

ARIC Manuscript Proposal # 811S

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SLEEP HEART HEALTH STUDY Manuscript Proposal:

1. a) Full Title: Sleep-disordered Breathing, Glucose Intolerance, and Insulin Resistance in the Sleep Heart Health Study.

b) Abbreviated Title: SDB and Impaired Glucose Metabolism
2. Lead Author: Naresh M. Punjabi, M.D., Ph.D.
3. Timeline: 07/01: Acquire proposal approval
09/01: Start date for proposed analysis
12/01: Start manuscript preparation (anticipate completion by 06/02)

4. Rationale:

We have been able to recently illustrate, using a community-based cohort of healthy men, that sleep-disordered breathing (SDB) is associated with glucose intolerance and insulin resistance independent of obesity.¹ The possibility of a causal link between SDB and glucose metabolism is based on a number of observations. First, it is well recognized that untreated SDB is associated with an increase in sympathetic neural traffic that is manifested by elevated levels of muscle sympathetic nerve activity and plasma and urinary catecholamines.²⁻⁸ Second, sleep disruption and the hypoxic stress that commonly accompany SDB have shown to be associated with altered corticotropic function.^{9,10} The impact of sleep disruption on glucocorticoid activity is supported by experimental sleep deprivation studies illustrating that sleep loss in normal volunteers is associated with higher levels of serum cortisol.¹¹ Third, there is also evidence that hypoxia alone may directly impair glucose metabolism. Studies in normal subjects and in individuals with chronic respiratory disease demonstrate that hypoxia is associated with impaired glucose tolerance and metabolic dysfunction.¹²⁻¹⁵ Collectively, the effects of elevated sympathetic nervous system activity, sleep induced alteration in glucocorticoid regulation, and intermittent hypoxemia may facilitate the development of metabolic disturbances in glucose homeostasis and insulin regulation in individuals with untreated SDB. Previous studies on the association between SDB and glucose metabolism have faced several difficulties including the use of clinic-based samples and failure to control for confounding factors (i.e., obesity).^{10,16-22} The use of SHHS data along with information obtained on glucose metabolism (fasting glucose and insulin levels, 2-hour glucose and insulin levels) from parent cohorts (i.e., ARIC, CHS, Strong Heart) offer the opportunity to examine an important relationship between SDB and glucose intolerance/insulin resistance, factors that have been associated with increased cardiovascular morbidity and mortality.

5. Hypothesis: SDB is associated with glucose intolerance, independent of obesity
SDB is associated with insulin resistance, independent of obesity

6. Data:

Study Design: Cross-sectional study to examine the relation between the severity of SDB fasting and 2-hour glucose and insulin levels.

Population: Eligible subjects will be SHHS participants who had an overnight sleep study and measurements of glucose and insulin levels. Exclusions include history of diabetes.

Variables of Interest:

SHHS Data – Information from the overnight polysomnogram will be used.

- Respiratory disturbance index (RDI) at various desaturation levels (2%, 3%, 4%, 5%)
- Sleep-stage dependent RDI (NREM-RDI and REM-RDI),
- Sleep architecture (time in sleep stage 1, 2, slow wave, and REM sleep),
- Arousal indices (arousals/hr)
- Hypoxia stress (percent time spent below set thresholds i.e., 90%, 80%, 70%)
- Demographic and anthropometric variables: BMI, neck circumference, waist-to-hip ratio, and history of prevalence diabetes

ARIC Data

- Visit 1
Fasting glucose and insulin levels
- Visit 2
Fasting glucose
- Visit 3
Fasting glucose
- Visit 4
Results of the oral glucose tolerance test (G_0 and G_{120})
Fasting insulin levels

CHS Data

- Visit 2
Results of oral glucose tolerance test (G_0 and G_{120})
Fasting insulin level
- Visit 5
Fasting glucose and insulin level
- Visit 9
Results of oral glucose tolerance test (G_0 and G_{120})

Strong Heart Data

- Phase II (Time frame 1991 – 1996)
Results of oral glucose tolerance test (G_0 and G_{120})
- Phase III (Time frame 1996 – 2000)
Results of oral glucose tolerance test (G_0 and G_{120})

Framingham Data

- Visit 5 (Time frame 1991 – 1995):
 - Height, weight, waist girth, and hip girth
 - Insulin Level
 - Results of oral glucose tolerance test (G_0 and G_{120})

- Visit 6 (Time frame 1996 – 1997)
 - Height, weight, waist girth, and hip girth
 - Fasting glucose (G_0)

7. Type of Study: Local Study

8. Type of Publication: Journal Article

9. Analysis Responsibility: Local

10. Introduction:

A number of parent cohorts of the Sleep Heart Health Study, have been performing fasting and 2-hour insulin and glucose levels in a majority of their participants. As discussed above, there is a great deal of interest in whether SDB is associated with alterations in metabolic function. Prior inferences about a possible relationship have been based on small, highly selected population studies with methodologic and analytical limitations.^{10;16-22} Available literature suggests that hypoxia and arousals can independently lead to metabolic dysfunction thus providing biologic plausibility to the hypothesis that SDB is associated with glucose intolerance and insulin resistance independent of obesity. Since glucose intolerance and insulin resistance increase blood pressure and cardiovascular risk, a positive independent association would further our understanding about the causal pathway between SDB and cardiovascular disease.

11. Analysis Plan:

Data on glucose and insulin levels (time window of three years around the overnight sleep study from SHHS) will be initially analyzed as follows. If available, two indices of insulin sensitivity will be examined: the ratio²³ of fasting glucose (G_0) to fasting insulin (I_0), and the homeostatic model assessment of insulin sensitivity (HOMA).²⁴ Insulin sensitivity according to the HOMA model is determined as $(G_0 \times I_0) / 22.5$. Two-hour glucose data from parent cohorts with available data will be used to assess glucose tolerance. Subjects will be considered diabetic²⁵ if they have a glucose level ≥ 200 mg/dL two hours after the glucose load. Impaired glucose tolerance²⁵ will be defined as a 2-hour glucose ≥ 140 mg/dL and < 200 mg/dL.

Preliminary analysis will consist of examining a number of descriptive statistics. Frequency distributions of polysomnographic and metabolic variables will be generated.

Analysis of variance will be used to determine whether polysomnographic variables, such as RDI quartile, are associated with indices of insulin sensitivity.

Multivariable methods will be used to examine the relationship between RDI and insulin sensitivity after adjusting for demographic and anthropometric (i.e., BMI, waist-to-hip ratio) variables. Residuals will be examined for evidence of outliers, poor fit to the data, and indications that there is interaction between variables that has not been adequately modeled.

Results of the glucose tolerance test from visit four will be analyzed with the technique of ordinal logistic regression. Since the results of the OGTT are expressed as normal, impaired, or a diabetic response, an ordinal logistic regression is the appropriate method to examine the independent predictors of glucose tolerance and adjust for potential confounders (i.e., BMI). In addition, multivariate methods will be used to model fasting and 2-hour glucose levels as a continuous outcome variable.

Cumulative data on glucose and insulin levels across visits (from cohorts that have the data) will be utilized to develop longitudinal models and examine whether SDB is associated with worsening glucose tolerance/insulin resistance independent of obesity. Since the clinical measurements of glucose and insulin over time will be correlated within individuals, method of generalized estimating equations (GEE) as described by Liang and Zeger²⁶ will be used to dealing with correlated data. The use of GEE will allow detailed exploration of how trajectories of glucose and insulin levels (and of derived indices from these two measurements) change over time in subjects with varying degrees of SDB.

All analyses will be repeated to determine whether there any differences by site.

12. Summary Section: SDB is highly prevalent in the general community. Obesity is a well-established risk factor for SDB. There is emerging evidence that implicates SDB as a risk factor for metabolic dysfunction. We have recently shown that SDB is independently associated with glucose intolerance and insulin resistance in a community sample of men without prevalence diabetes. However, there have been no large, well-controlled, studies to determine whether SDB is associated with metabolic dysfunction among a community-based population of subjects with SDB. In particular, there are no large studies analyzing the effects of hypoxemia and arousals on metabolic variables. Information from the parent cohorts (ARIC, Framingham, Strong Heart, and CHS) along with the polysomnographic data from the Sleep Heart Health Study provides the unique opportunity to answer the question of whether SDB is associated with a high risk of metabolic dysfunction.

13. Writing Group Members: a) FJ Nieto, b) E Sharar, c) J Samet, d) PL Smith

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