Global Features and Associated Outcomes of Dream Enactment Behavior and Isolated Insomnia Symptoms in the Canadian Population

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Abstract

Sleep disorders, including insomnia and REM sleep behavior disorder (RBD), have received increasing attention as prodromal (i.e., before fulfilling a clinical diagnosis) markers/symptoms of neurodegenerative diseases such as parkinsonism and dementia. Knowledge of the earliest phases of neurodegeneration can provide a window of opportunity, not only to understand disease in its earliest stage, but to facilitate design for future clinical trials aimed at preventing or slowing early neurodegeneration. This thesis is thus devoted to studying risk factors and neurodegeneration associated with RBD (Section 1) and insomnia (Section 2).

In the first two chapters of section one, we focus on describing RBD in both the general public and a clinical cohort, based on the existing knowledge from parkinsonism. Specifically, in chapter one, we enlist epidemiological studies describing RBD in the Canadian general population and challenges that come along with population screening. The second section looks at the disease progression among certain polysomnographic-proven RBD patients, who presented with an extensive period of prodromal phase without phenoconversion. The last chapter looks at a specific subtype of RBD, namely post-traumatic stress disorder-associated RBD, to examine whether it can be detected in the general population, and its overall presentation.

In the insomnia section, we assess neurodegenerative features and associated outcomes/differential diagnoses according to specifically delineated insomnia subtypes, namely sleep-onset insomnia (difficulty falling asleep), and sleep-maintenance insomnia (difficulty staying asleep). We found that the different insomnia subtypes had notable differences in neurological status and changes in health status over time, suggesting that treating insomnia as a single entity can obscure important associations.

Résumé

Les troubles du sommeil, y compris l'insomnie et les troubles du comportement en sommeil paradoxal (TCSP), ont reçu une attention croissante en tant que marqueurs/symptômes prodromiques (c'est-à-dire avant de poser un diagnostic clinique) de maladies neurodégénératives telles que le parkinsonisme et la démence. La connaissance des premières phases de la neurodégénérescence peut faciliter l'étudie de la maladie à ses débuts et la conception de futurs essais cliniques visant à prévenir ou à ralentir la neurodégénérescence précoce. Cette thèse est ainsi consacrée à l'étude des facteurs de risque et de la neurodégénérescence associés au TCSP (Section 1) et à l'insomnie (Section 2).

Dans les deux premiers chapitres de la première section, nous nous concentrons sur la description du TCSP à la fois dans le grand public canadien et dans une cohorte clinique, sur la base des connaissances existantes sur le parkinsonisme. Plus précisément, dans le premier chapitre, nous enrôlons des études épidémiologiques décrivant le TCSP dans la population générale canadienne et les défis qui accompagnent le dépistage de la population. La deuxième chapitre examine la progression de la maladie chez certains patients TCSP prouvés par polysomnographie, qui ont présenté une longue période de phase prodromique sans phénoconversion. Le dernier chapitre examine un sous-type spécifique de TCSP, à savoir le TCSP associé au trouble de stress post-traumatique, pour examiner s'il peut être détecté dans la population générale, et sa présentation globale.

Dans la section insomnie, nous évaluons les caractéristiques neurodégénératives et les résultats/diagnostics différentiels associés selon des sous-types d'insomnie spécifiquement définis, à savoir l'insomnie d'endormissement (difficulté à s'endormir) et l'insomnie de maintien du sommeil (difficulté à rester endormi). Nous avons constaté que les différents sous-types

d'insomnie présentaient des différences notables dans l'état neurologique et les changements dans l'état de santé au fil du temps, ce qui suggère que le traitement de l'insomnie comme une entité unique peut masquer des associations importantes.

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Preface

Dream Enactment Behavior

Dream enactment behavior is the real-life reflection of movements that occur within one's dream. It is best known for being one of the core symptoms of parkinsonism-related REM sleep behavior disorder. However, dream enactment behavior can also occur during non-REM sleep. Another aspect of dream enactment behavior is the aspect of dream recall, which is uncommon in those with sleepwalking (somnambulism) or sleep-talking (somniloquy). Although the exact mechanism of dream recall remains unknown, successful dream recalls are commonly associated with decreasing in sleep and increasing in awakening.[1] This is aligned with the typical patterns of dream enactment behavior, which most commonly occurs during the transition from sleep to waking.

Of the dream enactment behavior subtypes, REM sleep behavior disorder (RBD) is perhaps the most studied due to its role as a prodromal symptom for synucleinopathies, such as motor-first and dementia-first parkinsonism and multiple system atrophy. It is estimated that 80-85% of those with polysomnography confirmed idiopathic RBD will phenoconvert into parkinsonism or dementia.[2] Due to this unique position, RBD can provide a valuable window for future neuroprotective trials for synucleinopathies. Since most RBD patients come into sleep clinic only a few years prior to phenoconversion, identifying RBD at an even earlier stage via the associated risk factors and clinical features will help extend the effectiveness of a potential treatment, which is discussed in the first four chapters of the dream enactment behavior section in this thesis.

Another topic that has recently received an increase in attention is dream enactment behaviors in post-traumatic stress disorders (PTSD). Although documentation of dream

enactment behavior in PTSD predates the first RBD study by decades[3-5], it was not clearly differentiated in diagnosis until the recent proposal by Mysliwiec.[6, 7] In the original article, he noticed that when assessing polysomnography in veterans, a few of them showed sign of REM sleep without atonia (a sign of dream enactment behavior), of which he 'named' as trauma-associated sleep disorder. And, a few years after that, another case-series from Australia also found similar results, where veterans with PTSD showed signs of REM sleep without atonia or RBD. However, like most PTSD research, little is known among civilians with PTSD.[8] In section I chapter 3, we explored the usage of different terminologies to describe this phenomenon and its prevalence in the Canadian population. We also compared the overall clinical physiology to those with other dream enactment behaviors.

Insomnia

Insomnia is one of the most common sleep symptoms/disorders worldwide. In Canada, a federal survey estimated that 13.4% of Canadian aged 15 and above showed symptoms of difficulty initiating or maintaining asleep.[9] And, a later report from the same agency, suggested an increase in insomnia prevalence over the years, with more than 60% of insomnia-affected individuals experiencing symptoms for at least a year.[10] Similar findings had also been reported in the American National Health Interview Survey.[11] One possible explanation for this trend can be from the increase in average population age and reduction in birth rate, as the insomnia prevalence tends to increase with age.[11] Besides older age, insomnia is slightly more common among the female sex, with a greater propensity of experiencing sleep deprivation and poorer health outcome than those without insomnia.

Unlike dream enactment behavior and RBD, insomnia diagnoses are commonly made without polysomnography, although it can be useful to rule out insomnia as a secondary symptom to restless leg syndrome or apnea. Classifications of insomnia subtypes have varied drastically over the years among diagnostic guidelines and between iterations.[12, 13] In the latest edition, however, most guidelines have agreed on two major subtypes: sleep-onset and -maintenance insomnia. Although an official diagnosis for insomnia disorder requires confirmation of adequate sleep time and subsequent negative impact during the daytime, insomnia symptoms have also been shown predated neurological diseases such as parkinsonism and Alzheimer's dementia.[14-16]

Among the studies assessing the risk or associations between different insomnia symptoms and subsequent health events, most were assessed by simply comparing to those without insomnia symptoms. Since comorbidities among sleep disorders are common, it is difficult to comb through the direct contribution of each insomnia subtype among all comorbid sleep disorders. In section II chapter 1, we explored the potential association of each isolated insomnia symptom and clinical signs/symptoms associated with parkinsonism and dementia. And, in chapter 2, we would assess the direct risk of parkinsonism, dementia and associated differential diagnoses from isolated insomnia symptoms.

References:

1. Mangiaruga A, Scarpelli S, Bartolacci C, De Gennaro L. Spotlight on dream recall: the ages of dreams. Nature and Science of Sleep 2018;Volume 10:1-12.
2. 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.
3. Glaubman H, Mikulincer M, Porat A, Wasserman O, Birger M. Sleep of chronic post-traumatic patients. Journal of Traumatic Stress 1990;3:255-263.
4. Myers C. A CONTRIBUTION TO THE STUDY OF SHELL SHOCK. The Lancet 1915;185:316-320.
5. Crocq MA, Crocq L. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. Dialogues Clin Neurosci 2000;2:47-55.
6. Mysliwiec V, Brock MS. Time to recognize trauma associated sleep disorder as a distinct parasomnia. Sleep 2020;43.
7. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: A parasomnia induced by trauma. Sleep Med Rev 2018;37:94-104.
8. Van Ameringen M, Mancini C, Patterson B, Boyle MH. Post-Traumatic Stress Disorder in Canada. CNS Neuroscience & Therapeutics 2008;14:171-181.
9. Tjepkema M. Insomnia. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé 2005;17:9-25.
10. Chaput JP, Yau J, Rao DP, Morin CM. Prevalence of insomnia for Canadians aged 6 to 79. Health Rep 2018;29:16-20.
11. Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among US adults from 2002 to 2012. Sleep Medicine 2015;16:372-378.
12. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. World Psychiatry 2019;18:337-352.
13. Ito E, Inoue Y. [The International Classification of Sleep Disorders, third edition. American Academy of Sleep Medicine. Includes bibliographies and index]. Nihon Rinsho 2015;73:916-923.
14. Hung CM, Li YC, Chen HJ, et al. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatry 2018;18:38.
15. de Almondes KM, Costa MV, Malloy-Diniz LF, Diniz BS. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. J Psychiatr Res 2016;77:109-115.
16. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis 2017;3:9.

Section I: Dream Enactment Behavior

Chapter I & II - Idiopathic/Isolated REM Sleep Behavior Disorder in Synucleinopathy

- A Dream Enactment Behavior in Synuclienopathy

General Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized as loss of REM sleep atonia. Although the exact biological mechanism remains unclear, it is hypothesized that dream enactment may be induced by atrophy in the brainstem region, especially the pontine and ventromedial medulla.[1-4] Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), can also trigger RBD. The events of the dream enactment activities vary between and within subjects, from laughing, monologue-like sleep talking, running, to aggressive behavior.[5-7] Due to the potential unawareness of movement during sleep, patients are more likely to visit sleep clinics only after the occurrence of an injury or being informed by their bed partner.[8] With the additional issue of potential recall bias, it is difficult to pinpoint the onset of RBD.

Currently, the gold standard diagnosis for RBD relies solely on polysomnography (PSG), which may not be feasible and affordable for large-scale study. A detailed history of persistent dream enactment can serve as an alternative after ruling out other sleep disorders that may mimic dream enactment behavior, such as non-REM parasomnia, restless leg syndrome (RLS) and apnea.

The estimated prevalence of PSG-proven idiopathic RBD (iRBD) (ie. without defined neurodegenerative disease) is ~1% in Korea and Switzerland.[9, 10] Upon the initial assessment, 80% of these iRBD patients will phenoconvert into Parkinson's disease (PD) and multiple system atrophy (MSA) within 5 years. Ultimately, most iRBD patients will phenoconvert as the neurodegeneration progress continues.[11] Therefore, a better understanding of iRBD will aid the planning of future PD clinical trials. Centring on the goal, this proposed thesis will focus on studying the global features, biomarkers and disease progression in RBD.

Diagnostic Tools for RBD

Since polysomnography is a time-consuming process, leading to high expense for each patient[12], it is not plausible to apply it in a large-scale study. To address this issue, five questionnaires have been developed over the years (Appendix 1). Some brief information about the detail of each questionnaire were listed below by the year of the development.

RBD Screening Questionnaire (RBD-SQ), containing 13 questions, was first developed in 2007.[13] The questionnaire addresses three main aspects: 1) patients' awareness of the frequency and the content of dreams. 2) the awareness of dream enactment and the associated dream content. 3) the general sleep quality and comorbid neurological disorders. The later revised version, which removes item 10, yields a higher sensitivity (82.9%) and specificity (82.0%) at a cut-off of 8 than the originally suggested cut-off of 5 (sensitivity: 97.3%, specificity: 45.9%).[14]

Another similar detailed questionnaire, RBDQ-HK, published in 2010, contains two sections to assess: dream-related features and behavioural manifestation. The total score of the questionnaire adds up to 100. At a cut-off of 19, the questionnaire has an average sensitivity and specificity of 92.5% and 89.3%, (yielded from studies in China, Hong-Kong, Korea and Japan).[15-18] The advantage of RBDQ-HK is the inquiry into the frequency of dream enactment episodes, which may be used to measure RBD severity.

The Mayo Sleep Questionnaire was first introduced as a general sleep disorder questionnaire in 2009. Within it, a single question: 'Have you ever seen the patient appear to ''act out his/her dreams'' while sleeping? (punched or flailed arms in the air, shouted or screamed)' and 5 conditional subquestions were designed for RBD screening. The questionnaire has a generally good performance in both community-based and Alzheimer's disease and dementia cohorts (crude sensitivity and specificity: 96.6%, 84.7%).[8, 19, 20]

Appendix 1. REM Sleep Behavior Disorder Questionnaire

Questionnaire	REM Sleep Behavior Disorder Screening Questionnaire (RBD-SQ)		REM Sleep Behavior Disorder Questionnaire-Hong Kong (RBD-HK)	Mayo Sleep Questionnaire (MSQ)	RBD Single Question Questionnaire (RBD-1Q)	Innsbruk REM Sleep Behavior Disorder Inventory (RBD-I)
No. of Items	13		13	1 + 5 Conditional Questions	1	5
Interviewee	Patients (with/without Bed Partner)		Patients and/or Bed Partner	Bed Partner	Patients, Bed Partner, Caregiver	Patients (with/without Bed Partner)
Validation Place	China, USA, Italy, Korea, Japan, Germany, Turkey		Hong-Kong, Korea, Japan, China	USA	Canada	Austria
Cohort Detail	Sleep Disorder, PD		Sleep Disorder, Neurodegnerative Disease, Mental Illness	Community, Neurodegnerative Disease	Community, Sleep Disorder	Sleep Disorder, Neurodegenerative Disease
Cut-off	5[21]	8[14]	19/100[15-18]	1 (Positive)	1 (Positive)	25% Positive Rate
Polysomnogram	Yes	Yes	Yes	Yes	Yes	Yes
Sensitivity	97.6	82.9	92.5	96.6 [8, 19, 20]	93.8	91.4
Specificity	45.9	82.0	89.3	84.7	87.5	85.7
Estimated PPV	1.8	4.5	8.01	6.0	7.05	6.1
Estimated NPV	98.2	95.6	99.9	94.0	94.0	93.9
Note	- Remove item 10 Crude SN%: 91[85-95] Crude SP%: 77[66-85][21]		- Factor 2 may be used as an alternative - 2 apnes questions may be applied[18]	- Question 1 and the subquestions from the original questionnaire		$\frac{N\ of\ Positive\ Symptoms}{N\ of\ Answered\ Questions} = 25\%$

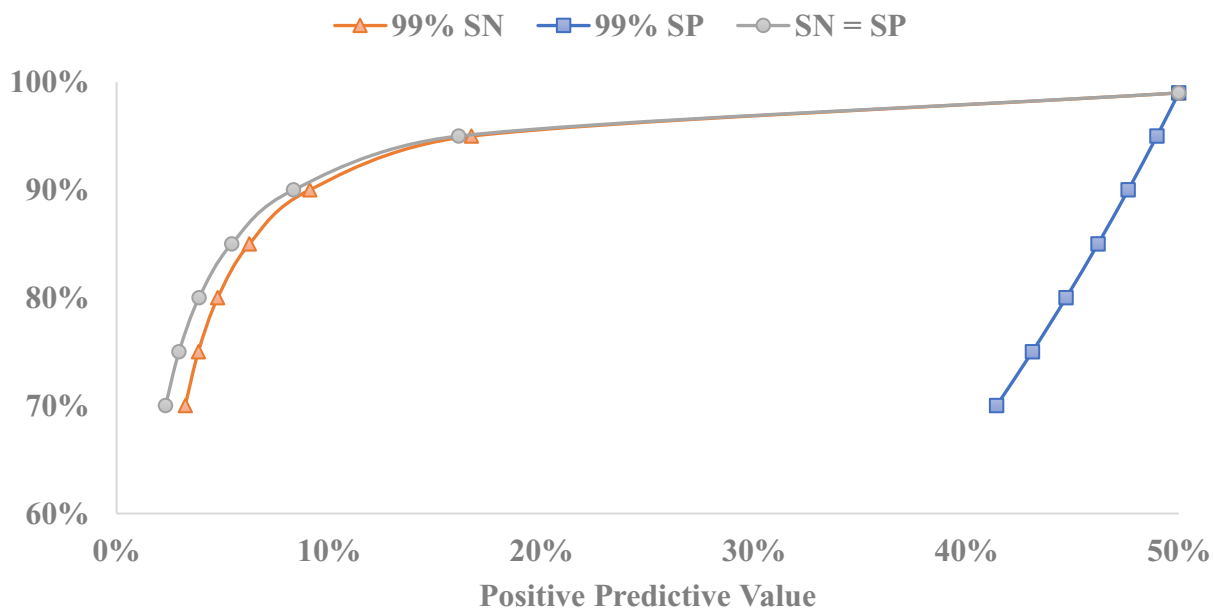
Sensitivity and specificity were the average values of the available large cohort validation (n>100). Both estimated positive predicted value and negative predicted value were recalculated under the assumption of 1% prevalence rate.

The RBD1Q is a single question screen: "Have you ever been told, or suspected yourself, that you seem to “act out your dreams" while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?". In the original 2012 validation study (n=242), RBD1Q yielded a 93.8% sensitivity and 87.2% specificity.[22] The questionnaire was designed to be performed directly by the patient (bed-partner and caregiver are encouraged to participate), unlike the Mayo questionnaire which screens caregivers.

In the same year as RBD1Q, the Innsbruck RBD Inventory (RBD-I) was introduced with 5 questions (9 questions were originally evaluated in the validation study, 7 for assessing RBD symptoms and 2 for differential diagnosis).[23] The design of the second part of the questionnaire: frequency of events in the past year, was based on the RBDQ-HK. Positive screening is defined as at least 25% of positive symptoms among all answered questions in part 1(sensitivity: 91.4%, specificity: 85.7%).

In general, most of the questionnaires have shown at least moderate to good performance. However, since the general prevalence of RBD is around 1%, the estimated positive predictive value (PPV) should be carefully considered when interpreting any large-scale study without PSG confirmation (Appendix 2).[9, 10] To illustrate, assume a new questionnaire has a sensitivity of 99% and specificity of 90%. In a clinic cohort with 35% of patients having RBD, the PPV would be 84.2%. However, when applying this same questionnaire in a population survey, where RBD prevalence is 1%, PPV would be only 9.1%.

Appendix 2.



The orange line represents the specificity value and the corresponding positive predictive value when the sensitivity value is fixed at 99%. On the contrary, the blue line represents the sensitivity value under the 99% specificity. At each point on the grey line, the value of sensitivity equals the value of specificity.

Risk Factors, Associated Factors and Drug-induced RBD:

Among the known preclinical symptoms, iRBD is by far the strongest predictor of parkinsonism.[24] As a prodromal symptom, RBD shares several similar sociodemographic features and risk factors to Parkinson's disease (PD). Both RBD and PD patients are predominantly male and are less physically active.[25, 26] Pesticide and occupational exposures (such as mining, industrial workers) have also been linked with both Parkinson's disease and RBD.[27-31] Lower education/socioeconomic status has been associated with RBD in both clinical and large-scale epidemiology studies.[27, 28, 32, 33] Depression and anxiety, as prodromal PD symptoms, are common in RBD, which may lead to increase in the use of antidepressants.[26, 27, 34-36] The reverse association is also possible since antidepressants can also trigger REM sleep without atonia (RSWA).[37] Both PD and RBD patients are more likely

to endorse risky behaviors and have similar personality features.[33, 38, 39] History of head injuries is positively associated with both RBD and PD.[27, 28, 32, 40]

In converse to PD, smoking, drinking and caffeine are not negatively associated with RBD.[9, 27, 28, 33] Moreover, smoking and drinking are positively associated with the occurrence of RBD. This does not imply causality, and both current and former daily smokers endorse RBD symptoms more than non-smokers.[41] Other explanations for these findings are possible; for example, these may be due to the increase in risky behaviors among RBD patients.[33] It is unclear if there is a dosage effect between RBD and the use of tobacco and alcohol.

Several medications have been shown to induce RBD-like symptoms. Of all the case-series, most were caused by the use of antidepressants, including nonselective monoamine oxidase inhibitors (MAOs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), which may also induce restless leg syndrome (RLS) and periodic leg movement during sleep (PLMS).[42-44] In one study, two patients had RBD-like symptoms during the treatment period of β-adrenoreceptor antagonist.[45] Although more study is needed to have a better understanding of potential mechanisms involved, this may be via a direct pharmacologic effect of serotonergic medications on spinal cord interneurons.[46, 47]

Disease Progression and Phenoconversion of Prodromal Synucleinopathies:

There are three primary neurodegenerative synculeinopathophies; Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). The clinical features of synucleinopathies consist of degenerative symptoms in both motor and non-motor functions. Although the diagnosis of PD is still defined by the motor manifestations and DLB by cognitive impairment, motor/cognitive symptoms are often not the initial symptoms of

disease. It has been shown that non-motor symptoms, such as olfactory dysfunction, orthostatic hypotension (OH), constipation and RBD may occur prior to the onset of motor disturbance.[41] Several studies have provided some insights into the evolution of the cardinal motor symptoms and some non-motor features, most notably the Rotterdam Study (a study of PD in the general population) and the Montréal Prospective RBD cohort.[48,49-52]

In our previous study, both olfactory loss and color vision abnormality were observed starting >10 years before phenoconversion (particularly for dementia-first phenoconverters).[53] The earliest motor symptoms were hypophonia and hypomimia (at year -9.8) following by cardinal manifestations (bradykinesia, rigidity, gait abnormalities and, last, resting tremor).[50] The onset of both bradykinesia (-5.2 vs. -7.5 year) and rigidity (-4.5vs. -4.8 year) were similar in between studies from Montreal and Rotterdam.[48, 50] A general trend of increase in laxative use (an indicator of constipation) was found in the Rotterdam cohort (statistically significant at -.24 years). No differences in levels of depression/anxiety were found in either cohort.

Of all non-motor symptoms, cognitive decline, olfaction loss and visual abnormality were fairly consistent in association to PD among studies.[49, 53-56] Olfactory dysfunction was significantly worse in PD phenoconverters (similar to the finding in the Honolulu-Asia Aging Study)[57] and might start years before initial RBD diagnosis.[52] The occurrence of color vision abnormality was also higher among phenoconverters in iRBD patients.[53] Decline in cognition was estimated to start approximately years before disease conversion in parkinsonism although it is more severe among dementia-first phenoconvertors.[49, 51] Despite the advance in the knowledge of parkinsonism disease models over the past few years, the nature of many parkinsonism symptoms' evolution during the prodromal stages remains unclear. A detailed forecast of PD symptoms may aid in future development of clinical trials.

Biomarkers of degeneration in RBD:

Over the years, several progressive markers (i.e. non-motor and motor manifestations)[52], biomarkers (e.g. synuclein deposit in cutaneous nerves and high echogenicity area in SN)[58, 59] and certain genetic variants (*LRRK2*, *PINK, PARK2, GBA and MAPT*)[60-64] have been suggested for either assessing the efficacy of future clinical trials or the search of a trial's target population. However, none of these markers can provide a long-term window before disease conversion and be used to examine the progression of neurodegeneration.

Medical imaging is useful for the understanding of the neurodegenerative evolution in parkinsonism. Recently, Bauckneht et.al. reviewed over 16 PET/SPECT studies with estimated 180 participants (excluding 11 duplicates) and found a general trend of decline in dopamine reuptake at putamen and caudate regions.[65] The model was able to successfully distinguish healthy controls, iRBD, PD and PD-RBD in most group comparisons (with an exception of iRBD vs. PD; overall AUC range from 0.79 to 0.99). Reduction in both substantial nigral volume measuring via structural MRI imaging ($p < 0.01$) and PET signal intensity ($p < 0.05$) were also found in both Oxford and Paris RBD cohorts.[66, 67] Although, these findings provide support for the nigrostriatal degeneration model, they cannot solely explain the mechanism of dream enactment behavior.

On the other hand, several studies have shown a decline in the volume of pontine region, which generates REM sleep muscular inhibition, in both iRBD and PD with RBD patients.[2, 68-70] Furthermore, microstructural changes in pons were found in both French and Denmark cohorts. Ehrminge study found a decrease in iRBD patients' both left and right locus coeruleus/subcoeruleus complex (LC) volumes compared to healthy controls ($n=21$, $p < 0.001$).[54] Another study done by Knudsen, shared similar findings of reduction in LC

volume and found a decrease in colonic isotope uptake, which suggests possible pathology in the peripheral autonomic nervous system.[71] Clonazepam has also been shown to promote the activation of the noradrenergic neurons, which are involved in the glutamatergic mechanism, in LC.[72] Although this evidence is partially aligned with existing knowledge of circuits controlling REM sleep and the hypothesized RBD disease mechanism,[73] more studies were required to determine the role of the brainstem in disease progression, as the brainstem degeneration is not uniformed across all cohorts.[74]

References:

1. Peever J, Luppi PH, Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. Trends Neurosci 2014;37:279-288.
2. Valencia Garcia S, Brischoux F, Clement O, et al. Ventromedial medulla inhibitory neuron inactivation induces REM sleep without atonia and REM sleep behavior disorder. Nat Commun 2018;9:504.
3. Vilas D, Iranzo A, Pont-Sunyer C, et al. Brainstem raphe and substantia nigra echogenicity in idiopathic REM sleep behavior disorder with comorbid depression. J Neurol 2015;262:1665-1672.
4. Tang WK, Hermann DM, Chen YK, et al. Brainstem infarcts predict REM sleep behavior disorder in acute ischemic stroke. BMC Neurol 2014;14:88.
5. Oudiette D, De Cock VC, Lavault S, Leu S, Vidailhet M, Arnulf I. Nonviolent elaborate behaviors may also occur in REM sleep behavior disorder. Neurology 2009;72:551-557.
6. Herlin B, Leu-Semenescu S, Chaumereuil C, Arnulf I. Evidence that non-dreamers do dream: a REM sleep behaviour disorder model. J Sleep Res 2015;24:602-609.
7. Fantini ML, Corona A, Clerici S, Ferini-Strambi L. Aggressive dream content without daytime aggressiveness in REM sleep behavior disorder. Neurology 2005;65:1010-1015.
8. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med 2011;12:445-453.
9. Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and Determinants of REM Sleep Behavior Disorder in the General Population. Sleep 2017;41:zsx197-zsx197.
10. 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;36:1147-1152.
11. Iranzo A, Stefani A, Serradell M, et al. Characterization of patients with longstanding idiopathic REM sleep behavior disorder. Neurology 2017;89:242-248.
12. Stewart SA, Penz E, Fenton M, Skomro R. Investigating Cost Implications of Incorporating Level III At-Home Testing into a Polysomnography Based Sleep Medicine Program Using Administrative Data. Can Respir J 2017;2017:8939461.
13. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. Mov Disord 2007;22:2386-2393.
14. Marelli S, Rancoita PM, Giarrusso F, et al. National validation and proposed revision of REM sleep behavior disorder screening questionnaire (RBDSQ). J Neurol 2016;263:2470-2475.
15. Li SX, Wing YK, Lam SP, et al. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). Sleep Med 2010;11:43-48.
16. You S, Moon HJ, Do SY, et al. The REM Sleep Behavior Disorder Screening Questionnaire: Validation Study of the Korean Version (RBDQ-KR). J Clin Sleep Med 2017;13:1429-1433.
17. Sasai T, Matsuura M, Wing YK, Inoue Y. Validation of the Japanese version of the REM sleep behavior disorder questionnaire (RBDQ-JP). Sleep Med 2012;13:913-918.
18. Chang Y, Gu Z, Zhan S, et al. Validation of the Beijing version of the REM sleep behavior disorder questionnaire (RBDQ-Beijing) in a mainland Chinese cohort. Tohoku J Exp Med 2014;234:7-15.
19. Chahine LM, Daley J, Horn S, et al. Questionnaire-based diagnosis of REM sleep behavior disorder in Parkinson's disease. Mov Disord 2013;28:1146-1149.
20. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. J Clin Sleep Med 2013;9:475-480.
21. Li K, Li SH, Su W, Chen HB. Diagnostic accuracy of REM sleep behaviour disorder screening questionnaire: a meta-analysis. Neurol Sci 2017;38:1039-1046.
22. 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.

23. Frauscher B, Ehrmann L, Zamarian L, et al. Validation of the Innsbruck REM sleep behavior disorder inventory. Mov Disord 2012;27:1673-1678.
24. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. Nat Rev Neurol 2016;12:622-634.
25. Schenck CH, Mahowald MW. Insights Into Polysomnography-Confirmed REM Sleep Behavior Disorder From New Prevalence and Gender Data in the General Population. Sleep 2018.
26. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 2011;26 Suppl 1:S1-58.
27. 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.
28. Wong JC, Li J, Pavlova M, et al. Risk factors for probable REM sleep behavior disorder: A community-based study. Neurology 2016;86:1306-1312.
29. Weisskopf MG, Knekt P, O'Reilly EJ, et al. Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology 2010;74:1055-1061.
30. Ascherio A, Chen H, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol 2006;60:197-203.
31. Rhodes SL, Fitzmaurice AG, Cockburn M, Bronstein JM, Sinsheimer JS, Ritz B. Pesticides that inhibit the ubiquitin-proteasome system: effect measure modification by genetic variation in SKP1 in Parkinsons disease. Environ Res 2013;126:1-8.
32. Ma JF, Qiao Y, Gao X, et al. A community-based study of risk factors for probable rapid eye movement sleep behavior disorder. Sleep Med 2017;30:71-76.
33. Baig F, Lawton MA, Rolinski M, et al. Personality and addictive behaviours in early Parkinson's disease and REM sleep behaviour disorder. Parkinsonism Relat Disord 2017;37:72-78.
34. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85:560-566.
35. Wing YK, Lam SP, Li SX, et al. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. J Neurol Neurosurg Psychiatry 2008;79:1415-1416.
36. Postuma RB, Gagnon JF, Tuineaig M, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013;36:1579-1585.
37. McCarter SJ, St Louis EK, Sandness DJ, et al. Antidepressants Increase REM Sleep Muscle Tone in Patients with and without REM Sleep Behavior Disorder. Sleep 2015;38:907-917.
38. Damholdt MF, Ostergaard K, Borghammer P, Larsen L. The parkinsonian personality and concomitant depression. J Neuropsychiatry Clin Neurosci 2011;23:48-55.
39. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. Brain 2009;132:3298-3307.
40. Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson disease: A systematic review and meta-analysis. Movement Disorders 2013;28:1222-1229.
41. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30:1600-1611.
42. Hoque R, Chesson AL, Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 2010;6:79-83.
43. Ryan Williams R, Sandigo G. Venlafaxine-induced REM sleep behavioral disorder presenting as two fractures. Trauma Case Rep 2017;11:18-19.
44. Tan L, Zhou J, Yang L, et al. Duloxetine-induced rapid eye movement sleep behavior disorder: a case report. BMC Psychiatry 2017;17:372.
45. Iranzo A, Santamaria J. Bisoprolol-induced rapid eye movement sleep behavior disorder. Am J Med 1999;107:390-392.

46. Zhang B, Hao Y, Jia F, et al. Sertraline and rapid eye movement sleep without atonia: an 8-week, open-label study of depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2013;47:85-92.
47. Arnulf I. REM sleep behavior disorder: Motor manifestations and pathophysiology. Movement Disorders 2012;27:677-689.
48. Darweesh SK, Verlinden VJ, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of prediagnostic functioning in Parkinson's disease. Brain 2017;140:429-441.
49. Darweesh SKL, Wolters FJ, Postuma RB, et al. Association Between Poor Cognitive Functioning and Risk of Incident Parkinsonism: The Rotterdam Study. JAMA Neurol 2017;74:1431-1438.
50. 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;135:1860-1870.
51. Genier Marchand D, Postuma RB, Escudier F, et al. How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. Ann Neurol 2018;83:1016-1026.
52. Postuma RB, Gagnon JF, Bertrand JA, Genier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015;84:1104-1113.
53. Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. Ann Neurol 2011;69:811-818.
54. Ehrminger M, Latimier A, Pyatigorskaya N, et al. The coeruleus/subcoeruleus complex in idiopathic rapid eye movement sleep behaviour disorder. Brain 2016;139:1180-1188.
55. Wu Y, Le W, Jankovic J. Preclinical biomarkers of Parkinson disease. Arch Neurol 2011;68:22-30.
56. Barber TR, Lawton M, Rolinski M, et al. Prodromal Parkinsonism and Neurodegenerative Risk Stratification in REM Sleep Behavior Disorder. Sleep 2017;40.
57. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Annals of Neurology 2008;63:167-173.
58. Antelmi E, Donadio V, Incensi A, Plazzi G, Liguori R. Skin nerve phosphorylated alpha-synuclein deposits in idiopathic REM sleep behavior disorder. Neurology 2017;88:2128-2131.
59. Iwanami M, Miyamoto T, Miyamoto M, Hirata K, Takada E. Relevance of substantia nigra hyperechogenicity and reduced odor identification in idiopathic REM sleep behavior disorder. Sleep Med 2010;11:361-365.
60. Saunders-Pullman R, Alcalay RN, Mirelman A, et al. REM sleep behavior disorder, as assessed by questionnaire, in G2019S LRRK2 mutation PD and carriers. Mov Disord 2015;30:1834-1839.
61. Gan-Or Z, Mirelman A, Postuma RB, et al. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol 2015;2:941-945.
62. Gan-Or Z, Ruskey JA, Spiegelman D, et al. Heterozygous PINK1 p.G411S in rapid eye movement sleep behaviour disorder. Brain 2017;140:e32.
63. Gan-Or Z, Girard SL, Noreau A, et al. Parkinson's Disease Genetic Loci in Rapid Eye Movement Sleep Behavior Disorder. J Mol Neurosci 2015;56:617-622.
64. Oczkowska A, Kozubski W, Lianeri M, Dorszewska J. Mutations in PRKN and SNCA Genes Important for the Progress of Parkinson's Disease. Curr Genomics 2013;14:502-517.
65. Baucknehtt M, Chincarini A, De Carli F, et al. Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: A systematic review and meta-analysis. Sleep Med Rev 2018.
66. Pyatigorskaya N, Gaurav R, Arnaldi D, et al. Magnetic Resonance Imaging Biomarkers to Assess Substantia Nigra Damage in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. Sleep 2017;40.
67. Rolinski M, Griffanti L, Piccini P, et al. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. Brain 2016;139:2224-2234.

68. Bianciardi M, Lewis LD, Wald LL, Rosen BR, Videnovic A. 0718 7 TESLA IMAGING OF MICROSTRUCTURAL BRAINSTEM CHANGES IN REM SLEEP BEHAVIOR DISORDER. Sleep 2017;40:A266-A266.
69. Vendette M, Gagnon JF, Soucy JP, et al. Brain perfusion and markers of neurodegeneration in rapid eye movement sleep behavior disorder. Mov Disord 2011;26:1717-1724.
70. Holtbernd F, Gagnon JF, Postuma RB, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology 2014;82:620-627.
71. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. Lancet Neurol 2018;17:618-628.
72. Nilsson LK, Schwieler L, Engberg G, Linderholm KR, Erhardt S. Activation of noradrenergic locus coeruleus neurons by clozapine and haloperidol: involvement of glutamatergic mechanisms. Int J Neuropsychopharmacol 2005;8:329-339.
73. McKenna D, Peever J. Degeneration of rapid eye movement sleep circuitry underlies rapid eye movement sleep behavior disorder. Mov Disord 2017;32:636-644.
74. Rahayel S, Postuma RB, Montplaisir J, et al. Abnormal Gray Matter Shape, Thickness, and Volume in the Motor Cortico-Subcortical Loop in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Association with Clinical and Motor Features. Cereb Cortex 2018;28:658-671.

Goals and Objectives

To extend the understanding and prepone the diagnosis of iRBD in synucleinopathy, several studies were performed and included in the first two chapters. They are:

- Risk Factor profiles and phenoconversion rate in the prospective population-based Canadian Longitudinal Study on Aging cohort

  1A: Risk Factors for possible REM Sleep Behavior Disorder

  1B: Phenoconversion from possible REM Sleep Behavior to Parkinsonism

  1C: Revisiting Idiopathic RBD Screening Definition

  1D: Revisiting Parkinsonism Risk Factors in Idiopathic RBD and RBD-Free Prodromal Parkinsonism

- Longstanding disease-free survival in idiopathic REM sleep behavior disorder in a prospective Montreal iRBD cohort.

Chapter IA - Risk Factors for possible REM Sleep Behavior Disorder: A CLSA Population-based Cohort

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Introduction

Risk factors for RBD are relatively understudied. Some studies have suggested that risk factors associated with PD or dementia (e.g. head trauma) are also present in RBD. However, some risk factors may differ, most notably smoking and caffeine use.[1, 2]

We used baseline data, collected between 2012 and 2015, from the Canadian Longitudinal Study on Aging Comprehensive sample of 30,097 participants. The CLSA included the RBD1Q, as well as additional questions to help rule out RBD mimics. In this study, we assessed sociodemographic, socioeconomic and clinical correlates of possible RBD.

Methods

Canadian Longitudinal Study of Aging Cohort

The Canadian Longitudinal Study on Aging (CLSA) is a prospective, national, population-based cohort, recruiting 51,338 participants, aged 45 to 85 years randomly sampled from 10 Canadian provinces, stratified by age.[3] Written informed consent was obtained from all participants (or guardians of participants) in the study. CLSA participants provide a core information set on demographics, lifestyle and behavior, social, physical, clinical, psychological, economic, and health status measures, including screens for selected neurological diseases. Of the entire cohort, 30,097 are included in a comprehensive cohort, recruited from 2012 to 2015, in which participants also have in-home face-to-face interviews (including a sleep questionnaire module that screens for sleep onset and maintenance insomnia, excessive somnolence, restless legs syndrome and RBD), physical assessments and biospecimen sampling; this is the sample for the current study.[3] Data access for the use of this study was reviewed and granted by the Data and Sample Access Committee (DSAC).

RBD Case Definition

In the comprehensive cohort, RBD was screened as a 'yes' response to the single-question RBD1Q: "Have you ever been told, or suspected yourself, that you seem to “act out your dreams" while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?". [4] Specificity has been estimated as 87%; false positives can occur if the RBD1Q detects other sleep disorders, especially NREM sleep disorders and obstructive sleep apnea. So for the primary analysis (Figure 1), to reduce false positives, we excluded screen positives with:

- onset under 20 years old - NREM parasomnia is generally a childhood onset disorder[5, 6], whereas synucleinopathy-mediated RBD starts generally after age 40[7].

- positive apnea screen defined as a "yes" response to either of the two symptom items from the STOP-BANG questionnaire (i.e. snoring loud enough to be heard in the next room and/or stopping breathing while sleeping)[8]

- any patient reporting a diagnosis of dementia / Alzheimer's disease (AD), or parkinsonism / Parkinson's disease (PD) (i.e. not idiopathic RBD).

In the risk factor assessment, these participants were excluded from both the RBD screen positive and RBD screen negative groups (i.e. the control group) to prevent bias related to risk factors for the excluded conditions (e.g. if apnea is removed from the RBD group but not the control group, apnea risk factors would be imbalanced between groups). Note that the use of the term risk factor here does not imply temporality or causality, as this is a cross-sectional study.

Sociodemographic and Life Style Variables

Educational levels were categorized in the CLSA as middle school and under, secondary school, bachelor degree and other diploma, and above. For the purposes of this analysis total years of education were imputed from the estimated years in the education categories and from information provided directly in follow-up questions (0-8 years imputed as the average = 4, 9-10 taken from follow-up questions, secondary school imputed as 12, post-secondary imputed according to average length of degree for each diploma type). Marital status was categorized into single/never married, married/common-law, widowed and divorced/separated. Annual personal income was grouped into four levels: $< 20000, 20-49000, 50-99000, ≥ 100,000. For ethnicity, participants were classified as Caucasian or Non-Caucasian (95.6% were Caucasian, so we did not have sufficient power to subdivide non-Caucasian ethnicities).

For lifestyle variables we analysed the average weekly walking hours during leisure time and their annual frequency of participating in social activities. Smoking status was categorized into three groups: never smoker (combining occasional smokers and non-smokers), past smoker and current smoker. We calculated pack years of smoking as packs/day x smoking years. Weekly alcohol consumption was based upon self-report using standard alcoholic beverage amounts (14 grams of ethanol). Binge drinking frequency was defined as >5 drinks per sitting for men (>4 for women). Moderate-heavy drinking was defined as drinking more than 7 drinks per week for females and 14 for males. Overall satisfaction level of life and self-rated social standing in the community was rated using the 10-point MacArthur scales.[9] Self-rated health profiles (healthy ageing, mental health and physical health) were assigned from 1 (poor) to 5 (excellent). Use of antidepressants and mental illness were assessed via self-report.

Statistical Analysis of Risk Factors

Prevalence odds ratios (OR) were estimated first based on logistic regression adjusting for age and sex (unweighted to the general Canadian population) with pRBD as the dependent variable. We then reassessed all OR in a more complete multivariable regression model that included age (continuous), sex (categorical), currently married or widowed (categorical), imputed years of education (continuous), income (ordinal), retirement (categorical), heavy drinking (categorical), daily smoking (categorical), having served in the military (categorical) and mental illness and/or use of antidepressant (categorical). To avoid repetition in analyses, similar variable structure to the regression model were used to replace the corresponding core variables (e.g. in analyzing the relationship between each age group and RBD, the ordinal variable “Age Group” would replace age as a continuous variable in the regression model). Statistical analyses were performed by PASW Statistics 18. We omitted any responses labeled as uncertain or 'refused to answer' in all analyses.

Sensitivity Analyses

In addition to the primary analysis, we performed three sensitivity analyses (fig e-1):

1) Including all RBD screen positives (i.e. including early onset and with positive apnea screen (still excluding dementia and parkinsonism)

2) Excluding those with mental illness (to assess possible role of post-traumatic stress disorder and/or antidepressant-caused RBD); in this analysis, those who screened positive on the Centre for Epidemiologic Studies Depression Scale Revised (CEDS-R-10)[10] or on the Primary Care PTSD Screen (PC-PTSD)[11], or who scored greater than 24 on the Kessler Psychological Distress Scale (K10)[12] or who self-reported a physician diagnosis of mood disorder, anxiety disorder or depressive disorder were excluded.

3) Excluding those screening positive for restless leg syndrome (RLS) (a possible mimic because of associated periodic leg movements of sleep), using sleep module questions adapted from the Johns Hopkins telephone interview for RLS[13, 14]

Results

Characteristics of the Cohort

Of the 30,097 included, 14,777 were male and 15,320 female. 64.7% were either married or in a common-law relationship. A total of 3,271 screened positive for possible RBD. Of these, 14 self-reported dementia and 44 self-reported PD/parkinsonism, 1386 screened positive for apnea, and 1529 had young onset dream enactment. This left 958 (4.9% of the remaining 19,584 participants; 3.2% of the 30,097-person cohort) considered as having possible RBD (pRBD) after removing potential false RBD mimics (table 1).

A. Simple Multivariable Analysis (Age and Sex-Adjusted only)

Sociodemographic Variables

The mean age was similar between pRBD participants and controls (63.0 vs. 63.5; OR_{adj}=0.994, 95%CI: [0.988, 1.001]). 58.9% with pRBD were male vs. 42.3% without ($OR_{adj.}$=1.97 [1.72, 2.25]). There was no evidence of an association with ethnicity (Caucasians vs. non-Caucasians $OR_{adj.}$=0.94 [0.70, 1.29]), but statistical power was limited as 95% of the cohort was Caucasian. Those with pRBD were more likely to be married or in a common-law relationship ($OR_{adj.}$=1.64 [1.22, 2.17]) or widowed ($OR_{adj.}$=1.47 [1.02, 2.12]). Those with pRBD had slightly less education (estimated mean years=13.2 vs. 13.6 years, OR_{adj}=0.94 [0.92, 0.96])., They also had lower income than those without. Moreover, pRBD participants reported having retired at a slightly younger age (57.5 vs. 58.6 years old, $OR_{adj.}$=0.98 [0.96, 0.99]) and were more likely to report that retirement was due to health issues (28.9 vs. 22.0%, OR_{adj}=1.22 [1.02, 1.46]). Although veterans did not have clearly higher occurrence of pRBD (OR=1.22 [0.99, 1.57]), there was a modest relationship between self-reported years of military service and pRBD among veterans (12.1 vs. 8.9 years, OR_{adj}=1.03 [1.01, 1.05]).

Activity and Self-Rated Health

pRBD participants were less likely to walk more than 7 hours per week (OR_{adj}=0.78 [0.62, 0.98]), although the average time spent walking did not differ between groups (4.2±4.3 vs. 4.7±4.7 hours) (table 2). The frequency of participation in either social activities or social sport did not differ between those with pRBD and controls. Those with pRBD were slightly less satisfied about their lives (life satisfaction score=27.2 vs. 28.1, OR_{adj}=0.98 [0.97, 0.99]), and were also more likely to rate their social standing in community as lower (mean social standing score=6.0 vs. 6.3, OR_{adj}=0.91 [0.88, 0.95]). Those with pRBD self-rated as having less healthy aging (score=3.6 vs. 3.8, OR_{adj}=0.81 [0.75, 0.87], physical health (3.6 vs. 3.8, OR_{adj}=0.80 [0.75, 0.86]) and mental health (3.8 vs. 4.0, OR_{adj}=0.75 [0.70, 0.81]).

Alcohol Use and Smoking

pRBD participants were more likely to drink more (100g vs. 70g/week, OR_{adj}=1.10 [1.03, 1.17]) and to be a moderate-heavy drinker (18.9% vs. 14.3%, OR_{adj}=1.32 [1.12, 1.56]). pRBD participants were also more likely to be current smokers (8.9% vs. 6.4%, OR_{adj}=1.61 [1.27, 2.04]) and past smokers (42.7% vs. 36.9%, OR_{adj}=1.29 [1.12, 1.47]). The average cigarette pack-year smoking dose was slightly greater in the pRBD group (8 vs. 6, OR_{adj}=1.01 [1.00, 1.01]).

Antidepressants and Mental Illness

Antidepressants were used more frequently used among pRBD participants (13.4% vs. 6.2%, OR_{adj}=2.71 [2.22, 3.31] table 3). pRBD participants scored higher on the Kessler Psychological Distress Scale (15.2±5.33 vs. 13.9±1.86, OR_{adj}=1.07 [1.05, 1.08]), and were more likely to report at least moderate psychological distress (10.9% vs. 6.6%, OR_{adj}=1.58 [1.43, 1.75]). Additionally, pRBD participants more often had a diagnosis of mental illness

(34.9% vs. 21.9%, OR_{adj}=1.91 [1.66, 2.19]), including a higher prevalence of physician-diagnosed anxiety (13.8% vs. 7.3%, OR_{adj}=2.24 [1.85, 2.72]) and depressive disorder (20.7% vs. 13.9%, OR_{adj}=1.84 [1.56 2.17]). The rate of positive screening of post-traumatic stress disorder was higher among those with pRBD (10.5% vs. 4.0%, OR_{adj}=3.19 [2.55, 3.99]).

B. Full Multivariable Analysis

Using multivariable logistic regression model (i.e. with all 10 variables, as listed in the methods), the association with male sex (OR_{mod}=2.14 [1.84, 2.50]) and with relationship status (OR_{mod}=1.77 [1.45, 2.16]) remained. Socioeconomically, lower education level still remained as a risk factor of pRBD in the multivariate model, but not income level, employment status, life satisfaction or self-rated social standing. Retirement age and having reporting retirement due to health issues remained significantly associated with pRBD, as were the amount of alcohol consumed weekly and moderate-heavy drinking (OR_{mod}=1.09 [1.02, 1.16], 1.25 [1.03, 1.50]). The average scores of life satisfaction and self-rated social standing still remained lower in pRBD. Overall, mental illness remained highly prevalent in pRBD participants compared to controls.

C. Sensitivity Analyses

Because RLS and periodic leg movements during sleep might be confused with dream enactment, we performed a sensitivity analysis omitting any RLS screen-positive participants from the pRBD group. Of the 16,552 remaining, 756 (4.6%) screened positive for possible RBD (representing 2.5% of the entire population before exclusions). No substantial change in results was observed (supplemental table e-2).

To further explore pRBD in the absence of mental illness, we also removed all participants reporting anxiety, depression, high psychological stress or post-traumatic stress disorder. Of

the 13,416 remaining, 543 participants (4.0%) screened positive for possible RBD (representing 1.8% of the entire population before exclusions). Results of risk factors were generally similar to the two primary multivariable analyses (supplemental table e-2).

Finally, to confirm our findings in absence of potential misclassification bias caused by both RLS symptoms or mental illness (including use of antidepressant), we performed an additional highly-restrictive sensitivity analysis excluding any pRBD participants endorsing either RLS or any self-reported mental illness. Of the 11,609 subjects remaining, 390 (3.3%) had possible RBD (1.3% of the total population). Risk factor results were similar to that of in the regression model (table 4). It is worth noting that pRBD participants were still more likely to have risky drinking habits and higher psychological distress level (12.9±2.8 vs. 12.6±1.3) than controls.

Discussion

In this 30,097-subject nation-wide study, we found that male sex, low education, heavy drinking, smoking, antidepressant use, and numerous indices of mental health are linked with possible RBD.

This is a large population-based study examining risk factors for possible RBD. Two previous large cross-sectional studies were conducted in Tangshan (n=12,784) and Shanghai (n=3,635), China[1, 15], which examined pRBD in selected populations. The Tangshan study found that age, male sex, marital status, low socioeconomic status and coal mining were associated with pRBD. pRBD participants were also more likely to smoke and drink alcohol and coffee, and were less active. The Shanghai report also found an association between risky drinking and pRBD. The Shanghai study found that those with pRBD were more likely to be single, and found no difference in risk between sexes. This may be due to the nature of the cohort (67% female participants) and the low specificity of the screening questionnaire (the RBDSQ was used, which includes some questions unrelated to dream-enactment[16]). Three other studies were conducted with polysomnogram-confirmed RBD.[2, 17] The largest, conducted by the RBD study group, found that RBD was more common in those with lower education, farmers, welders, and those exposed to pesticide; of note, there was no lowering of risk with caffeine and smoking (which are known to be associated with lower PD risk). A follow-up study from this group found that neither caffeine nor smoking were associated with more rapid conversion to defined PD or DLB; however, pesticide use was associated with a lower phenoconversion and family history of dementia with a higher conversion risk.[18] A second PSG-proven RBD study also found that participants were more likely to be smokers, with a mild association with lower alcohol use and no relationship with caffeine use.[17] Finally, a recent report from the Lausanne sleep registry again found that RBD participants were more likely to be smokers, and also had more antidepressant and antipsychotic use.[19]

The strongest relationships seen in our study were between measures of mental illness and pRBD. This same relationship has been seen in several studies, including cohorts of PSG-proven RBD, and RBD in association with PD.[17, 20-22] There are several possible explanations for this. One is that those with mental illness may tend to endorse multiple symptoms, including multiple sleep symptoms as part of their illness.[23-25] Another is th[20]at RBD itself can lead to psychosocial distress, via disruption in sleep patterns or bed partner relationships (this possibility does not accord with our clinical experience in RBD; sleep variables on polysomnogram are generally otherwise preserved in RBD[26], and patients themselves often express little concern about their dream enactment). Another more compelling hypothesis is that antidepressants are well known to trigger RBD and so we may be detecting antidepressant-triggered RBD.[22, 27] Note, however, the relationship with mental illness persisted even after adjustment for antidepressant use (OR_{adj}=1.78 [1.49, 2.14]). Another plausible explanation is that given depression and anxiety, like RBD, are well known risk factors for PD[22, 28], some of the effect seen may be due to a common underlying cause (i.e. prodromal PD and DLB). Finally, it is possible that there exists a subset of RBD in which people with preserved REM atonia mechanisms can nevertheless have dream enactment, because of very high intensity nightmares (common in PTSD), or general sleep-state disruption (as seen in narcolepsy). This would be consistent with the fact that the strongest relationship we observed was with PTSD and with previous descriptions of a trauma-associated sleep disorder, in which night terrors are common during both nREM and REM sleep.[29, 30] It is unclear whether this confound would explain all of our findings, however, as multicenter studies in PSG-confirmed cases have also found relationships between confirmed RBD and depression (OR=2.0) and antidepressant use (OR=2.4).[31]

Another unexplained finding, seen now in several studies is the relationship between lower education/socioeconomic status and pRBD.[1, 2, 32] With the comprehensive cohort of the

CLSA, we were able to assess this controlling for other key variables, particularly mental illness. We saw that some of this relationship was attenuated by this adjustment, suggesting that socioeconomic status and mental illness may have partially explained the relationship. However, the residual relationship with education after adjustment remains unexplained. This could be due to residual confounding from unmeasured mental illness, a different unmeasured confounding variable, or a true causal relationship. Studies have not generally found a connection between level of education and PD or DLB, suggesting that underlying synucleinopathy is not the cause. A final possibility is that dream content (which is related to daily activities) may differ in those with less education, with a differing likelihood of being recognized by patients or bed partners (e.g. if one enacts dreams about occupational activity, physical activity during RBD might differ between a college professor or construction worker[33]),

Given the strong and consistent inverse relationship between PD and smoking[1, 2, 17], the positive relationship seen here remains unexplained. Although OR overlapped, it appeared that current smokers had the strongest association, followed by past smokers and then non-smokers. It is known that smoking is correlated with alcohol use and mental illness.[2, 34] Here, with multivariable analysis, some of the relationship was attenuated after controlling for mental illness and alcohol use. It may be that non-synucleinopathy causes of dream enactment (e.g. false positives) are positively associated with smoking, counterbalancing a 'protective' role in synucleinopathy-mediated RBD. However, previous studies in PSG-confirmed RBD found that smoking was more common in RBD, and was not associated with progression from idiopathic RBD to PD and DLB. Alternatively, it has been recognized that RBD is strongly associated with disease subtype in PD and DLB.[35-38] It is possible that PD and DLB are epidemiologically heterogenous; some subtypes are associated with smoking risk and others not. Finally, given the complexity of factors that cause smoking behavior, and the partial

attenuation with multivariable adjustment, residual confounding related to unmeasured aspects of mental illness, impulse control, education, etc. make explain this relationship.

Strengths and Limitations

Some limitations of this study should be noted. First, the diagnosis of possible RBD, although done with a validated questionnaire, nevertheless relied entirely upon self-report. 3.18 % of our sample had possible RBD; however, studies that use polysomnogram (which should be considered the gold-standard studies) have found prevalences of approximately 1%.[19, 39, 40] This implies that even assuming high sensitivity, the majority of 'possible RBD' cases do not actually have RBD. This problem is shared by all large-scale risk factors studies of RBD.[1, 15] In particular, most patients with NREM parasomnia would screen positive on the RBD1Q (one study found that 69% of those with NREM parasomnia will screen positive on the RBD1Q)[41]; we attenuated this somewhat by selecting out those who had onset before age 20 (ages at which the majority of NREM parasomnia start). However, this would miss those who misattribute onset age, as well as all those who develop NREM parasomnia late in life. Periodic leg movements in sleep (PLMS) can also be a source of screen positives for possible RBD (noting that PLMS can also occur in true RBD).[42] Although the fact that we saw no change in point estimates on sensitivity analysis when removing participants with RLS makes this less likely, there still could be confounding by those reporting PLMS in the absence of RLS. It is possible also that adding frequency information (i.e. eliminating those with infrequent events) or restricting to those with current symptoms only would help reduce the false positive rate;[43] however, we do not have frequency information available. In general, incorrect diagnoses would result in a non-differential misclassification bias; that is, they would wash out differences between groups. If so, the significant relationships in our study would be generally stronger than what we observed, while some relationships would be missed. However,

differential misclassification is also possible, such that false positive screens could be driving some of the results (e.g. non-specific sleep disturbance with depression, post-traumatic stress disorder, apnea cases missed by screening questionnaires, periodic leg movements unassociated with restless legs syndrome, etc.). As discussed above, this may be particularly important for the relationship we observed between mental illness and possible RBD; those with post-traumatic stress, depression, or anxiety may be particularly prone to dream enactment unrelated to loss of REM atonia. Second, it is likely that many participants would be unaware of having dream enactment. This is underscored by our finding that being married or in a long-term relationship was associated with RBD, a finding likely explained by differential levels of awareness. Third, although the CLSA is relatively comprehensive, many variables of interest were not measured such as quantitative information of caffeinated products and other substance consumption (dietary information has been collected but analysis is pending). Fourth, because we were studying idiopathic RBD, we eliminated self-reported parkinsonism or PD. Overall sensitivity for self-report PD approximates 80%, meaning that some true PD patients might have been missed (note that dementia was eliminated both with self-report and cognitive examination, so this limitation would not apply for dementia).

On the other hand, the main advantages of our current study are the large sample size, the systematic population-based sampling, the capacity to adjust for diverse potential confounding variables, including mental illness and the ability to screen out RBD mimics such as apnea, RLS, and possible non-REM parasomnia.

Conclusions

This study has replicated findings originally seen in smaller scale cohorts that smoking, low education, and male sex are associated with RBD. We found a previously-unreported link with alcohol use. Finally, we found a strong connection between possible RBD and mental

illness in general, including depression, anxiety, and PTSD. Further clinical research on the comorbidity of mental illness and psychological health profile in iRBD is needed, to disentangle the complex interplay of sleep and mental health. Extra attention to mental health issues in clinical care of RBD patients may be warranted.

Reference

1. Wong JC, Li J, Pavlova M, et al. Risk factors for probable REM sleep behavior disorder: A community-based study. Neurology 2016;86:1306-1312.
2. 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.
3. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28:221-229.
4. 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.
5. Markov D, Jaffe F, Doghramji K. Update on parasomnias: a review for psychiatric practice. Psychiatry (Edgmont) 2006;3:69-76.
6. Fleetham JA, Fleming JA. Parasomnias. CMAJ 2014;186:E273-280.
7. Postuma RB, Gagnon JF, Bertrand JA, Genier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015;84:1104-1113.
8. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire: A Practical Approach to Screen for Obstructive Sleep Apnea. Chest 2016;149:631-638.
9. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;19:586-592.
10. Van Dam NT, Earleywine M. Validation of the Center for Epidemiologic Studies Depression Scale--Revised (CESD-R): pragmatic depression assessment in the general population. Psychiatry Res 2011;186:128-132.
11. Prins A, Bovin MJ, Smolenski DJ, et al. The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5): Development and Evaluation Within a Veteran Primary Care Sample. J Gen Intern Med 2016;31:1206-1211.
12. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002;32:959-976.
13. Hattan E, Chalk C, Postuma RB. Is there a higher risk of restless legs syndrome in peripheral neuropathy? Neurology 2009;72:955-960.
14. Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. Sleep Med 2008;9:283-289.
15. Ma JF, Qiao Y, Gao X, et al. A community-based study of risk factors for probable rapid eye movement sleep behavior disorder. Sleep Med 2017;30:71-76.
16. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. Mov Disord 2007;22:2386-2393.
17. Baig F, Lawton MA, Rolinski M, et al. Personality and addictive behaviours in early Parkinson's disease and REM sleep behaviour disorder. Parkinsonism Relat Disord 2017;37:72-78.
18. 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.
19. Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and Determinants of REM Sleep Behavior Disorder in the General Population. Sleep 2017;41:zsx197-zsx197.
20. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85:560-566.
21. Wing YK, Lam SP, Li SX, et al. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. J Neurol Neurosurg Psychiatry 2008;79:1415-1416.
22. Postuma RB, Gagnon JF, Tuineaig M, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013;36:1579-1585.

23. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci 2008;10:329-336.
24. Horvath A, Montana X, Lanquart JP, et al. Effects of state and trait anxiety on sleep structure: A polysomnographic study in 1083 subjects. Psychiatry Res 2016;244:279-283.
25. Baglioni C, Nanovska S, Regen W, et al. Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychol Bull 2016;142:969-990.
26. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis 2017;3:9.
27. Gagnon JF, Postuma RB, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. Neurology 2006;67:742-747.
28. Berg D, Postuma RB, Adler CH, et al. MDS Research Criteria for Prodromal Parkinson's Disease. Mov Disord 2015;30:1600-1611.
29. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: A parasomnia induced by trauma. Sleep Med Rev 2018;37:94-104.
30. Manni R, Ratti PL, Terzaghi M. Secondary ''incidental'' REM sleep behavior disorder: do we ever think of it? Sleep Med 2011;12 Suppl 2:S50-53.
31. Frauscher B, Jennum P, Ju YE, et al. Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. Neurology 2014;82:1076-1079.
32. Wing YK, Lam SP, Tsoh JM, Mok VC. Rapid eye movement sleep behaviour disorder and psychiatry: a case-control study. Hong Kong Med J 2015;21 Suppl 6:34-38.
33. Stiasny-Kolster K, Sixel-Doring F, Trenkwalder C, et al. Diagnostic value of the REM sleep behavior disorder screening questionnaire in Parkinson's disease. Sleep Med 2015;16:186-189.
34. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res 2008;10:1691-1715.
35. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain 2017;140:1959-1976.
36. Postuma RB, Bertrand JA, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord 2012;27:720-726.
37. Postuma RB, Adler CH, Dugger BN, et al. REM sleep behavior disorder and neuropathology in Parkinson's disease. Mov Disord 2015;30:1413-1417.
38. Dugger BN, Boeve BF, Murray ME, et al. Rapid eye movement sleep behavior disorder and subtypes in autopsy-confirmed dementia with Lewy bodies. Mov Disord 2012;27:72-78.
39. Pujol M, Pujol J, Alonso T, 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;40:116-121.
40. Baig F, Lawton M, Rolinski M, et al. Delineating nonmotor symptoms in early Parkinson's disease and first-degree relatives. Mov Disord 2015;30:1759-1766.
41. Haridi M, Weyn Banningh S, Cle M, Leu-Semenescu S, Vidailhet M, Arnulf I. Is there a common motor dysregulation in sleepwalking and REM sleep behaviour disorder? J Sleep Res 2017;26:614-622.
42. Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology 2002;59:1889-1894.
43. Nielsen T, Svob C, Kuiken D. Dream-enacting behaviors in a normal population. Sleep 2009;32:1629-1636.

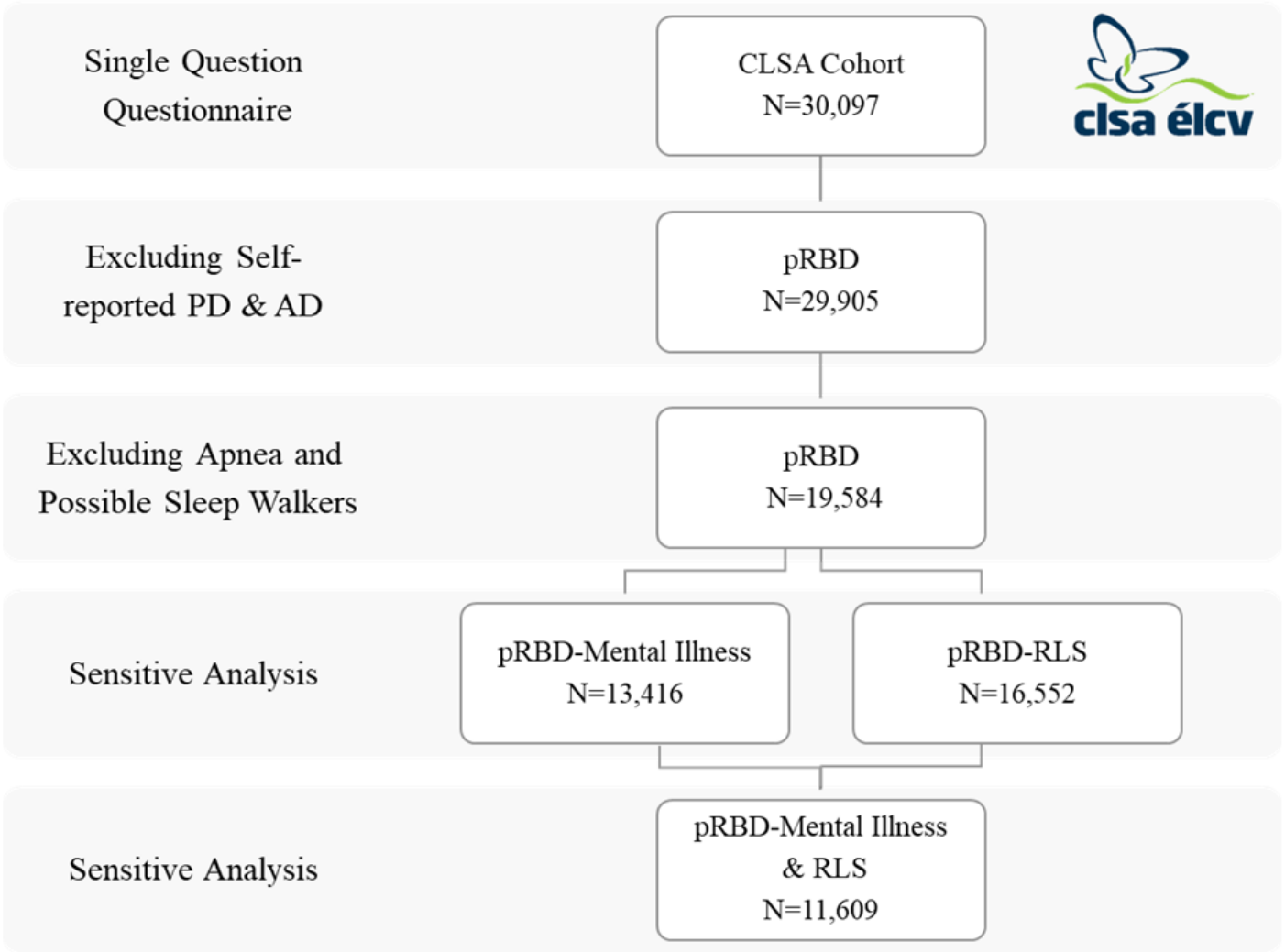


Figure 1. Flow Chart of CLSA Cohort Study

Table 1. Sociodemographic Variables

N total=19584		pRBD + (N=958)	pRBD - (N=18626)	OR (95% CI) Age/sex adjusted only	OR (95% CI) Multivariate Model
Age	Mean ± SD	63.0±10.5	63.5±10.5	0.994 (0.987, 1.000)	0.989 (0.980, 0.998)
	45-54 – n (%)	251 (26.2)	4592 (24.7)	-	-
	55-64 - n (%)	303 (31.6)	5721 (30.7)	0.97 (0.82, 1.15)	0.85 (0.69, 1.04)
	65-74 - n (%)	214 (22.3)	4624 (24.8)	0.85 (0.70, 1.02)	0.72 (0.56, 0.94)
	75-85 - n (%)	190 (19.8)	3689 (19.8)	0.94 (0.78, 1.14)	0.79 (0.59, 1.04)
Sex %	Male	564 (58.9)	7874 (42.3)	1.97 (1.72, 2.25)	2.09 (1.78, 2.44)
Ethnicity %	Caucasian	909 (99.2)	17794 (97.1)	0.94 (0.70, 1.29)	0.87 (0.60, 1.26)
Marital Status %	Single/Never Married	52 (6.1)	1492 (8.7)	-	-
	Married/Common-law	643 (75.1)	11335 (65.8)	1.59 (1.19, 2.12)	1.79 (1.32, 2.42)
	Widowed	82 (9.6)	1906 (11.4)	1.47 (1.02, 2.12)	1.54 (1.05, 2.27)
	Divorced/ Separated	79 (7.2)	2455 (14.2)	1.01 (0.71, 1.44)	0.98 (0.68, 1.42)
Education Level	BS and above	389 (40.6)	8572 (46.1)	-	-
	Secondary School	494 (51.8)	8982 (48.3)	1.77 (1.36, 2.31)	1.61 (1.18, 2.20)
	Primary / Middle School	73 (7.6)	1041 (5.6)	1.32 (1.15, 1.52)	1.25 (1.07, 1.47)
	Imputed Years of Education	13.2±2.8	13.6±2.6	0.94 (0.92, 0.96)	0.96 (0.93, 0.98)
Annual Income Level %	< 20,000	159 (17.3)	2799 (15.9)	-	-
	20-49,000	336 (36.6)	6680 (37.9)	0.81 (0.66, 0.98)	0.97 (0.77, 1.21)
	50-99,000	308 (33.6)	5851 (33.2)	0.73 (0.60, 0.90)	0.99 (0.78, 1.25)
	> 100,000	114 (12.4)	2302 (13.1)	0.60 (0.47, 0.78)	0.90 (0.67, 1.22)
Employment Status	Employed (%)	400 (41.9)	7885 (42.5)	-	-
	Retired (%)	554 (58.1)	10669 (57.5)	1.22 (1.02, 1.46)	1.12 (0.92, 1.36)
	Retirement Age	57.5±6.8	58.6±6.6	0.98 (0.96, 0.99)	0.983 (0.967, 0.999)
	Health Related Retirement	164 (28.9)	2393 (22.0)	1.46 (1.21, 1.77)	1.30 (1.05, 1.62)
Military Service	Yes (%)	116 (12.1)	1515 (8.1)	1.25 (0.99, 1.57)	1.22 (0.97, 1.54)
	Years of Service	12.11±12.47	8.93±11.07	1.03 (1.01, 1.05)	1.03 (1.01,1.05)

Table 2. Lifestyle and Life Satisfaction

N total=19584		pRBD + (N=958)	pRBD - (N=18626)	OR (95% CI) Age/sex adjusted only	OR (95% CI) Multivariate Model
Walk (hr/wk)	Hours/Week (Mean ± SD)	4.3±4.5	4.6±0.9	0.98 (0.97, 1.00)	0.99 (0.97, 1.00)
	0hr/wk (%)	137 (15.8)	2497 (14.3)	-	-
	<7hr/wk (%)	548 (63.2)	10832 (61.9)	0.91 (0.75, 1.10)	0.97 (0.79, 1.19)
	≥7hr/wk (%)	182 (21.0)	4161 (23.8)	0.78 (0.62, 0.98)	0.83 (0.65, 1.05)
Frequency of Social Activity (/year) Mean±SD	Social Sport	54.3±93.7	63.2±16.1	0.999 (0.998, 1.000)	1.000 (0.999, 1.000)
	Social Activity	25.0±26.0	26.6±4.9	0.998 (0.996, 1.001)	0.999 (0.996, 1.002)
Drinking	No Drink Last Year	106 (11.4)	3116 (11.7)	-	-
	Occasional Drinker (%)	97 (10.4)	2325 (12.8)	1.06 (0.86, 1.31)	1.17 (0.92, 1.49)
	Regular Drinker %	730 (78.2)	13701 (75.5)	0.83 (0.63, 1.10)	0.96 (0.69, 1.31)
	Alcohol amount (100g/wk)	1.0±2.1	0.7±1.0	1.10 (1.03, 1.17)	1.09 (1.02, 1.16)
	Binge Drinking Frequency/wk	1.3±4.6	1.0±3.7	1.013 (0.996, 1.030)	1.01 (0.99, 1.03)
	Moderate-Heavy Drinker	181 (18.9)	2792 (14.3)	1.38 (1.17, 1.63)	1.25 (1.04, 1.51)
Smoking	Cigarette Pack-Years	8.4±14.7	6.1±12.2	1.008 (1.003, 1.013)	1.01 (1.00, 1.01)
	Never Daily Smoker (%)	462 (48.9)	10269 (56.2)	-	-
	Ever Smoking (reference =never daily smoker) (%)	493 (51.6)	8235 (44.5)	1.28 (1.11, 1.48)	1.14 (0.99, 1.33)
	Past Daily Smoker (%)	408 (42.7)	7060 (36.9)	1.25 (1.09, 1.44)	1.12 (0.96, 1.31)
	Current Daily Smoker (%)	85 (8.9)	1175 (6.4)	1.53 (1.20, 1.95)	1.28 (0.97, 1.70)
Life Satisfaction scale Mean±SD	Score	27.2±6.8	28.1±6.2	0.98 (0.97, 0.99)	0.989 (0.975, 0.998)
Social Standing Scale Mean±SD		6.0±1.8	6.3±1.8	0.91 (0.88, 0.95)	0.93 (0.90, 0.97)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.6±1.0	3.8±0.5	0.81 (0.75, 0.87)	0.87 (0.80, 0.94)
	Physical Health	3.6±1.0	3.8±0.3	0.80 (0.75, 0.86)	0.97 (0.80, 0.94)
	Mental Health	3.8±1.0	4.0±0.5	0.75 (0.70, 0.81)	0.82 (0.75, 0.89)

Table 3. Mental Illness

N total=19584		pRBD + (N=958)	pRBD - (N=18626)	OR (95% CI) Age/sex adjusted only	OR (95% CI) Multivariate Model
Antidepressant Treatment %	Yes	128 (13.4)	1149 (6.2)	2.71 (2.22, 3.31)	2.77 (2.23, 3.45)
Psychological Distress	K10 Score (Mean±SD)	15.2±5.3	13.9±1.9	1.07 (1.05, 1.08)	1.07 (1.05, 1.08)
	Positive (%)	87 (10.9)	1109 (6.6)	1.58 (1.43, 1.75)	1.61 (1.44, 1.80)
Mental Illness %	Positive	334 (34.9)	4086 (21.9)	2.17 (1.89, 2.50)	2.13 (1.82, 2.48)
	Mood Disorder %	226 (23.7)	2682 (14.5)	2.08 (1.77, 2.43)	2.09 (1.75, 2.49)
	Anxiety Disorder %	132 (13.8)	1355 (7.3)	2.24 (1.85, 2.72)	2.18 (1.75, 2.70)
	Depressive Disorder%	197 (20.7)	2569 (13.9)	1.84 (1.56, 2.17)	1.84 (1.53, 2.21)
	Post-Traumatic Stress Disorder %	100 (10.5)	737 (3.98)	3.19 (2.55, 3.99)	2.68 (1.97, 3.65)

Table 4. A **Sensitivity Analysis after Excluding Mental Illness and Restless Leg Syndrome**

$N_{Total\ Subject}$=11609		RBD + (N=444)	RBD - (N=11165)	Unadjusted OR	OR (95% CI) Age/sex adjusted only
Age	Mean ± SD	64.1±10.7	63.7±10.6	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
	45-54 – n (%)	105 (23.6)	2730 (24.5)	-	-
	55-64 - n (%)	132 (29.7)	3393 (30.4)	1.01 (0.78, 1.31)	1.01 (0.78, 1.31)
	65-74 - n (%)	105 (23.6)	2773 (24.8)	0.98 (0.75, 1.30)	0.95 (0.72, 1.25)
	75-85 - n (%)	102 (23.0)	2269 (20.3)	1.17 (0.89, 1.54)	1.13 (0.85, 1.49)
Sex %	Male	301 (67.8)	5464 (48.9)	2.20 (1.79, 2.69)	2.20 (1.79, 2.69)
Ethnicity %	Caucasian	421 (99.8)	10637 (99.0)	0.86 (0.55, 1.35)	0.90 (0.58, 1.42)
Marital Status %	Single/Never Married	18 (4.5)	811 (7.8)	-	-
	Married/Common-law	326 (80.7)	7287 (70.0)	2.02 (1.25, 3.26)	1.89 (1.17, 3.06)
	Widowed	36 (8.9)	1069 (10.3)	1.52 (0.86, 2.69)	1.66 (0.92, 3.00)
	Divorced/ Separated	24 (5.9)	1238 (11.9)	0.87 (0.47, 1.62)	1.23 (0.72, 2.10)
Education Level	Imputed Years of Education	13.5±2.7	13.8±2.5	0.965 (0.932, 1.001)	0.957 (0.923, 0.993)
	BS and above	208 (46.9)	5528 (49.6)	-	-
	Secondary School	207 (46.6)	5099 (45.7)	1.48 (0.99, 2.20)	1.57 (1.04, 2.36)
	Primary / Middle School	29 (6.5)	522 (4.7)	1.08 (0.89, 1.31)	1.16 (0.96, 1.42)
Annual Income Level %	< 20,000	49 (11.5)	1286 (12.2)	-	-
	20-49,000	147 (34.6)	3781 (35.9)	1.02 (0.73, 1.42)	0.89 (0.64, 1.24)
	50-99,000	160 (37.7)	3808 (36.1)	1.10 (0.80, 1.53)	0.85 (0.61, 1.20)
	> 100,000	69 (16.2)	1671 (15.8)	1.08 (0.75, 1.57)	0.77 (0.52, 1.13)
Employment Status	Employed (%)	180 (40.6)	4763 (42.8)	-	-
	Retired (%)	263 (59.4)	6363 (57.2)	1.09 (0.90, 1.33)	1.11 (0.85, 1.45)
	Retirement Age	57.5±6.8	58.6±6.6	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)
	Health Related Retirement	44 (16.3)	1049 (16.1)	1.01 (0.73, 1.41)	1.04 (0.75, 1.45)
Military Service	Yes (%)	54 (12.2)	1037 (9.3)	1.35 (1.01, 1.81)	1.01 (0.75, 1.36)
	Years of Service	15.6±13.7	9.6±11.5	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)
Satisfaction with Life Score Mean±SD	Score	29.2±5.3	29.6±5.1	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Social Standing Mean±SD		6.3±1.6	6.4±1.8	0.97 (0.92, 1.03)	0.97 (0.92, 1.02)
Frequency of Social	Social Sport	64.2±102.5	68.1±13.1	1.000 (0.999, 1.000)	1.000 (0.999, 1.001)

Activity Mean±SD	Social Activity	26.8±26.7	28.1±4.0	0.998 (0.994, 1.002)	0.999 (0.995, 1.003)
Walk (hr/wk) Mean ± SD	Hours/Day	4.2±4.3	4.7±0.7	0.97 (0.75, 0.98)	0.87 (0.76, 0.96)
	0hr/wk	60 (14.7)	1387 (13.1)	-	-
	<7hr/wk	269 (65.8)	6515 (61.7)	0.95 (0.72, 1.27)	0.97 (0.73, 1.29)
	≥7hr/wk	80 (19.6)	2651 (25.1)	0.70 (0.50, 0.98)	0.70 (0.50, 0.99)
Drinking	Not Drink Last Year (%)	34 (7.9)	1097 (10.1)	-	-
	Occasional Drinker (%)	38 (8.8)	1244 (11.4)	1.36 (0.95, 1.95)	1.33 (0.93, 1.91)
	Regular Drinker (%)	361 (83.4)	8539 (78.5)	0.99 (0.62, 1.58)	1.09 (0.68, 1.74)
	100 Grams of Alcohol/wk	1.0±2.1	0.7±1.0	1.16 (1.10, 1.24)	1.12 (1.05, 1.21)
	Binge Drinking Frequency	1.5±4.9	1.0±3.7	1.03 (1.10, 1.05)	1.02 (1.00, 1.05)
	Moderate-Heavy Drinker	84 (18.9)	1630 (14.6)	1.37 (1.07, 1.74)	1.47 (1.15, 1.88)
Smoking	Cigarette Pack-Year All	7.5±14.6	5.6±11.6	1.011 (1.004, 1.017)	1.007 (1.001, 1.014)
	Never Daily Smoke (%)	241 (54.4)	6432 (57.9)	-	-
	Ever Smoking (reference to never daily smoker) (%)	202 (45.6)	4677 (42.1)	1.07 (0.87, 1.32)	1.02 (0.83, 1.26)
	Past Daily Smoker (%)	172 (38.8)	4119 (37.1)	1.11 (0.91, 1.36)	1.05 (0.86, 1.28)
	Current Daily Smoker (%)	30 (6.8)	558 (5.0)	1.44 (0.97, 2.13)	1.36 (0.92, 2.01)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.8±0.9	3.9±0.4	0.85 (0.76, 0.96)	0.87 (0.77, 0.97)
	Physical Health	3.9±0.9	4.0±0.4	0.89 (0.80, 1.00)	0.92 (0.82, 1.03)
	Mental Health	4.1±0.8	4.2±0.4	0.85 (0.75, 0.96)	0.85 (0.75, 0.96)
Psychological Distress	K10 Score	12.9±2.8	12.6±1.3	1.04 (1.01, 1.08)	1.05 (1.01, 1.08)
	Mild (%)	14 (3.5)	303 (2.9)	1.20 (0.69, 2.07)	1.22 (0.71, 2.11)

Supplementary Materials

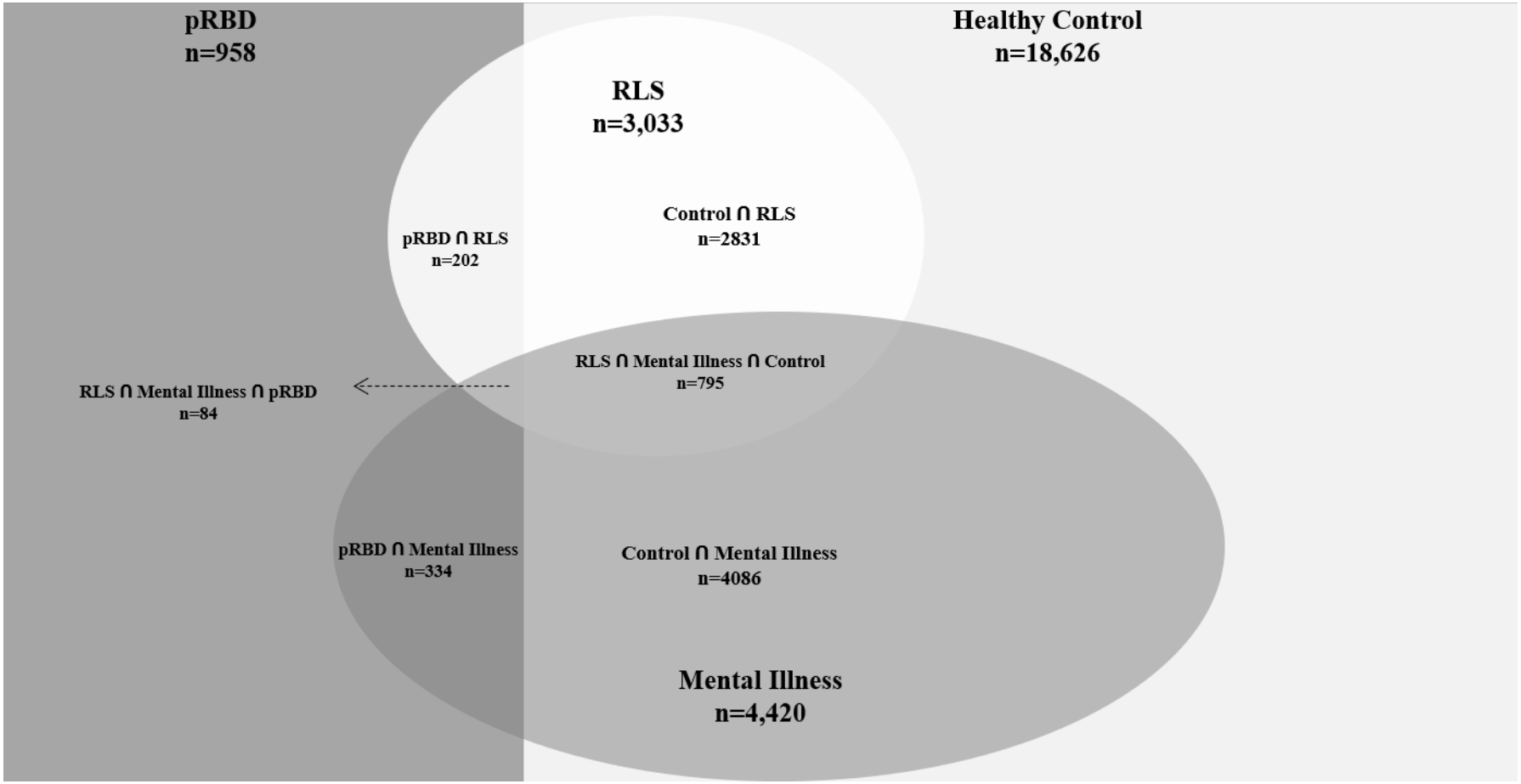
Several sensitivity and secondary analyses were performed after stratifying or adjusting for potential confounding factors such as apnea, RLS and mental illness. Text descriptions were embedded in the results and discussion section of the main text.

Table e-1. Sociodemographic and Lifestyle Characteristics of pRBD Cohort (of all people screened positive for pRBD)

$N_{Total\ Subject}$=29905		pRBD+ (N=3271)	pRBD- (N=26634)	Unadjusted OR	OR (95% CI) Age/sex adjusted only
Age	Mean ± SD	61.1±9.9	63.1±10.3	0.98 (0.98, 0.98)	0.98 (0.98, 0.98)
	45-54 – n (%)	1004 (30.7)	6577 (24.7)	-	-
	55-64 - n (%)	1141 (34.9)	8669 (32.5)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
	65-74 - n (%)	686 (21.0)	6624 (24.9)	0.68 (0.61, 0.75)	0.67 (0.61, 0.75)
	75-85 - n (%)	440 (13.5)	4764 (17.9)	0.61 (0.54, 0.68)	0.60 (0.53, 0.67)
Sex %	Male	1942 (59.4)	12721 (47.8)	1.60 (1.48, 1.72)	1.61 (1.50, 1.74)
Ethnicity %	Caucasian	3130 (99.4)	25458 (99.2)	1.06 (0.87, 1.28)	1.16 (0.95, 1.42)
Marital Status %	Single/Never Married	239 (7.8)	2090 (8.3)	-	-
	Married/Common-law	2248 (73.4)	17098 (68.1)	1.150 (0.999, 1.324)	1.14 (0.99, 1.32)
	Widowed	219 (7.2)	2539 (10.1)	0.75 (0.62, 0.91)	1.09 (0.89, 1.33)
	Divorced/ Separated	357 (11.7)	3395 (13.5)	0.92 (0.77, 1.09)	1.03 (0.86, 1.22)
Education Level	Imputed Years of Education	13.4±2.7	13.6±2.6	0.97 (0.96, 0.99)	0.95 (0.94, 0.97)
	BS and above	1393 (42.6)	12099 (45.5)	-	-
	Secondary School	1677 (51.3)	13068 (49.2)	1.20 (1.03, 1.41)	1.48 (1.26, 1.75)
	Primary / Middle School	197 (6.0)	1423 (5.4)	1.12 (1.03, 1.20)	1.20 (1.11, 1.29)
Annual Income Level %	< 20,000	498 (15.9)	3842 (15.2)	-	-
	20-49,000	1124 (35.9)	9337 (36.9)	0.93 (0.83, 1.04)	0.88 (0.78, 0.98)
	50-99,000	1055 (33.7)	8598 (34.0)	0.95 (0.85, 1.06)	0.75 (0.67, 0.85)
	> 100,000	455 (14.5)	3506 (13.9)	1.00 (0.88, 1.15)	0.69 (0.60, 0.80)
Employment Status	Employed (%)	1623 (49.8)	11645 (43.9)	-	-
	Retired %	1639 (50.3)	14891 (56.1)	3.28 (2.10, 5.13)	1.54 (0.89, 2.68)
	Retirement Age	57.6±6.6	58.5±6.6	0.98 (0.97, 0.99)	0.99 (0.98, 0.99)
	Health Related Retirement	541 (31.9)	3508 (23.0)	1.57 (1.41, 1.75)	1.54 (1.38, 1.72)
Military Service	Yes (%)	362 (11.1)	2344 (8.1)	1.29 (1.15, 1.45)	1.18 (1.04, 1.33)
	Years of Service	10.4±11.7	9.5±11.3	1.007 (0.997 1.016)	1.007 (0.998, 1.017)
Satisfaction with Life Scale Mean±SD	Score	26.8±7.0	27.9±6.3	0.97 (0.97, 0.98)	0.97 (0.97, 0.98)
Social Standing Mean±SD		6.1±1.9	6.2±1.9	0.95 (0.94, 0.97)	0.95 (0.93, 0.96)
Frequency of Social Activity Mean±SD	Social Sport	57.6±98.3	60.0±18.6	1.000 (0.999, 1.000)	1.000 (0.999, 1.000)
	Social Activity	24.7±25.0	25.9±5.6	0.998 (0.997, 1.000)	0.999 (0.998, 1.001)
Walk (hr/wk) Mean ± SD	Hours/Week	4.3±4.6	4.4±1.0	1.00 (0.96, 1.05)	0.99 (0.95, 1.04)

	0hr/wk	449 (14.4)	3826 (15.0)	-	-
	<7hr/wk	1978 (63.6)	15891 (62.4)	1.06 (0.95, 1.18)	1.02 (0.91, 1.14)
	≥7hr/wk	682 (21.9)	5754 (22.6)	1.01 (0.89, 1.15)	0.97 (0.86, 1.10)
Drinking	No Drink Last Year	382 (11.9)	3013 (11.6)	-	-
	Occasional Drinker (%)	366 (11.4)	3312 (12.8)	0.99 (0.88, 1.11)	0.92 (0.82, 1.033)
	Regular Drinker %	2461 (76.7)	19653 (75.7)	0.87 (0.75, 1.01)	0.90 (0.77, 1.04)
	Grams of Alcohol/wk	1.0±1.65	0.82±1.1	1.12 (1.09, 1.16)	1.08 (1.05, 1.12)
	Binge Drinking Frequency/wk	1.7±5.2	1.1±4.0	1.03 (1.02, 1.03)	1.02 (1.01, 1.03)
	Moderate-Heavy Drinker	596 (18.2)	3964 (14.9)	1.27 (1.16, 1.40)	1.30 (1.18, 1.43)
Smoking	Cigarette Pack-Year All	8.4±14.1	6.6±12.7	1.12 (1.09, 1.16)	1.08 (1.05, 1.12)
	Never Daily Smoker (%)	1525 (46.8)	14190 (53.6)	-	-
	Ever Smoking (reference to never daily smoker) (%)	1732 (53.2)	12283 (46.4)	1.29 (1.19, 1.39)	1.30 (1.21, 1.41)
	Past Daily Smoker (%)	1420 (43.6)	10516 (39.8)	1.28 (1.10, 1.49)	1.23 (1.06, 1.44)
	Current Daily Smoker (%)	312 (9.6)	1767 (6.7)	1.51 (1.15, 1.99)	1.45 (1.10, 1.91)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.6±1.0	3.7±0.6	0.81 (0.80, 0.84)	0.82 (0.79, 0.85)
	Physical Health	3.7±0.95	3.9±0.6	0.82 (0.79, 0.85)	0.82 (0.79, 0.85)
	Mental Health	3.6±1.0	3.7±0.6	0.78 (0.74, 0.81)	0.77 (0.74, 0.81)
Restless Leg Syndrome %	RLS Positive	733 (22.4)	4126 (15.5)	1.58 (1.44, 1.72)	1.73 (1.58, 1.89)
Antidepressant Treatment %	Yes	495 (15.2)	1907 (7.2)	2.32 (2.08, 2.58)	2.48 (2.22, 2.76)
Psychological Distress	K10 Score	15.6±5.4	25.1±2.3	1.06 (1.05, 1.07)	1.063 (1.056, 1.071)
	Positive	361 (12.6)	1785 (7.34	1.48 (1.40, 1.56)	1.49 (1.41, 1.58)
Mental Illness	Anxiety Disorder %	470 (92.1)	2102 (7.9)	1.96 (1.76, 2.18)	2.04 (1.83, 2.27)
	Depressive Disorder %	818 (25.2)	4067 (15.3)	1.86 (1.70, 2.02)	1.98 (1.81, 2.16)
	Mood Disorder %	858 (26.3)	4245 (16.0)	1.88 (1.73, 2.04)	1.98 (1.82, 2.16)
	Post-Traumatic Stress Disorder %	331 (10.2)	1148 (4.3)	2.51 (2.21, 2.86)	2.63 (2.31, 2.99)

Figure e-1. Venn Diagram of Comorbidities among symptoms



Distribution of comorbid disorders (RLS and mental illness) among possible RBD participants and controls. ∩ represents as intersection of two groups.

Table e-2. A **Sensitivity Analysis after Excluding Restless Leg Syndrome**

$N_{Total\ Subject}$=16,552		pRBD + (N=756)	pRBD - (N=15796)	Unadjusted OR	OR (95% CI) Age/sex adjusted only
Age	Mean ± SD	63.3±10.6	63.4±10.5	0.999 (0.992, 1.006)	0.997 (0.990, 1.004)
	45-54 – n (%)	197 (26.1)	3969 (25.1)	-	-
	55-64 - n (%)	233 (30.8)	4895 (31.0)	0.96 (0.79, 1.17)	0.95 (0.78, 1.16)
	65-74 - n (%)	171 (22.6)	3861 (24.4)	0.89 (0.72, 1.10)	0.86 (0.70, 1.07)
	75-85 - n (%)	155 (20.5)	3071 (19.4)	1.02 (0.82, 1.26)	0.98 (0.79, 1.21)
Sex %	Male	462 (61.1)	7050 (44.6)	1.95 (1.68, 2.26)	1.96 (1.68, 2.27)
Ethnicity %	Caucasian	719 (99.0)	15049 (99.0)	0.94 (0.65, 1.34)	0.99 (0.69, 1.42)
Marital Status %	Single/Never Married	41 (6.1)	1307 (8.9)	-	-
	Married/Common-law	516 (76.1)	9647 (65.9)	1.71 (1.23, 2.36)	1.64 (1.18, 2.26)
	Widowed	65 (9.6)	1620 (10.1)	1.28 (0.86, 1.90)	1.45 (0.96, 2.20)
	Divorced/ Separated	56 (8.3)	2057 (11.9)	0.87 (0.58, 1.31)	0.92 (0.61, 1.39)
Education Level	Imputed Years of Education	13.3±2.8	13.6±2.6	0.95 (0.93, 0.98)	0.94 (0.91, 0.96)
	BS and above	317 (41.9)	7459 (47.3)	-	-
	Secondary School	382 (50.5)	7470 (47.4)	1.59 (1.19, 2.13)	1.76 (1.31, 2.37)
	Primary / Middle School	57 (7.5)	843 (5.3)	1.20 (1.03, 1.40)	1.30 (1.11, 1.52)
Annual Income Level %	< 20,000	128 (17.7)	2276 (15.2)	-	-
	20-49,000	251 (34.7)	5530 (37.0)	0.81 (0.65, 1.00)	0.73 (0.58, 0.91)
	50-99,000	249 (34.4)	5089 (34.1)	0.87 (0.70, 1.08)	0.69 (0.55, 0.87)
	> 100,000	95 (13.1)	2045 (13.7)	0.83 (0.63, 1.08)	0.59 (0.44, 0.78)
Employment Status	Employed (%)	314 (41.8)	6809 (43.3)	-	-
	Retired (%)	438 (58.2)	8926 (56.7)	1.06 (0.91, 1.23)	1.18 (0.96, 1.44)
	Retirement Age	57.8±6.7	58.6±6.6	0.982 (0.968, 0.996)	0.978 (0.962, 0.994)
	Health Related Retirement	117 (26.0)	1937 (21.3)	1.30 (1.05, 1.62)	1.33 (1.06, 1.65)
Military Service	Yes (%)	92 (12.2)	1324 (8.4)	1.52 (1.21, 1.90)	1.19 (0.94, 1.50)
	Years of Service	12.9±12.3	9.3±11.2	1.03 (1.01 1.04)	1.03 (1.01, 1.04)
Satisfaction with Life Score Mean±SD	Score	27.4±6.7	28.3±6.2	0.991 (0.982, 0.999)	0.990 (0.981, 0.998)
Social Standing Mean±SD		6.1±1.8	6.3±1.8	0.94 (0.90, 0.98)	0.93 (0.90, 0.97)
Frequency of Social Activity	Social Sport	54.3±93.5	64.1±15.0	0.999 (0.998, 1.000)	0.999 (0.998, 1.000)
	Social Activity	25.1±26.2	26.9±4.6	0.997 (0.994, 1.000)	0.998 (0.995, 1.001)

Mean±SD					
Walk (hr/wk) Mean ± SD	Hours/Day	4.1±4.3	4.6±0.8	0.891 (0.795, 0.999)	0.89 (0.80, 1.00)
	0hr/wk	107 (15.6)	2121 (14.3)	-	-
	<7hr/wk	441 (64.4)	9126 (61.5)	0.96 (0.77, 1.19)	0.95 (0.77, 1.19)
	≥7hr/wk	137 (20.0)	35.91 (24.2)	0.76 (0.58, 0.98)	0.75 (0.58, 0.97)
Drinking	Not Drink Last Year	85 (11.5)	7867 (11.6)	-	-
	Occasional Drinker (%)	74 (10.03)	1924 (12.5)	1.04 (0.82, 1.31)	1.00 (0.79, 1.26)
	Regular Drinker (%)	579 (78.5)	11675 (75.9)	0.81 (0.59, 1.11)	0.86 (0.63, 1.19)
	100 Grams of Alcohol/wk	1.0±2.2	0.7±1.0	1.17 (1.11, 1.23)	1.13 (1.07, 1.19)
	Binge Drinking Frequency	1.6±5.0	1.0±3.8	1.03 (1.01, 1.04)	1.02 (1.01, 1.04)
	Moderate-Heavy Drinker	155 (20.5)	2344 (14.8)	1.48 (1.23, 1.78)	1.56 (1.30, 1.88)
Smoking	Cigarette Pack-Years All	8.2±14.5	6.0±12.2	1.01 (1.01, 1.02)	1.009 (1.004, 1.014)
	Never Daily Smoker (%)	371 (49.3)	8792 (56.0)	-	-
	Ever Smoking (reference to never daily smoker) (%)	382 (50.7)	6907 (44.0)	1.27 (1.09, 1.49)	1.24 (1.05, 1.45)
	Past Daily Smoker (%)	318 (42.2)	5903 (37.6)	1.28 (1.10, 1.49)	1.23 (1.06, 1.44)
	Current Daily Smoker (%)	64 (8.5)	1004 (6.4)	1.51 (1.15, 1.99)	1.45 (1.10, 1.91)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.6±1.0	3.8±0.5	0.81 (0.74, 0.88)	0.81 (0.74, 0.88)
	Physical Health	3.7±1.0	3.8±0.5	0.81 (0.75, 0.88)	0.82 (0.75, 0.88)
	Mental Health	3.8±0.9	4.0±0.3	0.79 (0.72, 0.85)	0.77 (0.71, 0.84)
Antidepressant Treatment %	Yes	83 (11.0)	912 (5.8)	2.01 (1.58, 2.55)	2.33 (1.83, 2.97)
Psychological Distress	K-10 Score	15.1±5.2	13.7±1.7	1.06 (1.05, 1.08)	1.07 (1.05, 1.09)
	Positive	65 (10.2)	867 (6.1)	1.54 (1.37, 1.73)	1.61 (1.43, 1.81)
Mental Illness	Anxiety Disorder %	102 (13.6)	1076 (6.8)	2.14 (1.72, 2.66)	2.36 (1.90, 2.95)
	Depressive Disorder %	138 (18.3)	2066 (13.1)	1.48 (1.23, 1.79)	1.69 (1.40, 2.06)
	Mood Disorder %	159 (21.1)	2148 (13.7)	1.70 (1.42, 2.03)	1.92 (1.60, 2.31)
	PTSD %	71 (9.4)	563 (3.6)	2.81 (2.17, 3.63)	3.17 (2.44, 4.12)

*The cohort was defined after we excluded subjects, who screened positive to RLS questionnaire.

Table e-3. A **Sensitivity Analysis after Excluding Mental Illness**

$N_{Total\ Subject}$=13,416		pRBD+ (N=543)	pRBD - (N=12873)	Unadjusted OR	OR (95% CI) Age/sex adjusted only
Age	Mean ± SD	63.6±10.6	63.8±10.6	0.997 (0.989, 1.005)	0.997 (0.989, 1.005)
	45-54 – n (%)	134 (24.7)	3085 (24.0)	-	-
	55-64 - n (%)	167(30.8)	3865 (30.0)	1.00 (0.79, 1.26)	1.00 (0.79, 1.35)
	65-74 - n (%)	126 (23.0)	3246 (25.2)	0.89 (0.69, 1.14)	0.86 (0.67, 1.10)
	75-85 - n (%)	117 (21.5)	2677 (20.8)	1.01 (0.78, 1.30)	0.97 (0.75, 2.65)
Sex %	Male	359 (66.1)	6047 (47.0)	2.20 (1.84, 2.64)	2.20 (1.84, 2.64)
Ethnicity %	Caucasian	513 (99.0)	12303 (99.0)	0.77 (0.51, 1.13)	0.82 (0.55, 1.22)
Marital Status %	Single/Never Married	20 (4.1)	906 (7.6)	-	-
	Married/Common-law	405 (82.0)	8392 (69.9)	2.19 (1.39, 3.44)	2.09 (1.32, 3.29)
	Widowed	40 (8.1)	1274 (10.6)	1.42 (0.83, 2.45)	1.71 (0.98, 3.00)
	Divorced/ Separated	29 (5.9)	1333 (11.9)	0.93 (0.53, 1.63)	0.98 (0.55, 1.74)
Education Level	Imputed Years of Education	13.5±2.7	13.7±2.5	0.966 (0.935, 0.999)	0.95 (0.92, 0.98)
	BS and above	246 (45.3)	6245 (48.6)	-	-
	Secondary School	262 (48.3)	5985 (46.6)	1.42 (0.99, 2.05)	1.60 (1.10, 2.31)
	Primary / Middle School	29 (5.9)	1333 (11.9)	0.92 (0.52, 1.63)	0.98 (0.55, 1.74)
Annual Income Level %	< 20,000	59 (11.4)	1529 (12.6)	-	-
	20-49,000	181 (34.9)	4472 (36.7)	1.05 (0.78, 1.42)	0.91 (0.67, 1.23)
	50-99,000	198 (38.2)	4316 (35.5)	1.19 (0.88, 1.60)	0.89 (0.66, 1.21)
	> 100,000	80 (15.4)	18.58 (15.3)	1.12 (0.79, 1.57)	0.74 (0.52, 1.06)
Employment Status	Employed (%)	229 (42.3)	5394 (42.1)	-	-
	Retired %	313 (57.8)	7435 (58.0)	0.99 (0.83, 1.18)	1.10 (0.86, 1.39)
	Retirement Age	58.4±6.3	58.8±6.5	0.99 (0.97, 1.01)	0.98 (0.97, 1.00)
	Health Related Retirement	53 (16.46)	1264 (16.63)	0.99 (0.73, 1.33)	1.02 (0.75, 1.38)
Military Service	Yes (%)	65 (11.97)	1172 (9.11)	1.52 (1.21, 1.90)	1.19 (0.94, 1.50)
	Years of Service	14.6±13.7	9.6±11.5	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)
Satisfaction with Life Score Mean±SDMeMean±SD	Score	29.3±5.2	29.5±5.2	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)
Social Standing Mean±SD		6.3±1.7	6.4±1.8	0.97 (0.92, 1.02)	0.96 (0.92, 1.01)
Frequency of Social	Social Sport	55.1±93.7	63.7±16.0	1.000 (0.999, 1.001)	1.000 (0.999, 1.001)

Activity Mean±SD	Social Activity	25.3±26.2	26.7±4.9	0.999 (0.995, 1.002)	1.000 (0.997, 1.003)
Walk (hr/wk) Mean ± SD	Hours/Week	4.2±4.2	4.7±0.7	0.98 (0.94, 1.02)	0.98 (0.94, 1.02)
	0hr/wk	74 (14.8)	1607 (13.2)	-	-
	<7hr/wk	326 (65.2)	7572 (62.2)	0.94 (0.72, 1.21)	0.93 (0.72, 1.21)
	≥7hr/wk	100 (20.0)	3000 (24.6)	0.72 (0.53, 0.98)	0.71 (0.52, 0.97)
Drinking	Not Drink Last Year	42 (7.9)	1284 (10.2)	-	-
	Occasional Drinker (%)	45 (8.5)	1437 (11.5)	1.38 (0.99, 1.90)	1.33 (0.96, 1.83)
	Regular Drinker (%)	442 (83.6)	9821 (78.3)	0.96 (0.63, 1.47)	1.05 (0.68, 1.61)
	100 Grams of Alcohol/wk	1.1±2.5	0.7±1.0	1.17 (1.10, 1.25)	1.13 (1.06, 1.20)
	Binge Drinking Frequency	1.5±4.9	0.9±3.5	1.03 (1.01, 1.05)	1.02 (1.01, 1.04)
	Moderate-Heavy Drinker	97 (17.9)	1906 (14.8)	1.251 (0.999, 1.567)	1.34 (1.07, 1.68)
Smoking	Cigarette Packs /Year All	8.2±14.5	6.0±12.2	1.01 (1.01, 1.02)	1.010 (1.004, 1.016)
	Never Daily Smoker (%)	285 (52.6)	7371 (57.6)	-	-
	Ever Smoking (reference to never daily smoker) (%)	257 (47.4)	5432 (42.4)	1.17 (0.98, 1.41)	1.14 (0.95, 1.37)
	Past Daily Smoker (%)	219 (40.4)	4798 (37.5)	1.18 (0.99, 1.41)	1.13 (0.94, 1.36)
	Current Daily Smoker (%)	38 (7.0)	634 (5.0)	1.55 (1.09, 2.20)	1.45 (1.03, 2.06)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.8±0.8	3.9±0.4	0.87 (0.79, 0.97)	0.89 (0.80, 0.98)
	Physical Health	3.9±0.8	3.9±0.5	0.91 (0.82, 1.01)	0.93 (0.84, 1.03)
	Mental Health	4.1±0.8	4.2±0.5	0.85 (0.76, 0.95)	0.84 (0.75, 0.94)
Psychological Distress	Score Mean±SD	13.0±2.9	12.7±1.4	1.034 (1.003, 1.066)	1.04 (1.01, 1.07)
	Mild	18 (3.6)	375 (3.1)	1.20 (0.69, 2.07)	1.22 (0.71, 2.11)

*The analysis was based on the cohort defined in the primary analysis after we omitted any subject screened positive or self-reported with depressive disorder, anxiety disorder, mood disorder or post-traumatic stress disorder. Subjects who scored greater than 24 on K-10, were also excluded from the cohort.

Table e-4. A **Sensitivity Analysis after Excluding Mental Illness and Restless Leg Syndrome (Civilian)**

$N_{Total\ Subject}$=11609		RBD + (N=390)	RBD - (N=10125)	Unadjusted OR	OR (95% CI) Age/sex adjusted only
Age	Mean ± SD	63.6±10.7	63.2±10.4	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
	45-54 – n (%)	97 (24.9)	2557 (25.3)	-	-
	55-64 - n (%)	120 (30.8)	3201 (31.6)	0.99 (0.75, 1.30)	0.99 (0.75, 1.30)
	65-74 - n (%)	89 (22.8)	2486 (24.6)	0.94 (0.70, 1.27)	0.93 (0.69, 1.25)
	75-85 - n (%)	84 (21.5)	1881 (18.6)	1.17 (0.87, 1.59)	1.19 (0.88, 1.60)
Sex %	Male	252 (64.6)	4555 (45.0)	2.23 (1.81, 2.76)	2.23 (1.81, 2.76)
Ethnicity %	Caucasian	370 (98.7)	9638 (98.9)	0.91 (0.56, 1.47)	0.96 (0.59, 1.57)
Marital Status %	Single/Never Married	17 (4.8)	752 (8.0)	-	-
	Married/Common-law	282 (79.2)	6593 (69.7)	1.89 (1.15, 3.11)	1.78 (1.09, 2.93)
	Widowed	34 (9.6)	972 (10.3)	1.55 (0.86, 2.79)	1.72 (0.94, 3.17)
	Divorced/ Separated	23 (6.5)	1146 (12.1)	0.89 (0.47, 1.67)	0.93 (0.49, 1.75)
Education Level	Imputed Years of Education	13.5±2.8	13.8±2.5	0.96 (0.93, 1.00)	0.95 (0.92, 0.99)
	BS and above	183 (46.9)	5017 (49.6)	-	-
	Secondary School	181 (46.4)	4620 (45.7)	1.50 (0.99, 2.29)	1.59 (1.03, 2.45)
	Primary / Middle School	26 (6.7)	475 (4.7)	1.07 (0.87, 1.32)	1.17 (0.96, 1.45)
Annual Income Level %	< 20,000	45 (12.0)	1251 (12.6)	-	-
	20-49,000	133 (35.5)	3444 (36.0)	1.04 (0.73, 1.46)	0.89 (0.63, 1.27)
	50-99,000	137 (36.5)	3388 (35.5)	1.08 (0.77, 1.53)	0.83 (0.58, 1.18)
	> 100,000	60 (16.0)	1519 (15.9)	1.06 (0.71, 1.57)	0.73 (0.48, 1.10)
Employment Status	Employed (%)	180 (40.6)	4763 (42.8)	-	-
	Retired (%)	263 (59.4)	6363 (57.2)	1.07 (0.88, 1.32)	1.06 (0.80, 1.40)
	Retirement Age	58.9±6.4	58.8±6.4	1.00 (0.98, 1.02)	0.99 (0.97, 1.02)
	Health Related Retirement	44 (16.3)	1049 (16.1)	0.98 (0.69, 1.40)	1.02 (0.71, 1.46)
Satisfaction with Life Score Mean±SD	Score	29.2±5.4	29.6±5.2	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Social Standing Mean±SD		6.3±1.6	6.4±1.7	0.96 (0.90, 1.02)	0.96 (0.90, 1.02)
Frequency of Social	Social Sport	63.0±100.4	68.4±106.5	0.999 (0.998, 1.000)	1.000 (0.999, 1.001)

Activity Mean±SD	Social Activity	26.0±24.52	28.2±26.5	0.997 (0.992, 1.001)	0.998 (0.994, 1.002)
Walk (hr/wk) Mean ± SD	Hours/Day	4.2±4.3	4.7±4.7	0.97 (0.92, 1.01)	0.97 (0.92, 1.01)
	0hr/wk	55 (15.3)	1256 (13.1)	-	-
	<7hr/wk	233 (64.9)	5929 (61.8)	0.90 (0.67, 1.21)	0.92 (0.68, 1.24)
	≥7hr/wk	71 (19.8)	2403 (25.1)	0.68 (0.47, 0.97)	0.69 (0.48, 0.98)
Drinking	Not Drink Last Year (%)	28 (7.4)	997 (10.1)	-	-
	Occasional Drinker (%)	33 (8.7)	1146 (11.6)	1.46 (0.99, 2.17)	1.43 (0.97, 2.12)
	Regular Drinker (%)	319 (84.0)	7713 (78.3)	1.02 (0.61, 1.70)	1.12 (0.67, 1.87)
	100 Grams of Alcohol/wk	0.9±1.1	0.7±1.0	1.15 (1.07, 1.24)	1.10 (1.01, 1.19)
	Binge Drinking Frequency	1.2±3.5	0.9±3.5	1.019 (0.995, 1.044)	1.01 (0.99, 1.04)
	Moderate-Heavy Drinker	84 (18.9)	1630 (14.6)	1.33 (1.03, 1.73)	1.45 (1.11, 1.88)
Smoking	Cigarette Pack-Year All	7.0±13.9	5.2±11.0	1.012 (1.004, 1.019)	1.008 (1.000, 1.016)
	Never Daily Smoke (%)	197 (54.4)	5935 (58.9)	-	-
	Ever Smoking (reference to never daily smoker) (%)	172 (44.2)	4143 (41.1)	1.057 (0.85, 1.32)	1.01 (0.81, 1.37)
	Past Daily Smoker (%)	154 (38.8)	3637 (36.1)	1.08 (0.87, 1.33)	1.02 (0.82, 1.27)
	Current Daily Smoker (%)	39 (6.8)	506 (5.0)	1.57 (1.05, 2.33)	1.493 (1.001, 2.227)
Self-rated Health Profile Mean±SD	Healthy Ageing	3.9±0.8	3.8±0.8	0.88 (0.78, 0.99)	0.90 (0.80, 1.02)
	Physical Health	3.9±0.9	4.0±0.8	0.86 (0.75, 0.99)	0.86 (0.75, 0.98)
	Mental Health	4.1±0.7	4.2±0.7	0.86 (0.76, 0.97)	0.88 (0.78, 0.99)
Psychological Distress	K10 Score	13.0±2.8	12.7±2.8	1.04 (1.01, 1.08)	1.05 (1.01, 1.09)
	Mild (%)	12 (3.4)	274 (2.9)	1.17 (0.65, 2.11)	1.19 (0.66, 2.15)

*The analysis was based on the cohort defined in the primary analysis after we omitted any subject screened positive or self-reported with depressive disorder, anxiety disorder, mood disorder or post-traumatic stress disorder. Subjects who scored greater than 24 on K-10, were also excluded from the cohort.

Chapter IB - Phenoconversion from possible REM sleep behavior to parkinsonism in the Canadian Population

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Introduction

Rapid eye movement sleep behavior disorder (RBD), characterized as dream enactment behavior due to loss of REM sleep paralysis, is a strong prodromal marker of synucleinopathy (Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy).[1, 2] To date, studies have estimated the phenoconversion rate from RBD to clinical disease in patients from sleep clinics, using polysomnography proven RBD participants.[3-7] However, no population-based estimates have been reported, and so it is unclear to what degree possible RBD, screened by questionnaire, is associated with risk of parkinsonism. Using the Canadian Longitudinal Study on Aging (CLSA) cohort, a prospective population-based study of 30,097 adults, we estimated the relationship between possible RBD (pRBD) and future diagnosis of parkinsonism.[8]

Method

Canadian Longitudinal Study on Aging (CLSA) Cohort:

This study was performed using the 30,097-person comprehensive subset of the CLSA, a population-based cohort of adults aged 45-85 recruited between 2012-2015.[9] As the primary question centered around new diagnosis of disease, those with self-reported diagnosis of parkinsonism or dementia at baseline were excluded. Patients were followed after 3-year interval, between 2015-2019.

Case Definition:

Dream enactment behavior (DEB, also considered as possible RBD; *pRBD*) was defined as a positive response to the single-question RBD-1Q during the baseline interview, namely "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?"[8, 10] The primary outcome was parkinsonism, which was defined by self-report of a physician diagnosis (i.e. "Has a doctor ever told you that you had Parkinsonism or Parkinson's Disease?"). To improve the accuracy of parkinsonism ascertainment, only those with either a positive screen for parkinsonism (i.e. ≥3 symptoms on the a 9-item Tanner screening Questionnaire[11, 12]) or those currently using parkinsonism medication (since medications may suppress symptoms on the Tanner questionnaire), were defined as de-novo parkinsonism. Time to phenoconversion was calculated based on age at the baseline interview and self-reported age of parkinsonism diagnosis. Time interval was calculated based on the dates between the first and the last available visit.

Statistical Analyses:

Relative risks were estimated using binomial estimate with log-link function for binary variables, adjusting for age, sex, time interval and follow-up status, and hazard ratios with Cox regression analysis adjusting for age and sex.[13] Phenoconversion and incidence rates were adjusted for follow-up status. To account for selection bias due to right censoring, all estimates were reassessed using inverse probability weighting (IPW).[14] 95% confidence intervals were estimated via the White's variance.[15] Last available value was carried forward for missing value imputation. Statistical analysis was performed using R version 4.0.3.

Sensitivity Analysis

Since several sleep disorders may mimic symptoms of RBD (namely, non-REM sleep parasomnia, apnea, and restless leg syndrome), the following sensitivity analyses were performed to remove possible RBD mimics at baseline.

1. Excluding participants with symptom onset before the age of 20 (may be more likely to represent non-REM-parasomnia)[16]

2. Excluding participants with possible sleep apnea, defined as one of the two core apnea symptoms (snoring loudly and stopping breathing during sleep) and scoring higher than 4 points on STOP-BANG (7 of 8 items were available, excluding neck circumference)[17]

3. Excluding participants with probable restless legs syndrome (RLS), defined as a positive screen on the 4 core RLS symptoms.[18]

4. Excluding those taking antidepressants, to remove the effect of possible antidepressant-triggered RBD

5. Excluding those with sleep deprivation, defined as less than 6 hours of sleep.[19]

Results

Characteristics of the Study Population

Of 30,097 participants recruited, 68 were excluded for self-reported dementia diagnosis at baseline and 112 for pre-existing parkinsonism diagnosis. Demographic information and other participant characteristics are provided in supplemental Table 1. At the 1st wave follow-up, 62 participants self-reported a new diagnosis of parkinsonism. We excluded 3 whose diagnosis was not confirmed on symptom/medication screen and 1 with missing information regarding baseline parkinsonism diagnosis, leaving 58 de-novo parkinsonism participants. The overall estimated incidence rate was 76.3 (95%CI=[59,98.6]); 100.9 for male and 49.1 for female participants.

When divided according to the response to RBD1Q, those endorsing DEB/pRBD had a 2.9-fold (95% CI=[1.57,5.38]) relative risk of de-novo parkinsonism diagnosis (Table 1) (Cox regression hazard ratio =2.95[1.6,5.5], Figure 1) . Using the simple likelihood ratio transformation[20], this corresponded to a positive likelihood ratio (+LR) of 2.2[1.39,3.47] and a negative (-LR) of 0.85[0.74,0.99]).

Secondary/Sensitivity Analyses

We observed an association between baseline DEB/pRBD and parkinsonism symptoms on the Tanner questionnaire (RR_{IPW}= 1.75 [1.56,1.96]) at follow-up (Table 1). After excluding sleep symptoms that may mimic the symptoms of dream enactment behaviors in RBD (e.g., early-onset dream enactment, apnea, restless leg syndrome, etc.), results were largely unchanged. (Table 1)

Discussion

Whereas the phenoconversion rates from RBD to neurodegenerative disease have been well established in patients who have been recruited from sleep clinics with full polysomnographic diagnosis, it has remained unclear to what degree screens for RBD are associated with future parkinsonism in the general population. With the advantage of the population based CLSA cohort, we assessed the relationship between the presence of self-reported dream enactment behavior and the risk of parkinsonism. We found a modest increase in the risk of parkinsonism that was similar in amplitude to predicted estimates from the MDS prodromal criteria.

We found a 2.9-fold increased rate of phenoconversion among those screening positive for RBD. This is in striking contrast to what has been observed for polysomnography confirmed iRBD; in a recent multicenter study of 1280 PSG-confirmed iRBD patients, 6.25% phenoconverted to dementia or parkinsonism per year.[21] Here, we observed an annual phenoconversion rate to parkinsonism of only 0.16% (95%CI=[0.14,4.19]). This striking difference undoubtedly reflects the low positive predictive value of RBD question screens, as would be expected given the low prevalence of iRBD (estimated prevalence ~1% in this age group)[22, 23] and a screen with moderate specificity (estimated as 87% in on clinic-based study).[24] This finding was, in fact, also anticipated by the MDS prodromal criteria. In the original criteria, it was posited that a screen positive RBD case should be associated with a +LR of 2.2; in this study, we observed a very similar +LR of 2.15.[20, 25]

Our findings also strongly suggest that the term 'probable RBD' should not be used to describe those who simply screen positive for RBD. This is illustrated both by the very large difference we observed in the phenoconversion rate verses the known rate in polysomnogram-confirmed RBD, and the contrast between a 11% prevalence of dream enactment in our cohort versus an 1% prevalence documented in studies that use polysomnographic confirmation .[22, 23] Given that the word 'probable' means more likely than not, use of the term 'probable RBD' is inappropriate to describe a positive symptom screen for RBD without further diagnostic confirmation.

Strengths and Limitations

The most important limitation of the study is that the diagnosis of RBD is via self-report; physician contact to confirm the diagnosis is not performed in the CLSA protocol. Our study findings should not, therefore, be interpreted as an estimate of the rate of phenoconversion of true RBD, rather they estimate of the utility of RBD population screens to identify elevated risk of parkinsonism. Second, PD diagnosis was also via self-report, and it should be expected that some patients will not have an accurate diagnosis. We were able to mitigate this somewhat via the inclusion of confirmatory screens for parkinsonism. Of note, in a recent meta-analysis, the estimated incidence rate of parkinsonism was 61.2[43.6,86.0] per-100,000-person-year for males aged 40 and above and 37.6[26.2,53.8]for females.[26] This is similar to what was found in our study (e-3) and the IR of 2013-2014 from a Canadian federal report (IR=55.1; male: 67.8, female:40.3).[27] Third, we were unable to include dementia as an outcome in our study; in the CLSA, only 56 developed de-novo dementia (based on self-report) in the first 3 years, much lower than expected worldwide; this may perhaps reflect healthy volunteer bias. We were also

unable to screen for hallmarks of dementia with Lewy bodies such as hallucinations and cognitive fluctuations.

On the other hand, this study has several advantages. The primary one is that it uses a population-based sample, and therefore is more generalizable than estimates coming from sleep centers. With the design of statistical weighting-based recruitment, the results from the CLSA cohort are mostly in-line with reports from the national representative source.[28] The loss-to-follow-up rate was low in the CLSA study. And, with the implantation of inverse probability weighting and White's estimate, we were able to provide more precise estimates than a complete case analysis.[29]

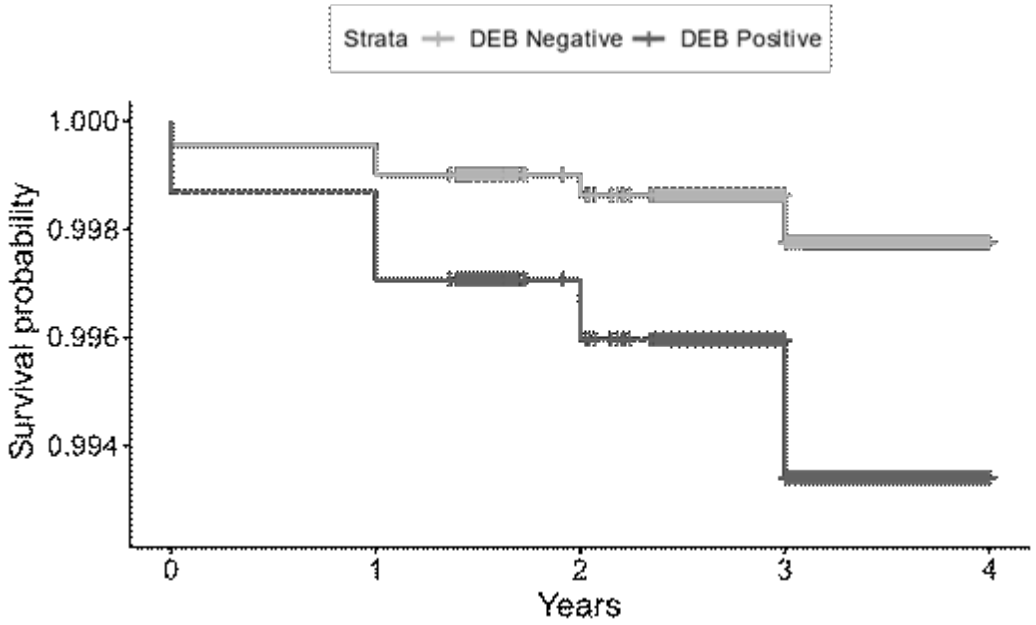
Conclusions

In conclusion, we confirm that questionnaire screening for RBD can identify patients at higher risk of future diagnosis of parkinsonism, with findings largely in line with the predictions of the MDS prodromal criteria.

References

1. Baltzan M, Yao C, Rizzo D, Postuma R. Dream enactment behavior: review for the clinician. J Clin Sleep Med 2020;16(11):1949-1969.
2. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011;77(9):875.
3. Wing YK, Li SX, Mok V, 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(4):470-472.
4. 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(2):e89741.
5. 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(8):744-748.
6. Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain 2019;142(7):2051-2067.
7. Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, others. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142(3):744-759.
8. Yao C, Fereshtehnejad S-M, Keezer MR, Wolfson C, Pelletier A, Postuma RB. Risk factors for possible REM sleep behavior disorder: A CLSA population-based cohort study. Neurology 2019;92(5):e475.
9. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28(3):221-229.
10. 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(7):913-916.
11. Tanner CM, Gilley DW, Goetz CG. A brief screening questionnaire for parkinsonism. Ann Neurol 1990;28:267-268.
12. Duarte J, Clavería LE, De Pedro-Cuesta J, Sempere AP, Coria F, Calne DB. Screening Parkinson's disease: A validated questionnaire of high specificity and sensitivity. Mov Disord 1995;10(5):643-649.
13. Venables WN, Ripley BD, Venables WN. Modern applied statistics with S. 4th ed. New York: Springer, 2002.
14. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168(6):656-664.
15. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica 1980;48(4):817-838.
16. Yao C, Fereshtehnejad S-M, Keezer MR, Wolfson C, Pelletier A, Postuma RB. Risk factors for possible REM sleep behavior disorder: A CLSA population-based cohort study. Neurology 2018.
17. Nagappa M, Liao P, Wong J, et al. Validation of the STOP-Bang Questionnaire as a Screening Tool for Obstructive Sleep Apnea among Different Populations: A Systematic Review and Meta-Analysis. PLoS One 2015;10(12):e0143697.
18. Medicine AAoS. International classification of sleep disorders. Diagnostic and coding manual 2005:51-55.
19. Nielsen T, Svob C, Kuiken D. Dream-enacting behaviors in a normal population. Sleep 2009;32(12):1629-1636.

20. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30(12):1600-1611.
21. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142(3):744-759.
22. 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(8):1147-1152.
23. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, others. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. Sleep 2018;41(2):zsx197-zsx197.
24. Postuma RB, Arnulf I, Hogl B, et al. A Single-Question Screen for REM Sleep Behavior Disorder: A Multicenter Validation Study. Mov Disord 2012;27(7):913.
25. Heinzel S, Berg D, Gasser T, et al. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord 2019;34(10):1464-1470.
26. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2016;46(4):292-300.
27. Canada TPHAo. Parkinsonism in Canada, including Parkinson's Disease. In: Minister of Health C, editor. Canada2018.
28. Raina P, Wolfson C, Kirkland S, et al. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). Int J Epidemiol 2019;48(6):1752-1753j.
29. Perkins NJ, Cole SR, Harel O, et al. Principled Approaches to Missing Data in Epidemiologic Studies. Am J Epidemiol 2018;187(3):568-575.



	RR	2.90 [1.57,5.38]			
IPW Weighted	Years	<Overall>			
	HR	3.09[1.35,7.05]	2.79[1.40,5.59]	2.96[1.60,5.50]	2.96[1.60,5.50]
	Years	1	2	3	4
Age and Sex	HR	3.08[1.37,6.94]	2.84[1.43,5.63]	2.83[1.53,5.24]	2.83[1.53,5.23]
Adjusted	Years	1	2	3	4

Figure 1 – Parkinsonism-free Survival according to baseline dream enactment behavior

The 4-year survival probability (Kaplan Meier analysis) was plotted based on the inverse probability weighted Cox-regression model.

Abbreviations:
DEB: dream enactment behavior
HR: Hazard Ratio

Table 1. Relative Risk of Phenoconversion in DEB/pRBD

	Primary Definition			*Sensitivity Analysis*			
	DEB-Free N=26,360	**DEB+ N=3271**		DEB+*Onset>20y.o. N=2228		DEB+*OSA- N=3172	
	Mean±SD or N(%)		**RR (1/IPW)**	Mean±SD or N(%)	RR (1/IPW)	Mean±SD or N(%)	RR (1/IPW)
Follow-Up							
De-novo Parkinsonism	44(0.18)	14(0.48)	**2.90 [1.57,5.38]**	11(0.54)	2.94 [1.48,5.85]	13(0.45)	2.83 [1.50,5.32]
Tanner's Questionnaire ≥ 3	1775(6.74)	337(10.3)	**1.75 [1.56,1.96]**	252(11.3)	1.70 [1.49,1.93]	309(9.75)	1.67 [1.49,1.88]

	Sensitivity Analysis					
	DEB+*RLS- N=2538		DEB+*SD- N=2776		DEB+*SSRI- N=1735	
	Mean±SD or N(%)	RR (1/IPW)	Mean±SD or N(%)	RR (1/IPW)	Mean±SD or N(%)	RR (1/IPW)
Follow-Up						
De-novo Parkinsonism	13(0.56)	3.30 [1.74,6.25]	11(0.43)	2.66 [1.35,5.25]	12(0.47)	2.78 [1.44,5.37]
Tanner's Questionnaire ≥ 3	232(9.16)	1.54 [1.35,1.77]	256(9.55)	1.59 [1.40,1.80]	243(8.76)	1.49 [1.31,1.70]

Descriptive analysis results were illustrated in mean± standard deviation or number (percentage %).

Abbreviations:

IPW: inverse probability weighting

DEB: dream enactment behavior

DEB+*Onset>20y.o.: dream enactment behavior without early onset

DEB+*OSA-: dream enactment behavior without possible apnea

DEB+*RLS-: dream enactment behavior without possible RLS

DEB+*SD-: dream enactment behavior without sleep deprivation (less than 6 hours)

DEB+*SSRI-: dream enactment behavior without use of antidepressants

Supplementary Materials

Questionnaires:

Self-reported dementia diagnosis was based on the response to the following question: "*Has a doctor ever told you that you have dementia or Alzheimer's disease?"*

Statistical Analysis:

Follow-up status adjusted annual incidence/phenoconversion rates of parkinsonism were calculated using Poisson regression.[13] The instantaneous event rate (i.e., hazard ratio) to parkinsonism was calculated using the adjusted Cox-regression model. The age and sex adjusted survival probability was plotted based on the predictive value from the Cox regression.

Consent Data Availability:

Written consent was obtained from all participants (or guardians of participants) in the study. Data access for the use of this study was reviewed and granted by the CLSA Data and Sample Access Committee. Data are available from the Canadian Longitudinal Study on Aging webpage (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

Proof of Backward Calculation for iRBD Prevalence:

With the population-based RBD phenoconversion rate and incident rate of parkinsonism known, we can provide an informative estimate of synuclienopathy-associated iRBD prevalence. For simplicity, we assume that both phenoconversion rate and incident rate obtained from our study are constant coefficients. And, based on systematic review, we assume that iRBD phenoconverted PD accounts for 20-30% of all PD.[30, 31] From here, we can estimate the prevalence of synuclienopathy-associated iRBD following the steps below. Our estimate was similar to that of Haba-Rubio's estimate from Swiss community cohort (1.06% [0.61,1.50]).[30]

<Calculation Process for iRBD Prevalence>

Assume the incidence rate of PD is a constant at 0.055 per-100-person.

0.055%*3=0.164% (cumulative 3-year incidence rate) and 3-year phenoconversion rate from RBD to PD is 0.4872%

∵ Prevalence of iRBD * Phenoconversion Rate of iRBD = Incidence Rate of PD from iRBD

∴ Incidence Rate of PD from iRBD ÷ Phenoconversion Rate of iRBD = Prevalence of iRBD

Let the incidence rate of PD from iRBD be IR_{PD}^{iRBD} and the proportion of PD from iRBD ranged from 25%. The phenoconversion rate of iRBD is denoted as PR_{PD}^{iRBD} and P_{iRBD} for the prevalence of iRBD.

$IR_{PD}^{iRBD} \sim (0.20, 0.30) * 0.164$

$\sim [0.0328, 0.0492]$

$IR_{PD}^{iRBD} \div PR_{PD}^{iRBD} \sim [0.0328, 0.0492] \div 0.04872$

$\sim [0.673234811,1.0098522]_{\#}$

e-References

1. Venables WN, Ripley BD, Venables WN. Modern applied statistics with S. 4th ed. New York: Springer, 2002.
2. Schenck C, Högl B, Videnovic A. Rapid-eye-movement sleep behavior disorder. Cham, Switzerland: Springer; 2019.
3. Ferri R, Cosentino FI, Pizza F, Arico D, Plazzi G. The timing between REM sleep behavior disorder and Parkinson's disease. Sleep Breath 2014;18(2):319-323.

Supplementary Table e1 Baseline Demographics

		Primary Definition			*Sensitivity Analysis*			
		DEB-Free N=26,360	**DEB+ N=3271**		DEB+*Onset>20y.o. N=2228		DEB+*OSA- N=3172	
		Mean±SD or N(%)		**OR**	Mean±SD or N(%)	OR	Mean±SD or N(%)	OR
Baseline (OR $_{\text{Age \& Sex Adjusted}}$ [95%CI]))								
Demography[$]	Age	63.1±10.3	61.1±10.0	**0.98 [0.98,0.98]**	62.5±10.1	0.99 [0.99,1.00]	61.1±10.0	0.98 [0.98,0.98]
	Sex (% Male)	12621(47.9)	1942(59.4)	**1.61 [1.49,1.73]**	1431(64.2)	1.96 [1.79,2.14]	1853(58.4)	1.55 [1.43,1.67]
	Years of Education	13.6±2.3	13.5±2.3	**0.95 [0.94,0.97]**	13.4±2.3	0.94 [0.92,0.96]	13.5±2.3	0.96 [0.94,0.97]

		Sensitivity Analysis					
		DEB+*RLS- N=2538		DEB+*SD- N=2776		DEB+*SSRI- N=1735	
		Mean±SD or N(%)	OR	Mean±SD or N(%)	OR	Mean±SD or N(%)	OR
Baseline (OR $_{\text{Age \& Sex Adjusted}}$ [95%CI]))							
Demography[$]	Age	61.1±10.1	0.98 [0.98,0.98]	61.3±10.1	0.98 [0.98,0.99]	61.4±10.2	0.98 [0.98,0.99]
	Sex (% Male)	1590(62.7)	1.84 [1.70,2.01]	1684(60.6)	1.69 [1.56,1.83]	1702(61.3)	1.74 [1.61,1.89]
	Years of Education	13.6±2.3	0.96 [0.95,0.98]	13.6±2.3	0.97 [0.95,0.99]	13.5±2.3	0.95 [0.93,0.97]

Descriptive analysis results were illustrated in mean± standard deviation or number (percentage %).
Abbreviations:
DEB: dream enactment behavior
DEB+*Onset>20y.o.: dream enactment behavior without early onset
DEB+*OSA-: dream enactment behavior without possible apnea
DEB+*RLS-: dream enactment behavior without possible RLS
DEB+*SD-: dream enactment behavior without sleep deprivation (less than 6 hours)
DEB+*SSRI-: dream enactment behavior without use of antidepressants

e-2 Characteristics of participants lost to follow-up

Demography & Presence of Symptoms related Sleep Disorders \ Follow-up Status		Followed-up N= 27209	Loss-to-Follow-up N=2888	OR_adj. [CI]
		N(%) or Mean±SD		$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]
Baseline				
Demography	Age	62.6±10.1	66.1±11.3	1.03 [1.03,1.04]
	Sex (% Male)	13379(49.2)	1398(48.4)	0.96 [0.89,1.03]
	Income (1,000 CAD)	58.4±35.8	46.6±32.3	0.99 [0.99,0.99]
	Years of Education	13.7±2.3	12.9±2.4	0.88 [0.86,0.89]
	Language – Anglophone	21997(80.8)	2350(81.4)	1.02 [0.92,1.12]
	Antidepressants	2135(7.90)	281(9.87)	1.40 [1.22,1.60]
Total Hours of Sleep		6.81±1.23	6.76±1.46	0.95 [0.92,0.98]
Less than 6 hours of Sleep		3262(12.0)	451(15.7)	1.39 [1.25,1.55]
Less than 4 hours of Sleep		203(0.75)	49(1.7)	2.47 [1.78,3.36]
Restless Leg Syndrome		4420(16.5)	481(16.8)	1.00 [0.90,1.11]
Stop Breathing/Snoring		6507(26.5)	412(24.2)	0.91 [0.81,1.03]
Stop Breathing & Snoring		2158(8.79)	146(8.57)	1.03 [0.86,1.23]
Dream Enactment Behavior	Positive	3009(11.2)	319(11.2)	1.07 [0.95,1.21]
	No Early Onset	2043(7.86)	235(8.47)	1.12 [0.97,1.29]

Supplementary e-3 Unweighted Relative Risk of Phenoconversion in RBD

	DEB+	DEB+*Onset>20yo vs. DEB-	DEB+*OSA- vs. DEB-	DEB+*RLS- vs. DEB-	DEB+*SD- vs. DEB-	DEB+*SSRI- vs. DEB-
	RR $_{\text{Age, Sex, Time Interval and Loss-to-follow-up Status Adjusted}}$ [95%CI]					
Follow-Up						
De-novo Parkinsonism	**2.76 [1.49,5.08]**	2.86 [1.46,5.59]	2.66 [1.42,4.99]	3.17 [1.69,5.93]	2.47 [1.26,4.84]	2.66 [1.40,5.08]
Tanner's Questionnaire ≥ 3	**1.73 [1.55,1.93]**	1.70 [1.50,1.92]	1.65 [1.47,1.84]	1.54 [1.36,1.75]	1.60 [1.42,1.80]	1.46 [1.29,1.65]

Abbreviations:
DEB: dream enactment behavior
DEB+*Onset>20y.o.: dream enactment behavior without early onset
DEB+*OSA-: dream enactment behavior without possible apnea
DEB+*RLS-: dream enactment behavior without possible RLS
DEB+*SD-: dream enactment behavior without sleep deprivation (less than 6 hours)
DEB+*SSRI-: dream enactment behavior without use of antidepressants

Supplementary e-4 Incidence/Phenoconversion Rate of Parkinsonism

			Unweighted	Weighted
			De-novo PD	
Demography	Age	45-54	14.3 [4.6,44.4]	15 [8.4,26.6]
		55-64	49.2 [28.6,84.7]	51.1 [37.3,70.1]
		65-74	116 [76.3,176.1]	121.7 [99,149.6]
		>75	157.4 [101.6,244]	168.5 [141.4,200.9]
	Sex	Female	49.2 [31.7,76.3]	49.8 [36.4,68]
		Female | Age	39.2 [24.4,63]	50.4 [37,68.7]
		Male	99.9 [72,136]	99.6 [79.7,124.5]
		Male | Age	77.3 [53.5,111.6]	98.3 [78.5,123.1]
RBD-1Q	DEB	Negative	63.1 [47,84.8]	63.1 [47.8,83.4]
		Positive	162.4 [96.2,274.2]	162.4 [136.4,193.3]
		Positive | Sex*Age	174.3[99.3,305.8]	179 [151.6,6,211.3]

Abbreviations:
DEB: dream enactment behavior

Chapter IC - Revisiting Idiopathic RBD Screening Definition

Introduction:

We previously reported a cross-sectional analysis of risk factors associated with questionnaire-screened REM sleep behavior disorder (i.e., possible RBD) in the Canadian Longitudinal Study on Aging cohort (CLSA, a population-based prospective cohort).[1] In a subsequent publication we found that after 3 years of follow-up, 14 possible RBD patients had phenoconverted to parkinsonism, 4 had recent onset prior to the parkinsonism diagnosis, and 1 at the same time (i.e., idiopathic RBD at baseline).[2]

In our previous study, we proposed exclusion criteria for population-based RBD screening to exclude potential false-positive cases mimicking RBD.[3] These included early dream enactment behavior onset (age of onset <20)[4], associated sleep apnea symptoms (which can mimic RBD)[5], and restless leg syndrome (with 80% of these patients also have periodic leg movement at night)[6]. In contrary to the 1% of point prevalence estimated via polysomnographic screening, over 9% of the CLSA cohort screened positive for possible RBD.[7-9] This has since been reflected in the population-based phenoconversion rate to parkinsonism, which was much lower than estimated from neurological clinics.[2, 10] These results are in line with the inevitable issue of low positive predictive value associated with a low prevalence condition screening tool. However, since iRBD accounts for a quarter to a third of de-novo parkinsonism, this gives us a 25 to 33 fold higher pretest probability compared to 1% in the general population. Therefore, given the same sensitivity and specificity, the majority of those screening positive for 'possible' RBD who eventually developed PD did indeed have RBD (see discussion for further detail). Since those who phenoconverted from questionnaire-screen RBD to parkinsonism were likely to have true RBD, we can re-assess whether the exclusion criteria based on comorbid sleep disorders/symptoms is appropriate.

Method:

Cohort Description and Case Definitions

We analyzed the 30,097-person comprehensive subset of the CLSA, a population-based cohort of adults aged 45-85 recruited between 2012-2015.[11] Those with self-reported diagnosis of parkinsonism or dementia at baseline were excluded. De-novo parkinsonism was defined by self-report of a 'new' physician diagnosis during the follow-up interview (median/mean interval ~ 3 years), plus either use of parkinsonism medication or endorsing at least 3 parkinsonism symptoms on a screening questionnaire.[2] Those who screened positive on the RBD-1Q[1] at either the baseline or the follow-up interview, with the symptom-onset that occurs prior to parkinsonism diagnosis, were defined as idiopathic REM sleep behavior disorder (iRBD) at the baseline. (Figure 1) Of note, one participant had RBD onset around the same time as the parkinsonism diagnosis. Dream enactment behavior-free was defined as negative screen on the RBD-1Q and free of parkinsonism throughout the study period.

RBD Screening Definition

To reduce the false positives, in our previous report, we had previously set a few exclusion criteria for the sensitivity analyses. These included:

<Primary Exclusion Criteria>

- symptom onset under 20 years old - NREM parasomnia is generally a childhood-onset disorder, whereas synucleinopathy-related RBD generally occurs after age 40

- apnea-related symptoms (i.e. snoring loud enough to be heard in the next room and/or stopping breathing while sleeping)

<Additional Exclusion Criterion>

- restless leg syndrome (RLS) screen positives, adapted from the Johns Hopkins telephone RLS interview.

Statistical Analysis

For comparison of sleep symptoms, we matched participants with prodromal parkinsonism (regardless of their RBD statuses) to ten participants free of dream enactment behavior based on age, sex, follow-up status and intervals using greedy match via *MatchIt.*[12] Associations between apnea/RLS and iRBD were assessed using logistic regression in R (version 4.0.3). Further details on the methods and results of the full cohort can be found in the supplementary material.

Results

At the follow-up (median/mean interval ~ 3 years), 62 participants self-reported a new diagnosis of parkinsonism. We excluded 3 whose diagnosis was not confirmed on symptom/medication screen and 1 with missing information regarding baseline parkinsonism diagnosis, leaving 58 de-novo parkinsonism participants. Of these, 19 had RBD onset prior to the parkinsonism diagnosis and can be considered as likely idiopathic RBD.

Of these 19 patients, when queried on the onset of the dream enactment behavior, 4 did not recall symptom duration, 3 reported symptom onset before age of 20 and 8 reported onset after 20 years of age. (Figure 2) Therefore, 7/19 patients would not have met the original definition of possible RBD based upon the age of onset. Of the sleep symptoms priorly excluded, 10 also had at least one apnea symptom (snoring and/or obstruction of the airway) and 2 screened positive for restless leg syndrome. (Table 2) When assessing the association, iRBD was associated with apnea (OR=2.80 [1.08,7.28]) but not restless leg syndrome. (Table 2) Of note, only one participant with iRBD screened positive for obstructive sleep apnea (cut-off >4). The results remained similar after reassessing the associations in comparison to disease-free (and dream enactment behavior-free). (Table e-1 & 2).

Discussion:

In this prospective nationwide study, we revisited the exclusion criteria of possible REM sleep behavior disorder (RBD) previously reported.[13] Of the comorbid sleep symptoms, iRBD was independently associated with apnea symptoms.

iRBD Estimate and PPV Calculation

Fortunately, with the proportion of iRBD-first parkinsonism among de-novo parkinsonism known (prior~0.25)[14], we can estimate the prevalence of iRBD based on the number of participants with de-novo parkinsonism (estimated number of iRBD=14-19 participants).[2] From a Bayesian's theorem standpoint, with the new 25-time-greater prior, this significantly improves RBD-1Q's positive predictive value (estimated PPV changes from 7% to 71.4%). Given that the number of participants screened positive of RBD, who later developed parkinsonism, were within the estimate, the majority of these RBD screened positive did indeed have RBD.

iRBD Onset Age, Apnea, Restless Leg Syndrome and Prodromal Parkinsonism

The typical age of RBD-related dream enactment behavior onset is believed to be after 40 years old (average age ranges: 54-69 years).[15] However, in our study, 46.7% of those iRBD who reported time of symptom onset had symptom onset before 20 years old (median = 29.6 years). This discrepancy may be the combined results of the difference in interviewing methods and the presence of parasomnia overlapping disorder. Of note, in this large-scale epidemiological cohort, all CLSA interviewers were trained to perform standardized interviews without querying additional details or providing additional clarifications (as would be routine in a clinical encounter with an expert sleep

clinician).[15] Therefore, it is likely that some participants were reporting other non-RBD symptoms (common in childhood), such as night terror, sleepwalking, restless sleep disorder (characterize as frequent movement at nighttime), etc. This could have been in association with true RBD: for example, 10.8 to 25.7% of polysomnography-confirmed iRBD patients have co-existing parasomnia overlap disorders at the time of diagnosis (and many more may have had childhood-onset parasomnias that have since resolved).[15]

The association between apnea symptoms and iRBD, found in our study, has also been indicating in a few other studies, including the international RBD study group.[15] Apnea has often been considered primarily as an RBD mimic. However, in the early 2012 study, obstructive sleep apnea was found present in 26% of the polysomnography-confirmed iRBD patients from multiple sleep centers across the world. Moreover, apnea was not associated with a lower rate phenoconversion among iRBD patients in these multicenter studies, as would be expected for an RBD mimic.[15] In our cohort, only one iRBD scored positive on the STOP-BAG screen for obstructive sleep apnea[16], suggesting it was not a common confound in our study, it is unclear how apnea symptoms play the role for the RBD mechanism.

In regards to RLS, if we were to also exclude participants with RLS, we will loss 2 participants who indeed have iRBD. As an additional exclusion criterion, we found no clear difference in restless leg syndrome prevalence between iRBD and disease-free (who are also free of dream enactment behavior). In the general adult population (i.e., >18 years old), the worldwide mean estimate of restless leg syndrome ranges from 9.4 to 15%, but can be more common among western counties and older age groups.[17] Interestingly, both our estimates (10.5 and 16.4%) and a recent multicenter iRBD study (17.7%) fall within the estimate, indicating no

clear association between iRBD and restless leg syndrome.[10] These results, however, challenge the notion of restless leg syndrome as a risk of parkinsonism.[18, 19] Future studies will be needed.

In conclusion, although early-onset dream enactment behavior is more common for non-REM sleep parasomnia, early symptom onset should not be considered as an exclusion for iRBD diagnosis. Apnea symptoms are common in those with iRBD.

References:

1. Yao C, Fereshtehnejad S-M, Keezer MR, Wolfson C, Pelletier A, Postuma RB. Risk factors for possible REM sleep behavior disorder: A CLSA population-based cohort study. Neurology 2019;92:e475.
2. Yao CW, Saha-Chaudhuri P, Zolfaghari S, Pelletier A, Postuma RB. Phenoconversion from Possible REM Sleep Behavior to Parkinsonism in the Population-Based CLSA. Mov Disord 2021.
3. 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;92:e475.
4. Schenck CH, Mahowald MW. Rapid eye movement and non-REM sleep parasomnias. Prim psychiatry 2005;12:67-74.
5. Iranzo A, Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep 2005;28:203-206.
6. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61-65.
7. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, others. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. Sleep 2018;41:zsx197-zsx197.
8. Sasai-Sakuma T, Takeuchi N, Asai Y, Inoue Y, Inoue Y. Prevalence and clinical characteristics of REM sleep behavior disorder in Japanese elderly people. Sleep 2020;43.
9. 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;36:1147-1152.
10. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142:744-759.
11. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28:221-229.
12. Stuart E, King G, Imai K, Ho D. MatchIT: Nonparametric Preprocessing for Parametric Causal Inference. Journal of Statistical Software 2011;42.
13. 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.
14. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord 2015;30:229-237.
15. Schenck C, Högl B, Videnovic A. Rapid-eye-movement sleep behavior disorder. Available at https://link.springer.com/book/10.1007/978-3-319-90152-72019.
16. Strange C, Richard CL, Shan S, et al. A population-based estimate of the health care burden of obstructive sleep apnea using a STOP-BAG questionnaire in South Carolina. J Clin Sleep Med 2021;17:367-374.
17. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev 2012;16:283-295.
18. Calzetti S, Bellanova MF, Negrotti A, Saccani E, Capozzi A, Pietrini V. Non-length-dependent somatosensory small fiber pathology presenting with restless legs syndrome in pre-motor Parkinson's disease. Evidence from skin biopsy in four patients. Journal of Clinical Neuroscience 2019;69:139-142.
19. Iwaki H, Hughes KC, Gao X, Schwarzschild MA, Ascherio A. The association between restless legs syndrome and premotor symptoms of Parkinson's disease. Journal of the Neurological Sciences 2018;394:41-44.
20. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

21. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-664.
22. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica 1980;48:817-838.
23. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. The Lancet Neurology 2019;18:307-318.
24. Mantovani S, Smith SS, Gordon R, O'Sullivan JD. An overview of sleep and circadian dysfunction in Parkinson's disease. Journal of Sleep Research 2018;27:e12673.
25. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis 2017;3:9.

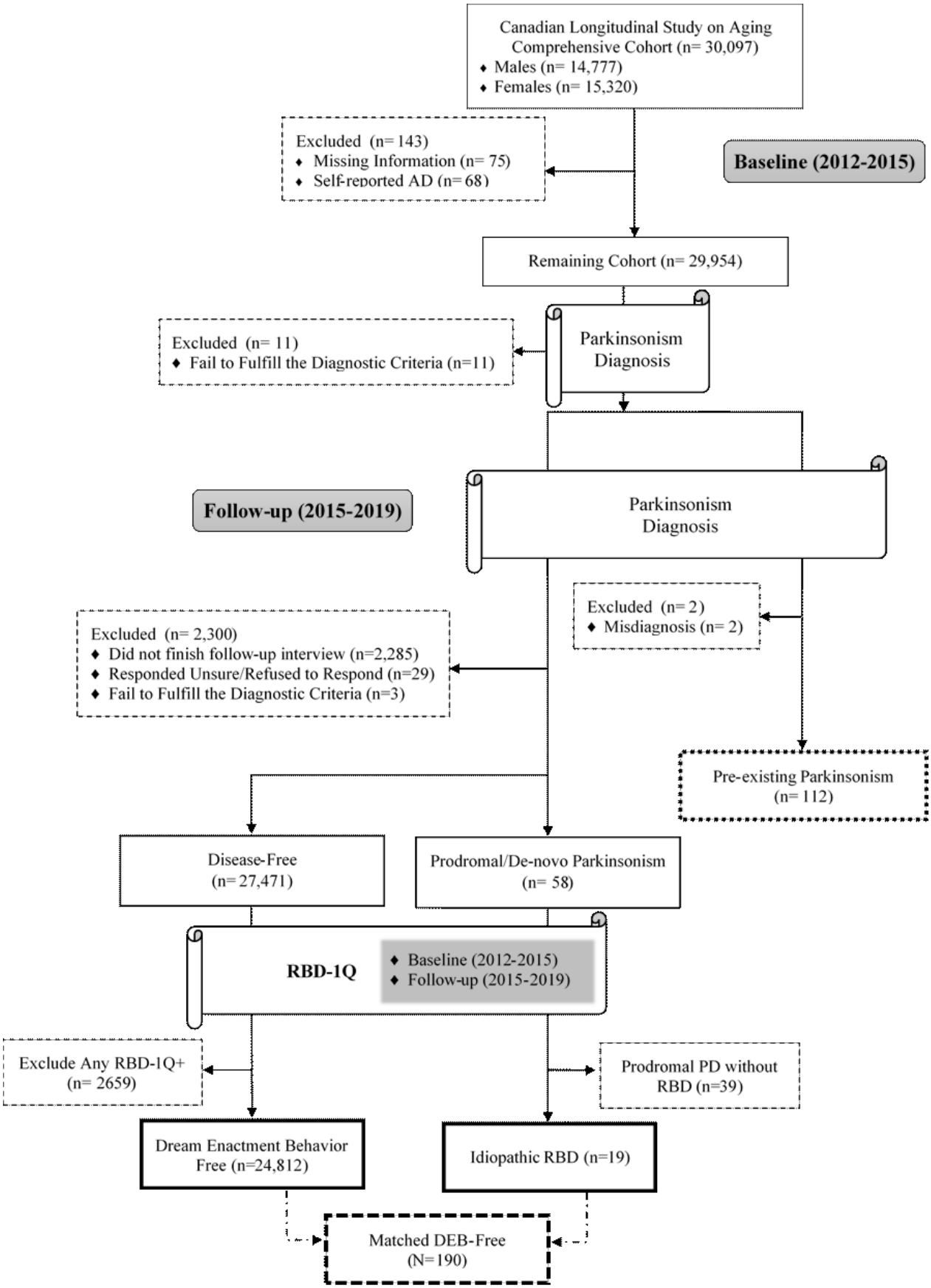


Figure 1. Flow Chart

Participants with prodromal parkinsonism were categorized into iRBD and RBD-free prodromal parkinsonism based on RBD-1Q screen results at both baseline and the follow-up.

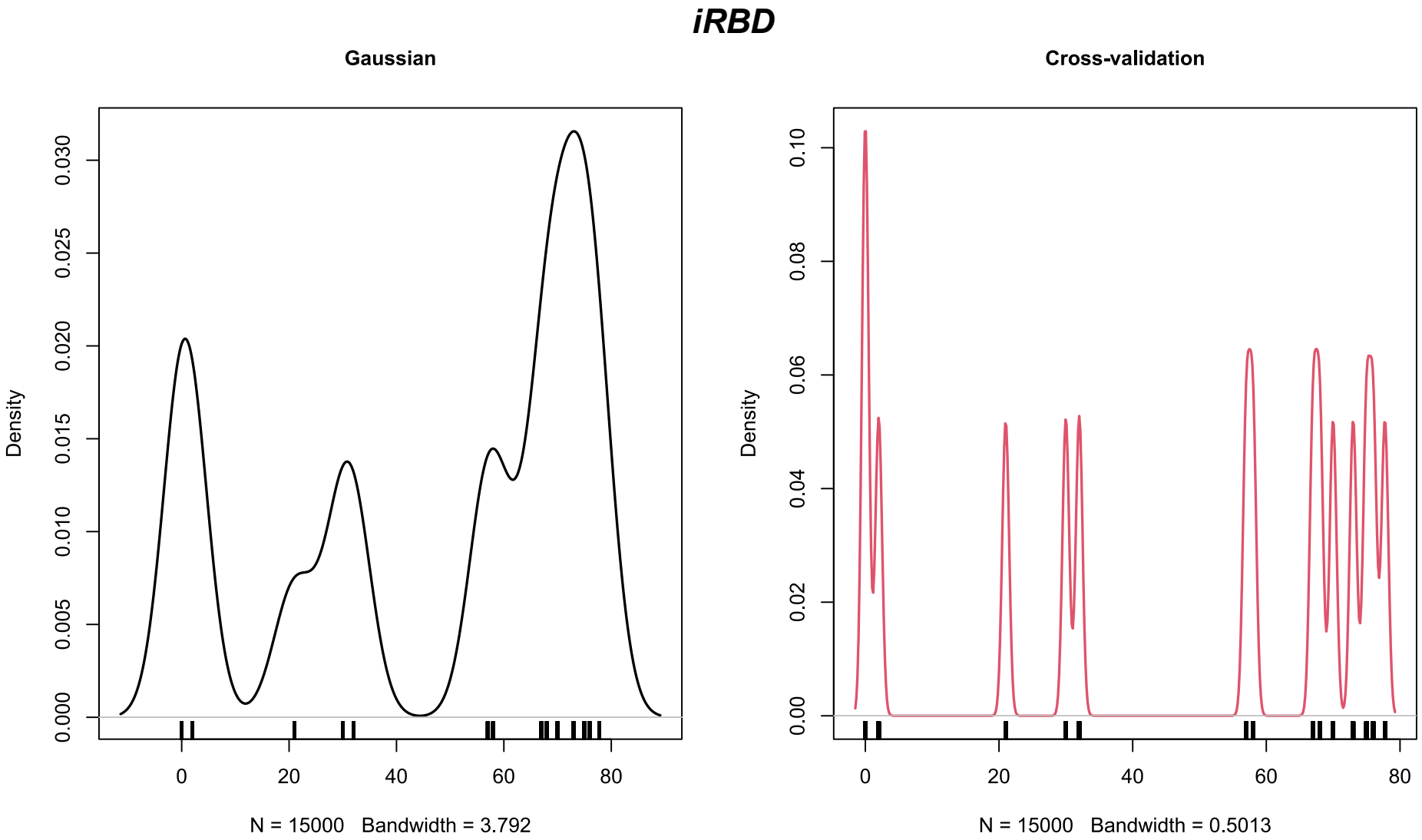
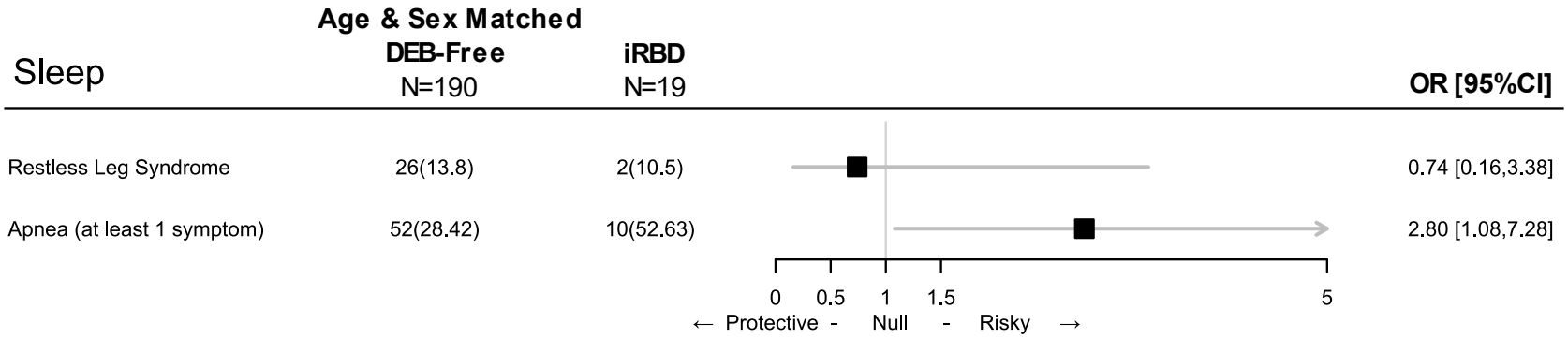


Figure 2 Age at dream enactment behavior onset in iRBD

Age of RBD onset was calculated based on the age at the interview and self-report duration of dream enactment behavior. Distribution were estimated via a Gaussian-based kernel after bootstrapping for 1000 iteration.

Table 2 Associated Sleep Symptoms/Disorders with idiopathic REM Sleep Behavior Disorder



A) 190 participants without dream enactment behavior during the entire follow-up period (i.e., 2012-2019) were matched to those with iRBD based on age, sex and follow-up status and interval, using the greedy match algorithm, at the ratio of 1 to 10. The associations between iRBD and sleep symptoms/disorders were assessed using logistic regression.

Abbreviations: DEB-Free - symptom-free (dream enactment behavior-free); iRBD - idiopathic REM sleep behavior disorder; Prodromal PD^{RBD-} - RBD-free prodromal parkinsonism

Supplementary Material

e-Methods

Additional Sleep Symptoms:

To assess if apnea symptoms and restless leg syndromes were independently associated with iRBD, we elected symptoms or causes related to circadian rhythm disorders for further analyses. Insufficient sleep was defined as less than 8 hours of sleep based on the self-reported average from the last 30 days. Insomnia and hypersomnolence were queried via questions adapted from the Pittsburgh Sleep Quality Index[20], namely:

1. Onset Insomnia: *"Over the last month, how often did it take you more than 30 minutes to fall asleep?"*
2. Maintenance Insomnia: *"Over the last month, how often did you wake in the middle of the night or too early in the morning and found it difficult to fall asleep again?"*
3. Hypersomnolence: *"Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?"*

A positive symptom of insomnia or hypersomnolence was defined as experiencing at least 3 days a week of the symptoms above.

For the matched cohort, the independent associations between apnea symptoms/restless leg syndrome and prodromal parkinsonism were assessed via conditional modeling adjusting for insufficient sleep, onset- and maintenance-insomnia and hypersomnolence. To account for loss-to-follow-up, associations within full cohort analyses were 'adjusted' via inverse probability weighting.[21]

Statistical Analysis:

We estimated associations between the elected risk factors and the prodromal parkinsonism subtypes, via logistic regression weighted for age, sex, time interval and follow-up status to account for selection bias.[21] 95% confidence intervals were estimated via White's variance.[22]

e-Discussion

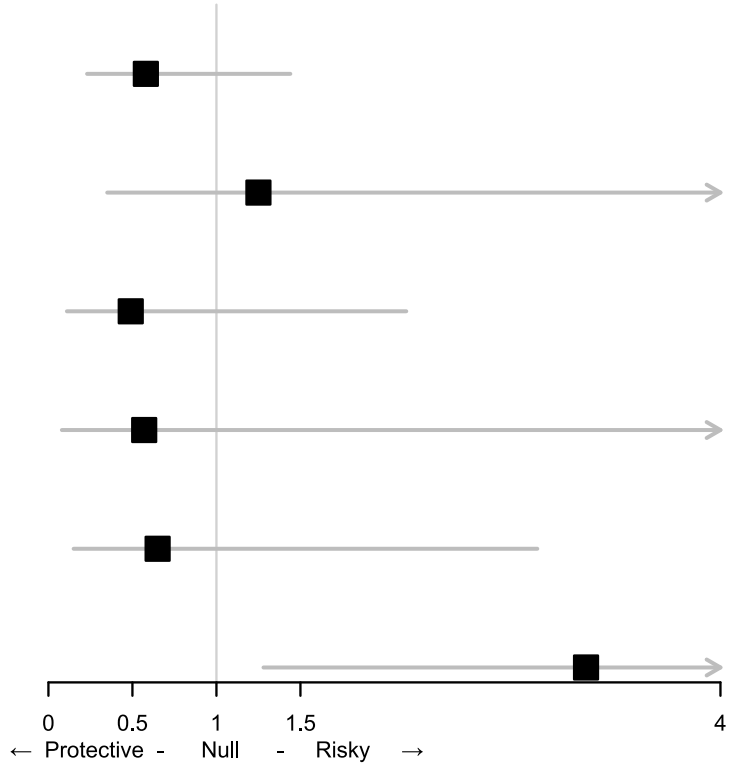
Several circadian rhythm disorders have been shown predating parkinsonism diagnosis.[23, 24] In our study, neither insomnia nor hypersomnolence was associated prodromal parkinsonism with or without RBD. This is slightly different from what was found in the Montréal prospective RBD cohort, where iRBD patients scored higher on the insomnia severity index than the age-and-sex matched symptom-free patients at the baseline.[25] However, the overall insomnia severity decreased overtime among iRBD patients and did not predict phenoconvertion.

e-References

1. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
2. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-664.
3. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica 1980;48:817-838.
4. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. The Lancet Neurology 2019;18:307-318.
5. Mantovani S, Smith SS, Gordon R, O'Sullivan JD. An overview of sleep and circadian dysfunction in Parkinson's disease. Journal of Sleep Research 2018;27:e12673.
6. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis 2017;3:9.

Table e-1 Associated Sleep Symptoms/Disorders with idiopathic REM Sleep Behavior Disorder

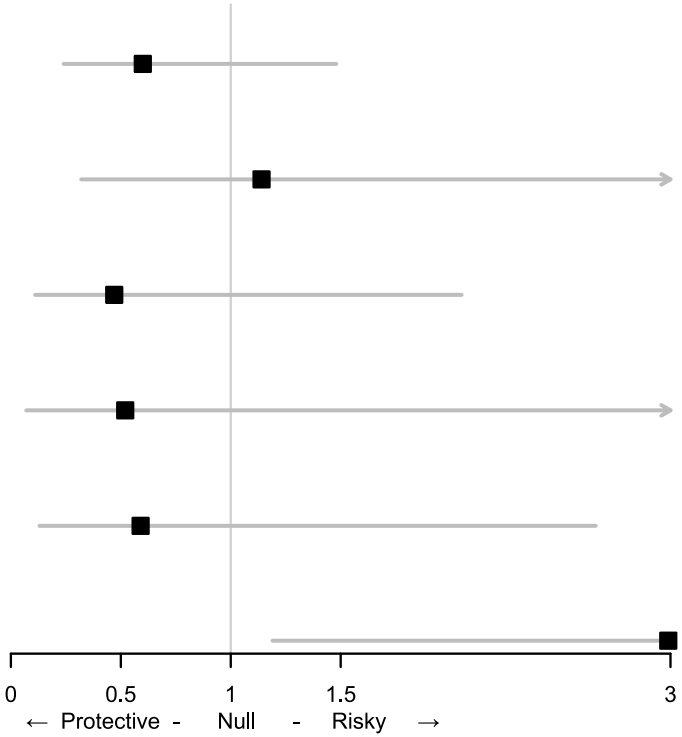
Sleep	DEB-Free N=24812	iRBD N=19	OR [95%CI]
Inefficient Sleep (< 8hrs)	17881(72.2)	11(57.9)	0.58 [0.23,1.44]
Onset Insomnia	3471(14)	3(15.8)	1.25 [0.35,4.43]
Maintenance Insomnia	5425(21.9)	2(10.5)	0.49 [0.11,2.13]
Hypersomnolence	1875(7.57)	1(5.26)	0.57 [0.08,4.25]
Restless Leg Syndrome	3797(15.5)	2(10.5)	0.65 [0.15,2.91]
Apnea (at least 1 symptom)	5849(24.9)	10(52.6)	3.20 [1.28,8.02]



The associations between prodromal parkinsonism and sleep symptoms/disorders were assessed using logistic regression 'adjusting' for age, sex, follow-up status and interval via inverse probability weighting. *Abbreviations: DEB-Free - symptom-free (dream enactment behavior-free); iRBD - idiopathic REM sleep behavior disorder*

Table e-2 Comorbid Sleep Symptoms among iRBD in comparison to Disease-free

Sleep	Disease-Free N=27471	iRBD N=19	OR [95%CI]
Inefficient Sleep (< 8hrs)	19762(72.1)	11(57.9)	0.60 [0.24,1.48]
Onset Insomnia	3966(14.5)	3(15.8)	1.14 [0.32,4.05]
Maintenance Insomnia	6089(22.2)	2(10.5)	0.47 [0.11,2.05]
Hypersomnolence	2170(7.91)	1(5.26)	0.52 [0.07,3.90]
Restless Leg Syndrome	4461(16.4)	2(10.5)	0.59 [0.13,2.66]
Apnea (at least 1 symptom)	7139(26.6)	10(52.63)	2.99 [1.19,7.48]



The associations between sleep symptoms/disorders were assessed using logistic regression 'adjusting' for age, sex, follow-up status and interval via inverse probability weighting. *Abbreviations: Disease-free (parkinsonism-free); iRBD - idiopathic REM sleep behavior disorder;*

Chapter I-D – Revisiting Parkinsonism Risk Factors in Idiopathic RBD and RBD-Free Prodromal Parkinsonism

Introduction:

We previously reported the risk factors of questionnaire-screened REM sleep behavior disorder (i.e., possible RBD) in the Canadian Longitudinal Study on Aging cohort (CLSA, a population-based prospective cohort), cross-sectionally.[1] After 3 years of follow-up, 14 of those with possible RBD had phenoconverted to parkinsonism. In addition, 5 patients developing parkinsonism who initially screened negative for RBD reported new onset of possible RBD prior to diagnosis of parkinsonism.[2]

Whereas over 9% of the CLSA cohort endorsed possible RBD, the true prevalence of RBD (using polysomnographic diagnosis) has been estimated to be approximately 1%.[3-5] This implies that the majority of patients with possible RBD (RBD screen-only on a questionnaire) do not have true RBD (as would be expected for a low prevalent condition). However, with a fourth of de-novo parkinsonism endorsing RBD prior to phenoconversion, one can assume that the positive predictive value would also greatly increase (estimated PPV~71.4%). Therefore, the majority of those screening positive for 'possible' RBD who eventually developed parkinsonism did indeed have RBD. This allows a direct comparison of previously described risk factors between possible idiopathic RBD and likely idiopathic RBD. Therefore, we reassessed the associations with male sex, fewer years of education, heavy drinking, daily smoking, psychological distress and use of antidepressants between participants with likely idiopathy RBD/prodromal parkinsonism, compared to both RBD-screen positives who remained disease-free and those reporting no RBD symptoms at baseline or follow-up. Since the previously assessed risk factors were selected based on the known associated factors of parkinsonism and iRBD, we also assessed the same associations among those with RBD-free prodromal parkinsonism.

Methods:

Cohort Description and Case Definitions

We analyzed the 30,097-person comprehensive subset of the CLSA, a population-based cohort of adults aged 45-85 recruited between 2012-2015.[6] Those with a self-reported diagnosis of parkinsonism or dementia at baseline were excluded. De-novo parkinsonism was defined by self-report of a 'new' physician diagnosis during the follow-up interview (median/mean interval ~ 3 years), plus either use of parkinsonism medication or endorsing at least 3 parkinsonism symptoms on a screening questionnaire.[2] Those who screened positive on the RBD-1Q[1] at either the baseline or the follow-up interview, with symptom-onset occuring prior to parkinsonism diagnosis, were defined as likely idiopathic REM sleep behavior disorder (iRBD) at the baseline. (Figure 1) Of note, one participant had RBD onset around the same time as the parkinsonism diagnosis. Those with a negative screen were defined as RBD-free prodromal parkinsonism (i.e., prodromal PD^{RBD-} in figures/tables). Of the participants who remained disease-free at the follow-up, those who screened negative on the RBD-1Q during both the baseline and the follow-up interviews were defined as free of dream enactment behavior (i.e., DEB-Free). The terminology 'disease-free' refers to those free of parkinsonism throughout the study period.

Risk Factors

Several risk factors associated with possible RBD were identified in our previous report.[7] These include male sex, fewer total years of education, heavy drinking, daily smoking, use of antidepressant, and mental illness.

Statistical Analysis

To conserve statistical power by reducing the variances between groups, we matched participants with prodromal parkinsonism (regardless of their RBD statuses) to ten participants free of dream enactment behavior based on age, sex, follow-up status and intervals using greedy match via *MatchIt.*[8] Associations between risk factors and iRBD/RBD-free prodromal parkinsonism were assessed using logistic regression in R (version 4.0.3). Further details on the methods and results of the full cohort can be found in the supplementary material.

Sensitivity Analysis

To conserve the benefits of population-based sampling, we also reassessed the associations using the full cohort. Each prodromal parkinsonism subtype was compared to two different reference groups: those without dream enactment behavior disorder (i.e., symptom-free) and those who remained free of parkinsonism through the study period (2012-2019). In addition, we also performed analyses to evaluate the associations among those with pre-existing parkinsonism (which is treated as a 'positive control' for replicating previous epidemiological findings).

Results

Of the 30,097 participants recruited at the baseline, 62 participants self-reported a new diagnosis of parkinsonism at the 3-year follow-up, of whom 58 fulfilled the diagnosis of de-novo parkinsonism (i.e. with additional confirmation via positive symptom-screen or use of medication). This translates to an estimated age-standardized incidence rate of 59.8 per-100,000-person-years. (Figure 1) The 4 excluded participants were excluded due to either missing information regarding baseline parkinsonism diagnosis or failing the confirmatory screen. Among the de-novo parkinsonism, 19 reported RBD symptoms with onset prior to the parkinsonism diagnosis (i.e., iRBD) and 39 did not report RBD symptoms (prodromal PD^{RBD-}).

Both iRBD and RBD-free prodromal parkinsonism were slightly older with more males compared to those disease-free and dream enactment behavior-free. (e-1 & 2) In comparison to the age-and-sex-matched symptom-free participants (DEB-free), participants with either iRBD or RBD-free prodromal parkinsonism were slightly less likely to be frequent binge drinkers compared to the matched symptom-free. (Table 1) Participantes with RBD-free prodromal parkinsonism were more likely to be a heavy drinker (OR=3.5; 95%CI=[1.57,7.77]) and past daily smoker comparing to the age-and-sex-matched symptom-free (OR=3.28 [1.54,7.01]). The association with past daily smoking remained at the time of phenoconversion (data not shown) but the association with drinking had attenuated. (Table e-3)

Of the mental illness associated with possible RBD, both likely iRBD (OR=1.16[1.04,1.30]) and RBD-free prodromal parkinsonism (OR=1.10[1.03,1.18]) were associated with slightly higher psychological distress comparing to the age-and-sex-matched symptom-free participants. Likely iRBD-to-parkinsonism was associated with a positive

depression screen (OR=3.71 [1.38,9.96]) and an increase in the use of antidepressants (OR=5.73 [1.31,25.1]).

Sensitivity Analyses

Full Cohort Analysis

To assess the representation of the findings within the Canadian population, we reassessed the associations in comparison to all those who remained free of dream enactment behavior and/or parkinsonism (i.e., DEB-free and disease-free). Overall, the associations were alike with the exception of use of antidepressant, which attenuated when comparing to the full cohort. (Figure 2) Detailed comparisons can be found in the supplementary materials.

Risk Profiles in Comparison to Pre-existing Parkinsonism

Since most parkinsonism risk factor studies were conducted retrospectively or cross-sectionally, we performed an additional sensitivity analysis on the associated risk factors among participants with (de-novo/pre-existing) parkinsonism in comparison to those who remained disease-free. Of the lifestyle factors assessed, those with pre-existing parkinsonism shared more similar profiles with likely iRBD than the RBD-free prodromal parkinsonism. (Figure 3) Psychological distress and depression were consistently associated with parkinsonism (before and after diagnosis). In contrary to the comparison between iRBD and disease-free, pre-existing parkinsonism was associated with hypersomnolence (OR= 2.25[1.1,4.6] and restless leg syndrome (OR=1.66[1.00,2.77]).

Discussion:

In this prospective nationwide study, we revisited associated/risk factors of possible REM sleep behavior disorder (RBD) previously reported.[7] Overall, older age and male sex were associated with parkinsonism, both with and without RBD. Of the risk factors previously assessed, use of antidepressants, psychological distress and depression remained associated with likely iRBD (iRBD). However, heavy drinking and smoking were no longer linked with likely iRBD, suggesting that these risk factors are associated with RBD mimics rather than true RBD.

Male Sex and Lifestyle Factors

Similar to most RBD clinical studies, both iRBD and parkinsonism were more common among men in the CLSA cohort.[9] Of note, upon analyzing large scale polysomnography screenings in communities, two studies from Switzerland and Japanese both showed no difference in the prevalence of iRBD between sexes.[3, 4] One potential explanation for this discrepancy may be that we selected likely iRBD from those who developed parkinsonism, which may introduce a selection bias due to parkinsonism being male predominant. If the true iRBD prevalence is not different between sexes, two potential hypotheses may be formed. These are 1) female sex is a protective factor for the progression of synucleinopathy in iRBD (which previous studies have not found) 2) male and female sex each poses different risks to different iRBD subtypes (with parkinsonism-related RBD being more common in male and another RBD subtype more common in female). Future studies will be needed to explore these associations.

Of the risk/associated factors known to parkinsonism, the roles of smoking and drinking in the parkinsonism mechanism are controversial. Of drinking, most meta-analyses showed

either a modest risk reduction of PD or no association.[10] In our study, both prodromal and pre-existing parkinsonism showed a trend towards a negative association with binge drinking frequency. (Table 1, e-1, e-2) However, when querying regarding the frequency of drinking per week, an association was found between RBD-free parkinsonism and heavy drinking at the baseline (Table 1, e-1, e-2), although, this association attenuated upon phenoconversion (e-3). A Swedish study also found a similar positive association between heavy drinking and parkinsonism in a 13-year-plus follow-up.[11] One possible explanation for this uncertainty in findings between studies may be the definition of alcohol use. Further analysis will be needed to assess this hypothesis.

In regards to daily smoking, like many previous studies, we found an inverse association between pre-existing parkinsonism and smoking.[12, 13] (Figure 3) Of prodromal parkinsonism, we also observed a negative trend of participants with iRBD being a daily smoker. This is notably different from other studies, including those from the international RBD study group in polysomnography-proven[14], although smoking was not a sufficient predictor for phenoconversion in the follow-up report.[15] In most RBD studies, ever smoking was used, as opposed to daily smoking used in our study.[14] And when we reclassified participants based on their status towards ever smoking (i.e. 100 cigarettes in life), the point estimate shifted towards positive association (OR=1.14[0.46,2.84], data not shown). This indicates that the difference in details of questions may affect the results. Future meta-analysis will need to take this into an account. On the other hand, we found a positive association between RBD-free prodromal parkinsonism and past daily smoking (Table 1, e-1, e-2), which is generally inversely associated with parkinsonism.[16] And, to confirm the reliability of self-report, we also found a positive association between RBD-free prodromal parkinsonism and pulmonary diseases, commonly

associated with smoking. (e-4) A similar positive association was also found in a recent study from the U.S.[17] One likely explanation aligned with their interpretation is the difference in the study design and age at recruitment. In the CLSA cohort, participants were recruited between the age of 45 and 85 at the baseline. And, similar to Kummer's study, both cohorts were much older than many previous studies.[18] Although false recruitment of vascular parkinsonism can also be a reason resulting in this discrepancy, the fact that both studies incorporated an additional confirmation (use of medication and positive symptom screen in ours) for disease screening, makes this confound less likely. The positive association with past daily smoking might also be consistent with the fact that prodromal parkinsonism patients were more likely to quit before phenoconverting to parkinsonism. This suggestion is in line with a Danish registry study, in which parkinsonism patients were found more likely to quit smoking than the age-and-sex matched control group.[19] Together, with the attenuation of drinking and RBD-free prodromal parkinsonism after phenoconversion (Figure 2 & e-3), our results could be consistent with the notion of a potential biological factor allowing parkinsonism patients to quit more easily.[13, 20] In regards to the "neuroprotective" aspect of smoking in parkinsonism, a recent male British doctor cohort study suggested a potential reduction of the "protective" effect for parkinsonism after quit smoking.[21] With the two hypotheses, it is possible that the positive link found between past daily smoking and parkinsonism, in our study, may be the results of losing the "neuroprotective" effect from tobacco after quitting smoking. However, it is advised that one should be careful of interpreting smoking as a true neuroprotective agent for parkinsonism, as nicotine failed to show any protective effect against parkinsonism in a recent NIC-PD randomized control trial.[22]

Psychiatric-related Risk Factors/Prodromal Symptoms

Of the psychiatric symptoms assessed, depression and anxiety have been well studied in prodromal parkinsonism. Studies from primary care/national health insurance database have shown an increase in the risk of future parkinsonism diagnosis among those with anxiety and depression (OR/RR ranging from 1.4-1.8).[23-25] Consistent with results from a systematic review, those with parkinsonism endorsed on average 1 to 2 more depressive/anxiety symptoms than those without parkinsonism.[26] (e-3) In addition to depression and anxiety, post-traumatic stress disorders have been also identified as independent risk/associated factors of REM sleep behavior disorders and parkinsonism.[27, 28] However, post-traumatic stress disorder was not associated with pre-existing parkinsonism or prodromal parkinsonism in our study. (e-1 & 3) Future studies will be needed to confirm the absence of these associations.

Strengths and Limitations

Several limitations should be noted. First, since the diagnoses of RBD and PD were based on questionnaire-guided self-reports, without physician examination or polysomnographic confirmation of RBD. Therefore, some participants may not have received the correct diagnosis. Although this comes from a large population-based study, the sample size for PD and particularly for probable RBD-parkinsonism (n=19) is small, limiting the power to detect the absence of associations. However, this study has several notable strengths including prospective design with standardized testing and complex sampling strategy, which has been shown to produce cohesive results based on the federal reports.[29] Second, to our knowledge, no population-based prior study has assessed the associations between risk factors and different prodromal parkinsonism with and without RBD.

Conclusions

In conclusion, whereas some risk factors were similar between possible RBD and probable RBD who phenoconverted to parkinsonism, daily smoking and heavy drinking were not clearly associated with the probable iRBD-to-parkinsonism group.

References:

1. Yao C, Fereshtehnejad S-M, Keezer MR, Wolfson C, Pelletier A, Postuma RB. Risk factors for possible REM sleep behavior disorder: A CLSA population-based cohort study. Neurology 2019;92:e475.
2. Yao CW, Saha-Chaudhuri P, Zolfaghari S, Pelletier A, Postuma RB. Phenoconversion from Possible REM Sleep Behavior to Parkinsonism in the Population-Based CLSA. Mov Disord 2021.
3. 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.
4. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28:221-229.
5. 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.
6. Ju Y-ES. Rapid eye movement sleep behavior disorder in adults younger than 50 years of age. Sleep Medicine 2013;14:768-774.
7. Haba-Rubio J AD, Bastardot F, Tobback N, Vollenweider P, Tafti M, Heinzer R. STOP-BANG Questionnaire as a Screening Tool for Obstructive Sleep Apnea in the General Population. Sleep: Associated Professional Sleep Societies, 2011: 128.
8. Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. Sleep Med 2008;9:283-289.
9. Stuart E, King G, Imai K, Ho D. MatchIT: Nonparametric Preprocessing for Parametric Causal Inference. Journal of Statistical Software 2011;42.
10. Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, others. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142:744-759.
11. Sasai-Sakuma T, Takeuchi N, Asai Y, Inoue Y, Inoue Y. Prevalence and clinical characteristics of REM sleep behavior disorder in Japanese elderly people. Sleep 2020;43.
12. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, others. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. Sleep 2018;41:zsx197-zsx197.
13. Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernández-Crehuet Navajas R. Smoking and Parkinson's disease: Systematic review of prospective studies. Movement Disorders 2004;19:614-621.
14. Marras C, Canning CG, Goldman SM. Environment, lifestyle, and Parkinson's disease: Implications for prevention in the next decade. Movement Disorders 2019;34:801-811.
15. 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.
16. 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.
17. Ellison Larry FL. Progress in net cancer survival in Canada over 20 years. Health Reports;29:10-18.
18. Gershon AS. Trends in Chronic Obstructive Pulmonary Disease Prevalence, Incidence, and Mortality in Ontario, Canada, 1996 to 2007. Archives of Internal Medicine 2010;170:560.
19. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2015;385:117-171.
20. Mappin-Kasirer B, Pan H, Lewington S, et al. Tobacco smoking and the risk of Parkinson disease. Neurology 2020;94:e2132-e2138.
21. Frauscher B, Gabelia D, Mitterling T, et al. Motor events during healthy sleep: A quantitative polysomnographic study. Sleep 2014;37:763-773.

22. Park J-H, Kim D-H, Park Y-G, et al. Cancer risk in patients with Parkinson's disease in South Korea: A nationwide, population-based cohort study. European Journal of Cancer 2019;117:5-13.
23. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. The Lancet Neurology 2016;15:1257-1272.
24. Oertel W, Müller H, Schade-Brittinger C, Kamp C, Balthasar K, Articus K. The NIC-PD-study –a randomized, placebo-controlled, double-blind, multi-centre trial to assess the disease-modifying potential of transdermal nicotine in early Parkinson's disease in Germany and N. America. Mov Disord 2018;33:S159.
25. Fang X, Han D, Cheng Q, et al. Association of Levels of Physical Activity With Risk of Parkinson Disease. JAMA Network Open 2018;1:e182421.
26. Gustafsson H, Nordstrom A, Nordstrom P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. Neurology 2015;84:2422-2429.
27. Fereshtehnejad S-M, Yao C, Pelletier A, Montplaisir JY, Gagnon J-F, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain 2019;142:2051-2067.
28. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. The Lancet Neurology 2015;14:57-64.
29. Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. Movement Disorders 2008;23:183-189.
30. Chan YLE, Bai YM, Hsu JW, et al. Post-traumatic Stress Disorder and Risk of Parkinson Disease: A Nationwide Longitudinal Study. American Journal of Geriatric Psychiatry 2017;25:917-923.
31. Elliott JE, Opel RA, Pleshakov D, et al. Posttraumatic stress disorder increases the odds of REM sleep behavior disorder and other parasomnias in Veterans with and without comorbid traumatic brain injury. Sleep 2020;43.
32. 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;39:121-132.
33. Zhou J, Zhang J, Du L, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case–control study. Sleep Med 2014;15:654-660.
34. Wolfson C, Raina PS, Kirkland SA, et al. The Canadian community health survey as a potential recruitment vehicle for the Canadian longitudinal study on aging. Can J Aging 2009;28:243-249.
35. Schenck CH, Howell MJ. Parasomnia Overlap Disorder: RBD and NREM Parasomnias. Rapid-Eye-Movement Sleep Behavior Disorder 2019:359-369.
36. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000;123:331-339.
37. Lin FC, Lai CL, Huang P, Liu CK, Hsu CY. The rapid-eye-movement sleep behavior disorder in Chinese-Taiwanese patients: Regular article. Psychiatry and Clinical Neurosciences 2009;63:557-562.
38. Ohayon MM, Guilleminault C, Priest RG. Night Terrors, Sleepwalking, and Confusional Arousals in the General Population. The Journal of Clinical Psychiatry 1999;60:268-276.
39. Hublin C, Kaprio J, Partinen M, Heikkila K, Koskenvuo M. Prevalence and Genetics of Sleepwalking: A Population-based Twin Study. Neurology 1997;48:177-181.
40. Jung YJ, Oh E. Is REM sleep behavior disorder a friend or foe of obstructive sleep apnea? Clinical and etiological implications for neurodegeneration. J Clin Sleep Med 2021.
41. Iwaki H, Hughes KC, Gao X, Schwarzschild MA, Ascherio A. The association between restless legs syndrome and premotor symptoms of Parkinson's disease. Journal of the Neurological Sciences 2018;394:41-44.
42. Qu Y, Zhang L, Shen D, Zhang W, Zhang M, Pan Y. Probable RBD Associates with the Development of RLS in Parkinson's Disease: A Cross-Sectional Study. Behavioural Neurology 2019;2019.

43. Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X. Restless Legs Syndrome: An Early Clinical Feature of Parkinson Disease in Men. Sleep 2014;37:369-372.
44. Szatmari S, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. Association of Restless Legs Syndrome With Incident Parkinson's Disease. Sleep 2017;40.
45. Gjerstad MD, Tysnes OB, Larsen JP. Increased risk of leg motor restlessness but not RLS in early Parkinson disease. Neurology 2011;77:1941-1946.
46. Angelini M, et al. A study of the prevalence of restless legs syndrome in previously untreated Parkinson's disease patients: Absence of co-morbid association. Journal of the Neurological Sciences 2011;310:286.
47. Adler CH, Hentz JG, Shill HA, et al. Probable RBD is increased in Parkinson's disease but not in essential tremor or restless legs syndrome. Parkinsonism & Related Disorders 2011;17:456-458.
48. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2016;46:292-300.
49. Canada TPHAo. Parkinsonism in Canada, including Parkinson's Disease. In: Minister of Health C, ed. Canada2018.
50. Raina P, Wolfson C, Kirkland S, et al. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). International Journal of Epidemiology 2019;48:1752-1753j.

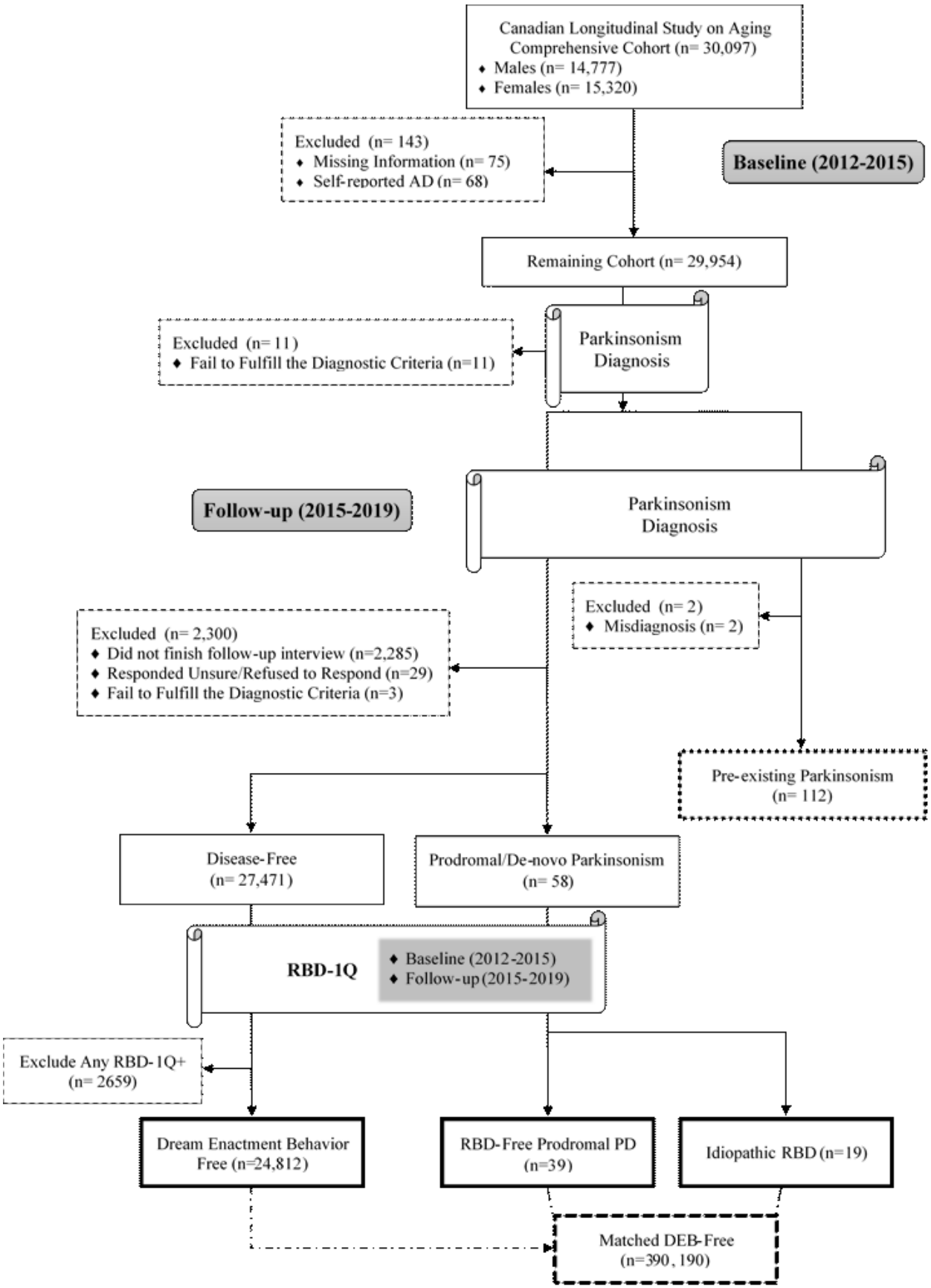


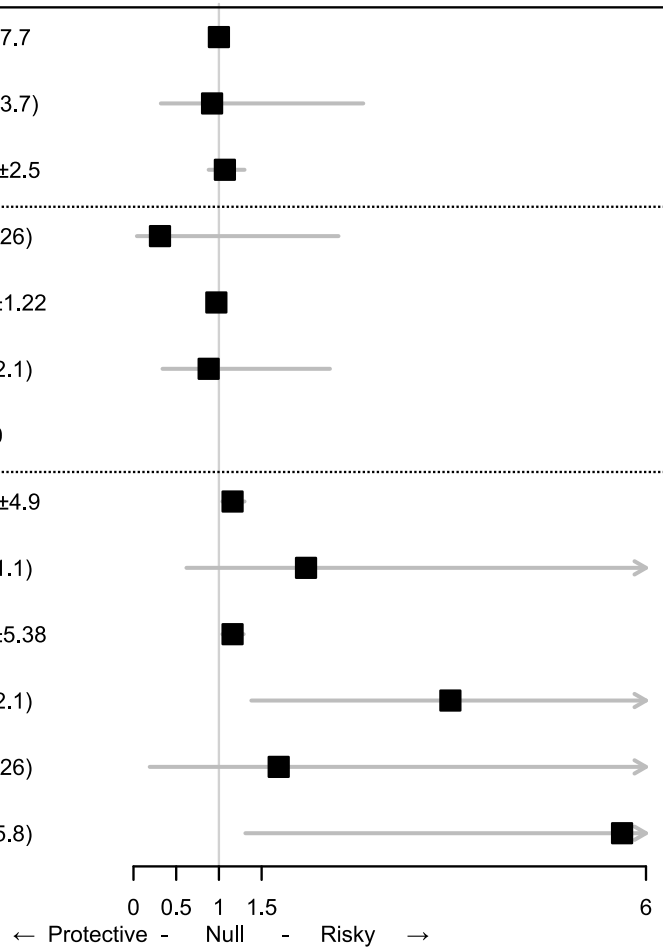
Figure 1. Flow Chart

Participants with prodromal parkinsonism were categorized into iRBD and RBD-free prodromal parkinsonism based on RBD-1Q screen results at both baseline and the follow-up.

Table 1 Risk Factors associated with probable iREM Sleep Behavior Disorder and RBD-Free Prodromal Parkinsonism

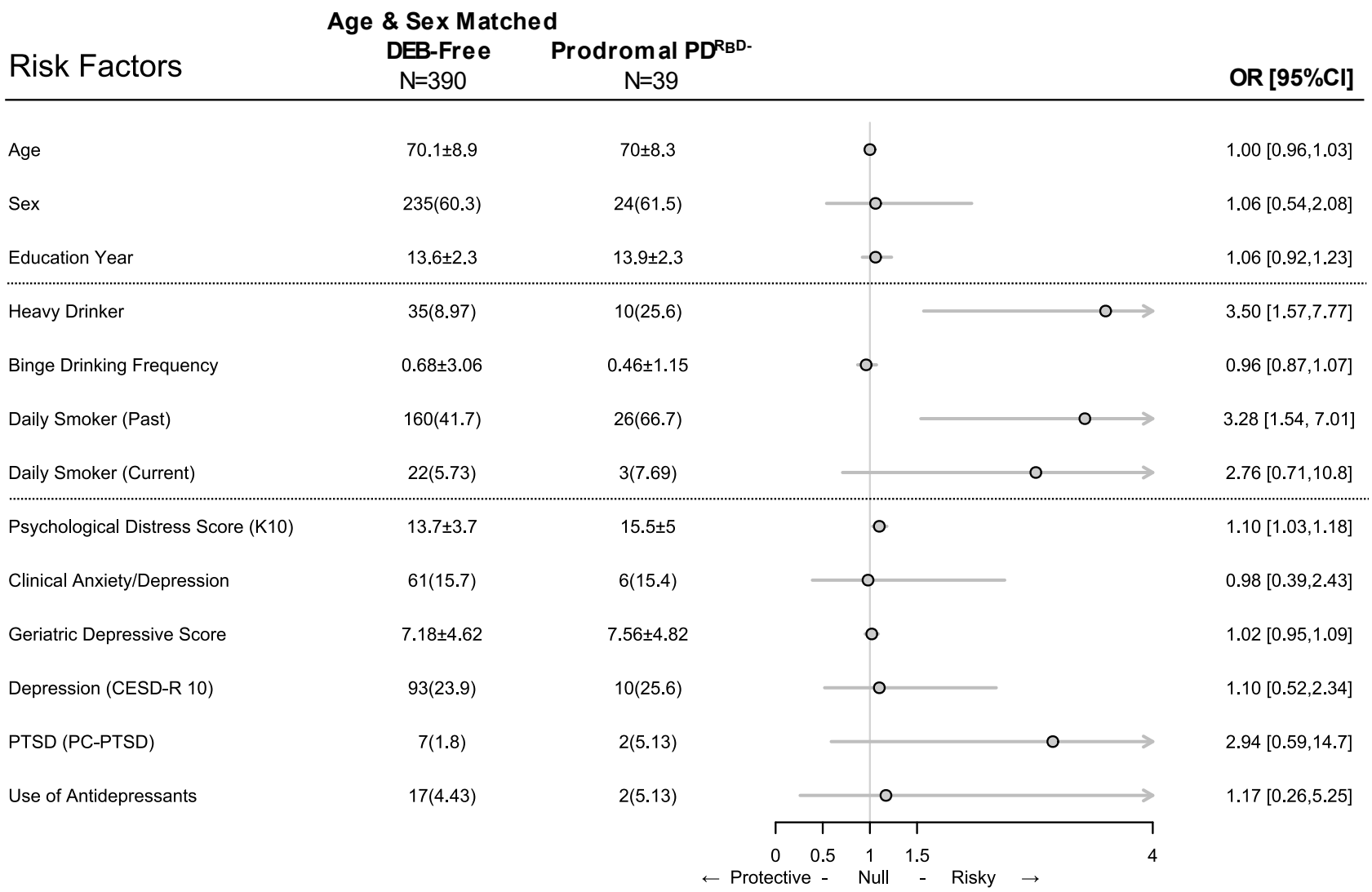
A

Risk Factors	Age & Sex Matched DEB-Free N=190	iRBD N=19	OR [95%CI]
Age	68.8±9.2	69±7.7	1.00 [0.96,1.05]
Sex	143(75.3)	14(73.7)	0.92 [0.32,2.69]
Education Year	13.5±2.5	13.9±2.5	1.07 [0.88,1.30]
Heavy Drinker	29(15.3)	1(5.26)	0.31 [0.04,2.40]
Binge Drinking Frequency	1.14±4.82	0.68±1.22	0.97 [0.90,1.04]
Daily Smoker (Past)	80(42.1)	8(42.1)	0.88 [0.34,2.30]
Daily Smoker (Current)	13(6.84)	0	-
Psychological Distress Score (K10)	13.1±3.3	15.5±4.9	1.16 [1.04,1.30]
Clinical Anxiety/Depression	22(11.6)	4(21.1)	2.02 [0.62,6.65]
Geriatric Depressive Score	6.09±3.58	8.74±5.38	1.16 [1.04,1.29]
Depression (CESD-R 10)	31(16.4)	8(42.1)	3.71 [1.38,9.96]
PTSD (PC-PTSD)	6(3.16)	1(5.26)	1.70 [0.19,15]
Use of Antidepressants	6(3.18)	3(15.8)	5.72 [1.31,25.1]



A) 190 participants without dream enactment behavior during the entire follow-up period (i.e., 2012-2019) were matched to those with iRBD based on age, sex and follow-up status and interval, using the greedy match algorithm, at the ratio of 1 to 10. Risk factors were identified based on the previously found associated factors reported in 2018. Odds ratios were assessed using logistic regression.

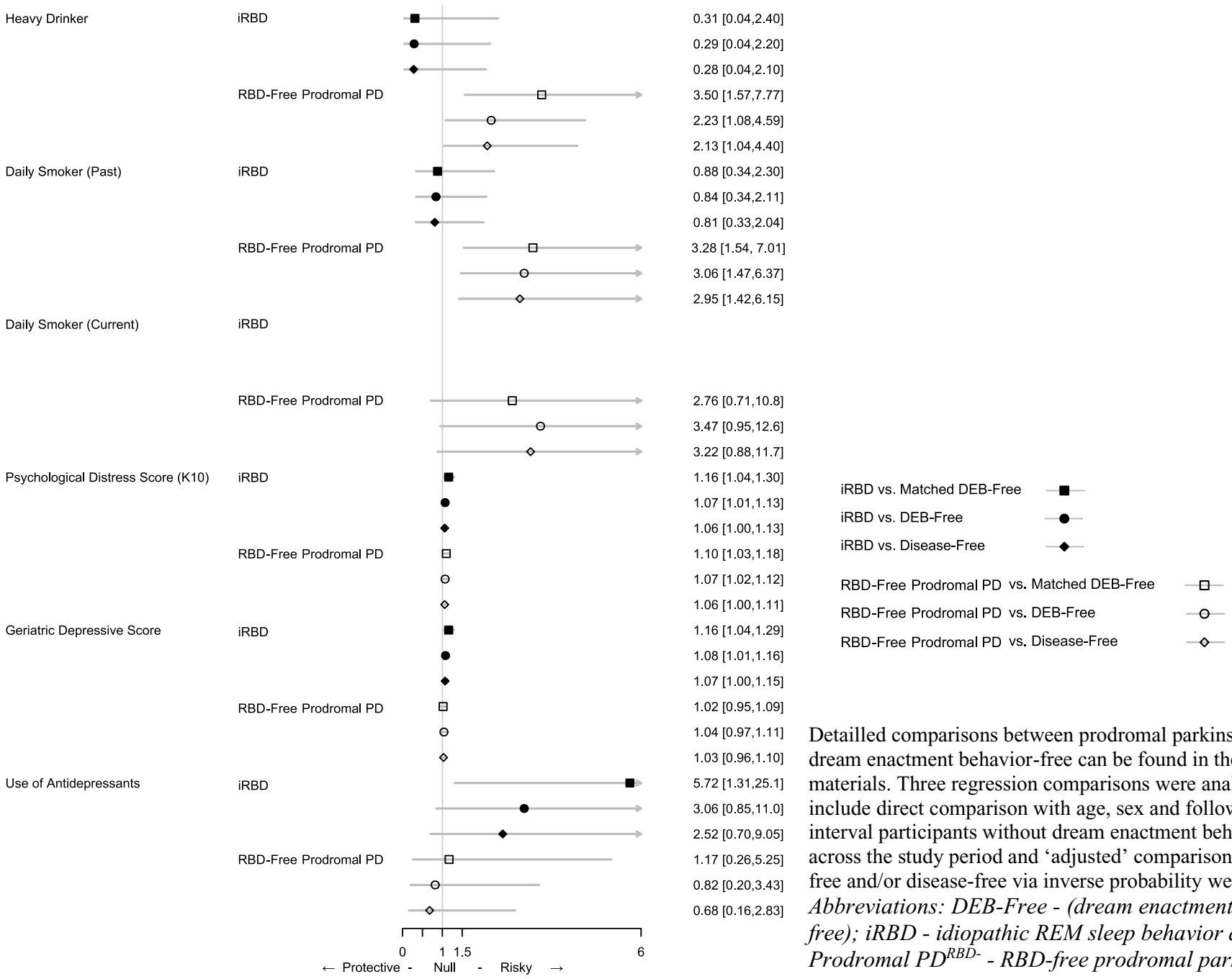
B



B) 390 participants without dream enactment behavior during the entire follow-up period (i.e., 2012-2019) were matched to those with RBD-free prodromal parkinsonism based on age, sex and follow-up status and interval, using the greedy match algorithm, at the ratio of 1 to 10. The associations between RBD-free prodromal parkinsonism and sleep symptoms/disorders were assessed using logistic regression.

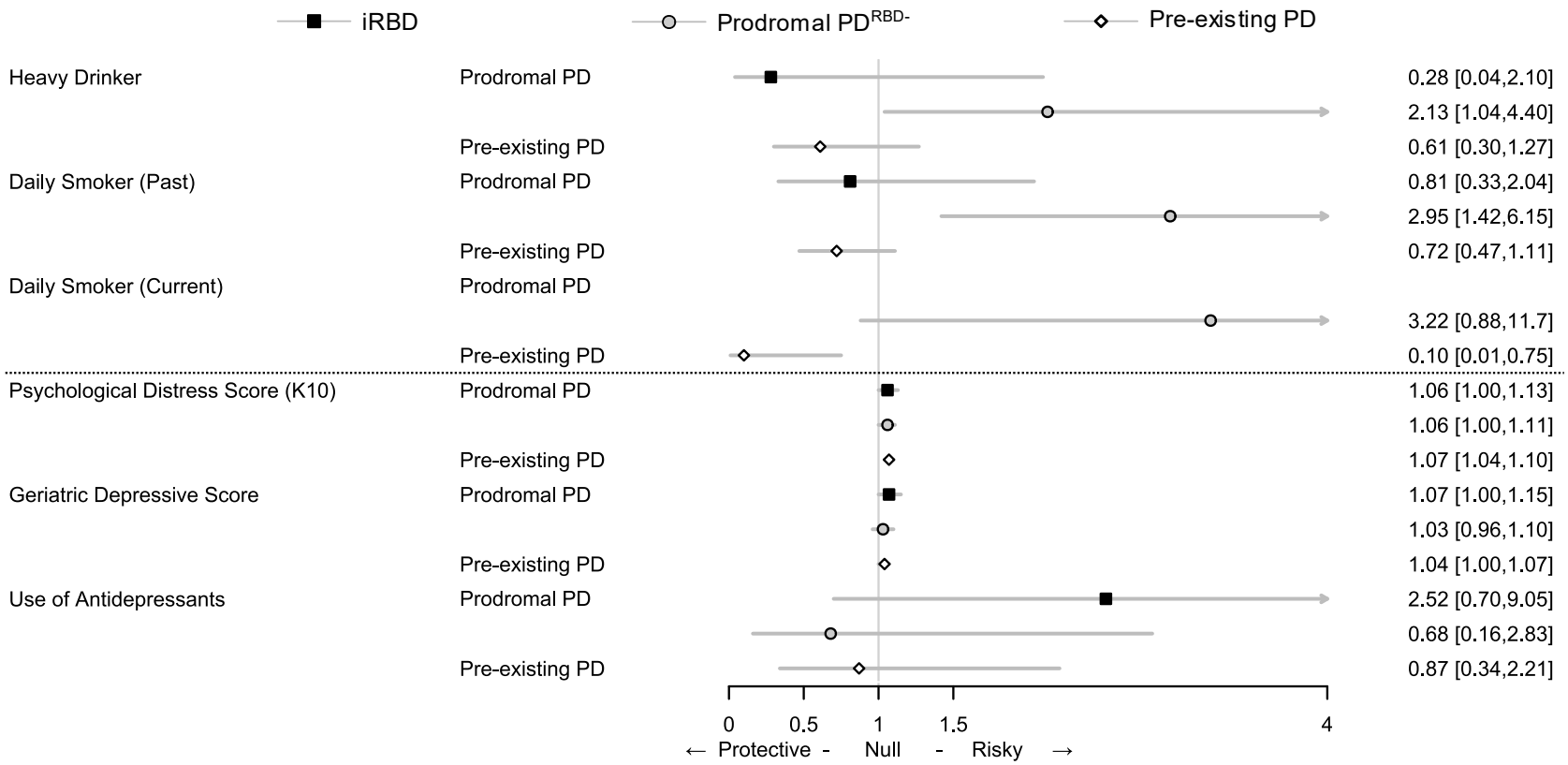
Abbreviations: DEB-Free - symptom-free (dream enactment behavior-free); iRBD - idiopathic REM sleep behavior disorder; Prodromal PD^{RBD-} - RBD-free prodromal parkinsonism

Figure 2. Summary Comparisons between Prodromal Parkinsonism and Parkinsonism-associated Risk Factors/Sleep Symptoms



Detailled comparisons between prodromal parkinsonism and dream enactment behavior-free can be found in the supplementary materials. Three regression comparisons were analyzed, these include direct comparison with age, sex and follow-up status and interval participants without dream enactment behavior (DEB) across the study period and 'adjusted' comparison with all DEB-free and/or disease-free via inverse probability weighting (IPW). *Abbreviations: DEB-Free - (dream enactment behavior-free); iRBD - idiopathic REM sleep behavior disorder; Prodromal PD^{RBD-} - RBD-free prodromal parkinsonism*

Figure 3. Summary Comparisons of Risk Factor Profiles between Prodromal Parkinsonism and Parkinsonism



Detail comparisons between prodromal parkinsonism and dream enactment behavior-free can be found in the supplementary materials. *Abbreviation: iRBD - idiopathic REM sleep behavior disorder; Prodromal PD^{RBD-} - RBD-free prodromal parkinsonism*

Supplementary Material

e-Methods

Pulmonary Diseases and Cancer

To assesses if the positive associations between smoking/drinking and RBD-free prodromal parkinsonism were due to false self-report, several health conditions commonly associated with drinking and smoking were elected for sensitivity analysis. These include:

1. Pulmonary Diseases/Conditions: flu (past year), pneumonia (past year), chronic obstructive pulmonary disease, asthma
2. Cancer: any positive diagnosis of cancer.

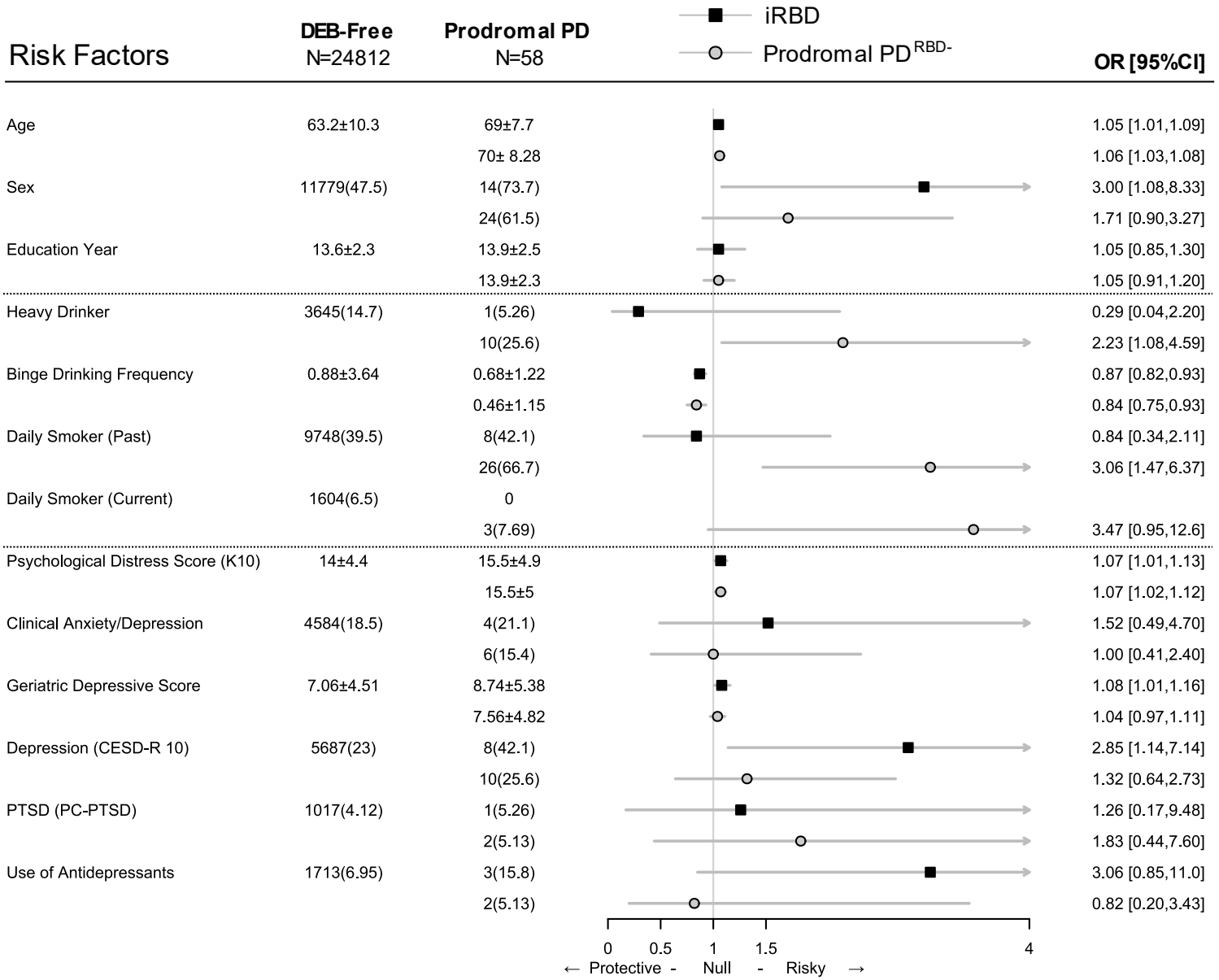
Statistical Analysis:

We estimated associations between the elected risk factors and the prodromal parkinsonism subtypes, via logistic regression weighted for age, sex, time interval and follow-up status to account for selection bias.[1] 95% confidence intervals were estimated via White's variance.[2]

e-References

1. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168(6):656-664.
2. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica 1980;48(4):817-838.

Table e-1 Associated Sleep Symptoms/Disorders with idiopathic REM Sleep Behavior Disorder and with RBD-Free Prodromal Parkinsonism



The associations between prodromal parkinsonism and risk factors were assessed using logistic regression 'adjusting' for age, sex, follow-up status and interval via inverse probability weighting. *Abbreviations: DEB-Free - (dream enactment behavior-free); iRBD - idiopathic REM sleep behavior disorder; Prodromal PD^{RBD-} - RBD-free prodromal parkinsonism*

Table e-2 Risk Factor Profile among Prodromal Parkinsonism in comparison to Pre-existing Parkinsonism

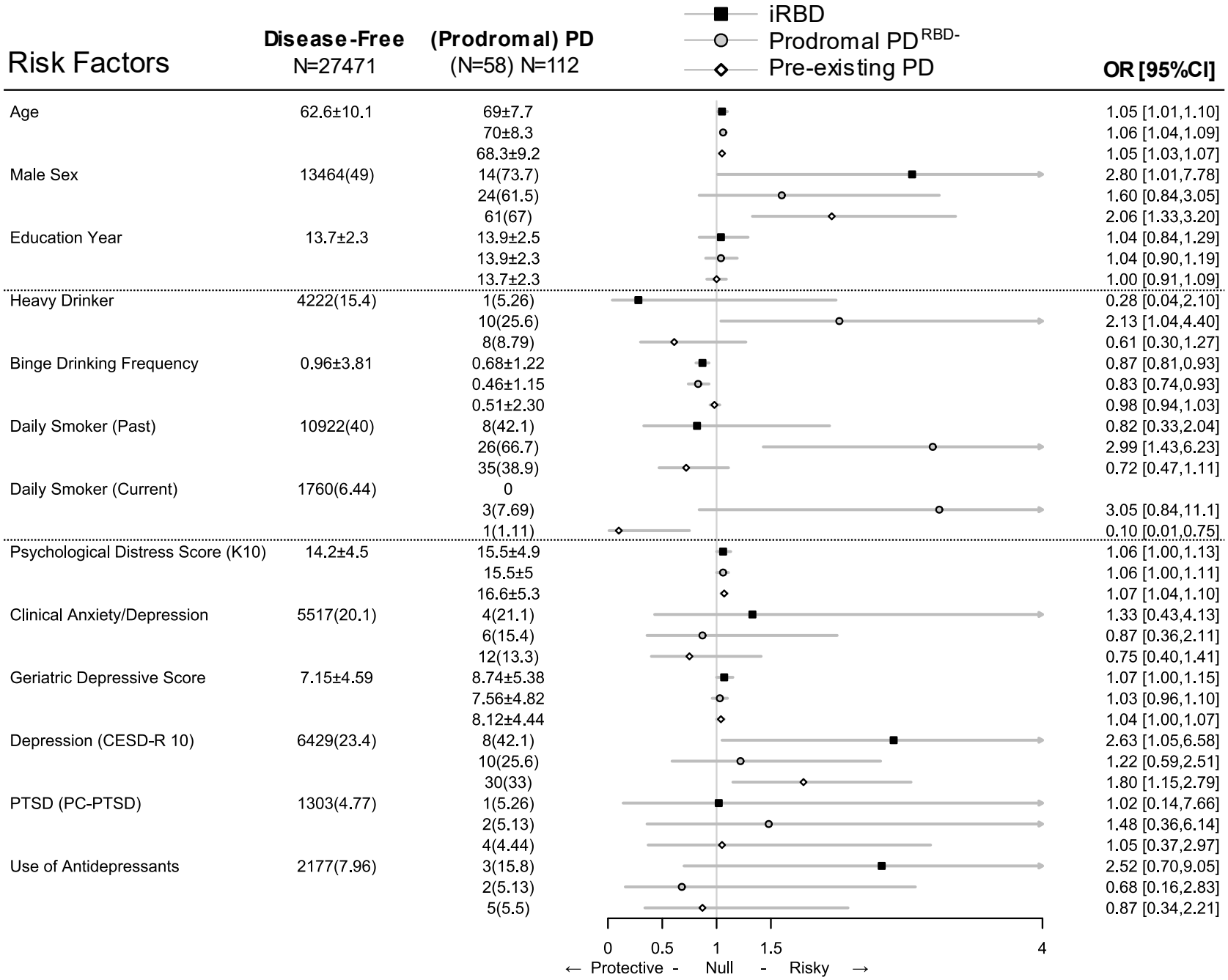
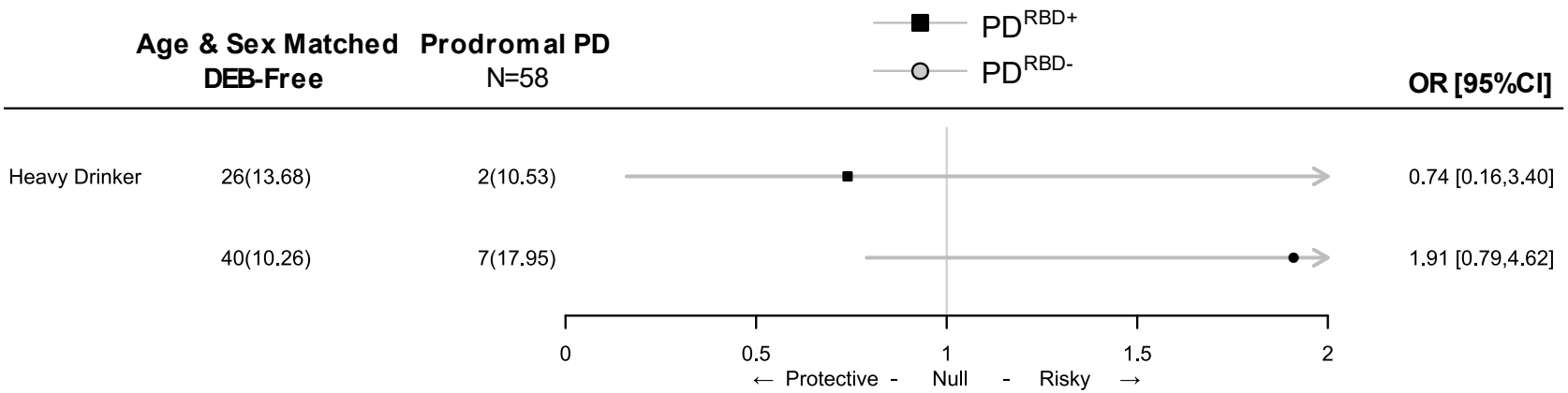


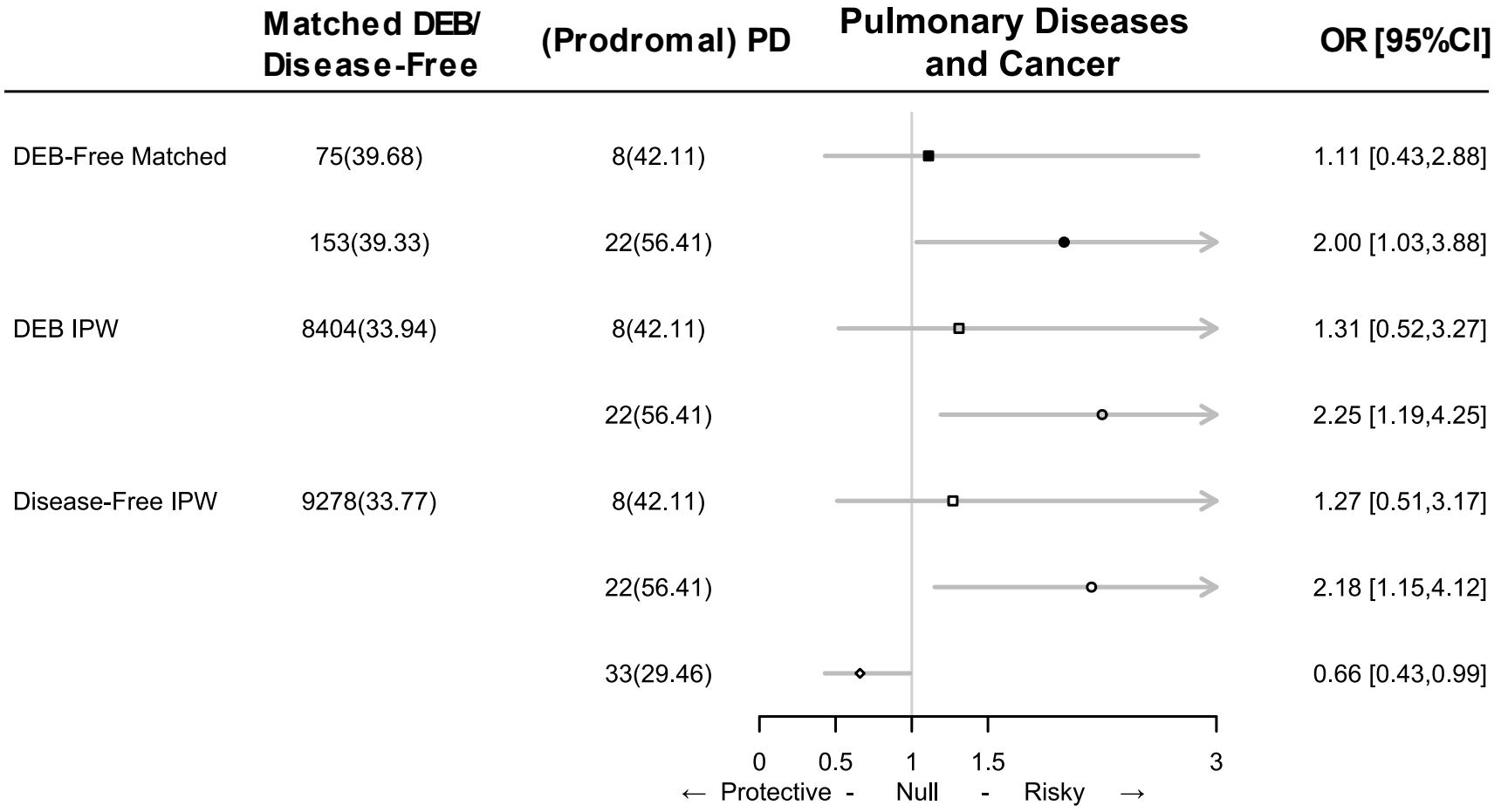
Table e-3. Associations with Drinking upon Phenoconversion



The associations with heavy drinking were reassessed at the follow-up (mean interval ~ 3 years) among de-novo parkinsonism (with/without RBD). Participants without dream enactment behavior during the entire follow-up period (i.e., 2012-2019) were matched to those with de-novo parkinsonism (with/without RBD) based on age, sex and follow-up status and interval, using the greedy match algorithm, at the ratio of 1 to 10. The associations between de-novo parkinsonism and heavy drinking were assessed using logistic regression.

Abbreviations: DEB-Free - symptom-free (dream enactment behavior-free); PD^{RBD+}- parkinsonism with RBD; PD^{RBD-} - RBD-free parkinsonism

Table e-4. Associations with Pulmonary Diseases and Cancer



Participants without dream enactment behavior during the entire follow-up period (i.e., 2012-2019) were matched to those with de-novo parkinsonism (with/without RBD) based on age, sex and follow-up status and interval, using the greedy match algorithm, at the ratio of 1 to 10. A list of pulmonary diseases/events and cancer were summarized into a single binary variable. These include having flu/pneumonia within the last 12 months, asthma, chronic obstructive pulmonary disease, and cancer. The associations between (prodromal) parkinsonism and the summary of pulmonary diseases/cancer were assessed using logistic regression.

Abbreviations: DEB-Free - symptom-free (dream enactment behavior-free); Disease-Free – free of parkinsonism

Chapter II - Longstanding disease-free survival in idiopathic REM sleep behavior disorder

- Is neurodegeneration inevitable?

Published as: **Yao C**, Fereshtehnejad SM, Dawson BK, et al. "Longstanding disease-free survival in idiopathic REM sleep behavior disorder: Is neurodegeneration inevitable?" Parkinsonism Relat Disord. Sep 2018;54:99-102. doi:10.1016/j.parkreldis.2018.04.010

Introduction

Idiopathic (or cryptogenic) REM sleep behavior disorder (iRBD) is the most powerful predictor of neurodegenerative synucleinopathies, with ≥80% converting to disease. We know little about the minority of iRBD patients who remain disease-free for many years. In particular, are all destined to develop disease, or do some have non-synucleinopathy causes? [1-3] Systematically evaluating long survivors provides a chance to determine whether a '*benign*' subtype of RBD exists.

Recently, Iranzo reported that Parkinson's disease (PD) prodromal markers are prevalent in iRBD patients followed >10-years[4], suggesting that neurodegeneration is almost inevitable.[4] This important result requires confirmation and further comparison with other RBD patients. In this study, we: 1) characterized longstanding iRBD subjects in our cohort; 2) compared prodromal symptom occurrence in these patients compared to controls, and to the baseline values of those with malignant course who phenoconverted quickly ('*early-converters*'); and 3) compared progression speed of prodromal features.

Methods

Study Participants

This study was based on data prospectively collected between 2004 and 2017 from an iRBD cohort. The project was approved by the local institutional review board and participants provided written consent.

All iRBD patients were diagnosed on polysomnography according to standard International Classification of Sleep Disorders-III criteria. Patients had a comprehensive annual examination, as previously described[5, 6], with the following markers assessed each visit:

- Motor function: UPDRS-Part III, Alternate Tap Test (hand motor speed). Purdue Pegboard Test (dexterity, coordination)
- Color vision: Farnsworth-Munsell 100 Hue test
- Olfaction: Cross-cultural 12-item University of Pennsylvania Smell Identification Test (UPSIT-12)
- Cognition: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA)
- Autonomic dysfunction: Unified Multiple System Atrophy Rating Scale. Cut-offs=≥2 for orthostatic hypotension, constipation, and urinary dysfunction, and ≥3 for erectile dysfunction. Blood pressure was measured supine and standing for 1 minute.
- Glucocerebrosidase (GBA) mutation status.[7]

Values were compared to age- and sex-matched controls (n=68) and 27 iRBD patients from the same cohort who phenoconverted rapidly within 4 years of diagnosis (11 developed parkinsonism first and 16 developed dementia first). [1, 5]

Prodromal Risk Assessment

In order to summarize evolution of all markers over time, the prodromal probability (i.e. % likelihood of having prodromal PD) was calculated annually, according to the MDS research criteria[8] (recently validated in iRBD[9]) To better illustrate annual change, we omitted the likelihood ratio for RBD itself (to avoid ceiling effects).

Statistical Analysis

For between-group comparisons, either independent *t*-test or Fisher's exact was used. Annual rate of progression of prodromal PD probability was compared between the two cohorts using Mann-Whitney U-test. Analyses were performed with IBM SPSS Statistics for Macintosh software (version 20.0).

Results

Of 168 patients, 56 had >10 years of potential follow-up (i.e. polysomnogram before September 2007). Of these, 8 were lost to follow-up (4 lost contact, 4 died without neurodegenerative disease), 1 had 10-year follow-up still pending (deferred at patient request), and 36 developed defined neurodegenerative disease. Therefore, 11 (8 males, 3 females) had not phenoconverted by last follow-up visit (**Supplementary 1**). Diagnosed RBD duration at last visit (from initial polysomnogram) was 16.2±4.6 years (range=11-23).

At last visit, 9/11 subjects had hyposmia, 6 had impaired color vision, and 5 had moderate-severe constipation. UPDRS part-III ranged from 1-11 (7 patients scored >3). Regarding cognition, 5 scored <26 on their last MoCA and had mild cognitive symptoms, suggesting mild cognitive impairment. Except for color vision, alternate tap test, and orthostatic blood pressure drop, all prodromal markers were significantly worse than controls (**Table 1**). Overall, 9/11 met criteria for prodromal PD, and 8/9 had a prodromal probability of >95%.

Since we followed all patients annually, we were able to track change with time (**Figure 1**). As measured by MDS prodromal probability, the longstanding iRBD group demonstrated clear progression over the 10 years. Their average post-test probability of prodromal PD at year 11 was similar to the early-convertors after 1-year follow-up (**Figure 1**). However, there was a significant difference in progression speed; the annual increase in prodromal PD probability was 3.9±3.2% in longstanding iRBD (3.9±3.2%) compared to 12.4±7.8% for early-convertors (*Mann-Whitney p*-value=0.002).

Finally, we compared the last visit of longstanding iRBD patients to the *initial baseline* values of 27 early convertors (conversion within 4 years). Duration of dream enactment symptoms was not significantly different between the two RBD cohorts at the

initial visit (12.5±8.4 vs. 8.1±10.0 years, p=0.231). Most prodromal measures were similar, including age, sex, total UPDRS (14.5±5.7 vs. 13.7±6.2), UPDRS part-II (4.0±3.0 vs. 3.0±2.2), quantitative motor tests (Purdue Pegboard = 9.7±2.0 vs. 10.0±1.7), cognition (MMSE=27.8±1.5 vs. 27.2±2.1) and all autonomic symptoms and signs. Only olfaction (UPSIT=85.0±21.1% vs. 58.0±26.6% of normal values, p=0.003) and baseline tonic REM (40.1±23.5% vs. 59.2±26.2%, p=0.045) was worse in early convertors. 0/10 longstanding iRBD patients were GBA mutation carriers, whereas 20% (3/15) of early convertors had GBA mutations.

Discussion

Whereas studies estimate that 80% of iRBD patients in sleep clinics eventually develop neurodegeneration, there are nonetheless long disease-free survivors. It is unclear whether they: 1) have a *'non-synucleinopathy*' subtype (and so should remain free of evident neurodegeneration), 2) have simply presented to medical attention earlier (so will progress at similar rates and convert at similar age/RBD symptom duration), or 3) have neurodegenerative synucleinopathy but with a slower-progressing subtype. We found that the large majority of long survivors have features of neurodegeneration, progress over time, and eventually meet criteria for prodromal PD, suggesting that *'synucleinopathy-free*' cases are rare. However, we found clear variability in progression speed, suggesting that subtypes with slower progression may exist, perhaps related to age, environment, or genetic factors.

Our findings echo several reports. There have been reports of disease converters with very longstanding history of iRBD.[10, 11] Although these cannot be considered definitive (mainly because one cannot prove that early symptoms were due to RBD), these studies suggest potential for very long prodromal periods. Recently *Iranzo et al* demonstrated that long survivors have objective smell loss, constipation, and mild parkinsonian signs, compared to age-matched controls.[4] Most patients also had abnormal DAT-SPECT imaging.[4] So, our results are supportive of these findings . We were now were able to add a systematic analysis of progression, and a direct comparison to those with a more malignant course.

We have previously shown that severity of REM atonia loss, advanced age, olfactory loss, abnormal color vision, and subtle motor dysfunction are risk factors for earlier phenoconversion in iRBD.[2, 12] Of note, longstanding disease-free survivors at final visit were similar on these measures to early convertors at baseline (with hyposmia as a notable exception). At baseline, however, the longstanding iRBD cohort were younger, had much fewer prodromal markers, and lower tonic REM. Moreover, it was clear that their overall

progression was slower (with a generally linear slope of prodromal probability), despite a similar baseline duration of RBD symptoms. Interestingly, though sample size was too small for statistical comparisons, none of the longstanding iRBD cohort had *GBA* mutations, which are associated with the both RBD prevalence and neurodegenerative outcomes.[7]

Strengths and Limitations

Some limitations should be noted. Of course, we cannot determine when long-standing iRBD patients might develop disease. In particular, given the similar age between last visit of longstanding iRBD and first visit of early convertors, we cannot determine whether there may be a future exponential progression in long-standing iRBD patients, as age-related compensatory mechanisms decline. Second, note that our cohort consists predominantly of older patients (generally >50), who had no other clear explanation for symptoms (e.g. stroke), and few with post-traumatic stress disorder (e.g. there are relatively few recent war veterans in Canada). Therefore, we cannot address whether there may exist a different subtype of young-onset RBD related to mental illness, autoimmunity, or other unrecognized factors.[2]

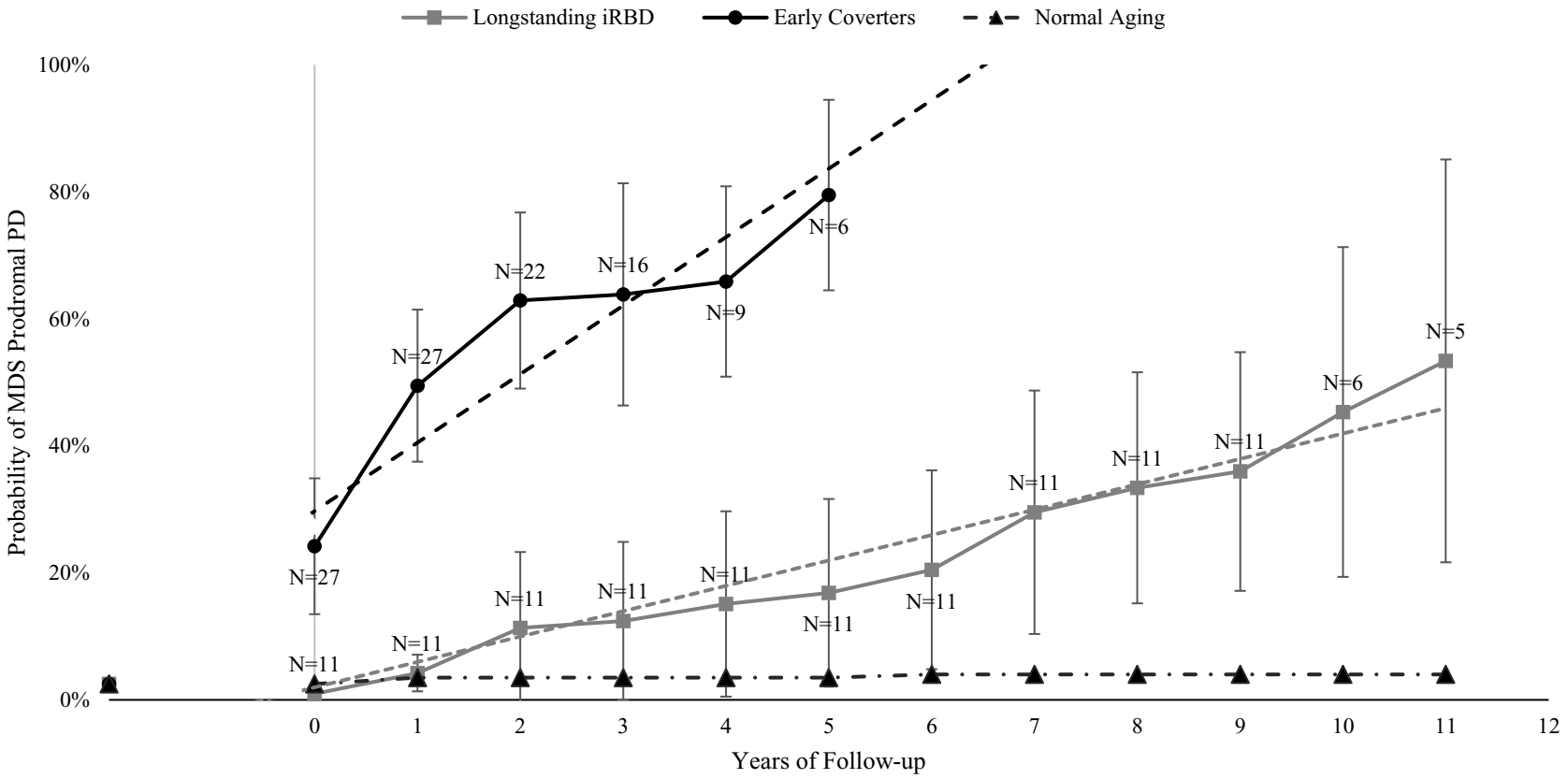
Conclusions

In conclusion, our study provides evidence that almost older iRBD patients with polysomnographic-proven iRBD exhibit neurodegeneration, similar in clinical characteristics to other RBD patients, yet differing in progression rate. The large prodromal window of iRBD provides a golden opportunity for neuroprotective trials; further studies are warranted to define potential iRBD subtypes and explore mechanisms for variable progression rates.

References

1. 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.
2. Postuma RB, Gagnon JF, Bertrand JA, Genier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015;84:1104-1113.
3. Al-Qassabi A, Fereshtehnejad SM, Postuma RB. Sleep Disturbances in the Prodromal Stage of Parkinson Disease. Curr Treat Options Neurol 2017;19:22.
4. Iranzo A, Stefani A, Serradell M, et al. Characterization of patients with longstanding idiopathic REM sleep behavior disorder. Neurology 2017;89:242-248.
5. Postuma RB, Gagnon JF, Pelletier A, Montplaisir J. Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. Mov Disord 2013;28:597-604.
6. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Mov Disord 2009;24:2225-2232.
7. Gan-Or Z, Mirelman A, Postuma RB, et al. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol 2015;2:941-945.
8. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30:1600-1611.
9. 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;32:865-873.
10. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology 2010;75:494-499.
11. Boeve BF, Silber MH, Ferman TJ, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14:754-762.
12. Postuma RB, Gagnon JF, Rompre S, Montplaisir JY. Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 2010;74:239-244.

Figure 1. MDS Prodromal PD % Probability Over Time among Longstanding iRBD Subjects and Early Converters



The figure illustrates the mean % probability of MDS prodromal PD, calculated according to Berg, D. et. al. 2015 (for each patient, an individualized calculation sums numerous risk and prodromal markers to calculate the % probability that this individual has prodromal PD at each time point). Note that for illustration purposes, RBD was removed from the calculations (to prevent ceiling effects).[7] The baseline probability (i.e. normal aging) was calculated with only age and sex. For early convertors, the horizontal axis represents the number of years of clinical visit before subjects converted into PD; for non-convertors, change from baseline is shown. Data were presented as mean±SEM. ** $p<0.01$ indicates statistical differences of slopes between early converters and longstanding iRBD subjects.

Table 1. Descriptive Characteristics for Control, Longstanding iRBD and Early Converters cohorts (N=106)

Characteristic	**Control** (n=68)	**Long-standing iRBD** (n=11), Baseline year	**Long-Standing iRBD** *(*n=11*)*, Final year	**Early Converters** (n=27) Baseline year	**Early Converters** (n=27), Final Year (i.e. Disease Onset)	**Control vs. Final Year Long-standing iRBD** p Value	**First Year Early Converter vs. Final Year Long-standing iRBD** p Value
Age (Years)	67.5±8.4	63.8±7.6	72.6±8.0	72.0±7.9	74.1±7.9	0.072	0.836
Male Sex (%)	47 (69.1%)	8 (72.7%)	8 (72.7%)	21 (77.8%)	21 (77.8%)	0.809	0.740
Family History of Movement Disorder/Dementia	9 (21.4%)	0 (0%)	-	5 (18.5%)	-	0.178	0.295
Duration of Follow-Up (Years)	-	-	11.1±1.4	-	4.1±1.7		
Dream Enactment Symptom Duration	-	12.5±8.4	25.8±9.9	8.1±10.0	11.1±10.4		
PSG-Proven RBD Duration	-	-	16.2±4.6	-	3.1±1.7		
Tonic REM %	-	40.1±23.5	-	59.2±26.2	-		
Phasic REM %	-	33.4±15.3	-	33.6±17.8	-		
GBA Mutation		0/10 (0%)		3/15 (20%)			
UPDRS-Total Score	3.0±2.5	5.5±4.5	14.5±5.7	13.7±6.2	28.8±18.6	<0.001	0.717
Motor Symptoms and Signs							
UPDRS-Part II	0.4±0.7	1.2±1.6	4.0±3.0	3.0±2.2	6.9±6.8	0.002	0.330
UPDRS -Part III	2.5±2.2	3.2±3.2	7.2±3.4	8.7±4.6	17.9±11.4	0.003	0.291
UPDRS -Part III ≥ 3	20/68 (29.4%)	3/10 (30.0%)	7/10 (70.0%)	27/27 (100%)	27/27 (100%)		
Alternate Tap Test, Average both Hands	194.8±27.5	196.8±37.3	176.0±34.0	152.6±29.0	126.8±40.2	0.145	0.090
Purdue Pegboard Test, Average 30s	12.0±2.0	11.2±1.5	9.7±2.0	10.0±1.7	8.6±2.6	0.010	0.748
Non-Motor Symptoms and Signs							
UPDRS-Part I	0.2±0.5	1.1±1.5	2.0±2.2	2.0±1.8	3.9±2.7	0.018	0.912

FM100 Total, % Normal	106.6±58.0	99.0±54.1	116.5±38.3	159.6±84.2	164.0±86.5%	0.514	0.480
Abnormal Colour Vision ≥ 1.25	22/61 (36.1%)	4/11 (36.4%)	6/9 (66.7%)	15/26 (57.7%)	19/26 (73.1%)		
MMSE	-	28.3±1.3	27.8±1.5	27.2±2.1	25.6±3.5		0.380
Drop in Systolic Blood Pressure (mmHg)	2.7±7.6	3.2±8.4	10.8±18.3	18.0±15.2	20.4±10.8	0.229	0.310
Drop in Systolic Blood Pressure > 20mmHg	1/51 (2.0%)	0/10 (0%)	5/9 (55.6%)	13/27 (48.1%)	13/27 (48.1%)	<0.001	0.700
UPSIT, % Normal	102.9±15.5	80.2±21.9	85.0±21.1	58.0±26.6	45.4±17.0	0.020	0.003
Hyposmia UPSIT % Normal ≤ 80%	3/65 (4.6%)	6/11 (54.5%)	4/11 (36.4%)	19/27 (70.4%)	27/27 (100%)		
Orthostatic UMSARS ≥ 2	1/63 (1.6%)	0/11 (0%)	2/11 (18.2%)	1/26 (3.8%)	3/26 (11.5%)	0.010	0.144
Constipation UMSARS ≥ 2	2/63 (3.1%)	1/11 (9.1%)	4/10 (40.0%)	7/26 (26.9%)	7/27 (25.9%)	<0.001	0.446
Urinary Dysfunction UMSARS ≥ 2	2/64 (3.1%)	0/11 (0%)	1/10 (10.0%)	5/25 (20%)	5/27 (18.5%)	0.013	0.478
Impotence UMSARS ≥ 3	1/49 (2.0%)	1/8 (12.5%)	5/8 (62.5%)	9/20 (45%)	14/21 (66.7%)	<0.001	0.403

*Abbreviation: REM Sleep Behaviour Disorder (RBD), Orthostatic Hypotension (OH), University of Pennsylvania Smell Identification Test (UPSIT), Farnsworth-Munsell 100 Hue Test (FM100), Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA), Mini–Mental State Examination (MMSE), Parkinson's Disease (PD)

Supplementary 1. Prodromal Markers of Longstanding iRBD Subjects on the Last Visit. Ages are rounded to deciles to preserve confidentiality.

	1 [a]	***2***	***3*** [a]	***4*** [a]	***5*** [a]	***6*** [a]	***7*** [a]	***8*** [a]	***9*** [a]	***10***	***11*** [a]
Age	70-9	50-9	80-9	60-9	70-9	70-9	70-9	60-9	70-9	80-9	70-9
Sex	M	M	M	M	F	M	M	F	M	F	M
Years of RBD	23	22	21	15	14	12	13	14	11	21	12
Smoker	Former	Former	Former	N	Former	N	Former	Former	Former	N	Y
Constipation	N	N	Y	N	N	N	Y	Y	Y	N	N
Laxative Use	N	N	Y	N	N	Y	Y	Y	Y	N	N
Urinary Symptoms	N	N	N	N	N	Y	N	N	N	N	N
Impotence	N/A	N/A	Y	Y		Y	Y		Y		Y
OH	N	N	Y	N	Y	Y	N	Y	Y	N/A	N
UPSIT % Normal	0.76	0.46	0.96	1.16	0.99	0.87	0.75	0.96	0.54	1.06	0.85
FM100 % Normal	1.61	1.68	1.51	0.93	1.37	0.81	1.36	0.7	1.52	0.96	0.66
Antidepressant	N	N	N	Y	Y	Y	N	Y	Y	N	Y
Depression	N	N	N	Y	Y	N	N	Y	N	N	N
UPDRS 2	4	0	5	2	6	3	1	3	3	1	0
UPDRS 3	10	2	11	10	8	1	10	3	6	2	6
MoCA	26	N/A	28	25	27	28	23	30	23	25	25
MMSE	28	29	29	27	28	29	25	30	27	28	27
GBA Mutation	N	N	N/A	N	N	N	N	N	N	N	N
Prodromal PD Risk	0.996	0.726	0.994	0.955	0.941	0.980	0.997	0.982	0.999	0.568	0.919
Prodromal PD Risk Ignoring RBD	0.63	0.02	0.55	0.14	0.11	0.27	0.75	0.30	0.87	0.01	0.08

*Abbreviation: Idiopathic REM Sleep Behaviour Disorder (iRBD), Orthostatic Hypotension (OH), University of Pennsylvania Smell Identification Test (UPSIT), Farnsworth-Munsell 100 Hue Test (FM100), Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA), Mini–Mental State Examination (MMSE), Parkinson's Disease (PD)

[a] Subject is clinically abnormal.

Chapter III –Trauma-associated Sleep Disorder: a Post-traumatic Stress Disorder-associated RBD Subtype

Introduction

Trauma-associated sleep disorder (TSD) is a newly proposed terminology to refer to dream enactment occurring in the setting of post-traumatic stress disorder (PTSD). It has been proposed as distinct from REM sleep behavior disorder (RBD), in which the normal REM sleep without atonia is lost, allowing patients to 'act out' dreams at night. Of note, RBD is a strong marker of prodromal neurodegenerative disease, particularly neurodegenerative synucleinopathies (Parkinson's disease, Dementia with Lewy bodies and Multiple System Atrophy). In sleep clinics, 80-85% of patients with idiopathic RBD will ultimately phenoconvert to a full neurodegenerative synucleinopathy within 15 years.[1, 2]

Although RBD-like behavior such as nocturnal screaming and motor activities have been reported in veterans with PTSD since WWI[3] (with descriptions such as shell-shock and night-terror), little is known about RBD in PTSD and other psychiatric disorders.[4, 5] In one of the earliest polysomnography studies in the late 90s, RBD was noted in 11 male veterans with PTSD, with an increase in leg EMG during the phasic phase of REM sleep.[4] In a later case-series, Mysliwiec proposed the term trauma-associated sleep disorder (TSD) as a separate PTSD-associated subtype different from the commonly known synucleinopathy-associated RBD.[6, 7] Within the initial proposed diagnostic criteria, TSD was noted to be more common among the younger population and may be proceeded after a traumatic event. However, as in the case with most PTSD studies, general clinical knowledge and treatment were mostly based on veterans leading to a lack of information from the greater general population.

In a recent Canadian population-based study, we found a persistent association between PTSD and RBD after conducting a series of subgroup analyses and adjusting for various confounding factors, suggesting an independent association between the two.[8] And, with the increase of victims experiencing sexual assault and/or domestic abuse willing to coming forward in recent years, further understanding of PTSD and the associated determinants for TSD in the general population is becoming important for future

clinical practice and prevention for patients injuring themselves and their bed partners.[9-11] To assess the potential clinical determinants associated with TSD, we used the Canadian Longitudinal Study on Aging (CLSA), a large prospective nationwide population-based longitudinal cohort study.[12] Capitalizing on its rich interview details and physiological/physical assessments, we set out two primary goals for this study. They are:

1. Estimating point prevalence of PTSD-associated dream enactment behavior in the Canadian population
2. Assessing traumatic events and clinical determinants associated with TSD and PTSD

Method

Canadian Longitudinal Study on Aging Cohort

This study was performed using the 30,097-person comprehensive cohort, at the baseline, aged 45-85 years, recruited from the Canadian Longitudinal Study on Aging (CLSA) population-based cohort, as described previously.[13] To avoid dream enactment behavior secondary to an established disease or recall bias due to dementia, any participants reporting a diagnosis of dementia/Alzheimer's disease (AD) or parkinsonism/Parkinson's disease (PD) were excluded (Figure 1).

Case Definition

Participants were screened for post-traumatic stress disorder (PTSD) and dream enactment behavior via two questionnaires, with good to excellent sensitivity and specificity in large sample size validation studies, during the interviews[14], namely:

1. Primary Care PTSD Screening Questionnaire (PC-PTSD), the 4-question version assessing symptoms associated with PTSD, as following: "In the past month, have you...

-1 Had nightmares about the event(s) or thought about the event(s) when you did not want to?

-2 Tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)?

-3 Been constantly on guard, watchful, or easily startled?

-4 Felt numb or detached from people, activities, or your surroundings?"

with a 78% sensitivity and 87% specificity among veterans and 85.1% and 82% in the general public.[15, 16]

2. Single Question REM Sleep Behavior Disorder Screening Questionnaire (RBD-1Q)[17], which queries dream enactment behavior via - "Have you ever been told, or suspected yourself, that you seem to “act out your dreams" while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?", with an estimate of 93.8% sensitivity and 87.2% specificity from large scale screening results.[18]

Those who screened positive of PC-PTSD and RBD-1Q were defined as having trauma-associated sleep disorders (TSD), based on the proposed diagnostic criteria.[19] (Figure 1) Of the remaining cohort, those with a positive screen on PC-PTSD (with a negative screen on RBD-1Q) were defined as dream enactment behavior-free PTSD positive ($PTSD^{DEB-}$) and RBD-1Q for PTSD-free dream enactment behavior disorder positive (DEB^{PTSD-}). Symptom-free was defined as negative on both RBD-1Q and PC-PTSD.

Point Prevalence Estimate

Prevalence of $PTSD^{DEB-}$ and TSD were bootstrapped for 1000 iterations with inflation weight, calculated based on the inclusion probabilities for each individual during sampling, and bootstrapped for 1000 iterations. All prevalences were also recalculated within each stratum based on age group (10-year interval) and biological sex. Estimates were computed using the *survey* package in R.

Sociodemographic Statuses

A comprehensive list of sociodemographic variables was collected during the interview. These include age, biological sex (male vs female), marital statuses, ethnicity, immigration statuses, LGBTQ+ identity, annual household income, years of education, military record

(including years of service), and retirement status (including age at retirement).[8] Since the CLSA cohort population is composed of primarily Caucasians, ethnicity statuses were recategorized into Caucasian and non-Caucasian. LGBTQ+ identity was defined according to self-reported sexual orientation and the cross-tabulated results of self-reported gender and biological sex.

History of Childhood Maltreatment and related Events

Besides occupational hazards such as military service and social workers in child protection services, childhood maltreatment and traumatic experiences are common causes of post-traumatic stress disorder. Since the majority of the population within the cohort were civilians, we included a list of questions originated from the Childhood Experiences of Violence Questionnaire, which queried traumatic events that occurred before age of 16[20], in the interest of confirming possible causes of the trauma.[21] These include:

1. Domestic Events: negligence, witness verbal or physical abuse, verbal, or physical abuse
2. General Events: police involvement, physical violence (mild, moderate and severe), sexual harassment and sexual assault.

A positive response was defined as experiencing at least once of the traumatic event queried. Three additional questions from the National Longitudinal Study of Adolescent to Adult Health Wave III Questionnaire[22] were also included in the study to assess the associations with a family history of mental illness, parental divorce, and the parents being severely ill or passing before age of 18. Further details of these questionnaires can be found in the e-material.

Clinical Presentation and Sleep Profiles

To assess the differences in clinical presentations between groups, a list of psychiatric batteries were included. They are:

1. Physician Diagnosis and Prescription: use of antidepressant and physician diagnosis of depressive or anxiety disorder,
2. Questionnaires: Kessler Psychological Distress Scale (10-item interviewer module)[23], and revised Center for Epidemiologic Studies Depression Scale (CESD-R-10)[24].

In addition to the psychiatric presentation, we also included a list of sleep symptoms to explore the potential correlates and secondary causes of dream enactment behavior due to other sleep disorders. These include:

1. Dyssomnia and Overall Sleep Profiles: self-rated sleep quality, self-reported average hours of sleep per night, insomnia symptoms (sleep-onset and -maintenance subtype), and hypersomnolence (a question adapted from Pittsburgh Sleep Quality Index)[25]
2. Sleep-related Breathing Disorder and Movement Disorders: presentation of apnea symptoms (including snoring and/or obstruction of the airway), STOP-BAG index (a screen for obstructive sleep apnea)[26, 27] and restless leg syndrome screen (based on ICSD-2)[28, 29]

Details of clinical definitions can be found in supplementary materials.

Statistical Analyses

- Prevalence Odds Ratio and Associations

Prevalence odds ratios (OR) were estimated first via logistic regression adjusting for age and sex with the dependent variables (i.e., $PTSD^{DEB-}$, TSD and DEB^{PTSD-}) in comparison to the symptom-free. Differences in association strength between $PTSD^{DEB-}$ and TSD were also

assessed with the former being the reference in regression. Any responses labelled as uncertain or 'refused to answer' were omitted in all analyses. Missing rates of most variables were limited to less than 5%, with the exception of the history of childhood maltreatment and related event at 8.4% Results of participants who did not participate in the history of childhood maltreatment and related event interview were imputed using multiple imputations by chained equations (i.e., *mice algorithm*) incorporated with random forest algorithm.[30] In addition, we also incorporated inverse probability weighting (IPW) when assessing the association with traumatic events, to account for the uncertainty due to selection bias (i.e., failed to attend the interview). Confidence intervals were estimated using White's estimate for robust standard error.[31] Statistical analysis was performed using R version 4.1.0.

Sensitivity Analysis and Subgroup Analysis

- Permutation Test

To assess the likely predictors from variables associated with TSD among those with PTSD, all the associated clinical correlates and military service status passed through a Random Forest-based permutation test (i.e., Boruta algorithm).[32] In addition, we also added LGBTQ+ statuses due to the greater cultural discrimination and related trauma that these minority groups faced to which positively associated with PTSD.[33] Variables were then grouped into 'confirmed predictor' and 'rejected predictor' based on the results from the permutation test.

- Stratification by Biological Sex

Since clinical presentations may often vary by sex, all the analyses were reassessed among only male or female. The variable - biological sex, was left out for all subsequent analyses for which was adjusted or weighted.

Consent Data Availability

Written consent was obtained from all participants (or guardians of participants) in the study. Data access for the use of this study was reviewed and granted by the CLSA Data and Sample Access Committee (DSAC). Applicants with a CLSA approved the project and the members of the project teams, with a signature on Schedule F of the CLSA Access Agreement form, are allowed to have direct access to the raw data.

Results

Characteristics of Study Population

Of the 30,097 participants recruited in the comprehensive CLSA cohort, 289 were excluded for either having or absence of information on the prior diagnosis of dementia or parkinsonism. (Figure 1.) Among the remaining 29,808 participants, 172 were excluded for having missing information on the Primary Care Post-Traumatic Stress Disorder Screen (PC-PTSD) and 265 on the REM sleep behavior disorder single question questionnaire (RBD-1Q, screening for dream enactment behavior; DEB). This left us with 27,919 PTSD screened negative and 1,453 positive and 3,328 positives of RBD-1Q and 26,145 negative. Together with the two screening questionnaires, 331 screened positive of both PC-PTSD and RBD-1Q (i.e., trauma-associated sleep disorder; TSD) and 1,122 dream enactment behavior-free PTSD (i.e., $PTSD^{DEB-}$), 2,897 with PTSD-free dream enactment behavior (i.e., DEB^{PTSD-}) and 25,021 negatives of both screens (i.e., symptom-free). This translated to an unadjusted point-prevalence of 1.26% (95%CI=[1.09,1.43]) for TSD among Canadians aged 45-85 (with a prevalence of 4.18% (95%CI=[3.88,4.48]) for dream enactment behavior-free PTSD . (Figure 1). Among those with PTSD, 23.5% (95%CI=[20.8,26.2]) endorsed symptoms consistent with TSD.

Sociodemographic Features

Regarding all symptom groups (i.e. TSD, $PTSD^{DEB-}$, DEB^{PTSD-}), participants tend to be slightly younger (OR ranged from 0.96-0.98) with the point estimate of prevalence decreased by age. (Figure 1, Table 1) Participants in all symptom groups had on average, fewer total years of education (OR=0.85-0.96) than that of symptom-free (i.e., free of both PTSD and DEB). (Table 1) $PTSD^{DEB-}$ were more prevalent among female sex (69.2% female, OR=2.11[1.85,2.40]),

whereas DEB^{PTSD-} for male sex (72.3% male, OR=1.69[1.56,1.82]) when comparing to symptom-free. Although there was no clear difference in biological sex between those with TSD and symptom-free, female sex was less likely to have TSD (55.9%) than PTSD^{DEB-} (OR= 0.56[0.44,0.73]). This translated to an estimated prevalence of 30.6% (95%CI=[25.5,35.7]) among Canadian males with PTSD who also had TSD and 19.5% (95%CI=[16.5,22.6]) for females. (e-1) Those with post-traumatic stress disorder, regardless of the presence of dream enactment behavior, were less likely to have been in a relationship (PTSD^{DEB-}: 63.9%; OR=0.52[0.46,0.59], TSD: 66.6%; OR=0.55[0.43,0.70]), which was the opposite in those with DEB^{PTSD-} (82.1%; OR=1.16[1.05,1.29]), than symptom-free (79.2%).

Those with PTSD (including both PTSD^{DEB-} and TSD) were slightly lower in socioeconomic statuses in comparison to symptom-free (OR=0.99[0.98,0.99]). The non-Caucasian to Caucasian ratio was higher among those with PTSD^{DEB-} (5.49%, OR=1.47[1.12,1.92]) when comparing to symptom-free (3.67%). Those with TSD were less likely to be immigrants (OR=0.68 [0.49,0.95]) and more likely to be part of the LGBTQ+ community than symptom-free. More participants with TSD have/had served in the military than those with PTSD^{DEB-} or symptom-free. Both TSD (OR=1.83[1.33,2.51]) and PTSD^{DEB-} (OR=1.32[1.11,1.56]) were associated with higher retirement rate comparing to symptom-free.

Childhood Traumatic Experiences

In comparison to those who were symptom-free, most assessed events were commonly experienced in all symptom groups, except for domestic physical punishment and social service involvement. (Table 2) And, of all non-spatial specific events assessed, more participants with TSD experienced severe physical violence (24.2% verse 17.4%, OR=1.38[1.02,1.87]), sexual

harassment (33.5% verse 27.4%, OR=1.52[1.15,2.00]), and sexual assault (23% verse 19.3%, OR=1.39[1.02,1.88]) than those with $PTSD^{DEB-}$. Among the events that occurred domestically, participants with TSD were more likely to have been witnesses (OR=1.40[1.05,1.87]) or victims of verbal abuse (OR=1.85[1.43,2.41]) comparing to $PTSD^{DEB-}$. Despite having no difference statistically between groups, more than half of the participants self-reported witnessing physical abuse among those with TSD or $PTSD^{DEB-}$. Similar to the traumatic experiences assessed above, more participants in symptomatic groups had a family history of mental illness and experience of parents being severely ill or deceased before age of 18. And among the events queried, more participants with TSD were likely to have a family history of mental illness than $PTSD^{DEB-}$.

Clinical Signs and Symptoms

In terms of clinical presentations, all symptom groups (i.e., TSD, $PTSD^{DEB-}$ and DEB^{PTSD-}) showed greater psychological distress and were more likely to have a prior diagnosis of mood disorders (including depressive disorders), anxiety disorder and on the treatment of antidepressant. (Table-3) And, when comparing to $PTSD^{DEB-}$, all associations were stronger for those with TSD.

Similar to psychiatric presentations, all symptom groups presented more comorbid sleep symptoms including poor sleep quality, circadian rhythm disorders, sleep breathing disorder and restless leg syndrome than symptom-free. (Table-3) And, when comparing within those with PTSD, TSD showed increases in associations with poor sleep quality (OR=1.33[1.04,1.71]), hypersomnolence (OR=1.62[1.22,2.16]), apnea symptoms (obstruction/snore: 1.44[1.06,1.96], obstruction and snore: 2.39[1.64,3.50]) and positive restless leg syndrome screen

(OR=1.96[1.50,2.57]) than $PTSD^{DEB-}$. No clear difference in average sleeping hours was found between TSD and $PTSD^{DEB-}$.

Subgroup Analysis – Male and Female

Since sociodemographic and perception of symptoms are often confounded by sex, we reassessed the associations after stratifying by biological sex. (Table e-2) Among male participants, there was no clear difference in demographical statuses when comparing between TSD and $PTSD^{DEB-}$. Whereas, among females, participants with TSD were more likely to self-identify as LGBTQ+ (5.95% verse 1.82%, OR_{female}=3.34[1.49,7.49]) and be retired (53.3% verse 48.5%, OR_{female}=1.67[1.10,2.53]) than those with $PTSD^{DEB-}$.

Of the traumatic events assessed, sexual harassment (43.5% verse 32.4%, OR_{female}=1.58[1.13,2.20]) and sexual assaults (31.1% verse 22.5%, OR_{female}=1.52[1.06,2.19]) remained more common among female TSD compared to PTSD participants without DEB. (Table e-3) Domestically, participants with TSD in both sexes remained more likely to be a victim of verbal abuse (OR_{male}=1.78[1.19,2.66], OR_{female}=1.91[1.36,2.70]) than those with $PTSD^{DEB-}$, with more than half of the participants ever been witnesses of domestic violence in all subgroups. No clear difference in the family history of mental illness was found after stratifying by sex.

In regard to the clinical presentation/history assessed, TSD remained to associate with greater degrees of psychological distress, mood disorders and use of antidepressant than $PTSD^{DEB-}$ among both sexes, with the exception of anxiety disorders among females. (Table e-4) In terms of comorbid sleep symptoms, the associations varied by sexes. Among males, TSD was

associated with hypersomnolence (OR_{male}=2.12[1.39,3.22]), restless leg syndrome (OR_{male}=1.73[1.09,2.73]) and greater STOP-BAG score (3.26 verse 2.90) but not apnea symptoms when comparing $PTSD^{DEB-}$. On the other hand, of the female participants, TSD was associated with apnea symptoms (obstruction/snore: 1.89[1.27,2.83], obstruction and snore: 3.48[2.13,5.68]), maintenance insomnia (OR_{female}=1.54[1.12,2.13]) and restless leg syndrome (OR_{female}=2.10[1.50,2.94]).

Sensitivity Analysis

- Permutation Test

To identify if the variables (as a predictor) associated with TSD were only specific to the cohort, we performed a series of permutation tests using a Random-Forest based algorithm. Within all participants with PTSD, male sex, experiences of certain traumatic events (including sexual harassment, sexual assault, and verbal abuse), greater psychological distress, prior diagnosis of mood disorder, use of antidepressant, hypersomnolence and apnea symptoms remained associated with the occurrence of dream enactment behavior in PTSD (i.e., TSD). (Figure 2)

When reassessing the results after stratifying the cohort by sex, mood disorder and experience of verbal abuse remained as common associated factors among both sexes. Within female participants, sexual harassment, sexual assault, and apnea symptoms were additional predictors for TSD from PTSD. And, of male participants, TSD was associated with more prevalent anxiety disorder, use of antidepressant and hypersomnolence than $PTSD^{DEB-}$.

Discussion

With the advantage of the population-based CLSA cohort, we were able to estimate the prevalence of questionnaire-screen trauma-associated sleep disorder - 1.26% (95%CI=[1.09,1.43]) among middle-aged and older Canadians. Among participants with PTSD, TSD was more prevalent in men, those reporting experience of certain traumatic events (including sexual harassment, sexual assault, and verbal abuse), those with a prior diagnosis of mood disorders and/or anxiety disorder and those treated with antidepressant.

Trauma-associated Sleep Disorder: a PTSD-associated subtype of RBD

Since the proposal of TSD as an independent parasomnia is relatively new, descriptions of its clinical etiology and presentation in the population are limited.[34] Most polysomnography and questionnaire-based studies to-date centred on the association between PTSD and RBD or dream enactment behavior among male veterans and first responder.[4, 7, 35, 36]

In our previous study, PTSD was found positively associated with dream enactment behavior after accounting for use of antidepressant, apnea symptoms, restless leg syndrome and other confounders (OR=2.68[1.97,3.65]).[8] This has also been observed in a few studies including one of the earliest case-control studies of TSD by Ross R.J. et. al.[4] Of the 11 male veterans with PTSD included and their age-matched control group, PTSD patients showed a significant increase in REM sleep phasic leg activity (i.e., a sign of REM sleep without atonia, index score: 4.6 vs. 1.3). A later study from Australia found that 10 of the 35 patients with PTSD (including mostly male military and emergency personnel) were aroused from a nightmare (a potential sign of RBD) during REM sleep and 14 awakened during non-REM sleep.[37] In addition to nightmare awakening, 6 also had clear RBD activities during polysomnography recording. This translated

to a raw estimate of 17.1-28.6% of RBD among all PTSD (i.e., TSD prevalence), similar to our estimate (23.5% for all and 30.6% for males). In a recent VA study, 19 of the 394 U.S. veterans (4.82%) were diagnosed with both RBD and PTSD (i.e., TSD), which accounts for a point prevalence of 16.8% of all patients with PTSD.[38] Despite 114 patients were excluded from the study, their point prevalence of TSD was twice our estimate for Canadian veterans (2.40%). (Table e-1) One possible explanation accounting for this difference may be that Canada has a much lower rate in general deployment and peacekeeping involvement than the U.S. (i.e., lower trauma-exposure rate). Nonetheless, PTSD was independently associated with RBD in both theirs and our study (results were similar to that of adjusted for apnea symptoms and restless leg syndrome, data not shown).

Similar findings were also reported in another Australian Vietnam War Veteran study.[35] In comparison to PTSD-free veterans who experienced similar trauma, PTSD remained as an independent predictor for RBD-related dream enactment behavior (screened via Mayo Sleep Questionnaire[39]) after adjusting for comorbid sleep disorders and confounders (60.2% verse 11.3%, OR=5.65[2.92,10.9]). Another recent study from Tasmania also reported that patients with PTSD (n=30) scored higher on the RBDSQ (a RBD questionnaire developed in Germany) than those with/without traumatic experience.[40] Together with our results, it supports the notion that trauma by itself may induce RBD-related dream enactment behavior, but the propensity greatly increases when PTSD arose from a traumatic experience. (Table 2) On the other hand, certain traumatic events (e.g., sexual harassment/assault) sustained the permutation tests in our study but not military service nor LGBTQ+ identity, indicating that the importance of traumatic events in the role of predicting TSD within those with PTSD. (Figure 2)

- Traumatic Events, Dream Enactment Behavior and Nightmare

Among participants with PTSD, childhood experience of domestic verbal abuse, in both sexes, and sexual harassment/assaults among females were associated with TSD in our study. (Table 2, Figure 2) Although direct associations between sexual assault or domestic violence and TSD have not been well established in the literature, several studies reported an increase in nightmare experience and frequency among sexual assault and/or domestic violence survivors, who are more likely to develop complex PTSD.[41-44] Note that although not all nightmares trigger dream enactment behavior, both symptoms often coexist.[1] In fact, in the two Australian studies, described earlier, both reported relatively a high percentage of nightmare experiences among patients with PTSD (82.9 and 90.7%).[35, 37] Therefore, the increase in nightmare frequency may imply an increase in the likelihood of TSD among sexual assault and/or domestic violence survivors.

Male Sex, Antidepressant, Apnea, and Restless Leg Syndrome

We found that antidepressant treatment was directly associated with TSD in men, but not women. (Figure 2) Antidepressants (including MOI, TCA, SSRI and SNRI) and their link to RBD have been well documented.[1, 45] Both prospective and retrospective studies have shown that antidepressants are associated with REM sleep without atonia during tonic and phasic REM sleep. However, antidepressants can also trigger early presentation of an underlying RBD due to syncucleinopathy. Together with our previous findings, we found similar bilateral independent associations – PTSD-associated dream enactment behavior[8] and antidepressant-associated dream enactment behavior (Figure 2), indicating a potential independent mechanism related to PTSD. Along with these findings, we also noted that antidepressant-triggered dream enactment behavior

was a male-predominant feature. (Figure 2) Interestingly, although antidepressant treatment was more common among female participants in our study, similar to most literature, antidepressant failed to be an independent correlate from the permutation test. (Figure2) Therefore, to a certain extent, our results support the notion that men have a slightly higher propensity of developing RBD in both parkinsonism (a male-predominant disease)[1] and PTSD (despite it being more commonly reported among females). (Table 1, e-4 and Figure 2) It is worth noting that, in our study, TSD was also equally distributed between sexes in the Canadian population (Table e-1), as was seen in a large Swiss community polysomnography screen for RBD.[46] Future studies will be needed to explore possible sex-specific links between antidepressants and dream enactment behavior.

TSD verse Parkinsonism-associated RBD

In comparison to parkinsonism-associated RBD, patients with TSD or PTSD-associated RBD subtype tend to occur in the younger generation and are more evenly distributed among males and females.[47] On the other hand, both parkinsonism-associated RBD and TSD are associated with depression, anxiety, use of antidepressants and hypersomnolence although the symptom-manifestation may be different.[48] Interestingly, besides the commonly shared male-dominant association with the use of antidepressants, hypersomnolence was also commonly associated with both TSD and parkinsonism-associated RBD. In parkinsonism, the presence of hypersomnolence is often seen as a sign of medication wearing off or poor sleep quality. Although the exact association between TSD and hypersomnolence is unclear, hypersomnolence was associated with several sleep determinants among TSD, with the strongest being poor sleep

quality. (e-5) Since as opposed to females, male participants with TSD were less likely to be retired, hypersomnolence may be a reflection of poor daytime performance. (Table 2)

In our study, we also noted that TSD also frequently overlap with apnea and restless leg syndrome. (Table 2, e-4) For apnea, this is similar to what was found in the multicenter RBD studies, where 27-28% of patients with parkinsonism-related RBD were also diagnosed with obstructive sleep apnea (AHI index≥15).[49] Similar findings have also been reported in some male-predominant TSD studies.[4, 35] One possible explanation for this is phenomenon is the anatomical proximity of respiratory rhythmic generator and subcoeruleus nucleus in the brainstem region.[50] We also found an association between maintenance insomnia and TSD. Frequent co-presentation of restless leg syndrome has also been noted in an early TSD polysomnography study, in particular during NREM sleep.[4] However, the percentage of co-expression of restless leg syndrome in parkinsonism-associated RBD from a recent international RBD study group study (n=1280) was similar to the population estimate[49, 51], indicating that the association may be unique to TSD. Future studies will be needed to confirm this association.

Strength and Limitations

Several limitations should be noted in our study. First, within this large sample size population-based cohort, our case definitions were based on the screening results of PC-PTSD questionnaire and RBD-1Q. Although both questionnaires have been demonstrated with good sensitivity and specificity in large sample size studies[16, 17, 52], a certain degree of misclassification is inevitable. This problem is shared by all large-scale studies. To limit the effect of misclassification bias, in particular possible false-positive results driven by differential misclassification bias, we performed several sensitivity analyses including randomization and

permutation tests to ensure the precision of the results. Second, because the CLSA recruitment started prior to the development of PC-PTSD-5, we were unable to assess the association between RBD and complex PTSD (which requires the fifth component of self-organization). Third, since the acquisition of childhood maltreatment and related events information was performed in the follow-up, not all participants participated in the interview (i.e., right censoring). However, with the combination of multiple imputations by chained equations and inverse probability weighting, we can reduce this bias.[53]

On the other hand, this study has several advantages. The primary one is that it uses a population-based sample, and therefore is more generalizable than estimates coming from sleep centers. With the design of statistical weighting-based recruitment, the results from the CLSA cohort are mostly in line with reports from the national representative source.[54] Moreover, using the inflation weight generated along the recruitment allowed us to calculate precise prevalence estimates that can reflect the Canadian population. Third, our study provided insight into differences in clinical presentations and associates of PTSD among male and female sex, separately. Since clinical presentations vary greatly between sexes and genders among psychiatric patients, our results can provide useful suggestions in clinical practice.

Capitalizing upon a large population-based cohort, we found that 1.26% of the population aged 45-85 endorsed symptoms of both PTSD and dream enactment (i.e. traumatic sleep disorder). Dream enactment behavior was more common among those with PTSD compared to those without. Among PTSD, participants with TSD were more likely to be male, survivors of, domestic and/or sexual adverse events, and treated with antidepressants.

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References:

1. Schenck C, Högl B, Videnovic A. *Rapid-eye-movement sleep behavior disorder*. Springer; 2019. https://link.springer.com/book/10.1007/978-3-319-90152-7
2. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. 2019/2/20 2019;142(3):744-759. doi:10.1093/brain/awz030
3. Crocq MA, Crocq L. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. *Dialogues Clin Neurosci*. 2000;2(1):47-55. doi:10.31887/DCNS.2000.2.1/macrocq
4. Ross RJ, Ball WA, Dinges DF, et al. Motor Dysfunction During Sleep in Posttraumatic Stress Disorder. *Sleep*. 1994;17(8):723-732. doi:10.1093/sleep/17.8.723
5. Elliott JE, Opel RA, Pleshakov D, et al. Posttraumatic stress disorder increases the odds of REM sleep behavior disorder and other parasomnias in Veterans with and without comorbid traumatic brain injury. *Sleep*. 2020/3 2020;43(3)doi:10.1093/sleep/zsz237
6. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: A parasomnia induced by trauma. *Sleep Medicine Reviews*. 2018;37:94-104. doi:10.1016/j.smrv.2017.01.004
7. Mysliwiec V, O'Reilly B, Polchinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia encompassing disruptive nocturnal behaviors, nightmares, and REM without atonia in trauma survivors. *J Clin Sleep Med*. Oct 15 2014;10(10):1143-8. doi:10.5664/jcsm.4120
8. 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*. Dec 26 2018;doi:10.1212/WNL.0000000000006849
9. Janiri D, Carfì A, Kotzalidis GD, Bernabei R, Landi F, Sani G. Posttraumatic Stress Disorder in Patients After Severe COVID-19 Infection. *JAMA Psychiatry*. 2021;78(5):567. doi:10.1001/jamapsychiatry.2021.0109
10. Survey on COVID-19 and Mental Health, September to December 2020 (Statistics Canada) (2021).
11. Galea S, Merchant RM, Lurie N. The Mental Health Consequences of COVID-19 and Physical Distancing. *JAMA Internal Medicine*. 2020;180(6):817. doi:10.1001/jamainternmed.2020.1562
12. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). *Can J Aging*. 2009 2009;28(3):221-229. doi:10.1017/s0714980809990055
13. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). *Can J Aging*. Sep 2009;28(3):221-9. doi:10.1017/s0714980809990055
14. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. May 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
15. Prins A, Bovin MJ, Smolenski DJ, et al. The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5): Development and Evaluation Within a Veteran Primary Care Sample. *J Gen Intern Med*. 2016/10 2016;31(10):1206. doi:10.1007/s11606-016-3703-5
16. Freedy JR, Steenkamp MM, Magruder KM, et al. Post-traumatic stress disorder screening test performance in civilian primary care. *Family Practice*. 2010;27(6):615-624. doi:10.1093/fampra/cmq049
17. Postuma RB, Arnulf I, Hogl B, et al. A Single-Question Screen for REM Sleep Behavior Disorder: A Multicenter Validation Study. *Mov Disord*. 2012/6 2012;27(7):913. doi:10.1002/mds.25037
18. 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*. Jun 2012;27(7):913-6. doi:10.1002/mds.25037

19. Brock MS, Powell TA, Creamer JL, Moore BA, Mysliwiec V. Trauma Associated Sleep Disorder: Clinical Developments 5 Years After Discovery. *Current Psychiatry Reports*. 2019/08/13 2019;21(9):80. doi:10.1007/s11920-019-1066-4
20. Walsh CA, MacMillan HL, Trocmé N, Jamieson E, Boyle MH. Measurement of victimization in adolescence: Development and validation of the Childhood Experiences of Violence Questionnaire. *Child Abuse & Neglect*. 2008/11/01/ 2008;32(11):1037-1057. doi:https://doi.org/10.1016/j.chiabu.2008.05.003
21. Joshi D, Raina P, Tonmyr L, Macmillan HL, Gonzalez A. Prevalence of adverse childhood experiences among individuals aged 45 to 85 years: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. *CMAJ Open*. 2021;9(1):E158-E166. doi:10.9778/cmajo.20200064
22. Harris KM, Halpern CT, Whitsel EA, et al. Cohort Profile: The National Longitudinal Study of Adolescent to Adult Health (Add Health). *International Journal of Epidemiology*. 2019;48(5):1415-1415k. doi:10.1093/ije/dyz115
23. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). *Aust N Z J Public Health*. Dec 2001;25(6):494-7. doi:10.1111/j.1467-842x.2001.tb00310.x
24. Björgvinsson T, Kertz SJ, Bigda-Peyton JS, McCoy KL, Aderka IM. Psychometric Properties of the CES-D-10 in a Psychiatric Sample. *Assessment*. 2013;20(4):429-436. doi:10.1177/1073191113481998
25. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Dec 2002;73(6):629-35. doi:10.1136/jnnp.73.6.629
26. Haba-Rubio J AD, Bastardot F, Tobback N, Vollenweider P, Tafti M, Heinzer R. STOP-BANG Questionnaire as a Screening Tool for Obstructive Sleep Apnea in the General Population. presented at: Sleep; 2011;
27. Strange C, Richard CL, Shan S, et al. A population-based estimate of the health care burden of obstructive sleep apnea using a STOP-BAG questionnaire in South Carolina. *Journal of Clinical Sleep Medicine*. 2021;17(3):367-374. doi:doi:10.5664/jcsm.8860
28. Medicine AAoS. *International Classification of Sleep Disorders. 2nd ed.* American Academy of Sleep Medicine; 2005.
29. Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. *Sleep Med*. 2008 2008;9(3):283-289. doi:10.1016/j.sleep.2007.04.021
30. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *2011*. 2011-12-12 2011;45(3):67. doi:10.18637/jss.v045.i03
31. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. *Econometrica*. 1980 1980;48(4):817-838.
32. Kursa MB, Rudnicki WR. Feature Selection with the Boruta Package. *2010*. 2010-09-16 2010;36(11):13. doi:10.18637/jss.v036.i11
33. Roberts AL, Austin SB, Corliss HL, Vandermorris AK, Koenen KC. Pervasive Trauma Exposure Among US Sexual Orientation Minority Adults and Risk of Posttraumatic Stress Disorder. *American Journal of Public Health*. 2010;100(12):2433-2441. doi:10.2105/ajph.2009.168971
34. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: A parasomnia induced by trauma. *Sleep Med Rev*. 2018/2/1 2018;37:94-104. doi:10.1016/j.smrv.2017.01.004
35. Baird T, McLeay S, Harvey W, Theal R, Law D, O'Sullivan R. Sleep Disturbances in Australian Vietnam Veterans With and Without Posttraumatic Stress Disorder. *Journal of Clinical Sleep Medicine*. 2018;14(05):745-752. doi:10.5664/jcsm.7096

36. Feemster JC, Smith KL, McCarter SJ, St Louis EK. Trauma-Associated Sleep Disorder: A Posttraumatic Stress/REM Sleep Behavior Disorder Mash-Up? *J Clin Sleep Med*. Feb 15 2019;15(2):345-349. doi:10.5664/jcsm.7642
37. Phelps AJ, Kanaan RAA, Worsnop C, Redston S, Ralph N, Forbes D. An Ambulatory Polysomnography Study of the Post-traumatic Nightmares of Post-traumatic Stress Disorder. *Sleep*. 2018;41(1)doi:10.1093/sleep/zsx188
38. Elliott JE, Opel RA, Pleshakov D, et al. Posttraumatic stress disorder increases the odds of REM sleep behavior disorder and other parasomnias in Veterans with and without comorbid traumatic brain injury. *Sleep*. 2019 2019;doi:10.1093/sleep/zsz237
39. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. *J Clin Sleep Med*. May 15 2013;9(5):475-80. doi:10.5664/jcsm.2670
40. Ney LJ, Hsu CMK, Nicholson E, et al. The Effect of Self-Reported REM Behavior Disorder Symptomology on Intrusive Memories in Post-Traumatic Stress Disorder. *Behavioral Sleep Medicine*. 2021;19(2):178-191. doi:10.1080/15402002.2020.1722127
41. Krakow B, Schrader R, Tandberg D, et al. Nightmare frequency in sexual assault survivors with PTSD. *Journal of Anxiety Disorders*. 2002;16(2):175-190. doi:10.1016/s0887-6185(02)00093-2
42. Belleville G, Dubé-Frenette M, Rousseau A. Sleep disturbances and nightmares in victims of sexual abuse with post-traumatic stress disorder: an analysis of abuse-related characteristics. *European Journal of Psychotraumatology*. 2019;10(1):1581019. doi:10.1080/20008198.2019.1581019
43. Krakow B, Germain A, Tandberg D, et al. Sleep breathing and sleep movement disorders masquerading as insomnia in sexual-assault survivors. *Comprehensive Psychiatry*. 2000;41(1):49-56. doi:10.1016/s0010-440x(00)90131-7
44. Hyland P, Shevlin M, Fyvie C, Cloitre M, Karatzias T. The relationship between ICD-11 PTSD, complex PTSD and dissociative experiences. *Journal of Trauma & Dissociation*. 2020;21(1):62-72. doi:10.1080/15299732.2019.1675113
45. Baltzan M, Yao C, Rizzo D, Postuma R. Dream enactment behavior: review for the clinician. *J Clin Sleep Med*. 2020/11/15 2020;doi:10.5664/jcsm.8734
46. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, others. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. *Sleep*. 2018 2018;41(2):zsx197-zsx197. doi:10.1093/sleep/zsx197
47. Postuma RB, Gagnon JF, Montplaisir JY. REM sleep behavior disorder: from dreams to neurodegeneration. *Neurobiol Dis*. Jun 2012;46(3):553-8. doi:10.1016/j.nbd.2011.10.003
48. Baig F, Lawton MA, Rolinski M, et al. Personality and addictive behaviours in early Parkinson's disease and REM sleep behaviour disorder. *Parkinsonism Relat Disord*. Apr 2017;37:72-78. doi:10.1016/j.parkreldis.2017.01.017
49. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. Mar 1 2019;142(3):744-759. doi:10.1093/brain/awz030
50. Jung YJ, Oh E. Is REM sleep behavior disorder a friend or foe of obstructive sleep apnea? Clinical and etiological implications for neurodegeneration. *Journal of Clinical Sleep Medicine*. 2021;17(6):1305-1312. doi:doi:10.5664/jcsm.9144
51. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: A synthesis of the literature. *Sleep Medicine Reviews*. 2012;16(4):283-295. doi:10.1016/j.smrv.2011.05.002
52. Cameron RP, Gusman D. The primary care PTSD screen (PC-PTSD): development and operating characteristics. *Primary care psychiatry*. 2003;9(1):9-14.
53. Seaman SR, White IR, Copas AJ, Li L. Combining Multiple Imputation and Inverse-Probability Weighting. *Biometrics*. 2012;68(1):129-137. doi:10.1111/j.1541-0420.2011.01666.x

54. Raina P, Wolfson C, Kirkland S, et al. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). *Int J Epidemiol*. Dec 1 2019;48(6):1752-1753j. doi:10.1093/ije/dyz173
55. Kursa MB, Rudnicki WR. Feature Selection with the Boruta Package. *Journal of Statistical Software*. Sep 2010;36(11):1-13. doi:DOI 10.18637/jss.v036.i11

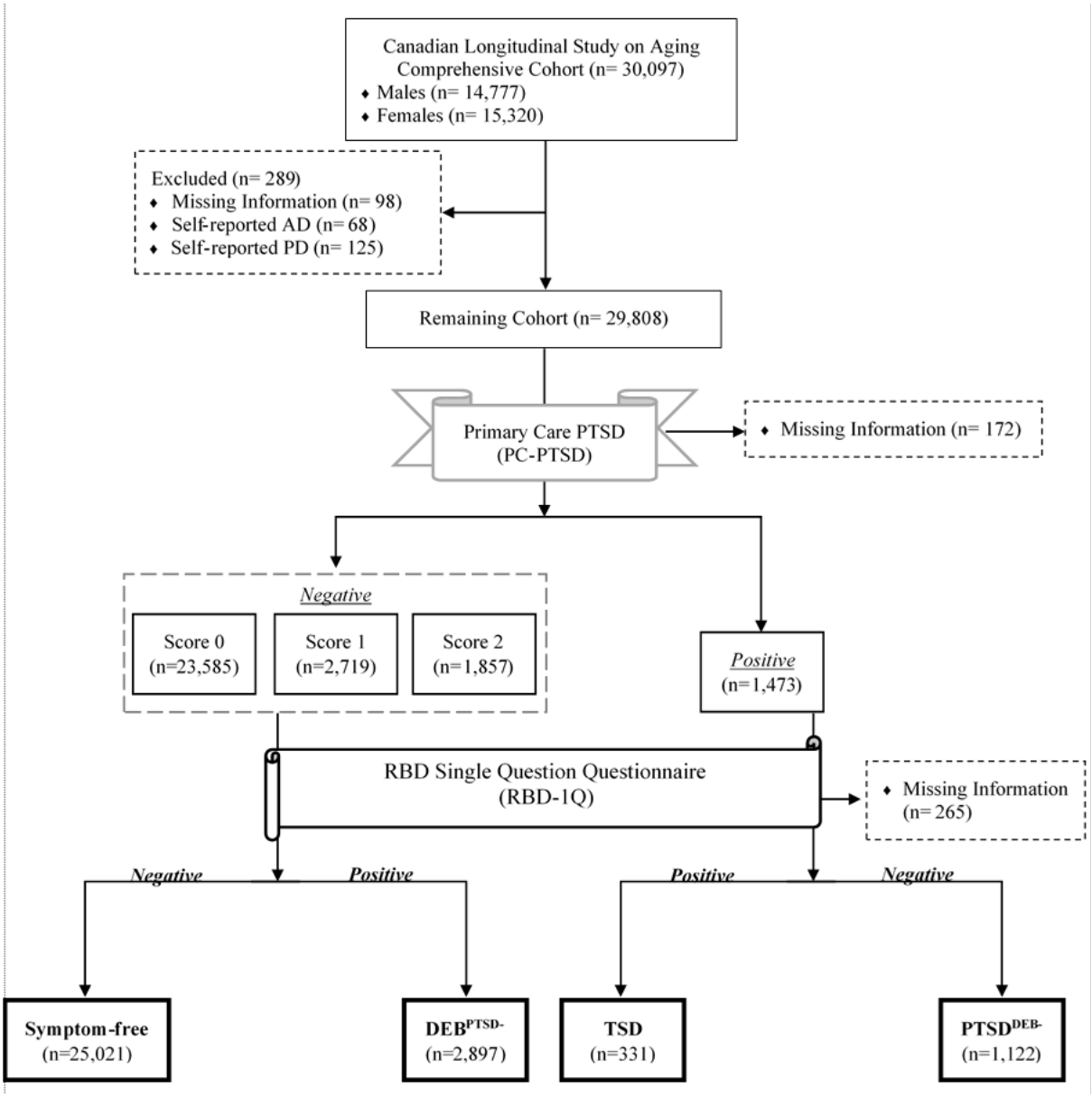

Figure 1. STROBE Flow Diagram and Prevalence Estimate

Estimated Point Prevalence		PTSD	PTSD^{DEB-}	TSD
		Point Prevalence (per-100-person)		
Unstratified		5.45 [5.12,5.79]	4.18 [3.88,4.48]	1.26 [1.09,1.43]
Age Group	45-54	6.42 [5.80,7.04]	4.83 [4.28,5.37]	1.62 [1.28,1.96]
	55-64	5.66 [5.12,6.20]	4.40 [3.93,4.87]	1.23 [0.97,1.49]
	65-74	4.11 [3.55,4.67]	3.22 [2.74,3.71]	0.81 [0.57,1.05]
	75+	3.28 [2.60, 3.95]	2.59 [2.00,3.17]	0.67 [0.35,0.99]
Biological Sex	Male	3.92 [3.49,4.35]	2.73 [2.36,3.10]	1.18 [0.94,1.43]
	Female	6.96 [6.46,7.46]	5.61 [5.15,6.06]	1.34 [1.11,1.57]

Primary case definitions were highlighted in broad edged cell. The connected arrows indicate the case-definition criteria. Prevalence was estimated using the inflation weight calculated to reflect the distribution in Canada.

< Abbreviation > TSD: trauma-associated sleep disorder

DEB^{PTSD-}: PTSD-free dream enactment behavior

PTSD^{DEB-}: DEB-free post-traumatic stress disorder

Table 1. Sociodemographic Status

		Symptom-free N=25,021	PTSD^{DEB-} N=1,122	TSD N=331	DEB^{PTSD-} N=2,897	PTSD^{DEB-} vs Symptom-free	TSD vs Symptom-free	TSD vs PTSD^{DEB-}	DEB^{PTSD-} vs Symptom-free
		N (%) or Mean±SD				$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]			
Demographic Profile									
Age		63.2±10.3	60.1± 9.3	59.3± 9.2	61.3±10	0.97 [0.96,0.98]	0.96 [0.95,0.97]	0.99 [0.98,1.00]	0.98 [0.98,0.99]
Biological Sex (Female %)		12853 (51.4)	776 (69.2)	185 (55.9)	1122 (38.7)	2.11 [1.85,2.40]	1.19 [0.96,1.48]	**0.56 [0.44,0.73]**	0.59 [0.55,0.64]
Married/Common-law		18720 (79.2)	660 (63.9)	203 (66.6)	2231 (82.1)	0.52 [0.46,0.59]	0.55 [0.43,0.70]	1.08 [0.82,1.42]	1.16 [1.05,1.29]
Years of Education		13.7±2.3	12.9±2.3	13±2.4	13.6±2.3	0.85 [0.83,0.88]	0.85 [0.80,0.90]	0.99 [0.94,1.05]	0.96 [0.94,0.97]
Socioeconomical Statuses and Social Minority Status									
Annual Income (per 1,000 CAD)		58.1±35.6	43.3±32.5	45.2±33.9	59.1±36.1	0.99 [0.98,0.99]	0.99 [0.98,0.99]	1.00 [1.00,1.00]	1.00 [1.00,1.00]
Ethnicity (Non-caucasian %)		911 (3.67)	61 (5.49)	13 (3.95)	99 (3.45)	1.47 [1.12,1.92]	0.97 [0.55,1.71]	0.65 [0.35,1.20]	0.85 [0.69,1.05]
Immigration Status		4590 (18.4)	188 (16.8)	41 (12.4)	473 (16.3)	0.99 [0.84,1.16]	0.68 [0.49,0.95]	**0.69 [0.48,0.99]**	0.88 [0.79,0.98]
LGBTQ+ Status		565 (2.26)	29 (2.6)	17 (5.17)	72 (2.49)	1.15 [0.79,1.68]	2.12 [1.28,3.49]	**1.86 [0.97,3.54]**	0.98 [0.76,1.27]
Military and Retirement Status									
Military Service	Yes	2229 (8.91)	73 (6.51)	40 (12.1)	320 (11.1)	1.14 [0.89,1.47]	1.86 [1.31,2.65]	**1.55 [1.01,2.38]**	1.14 [1.00,1.30]
	Years of Service	9.3±11.3	8.3±10.3	13.5±12.3	9.8±11.6	0.99 [0.97,1.02]	1.03 [1.01,1.06]	1.04 [1.01,1.08]	1.00 [0.99,1.01]
Retirement Status	Retired	14028 (56.3)	561 (50.3)	169 (51.5)	1447 (50)	1.32 [1.11,1.56]	1.83 [1.33,2.51]	1.27 [0.92,1.75]	1.03 [0.93,1.15]
	Retired Age	58.5±6.5	56.1±7	54.9±7.6	57.9±6.5	0.97 [0.96,0.98]	0.95 [0.92,0.97]	0.98 [0.95,1.01]	0.99 [0.98,1.00]

< Abbreviation >
TSD: trauma-associated sleep disorder
DEB^{PTSD-}: PTSD-free dream enactment behavior
PTSD^{DEB-}: DEB-free post-traumatic stress disorder

Table 2. Childhood Traumatic Experience and Associations to Dream Enactment Behavior

		Symptom-free N=25,021	$PTSD^{DEB-}$ N=1,122	TSD N=331	DEB^{PTSD-} N=2,897	$PTSD^{DEB-}$ vs Symptom-free	TSD vs Symptom-free	TSD vs $PTSD^{DEB-}$	DEB^{PTSD-} vs Symptom-free
		N (%) or Mean±SD				$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]			
Events Occur Before the Age of 16									
Non-spatial Specific Events									
Physical Violence	Mild	3549 (14.4)	310 (28.4)	112 (34.8)	599 (21.1)	2.39 [2.08,2.74]	2.98 [2.36,3.76]	1.24 [0.95,1.62]	1.45 [1.32,1.60]
	Moderate	9589 (38.8)	546 (50.1)	186 (57.8)	1346 (47.3)	1.70 [1.50,1.92]	2.13 [1.69,2.67]	1.28 [0.99,1.65]	1.29 [1.19,1.40]
	Sever	1570 (6.4)	190 (17.4)	78 (24.2)	298 (10.5)	3.19 [2.69,3.77]	4.44 [3.42,5.77]	**1.38 [1.02,1.87]**	1.57 [1.38,1.80]
Sexual Harassment		3404 (13.8)	299 (27.4)	108 (33.5)	458 (16.1)	1.94 [1.68,2.24]	3.09 [2.42,3.94]	**1.52 [1.15,2.00]**	1.37 [1.23,1.53]
Sexual Assault		1785 (7.2)	210 (19.3)	74 (23)	261 (9.2)	2.54 [2.16,2.99]	3.62 [2.77,4.74]	**1.39 [1.02,1.88]**	1.43 [1.25,1.64]
Domestic Events									
Witness Domestic Violence	Verbal	2834 (11.5)	224 (20.6)	86 (26.7)	421 (14.8)	1.84 [1.58,2.14]	2.57 [2.00,3.31]	**1.40 [1.05,1.87]**	1.29 [1.16,1.45]
	Physical	8386 (34)	551 (50.6)	178 (55.3)	1162 (40.8)	1.78 [1.57,2.01]	2.13 [1.70,2.66]	1.16 [0.90,1.50]	1.28 [1.18,1.39]
Physical Punishment		17499 (70.9)	805 (73.9)	242 (75.2)	2111 (74.2)	1.11 [0.96,1.27]	1.10 [0.86,1.42]	0.99 [0.74,1.33]	1.07 [0.97,1.17]
Verbal Abuse		6774 (27.4)	517 (47.4)	200 (62.1)	1023 (36)	2.13 [1.88,2.41]	3.90 [3.10,4.91]	**1.85 [1.43,2.41]**	1.43 [1.32,1.55]
Negligence		713 (2.9)	98 (9)	36 (11.2)	116 (4.1)	3.06 [2.44,3.83]	4.03 [2.82,5.75]	1.33 [0.88,2.02]	1.45 [1.19,1.78]
Social Service Involvement		527 (2.13)	66 (6.06)	16 (4.97)	69 (2.43)	2.40 [1.84,3.13]	2.12 [1.27,3.56]	0.82 [0.46,1.46]	1.20 [0.93,1.55]
Events Occur Before the Age of 18									
Family History of Mental Illness		4966 (20.1)	373 (34.2)	129 (40.1)	705 (24.8)	1.80 [1.58,2.05]	2.37 [1.89,2.99]	**1.34 [1.03,1.75]**	1.29 [1.18,1.42]
Divorced Parents		2283 (9.2)	173 (15.9)	42 (13)	312 (11)	1.62 [1.37,1.93]	1.24 [0.89,1.74]	0.81 [0.59,1.11]	1.13 [1.00,1.28]
Deceased/Severely Ill Parents		3822 (15.5)	245 (22.5)	61 (18.9)	482 (16.9)	1.70 [1.46,1.97]	1.38 [1.04,1.83]	0.76 [0.53,1.11]	1.15 [1.03,1.28]

< Abbreviation >
TSD: trauma-associated sleep disorder
DEB^{PTSD-}: PTSD-free dream enactment behavior
$PTSD^{DEB-}$: DEB-free post-traumatic stress disorder

Table 3. Summary Psychiatric Signs/Symptoms and Comorbid Sleep Symptoms

		Symptom-free N=25,021	$PTSD^{DEB-}$ N=1,122	TSD N=331	DEB^{PTSD-} N=2,897	$PTSD^{DEB-}$ vs Symptom-free	TSD vs Symptom-free	TSD vs $PTSD^{DEB-}$	DEB^{PTSD-} vs Symptom-free
		N(%) or Mean±SD				$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]			
Psychiatric Signs/Symptoms									
Distress	K-10 Score	13.9±4.1	18.9±7.1	20.7±7.2	15±4.8	1.16 [1.14,1.17]	1.19 [1.17,1.21]	**1.04 [1.02,1.05]**	1.06 [1.05,1.07]
	Clinically Distressed	641 (2.71)	196 (19)	90 (29.8)	130 (4.76)	7.44 [6.21,8.92]	14.2 [10.9,18.6]	**1.80 [1.34,2.41]**	1.85 [1.53,2.25]
Mood Disorder	Positive Diagnosis	3670 (14.7)	467 (41.7)	186 (56.2)	660 (22.8)	3.62 [3.19,4.12]	7.11 [5.65,8.95]	**1.82 [1.42,2.34]**	1.83 [1.66,2.01]
	Anxiety Disorder	1755 (7)	294 (26.4)	120 (36.5)	340 (11.8)	4.17 [3.61,4.82]	7.13 [5.63,9.03]	**1.64 [1.26,2.13]**	1.84 [1.62,2.09]
	Depressive Disorder	3484 (14)	471 (42.4)	178 (54.1)	630 (21.8)	3.94 [3.46,4.47]	6.95 [5.52,8.73]	**1.66 [1.29,2.14]**	1.84 [1.67,2.03]
	CESD-10-R Score	6.9±4.3	12.2±6.6	13.9±6.8	7.6±4.7	1.18 [1.16,1.19]	1.22 [1.20,1.24]	**1.04 [1.02,1.06]**	1.04 [1.04,1.05]
	Antidepressant Use	1598 (6.4)	260 (23.6)	115 (35.4)	372 (12.9)	3.80 [3.27,4.43]	7.54 [5.90,9.64]	**1.85 [1.41,2.43]**	2.34 [2.07,2.65]
Comorbid Sleep Symptoms									
Poor Sleep Quality		6047 (24.2)	468 (41.7)	161 (48.7)	837 (28.9)	2.07 [1.83,2.34]	2.85 [2.29,3.54]	**1.33 [1.04,1.71]**	1.31 [1.20,1.43]
Circadian Rhythm	Sleep Hours	6.82±1.21	6.54±1.58	6.62±1.92	6.8±1.33	0.85 [0.80,0.90]	0.89 [0.77,1.02]	1.03 [0.96,1.12]	1.00 [0.97,1.04]
	Onset Insomnia	3341 (13.4)	340 (30.4)	111 (33.5)	533 (18.4)	2.59 [2.26,2.97]	3.27 [2.59,4.14]	1.20 [0.93,1.57]	1.60 [1.45,1.78]
	Maintenance Insomnia	5265 (21.1)	435 (38.8)	144 (43.5)	716 (24.8)	2.27 [2.01,2.58]	2.88 [2.31,3.58]	1.24 [0.97,1.60]	1.28 [1.17,1.41]
	Hypersomnolence	1788 (7.2)	202 (18.1)	90 (27.4)	277 (9.6)	3.15 [2.68,3.71]	5.35 [4.18,6.86]	**1.62 [1.22,2.16]**	1.40 [1.23,1.60]
Sleep Breathing Disorder	Obstruction/Snore	5545 (25.3)	284 (29.8)	98 (34.5)	821 (32)	1.52 [1.31,1.76]	2.18 [1.66,2.86]	**1.44 [1.06,1.96]**	1.45 [1.32,1.59]
	Obstruction+Snore	1723 (7.9)	106 (11.1)	61 (21.5)	364 (14.2)	2.00 [1.60,2.49]	4.49 [3.21,6.28]	**2.39 [1.64,3.50]**	1.94 [1.71,2.20]
	STOP-BAG Score	1.95±1.06	2.02±1.18	2.56±1.33	2.26±1.17	1.50 [1.40,1.60]	2.05 [1.85,2.28]	**1.40 [1.24,1.59]**	1.26 [1.20,1.31]
Restless Leg Syndrome (ICSD-2)		3752 (15.2)	278 (25.1)	119 (37.1)	602 (21.1)	1.78 [1.54,2.05]	3.42 [2.72,4.31]	**1.96 [1.50,2.57]**	1.64 [1.49,1.81]

< Abbreviation >
TSD: trauma-associated sleep disorder
DEB^{PTSD-}: PTSD-free dream enactment behavior
$PTSD^{DEB-}$: DEB-free post-traumatic stress disorder
K10: Kessler Psychological Distress Scale
CESD-10-R: Center for Epidemiologic Studies Depression Scale Revised
Obstruction: obstruction of airway
STOP-BAG: snoring, tiredness, obstruction of airway, hypertension, high BMI, older age, and male gender
ICSD: International Classification of Sleep Disorders

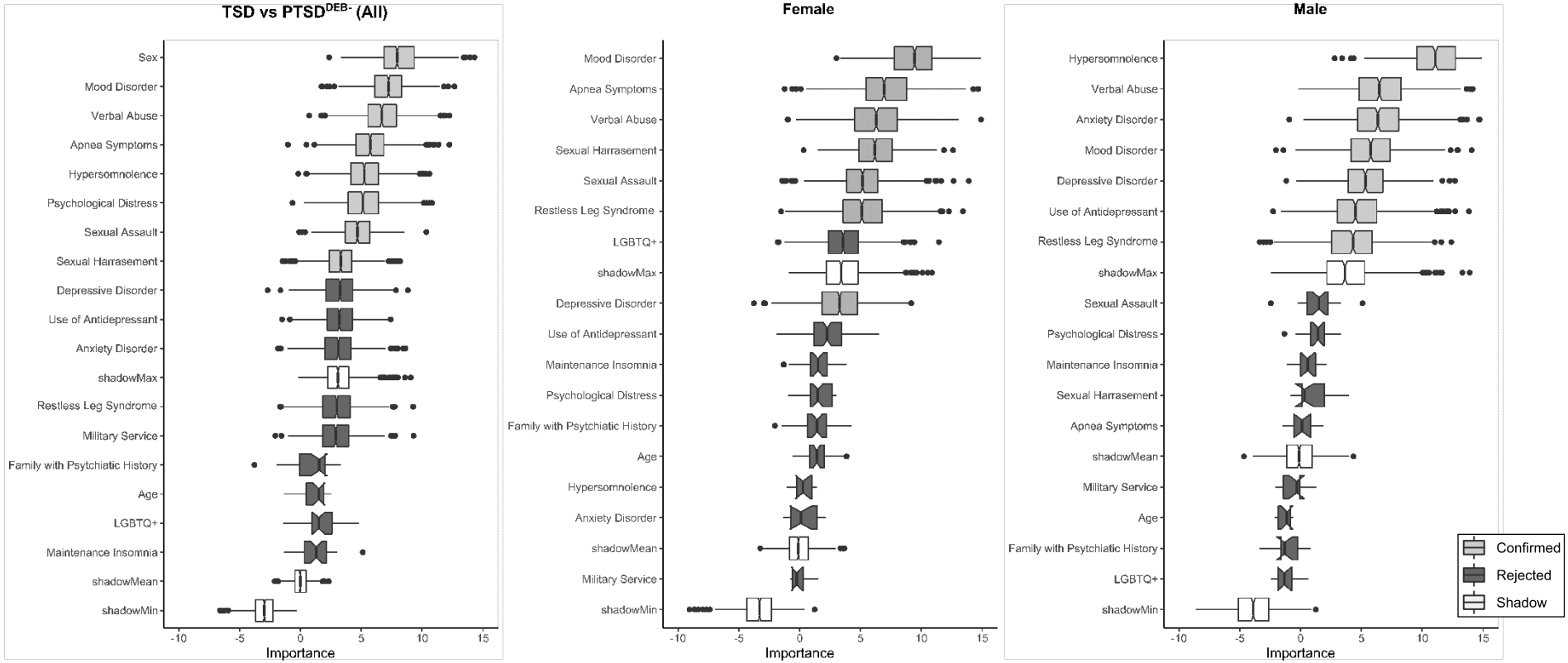

Figure 2. Robust Clinical Determinants – TSD verse PTSD^{DEB-}

To assess importance and robustness of the associated variables/predictors individually, all the associated variables from primary analysis were re-evaluated using the Boruta algorithm, a Random Forest classification-based permutation and feature ranking algorithm.[55] Variables were either confirmed or rejected based on permutation tests (with 1000 iterations). The results were then reassessed among female and male participants separately. Variables failed permutation tests were colored in dark grey with the descriptive summary of the 'shadow' variables in white. Note that no statistical adjustment was performed in all permutation tests.

Apnea symptoms were recorded in three levels: no symptom, obstruction of airway/snoring, or presenting with both symptoms.

e-Methods

Detailed Questions

Information regarding to childhood maltreatment and related events were queried via questions from the Childhood Experiences of Violence Questionnaire.[1]

Before age 16, how many times did…

<Domestic>	
Witness Verbal Violence	you see or hear any one of your parents, step-parents or guardians say hurtful or mean things to each other or to another adult in your home?
Witness Physical Violence	you see or hear any one of your parents, step-parents or guardians hit each other or another adult in your home? By adult, I mean anyone 18 years and over.
Physical Punishment	a parent or caregiver spank you with their hand on your bottom (bum), or slap you on your hand?
Verbal Abuse	any one of your parents, step-parents or guardians swear at you, or say hurtful, insulting things that made you feel like you were not wanted or loved?
Negligence	your parents, step-parents or guardians not take care of your basic needs, such as keeping you clean or providing food or clothing?
Police Involvement	did you ever see or talk to the police or anyone from child protective services about any of the things you mentioned?
<Non-spatial Specific>	
Physical Violence Mild	an adult push, grab, shove or throw something at you to hurt you?
Physical Violence Moderate	an adult slap you on the face, head or ears or hit or spank you with something hard to hurt you?
Physical Violence Severe	an adult kick, bite, punch, choke, burn you, or physically attack you in some way?
Sexual Harassment	an adult touch you against your will in any sexual way? By this, I mean anything from unwanted touching or grabbing, to kissing or fondling.
Sexual Assault	an adult force you or attempt to force you into any unwanted sexual activity, by threatening you, holding you down or hurting you in some way?

Three additional related questions were adapted from the National Longitudinal Study of Adolescent to Adult Health Wave III Questionnaire.[2]
Before the age of 18, did…

Family History of Mental Illness	did anyone in your family ever suffer from mental or psychiatric illness or have a “breakdown” ?
Divorced Parents	you experience the divorce or separation of your parents?
Physical	you ever experience the death or serious illness of a parent or a primary caretaker?

Additional Case Definition

Sleep Disorders/Symptoms

Participants were screened for insomnia symptoms with two questions during the initial interview, adapted from the Pittsburgh Sleep Quality Index[3], namely:

1. "Over the last month, how often did it take you more than 30 minutes to fall asleep?" and
2. "Over the last month, how often did you wake in the middle of the night or too early in the morning and found it difficult to fall asleep again?".

Those who answered 'yes' to either of the two questions, with symptom frequency of at least 3 nights-per-week were considered as having insomnia symptoms. To avoid transient insomnia symptoms, participants with symptom onset within 3 months were defined as negative of insomnia symptom.

Following the similar logic, hypersomnolence (a.k.a. daytime sleepiness) was defined as positive of subjective experience of trouble staying awake during daytime at least 6 days per week for minimum of 3 month.

Psychological Distress Symptom Profile

Symptoms of psychological distress assessed via Kessler's questionnaire[4] were first dichotomized into two categories: increase in symptom frequency and nil. Both continuous and factorial forms of individual items were then profiled via mixed data factor analysis separately to assess the stability of the features.[5] Differences among individual symptoms between TSD and $PTSD^{DEB-}$ were assessed via logistic regression after adjusting for age and sex. To explore the effect of antidepressant treatment, additional adjustment via regression modeling was performed.

Subgroup analyses after stratifying by biological sex, were also performed after excluding biological sex from the regression model.

Additional Point Prevalence Estimate

Prevalence of $PTSD^{DEB-}$ and TSD were bootstrapped for 1000 iteration with/without inflation weight, calculated based on the inclusion probabilities for each individual during sampling, and bootstrapped for 1000 iteration. All prevalence were also recalculated within each stratum based on age groups (10-year interval) sex, ethnicity, immigration status, LGBTQ+ identity and military service. Estimates were computed using in R via the *survey* package.

Intervariable Associations

To further understand the complex associations between predictors and sleep symptoms found associated with TSD, we performed a series of analysis using logistic regression adjusting for age and sex. For apnea symptoms, the point estimates were assessed in both multinomial (lognorm-link) and logistic regression (as a predictor). Since the results were similar in both cases, only results assessed via logistic regression were presented. Statistical significance was determined based on the 95% confidence interval.

e-Results

Sleep

No clear difference in average hours of sleep among groups except for PTSD^{DEB-} having slightly less than the average of symptom-free (6.54±1.58 verse 6.82±1.21 hours). But when assessing if participants were more likely sleep less than 8 hours-per-night, there was no difference across the groups, indicating the associations been driven by a small group of individuals.

Associations between Variables and Predictors among participants with TSD

Among the variables assessed, an increase in association between antidepressant and apnea symptoms was noted. (e-5) However, this association was more prominent among female sex. In addition, we also noted an increase in association between antidepressants and hypersomnolence, which was a male-dominant feature. (e-4) Interestingly, poor sleep quality was strongly associated with maintenance insomnia, which was rejected as an independent predictor in the permutation test, among TSD. Of male participants with TSD, poor sleep quality was associated with hypersomnolence.

e-References

1. Walsh CA, MacMillan HL, Trocmé N, Jamieson E, Boyle MH. Measurement of victimization in adolescence: Development and validation of the Childhood Experiences of Violence Questionnaire. *Child Abuse & Neglect*. 2008/11/01/ 2008;32(11):1037-1057. doi:https://doi.org/10.1016/j.chiabu.2008.05.003
2. Harris KM, Halpern CT, Whitsel EA, et al. Cohort Profile: The National Longitudinal Study of Adolescent to Adult Health (Add Health). *International Journal of Epidemiology*. 2019;48(5):1415-1415k. doi:10.1093/ije/dyz115
3. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. May 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
4. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). *Aust N Z J Public Health*. Dec 2001;25(6):494-7. doi:10.1111/j.1467-842x.2001.tb00310.x
5. J. P. Analyse factorielle de données mixtes. *Revue de statistique appliquée*. 2004;52(4):93-111.

Table e-1. Prevalence of PTSD, TSD and PTSD^{DEB-} among Canadians aged 45-85

		Unweighted			Weighted		
		PTSD	PTSD^{DEB-}	TSD	PTSD	PTSD^{DEB-}	TSD
		Point Prevalence (per-100-person)			Point Prevalence (per-100-person)		
Unstratified		4.97 [4.77,5.22]	3.83 [3.61,4.05]	1.11 [1.00,1.23]	5.45 [5.12,5.79]	4.18 [3.88,4.48]	1.26 [1.09,1.43]
Age Group	45-54	6.63 [6.05,7.21]	5.05 [4.55,5.56]	1.60 [1.32,1.88]	6.42 [5.80,7.04]	4.83 [4.28,5.37]	1.62 [1.28,1.96]
	55-64	5.72 [5.26,6.17]	4.44 [4.04,4.85]	1.25 [1.03,1.15]	5.66 [5.12,6.20]	4.40 [3.93,4.87]	1.23 [0.97,1.49]
	65-74	3.88 [3.44,4.34]	3.01 [2.613.42]	0.83 [0.63,1.02]	4.11 [3.55,4.67]	3.22 [2.74,3.71]	0.81 [0.57,1.05]
	75+	2.65 [2.21,3.09]	2.06 [1.67,2.45]	0.54 [0.34,0.74]	3.28 [2.60, 3.95]	2.59 [2.00,3.17]	0.67 [0.35,0.99]
Biological Sex	Male	3.42 [3.13,3.71]	2.41 [2.15,2.66]	1.00 [0.84,1.16]	3.92 [3.49,4.35]	2.73 [2.36,3.10]	1.18 [0.94,1.43]
	Female	6.46 [6.06,6.87]	5.21 [4.84,5.57]	1.22 [1.05,1.39]	6.96 [6.46,7.46]	5.61 [5.15,6.06]	1.34 [1.11,1.57]
Social Minority Status							
Ethnicity	Caucasian	4.89 [4.64,5.13]	3.75 [3.52,3.97]	1.11 [0.94,1.23]	5.37 [5.03,.571]	4.10 [3.79,4.40]	1.26 [1.09,1.44]
	Non-Caucasian	6.86 [5.33,8.38]	5.65 [4.28,7.02]	1.18 [0.54,1.82]	7.07 [5.23,8.91]	5.71 [4.07,7.36]	1.28 [0.43,2.13]
Immigration Status	Immigrant	5.10 [4.83,5.38]	3.90 [3.65,4.14]	1.19 [1.06,1.32]	5.58 [5.21,5.95]	4.23 [3.90,4.56]	1.35 [1.16,1.55]
	Non-Immigrant	4.36 [3.82,4.91]	3.55 [3.05,4.05]	0.76 [0.53,1.00]	4.87 [4.15,5.58]	3.95 [3.31,4.59]	0.84 [0.52,1.16]
LGBTQ+ Status	Straight	4.91 [4.66,5.16]	3.81 [3.58,4.04]	1.08 [0.96,1.19]	5.39 [5.06,5.73]	4.16 [3.86,4.46]	1.22 [1.05,1.39]
	LGBTQ+	6.89 [4.97,8.81]	4.28 [2.77,5.79]	2.44 [1.28,3.60]	7.40 [4.89,9.92]	4.44 [2.42,6.46]	2.81 [1.20,4.41]
Military and Retirement Status							
Military Service	Civilian	5.04 [4.78,5.31]	3.94 [3.70,4.17]	1.08 [0.96,1.20]	5.40 [5.06,5.74]	4.21 [3.91,4.51]	1.17 [1.01,1.33]
	Veterans	4.25 [3.49,5.00]	2.76 [2.14,3.38]	1.48 [1.02,1.95]	6.16 [4.74,7.58]	3.84 [2.74,4.94]	2.40 [1.44,3.35]

Prevalence was estimated using the inflation weight calculated to reflect the distribution in Canada.

< Abbreviation >
PTSD: post-traumatic stress disorder
TSD: trauma-associated sleep disorder
PTSD^{DEB-}: DEB-free post-traumatic stress disorder

Table e-2. Sociodemographic Status by Sex

		Male			***Female***		
		$PTSD^{DEB-}$ N= 346	TSD N= 146	TSD vs $PTSD^{DEB-}$	$PTSD^{DEB-}$ N= 776	TSD N= 185	TSD vs $PTSD^{DEB-}$
		N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]	N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]
Demographic Profile							
Age		60.3±9.2	59.5±9	1.00 [0.97,1.02]	60.1±9.3	59.2±9.4	0.99 [0.98,1.01]
Married/Common-law		221 (70.4)	98 (73.1)	1.16 [0.74,1.83]	439 (61.1)	105 (61.4)	1.04 [0.74,1.47]
Years of Education		13.1±2.4	13.5±2.5	1.07 [0.98,1.16]	12.9±2.3	12.6±2.3	0.94 [0.88,1.02]
Socioeconomical Statuses and Social Minority Status							
Annual Income (per 1,000 CAD)		52.6±37.9	59.8±37.7	1.01 [1.00,1.01]	39.1±28.9	33±24.5	1.00 [0.99,1.00]
Ethnicity (Non-caucasian %)		24 (7.04)	8 (5.52)	0.77 [0.34,1.75]	37 (4.81)	5 (2.72)	0.54 [0.21,1.41]
Immigration Status		65 (18.8)	22 (15.8)	0.78 [0.46,1.33]	123 (15.9)	19 (10.3)	0.62 [0.37,1.03]
LGBTQ+ Status		15 (4.37)	6 (4.17)	0.91 [0.35,2.39]	14 (1.82)	11 (5.95)	**3.34 [1.49,7.49]**
Military and Retirement Status							
Military Service	Yes	57 (16.5)	34 (23.3)	1.55 [0.96,2.50]	16 (2.07)	6 (3.25)	1.58 [0.62,4.04]
	Years of Service	7.6± 9.9	14.4±12.7	1.06 [1.02,1.10]	10.9±11.8	8±9.1	0.94 [0.85,1.04]
Retirement Status	Retired	187 (54.2)	72 (49.3)	0.88 [0.54,1.44]	374 (48.5)	97 (53.3)	**1.67 [1.10,2.53]**
	Retired Age	56±7.1	55.5±7.4	1.00 [0.96,1.03]	56.2±7	54.5±7.8	0.98 [0.94,1.01]

< Abbreviation >
TSD: trauma-associated sleep disorder
$PTSD^{DEB-}$: DEB-free post-traumatic stress disorder

Table e-3. Childhood Traumatic Experience and Associations to Dream Enactment Behavior by Sex

		Male			***Female***		
		$PTSD^{DEB-}$ N= 346	TSD N= 146	TSD vs $PTSD^{DEB-}$	$PTSD^{DEB-}$ N= 776	TSD N= 185	TSD vs $PTSD^{DEB-}$
		N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]	N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]
Events Occur Before the Age of 16							
Non-spatial Specific Events							
Physical Violence	Mild	112 (33.6)	61 (42.1)	1.42 [0.95,2.12]	198 (26.2)	51 (28.8)	1.12 [0.78,1.60]
	Moderate	192 (57.7)	86 (59.3)	1.06 [0.71,1.58]	354 (46.8)	100 (56.5)	1.45 [1.04,2.02]
	Sever	78 (23.4)	42 (29)	1.32 [0.85,2.05]	112 (14.8)	36 (20.3)	1.45 [0.96,2.19]
Sexual Harassment		54 (16.2)	31 (21.4)	1.39 [0.85,2.27]	245 (32.4)	77 (43.5)	**1.58 [1.13,2.20]**
Sexual Assault		40 (12)	19 (13.1)	1.09 [0.61,1.95]	170 (22.5)	55 (31.1)	**1.52 [1.06,2.19]**
Domestic Events							
Witness Domestic Violence	Verbal	66 (19.8)	40(27.6)	1.53 [0.97,2.42]	158 (20.9)	46 (26)	1.31 [0.90,1.92]
	Physical	173 (52)	82 (56.6)	1.18 [0.80,1.76]	378 (49.9)	96 (54.2)	1.15 [0.82,1.60]
Physical Punishment		257 (77.2)	115 (79.3)	1.10 [0.68,1.79]	548 (72.4)	127 (71.8)	0.93 [0.65,1.34]
Verbal Abuse		147 (44.2)	85 (58.6)	**1.78 [1.19,2.66]**	370 (48.9)	115 (65)	**1.91 [1.36,2.70]**
Negligence		27 (8.11)	11 (7.59)	0.93 [0.44,1.93]	71 (9.4)	25 (14.1)	1.60 [0.98,2.60]
Social Service Involvement		17 (5.11)	5 (3.45)	0.64 [0.23,1.80]	49 (6.5)	11 (6.2)	0.93 [0.47,1.84]
Events Occur Before the Age of 18							
Family History of Mental Illness		93 (27.9)	50 (34.5)	1.35 [0.88,2.06]	280 (37)	79 (44.6)	1.34 [0.96,1.88]
Divorced Parents		82 (24.6)	29 (20)	0.78 [0.49,1.26]	163 (21.5)	32 (18.1)	0.82 [0.54,1.26]
Deceased/Severely Ill Parents		58 (17.4)	16 (11)	0.58 [0.32,1.04]	115 (15.2)	26 (14.7)	0.92 [0.58,1.47]

< Abbreviation >
TSD: trauma-associated sleep disorder
$PTSD^{DEB-}$: DEB-free post-traumatic stress disorder

Table e-4. Summary Psychiatric Signs/Symptoms and Comorbid Sleep Symptoms by Sex

		Male			***Female***		
		PTSD^{DEB-} N= 346	TSD N= 146	TSD vs PTSD $^{DEB-}$	PTSD^{DEB-} N= 776	TSD N= 185	TSD vs PTSD $^{DEB-}$
		N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]	N (%) or Mean±SD		$OR_{Age\ Adjusted}$ [95%CI]
Psychiatric Signs/Symptoms							
Distress	K-10 Score	18.8±6.9	20.5±7.1	**1.04 [1.01,1.07]**	19±7.1	21±7.3	**1.04 [1.02,1.06]**
	Clinically Distressed	63 (19.9)	36 (27.1)	1.48 [0.93,2.37]	133 (18.6)	54 (32)	**2.06 [1.42,2.99]**
Mood Disorder	Positive Diagnosis	128 (37.2)	82 (56.2)	**2.15 [1.45,3.18]**	339 (43.8)	104 (56.2)	**1.66 [1.20,2.29]**
	Anxiety Disorder	73 (21.2)	56 (38.4)	**2.30 [1.51,3.50]**	221 (28.7)	64 (35)	1.34 [0.95,1.89]
	Depressive Disorder	123 (36.1)	75 (51.7)	**1.88 [1.27,2.79]**	348 (45.1)	103 (56)	**1.55 [1.12,2.14]**
	CESD-10-R Score	11.7±6.7	13.9±6.9	**1.05 [1.02,1.08]**	12.4±6.6	13.9±6.8	**1.04 [1.02,1.06]**
	Antidepressant Use	57 (16.9)	49 (34.3)	**2.54 [1.61,3.99]**	203 (26.6)	66 (36.3)	**1.57 [1.12,2.22]**
Comorbid Sleep Symptoms							
Poor Sleep Quality		137 (39.6)	69 (47.3)	1.36 [0.92,2.01]	331 (42.7)	92 (49.7)	1.31 [0.95,1.81]
Circadian Rhythm	Sleep Hours	6.53±1.63	6.60±2.12	1.03 [0.92,1.15]	6.56±1.57	6.64±1.77	1.04 [0.93,1.16]
	Onset Insomnia	92 (26.6)	40 (27.4)	1.03 [0.67,1.58]	248 (32.1)	71 (38.4)	1.32 [0.95,1.84]
	Maintenance Insomnia	132 (38.2)	52 (35.6)	0.90 [0.60,1.34]	303 (39.1)	92 (49.7)	**1.54 [1.12,2.13]**
	Daytime Sleepiness[a]	78 (22.6)	55 (37.7)	**2.12 [1.39,3.22]**	124 (16)	35 (19.1)	1.27 [0.84,1.92]
Sleep Breathing Disorder	Obstruction/Snore	118 (39.9)	47 (36.7)	0.98 [0.62,1.55]	166 (25.3)	51 (32.7)	**1.89 [1.27,2.83]**
	Obstruction+Snore	46 (15.6)	27 (21.1)	1.43 [0.81,2.53]	60 (9.14)	34 (21.8)	**3.48 [2.13,5.68]**
	STOP-BAG Score	2.90±1.01	3.26±1.15	**1.40 [1.15,1.71]**	1.63±1.03	1.99±1.2	**1.41 [1.20,1.65]**
Restless Leg Syndrome (ICSD-2)		62 (18)	39 (27.3)	**1.73 [1.09,2.73]**	216 (28.3)	80 (45)	**2.10 [1.50,2.94]**

[a] Daytime sleepiness was defined as subjects experiencing trouble staying awake during daytime at least 6 days per week for minimum of 3 month. Participants who slept less than 6 hours on average per night or self-reported endorsing narcolepsy, were excluded.

< Abbreviation >
TSD: trauma-associated sleep disorder
PTSD^{DEB-}: DEB-free post-traumatic stress disorder

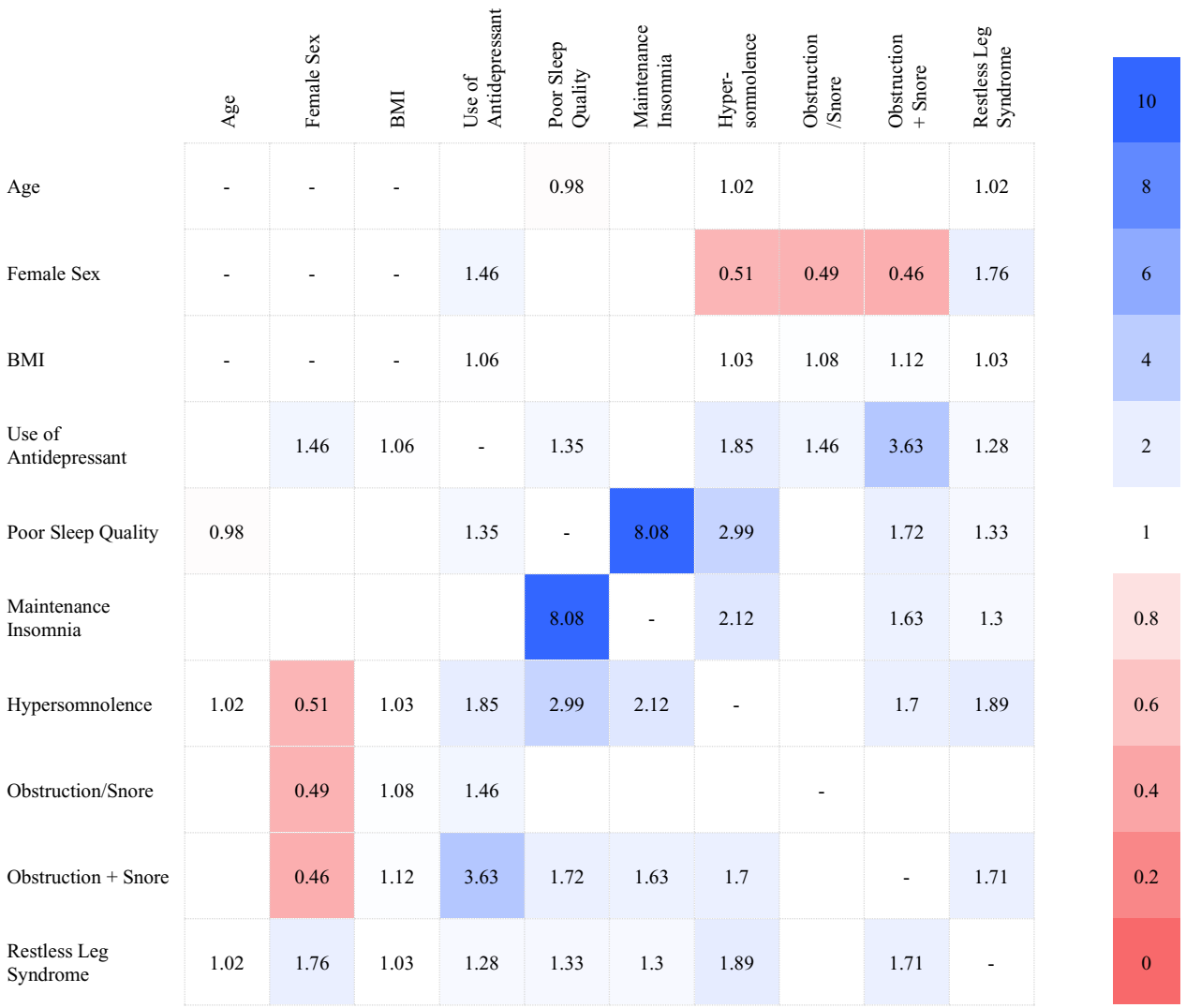

Figure e-5. Association Matrix of Predictors/Independent Variables within Participants with Post-traumatic Stress Disorder

To further understand the associations among predictors and associated factors of trauma-associated sleep disorder, a list of variables known to associate with REM sleep behavior disorder was elected. Associations between variables were assessed using logistic regression adjusting for age and sex. Statistical significance was determined based on the estimated 95% confidence interval. Associations failed to reject the null hypothesis were left blank. Associations among age, sex and BMI were not computed.

Section II – Insomnia and its Subtypes

General Introduction

Insomnia is one of the most common sleep-related disorders and symptoms. It is estimated that 16-21% of the general population experiences some difficulty initiating or maintaining sleep at least 3 nights per week, and prevalence rises with age worldwide.[1] When assessing based on different criteria, insomnia prevalence may alter from half of this estimate, as a disorder, to twice or three times higher of this estimate, as a symptom.[2,3] Although insomnia has been commonly regarded as a by-product of normal aging or a symptom of a predisposed condition (e.g., stress and illness)[4-7], recent studies have indicated that insomnia may serve as a risk/causal factor to certain health events. This is perhaps best exemplified by the recent surge of evidence showing the bi-directional causal relationship between insomnia and anxiety/depressive disorders.[3]

Clinical Diagnosis, Screening Tools and Definitions

In clinical practice, insomnia diagnoses are made mostly without polysomnography, although it can be useful to rule out insomnia as a secondary symptom to restless leg syndrome or apnea. Although the concept of diagnostic criteria for insomnia has been available for quite some time, insomnia classifications are not uniformed till recent years. Historically, insomnia diagnosis can be further subtyped into psychophysiological, paradoxical, psychiatric or behavioral insomnia depending on the iteration and the referenced diagnostic guidelines [3,8,9] One primary reason for the unification of diagnosis in the latest DSM (termed, persistent insomnia disorder) and ICSD (chronic insomnia) guidelines is that lack of evidence for independent mechanisms underlying each priorly proposed subtypes.[10] Besides chronic insomnia diagnosis, most guidelines have also agreed on two major symptomatic subtypes: sleep-onset and -maintenance insomnia.

Many questionnaires have been adapted or developed for the use of both clinical diagnosis and research purposes, with a few commonly used ones including the Insomnia Severity Index[11-13], the Insomnia Screening Scale[14], the Women's Health Initiative Insomnia Rating Scale[15], the Pittsburgh Sleep Quality Index[16], the modified Karolinska Sleepiness Scale[11], and the Athens Insomnia Scale[17]. And, of all, both the Insomnia Severity Index (cut-off ≥11) and the Pittsburgh Sleep Quality Index (cut-off ≥5) are the two earliest developed tools but still maintain good-to-excellent accuracy based on the current DSM-V and ICSD-3 diagnostic criteria.[11,17,18]

Most insomnia research to-date can be categorized into symptomatic- and disorder-based studies. With regards to the effect of the recent changes in criteria, these alterations have a heavier impact in studies either relying on digital diagnostic registries or of insomnia disorders than that of insomnia symptoms.[3,8,9] This is because most studies focus on three major symptomatic subtypes: difficulty initiating sleep (i.e., sleep-onset insomnia), difficulty maintaining sleep (i.e., sleep-maintenance insomnia) and waking up earlier than desired (i.e., terminal insomnia). Of note, definitions of both sleep-onset and -maintenance insomnia symptoms are much more consistent throughout studies and across diagnostic guidelines than the latter.

Chronic Insomnia and associated Health Outcome

Besides the alteration in symptomatic description and frequency of insomnia diagnosis, the latest insomnia diagnostic criteria also emphasize the importance of insomnia symptom duration, which often varies greatly among studies.[19,20] As illustrated in prior paragraphs, precipitating factors such as stress, recent events, shiftwork and jetlag, can often trigger insomnia symptoms. In general, most insomnia symptoms resolve after the withdrawal of the external triggers.[21,22] Of the

studies to-date, most suggested that patients who developed chronic (duration ≥3 months) or recurrent insomnia, are more likely to have health burdens compared to those with transient/acute insomnia.[21]

Insomnia disorders have been shown as a risk factor and as prodromal symptoms predating cardiological, psychiatric and neurological conditions.[4,5,23-26] Of the psychiatric conditions assessed, a recent systematic meta-analysis found insomnia disorder to be a significant predictor for depression (OR=2.83, 95%CI=[1.55,5.17]) and anxiety (OR=3.23[1.52,6.85]) calculated via mixed-effect modelling.[5] Interestingly, the same study also noted that the negative daytime impact required for making an insomnia diagnosis only moderately elevated the association between depression and insomnia based on results of prior meta-analyses (OR=2.60 [1.98,3.42], 2.27[1.89,2.71]).[27,28] Another systematic-meta analysis also found no clear difference between insomnia disorders and insomnia symptoms in association with all-cause mortality in sensitivity analyses.[20] Of note, since most reviews did not assess the difference between insomnia disorders and insomnia symptoms in association with the subsequent health outcomes, it is difficult to determine if negative daytime impact draws a significant contribution in the associations. Future studies will be needed.

Neurodegeneration and Health Outcomes Associated with different Insomnia Symptoms

As symptoms, studies have found positive associations between insomnia and several health events, including depression/anxiety disorders, cardiovascular diseases, parkinsonism and Alzheimer's dementia.[20,26,29,30] In parkinsonism, studies have shown an increase in sleep-maintenance insomnia before and after phenoconversion.[6,31] In dementia, associations with specific subtypes of insomnia symptoms are less clear although insomnia symptoms have been

found predating dementia diagnosis in several studies.[32-35] And, with the increase in absence of associations between insomnia and cognitive decline found in recent studies, the role of insomnia symptoms as a marker or prodromal symptom of dementia becomes questionable.[36,37] Similarly, in parkinsonism, although sleep-maintenance insomnia has been found in patients with idiopathic REM sleep behavior disorder, both local and large-scale international studies found no link between insomnia and phenoconversion rate.[38] Besides neurological events, insomnia symptoms have also been found associated with cardio- and cerebrovascular events in previous studies.[4,20,39] In a Taiwan National Health Insurance Research Database study, insomnia was found as a risk factor for heart attack (HR=1.68 [1.31,2.16]) and stroke (HR=1.85 [1.62,2.12]).[40] Another population-based study using the Nord Trøndelag Health Study cohort also found an increase in the relative risk rate of heart attack in both insomnia subtypes (all insomnia HR=1.45 [1.18 ,1.80], sleep-onset HR=1.30 [1.01,1.68], sleep-maintenance HR=1.27 [1.03,1.57]).[41] Interestingly, only sleep-onset insomnia was found associated with future cardiovascular disease-related mortality in a recent systematic meta-analysis.[20] One possible reason for the variability in the associations discussed above may be the comorbidities of multiple insomnia symptoms. The mix of different classifications can often result in biases similar to the results of differential misclassification. And, with the commonly comorbid sleep deprivation confounding the results, it is hard to assess the independent association between the outcome and a specific insomnia symptom subtype.

Goals and Objectives

To untangle this complex association network for cardiovascular, parkinsonism and dementia-related neurodegeneration with insomnia, the second section of this thesis focuses on assessing neurodegenerative risks in those with isolated insomnia symptom subtypes (i.e., sleep-

onset or -maintenance insomnia). Two chapters were set up to assess the neurodegenerative risks and outcomes associated with insomnia in the Canadian population:

- Isolated Insomnia Symptom Subtypes and Manifestations of Prodromal Neurodegeneration
- Prospective Health Outcome of Isolated Insomnia Symptom

References

1. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002; 6 (2): 97-111.
2. Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M. Prevalence of insomnia in a survey of 12 778 adults in France. Journal of Sleep Research. 2000; 9 (1): 35-42.
3. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. World Psychiatry. 2019; 18 (3): 337-352.
4. Javaheri S, Redline S. Insomnia and Risk of Cardiovascular Disease. Chest. 2017; 152 (2): 435-444.
5. Hertenstein E, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. Sleep Medicine Reviews. 2019; 43: 96-105.
6. Tholfsen LK, Larsen JP, Schulz J, Tysnes O-B, Gjerstad MD. Changes in insomnia subtypes in early Parkinson disease. Neurology. 2017; 88 (4): 352-358.
7. Shi L, Chen S-J, Ma M-Y, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med Rev. 2018; 40: 4-16.
8. Ito E, Inoue Y. [The International Classification of Sleep Disorders, third edition. American Academy of Sleep Medicine. Includes bibliographies and index]. Nihon Rinsho. 2015; 73 (6): 916-923.
9. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Press; 2000. 553–557.
10. American Psychiatric A. *Diagnostic and statistical manual of mental disorders : DSM-5.* 5th ed. ed. Arlington, VA

Washington, D.C.: American Psychiatric Association; 2013.
11. Filosa J, Omland PM, Langsrud K, et al. Validation of insomnia questionnaires in the general population: The Nord-Trondelag Health Study (HUNT). J Sleep Res. 2021; 30 (1): e13222.
12. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin. 2009; 25 (10): 2487-2494.
13. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001; 2 (4): 297-307.
14. Yeh Z-T, Chiang RP-Y, Kang S-C, Chiang C-H. Development of the Insomnia Screening Scale Based on ICSD-II. International Journal of Psychiatry in Clinical Practice. 2012; 16 (4): 259-267.
15. Levine DW, Kripke DF, Kaplan RM, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess. 2003; 15 (2): 137-148.
16. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28 (2): 193-213.
17. Ali RM, Zolezzi M, Awaisu A. A Systematic Review of Instruments for the Assessment of Insomnia in Adults. Nat Sci Sleep. 2020; 12: 377-409.
18. Dietch JR, Taylor DJ, Sethi K, Kelly K, Bramoweth AD, Roane BM. Psychometric Evaluation of the PSQI in U.S. College Students. Journal of Clinical Sleep Medicine. 2016; 12 (08): 1121-1129.
19. Berry RB. Insomnia. In: Elsevier; 2012: 481-514.
20. Ge L, Guyatt G, Tian J, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. Sleep Med Rev. 2019; 48: 101215.
21. Yang C-M, Lin S-C, Cheng C-P. Transient Insomnia Versus Chronic Insomnia: A Comparison Study of Sleep-Related Psychological/Behavioral Characteristics. Journal of Clinical Psychology. 2013; 69 (10): 1094-1107.

22. Perlis ML, Vargas I, Ellis JG, et al. The Natural History of Insomnia: the incidence of acute insomnia and subsequent progression to chronic insomnia or recovery in good sleeper subjects. Sleep. 2020; 43 (6).
23. Shamim SA, Warriach ZI, Tariq MA, Rana KF, Malik BH. Insomnia: Risk Factor for Neurodegenerative Diseases. Cureus. 2019.
24. Almondes KMD, Costa MV, Malloy-Diniz LF, Diniz BS. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. Journal of Psychiatric Research. 2016; 77: 109-115.
25. Morin CM, Jarrin DC. Epidemiology of Insomnia. Sleep Medicine Clinics. 2013; 8 (3): 281-297.
26. Hung CM, Li YC, Chen HJ, et al. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatry. 2018; 18 (1): 38.
27. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011; 135 (1-3): 10-19.
28. Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. BMC Psychiatry. 2016; 16 (1): 375.
29. de Almondes KM, Costa MV, Malloy-Diniz LF, Diniz BS. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. J Psychiatr Res. 2016; 77: 109-115.
30. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis. 2017; 3: 9.
31. Loddo G, Calandra-Buonaura G, Sambati L, et al. The Treatment of Sleep Disorders in Parkinson's Disease: From Research to Clinical Practice. Frontiers in neurology. 2017; 8: 42-42.
32. Hoile R, Tabet N, Smith H, Bremner S, Cassell J, Ford E. Are symptoms of insomnia in primary care associated with subsequent onset of dementia? A matched retrospective case-control study. Aging Ment Health. 2019: 1-6.
33. Osorio RS, Pirraglia E, Agüera-Ortiz LF, et al. Greater risk of Alzheimer's disease in older adults with insomnia. Journal of the American Geriatrics Society. 2011; 59 (3): 559-562.
34. Yaffe K, Nettiksimmons J, Yesavage J, Byers A. Sleep Quality and Risk of Dementia among Older Male Veterans. American Journal of Geriatric Psychiatry. 2015; 23 (6): 651-654.
35. Benedict C, Byberg L, Cedernaes J, et al. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. Alzheimer's and Dementia. 2015; 11 (9): 1090-1097.
36. Foley D, Monjan A, Masaki K, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. Journal of the American Geriatrics Society. 2001; 49 (12): 1628-1632.
37. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep. 2012; 35 (9): 1201-1207.
38. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain. 2019; 142 (3): 744-759.
39. Molano J, Vaughn BV. Approach to insomnia in patients with dementia. Neurology: Clinical Practice. 2014; 4 (1): 7-15.
40. Hsu C-Y, Chen Y-T, Chen M-H, et al. The Association Between Insomnia and Increased Future Cardiovascular Events: A Nationwide Population-Based Study. Psychosomatic Medicine. 2015; 77 (7): 743-751.
41. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the Risk of Acute Myocardial Infarction. Circulation. 2011; 124 (19): 2073-2081.

Section 1, Chapter I – Isolated Insomnia Symptom Subtypes and Manifestations of Prodromal Neurodegeneration

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Introduction

Symptoms of insomnia are common in neurological diseases of aging, including parkinsonism, dementia and cerebral vascular events.[1, 2] They are common early in the disease course, suggesting that they may be present before diagnosis. A recent meta-analysis suggested that insomnia symptoms may increase risk of dementia (including Alzheimer's disease) in later life.[1] Another recent study from our study group found that insomnia disorder was associated with lower cognitive performance on objective neuropsychological tests compared to individuals without insomnia.[3] Insomnia was also found to be more prevalent in probable prodromal parkinsonism in two studies.[4, 5]

Among studies to-date, most have focused primarily on the association of primary insomnia, as a whole entity, but not the subtypes within.[1] This leaves an important gap, as not all insomnia is the same; for example, Parkinson's disease is more-commonly associated with sleep-maintenance insomnia[6] (falling asleep easily and early, but then waking too early), but not difficulty falling asleep (sleep-onset insomnia), whereas Alzheimer disease is associated with a general circadian rhythm disruption.[7] Combining insomnia subtypes together may then mask important differences in neurodegenerative associations.

In this study, we used the baseline data from the Canadian Longitudinal Study on Aging (CLSA), a cohort focused on detecting early signs of aging, recruiting 51,338 participants, aged 45 to 85 years randomly sampled from 10 Canadian provinces, stratified by age.[8] The primary focus of the study was to examine to what degree insomnia and its subtypes were associated with objective prodromal motor, cognitive, and autonomic markers of neurodegeneration.

Methods

Canadian Longitudinal Study on Aging Cohort

This study was performed using the 30,097-person comprehensive cohort, at the baseline, aged 45-85 years, recruited from the 51,000-person Canadian Longitudinal Study on Aging (CLSA) population-based cohort, as described previously.[9] Since the purpose of the study was to assess the associations between insomnia symptoms and risk of parkinsonism and dementia, any participants reporting a diagnosis of dementia/Alzheimer's disease (AD) or parkinsonism/Parkinson's disease (PD) were excluded (details regarding to the questionnaires were listed in the e-method) (Figure 1).

Case Definition

Participants were screened for insomnia symptoms with two questions during the initial interview, adapted from the Pittsburgh Sleep Quality Index[10], namely:

1. "Over the last month, how often did it take you more than 30 minutes to fall asleep?" and
2. "Over the last month, how often did you wake in the middle of the night or too early in the morning and found it difficult to fall asleep again?".

Those who answered 'yes' to either of the two questions, with symptom frequency of at least 3 nights-per-week were considered as having insomnia symptoms. Note that a clinical diagnosis of insomnia disorder requires that symptoms also have a detrimental impact on quality of life.[11, 12] Since our primary research question was centered around the relationship of sleep symptoms per se to neurodegenerative markers, we did not require symptoms to be distressing to participants or to impact their daily function. On secondary analysis, we also assessed relationships between full insomnia disorder and the same neurodegenerative markers, according to ICSD-3 criteria.[13] To

avoid measuring acute transient insomnia symptoms, those with symptom onset within 3 months (n=197) were excluded from the analysis.

Neurodegenerative Signs and Symptoms

A comprehensive list of self-reported symptoms and functional measures, associated with prodromal parkinsonism or dementia, were pre-selected to assess the risk of neurodegeneration. All degenerative signs/symptoms were assessed at baseline, expect for the incidence of falls, for which data was acquired approximately one year after the baseline visit. The primary variables of interest were objective markers of potential neurodegeneration (i.e., dementia and gait/parkinsonism signs). These included:

1. Quantitative Motor Tasks: standing balance task (amount of time one can retain balanced while standing on one leg), timed Sit-to-Stand task (in absence of additional support, the total time needed to rise from sitting on a chair, with both feet on the ground, repeated five times), timed 4-meter walk task (the amount of time to walk 4-meters), timed Up-and-Go task (time needed to rise up from a chair, walk for 3 meters, then return to the chair and sit back down)[14], hand grip strength test (the strength exerted to squeeze a dynamometer with the dominant hand)[15]
2. Cognitive Assessments: verbal fluency (FAS task), recall task (immediate and delayed modules), Miami Prospective Memory Test (MPMT)[16]
3. Autonomic Neurological Assessments: heart rate variability (HRV). This was defined as the variation in heart rate between five different 1-minute measures separated by 1 minute. HRV was calculated based on the equation for calculating the root mean square of successive RR interval differences.[17] This serves as an indirect index of the root mean square standard deviation – a time-domain index that is believed to reflect parasympathetic activities.[18] (Equation -1)

Equation -1

$$Heart\ Rate\ Variability = \sqrt[2]{\frac{\sum(T_{i+1} - T_i)^2}{N-1}}$$

$$Estimated\ Period\ of\ 1\ Heart\ Beat\ (T)$$

$$= 60\ seconds/\ Heart\ Rate$$

$$N: Number\ of\ Pulse\ Measures$$

In addition, we assessed several potential symptoms of neurodegenerative disease. These included:

1. Motor Symptoms: Tanner's Parkinson's disease questionnaire (a screening questionnaire for Parkinson's disease that queries 9 different potential symptoms)[19], plus the incidence of falls

2. Other Sleep symptoms: Total hours of sleep < 6 (based on self-reported average hours of sleep), RBD-1Q (a single question screen for REM sleep behavior disorder)[20], daytime somnolence (a question adapted from Pittsburgh Sleep Quality Index)[21]

3. Psychological and Psychiatric Batteries: physician diagnosis of memory problem, physician diagnosis of depressive or anxiety disorder, prior and current use of antidepressants

4. Somatosensory Symptoms: self-reported chronic pain, assessed via a single question - "Are you usually free of pain or discomfort?"

To assess the associations with potential clinical neurodegenerative signs/symptoms, a cut-off of the bottom 15th percentile of performance was set based on the ranking of raw values.

Sociodemographic variables were assessed as previously defined[22]

Statistical Analyses

Associations between insomnia (as a dependent variable) and assessed variables were estimated using logistic regression analysis adjusting for age and sex. For cognitive variables, we also adjusted for years of education. Any responses labeled as uncertain or 'refused to answer' were omitted in all analyses. For heart rate variability analysis, outliers (defined as 1.5 interquartile range below the first quartile or above the third quartile) within each group were excluded. Statistical analysis was performed using R version 3.5.1.

Sensitivity Analyses

Because of the differences in age, sex, education, and BMI, we also conducted a sensitivity analysis using propensity score matching for these four using the nearest neighbor matching method in *MatchIt*, using a ratio of 1:1.[23] Since restless legs syndrome may trigger symptoms of insomnia, and may be an independent risk factor for disease, we reassessed the associations by (1) adjusting for presence of RLS symptoms and (2) excluding insomnia participants with RLS symptoms. To address potential confounding by other health conditions, we also conducted analyses adjusting for potential confounders that could also cause positive clinical abnormalities. These included:

1. Motor Signs: adjusted for arthritis, swelling joins, injuries or surgeries in lower extremity, polio, stroke, transient ischemic attack, diabetes, multiple sclerosis, BMI, age and sex
2. Psychiatric and Cognitive Symptoms: stroke, transient ischemic attack, diabetes, diagnosis of depression or anxiety (not used when assessing depression/anxiety), age and sex
3. Possible RBD: use of antidepressant, post-traumatic stress disorder, age and sex
4. Low HRV: any pre-existing cardiological condition, age and sex
5. Total Number of Abnormal Items: all of the selected confounding variables listed above.

To address potential associations of insomnia between men and women, we conducted a secondary analyses stratified to sex. Finally, since late-onset insomnia symptoms may be more likely to reflect a recent-onset prodromal neurodegenerative symptom (i.e. a prodromal sign rather than a risk factor), we conducted a secondary analysis stratifying insomnia participants to older age of insomnia onset (>55) versus those with young onset (before age 40). The two diverging cut-off points for age was to explore differences between insomnia as a lifelong/longstanding 'risk factor' vs. a recent-onset prodromal disease marker (i.e. prodromal neurodegeneration causes insomnia). We chose the cut-offs to allow clear distinction (most neurodegenerative diseases do not start before age 40), and to avoid confounds of the peri-menopausal state in women.[24]

Consent Data Availability

Written consent was obtained from all participants (or guardians of participants) in the study. Data access for the use of this study was reviewed and granted by the CLSA Data and Sample Access Committee (DSAC). Applicants with a CLSA approved project and the members of the project teams, with a signature on Schedule F of the CLSA Access Agreement form, are allowed to have direct access to the raw data.

Results

Characteristics of Study Population

Of 30,097 cohort participants, 289 were excluded due to possible dementia/parkinsonism, and 199 were excluded for missing information on one of the insomnia questions. Among the remaining 29,155 participants, 8,755 (29.6%) endorsed symptoms of insomnia starting at least 3 months ago. 2,371 (8.0%) had both sleep-onset and sleep-maintenance insomnia, 2,051 (6.9%) had isolated sleep-onset symptoms (OI) and 4,333 (14.6%) had isolated sleep-maintenance symptoms (MI) (Figure 1). Less than 5% of participants have at least one missing information on any of the sleep variables assessed in this study.

Sociodemographic Features

Regarding all subtypes of insomnia, women were more likely to endorse insomnia symptoms (58.4% with insomnia were female vs. 47.6% without) (Table 1). Although both sleep-onset and sleep-maintenance insomnia symptoms were more common among women, women were more likely to endorse sleep-onset difficulties (adjusted OR onset vs. maintenance=1.51, 95% CI [1.35,1.68]) Age was similar between those with insomnia and those without (63.0±10.2 vs. 62.6±10.2). No obvious difference in age was found between sleep-onset and -maintenance insomnia subtypes (OI: 62.6±10.2 vs. MI: 62.5±10.2); all subsequent estimates were adjusted by age and sex.

Participants with sleep-onset insomnia were less likely to have been married or in a common-law relationship (OR to controls=0.81 [0.72, 0.90]), whereas the opposite relationship to controls was seen among those with sleep-maintenance insomnia(OR=1.13 [1.04, 1.23]). Compared to both controls and those with sleep-maintenance insomnia, those with sleep-onset

insomnia had slightly increased weight (0.2 kg difference on average), had slightly fewer total years of education, lower annual income, and were more likely to have retired. Participants with sleep-onset insomnia were likely to report having a non-daytime work shift (8.5%) than sleep-maintenance insomnia participants (6.8%).

Prodromal Neurodegenerative Signs

Objective Motor Signs

Overall, those with any type of insomnia symptom were slower at numerous quantitative gait tests, including Timed-Up-and-Go (9.7 vs. 9.5 seconds), 4-meter walking speed (4.34 vs. 4.25 seconds), and Sit-to-Stand task speed (2.70 vs. 2.66 seconds) (Table 2 & 3). However, when divided according to subtypes, only those with sleep-onset insomnia demonstrated gait abnormalities. No significant differences in motor performance were observed between controls and those with sleep-maintenance insomnia. All motor tests were significantly worse in sleep-onset insomnia vs. sleep-maintenance insomnia participants (balance time in OI=36.6 seconds, vs. MI=40.3, Timed-Up-and-Go=9.9 vs. 9.5 seconds, 4-meter walk=4.34 vs. 4.26 seconds).

Neuropsychiatric Assessments

The combined insomnia group did not, on average, differ from controls on cognitive performance except for reduced performance in task switching (Stroop OR_{adj}=1.07[1.01,1.13]) and prospective memory task (OR_{adj}=1.13[1.05,1.21]). However, when differentiated by subtype, participants with sleep-onset insomnia were more likely to score >1 standard deviation below mean on numerous measures than both controls and those with sleep-maintenance insomnia. These included verbal fluency (adjusted OR of lower 15^{th} percentile= 1.15[1.01, 1.30] to

controls), memory (immediate recall OR_{adj}=1.127[1.004,1.264], prospective memory OR_{adj}=1.24[1.09,1.40]), task switching (Stroop OR_{adj}=1.13[1.02,1.26], mental alternation OR_{adj}=1.16[1.03,1.32]) and psychomotor speed (OR_{adj}=1.19[1.07,1.32]). There was no difference in any neuropsychological measure between maintenance insomnia participants and controls.

Heart-rate Variability

On the index of heart rate variability (HRV), participants with insomnia overall had less fluctuation in between heartbeats (index=29.4 vs 28.5) than controls, indicating possible sympathetic autonomic denervation (Table 2). When differentiated by subtype, sleep-onset participants had lower HRV (27.6) and were more likely to fall within the lowest 15th percentile of HRV (17.1 vs.14.7% in control; OR_{adj}=1.20[1.06,1.36]). However, neither measure of HRV in sleep-maintenance insomnia group was significantly different from controls.

Subjective Measures

Motor Symptoms

In terms of motor symptoms, the combined insomnia group reported more motor symptoms than controls (0.7 vs. 0.5 symptoms on the 9-item Tanner Parkinson screening questionnaire) (Table 4). When differentiated by subtype, onset-insomnia participants reported more motor symptoms than sleep-maintenance insomnia (0.7 vs 0.6, OR=1.13 [1.07,1.18]). 8.7% of sleep-onset insomnia participants endorsed ≥3 symptoms (the threshold for a positive parkinsonism screen), compared to 4.5% of controls and 5.4% of those with sleep-maintenance insomnia) (Table 5). Among the individual motor symptoms assessed in Tanner's questionnaire, most symptoms were associated with both insomnia subtypes (Table e-2) except that gait

freezing and festination were similar between those with sleep-maintenance insomnia and controls. Other than gait freezing, all symptoms related to poor function in lower extremities were more common in sleep-onset insomnia than sleep-maintenance insomnia groups. Sleep-onset insomnia participants were more likely to report having a fall in the following year after the initial interview (13.2%) than controls (10.0%) or sleep-maintenance insomnia participants (11.2%).

Other Non-motor symptoms

With regards to other sleep problems, insomnia participants overall slept less than controls (6.0 vs. 7.1 hours) and were more likely to report poor sleep quality (58.3% vs. 11.0% in controls), daytime sleepiness (14.4% vs. 6.3%) and possible REM sleep behavior disorder (pRBD)-related dream enactment behavior (7.8% vs. 4.5%). Divided according to subtype, both sleep-onset and -maintenance subtypes had fewer hours of sleep than controls, with sleep-maintenance insomnia participants having less sleep than the sleep-onset insomnia (controls=7.1, OI=6.5; MI=6.1 hours). Although both insomnia sub-groups endorsed daytime somnolence, those with sleep-maintenance insomnia reported this more often (OI=10.6%; MI=13.2%). On the contrary, the prevalence of pRBD-related symptoms, although higher in both groups (OI=7.2%, MI=5.7%, controls=4.5%), was highest among sleep-onset participants (OR_{adj}=1.82 [1.44,2.29] to controls).

Whereas insomnia combined was associated with increase in self-reported memory troubles compared to controls (2.0% vs. 1.3%), this difference was driven mainly by sleep-onset participants (OI=2.1%, MI=1.6%) (Table 3). Although clinically diagnosed depression and/or anxiety were more prevalent in both insomnia groups than controls, the prevalence was much

larger in sleep-onset insomnia (OI=32.6%, MI=20.6%, controls=17.8%). Use of antidepressants was the most common among sleep-onset insomnia participants (OI=15.3%, controls=7.2%) but was less common in sleep-maintenance group (5.8%). Both groups of insomnia participants were more likely to report frequent pain than controls, again with sleep-onset insomnia participants more likely to report having pain than sleep-maintenance participants (controls=32.9%, OI=47.1%, MI=41.3%).

Sensitivity Analyses

Modeling and Adjustment

Since restless leg syndrome may induce insomnia, we reassessed after adjusting for the presence of RLS symptoms, and performed a subgroup analysis of those without RLS symptoms. After adjusting for RLS, most associations remained similar except for an attenuation of relationships with verbal fluency, memory tasks (immediate and delay recall) and task switching (Figure 2). Results remained similar after excluding those with RLS symptoms among insomnia participants. To address potential confounding between insomnia and other health events, we also assessed the relationship between insomnia and several preselected disease comorbidities, and conducted regression analyses with these additional covariates. Sleep-maintenance insomnia participants, but not sleep-onset insomnia participants, were more likely to have history of both cerebral vascular attack (CVA) (1.89 vs. 1.50%; OR_{adj}=1.33 [1.03, 1.69]) and/or transient ischemic attack (TIA) (3.41 vs. 2.91%; OR_{adj}=1.24 [1.03, 1.49]) compared to controls. (Table e-4) Diabetes was more common sleep-onset insomnia participants than the controls (21.2% vs. 16.8%, OR=1.43[1.26,1.59]) and sleep-maintenance insomnia participants (17.90%;

OR_{adj}=1.29[1.13,1.47]). Adding these variables to the model had modest effects, again with attenuation of some cognitive measures (Figure 2).

Demographic Matching

Due to the differences in demographic characteristics among the three study groups, we performed a sensitivity analysis on a subsample that was closely matched for age, sex, BMI and years of education (n=2,041 participants for each group). Point estimates of all OR were broadly similar to that of the primary analysis (Table e-3), although in some cases, the previous observed associations within this smaller subgroup became nonsignificant (e.g. diagnosis of poor cognition and averagely low HRV were significantly more common in sleep-onset than -maintenance insomnia, but not more when comparing to controls).

Insomnia Disorder

We re-assessed all the associations in a subgroup of individuals who fulfilled the clinical diagnosis of insomnia disorder (i.e. adding a requirement for impact of sleep symptoms on function). Overall, patterns of effects were similar to the broader group. As in the broader group, insomnia disorders were more common in female participants and associated with fewer total years of education and younger age. Onset insomnia disorder participants were also slightly heavier than the controls. (Table 6). Isolated sleep-onset insomnia disorder was associated with poorer motor function those without insomnia and those with maintenance insomnia disorder. Of the cognitive tasks, poor verbal fluency and choice reaction retained their associations with isolated sleep-onset insomnia disorder, with no associations found in those with the sleep-maintenance insomnia. Anxiety/depression were strongly associated with both insomnia

disorders. Possible RBD and low HRV were associated with isolated sleep-onset insomnia disorders but not the sleep-maintenance insomnia. Results were similar after adjustment for the presence of RLS symptoms.

Secondary Analyses

Men vs. Women

The relationship between prodromal markers and insomnia was present in both sexes (Table e-5). However, associations were generally more robust in men than in women. Except for heart rate variability, the point estimate of each marker's OR was higher in men. In the case of verbal fluency and possible RBD, the 95% CI between men and women did not overlap, and the strength of association was stronger in men.

Age of Onset

To address the potential differences between lifelong insomnia (as a potential risk factor for disease) and recent-onset insomnia (as a possible prodromal marker of disease), we stratified groups into young-onset (≤ 40 years old) and older-onset (≥ 55 years old) insomnia. (Table e-6 and e-7) The older-onset group was generally more likely to endorse isolated sleep-maintenance rather than sleep-onset insomnia. Self-reported motor symptoms were more common in young-onset sleep-maintenance insomnia than those with older-onset (e.g. OR falls= 1.30 [1.03,1.63] for young-onset maintenance group vs. 1.01 [0.86,1.18] for the older-onset maintenance group). However, for all objective neurodegenerative markers, no clear differences between early and late onset were seen.

Other confounders

We conducted additional analysis adjusting for additional confounders, including numerous major health events, smoking and heavy drinking. Results were generally similar to models without these variables (e.g. see Supplementary e-4, other data not shown)

Discussion

Capitalizing upon a large population-based cohort, in which array of objective neurological markers were assessed, we were able to explore the relationship between symptoms/subtypes of insomnia and signs of potential prodromal neurodegeneration. On numerous objective measures, participants with insomnia overall had worse gait function (balance and transfer/gait speed/turning), cognition (prospective memory and choice reaction task) and lower heart rate variability than controls. This was in addition to numerous self-reported motor/cognitive symptoms. However, when divided according to subtype, most of these differences were seen specifically in those with sleep-onset insomnia, with few differences between sleep-maintenance insomnia participants and controls. Stratifying the cohort by sex or age-at-symptom-onset produced similar results.

Motor Dysfunction

Our study found that those with insomnia symptoms, particularly sleep-onset insomnia, were more likely to endorse motor symptoms and have motor slowing on objective gait tests. Our findings are consistent with prior studies. In a study using the Taiwan National Health Insurance program, insomnia (as a global symptom) marked an increased risk of developing parkinsonism[25]. In the UK primary care database[5], PD patients were 1.4-times more likely to have visited a health care professional for insomnia 0-2 years before PD diagnosis (no significant relationship was seen at longer prediagnostic intervals). In a Taiwanese retrospective study insomnia was associated with a 2-fold increased risk of PD, from as long as 7-to-10 years from baseline evaluation.[25] Neither of these studies assessed sleep-onset vs. sleep-maintenance insomnia subtypes. A study of patients with idiopathic REM sleep behavior disorder (the

strongest known prodromal marker of PD) found higher prevalence of insomnia compared to controls. However, insomnia symptoms in RBD patients at baseline did not increase the risk of phenoconversion later on.[4] This study did compare insomnia subtypes, finding that sleep-maintenance insomnia was more common among iRBD patients at baseline, but resolved over time (perhaps reflecting either progressive somnolence/sleep drive, or treatment-related reduction in arousals caused by directly by RBD).

The fact that sleep-onset but not sleep-maintenance insomnia was associated with motor deficits is somewhat surprising, considering that sleep-maintenance insomnia is the most common subtype observed in PD. Of note, the objective measures in this study were gait measures; therefore, gait problems unrelated to PD may underlie the effect; these might include consequences of cerebrovascular lesions, prodromal Alzheimer dementia symptoms (AD is much more common than PD, so even smaller prodromal motor changes could drive differences[26, 27]), or other unrecognized confounds/conditions. Falling and other gait dysfunction may predate diagnosis of 'vascular parkinsonism', which is consistent with the findings in a recent meta-analysis suggesting that insomnia disorder is a risk factor for stroke.[28] Several previous meta-analysis studies have identified that insomnia symptoms as a whole are associated with new incidence of stroke and cerebral vascular events but do not contribute to mortality.[29, 30] Prospective follow-up will be able to address whether sleep-onset insomnia is a risk factor for (vascular) parkinsonism in our population.

Cognition and Non-motor Symptoms

Overall, we found a modest association between insomnia symptoms and poor cognitive

performance on certain tasks, which was evident only in those with sleep-onset insomnia, even after adjusted for depression/anxiety, stroke, transient ischemic attack, diabetes, pain, apnea, RLS and possible comorbid conditions. (Figure 2, Table e-4,9,10) These results are broadly similar to a recent study using the same cohort, in which patients with full defined insomnia disorder had increased cognitive impairment, without any clear differences between maintenance and onset insomnia (although power was insufficient for direct comparison).[3] Note that the case definition of insomnia was not the same as the current study; here we were interested in studying whether changes in sleep *per se* are associated with neurodegenerative markers (i.e. irrespective of a perceived negative impact upon quality of life, which is required for an insomnia clinical diagnosis). Our results are consistent with other prospective studies suggesting that insomnia may be a prodromal dementia symptom. These include two Taiwanese population-based studies which found that insomnia increases patients' risk of developing dementia after adjusting for vascular-events and other related confounders.[31, 32] Hoile et. al. noted an increase in risk of developing dementia retrospectively among those with prior diagnosis of insomnia up to a decade.[33] Similarly, Osorio et. al. also reported a 2.39-fold increased dementia risk among 655 New Yorkers with insomnia.[34] In a retrospective all-male-veteran U.S. study (aged 55 and above), insomnia at midlife was associated with 27% increased risk of developing various dementia subtypes, except vascular and Lewy body dementia.[35] A Swedish study also found an increased risk in the occurrence of dementia among those with long-term insomnia.[36] By contrast, the Honolulu-Asia Aging Study reported that insomnia was not able to predict the occurrence of cognitive decline or dementia among Asian men.[37] Moreover, the prospective French Three-City Study found no association between insomnia and cognitive decline over an 8-year follow-up period[38]; this study also found that those endorsing sleep-maintenance insomnia

were less likely to experience cognitive decline. Therefore, these findings suggest that any future study measuring insomnia as a risk factor for dementia should carefully delineate onset vs. maintenance subtypes (Table S2).

Among the specific cognitive assessments, poor performance in prospective memory and choice reaction task were persistently associated with sleep-onset insomnia, even after adjusting for cerebral vascular events and related-health events (Figure 2). Since no difference was found when assessing the time needed to complete the tasks, the observed pattern may be associated with attention deficit and poor execution. Abnormalities on these tests can be associated with Alzheimer disease, vascular dementia, and Lewy body dementia, even during their prodromal phases.[39-42] However, two recent UK bio-bank mendelian randomized studies found no association between overall insomnia and Alzheimer's disease-related genetic risks.[43, 44] In our study, when assessing the cardinal signs of Alzheimer's dementia, using the recall tasks, we found no association when pooling all insomnia symptoms together, either (Table 2). Although we did observe a mild association between onset-insomnia symptom and poor immediate recall, the associations were stronger with non-Alzheimer's dementia specific signs (such as poor choice reaction and mental alternation tests). Prospective follow-up will help to determine whether these tests can identify specific subtypes of dementia for which sleep-onset insomnia is a risk factor.

Besides the motor signs, we also observed a relatively persistent association between sleep-onset insomnia and non-motor signs/symptoms even after adjusting for multiple comorbidities. Depression and anxiety were associated with insomnia; these are well-established but non-specific risk factors for many diseases and health event and may predate the phenoconversion up-to 2 decades.[45-48] There is also growing evidence showing that cardiac

autonomic dysfunction manifested as loss of the normal heart rate variability during midlife is a risk factor for developing cognitive impairment and dementia later in life.[49, 50] Interestingly, in our study, participants with sleep-onset insomnia had lower heart rate variability and endorsed poorer performance in certain cognitive batteries.

Limitations and Strengths

Some limitations of this study should be noted. Since insomnia diagnosis is primarily based on self-report, it is, by definition, subject to recall/reporting bias. This may manifest itself as differences in recognition of symptoms (e.g. poor insight into insomnia may be more common in those with memory impairment), inaccurate recall of time of onset, or potential overreporting of symptoms among patients with anxiety or depressive disorders (although we saw no clear differences in effect when adjusting for mental illness) (Figure 2). The absence of information on sleep medications is another unmeasured confounder in this study, as long term usage of certain medications (e.g., long-acting benzodiazepines) may impair cognition (note that this should not clearly account for the observed differences in sleep onset vs. maintenance insomnia). Although we were able to adjust for the potential confounding effects of comorbid sleep symptoms, comorbid medical conditions and smoking/drinking in the sensitivity analyses, additional unmeasured confounds may still exist. Motor assessments were limited to gait measures; studies in other populations have suggested that upper limb tests (e.g. Purdue Peg Board or Alternative Finger Tap Test) may be more sensitive for detecting early prodromal parkinsonism.[47] Assessment of heart rate variability used only the variation in pulse between five consecutive measures and should be considered exploratory. Because of the nature of the pulse data (5 independent pulse rates) we were unable to examine specific patterns of abnormality such as

high frequency, low frequency, and very-low-frequency alterations. The recruitment procedures of the CLSA exclude those with baseline dementia from assessment; thus we are unable to assess links between insomnia and dementia in this cross-sectional study. It is notable that participants with sleep-onset insomnia seem to be worse on numerous measures of health, depression, etc; this might suggest that unmeasured confounds could underlie the association between sleep and neurodegenerative markers. Finally, this is a cross-sectional study; prospective follow-up (ongoing) will allow direct assessment of whether insomnia predicts dementia or (vascular) parkinsonism.

On the other hand, this study has some important advantages. Because the study has a large sample size that used population-based sampling, the association between sleep onset-insomnia and neurodegeneration signs/symptoms were likely to be representative to the true population. With detailed assessment of general health events, we were able to adjust for multiple potential confounders. The fact that gait and cognition were assessed with standardized objective measures minimizes effects of response bias. Because we also screened for RLS, we were able to address confounding by potential RLS symptoms, finding results that relatively similar (noting, however, that RLS screen does not include clinician interview to rule out mimics). Similarly, none of the potential interaction-terms between other sleep disorders and the use of antidepressant significantly alter the associations (among the non-psychiatric variables) found in the primary analyses.

Conclusions

In summary, our study found several objective motor and cognitive abnormalities in those with symptoms of insomnia. These appear to be largely driven by abnormalities in sleep-

onset, rather than sleep-maintenance insomnia. Future prospective studies will help confirm to what degree insomnia subtypes predict neurodegenerative disorders (e.g. dementia, vascular diseases and parkinsonism).

References

1. Shi L, Chen S-J, Ma M-Y, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Medicine Reviews 2018;40:4-16.
2. Ju Y-ES, Videnovic A, Vaughn BV. Comorbid Sleep Disturbances in Neurologic Disorders. CONTINUUM: Lifelong Learning in Neurology 2017;23:1117-1131.
3. Cross NE, Carrier J, Postuma RB, et al. Association between insomnia disorder and cognitive function in middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. Sleep 2019.
4. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Parkinsons Dis 2017;3:9.
5. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol 2015;14:57-64.
6. Loddo G, Calandra-Buonaura G, Sambati L, et al. The Treatment of Sleep Disorders in Parkinson's Disease: From Research to Clinical Practice. Frontiers in neurology 2017;8:42-42.
7. Homolak J, Mudrovčić M, Vukić B, Toljan K. Circadian Rhythm and Alzheimer's Disease. Med Sci (Basel) 2018;6:52.
8. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28:221-229.
9. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). Can J Aging 2009;28:221-229.
10. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
11. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Association, 2013.
12. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.
13. Ito E, Inoue Y. [The International Classification of Sleep Disorders, third edition. American Academy of Sleep Medicine. Includes bibliographies and index]. Nihon Rinsho 2015;73:916-923.
14. Avila-Funes JA, Gray-Donald K, Payette H. Association of nutritional risk and depressive symptoms with physical performance in the elderly: the Quebec longitudinal study of nutrition as a determinant of successful aging (NuAge). Journal of the American College of Nutrition 2008;27:492-498.
15. L Ashton SM. Serial Grip Strength Testing- Its Role In Assessment Of Wrist And Hand Disability. The Internet Journal of Surgery 2003;5.
16. Capp K, Diaz-Santos A, Raffo A, et al. A-23The Miami Prospective Memory Test (MPMT) in Discriminating Community-Dwelling Older Adults with Amnestic MCI from Cognitively Normal Elders. Archives of Clinical Neuropsychology 2016;31:592-592.
17. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
18. Zygmunt A, Stanczyk J. Methods of evaluation of autonomic nervous system function. Arch Med Sci 2010;6:11-18.
19. Tanner CM, Gilley DW, Goetz CG. A brief screening questionnaire for parkinsonism. Ann Neurol 1990;28:267-268.
20. 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.
21. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:629-635.

22. 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.
23. Ho D, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. 2011 2011;42:28.
24. Zolfaghari S, Yao C, Thompson C, et al. Effects of menopause on sleep quality and sleep disorders: Canadian Longitudinal Study on Aging. Menopause 2020;27:295-304.
25. Hsiao YH, Chen YT, Tseng CM, et al. Sleep disorders and an increased risk of Parkinson's disease in individuals with non-apnea sleep disorders: a population-based cohort study. Journal of Sleep Research 2017;26:623-628.
26. Buchman AS, Bennett DA. Loss of motor function in preclinical Alzheimer's disease. Expert review of neurotherapeutics 2011;11:665-676.
27. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor Dysfunction in Mild Cognitive Impairment and the Risk of Incident Alzheimer Disease. JAMA Neurology 2006;63:1763-1769.
28. Koo DL, Nam H, Thomas RJ, Yun CH. Sleep Disturbances as a Risk Factor for Stroke. J Stroke 2018;20:12-32.
29. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol 2014;21:57-64.
30. Ge L, Guyatt G, Tian J, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. Sleep Med Rev 2019;48:101215.
31. Hung C-M, Li Y-C, Chen H-J, et al. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatry 2018;18:38.
32. Chen PL, Lee WJ, Sun WZ, Oyang YJ, Fuh JL. Risk of Dementia in Patients with Insomnia and Long-term Use of Hypnotics: A Population-based Retrospective Cohort Study. PLoS One 2012;7.
33. Hoile R, Tabet N, Smith H, Bremner S, Cassell J, Ford E. Are symptoms of insomnia in primary care associated with subsequent onset of dementia? A matched retrospective case-control study. Aging Ment Health 2019:1-6.
34. Osorio RS, Pirraglia E, Agüera-Ortiz LF, et al. Greater risk of Alzheimer's disease in older adults with insomnia. Journal of the American Geriatrics Society 2011;59:559-562.
35. Yaffe K, Nettiksimmons J, Yesavage J, Byers A. Sleep Quality and Risk of Dementia among Older Male Veterans. American Journal of Geriatric Psychiatry 2015;23:651-654.
36. Benedict C, Byberg L, Cedernaes J, et al. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. Alzheimer's and Dementia 2015;11:1090-1097.
37. Foley D, Monjan A, Masaki K, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. Journal of the American Geriatrics Society 2001;49:1628-1632.
38. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep 2012;35:1201-1207.
39. Crossley M, D'Arcy C, Rawson NSB. Letter and category fluency in community-dwelling canadian seniors: A comparison of normal participants to those with dementia of the Alzheimer or vascular type. Journal of Clinical and Experimental Neuropsychology 1997;19:52-62.
40. Jones S, Laukka EJ, Bäckman L. Differential Verbal Fluency Deficits in the Preclinical Stages of Alzheimer's Disease and Vascular Dementia. Cortex 2006;42:347-355.
41. Williams VG, Bruce JM, Westervelt HJ, et al. Boston naming performance distinguishes between Lewy body and Alzheimer's dementias. Arch Clin Neuropsychol 2007;22:925-931.
42. Genier 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:zsw014-zsw014.

43. Anderson EL, Richmond RC, Jones SE, et al. Is disrupted sleep a risk factor for Alzheimer's disease? Evidence from a two-sample Mendelian randomization analysis. International Journal of Epidemiology 2020.
44. Huang J, Zuber V, Matthews PM, Elliott P, Tzoulaki J, Dehghan A. Sleep, major depressive disorder, and Alzheimer disease: A Mendelian randomization study. Neurology 2020;95:e1963-e1970.
45. Ismail Z, Gatchel J, Bateman DR, et al. Affective and emotional dysregulation as pre-dementia risk markers: exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. Int Psychogeriatr 2018;30:185-196.
46. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. Stroke 2012;43:32-37.
47. Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain 2019;142:2051-2067.
48. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BH. Meta-Analysis of Anxiety as a Risk Factor for Cardiovascular Disease. Am J Cardiol 2016;118:511-519.
49. Vanessa Pereira da S, Bruno Ribeiro Ramalho O, Roger Gomes Tavares M, Helena M, Andrea Camaz D, Jerson L. Heart Rate Variability Indexes in Dementia: A Systematic Review with a Quantitative Analysis. Current Alzheimer Research 2018;15:80-88.
50. Forte G, Favieri F, Casagrande M. Heart Rate Variability and Cognitive Function: A Systematic Review. Front Neurosci 2019;13:710.

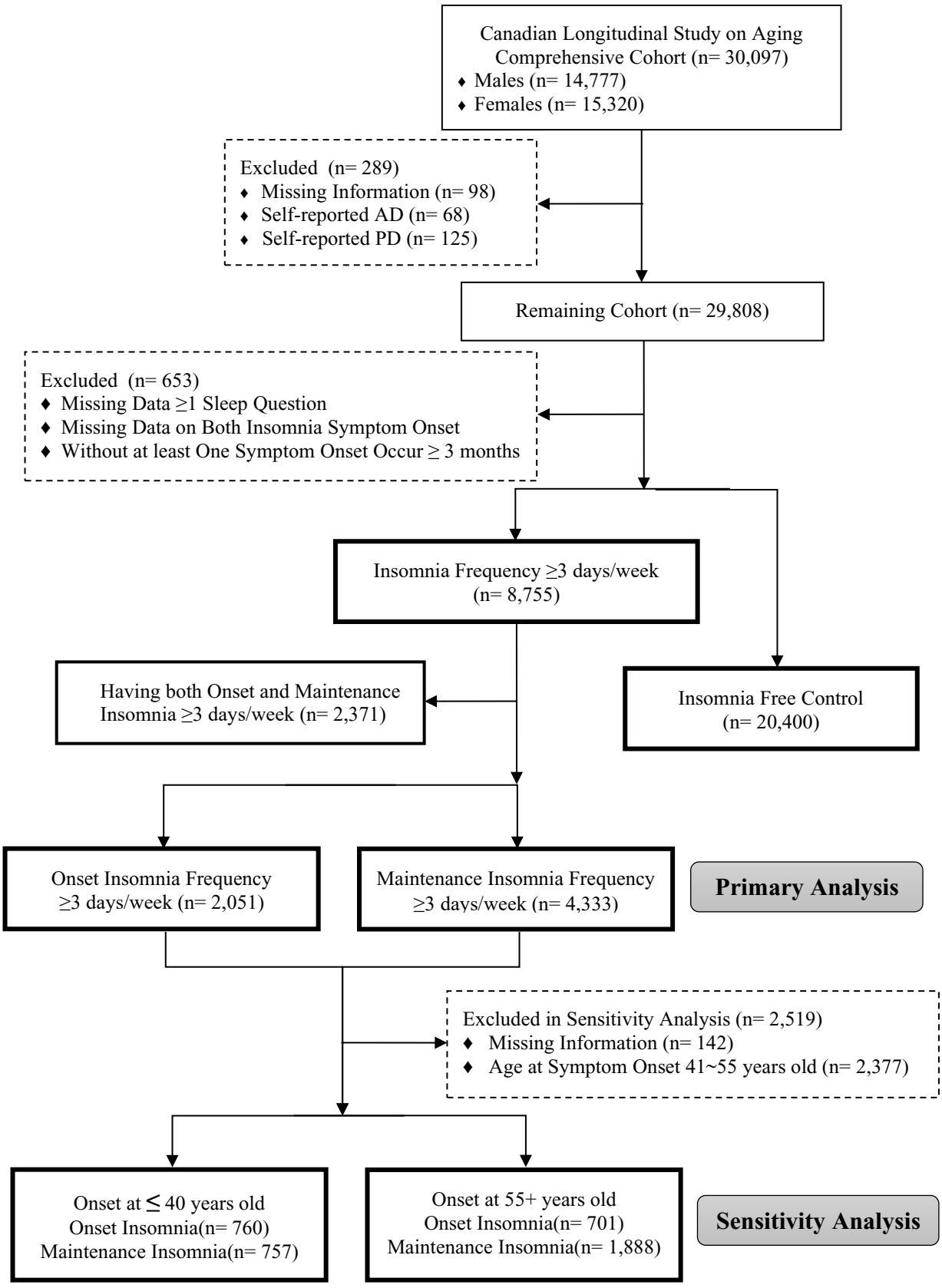


Figure 1. STROBE Flow Diagram

Sociodemographic Status		No Insomnia (n=20,400)	All Insomnia (8,755)	Onset Insomnia (2,051)	Maintenance Insomnia (4,333)	All Insomnia vs. Ctrl	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
		% or Mean±SD				$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]			
Sex (% female)		9708 (47.6)	5109 (58.4)	1280 (62.4)	2273 (52.5)	1.54 [1.46,1.62]	1.83 [1.66,2.01]	1.21 [1.14,1.29]	1.51 [1.35,1.68]
Age		63.0±10.2	62.6±10.2	62.6±10.3	62.5±10.2	1.00 [0.99,1.00]	1.00 [0.99,1.00]	1.00 [0.99,1.00]	1.00 [1.00,1.01]
Body Mass Index		28.0±5.3	28.2±5.7	28.5±5.7	27.9±5.5	1.008 [1.004,1.012]	1.02 [1.01,1.03]	1.00[0.99,1.01]	1.02 [1.01,1.03]
Ethnicity (Caucasian %)		19486 (96.1)	8399 (96.7)	1946 (95.7)	4188 (97.3)	1.16 [1.01,1.33]	0.86 [0.69,1.09]	1.43 [1.18,1.75]	0.61 [0.46,0.81]
Married/Common-law		15317 (79.3)	6284 (76.9)	1405 (74.0)	3296 (80.6)	0.92 [0.87,0.98]	0.81 [0.72,0.90]	1.13 [1.04,1.23]	0.71 [0.62,0.80]
Annual Income (per 1,000 CAD)		59.2±35.7	53.3±35.3	48.5±33.5	58.9±36.3	0.9963 [0.9955,0.9971]	0.992 [0.991,0.994]	1.000 [0.999,1.001]	0.992 [0.991,0.994]
Years of Education		13.7±2.3	13.4±2.3	13.2±2.3	13.6±2.3	0.94 [0.93,0.95]	0.92 [0.90,0.94]	0.98 [0.97,0.99]	0.94 [0.92,0.96]
Employment Status and Work Schedule	Retired	11239 (55.3)	4855 (55.6)	1182 (57.9)	2333 (54.0)	1.11 [1.04,1.19]	1.30 [1.14,1.47]	1.03 [0.94,1.12]	1.26 [1.09,1.45]
	Daytime Job	18758 (92.6)	8005 (92.2)	1848 (91.5)	4021 (93.2)	-	-	-	-
	Non-Daytime Job	1494 (7.4)	680 (7.8)	171(8.5)	292 (6.8)	1.06 [0.96,1.16]	1.16 [0.98,1.37]	0.89 [0.77,1.01]	1.31 [1.07,1.61]

Table 1. Sociodemographic Status

Prodromal Neurodegenerative Signs			No Insomnia (n=20,400)	All Insomnia (8,755)	All Insomnia vs. Ctrl
			% or Mean±SD		$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]
Motor Signs					
Balance Task	Best Performance (seconds)		39.7±23.3	38.51±23.48	-
	<15th percentile		2799 (14.5)	1271(15.6)	1.16 [1.07,1.25]
Timed-Up-and-Go	Total Time		9.51±2.39	9.69±2.89	-
	<15th percentile		2862 (14.2)	1384(16.1)	1.23 [1.14,1.32]
4-meter Walk Task			4.25±1.04	4.34±1.17	1.08 [1.06,1.11]
Sit-to-Stand	Average Time/Trial		2.66±0.75	2.70±0.86	1.07 [1.04,1.11]
Neuropsychiatric Signs					
F-A-S Verbal Fluency Task	Total Score		39.3±12.7	39.08±12.83	-
	<15th percentile		3090 (15.7)	1412(16.7)	1.06 [0.99,1.14]
Recall Task	Immediate Recall		5.85±1.91	5.90±1.89	-
	<15th percentile		4705 (23.8)	1928(22.8)	1.01 [0.94,1.07]
	Delayed Recall		4.04±2.17	4.11±2.14	-
	<15th percentile		4628 (23.5)	1834(21.7)	0.96 [0.90,1.03]
Miami Prospective Memory Task	Time-based Score		8.67±0.94	8.65±0.95	0.97 [0.94,0.99]
	Event-based Score		8.45±1.39	8.43±1.39	0.98 [0.97,1.00]
	Accuracy		11.2±1.7	11.2±1.7	0.98 [0.96,0.99]
	<15th percentile		3025 (15.1)	1394(16.2)	1.13 [1.05,1.21]
Psychomotor Speed Task & Task switching	Stroop Interference Error		0.68±2.02	0.71±2.01	-
	>85th percentile		5180(25.83)	2347(27.32)	1.07 [1.01,1.13]
	Mental Alternation Task (MMSE)		26.68±8.78	26.42±8.57	-
	<15th percentile		3009(15.5)	1340(16.08)	0.998 [0.927,1.074]
	Choice Reaction Task	Accuracy	98.86±3.03	98.88±3.03	-
		<15th percentile	5359(26.63)	2288(26.53)	1.04 [0.98,1.10]
Nonmotor Signs					
Autonomic Abnormality	Heart Rate Variability		29.4±28.6	28.5±28.3	-
	<15th percentile		2924 (14.7)	1331(15.6)	1.08 [1.01,1.16]

Table 2. Prodromal Neurodegenerative Signs in All Insomnia Combined

Prodromal Neurodegenerative Signs			Onset Insomnia (2,051)	Maintenance Insomnia (4,333)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
			% or Mean±SD		$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]		
Motor Signs							
Balance Task	Best Performance (seconds)		36.6±23.7	40.3±23.	-	-	-
	<15th percentile		330 (17.4)	592 (14.4)	1.33 [1.16,1.52]	1.05 [0.94,1.16]	1.28 [1.09,1.50]
Timed-Up-and-Go	Total Time		9.90±3.64	9.50±2.66	-	-	-
	<15th percentile		378 (18.8)	576 (13.5)	1.52 [1.34,1.73]	0.98 [0.89,1.09]	1.55 [1.33,1.80]
4-meter Walk Task			4.34±1.17	4.26±1.17	1.13 [1.08,1.17]	1.01 [0.98,1.04]	1.11 [1.06,1.17]
Sit-to-Stand	Average Time/Trial		2.79±1.06	2.63±072	1.21 [1.14,1.28]	0.95 [0.91,1.00]	1.27 [1.18,1.36]
Neuropsychiatric Signs							
F-A-S Verbal Fluency Task	Total Score		38.4±12.9	39.8±12.8	-	-	-
	<15th percentile		364 (18.3)	630 (15.0)	1.15 [1.01,1.30]	0.97 [0.88,1.07]	1.18 [1.01,1.37]
Recall Task	Immediate Recall		5.83±1.94	5.95±1.88	-	-	-
	<15th percentile		496 (25.0)	918 (21.9)	1.127 [1.004,1.264]	0.96 [0.88,1.04]	1.19 [1.04,1.37]
	Delayed Recall		4.06±2.18	4.14±2.15	-	-	-
	<15th percentile		461 (23.2)	897 (21.4)	1.07 [0.95,1.20]	0.93 [0.86,1.02]	1.17 [1.02,1.35]
Miami Prospective Memory Task	Time-based Score		8.63±0.98	8.69±0.88	0.95 [0.91,1.00]	1.01 [0.97,1.05]	0.94 [0.89,1.00]
	Event-based Score		8.37±1.50	8.48±1.32	0.96 [0.93,0.99]	1.01 [0.98,1.04]	0.95 [0.91,0.99]
	Accuracy		11.1±1.8	11.3±1.6	0.96 [0.94,0.99]	1.00 [0.98,1.02]	0.96 [0.93,0.99]
	<15th percentile		359 (17.8)	614 (14.4)	1.24 [1.09,1.40]	0.98 [0.88,1.07]	1.27 [1.09,1.47]
Psychomotor Speed Task & Task switching	Stroop Interference Error		0.77±1.98	0.63±1.96	-	-	-
	>85th percentile		578(28.73)	1050(24.59)	1.13 [1.01,1.25]	0.95 [0.88,1.03]	1.19 [1.05,1.35]
	Mental Alternation Task		25.83±8.9	27.16±8.35	-	-	-
	<15th percentile		367(18.82)	561(13.55)	1.16 [1.02,1.32]	0.86 [0.78,0.95]	1.38 [1.18,1.60]
	Choice Reaction Task	Accuracy	98.72±3.28	98.97±2.93	-	-	-
		<15th percentile	595(29.4)	1056(24.71)	1.19 [1.07,1.32]	0.94 [0.87,1.02]	1.27 [1.13,1.44]
Nonmotor Signs							
Autonomic Abnormality	Heart Rate Variability		27.6±24.0	29.7±30.5	-	-	-
	<15th percentile		340 (17.1)	605 (14.3)	1.20 [1.06,1.36]	0.98 [0.89,1.08]	1.24 [1.07,1.43]

Table 3. Prodromal Neurodegenerative Signs among Sleep maintenance vs. Sleep onset Insomnia Subtypes

Prodromal Neurodegenerative Symptoms		No Insomnia (n=20,400)	All Insomnia (8,755)	All Insomnia vs. Ctrl
		% or Mean±SD		$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]
Motor Symptoms				
Tanner Questionnaire	Overall Score	0.46±0.92	0.67±1.14	1.22 [1.19,1.25]
	Score ≥ 3	909 (4.46)	669 (7.64)	1.86 [1.68,2.07]
Fall (last year)	At least One Fall	1959 (10.0)	1047 (12.6)	1.26 [1.16,1.36]
	Number of Falls	1.40±1.57	0.20±0.90	1.11 [1.07,1.15]
Neuropsychiatric Symptoms				
Psychiatric and Cognitive Symptoms	Self-Reported Memory Problem	270 (1.33)	171 (1.95)	1.52 [1.25,1.84]
	Depression/Anxiety	3618 (17.8)	2271 (26.0)	1.53 [1.44,1.62]
	Prescribed Antidepressant	1474 (7.24)	868 (9.96)	1.31 [1.20,1.43]
Non-motor Symptoms				
Sleep	Sleep Hours	7.14±1.06	6.03±1.30	0.41 [0.40,0.42]
	Poor Sleep Quality	2239 (11.0)	5104 (58.3)	11.3 [10.6,12.0]
	Daytime Sleepiness[a]	1292 (6.34)	1253 (14.3)	2.55 [2.35,2.77]
	Possible RLS Symptoms	2796(13.84)	1924(22.33)	1.71 [1.60,1.82]
	Possible RBD	517(3.07)	279(4.08)	1.41 [1.21,1.64]
Pain	Chronic pain (most days)	6432 (32.9)	3798 (45.7)	1.68 [1.59,1.77]

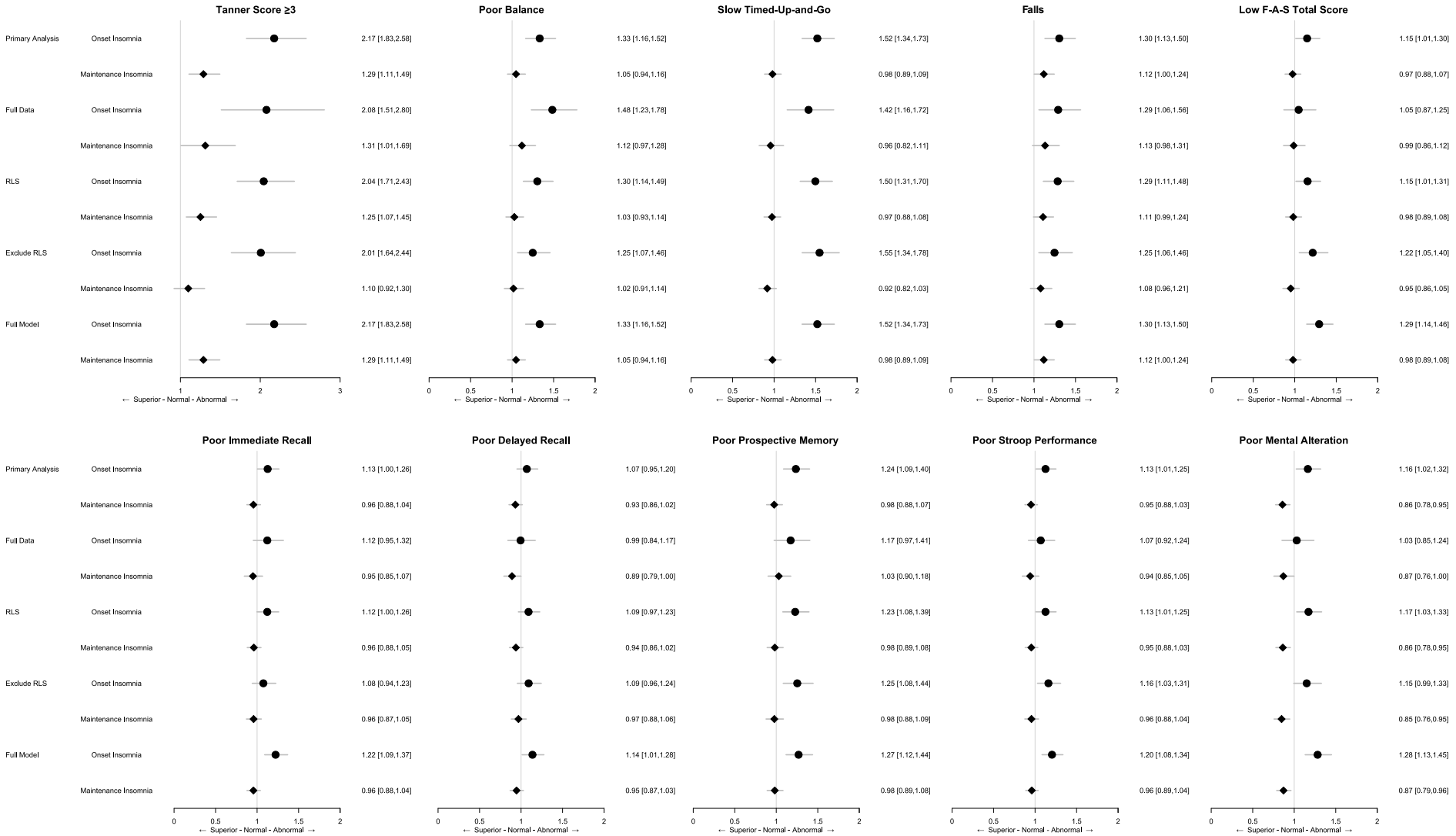
Table 4. Prodromal Neurodegenerative Symptoms in All Insomnia Combined

[a] Daytime sleepiness was defined as subjects experiencing trouble staying awake during daytime at least 6 days per week for minimum of 3 month. Participants who slept less than 6 hours on average per night or self-reported endorsing narcolepsy, were excluded.

Prodromal Neurodegenerative Symptoms		Onset Insomnia (2,051)	Maintenance Insomnia (4,333)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
		% or Mean±SD		$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]		
Motor Symptoms						
Tanner Questionnaire	Overall Score	0.70±1.19	0.57±1.00	1.26 [1.21,1.31]	1.14 [1.10,1.18]	1.13 [1.07,1.18]
	Score ≥ 3	179 (8.73)	235 (5.42)	2.17 [1.83,2.58]	1.29 [1.11,1.49]	1.68 [1.37,2.07]
Fall (last year)	At least One Fall	255 (13.2)	463 (11.2)	1.30 [1.13,1.50]	1.12 [1.00,1.24]	1.17 [1.00,1.38]
	Number of Falls	1.65±2.60	1.40±1.05	1.06 [1.00,1.12]	1.00 [0.93,1.07]	1.09 [1.00,1.21]
Neuropsychiatric Symptoms						
Psychiatric and Cognitive Symptoms	Self-Reported Memory Problem	43 (2.10)	69 (1.59)	1.65 [1.17,2.26]	1.23 [0.94,1.60]	1.40 [0.94,2.05]
	Depression/Anxiety	666 (32.6)	889 (20.6)	2.06 [1.86,2.28]	1.15 [1.06,1.25]	1.81 [1.61,2.05]
	Prescribed Antidepressant	311 (15.3)	251 (5.82)	2.09 [1.82,2.38]	0.76 [0.66,0.87]	2.82 [2.36,3.36]
Non-motor Symptoms						
Sleep	Sleep Hours	6.5±1.3	6.1±1.2	0.57 [0.55,0.59]	0.40 [0.39,0.42]	1.30 [1.24,1.35]
	Poor Sleep Quality	901 (44.0)	2446 (56.5)	6.27 [5.68,6.92]	10.5 [9.8,11.3]	0.59 [0.53,0.66]
	Daytime Sleepiness[a]	216 (10.6)	571 (13.2)	1.82 [1.56,2.11]	2.30 [2.07,2.55]	0.80 [0.67,0.94]
	Possible RLS Symptoms	494(24.56)	824(19.27)	1.90 [1.70,2.12]	1.46 [1.34,1.59]	1.31 [1.15,1.49]
	Possible RBD	67(4.29)	128(3.65)	1.54 [1.17,1.98]	1.22 [1.00,1.48]	1.23 [0.91,1.67]
Pain	Chronic pain (most days)	912 (47.1)	1713 (41.3)	1.75 [1.59,1.92]	1.43 [1.33,1.53]	1.23 [1.10,1.37]

Table 5. Prodromal Neurodegenerative Symptoms among Sleep maintenance vs. Sleep onset Insomnia Subtypes

[a] Daytime sleepiness was defined as subjects experiencing trouble staying awake during daytime at least 6 days per week for minimum of 3 month. Participants who slept less than 6 hours on average per night or self-reported endorsing narcolepsy, were excluded.


Tanner Score ≥3
Poor Balance
Slow Timed-Up-and-Go
Falls
Low F-A-S Total Score
Poor Immediate Recall
Poor Delayed Recall
Poor Prospective Memory
Poor Stroop Performance
Poor Mental Alteration
Primary Analysis
Full Data
RLS
Exclude RLS
Full Model
Onset Insomnia
Maintenance Insomnia
2.17 [1.83,2.58]
1.29 [1.11,1.49]
2.08 [1.51,2.80]
1.31 [1.01,1.69]
2.04 [1.71,2.43]
1.25 [1.07,1.45]
2.01 [1.64,2.44]
1.10 [0.92,1.30]
2.17 [1.83,2.58]
1.29 [1.11,1.49]
1.33 [1.16,1.52]
1.05 [0.94,1.16]
1.48 [1.23,1.78]
1.12 [0.97,1.28]
1.30 [1.14,1.49]
1.03 [0.93,1.14]
1.25 [1.07,1.46]
1.02 [0.91,1.14]
1.33 [1.16,1.52]
1.05 [0.94,1.16]
1.52 [1.34,1.73]
0.98 [0.89,1.09]
1.42 [1.16,1.72]
0.96 [0.82,1.11]
1.50 [1.31,1.70]
0.97 [0.88,1.08]
1.55 [1.34,1.78]
0.92 [0.82,1.03]
1.52 [1.34,1.73]
0.98 [0.89,1.09]
1.30 [1.13,1.50]
1.12 [1.00,1.24]
1.29 [1.06,1.56]
1.13 [0.98,1.31]
1.29 [1.11,1.48]
1.11 [0.99,1.24]
1.25 [1.06,1.46]
1.08 [0.96,1.21]
1.30 [1.13,1.50]
1.12 [1.00,1.24]
1.15 [1.01,1.30]
0.97 [0.88,1.07]
1.05 [0.87,1.25]
0.99 [0.86,1.12]
1.15 [1.01,1.31]
0.98 [0.89,1.08]
1.22 [1.05,1.40]
0.95 [0.86,1.05]
1.29 [1.14,1.46]
0.98 [0.89,1.08]
1.13 [1.00,1.26]
0.96 [0.88,1.04]
1.12 [0.95,1.32]
0.95 [0.85,1.07]
1.12 [1.00,1.26]
0.96 [0.88,1.05]
1.08 [0.94,1.23]
0.96 [0.87,1.05]
1.22 [1.09,1.37]
0.96 [0.88,1.04]
1.07 [0.95,1.20]
0.93 [0.86,1.02]
0.99 [0.84,1.17]
0.89 [0.79,1.00]
1.09 [0.97,1.23]
0.94 [0.86,1.02]
1.09 [0.96,1.24]
0.97 [0.88,1.06]
1.14 [1.01,1.28]
0.95 [0.87,1.03]
1.24 [1.09,1.40]
0.98 [0.88,1.07]
1.17 [0.97,1.41]
1.03 [0.90,1.18]
1.23 [1.08,1.39]
0.98 [0.89,1.08]
1.25 [1.08,1.44]
0.98 [0.88,1.09]
1.27 [1.12,1.44]
0.98 [0.89,1.08]
1.13 [1.01,1.25]
0.95 [0.88,1.03]
1.07 [0.92,1.24]
0.94 [0.85,1.05]
1.13 [1.01,1.25]
0.95 [0.88,1.03]
1.16 [0.99,1.33]
0.96 [0.88,1.04]
1.20 [1.08,1.34]
0.96 [0.89,1.04]
1.16 [1.02,1.32]
0.86 [0.78,0.95]
1.03 [0.85,1.24]
0.87 [0.76,1.00]
1.17 [1.03,1.33]
0.86 [0.78,0.95]
1.15 [0.99,1.33]
0.85 [0.76,0.95]
1.28 [1.13,1.45]
0.87 [0.79,0.96]
← Superior - Normal - Abnormal →

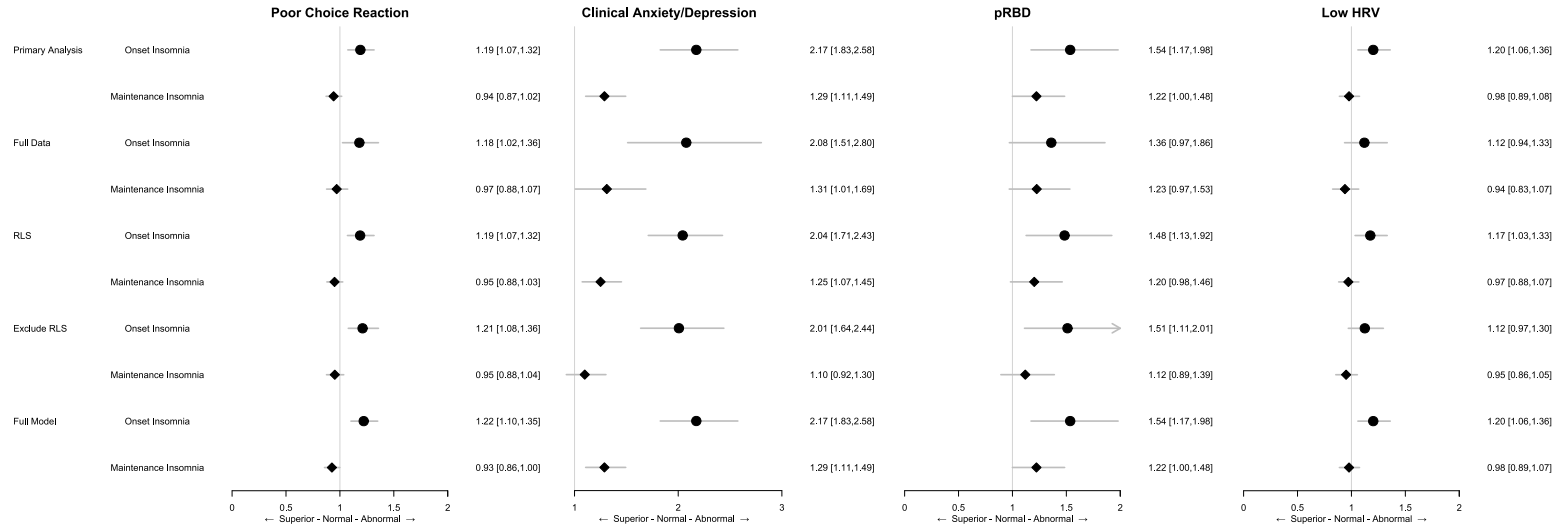


Figure 2. Associations between Neurodegenerative Signs/Symptoms and Insomnia Subtypes

- Primary Analysis: Age and Sex (+ Education & Language)
- Full Data: Age and Sex (+ Education & Language) among participants with complete information of the assessed neurodegenerative sign/symptoms
- RLS: Primary Analysis + RLS
- Exclude RLS: Age and Sex (+ Education & Language) with insomnia positive participants without RLS
- Full Model: Adjusted with RLS, and the following classified according to the variable categories (a-e).

[a]Motor Sign: arthritis, injuries or surgeries, swelling joins in lower extremity, polio, stroke, transient ischemic attack, diabetes, multiple sclerosis, age and sex
[b]Psychiatric and Psychological Symptoms: stroke, transient ischemic attack, diabetes, depression/anxiety, age, sex and total years of education
[c]Possible RBD: use of antidepressant, post-traumatic stress disorder, age and sex
[d]Low HRV: any pre-existing cardiological condition, age and sex
[e]Numbers of Abnormal Items: all of the selected confounding variables listed above.

		Isolated Onset Insomnia (473)	Isolated Maintenance Insomnia Disorder (1,044)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
		Mean±SD or %		$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]		
Demography Disorder						
Sex (% female)		317(67.0)	584(55.9)	2.21 [1.83,2.69]	1.38 [1.22,1.57]	1.60 [1.28,2.01]
Age		60.4±9.8	60.1±9.7	0.97 [0.96,0.98]	0.97 [0.97,0.98]	1.00 [0.99,1.01]
Body Mass Index		27.8±5.6	29.3±6.4	1.04 [1.02,1.05]	0.99 [0.98,1.01]	1.05 [1.03,1.06]
Years of Education		13.7±2.2	13.3±2.2	0.91 [0.88,0.95]	0.98 [0.95,1.01]	0.93 [0.88,0.98]
Clinical Signs/Symptoms						
Motor Sign	Tanner Score >3	56(11.8)	66(6.32)	3.81 [2.80,5.09]	1.82 [1.38,2.35]	2.17 [1.47,3.20]
	Poor Balance	72(16.5)	115(11.6)	1.62 [1.22,2.12]	1.00 [0.81,1.23]	1.66 [1.17,2.35]
	Slow Timed-Up-and-Go	110(23.8)	135(13.1)	2.81 [2.21,3.55]	1.17 [0.96,1.42]	2.30 [1.70,3.11]
	Fall (in last year)	68(15.3)	122(12.2)	1.57 [1.19,2.02]	1.25 [1.02,1.51]	1.27 [0.91,1.74]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	84(18.5)	134(13.2)	1.33 [1.03,1.70]	0.92 [0.76,1.12]	1.44 [1.04,1.97]
	Poor Immediate Recall	98(21.4)	184(18.3)	1.14 [0.89,1.44]	0.89 [0.75,1.05]	1.32 [0.97,1.78]
	Poor Delayed Recall	88(19.1)	183(18.1)	1.00 [0.78,1.28]	0.87 [0.73,1.04]	1.17 [0.86,1.59]
	Poor Prospective Memory	118(25.4)	250(24.2)	1.08 [0.87,1.34]	1.04 [0.89,1.21]	1.06 [0.81,1.37]
	Poor Stroop Performance	79(17.5)	137(13.7)	1.24 [0.95,1.59]	0.98 [0.81,1.18]	1.23 [0.89,1.69]
	Poor Mental Alteration	132(28.1)	254(24.6)	1.21 [0.98,1.48]	0.98 [0.84,1.13]	1.27 [0.99,1.63]
	Poor Choice Reaction	95(20.4)	144(14.1)	1.80 [1.41,2.28]	1.10 [0.91,1.32]	1.61 [1.18,2.17]
	Clinical Anxiety/Depression	230(48.9)	290(27.8)	3.85 [3.19,4.64]	1.63 [1.41,1.88]	2.40 [1.91,3.02]
Non-motor Signs	pRBD	18(5.08)	29(3.58)	1.86 [1.11,2.93]	1.22 [0.82,1.76]	1.52 [0.81,2.76]
	Low HRV	84(18.3)	143(14)	1.43 [1.12,1.82]	1.03 [0.85,1.23]	1.42 [1.05,1.91]
Other Sleep Symptoms						
Sleep	Poor Sleep Quality	267(56.57)	689(66)	9.99 [8.28,12.1]	15.2 [13.3,17.4]	0.67 [0.54,0.84]
	Possible RLS Symptoms	131(28.7)	215(20.9)	2.34 [1.89,2.87]	1.62 [1.38,1.89]	1.46 [1.13,1.89]

Table 6. Prodromal Neurodegenerative Signs and Symptoms according to diagnosis of possible insomnia disorder.

Supplementary Materials:

Questionnaires:

Self-reported dementia diagnosis was based on the response to the following question: "*Has a doctor ever told you that you have dementia or Alzheimer's disease?"*

The status of parkinsonism diagnosis was inquired via a single question: *"Has a doctor ever told you that you had Parkinsonism or Parkinson's Disease?"*

Sensitivity Analyses:

Several additional sensitivity analyses were performed to control or adjust for potential confounders. These include a model adjusting for any major health events (i.e., surgical treatment in the past 3 months, polio, aneurysm, pacemaker, major heart conditions, thyroid disorders, arthritis, multiple sclerosis, post-traumatic stress disorder, stroke, transient ischemic attack, nephrological disorders and diabetes).

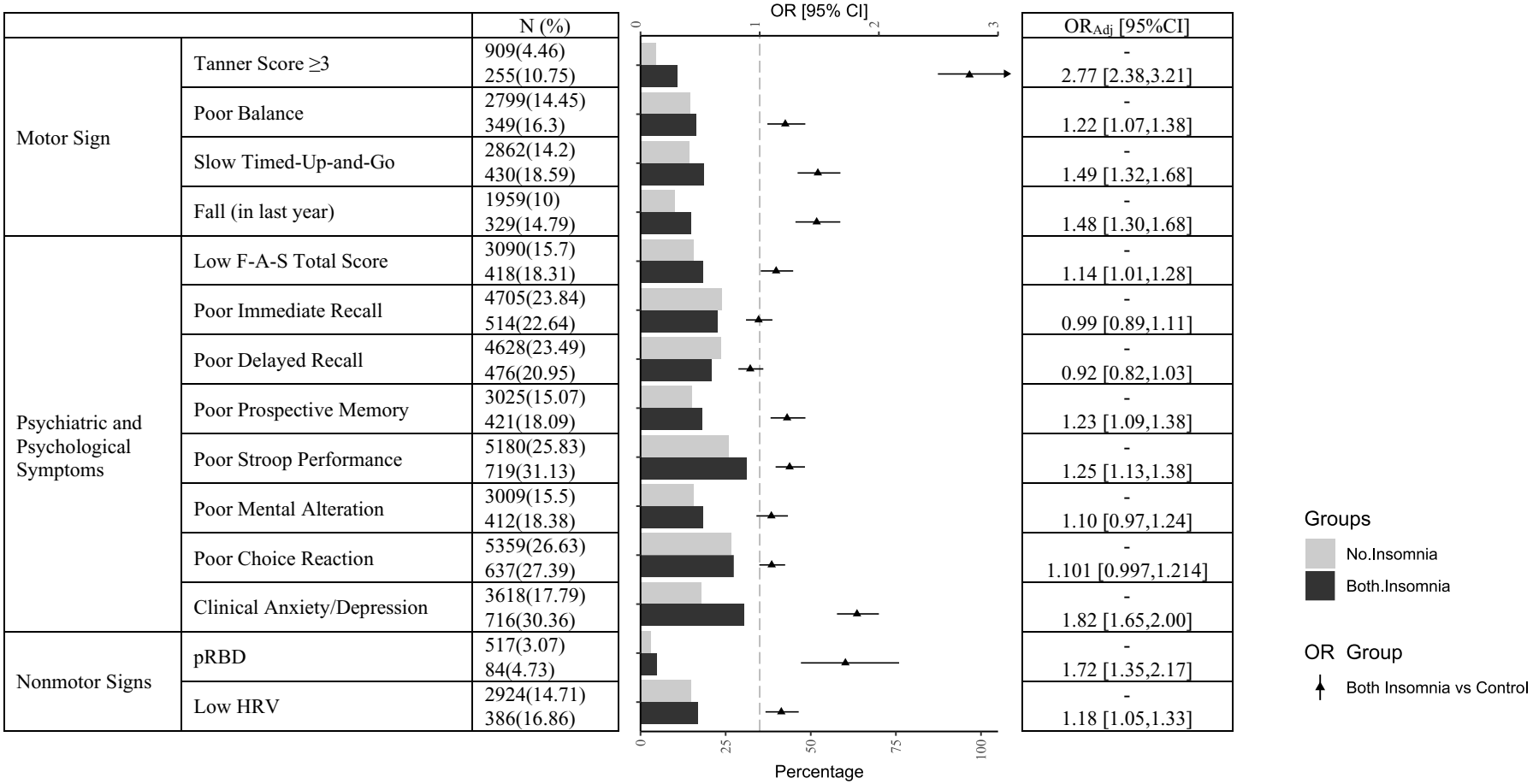


Figure e-1 Comorbidities and possible indicators of neurodegeneration among all participants with insomnia and those with combined onset and maintenance insomnia

A) Comorbidities and possible indicators of neurodegeneration in all insomnia participants comparing to the those without symptoms. B) Those endorsing both onset and maintenance insomnia symptoms' neurodegenerative risks and its comparisons (the control group and the isolated sleep-onset insomnia group).

Additional motor symptoms and sleep disorder history		No Insomnia (20,400)	Onset Insomnia (2,051)	Maintenance Insomnia (4,333)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
		N (%) or Mean±SD			$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]		
Motor Symptoms							
Tremor at Distal Limbs		1251 (6.14)	174 (8.48)	305 (7.04)	1.47 [1.24,1.73]	1.19 [1.04,1.35]	1.28 [1.05,1.56]
Resting Tremor		408 (2.01)	64 (3.13)	121 (2.81)	1.67 [1.26,2.17]	1.44 [1.17,1.77]	1.19 [0.87,1.61]
Micrographia		1161 (5.77)	161 (7.99)	305 (7.14)	1.46 [1.22,1.73]	1.30 [1.13,1.48]	1.12 [0.92,1.37]
Trouble buttoning buttons		1150 (5.64)	158 (7.71)	293 (6.76)	1.42 [1.19,1.69]	1.26 [1.10,1.44]	1.13 [0.92,1.39]
Microphonia		939 (4.62)	112 (5.48)	257 (5.95)	1.31 [1.07,1.60]	1.38 [1.19,1.58]	0.96 [0.76,1.20]
Gait Freeze		107 (0.53)	22 (1.07)	32 (0.74)	2.07 [1.27,3.23]	1.43 [0.95,2.10]	1.45 [0.83,2.50]
Festinating Gait		784 (3.85)	139 (6.79)	180 (4.16)	1.91 [1.57,2.30]	1.12 [0.95,1.33]	1.71 [1.36,2.16]
Poor Balance		2276 (11.2)	357 (17.4)	592 (13.7)	1.70 [1.49,1.92]	1.31 [1.18,1.45]	1.32 [1.14,1.53]
Hypomimia		638 (3.21)	105 (5.30)	204 (4.85)	1.78 [1.43,2.20]	1.57 [1.33,1.84]	1.15 [0.90,1.46]
Trouble rising from chair		1163 (5.71)	204 (9.95)	299 (6.91)	1.81 [1.54,2.12]	1.26 [1.10,1.43]	1.46 [1.21,1.77]
History of Sleep Disorders							
Total Hours of Sleep < 6		971(4.77)	419(20.52)	1166(26.95)	5.22 [4.59,5.92]	7.39 [6.73,8.11]	0.70 [0.61,0.79]
Insomnia Severity	Years	-	19.8±20.40	10.8±13.46	-	-	1.03 [1.03,1.04]
	Level of Influence	-	0.72±0.63	0.81±0.60	-	-	0.75 [0.68,0.82]
Daytime Somnolence	Duration (Years)	1.39±6.22	8.72±12.11	8.34±11.26	1.00 [0.99,1.00]	0.99 [0.99,1.00]	1.00 [0.99,1.01]
	Screen Positive	1087 (5.36)	216(10.56)	571(13.19)	1.82 [1.56,2.11]	2.30 [2.07,2.55]	0.80 [0.67,0.94]
	Level of Influence	0.08±0.31	0.19±0.47	0.23±0.49	2.02 [1.82,2.24]	2.54 [2.35,2.74]	0.82 [0.73,0.92]
Apnea-related Symptoms	Snores loudly	4946 (27.70)	465(26.56)	1107(29.19)	1.04 [0.93,1.16]	1.11 [1.03,1.20]	0.94 [0.83,1.07]
	Stopped breathing in sleep	2777 (14.44)	286(15.18)	683(16.78)	1.22 [1.07,1.40]	1.26 [1.15,1.38]	0.98 [0.84,1.14]

Table e-2. Additional motor symptoms and sleep disorder history.
The additional motor symptoms were assessed using the Tanner's Parkinson's Disease Screening Questionnaire.

A.

Sociodemographic Status	No Insomnia (2,041)	Onset Insomnia (2,041)	Maintenance Insomnia (2,041)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
	% or Mean±SD			$OR_{Age\_\&\_Sex\_Adjusted}$ [95%CI]		
Sex	1267(62.08)	1275(62.47)	1278(62.62)	1.02 [0.89,1.15]	1.02 [0.90,1.16]	0.99 [0.88,1.12]
Age	62.86±10.16	62.59±10.25	62.51±10.18	1.00 [0.99,1.00]	1.00 [0.99,1.00]	1.00 [1.00,1.01]
Ethnicity (Caucasian %)	1941 (95.7)	1941 (95.7)	1950 (96.2)	1.00 [0.74,1.36]	1.11 [0.81,1.52]	0.90 [0.66,1.24]
Total Education Year	13.21±2.28	13.25±2.31	13.26±2.25	1.01 [0.98,1.04]	1.00 [0.97,1.03]	1.01 [0.98,1.04]
BMI	28.54±6.09	28.49±5.71	28.45±5.75	1.00 [0.99,1.01]	1.00 [0.99,1.01]	1.00 [0.99,1.02]

B.

		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	99(4.85)	-
		172(8.43)	1.87 [1.44,2.42]
		102(5)	1.06 [0.80,1.41]
	Poor Balance	277(13.77)	-
		377(18.76)	1.56 [1.30,1.86]
		288(14.24)	1.09 [0.90,1.31]
	Slow Timed-Up-and-Go	303(15.63)	-
		328(17.27)	1.22 [1.01,1.47]
		305(15.71)	1.06 [0.88,1.28]
	Fall (in last year)	203(10.34)	-
		253(13.12)	1.31 [1.08,1.60]
		228(11.59)	1.14 [0.93,1.39]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	340(17.38)	-
		359(18.16)	1.07 [0.90,1.27]
		297(14.92)	0.88 [0.74,1.05]
	Poor Immediate Recall	473(24.11)	-
		490(24.8)	1.06 [0.90,1.23]
		422(21.2)	0.89 [0.76,1.04]
	Poor Delayed Recall	423(21.61)	-
		457(23.13)	1.13 [0.97,1.33]
		423(21.22)	1.02 [0.87,1.20]
	Poor Prospective Memory	311(15.54)	-
		357(17.8)	1.21 [1.02,1.44]
		293(14.61)	0.97 [0.81,1.16]
	Poor Stroop Performance	555(27.75)	-
		574(28.66)	1.07 [0.92,1.23]
		493(24.48)	0.86 [0.74,0.99]
	Poor Mental Alteration	304(15.73)	-
		365(18.8)	1.28 [1.08,1.52]
		276(14.03)	0.91 [0.76,1.10]
	Poor Choice Reaction	528(26.24)	-
		504(25.07)	1.17 [1.01,1.34]
		390(19.18)	0.97 [0.84,1.12]
	Clinical Anxiety/Depression	661(32.51)	-
		453(22.24)	2.05 [1.77,2.37]
		33(1.95)	1.20 [1.03,1.40]
Nonmotor Signs	pRBD	67(4.31)	-
		59(3.57)	2.29 [1.51,3.54]
		291(14.62)	1.87 [1.22,2.91]
	Low HRV	336(16.98)	-
		286(14.31)	1.21 [1.02,1.43]
		504(25.07)	0.98 [0.82,1.17]

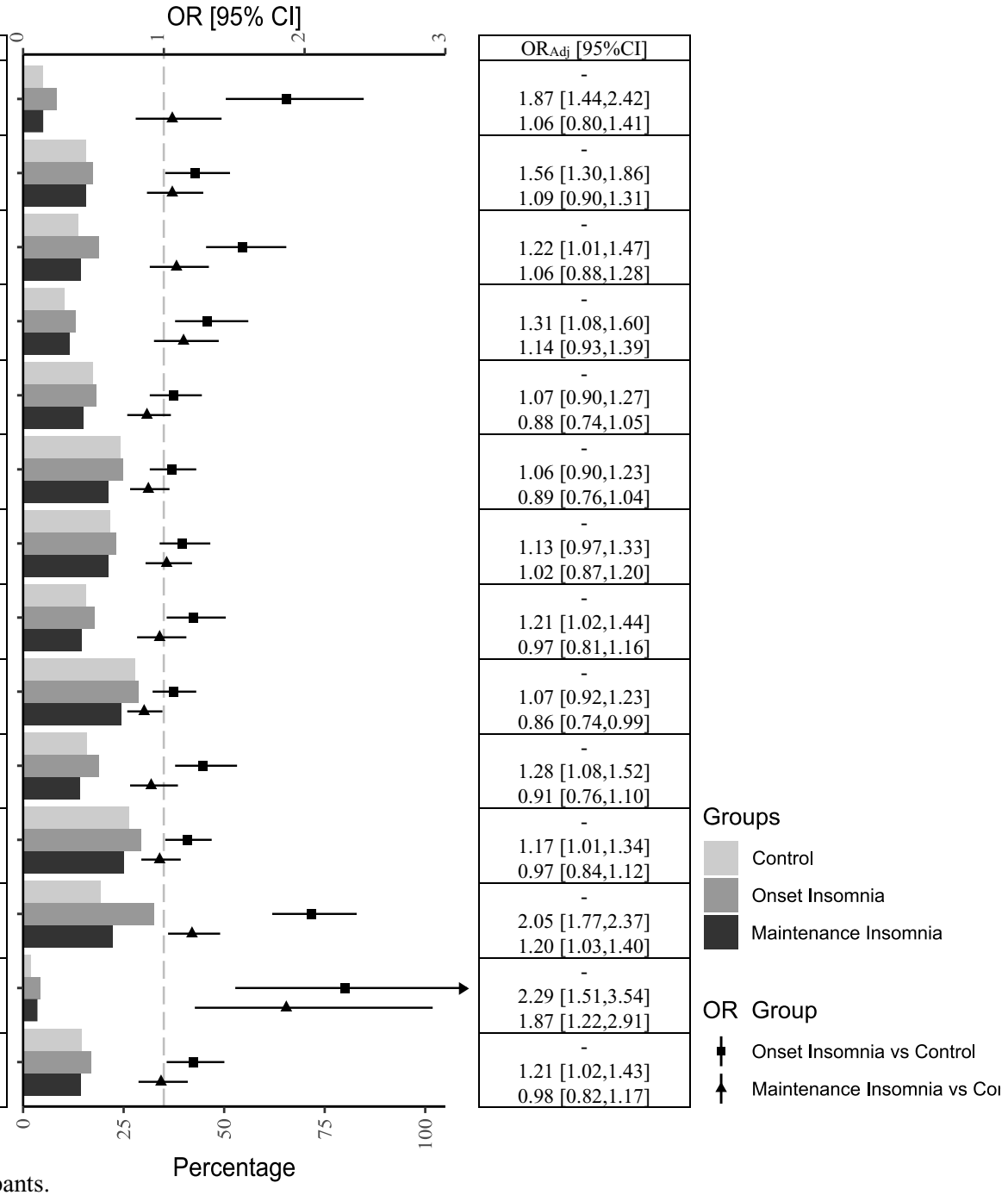


Table e-3. Neurodegenerative Risk Among Matched Participants.
A) sociodemographic distribution after propensity score matching. B) prodromal neurodegenerative symptoms among propensity score matched participants.

A.

Events that May Influenced Motor Function or Caused Motor Symptoms	No insomnia (20,400)	Onset Insomnia (2,051)	Maintenance Insomnia (4,333)	Onset vs. Ctrl	Maintenance vs. Ctrl	Onset vs. Maintenance
	% or Mean±SD			$OR_{Age\_\&\_Sex\_(+Education)\_Adjusted}$ [95%CI]		
Vascular Neurological Event						
Cerebral Vascular Attack	306 (1.50)	33 (1.62)	82 (1.89)	1.16 [0.79,1.64]	1.33 [1.03,1.69]	0.88 [0.57,1.31]
Transient Ischemic Attack	591 (2.91)	68 (3.35)	147 (3.41)	1.21 [0.93,1.56]	1.24 [1.03,1.49]	0.98 [0.73,1.31]
Diabetes Mellitus	3415 (16.8)	434 (21.2)	775 (17.9)	1.42 [1.26,1.59]	1.12 [1.02,1.22]	1.29 [1.13,1.47]
Multiple Sclerosis	126 (0.62)	25 (1.22)	29 (0.67)	1.76 [1.11,2.66]	1.03 [0.68,1.53]	1.72 [1.00,2.95]
Polio	189 (0.93)	23 (1.12)	36 (0.83)	1.28 [0.81,1.94]	0.93 [0.64,1.32]	1.34 [0.78,2.26]
Events related to Limitation on Lower Extremity Motor Function						
Motion Limitation and Swollen Joints	8118 (40.4)	1012 (50.1)	1975 (46.2)	1.41 [1.29,1.55]	1.27 [1.18,1.36]	1.12 [1.00,1.24]
Any Surgery Lower Extremity	1753 (8.60)	209 (10.2)	350 (8.08)	1.20 [1.03,1.40]	0.95 [0.84,1.08]	1.26 [1.05,1.52]
Any Health Event	12534 (62.4)	1391 (69.0)	2803 (65.6)	1.36 [1.23,1.51]	1.19 [1.11,1.29]	1.14 [1.01,1.29]

B.

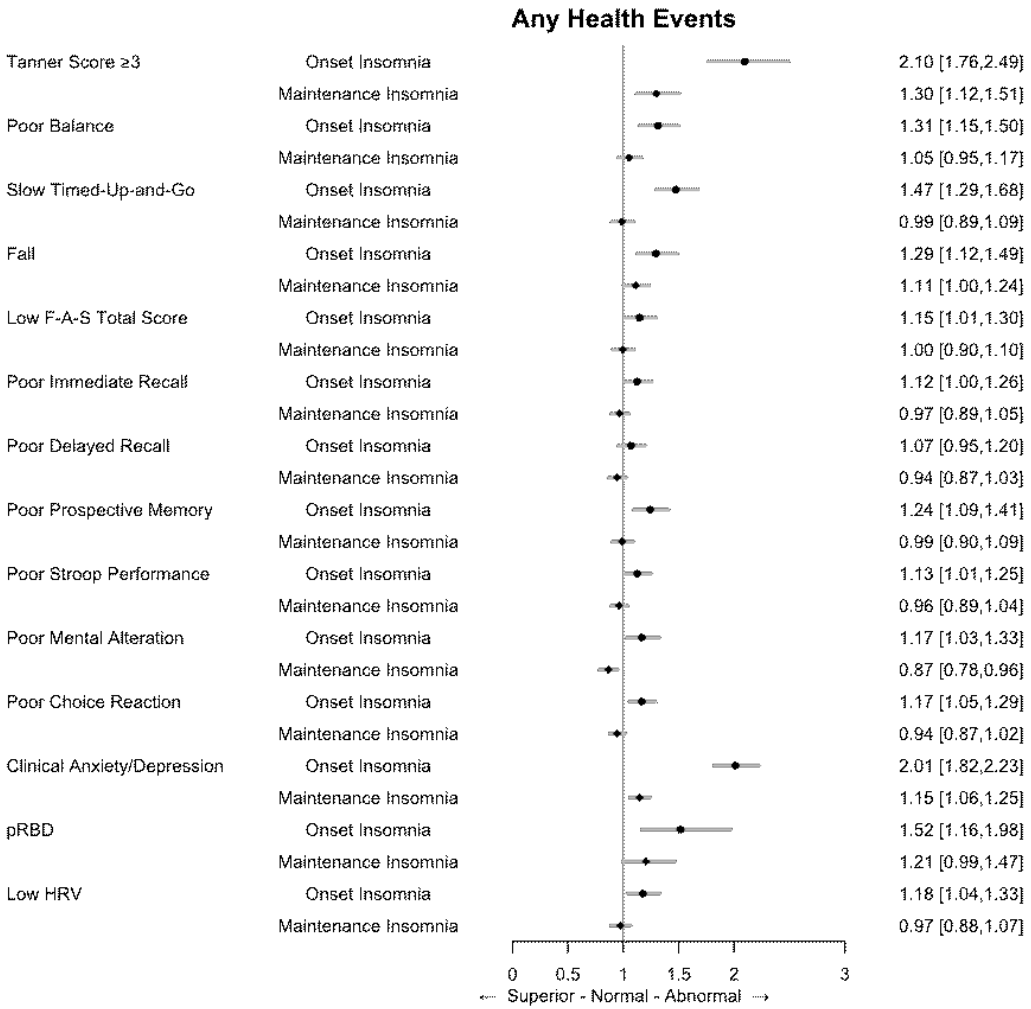
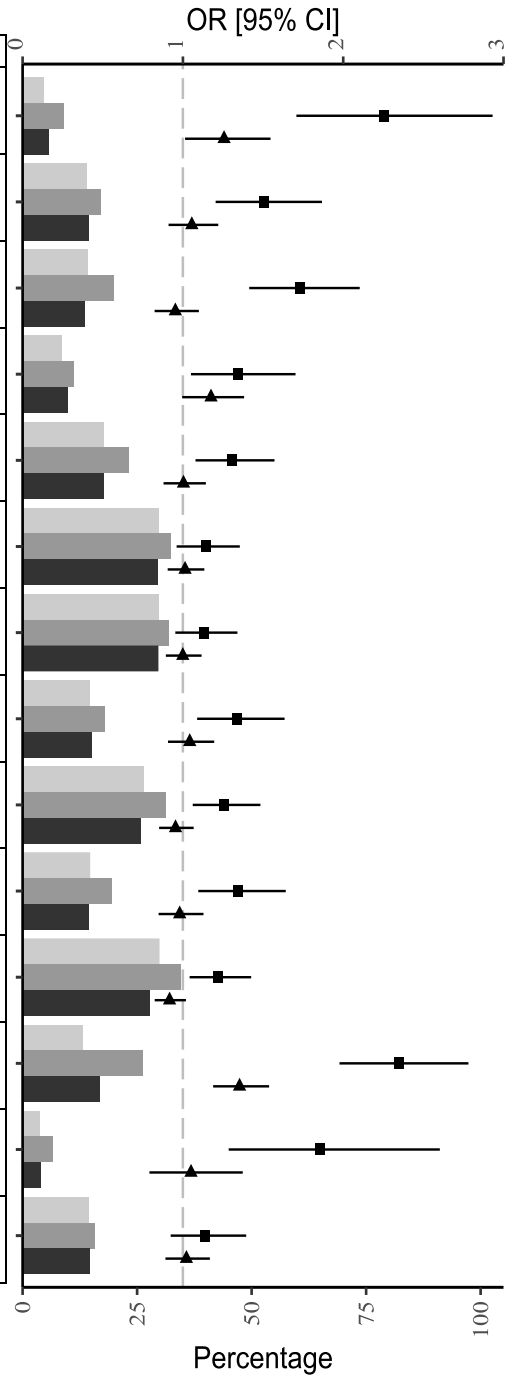
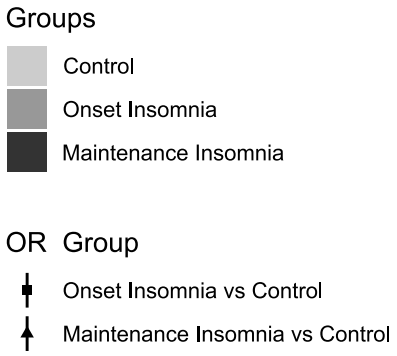


Table e-4 Events that may Influenced Motor/Cognitive Functions or Caused Motor Symptoms

Any health event was compiled of a list of health events provided in the CLSA. This includes: having an operation in the past 3 months, polio, aneurysm, pacemaker, major heart conditions, thyroid disorders, arthritis, multiple sclerosis, post-traumatic stress disorder, stroke, transient ischemic attack, nephrological disorders and diabetes.

A. Male		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	492 (4.60)	-
		69 (8.95)	2.25 [1.71,2.93]
		116 (5.63)	1.26 [1.01,1.55]
	Poor Balance	1436 (14.1)	-
		121 (17.1)	1.50 [1.20,1.87]
		284 (14.5)	1.06 [0.91,1.22]
	Slow Timed-Up-and-Go	1501 (14.2)	-
		150 (19.9)	1.73 [1.41,2.10]
		275 (13.5)	0.95 [0.82,1.10]
	Fall (in last year)	877 (8.55)	-
		81 (11.1)	1.35 [1.05,1.70]
		193 (9.88)	1.18 [1.00,1.38]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	1828 (17.7)	-
		172 (23.1)	1.30 [1.08,1.57]
		354 (17.8)	1.00 [0.88,1.14]
	Poor Immediate Recall	3070 (29.7)	-
		240 (32.4)	1.14 [0.96,1.35]
		589 (29.6)	1.01 [0.90,1.13]
	Poor Delayed Recall	3064 (29.7)	-
		236 (31.9)	1.13 [0.95,1.34]
		590 (29.7)	1.00 [0.89,1.12]
	Poor Prospective Memory	1553 (14.8)	-
		135 (17.9)	1.34 [1.09,1.63]
		307 (15.2)	1.04 [0.91,1.20]
	Poor Stroop Performance	2775 (26.5)	-
		235 (31.3)	1.26 [1.06,1.48]
		522 (25.8)	0.95 [0.85,1.07]
	Poor Mental Alteration	1495 (14.8)	-
		142 (19.5)	1.35 [1.10,1.64]
		286 (14.6)	0.98 [0.85,1.13]
	Poor Choice Reaction	3153 (29.9)	-
		262 (34.6)	1.22 [1.04,1.43]
		566 (27.8)	0.92 [0.82,1.02]
	Clinical Anxiety/Depression	1393 (13.1)	-
		203 (26.4)	2.35 [1.98,2.78]
		348 (16.9)	1.35 [1.19,1.54]
Nonmotor Signs	pRBD	323 (3.71)	-
		37 (6.63)	1.86 [1.29,2.60]
		63 (3.89)	1.05 [0.79,1.37]
	Low HRV	1503 (14.4)	-
		117 (15.8)	1.14 [0.92,1.39]
		296 (14.7)	1.02 [0.89,1.17]





B. Female		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	417 (4.30)	-
		110 (8.59)	2.13 [1.70,2.65]
		119 (5.24)	1.32 [1.06,1.63]
	Poor Balance	1363 (14.9)	-
		209 (17.5)	1.23 [1.04,1.46]
		308 (14.3)	1.04 [0.90,1.20]
	Slow Timed-Up-and-Go	1361 (14.2)	-
		228 (18.1)	1.39 [1.17,1.64]
		301 (13.4)	1.01 [0.88,1.17]
	Fall (in last year)	1082 (11.6)	-
		174 (14.4)	1.28 [1.07,1.52]
		270 (12.3)	1.08 [0.93,1.24]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	1262 (13.5)	-
		192 (15.5)	1.04 [0.88,1.24]
		276 (12.5)	0.94 [0.81,1.08]
	Poor Immediate Recall	1635 (17.4)	-
		256 (20.6)	1.13 [0.97,1.32]
		329 (14.9)	0.87 [0.76,0.99]
	Poor Delayed Recall	1564 (16.7)	-
		225 (18.1)	1.03 [0.88,1.21]
		307 (13.9)	0.83 [0.72,0.95]
	Poor Prospective Memory	1472 (15.4)	-
		224 (17.8)	1.18 [1.00,1.38]
		307 (13.7)	0.91 [0.79,1.05]
	Poor Stroop Performance	2405 (25.1)	-
		343 (27.2)	1.05 [0.91,1.20]
		528 (23.5)	0.95 [0.85,1.06]
	Poor Mental Alteration	1514 (16.3)	-
		225 (18.4)	1.06 [0.90,1.25]
		275 (12.6)	0.76 [0.66,0.88]
	Poor Choice Reaction	2206 (23.0)	-
		333 (26.3)	1.16 [1.02,1.33]
		490 (21.9)	0.97 [0.87,1.09]
	Clinical Anxiety/Depression	2225 (23.0)	-
		463 (36.4)	1.93 [1.70,2.18]
		541 (23.9)	1.03 [0.93,1.15]
Nonmotor Signs	pRBD	194 (2.39)	-
		30 (2.99)	1.27 [0.84,1.84]
		65 (3.45)	1.46 [1.09,1.93]
	Low HRV	1421 (15.0)	-
		223 (17.9)	1.23 [1.05,1.44]
		309 (13.9)	0.94 [0.82,1.08]

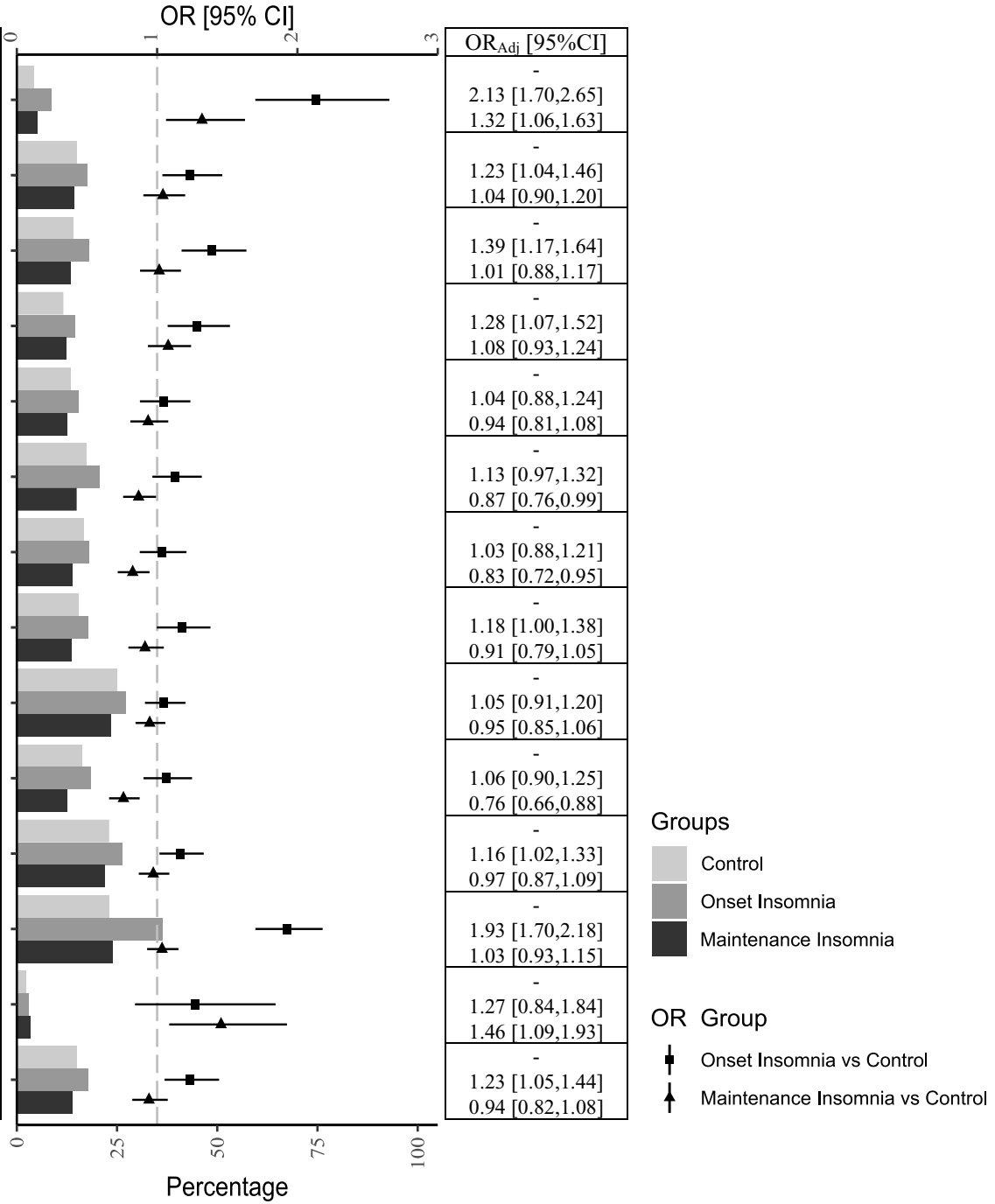


Table e-5 Neurodegeneration Features among Men and Women with Insomnia

Early Onset: ≤ 40 years old		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	909 (4.46)	-
		47 (6.18)	1.92 [1.39,2.59]
		39 (5.15)	1.75 [1.23,2.41]
	Poor Balance	2799 (14.5)	-
		89 (12.4)	1.26 [0.99,1.59]
		67 (9.31)	1.00 [0.76,1.30]
	Slow Timed-Up-and-Go	2862 (14.2)	-
		103 (13.8)	1.43 [1.14,1.78]
		76 (10.2)	1.12 [0.86,1.43]
	Fall (in last year)	1959 (10)	-
		86 (12.0)	1.27 [1.00,1.59]
		87 (12.1)	1.30 [1.03,1.63]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	3090 (15.7)	-
		120 (16.3)	1.09 [0.88,1.33]
		115 (15.6)	1.15 [0.92,1.41]
	Poor Immediate Recall	4705 (23.8)	-
		161 (22.1)	1.08 [0.89,1.30]
		128 (17.4)	0.90 [0.73,1.10]
	Poor Delayed Recall	4628 (23.5)	-
		149 (20.3)	1.00 [0.83,1.21]
		131 (17.7)	0.93 [0.76,1.14]
	Poor Prospective Memory	3025 (15.1)	-
		101 (13.5)	1.15 [0.92,1.43]
		83 (11.2)	1.01 [0.79,1.28]
	Poor Stroop Performance	5180 (25.8)	-
		190 (25.5)	1.12 [0.94,1.33]
		166 (22.3)	1.03 [0.85,1.23]
	Poor Mental Alteration	3009 (15.5)	-
		104 (14.3)	1.01 [0.81,1.25]
		87 (12.1)	0.94 [0.73,1.18]
	Poor Choice Reaction	5359 (26.6)	-
		219 (29.2)	1.17 [0.99,1.38]
		176 (23.7)	0.92 [0.78,1.10]
	Clinical Anxiety/Depression	3618 (17.8)	-
		248 (32.8)	2.12 [1.81,2.48]
		197 (26.1)	1.51 [1.27,1.78]
Nonmotor Signs	pRBD	517 (3.07)	-
		29 (5.05)	1.68 [1.12,2.43]
		23 (3.88)	1.29 [0.82,1.93]
	Low HRV	2924 (14.7)	-
		111 (15.0)	1.16 [0.94,1.42]
		95 (12.8)	1.00 [0.80,1.24]

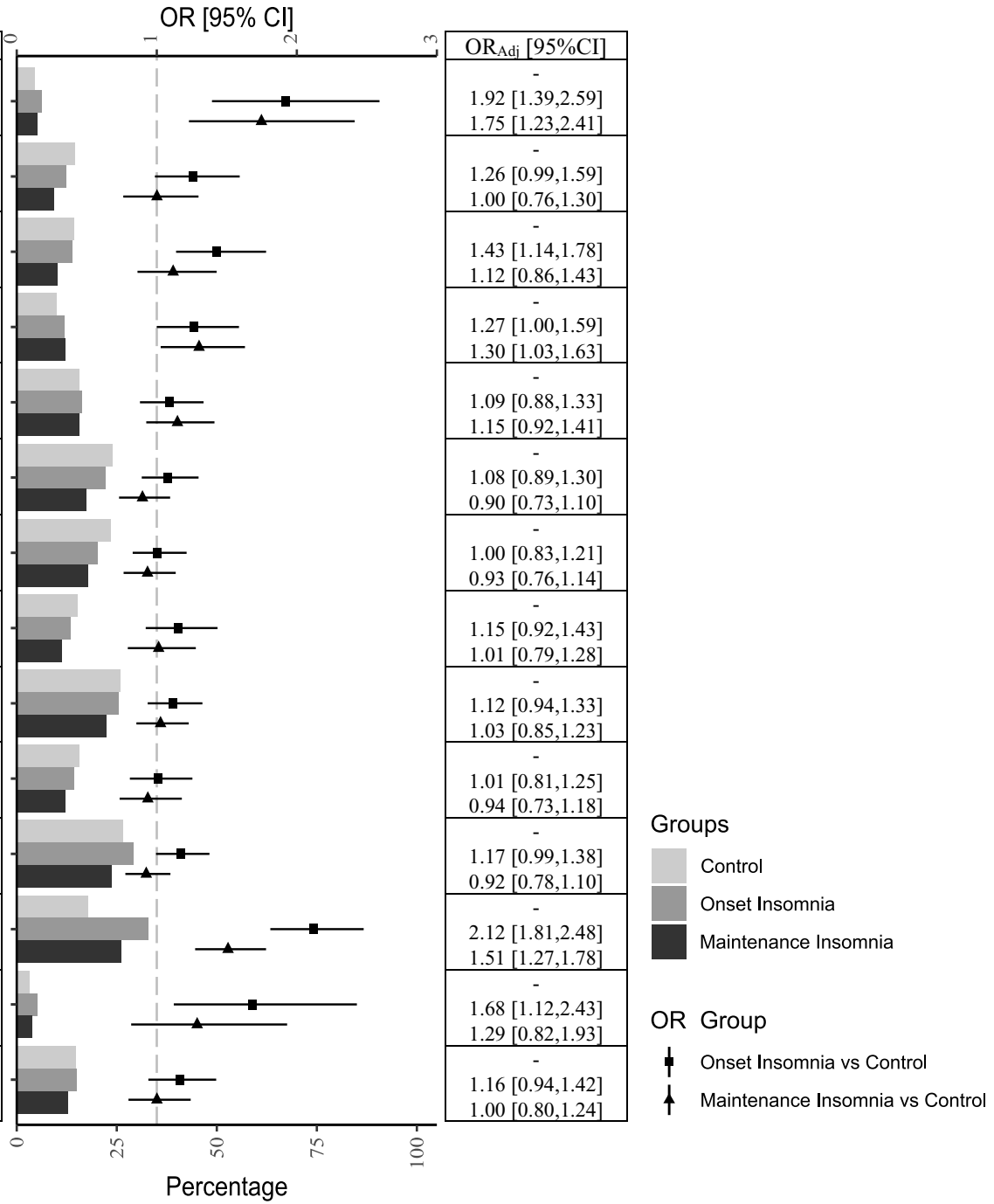


Table e-6 Abnormal Neurodegenerative Signs and Symptoms Onset ≤ 40

Late Onset: Onset ≥ 55 years old		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	909 (4.46) 91 (13.0) 142 (7.52)	- 2.00 [1.57,2.52] 1.08 [0.89,1.30]
	Poor Balance	2799 (14.5) 185 (29.8) 421 (24.1)	- 1.35 [1.11,1.63] 1.00 [0.88,1.13]
	Slow Timed-Up-and-Go	2862 (14.2) 194 (28.4) 387 (20.8)	- 1.34 [1.11,1.60] 0.85 [0.75,0.97]
	Fall (in last year)	1959 (10.0) 101 (15.2) 195 (10.9)	- 1.48 [1.18,1.84] 1.01 [0.86,1.18]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	3090 (15.7) 149 (21.9) 317 (17.4)	- 0.99 [0.81,1.21] 0.89 [0.78,1.02]
	Poor Immediate Recall	4705 (23.8) 240 (35.1) 551 (30.3)	- 0.99 [0.83,1.18] 0.88 [0.78,0.99]
	Poor Delayed Recall	4628 (23.5) 220 (32.2) 542 (29.8)	- 0.92 [0.78,1.10] 0.88 [0.79,0.99]
	Poor Prospective Memory	3025 (15.1) 177 (25.8) 382 (20.6)	- 1.16 [0.96,1.39] 0.88 [0.78,1.00]
	Poor Stroop Performance	5180 (25.8) 239 (34.9) 564 (30.4)	- 1.01 [0.85,1.20] 0.89 [0.80,1.00]
	Poor Mental Alteration	3009 (15.5) 162 (24.6) 299 (16.7)	- 1.06 [0.87,1.28] 0.73 [0.63,0.84]
	Poor Choice Reaction	5359 (26.6) 208 (30.1) 519 (27.8)	- 1.00 [0.84,1.18] 0.95 [0.85,1.06]
	Clinical Anxiety/Depression	3618 (17.8) 203 (29.1) 322 (17.1)	- 2.34 [1.97,2.78] 1.14 [1.00,1.29]
Nonmotor Signs	pRBD	517 (3.07) 19 (3.57) 53 (3.47)	- 1.15 [0.69,1.78] 1.12 [0.82,1.48]
	Low HRV	2924 (14.7) 143 (21.3) 327 (17.9)	- 1.29 [1.06,1.56] 1.05 [0.92,1.19]

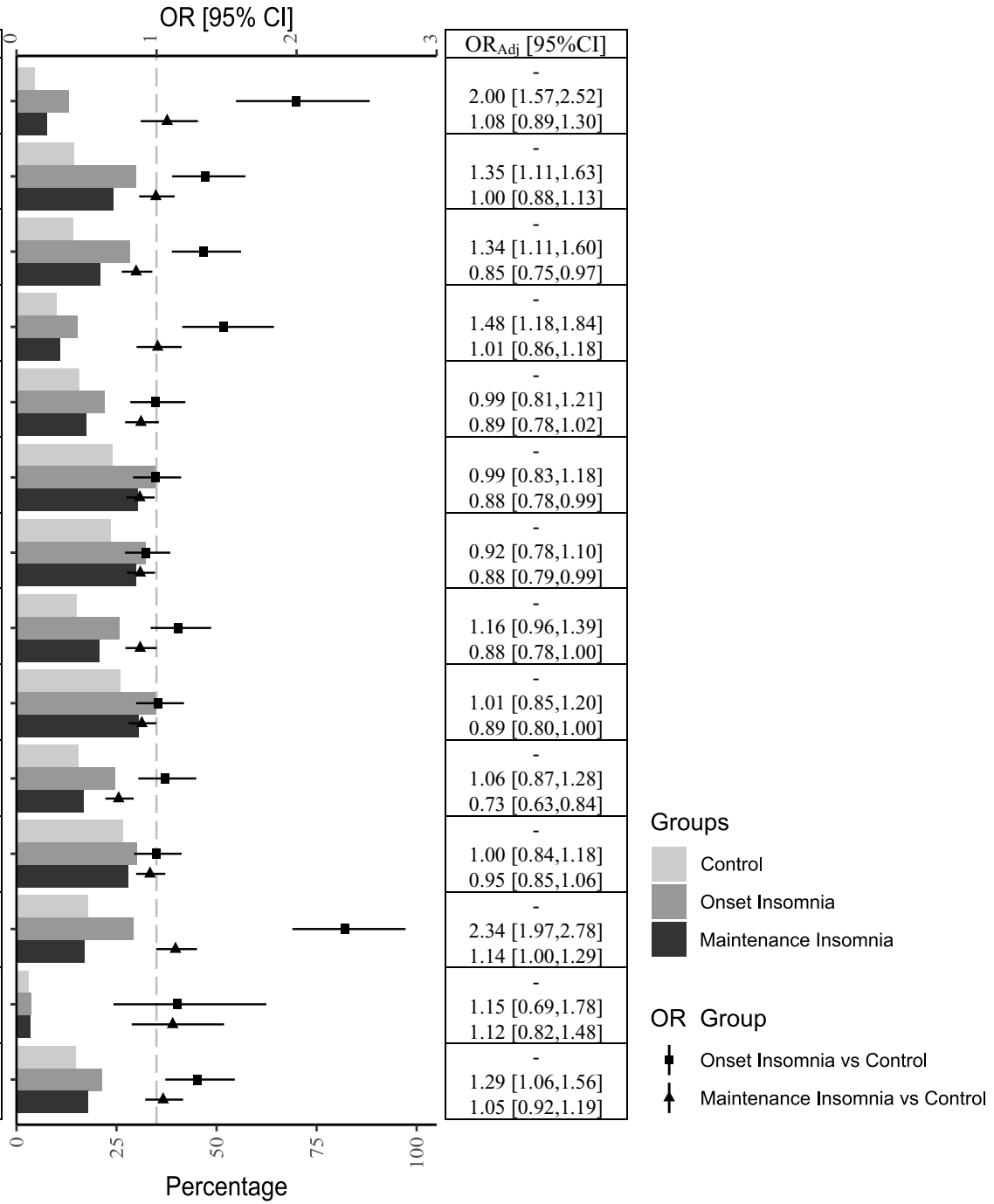


Table e-7 Abnormal Neurodegenerative Signs and Symptoms Onset ≥ 55.
Only participants aged at least 55 years were included in the analysis

Age >65 years old		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	635(7.34) 110(13.73) 161(9.42)	- 2.01 [1.60,2.51] 1.31 [1.09,1.57]
	Poor Balance	2108(26.56) 241(34.18) 441(28.29)	- 1.37 [1.15,1.63] 1.08 [0.95,1.22]
	Slow Timed-Up-and-Go	2134(25.01) 239(30.72) 417(24.79)	- 1.28 [1.08,1.51] 0.97 [0.85,1.10]
	Fall (in last year)	905(10.92) 106(13.98) 197(12.12)	- 1.24 [1.00,1.54] 1.11 [0.94,1.31]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	1750(21.02) 195(25.39) 344(20.84)	- 1.22 [1.02,1.46] 1.03 [0.89,1.18]
	Poor Immediate Recall	2967(35.6) 282(36.34) 574(35.09)	- 1.08 [0.91,1.27] 1.00 [0.89,1.13]
	Poor Delayed Recall	2881(34.73) 269(34.8) 556(33.94)	- 1.09 [0.92,1.28] 0.97 [0.87,1.10]
	Poor Prospective Memory	2044(24.06) 225(28.81) 419(25.12)	- 1.20 [1.01,1.42] 1.04 [0.92,1.18]
	Poor Stroop Performance	3010(35.45) 310(39.69) 578(34.51)	- 1.13 [0.97,1.32] 0.96 [0.86,1.07]
	Poor Mental Alteration	1873(23.04) 200(26.67) 327(20.37)	- 1.06 [0.89,1.27] 0.84 [0.73,0.96]
	Poor Choice Reaction	2551(29.91) 262(33.29) 463(27.45)	- 1.16 [0.99,1.37] 0.91 [0.81,1.03]
	Clinical Anxiety/Depression	1278(14.8) 224(28.07) 274(16.02)	- 2.11 [1.78,2.50] 1.09 [0.94,1.26]
Nonmotor Signs	pRBD	227(3.24) 16(2.64) 48(3.49)	- 0.92 [0.55,1.55] 1.11 [0.81,1.52]
	Low HRV	1574(18.91) 161(21.1) 302(18.31)	- 1.10 [0.92,1.32] 0.96 [0.83,1.09]

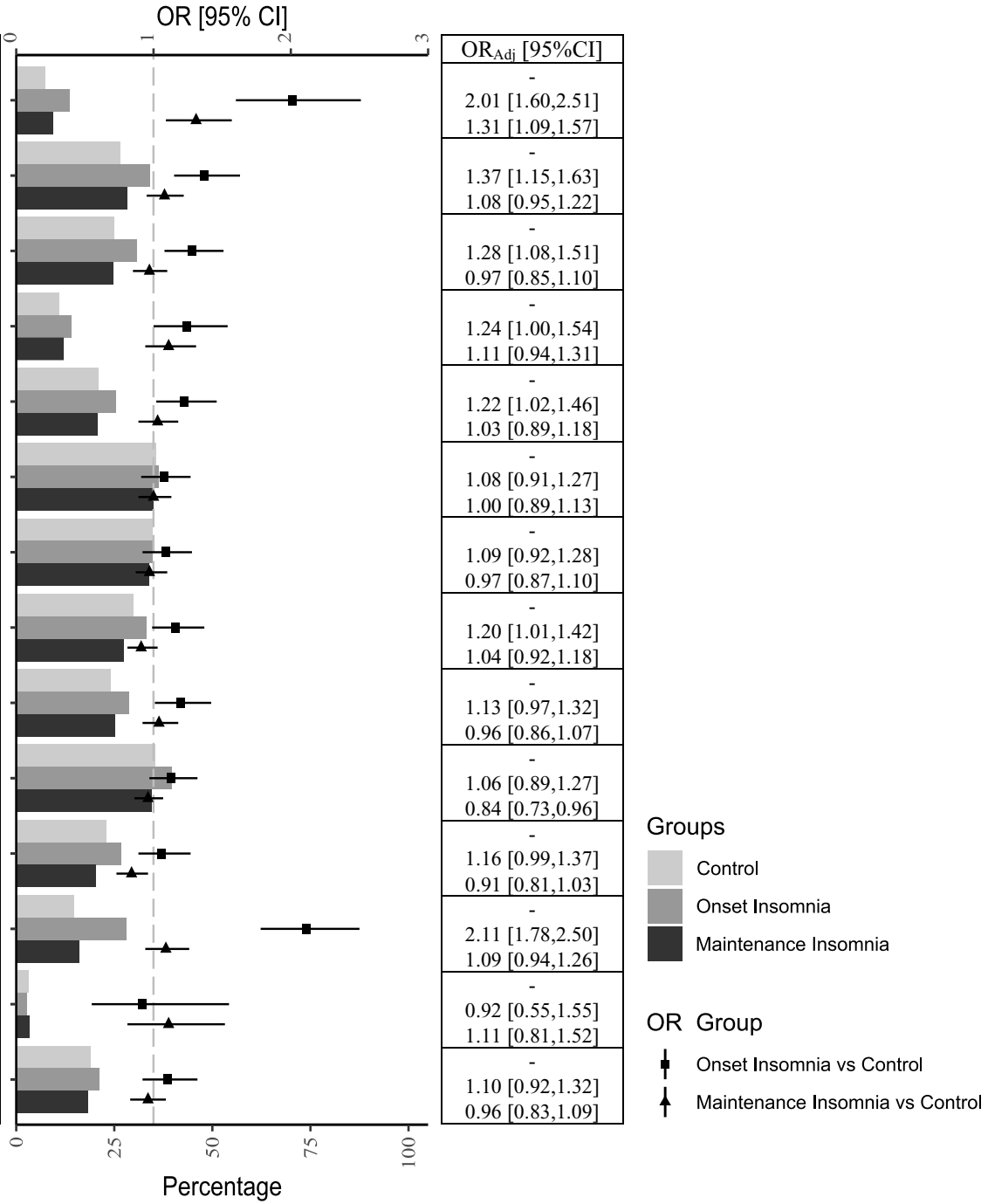


Table e-8 Abnormal Neurodegenerative Signs and Symptoms in Participants aged 65 and above. Only participants aged at least 65 years were included in the analysis

No Memory Complaints		N (%)	OR_{Adj} [95%CI]
Motor Sign	Tanner Score ≥3	840(4.18)	-
		162(8.08)	2.12 [1.77,2.54]
		219(5.14)	1.30 [1.12,1.52]
	Poor Balance	2732(14.28)	-
		319(17.12)	1.32 [1.15,1.51]
		573(14.16)	1.04 [0.94,1.15]
	Slow Timed-Up-and-Go	2768(13.93)	-
		363(18.44)	1.52 [1.33,1.73]
		555(13.17)	0.98 [0.88,1.09]
	Fall (in last year)	1921(9.95)	-
		248(13.07)	1.30 [1.13,1.50]
		455(11.16)	1.13 [1.01,1.25]
Psychiatric and Psychological Symptoms	Low F-A-S Total Score	3012(15.53)	-
		350(18.03)	1.14 [1.01,1.30]
		608(14.7)	0.97 [0.88,1.07]
	Poor Immediate Recall	4568(23.48)	-
		481(24.76)	1.14 [1.01,1.28]
		880(21.33)	0.95 [0.87,1.03]
	Poor Delayed Recall	4500(23.16)	-
		445(22.9)	1.07 [0.95,1.21]
		862(20.88)	0.92 [0.85,1.01]
	Poor Prospective Memory	2934(14.83)	-
		344(17.46)	1.23 [1.08,1.40]
		593(14.16)	0.98 [0.88,1.08]
	Poor Stroop Performance	5075(25.67)	-
		565(28.72)	1.14 [1.02,1.27]
		1025(24.41)	0.95 [0.88,1.03]
	Poor Mental Alteration	2925(15.29)	-
		351(18.39)	1.15 [1.01,1.31]
		542(13.3)	0.86 [0.77,0.95]
	Poor Choice Reaction	5259(26.51)	-
		580(29.31)	1.19 [1.07,1.32]
		1037(24.68)	0.95 [0.88,1.02]
	Clinical Anxiety/Depression	3492(17.42)	-
		639(31.98)	2.05 [1.85,2.27]
		862(20.27)	1.16 [1.07,1.26]
Nonmotor Signs	pRBD	512(3.08)	-
		66(4.29)	1.53 [1.18,2.00]
		125(3.62)	1.21 [0.99,1.48]
	Low HRV	2866(14.63)	-
		333(17.12)	1.21 [1.07,1.37]
		595(14.28)	0.98 [0.89,1.08]

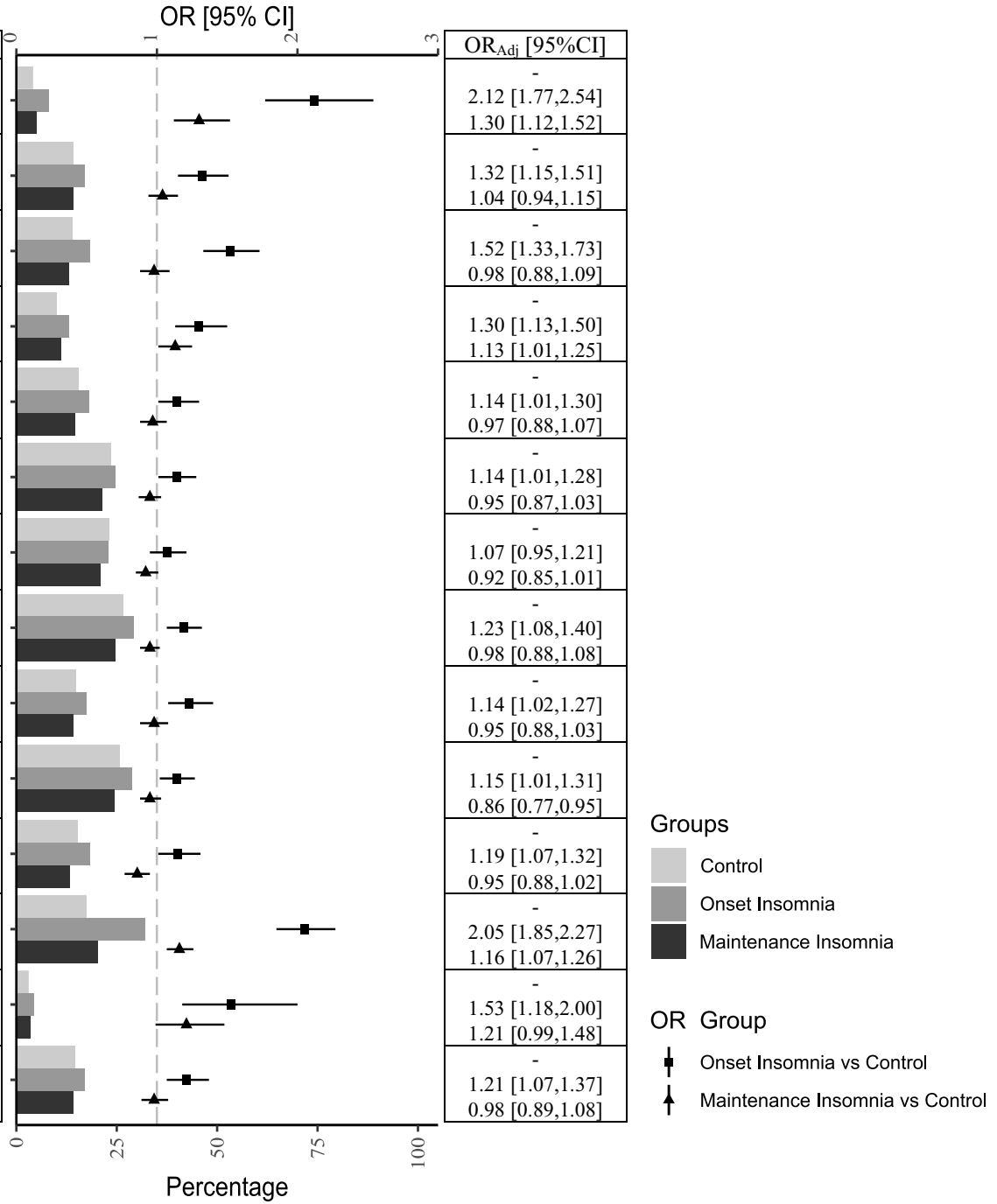
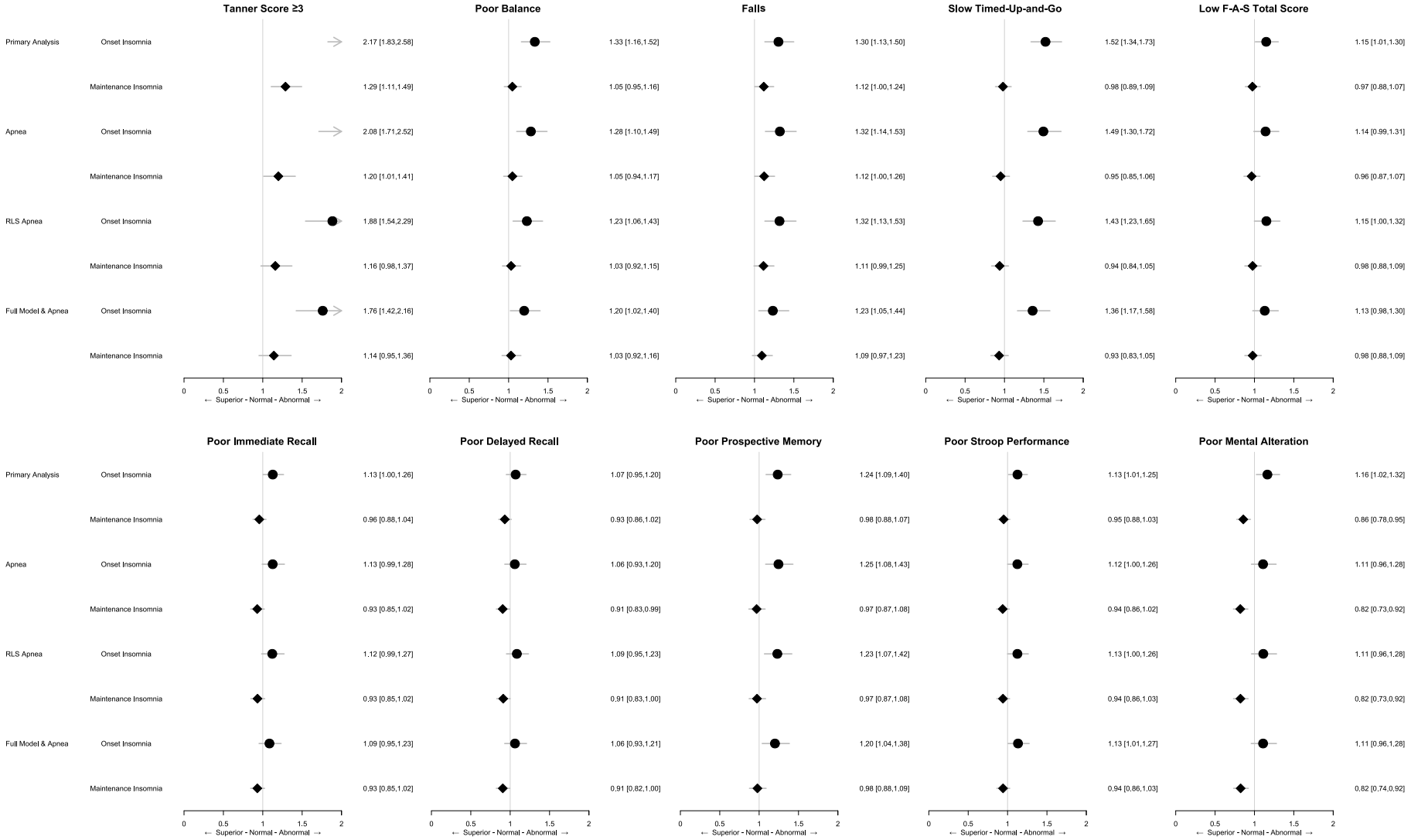


Table e-9 Abnormal Neurodegenerative Signs and Symptoms among Participants without Clinical Memory Complaints.


Tanner Score ≥3
Poor Balance
Falls
Slow Timed-Up-and-Go
Low F-A-S Total Score
Primary Analysis
Onset Insomnia
2.17 [1.83,2.58]
1.33 [1.16,1.52]
1.30 [1.13,1.50]
1.52 [1.34,1.73]
1.15 [1.01,1.30]
Maintenance Insomnia
1.29 [1.11,1.49]
1.05 [0.95,1.16]
1.12 [1.00,1.24]
0.98 [0.89,1.09]
0.97 [0.88,1.07]
Apnea
Onset Insomnia
2.08 [1.71,2.52]
1.28 [1.10,1.49]
1.32 [1.14,1.53]
1.49 [1.30,1.72]
1.14 [0.99,1.31]
Maintenance Insomnia
1.20 [1.01,1.41]
1.05 [0.94,1.17]
1.12 [1.00,1.26]
0.95 [0.85,1.06]
0.96 [0.87,1.07]
RLS Apnea
Onset Insomnia
1.88 [1.54,2.29]
1.23 [1.06,1.43]
1.32 [1.13,1.53]
1.43 [1.23,1.65]
1.15 [1.00,1.32]
Maintenance Insomnia
1.16 [0.98,1.37]
1.03 [0.92,1.15]
1.11 [0.99,1.25]
0.94 [0.84,1.05]
0.98 [0.88,1.09]
Full Model & Apnea
Onset Insomnia
1.76 [1.42,2.16]
1.20 [1.02,1.40]
1.23 [1.05,1.44]
1.36 [1.17,1.58]
1.13 [0.98,1.30]
Maintenance Insomnia
1.14 [0.95,1.36]
1.03 [0.92,1.16]
1.09 [0.97,1.23]
0.93 [0.83,1.05]
0.98 [0.88,1.09]
0 0.5 1 1.5 2
← Superior - Normal - Abnormal →
Poor Immediate Recall
Poor Delayed Recall
Poor Prospective Memory
Poor Stroop Performance
Poor Mental Alteration
Primary Analysis
Onset Insomnia
1.13 [1.00,1.26]
1.07 [0.95,1.20]
1.24 [1.09,1.40]
1.13 [1.01,1.25]
1.16 [1.02,1.32]
Maintenance Insomnia
0.96 [0.88,1.04]
0.93 [0.86,1.02]
0.98 [0.88,1.07]
0.95 [0.88,1.03]
0.86 [0.78,0.95]
Apnea
Onset Insomnia
1.13 [0.99,1.28]
1.06 [0.93,1.20]
1.25 [1.08,1.43]
1.12 [1.00,1.26]
1.11 [0.96,1.28]
Maintenance Insomnia
0.93 [0.85,1.02]
0.91 [0.83,0.99]
0.97 [0.87,1.08]
0.94 [0.86,1.02]
0.82 [0.73,0.92]
RLS Apnea
Onset Insomnia
1.12 [0.99,1.27]
1.09 [0.95,1.23]
1.23 [1.07,1.42]
1.13 [1.00,1.26]
1.11 [0.96,1.28]
Maintenance Insomnia
0.93 [0.85,1.02]
0.91 [0.83,1.00]
0.97 [0.87,1.08]
0.94 [0.86,1.03]
0.82 [0.73,0.92]
Full Model & Apnea
Onset Insomnia
1.09 [0.95,1.23]
1.06 [0.93,1.21]
1.20 [1.04,1.38]
1.13 [1.01,1.27]
1.11 [0.96,1.28]
Maintenance Insomnia
0.93 [0.85,1.02]
0.91 [0.82,1.00]
0.98 [0.88,1.09]
0.94 [0.86,1.03]
0.82 [0.74,0.92]
0 0.5 1 1.5 2
← Superior - Normal - Abnormal →

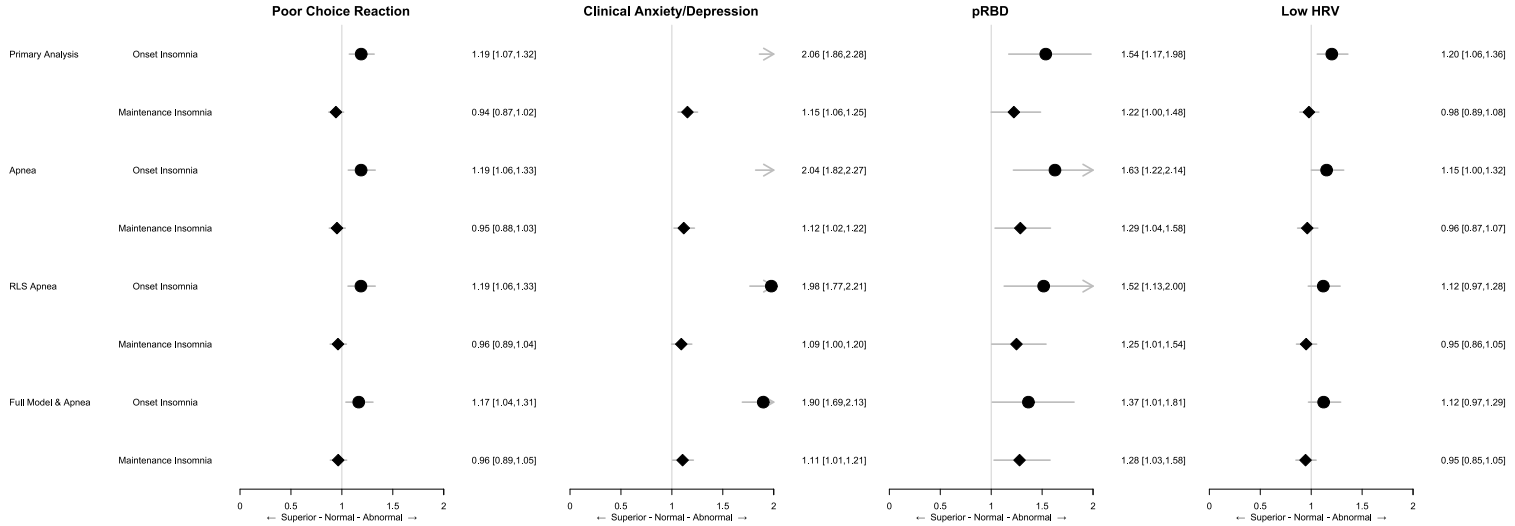


Table e-10. Associations between Neurodegenerative Signs/Symptoms and Insomnia Subtypes

- Primary Analysis: Age and Sex (+ Education & Language)
- Apnea: Primary Analysis + Apnea Symptoms (Snoring and/or Stop Breathing)
- RLS/Apnea: Analysis + Apnea Symptoms (Snoring and/or Stop Breathing) + RLS
- Full Model & Apnea: Adjusted with apnea symptoms, RLS, and the following variables for the corresponding variable categories (a-e).

[a]Motor Sign: arthritis, injuries or surgeries, swelling joins in lower extremity, polio, stroke, transient ischemic attack, diabetes, multiple sclerosis, age and sex
[b]Psychiatric and Psychological Symptoms: stroke, transient ischemic attack, diabetes, depression/anxiety, age, sex and total years of education
[c]Possible RBD: use of antidepressant, post-traumatic stress disorder, age and sex
[d]Low HRV: any pre-existing cardiological condition, age and sex
[e]Numbers of Abnormal Items: all of the selected confounding variables listed above.

Chapter II - Prospective Health Outcome of Isolated Insomnia Symptoms

Insomnia is one of the most prevalent sleep symptoms/disorders. Over the years, diagnostic criteria for insomnia classification have varied drastically across iterations. In Chapter 2-1, we assessed neurodegeneration signs and symptoms in those with insomnia symptoms. Of the isolated insomnia symptoms (i.e., with only trouble initiating or maintaining sleep), sleep-onset insomnia was associated with parkinsonism-related symptoms, poor motor performance and cognitive decline but not sleep-maintenance insomnia.[1] In this follow-up study, we set out to explore the health outcomes associated with diagnosed neurodegeneration.

We prospectively assessed the population-based comprehensive CLSA cohort, which composed of 30,097 adults aged 45-85 recruited between 2012-2015.[2] Several health outcomes that share similar clinical presentations as parkinsonism and/or dementia, were elected for analyses. These were: cerebral vascular attack, clinical diagnosis of parkinsonism (cross-verified with parkinsonism treatment and symptom-screen) and dementia. We also assessed the risk known to the assessed health outcomes of interest, including myocardial infarction, hypertension, angina, transient ischemic attack, and clinical memory impairment. De-novo diagnosis for each assessed health outcome was defined as negative of baseline diagnosis but reporting a 'new' diagnosis at the 3-year follow-up. Those with negative diagnoses throughout the follow-up period were defined as disease-free for the assessed outcome. The last available status for each outcome was carried forward for missing value imputation. We estimated relative risks from insomnia symptom subtype to the outcome of interest using binomial estimate with log-link function weighted for age, sex time interval, follow-up statuses to account for selection bias.[3] 95% confidence intervals were estimated via White's variance.[4] Statistical analysis was performed using R version 4.1.0.

At the 3-year follow-up, most assessed health outcomes were associated with older age, male sex, and increase in total body fat. (e-1) Overall, participants with insomnia showed an increase in the risk of developing de-novo vascular events (i.e., hypertension, peripheral vascular disease, angina, and myocardial infarction), cerebrovascular events (transient ischemic attack and cerebrovascular attack) and clinical memory impairment but not with dementia nor parkinsonism. (Figure 1-A) Besides those endorsing both insomnia symptoms, who posed the greatest risks of all the associated outcomes, sleep-onset insomnia was also found associated with hypertension (RR=1.17, 95%CI=[1.11,1.24]), cerebrovascular attack (RR=1.45[1.05,2.01]), myocardial infarction (RR=1.31[1.24,1.38]), and memory impairment (1.61[1.17,2.22]). Sleep-maintenance insomnia was not associated with any of the health outcomes assessed. When re-assessing the associations with cardiovascular risk factors at baseline, we noticed that participants with insomnia (except isolated sleep-maintenance insomnia), also had higher total body fat on average than the insomnia-free. (e-2)

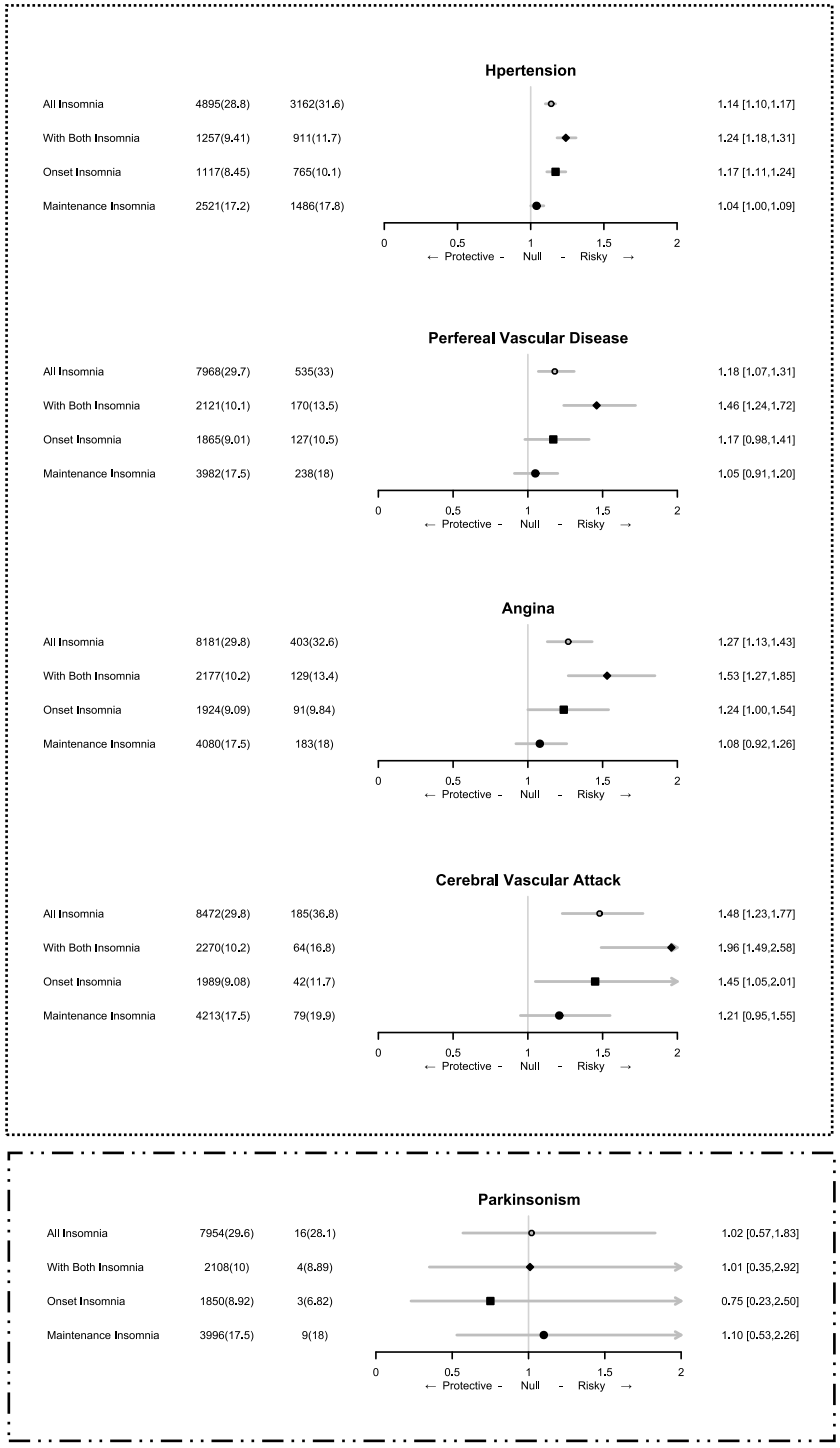
To futher evaluate whether the observed associations could confounded by other underlying risk factors, a series of sensitivity analyses were conducted to reassess the causal relationship via inverse probability weighting. Sleep-onset insomnia remained as an independent risk factor for hypertension and myocardial infraction comparing to those with sleep-maintenance insomnia and insomnia-free after accounting for various confounders. (Figure 1-B) The results also remained similar upon stratification by biological sex. (e-3)

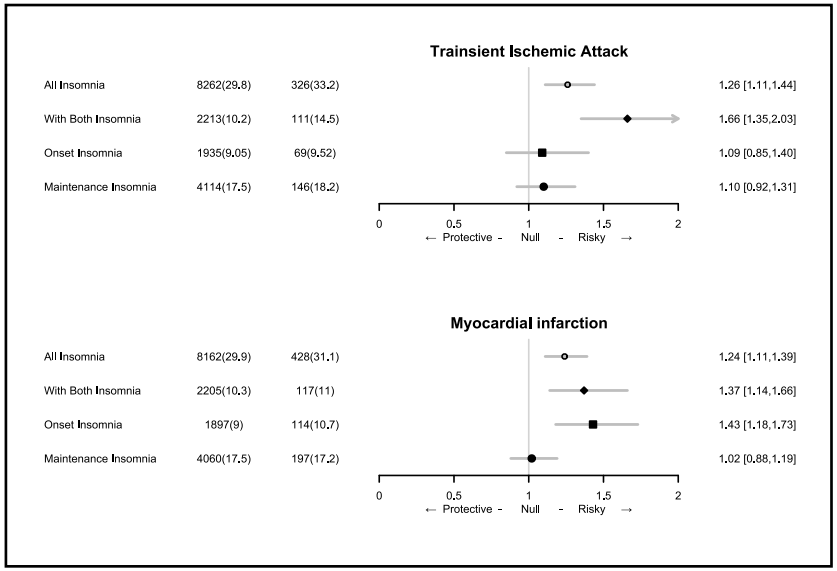
Associations between insomnia and subsequent risk of myocardial infraction had also been reported in a few reports but most did not assess the separate risks between the subtypes.[5] One study using the Nord-Trondelag Health Study cohort found that severe sleep-onset insomnia (i.e., almost every night) increased the prospective risk of myocardial infarction

(HR=1.30[1.01,1.68]) over the course of 11 years. Interestingly, they also found a similar result in those with difficulties maintaining sleep (HR=1.27[1.03,1.57]), whereas we did not. One possible explanation for this difference could be the definition of insomnia. Since our study focused primarily on isolated insomnia symptoms, those endorsing both insomnia subtypes were grouped separately for analyses. Further longitudinal causal mediation analyses will be needed to confirm if sleep-onset insomnia is the primary risk source.

Our results did not find that insomnia was associated with the risk of parkinsonism and/or dementia.[1] Instead, the intervariable association matrix suggested that previously found an association between sleep-onset insomnia and poor cognition may be resulting from cerebro-/ cardiovascular events. (e-4) Future mediation analysis study will help clarify the relationship.

In this large sample size population-based study, those with sleep-onset insomnia pose a greater risk of developing hypertension and having myocardial infractions within 3 years. However, insomnia was not associated with the future diagnosis of either dementia or parkinsonism.





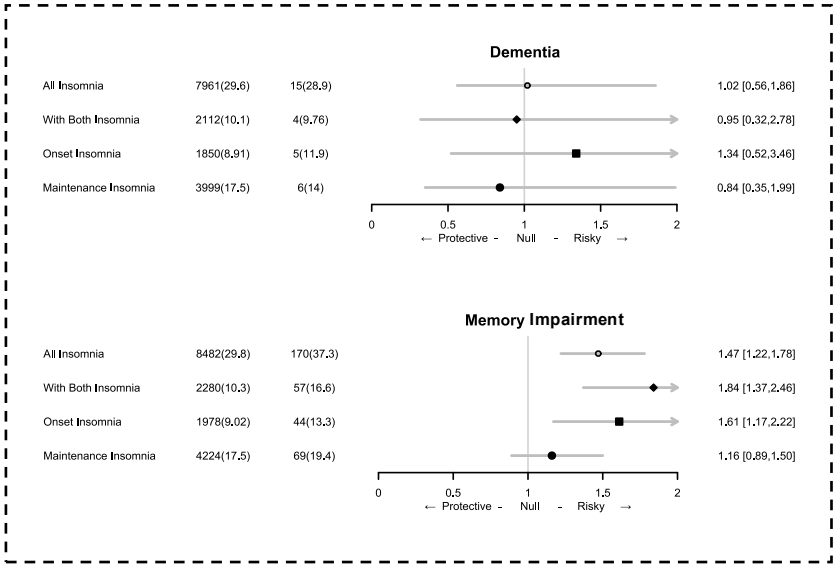


Figure 1-A Prospective De-novo Health Outcome from Insomnia

Relative risk was computed via generalized linear regression with (binomial lognormal link). De-novo health outcome was defined as negative of the assessed health event at the baseline but receiving a 'new' diagnosis at the follow-up. Disease-free for each health outcome was defined as negative at both baseline and follow-up.

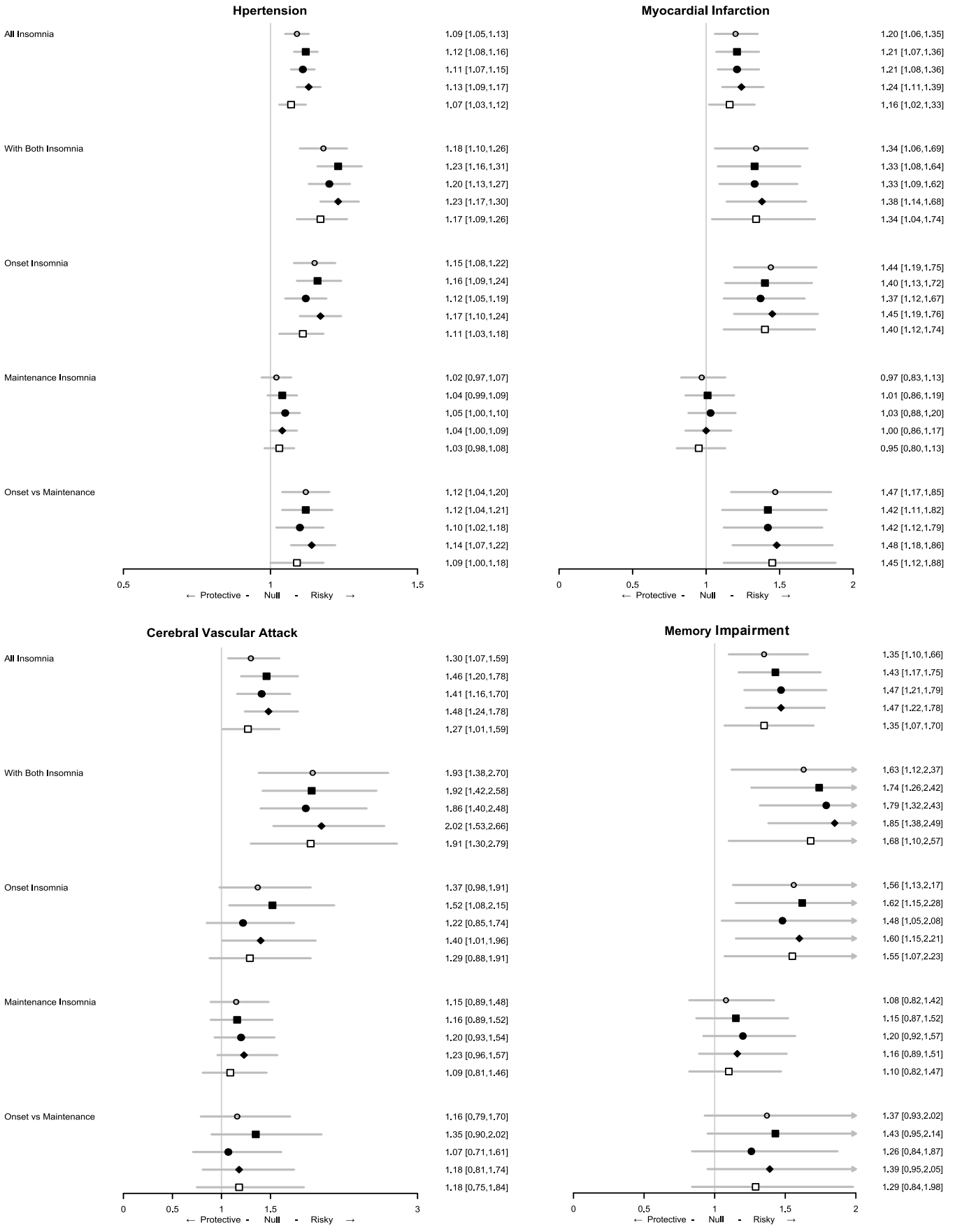


Figure 1-B Sensitivity Analysis

Relative risks were reassessed after accounting for confounding variables, including, sleep deprivation (<6 hours), apnea symptom, restless leg syndrome (RLS), percentage of total body fat (measured via DEXA), and clinical categories of heart rate, blood pressure.

References:

1. Yao CW, Pelletier A, Fereshtehnejad SM, Cross N, Dang-Vu T, Postuma RB. Insomnia symptom subtypes and manifestations of prodromal neurodegeneration: a population-based study in the CLSA. *J Clin Sleep Med*. Jul 27 2021;doi:10.5664/jcsm.9562
2. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). *Can J Aging*. Sep 2009;28(3):221-9. doi:10.1017/s0714980809990055
3. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. Sep 15 2008;168(6):656-64. doi:10.1093/aje/kwn164
4. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. *Econometrica*. 1980 1980;48(4):817-838.
5. Javaheri S, Redline S. Insomnia and Risk of Cardiovascular Disease. *Chest*. 2017;152(2):435-444. doi:10.1016/j.chest.2017.01.026

Supplementary Materials

e-Methods:

Additional Questions

Outcome	Question
Memory Problem	Has a doctor ever told you that you have a memory problem?
Dementia	Has a doctor ever told you that you have dementia or Alzheimer's disease?
Hypertension	Has a doctor ever told you that you have high blood pressure or hypertension?
Peripheral Vascular Disease	Has a doctor ever told you that you have peripheral vascular disease or poor circulation in your limbs?
Transient Ischemic Attack	Has a doctor ever told you that you have experienced a ministroke or TIA (Transient Ischemic Attack)?
Cerebrovascular Attack	Has a doctor ever told you that you have experienced a Stroke or CVA? (cerebrovascular accident)?
Angina	Has a doctor ever told you that you have angina (or chest pain due to heart disease)?
Myocardial Infraction	Has a doctor ever told you that you have had a heart attack or myocardial infarction?
Parkinsonism	Has a doctor ever told you that you had Parkinsonism or Parkinson's Disease?

Consent Data Availability

All participants (or guardians of participants) have provided written consent for the study. Data access for the use of this study was reviewed and granted by the CLSA Data and Sample Access Committee. Data are available from the Canadian Longitudinal Study on Aging webpage (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

Acknowledgement and Disclaimer

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151284 (E.F.). This research has been conducted using the CLSA Baseline and first wave Follow-up Comprehensive Dataset version 3.1, under Application Number 160607. The CLSA is led by Drs. Parminder Raina, Christina Wolfson, and Susan Kirkland. We are grateful for all participants' contribution to the study and the opportunity provided by CLSA. This research was funded by Canadian Institutes of Health Research, the Webster foundation, and le Fonds de Recherche du Québec - Santé. The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

e-1 Risk Factor Profiles – Prospective Health Outcome

		Negative	Hypertension	RR [95% CI]	Negative	Peripheral Vascular Disease	RR [95% CI]
		Mean±SD, N (SD)		$IPW_{Primary}$	Mean±SD, N (SD)		$IPW_{Primary}$
Age		60.6±9.9	65.8±9.7	1.02 [1.02,1.03]	62.5±10.2	66.8±10.3	1.04 [1.02,1.06]
Sex		8151(46.9)	5343(51.9)	1.08 [0.95,1.22]	13544(49.4)	729(43.5)	0.76 [0.50,1.14]
Years of Education		13.8±2.2	13.4±2.3	0.996 [0.948,1.047]	13.7±2.3	13.1±2.4	0.98 [0.69,1.39]
Heart Rate	Bradycardia	2451(14.2)	1655(16.3)	0.97 [0.93,1.02]	4028(14.8)	282(17.1)	1.09 [0.95,1.24]
	Tachycardia	213(1.24)	171(1.68)	1.30 [1.17,1.45]	408(1.51)	25(1.52)	1.15 [0.78,1.69]
Blood Pressure	Hypertension	1317(7.7)	2512(24.7)	1.96 [1.90,2.02]	3972(14.6)	272(16.5)	1.13 [0.99,1.29]
	Hypotension	1320(7.67)	634(6.23)	0.74 [0.68,0.81]	1833(6.75)	216(13.1)	1.81 [1.55,2.12]
Total percentage of Body Fat		32.8±8	35.3±7.9	1.03 [1.03,1.04]	33.7±8	36.2±8.3	1.002 [1.001,1.002]

		Negative	Angina	RR [95% CI]	Negative	Myocardial Attack	RR [95% CI]
Age		62.5±10.2	69.4±9	1.04[1.02,1.07]	62.5±10.2	68.7± 9.2	1.05 [1.03,1.07]
Sex		13508(48.2)	834(65.2)	1.56 [0.96,2.52]	13256(47.4)	1076(75.5)	2.87 [1.76,4.69]
Years of Education		13.7±2.3	13.1±2.5	0.74 [0.67,0.82]	13.7±2.3	13.1±2.4	0.75 [0.67,0.83]
Heart Rate	Bradycardia	3929(14.2)	383(30.2)	1.88 [1.66,2.12]	3886(14)	450(31.9)	1.96 [1.75,2.19]
	Tachycardia	423(1.53)	12(0.95)	0.87 [0.49,1.53]	427(1.55)	10(0.71)	0.60 [0.32,1.12]
Blood Pressure	Hypertension	4089(14.7)	199(15.7)	1.03 [0.88,1.20]	4059(14.7)	223(15.8)	0.98 [0.85,1.14]
	Hypotension	1859(6.7)	197(15.6)	2.18 [1.84,2.57]	1889(6.83)	186(13.17)	1.99 [1.69,2.35]
Total percentage of Body Fat		33.8±8.1	33.9±7.9	1.02 [1.01,1.03]	33.9±8.1	32.8±7.3	1.010 [1.003,1.017]

		Negative	Transient Ischemic Attack	RR [95% CI]	Negative	Cerebrovascular Attack	RR [95% CI]
Age		62.5±10.1	70.1± 9.7	1.003 [1.002,1.004]	62.7±10.2	68.7± 9.5	1.06 [1.02,1.09]
Sex		13858(48.9)	543(53.2)	0.96 [0.55,1.67]	14193(48.8)	291(55.9)	1.27 [0.59,2.75]
Years of Education		13.7±2.3	13.2±2.4	0.75 [0.67,0.83]	13.6±2.3	13.1±2.5	1.006 [0.986,1.026]
Heart Rate	Bradycardia	4150(14.8)	205(20.2)	1.16 [0.99,1.36]	4311(15)	80(15.5)	0.85 [0.66,1.10]
	Tachycardia	421(1.5)	13(1.29)	1.12 [0.65,1.92]	431(1.5)	9(1.75)	1.35 [0.70,2.62]
Blood Pressure	Hypertension	4114(14.7)	171(16.9)	1.04 [0.88,1.23]	4236(14.7)	81(15.7)	0.96 [0.75,1.23]
	Hypotension	1975(7.04)	115(11.34)	1.29 [1.04,1.61]	2056(7.15)	49(9.52)	1.21 [0.88,1.68]
Total percentage of Body Fat		33.8±8	35±7.9	1.02 [1.01,1.04]	33.8±8	34.5±8.4	1.01 [1.00,1.03]

		Negative	Memory Impairment	RR [95% CI]	Negative	Dementia	RR [95% CI]
		Mean±SD, N (SD)		$IPW_{Primary}$	Mean±SD, N (SD)		$IPW_{Primary}$
Age		62.8±10.2	64.5±10.7	1.02 [0.98,1.06]	62.6±10.1	74.6± 8.1	1.20[1.12,1.28]
Sex		14230(48.9)	262(54.7)	1.15 [0.56,2.40]	13476(49)	25(47.2)	0.26 [0.05,1.31]
Years of Education		13.6±2.29	13.3±2.4	1.002 [0.993,1.011]	13.7±2.3	13.5±2.4	0.76 [0.67,0.86]
Heart Rate	Bradycardia	4311(15)	81(17.1)	1.04 [0.81,1.34]	4148(15.2)	10(18.9)	1.02 [0.48, 2.20]
	Tachycardia	429(1.49)	6(1.27)	1.01 [0.45,2.24]	373(1.37)	1(1.89)	1.51 [0.21,10.96]
Blood Pressure	Hypertension	4248(14.8)	68(14.4)	0.96 [0.74,1.26]	3910(14.4)	13(24.5)	1.32 [0.70,2.52]
	Hypotension	2075(7.21)	36(7.6)	1.03 [0.71,1.49]	1914(7.03)	5(9.44)	1.21 [0.45,3.25]
Total percentage of Body Fat		33.8±8	33.9±8.3	1.00 [0.99,1.02]	33.8±8	33.5±7.5	0.95 [0.88,1.02]

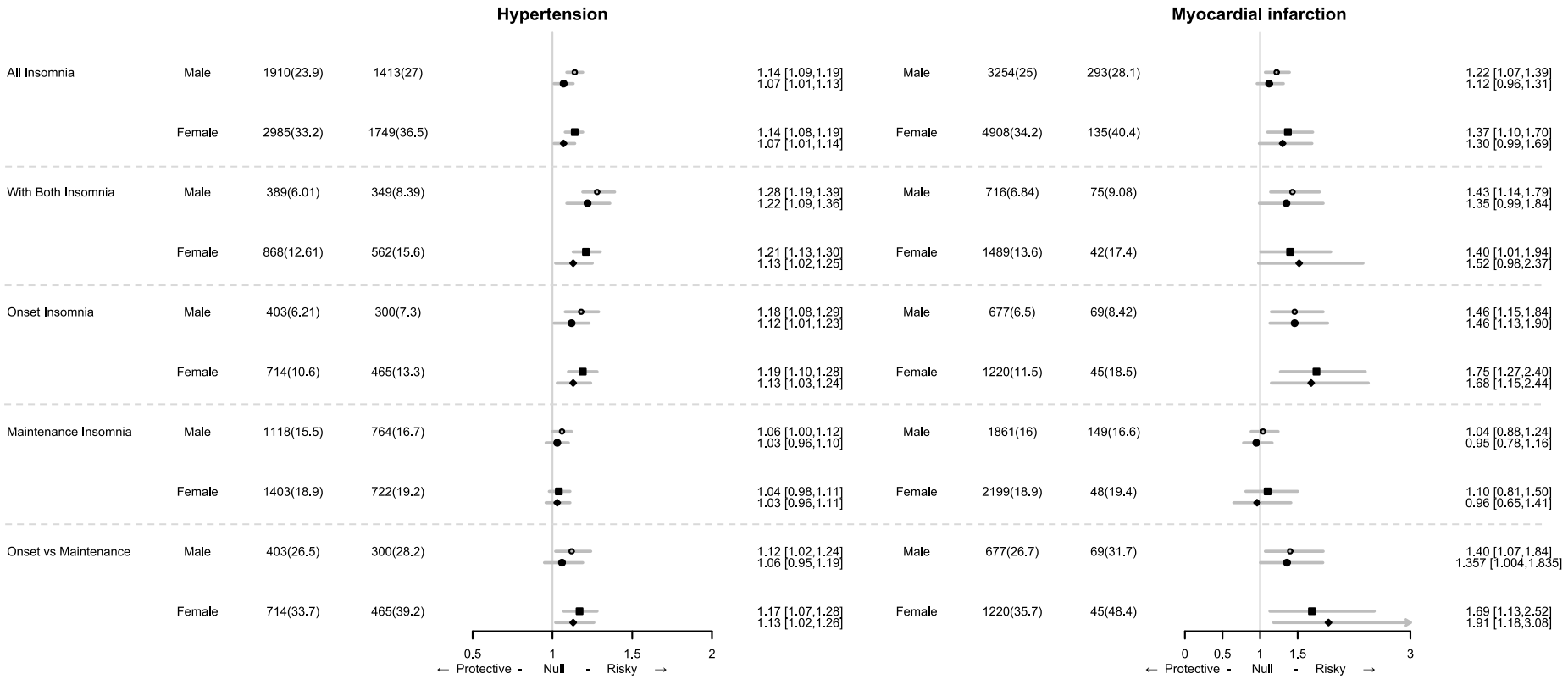
		Negative	Parkinsonism	RR [95% CI]
Age		62.6±10.1	69.7± 8	1.08 [1.06, 1.11]
Sex		13464(49)	38(65.5)	2.78 [1.60,4.81]
Years of Education		13.7±2.3	13.9±2.3	0.79 [0.69,0.90]
Heart Rate	Bradycardia	4148(15.2)	9(15.5)	0.69 [0.33, 1.43]
	Tachycardia	372(1.37)	1(1.73)	1.53 [0.21,11.01]
Blood Pressure	Hypertension	3914(14.4)	10(17.3)	1.08 [0.54,2.18]
	Hypotension	1914(7.04)	5(8.63)	0.93 [0.37,2.38]
Total percentage of Body Fat		33.8±8	33±7.2	1.00 [1.00,1.00]

All risk ratios were weighted for age, sex, follow-up intervals and statuses. Several variables were assessed using quassipoisson function due to being overdispersed.

e-2 Risk Factor Profiles - Insomnia

		Insomnia-free	All Insomnia	Both Insomnia	All Insomnia vs. Insomnia-free	Both Insomnia vs. Insomnia-free
		Mean±SD, N (SD)			OR [95% CI]	
Age		62.99±10.23	62.57±10.18	62.70±10.12	1.00 [1.00,1.00]	1.00 [1.00,1.01]
Sex		10692(52.42)	3646(41.65)	815(34.38)	0.65 [0.62,0.69]	0.48 [0.44,0.53]
Years of Education		13.73±2.29	13.38±2.29	13.06±2.30	0.94 [0.93,0.96]	0.89 [0.87,0.91]
Heart Rate	Bradycardia	3111(15.39)	1224(14.15)	291(12.46)	0.99 [0.92,1.07]	0.90 [0.79,1.03]
	Tachycardia	297(1.47)	136(1.58)	40(1.72)	1.10 [0.90,1.36]	1.23 [0.88,1.72]
Blood Pressure	Hypertension	2977(14.74)	1294(14.96)	372(15.93)	1.07 [1.00,1.15]	1.17 [1.04,1.32]
	Hypotension	1414(7)	665(7.69)	179(7.67)	1.06 [0.96,1.17]	1.01 [0.86,1.19]
Total percentage of Body Fat		33.35±8.01	34.90±7.98	36.18±7.90	1.02 [1.01,1.02]	1.03 [1.02,1.04]

		Onset Insomnia	Maintenance Insomnia	Onset Insomnia Vs. Insomnia-free	Maintenance Insomnia vs. Insomnia-free	Onset vs. Maintenance Insomnia
		Mean±SD, N (SD)		OR [95% CI]		
Age		62.60±10.26	62.48±10.19	1.00 [1.00,1.01]	1.00 [1.00,1.00]	1.01 [1.00,1.01]
Sex		771(37.6)	2060(47.55)	0.55 [0.50,0.61]	0.83 [0.78,0.89]	0.67 [0.60,0.74]
Years of Education		13.25±2.32	13.62±2.25	0.92 [0.91,0.94]	0.98 [0.97,1.00]	0.94 [0.92,0.96]
Heart Rate	Bradycardia	256(12.66)	677(15.76)	0.90 [0.78,1.03]	1.08 [0.99,1.19]	0.83 [0.71,0.96]
	Tachycardia	34(1.69)	62(1.45)	1.19 [0.83,1.70]	1.01 [0.77,1.33]	1.16 [0.76,1.77]
Blood Pressure	Hypertension	289(14.31)	633(14.75)	1.03 [0.90,1.17]	1.05 [0.95,1.15]	0.99 [0.85,1.15]
	Hypotension	155(7.68)	331(7.71)	1.01 [0.85,1.20]	1.11 [0.98,1.26]	0.92 [0.75,1.12]
Total percentage of Body Fat		35.97±8.19	33.71±7.75	1.04 [1.03,1.04]	1.01 [1.00,1.01]	1.04 [1.03,1.05]



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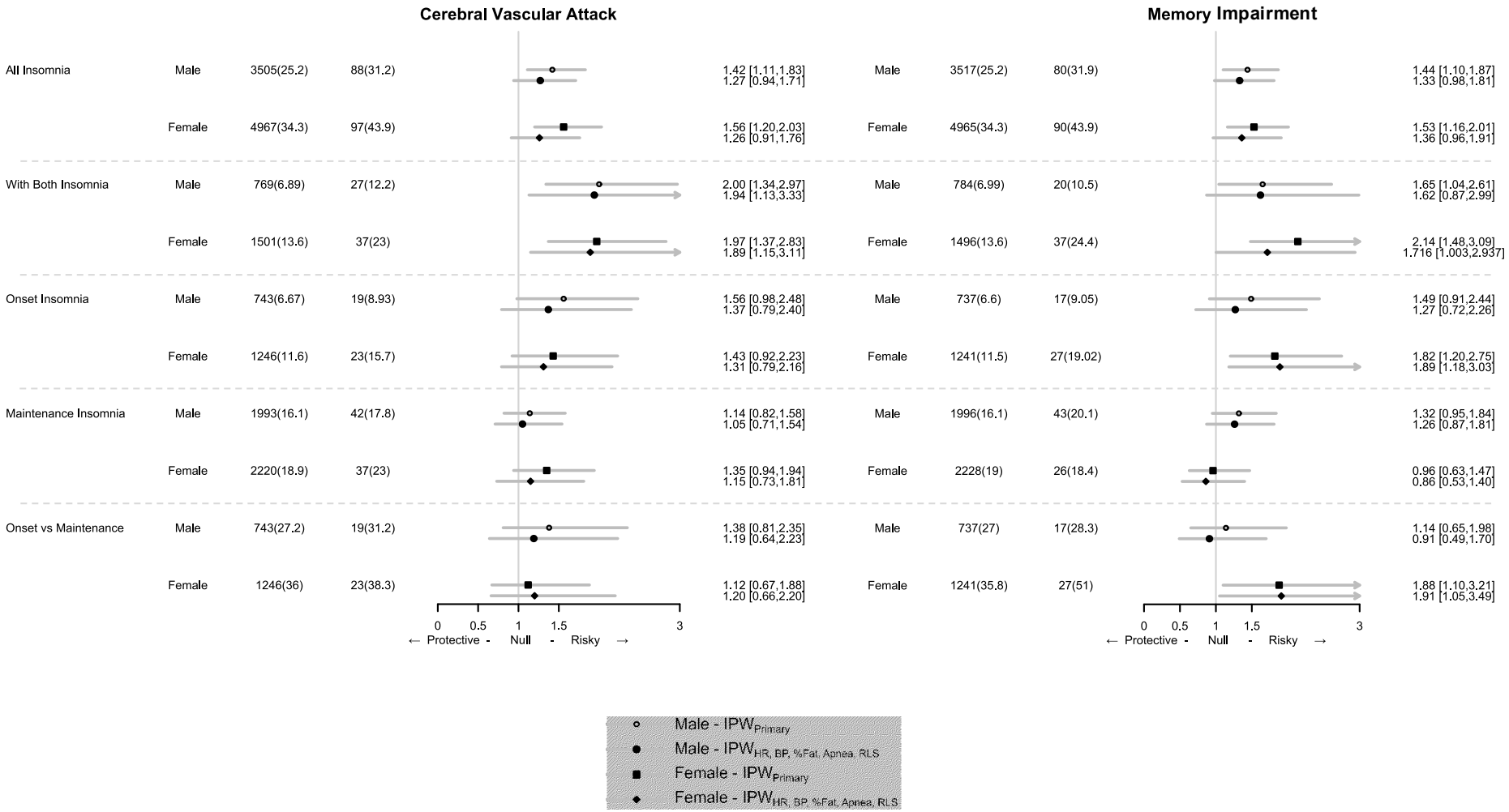
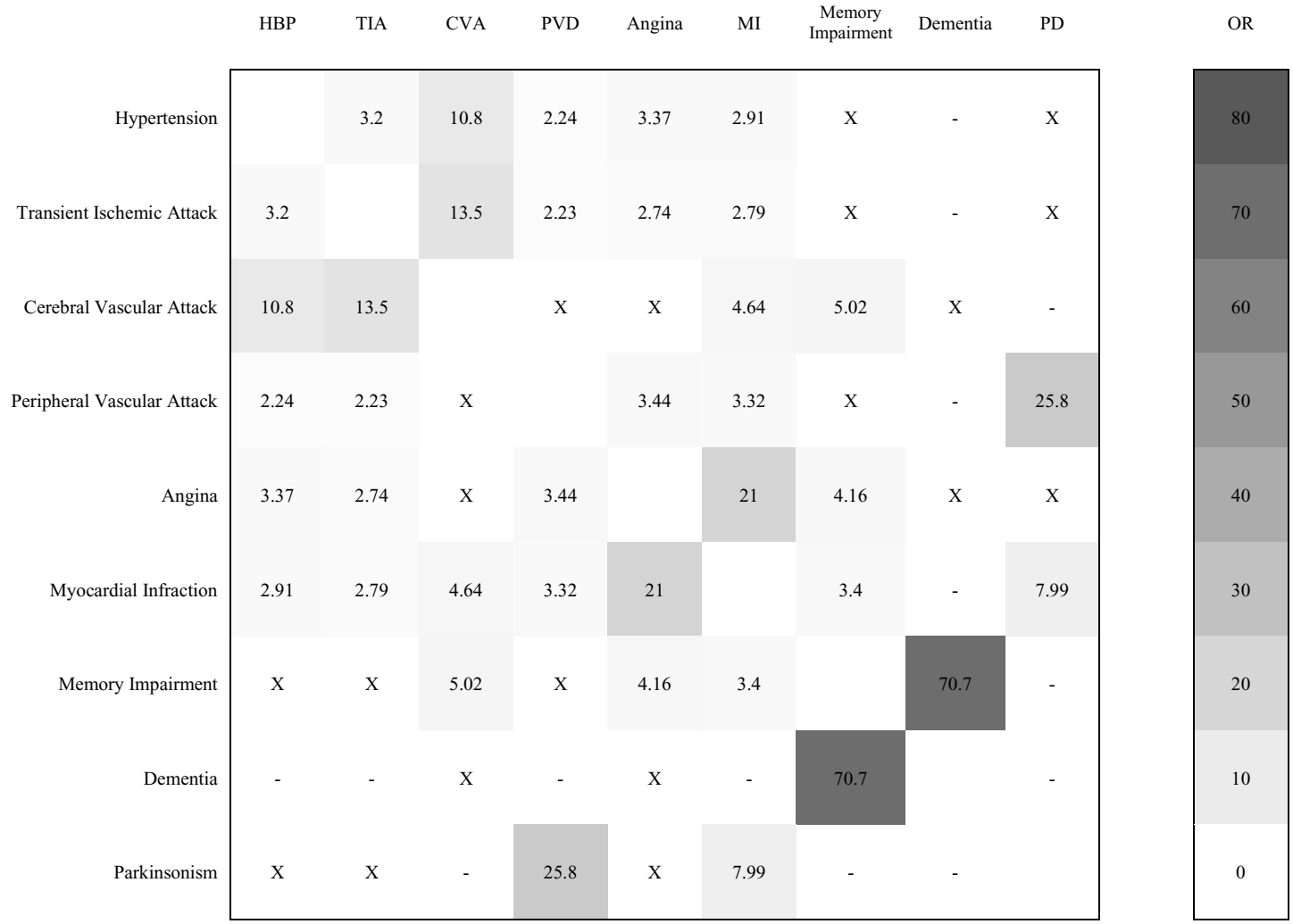


e-3 Subgroup Analysis – Insomnia Subtypes and Prospective Outcome Risk

Direct associations between insomnia subtypes and prospective health outcome after accounting for primary factors: age, loss-to-follow-up, follow-up interval. We also performed an extra series of analyses after adding blood pressure, heart rate, total percentage of body fat, apnea symptoms and restless leg syndrome statuses at the baseline when calculating the propensity score. All inverse probability weights were calculated after stratifying the cohort by biological sex.



e-4 Within Outcome Associations among Onset-insomnia

Associations between variables were assessed using logistic regression adjusted for age and sex. Since each outcome was alternated between being a predictor or a dependent variable in regression analysis, the presented OR was computed based on the average of the associations between the outcome pairs. Absence of coexisting outcome was denoted as "-" in the graph. X was used to indicate insignificant association.