ARIC Manuscript Proposal # 3217

PC Reviewed:  8/14/18       Status: _____       Priority: 2
SC Reviewed: _________       Status: _____       Priority: _____

1.a. Full Title:
Long-term respiratory effects of cigar and pipe use in the NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters):
Pipe/cigar use and the lung

2. Writing Group:
Writing group members:
Tiffany R. Sanchez, Columbia University, New York, NY, USA, trs2111@cumc.columbia.edu
Pallavi Balte, Columbia University, New York, NY, USA, ppb2119@cumc.columbia.edu
Surya Bhatt, University of Alabama at Birmingham, Birmingham, AL, USA, sbhatt@uabmc.edu
Pat Cassano, Cornell University, Ithaca, NY, USA, pac6@cornell.edu
David Couper, University of North Carolina, Chapel Hill, NC, USA, david_couper@unc.edu
Pam Lutsey, University of Minnesota, Minneapolis, MN, USA, lutsey@umn.edu
David Jacobs, University of Minnesota, Minneapolis, MN, USA, jacob004@umn.edu
Ravi Kalhan, Northwestern University, Chicago, IL, USA, RKalhan@nm.org
Richard Kronmal, University of Washington, Seattle, WA, USA, kronmal@u.washington.edu
Robert Kaplan, Albert Einstein College of Medicine, New York, NY, USA, Robert.kaplan@einstein.yu.edu
Laura Loehr, University of North Carolina, Chapel Hill, NC, USA, lloehr@email.unc.edu
Stephanie London, NIH/NIEHS, Research Triangle Park, NC, USA, london2@niehs.nih.gov
Anne Newman, University of Pittsburgh, Pittsburgh, PA, USA, NewmanA@edc.pitt.edu
George O’Connor, Boston University, Boston, MA, USA, goconnor@bu.edu
Joseph Schwartz, Columbia University, New York, NY, 10032, jes2226@cumc.columbia.edu
Wendy White, Tougaloo College, Tougaloo, MS, USA, wendywhite2001@yahoo.com
Sachin Yende, University of Pittsburgh, Pittsburgh, PA, USA, Yendes@upmc.edu
Neal Freedman, National Cancer Institute, Rockville, MD, USA, freedmanne@mail.nih.gov
Ana Navas-Acien, Columbia University, New York, NY, USA, an2737@cumc.columbia.edu
Elizabeth Oelsner, Columbia University, New York, NY, USA, eco7@cumc.columbia.edu

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

First author: Tiffany R. Sanchez
Address:  722 West 168 Street
          Suite 1105
          New York, NY 10032
Phone: cell: (505)688-0191   Fax: n/a
E-mail: trs2111@cumc.columbia.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: Pamela Lutsey  
Address: 1300 S 2nd St  
300 West Bank Office Building  
Minneapolis, MN 55454  
Phone: 612-624-5812 Fax: n/a  
E-mail: lutsey@umn.edu

3. **Timeline:**  
We plan to submit an abstract for 2019 ATS (abstract deadline November 2018). Manuscript by March 2019.

4. **Rationale:**  
Active smoking is an established cause of chronic respiratory disease.\(^1\) While less common than cigarette use, cigar and pipe use in the U.S. is on the rise. From 2000 to 2015, cigar and pipe tobacco consumption increased by 180% and 556%, respectively, while total cigarette consumption decreased by 39%.\(^2\) In 2016, an estimated 12.3 million people in the U.S. (4.6%) aged 12+ were current cigar smokers and 2.3 million (0.8%) were current pipe smokers.\(^3\) While health risks for cigarette smokers in the U.S. have been extensively studied, estimates for noncigarette tobacco products, such as cigars and pipes, are more limited, particularly over the past two decades\(^4\). Given the changes in cigar and pipe use patterns in the US, studies are needed to understand the contemporary health risks for noncigarette tobacco use. A recent publication in the National Longitudinal Mortality study found that current or former exclusive cigar or pipe use was associated with an elevated risk of dying from a tobacco-related cancer.\(^5\) A major limitation of available research is the relatively limited sample sizes for lung disease morbidity and limited confounder control in assessing the association between cigar and pipe smoking with lung disease.

Research is needed to elucidate the relationship of noncigarette tobacco use, including distinguishing primary from secondary cigar/pipe smokers, with subclinical and clinical respiratory health effects leveraging data from diverse populations across the US and controlling for potential confounding variables.

5. **Main Hypothesis/Study Questions:**  
We hypothesize that noncigarette tobacco use is associated with adverse respiratory outcomes, independently of cigarette smoking, and that examining cigar and pipe use in the NHLBI Pooled Cohorts Study will allow us to explore this relationship in greater depth.

1) What is the association between pipe and cigar use (measured as current use, ever use, number smoked per week, and years of use) and lung function and changes in lung function over time, as measured by forced expiratory volume in 1 second (FEV\(_1\)), forced vital capacity (FVC) and FEV1/FVC on spirometry?  
   **Hypothesis:** Cigar/pipe use is associated with lower lung function and accelerated lung function decline.

2) What is the association between pipe and cigar use and respiratory-related hospitalizations and mortality?  
   **Hypothesis:** Cigar/pipe use is associated with greater risk of respiratory-related hospitalizations and mortality.

3) What is the association between pipe and cigar use and self-reported respiratory symptoms and physician diagnosed respiratory disease.
Hypothesis: Cigar/pipe use is associated with increased report of respiratory symptoms and respiratory disease.

4) Explore the consistency of the association between pipe and cigar use and lung outcomes by sex, age, race/ethnicity, education levels, and former/current smoking status.

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).

Sample: We propose to use cohorts with information on noncigarette tobacco use, spirometry, clinical, and events data that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study:

1. Atherosclerosis Risk in Communities (ARIC) Study
2. Coronary Artery Risk Development in Young Adults (CARDIA) Study
3. Cardiovascular Health Study (CHS)
4. Framingham Heart Study (FHS)
5. Health Aging and Body Composition (HABC) Study
6. Hispanic Community Health Study/Study of Latinos (HCHS/SOL)
7. Multiethnic Study of Atherosclerosis (MESA)
8. Strong Heart (SH) Study

The total pooled sample includes 58,496 adults with at least one valid spirometry exam, all of whom have follow-up for all-cause mortality and respiratory mortality. Four of the included cohorts have additional follow-up data on CLRD hospitalizations. Most of the required data have already been harmonized and pooled at Columbia University, where the proposed analyses will be performed.

Exposure: Self-reported pipe/cigar use: We plan to evaluate self-reported pipe and cigar use using relevant questionnaire data available in 8 of the 9 NHLBI pooled cohort studies (1 cohort study did not include question on pipe/cigar use). We proposed the following primary exposure variables: 1) Current use reported at baseline. This information is available in 7 of 8 cohort studies in a relatively consistent manner. For CHS and HABC, the question was asked about combined pipe and cigar use. 2) Ever use reported at baseline. This information is available in 6 of 8 in a relatively consistent manner. It is not available for CHS or FHS. For HABC, the question was asked about combined pipe and cigar use. 3) Number smoked per week. This information is available in ARIC, CARDIA, FHS and MESA. In FHS and MESA, the questions ask about number per day. We will convert this variable into number per week. 4) Years of use. This information is available in ARIC, HABC and MESA. Smokeless tobacco: Only 4 cohorts included questions on smokeless tobacco use. If the sample size is large enough, we will also run analyses for smokeless tobacco. Cotinine: We will use cotinine levels to validate self-reported current pipe/cigar use in non-cigarette smokers, to confirm that those who claim to use pipe/cigars have elevated cotinine levels compared to non-tobacco users. Cotinine levels are available in CARDIA and MESA.

Table 1. Noncigarette tobacco-related variables available by cohort

<table>
<thead>
<tr>
<th>Current use</th>
<th>Ever use</th>
<th># Smoked/week</th>
<th>Years used</th>
<th>Cotinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigar</td>
<td>Pipe</td>
<td>Smokeless</td>
<td>Cigar</td>
<td>Pipe</td>
</tr>
<tr>
<td>ARIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CARDIA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CHS</td>
<td>Pipe/cigar</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FHS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HABC</td>
<td>Pipe/cigar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCHS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MESA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Primary endpoint(s)
• Lung function: FEV₁, FVC and FEV₁/FVC
  o Cross-sectional lung function
  o Rate of decline in lung function
  o Rate of incident airflow limitation, defined as FEV1/FVC < lower limit of normal (LLN)
  o Rate of incident restrictive ventilatory pattern, defined as FVC<LLN and FEV1/FVC > LLN
• Composite of first respiratory hospitalization and respiratory mortality
  o Respiratory hospitalization: hospitalizations adjudicated or administratively coded as caused by COPD, chronic bronchitis, or emphysema (ICD-9 490-492, 496, 506.4; ICD-10 J40-J44), pneumonia (ICD-9 480-487, ICD-10 J18), or interstitial lung disease (ICD-9 516, ICD-10 J84)
  o Respiratory mortality: deaths adjudicated or administratively coded as caused by respiratory disease (ICD 9 and ICD-10 codes as specified above) Events will be sub-classified by code position (primary diagnosis code or underlying cause of death versus any code position)

Secondary endpoints
• Self-reported respiratory symptoms and physician diagnosed respiratory disease
  o Incidence of self-reported respiratory symptoms including dyspnea, wheeze, cough, and modified Medical Research Council (mMRC) chronic bronchitis
  o Incidence of self-reported physician diagnosis of COPD or asthma
• All-cause mortality

Additional variables:
• Socio-demographics: age, sex, race/ethnicity, educational attainment, alcohol use, physical activity
• Anthropometrics: height, weight, BMI
• Medical history: history of COPD, asthma, coronary artery disease, diabetes, hypertension, lung cancer
• Medications: inhalers, oral steroids
• Cigarette smoking history: pack-years, cigarettes per day smoked, years smoked, age started, and years since quitting

Proposed Analysis Plan
We will examine associations for pipe or cigar use separately and combined. If there are a sufficient number of exclusive cigar and pipe users, our primary analyses will be conducted among never cigarette smokers. We will also conduct analyses of cigar/pipe use separately for current cigarette smokers and former cigarette smokers to evaluate the consistency of the findings across groups.

We will describe baseline demographic features associated with pipe/cigar use vs. no pipe/cigar use, including: age at enrollment, gender, ethnicity/race, center, education, body mass index, and diabetes. Initial univariate comparisons will be made using Chi-Square or Fisher’s exact test for categorical data, and a Student’s t-test or Wilcoxon rank sum test for continuous variables, as appropriate. The four dimensions of pipe/cigar use to be examined in the descriptive analyses as well as in the regression models will include 1) Current use reported at baseline. 2) Ever use reported at baseline. 3) Baseline pipe/cigar use intensity (number smoked/week). 4) Years of use reported at baseline.

The following models will be sequentially adjusted for potential confounders and precision variables, such as age, birth-year, sex, race/ethnicity, study site, education, alcohol intake, height, weight, prior physician diagnosis of asthma or COPD. For analyses including former or current cigarette smokers, we will further adjust for smoking history using variables such as pack-years, cigarettes per day smoked, years smoked, age started, and years since quitting (for former smokers).
Research question 1: We will examine cross-sectional and longitudinal associations between our pipe/cigar use variables (to be run in separate models) and lung function (FEV1, FVC and FEV1/FVC) using linear mixed-models with cohort-specific unstructured covariance matrices. We will report both the baseline difference and the annual change in lung function measures comparing increasing number smoked/week, years used, or exposed vs. unexposed. We will conduct additional analyses stratifying by presence/absence of spirometry abnormalities and/or clinical lung disease and examining rate of incident spirometry abnormalities (air flow limitation and restrictive ventilatory pattern) using Cox proportional hazard models. Time-to-event will be biological age at event, with left truncation at age at study entry. Cohort will be included as a stratum term.

Research question 2: We will examine associations between pipe/cigar use and respiratory-related hospitalizations and clinical endpoints (e.g. respiratory hospitalization, death) using Cox proportional hazards models as described above. In secondary analysis, we will also perform competing risks analysis and will examine associations between pipe/cigar use and all-cause mortality.

Research question 3: We will examine associations between pipe/cigar use and self-reported respiratory symptoms and physician diagnosed respiratory disease using mixed effects logistic regression accounting for cohort study clustering.

Research question 4: We will assess potential effect modification by sex, quartiles of age, race/ethnicity, education levels and cigarette smoking status.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ 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? __X__ 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”? ____ 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/mantrack/maintain/search/dtSearch.html

    ___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)?

    N/A
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
   ___  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)* __________   __________ __________)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.