ARIC Manuscript Proposal # 1135S
SHHS Manuscript/Abstract Proposal Format

1.a. Full title: **Restless Legs Syndrome, Obstructive Sleep Apnea, and Cardiovascular Disease**

  b. Abbreviated title: **RLS, OSA and CVD**

2.　Lead Author: **John W. Winkelman MD PhD**

3.　Timeline: Start on **1/1/06**　　　　Finish on **6/1/06**

4. **Rationale**:
    There is a suggestion that Obstructive Sleep Apnea (OSA) is an independent risk factor for RLS (1), potentially by producing sleep deprivation, which is known to worsen RLS (2).

    There are a number of reasons to suspect that RLS is associated with incident hypertension, diabetes, and cardiovascular disease. RLS produces both sleep deprivation and sleep fragmentation (3,4), both of which are identified risk factors for incident diabetes (5) and cardiovascular disease (6). Furthermore, PLMS, which are present in roughly 80% of those with RLS, produce repetitive autonomic arousals (7), which may also predispose to cardiovascular disease. Finally, two cross-sectional epidemiologic studies have found an independent association of RLS with either cardiovascular disease (8) or hypertension (9).

5. **Hypotheses**:
    a) Individuals with OSA have a higher prevalence of RLS than those without OSA, even after controlling for age, gender, and other important potential confounds.
    b) RLS has a cross-sectional association with hypertension, diabetes, and cardiovascular disease, and is a predictor of *incident* hypertension, diabetes and cardiovascular disease.

6. **Data**: Cardinal symptoms of Restless Legs Syndrome; polysomnographic assessment of hypopneas, apneas, oxygen desaturation, total sleep time (to make diagnoses of OSA); diagnoses of hypertension, diabetes, cardiovascular (for cross-sectional analysis).

7.　Type of Study: [**Secondary Study**]

8. Type of Publication: [**Journal Article**]

9. Analysis Responsibility: [**Distributed Analysis**]

Please attach or include below:

10. **Introduction**
    Restless Legs Syndrome (RLS) is a sensory-motor disorder characterized by dysesthesia and leg restlessness occurring predominantly at night during periods of immobility (10). The sensations and the need to move usually interfere with the ability to fall and/or stay asleep. The prevalence of RLS is roughly 5-10% of the adult population. Roughly 80% of those with RLS have periodic leg movements of sleep, which are repetitive, stereotyped dorsoflexive movements of the toe and foot during sleep, which produce consistent increases in heart rate and blood pressure and may produce arousal from sleep (7). Increasing age,

female gender, first degree family members with RLS, and certain medical disorders (iron deficiency, renal failure) all increase the likelihood of RLS (11).

Obstructive sleep apnea (OSA) is a common sleep disorder in which obstruction of the upper airway during sleep produces repetitive arousals and oxygen desaturation. Obesity and male gender are the most common risk factors for OSA (12). Sleep deprivation and fragmentation from OSA may predispose to RLS (2) producing relationships between the two disorders. However, the coexistence of OSA and RLS in previous case series' (13) does not establish whether one is a risk factor for the other. One previous study (1) using telephone interviews for as the basis of diagnoses, suggested that both loud snoring (OR=1.77, 1.41-2.21) and OSA (1.45, 1.03-2.05) were independent risk factors for RLS. However, no study of this relationship has been performed using subjects assessed by polysomnography and with current diagnostic definitions for RLS.

Previous epidemiologic studies demonstrate an association of cardiovascular disease and/or hypertension with RLS (9,8). The basis for this relationship may be the repetitive EEG and autonomic arousals observed in patients with RLS and associated PLMS (7). However, such cross-sectional relationships do not establish whether RLS predisposes to cardiovascular disease, vice versa, or whether a third variable causes both. For this reason, we would like to assess whether these cross-sectional relationships exist in this cohort, as well as assess these relationships prospectively. Similarly, numerous recent epidemiologic studies have established a prospective association of sleep disruption and sleep deprivation with glucose intolerance or diabetes (5,14,15). We would like to explore this relationship in subjects identified as having RLS.

11. **Brief Analysis Plan**

Although the ultimate goal of this investigation is to assess the independent relation of RLS to incident cardiovascular disease, this manuscript will address the cross-sectional relationships at the time of RLS questionnaire administration (i.e., SHHS-2). Data will be obtained from the CC, including SHHS-2 variables for age, sex, race, waist girth, BMI, rdi4p; insomnia symptoms, snoring, tobacco, alcohol and caffeine consumption from the Sleep Habits Questionnaire; RLS symptoms from the Health Interview (hi208-hi216); use of antihypertensive or oral hypoglycemic medication or insulin; measured SBP and DBP; and self-reported prevalent CVD (from self-reported CVD at SHHS-1 plus screening form questions at SHHS-2).

For the analyses, a categorical definition of the presence of RLS will be obtained from the RLS questions on the HI form. RLS diagnosis will be based on positive responses to the four cardinal symptoms of RLS and a minimum symptom frequency of once per week.

The relation of SDB to RLS symptoms will be evaluated using both categorical (rdi4p quartiles or clinical categories) and continuous (rdi4p) measures of SDB. The association of RLS with categorical SDB variables will be assessed using contingency table analysis for unadjusted associations and logistic regression analysis to adjust for potential confounders including age, sex, and body habitus. The association of RLS symptoms with RDI as a continuous measure will be examined using linear regression models, adjusting for these covariates. For analyses of the relation of RLS symptoms to prevalent hypertension, cardiovascular disease, and DM, operational definitions will be created from the available data (hypertension defined as SBP>140, DBP>90, or use of antihypertensive medications; CVD defined as self-reported presence of CVD at baseline SHHS exam or screening questionnaire at SHHS-2; DM defined as use of antidiabetic medication). With each of

these dichotomous variables as the dependent variable in a separate analysis, logistic regression will be used to assess the association with RLS, adjusting for age, sex, body habitus, smoking status, and other potential confounders (including SBP and use of antihypertensive medications in analyses of CVD variables).

12. **Summary Section**

This manuscript will explore the cross-sectional associations of restless legs syndrome with sleep-disordered breathing and with prevalent hypertension, diabetes mellitus, and cardiovascular disease. Follow-up analyses will assess the relationship of RLS with incident hypertension, diabetes mellitus, and cardiovascular disease, when data on these latter measures are available.

13. **References**

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