ARIC Manuscript Proposal #2262

PC Reviewed: 11/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cigarette smoking in midlife and subsequent 23-year cognitive decline: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): smoke, NCS cog change

2. Writing Group: (Alphabetical) Alvaro Alonso, Karen Bandeen-Roche, Jennifer A. Deal, Priya Palta, Kelly Perryman, Melinda C. Power, Andrea Schneider, A. Richey Sharrett, Lisa Wruck

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

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3. Timeline:
Manuscript will be completed in 6 months.

4. Rationale:
Cigarette smoking results in detrimental, well-documented vascular effects, and is a cause of both clinical and subclinical cardiovascular disease, and of stroke.[1, 2] Smoking is hypothesized to be a risk factor for dementia and for cognitive decline through these mechanisms.

In a meta-analysis of prospective studies in 2004, current smoking was associated with increased risk of both Alzheimer's disease, vascular dementia, and change in Modified Mini-Mental State Exam,[3] a commonly used screen for dementia.[4] In ARIC, midlife

smoking in was associated with increased risk of a later hospitalization with dementia (hazard ratio comparing current smokers to never smokers at Visit 2: 1.7, 95% CI: 1.2, 2.5).[5]

Results from longitudinal epidemiologic studies of the effect of smoking on cognitive decline are mixed. The lack of consistent findings may be due, at least in part, to the selective loss of smokers from a cohort study over time. In ARIC, although baseline smoking status (Visit 2) is associated with poorer cognitive test performance cross-sectionally[6], it was not associated with cognitive change during the 6 years between Visits 2 and 4.[7] The latter result could be due to a selection bias in which smokers are more likely than nonsmokers to experience cognitive decline, but are also more likely to be lost to follow-up before that decline is observed. Lending support to this hypothesis, Knopman and al. report that data on cognitive change between Visits 2 and 4 was available for 42% of nonsmokers (as reported at Visit 2), but only 19% of current smokers ($p<0.001$).[7]

In published analyses of smoking and cognitive change in two longitudinal cohorts, the estimated effect of smoking on cognitive decline was increased when methodologies that account for informative dropout were used. In a cohort of employees of the British Civil Service, smoking in midlife was associated with a faster rate of change in global (mean difference in the rate of standardized change = -0.09, 95% CI: =0.15, -0.03) and domain specific function (mean difference in executive function change = -0.011, 95% CI: =0.17, -0.05), in men. When a shared parameter model that jointly estimates rate of longitudinal change and survival to death or dropout was used to incorporate information on time to death into the model, estimates of the association between smoking and cognitive decline were 1.2-1.5 times larger. No associations were observed for either analysis in women.[8] In analysis of 3,713 older adults enrolled in the Chicago Health and Aging Project, Weuve and colleagues compared rates of cognitive decline over 12 years in smokers and nonsmokers. Estimates of the difference in the rates of change increased 56-86% when weights were included in the models to account for informative dropout.[9]

In this study, we propose to expand upon the previous longitudinal study of smoking and cognitive change in this cohort,[7] incorporating the 23 years of follow-up now currently available. In sensitivity analyses, we will utilize methodologies tailored to address potential selection bias, as currently recommended by the ARIC NCS Analysis Workgroup.

5. Main Hypothesis/Study Questions:

To test the hypothesis that cigarette smoking status in midlife is a risk factor for cognitive decline over 23 years in adults.

We hypothesize that, compared to nonsmokers, persons who self-report as current smokers have a faster average rate of global and test-specific cognitive decline

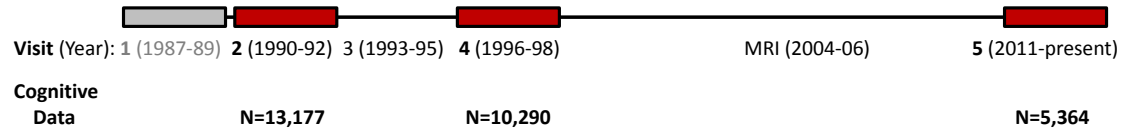
during follow-up, and that among those who smoke, the rate of cognitive decline is faster as the average quantity of cigarettes smoked increases.

We hypothesize that the rate of cognitive decline over time in persons who self-report as former smokers is slower that the rate of cognitive decline in persons who identify as current smokers, but this rate may or may not differ compared to nonsmokers, as the vascular effects of tobacco use may be mitigated by cessation.

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 observational study of N=13,177 men and women (N=28,831 total observations) who completed 3 neuropsychological tests at Visit 2 and up to 2 additional visits during 23 years of follow-up (1990-present). Exposure information (smoking status) is available for all participants with cognitive data at Visit 2.

Figure 1. Study design



Outcome: 23-year trajectories of global and test-specific cognitive function. Cognitive function was measured in the entire cohort at up to 3 time points (Fig.1) using three standardized, neuropsychological tests: the **Delayed Word Recall Test (DWRT)**, the **Digit Symbol Substitution Test (DSST)**, and the **Word Fluency Test (WFT)**.

In the **DWRT**,[10] participants are asked to learn 10 common nouns by reading each noun and using it in a sentence. After an interval filled with a different neurocognitive test, participants are asked to recall the 10 nouns. The DWRT is scored as the total number of words correctly recalled and ranges from 0-10.

The **DSST**[11] is a test of speed and executive attention. Participants are provided with a key that uniquely associates a number with a nonsense symbol and then asked to translate a series of numbers to the corresponding symbol. The DSST is scored as the total number of symbols correctly completed within 90 seconds.

The **WFT**[12] is a test of verbal fluency consisting of 3 consecutive 1-minute word-naming trials. Participants are asked to list as many words as possible (excluding proper nouns) that begin with the letter "F", "A" and "S" in each trial, respectively. WFT is scored as the total number of words generated during the 3 trials.

In order to facilitate comparisons of decline across tests, all tests will be standardized to z-scores in the primary analysis: z-score = (observed test score – mean test score)/ standard deviation of test score at baseline Visit 2.

A **GLOBAL** cognitive score, as described by Gottesman et al (ARIC Manscript Proposal (MP) 1982, submitted), will be created using the three neurocognitive tests.

Exposure:
Self-reported information on current and past cigarette smoking status was collected at each study visit (Table 1, Figure 2). Quantity of lifetime tobacco use among ever smokers was calculated at Visit 1 (Table 2, Figure 3).

Table 1. Determination of smoking status by participant self-report

Questionnaire item (self-report):	**Participant response**			
"Have you ever smoked cigarettes?"*	No	Yes	Yes	No
"Do you now smoke cigarettes?"*	No	No	Yes	Yes
Smoking classification:	Never	Former	Current	Missing

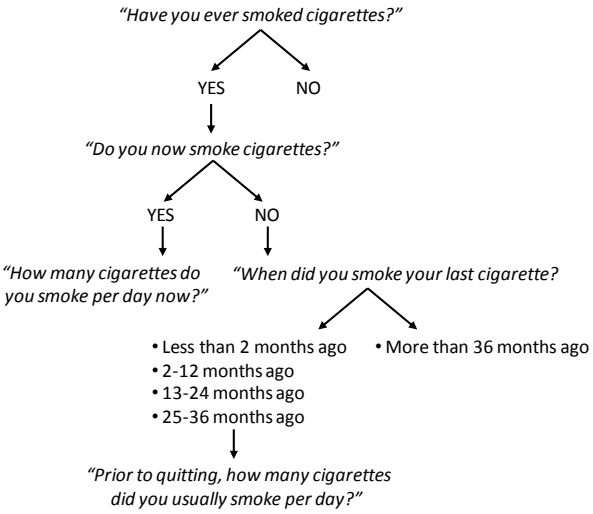
*Participants missing information on either question were classified as missing.

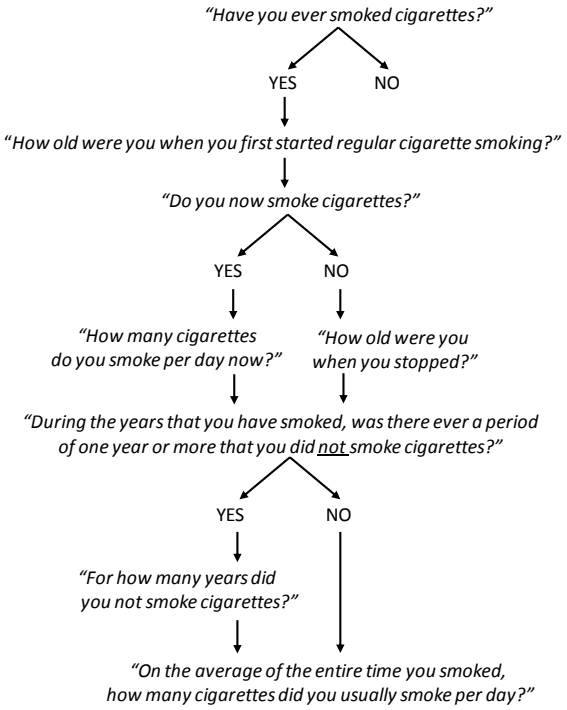
Table 2. Calculation of cigarette years of smoking at Visit 1

Smoking status	**Calculation**
Former	$cigarettes/day \times [(age_{quit} - age_{initiation}) - years\ quit]$
Current	$cigarettes/day \times [(age_{Visit\ 1} - age_{initiation}) - years\ quit]$

Figure 2. Smoking questionnaire items from Visit 2

Figure 3. Smoking questionnaire items from Visit 1





Additional independent variables: Demographic information was collected at Visit 1, including age (years), sex, self-reported race and education (highest grade or year of school completed). Race and education will be categorized according to standardized ARIC algorithms. Because of the small number of participants of Asian or Pacific Islander (N=33), or of American Indian or Alaskan Indian (N=10) race, analyses will be limited to African Americans and Whites. Education will be categorized as basic (≤ 11 years), intermediate (12-16 years), or advanced (≥ 17 years).

Drinking status (former, current, never) was collected at each study visit and adjudicated according to a standardized algorithm.

Disease covariates were collected at each study visit, and adjudicated according to standardized algorithms. Hypertension will be considered present based on a diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥140 mmHg, or use of hypertensive medications. Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes. A participant will be considered to have prevalent coronary heart disease (CHD) or prevalent stroke at Visit 2 if CHD or stroke, respectively, was reported by the participant at Visit 1, or CHD or stroke events were adjudicated by Visit 2. Apolipoprotein E (APOE) polymorphisms were sequenced by Taqman assay (Applied Biosystems, Foster City, CA). ABI 7900 and Sequence Detection System software (Applied Biosystems) were utilized for allele detection and genotype calling. APOE variants at codons 112 and 158 were detected separately during the assay, but later combined, resulting in six possible APOE genotypes: ε2/2, ε2/3, ε3/3, ε4/2, ε4/3, and

ε4/4.[13] The primary analysis will utilize an ordinal variable for number of ε4 alleles (0, 1 or 2).

Statistical analysis: Generalizing estimating equations[14] with an unstructured correlation matrix (to account for the correlation between repeated cognitive measures in an individual over time) and robust variance will be used to estimate the average difference in the estimated average trajectories of cognitive change over time by smoking status as reported at Visit 2. An interaction term between smoking status and time will be included in the models in order to test whether rates of cognitive change over time differ by smoking status. In addition to reporting the difference in rates of cognitive change by smoking status (both before and after Visit 4), we will also test the global hypothesis that the average 20-year trajectory of cognitive decline differs by smoking status. Time on study will be used as the time scale, with a two-piece linear spline with knot at Year 6 in order to allow for differential rates of cognitive change before and after Year 6. Year 6 was chosen a priori as the knot for the spline, as year 6 is the mean follow-up time for participants at Visit 4, and the largest gap in time between study visits was between Visits 4 and 5, resulting in sparse outcome data between Year 6 and the start of Visit 5. Alternative splines will be explored. Model fit will be assessed using diagnostic plots, including residual plots, and through statistics such asthe Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and likelihood ratio tests.

Because persons who smoke are more likely than nonsmokers to be lost to follow-up, and because we hypothesize that smokers are more likely to experience cognitive decline, we will evaluate the effect of potential selection bias through several sensitivity analyses, including the use of inverse probability attrition weights (as in Gottesman et al, ARIC MP 1982, submitted). Additionally, the Telephone Interview for Cognitive Status (TICS)[15] in persons who failed to be examined at visit 5 will be used to complete cognitive performance at Visit 5 in supplementary analyses to examine the influence of attrition of the primary estimates. Following recommendations from the ARIC NCS Analysis Workgroup, an additional alternative measurement sensitivity analysis will utilize information on the cognitive performance of participants who were lost to follow-up, but were subsequently hospitalized with a diagnosis of dementia in the medical records.

Because preliminary data analysis suggests a difference in the estimated effect of smoking on cognitive decline by race, the primary analyses will be stratified by race (White, African American). We will also test for a possible statistical interaction between smoking and APOE status on the estimated rate of cognitive change.

We will employ a two-step model building process for adjustment. Model 1 will incorporate demographic covariates, including age, sex, and ARIC clinic site. Interaction terms between these variables and time will also be included if shown to have statistical support for inclusion (e.g., significant p-value, improved model fit statistics) or based on a priori knowledge of the longitudinal relationship with the variable and cognitive decline. Based on previous analyses, we will include both a linear term and a quadratic spline for age, in order to allow for the non-linear association of age with cognitive

performance. Model 2 will include those covariates in Model 1, as well as additional risk factors for cognitive decline, including drinking status, prevalent (at Visit 2) coronary heart disease, prevalent (at Visit 2) stroke, diabetes, and hypertension.

References:

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15. Brandt J, Spencer M, Folstein MF. The telephone interview for cognitive status. *Neuropsychiatry, neuropsychology, and behavioral neurology*. 1988;1:111-117.

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? N/A
____ 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?
____ 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"? N/A
____ 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)?

MP1967. Adjusting for Measurement Error in Baseline Measures of Cognitive Function: The ARIC Neurocognitive Study. Wruck L et al.

MP1982. Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS. Gottesman R. et al.

MP2033. Cognitive domains in elderly ARIC blacks and whites. Rawlings et al.

MP2115. Sensitivity Analyses with Shared-Parameter Models for studying Cognitive Change in the presence of potentially Informative Dropout – the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. Griswold et al.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____Yes __ X __ No

11.b. If yes, is the proposal N/A
___ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _1999.01____ _____)

*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.