prevalence of dRBD in our sample was closer to the Spanish one (1.18%). Another similar 3-stage survey has been carried out in Japan, where a prevalence of dRBD of 0.54% was reported.[23] In this latter study, prevalence rose up to 1.23% when provisional RBD was also considered. This estimate is close to that obtained in our survey when patients with provRBD were included. Interestingly, the adjusted prevalence rates of dRBD (1.18%) and dRBD plus provRBD (2.62%) in our study were almost double when compared to this study where the participation rate was slightly above 50%.[23]

Finally, a third 3-stage survey was carried out in China where, considering only isolated dRBD, prevalence was 0.29%.[24] Comparison with the other 2 studies is limited because of different inclusion criteria and procedures.[6,25]

Weaknesses and strengths

Our survey confirms that isolated RBD is a disease with a very low prevalence rate in the general population, considering both pRBD and dRBD, and underlines the difficulties in carrying out population-based surveys above all for dRBD.

One of the main pitfalls in conducting a prevalence survey to estimate RBD prevalence is related to the participation rate, especially for the diagnosis of dRBD that requires the VPSG recording.

Participation rates, across the different stages, vary widely between studies, with some having low participation rates[20,23] and others higher.[14,24,25] In our survey, the participation rate was good (almost 70%) for the Stage II (clinical evaluation), but very low (33%) at Stage III (VPSG examination). In particular, participation rate at Stage III was lower than that recorded in

the Spanish study,[14] but higher compared to a Japanese study where none of the participants agreed to a VPSG.[20] The issue of participation rate has a relevant impact in interpreting prevalence estimates, since the low participation rate can lead to an underestimation of the true prevalence when rates are not adjusted by the number of nonparticipants and can also lead to a selection bias limiting the generalizability of the results.

There are different factors that might have contributed to the low participation rate at the VPSG examination. First, patients affected by RBD are often not aware of their disorder, which is usually considered as a paraphysiological behavior. For this reason they often do not agree to spend a night at the hospital to undergo VPSG. Another cause for refusal reported by the enrolled participants was related to the fact that they had been informed about the possible association between RBD and PD and, for this reason, preferred to avoid further investigations. Indeed, ethical issues in RBD epidemiological studies are a delicate matter balancing between advantages and disadvantages of disclosing alpha-synucleinopathy risk information in such research settings.[26] In our study we chose an approach based on full disclosure of the scope of the study, explaining also the associated risk of developing an alpha-synucleinopathy, albeit underlining that the real extent of the risk is not well understood.

A further important limit in interpreting the estimates of dRBD reported in literature is related to the VPSG procedure. The rate of pRBD confirmed by VPSG is generally very low.[14] Indeed, if the diagnosis based on clinical grounds (pRBD) tends to be overestimated, the true prevalence of dRBD confirmed by VPSG could be underestimated. VPSG, in fact, might fail to capture the presence of RBD because of the first-night effect and, more importantly, because of the nonpersistence of RBD symptomatology through every night,[27] especially when patients are actively screened in a population-based setting, where symptoms are deemed so mild that they are not considered worthy of medical assistance. From this point of view, the inclusion of provRBD could be important in reducing the number of false negative cases.

We also acknowledge that our prevalence estimates could be lower than the true population prevalence of RBD due to several pitfalls. Indeed, nonparticipants at Stage I were older and less educated compared to participants, both considered factors associated with RBD.[28] Moreover, participants sleeping alone might not be aware of mild movements during sleep and thus not considered to have a sleep disorder, reducing the prevalence estimates. Furthermore, it has been demonstrated[6] that a certain portion of patients without clear evidence of movements during sleep may just present features of RSWA (isolated RSWA).[6] Because of this, VPSG should be performed in a random sample of the screened negative participants to estimate the percentage of false negatives on the basis of the clinical history, but these kinds of studies are difficult to perform. Indeed, considering the low prevalence of RBD, a large number of negative participants should undergo VPSG to obtain accurate estimates. Nevertheless, it should be noted that the presence of isolated RSWA is not sufficient to diagnose RBD,[2] and thus even these results should be interpreted with caution.

Finally, another potential source of selection bias is represented by the sampled populations. In our study, the selected population has been drawn from the GPs' offices. Considering the characteristics of the study outcome, door-to-door design could be a better approach, but it is extremely expensive and time consuming, thus poorly feasible. On the other hand, a study design including participants admitted for general consultation in their local GPs' studies represents a good compromise, as other studies have already done.[9,14] Nonetheless, even if we randomly selected a sample of GPs working in the city of Catania, participants enrolled were those who visited the GPs' offices, thus we cannot be sure that they were truly representative of the study population.

However, regardless of the above-mentioned limits, our study has many strengths, of which the large sample size and the 3-stage design represent the main ones. This is, in fact, the first survey conducted in Italy, and one of the largest, to determine the prevalence of isolated dRBD using a population-based design. The size of the study was determined according to a specific sample size calculation, and to obtain a representative sample of the population, GPs were randomly selected from the roster of the province of Catania. A further important strength is related to the confirmation of pRBD by a certified sleep specialist, which allowed us to reduce the number of false positives from Stage I to Stage II and to correctly classify the other sleep disorders reported by non-RBD cases at Stage II. As consequence, on one hand, a lower prevalence pRBD has been detected, and on the other hand, the confirmation rate at Stage III was quite high when dRBD and provRBD were considered. Furthermore, patients with suspicion of RBD at Stage II were also extensively evaluated by a movement disorders specialist also able to recognize early stages of alpha-synucleinopathies and to correctly apply the diagnostic criteria to exclude secondary RBD.

In conclusion, our study confirms that isolated RBD is a disease with a low prevalence and has underlined important limits in carrying out population-based surveys to detect dRBD. From an epidemiological point of view, surveys aimed to estimate isolated pRBD are more feasible, even if this kind of study could lead to an overestimation of the outcome. The 2-stage design and the use of sleep specialists to confirm pRBD cases represent an important requirement to reduce the number of false positive patients. Considering that isolated RBD is considered the best "window of time" to test a potential neuroprotective drug that might hinder or stop the progression to an alpha-synucleinopathy,[29] epidemiological guidelines to perform surveys on RBD prevalence are needed to obtain more homogeneous estimates.

ABBREVIATIONS

CI, confidence interval
dRBD, definite RBD
GPs, general practitioners
PD, Parkinson disease
pRBD, probable RBD
provRBD, provisional RBD
RBD, rapid eye movement sleep behavior disorder
RSWA, rapid eye movement sleep without atonia
VPSG, video polysomnography

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