Risk factors for phenoconversion in Idiopathic REM sleep behavior disorder.

[1,2]H. Zhang, MD, PhD, [3]A Iranzo, MD, [4]B Hogl, MD, [5]I Arnulf, MD, PhD, [6]L Ferini-Strambi, MD, PhD, [7]R Manni, MD, [8]T. Miyamoto, MD, PhD, [9]W Oertel, MD, [10]Y Dauvilliers, MD, PhD, [11]Y Ju, MD, [12]M Puligheddu, MD, [13]K Sonka, MD, PhD, [16]A Pelletier, PhD, [16,17]JY Montplaisir, MD, PhD, [3]J Santamaria, MD, [1]B Frauscher, MD, [5]S Leu-Semenescu, MD, [6]M Zucconi, MD, [7]M Terzaghi, MD, [14]M. Miyamoto, MD, PhD, [9]MM Unger, [10]B Carlander, [12,15]ML Fantini, MD, MSc, MD, [1,16]*RB Postuma, MD, MSc

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada, [2]Department of Neurology, Xuanwu Hospital Capital Medical University, Beijing, China, [3]Neurology Service, Hospital Clinic de Barcelona, IDIBAPS, CIBERNED, Barcelona, Spain, [4]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria. [5]Sorbonne University, Paris Brain Institute and sleep disorder unit, Pitie-Salpetriere Hospital, APHP, Paris, France. [6]Sleep Disorders Center, Università Vita-Salute San Raffaele, Milan, Italy, [7]C. Mondino. National Neurological Institute, Pavia, [8]Department of Neurology Dokkyo Medical University Koshigaya Hospital, Saitama, Japan, [9]Department of Neurology, Philipps-Universität, Marburg, Germany, [6]Department of Neurology, Hôpital Gui de Chauliac, Montpellier, INSERM U1061, Montpellier, F-34093 Cedex 5 France, [11]Washington University Multidisciplinary Sleep Center, St. Louis, MO, USA, [12]Sleep Center, Department of Cardiovascular and Neurological Sciences, University of Cagliari. Italy, [13]Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [14]Department of Neurology Dokkyo Medical University School of Medicine, Tochigi, Japan, [15]Department of Neurology Université d'Auvergne, Clermont-Ferrand, France. [16]Centre d'Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Cœur de Montréal, Montréal, Canada. [17]Department of Psychiatry, University of Montreal

*Correspondence to: Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G1A4; ron.postuma@mcgill.ca (email can be published)

Support: This study was supported by the Fonds de la Recheche en Sante Quebec and the Canadian Institute of Health Research

Running Head: Risk factors for RBD phenoconversion

Word Count: Manuscript Words, Abstract Words

Figures: 1, Tables: 4, Supplemental Tables: 5

Disclosures

Dr. Postuma reports grants and personal fees from Fonds de la Recherche en Sante, the Canadian Institute of Health Research, Parkinson Canada, the Weston-Garfield Foundation, the Michael J. Fox Foundation, the Webster Foundation, and personal fees from Takeda, Roche/Prothena, Teva Neurosciences, Novartis, Biogen, Boehringer Ingelheim, Theranexus, GE HealthCare, Jazz Pharmaceuticals, Abbvie, Jannsen, Curasen and Otsuko, outside the submitted work; . Dr. Arnulf reports consultancy fees from Ono Pharma, Idorsia Pharma and UCB Pharma, outside the submitted work; The present work was helped by an Icrin grant from Paris Brain Institute. Dr. Šonka has served on the speakers' bureau for Sanofi, Angelini, and Stada and as a consultant for AOP Orphan and participated in advisory board for UCB and in clinical trials for Jazz Pharmaceuticals and Flamel-Avadel, all outside the submitted work.

Dr. Stefani has nothing to disclose.

The final article is available at: Zhang, H., Iranzo, A., Högl, B., Arnulf, I., Ferini-Strambi, L., Manni, R., Miyamoto, T., Oertel, W. H., Dauvilliers, Y., Ju, Y. E., Puligheddu, M., Sonka, K., Pelletier, A., Montplaisir, J. Y., Stefani, A., Ibrahim, A., Frauscher, B., Leu-Semenescu, S., Zucconi, M., Terzaghi, M., … Postuma, R. B. (2022). Risk Factors for Phenoconversion in Rapid Eye Movement Sleep Behavior Disorder. *Annals of Neurology*, *91*(3), 404–416. https://doi.org/10.1002/ana.26298

Abstract

Objectives: To follow-up predictive factors for clinical neurodegeneration in a multicenter cohort of idiopathic/isolated REM sleep behavior disorder (iRBD).

Methods: Patients with iRBD from 12 centres underwent a detailed assessment for potential environmental and lifestyle risk factors via a standardized questionnaire at baseline. Patients were then prospectively followed and received assessments for parkinsonism or dementia during follow-up. The risk of parkinsonism or dementia was estimated with Kaplan-Meier analysis. Cox regression analyses were used to evaluate the predictive value of environmental/lifestyle factors over a follow-up period of 11 years, adjusting for age and sex.

Results: Of 319 patients who were at baseline free of parkinsonism or dementia, 281 provided follow-up information. After a mean follow-up of 5.8 years, 130 patients developed neurodegenerative disease. The overall phenoconversion rate was 24.2% after 3 years, 44.8% after 6 years, and 68.1% after 10 years. Patients with older age (adjusted hazard ratio (HR) 1.06), a positive family history of cognitive loss (adjusted HR 1.56), clonazepam use (adjusted HR 1.50), and nitrate derivative use (adjusted HR 2.54) were more likely to phenoconvert, whereas prior pesticide exposure (adjusted HR 0.21–0.68), hypercholesterolemia (adjusted HR 0.64), and respiratory drug use (adjusted HR 0.40) were associated with lower phenoconversion risk. Risk factors for those converting to primary dementia and parkinsonism were generally similar, except for a lower coffee intake and higher prevalence of clonazepam use in dementia converters.

Conclusion: Our findings elucidate the predictive values of environmental factors and comorbid conditions in identifying RBD patients at higher risk of phenoconversion.

Introduction

Idiopathic/isolated REM behavior disorder (iRBD) is a parasomnia characterized by loss of normal muscle atonia during REM sleep and dream-enacting behaviors[1]. Numerous studies have demonstrated a strong association between iRBD and the development of neurodegenerative α-synucleinopathies (i.e. Parkinson's disease (PD), Dementia with Lewy-bodies (DLB), and multiple system atrophy (MSA))[2-4]. iRBD is now considered to be an early stage of these α-synucleinopathies, with patients often developing defined neurodegenerative disease after a decade or more. Therefore, iRBD allows a window into early stages of neurodegenerative disease.

In 2008, 13 centers of the International RBD Study Group (IRBDSG) recruited patients with iRBD to assess environmental, lifestyle and medical risk factors for RBD[5]. After 4-year follow up, we reported that 33.3% of a series of 279 patients with iRBD developed a neurodegenerative disease[6]. In that report, we found that family history of dementia, age, and prodromal autonomic and motor symptoms of disease were associated with higher rate of disease progression, while pesticide use was associated with lower progression rate. Since publication of the baseline cohort, patients were still being continuously prospectively followed in each center. We now provide a 6-year update from our 2015 report, with the primary focus being to assess the predictive factors for disease conversion from iRBD to neurodegenerative synucleinopathies. An additional secondary analysis was to investigate whether risk factors were associated differently with primary parkinsonism vs. primary dementia.

Methods

Patients and Centers

Patients with polysomnography-confirmed iRBD were recruited from 13 member centers from IRBDSG from 2008 to 2011. The diagnosis of iRBD was made based on the standard International Classification of Sleep Disorders criteria (ICSD-II)[7]. All participants underwent neurological examinations to exclude dementia or parkinsonism. Patients with mild cognitive impairment (MCI) could be included except that the

Barcelona center excluded patients with MCI from their baseline cohort. All participants provided written informed consents according to the Declaration of Helsinki, and ethics approval was obtained from the local research ethics board of each center.

Baseline Questionnaire

A structured questionnaire assessed a set of risk factors previously reported to be associated with PD or dementia. Detailed information and findings of the questionnaire study have been described previously[5, 6, 8-10]. The questionnaire included: (1) demographics (i.e. age, sex, years of education, marital status, history of rural living, and occupation, specifically questioning for history of farming, welding, mining, health care, and teaching); (2) lifestyle risk factors (coffee and caffeinated tea intake, alcohol consumption, and smoking history); (3) exposure history (occupational and nonoccupational exposure to pesticides (herbicides and insecticides), well water use); (4) comorbid conditions (history of traumatic head injury, cardio/cerebrovascular disease, migraine, depression, hypertension, diabetes, hypercholesterolemia); (5) BMI with obesity defined as BMI $\geqslant$30 kg/m^2; (6) Family history of neurological diseases (tremor, Parkinson's disease, Alzheimer's disease, cognitive decline, waking trouble, decreased balance) and sleep disturbances (dream enactment behaviors, possible sleep apnea); (7) current and past medication use.

Follow-up study and disease conversion

All centers prospectively followed patients to diagnose phenoconversion to defined parkinsonism or dementia. To ensure eligibility of a center, more than 70% of the enrolled patients had to have at least one in-person follow-up neurological examination conducted at least two years after baseline questionnaire administration. Parkinsonism was defined as the presence of bradykinesia plus either rigidity or rest tremor[11]. Dementia was defined according to the Movement Disorders Society criteria for dementia in PD[12] (both level 1 and level 2 testing could be used as screening tools, except that major depression was not an exclusion criterion) or consensus criteria for dementia with Lewy bodies[13]. For patients with parkinsonism-first manifestations, clinical diagnoses of PD or MSA were made according to best clinical impression, supplemented by diagnostic criteria described by the MDS/UK brain bank and Gilman et al[11, 14]. All follow-up information was used to make the differential diagnosis (i.e. a patient initially diagnosed as PD but later found to have MSA would be included as MSA). All patients with dementia conversion meet criteria for probable DLB according to the 2017 criteria[13] in which a core clinical feature (dream enactment behavior) plus the indicative biomarker of PSG-confirmed REM sleep without atonia makes a diagnosis of probable DLB.

Statistical Analysis

To analyze disease risk, we performed Kaplan-Meier analysis to estimate the rates of disease progression-free survival. Time=0 was the time of baseline questionnaire administration, and the time variable was set as years from baseline questionnaire administration to the censoring date (date of last follow-up visit or death) for non-converters, or to the date of neurodegenerative disease onset for converters. For assessing predictive values of risk factors for disease conversion, the primary analysis was Cox proportional hazards analysis. Each baseline questionnaire variable was analyzed using Cox regression, with hazardsratios (HRs) adjusted for baseline age and sex. On secondary analysis, among the converters who were diagnosed with Lewy body disease (excluding MSA), we performed logistic regression analyses to compare the variables between those who eventually developed dementia as the primary disease manifestation and those who developed parkinsonism as primary disease manifestation, again adjusting for age and sex.

Results

Participants characteristics and overall outcomes during follow-up

A total of 319 patients with iRBD from 12 centers participated in the follow-up study. Recruitment information from each center is summarized in Table S4. Of the 319 patients included, 281 (88.1%) had available follow-up information. 251 (89.3%) patients had in-person examination of last visit and the remaining 30 (10.7%) had telephone interview.

During follow-up, 130 of 281 (46.3%) patients developed an overt neurodegenerative synucleinopathy (Figure 1). The mean interval between baseline questionnaire and disease diagnosis was 4.02 ± 2.50 years. The median time to phenoconversion was 3.5 years. Kaplan-Meier curve showed that the risk of neurodegenerative disease was 14.5% after 2 years, 24.2% after 3 years, 44.8% after 6 years, 60.1% after 8 years, and 68.1% after 10 years. The diagnosis was PD in 61 patients (46.9%), DLB in 60 patients (46.2%), and MSA in 9 patients (6.9%).

Demographics and lifestyle factors

The mean age at baseline was 68.5 ± 8.5 years and 227 (80.8%) were male. Patients who developed neurodegenerative diseases were 3.6 years older than those who remained disease-free ($p<0.001$). There was no difference in sex, marital status, rural residence, or occupation between converters and non-converters. The median RBD symptom duration prior to diagnosis was 8.0 years in converters versus 7.3 years in non-converters ($p>0.05$). Converters had slightly less of years of education compared with non-converters (mean years of education: 10.2 vs. 12.0 years), but this did not reach statistical significance after adjusting for age and sex.

Although coffee use was previously reported as a protective factor for PD[15, 16], we found no association between coffee intake and RBD phenoconversion. There was also no difference in baseline caffeinated tea use between converters and non-converters. Smoking has been reported to be a risk factor for iRBD in previous epidemiological studies[5, 17, 18], however, we found no association in either current smoking or ever-smoking with RBD conversion risk. Converters had slightly lower total pack-years compared with non-converters at baseline (15.7±20.7 vs. 21.0±27.9), although this did not reach statistical significance after adjusting for age and sex. There was no significant association between baseline alcohol consumption and RBD conversion risk.

Although pesticide exposure was increased in RBD patients compared to controls in this cohort[5,19], on follow-up we found that patients with occupational pesticide exposure were less likely to develop a defined neurodegenerative disease (age- and sex-adjusted HR 0.47, 95% confidence interval (CI) 0.22–0.99). This inverse association was mainly driven by occupational insecticide exposure (adjusted HR 0.21, 95% CI 0.06–0.72); occupational herbicide exposure had no association with the lower conversion risk. In addition, non-occupational insecticide exposure was also associated with a lower risk of disease conversion from iRBD to neurodegenerative disease (adjusted HR 0.68, 95% CI 0.45–0.98).

Family History of Neurological disease

There was no difference in reported family history of possible RBD symptoms or possible sleep apnea between patients who converted to neurodegenerative disease and those who remained disease-free. No significant difference was observed in reported family history of tremor, walking trouble, decreased balance, PD, or memory loss/Alzheimer's disease between converters and non-converters. However, patients who reported a family history of any cognitive loss had a higher risk of developing neurodegenerative disease (converters vs. non-converters 31.8% vs. 24.5%, adjusted HR 1.56, 95% CI 1.07–2.26).

Medical comorbidity and baseline medication history

We found no significant difference in the frequency of comorbid cardiovascular or cerebrovascular disease, migraine, cancer, hypertension, diabetes, or obesity between converters and non-converters. Both head injury and depression did not predict disease conversion in the current study. Patients with comorbid hypercholesterolemia were found to have a significantly lower risk of developing neurodegenerative disease (adjusted HR 0.64, 95% CI 0.43–0.96).

Among the medications used at baseline, we found that concurrent usage of nitrate derivatives was associated with an increased risk of RBD phenoconversion (adjusted HR 2.54, 95%CI 1.26–5.12). β2-adrenoreceptor agonist has been associated with a decreased PD risk and β2-adrenoreceptor antagonist may be associated with PD risk[20, 21]. Patients taking respiratory drugs (which would include β2-adrenoreceptor agonists) at baseline had a lower risk of developing neurodegenerative disease (adjusted HR 0.40, 95% CI 0.16-0.99). Given that smoking is a protective factor for PD and smoking-related pulmonary conditions are important indications for β_2-adrenoreceptor agonists[16], we further examined the predictive value of respiratory drugs in Cox regression analysis with additional adjustment for smoking. The inverse association between β_2-adrenoreceptor agonist use and RBD phenoconversion remained unchanged after additional adjustment for smoking (adjusted HR 0.39, 95% CI 0.16-0.97). However, the effect appeared to be similar between those using B-agonists and other inhaled preparations such as corticosteroids, suggesting possible confounding by indication. No difference was observed in the beta-blocker use at baseline between converters and non-converters. Calcium channel blockers were also not predictive of disease conversion from iRBD to neurodegenerative disease. Of note, patients with clonazepam use had a higher risk of developing neurodegenerative disease in iRBD (adjusted HR 1.50, 95% CI 1.05–2.15).

PD versus Dementia

We further evaluated the association between epidemiologic factors and clinical phenotype of Lewy body disease by comparing patients who converted to dementia first and those who converted to PD first. Among the 121 patients diagnosed with Lewy body disease (MSA was excluded), very few differences existed between the two groups. Patients who converted to PD first drank more coffee at baseline compared with patients who developed primary dementia (11.5 cups per week in PD vs. 7.9 cups per week in dementia, adjusted odds ratio (OR) 1.06, 95% CI 1.003–1.13). Dementia-first patients had a slightly higher reported prevalence of family history of memory loss or Alzheimer's disease than PD-first patients, but the difference did not reach statistical significance. Patients who converted to PD first were less likely to use clonazepam (45.0% vs. 67.2%, adjusted OR 0.39, 95% CI 0.18–0.84) or all combined benzodiazepines (38.3% vs. 62.1%, adjusted OR 0.40, 95% CI 0.19–0.86) at baseline compared with those who developed dementia first.

Discussion

In this large multicenter study, we provide updated estimates of environmental/lifestyle conditions, comorbidities, and medication as risk factors for phenoconversion from iRBD to defined neurodegenerative disease. In line with the previous findings in 2015, we confirmed that age, family history of cognitive loss, and clonazepam use were associated with higher risk of disease conversion, whereas prior pesticide exposure, and history of hypercholesterolemia were associated with lower risk. With longer follow-up and consequent larger number of convertors, we now have found that respiratory drug use was associated with lower phenoconversion risk, while nitro derivatives were associated with higher risk. Risk factors were similar between those converting to dementia first vs. parkinsonism-first, except for reduced caffeine intake and increased benzodiazepine use, which represented risk factors for dementia-first conversion.

Several clinical markers have been shown to predict the risk of conversion to α-synucleinopathies in patients with iRBD, including prodromal nonmotor symptoms, brain imaging markers, and motor/cognitive testing[22]. Few studies have investigated the predictive values of environmental factors in identifying RBD patients at higher risk of disease conversion. This study revealed that most environmental risk factors for PD/DLB did not predict clinical neurodegeneration in RBD. For example, smoking and caffeine use are clearly associated with lower risk of PD, but were not associated with RBD conversion to α-synucleinopathies. As previously discussed[6], protective factors against PD could possibly selectively protect nigral dopaminergic neurons, but not the non-dopaminergic neurons in extranigral structures involved in prodromal synucleinopathy (i.e. iRBD). Alternatively, RBD may mark a unique subtype within neurodegenerative diseases, with different clinical and genetic profiles[23-25], indicating that RBD-PD and RBD-DLB may have an independent risk factor profile. Of note, all the hazard ratios of the variables associated with smoking and caffeine use were less than 1; thus, future large-scale prospective studies are needed to clarify whether smoking and caffeine use could slow the disease progression and reduce phenoconversion risk.

The strongest risk factors for iRBD are increased age and male sex[26]; however, we only found advanced age predicted neurodegeneration in iRBD. This supports the fundamental role of aging in neurodegeneration. Pesticide exposure is another well-known risk factor for PD, which we also saw was associated with iRBD[5, 19]; nonetheless, it was found to be associated with a slower disease progression from iRBD to Lewy body disease in both our 2015 report and in our updated study. The effect was mainly driven by occupational and non-occupational exposure to insecticides. One possible explanation is that pesticide exposure may be only associated with the static risk of PD and be independent of progression rate through the prodromal stage of synucleinopathies. That is, pesticides, might increase PD risk by producing an early reserve-reducing single 'hit' to vulnerable areas, but then with subsequent relatively slow progression from prodromal stages to defined neurodegenerative disease. However, since there were a limited number of patients with occupational pesticide exposure, large-scale prospective study is warranted to validate this speculation and further elucidate the exposure-response relationship between pesticide exposure and RBD conversion rate.

Regarding medication use as predictive marker, several new findings should be noted as compared with the 2015 report. First, we found that patients taking respiratory drugs (including β_2-adrenoreceptor agonists) were less likely to develop a defined neurodegenerative disease. Recent induced pluripotent stem cells (iPSC)-derived neuronal culture and animal studies have suggested that α-synuclein can be regulated by modulation of the β_2-adrenoreceptor[27], and the β_2-adrenoreceptor is associated with neuronal SNCA expression and risk of PD[27]. Two large population-based epidemiologic studies also suggested that β_2-adrenoreceptor agonists were associated with a reduced risk of PD [20, 21]and one of the two studies indicated that β_2-adrenoreceptor antagonists markedly increased PD risk[20]. However, it has been suggested that this finding may be due to confounding by smoking – smokers are more likely to require respiratory drugs, but are also at decreased risk of PD[28]. Of note, our association was not attenuated after adjustment for smoking (HR = 0.40 vs. 0.39 with smoking adjustment). However, use of non β_2-agonist inhaled medications had a similar direction of effect. Since numbers were low, and since many patients take both medications, we were not able to reliably disentangle β_2-agonists from other preparations; however, the fact that 4/5 patients taking only non-β_2-agonist inhaled medications were in the non-converted group suggests that confounding by indication (i.e. respiratory disease rather than β_2-agonist use) is a strong possibility.

Our second new finding is that patients with nitrate derivative use were found to have a 2.5-fold greater risk of disease phenoconversion. Here again, there is a strong possibility of confounding by indication, as nitrate derivatives are used in the treatment of serious cardiovascular diseases. However, we did not observe evidence of any other cardiac risk factor and conversion (except for a lower rate of hypercholesterolemia in convertors). Evidence of potential mechanisms is limited. Nitrate derivatives exert their action by releasing endothelial nitric oxide (NO)[29], and NO produced in high concentration has been associated with neurodegeneration[30]. Interestingly, NO is also closely related with iron homeostasis, which is critical for iron accumulation in substantia nigra in PD[31]. Animal studies have revealed that inducible NO synthase (iNOS) stimulates dopaminergic neurons in the MPTP model of PD[32]. Although there have been no epidemiologic studies on the association between nitrate derivatives and PD risk, it would be worth exploring whether nitrate derivatives increase PD risk in large population studies independent of vascular disease.

The final potential link with medication use was a lower occurrence of hypercholesterolemia among convertors accompanied by a very similar (but non-significant) relationship with a lower use of lipid-lowering agents. It is impossible to distentangle potential effects of hypercholesterolemia and statin use in this study, since diagnosis of hypercholesterolemia generally leads to statin use. Note that we had originally found no difference in occurrence of hypercholesterolemia in RBD patients compared to controls, despite an increase in cardiovascular disease in RBD patients[5]. There have been conflicting studies of the risk of PD in patients with diagnosis of hypercholesterolemia or with use of statins[33, 34], and further study is required.

In the 2015 report, we observed a relationship between clonazepam use and dementia risk. Now in the updated study, an additional relationship between clonazepam use and overall RBD phenoconversion risk was found. This may be an artifact of disease severity, in that RBD patients with higher severity may be more likely to develop neurodegenerative disease[35, 36] and clonazepam may be more likely to be used in patients with severe RBD symptoms. This drug can decrease sleep-related injury but also can cause adverse effects, including psychiatric symptoms and gait disorder[37]. One could speculate direct effects on cognition by clonazepam could have resulted in an early manifestation and diagnosis of dementia rather than parkinsonism first. This finding also suggests that of clonazepam should be used with caution in clinical practice, perhaps reserved for cases in which RBD symptoms cause clear impairment of quality of life.

Both the 2015 report and the updated study observed that a positive family history of any cognitive loss was associated with a higher risk of RBD phenoconversion. In addition, there was a nonsignificant trend towards more reported family history of cognitive loss in dementia-first patients compared with parkinsonism-first patients. Family history of cognitive loss might be associated with a greater risk of amyloid deposition or mixed pathology, resulting in an early clinical manifestation of dementia rather than parkinsonism. Alternatively, it is now well known that mutations in GBA are common in iRBD[38] and GBA mutations are a strong risk factor for DLB (perhaps even stronger than PD). In a recent study, iRBD patients with GBA mutations had faster phenoconversion to defined neurodegenerative disease[39]. Additionally, SNCA polymorphisms are also present in iRBD with a profile similar to the polymorphisms linked to DLB[25]. Therefore, since our original publication in 2015, we now have increasing evidence to suggest that genetic factors underlie not only iRBD but also its phenoconversion to neurodegenerative disease.

The comparison between primary dementia and primary parkinsonism patients among RBD converters was remarkable for the similarity in the predictive values across the environmental risk factors. Overall, only coffee intake quantity and clonazepam use were significantly different between parkinsonism and dementia patients. Coffee use is associated with reduced risk of both PD and DLB in epidemiologic studies[16, 40]. In a retrospective study, when compared with published risk estimates, caffeine use was found to reduce the risk of DLB more strongly than in PD (OR in DLB 0.29 vs. relative risk (RR) in PD 0.69)[40]. Consistent with this finding, our study also found that patients converting to dementia had less coffee intake than patients converting to primary parkinsonism. Whether this is a direct effect or related to confounding or reverse causality (e.g. patients with prodromal dementia lose self-perceived benefit of caffeine) is unclear. Dementia-first patients also were 2.5 years older than parkinsonism-first patients, which suggested that aging-related cortical pathology might trigger a rapid cortical neurodegeneration and then result in a dementia-first phenotype.

Several limitations of this study should be noted. First, 11.9% of the patients were lost to any follow-up and 9.4% only received telephone interview at last follow-up. The patients lost to follow-up may have comorbid medical conditions with a higher risk of disease conversion.[1] In addition, in-person follow-up frequency and intensity varied, and may also have an impact on the estimation of disease phenoconversion rates, because many patients may not recognize the early symptoms of parkinsonism or cognitive decline. Second, whenever follow-up was less frequent, neurodegenerative disease may have been developed earlier or later than the reported time of disease diagnosis. The final diagnosis may also be subject to change with time (e.g. patients diagnosed with PD may eventually receive MSA diagnoses as atypical features emerge). Third, environmental and lifestyle exposure information at baseline was evaluated via questionnaire, implying potential recall bias. In particular, the family history information was determined by proxy report, which is less reliable. Fourth, all patients with iRBD were recruited from sleep laboratory or sleep clinics, and generalizability of our findings to all iRBD patients is unclear. Fifth, the protocol for patient recruitment differed between centers, in that the Barcelona center excluded patients with MCI at baseline and defined *de novo* MCI as disease conversion. However, to avoid the overestimation of disease risk, we chose dementia rather than MCI as the disease outcome. This study assessed many risk factors, and given sample size, there was no adjustment for multiple comparisons; therefore, findings should be considered exploratory in nature[41]. Finally, for some uncommon risk factors, only a limited number of patients had exposure history which would weaken the statistical power.

In conclusion, this updated study confirmed that age, family history of cognitive loss, nitrate derivatives, and clonazepam use predicted RBD conversion to synucleinopathies, whereas prior pesticide exposure, hypercholesterolemia, and respiratory medications were associated with lower phenoconversion risk. Considering the profound importance of the field of iRBD for developing potential neuroprotective therapies, future large-scale prospective studies are still needed to further validate our findings.

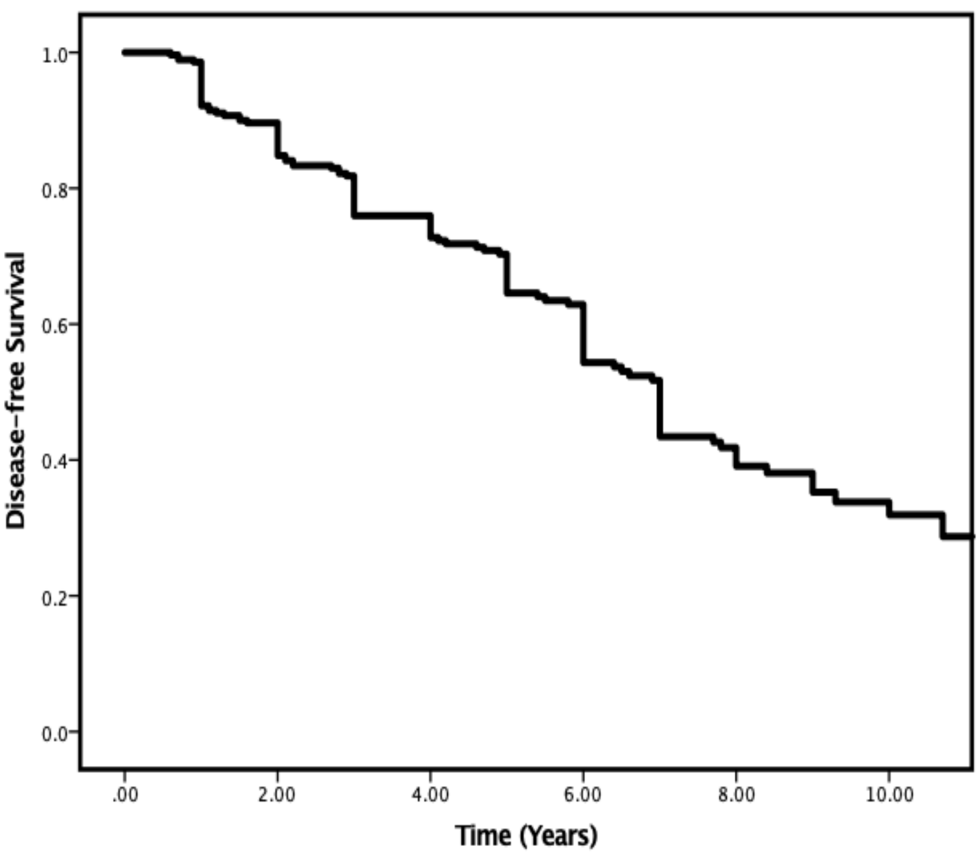
Reference

1. Schenck CH, Montplaisir JY, Frauscher B, et al. Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy--a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group. Sleep Med 2013;14:795-806.
2. Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9:e89741.
3. 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;72:1296-1300.
4. 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;14:744-748.
5. Postuma RB, Montplaisir JY, Pelletier A, et al. Environmental risk factors for REM sleep behavior disorder: A multicenter case-control study. Neurology 2012;79:428-434.
6. Postuma RB, Iranzo A, Hogl B, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. Ann Neurol 2015;77:830-839.
7. AASM. The International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd ed. Westchester: American Academy of Sleep Medicine 2005.
8. Postuma RB, Arnulf I, Hogl B, et al. A single-question screen for rapid eye movement sleep behavior disorder: A multicenter validation study. Mov Disord 2012;27:913-916.
9. Ferini-Strambi L, Oertel W, Dauvilliers Y, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study. J Neurol 2014;261:1112-1118.
10. Dauvilliers Y, Postuma RB, Ferini-Strambi L, et al. Family history of idiopathic REM behavior disorder: A multicenter case-control study. Neurology 2013;80:2233-2235.
11. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2015;30:1591-1601.
12. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Movement disorders : official journal of the Movement Disorder Society 2007;22:2314-2324.
13. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.
14. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670-676.
15. Benedetti MD, Bower JH, Maraganore DM, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. Neurology 2000;55:1350-1358.
16. Liu R, Guo X, Park Y, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. Am J Epidemiol 2012;175:1200-1207.
17. Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. Sleep 2018;41:zxs197.
18. Yao C, Fereshtehnejad SM, Keezer MR, Wolfson C, Pelletier A, Postuma RB. Risk factors for

possible REM sleep behavior disorder: A CLSA population-based cohort study. Neurology 2018.
19. Lai BC, Marion SA, Teschke K, Tsui JK. Occupational and environmental risk factors for Parkinson's disease. Parkinsonism & related disorders 2002;8:297-309.
20. Gronich N, Abernethy DR, Auriel E, Lavi I, Rennert G, Saliba W. beta2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2018;33:1465-1471.
21. Searles Nielsen S, Gross A, Camacho-Soto A, Willis AW, Racette BA. beta2-adrenoreceptor medications and risk of Parkinson disease. Annals of neurology 2018;84:683-693.
22. Hogl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. Nat Rev Neurol 2018;14:40-55.
23. Romenets SR, Gagnon JF, Latreille V, et al. Rapid eye movement sleep behavior disorder and subtypes of Parkinson's disease. Mov Disord 2012;27:996-1003.
24. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. JAMA Neurol 2015;72:863-873.
25. Krohn L, Wu RYJ, Heilbron K, et al. Fine-Mapping of SNCA in Rapid Eye Movement Sleep Behavior Disorder and Overt Synucleinopathies. Ann Neurol 2020;87:584-598.
26. Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. Nature reviews Disease primers 2018;4:19.
27. Mittal S, Bjornevik K, Im DS, et al. beta2-Adrenoreceptor is a regulator of the alpha-synuclein gene driving risk of Parkinson's disease. Science 2017;357:891-898.
28. Hopfner F, Wod M, Hoglinger GU, et al. Use of beta2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson disease. Neurology 2019;93:e135-e142.
29. Porsti I, Paakkari I. Nitric oxide-based possibilities for pharmacotherapy. Annals of medicine 1995;27:407-420.
30. Tse JKY. Gut Microbiota, Nitric Oxide, and Microglia as Prerequisites for Neurodegenerative Disorders. ACS chemical neuroscience 2017;8:1438-1447.
31. Liu C, Liang MC, Soong TW. Nitric Oxide, Iron and Neurodegeneration. Frontiers in neuroscience 2019;13:114.
32. Liberatore GT, Jackson-Lewis V, Vukosavic S, et al. Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease. Nature medicine 1999;5:1403-1409.
33. Poly TN, Islam MM, Walther BA, et al. Exploring the Association between Statin Use and the Risk of Parkinson's Disease: A Meta-Analysis of Observational Studies. Neuroepidemiology 2017;49:142-151.
34. Jeong SM, Jang W, Shin DW. Association of statin use with Parkinson's disease: Dose-response relationship. Mov Disord 2019;34:1014-1021.
35. Postuma RB, Gagnon JF, Rompre S, Montplaisir J. Severity of REM Atonia Loss in Idiopathic REM Sleep Behavior Disorder Predicts Parkinson Disease. Neurology 2010;74:239-244.
36. McCarter SJ, Sandness DJ, McCarter AR, et al. REM sleep muscle activity in idiopathic REM sleep behavior disorder predicts phenoconversion. Neurology 2019;93:e1171-e1179.
37. Dokkedal-Silva V, Berro LF, Galduroz JCF, Tufik S, Andersen ML. Clonazepam: Indications, Side Effects, and Potential for Nonmedical Use. Harvard review of psychiatry 2019;27:279-289.
38. Krohn L, Ruskey JA, Rudakou U, et al. GBA variants in REM sleep behavior disorder: A

multicenter study. Neurology 2020;95:e1008-e1016.
39. Honeycutt L, Montplaisir JY, Gagnon JF, et al. Glucocerebrosidase mutations and phenoconversion of REM sleep behavior disorder to parkinsonism and dementia. Parkinsonism Relat Disord 2019;65:230-233.
40. Boot BP, Orr CF, Ahlskog JE, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology 2013;81:833-840.
41. Bender R, Lange S. Adjusting for multiple testing--when and how? JClinEpidemiol 2001;54:343-349.

Figure 1. Shown is a Kaplan-Meier analysis plotting disease-free survival (i.e. Parkinson’s disease, Multiple System Atrophy and Dementia with Lewy Bodies) in patients with iRBD



Number at risk	281	243	164	103	46	18

Table 1. Demographics, occupation and lifestyle factors

	RBD converters (n=130)	RBD non-converters (n=151)	Age and sex adjusted HR (95%CI)
Age, years	70.38 ± 7.11	66.81 ± 9.18	**1.06 (1.03, 1.08)**
Male, n (%)	103 (79.2%)	124 (82.1%)	1.09 (0.71, 1.67)
Years of education	10.17 ± 4.57	11.97 ± 4.30	0.95 (0.90, 1.00)
Follow-up duration, years	5.85 ± 2.60	5.77 ± 2.80	**N/A**
Interval between baseline to disease onset, years	4.02 ± 2.50	——	
RBD symptom duration, years	10.21 ± 8.90	11.14 ± 10.88	0.996 (0.98, 1.02)
Marital status, n (%)			
Single	3 (2.3%)	4 (2.6%)	ref
Married/common in law	107 (82.9%)	129 (85.4%)	0.66 (0.20, 2.11)
Widowed/Divorced/separated	19 (14.7%)	18 (11.9%)	0.73 (0.21, 2.50)
Living with someone, n (%)	113 (88.3%)	130 (86.7%)	1.29 (0.74, 2.24)
Coffee use, ever, n (%)	109 (85.2%)	130 (86.1%)	0.98 (0.60, 1.61)
Coffee use, current, n (%)	93 (72.7%)	111 (75.5%)	0.97 (0.65, 1.44)
Coffee use (average cups per week)	9.91 ± 8.17	11.69 ± 8.80	0.99 (0.97, 1.01)
Caffeinated tea use, ever, n (%)	36 (28.3%)	52 (35.9%)	0.81 (0.55, 1.20)
Current alcohol use frequency, (0-6)	3.36 ± 2.35	3.39 ± 2.25	0.98 (0.90, 1.07)
Alcohol >5 drinks, (0-6)	0.57 ± 1.36	0.84 ± 1.50	0.86 (0.73, 1.01)
Past alcohol frequency, (0-6)	3.49 ± 2.36	3.36 ± 2.15	1.02 (0.94, 1.12)
Smoker, ever, n (%)	89 (68.5%)	97 (64.7%)	0.99 (0.67, 1.46)
Regular smoking, n (%)	82 (63.1%)	93 (61.6%)	0.90 (0.62, 1.31)
Current smoker, n (%)	12 (10.2%)	16 (11.5%)	0.91 (0.50, 1.66)
Smoking pack-years	15.70 ± 20.74	21.01 ± 27.87	0.99 (0.99, 1.002)
Rural living, n (%)	49 (38.9%)	85 (57.4%)	0.72 (0.50, 1.04)
Well water exposure, n (%)	52 (40.3%)	58 (40.0%)	0.85 (0.60, 1.21)

Occupation, n (%)			
Farming	18 (13.8%)	37 (24.7%)	0.61 (0.37, 1.02)
Welding	18 (13.8%)	26 (17.8%)	1.20 (0.71, 2.02)
Teaching	9 (7.1%)	20 (13.8%)	0.96 (0.48, 1.89)
Health care	11 (8.5%)	18 (12.3%)	0.82 (0.44, 1.54)
Mining	3 (2.3%)	3 (2.1%)	1.75 (0.55, 5.54)
Pesticide: occupational use, n (%)	7 (5.4%)	17 (11.8%)	**0.47 (0.22, 0.99)**
Occupational herbicide, n (%)	7 (5.5%)	12 (7.9%)	0.96 (0.29, 3.16)
Occupational insecticide, n (%)	5 (3.9%)	16 (10.6%)	**0.21 (0.06, 0.72)**
Any non-occupational pesticide use, n (%)	56 (43.8%)	83 (56.1%)	0.76 (0.53, 1.08)
Non-occupational herbicide, n (%)	30 (23.4%)	54 (37.8%)	0.70 (0.46, 1.07)
Non-occupational insecticide, n (%)	42 (33.3%)	71 (50.0%)	**0.68 (0.47, 0.98)**
Regular non-occupational pesticide use, n (%)	10 (7.8%)	17 (11.4%)	0.75 (0.40, 1.40)
Regular herbicide, n (%)	2 (1.6%)	10 (7.0%)	0.27 (0.07, 1.03)
Regular insecticide, n (%)	8 (6.3%)	13 (9.0%)	0.90 (0.45, 1.82)

Table 2. Family history

	RBD converters (n=130)	RBD non-converters (n=151)	Age and sex adjusted HR (95%CI)
Dream enactment behavior	13 (10.3%)	24 (17.8%)	0.88 (0.51, 1.50)
Sleep apnea	18 (14.8%)	33 (23.9%)	1.02 (0.63, 1.64)
Essential Tremor	3 (2.4%)	10 (7.3%)	0.96 (0.36, 2.55)
Any tremor	9 (7.0%)	19 (13.5%)	0.87 (0.46, 1.67)
Shaking head/voice	5 (3.9%)	5 (3.6%)	1.34 (0.59, 3.08)
Walking trouble	17 (13.3%)	17 (12.2%)	1.13 (0.67, 1.88)
Decreased balance	11 (8.6%)	23 (16.7%)	0.87 (0.48, 1.58)
Parkinson disease	10 (8.1%)	10 (7.3%)	1.79 (0.94, 3.41)
Memory problem	31 (24.2%)	28 (20.1%)	1.39 (0.93, 2.10)
Alzheimer's disease	17 (13.4%)	15 (10.9%)	1.34 (0.79, 2.26)
Any cognitive loss	41 (31.8%)	34 (24.1%)	**1.56 (1.07, 2.26)**

Table 3. Comorbidities and medication use at baseline

	RBD converters (n=130)	RBD non-converters (n=151)	Age and sex adjusted HR (95%CI)
Comorbidities, n (%)			
Head injury	24 (18.6%)	29 (19.2%)	1.03 (0.65, 1.63)
Head injury resulted in hospital	13 (10.1%)	13 (8.6%)	0.97 (0.54, 1.72)
Cardiovascular disease	35 (27.3%)	37 (26.2%)	0.85 (0.57, 1.27)
Cerebrovascular disease	8 (6.5%)	15 (10.9%)	0.55 (0.28, 1.07)
Migraine	26 (21.3%)	26 (18.8%)	1.03 (0.66, 1.60)
Depression	41 (32.8%)	39 (27.9%)	1.33 (0.90, 1.96)
Cancer	17 (14.0%)	18 (13.2%)	0.95 (0.57, 1.59)
Hypertension	48 (38.1%)	52 (36.9%)	0.90 (0.62, 1.29)
Diabetes	14 (11.4%)	20 (14.3%)	0.81 (0.47, 1.42)
High Cholesterol	28 (22.2%)	47 (33.8%)	**0.64 (0.43, 0.96)**
Obesity	16 (13.0%)	28 (19.0%)	0.88 (0.51, 1.50)
BMI current	25.91 ± 3.67	26.67 ± 6.36	0.99 (0.95, 1.03)
Obesity (age of 40)	4 (3.3%)	15 (10.6%)	0.47 (0.17, 1.27)
BMI (age of 40)	23.95 ± 2.70	25.10 ± 6.03	0.97 (0.92, 1.01)
Medications, n (%)			
All Antihypertensives	53 (41.7%)	65 (43%)	0.74 (0.52, 1.07)
Beta-blockers	22 (17.3%)	22 (14.6%)	0.93 (0.58, 1.48)
Calcium antagonists	15 (11.8%)	19 (12.6%)	0.66 (0.38, 1.13)
Nitrate derivatives	9 (7.1%)	3 (2.0%)	**2.54 (1.26, 5.12)**
Vitamins	27 (21.3%)	26 (17.2%)	1.41 (0.91, 2.17)
Analgesics	13 (10.2%)	19 (12.6%)	0.91 (0.51, 1.63)
Respiratory	5 (3.9%)	15 (9.9%)	**0.40 (0.16, 0.99)**
Inhaled B-agonists	4 (3.3%)	8 (5.3%)	0.50 (0.18-1.36)
Other inhaled	4 (3.3%)	11 (7.3%)	0.46 (0.17-1.25)

B-agonists, alone	1 (0.8%)	1(0.7%)	0.49 (0.17-3.52)
Other inhaled, alone	1 (0.8%)	4 (2.6%)	0.36 (0.05-2.62)
Gastrointestinal	28 (22%)	38 (25.2%)	0.92 (0.60, 1.41)
Urinary System	21 (16.5%)	20 (13.2%)	1.09 (0.68, 1.75)
Metabolic	30 (23.6%)	48 (31.8%)	0.67 (0.44, 1.02)
Anti-diabetic	13 (10.2%)	16 (10.6%)	0.90 (0.50, 1.61)
Lipid lowering	28 (22%)	44 (29.1%)	0.65 (0.43, 1.00)
Urostatics (Anti-hyperuricemia)	5 (3.9%)	5 (3.3%)	1.13 (0.46, 2.78)
Thyroid	11 (8.7%)	9 (6.0%)	1.22 (0.64, 2.32)
Osteoporosis	10 (7.9%)	11 (7.3%)	1.52 (0.78, 2.97)
Dopaminergic	11 (8.7%)	12 (7.9%)	1.08 (0.58, 2.01)
Neuroleptics	4 (3.1%)	0	2.34 (0.86, 6.39)
Anticonvulsants	6 (4.7%)	10 (6.6%)	1.26 (0.54, 2.90)
Anticoagulants /Antiplatelets	43 (33.9%)	53 (35.1%)	0.86 (0.59, 1.25)
Anti-depressants	20 (15.4%)	29 (19.2%)	0.91 (0.57, 1.48)
Melatonin	17 (13.4%)	12 (7.9%)	1.59 (0.94, 2.67)
Benzodiazepines	65 (51.2%)	56 (37.1%)	1.30 (0.91, 1.86)
Clonazepam	70 (55.1%)	55 (36.4%)	**1.50 (1.05, 2.15)**

Table S1. Demographics, occupation and lifestyle factors in dementia-first vs. parkinsonism-first phenoconvertors (excluding MSA phenoconversion)

	Dementia (n=60)	Parkinsonism (n=61)	Age and sex adjusted OR (95%CI)
Age, years	72.18 ± 6.78	69.72 ± 6.61	0.95 (0.90, 1.002)
Male, n (%)	52 (86.7%)	46 (75.4%)	0.50 (0.19, 1.29)
Years of education	10.50 ± 3.93	10.10 ± 5.14	0.97 (0.89, 1.05)
Interval between baseline to disease onset (years)	3.55 ± 2.52	4.55 ± 2.51	1.13 (0.97, 1.32)
RBD symptom duration, years	9.80 ± 8.82	10.82 ± 9.16	1.03 (0.98, 1.07)
Marital status, n (%)			
single/widowed/divorced/separated	13 (21.7%)	7 (11.7%)	ref
Married/common in law	47 (78.3%)	53 (88.3%)	2.47 (0.86, 7.12)
Living with someone, n (%)	50 (84.7%)	56 (91.8%)	2.26 (0.67, 7.57)
Coffee use, ever, n (%)	48 (81.4%)	53 (88.3%)	1.45 (0.48, 4.38)
Coffee use, current, n (%)	42 (71.2%)	44 (73.3%)	0.88 (0.37, 2.12)
Coffee use (average cups per week)	7.86 ± 5.42	11.54 ± 9.59	**1.06 (1.003, 1.13)**
Caffeinated tea use, ever, n (%)	18 (30.5%)	17 (28.8%)	0.89 (0.40, 2.01)
Current alcohol use frequency, (0-6)	3.54 ± 2.32	3.29 ± 2.37	0.96 (0.79, 1.15)
Alcohol >5 drinks, (0-6)	0.67 ± 1.52	0.51 ± 1.29	0.92 (0.68, 1.24)
Past alcohol frequency, (0-6)	3.56 ± 2.40	3.38 ± 2.33	0.99 (0.82, 1.21)
Smoker, ever, n (%)	40 (66.7%)	42 (68.9%)	1.50 (0.61, 3.67)
Regular smoking, n (%)	35 (58.3%)	40 (65.6%)	1.88 (0.80, 4.43)
Current smoker, n (%)	7 (13.2%)	4 (7.1%)	0.44 (0.11, 1.70)
Smoking pack-years	17.04 ± 23.64	14.20 ± 17.89	1.00 (0.98, 1.02)
Rural living, n (%)	21 (36.8%)	25 (41.7%)	1.18 (0.55, 2.53)
Well water exposure, n (%)	27 (45.8%)	24 (39.3%)	0.68 (0.32, 1.44)
Occupation, n (%)			
Farming	9 (15.0%)	9 (14.8%)	1.19 (0.42, 3.34)

Welding	8 (13.3%)	9 (14.8%)	1.06 (0.36, 3.17)
Teaching	3 (5.1%)	6 (10.2%)	1.88 (0.43, 8.22)
Health care	3 (5.1%)	7 (11.5%)	2.41 (0.57, 10.17)
Mining	2 (3.3%)	1 (1.6%)	0.47 (0.04, 5.37)
Pesticide: occupational use, n (%)	4 (6.8%)	3 (4.9%)	0.78 (0.17, 3.63)
Occupational herbicide, n (%)	4 (6.8%)	3 (4.9%)	0.82 (0.09, 7.44)
Occupational insecticide, n (%)	3 (5.1%)	2 (3.3%)	0.48 (0.03, 9.12)
Any non-occupational pesticide use, n (%)	23 (39.7%)	29 (47.5%)	1.24 (0.57, 2.70)
Non-occupational herbicide, n (%)	8 (13.8%)	19 (31.1%)	2.59 (0.98, 6.88)
Non-occupational insecticide, n (%)	22 (37.9%)	18 (30.5%)	0.71 (0.32, 1.58)
Regular non-occupational pesticide use, n (%)	7 (12.1%)	3 (4.9%)	0.44 (0.11, 1.72)
Regular herbicide, n (%)	2 (3.5%)	0	—
Regular insecticide, n (%)	5 (8.6%)	3 (5.1%)	0.81 (0.19, 3.45)

Table S2. Family history in dementia-first vs. parkinsonism-first phenoconvertors (excluding MSA phenoconversion)

	Dementia (n=60)	Parkinsonism (n=61)	Age and sex adjusted OR (95%CI)
Dream enactment behavior	4 (6.8%)	8 (13.6%)	1.16 (0.36, 3.77)
Sleep apnea	9 (16.1%)	9 (15.5%)	1.23 (0.45, 3.37)
Essential Tremor	1 (1.8%)	2 (3.4%)	1.71 (0.20, 14.60)
Tremor	5 (8.5%)	4 (6.7%)	0.91 (0.24, 3.56)
Shaking head/voice	1 (1.7%)	4 (6.7%)	3.98 (0.49, 32.22)
Walking trouble	7 (11.9%)	8 (13.3%)	1.42 (0.47, 4.34)
Decreased balance	4 (6.8%)	5 (8.3%)	0.65 (0.17, 2.54)
Parkinson disease	4 (7.0%)	6 (10.0%)	2.06 (0.53, 7.97)
Memory problem	17 (28.8%)	11 (18.3%)	0.55 (0.23, 1.34)
Alzheimer's disease	10 (16.9%)	5 (8.3%)	0.38 (0.12, 1.23)
Any cognitive loss	23 (38.3%)	14 (23.3%)	0.48 (0.21, 1.08)

Table S3. Comorbidities and medication use at baseline in dementia-first vs. parkinsonism-first phenoconvertors (excluding MSA phenoconversion)

	Dementia (n=60)	Parkinsonism (n=61)	Age and sex adjusted OR (95%CI)
Comorbidities, n (%)			
Head injury	10 (16.9%)	12 (19.7%)	1.15 (0.44, 3.01)
Head injury resulted in hospital	5 (8.5%)	7 (11.5%)	1.27 (0.36, 4.47)
Cardiovascular disease	16 (27.1%)	17 (28.3%)	1.42 (0.60, 3.37)
Cerebrovascular disease	6 (10.7%)	2 (3.4%)	0.30 (0.06, 1.52)
Migraine	11 (19.6%)	12 (21.1%)	0.91 (0.34, 2.41)
Depression	21 (36.8%)	16 (27.1%)	0.46 (0.18, 1.13)
Cancer	9 (16.4%)	7 (12.3%)	0.75 (0.25, 2.23)
Hypertension	25 (43.9%)	19 (31.7%)	0.68 (0.31, 1.50)
Diabetes	7 (12.5%)	6 (10.3%)	1.23 (0.37, 4.09)
High Cholesterol	12 (20.7%)	12 (20.3%)	1.16 (0.46, 2.91)
Obesity	7 (12.5%)	8 (13.8%)	0.77 (0.24, 2.44)
BMI current	25.43± 3.43	26.44 ± 3.67	1.07 (0.96, 1.20)
Obesity (age of 40)	0	3 (5.3%)	0
BMI (age of 40)	23.67 ± 2.39	24.00 ± 2.91	1.07 (0.92, 1.24)
Medications, n (%)			
All Antihypertensives	24 (41.4%)	23 (38.3%)	1.31 (0.58, 2.97)
Beta-blockers	7 (12.1%)	12 (20.0%)	2.51 (0.86, 7.35)
Calcium antagonists	8 (13.8%)	7 (11.7%)	1.10 (0.36, 3.42)
Nitroderivates	5 (8.6%)	4 (6.7%)	1.27 (0.30, 5.43)
Vitamins	12 (20.7%)	20 (20.0%)	0.80 (0.32, 2.05)
Analgetics	4 (6.9%)	7 (11.7%)	1.75 (0.47, 6.53)
Respiratory	3 (5.2%)	2 (3.3%)	0.67 (0.10, 4.39)
Gastrointestinal	11 (19.0%)	16 (26.7%)	1.53 (0.62, 3.77)

Urinary System	11 (19.0%)	10 (16.7%)	1.09 (0.41, 2.91)
Metabolic	17 (29.3%)	11 (18.3%)	0.72 (0.29, 1.81)
Anti-diabetic	7 (12.1%)	5 (8.3%)	0.89 (0.26, 3.10)
Lipid lowering	13 (22.4%)	12 (20.0%)	1.09 (0.44, 2.75)
Urostatics (Anti-hyperuricemia)	3 (5.2%)	2 (3.3%)	1.02 (0.15, 6.68)
Thyroid	4 (6.9%)	5 (8.3%)	1.46 (0.35, 6.08)
Osteoporosis	5 (8.6%)	4 (6.7%)	0.47 (0.10, 2.13)
Dopaminergic	7 (12.1%)	3 (5.0%)	0.44 (0.10, 1.88)
Neuroleptics	2 (3.4%)	2 (3.3%)	0.84 (0.11, 6.33)
Anticonvulsants	2 (3.4%)	3 (5.0%)	1.02 (0.15, 6.88)
Anticoagulants /Antiplatelets	22 (37.9%)	20 (33.3%)	1.08 (0.48, 2.42)
Anti-depressants	9 (15.0%)	9 (14.8%)	0.89 (0.32, 2.49)
Melatonin	9 (15.5%)	7 (11.7%)	0.58 (0.19, 1.81)
Benzodiazepines	36 (62.1%)	23 (38.3%)	**0.40 (0.19, 0.86)**
Clonazepam	39 (67.2%)	27 (45.0%)	**0.39 (0.18, 0.84)**

Table S4. Centers participating in the current prospective study

Center	Number
Montreal	56
Barcelona	39
Paris	33
Montpellier	12
Tochigi	20
Milan	28
Pavia	18
Clagari	10
Prague	8
Innsbruck	31
Marburg	15
St. Louis	11
Total	281