ARIC Manuscript Proposal #3209

1.a. Full Title:
Long-term respiratory effects of secondhand smoke exposure among non-smokers in the NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters):
Secondhand smoke and the lung

2. Writing Group:
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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]

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

4. Rationale:  
Chronic obstructive pulmonary disease ranks as the 4th leading cause of death worldwide (The US Burden of Disease Collaborators, 2018). In the United States, the mortality rate for chronic respiratory disease has continued to increase between 1980 and 2014 (Dwyer-Lindgren et al., 2017). While active smoking is an established cause of chronic respiratory disease (U.S. Department of Health and Human Services, 2010), the 2006 Surgeon General’s report on The Involuntary Consequences of Tobacco Smoke concluded that there is plausible but not sufficient evidence to infer whether the association between secondhand tobacco smoke (SHS) exposure and respiratory disease is causal (US Department of Health and Human Services, 2006). Evidence for SHS exposure and lung disease continues to grow. In a cohort of Singaporeans of Chinese ethnicity, living with smokers in childhood was related to chronic dry cough in adulthood (David et al., 2005). In the multi-ethnic study of atherosclerosis (MESA) cohort, self-reported childhood SHS exposure among non-smokers was associated with the development of emphysema during adulthood (Lovasi et al., 2009). Recently, the 2014 Surgeon General’s report causally linked SHS exposure to respiratory symptoms and lower respiratory illness in children (United States Department of Health and Human Services, 2014). A major limitation of available research in adults is the relatively limited sample size and lack of power to assess the association between SHS exposure, including current exposure, with lung disease in adulthood. Globally, it is estimated that at least a third of non-smoking adults are exposed to SHS (Öberg et al., 2011). In the United States, around 25% of the population remains exposed to SHS, disproportionately affecting communities with low income (Homa et al., 2015). Because of the large proportion of the population exposed, even a relatively small effect of SHS smoke on lung health could have a major public health impact in the population. Research is needed to elucidate the relationship of SHS exposure among non-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 SHS exposure is associated with adverse respiratory outcomes and that examining SHS exposure in the NHLBI Pooled Cohorts Study will allow us to explore the following:

1) Describe SHS exposure (measured as baseline hours per week of SHS exposure, living with at least one smoker, living with a smoker in early life/childhood, and urinary cotinine levels) and other potential risk factors (education level) across multiple race/ethnic groups in the PCS populations.

2) Examine the associations between SHS exposure, measured as above, among non-smokers with the following respiratory endpoints:
a) Examine the associations between SHS exposure among non-smokers and lung function and changes in lung function over time, as measured by forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC on spirometry.

b) Examine the associations between SHS exposure among non-smokers and respiratory-related hospitalizations and mortality.

c) Examine the associations between SHS exposure among non-smokers and self-reported respiratory symptoms and physician diagnosed respiratory disease.

3) Explore the consistency of the association between SHS and lung outcomes by sex, age, race/ethnicity, education levels, former/current smoking status, smoking prevalence in the city/state, and smoke-free legislation in the city/state.

The study provides an extraordinary opportunity to understand the effects of SHS exposure on pulmonary diseases and will help define the dose-response relationship between SHS and lung function in a large and diverse sample of the US population.

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 secondhand smoke exposure information, 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. Hispanic Community Health Study/Study of Latinos (HCHS/SOL)
6. Multiethnic Study of Atherosclerosis (MESA)
7. 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 secondhand smoke exposure
We plan to evaluate self-reported SHS exposure using questions relating to secondhand tobacco smoke collected via questionnaires in 7 of the 9 NHLBI pooled cohort studies (2 cohort studies did not include question on SHS exposure). We proposed the following primary SHS exposure variables: 1) Hours/week of SHS exposure reported at baseline. This information is available in 6 of 7 cohort studies in relatively consistent manner. In the Strong Heart Study, the question was about hours per day of SHS exposure. We will convert this variable into hours per week. In the CHS study, information on hours per week or day of SHS was not collected. 2) Living with at least one smoker. This information is available in CHS, FHS, HCHS and MESA. 3) Living with a smoker in early life/childhood. This information is available in CHS, HCHS and MESA.

Urinary cotinine
As a secondary marker of exposure, we will use urinary cotinine to validate self-reported secondhand smoke exposure. Cotinine levels are available in CARDIA and MESA.

**Table 1. SHS-related variables available by cohort**

<table>
<thead>
<tr>
<th>Secondhand smoke exposure variables</th>
<th>1) Hours/week of SHS exposure</th>
<th>2) Living with ≥1 smoker</th>
<th>3) Living with a smoker in early life/childhood</th>
<th>4) Urinary cotinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CARDIA</td>
<td>X</td>
<td></td>
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<td>X</td>
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<tr>
<td>CHS</td>
<td>X</td>
<td>X</td>
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<tr>
<td>FHS</td>
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<td>HCHS</td>
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<td>X</td>
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<tr>
<td>MESA</td>
<td>X</td>
<td>X</td>
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<tr>
<td>SH</td>
<td>X</td>
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</tbody>
</table>

**Endpoints:**

**Primary endpoint(s)**
- Lung function: FEV₁, FVC and FEV₁/FVC
  - Cross-sectional lung function
  - Rate of decline in lung function
  - Rate of incident airflow limitation, defined as FEV₁/FVC < lower limit of normal (LLN)
  - Rate of incident restrictive ventilatory pattern, defined as FVC<LLN and FEV₁/FVC > LLN
- Composite of first respiratory hospitalization and respiratory mortality
  - 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)
  - 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
  - Incidence of self-reported respiratory symptoms including dyspnea, wheeze, cough, and modified Medical Research Council (mMRC) chronic bronchitis
  - Incidence of self-reported physician diagnosis of COPD or asthma
- All-cause mortality

**Additional variables:**
- **Socio-demographics:** age, sex, race/ethnicity, educational attainment, country of birth
- **Anthropometrics:** height, weight, BMI
- **Medical history:** history of COPD, asthma, coronary artery disease, diabetes, hypertension
- **Medications:** inhalers, oral steroids
- **Contextual factors:** smoke-free legislation city/state (Center for Disease Control and Prevention, 2018), smoking prevalence in the city/state (Center for Disease Control and Prevention, 2016)

**Proposed Analysis Plan**
All the analyses will be conducted among current non-smokers, including never smokers and former smokers. Sensitivity analyses by smoking status (never/former) will be conducted to evaluate the consistency of the findings across both groups.

**Research question 1**
We will describe baseline demographic features associated with SHS exposure vs. no SHS exposure among non-smoking individuals, including: age at enrollment, gender, ethnicity/race, center, education, state smoking legislation, body mass index, diabetes and air pollution. 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 SHS exposure to be examined in the descriptive analyses as well as in the regression models will include 1) baseline SHS exposure intensity (hours/week), 2) living with a smoker as an adult, 3) living with a smoker as a child and 4) urinary cotinine.

**Research question 2**
We will examine cross-sectional and longitudinal associations between our SHS exposure 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 hours of SHS/week 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.

We will examine associations between SHS exposure 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 SHS exposure and all-cause mortality.

We will examine associations between SHS exposure and self-reported respiratory symptoms and physician diagnosed respiratory disease using mixed effects logistic regression accounting for cohort study clustering with adjustment for the appropriate covariates.

All models will be sequentially adjusted for potential confounders and precision variables, such as age, birth-year, sex, race/ethnicity, study site, education, height, weight, smoking status (never/former), pack-years, prior physician diagnosis of asthma or COPD.

**Research question 3**
We will assess potential effect modification by sex, race and quartiles of age, race/ethnicity, education levels, former/current smoking status, smoking prevalence in the city/state, and smoke-free legislation in the city/state. For smoke-free legislation, we will explore categorizing cities/states based on 1) 100% smoke-free legislation in workplaces, restaurants and bars; 2) some smoke-free legislation in workplaces, restaurants or bars; or 3) no smoke-free legislation and will account for changes in legislation over time.

At the conclusion of these analyses, we will be able to characterize the long-term pulmonary effects associated with SHS exposure.
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

12.a. 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://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.