ARIC Manuscript Proposal #2842

1.a. Full Title: The prevalence of probable RBD and associated factors

b. Abbreviated Title (Length 26 characters): RBD epidemiology

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___HL___ [please confirm with your initials electronically or in writing]

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3. Timeline: Manuscript submitted by July 2017

4. Rationale:

Rapid eye movement sleep Behavior Disorder (RBD) is a parasomnia disorder that is characterized by “acting out of dream” behaviors that are associated with loss of muscle atonia and vivid dreaming during REM sleep. As results, patients often suffer from restless sleep and sometimes serious injuries to self and/or bed partner\(^1\). A clinical
diagnosis of RBD requires both clinical symptoms and abnormal polysomnograph readings. Based on clinical studies, it was estimated that RBD affects about 0.5-0.8% of the population with a clear male predominance of up to 8 to 1. Clinical studies further showed that up to 80% of PSG-confirmed RBD developed Parkinson’s disease (PD) or a related synucleinopathy, suggesting RBD as a prodromal stage of α-synuclein related neurodegeneration. As PSG requires an overnight stay at the sleep lab and an expensive sleep study, several simple questionnaires have been designed to screen for dream enacting behaviors that are often consistent with a probable RBD. Based on clinical samples, these questionnaires demonstrated excellent sensitivity and specificity when compared with PSG confirmed RBD diagnosis. Interestingly, using the same questionnaires, the few population-based studies showed that probable RBD has a much higher prevalence (~4-6%) than clinical estimate and a much smaller male to female ratio (~1.5-2) \(^2,3\). While false positives are likely, it is also possible that RBD patients with mild symptoms may not visit a sleep clinic. One of these population based studies further found that individuals with probable RBD were twice likely to develop mild cognitive impairment (MCI) than those without \(^2\), suggesting that even probable RBD or dream enacting behaviors may have neurodegenerative consequences that are yet to be understood.

For these reasons, there has been substantial clinical interest to study RBD with the hope of early identification and intervention of neurodegenerative diseases. Equally important, studies of potential risk factors for RBD may also eventually lead to a better understanding of early development and progression of neurodegenerative diseases.

To the best of our knowledge, only two studies have explored factors that are potentially associated with RBD \(^3\). In one case-control study \(^4\), PSG confirmed RBD was associated with smoking, previous head injury, less education, and exposure to pesticides. Caffeine and alcohol use were however not different between cases and controls. In a cross-sectional analysis of Chinese coal miners, probable RBD identified from screening questionnaire were associated with lower education level, labor occupation, lower physical activity level, head injury, self-reported olfactory/taste dysfunction and various cardiovascular factors \(^3\). We therefore propose to examine the prevalence of RBD and its potential risk factors in the ARIC study.

### 5. Main Hypothesis/Study Questions:

There are two aims of the current manuscript:

1) Examine the prevalence of RBD in older US population. We hypothesize about 4% of ARIC participants may have probable RBD and the prevalence is higher in men than in women and in whites than in blacks.

2) Examine factors that are associated with probable RBD in cross-sectional analyses among ARIC participants without PD and dementia. In particular, we hypothesize that RBD was associated with other prodromal symptoms of PD (e.g. poor sense of smell and lower cognitive score), lifestyle (e.g. smoking, and
physical activity), and cardiovascular risk factors (e.g. BMI, plasma LDL and plasma urate).

The current analyses will be conducted among ARIC participants who answered the GEN questionnaire in 2011-2012. Based on the findings, we will propose more focused research in the future to investigate individual (e.g smoking) or a few related risk factors (e.g. plasma lipids) for RBD using exposure data from ARIC previous clinical visits.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: We propose a cross-sectional analysis using data from GEN and visit 5/NCS in 2011-2013. Main analytic variables are listed in the table below.

<table>
<thead>
<tr>
<th>Table Main outcome and exposure variables and collection time</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Probable RBD</td>
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<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td>Parkinson’s disease</td>
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<td>Dementia/MCI</td>
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<td><strong>Medication use</strong></td>
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<td><strong>Prodromal nonmotor</strong></td>
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<td>Sense of smell</td>
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<td>Depression</td>
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<td>Daytime sleepiness</td>
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<td>Cognitive function</td>
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<td><strong>Motor symptoms</strong></td>
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<td>Tremor</td>
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<td>Small handwriting</td>
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<td>Finger tapping</td>
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<tr>
<td><strong>Genetics</strong></td>
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<tr>
<td>Genetic risk score for PD</td>
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<tr>
<td>Genetic risk score for AD</td>
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</tbody>
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Inclusion and exclusion criteria: All ARIC participants with valid RBD data form the 2011-2012 GEN will be eligible for the current analysis. The actual analytic sample size may however differ by analysis, mainly depending whether the exposure of interest was from visit 5 or GEN. The primary analyses on prevalence and associated factors will also be limited to participants without PD or dementia. We however plan to present overall data, including PD and dementia cases, as supplemental information.

Outcome – probable RBD: The ARIC study screened for probable RBD using a validated screening question “Have you ever been told, or suspected yourself, that you “act out your dreams” while you sleep, for example, punching or flailing your arms in the air, making running movements, shouting, or screaming?” We further queried the frequency
of this symptom and the age of first occurrence. This screening question was clinically validated against polysomnograph confirmed patients with a sensitivity of 93.8% and a specificity of 87.2%\textsuperscript{5}. While it is uncertain whether these characteristics could be generalized to community-based studies, this screening question is strongly associated with prevalent PD in our preliminary analyses.

**Data analyses:** Probable RBD will be defined as a dichotomous variable. We will first estimate the prevalence of probable RBD overall, and by age, sex and race. For potential exposures of interest, we will calculate odds ratios and 95% confidence intervals using logistic regression model, adjusting for age, sex, and race. Exposures that show significant associations in these analyses will enter into a mutually adjusted model to evaluate their independent associations with RBD.

**Potential method limitations and challenges:** The outcome is defined based on a screening question; misclassification is likely. Further, the analyses will be limited to individuals who participated in GEN survey, which may limit the generalizability of study findings.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES\_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES\_DNA = “CVD Research” would be used? __X__ Yes ___ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __X__ Yes ___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = “No use/storage DNA”? __X__ Yes ___ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: [http://www.csec.unc.edu/ARIC/search.php](http://www.csec.unc.edu/ARIC/search.php)

__X__ Yes ______ No
10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
This project will be conducted by the PD working group of ARIC. We have four recent publications: 1) HRV and PD on *Annals of Neurology*; 2) cholesterol and PD on *Movement Disorders*; 3) vitamin D and PD on *Movement Disorders*; and 4) GWAS analyses of the sense of smell on *Medicine*. To the best of our knowledge, this proposal has no overlap with any other proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 
   **X** Yes  ____ No

11.b. If yes, is the proposal
   ____ A. primarily the result of an ancillary study (list number)
   **X** B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s))*  2010.17, 2009.19, 2014.25*

*ancillary studies are listed by number at [http://www.cscu.unc.edu/aric/forms/](http://www.cscu.unc.edu/aric/forms/)

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire. Understood.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from [http://publicaccess.nih.gov/](http://publicaccess.nih.gov/) are posted in [http://www.cscu.unc.edu/aric/index.php](http://www.cscu.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central. Understood.

References: