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Probable REM Sleep Behavior Disorder Increases Risk for Mild Cognitive Impairment and Parkinson's Disease: A Population-Based Study

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Abstract

Objective—REM sleep behavior disorder (RBD) is associated with neurodegenerative disease and particularly with the synucleinopathies. Convenience samples involving subjects with idiopathic RBD have suggested an increased risk of incident mild cognitive impairment (MCI), dementia (usually dementia with Lewy bodies) or Parkinson’s disease (PD). There is no data on such risk in a population-based sample.

Methods—Cognitively normal subjects aged 70–89 in a population-based study of aging who screened positive for probable RBD using the Mayo Sleep Questionnaire were followed at 15 month intervals. In a Cox Proportional Hazards Model, we measured the risk of developing MCI, dementia, PD among the exposed (pRBD+) and unexposed (pRBD–) cohorts.

Results—Forty-four subjects with pRBD+ at enrollment (median duration of pRBD features was 7.5 years), and 607 pRBD– subjects, were followed prospectively for a median of 3.8 years. Fourteen of the pRBD+ subjects developed MCI and one developed PD (15/44=34% developed MCI / PD); none developed dementia. After adjustment for age, sex, education, and medical comorbidity, pRBD+ subjects were at increased risk of MCI / PD [Hazard Ratio (HR) 2.2, 95% Confidence Interval (95%CI) 1.3 – 3.9; p=0.005]. Inclusion of subjects who withdrew from the study produced similar results, as did exclusion of subjects with medication-associated RBD. Duration of pRBD symptoms did not predict the development of MCI / PD (HR 1.05 per 10 years, 95%CI 0.84 – 1.3; p=0.68).

Interpretation—In this population-based cohort study, we observed that pRBD confers a 2.2-fold increased risk of developing MCI / PD over four years.

Keywords

sleep disorders; parasomnias; dementia; Alzheimer’s disease; dementia with Lewy bodies; parkinsonism; synuclein

INTRODUCTION

REM sleep behavior disorder (RBD) is a parasomnia in which subjects appear to act out their dreams. It is associated with the synucleinopathies of Parkinson’s disease (PD), PD with Dementia (PDD), Dementia with Lewy Bodies (DLB), Multiple System Atrophy (MSA) and Pure Autonomic Failure.¹ Autopsy studies support a reasonably specific association of RBD with synuclein disorders.^{2, 3} The onset of RBD typically precedes the development of cognitive impairment and/or parkinsonism by years or even decades.⁴ Finally, persons with “idiopathic” RBD appear to have an increased risk of cognitive impairment and/or parkinsonism.^{5–8} These findings, suggesting that RBD represents an evolving synucleinopathy, raise the possibility that selected subjects with RBD might be enrolled in therapeutic trials to prevent progression of the pathology.^{9, 10}

Estimates of the risk of parkinsonism or dementia associated with RBD vary from 18%⁵ to over 65%.^{6, 11} When mild cognitive impairment (MCI) is included in these calculations, the five-year risk of developing a neurodegenerative syndrome is 45%.⁷ However, all risk estimates to date have been determined from clinical samples from sleep or movement disorder clinics. These high estimates could therefore be due to referral bias. Compared to

persons in the general population, subjects recruited from the clinical setting may have a more severe form of the disorder in regard to the frequency, severity, or type of RBD behaviors. More severe REM atonia is associated with a greater risk of developing a neurodegenerative syndrome.¹² A population based estimate would give a more valid estimate across the range of RBD severity. To our knowledge, such an estimate has not been previously reported. We sought to address these issues by identifying and following subjects with probable RBD in a population-based sample.

DESIGN/METHODS

Subjects

Subjects were 70–89 year-old residents of Olmsted County, Minnesota, USA at enrollment in October, 2004. Using the medical records linkage system of the Rochester Epidemiology Project, we randomly selected subjects from the population to participate in the Mayo Clinic Study of Aging, a longitudinal population-based study of aging and MCI.¹³ Written consent for participation was provided by the subjects and their informants, which was typically the spouses or adult children of the subject. All study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.¹³

Diagnostic evaluation

Subjects are evaluated using a standardized clinical protocol and followed prospectively at 15-month intervals using the same protocol as at baseline. A clinician obtains a medical history from the subject and performs a comprehensive neurological examination. The clinician routinely asks about pre-existing dream enactment behavior, and always asks about new-onset dream enactment as part of the structured interview. Particular attention is paid to detecting the cardinal features of PD, and the modified part III of the Unified Parkinson Disease Rating Scale (UPDRS) is completed. The Charlson Comorbidity Index, a measure of illness burden, is computed using information from the participant's medical record.¹³ The clinician, study coordinator and neuropsychologist evaluate and/or diagnose the subject independently prior to a weekly consensus meeting. A consensus diagnosis of normal cognition, or one of the neurodegenerative syndromes (e.g., MCI, dementia, PD) as defined by published criteria, is determined for each subject.¹³ Ninety-one percent of eligible subjects had at least one follow-up visit. Additional details of the MCSA are published elsewhere.¹³

Only cognitively normal subjects without PD at enrollment and with at least one follow-up evaluation were included in the present study. Patients unable to attend the clinic and unwilling to have a home visit were followed with in-depth telephone interviews. Almost all MCSA subjects seek their medical care from one of two provider systems: both use a medical records-linkage system that enables tracking of all patient information. We systematically reviewed the clinical records of participants who withdrew from the study for evidence of neurodegenerative syndrome.¹³ If no clinical diagnosis is made, the subjects were assumed to be cognitively normal. These data are included in a sensitivity analysis.

Probable RBD diagnosis

Assessment for RBD was based on information from the Mayo Sleep Questionnaire (MSQ) provided by someone who sleeps in the same room as the participant. The diagnosis of pRBD is less reliable if informants do not sleep in the same room as the subject; therefore we excluded those subjects. The presence of pRBD is based on an affirmative response to the question: "Have you ever seen the patient appear to 'act out his/her dreams' while sleeping? (punched or flailed arms in the air, shouted or screamed)." Informants answer yes only if dream enactment behavior has occurred at least three times. The MSQ is a validated

screening measure¹⁴ which has 100% sensitivity and 95% specificity for polysomnogram (PSG)-confirmed RBD in this population;¹⁵ it is freely available from <http://www.mayoclinic.org/sleep-disorders/research.html>.

Statistical analysis

We used the Cox proportional hazards model to compute Hazards Ratios, and Kaplan-Meier curves to display the data. The analyses were made to: (a) compare rates of MCI, dementia and PD in subjects with and without pRBD, (b) estimate risk at four years, (c) determine if duration of pRBD predicted diagnosis, and (d) determine if measures of mild Parkinsonism (UPDRS) at enrollment, or changes in these scores over time, differed between the pRBD+ and pRBD− groups. We conducted a stratified analysis to compare rates of MCI, dementia and PD within the groups of patients taking, or not taking, antidepressant medications.

Sensitivity Analyses

Obstructive sleep apnea—Some patients with obstructive sleep apnea (OSA) exhibit dream enactment behavior, and upon detailed questioning of patients and their bed-partners, many of the other historical features of RBD may be present.^{2, 16} If electromyographic atonia is present during REM sleep, then such patients have OSA only, and are often said to have “pseudo-RBD.” Thus a false-positive diagnosis of pRBD can be made in subjects with OSA whose RBD has not been confirmed by polysomnography. We reviewed the data from all available polysomnograms from pRBD+ subjects. We also compared the frequency of OSA features queried on the MSQ between pRBD+ and pRBD− subjects, and added them to our statistical model in a sensitivity analysis. OSA features are captured on the MSQ by the questions, “Has the patient ever snorted or choked him/herself awake?” and “Does the patient ever seem to stop breathing during sleep?”

Antidepressants—Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tri- and tetra-cyclic antidepressants can precipitate or aggravate RBD.^{2, 17, 18} Therefore, we compared the use of these medications (collectively referred to as “antidepressants” henceforth) between the pRBD+ and pRBD− groups. Subjects whose pRBD features began within six months of drug commencement were defined as having medication-associated pRBD. We performed a sensitivity analysis to determine if the exclusion of medication-associated pRBD subjects affected results.

Inclusion of subjects with prevalent MCI—We also determined if pRBD is associated with subsequent diagnosis of dementia or PD when patients with prevalent MCI at enrollment are included. We also adjusted for baseline cognitive status in this model.

Role of the funding sources

The funding sources had no role in the design, data collection, analysis, interpretation or reporting. The corresponding author had full access to all data and was responsible for the decision to publish the report.

RESULTS

Sample characteristics

Of the 1631 subjects who were cognitively normal at baseline, 727 completed the MSQ. Of these, 651 had at least one follow-up evaluation and are included in the analyses (Figure 1, Table 1). None of the incident MCI subjects in the pRBD+ group were taking cholinesterase inhibitors at enrollment when the MSQ was originally completed; one started a cholinesterase inhibitor after development of MCI.

Cognitive and parkinsonism diagnoses

Forty-four subjects with pRBD at enrollment, and 607 without pRBD, were followed for a median of 46 months. Fourteen subjects in the pRBD+ group developed MCI and one developed PD; none developed dementia. Therefore, 15/44=34% of the pRBD+ group developed MCI / PD compared to 94/607=15% in the pRBD- group. Because of the large size of the pRBD- group, most of the subjects that developed a neurodegenerative syndrome were pRBD- at baseline: MCI (90 vs. 14), dementia (8 vs. 0) and PD (4 vs. 1). UPDRS scores did not differ between pRBD+ and pRBD- subjects at enrollment (see Table 1), nor was the change over time in UPDRS scores different between the groups (0.13 per year decrease in both groups, $p=0.76$).

After adjustment for age, sex, education, and medical comorbidity, pRBD+ subjects were at increased risk of MCI / PD [Hazard Ratio (HR) 2.2, 95% CI 1.3 – 3.9; $p=0.005$, Figure 2). Results were similar after additionally adjusting for OSA symptoms [HR 2.0, 95% CI 1.1 – 3.7; $p=0.016$]. Inclusion of subjects who withdrew from the study led to similar results [HR 2.0, 95% CI 1.2 – 3.5; $p=0.01$], as did exclusion of the two pRBD+ subjects with medication-associated RBD [HR 2.4, 95% CI 1.3 – 4.1; $p=0.003$]. A post-hoc within groups analysis revealed a significantly increased risk of MCI / PD associated with pRBD+ among those not taking an antidepressant at enrollment (HR 2.7, 95% CI 1.5 – 5.1, $p=0.002$), but no significant effect among those taking antidepressants (HR 0.74, 95% CI 0.20 – 2.8, $p=0.66$).

RBD characteristics

The median duration of pRBD symptoms was 7.5 years at enrollment (mean 18.7; range: 2 months – 60 years; inter-quartile range (years): 2.0 – 41.5). The median time between onset of dream enactment behavior and diagnosis of MCI / PD was 20.7 years. Despite this apparent difference in duration of pRBD between those who developed MCI / PD and those that did not, duration of pRBD did not predict the outcome in parametric (HR 1.05 per 10 years, 95% CI 0.84 – 1.3; $p=0.68$) or non-parametric analyses (HR 1.07 per 2-fold increase, 95% CI 0.86 – 1.3; $p=0.55$).

Potential confounds in RBD determination

Medication-associated pRBD—pRBD+ subjects were significantly more likely to be taking an antidepressant (23% vs. 7%, $p=0.001$). Ten of the 44 pRBD+ subjects were taking an antidepressant. Two had medication-associated pRBD;^{2, 17, 18} the eight remaining subjects had pRBD symptom onset 2.5– 51 years before antidepressant treatment.

OSA features—Significant differences in the features of OSA were found between the pRBD+ and pRBD- groups (Table 1). Six of the 44 pRBD+ subjects had previously undergone a PSG: all six had periodic limb movements during sleep, and five had OSA (apnea-hypopnea index ≥ 5). Three had undergone PSG within two years of enrollment into the MCSA and so their PSG's were available for blinded, randomized review as part of another study protocol. All three demonstrated the electrophysiologic substrate for RBD: REM sleep without atonia.

Inclusion of subjects with prevalent MCI

When subjects with prevalent MCI at enrollment are added to the original analysis and the outcome measure is changed to dementia or PD, the risk associated with pRBD is no longer significant (HR 0.69, $p=0.48$). Amongst the subjects with MCI at enrollment, 31 of 104 pRBD- subjects developed dementia or PD, whereas 3 of 16 pRBD+ subjects developed dementia or PD.

DISCUSSION

In this population-based cohort of cognitively-normal 70–89 year-olds, pRBD confers a 2.2-fold increased risk of developing MCI / PD within four years. MCI predicts subsequent progression to dementia,¹⁹ and in this population the risk is increased 2.1-fold (Petersen RC et al., unpublished data). These results support and extend the previous clinic-based findings of risk associated with RBD.^{5–7} Despite not coming to clinical attention, the risk of MCI / PD associated with pRBD in the older, cognitively intact population is still quite high. pRBD is worth identifying for clinical and research purposes, and may become far more important for experiment trials of α -synuclein disease-modifying therapies, particularly considering that therapy may be most effective if started early in the disease.

Many patients with apparently idiopathic RBD subsequently develop PD (Table 2). In this study, however, subjects with pRBD developed a cognitive disorder far more frequently than a movement disorder (i.e. 14 patients with MCI vs. 1 patient with PD). Since the development of both cognitive and movement disorders were rigorously assessed by evaluators blinded to the MSQ data and previous evaluations, ascertainment bias is unlikely. Nor do the relatively stringent diagnostic criteria for PD (e.g. requiring akinesia plus one other cardinal feature) account for the findings: there was no between-group difference in the degree or progression of mild parkinsonism (as reflected by the UPDRS scores). Instead the different pattern may reflect clinical sample bias in earlier studies^{5–7} in which subjects had presented to a sleep disorder centre, and not all subjects were rigorously assessed for possible mild cognitive impairment. Conversely, by including only subjects with bed-partners, we may have excluded many subjects with severe RBD. The pattern could also relate to the advanced age of our cohort at enrollment. We suspect that many patients with RBD had developed PD prior to age 70 and thus were excluded from our analysis. This suspicion is heightened further as the median age of onset of PD in Olmsted County, Minnesota, is 71 years.^{20, 21} Enrolling and following a younger cohort of subjects using a similar methodology is warranted.

False-positive pRBD cases suggest true risk of RBD is underestimated

While some of the pRBD+ subjects developed cognitive impairment and/or parkinsonism, many more did not. Some of these subjects may not have RBD (i.e. represent false-positives), and hence their risk of developing cognitive impairment and/or parkinsonism is similar to the normal population. Polysomnography in those who screen positive will allow identification of those with definite RBD. Using the sensitivity and specificity of the Mayo Sleep Questionnaire for true RBD, and the prevalence of RBD, one can determine the positive predictive value of the questionnaire. The sensitivity and specificity of the Mayo Sleep Questionnaire for RBD are 100% and 95% respectively,¹⁵ but the prevalence of RBD is not known. However, we have determined that the prevalence of pRBD in this population is 8.9%.²² Keeping in mind the risk of circularity related to the use of pRBD rather than RBD prevalence data, and noting that subjects are excluded from the Mayo Clinic Study of Aging if they already carry a diagnosis of dementia, we can estimate the positive predictive value of the Mayo Sleep Questionnaire to be 0.66. Therefore our reported hazard ratios likely underestimate the true risk of MCI / PD associated with RBD by this fraction.

Inclusion of subjects with MCI

We did not find an increased risk of dementia or PD when we added subjects with prevalent MCI to our analysis. The strength of the association between MCI and dementia may overshadow the association between RBD and dementia/PD, or may reflect the differing rate at which RBD-associated and non-RBD-associated dementias progress.

Comparison with previous studies

Important differences exist between our study and the others which have characterized RBD-associated risk (Table 2). Subjects in those studies were patients referred to a sleep disorder centre for clinical investigation who had PSG-confirmed RBD and were prospectively followed, or whose data was analyzed retrospectively. In contrast, we prospectively studied cognitively normal, community-dwelling subjects whose bed-partners witnessed recurrent dream enactment behavior. After nearly four years of follow-up, only one subject (2.3%) in the pRBD+ group was diagnosed with dementia or PD. This rate is significantly lower than the lowest 5-year risk estimate (18% of subjects) observed in sleep disorder centre samples.⁵ When MCI is included in the calculations, the five-year risk was 45%,⁷ compared to 39% (after four years) in our sample. Despite these differences, the five-year risk of a neurodegenerative syndrome in our cohort may yet approach those of the clinic-based samples.^{5, 23} The frequency of MCI is higher in the pRBD+ group (31.8% vs. 14.7%), and those with MCI convert to dementia at twice the rate of those without (8.4% vs. 4.0% per year; Petersen et al, unpublished data). Therefore we can expect greater rates of dementia in the pRBD+ vs. pRBD- groups over a longer duration of follow-up. Recent clinicopathologic analyses suggest that those with RBD and MCI – regardless of the MCI subtype – very likely reflect evolving Lewy body disease.^{1–4, 7, 23} All four subtypes of MCI (as represented by amnesic vs. non-amnesic, and single vs. multi-domain dichotomies) were observed in the 14 pRBD+ subjects who developed MCI. This was also the case among several subjects with RBD who evolved from MCI to DLB before Lewy body disease was diagnosed at autopsy in this population.²⁴ Whether those in this cohort with pRBD plus MCI will evolve into DLB will be determined in future assessments.

Confounds and limitations

OSA—A major limitation of the current study is that we rely on bed-partner reports of dream enactment behavior to define pRBD, rather than establishing the diagnosis with a PSG. The bed-partners of pRBD+ subjects were significantly more likely to report features of OSA. Patients with OSA can mimic the symptoms of RBD,¹⁶ and hence some of our pRBD+ subjects may not in fact have RBD. Because OSA has not been shown to be associated with an increased risk of neurodegenerative syndromes, the hazard ratios reported here may represent under-estimates of the true population RBD risk. However, adding OSA symptoms to our statistical model did not substantially change our results. We plan to investigate our pRBD+ subjects with PSG in order to better assess this risk.

Medication-associated RBD—Subjects with pRBD were significantly more likely to be taking antidepressant medications known to be associated with RBD (22.7 vs. 5.4%, $p < 0.001$). In eight of the ten RBD+ subjects taking antidepressants, the onset of dream enactment behavior substantially preceded antidepressant use. We conducted a separate analysis which excluded the remaining two subjects and this did not significantly affect the MCI / PD risk estimates. It is unclear if previous clinic-based studies of RBD associated cognitive impairment or parkinsonism sufficiently accounted for medication-associated RBD. Iranzo et al⁷ included only “idiopathic RBD” subjects, Schenck et al⁶ withdrew “psychotropic medication” for one month prior to PSG, and Postuma et al⁵ withdrew all medications “known to affect sleep” at least two weeks prior to the PSG. While a two- to four-week medication washout is certainly reasonable, there are no data on the natural history of medication-associated RBD after cessation of such drugs. Given the very slow offset of action of these medications,^{25, 26} patients with medication-associated RBD may have been included in previous risk estimates. Whether their inclusion would falsely decrease RBD associated neurodegenerative risk estimates is unknown.

Separate from the possible direct effect of antidepressant medications on RBD is the association of depression and neurodegenerative disease. It is likely that depression is both a prodromal feature of neurodegenerative disease and a reaction to the sense of loss associated with incipient cognitive decline. This may account for the high proportion (23%) of subjects in the pRBD+ group taking antidepressant medication. Given that depression is an independent risk factor for neurodegenerative disease^{27, 28} and that antidepressant medications can precipitate RBD, inclusion of subjects with RBD, depression and antidepressant medication may confound RBD-associated neurodegenerative disease risk assessment. This was reflected in our data: pRBD was associated with a significantly increased risk of MCI / PD among subjects not taking antidepressants (HR 2.7, $p=0.002$), whereas there was no significant association among subjects on an antidepressant (HR 0.74, $p=0.66$).

Clinician not blind to possible RBD—Although clinicians in this study are blind to the MSQ data, they always ask subjects about a history of dream enactment behavior as part of the structured interview. This knowledge could potentially increase their willingness to diagnose MCI, PD or dementia and thus produce an artificially high estimate of the risk associated with pRBD. This is unlikely for several reasons. The diagnosis of normal cognition, MCI, or dementia used in this analysis is based on formal criteria and is made by consensus: the clinician's diagnosis cannot “trump” the others' diagnoses. Furthermore, we reviewed the independent diagnoses at each wave of the study: agreement between the three groups (clinician, study coordinator and neuropsychologist) was 89–92%. The clinicians did not diagnose disease at a rate greater than the other study members ($p \geq 0.5$).

These findings underscore the value of using a sensitive and specific measure for probable RBD in epidemiologic research, particularly to assess the association of RBD with neurodegenerative syndromes and to assess risk that pRBD portends to future course. Screening for RBD will become increasingly important as investigators identify subjects with pRBD, confirm or refute the diagnosis by PSG, and prepare for experimental trials of disease-modifying therapies in neurodegenerative diseases.

ABBREVIATIONS

AD	clinically probable Alzheimer's disease
DLB	dementia with Lewy bodies (as defined by the clinical syndrome)
FTD	behavioral variant frontotemporal dementia
HR	hazard ratio
LBD	Lewy body disease (as defined by pathology)
MCI	mild cognitive impairment
MCSA	Mayo Clinic Study of Ageing
MSA	multiple system atrophy
MSQ	Mayo Sleep Questionnaire
OSA	obstructive sleep apnea
PD	Parkinson's disease
pRBD	probable REM sleep behavior disorder
PSG	polysomnography

RBD	REM sleep behavior disorder
REM	rapid eye movement

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Figure One.
Study participants.

Figure Two.

Neurodegenerative syndrome-free survival adjusted for age (a), or over time in the study (b), in subjects with (+) and without (–) probable REM sleep behavior disorder (pRBD).

Table 1

Demographic Characteristics At Enrollment of Participants with MCSA Study Follow-up

	pRBD+	pRBD–	Total	p value
Subjects	44	607	651	
Age (years)	78 (75, 82)	77 (74, 82)	77 (74, 82)	0.36
Male gender	34 (77.3)	421 (69.4)	455 (69.9)	0.27
Education (years)	12 (12, 16)	14 (12, 16)	14 (12, 16)	0.38
Charlson Index of Comorbid Disease	2 (1, 4)	2 (0, 3)	2 (0, 4)	0.13
Parkinsonism				
UPDRS Motor Subtest – Total	0 (0, 5)	0 (0, 2)	0 (0, 2)	0.63
Total ≥ 4	12 (27.3)	111 (18.3)	123 (18.9)	0.16
Total ≥ 10	2 (4.5)	33 (5.4)	35 (5.4)	1.00
Kokmen Short Test of Mental Status	34 (33, 36)	35 (33, 36)	35 (33, 36)	0.49
Study Follow-up (months)	46 (31, 47)	46 (33, 48)	46 (33, 48)	
Neurodegenerative Syndrome Evolved	15 (34.1)	94 (15.5)	109 (16.7)	
MCI [†]	14 (31.8)	90 (14.8)	104 (16.0)	
Dementia [†]	0 (0.0)	8 (1.3)	8 (1.2)	
PD [†]	1 (2.3)	4 (0.7)	5 (0.8)	
Age at onset of pRBD (years)	69 (35, 76)			
Duration of pRBD [median; mean (25 th , 75 th percentile)]	7.5; 18.7 (2.0, 41.5)			
Use of antidepressant[#]	10 (22.7)	40 (6.6)	50 (7.7)	0.001
pRBD temporally related to use	2 (4.5)			
OSA features				
Snorted/choked themselves awake	20 (45.5)	139 (22.9)	159 (24.4)	0.002
Stopped breathing when asleep	12 (27.3)	92 (15.2)	104 (16.0)	0.052

Numbers in table are N (%) or Median (25th percentile, 75th percentile). Data at enrollment are presented, unless otherwise indicated. MCI: Mild Cognitive Impairment, MCSA: Mayo Clinic Study of Ageing, OSA: Obstructive Sleep Apnoea, PD: Parkinson's Disease, pRBD: probable REM Sleep Behavior Disorder, UPDRS: Unified Parkinson's Disease Rating Scale (Part III).

[†] Subjects can be included in multiple categories: 2 pRBD- subjects developed PD then MCI, 6 pRBD- subjects developed MCI then dementia. 2 pRBD- subjects did not have MCI detected before dementia and are only counted as dementia.

[#] Includes selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and tri- and tetra-cyclic antidepressants. Data includes incident use.

Table 2
Studies of the Risk of Developing a Neurodegenerative Syndrome Associated with Probable or Definite RBD^a

Study	Setting	Cohort N	Percent Male	Mean Age at RBD / pRBD Diagnosis ^c	Developed Degenerative Syndrome N	Mean Years of RBD Symptoms Prior to Degenerative Syndrome	Diagnoses (%)					Cohort Neurodegenerative Syndrome Risk
							MCI	AD	DLB	MSA	PD	
Schenck et al, 1996 ⁵	Patients referred to sleep disorder center	29	100 ^b	52	12	12.7 ^e	n.a.	8	0	0	92	39% at 3.7 years ^f
Iranzo et al, 2006 ⁶	Patients referred to sleep disorder center	44	89	69	20	10.7	20	0	30	5	45	45% at 5 years
Postuma et al, 2009 ⁴	Patients referred to sleep disorder center	93	80	65	26	11.5	n.a.	15	27	4	54	18% at 5 years ^f
This study	Cognitively normal community dwellers	44	70	78 ^d	15	23.9	93	0	0	0	7	41% at 10 years ^f
												34% at 4 years

AD: Alzheimer's disease, DLB: dementia with Lewy bodies, MCI: mild cognitive impairment, MSA: multiple system atrophy, N: number, n.a.: not assessed, PD: Parkinson's disease, pRBD: probable REM sleep behavior disorder, RBD: REM sleep behavior disorder.

^a Important methodological differences exist between these studies which limit direct comparisons, see text.

^b 88% of original cohort of 96 subjects were male.

^c All subjects.

^d Enrolled 70 – 89 year old subjects only.

^e PD subjects only.

^f Does not include MCI.