

## ARIC Manuscript Proposal # 1638

PC Reviewed: 4/13/10  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Burden of smoking-related morbidity and mortality and benefits associated with smoking cessation in a middle-aged US population: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** Impact of smoking and quitting

### 2. Writing Group:

Rachel Huxley, Pamela L. Lutsey, Suma Konety, Mark Woodward, Alvaro Alonso, Aaron R. Folsom, others welcome

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

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### 3. Timeline:

Data analysis – 3 months

First draft of the manuscript – 3 months

### 4. Rationale:

Despite decades of anti-smoking campaigns cigarette smoking remains the leading cause of morbidity and mortality in the United States with more than 430,000 deaths directly attributed to smoking occurring each year primarily from cardiovascular disease,

respiratory disease and cancer [1]. Currently, it is estimated that one in five adult Americans smokes (approximately 45 million people) of whom 80% smoke every day [1]. Importantly, 44% of current smokers had reported not to have smoked for one day in an attempt to quit the habit but had subsequently continued to smoke. Whilst the current prevalence represents a substantial reduction in smoking rates since its peak in the 1950's, there is evidence that the decline in smoking rates in the US has reached a plateau in recent years. For example, between 1997 and 2004 the prevalence of smoking fell by 15% to 20.9% but there has been no indication of any improvement since then [1].

The prevalence of smoking varies widely across the population and differs by race, gender, education level and other sociodemographic characteristics. For example, the prevalence among White and Black males is 23.1% and 24.8%, respectively [1] but lower in Black compared with White women (15.8 versus 19.8%) and is inversely associated with attained educational level [2]. A national health objective for 2010 is to reduce the prevalence of smoking in adults to less than 12% [3]. However, in order to achieve this reduction more information is required regarding both the hazards of smoking and the benefits of smoking cessation among different population sub-groups as well as the identification of those sociodemographic characteristics that are most frequently associated with smoking cessation [4].

For example, although data on the risks of smoking-related mortality are well known for men and women and for specific diseases, there are currently no published data specifically pertaining to African-Americans [1]. Moreover, a recent economic analysis of the costs of smoking in California indicate that African-Americans are more likely to die at younger ages from smoking-related diseases compared with other Californians: the years of potential life lost per death were 16.3 years versus 12.5 years in African Americans and other Californians, respectively [5]. The reasons for this mortality differential are unknown but may be due in part to greater absorption of nicotine and other chemicals per cigarette among Blacks, and also the greater exposure to secondhand smoke than in Whites. Such information is essential for the development of culturally specific smoking cessation programs and in targeting those individuals who may require more intensive interventions to quit smoking.

The ARIC study represents an ideal opportunity to study prospectively the aforementioned associations in both Whites and African-Americans and to investigate those characteristics that are associated with smoking cessation. Such information will help to inform on future smoking intervention strategies.

## **5. Main Hypothesis/Study Questions:**

The objectives of the proposal are five-fold and are as follows; separately for White and Black men and women we will estimate the:

- i. risk of smoking-related cardiovascular, respiratory and cancer morbidity and mortality
- ii. effect of age at initiation of smoking on outcomes

- iii. population attributable fraction for cardiovascular diseases, respiratory diseases and cancer and due to smoking
- iv. the benefits of smoking cessation for each of these outcomes both overall and by the duration of cessation (i.e.  $\leq 5$  yrs,  $5 - 10$  yrs,  $\geq 10$  yrs)
- v. investigation of the sociodemographic characteristics associated with quitting smoking

We hypothesize that the hazards and benefits association with smoking and cessation respectively differ between Whites and African-Americans and given the higher prevalence of smoking in African-Americans we hypothesize that the population attributable risks from smoking will be higher in African-Americans than Whites.

Given the amount of information that is expected to be generated from these analyses we may publish the findings in two separate manuscripts.

**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).**

We will assess the association of smoking and smoking cessation with morbidity and mortality from cardiovascular disease, respiratory disease and cancer using a cohort approach. Estimates of effect will be provided separately by gender and ethnic group.

*Exposure*

In addition to smoking status being measured during the four study visits, it was also recorded at yearly intervals via a telephone questionnaire. Hence, to exploit both the cross-sectional and longitudinal data available on smoking habit, an individuals' smoking status will be categorized in two ways:

**i. Baseline assessment:** Study participants will be grouped as 'current' smokers if they reported smoking at study baseline, 'former' smoker if they reported having quit and 'never' smoker if they reported having never smoked at baseline. For current and former smokers the number of cigarettes smoked per day (CPD) will be classified into three approximately equal sized groups:  $<15$ ,  $15-24$ , and  $> 25$  CPD. Information on age of initiation of smoking and age at quitting will also be obtained. Pack-years of smoking will be calculated by calculating the average number of cigarettes smoked per day multiplied by the years of smoking divided by 20. The number of years since quitting before baseline will be obtained by subtracting the age at quitting from baseline age.

**ii. Follow-up assessment:** Smoking status will be categorized into the following: never smoker, sustained former smoker (former smoker at baseline and throughout follow-up), newly quit, current smoker at baseline and former smoker at some point during follow-up) and current smoker.

### *Outcome*

Incident cases and deaths from cardiovascular disease and total cancer identified in the follow-up through the end of 2007 will be included using ARIC adjudicated events for CHD, stroke (total, ischemic, and hemorrhagic), heart failure, total CVD, and CV mortality, and discharge codes from hospitalizations and death certificates for other outcomes: Outcomes will be classified according to the ninth revision of the International Classification of Diseases (ICD 9 and 10—ICD9 codes shown); cancer (ICD 140 – 239, except 173 (non-malignant melanoma)); and respiratory disease (490 – 496).

### *Exclusions*

Study participants will be excluded from the analysis if they fulfill at least one of the following criteria:

- ethnicity other than Black or White
- missing data on smoking status at any of the study visits for which they were able to attend
- prevalent cardiovascular disease, respiratory disease or cancer at study baseline

### *Statistical analysis*

Aim 1: Cox proportional hazard models that are adjusted for age, gender (where appropriate), race (where appropriate), BMI, study site, education, income and associated cardiovascular co-morbidities including hypertension, type-2 diabetes and dyslipidemia will be used to derive the hazard ratios, and corresponding 95% confidence intervals, for death for ‘former smokers’ as compared with ‘current’ and for ‘current’ as compared with ‘never smoked’ at study baseline. Hazard ratios for dose-response of cigarettes per day will also be estimated, taking ‘never-smoked’ as the reference group. Confidence intervals will be calculated using the method of floating absolute risk [6]. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and by inspection of the log (-log[survival function]) curves.

Aim 2: To examine the impact of age of smoking initiation we will stratify according to the following age-groups corresponding to age of smoking initiation: <19 yrs, 20 – 25 yrs, 26 + yrs. Cox proportional hazard models that are adjusted for pack-years of smoking in addition to those variables given in Aim 1 will be used to derive the hazard ratios, and corresponding 95% confidence intervals, for death for ‘former smokers’ as compared with ‘current’ and for ‘current’ as compared with ‘never smoked’ at study baseline.

Aim 3: Population attributable fractions for cardiovascular disease, respiratory disease and cancer due to smoking will be computed according to the following formula [9]:

$$PAF = \sum_{i=0}^k pd_i \left( \frac{RR_i - 1}{RR_i} \right)$$

where  $pd_i$  is the proportion of cases falling into  $i$ th exposure level and  $RR_i$  is the relative risk comparing  $i$ th exposure level with unexposed group ( $i=0$ ).

Aim 4: To estimate the benefits associated with sustained smoking cessation Cox proportional hazard models, adjusted for age, gender (where appropriate), race (where appropriate), study site, education and income will be used to derive the hazard ratios, and corresponding 95% confidence intervals, for combined fatal and non-fatal cardiovascular, respiratory and cancer outcomes for ‘former smokers’ at baseline as compared with ‘current smokers’. We will also estimate the benefits associated with quitting smoking during follow-up by examining the risks in those individuals who reported being a current smoker at baseline but a ‘former’ smoker at any of the visits or via the annual follow-up calls that occurred prior to the penultimate study visit. Smoking cessation will be modeled as a time-dependent covariate. Data will be censored at the study visit prior to the event to minimize the impact that individuals who quit smoking did so for reasons of ill-health. Further analyses will examine the relationship between duration of smoking cessation with outcomes by stratifying into three groups.

Aim 5: To investigate the relationship between sociodemographic characteristics at baseline with sustained smoking cessation, logistic regression models that are adjusted for sex, race, age and ARIC study centre will be used. Adjusted means and mean differences and corresponding 95% confidence intervals comparing sustained quitters with current smokers will be derived using pooled logistic regression models. Test of significance will be performed and statistical significance will be set at  $p = 0.05$ .

#### *Limitations*

In our primary analysis, we will be reliant upon self-reported smoking habits as there is no biochemical measure of smoking status in ARIC. Hence, the main concern is that misclassification of exposure may exist with some individuals being classified incorrectly as never-smokers or former-smokers which may dilute the magnitude of the observed associations.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**    ☒ Yes    ☐ 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    ☒ 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

8.c. If yes, is the author aware that the participants with RES\_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

☐ 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.csc.unc.edu/ARIC/search.php>

☒ 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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☐ Yes ☒ No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number\* 2008.09)

☐ 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.csc.unc.edu/aric/forms/>

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.

### References

1. Center for Disease Control and Prevention. Cigarette smoking among adults---United States, 2004. MMWR 2007;56:1157-61.
2. Center for Disease Control and Prevention. Cigarette Smoking Among Adults and Trends in Smoking Cessation—United States. JAMA 2009; 302: 2651 - 2654.
3. US Department of Health and Human Services. Healthy people 2010 (conference ed, in 2 vols). Washington, DC: US Department of Health and Human Services; 2000. Available at <http://www.health.gov/healthypeople>.
4. Institute of Medicine. Ending the tobacco problem: a blueprint for the nation. Washington, DC: The National Academies Press; 2007.

5. Max W, Sung HY, Tucker LY, Stark B. The disproportionate cost of smoking for African Americans in California. *Am J Public Health*. 2010;100:152-8
6. Woodward M. *Epidemiology: study design and data analysis*. 2nd ed. Boca Raton: Chapman and Hall/CRC, 2004.