1. **Full Title:** The relative contribution of apneas and hypopneas to impaired glucose metabolism

   b) **Abbreviated Title:** Apneas, hypopneas, and metabolism

2. **Lead Author:** Katherine A. Stamatakis, PhD, MPH. (Naresh M. Punjabi, MD, PhD)

3. **Timeline:**
   - 10/04: Acquire approval from the SHHS P & P committee
   - 10/04: Start date for proposed analysis
   - 12/04: Manuscript preparation

4. **Rationale:**

   Objective: To determine the relationship between varying degrees of sleep related hypoxic and prevalent metabolic impairment.

   Sleep-disordered breathing (SDB) is characterized by the presence of apneas and hypopneas during sleep. An apnea is defined as the cessation for airflow for at least 10 seconds. A hypopnea is defined as a reduction of oronasal airflow associated with either oxyhemoglobin desaturation or arousal from sleep. Varying degrees of oxyhemoglobin desaturation are used in clinical practice to define a hypopnea. Although hypopneas in most sleep laboratories are based on identifying an oxygen desaturation of 4%, there are no data to indicate whether lower levels of oxygen desaturation do not predict a higher likelihood of adverse outcomes. Data from the Sleep Heart Health Study provide the unique opportunity to explore whether different degrees of sleep related hypoxemia are associated with a higher prevalence of impaired metabolism. The overarching goal of this proposal is to examine whether there is a specific threshold in oxygen desaturation associated with apneas and hypopneas that predicts an increase in prevalent odds of glucose intolerance.

4. **Hypothesis:**

   Hypopneas with lower than a 4% oxygen desaturation will be associated with an increase odds of prevalent glucose intolerance.

5. **Data:**

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

   **PSG Parameters:**
   - Event frequency (apnea and hypopneas) at different levels of oxygen desaturation.
   - PSG defined total sleep time
   - Variables on sleep staging and oximetry quality
Anthropometrics: BMI and waist circumference
Demographic data: Age, gender, and race

Study Design: Cross-sectional study

Population: SHHS participants with overnight sleep study and measurements of glucose and insulin levels. Exclusionary criteria include poor quality polysomnograms based on quality of sleep stage and oximetry data.

7. Type of Study: Secondary Study
8. Type of Publication: Journal Article
9. Analysis Responsibility: Local Analysis
10. Introduction:

Previous analyses of the SHHS data have demonstrated a relationship between a commonly used measure of sleep-disordered breathing, the respiratory disturbance index (RDI), and glucose intolerance and insulin resistance (SHHS 050). The RDI is defined as the number of apneas or hypopneas that were associated with a 4 percent decrease in oxygen saturation per hour of sleep. Although the cut-point of 4% is commonly used, it remains to be determined whether sleep-related respiratory events that are associated with lower levels of oxygen desaturation carry any clinical significance. Analyses reported in SHHS 050 focused on using the RDI as the primary predictor. Only those respiratory events (apneas or hypopneas) with a 4% desaturation were considered in that analysis. Sleep-related hypoxia, as assessed by average oxygen saturation and the percent time spent below 90%, was associated with prevalent metabolic abnormalities. However, these results cannot be applied toward defining sleep-related respiratory events that are associated with an increased risk for metabolic dysfunction.

11. Analysis Plan:

Data on glucose levels will be modeled as previously done in SHHS050. Fasting and 2-hour levels will be used to classify individuals into normal, impaired, or diabetic groups. Subjects will be considered diabetic if they have a glucose level ≥200mg/dL two hours after the glucose load. Impaired glucose tolerance will be defined as a 2-hour glucose ≥140mg/dL and <200mg/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. Separate models will be constructed for fasting and 2-hour classification of the glucose status.
The primary predictors will include the apnea index (AI), hypopnea index (HI), and the apnea-hypopnea index (AHI). Each of these indices will be defined at varying levels of oxygen desaturation ($\geq 0\%$, $\geq 2\%$, $\geq 3\%$, $\geq 4\%$, $\geq 5\%$). Separate multivariable models will be developed for each level of desaturation. To delineate whether a threshold exists in the predicting prevalent metabolic disturbance, event frequencies will also be computed for specific levels of oxygen desaturation. For example, we will calculate the AI, HI, and AHI for events with 2-3%, 3-4%, and 4-5%. In addition, other ranges of oxygen desaturation will also be examined. Each multivariable model will include adjustments for age, race, gender, body mass index, waist circumference, and smoking status. Model fit will be assessed by the Hosmer-Lemeshow goodness-of-fit test. The assumption of proportional odds across categories of glucose tolerance will be examined. If the assumption is violated, we will then use the generalized logistic model to calculate level specific odds ratio for each predictor variable.

12. **Summary Section:**

Data from several epidemiologic data has demonstrated that SDB symptoms are associated with an increased risk of incident diabetes. Physiologic mechanisms through which sleep-related respiratory disturbance could cause changes in metabolic function include hypoxic stress and fragmentation of sleep. Although data from SHHS has shown a link between polysomnographically defined SDB and metabolic dysfunction, it remains to be determined whether currently used definitions for respiratory events encompass the entire spectrum that predispose to adverse health outcomes. The primary objective of this proposal is to define whether there is a threshold in the level of oxygen desaturation that would predict the presence of glucose intolerance and insulin resistance.

13. **Writing Group Members:**

Stamatakis, K, Punjabi NM, and others as selected by the Steering Committee.