

ARIC Manuscript Proposal # 3067

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1.a. Full Title: The prognostic significance of simple chronic bronchitis in the general population: the NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters): Simple chronic bronchitis in the general population

2. Writing Group:

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

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3. Timeline:

Data from all cohorts have already been obtained, harmonized, and pooled under the auspices of approved paper/ancillary study proposals relating to specific biological hypotheses that are to be tested in this data. We hope to submit an abstract on simple chronic bronchitis in the general population for the 2018 American Thoracic Society Conference and to prepare the relevant manuscript in spring 2018.

4. Rationale:

Chronic obstructive pulmonary disease (COPD) is the third leading cause-of-death worldwide (1). Despite large reductions in the prevalence and intensity of smoking over the last 50 years, age-adjusted COPD mortality has remained high, and most cases of incident COPD occur now in former smokers and persons who have never smoked (2-7). Although smoking, occupational and environmental exposures, gene variants, and early life factors have been identified as risk factors for COPD (8), researchers have acknowledged considerable heterogeneity in the clinical presentation and progression of COPD (9, 10). Hence, there is an ongoing effort to define specific COPD endotypes that would allow for improved risk stratification and targeted therapies for both primary and secondary prevention (11).

Chronic bronchitis (CB), which is characterized by cough and sputum production that may be assessed by the modified British Medical Research Council (mMRC) questionnaire (12), occurs frequently in COPD (13), but it is also a common condition in persons with preserved lung function, among whom it is often called “simple chronic bronchitis” (SCB) (14). The prognostic significance of SCB remains controversial. Once considered as significant step in development of airflow limitation, research interest in SCB diminished over the years due to lack of association between SCB and decline in FEV1 demonstrated by several studies (7, 14-19). However, more recent studies have shown an association between SCB and increased COPD exacerbations (20, 21), decline in lung function (9, 22), more frequent hospitalizations (22), and higher all-cause mortality and mortality associated with COPD (23, 24). In smokers with preserved lung function, the presence of CB symptoms has recently been correlated with poor clinical outcomes (25).

In the context of conflicting results from prior studies that were limited to small, case-control, heavy smoking, and/or European samples – as well as compelling recent findings suggesting that airway mucin could be a therapeutic target in CB (26) – we therefore propose to test the associations between SCB and prospective lung function and clinical outcomes in a large, multiethnic, US population-based sample. Using data that were harmonized and pooled across nine cohorts in the NHLBI Pooled Cohorts Study (27), we will furthermore conduct stratified analyses according to age, sex, race/ethnicity, smoking history, and cardiovascular comorbidities.

5. Main Hypothesis/Study Questions:

1. Is SCB associated with low lung volumes, lung function decline, and incident airflow limitation?
2. Is SCB associated with incident clinical events, such as severe obstructive lung events (SOLE); lung cancer; pneumonia; myocardial infarction; and all-cause mortality?
3. Are these associations modified by age, sex, race/ethnicity, smoking history, and cardiovascular comorbidities?
4. Do these associations differ for SCB versus CB with airflow limitation, or “obstructive chronic bronchitis” (OCB)?

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 data from nine cohorts that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study (27):

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 (Health ABC) Study
6. Hispanic Community Health Study/ Study of Latinos (HCHS/SOL)
7. Jackson Heart Study (JHS)
8. Multiethnic Study of Atherosclerosis (MESA)
9. Strong Heart Study (SHS)

For the primary analyses of SCB, we will exclude all participants who, at the time of CB classification, were characterized by:

- Prevalent airflow limitation, defined as $FEV1/FVC < \text{lower limit of normal (LLN)}$ (28).
- Prevalent chronic lower respiratory disease (CLRD), defined by self-reported COPD, chronic bronchitis, emphysema, or asthma, or inhaler therapy.

This will leave 44,104 participants, with 83,072 valid spirometry measures, and 359,916 person-years of follow-up for clinical events. The composition of the sample will be 42% European

Americans (EAs), 22% African-Americans (AAs), 31% Hispanics, 4% American Indians (AIs), 1% Asian Americans (AAs), 53% never-smokers, and 19% current smokers.

Participants with airflow limitation and/or prevalent CLRD at the time of CB classification (N=11,233) will be used for secondary analyses of OCB.

Exposure

SCB will be defined by mMRC criteria as the presence of cough and sputum production for at least three months of two consecutive years (12). In five cohorts (N=36,883), we will directly apply this definition. In three cohorts (N=7,221), we will define SCB as chronic cough with sputum for three months. mMRC and/or chronic cough were assessed at baseline in six cohorts including ARIC, CARDIA, CHS, HCHS/SOL AND JHS. For FHS-O, MESA and SHS CB was assessed at subsequent cohort exams.

For secondary analyses, OCB will be defined by the same criteria as SCB, but among participants with airflow limitation and/or prevalent CLRD at the time of CB classification.

Alternative definitions for CB (e.g., SGRQ) will be applied, depending on data availability, in sensitivity analyses (29).

Endpoints

- Lung function
 - Initial and annual decline in FEV1, FVC, FEV1/FVC, using spirometry data that has been validated, harmonized, and pooled by the NHLBI Pooled Cohorts Study (27).
 - Incident airflow limitation.
- Incident clinical events
 - Lung disease: classified by adjudication and/or administrative definitions as applied to prospectively ascertained hospitalizations and mortality.
 - Incident CLRD: first hospitalization or death adjudicated as primarily or secondarily attributable to CLRD, or, if adjudication was lacking, those with CLRD listed in any ICD code position. In prior work in MESA and HCHS/SOL, 82% of such administratively-defined events were physician-confirmed as evidence of clinical CLRD (30).
 - Incident SOLE: first hospitalization or death adjudicated as primarily attributable to CLRD or, if adjudication was lacking, with CLRD coded as the primary discharge diagnosis or the underlying cause-of-death. This administrative definition was previously found to have a positive predictive value of 97% for physician-adjudicated CLRD exacerbations (30).
 - Incident lung cancer: first hospitalization or death adjudicated as primarily or secondarily attributable to lung cancer (31).
 - Incident pneumonia: first hospitalization or death adjudicated as primarily attributable to pneumonia.

- Heart disease: classified by adjudication of prospectively ascertained hospitalizations and mortality, and defined among participants without prevalent cardiovascular disease at baseline.
 - Incident coronary heart disease: adjudication as physician-adjudicated MI, resuscitated cardiac arrest, or CHD death.
 - Incident congestive heart failure: adjudicated, where available.
- All-cause mortality

Covariates

- Socio-demographics: age, sex, race/ethnicity, educational attainment
- Anthropometric: height, weight, BMI
- Smoking: smoking status, cigarettes per day, pack-years, pipe use, cigar use
- Medical history: medical comorbidities and medications (e.g., steroids, HRT, anti-hypertensives, statins, antiplatelets)
- Other exposures: occupational history/exposures, air pollution exposure (as available)

Of note, data from all cohorts have already been obtained, harmonized, and pooled under the auspices of approved paper/ancillary study proposals relating to other specific biological hypotheses.

Analysis plan and methods

- Participants characteristics will be tabulated by SCB status as well as by cohort.
- Associations between SCB and longitudinal lung function will be assessed using generalized estimating equations and generalized linear mixed models to characterize population mean changes in lung function over time. In the pooled data, we will use a cohort-specific unstructured covariance matrix, akin to a “stratified MANOVA” approach.
- Associations between SCB and incident airflow limitation and incident clinical events will be analyzed via survival models with time-to-event defined as biological age at event, and left-truncation for age at study entry. For significantly associated endpoints, the prognostic significance of CB will be assessed via logistic regression (i.e., ROC curves, c-statistics) and the net reclassification index (32).
- Models will be sequentially adjusted for covariates, including time-varying height, weight, and smoking status.
- Effect modification by age, sex, race/ethnicity, smoking history, and cardiovascular comorbidities will be assessed by interaction terms and in stratified models.
- Sensitivity analyses will be performed to assess the impact of using alternative definitions of CB.
- In addition to complete case analysis, alternative strategies to address missing data, such as inverse-probability weighting and multiple imputation, will be explored.
- In secondary analyses, models will be repeated with OCB as the exposure among participants with prevalent airflow limitation and/or clinical CLRD, so that results for SCB and OCB can be compared. Furthermore, pooled analyses will also be performed in the total NHLBI Pooled Cohorts sample to test the main effects of chronic bronchitis and presence/absence of

concomitant airflow limitation, as well as their multiplicative interaction term, in order to assess for statistical evidence of effect measure modification.

Statistical analyses will be performed in R or SAS, Version 9.4.

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 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 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.csc.c.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)?

The authorship group for this proposal has several approved proposals that test non-overlapping, specific biological hypotheses in the harmonized and pooled data (AS 2013.04, 2014.41, 2016.09).

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* _____)

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.c.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.csc.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes No.