# The webinar, "Clinical Features of REM Sleep Behavior Disorder in the Population-based CLSA Cohort: Can we improve the screening tools?," will begin shortly.

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- This webinar will use VoIP only. Upon entering the session, you will be asked to join an integrated voice conference. Please select "yes". If you are not prompted with this message, please go to the main toolbar and select Audio>Integrated Audio Conference>Start Conference. If you continue to have audio issues, please go to Audio>Speaker/Microphone Audio Test.

- The only people in the session who can speak and be heard are the host and panelists.

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# CLSA Webinar Series

## Clinical Features of REM Sleep Behavior Disorder in the Population-Based CLSA Cohort: Can We Improve the Screening Tools?

Chun Yao, MSc, PhD Candidate at McGill University

**12 pm to 1 pm ET | December 12, 2018**

REM sleep behavior disorder (RBD), featured as acting out of dream, is the strongest known predictor for parkinsonism. It is estimated that idiopathic RBD patients have around 80-85% of phenoconversion rate to parkinsonism within five years, upon the first clinical visit. Since polysomnography sleep testing is expensive and time-consuming, several questionnaires were developed over the years to pre-screen for possible RBD patients in clinic. This webinar presents research that aims to improve the accuracy of RBD screening tools using the population-based cohort from the Canadian Longitudinal Study on Aging (CLSA).

Chun Yao is a PhD candidate in Neuroscience at McGill University. His work focuses primarily on studying the clinical features and disease progression in REM sleep behavior disorder under the supervision of Dr. Ronald B. Postuma. Chun completed his Master of Science in Chinese Medicine training in preventive medicine at China Medical University, Taiwan.

Register online at:
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# Clinical Features of REM Sleep Behavior Disorder in the CLSA:

## Can we improve the screening tools?


Presenter: Chun Yao, *PhD Candidate*

PI: Ronald B. Postuma, *MD. MSc.*

*Email: chun.yao@mail.mcgill.ca*


Centre universitaire de santé McGill | McGill University Health Centre | McGill

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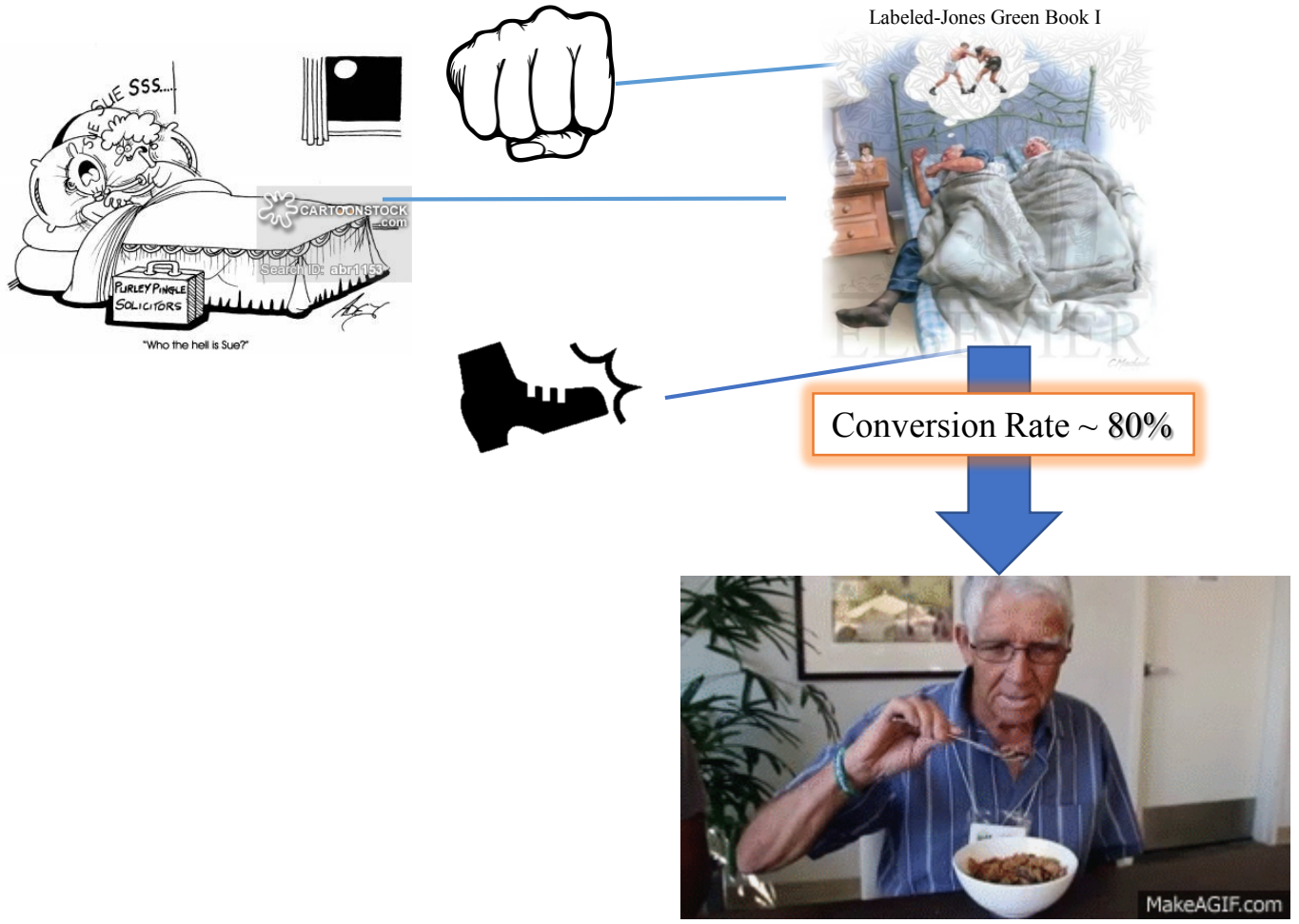
# What is REM Sleep Behavior Disorder?



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http://www.freepik.com/free-icon/kick-boot_696486.htm

# What is REM Sleep Behavior Disorder?




Labeled-Jones Green Book I

Male

Smoking

Married

Antidepressant

>40 y.o.

Conversion Rate ~ 80%




https://www.cartoonstock.com/directory/s/sleep-talk.asp
http://www.clipartpanda.com/clipart_images/hulk-fist-punch-clipart-70289757

https://www.youtube.com/watch?v=CTG5WCHe-zw
http://www.freepik.com/free-icon/kick-boot_696486.htm

# What is REM Sleep Behavior Disorder?




Labeled-Jones Green Book I

Male

Smoking

Married

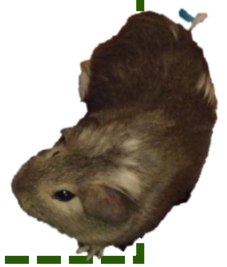
Antidepressant

>40 y.o.

Conversion Rate ~ 80%

So far, studies had shown us what RBD patients may look like in clinic.

But… who are these people endorsing RBD in a general population?



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https://www.youtube.com/watch?v=CTG5WCHe-zw
http://www.freepik.com/free-icon/kick-boot_696486.htm

# Gold Standard

# RBD Diagnosis

- Loss of atonia during REM Sleep
- History of sleep-related injurious behaviors
- Absence of epileptiform activity during REM sleep (unless RBD can be distinguished)
- Sleep disturbance is not better explained by another disorder (ex. psychological disorders)
- Questionnaires can be used to screen pRBD in absence of polysomnography.

## Introduction

REM sleep behavior disorder (RBD) was first described in humans in 1986 after a series of patients reported curious nocturnal behaviors that resulted in injury to patients or their bedpartners [1]. Due to the loss of normal REM sleep muscle atonia, RBD patients often "act out their dreams," most commonly expressing violent complex movements that often mirror dream content [1–10]. RBD patients are primarily divided into two groups: idiopathic RBD, with no obvious cause, and symptomatic RBD, which is primarily associated with synucleinopathy neurodegenerative disorders, including Parkinson's disease (PD), Lewy body dementia (DLB), and multiple system atrophy (MSA) [3–12]. However, RBD is also common in patients with narcolepsy and in patients receiving antidepressant treatment and may be seen rarely in hose with brainstem lesions in dorsal pons and medulla [10, –26]. In addition, RBD has also been associated with the or withdrawal of drugs or alcohol, high chocolate intake and migraine headaches [27–31]. However, because up % of idiopathic RBD patients develop parkinsonism or ia over longitudinal follow-up, growing evidence that idiopathic RBD may be a prodromal feature of generative disease, often preceding other characve overt neurological manifestations by several des [3, 5, 7, 8, 12, 32–37]. In addition, recent data suggest that up to 94 % of patients with % of RBD patients confirmed by (PSG), have synucleinopathy neurode-

ouis · B.F. Boeve
Clinic and Foundation, Mayo
Street Southwest, Rochester,

generation at autopsy, furthering the presumption that RBD may represent the *forme fruste of* neurodegeneration in many patients [37].

## Diagnosis and Classification of RBD

The minimal diagnostic criteria according to the International Classification of Sleep Disorders (ICSD) 2 include: (A) presence of REM sleep without atonia on PSG; (B) sleep-related injurious or potentially injurious disruptive behaviors by history, and/or abnormal REM sleep behaviors during PSG; (C) absence of epileptiform activity during REM sleep (unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder); and (D) sleep disturbance is not better explained by another disorder [38]. However, an evolving diagnostic standard for probable RBD (pRBD) for patients having dream enactment behaviors but who lack PSG evidence for RSWA (due to either unavailability of PSG or failure to record REM sleep) is included in ICSD 3, given the resource intensive nature of confirmatory PSG (38a).

The core clinical feature of RBD is a history of witnessed dream enactment by the patient's bed partner, with or without recall of dream mentation by the patient himself or herself [1, 5, 11, 34, 39]. Patients are often able to vividly recall their dreams for weeks or longer, and when enacted dreams are recalled, patients typically report that their dream mentation contains a theme of being chased, or defense against an attack by animals or people [11, 40]. However, less aggressive themes such as playing sports or performing household chores are also common [41, 42]. Collateral history obtained from the patient's bed partner is crucial in diagnosing RBD patients, since NREM parasomnias like sleep walking or sleep terrors also often report frightening dream content. However, dreams of patients with sleep walking or sleep terrors more often involve natural disasters with a "flight" response, as opposed to the "fight" response reported by patients with RBD [5, 11, 39, 42, 43].


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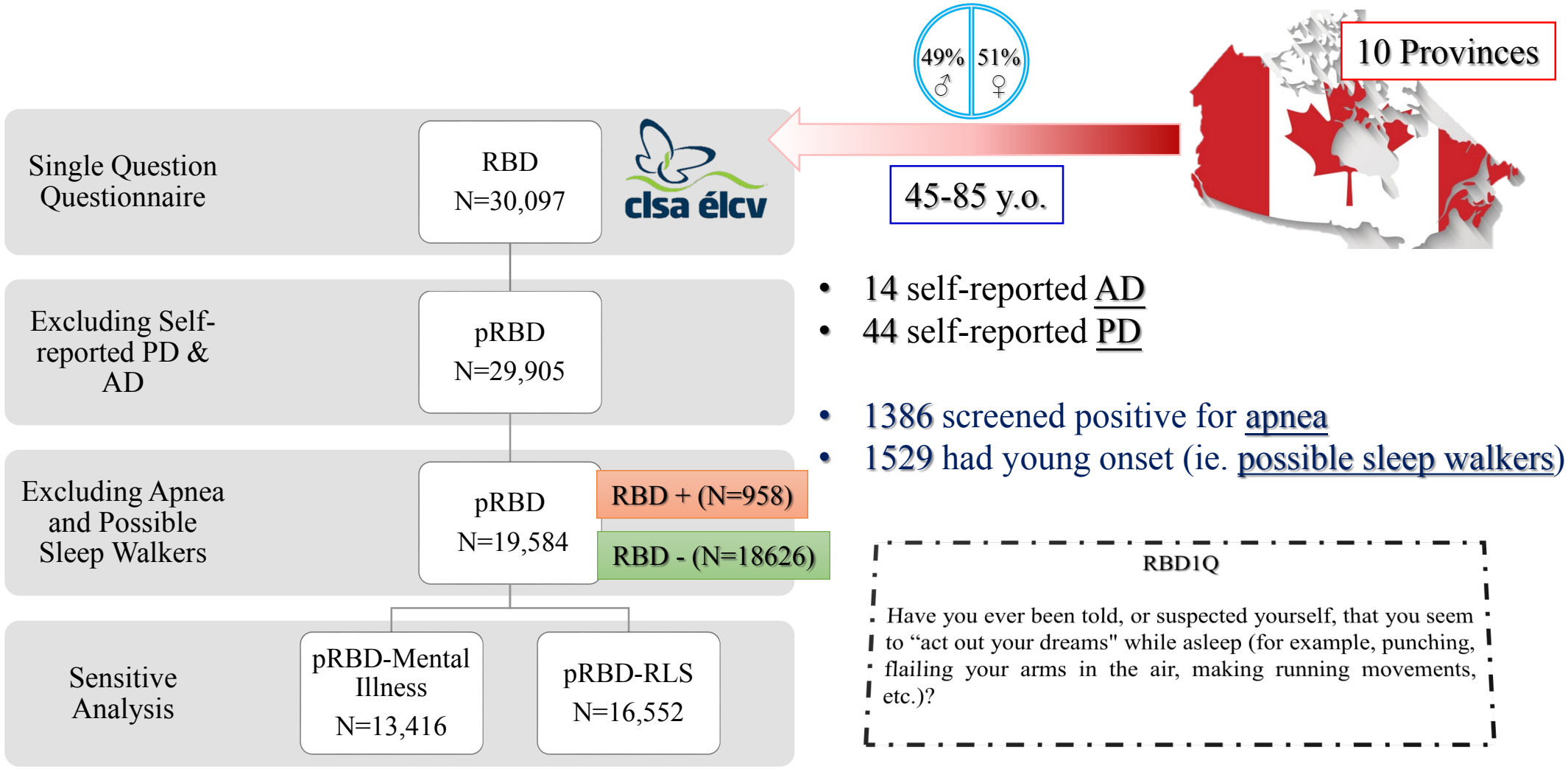
# Table of Content

# Case Definition of possible RBD, Early Parkinsonism and PD






- 14 self-reported AD
- 44 self-reported PD

- 1386 screened positive for apnea
- 1529 had young onset (ie. possible sleep walkers)

**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.)?

# Sociodemographic Statuses

| | pRBD+ vs. pRBD- | Adjusted by age & sex OR [95%CI] |
|---|---|---|
| • Age: no differences | 63±10 vs. 64±11 | 0.99 [0.99, 1.00] |
| • Men ♂ were more likely to have pRBD. | 58.9% vs. 42.3% | 1.97 [1.72, 2.25] |
| • Subjects were more likely to be in any form of long-term relationship. | 84.7% vs. 77.2% | 1.97 [1.72, 2.25] |
| • pRBD is linked with lower education level. | | |
| ➢ Secondary School | 51.8% vs. 48.3% | 1.77 [1.36, 2.31] |
| ➢ Below Grade 11 | 7.62% vs. 5.60% | 1.32 [1.15, 1.52] |
| • Subjects were more likely to be retired. | 58.1% vs. 57.5% | 1.97 [1.72, 2.25] |
| • pRBD subjects were negatively associated income level. | 2.45 vs. 2.51 | 0.86 [0.79, 0.93] |

**Annual Income Level %**

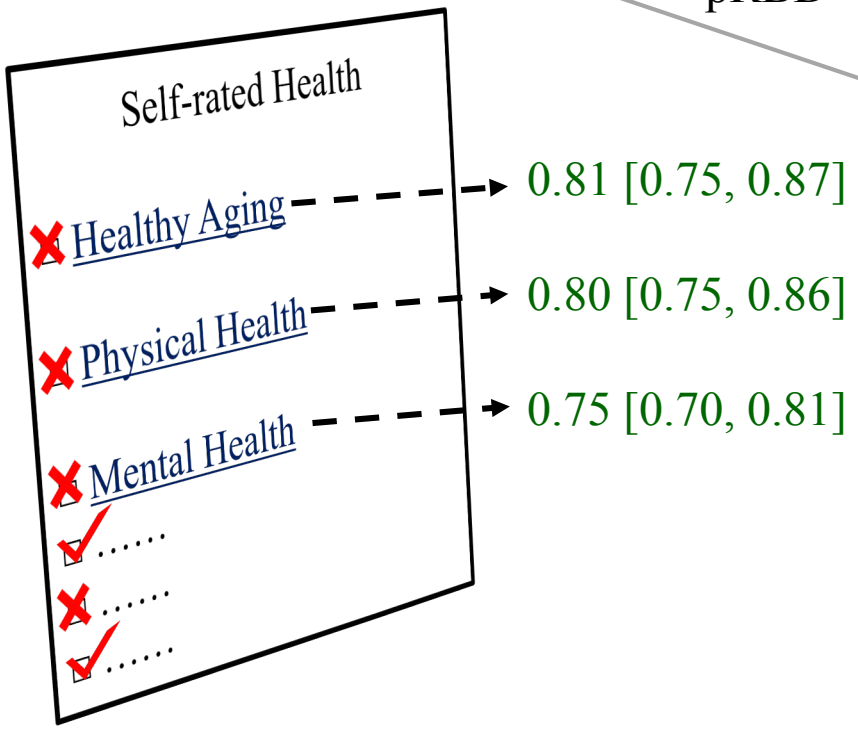
| | |
|---|---|
| 1 | < 20,000 |
| 2 | 20-49,000 |
| 3 | 50-99,000 |
| 4 | > 100,000 |

# Life Style and Satisfaction of Life

Healthy Control 4.6±0.9 (hrs/week)

pRBD + 4.3±4.5

**No Difference**




0.81 [0.75, 0.87]

0.80 [0.75, 0.86]

0.75 [0.70, 0.81]

**Social Sport**

Healthy Control 63.2±16.1 (days)

pRBD + 54.3±93.7

**No Difference**

**Social Sport**

Healthy Control 26.6±4.9 (days)

pRBD + 25.0±26.0



https://giphy.com/gifs/walking-UXbxS9krBsjxC/download

https://www.freevector.com/smoking-cartoon-woman

https://popkey.co/search/drinking%20drunk%20drink%20wine

# Risky Behaviors

| **Drinking Patterns:** | **pRBD** | **Healthy Controls** | **OR [95%CI]** |
|---|---|---|---|
| Occasional Drinkers: | 97 (10.4%) | 2325 (12.8%) | 1.06[0.86, 1.31] |
| Regular Drinkers: | 730 (78.2%) | 13701 (75.5%) | 0.83[0.63, 1.10] |

**Binge Drinking Frequency:** >5 drinks per sitting/week for men
>4 for women

| | | |
|---|---|---|
| 1.3±4.6 | 1.0±3.7 (day/week) | 1.01[1.00,1.03] |

**Moderate-heavy Drinking:** >14 drinks/week for males
>7 drinks/week for females

| | | |
|---|---|---|
| 181 (18.9%) | 2792 (14.3%) | 1.38 [1.17, 1.63] |

# Risky Behaviors

| | pRBD | Healthy Control | OR [95%CI] |
|---|---|---|---|
| **Cigarette Pack-Years** | pack years of smoking as packs/day x smoking years | | |
| | 8.4±14.7 | 6.1±12.2 | 1.008 [1.003, 1.013] |
| **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] |
| **Past Daily Smoker (%)** | 408 (42.7) | 7060 (36.9) | 1.25 [1.09, 1.44] |
| **Current Daily Smoker (%)** | 85 (8.9) | 1175 (6.4) | 1.53 [1.20, 1.95] |

# Mental Illness and Use of Antidepressants

**Kessler Psychological Distress Scale (K10)**

| Please tick the answer that is correct for you: | All of the time (score 5) | Most of the time (score 4) | Some of the time (score 3) | A little of the time (score 2) | None of the time (score 1) |
|---|---|---|---|---|---|
| 1. In the past 4 weeks, about how often did you feel tired out for no good reason? | | | | | |
| 2. In the past 4 weeks, about how often did you feel nervous? | | | | | |
| 3. In the past 4 weeks, about how often did you feel so nervous that nothing could calm you down? | | | | | |
| 4. In the past 4 weeks, about how often did you feel hopeless? | | | | | |
| 5. In the past 4 weeks, about how often did you feel restless or fidgety? | | | | | |
| 6. In the past 4 weeks, about how often did you feel so restless you could not sit still? | | | | | |
| 7. In the past 4 weeks, about how often did you feel depressed? | | | | | |
| 8. In the past 4 weeks, about how often did you feel that everything was an effort? | | | | | |
| 9. In the past 4 weeks, about how often did you feel so sad that nothing could cheer you up? | | | | | |
| 10. In the past 4 weeks, about how often did you feel worthless? | | | | | |

**Kessler Psychological Distress Scale (K10)**
Source: Kessler R. Professor of Health Care Policy, Harvard Medical School, Boston, USA.

This is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4 week period.

| | pRBD | Healthy Controls | OR [95%CI] |
|---|---|---|---|
| **Score** | 15.2±5.33 | 13.9±1.86 | **1.07 [1.05, 1.08]** |
| **≥24** | 87 (10.9%) | 1109 (6.6%) | **1.58 [1.43, 1.75]** |

**Australian and New Zealand Journal of Public Health (2001) 25,** 494-497

**Antidepressants:**

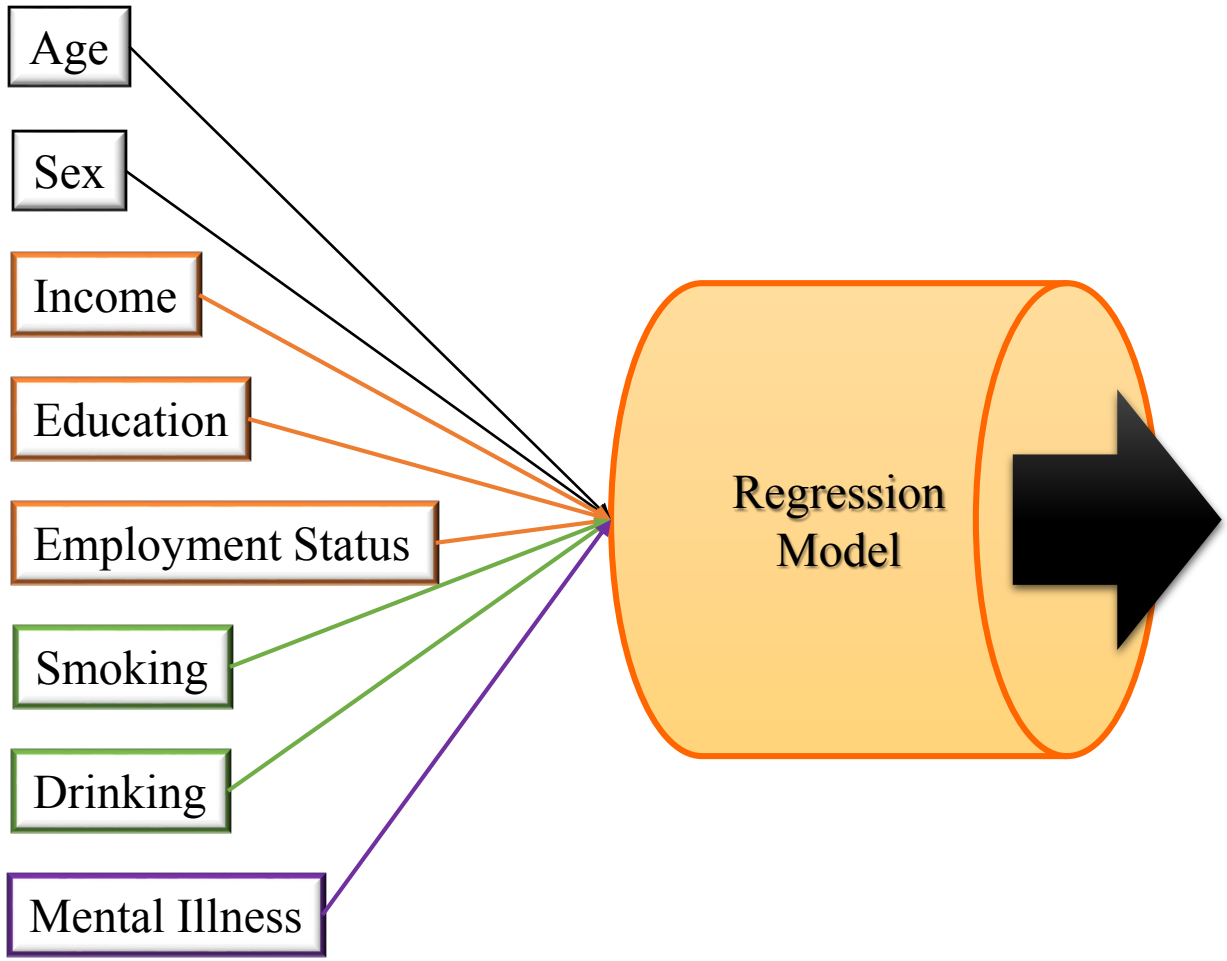
| | | |
|---|---|---|
| 128 (13.4%) | 1149 (6.2%) | **2.71 [2.22, 3.31]** |

# Mental Illness and Use of Antidepressants

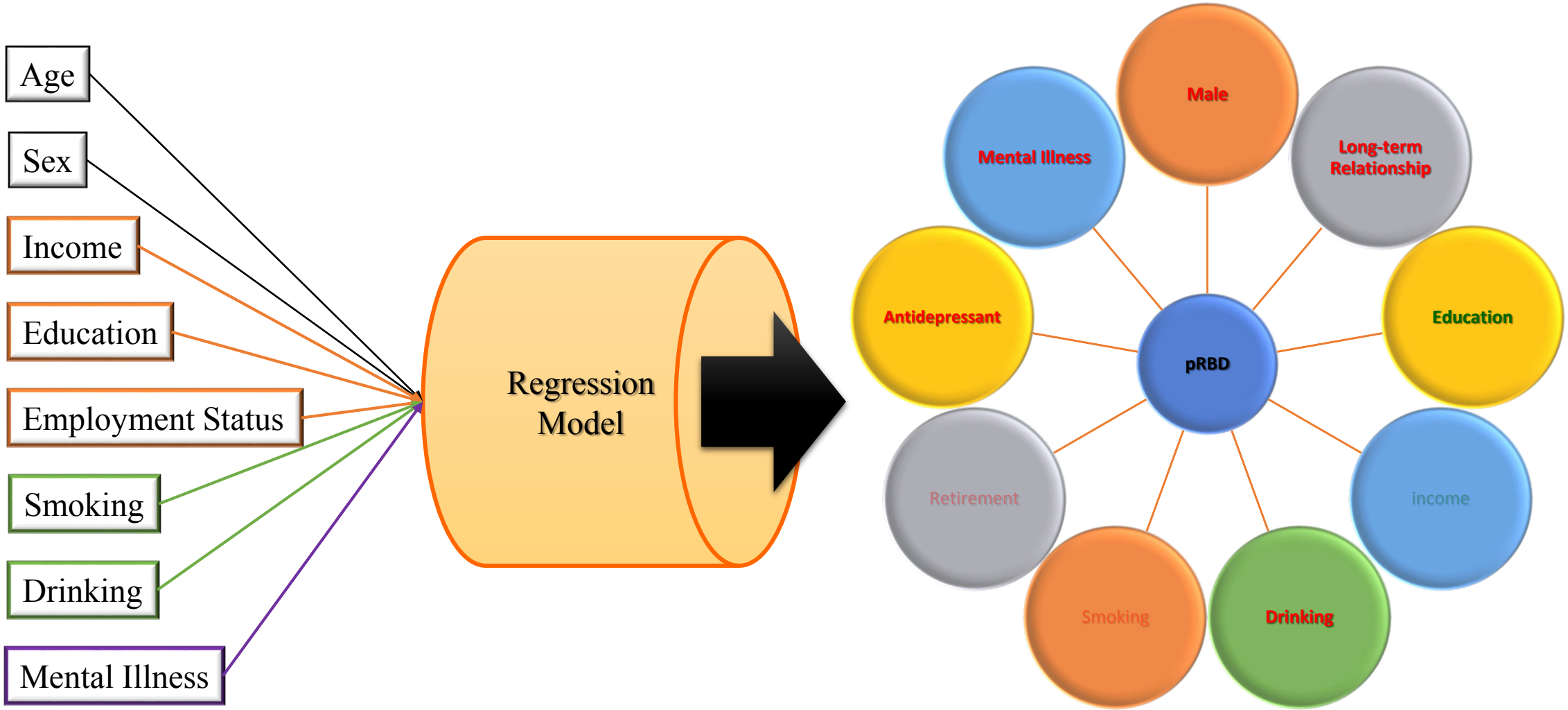
| | | pRBD | Healthy Control | OR (95% CI) |
|---|---|---|---|---|
| | Positive | 334 (34.9) | 4086 (21.9) | 2.17 (1.89, 2.50) |
| | Mood Disorder % | 226 (23.7) | 2682 (14.5) | 2.08 (1.77, 2.43) |
| **Mental Illness %** | Anxiety Disorder % | 132 (13.8) | 1355 (7.3) | 2.24 (1.85, 2.72) |
| | Depressive Disorder% | 197 (20.7) | 2569 (13.9) | 1.84 (1.56, 2.17) |
| | Post-Traumatic Stress Disorder + % | 100 (10.5) | 737 (3.98) | 3.19 (2.55, 3.99) |

# Risk Factor Profile

# Risk Factor Profile

# Risk Factor Profile



# Conclusion and Discussions

- Men ♂ were more likely to have pRBD.
- pRBD may be linked with lower socieoecnomical status.
- Drinking and Smoking were both positively linked with pRBD.
- Use of antidepressant and mental illness were associated with pRBD.

***Neurology*® 2012;79:428–434**

***Neurology*® 2016;86:1306–1312**

***Sleep Medicine* 30 (2017) 71e76**

**Parkinsonism Relat Disord. 2017 Apr; 37: 72–78.**

- This is the first population and the largest study on REM sleep behaviour study.
- Like all large cohort study, we are unfortunately unable to obtain PSG data from each subject.
- Researchers and physicians may need to be aware of the possible mental health issue in pRBD subjects.

# Table of Content

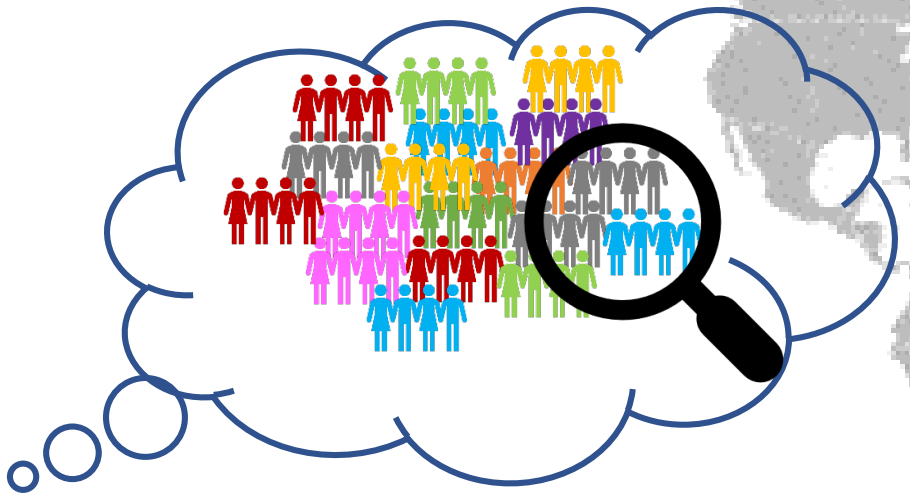
1. Associated Factors of Possible REM Sleep Behavior Disorder (pRBD)

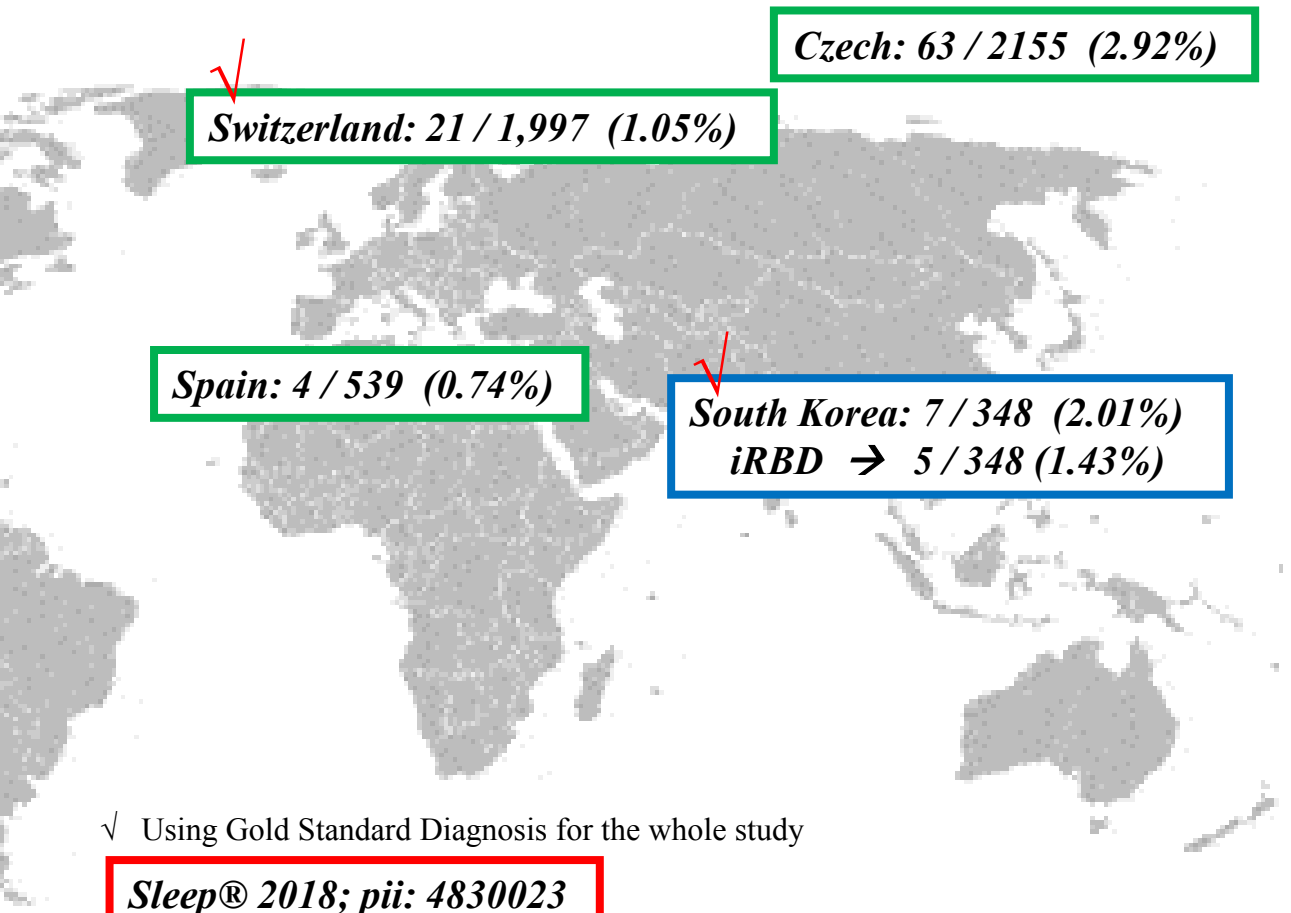
Goal:
Screening RBD and "checking" the risk factor association in population

**2. Global Clinical Features of Possible REM Sleep Behavior Disorder**

**Goal:**
**To confirm the clinical presentations among RBD screened positives**

# Which of these participants possibly have "TRUE" iRBD?





*Czech: 63 / 2155 (2.92%)*

√ *Switzerland: 21 / 1,997 (1.05%)*

*Spain: 4 / 539 (0.74%)*

√ *South Korea: 7 / 348 (2.01%)*
*iRBD → 5 / 348 (1.43%)*

√ Using Gold Standard Diagnosis for the whole study

***Sleep® 2018; pii: 4830023***

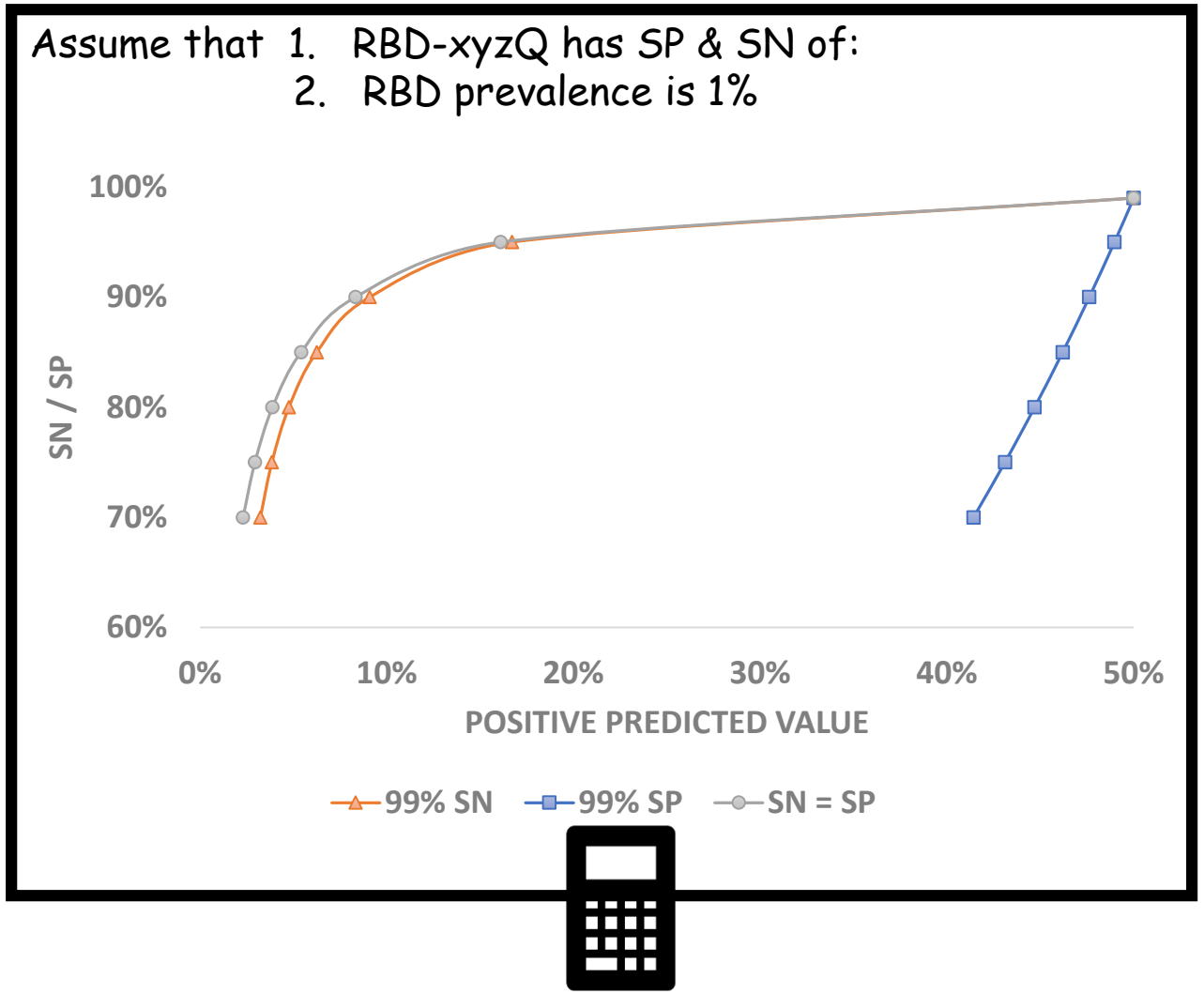
# Why to improve the screening accuracy in RBD?




Positive Rate: 3.2%

# Why to improve the screening accuracy in RBD?






| Status / Screen | Healthy Control | pRBD |
|---|---|---|
| Negative | True Negative | False Negative |
| Positive | False Positive | True Positive |

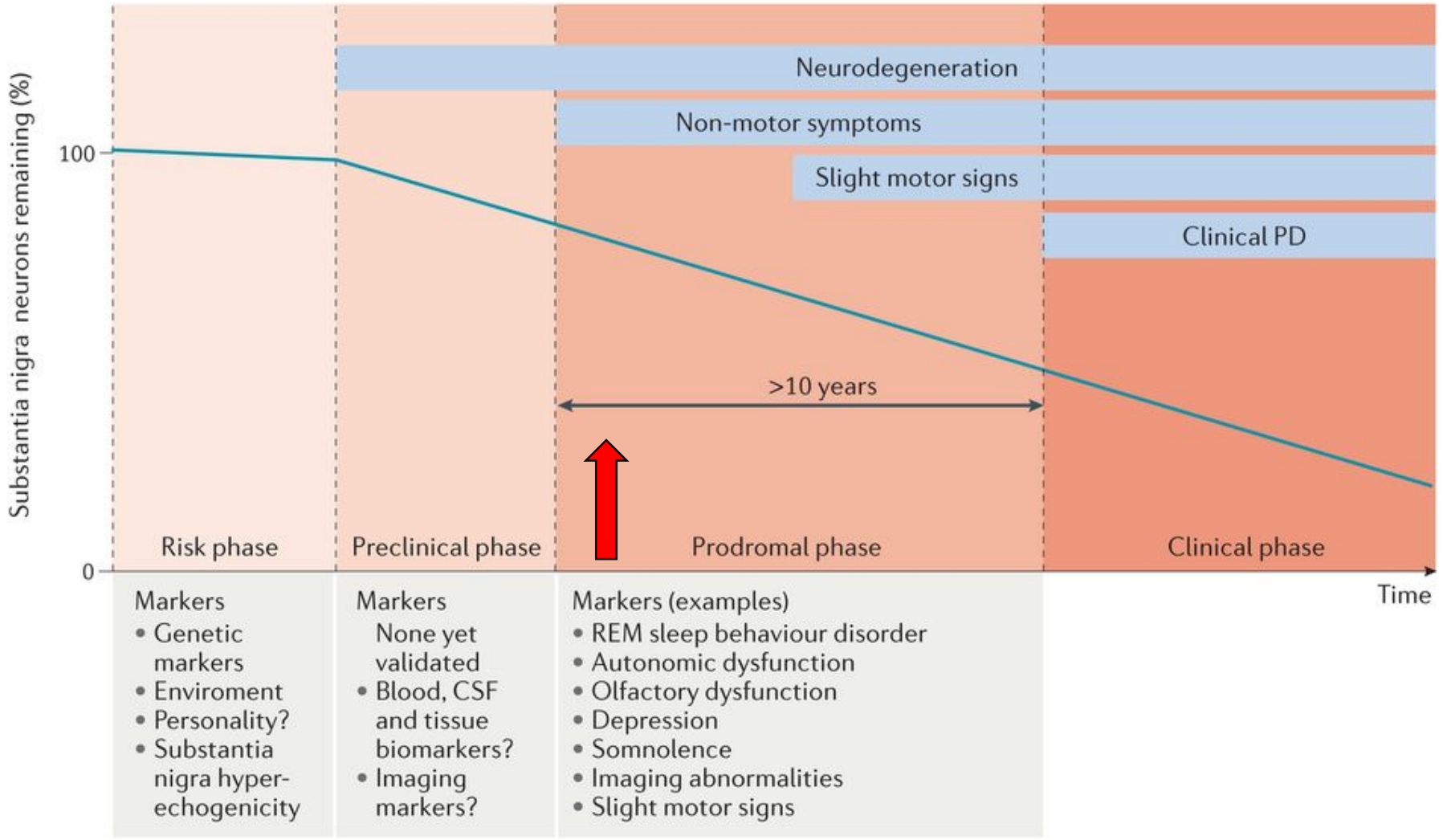
Sensitivity = TP/ (TP + FN)

Specificity = TN/ (TN + FP)

PPV = TP/ (TP + FP)

# How does iRBD progress?





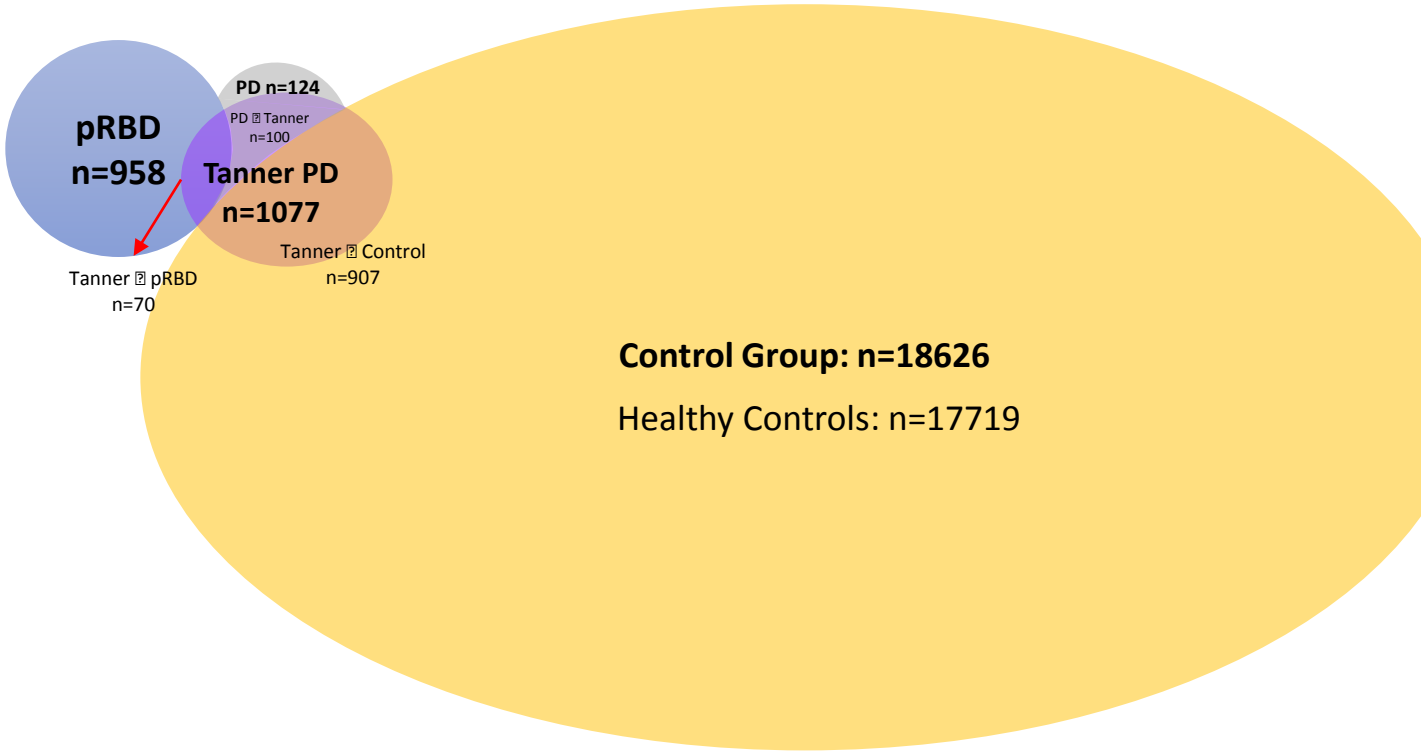

*Nature Reviews Neurology 2017;*12: 622–634

# What are **the differences** between **pRBD-Tanner** vs. **PD?**



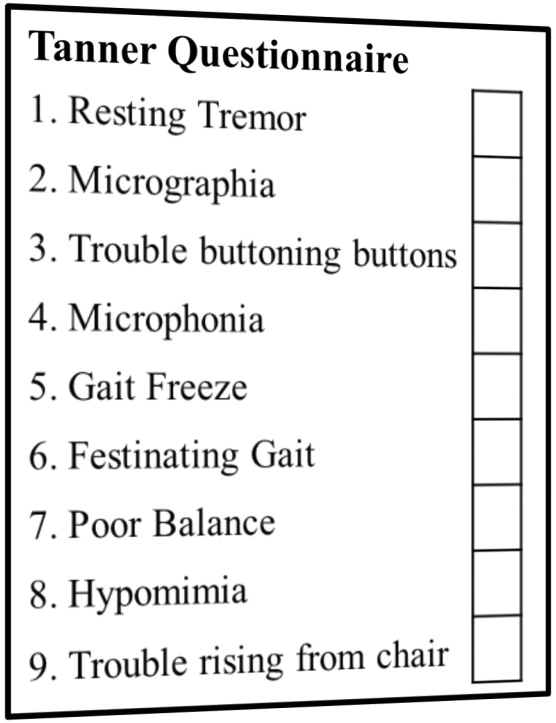
**Tanner Questionnaire**

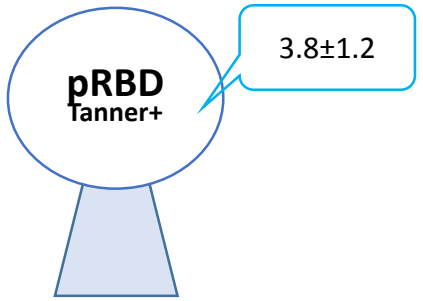
1. Resting Tremor
2. Micrographia
3. Trouble buttoning buttons
4. Microphonia
5. Gait Freeze
6. Festinating Gait
7. Poor Balance
8. Hypomimia
9. Trouble rising from chair

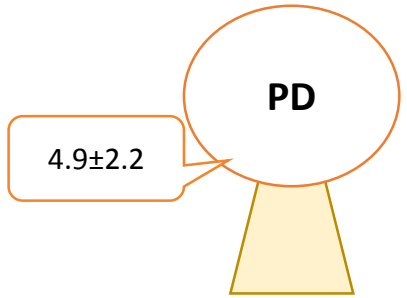


# What are **the differences** between **pRBD-Tanner** vs. **PD?**





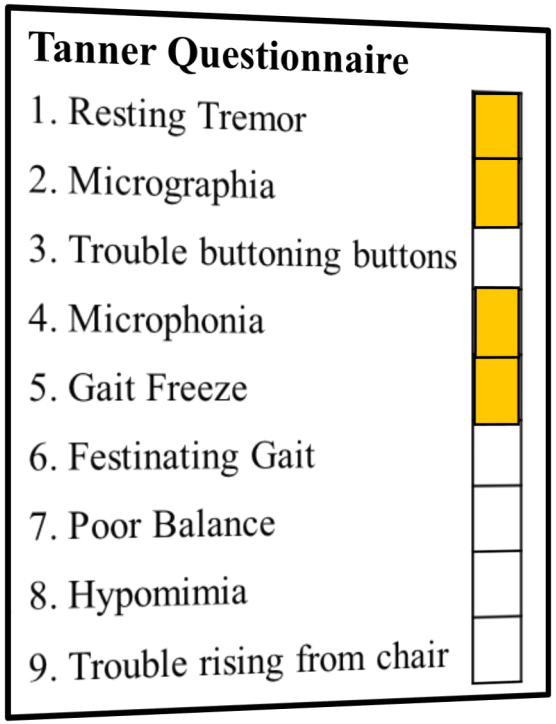



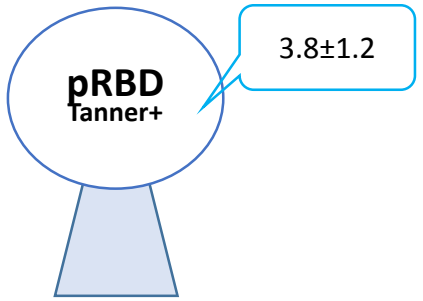



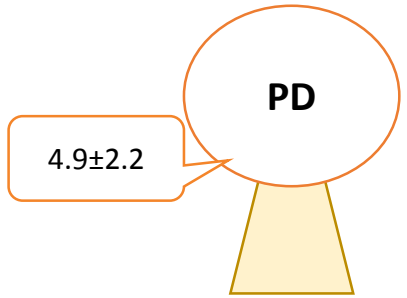

| | | | |
|---|---|---|---|
| **21.7%** | **5.93** | **[2.99,12.31]** | **62.2%** |
| **38.6%** | **5.93** | **[3.03,11.94]** | **79.0%** |
| 50.0% | 1.53 | [0.82,2.87] | 47.1% |
| **37.1%** | **1.92** | **[1.02,3.64]** | **53.9%** |
| **4.3%** | **7.74** | **[2.58,33.49]** | **26.2%** |
| 47.1% | 1.47 | [0.79,2.74]] | 54.3% |
| 64.3% | 0.72 | [0.38,1.35] | 56.9% |
| 35.8% | 1.31 | [0.68,2.56] | 40.6% |
| 54.3% | 0.54 | [0.29,1] | 39.2% |

# What are **the differences** between **pRBD-Tanner** vs. **PD?**






| | | | |
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| **4.3%** | **7.74** | **[2.58,33.49]** | **26.2%** |

# Poorer in Motor Functions and Postural Instability



| Healthy Control | pRBD | pRBD-Tanner | PD |
|---|---|---|---|
| 39.21±23.05 | 39.74±23.05 | 20.7±22.7 | 26.26±24.07 |
| 9.28±1.83 | 9.45±3.54 | 10.96±3.0 | 10.3±2.21 |
| 35.11±10.98 | 35.04±11.44 | 31.04±11.43 | 30.8±10.42 |


https://www.fysiopartner.no/produkt/19502534/120605/jamar-plus-digital-handdynamometer/18169764/1
(Dzhagaryan, Milenkovic et al. 2015)
www.homefitnesstest.com/tests/balance.htm

# Insomnia as a Comorbid Sleep Disorder

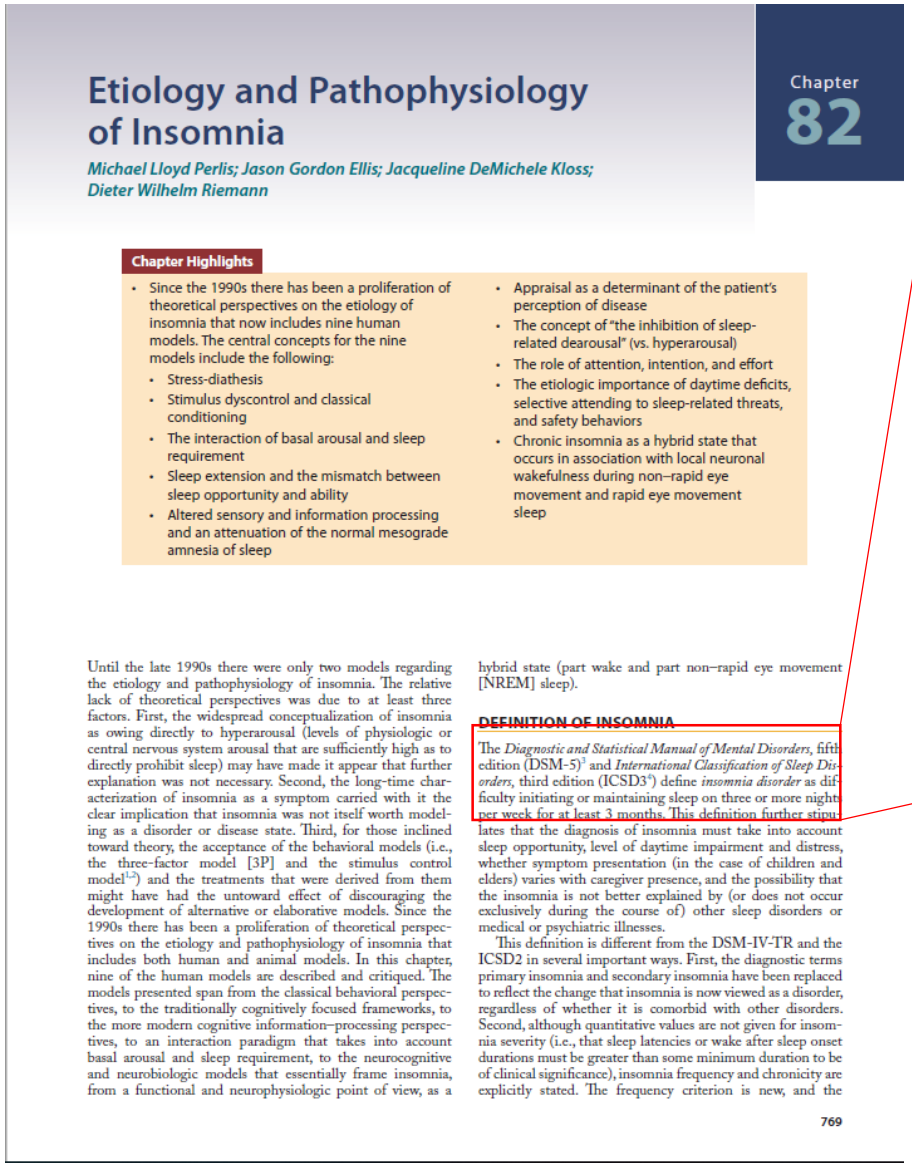
Introduction

**Case Definition**

Results

Discussions

Acknowledgment



Chapter 82

## Etiology and Pathophysiology of Insomnia

*Michael Lloyd Perlis; Jason Gordon Ellis; Jacqueline DeMichele Kloss; Dieter Wilhelm Riemann*

**Chapter Highlights**

- Since the 1990s there has been a proliferation of theoretical perspectives on the etiology of insomnia that now includes nine human models. The central concepts for the nine models include the following:
  - Stress-diathesis
  - Stimulus dyscontrol and classical conditioning
  - The interaction of basal arousal and sleep requirement
  - Sleep extension and the mismatch between sleep opportunity and ability
  - Altered sensory and information processing and an attenuation of the normal mesograde amnesia of sleep
  - Appraisal as a determinant of the patient's perception of disease
  - The concept of "the inhibition of sleep-related dearousal" (vs. hyperarousal)
  - The role of attention, intention, and effort
  - The etiologic importance of daytime deficits, selective attending to sleep-related threats, and safety behaviors
  - Chronic insomnia as a hybrid state that occurs in association with local neuronal wakefulness during non–rapid eye movement and rapid eye movement sleep

Until the late 1990s there were only two models regarding the etiology and pathophysiology of insomnia. The relative lack of theoretical perspectives was due to at least three factors. First, the widespread conceptualization of insomnia as owing directly to hyperarousal (levels of physiologic or central nervous system arousal that are sufficiently high as to directly prohibit sleep) may have made it appear that further explanation was not necessary. Second, the long-time characterization of insomnia as a symptom carried with it the clear implication that insomnia was not itself worth modeling as a disorder or disease state. Third, for those inclined toward theory, the acceptance of the behavioral models (i.e., the three-factor model [3P] and the stimulus control model[1,2]) and the treatments that were derived from them might have had the untoward effect of discouraging the development of alternative or elaborative models. Since the 1990s there has been a proliferation of theoretical perspectives on the etiology and pathophysiology of insomnia that includes both human and animal models. In this chapter, nine of the human models are described and critiqued. The models presented span from the classical behavioral perspectives, to the traditionally cognitively focused frameworks, to the more modern cognitive information–processing perspectives, to an interaction paradigm that takes into account basal arousal and sleep requirement, to the neurocognitive and neurobiologic models that essentially frame insomnia, from a functional and neurophysiologic point of view, as a hybrid state (part wake and part non–rapid eye movement [NREM] sleep).

**DEFINITION OF INSOMNIA**

The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5)[3] and *International Classification of Sleep Disorders*, third edition (ICSD3[4]) define *insomnia disorder* as difficulty initiating or maintaining sleep on three or more nights per week for at least 3 months. This definition further stipulates that the diagnosis of insomnia must take into account sleep opportunity, level of daytime impairment and distress, whether symptom presentation (in the case of children and elders) varies with caregiver presence, and the possibility that the insomnia is not better explained by (or does not occur exclusively during the course of) other sleep disorders or medical or psychiatric illnesses.

This definition is different from the DSM-IV-TR and the ICSD2 in several important ways. First, the diagnostic terms primary insomnia and secondary insomnia have been replaced to reflect the change that insomnia is now viewed as a disorder, regardless of whether it is comorbid with other disorders. Second, although quantitative values are not given for insomnia severity (i.e., that sleep latencies or wake after sleep onset durations must be greater than some minimum duration to be of clinical significance), insomnia frequency and chronicity are explicitly stated. The frequency criterion is new, and the

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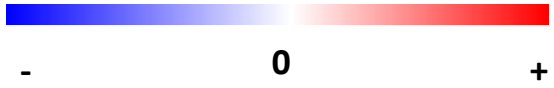
# Insomnia as a Comorbid Sleep Disorder





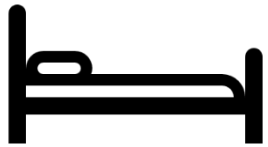


Onset Insomnia

Control: 14.6%
**pRBD: 20.1%**
**pRBD–Tanner: 41.4 %**
PD: 14.6 %

2.04 [1.19, 3.85]

Maintenance Insomnia



Control: 27.9%
pRBD: 23.8%
**pRBD-Tanner: 17.1%**
**PD: 30.1%**

No Difference Across the Board

https://thepenal.com/wall-clocks/black-white-wall-clock.php
https://www.hercampus.com/school/butler/narcolepsy-told-gif
https://giphy.com/gifs/RbLhosb3cxhvy

# Insomnia as a Comorbid Sleep Disorder




## Onset Insomnia

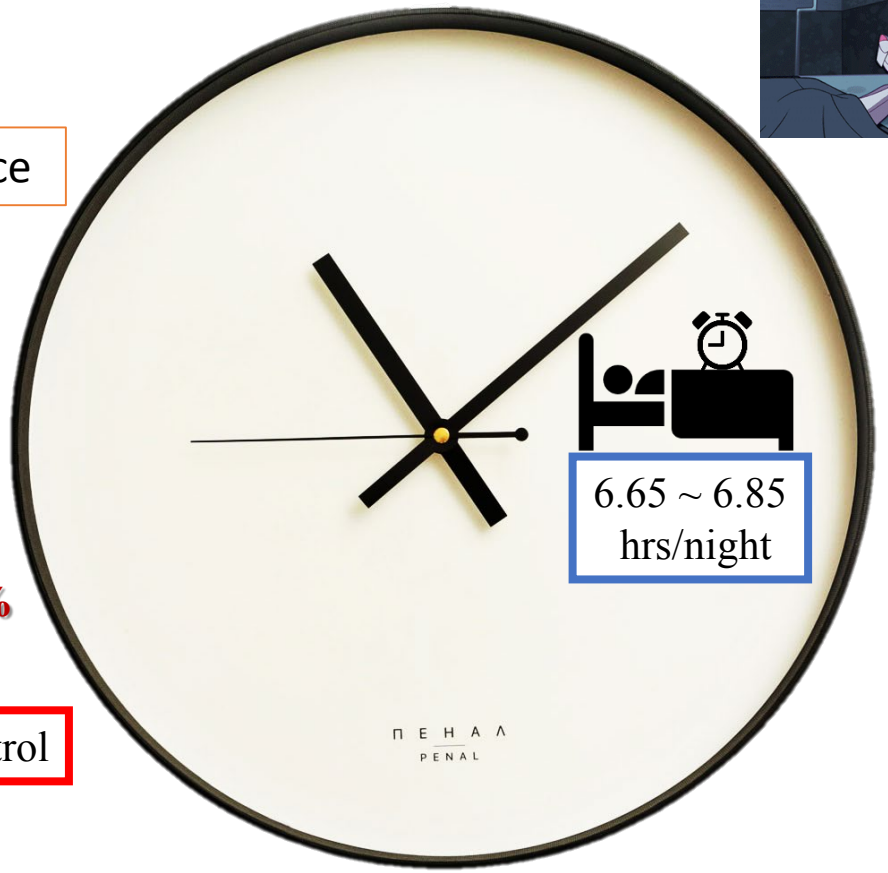
Control: 14.6%
**pRBD: 20.1%**
**pRBD–Tanner: 41.4 %**
PD: 14.6 %

2.04 [1.19, 3.85]

## Daytime Somnolence

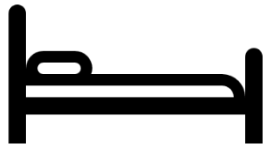
Control: 6.7%
pRBD: 11.6%
**pRBD-Tanner: 21.4%**
**PD: 18.5%**

Only Worse than Control




6.65 ~ 6.85 hrs/night

## Maintenance Insomnia



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https://thepenal.com/wall-clocks/black-white-wall-clock.php
https://www.hercampus.com/school/butler/narcolepsy-told-gif
https://giphy.com/gifs/RbLhosb3cxhvy

# Worsen in Cognition

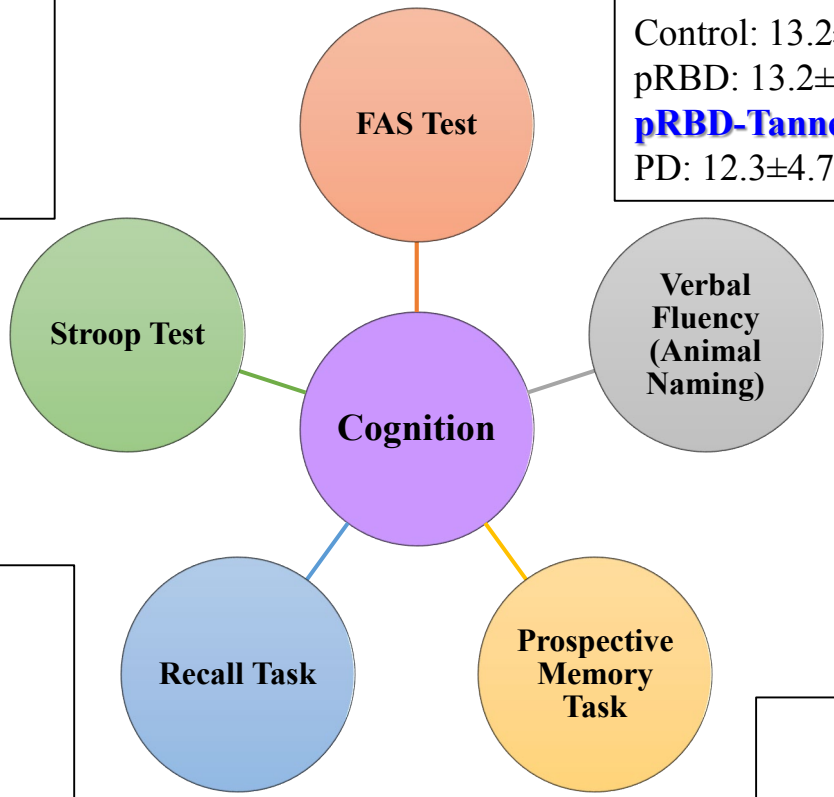


**Interference Error/Dot Error**

Control: 1.61±1.88
pRBD: 1.74±2.28
**pRBD-Tanner: 2.17±2.58**
**PD: 2.29±3.32**

**Mean FAS Score**

Control: 13.2±4.3
pRBD: 13.2±4.2
**pRBD-Tanner: 11.3±4.3**
PD: 12.3±4.7




**Mean Animal Naming**

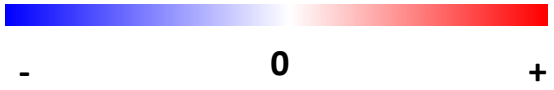
Control: 20.5±6.0
pRBD: 20.4±6.0
**pRBD-Tanner: 17.2±5.2**
PD: 18.1±6.0

**Delayed Recall Score**

Control: 4.11±2.0
pRBD: 4.02±2.12
pRBD-Tanner: 3.18±1.87
**PD: 2.80±2.11**

**Total Score < 14**

Control: 2.8%
pRBD: 2.8%
**pRBD-Tanner: 11.8%**
PD: 4.9%



# Increase in the occurrence of Psychiatric Events




**pRBD:** 2.24 [1.85, 2.72]
**pRBD-Tanner:** 6.34 [3.55, 10.84]
PD: 1.38 [0.58 , 2.79]


**pRBD:** 1.07 [1.05, 1.08]
**pRBD-Tanner:** 8.40 [4.18, 16.03]
**PD:** 3.78 [2.06 , 6.42]

**Kessler Psychological Distress Scale (K10)**
Source: Kessler R. Professor of Health Care Policy, Harvard Medical School, Boston, USA.

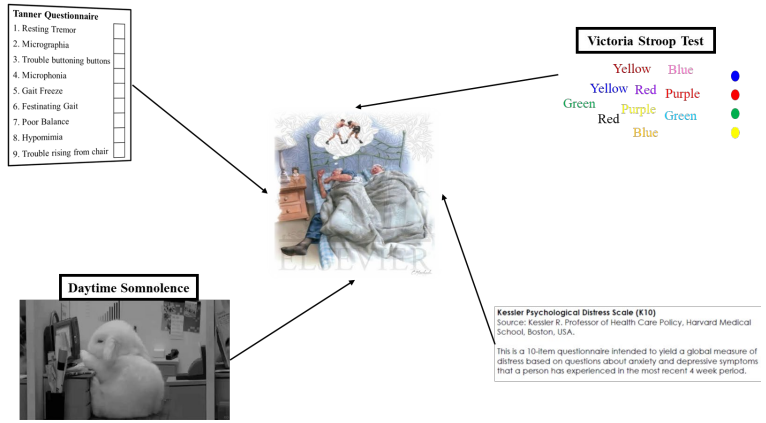
This is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4 week period.

**pRBD:** 1.84 [1.56, 2.17]
**pRBD-Tanner:** 7.07 [4.29, 11.54]
PD: 1.59 [0.87 , 2.70]


# Take Home Message & Future Plan



1. Even high specificity screens still have low PPV with uncommon diseases
2. Overall PPV of RBD-1Q ≤ 30%
3. pRBD–Tanner + ≈ true PD




4. However. without prospective, it is hard to be sure who really have RBD.

**Missing prospective! Available next year.**

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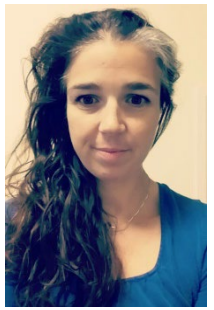

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RI-MUHC:
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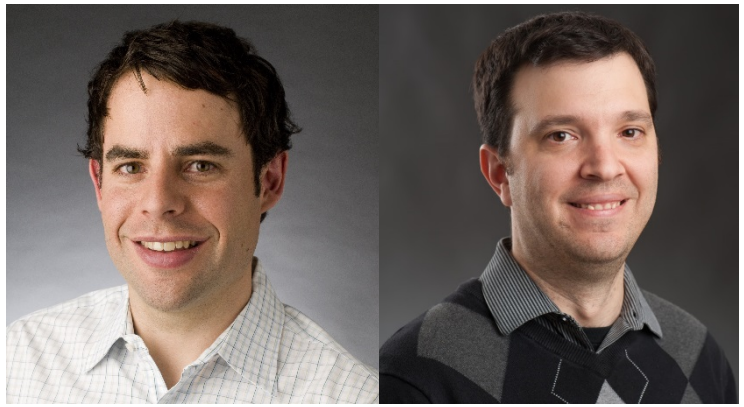
# Upcoming CLSA Webinars

**Availability and quality assessment of genome-wide genetic data on 9,900 participants in the CLSA**

**Brent Richards, MD, MSc**
**Vince Forgetta, MSc, PhD**

**January 15, 2019 | 12 p.m. ET**



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