SHHS Manuscript/Abstract Proposal Format
1. a. Full Title: Abnormalities in Glucose Metabolism in Sleep Disordered Breathing and Implications for Cardiovascular Risk
1. b. GT aspects in SDB and CVD risk
2. Lead Author: Sinziana Seicean MD (Susan Redline, MD, MPH, and Mendel E. Singer, PhD, mentors)
   09-10/04: Start date for proposed analysis.
   12/04: Start manuscript preparation (anticipate completion by 04/05).
4. Rationale:

   Sleep Disorder Breathing (SDB) is associated with diabetes and insulin resistance (1, 2). The “Metabolic Syndrome” or/and diabetes have been reported in 30-90% of SDB patients (3-8, 12, 13). Causal association are supported by longitudinal studies which showed the relative risk for incident diabetes (over 10 years) to be higher (7.0 vs. 5.1, p<0.05) in obese snorers compared with obese non-snorers (Swedish Cohort Study), or two fold increased risk in females snorers after adjusting for BMI, and other potential confounders ( Nurses Health Study) (9, 10).

   Insulin resistance may be measured by responses to oral glucose loading (Impaired Glucose Tolerance; IGT) or by abnormal fasting glucose levels (Impaired Fasting Glucose, IFG). The prevalence and outcomes of insulin resistance may vary according to whether insulin resistance is defined by abnormal fasting versus post-glucose loading values. The relative predictive value of each test of glucose metabolism also may vary among population subgroups. Preliminary data from the Cleveland Family Study suggest that in individuals with SDB, insulin resistance is much more prevalent when defined using IGT than IFG criteria. Furthermore, data indicate that the risks of diabetes and macrovascular disease are greater in individuals with both IGT and IFG (11) than in individuals with either abnormality. Variation in test performance may relate to differences in the pathophysiological abnormalities detected by each test. Abnormal IGT from glucose load testing likely identifies abnormalities in sensitivity to peripheral insulin; in contrast, FPG may more closely identify raised hepatic glucose output, with increased sensitivity to defects in early insulin secretion (11, 15-18); the first test could capture a specific subpopulation with higher diabetes, cardiovascular and mortality risk factors. Thus, there is a need to identify the role of each test in identifying insulin resistance, and to assess whether individuals with SDB are more likely to require 2 hour glucose tolerance tests relative to other population groups.

   Fully understanding the role of tests of glucose intolerance in SDB relates to the need to: 1. define which test(s) identify metabolic abnormalities in SDB; 2. which tests best predict co-morbidity and/or progression to diabetes. The latter is of especial interest since SDB may act either additively or synergistically with insulin resistance to increase risk of CVD-associated co-morbidities. For example, SDB-related hypoxemia and autonomic dysregulation may be postulated to play a
role in both causing metabolic changes associated with insulin resistance (1, 2), as well as a role in exacerbating vascular disease in subjects with existing diabetes. There has only been little work, however, that has examined whether SDB occurring in the setting of insulin resistance, modifies the risk of CVD. It is possible that the recurrent intermittent nocturnal hypoxemia and autonomic nervous system activation, characteristic of SDB, not only increases risk of insulin resistance, but also increases risk of CVD co-morbidity. However, fully addressing this question will also require identifying which measures of insulin resistance are the most relevant exposures in studies of SDB.

Finally, most of the literature describing metabolic abnormalities and CVD has focused on the predictive value of threshold levels defining “borderline” or “abnormal” values. However, little more has rigorously explored the overall shape of any dose-response relationship, and whether such relationships vary in groups defined by obesity and SDB.

5. Hypotheses:
   a) In SDB, the 2 hour oral glucose tolerance test (2h OGTT), is more sensitive (identifies a higher proportion of individuals) than fasting plasma glucose testing, and the relative difference in sensitivity of the two tests is greater than what is observed among other groups, including obese non-SDB individuals and non-obese, non-SDB individuals.
   The rationale is that the 2h OGTT is likely to be a peripheral insulin resistance marker which is more likely to be abnormal in the setting of obesity and intermittent nocturnal hypoxemia than the FPG, which rather captures raised hepatic glucose output and detects defects in early insulin secretion (11), which may be less influenced by SDB-associated stresses. Additionally, IGT, contrasted to IFG, may better identify subgroups with higher diabetes, cardiovascular and mortality risk factors.
   b) Subjects with both SDB (RDI > 5) and with abnormal values for IGT on the 2h OGTT test are more likely to have other features of metabolic syndrome (as hypertension and dyslipidaemia), compare with individuals with SDB who either have normal values of IGT and FPG or abnormal FPG levels alone, with the highest prevalence of CVD risk occurring in subjects with both abnormal IGT and FPG levels.
   c) In non-diabetic SDB, 2h OGTT and FPG values will each predict CVD in a linear dose–response relationship; however, the slopes (or effects) will be stronger for 2h OGTT.
   d) There will be a multiplicative effect between SDB and IGT (defined by the optimal measure of IGT defined in #c) co-morbidity as evidenced by a higher odds of self-reported macrovascular disease (coronary heart disease and stroke), in individuals with both SDB and IGT compared to groups with neither or only one risk factor. Such associations will persist after adjusting for other CVD risk factors (BMI, age, sex, race, and smoking habits).

6. Data:
   Study design: Cross-sectional study to examine a potential multiplicative association between SDB and IGT and self-reported macrovascular disease (an aggregate measure of self reported coronary heart disease, CHD, and Stroke)
Population: SHHS participants who had an overnight PSG and measurements of FPG and 2h OGTT. Exclusion includes history of diabetes mellitus with use of insulin or an oral hypoglycemic medication.

Variables of interest: The following proposed analyses will use SHHS 1 collected Data. However, if SHHS 2 data are available, and approved to be used, the following analyses will be modified to capture the incident CVD risk.

SHHS data:
1. Indices of SDB breathing (RD13P, RDI4P, percent time <90 oxygen saturation).
2. Demographic and anthropometrical variables: age, race, sex, BMI, waist circumference.
3. History and prevalence of diabetes, diabetes and anti lipid medications, smoking status, alcohol drinking, total and HDL cholesterol, systolic and diastolic blood pressure, self reported prevalent coronary heart disease (will include self reported myocardial infarction, angina, coronary artery bypass surgery, or angioplasty as recorded on the night of the PSG study), and self reported prevalent cardiovascular disease (CHD or stroke).

ARIC Data: visit 1, 2, 3, fasting glucose; visit 4 - Oral glucose tolerance test (Go and G120)
CHS Data visit 2 and visit 9: Oral tolerance test (Go and G120); visit 5 Fasting glucose test
Strong Heart Data: Phase II (Time frame 1991-1996) Oral glucose tolerance test (Go and G120), Phase III (Time frame 1991-1995): Height, weight, waist girth and hip girth and Oral glucose tolerance test (Go and G120)
Framingham Data: Visit 5 (Time frame 1991-1995): Height, weight, waist girth and hip girth and Oral glucose tolerance test (Go and G120) and visit 6 (Time frame 1996-1997) Height, Weight, waist girth and hip girth and Fasting glucose (Go)

7. Type of study: Cross-sectional analyses of pooled data from ARIC, CHS, Strong Heart and Framingham sites.

8 Type of Publication: Journal article
9. Analyses Responsibility: Local

10. Introduction:
The co-occurrence of SDB and IGT has been described in several studies, including the SHHS (1, 2, and 14). An increased risk of abnormal glucose metabolism in SDB is evident even after controlling for BMI, age, sex, gender. The role of IGT in modifying risk of CVD, and the converse, the role of SDB in modifying diabetes-associated co-morbidities, however, are poorly understood. A better understanding of the potential interactive effects of each condition, however, requires an improved understanding of the range of glucose metabolic derangements that occur in SDB, and which test of glucose metabolism (FPG or 2h OGTT) is most sensitive and most predictive of co-morbidities. Although the most common practice is to screen for diabetes using a fasting glucose level, it is possible that this test is not as sensitive or predictive as tests of IGT using glucose load responses. The 2h OGTT, as a peripheral insulin resistance marker, may better capture the metabolic imbalance in groups such as
individuals with SDB who are commonly obese and also experience recurrent nocturnal hypoxemia, which may especially impair peripheral insulin sensitivity. Individuals with both co-morbidities (SDB and IGT) may be at higher risk for cardiovascular disease compared to other groups. SDB-induced physiological stresses, notably hypoxia and oxidative stress, may stimulate sympathetic over-activity (19, 20) and contribute to worsening the insulin resistance by secretion of insulin antagonists (e.g. catecholamine) (21). They also could lead to a cascade of inflammatory and hormonal responses, as well as to the release of a number of cytokines, adhesion factors and other hormones that may alter endothelial function (22-25). Together, these will exacerbate the process of atherosclerosis, independent of visceral obesity and adipocyte dysfunction (26-27), and may enhance the propensity for oxidation of serum and tissue proteins, and adversely effect lipid and carbohydrate metabolism, by reducing the fibrinolytic potential, with subsequent damage of the vascular endothelium (28-30). As the result, the overall cardiovascular risk may be multiplicative in this population (SDB and IGT).

Defining such associations could be of great value in the development of informed approaches for health screening and early intervention.

11. Preliminary Analyses Plan:

Descriptive Statistics:
- Identify “metabolic” groups defined by abnormalities in FPG and IGT (both abnormal, one abnormal, both normal) and describe the underlying characteristics (BMI, CVD risk factors, SDB level, etc.), testing whether levels of BMI, SDB, percent male, etc are greatest as follows: abnormal FPG and IGT; abnormal IGT alone; abnormal FPG alone, neither abnormal. Repeat analyses stratifying by obesity and SDB level to identify potential interactions.

Metabolic group definitions:
1. Positive borderline FPG (110-125mg/dl) or/and abnormal (FPG>=126 mg/dl) with normal 2h OGTT (<140 mg/dl)
2. Normal (negative abnormal/borderline) FPG (<110mg/dl) with positive borderline 2h OGTT(140-199mg/dl) or/and abnormal 2h OGTT(>=200 mg/dl)
3. Positive borderline FPG (110-125mg/dl) or/and abnormal (FPG>=126 mg/dl) with positive borderline 2h OGTT(140-199mg/dl) or/and abnormal 2h OGTT(>=200 mg/dl)
4. Normal (negative abnormal/borderline) FPG (<110mg/dl) with normal 2h OGTT(<140 mg/dl)

SDB, obesity definitions for descriptive analyses:
- SDB levels: (RDI < 5 events/hour, 5-25 events/hour, 15-30 events/hour, ≥30 events/hour)
- Obesity levels: BMI :< 18.5kg/m2, 18.5 to <25 kg/m2, 25 to <30 kg/m2 and >=30 kg/m2.)

- Use multivariable methods (logistic for SDBD as a binary variable, multiple regression for RDI as outcome) to examine the relative predictive value for IGT, FPG, and combinations of each, with and without adjusting for other covariates (BMI, race, sex, RDI); and also stratifying by obesity and SDB in other models, relationship between SDB with positive values for IGT on 2h OGTT test and
other Model dose-response relationships of FPG and 2h OGTT with odds of CHD/stroke. Performing cubic spline logistic regression to identify the patterns of response (linear vs. nonlinear) of 1) FPG and 2) 2h OGTT relative to the odds of CVD risk (self reported coronary heart disease and stroke) in this group. Stratify analyses by SDB levels; alternatively, use as RDI level as a covariate.

- Perform hierarchical models, predicting CVD outcomes, initially as a function of traditional demographic and anthropometrical factors, then adding CVD co-risk factors; and then with the optimal functional form describing IGT/FPG (identified above). Finally, add indices of SDB and include SDB*IGT interactions.

12. Summary Section:

The results of these analyses will better define the associations of metabolic abnormalities to SDB, including identifying the optimal measure for defining glucose abnormalities in the SDB population and addressing whether subjects with both metabolic abnormalities and SDB have greater CVD risk than subjects with either condition alone.

13. References:

1. Punjabi N M; Shahar E; Redline S; Gottlieb D; Givelber R; Resnick H E; Sleep disordered breathing, glucose intolerance and insulin resistance: The sleep Heart Health Study


