Manuscript Proposal:

1. a) Full Title: The association between snoring, nocturnal arousals, and metabolic dysfunction
   b) Abbreviated Title: Snoring, arousals, and metabolism

2. Lead Author: Naresh M. Punjabi, MD, PhD

3. Timeline:
   04/03: Acquire approval from the SHHS P & P committee
   04/03: Start date for proposed analysis
   08/03: Manuscript preparation

4. Rationale:
   In the manuscript proposal entitled ‘Sleep-disordered breathing, Glucose Intolerance, and Insulin Resistance’ (SHHS 050), a cross-sectional association was observed between the severity of sleep-disordered breathing (SDB), as assessed by the respiratory disturbance index (RDI), and measures of glucose tolerance and insulin resistance. Individuals in the highest RDI quartile (RDI > 11.4 events/hr) were noted to have an increased odds ratio for glucose intolerance based on fasting and 2-hour values. Recent experimental data on sleep restriction in healthy volunteers shows that a decrease in nocturnal sleep time even for a few days is associated impairment in glucose tolerance but not insulin resistance (1).

   Continuity of nocturnal sleep can be disturbed for a variety of reasons. Pathological states such as SDB induce recurrent arousals due to the occurrence of disordered breathing events that are often associated with oxyhemoglobin desaturation. Even habitual snoring in the absence of apneas or hypopneas can disrupt sleep continuity due to the occurrence of brief arousals. Although arousals are part of the normal sleep cycle, their frequent occurrence, for any reason, can induce a state of chronic sleep insufficiency.

   Currently, the relationship between snoring, frequent arousals, and glucose metabolism in individuals without SDB is not known. Data from the Nurses Health Study (2) and the Cardiovascular Health Study (3) indicate that self-reported snoring is independently associated with incident and prevalent diabetes, respectively. Whether the relationship between snoring and altered metabolism in these studies is attributable to the presence of SDB is not known. Moreover, there are no data on whether recurrent arousals can alter glucose metabolism in individuals without SDB. The baseline data from the SHHS along with metabolic parameters derived from the parent cohorts (Framingham, CHS, ARIC) provide the opportunity to determine whether habitual snoring and nocturnal arousals (in individuals without SDB) are cross-sectionally associated with the occurrence of glucose intolerance and insulin resistance.

5. Hypothesis:
   a. Habitual snoring is associated with glucose intolerance or insulin resistance
   b. Arousal frequency is associated with glucose intolerance and insulin resistance

6. Data:
**Study Design**: Cross-sectional study to examine the relation between:
   a) Self-reported snoring and glucose tolerance and insulin resistance
   b) Nocturnal arousal frequency and glucose tolerance and insulin resistance

**Population**: SHHS participants with overnight sleep study and measurements of glucose and insulin levels. Exclusionary criteria include: use of oral hypoglycemic agents, insulin, and SDB (defined as an RDI ≥ 5 events/hr)

**Variables of Interest**:

- **Metabolic Parameters**: Fasting glucose and insulin values
  2-hour glucose during the oral glucose tolerance test

- **PSG Parameters**: Respiratory disturbance index
  PSG defined total sleep time
  Arousal frequency
  Distribution of NREM (I, II, III, IV) and REM sleep stages

- **Questionnaire data**: Snoring history

- **Anthropometrics**: BMI and waist circumference

- **Demographic data**: Age, gender, and race

7. **Type of Study**: Secondary

8. **Type of Publication**: Journal Article (SLEEP)

9. **Analysis Responsibility**: Local

10. **Introduction**:

    Over the course of the last few years, the significance of sleep as a determinant of metabolic dysfunction has been of significant research interest. The current proposal is based on the findings of the novel experiment conducted by Spiegel et al. (1) demonstrating that sleep loss is associated with glucose intolerance in healthy men. Cross-sectional analyses from the SHHS data also demonstrate that RDI is a predictor of impaired metabolism. The question of whether snoring and nocturnal arousals in the absence of SDB predict metabolic dysfunction remains to be determined.

11. **Analysis Plan**:

    Data on glucose levels will be modeled as previously done in SHHS manuscript 50. Fasting and 2-hour levels will be used to classify individuals into normal, impaired, or diabetic groups based on the current American Diabetes Association criteria (4). Subjects will be considered diabetic if they have a glucose level ≥ 200 mg/dL two hours after the glucose load. Impaired glucose tolerance will be defined as a 2-hour glucose ≥140 mg/dL and <200 mg/dL. In the absence of 2-hour glucose data, individuals will be considered diabetic if the fasting glucose is
≥ 126 mg/dl. Impaired fasting glucose will be defined as a fasting glucose level between 110 to 125 mg/dl. Ordinal logistic regression will be used to determine whether (independent of known confounders such as age, gender, BMI, and waist circumference) snoring and arousal frequency predict glucose tolerance in individuals without SDB. Separated models will be constructed for fasting and 2-hour classification of the glucose status. If available, the homeostatic model assessment (HOMA), which is determined as the product of fasting glucose and fasting insulin, will be used as an index of insulin sensitivity. Analysis of covariance will be used to determine the adjusted HOMA levels based on snoring status and as a function of arousal frequency. Multivariable analyses will also examine whether parameters of sleep architecture (distribution of sleep stages) are associated with glucose tolerance (based on fasting or 2-hour data) and insulin resistance. Covariates in all multivariable models will include: age, gender, race, body mass index, smoking status, and waist circumference.

12. Sample Size and Power Analysis:

Sample size projections were based on constructing a multivariable logistic regression model for fasting glycemic status (normal, impaired, diabetic) as a function of arousal frequency. The proposed analyses will use quartiles of the primary predictor (i.e., arousal frequency) to test for associations with glucose intolerance after adjusting for other covariates (e.g., age, BMI). The following assumptions were used in calculating the necessary sample size for these analyses: a) 8.3% prevalence of impaired or diabetic fasting glucose in the lowest quartile of arousal frequency; b) 14% or higher prevalence of impaired or fasting glucose tolerance in the highest quartile of arousal frequency; and c) 10% variability (r²) due to other covariates (e.g., BMI, waist circumference) in the multivariable model. The aforementioned assumptions are based on data used for SHHS manuscript 50. The following graph illustrates the power to detect a range of differences (6% to 12%) in the prevalence of impaired or diabetic fasting glucose between the lowest and the highest quartile of arousal frequency as a function of sample size. A sample size of at least 1200 individuals is necessary to detect a 6% difference in the prevalence of impaired or diabetic fasting glucose between the lowest and the highest quartile of arousal frequency as a function of sample size. A sample size of at least 1200 individuals is necessary to detect a 6% difference in the prevalence of impaired or diabetic fasting glucose between the lowest and the highest quartiles of arousal frequency (power ~ 76%, α = 0.05). The SHHS cohort consists of 1,775 and 1,390 individuals with a respiratory disturbance index (RDI 4%) less than 5 events/hr and fasting glucose data within 18 and 12 months, respectively, of the baseline SHHS polysomnogram. Thus, the currently available data will have sufficient power to examine the relationship between arousal frequency and fasting glycemic status in participants without sleep-disordered breathing (RDI < 5 events/hr).
13. **Summary Section:** Diabetes and impaired glucose tolerance are prevalent in the general population. Snoring in the absence of SDB is also a common occurrence. In light of the fact that experimentally induced sleep loss can induce glucose intolerance in otherwise healthy individuals raises the concern on whether frequent nocturnal arousals and snoring are also associated with impaired metabolism. Data from the Nurses Health Study (2) and Cardiovascular Health Study (3) show that snoring is associated with incident and prevalent diabetes, respectively. The polysomnographic data from the SHHS provide the opportunity to exclude individuals with SDB and probe the question of whether snoring and nocturnal arousals are related with glucose intolerance and insulin resistance.

14. **Writing Group Members:** a) Punjabi NM, b) Resnick HE, c) Gottleib DJ

**References:**


