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Risk Factors for Neurodegeneration in Idiopathic REM sleep Behavior Disorder: A Multicenter Study

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Abstract

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Disclosure

The authors have nothing to disclose in relation to this paper.

Objective—To assess whether risk factors for Parkinson's disease and Dementia with Lewy bodies increase rate of defined neurodegenerative disease in idiopathic REM sleep behavior disorder

Methods—12 centers administered a detailed questionnaire assessing risk factors for neurodegenerative synucleinopathy to patients with idiopathic REM sleep behavior disorder. Variables included demographics, lifestyle factors, pesticide exposures, occupation, co-morbid conditions, medication use, family history, and autonomic/motor symptoms. After 4-years follow-up, patients were assessed for dementia or parkinsonism. Disease risk was assessed with Kaplan-Meier analysis, and epidemiologic variables were compared between convertors and those still idiopathic using logistic regression.

Results—Of 305 patients, follow-up information was available for 279, of whom 93 (33.3%) developed defined neurodegenerative disease. Disease risk was 25% at 3 years, and 41% after 5 years. Patients who converted were older (difference=4.5 years, $p<0.001$), with similar sex distribution. Neither caffeine, smoking, nor alcohol exposure predicted conversion. Although occupation was similar between groups, those who converted had a lower likelihood of pesticide exposure (occupational insecticide=2.3% vs. 9.0%). Convertors were more likely to report family history of dementia (OR=2.09), without significant differences in Parkinson's disease or sleep disorders. Medication exposures and medical history were similar between groups. Autonomic and motor symptoms were more common among those who converted. Risk factors for primary dementia and parkinsonism were generally similar, except for a notably higher clonazepam use in dementia convertors (OR=2.6).

Interpretation—Patients with idiopathic RBD are at very high risk of neurodegenerative synucleinopathy. Risk factor profiles between convertors and non-convertors have both important commonalities and differences.

Introduction

Idiopathic REM sleep behavior disorder (RBD) is characterized by loss of the normal atonia of REM sleep, resulting in apparent acting out of dream content[1]. Numerous single-center prospective cohort studies have now suggested that the majority of patients with idiopathic RBD are in fact in prodromal stages of neurodegeneration, most commonly the synucleinopathies Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA)[2–4]. In single-center studies, conversion rates from idiopathic RBD to full clinical stages have ranged from 8–45% over 5 years[2–6]. Therefore, studying RBD provides a window to observe neurodegenerative synucleinopathies in their prodromal stages, before parkinsonism or dementia become fully manifest.

In 2008, 13 member centers of the International REM Sleep Behavior Disorder Study Group (IRBDSG) began a study to assess risk factors for RBD. We found that like PD, RBD was associated with prior head injury, farming as an occupation, and pesticide exposure. Like DLB, RBD was associated with lower levels of education. Unlike PD and DLB, however, idiopathic RBD patients had no reduction in caffeine use and had an increased likelihood of smoking. Idiopathic RBD patients were more likely to take antidepressants and were more likely to report cardiovascular disease[7]. Although there was no increased prevalence of

proxy-reported PD or dementia among family members, RBD patients were more likely to report a family history of dream-enactment behavior[8]. Finally, patients were more likely to report autonomic symptoms, particularly in gastrointestinal, urinary, and cardiovascular domains[9].

Since publication of the baseline cohort, patients have continued to be prospectively followed in each center. This provides an opportunity to assess if baseline risk factors affect outcome to neurodegenerative disease. It also provides the opportunity to assess neurodegenerative risk for the first time in a multicenter cohort. Therefore, we conducted a prospective follow-up study of patients in the IRBDSG to:

1. Quantify the risk of defined neurodegenerative disease in patients with idiopathic RBD, and
2. Assess whether PD and DLB risk factors may influence the progression of synucleinopathy from prodromal RBD stages to full clinical disease.

Methods

Patients and Centers

Details of recruitment of participants and centers in the baseline study have been previously described[10]. Briefly, 13 centers from the IRBDSG recruited patients with idiopathic RBD (according to standard criteria[11]). All cases had neurologic examination confirming that dementia and parkinsonism were absent. Patients with mild cognitive impairment (MCI) could be included (although the Barcelona and Innsbruck centers did not include MCI patients). All participants provided written informed consent to participate and the research ethics boards of each center gave approval for the study.

Questionnaires

A structured questionnaire queried a diverse set of variables, including:

- **a.** demographics (age, sex, years of education, history of rural living)[10],
- **b.** lifestyle factors - caffeine use, smoking history, alcohol intake[10]
- **c.** exposures - herbicides, insecticides, well water use[10]
- **d.** occupational history, focused particularly on farming, welding, mining, health care and teaching[10],
- **e.** co-morbid conditions[7], particularly neurologic conditions, head injury and atherosclerotic disease
- **f.** current and past medication use[7]
- **g.** family history of neurologic disease and sleep disorders[8]
- **h.** symptoms of parkinsonism, assessed with a four-item questionnaire[12]
- **i.** autonomic symptoms, assessed by the SCOPA-AUT[9, 13]. (participants from the Montreal center did not perform the SCOPA-AUT).

Follow-up study

All centers that participated in the initial cross-sectional study were invited to participate in the follow-up. In order for a center to be eligible, over 70% of their patients had to have had an in-person follow-up examination that was conducted at least two years after the baseline questionnaire administration. Centers recorded the final diagnostic status as of last visit according to the presence or absence of dementia and parkinsonism. Parkinsonism was diagnosed according to the presence of bradykinesia, in association with rigidity or rest tremor. Dementia was diagnosed according to MDS criteria[14], except that depression was not considered an exclusion criteria[15]; either level 1 or level 2 procedures could be used (note that by consensus criteria, all patients meet criteria for possible DLB[16, 17]). To prevent selection bias, any residual patients not be seen in person were evaluated with telephone consultation and chart review. Because there could be up to a 1-year lag between baseline examination and baseline questionnaire administration, we excluded from the analysis any patient who had self-reported baseline PD or dementia and was taking medications for parkinsonism or dementia (even if the most recent examination of the neurologist had not found this).

Analysis

To calculate risk of disease, a Kaplan-Meier Analysis was performed. Time 0 was set at the time of questionnaire administration, with the interval between questionnaire administration and disease onset calculated for each patient (rounded by most centers to the year). For assessing risk factors for conversion, the primary analysis was a comparison of baseline questionnaire variables between RBD patients who eventually developed defined neurodegenerative dementia and/or parkinsonism, and those who remained disease-free. Each variable was assessed using logistic regression, with odds ratios adjusted for age and sex. In addition, to assess whether variables altered the type of clinical presentation, a secondary subanalysis divided Lewy body disease into presentation with primary dementia or primary parkinsonism (excluding multiple system atrophy).

Results

Participants and Disease Outcomes at Follow-up

A total of 12 centers participated in the follow-up study, representing 319 patients diagnosed with idiopathic RBD (Table S5). We excluded 14 patients with possible baseline parkinsonism/dementia, leaving 305 available for analysis. Of these, follow-up information was available for 279 (91.5%). 263 (94.3%) had an in-person examination, and the remaining 16 (5.7%) had telephone follow-up and chart review. The mean follow-up duration (between questionnaire administration and last contact) was 3.8+/−1.4 years.

During follow-up, 93 (33.3%) developed a neurodegenerative disease (Figure 1). The mean interval between questionnaire and disease diagnosis was 2.5+/−1.7 years. On Kaplan-Meier analysis, the risk of neurodegenerative disease was 15% after 2 years, 25% after 3, 36% after 4, and 41% after 5 years. The final diagnosis was PD in 39 (41.9%), dementia in 47 (50.5%) and multiple system atrophy in 7 (7.5%). Of the 37 dementia patients for whom we had full information on clinical DLB hallmarks, 28 (76%) met consensus criteria for probable DLB.

Since the presence of RBD implies at least possible DLB, all met criteria for possible DLB[16].

Risk Factors for Conversion to Disease

Demographics and Lifestyle Factors

Patients who converted to disease were 4.5 years older than those who remained disease free ($p<0.001$) (Table 1). There was no difference between men and women. Median RBD duration was 7 years in convertors and 8 years in non-convertors; this difference was not significant. Convertors had slightly lower education, a difference that became non-significant after adjusting for age and sex.

There was no difference in baseline caffeine use among convertors vs. non-convertors. Whereas we previously found that smoking was a risk factor for RBD, we saw no clear effect upon conversion risk; convertors may have had a slight reduction in smoking exposure as measured by total pack-years (14.6+/−20.2 vs. 18.9+/−23.3), and were half as likely to be current smokers (7.1% vs. 12.4%), but neither of these comparisons were significantly different between groups. There was no difference in baseline alcohol use between those who converted to disease and those who remained disease free. There were no differences in occupation between groups.

Previous pesticide exposure was associated with a *lower* risk of conversion to defined neurodegenerative disease, an effect found for both occupational (insecticide = 2.3% vs. 9.0%) and non-occupational exposure (30% vs. 48%). This effect was primarily driven by insecticide exposure; herbicide exposure was not clearly associated with lower risk. Note that exposure to frequent or occupational pesticides was relatively uncommon in both groups.

Family History of Neurological Disease

Patients who converted to disease had no differences in the reported prevalence of either possible RBD or sleep apnea among family members (Table 2). There was no difference in familial tremor or gait dysfunction. However, patients who converted to disease were more than twice as likely to report a family history of Alzheimer's disease (21.3% vs. 10.7%, OR=2.6 (1.2–5.5)), or any cognitive loss among family members (37.8% vs. 22.6%, OR=2.2 (1.2,3.9)). There was a small increase in family history of Parkinson's disease (9.1% vs. 7.1%), but this difference was not significant.

Medical Co-morbidities/Medications at Baseline

We found no difference in the occurrence of any major medical co-morbidity between those who converted to disease or not (Table 3). In particular, although both cardiovascular disease and depression were risk factors for RBD compared to controls, they did not predict conversion. The only medical co-morbidity with a significant association was hypercholesterolemia, which was lower in those who converted to disease.

Among medications used at baseline, 7.7% of convertors were taking nitro derivatives vs. 1.6% of non-convertors, and 4.4% of convertors were taking neuroleptics, compared to only

0.5% of non-convertors; however, these differences were not significant (Table 3). Although calcium channel blockers have been linked with a lower risk of PD, we found no effect on disease conversion from RBD. Of note, antidepressants, common triggers of RBD, were not associated with risk of conversion. Finally, there was a non-significant increase in both clonazepam (53% vs. 40%) and melatonin use (13% vs. 9%) among convertors.

Autonomic and Motor Symptoms

We found substantial increases in other prodromal symptoms of synucleinopathy between convertors and non-convertors (Table 4). On the SCOPA-AUT, converters had a higher total score than non-convertors (total=14.1+/−6.1 vs. 12.0+/−6.9). This was primarily related to increases in the gastrointestinal (4.5+/−2.6 vs. 3.3+/−2.9) and cardiovascular domains (0.90+/−1.3 vs. 0.58+/−1.07), with an additional non-significant increase in urinary symptoms. Subtle motor symptoms (slowness/stiffness, stooped posture, reduced arm swing, tremor) were also endorsed more frequently in those who converted to disease, with OR ranging from 1.4 - 2.0.

PD vs. Dementia

We then explored whether risk factors could modulate the clinical presentation of Lewy body disease by comparing those with a primary diagnosis of PD vs. dementia (note that power for this comparison is limited) (Table S1-S4). Most variables were similar between groups. Patients who developed primary dementia were 3 years older than those who developed primary PD. Dementia patients drank less coffee at baseline (8.0 cups per week vs. 12.9 for PD). Smoking rates were slightly and nonsignificantly higher in those who were destined to develop dementia. Dementia-first patients had a 2.3-fold OR of reported family history of dementia/cognitive loss compared to PD patients, although this difference did not meet statistical significance. Dementia patients had a non-significant 4-fold increase in reported occurrence of cerebrovascular disease, despite having a borderline lower BMI. Of note, patients diagnosed with dementia were more likely to be taking clonazepam at baseline than those who developed PD (64% vs. 42%, adjusted OR=2.57 (1.01–6.58)). Odds ratio for melatonin use was also increased, although not significantly. There were no differences in prodromal autonomic or motor symptoms among PD or dementia patients.

Discussion

This multicenter study of conversion from RBD to defined neurodegenerative disease has found an overall risk very similar to previously-published single-center estimates. Most risk factors for PD, DLB and idiopathic RBD did not clearly affect progression rate. Notably absent for their effects were caffeine use, smoking, use of dihydropyrimadine calcium channel blockers, and family history of RBD. However, family history of dementia, age, and prodromal autonomic and motor symptoms of disease were associated with higher rate of progression, while prior pesticide use was associated with lower progression rate.

Some limitations should be noted. Although follow-up was relatively complete, 8.5% were lost-to-follow-up, and 6% had telephone follow-up only. It is possible that these patients were more likely to have developed neurodegenerative syndromes. Although we followed

standard diagnostic criteria, diagnosis of disease remains partially subjective; disease may have started earlier or later than diagnosed. However, combining 12 different centers minimizes a single examiners' bias, increasing generalizability of findings. All patients were from sleep disorder clinics; patients screened for RBD from the general population would likely have a different (possibly lower) disease risk. Risk factors were restricted to variables assessable in questionnaires; it is important to continue assessing the predictive value of other more sophisticated markers of prodromal neurodegeneration. Family history data was proxy-reported, which is less reliable; in particular, family members with 'Alzheimer's disease' may actually have had alternate dementia syndromes (particularly DLB, which is commonly misdiagnosed as AD). We did not select a single primary outcome and results are not adjusted for multiple comparisons; therefore, some findings could be due to chance, and this should be considered an exploratory analysis[18]. We chose dementia rather than MCI as the defined cognitive disease; if MCI were considered a disease outcome, risk estimates would differ (unpredictably, since MCI patients would be removed at baseline). Finally, although this is a relatively large study, there is still insufficient power to detect modest differences, particularly for uncommon risk factors.

This study assessed PD/DLB risk factors as modifiers of disease conversion. The relationship between a disease's risk factors and progression from prodromal stages may be more complex than simply 'risk factor=higher progression rate'. Several possible scenarios could include:

1. Risk factors act selectively on only one vulnerable region. A protective factor against PD that protects the substantia nigra but *not* other structures involved in synucleinopathies may not lower risk of its non-motor prodromal syndrome (RBD). Similarly, a risk factor that increases nigral but not cortical degeneration may convert more to 'parkinsonism-first' rather than 'dementia-first' degeneration, and vice versa. For example, if smoking was truly neuroprotective, but worked selectively upon nigral dopaminergic neurons, smokers would not be protected from a non-dopaminergic prodromal state (e.g. idiopathic RBD[10]). Once in this prodromal state, however, they may have higher proportion of 'dementia-first' conversion.

2. Risk factors for PD/DLB may not always increase progression rates. In fact, depending on their mechanism, factors that increase risk of disease may be completely independent of progression rate through a disease's prodromal/clinical stages (or may even associate with slower progression). For example, if risk factors work by producing only an early reserve-reducing 'one-hit', without accelerating progression, they might be associated with RBD, but not with faster progression from RBD to defined disease.

3. Risk factors may also be early disease manifestations. If some 'risk factors' are actually symptoms or signs of PD or DLB, they should increase likelihood of progression from prodromal stages to full clinical disease.

4. Finally, differences between disease convertors and non-convertors can also be due to non-synucleinopathy RBD causes (unrecognized brainstem stroke, 'pure' pharmacologic-caused RBD, etc.). However, long-term cohort studies suggest

that the large majority aged >50 do have underlying synucleinopathy, arguing that our findings relate most to progression rate rather than presence or absence of synucleinopathy[2, 3, 6].

Overall, most environmental risk factors were similar between progressors and non-progressors. This suggests that idiopathic RBD is predominantly a single entity (i.e. prodromal synucleinopathy), rather than a heterogeneous syndrome (with many non-synucleinopathy cases). The positive association with age may suggest that older patients have less compensatory mechanisms to prevent clinical expression of disease. Also, note that although idiopathic RBD is diagnosed much more commonly in men, women had similar risk of neurodegeneration.

The absence of clear protection of caffeine and smoking against both idiopathic RBD[10] and its progression to PD/DLB is intriguing. The inverse relationship between caffeine/smoking and PD is among the most robust findings in epidemiology. Non-use of caffeine may also increase DLB[19]. Numerous studies suggest that RBD in PD marks a disease subtype, characterized particularly by prominent gait impairment, autonomic dysfunction, and increased dementia risk[20–22]. This may suggest that PD is broadly heterogenous, not only in its clinical symptoms, but also in its risk factors, with the RBD-PD/DLB subtype exhibiting a unique risk factor profile. It should be noted, however, that confidence intervals of caffeine and smoking effects in our study include OR as low as 0.4; therefore, a larger study might have demonstrated a protective effect.

Also puzzling is the connection between pesticide exposure and slower progression, given that pesticides are a well-established risk factor for PD, and that exposure is more common among idiopathic RBD patients than controls[10]. Given the age of the cohort, most pesticide exposure (especially occupational exposure) would have been in the past. This could suggest that pesticides increase PD by producing a ‘single-hit’ reserve-reducing lesion, with subsequent slower progression through prodromal stages. It would be of considerable interest to see if PD patients with occupational pesticide exposure also have slower progression once clinical disease has started.

With regards to medications as risk factors, there were two notable negative findings. First, there was no relationship between antidepressant use and a lower risk of progression, as was previously reported[23]. This may reflect patient selection differences. If a center systematically excludes patients taking antidepressants at diagnosis, then any patients with newly prescribed antidepressants at the time of questionnaire are likely to have developed new depression, a prodromal sign of neurodegeneration. This might ‘cancel out’ lower conversion risk among centers that include antidepressant-triggered RBD. The second negative finding is the absence of protection by calcium channel blockers, either from progression, or from idiopathic RBD[7]. There have been suggestions that dihydropyridamine calcium channel blockers prevent nigral degeneration by reducing excitoxicity[24], but epidemiologic studies are contradictory[25]. A randomized trial of isradipine for PD is ongoing[24], which will more definitively assess whether calcium channel blockers protect against neurodegeneration.

There was a concerning relationship between clonazepam use and dementia risk. This may represent confounding by indication; more severely-affected RBD patients could have a higher risk of disease, so require more medications. However, clonazepam might impair cognition, allowing dementia to be diagnosed earlier, or may even worsen cortical function irreversibly[26]. Regardless, this suggests that clonazepam should be used with caution in RBD, perhaps reserved for treatment-resistant patients at risk of injury.

Unlike environmental risk factors, prodromal symptoms of synucleinopathy clearly increased conversion risk. The predictive value of motor symptoms is consistent with single-center studies that document a relatively long motor prodrome of PD[27]. The autonomic findings are new. The only studies that assessed whether baseline autonomic dysfunction predicts outcome in RBD failed to find clear differences[28, 29]; however, point estimates were similar to the current study, suggesting that the negative findings simply reflected lack of power.

Finally, the ability to compare primary parkinsonism vs. primary dementia allowed us to test two what extent these are independent diseases, and if certain risk factors selectively work upon cortical vs. nigral structures. In general, risk factors were very similar, suggesting that ‘RBD-to-DLB’ and ‘RBD-to-PD’ are, from an epidemiologic standpoint, a unified condition. We noted striking similarity in motor and autonomic symptoms between prodromal DLB and PD, similar to single-center studies[27, 28]. The only major difference was that patients converting to dementia were older, perhaps suggesting that dementia will emerge first if there is age-dependent co-morbid cortical pathology, such as amyloid deposition or microvascular disease. Consistent with this, there were nonsignificant trends towards more cerebrovascular disease and family history of dementia in ‘dementia-first’ convertors.

Although our primary aim was to assess epidemiologic risk factors, this also represents the first multicenter study assessing neurodegenerative disease risk in idiopathic RBD. Of note, 10/12 participating centers had not previously published risk estimates[3, 4]. Our findings broadly confirm previous single-center studies; in fact, our overall estimate is remarkably similar to the original paper describing the link between RBD and neurodegeneration (33% at 3.8 years follow-up vs. 38% at 3.7 years)[30]. With observed annual conversion rates of 8–9%, we therefore confirm the very high risk of neurodegenerative synucleinopathy. Moreover, proportion of convertors will continue to increase with further follow-up; the longest-term studies have found near-inevitability of dementia or parkinsonism[2, 3, 6]. This has critical implications, particularly for developing neuroprotective therapy. RBD is by an order of magnitude the most powerful clinical identifier of prodromal PD, DLB and MSA, and so allows a unique opportunity to test potential neuroprotective therapy before symptomatic medications confound assessment and before neurodegenerative processes are too advanced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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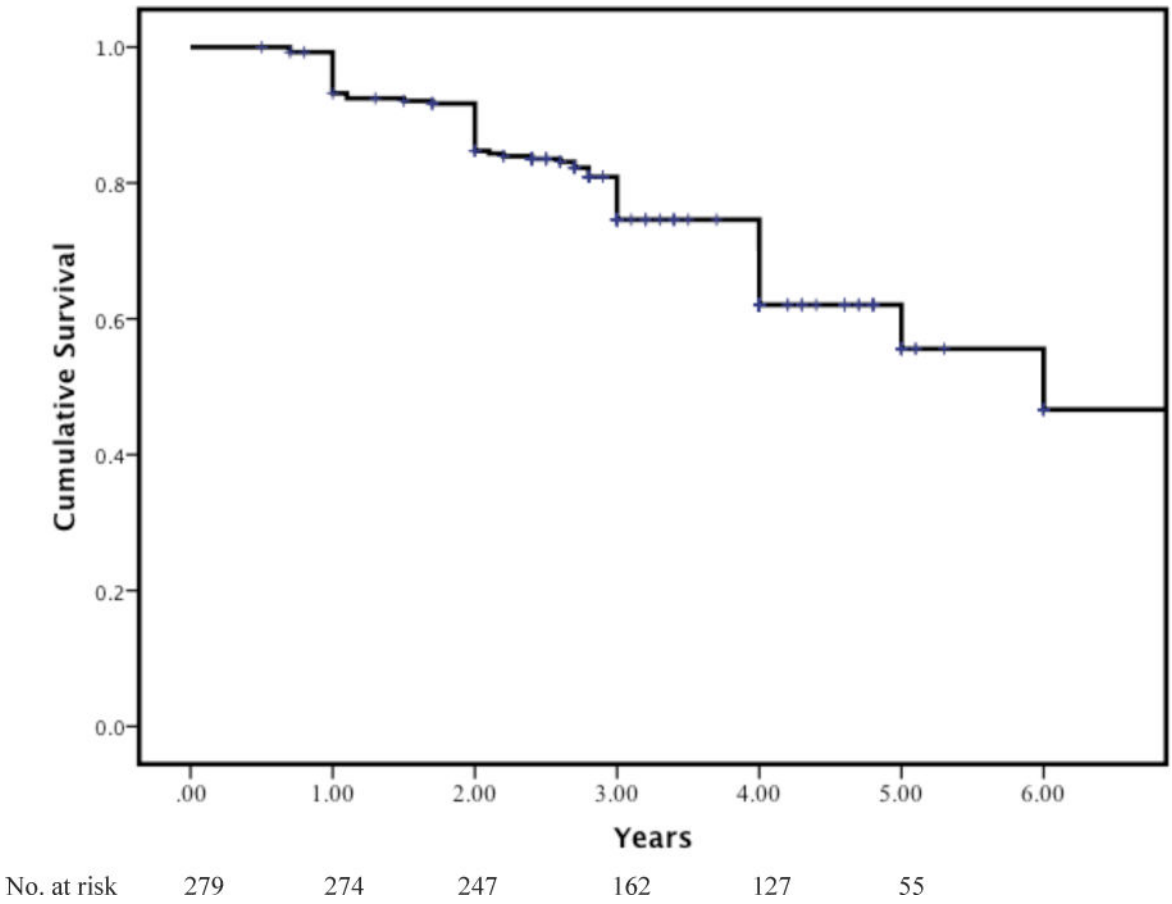

Figure 1.

Shown is a Kaplan-Meier analysis plotting disease-free survival (i.e. Parkinson's disease, Dementia with Lewy Bodies and Multiple System Atrophy) in patients with Idiopathic REM sleep behavior disorder

Table 1

Demographics, coffee, alcohol, smoking, occupation

	RBD converters (n=93)	RBD non-converters (n=186)	Adjusted OR (95% CI)
Age	71.32 ± 7.3	66.82 ± 9.5	**1.07 (1.03–1.10)**
Female	19.4 %	21.0 %	0.87 (0.46–1.66)
Years of education	10.2 ± 4.5	11.3 ± 4.5	0.97 (0.92–1.03)
RBD symptom duration (median,y)	7	8	0.98 (0.95–1.01)
Coffee use, ever	84.8 %	87.0 %	0.88 (0.42–1.88)
Coffee use, current	70.7 %	76.2 %	0.89 (0.49–1.60)
Coffee (cups/week)	10.6 ± 8.9	11.3 ± 8.6	0.998 (0.97–1.03)
Alcohol frequency (0–6)	4.18 ± 2.21	4.48 ± 2.34	0.95 (0.84–1.08)
Alcohol >5 drinks (0–6)	1.63 ± 1.47	1.79 ± 1.46	0.94 (0.77–1.16)
Past alcohol frequency (0–6)	4.44 ± 2.28	4.40 ± 2.25	1.01 (0.88–1.15)
Smoker, ever	64.5 %	62.7 %	1.08 (0.61–1.91)
Current smoker	7.1 %	12.4 %	0.53 (0.20–1.40)
Total Pack-years	14.6 ± 20.2	18.9 ± 23.3	0.99 (0.98–1.002)
Rural living	44.0 %	53.6 %	0.69 (0.41–1.17)
Well water use	41.3 %	40.6 %	0.95 (0.56–1.62)
Farming occupation	18.3 %	21.1 %	0.94 (0.48–1.82)
Welding occupation	20.4 %	14.4 %	2.04 (0.997–4.16)
Teaching occupation	5.4 %	13.4 %	0.42 (0.15–1.17)
Health care occupation	7.6 %	12.7 %	0.55 (0.23–1.33)
Mining occupation	3.2 %	2.8 %	1.19 (0.27–5.19)
Pesticide: occupational use	6.5 %	11.7 %	0.49 (0.19–1.29)
Occupational Herbicide	5.3 %	6.0 %	0.94 (0.23–3.94)
Occupational Insecticide	2.3 %	9.0 %	**0.12 (0.02–0.82)**
Any Non-Occupational Pesticide use	41.8 %	52.0 %	0.72 (0.42–1.22)
Any Herbicide	24.2 %	36.0 %	0.69 (0.38–1.25)
Any Insecticide	30.0 %	47.7 %	**0.56 (0.32–0.97)**
Regular Non-Occupational Pesticide use	4.4 %	14.6 %	**0.25 (0.09–0.72)**
Regular herbicide	1.1 %	5.9 %	0.18 (0.03–1.20)
Regular Insecticide	3.3 %	10.8 %	**0.23 (0.07–0.82)**

Table 2

Family History

	RBD converters (n=93)	RBD non-converters (n=186)	Adjusted OR (95% CI)
Dream-enactment behavior	13.8 %	14.0 %	1.15 (0.51–2.60)
Sleep apnea	14.7 %	23.8 %	0.58 (0.28–1.23)
Essential tremor	3.0 %	6.1 %	0.42 (0.09–1.84)
Any Tremor	11.7 %	10.5 %	1.11 (0.48–2.59)
Walking Trouble	13.0 %	12.9 %	0.996 (0.46–1.77)
Decreased balance	9.3 %	15.4 %	0.63 (0.27–1.49)
Parkinson Disease	9.1 %	7.1 %	1.36 (0.52–3.58)
Alzheimer Disease	21.0 %	10.9 %	**2.47 (1.16–5.27)**
Any Cognitive loss	37.4 %	23.0 %	**2.09 (1.17–3.72)**

Adjusted OR are via logistic regression, adjusting for age and sex.

Table 3

Comorbidities and Medications Used at Baseline

	RBD converters (n=93)	RBD non-converters (n=186)	Adjusted OR (95% CI)
Comorbidities	9.8 %	9.0 %	1.14 (0.47–2.76)
Head Injury (hospitalization)			
Cardio/Cerebrovascular Disease	21.1 %	24.2 %	0.66 (0.35–1.25)
Cardiovascular	15.1 %	16.7 %	0.71 (0.35–1.46)
Cerebrovascular	6.7 %	9.2 %	0.53 (0.19–1.46)
Migraine	17.0 %	21.6 %	0.74 (0.37–1.49)
Depression	33.3 %	27.8 %	1.40 (0.80–2.47)
Hypertension	39.3 %	34.3 %	1.01 (0.58–1.76)
Diabetes	12.5 %	13.4 %	0.50 (0.34–1.66)
Cholesterol	20.2 %	35.4 %	**0.39 (0.21–0.73)**
Obesity	12.9%	19.9%	0.74 (0.36–1.52)
Metabolic Syndrome (at least 2 of above 4)	23.9 %	30.4 %	0.63 (0.35–1.13)
BMI (Current)	25.62 ± 3.50	26.69 ± 5.99	0.96 (0.91–1.02)
Obesity (Age of 40)	4.6 %	10.9 %	0.43 (0.14–1.32)
BMI (Age of 40)	23.76 ± 2.74	24.97 ± 5.52	0.94 (0.87–1.01)
Medications	39.6%	41.9%	0.71 (0.41–1.11)
All Antihypertensives			
Calcium antagonists	11.0%	11.3%	0.83 (0.36–1.89)
Dihydropyridine	11.0 %	7.5 %	
Non-dihydropyridine	0 %	3.8 %	
Nitroderivates	7.7 %	1.6 %	3.60 (0.88–14.83)
Vitamins	19.8 %	19.4 %	1.07 (0.56–2.06)
Analgetics	9.9 %	12.4 %	0.82 (0.35–1.88)
Respiratory	5.5 %	9.7 %	0.50 (0.18–1.42)
Gastrointestinal	24.2 %	24.7 %	0.90 (0.49–1.65)
Urinary System	17.6 %	15.6 %	0.99 (0.50–1.99)
Metabolic	24.2 %	30.1 %	0.60 (0.33–1.09)
Anti-diabetic	12.1 %	10.2 %	1.03 (0.46–2.31)
Lipid lowering	24.2 %	28.0 %	0.69 (0.38–1.25)
Thyroid	7.7 %	6.5 %	1.20 (0.42–3.43)
Osteoporosis	8.8 %	7.0 %	1.50 (0.57–3.94)
Dopaminergic	6.5 %	8.6 %	0.76 (0.28–2.06)
Neuroleptics	4.4 %	0.5 %	8.75 (0.95–80.81)
Anticonvulsants	4.4 %	6.5 %	1.01 (0.29–3.44)
Anticoagulants /Antiplatelets	41.8 %	33.9 %	1.06 (0.62–1.83)
Anti-depressants	6.1 %	4.4 %	1.71 (0.53–5.53)
Past use	18.7 %	20.4 %	0.90 (0.47–1.74)
Ever	19.5 %	17.6 %	1.18 (0.59–2.35)
Current			
Melatonin	14.3 %	9.1 %	1.70 (0.76–3.81)
Clonazepam	51.6 %	41.4 %	1.34 (0.79–2.25)

Adjusted OR are via logistic regression, adjusting for age and sex. Abbreviations: BMI = body mass index

Table 4

Prodromal Symptoms - Motor and Autonomic

	RBD converters (n=72)	RBD non-converters (n=169)	Adjusted OR (95% CI)
Autonomic Symptoms Gastrointestinal	4.44 ± 2.58	3.37 ± 2.89	**1.13 (1.01–1.25)**
Urinary	5.39 ± 2.84	4.63 ± 3.27	1.07 (0.98–1.17)
Cardiovascular	0.90 ± 1.30	0.58 ± 1.07	**1.28 (1.010–1.61)**
Thermoregulatory	1.71 ± 1.85	1.68 ± 1.71	1.04 (0.88–1.23)
Pupillomotor	0.51 ± 0.65	0.50 ± 0.74	1.07 (0.72–1.60)
Sexual (men)	1.26 ± 1.51	1.18 ± 1.56	1.01 (0.83–1.24)
Sexual (women)	0.50 ± 1.401	1.59 ± 2.02	0.73 (0.42–1.25)
Total SCOPA-AUT	14.07 ± 6.05	11.97 ± 6.93	**1.047 (1.003–1.093)**
Motor Symptoms Slow/stiff	55.9 %	42.7 %	1.53 (0.91–2.58)
Stooped posture	42.2 %	25.9 %	**1.88 (1.08–3.29)**
Swing arms	24.4 %	18.4 %	1.16 (0.61–2.20)
Tremor	38.0 %	22.8 %	**2.03 (1.15–3.61)**
Total PD Screen	1.59 ± 1.28	1.08 ± 1.16	**1.32 (1.07–1.63)**

Adjusted OR are via logistic regression, adjusting for age and sex. Abbreviations: SCOPA-AUT = Scale for Outcomes in PD – Autonomic