ARIC Manuscript Proposal # 921S

1. a. Full Title:
   Prospective longitudinal analysis of sleep-disordered breathing and hypertension: the Sleep Heart Health Study

   b. Abbreviated Title [Length, total of 26 letters + spaces]:
   Longitudinal SDB and BP

2. Lead Author: George O’Connor

3. Timeline: To start immediately

4. Rationale:
   Sleep-disordered breathing (SDB) has been associated with hypertension in cross-sectional studies 1 including SHHS 2. The cross-sectional nature of such studies precludes definitive causal inferences regarding the observed association. Among 709 participants in the Wisconsin Sleep Cohort, Peppard and coworkers 3 found a significant dose-response association between sleep-disordered breathing at baseline and the presence of hypertension four years later that was independent of known confounding factors. The odds ratio estimate associated with an AHI of 15 or greater was 2.89. The Peppard analysis was based on a single assessment of SDB at the beginning of the follow-up interval. The current SHHS data allow us to confirm the findings of Peppard and to examine in addition the relation of longitudinal change in SDB to the risk of developing hypertension.

5. Hypotheses

   Hypotheses to be addressed among all subjects with a baseline PSG:
   1. Among persons with normal baseline BP and taking no antihypertensive medications at baseline, SDB at baseline is associated with an increased risk of incident hypertension (BP > 140/90 or taking anti-hypertensive medications) during follow-up.
   2. Among persons taking no antihypertensive medications at either the baseline or the follow-up examination, SDB at baseline is associated with a greater increase in BP over time.

   Hypotheses to be addressed among subjects with two PSGs:
   3. Among persons with normal baseline BP and taking no antihypertensive medications at baseline, SDB at baseline and the change in SDB over the subsequent 5 years are each independently associated with the risk
of incident hypertension (BP > 140/90 or taking anti-hypertensive medications).

4. Among persons taking no antihypertensive medications at either the baseline or the follow-up examination, SDB at baseline and the change in SDB over the subsequent 5 years are each independently associated with a greater increase in BP over time.

6. Data [variables, time window, source, inclusions/exclusions]

Sample: All 6,441 subjects in SHHS

Exclusions:
- technically inadequate SDB assessments
- taking anti-hypertensive medications at SHHS baseline examination
- missing baseline data on BP or medications
- no follow-up data on BP or medications

Variables needed:
- SHHS baseline exam: age, gender, race/ethnicity, CVD status (MI, CHF, stroke)
- SHHS baseline, F/U-1, F/U-2: SBP, DBP, medications, BMI, waist:hip ratio, smoking status, alcohol intake
- SHHS baseline and F/U-2 PSG variables: RDI4p, arousal index, % time < 90% sat

7. Type of study: Mainline

8. Type of publication: Journal article

9. Analysis responsibility: Central

10. Brief analysis plan

In all analyses, three alternative SDB metrics will be examined separately: RDI4p, arousal index, % time < 90% saturation. In all analyses, multivariate models will be used to adjust for potential confounders including age, gender, BMI, waist:hip ratio, smoking status, alcohol intake.

Hypothesis 1. Baseline SDB as a predictor of incident HTN (restricted to subjects without HTN at baseline)
- For some subjects, outcome data will only be available for SHHS F/U 1. For others, there will only be data for SHHS F/U 2. For others, data from both exams available.
- HTN will be a dichotomous outcome defined as SBP >90 or DBP > 90 or on medication for HTN. (Note: This requires data on the indication for medication being taken.) One approach would be Cox proportional hazards model in light of varying follow-up intervals. (This assumes we consider HTN as an absorbing
outcome, not allowing transitions to and from HTN.) Alternatively, we can use logistic regression with GEE approach (as done by Peppard et al. 3).

Hypothesis 2. Baseline SDB as a predictor of longitudinal change in SBP and DBP (restricted to subjects not taking antihypertensive meds at baseline or follow-up exams)
- For some subjects, outcome data only available for SHHS F/U 1. For others, data for only SHHS F/U 2. For others, data from both exams available.
- Best approach may be to use GEE to maximize use of data, some subjects contributing only one follow-up observation and some subjects contributing two. A model with outcome variable SBP at time $t$ could be adjusted for SBP at time 0 (baseline) as a means of capturing the longitudinal change. Alternatively, a SBP slope could be calculated for each subject and this could be used as the outcome variable.

Hypothesis 3. Baseline SDB and SDB over time are both independently associated with risk of HTN (restricted to subjects without HTN at baseline)
- Limited to subjects with two PSGs.
- HTN will be a dichotomous outcome, determined at the time of the second PSG, defined as SBP >90 or DBP > 90 or on medication for HTN. (Note: This requires data on the indication for medication being taken.)
- Logistic regression model should suffice here inasmuch as all subjects will have data at the same two time points. The model could include both baseline SDB and change in SDB during follow-up as independent variables.

Hypothesis 4. Baseline SDB and SDB over time as independent predictors of longitudinal change in SBP and DBP (restricted to subjects not taking antihypertensive meds at baseline or follow-up exams)
- Limited to subjects with two PSGs.
- To be determined: Shall we only consider BP at the time of the baseline and follow-up PSGs, or shall we also consider the interim BP at SHHS F/U 1 for those subjects who have data? (I am inclined to ignore the interim BP, which will only be available in a subset.)
- If the straightforward approach of SDB data and BP data at two time points is used, then a simple GLM approach should suffice.

[Note: For hypotheses 1 and 3, there is an alternative approach that may be used instead of restricting the analysis to subjects without hypertension at baseline. This is the approach used by Peppard et al. 3 in their 2000 NEJM paper: “Because of variability within subjects and measurement error in assessing blood pressure, some misclassification of hypertension status was inevitable. Thus, we could not precisely identify a cohort of participants who were free of hypertension at base line to follow for a determination of the incidence of hypertension. Instead, in all models, we controlled for hypertension status at base line. This approach allowed us simultaneously to examine the association between sleep-disordered breathing at base line and]
hypertension at follow-up in participants classified as normotensive at base line and the association between sleep-disordered breathing and persistent hypertension in participants classified as hypertensive at base line. We used an interaction term to assess whether these two associations were different. As a check for a possible bias resulting from the misclassification of hypertension, we performed Monte Carlo simulations in which a random error was added to the measurement of participants' blood pressure. Using conservative (larger than likely) estimates of the error in blood-pressure measurements calculated from the variability between participants' base-line and follow-up measurements, we determined that the misclassification of hypertension might lead to slight underestimates of the odds ratios for the likelihood of hypertension at follow-up."

**Power considerations:** Peppard et al. (author reply to comment by Pankow et al., 2000) have reported the relation of baseline AHI to the incidence of hypertension (HTN) four years later among 641 adults who were classified as normotensive at baseline. Among these subjects, those in the lowest AHI category had a HTN incidence of 9.7% and those with AHI ≥ 15 had a HTN incidence of 32.1%. The adjusted OR for HTN in this highest AHI group was 3.15.

Based on the 6,132 SHHS subjects described in the Nieto paper in JAMA, our cohort includes approximately 1,000 subjects who had an AHI < 1.5 and were normotensive at baseline and approximately 400 subjects who had an AHI ≥ 15 and were normotensive at baseline. We can conservatively estimate power as the power to detect a difference in the 5-year incidence of HTN between these two groups. (Power will actually be greater than this because we will be able to test for the trend across AHI categories.) The power to detect a difference in incident HTN with two-sided alpha error of 0.05 is shown in the table below for alternative HTN incidence rates in the low AHI (referent) group and alternative odds ratios for high vs. low AHI.

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Incidence of HTN in low AHI group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>2.0</td>
<td>84</td>
</tr>
<tr>
<td>3.0</td>
<td>&gt; 99</td>
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Thus, the proposed analysis will have ample power to detect an effect size as large as that reported by Peppard et al., and excellent power to detect an even smaller effect size.

**10. Summary:** As requested by the Longitudinal Analysis working group and the Steering Committee, this analysis will take advantage of longitudinal data on SDB, blood pressure, and other covariates to examine the relation of SDB and change in SDB over time on the change in blood pressure over time and the risk of developing hypertension.
11. References


