ARIC Manuscript Proposal #909S

PC Reviewed:	09/10/02	Status:	_A	Priority:	_2
SC Reviewed:	09/13/02	Status:	_A	Priority:	_2

- 1. a) Full Title: Cigarette smoking and sleep architecture
 - b) Abbreviated Title: Smoking and disruption of nocturnal sleep
- 2. <u>Lead Author</u>: Lin Zhang (Ph.D. student mentored by Dr. Punjabi and Dr. Samet)
- 3. <u>Timeline</u>: 10/02: Acquire approval from P and P committee and request data set 11/02: Start date for proposed analysis
 - 02/03: Start manuscript preparation (anticipated completion by 6/03)

4. Rationale:

In spite of well-documented hazards, tobacco smoking remains the one of the strongest causes of avoidable morbidity and mortality. While its effects in causing acute and chronic diseases have been well documented, there has been little research on the effects of smoking on sleep. Smoking may affect sleep structure through three mechanisms. First, nicotine has stimulating effects on sleep through its effects on nicotine receptors that lead to release of neurotransmitters including acetylcholine (Ach), norephinephrine (NE), serotonin (5-HT), gamma-aminobutyric acid (GABA), and dopamine (DA) – neurotransmitters that play an important role in sleep regulation (3, 14). Both animal studies and human studies have demonstrated that acute nicotine administration can reduce the amount of rapid eye movement (REM) sleep and slow wave sleep, although findings did not achieve statistical significance in all studies (1, 2, 4, 5, 10-12, 15, 16). Second, addicted smokers go through withdrawal every night; the regular intake of nicotine during the day (over 200 puffs or "hits" for typical U.S. smokers) is interrupted. Numbers of dopamine receptors are increased and withdrawal across the night may affect the sleep stage architecture. Epidemiological studies have shown that smoking cessation worsens sleep quality over the -short term, while improving over the long term (1, 13, 17). Finally, smoking causes pulmonary and cardiovascular diseases that can also directly affect sleep

Although there is a plausible basis for investigating the effects of smoking on sleep, research has been relatively limited, both its effects on sleep and on sleep-disordered breathing. Studies with subjective measurements of sleep have linked smoking with poor sleep quality, but only one study has included actual measurement of sleep (13). In that study of 100 subjects, current smokers compared to non-smokers showed decreased percentage of REM and slow wave sleep, and increased percentage of stage 1 and 2 sleep, but the differences were relatively small and none achieved statistical significance. With a limited sample size, the study could not consider potential confounders or explore causal pathways.

The large sample size of the SHHS affords an opportunity to both control for potential confounding and to explore causal pathways linking smoking to altered sleep. Smoking has a number of relevant lifestyle correlates: in comparison with nonsmokers, smokers tend to drink more alcohol and caffeine-containing beverages, agents that can alter sleep architecture (1, 6, 7). In addition, animal studies have demonstrated that nicotine and alcohol have a common target, the mesolimbic dopamine system, which is important in regulation of sleep (6). Thus, alcohol and caffeine consumption are potentially important confounders and effect modification is also plausible. There are also differences in weight across categories of smokers. Current smokers on average tend to be thinner than nonsmokers and former smokers may have substantial weight gain after successfully quitting. Finally, nicotine has been shown to stimulate upper airway musculature and decrease upper airway resistance in animals, effects that would tend to reduce the occurrence of sleep-disordered breathing (8). Thus, an increased rate of apneas and hypopneas in some smokers could also contribute to changes in sleep architecture.

In summary, self-reported measures of sleep have been previous employed in most studies and the effects of smoking on sleep architecture have not been critically examined in a large group with objective physiologic measures of sleep. The only study that used polysomnography to investigate the relationship failed to show significant changes in sleep structure, and this may be due to the limitations discussed above. With full night polysomnography in a large cohort, the SHHS provides a unique opportunity to test the relationship between smoking and alterations in sleep architecture changes. A previous study from SHHS (to be published) showed that current smokers have a lower percentage of slow wave sleep and a higher percentage of stage 1/2 sleep before adjusting for alcohol and caffeine consumption (9). We propose to further analyze the SHHS baseline PSG data to better characterize the relationship of smoking with sleep architecture.

- 5. <u>Hypothesis</u>: The overarching hypothesis of this proposal is that current smoking is associated with alterations in sleep structure and the minor nicotine withdrawal overnight plays an import role in this process. We hypothesize that current smokers will have decreased sleep efficiency, longer sleep latency, reduced total sleep time, lower percentage of stage3/4 sleep and REM sleep, higher percentage of stage 1 and 2 sleep.
- 6. <u>Data</u>: <u>Study Design</u>: Cross-sectional study

<u>Population</u>: Current smokers, former smokers and nonsmokers in the SHHS baseline cohort will be included. Former smokers will provide an additional comparison group. Exclusionary criteria will include individuals that had poor quality studies and polysomnography that could not be scored.

Variables of Interest:

Outcome variables will include a) sleep efficiency, b) initial sleep latency, c) total sleep time and d) percentages in sleep stage 1, 2, Slow Wave, and REM sleep.

Smoking status will be primary independent variable and will be defined based on self-reported data. A number of different approaches will be used to compare smokers versus non-smokers. First, the comparison will be restricted to current smokers and nonsmokers. Second, comparisons will include current smokers and former smokers so that comparison can be made between current smokers and nonsmokers and also current smokers and similar persons who previously smoked. Finally, pack-years and amount smoked will also be used to determine whether there is a dose-response relationship between the extent of smoking and the outcome(s) of interest. Other covariates will include gender, race, age, caffeine consumption, alcohol consumption, BMI, neck circumference, waist-to-hip ratio, respiratory disturbance index (RDI).

- 7. <u>Type of Study</u>: Local Study
- 8. <u>Type of Publication</u>: Journal Article
- 9. Analysis Responsibility: Local

Manuscript proposal for SHHS

10. Introduction:

A number of cross-sectional studies have reported significant impairment in sleep quality in smokers compared to non-smokers. Alterations in sleep architecture among smokers include increased latency to sleep onset, reduction in total sleep time, and a reduction in the amount of REM sleep. Smokers have also been noted to be at increased risk for sleep-disordered breathing which can independently alter the normal progression of sleep. Although a number of studies have been conducted to examine the mechanistic links between nicotine and sleep, the etiologic link between smoking and sleep disruption remains largely unknown. Data from intervention studies suggests that nicotine can significantly disrupt sleep architecture and invoke changes in sleep that are more common in smokers(1).

The proposed study will further our understanding of the effects of smoking on sleep. We anticipate further analyses directed at changes across the night in smokers and also using the follow-up polysomnography to assess changes after quitting.

11. Analysis Plan:

Exploratory data analysis will include examining the baseline distributions of the independent variables, comparing them between current smokers and nonsmokers, current smokers and former smokers. Chi-square tests or Fisher's exact tests will be used to compare categorical variables. t-tests or non-parametric tests will be used to compare all outcome variables and continuous independent variables. Comparisons will be made across strata of smoking status (never, current, and former), within current smokers by numbers of cigarettes smoked, and among former smokers by duration of successful quitting.

For the outcome variable of sleep latency, the Kaplan-Meier method will be used and nonparametric curves will be created stratified by smoking status. Multivariable proportional hazards model will be used to assess the association between smoking status and sleep latency. Constant hazard assumption will be checked through scaled schoenfeld residuals.

Multivariable models will explore the distributions of sleep stages across the various smoking groups. Several modeling strategies will be used, including linear or logistic regression models for percentage time in various sleep stages or using multi-level outcomes to model the distribution of sleep time across sleep stages. We will explore dose-response relationships in current smokers with number of cigarettes smoked. The log-log transformation of variable percentage of stage 1 and stage3/4 sleep as recommended by some SHHS investigators will be tried.

Our modeling approach will explore alternative models for the relationship between smoking and sleep. As described, there are several causal pathways by which smoking might affect sleep architecture. *A priori*, we will specify models for these alternative pathways. Alcohol and caffeine consumption will be treated as potential confounders and effect modifiers. BMI may be an intermediate variable in the causal pathway from smoking to altered sleep architecture. The analyses will be conducted with and without inclusion of persons with the major smoking-related cardiovascular and pulmonary diseases.

12. <u>Summary Section</u>:

Although associations between smoking and sleeping have been documented by several observational studies, the effects of smoking are not well characterized and underlying mechanisms still remain undetermined. Hypotheses have been proposed but have not been tested. The Sleep Heart Health Study provides a unique opportunity to test these hypotheses.

13. Writing Group Members: a) NM Punjabi, b) J Samet and others to be identified

References

- 1. Davila DG et al. Acute effects of transdermal nicotine on sleep architecture, snoring, and sleep-disordered breathing in nonsmokers. Am.J.Respir.Crit Care Med. 1994;150:469-74.
- 2. Domino EF, Yamamoto KI. Nicotine: effect on the sleep cycle of the cat. Science 1965;150:637-8.
- 3. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J.Am.Acad.Child Adolesc.Psychiatry 2001;40:630-41.
- 4. Gillin JC et al. Dose-dependent effects of transdermal nicotine on early morning awakening and rapid eye movement sleep time in nonsmoking normal volunteers. J.Clin.Psychopharmacol. 1994;14:264-7.
- 5. Guzman-Marin R et al. Subcutaneous administration of nicotine changes dorsal raphe serotonergic neurons discharge rate during REM sleep. Brain Res. 2001;888:321-5.
- 6. Martinez-Gonzalez D et al. Effects of nicotine on alcohol intake in a rat model of depression. Pharmacol.Biochem.Behav. 2002;72:355-64.
- 7. Obermeyer WH, Benca RM. Effects of drugs on sleep. Neurol.Clin. 1996;14:827-40.
- 8. Phillips BA, Danner FJ. Cigarette smoking and sleep disturbance. Arch.Intern.Med. 1995;155:734-7.
- 9. Redline S et al. The Effects of Age, Sex, Ethnicity and Sleep Disordered Breathing on Sleep Architecture. 2. Ref Type: Generic
- 10. Salin-Pascual RJ. Relationship between mood improvement and sleep changes with acute nicotine administration in non-smoking major depressed patients. Rev.Invest Clin. 2002;54:36-40.
- 11. Salin-Pascual RJ et al. Effects of transderman nicotine on mood and sleep in nonsmoking major depressed patients. Psychopharmacology (Berl) 1995;121:476-9.
- 12. Salin-Pascual RJ et al. Changes in sleep after acute and repeated administration of nicotine in the rat. Psychopharmacology (Berl) 1999;145:133-8.
- 13. Soldatos CR et al. Cigarette smoking associated with sleep difficulty. Science 1980;207:551-3.
- 14. Stitzel JA et al. Long sleep and short sleep mice differ in nicotine-stimulated 86Rb+ efflux and alpha4 nicotinic receptor subunit cDNA sequence. Pharmacogenetics 2001;11:331-9.
- 15. Vazquez J et al. Transdermal nicotine on sleep and PGO spikes. Brain Res. 1996;737:317-20.
- 16. Velazquez-Moctezuma J et al. Microinjections of nicotine in the medial pontine reticular formation elicits REM sleep. Neurosci.Lett. 1990;115:265-8.
- 17. Wolter TD et al. Effects of 24-hr nicotine replacement on sleep and daytime activity during smoking cessation. Prev.Med. 1996;25:601-10.