ARIC Manuscript Proposal #2135

PC Reviewed: 5/14/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Abnormal sleep characteristics and cognitive change: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Sleep & cognitive change

2. Writing Group: Pamela L Lutsey, Alvaro Alonso, Thomas Mosley, Rebecca Gottesman, Eyal Shahar, Naresh Punjabi, Richard MacLehose, Lisa Wruck. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __X__

First author: **Pamela L Lutsey**
Address: 1300 South 2nd St, Suite 300
Minneapolis, MN 55126

Phone: (612) 624-5812 Fax: (612) 624-0315
E-mail: Lutsey@umn.edu

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: **Alvaro Alonso**
Address: 1300 South 2nd St, Suite 300
Minneapolis, MN 55126

Phone: (612) 626-8597 Fax: (612) 624-0315
E-mail: alonso@umn.edu

3. Timeline: We anticipate data analyses to be complete within ~ 1.5 years of when final ARIC NCS data are available.

4. Rationale:

Dementia and mild cognitive impairment (MCI) are common among U.S elderly[1], yet despite their immense and growing burden relatively little is known about characteristics which lead to cognitive decline. Recent evidence, both epidemiological and pathophysiological, has suggested a possible relation between abnormal sleep

characteristics and cognitive impairment due to both cerebral vascular etiologies and Alzheimer's disease. However, understanding of this relation is incomplete.

In an acute setting, it is well established that poor sleep quality/duration is associated with worse cognitive function[2]. However, it is not known whether chronic exposure to abnormal sleep characteristics has long-lasting effects on cognitive function. There are several mechanisms through which disordered sleep may impact cognitive decline[2, 3]: Chronic nocturnal hypoxia[4 5, 6], sleep fragmentation[7], mediation through cardiovascular disease risk factors (e.g. hypertension, diabetes, inflammation), stroke (both clinical and subclinical) [6, 8, 9], Aβ plaque build-up[10], and interaction with the APOE ε4 risk allele[11, 12].

Several prior cross-sectional studies[13-24], including an ARIC publication (Shahar second author)[17], have evaluated the relation between abnormal sleep and cognition. As a whole, they generally found adverse sleep characteristics to be associated with lower cognition, with the greatest deficits occurring in the executive function and attention domains[13, 22, 25]. Consistent with pathophysiologic evidence, two reported an interaction whereby individuals with both obstructive sleep apnea (OSA) and APOE ε4 had more cognitive impairment[14, 26]. Notably, the prior cross-sectional ARIC publication reported no relation between sleep and cognitive performance[17]. Yet, ARIC participants were 53-74 years old at the time, and the analysis may have taken place too early in the natural history of the disease.

The relation between subjectively measured sleep characteristics and incident cognitive decline has been evaluated in four prior publications[27-31]. Results have been mixed, but the studies were limited by short follow-up (at most three years), and utilized varying measures of sleep disturbances and cognition.

Additionally, as reviewed recently[32], several small, short, randomized trials of OSA patients have reported modest improvements in cognitive functioning after CPAP therapy, with the greatest gains observed in the executive function domain[22].

5. Main Hypothesis/Study Questions:

Study question: Assess whether abnormal sleep characteristics (inclusive of measures of hypoxia and disordered breathing, sleep fragmentation, and sleep duration) are associated with change in cognitive functioning, as assessed by change in results on 3 cognitive tests administered at ARIC Visit 4 (1996-1998) and repeated in ARIC NCS (2011-2013): Delayed Word Recall (DWR), Word Fluency (WF), Digit Symbol Substitution (DSS).

Hypothesis: Participants with abnormal sleep characteristics will experience a greater decline in scores on these tests, relative to participants who do not have abnormal sleep characteristics.

Secondary study question: Examine the relation between sleep characteristics and 14 additional tests spanning 7 domains of cognitive functioning assessed as part of ARIC NCS. These tests were not administered previously in the entire ARIC cohort.

Hypothesis: Participants with abnormal sleep characteristics will perform more poorly on additional cognitive function tests administered in the ARIC NCS exam, relative to those

without abnormal sleep characteristics. This will be particularly true for tests of the executive function and attention domains.

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. We will link data from 1,892 individuals who participated in both ARIC Visit 4 and had an in-home overnight polysomnography (PSG) as part of the Sleep Heart Health Study (SHHS) with outcome data presently being collected as part of the ARIC NCS exam. We anticipate that about 1,000 participants will be included in this analysis.

Inclusion/Exclusion

Participants who at visit 4 scored below the sex- and race-specific 5th percentile in any of the cognitive tests will be excluded, as they may have had prevalent dementia at visit 4[33]. All other participants with SHHS, visit 4, and NCS data will be included.

Exposures

Measures of hypoxia and disordered breathing, sleep fragmentation, and sleep duration, as previously defined in SHHS.

Hypoxia and disordered breathing

- Obstructive sleep apnea (Respiratory Disturbance Index of ≥/< 15 events/h)
- Oxygen saturation <90% (≥/<1% of sleep time)
- Sleep time in apnea or hypopnea, % (continuous)
- Total apnea or hypopnea events, n events/night

Sleep fragmentation

- Arousal index, arousals/hour (continuous)
- Wake after sleep onset, min (continuous)

Sleep duration

- Time in sleep, min (categorical; will not assume linearity)

Outcomes

Primary outcomes: Change in scores on 3 cognitive tests (DWR, DSS, WF) conducted at visit 4 and repeated in ARIC-NCS. Each cognitive test will be analyzed separately.

Secondary outcomes: Additional cognitive tests measured through ARIC-NCS.

Confounders and effect modifiers

Age, race, sex, education, physical activity, smoking status, BMI, diabetes, inflammatory markers, hypertension, APOE ε4 risk allele.

Data analysis

Our analysis will follow recommendations presently being developed by the ARIC-NCS Analysis Committee. The date of the SHHS exam will serve as baseline for the current analysis. Visit 4 participant characteristics will be described using means and proportions stratified by levels of the exposures.

For the primary analysis, linear regression will be used to estimate the association between sleep characteristics (independent variable) and the difference in test scores between ARIC visit 4 and ARIC NCS (dependent variables). We anticipate running a series of models, using 'baseline' covariates collected at ARIC visit 4. The first will likely adjust for demographics (age, race, sex), while further models will additionally adjust for behaviors, psychological characteristics (e.g. depressive symptoms), and physiologic characteristics (e.g. BMI, inflammatory markers, diabetes, hypertension). We also anticipate exploring whether age, sex, and APOE ε4 modify relations between sleep and cognitive impairment by including interaction terms in the models.

In secondary analyses we will evaluate relations of sleep characteristics to cognitive tests measured only at visit 5. For these secondary analyses, we will employ methods recommended by the ARIC-NCS analysis committee.

Selection bias is of concern in this analysis, as people who attend the ARIC-NCS exam may have better cognitive functioning than those who do not attend or died, and may also differ from the rest of the ARIC population in regard to their sleep characteristics. To help address this, inverse probability weighting will be used to model selection into the study using information in ARIC as well as TICS and hospital records[34-36].

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 ICTDER 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?
__X (only APOE ε4)__ Yes ____ 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"?
__X__ 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#884: Measures of Cognitive Function in Persons with Varying Degrees of Sleep-Disordered Breathing: The Sleep Heart Health Study (Shahar 2nd author).

MS#1298: Sleep-disordered breathing and risk of incident cerebrovascular disease: The Sleep Heart Health Study (Shahar coauthor, Punjabi senior author)

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

_X__ A. primarily the result of an ancillary study

1995.12 Sleep Heart Health Study (SHHS) (PI: Punjabi NM)

2008.06 Prediction of cognitive impairment from mid-life vascular risk factors and markers: The ARIC Neurocognitive Study (ARIC-NCS) (PI: Coresh J)

(Under review)
2013.02 Sleep disordered breathing and incident cognitive decline and dementia: The ARIC Study (PI: Lutsey PL)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References

1. Fitzpatrick AL, Kuller LH, Ives DG, Lopez OL, Jagust W, Breitner JCS, Jones B, Lyketsos C, Dulberg C. Incidence and prevalence of dementia in the cardiovascular health study. *Journal of the American Geriatrics Society*. 2004;52:195-204
2. Amlander C, Fuller P. *Basics of sleep guide*. Westchester, Illinois: Sleep Research Society; 2009.
3. Yaffe K, Laffan AM, Harrison S, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA: The Journal of the American Medical Association*. 2011;306:613-619
4. Bliwise DL. Sleep apnea, apoe4 and alzheimer's disease 20 years and counting? *Journal of Psychosomatic Research*. 2002;53:539-546
5. Durgan DJ, Bryan RM. Cerebrovascular consequences of obstructive sleep apnea. *Journal of the American Heart Association*. 2012;1
6. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea–hypopnea and incident stroke: The sleep heart health study. *American Journal of Respiratory and Critical Care Medicine*. 2010;182:269-277
7. Born J, Wilhelm I. System consolidation of memory during sleep. *Psychological Research*. 2012;76:192-203
8. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine*. 2005;353:2034-2041
9. Munoz R, Duran-Cantolla J, Martínez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke*. 2006;37:2317-2321
10. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*. 2009;326:1005-1007
11. Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein e ∈4 and sleep-disordered breathing in adults. *JAMA*. 2001;285:2888-2890
12. Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, Young T. Apoe epsilon4 is associated with obstructive sleep apnea/hypopnea: The sleep heart health study. *Neurology*. 2004;63:664-668
13. Sforza E. Sleep apnea syndrome and cognition. *Frontiers in Neurology*. 2012;3
14. Spira AP, Blackwell T, Stone KL, Redline S, Cauley JA, Ancoli-Israel S, Yaffe K. Sleep-disordered breathing and cognition in older women. *Journal of the American Geriatrics Society*. 2008;56:45-50
15. Dealberto MJ, Pajot N, Courbon D, Alperovitch A. Breathing disorders during sleep and cognitive performance in an older community sample: The eva study. *J Am Geriatr Soc*. 1996;44:1287-1294
16. Ancoli-Israel S, Klauber MR, Butters N, Parker L, Kripke DF. Dementia in institutionalized elderly: Relation to sleep apnea. *J Am Geriatr Soc*. 1991;39:258-263
17. Boland LL, Shahar E, Iber C, Knopman DS, Kuo TF, Nieto FJ, For the Sleep Heart Health Study I. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: The sleep heart health study. *Journal of Sleep Research*. 2002;11:265-272
18. Kim HC, Young T, Matthews CG, Weber SM, Woodard AR, Palta M. Sleep-disordered breathing and neuropsychological deficits: A population-based study. *American Journal of Respiratory and Critical Care Medicine*. 1997;156:1813-1819
19. Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd DG, Suratt PM. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. *Chest*. 1986;90:686-690
20. Naegele B, Thouvard V, Pepin JL, Levy P, Bonnet C, Perret JE, Pellat J, Feuerstein C. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep*. 1995;18:43-52
21. Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, Cappa SF. Cognitive dysfunction in patients with obstructive sleep apnea (osa): Partial reversibility after continuous positive airway pressure (cpap). *Brain Research Bulletin*. 2003;61:87-92

22. Saunamäki T, Jehkonen M. A review of executive functions in obstructive sleep apnea syndrome. *Acta Neurologica Scandinavica*. 2007;115:1-11
23. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: A critical review. *Journal of the International Neuropsychological Society*. 2004;10:772-785
24. Aloia MS, Ilniczky N, Di Dio P, Perlis ML, Greenblatt DW, Giles DE. Neuropsychological changes and treatment compliance in older adults with sleep apnea. *Journal of Psychosomatic Research*. 2003;54:71-76
25. Jackson ML, Howard ME, Barnes M. Chapter 3 - cognition and daytime functioning in sleep-related breathing disorders. In: Hans PAVD, Gerard AK, eds. *Progress in brain research*. Elsevier; 2011:53-68.
26. O'Hara R, Schroder CM, Kraemer HC, Kryla N, Cao C, Miller E, Schatzberg AF, Yesavage JA, Murphy GM, Jr. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in apoe epsilon4 carriers. *Neurology*. 2005;65:642-644
27. Potvin O, Lorrain D, Forget H, Dube M, Grenier S, Preville M, Hudon C. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep*. 2012;35:491-499
28. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. *Journal of the American Geriatrics Society*. 2001;49:1185-1189
29. Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, Launer L. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older japanese-american men. *Journal of the American Geriatrics Society*. 2001;49:1628-1632
30. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. *Alzheimer Disease & Associated Disorders*. 2006;20:41-48 10.1097/1001.wad.0000201850.0000252707.0000201880
31. Jelicic M, Bosma H, Ponds RWHM, Van Boxtel MPJ, Houx PJ, Jolles J. Subjective sleep problems in later life as predictors of cognitive decline. Report from the maastricht ageing study (maas). *International Journal of Geriatric Psychiatry*. 2002;17:73-77
32. Sanchez AI, Martinez P, Miro E, Bardwell WA, Buela-Casal G. Cpap and behavioral therapies in patients with obstructive sleep apnea: Effects on daytime sleepiness, mood, and cognitive function. *Sleep medicine reviews*. 2009;13:223-233
33. Alonso A, Mosley TH, Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: The atherosclerosis risk in communities (aric) study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2009;80:1194-1201
34. Robins JM, Hernán MÁ, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550-560
35. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15:615-625
36. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, Evans DA, Mendes de Leon CF. Accounting for bias due to selective attrition: The example of smoking and cognitive decline. *Epidemiology*. 2012;23:119-128 110.1097/EDE.1090b1013e318230e318861