PC Reviewed: 8/13/13 **Status: <u>A</u>** **Priority: <u>2</u>**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Sleep Disordered Breathing, Sleep Duration and the Risk of Incident Self-Reported Diabetes: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Sleep and Incident Diabetes

2. Writing Group:
Mako Nagayoshi, PhD; Naresh Punjabi, MD, PhD; James S. Pankow, PhD, MPH; Elizabeth Selvin, PhD, MPH; Eyal Shahar, MD, MPH; Hiroyasu Iso, MD, PhD; Pamela L. Lutsey, PhD MPH; <u>Others welcome</u>.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MN_ **[please confirm with your initials electronically or in writing]**

> **First author**: **Mako Nagayoshi, PhD**
> **Address:** Division of Epidemiology and Community Health
> 1300 South 2nd Street, Suite 300,
> Minneapolis, MN 55454
> Phone: 612-626-8598   Fax: 612-624-0315
> E-mail: nmako@hotmail.com

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

> **Name: Pamela L. Lutsey**
> **Address:** 1300 South 2nd Street, Suite 300,
> Minneapolis, MN 55454
> Phone: 612-624-5812   Fax: 612-624-0315
> E-mail: lutsey@umn.edu

3. Timeline:
• Analysis to be completed by: August 31, 2013
• Initial draft of manuscript to be completed by: September 31, 2013
• Manuscript to be submitted for publication by: December 31, 2014

4. Rationale:

Worldwide, the prevalence of diabetes has increased dramatically over time, in parallel with the increases in the prevalence of overweight and obesity[1]. In 2010, an estimated 19.7 million (8.3%) Americans had diagnosed diabetes, an additional 8.2 million (3.5%) had undiagnosed diabetes, and 19.7 million (38.2%) had prediabetes, as defined by abnormal fasting glucose levels [2]. The prevention of diabetes is a public health priority because diabetes is associated with increased risk of retinopathy, renal failure, cardiovascular disease, and mortality[2].

Sleep disordered breathing (SDB) is characterized by repetitive episodes of upper airway collapse during sleep, which cause enhanced sympathetic activity, increased cytokine levels, elevated oxidative stress and sleep fragmentation. SDB has been correlated with diabetes in many cross-sectional studies [3]. For example, in the Sleep Heart Health Study the prevalence of type 2 diabetes was 1.7-fold higher among persons with SDB than in those without SDB after adjustment for age, sex, body mass index (BMI) and waist circumference [4].

Evidence of the association between objectively measured SDB and incident diabetes is, however, limited [5]. In a Japanese population moderate-to severe SDB was associated with a 1.7-fold higher risk of incident diabetes, however this study is limited in that it used pulse-oximetry to assess nocturnal intermittent hypoxia as surrogate marker of SDB [6]. This finding supports the results from longitudinal studies which have found SDB symptoms, such as self-reported habitual snoring, to be associated with higher risk of incident diabetes [3]. However, in longitudinal analysis of the Wisconsin Sleep Cohort Study SDB was not associated with incident diabetes after adjustment for waist circumference [7].

There are several mechanisms may underlie the association between SDB and incident diabetes. Frist, hypoxia may lead to a direct or chemoreflex-mediated increase in sympathetic nerve activity [8], which may raise serum catecholamine levels and lead to elevated serum glucose [9]; Second, sleep fragmentation as a result of OSA may lead to alterations in the hypothalamic–pituitary–adrenal axis, which can cause marked elevation in serum cortisol levels, potentially leading to insulin resistance and hyperglycaemia [10]. Third, hypoxia and oxidative stress may lead to elevation in cytokine levels (e.g. TNF-α) [11], which may precede increased insulin resistance [12].

Both short and long sleep duration have also been associated with incident diabetes in epidemiologic studies[13]. In a recent meta-analysis, relative to reference sleep categories, short sleep duration was associated with a HR for incident diabetes of 1.28 (95% CI: 1.03-1.60) while for long sleep duration the HR for incident diabetes was 1.48 (95% CI: 1.13-1.96). Several possible mechanisms have also been posited for the association between short sleep duration and incident diabetes. Reciprocal changes in circulating levels of leptin and ghrelin [1415] may facilitate the development of obesity [1416] and impaired glycemic control

[17] via increased appetite and caloric intake, and reduced energy expenditure [1618]. Short sleep duration may also lead to diabetes through increased cortisol secretion and altered growth hormone metabolism [19], and low-grade inflammation activated by short sleep duration [20]. The mechanisms for the association between long sleep duration and incident diabetes are less clear, because long sleep duration may be intricately linked to depressive symptoms, low socioeconomic status, unemployment, a low level of physical activity, undiagnosed health conditions, and poor general health.

5. Main Hypothesis/Study Questions:

The aim of this study is to determine whether SDB and abnormal sleep duration are associated with incident diabetes independent of behavioral factors, and anthropometry.

We hypothesize that individuals with SDB (RDI>15), and individuals with short (< 6 hrs/night) and long sleep duration (>9 hrs/night) will be at higher risk of developing diabetes, independent of behavioral factors and anthropometry.

We will also explore whether the magnitude of these relations differs by sex.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Prospective cohort starting at ARIC visit 4 (1996-1998), which approximately corresponds to when in-home overnight polysomnography (PSG) was conducted in a subset of ~1,892 ARIC participants who also took part in the Sleep Heart Health Study (SHHS). Incident self-reported diabetes will be ascertained through Annual Follow-Up (AFU) phone call responses from visit 4 through the end of follow-up (2010).

Inclusion/Exclusion: Only participants who took part in ARIC Visit 4 and SHHS will be eligible for the analysis. We will also exclude those with prevalent diabetes at visit 4.

Outcome variable: Incident diabetes from visit 4 onward, as defined by self-reported diabetes assessed during annual follow-up telephone calls. Based on crude calculations, we estimate that there will be at least 175 cases of incident self-reported diabetes among ARIC SHHS participants over the course of follow-up. Previous work in ARIC has shown the sensitivity of incident self-reported diabetes to be 55.9% - 80.4%, and specificity 84.5% - 90.6% when compared with reference definitions defined by fasting glucose, hemoglobin A1c, and medication use obtained during an in-person visit attended by a subsample of participants (n = 1,738) in 2004–2005 [21].

Follow-up time will be calculated from the date of the visit 4 exam until the date of the telephone call that resulted in a diagnosis of incident diabetes, the date of last contact if the subject was lost to follow-up, or the date of the most recent AFU contact, whichever comes first.

We will also conduct sensitivity analyses, in which only persons who reported taking diabetes medications will be classified as having incident diabetes. In another sensitivity analyses, we will also include as cases participants with incident diabetes at visit 5, as defined by fasting glucose ≥126 mg/dL or HbA1c ≥6.5% or diabetes medication use.

Independent variable:
- SDB is the primary exposure of interest, and will be calculated as has been done previously in SHHS [22]. Analytically, we will define SDB by a Respiratory Disturbance Index (RDI) of >15 per hour.
- Sleep duration will be calculated by time in sleep (hours/night, categorical; will not assume linearity).
- In secondary analyses, we will also explore the following exposures: total apnea or hypopnea events (events/night sleep), time in apnea or hypopnea (%, continuous), lowest SpO2, duration of SpO2 <90% (%, continuous), sleep fragmentation including arousal index (arousals/hour, continuous) and wake after sleep onset (min, continuous).

Covariates:
- Age, gender, race-center, educational attainment, income, marital status, smoking status, alcohol use, physical activity, BMI, waist circumference, hypertension and hypercholesterolemia.

Analyses: Descriptive statistics will be generated for potential covariates. For the primary analysis we will use the Cox Proportional hazards model to estimate hazards ratios for incident diabetes, stratified by categories of sleep phenotype (e.g. RDI≥15, lowest SpO2, duration of SpO2 <90%, arousal index and sleep duration).

 Model 1: Adjust for age, gender, center
 Model 2: Adjusted for Model 1 + educational attainment, income, marital status
 Model 3: Adjusted for Model 2 + smoking status, alcohol use, physical activity
 Model 4: Adjusted for Model 3 + BMI, waist circumference
 Model 5: Adjusted for Model 4 + hypertension, hypercholesterolemia

We will also separately examine whether gender modifies associations between SDB, sleep duration, and incident diabetes, by including cross-product terms in the models.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No
b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons
with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA
analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains
the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating
Center must be used, or the file ICTDER03 must be used to exclude those with value
RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC
Study manuscript proposals and has found no overlap between this proposal and
previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area
of the web site at: http://www.cscc.unc.edu/ARIC/search.php   ___X___ Yes _____ No
10. What are the most related manuscript proposals in ARIC (authors are encouraged
to contact lead authors of these proposals for comments on the new proposal or
collaboration)?
MS # **811S** Sleep-disordered Breathing, Glucose Intolerance, and Insulin Resistance
 in the Sleep Heart Health Study, NM Punjabi, FJ Nieto, E Sharar, J Samet, PL Smith.

There are authors from this manuscript that are included in this proposal.
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any
ancillary study data? __ X __ Yes __ __ No
11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
_ X _ B. primarily based on ARIC data with ancillary data playing a minor role (usually
control variables; list number(s)* _____ _____ _____)
*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

1995.12 (Punjabi PI)
- Sleep Heart Health Study (SHHS)
- We have been working with both Naresh and the SHHS Coordinating Center to get access
to the ARIC-SHHS data.   At present, the ARIC CC does not have this data.

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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