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CLINICAL REVIEW

The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies

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SUMMARY

Several studies report an association between REM Sleep Behavior Disorder (RBD) and neurodegenerative diseases, in particular synucleinopathies. Interestingly, the onset of RBD precedes the development of neurodegeneration by several years. This review and meta-analysis aims to establish the rate of conversion of RBD into neurodegenerative diseases. Longitudinal studies were searched from the PubMed, Web of Science, and SCOPUS databases. Using random-effect modeling, we performed a meta-analysis on the rate of RBD conversions into neurodegeneration. Furthermore, we fitted a Kaplan-Meier analysis and compared the differences between survival curves of different diseases with log-rank tests. The risk for developing neurodegenerative diseases was 33.5% at five years follow-up, 82.4% at 10.5 years and 96.6% at 14 years. The average conversion rate was 31.95% after a mean duration of follow-up of 4.75 ± 2.43 years. The majority of RBD patients converted to Parkinson's Disease (43%), followed by Dementia with Lewy Bodies (25%). The estimated risk for RBD patients to develop a neurodegenerative disease over a long-term follow-up is more than 90%. Future studies should include control group for the evaluation of REM sleep without atonia as marker for neurodegeneration also in non-clinical population and target RBD as precursor of neurodegeneration to develop protective trials.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia characterized by a consistent loss of the skeletal muscle atonia typically observed during REM sleep in healthy subjects. These periods of REM sleep without atonia allow patients to enact their dreams, which are often characterized by violent behaviors and may result injurious for themselves or their bed partners [1]. According to the 3rd edition of the International classification of sleep disorders (ICSD-3), in order to be diagnosed as RBD, patients have to exhibit repeated episodes of vocalization or complex motor behaviors during REM sleep documented by polysomnography (PSG) or based on clinically history of dream enactment; furthermore, PSG recording is crucial to demonstrate the REM sleep period without atonia [2].

Several studies attested the prevalence of RBD to be between 0.5% and 2.01% in general population [2–5], with a higher incidence in men after the age of 50 [6]. Recently, Haba-Rubio and colleagues [4] performed a full PSG investigation in 1997 participants from the general population and found a prevalence of 1.06% in this sample. The control of environmental safety—such as removing dangerous objects—is crucial for RBD management [7]. Nevertheless, the mainstay for the treatment of this pathology is represented by pharmacological agents. In particular, clonazepam and melatonin have shown clinical effectiveness in reducing RBD symptoms [8,9].

RBD is defined as secondary when it is associated with other neurological diseases, often including α-synucleinopathies such as Parkinson disease (PD), Dementia with Lewy bodies (DLB), and Multiple system atrophy (MSA) [10]. Differently, RBD may be defined as primary (or idiopathic) when it occurs in the absence of any other disorder. However, even in this idiopathic form, RBD often precedes the development of neurodegenerative diseases, in

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Abbreviations

AD	Alzheimer's disease
DLB	Dementia with Lewy bodies
ICSD	International classification of sleep disorders
MCI	Mild cognitive impairment
MSA	Multiple system atrophy
PD	Parkinson disease
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSG	Polysomnography
RBD	REM sleep behavior disorder
REM	Rapid eye movements
RSWA	REM sleep without atonia

particular synucleinopathies. In a seminal work describing this finding, Schenck and collaborators [11] reported that 11 out 29 (38%) patients developed parkinsonism after a mean follow-up of 3.7 ± 1.4 years from the initial diagnosis of RBD. The authors recently published a 16 years update on the same cohort of patients, showing that 21 out of 26 (80.8%) patients who completed the follow-up developed parkinsonism or dementia [12]. This evidence suggests that the duration of follow-up is a critical factor to determine a reliable conversion rate and it led the way to several longitudinal studies suggesting an increasing conversion with increasing follow-up time [13].

Several biomarkers of neurodegeneration have been identified in RBD, including imaging data showing a reduction in dopamine transporter [14], impaired color vision and olfactory function [15], electroencephalography slowing [16], and neurocognitive impairments [17,18]. Taken together, these findings have challenged the existence of an idiopathic form of RBD and the alternative term “cryptogenic” has been proposed to better characterize the complex etiopathogenesis and the high risk of conversion into a neurodegenerative disease [19].

In light of this evidence the aim of the present work is to provide a quantitative evaluation of the risk of conversion from RBD into a neurodegenerative disease, through a systematic review and meta-analysis of longitudinal studies conducted thus far.

Methods

Search method and studies selection

Two researchers (A.G. and L.V.) independently performed a systematic search of the relevant literature up to October 2017 in PUBMED, SCOPUS, and Web of Science. Key terms used were “rapid-eye movement sleep behavior disorder”, “REM sleep behavior disorder”, “RBD”, in combination with “conversion”, “neurodegenerative”, “neurodegeneration”, “synucleinopathies”. These terms could appear everywhere in the body of the manuscript. Further studies were identified by examining the reference list of retrieved papers. To reduce publication bias, both published (i.e., peer reviewed papers) as well as unpublished (i.e., abstract of posters or oral presentations) studies were considered; to this aim, Special Issues of journals reporting conference abstracts (i.e., Sleep, Journal of Sleep Research, Journal of Clinical Sleep Medicine, European Journal of Neurology, Neurological Sciences, Movement Disorders, Sleep Medicine) were also scanned. To reduce language bias the relevant literature was searched for in several languages; however, only English works were deemed suitable. Findings are reported according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [20], elaboration, and explanation [21].

Inclusion and exclusion criteria

In a first step, the eligibility of each manuscript abstract was assessed independently by two investigators (A.G. and L.V.), and disagreements were discussed to reach a common conclusion. Studies meeting the following criteria were included in the review: 1) RBD was confirmed by PSG, according to standard criteria of the ICSD, 2nd edition [22]; 2) the follow-up time was clearly reported. If the follow-up was not reported, the study was included in the review but not in the meta-analysis; 3) the study subjects were human participants; 4) the study reported the rate of RBD phenoconversion.

Studies were excluded if: 1) the manuscript reported a single-case study; 2) the manuscript reported a correlational study or a review; 3) the study was a retrospective study investigating RBD in patients with an outcome of neurodegenerative disease, as in this case the conversion rate would be necessarily 100%; 4) study subjects were animals. An overview of the selection process is depicted by the PRISMA flow diagram in Fig. 1.

Data extraction

The selected manuscripts and abstracts were scanned independently by A.G. and L.V. The extracted data were then compared to ensure that information was correctly assessed. The following variables were deemed relevant: Country where the study was conducted, number of patients being tested, mean follow-up duration (from first visit to diagnosis of conversion or second visit), standard deviation of follow-up, participants' gender, number of patients who converted to a degenerative disease, percentage of converters on the total, type of disease patients converted to (PD, MSA, DLB, Mild cognitive impairment [MCI], not otherwise specified dementia, Alzheimer's disease [AD], others). When patients were lost to follow-up due to death, relocation, or other similar causes, conversion rates were calculated only if demographic details and disease of conversion of the removed participant were provided; otherwise these patients were excluded also from the original sample (e.g., [23]).

Specific methods for the systematic review

The quality of the studies selected for systematic review was assessed using the critical appraisal skills program for cohort studies tool (Critical appraisal skills programme [24]). This checklist is intended to reliably evaluate each study in a systematic way. A.G. and L.V. rated independently the quality of each study; results of this assessment were compared, and disagreements were solved by discussion. For the aim of the present study, the quality assessment focused on the following aspects: Clarity of the research question (Question 1), cohort recruitment (Question 2), selection bias (Question 3), outcome measures (Question 4), possible confounding factors (Question 5, a & b), follow-up completeness (Question 6a) and length (Question 6b), relevance, reliability, and credibility of the results (Question 7, Question 8, and Question 9), applicability of the results (Question 10), and lastly fitness of the results within other available evidence (Question 11). Each study could reach a maximum of 13 points; the average quality score for the selected studies was 11.09. Since all studies scored above 50% of the maximum result, none was excluded from subsequent analyses based on the quality ratings.

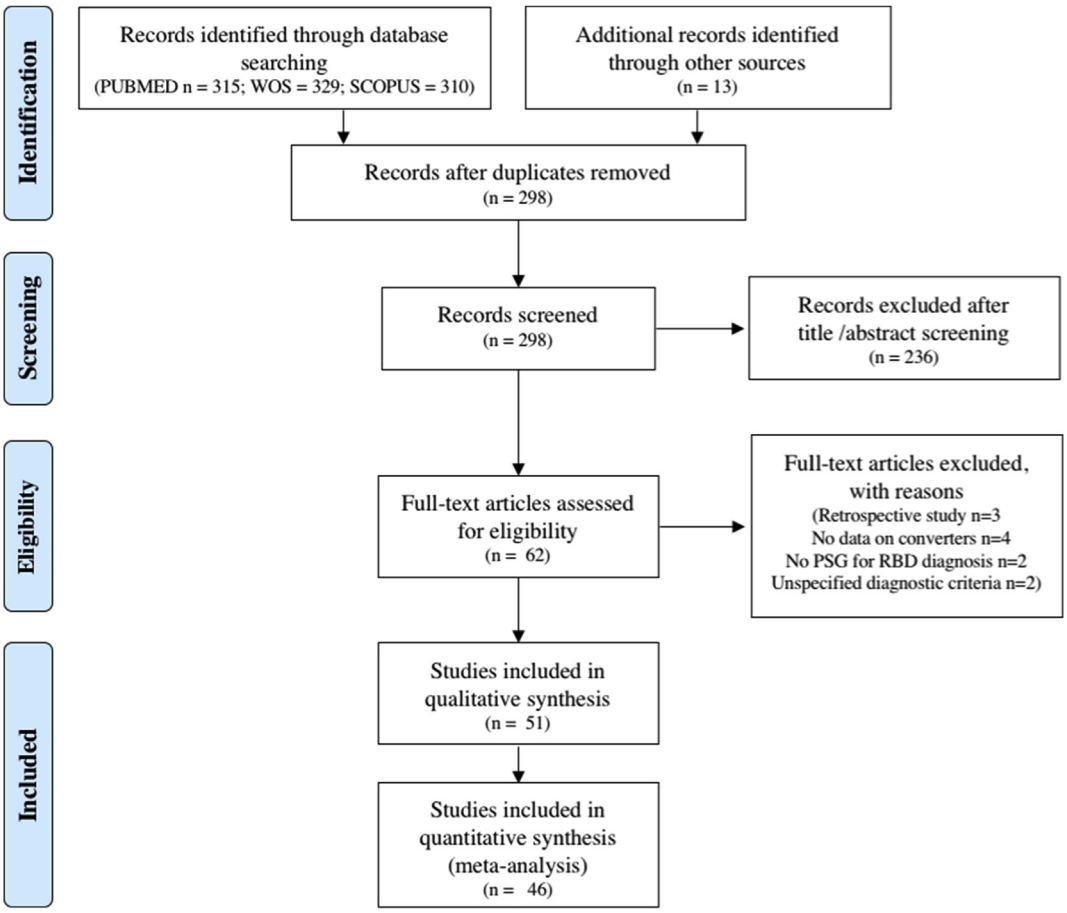

Fig. 1. PRISMA flow diagram summarizing the selection procedure.

Specific methods for meta-analysis

Analyses were conducted using the software R Studio version 1.1.383 (R Studio Inc., Boston, USA) supporting R version 3.4.3 (http://www.R-project.org/). Effects sizes were calculated using the package metafor [25] as log-transformed incidence rates. I^2 statistics was calculated to investigate heterogeneity between studies. Publication bias was controlled for a-priori by including published and non-published material in the systematic review, and assessed for a-posteriori by visual inspection of the corresponding funnel plot. Given the high heterogeneity between studies, a random effects model was employed for the meta-analytic investigation.

In addition, a Kaplan-Meier survival analysis was conducted using the R survival package [26,27] on the conversion rates from the included studies, with number of converters as a dichotomous variable (0 = disease free at follow-up time, 1 = converted) and mean follow-up of each study as the timing variable. The R Survminer package [28] was then used to perform a pairwise log-rank test with a False Discovery rate (FDR) correction on pairwise combinations of treatments.

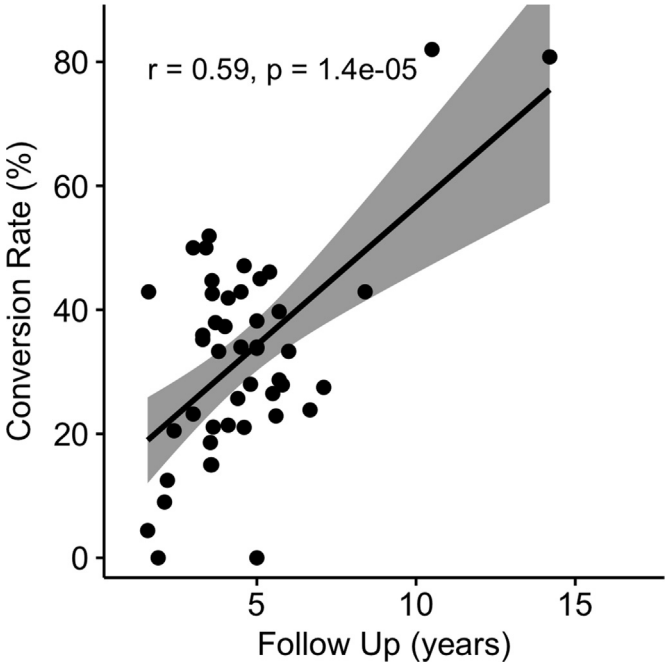

Fig. 2. Correlation between follow-up duration and conversion rate.

Results

Systematic review

The systematic review analyzed 51 studies, including papers published in peer-reviewed journals (N = 43) as well as conference

Table 1
Study characteristics.

Study Number	First author and year	Country	Number of Patients	Follow-up (years)	Age	Gender	Converters	Conversion rate (%)	Disease type							Publication Type
									PD	MSA	DLB	MCI	Dementia	AD	Other	
1	Schenck et al., 1996 [11]	USA	29	3.7 ± 1.4	/	29 M	11	37.93	11	0	0	0	0	1[a]	1[a] cerebro-vascular disease	Paper
2	Fantini et al., 2001 [36]	Canada	19	4.6 ± 2.4	70 ± 4.7	17 M, 2 F	4	21.05	4	0	0	0	0	0	0	Abstract
3	Iranzo et al., 2006 [37]	Spain	44	5.10 ± 2.7	74.1 ± 6.5	39 M, 5 F	20	45.0	9	1	6	4	0	0	0	Paper
4	Stavros et al., 2006[b] [32]	Greece	4	/	/	/	1	25	1	0	0	0	0	0	0	Abstract
5	Iranzo et al., 2009 [30]	Spain	11	5.0 ± 1.9	73.2 ± 5.4	9 M, 2 F	0	0	0	0	0	0	0	0	0	Paper
6	Postuma et al. 2009[b] [33]	Canada	67	/	/	/	17	25.4	6	0	0	0	11	0	0	Paper
7	Postuma et al., 2009 [13]	Canada	93	4.8 ± 3.6	65.4 ± 9.3	75 M, 18 F	26	28.0	14	1	7	0	0	4	0	Paper
8	Iranzo et al., 2010 [38]	Spain	43	3.54 ± 3.00	70.1 ± 6.8	37 M, 6 F	8	18.6	5	1	2	0	0	0	0	Paper
9	Postuma et al., 2010 [23]	Canada	88	6.67 ± 0.59	/	/	21	23.86	11	1	5	0	0	4	0	Paper
10	Postuma et al., 2010 [34],[b]	Canada	52	/	/	/	26	50.0	12	1	7	0	0	6	0	Paper
11	Fantini et al., 2011 [39]	Italy	24	2.19 ± 0.42	69.5 ± 7.3	18 M, 6 F	3	12.5	3	0	0	0	0	0	0	Paper
12	Iranzo et al., 2011 [40]	Spain	20	3.55 ± 2.67	70.55 ± 6.02	18 M, 2 F	3	15	3	0	0	0	0	0	0	Paper
13	Postuma et al., 2011 [15]	Canada	59	5 interval	67.8 ± 9.9	47 M, 15 F	21	33.8	4	0	0	0	17	0	0	Paper
14	Postuma et al., 2012 [41]	Canada	78	3.3 ± 1.8	/	/	28	35.9	12	1	9	0	6	0	0	Paper
15	Dang-Vu et al., 2012 [42]	Canada	20	3.0 ± 0.0	/	/	10	50.0	5	0	5	0	0	0	0	Paper
16	Wing et al., 2012 [43]	China	83	5.6 ± 3.30	/	68 M, 15 F	19	22.89	8	0	1	0	2	8	0	Paper
17	Iranzo et al., 2013 [44]	Spain	19	3.63 ± 2.72	70.78 ± 6.08	17 M, 2 F	4	21.1	3	1	0	0	0	0	0	Paper
18	Iranzo et al., 2013 [45]	Spain	44	Median 10.5	74.0 ± 0.0	39 M, 5 F	36	82	16	1	14	5	0	0	0	Paper
19	Postuma et al., 2013 [46]	Canada	84	4.5	/	/	36	42.9	15	3	18	0	0	0	0	Paper
20	Postuma et al., 2013 [47]	Canada	91	3.30 ± 2.30	70.3 ± 9.4	70 M, 21 F	32	35.2	16	1	15	0	0	0	0	Paper
21	Schenck et al., 2013 [12]	USA	26	14.2 ± 6.2	/	/	21	80.8	13	2	3	0	1	2	0	Paper
22	Terzaghi et al., 2013 [48]	Italy	20	3.58 ± 1.58	66.1 ± 7.1	19 M, 1 F	3	15	2	1	0	0	0	0	0	Paper
23	Holtbernd et al., 2014 [49]	Canada	17	4.60 ± 2.50	68.9 ± 4.8	14 M, 3 F	8	47.1	5	0	3	0	0	0	0	Paper
24	Iranzo et al., 2014 [50]	Spain	55	5.0 ± 0.0	68.9 ± 7.8	47 M, 8 F	21	38.2	11	1	9	0	0	0	0	Paper
25	Iranzo et al., 2014 [51]	Spain	174	Median 4	68.82 ± 6.44	136 M, 38 F	65	37.3	22	2	29	12	0	0	0	Paper
26	Sakurai et al., 2014 [31]	Japan	9	1.90 ± 0.77	71.1 ± 3.2	7 M, 2 F	0	0	0	0	0	0	0	0	0	Paper
27	Zhou et al., 2014 [52]	China	90	1.57 ± 0.82	59.1 ± 15.5	63 M, 27 F	4	4.4	3	0	0	0	1	0	0	Paper
28	Mahlknecht et al., 2014 [53]	Austria, Spain	35	4.40 ± 0.70	/	/	9	25.71	6	0	3	0	0	0	0	Abstract
29	Kim et al., 2014 [54]	South Korea	21	8.40 ± 0.60	66.8 ± 4.7	16 M, 5 F	9	42.9	5	1	2	0	0	0	1	Abstract
30	Rodrigues Brazète et al., 2014 [55]	Canada	52	3.40 ± 0.00	/	/	26	50	/	/	/	/	/	/	/	Abstract
31	Génier Marchand et al., 2014 [56]	Canada	63	1.60 ± 1.10	/	/	27	42.9	11	2	14	0	0	0	0	Abstract
32	Arnulf et al., 2015 [57]	France	69	Median 3	/	/	16	23.2	6	2	0	0	6	0	2 Parkinsonism + dementia	Paper
33	Mahlknecht et al., 2015 [58]	Austria, Spain	34	5.5 ± 4.7	67.8 ± 5.8	29 M, 5 F	9	26.5	6	0	3	0	0	0	0	Paper
34	Postuma et al., 2015 [59]	Canada	89	5.40 ± 2.90	66.9 ± 9.3	73 M, 16 F	41	46.1	17	3	0	0	21	0	0	Paper
35	Postuma et al., 2015 [60]	International	279	3.80 ± 1.40	69.07 ± 8.4	222 M, 57 F	93	33.3	39	7	28	0	19	0	0	Paper
36	Youn et al., 2016 [18]	South Korea	84	4.10 ± 2.12	65.49 ± 6.66	/	18	21.4	9	1	4	0	0	3	1 ataxia	Paper
37	Gan-Or et al., 2015 [35]	International	56	4.50 ± 1.50	/	/	19	34	9	0	10	0	0	0	0	Paper
38	Li et al., 2016 [9]	China	39	2.40 ± 1.11	68.3 ± 7.8	29 M, 10 F	8	20.5	/	/	/	/	/	/	/	Paper
39	Mahlknecht et al., 2016 [61]	Austria	24	6.00 ± 0.00	66.0 ± 5.0	21 M, 3 F	8	33.3	8	0	0	0	0	0	0	Paper
40	Fernandez-Arcos et al., 2016 [62]	Spain	203	5 median	68 median	162 M, 41 F	69	34.0	22	2	32	13	0	0	0	Paper
41	Rodrigues Brazète et al., 2016 [63]	Canada	61	3.60 ± 0.00	/	/	26	42.6	/	/	/	/	/	/	/	Abstract
42		Canada	54	3.50 ± 2.20	66.9 ± 7.6	41 M, 13 F	28	51.9	12	2	14	0	0	0	0	Paper

	Rodrigues Brazète et al., 2016 [64]															
43	Zhou et al., 2016 [65]	China	182	7.10 ± 4.50	/	/	50	27.5	/	/	/	/	/	/	/	Paper
44	Gan-Or et al., 2017 [66],[b]	International	480	/	/	/	140	29.2	98	14	28	0	0	0	0	Paper
45	Li et al., 2017 [67]	China	43	4.1 median	65.15 ± 5.50	34 M, 9 F	18	41.9	12	3	2	0	0	0	0	Paper
46	Génier Marchand et al., 2017 [17]	Canada	76	3.59 ± 2.36	67.36 ± 7.13	56 M, 20 F	34	44.7	17	2	15	0	0	0	0	Paper
47	Zhou et al., 2017 [68]	China	179	5.80 ± 4.30	66.3 ± 9.8	142 M, 37 F	50	27.9	27	2	7	0	0	14	0	Paper
48	Fereshtehnejad et al., 2017 [69]	Canada	121	5.70 ± 3.70	66.40 ± 9.10	90 M, 31 F	48	39.7	/	/	/	/	/	/	/	Paper
49	Tabatabai et al. 2017[b,c] [29].	USA	77	11.7 median	/	77 F	/	/	/	/	/	/	/	/	/	Abstract
50	Barber et al., 2017 [70]	UK	171	2.10 ± 1.25	64.7 ± 9.0	151 M, 20 F	16	9	9	2	1	0	3	0	1 pure autonomic failure	Paper
51	Iranzo et al., 2017 [14]	Spain	87	5.7 ± 2.2	70.0 ± 6.7	67 M, 20 F	25	28.7	11	1	13	0	0	0	0	Paper

[a] Not computed in the original work for conversion rate.
[b] Not included in the meta-analytic calculations.
[c] This abstract report a conversion rate of 91.5% at 21.7% based on survival estimations performed with the Kaplan-Meier method.

abstracts (N = 8) to minimize file drawer effect (publication bias), namely the tendency not to publish negative or null results in peer-reviewed journals. In total, these studies evaluated the rate of conversion of 3942 patients with polysomnographic confirmed idiopathic RBD. However, one study did not report the number of converters [29]; hence, the patients included in this study (N = 77) are not calculated in the total rate of conversion. Of the remaining 3865 patients, 1235 (31.95%) converted into a neurodegenerative disease with a mean follow-up duration of 4.75 ± 2.43 years. Reported diseases of conversion were PD (538 patients, 44% of converters), MSA (62 patients, 5%), DLB (309 patients, 25%), MCI (34 patients, 3%), not better specified dementia (87 patients, 7%), AD (42 patients, 3%), other type of degenerative diseases (6 patients, 0.5%).

The selected studies covered a large variety of follow-up durations and conversion rates, as illustrated by the fact that the lowest conversion rate was 0%, reported by Iranzo and colleagues [30] after a follow-up of five years, and by Sakurai et al. [31] after a follow-up of 1.9 years on average. The highest conversion rate was described by Schenck et al. [12] reporting that 81% of the patients converted into a neurodegenerative disease 14 years after RBD diagnosis.

Duration of follow-up and percentage of converters were significantly correlated ($r = 0.59$, $p < .001$; Fig. 2). 18 studies did not report the mean age of participants at the beginning of the study; those who did (N = 34) revealed an average age of 68.24 ± 2.97 years, with a predominance of males (N = 1902) as compared to females (N = 542).

The studies reported in the systematic review were conducted in 13 different countries. The vast majority was carried out in Canada (13 studies) and Spain (12 studies). Other studies have been executed in Austria (two studies), China (six studies), France (one study), Greece (one study), Italy (two studies), Japan (one study), Korea (two studies), United Kingdom (one study), United States of America (three studies). Two studies were conducted within multiple centers.

The studies included in the systematic review and the corresponding data are summarized in Table 1.

Meta-analysis

The meta-analysis took into account 46 studies including in total 3262 patients. Five studies included in the systematic review were not included in the meta-analysis [29,32–35], because they lacked information on the duration of follow-up.

Heterogeneity between studies was high ($I^2 = 69.93\%$; $Q = 150$). A graphical summary of the results is presented in Fig. 3. The estimated rate of conversion across all studies was 33% [95% C.I. 29.39 to 37.35].

The Kaplan-Meier survival analysis based on the overall conversion rate shows a significant conversion rate from RBD to either one of the selected diseases with an increasing risk over time (Log–Rank test $p < .001$; Fig. 4).

As anticipated by the summary statistics of the systematic review, PD was the main disease of conversion followed by DLB. Pairwise comparisons between different types of diseases were calculated with a log-rank test, FDR adjusted for multiple comparisons. These results are presented in Table 2 and Fig. 5.

Discussion

The aim of this systematic review and meta-analysis was to quantitatively estimate the risk of developing a neurodegenerative disease in patients affected by RBD. Our analysis included all longitudinal studies present in the scientific literature regarding RBD and responding to stringent qualitative criteria.

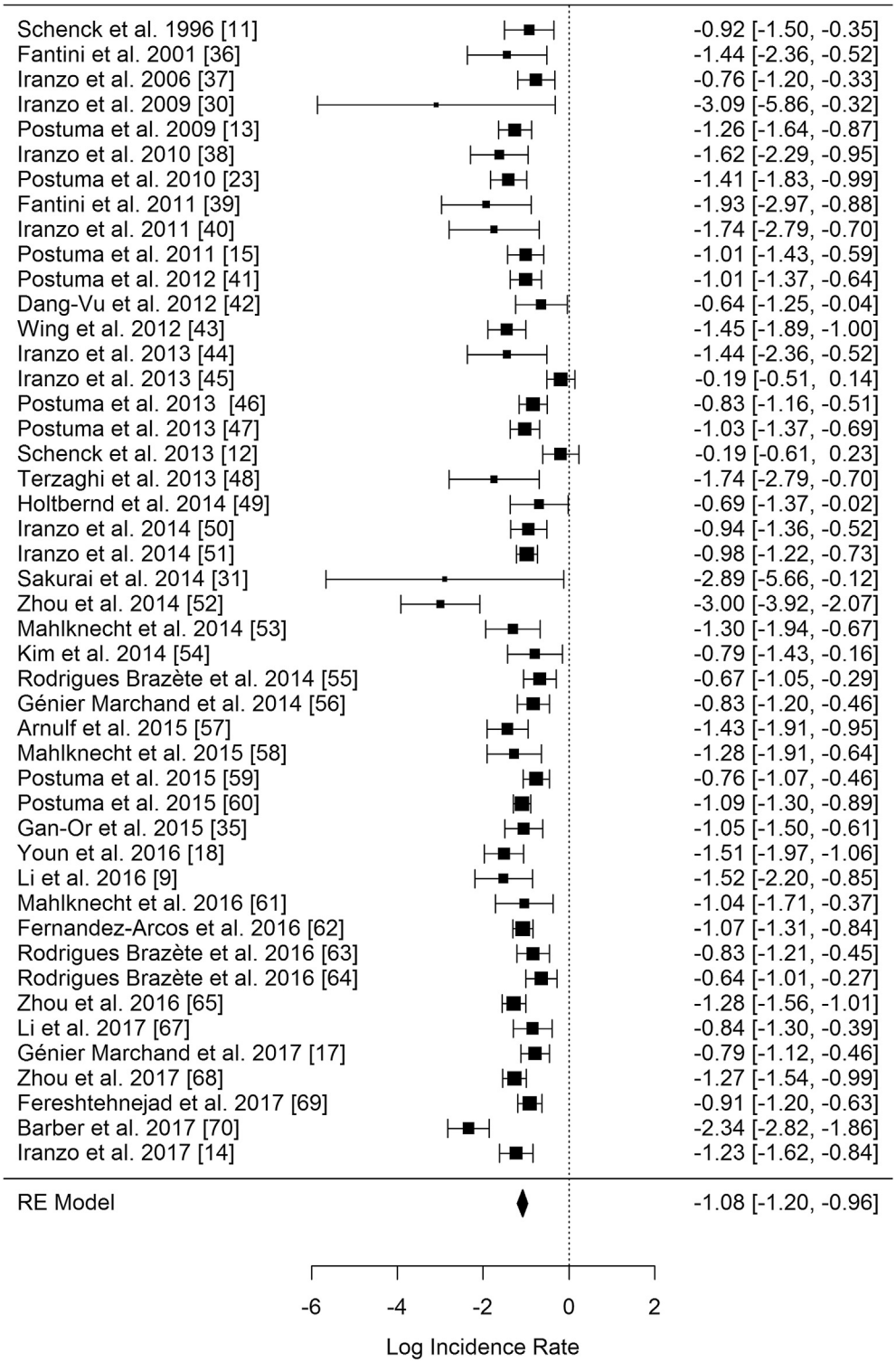

Fig. 3. Graphical summary of the meta-analytic results.

We found a significant risk for developing a neurodegenerative disease: After a mean follow-up of 4.75 ± 2.43 years, 31.95% of RBD patients converted into a neurodegenerative disorder. The most frequent condition was represented by PD (44% of converters), followed by DLB (25%), not otherwise specified forms of dementia (7%), MSA (5%), AD (3%), MCI (3%), and other forms of neurodegenerative disorders (0.5%). By employing a Kaplan-Meier analysis we estimated a conversion risk of 97% after a follow-up of 14.2 years, and a significantly higher risk for developing PD than for any other disorder (Table 2). Furthermore, we found a significant positive correlation between conversion rate and duration of the follow-up (Fig. 2), indicating that the risk of conversion increases over years after RBD diagnosis.

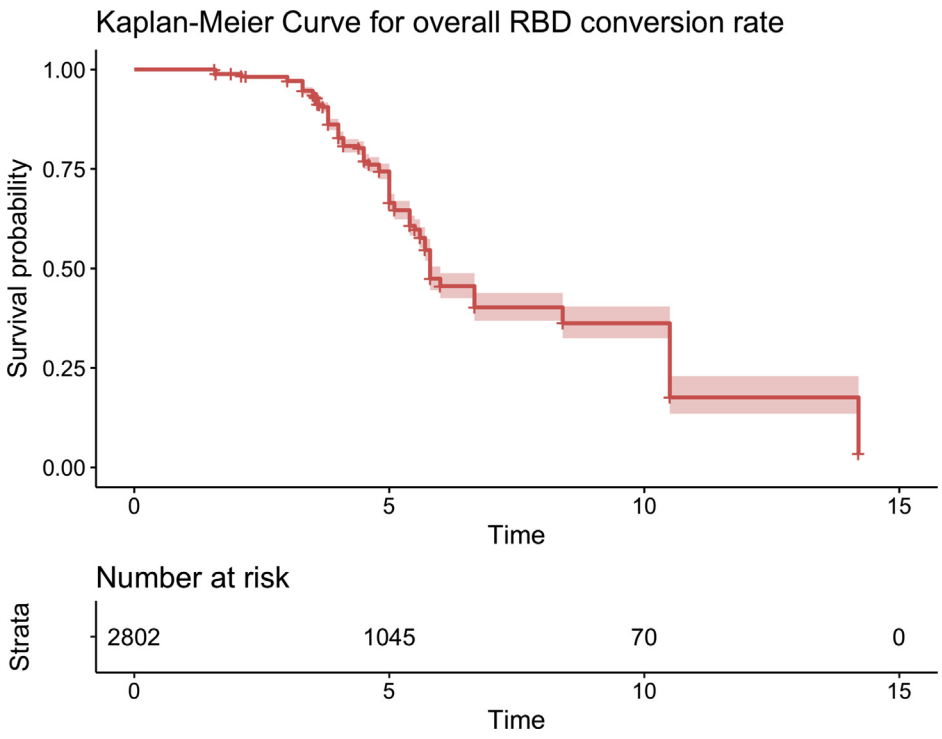

Fig. 4. Kaplan-Meier analysis plotting disease-free survival in RBD patients.

Table 2
Results of the log-rank test comparing the fitted Kaplan-Meier estimates stratified for each disease of conversion.

	PD	MSA	DLB	MCI	Dementia	AD
MSA	<.001					
DLB	<.001	<.001				
MCI	<.001	0.16	<.001			
dementia	<.001	<.05	<.001	<.001		
AD	<.001	0.19	<.001	0.90	<.001	
Other	<.001	<.001	<.001	<.001	<.001	<.001

Since the seminal work by Schenck and collaborators [11] and its subsequent update [12], it has become clear that RBD can precede the onset of parkinsonism and dementia. In those studies, the conversion rate from RBD to a neurodegenerative disease was found to be 38% at 3.7 years with an increase at 80.8% after a mean follow-up of 14.2 years. This observation was recently confirmed by Iranzo and colleagues who showed that the risk of developing an overt neurodegeneration exceeds 90% [51]. The current meta-analysis further confirms a risk higher than 90% at 14 years. Furthermore, it highlights a positive correlation between rate of conversion and length of the follow-up indicating that the risk increases with time in agreement with previous results [11,12].

In patients who develop neurodegeneration, RBD most frequently converts into a synucleinopathy. It is now well established that RBD is a consistent precocious indicator for the insurgence of PD, PD with dementia, DLB, and—only in few cases—MSA [10]. Accordingly, the largest series of idiopathic RBD patients who underwent neuropathological investigation reported clear signs of an underlying synucleinopathy in most cases [71]. DAT-SCAN abnormalities in the substantia nigra and putamen of idiopathic RBD patients have been also found to predict the development of a clinically defined synucleinopathy [14]. Taken together these findings are consistent with the pathological staging hypothesized by Braak and collaborators [72]. In this model neuronal degeneration proceeds upwards from the brainstem, involving structures fundamental for the control of REM sleep atonia—thus causing RBD—, then reaching the midbrain, in particular the substantia nigra—causing parkinsonism. Our study also highlights that not every RBD patient converts to a defined neurodegeneration: RBD may remain idiopathic even after a decade from its diagnosis. However, it is plausible to think that even these long-term idiopathic cases would convert given sufficient follow-up time. This hypothesis is in line with a recent work by Iranzo and collaborators [73] who assessed 20 longstanding idiopathic RBD patients. Results showed the presence of clinical, neuroimaging, and pathological markers for PD, suggesting that also these patients are subject to an underlying neurodegeneration despite not being overtly diagnosed.

Conversion in MCI and AD was far less frequent and comparable to that observed in healthy population [74,75]. This conversion rate challenges the interpretation of MCI and AD as a consequence of RBD in these patients and raises the question if RBD may exhibit pathophysiological relationship with the tauopathies progression or with tauopathies at all [76]. If MCI can be interpreted as an early stage of DLB [77], given sufficient time these patients could evolve in an overt synucleinopathy. The issue is different for AD, which belongs to a different family of neurodegenerative diseases. Only few longitudinal studies reported the development of AD [11–13,18,23,34,68] and only one study reported a post-mortem neuropathological examination demonstrating the presence of AD and DLB histopathological features [12]. These findings suggest that those patients converting from RBD to AD can in reality represent the coexistence of two different dementias, i.e., AD and DLB. However, given the lack of systematical studies future neuropathological examinations are required to confirm this hypothesis.

The discrepancy between the conversions rate in DLB, AD, and other forms of dementia can also have clinical implications. Although the presence of RBD has been included in the core clinical feature for the diagnosis of DLB [78], only one study systematically investigated if adding RBD to diagnostic criteria

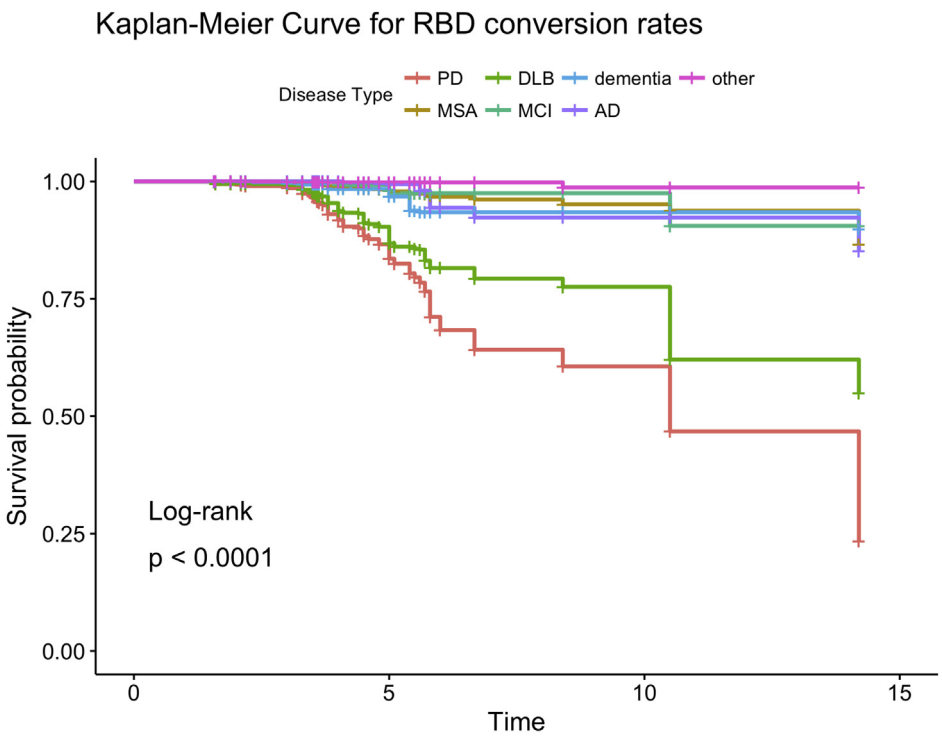

Fig. 5. Kaplan-Meier analysis plotting disease-free survival in RBD patients, stratified for neurodegenerative disease of conversion.

boosts accuracy of autopsy-confirmed DLB [79]. In this remarkable investigation, 234 patients with dementia (DLB, AD, corticobasal and frontotemporal dementia) were followed until autopsy. The inclusion of RBD as a core clinical feature increased the odds of autopsy confirmed DLB by 6-fold. However, it is important to underline that in this study PSG recordings were available for a minority of patients (36 out of 74 DLB patients) and a complete evaluation REM sleep without atonia (RSWA) was not performed. Future studies are needed in order to fully address this point. Concerning AD, the presence of RBD in AD patients or the conversion from RBD into AD may be instead explainable by a "mixed pathology", i.e., the presence of neuropathological features of more than one neurodegenerative disease in the same patient (in this case AD and DLB) [80]. Given this evidence, the employment of PSG-investigation in clinical setting could be useful to differentiate between DLB and AD.

Our meta-analysis considered all longitudinal studies where RBD diagnosis was performed throughout PSG evaluation, following the diagnostic criteria determined by the ICSD-2 [22] and a conversion rate and follow-up length were provided. A careful analysis of these studies revealed some methodological issues that should be taken into account. First, the lack of a healthy control group in a consistent number of longitudinal studies does not allow to quantitatively determining a conversion risk for RBD in comparison to healthy population. In addition, RBD represents a selected clinical population primarily characterized by the loss of physiological REM sleep atonia; however, RSWA may occur even without a diagnosis of RBD. If this neurophysiologic hallmark is able to pinpoint subjects at risk for neurodegenerative diseases, longitudinal studies investigating RSWA also in healthy controls are required to fully address this point. Another relevant matter concerns the diagnostic criteria for neurodegenerative diseases. Clinical diagnosis and the International and Parkinson movement disorder society unified Parkinson's disease rating scale are frequently employed but there is a certain degree of heterogeneity among studies. The picture is even more complex for dementias. Only few studies had autopsy confirmed diagnosis for AD and DLB; furthermore, the employment of outdated diagnostic criteria is frequent. Therefore, future investigations must use updated diagnostic criteria in order to improve classification accuracy. Lastly, it is likely that a certain degree of overlap exists in cohorts of patients reported in different studies conducted by the same authors or belonging to multi-centric studies. While we are aware of this possibility, this has not been fully controlled for in the meta-analysis. Therefore, the risk of conversion here reported might be affected by this confounding factor.

In conclusion, this meta-analysis identified RBD as a strong predictor of neurodegenerative diseases. Synucleinopathies represent the most common outcome for RBD patients. In particular, the risk of conversion to PD is the greatest among all other neuropathologies, followed by DLB—whose risk is significantly greater in comparison to MSA, AD, and MCI (Table 2). The duration of the follow-up is crucial in order to reliably determine the development of a neurodegeneration, as highlighted by the positive correlation between follow-up and conversion rate (Fig. 2). PD prevalence is more than doubled from 1990 to 2015 and this led some authors to refer to a PD pandemic [81]. This might reflect also on the prevalence and conversion rate of RBD. Future systematic longitudinal studies investigating the development of neurodegenerative diseases in RBD patients should focus on improving diagnostic accuracy by employing the most updated criteria, in particular for a consistent differential diagnosis among dementias, and control group for the evaluation of RSWA as a marker for neurodegeneration also in non-clinical populations.

Practice points

1. The conversion of RBD patients into neurodegenerative disease has been extensively investigated.
2. The development of neurodegeneration over time is frequent in RBD patients.
3. Synucleinopathy— in particular PD and DLB—is the most frequent outcome.
4. The length of the follow-up is crucial in order to determine a reliable rate of conversion.

Research agenda

1. Control group should be included in order to determine a conversion risk comparable to healthy population.
2. The employment of the most updated diagnostic criteria should be mandatory and autopsy-confirmed diagnosis is recommendable.
3. Longitudinal studies evaluating RSWA in general population are needed.
4. The possibility to include PSG recordings in clinical routine to perform differential diagnoses among dementias should be evaluated.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

References

[1] Silber M, St Louis E, Boeve B. Rapid eye movement sleep parasomnias. In: Kryger MH, Roth T, editors. Principles and practice of sleep medicine. 6th ed. Philadelphia: Elsevier; 2017. p. 993–1001.

[2] American Academy of Sleep Medicine. International classification of sleep disorders (ICSD-3). 3rd ed. Darien, Illinois: American Academy of Sleep Medicine; 2014.

[3] Kang SH, Yoon IY, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. Sleep 2013;36:1147–52. https://doi.org/10.5665/sleep.2874.

[4] Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, et al. Prevalence and determinants of REM sleep behavior disorder in the general population. Sleep 2018;41:1–8. https://doi.org/10.1093/sleep/zsx197/4690595.

[5] Pujol M, Pujol J, Alonso T, Fuentes A, Pallerola M, Freixenet J, et al. Idiopathic REM sleep behavior disorder in the elderly Spanish community: a primary care center study with a two-stage design using video-polysomnography. Sleep Med 2017;40:116–21. https://doi.org/10.1016/j.sleep.2017.07.021.

[6] Rodriguez CL, Jaimchariyatam N, Budur K. Rapid eye movement sleep behavior disorder: a review of the literature and update on current concepts. Chest 2017;152:650–62. https://doi.org/10.1016/j.chest.2017.03.015.

[7] Galbiati A, Rinaldi F, Giora E, Ferini-Strambi L, Marelli S. Behavioural and cognitive-behavioural treatments of parasomnias. Behav Neurol 2015:1–8. https://doi.org/10.1155/2015/786928.

[8] McCarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF, et al. Treatment outcomes in REM sleep behavior disorder. Sleep Med 2013;14:237–42. https://doi.org/10.1016/j.sleep.2012.09.018.

[9] Li SX, Lam SP, Zhang J, Yu MWM, Chan JWY, Liu Y, et al. A prospective, naturalistic follow-up study of treatment outcomes with clonazepam in rapid eye movement sleep behavior disorder. Sleep Med 2016;21:114–20. https://doi.org/10.1016/j.sleep.2015.12.020.

[10] Ferini-Strambi L, Marelli S, Galbiati A, Rinaldi F, Giora E. REM Sleep Behavior Disorder (RBD) as a marker of neurodegenerative disorders. Arch Ital Biol 2014;152:129–46. https://doi.org/10.12871/000298292014238.

[11] Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older, men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. Neurology 1996;46:388–93. https://doi.org/10.1212/WNL.46.2.388.

*[12] Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 2013;14:744–8. https://doi.org/10.1016/j.sleep.2012.10.009.

*[13] Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296–300. https://doi.org/10.1212/WNL.0b013e3181a52fbe.

*[14] Iranzo A, Santamaría J, Valldeoriola F, Serradell M, Salamero M, Gaig C, et al. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol 2017;82:419–28. https://doi.org/10.1002/ana.25026.

[15] Postuma RB, Gagnon J-FO, Vendette ML, Desjardins C, Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. Ann Neurol 2011;69:811–8. https://doi.org/10.1002/ana.22282.

[16] Sasai T, Matsuura M, Inoue Y. Electroencephalographic findings related with mild cognitive impairment in idiopathic rapid eye movement sleep behavior disorder. Sleep 2013;36:1893–9. https://doi.org/10.5665/sleep.3224.

[17] Génier Marchand D, Montplaisir J, Postuma RB, Rahayel S, Gagnon JF. Detecting the cognitive prodrome of dementia with Lewy bodies: a prospective study of REM sleep behavior disorder. Sleep 2017;40:1–11. https://doi.org/10.1093/sleep/zsw014.

[18] Youn S, Kim T, Yoon I-Y, Jeong J, Kim HY, Han JW, et al. Progression of cognitive impairments in idiopathic REM sleep behaviour disorder. J Neurol Neurosurg Psychiatry 2016;87:890–6. https://doi.org/10.1136/jnnp-2015-311437.

*[19] Ferini–Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): does the idiopathic form of RBD really exist? Neurology 2004;62:41–5.

[20] Moher D, Liberati A, Tetzlaff J, Altman DG. Systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9. https://doi.org/10.1371/journal.pmed1000097.

[21] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6, e1000100. https://doi.org/10.1371/journal.pmed.1000100.

[22] American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual (ICSD-2). 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine; 2005. https://doi.org/10.1111/febs.12678.

[23] Postuma RB, Lanfranchi PA, Blais H, Gagnon JF, Montplaisir JY. Cardiac autonomic dysfunction in idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2304–10. https://doi.org/10.1002/mds.23347.

[24] Programme CAS. CASP cohort study checklist. 2017. http://www.casp-uk.net. [Accessed 7 February 2017].

[25] Viechtbauer W. Conducting meta-analyses in {R} with the {metafor} package. J Stat Software 2010;36:1–48.

[26] Therneau TM, Grambsch PM. Modeling survival data: extending the cox model. New York: Springer; 2000. https://doi.org/10.1007/978-1-4757-3294-8.

[27] Therneau TM. A package for survival analysis in S. 2015.

[28] Kassambara A, Kosinski M. survminer: drawing Survival Curves using "ggplot2". 2017.

[29] Tabatabai G, Boeve A, Commers N, McCarter S, McCord S, Sandness D, et al. Time course for phenoconversion to a defined neurodegenerative disease in women with idiopathic REM sleep behavior disorder with and without antidepressant use. Sleep 2017;40:A268.

[30] Iranzo A, Ratti PL, Casanova-Molla J, Serradell M, Vilaseca I, Santamaría J. Excessive muscle activity increases over time in idiopathic REM sleep behavior disorder. Sleep 2009;32:1149–53. https://doi.org/10.1093/sleep/32.9.1149.

[31] Sakurai H, Hanyu H, Inoue Y, Kanetaka H, Nakamura M, Miyamoto T, et al. Longitudinal study of regional cerebral blood flow in elderly patients with idiopathic rapid eye movement sleep behavior disorder. Geriatr Gerontol Int 2014;14:115–20. https://doi.org/10.1111/ggi.12068.

[32] Stavros B, Anna K, Petros A, Aggeliki B, Georgia A, Konstantinos S, et al. REM behaviour disorder (RBD). J Sleep Res 2006;15:214.

[33] Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Mov Disord 2009;24:2225–32. https://doi.org/10.1002/mds.22757.

[34] Postuma RB, Gagnon JF, Rompré S, Montplaisir JY. Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 2010;74:239–44.

[35] Gan-Or Z, Girard SL, Noreau A, Leblond CS, Gagnon JF, Arnulf I, et al. Parkinson's disease genetic loci in rapid eye movement sleep behavior disorder. J Mol Neurosci 2015;56:617–22. https://doi.org/10.1007/s12031-015-0569-7.

[36] Fantini L, Filipini D, Montplaisir J. Idiopathic REM behavior disorder: a longitudinal study. Mov Disord 2001;16:S58.

* The most important references are denoted by an asterisk.

*[37] Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006;5:572–7. https://doi.org/10.1016/S1474-4422(06)70476-8.

*[38] Iranzo A, Lomeña F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 2010;9:1070–7. https://doi.org/10.1016/S1474-4422(10)70216-7.

[39] Fantini ML, Farini E, Ortelli P, Zucconi M, Manconi M, Cappa S, et al. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. Sleep 2011;34:619–25. https://doi.org/10.1093/sleep/34.5.619.

[40] Iranzo A, Valldeoriola F, Lomeña F, Molinuevo JL, Serradell M, Salamero M, et al. Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 2011;10:797–805. https://doi.org/10.1016/S1474-4422(11)70152-1.

[41] Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. Brain 2012;135:1860–70. https://doi.org/10.1093/brain/aws093.

[42] Dang-Vu TT, Gagnon JF, Vendette M, Soucy JP, Postuma RB, Montplaisir J. Hippocampal perfusion predicts impending neurodegeneration in REM sleep behavior disorder. Neurology 2012;79:2302–6. https://doi.org/10.1212/WNL.0b013e318278b658.

[43] Wing YK, Li SX, Mok V, Lam SP, Tsoh J, Chan A, et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:470–2. https://doi.org/10.1136/jnnp-2011-301232.

[44] Iranzo A, Serradell M, Vilaseca I, Valldeoriola F, Salamero M, Molina C, et al. Longitudinal assessment of olfactory function in idiopathic REM sleep behavior disorder. Park Relat Disord 2013;19:600–4. https://doi.org/10.1016/j.parkreldis.2013.02.009.

*[45] Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol 2013;12:443–53. https://doi.org/10.1016/S1474-4422(13)70056-5.

[46] Postuma RB, Gagnon J-F, Tuineaig M, Bertrand J-A, Latreille V, Desjardins C, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013;36:1579–85. https://doi.org/10.5665/sleep.3102.

[47] Postuma RB, Gagnon J-F, Pelletier A, Montplaisir J. Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. Mov Disord 2013;28:597–604. https://doi.org/10.1002/mds.25445.

[48] Terzaghi M, Zucchella C, Rustioni V, Sinforiani E, Manni R. Cognitive performances and mild cognitive impairment in idiopathic rapid eye movement sleep behavior disorder: results of a longitudinal follow-up study. Sleep 2013;36:1527–32. https://doi.org/10.5665/sleep.3050.

[49] Holtbernd F, Gagnon J-F, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology 2014;82:620–7. https://doi.org/10.1212/WNL.0000000000000130.

[50] Iranzo A, Stockner H, Serradell M, Seppi K, Valldeoriola F, Frauscher B, et al. Five-year follow-up of substantia nigra echogenicity in idiopathic REM sleep behavior disorder. Mov Disord 2014;29:1774–80. https://doi.org/10.1002/mds.26055.

[51] Iranzo A, Fernández-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9, e89741. https://doi.org/10.1371/journal.pone.0089741.

[52] Zhou J, Zhang J, Du L, Li Z, Li Y, Lei F, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case-control study. Sleep Med 2014;15:654–60. https://doi.org/10.1016/j.sleep.2013.12.020.

[53] Mahlknecht P, Seppi K, Iranzo A, Santamaria J, Tolosa E, Serradell M, et al. Olfactory assessment for predicting transition to neurodegenerative parkinsonian disorders in subjects with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective cohort study. Eur J Neurol 2014;21(S1):37.

[54] Kim YE, Kim JM, Lee BC, Kim SE. Development of neurodegenerative disease and dopamine transporter imaging in patients with idiopathic REM sleep behavior disorder: an 8-year follow-up. Mov Disord 2014;29:S293.

[55] Rodrigues-Brazète J, Gagnon J-F, Postuma RB, Bertrand J-A, Petit D, Montplaisir JY. Electroencephalogram slowing as a potential marker for the development of a neurodegenerative disease in REM sleep behavior disorder. Mov Disord 2014;29:S296.

[56] Génier Marchand D, Montplaisir J, Postuma R, Bertrand JA, Paquet J, Desjardins C, et al. Mild cognitive impairment and risk of conversion in rapid eye movement sleep behavior disorder. Mov Disord 2014;29:S344.

*[57] Arnulf I, Neutel D, Herlin B, Golmard J-L, Leu-Semenescu S, Cochen de Cock V, et al. Sleepiness in idiopathic REM sleep behavior disorder and Parkinson disease. Sleep 2015;38:1529–35. https://doi.org/10.5665/sleep.5040.

[58] Mahlknecht P, Iranzo A, Högl B, Frauscher B, Müller C, Santamaría J, et al. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. Neurology 2015;84:654–8. https://doi.org/10.1212/WNL.0000000000001265.

[59] Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015;84:1104–13. https://doi.org/10.1212/WNL.0000000000001364.

*[60] Postuma RB, Iranzo A, Hogl B, Arnulf I, Ferini-Strambi L, Manni R, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. Ann Neurol 2015;77:830–9. https://doi.org/10.1002/ana.24385.

[61] Mahlknecht P, Pechlaner R, Boesveldt S, Volc D, Pinter B, Reiter E, et al. Optimizing odor identification testing as quick and accurate diagnostic tool for Parkinson's disease. Mov Disord 2016;31:1408–13. https://doi.org/10.1002/mds.26637.

[62] Fernández-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. Sleep 2016;39:121–32. https://doi.org/10.5665/sleep.5332.

[63] Rodrigues-Brazète J, Gagnon J-F, Postuma R B, Bourgouin P-A, Petit D, Montplaisir J. Spectral analysis of rapid eye movement (REM) sleep as a potential marker of neurodegenerative disease in REM sleep behavior disorder. Mov Disord 2016;31:S433.

[64] Rodrigues-Brazète J, Gagnon JF, Postuma RB, Bertrand JA, Petit D, Montplaisir J. Electroencephalogram slowing predicts neurodegeneration in rapid eye movement sleep behavior disorder. Neurobiol Aging 2016;37:74–81. https://doi.org/10.1016/j.neurobiolaging.2015.10.007.

[65] Zhou J, Zhang J, Lam SP, Mok V, Chan A, Li SX, et al. Mortality and its risk factors in patients with rapid eye movement sleep behavior disorder. Sleep 2016;39:1543–50. https://doi.org/10.5665/sleep.6016.

[66] Gan-Or Z, Montplaisir J, Ross JP, Poirier J, Warby SC, Arnulf I, et al. The dementia-associated APOE ε4 allele is not associated with rapid eye movement sleep behavior disorder. Neurobiol Aging 2017;49. https://doi.org/10.1016/j.neurobiolaging.2016.10.002. 218.e13-e218.e15.

[67] Li Y, Kang W, Yang Q, Zhang L, Zhang L, Dong F, et al. Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases. Neurology 2017;88:1493–500. https://doi.org/10.1212/WNL.0000000000003838.

[68] Zhou J, Zhang J, Lam SP, Chan JW, Mok V, Chan A, et al. Excessive daytime sleepiness predicts neurodegeneration in idiopathic REM sleep behavior disorder. Sleep 2017;40:1–7. https://doi.org/10.1093/sleep/zsx041.

[69] Fereshtehnejad SM, Montplaisir JY, Pelletier A, Gagnon JF, Berg D, Postuma RB. Validation of the MDS research criteria for prodromal Parkinson's disease: longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. Mov Disord 2017;32:865–73. https://doi.org/10.1002/mds.26989.

[70] Barber TR, Lawton M, Rolinski M, Evetts S, Baig F, Ruffmann C, et al. Prodromal parkinsonism and neurodegenerative risk stratification in REM sleep behavior bisorder. Sleep 2017;40:1–10. https://doi.org/10.1093/sleep/zsx071.

*[71] Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14:754–62. https://doi.org/10.1016/j.sleep.2012.10.015.

[72] Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 2003;110:517–36. https://doi.org/10.1007/s00702-002-0808-2.

[73] Iranzo A, Stefani A, Serradell M, Martí MJ, Lomeña F, Mahlknecht P, et al. Characterization of patients with longstanding idiopathic REM sleep behavior disorder. Neurology 2017;89:242–8. https://doi.org/10.1212/WNL.0000000000004121.

[74] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15:455–532. https://doi.org/10.1016/S1474-4422(16)00062-4.

[75] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: mild cognitive impairment. Neurology 2018;90:126–35. https://doi.org/10.1212/WNL.0000000000004826.

[76] Galbiati A, Carli G, Hensley M, Ferini-Strambi L. REM sleep behavior disorder and Alzheimer's disease: definitely no relationship? J Alzheim Dis 2018;63:1–11. https://doi.org/10.3233/JAD-171164.

[77] Cagnin A, Bussè C, Gardini S, Jelcic N, Guzzo C, Gnoato F, et al. Clinical and cognitive phenotype of mild cognitive impairment evolving to dementia with Lewy bodies. Dement Geriatr Cogn Dis Extra 2015;5:442–9. https://doi.org/10.1159/000441184.

[78] McKeith IG, Boeve BF, DIckson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies. Neurology 2017;89:88–100. https://doi.org/10.1212/WNL.0000000000004058.

[79] Ferman TJ, Boeve BF, Smith GE, Lin S, Silber MH, Pedraza O, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011;77:875–82. https://doi.org/10.1212/WNL.0b013e31822c9148.

[80] Jellinger KA, Attems J. Neuropathological evaluation of mixed dementia. J Neurol Sci 2007;257:80–7. https://doi.org/10.1016/j.jns.2007.01.045.

[81] Dorsey ER, Bloem BR. The Parkinson pandemic - a call to action. JAMA Neurol 2018;75:9–10. https://doi.org/10.1001/jamaneurol.2017.3299.