ARIC Manuscript Proposal #3846

PC Reviewed: 5/11/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Assessment of Diagnostic Criteria of Early COPD: NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters):
Early COPD

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

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3. Timeline: Analysis 6 months, manuscript preparation 6 months, totaling 12 months after approval.

4. Rationale:

Chronic obstructive pulmonary disease (COPD) affects over 29 million people and is the 4th leading cause of death in the United States.[1,2] The disease develops slowly over many years and is typically diagnosed when patients are over 60 years old and have substantial airflow obstruction, making therapies less effective.[3,4] Because of this, experts have proposed to shift the focus to detecting COPD among individuals <50 years of age and coined the term Early COPD.[5-8] The proposed definition criteria of Early COPD are the following: Required: <50 yr. of age and ≥10 pack-years of smoking history. Others: 1) FEV1/FVC below the lower limit of normal (LLN); 2) Compatible computed tomography abnormalities (visual emphysema, air trapping, or bronchial thickening graded mild or worse); and 3) Evidence of accelerated FEV1 decline (>60 ml/yr). However, the proposed definition has not been formally examined and lacks respiratory symptoms, even though young adults who suffer from respiratory symptoms are at higher risk of developing COPD later.[9] To examine the proposed Early COPD definition, we will estimate longitudinal associations of its diagnostic criteria (e.g., pack years of smoking, low FEV1/FVC ratio, and accelerated FEV1 decline) with respiratory endpoints, including COPD-related hospitalization and mortality. We will also examine whether the spirometry components of the Early COPD definition predict COPD-related outcomes in participants with lesser or no smoking history. In addition, we will examine whether adding respiratory symptoms provides further information to identify individuals at higher risk of COPD-related hospitalization and mortality.

We will assess the proposed definition of Early COPD in over 20,000 participants who were less than 50 years old at time of baseline spirometry and have respiratory events followed-up in the NHLBI Pooled Cohorts Study.[10] This assessment will allow to validate the proposed definition of Early COPD and

identify which diagnostic criteria relate to relevant respiratory endpoints. Ultimately, this analysis will provide a foundation to a validated definition of Early COPD that may be used in future prospective studies. We will not evaluate the imaging criterion, since the NHLBI Pooled Cohort has not yet harmonized data on lung imaging.

The NHLBI Pooled Cohorts Study is a source to conduct this analysis, as it provides a large sample of individuals, long-term follow-up, and an adequate number of events over time from richly characterized cohorts.[10]

5. Main Hypothesis/Study Questions:

We will test the following hypotheses:

a) The proposed diagnostic criteria for Early COPD are associated with respiratory endpoints (COPD-related events, COPD-related hospitalization and respiratory and all-cause mortality) among 10+ pack-year smokers who were <50 years old at baseline spirometry.

b) The proposed diagnostic criteria for Early COPD are associated with respiratory endpoints among never-smokers and <10-pack-year smokers who were <50 years old at baseline spirometry.

c) Respiratory symptoms before age 50, which are not currently included as criteria for Early COPD, are associated with respiratory endpoints.

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).

1. Samples

Based on a preliminary analysis, six cohorts contribute data to this analysis, totaling over 20,000 participants with spirometry performed before age 50. The cohorts are:

Atherosclerosis Risk in Communities (ARIC) Study; Coronary Artery Risk Development in Young Adults (CARDIA) Study; Framingham Heart Study (FHS)-Offspring; Multiethnic Study of Atherosclerosis (MESA); Jackson Heart Study (JHS); Strong Heart Study (SHS)

2. Inclusion criteria

-Participants <50 years of age

-Participants with a valid spirometry at baseline

3. Exclusion criteria

-Participants aged 50 years or older at baseline and those without at least one valid spirometry.

-Participants with respiratory diseases (e.g., lung cancer) other than COPD and asthma.

4. Exposures

We will use the following proposed diagnostic criteria for Early COPD

4.1 Low FEV1/FVC ratio: It will be defined as FEV1/FVC below LLN. We will use Global Lung Initiative and NHANES equations to determine the normative values.[11,12]

4.2 Decline in FEV1: It will be defined as FEV1 drop of 60 ml per year calculated as FEV1 at time 2 minus FEV1 at time 1, divided by the years elapsed between the two measures, with minimum interval of one year before age of 50 years. We will perform sensitivity analyses

restricted to the subsets of participants with both first and second spirometry measures occurring (a) within <6 years and (b) prior to age 50 years.

4.3 Pack Years: 10+ pack years of smoking history.

Given recent evidence suggesting that the 10 pack-year criterion may not capture relevant smoking exposures[13] and the substantial burden of COPD in never smokers,[14] we will also examine other smoking-based risk criteria including ever-smoking, low (<10-year) pack-year of smoking, and never-smoking.

4.4 Respiratory symptoms: We will consider cough, phlegm, and dyspnea if participants report any of them at least once at any time before age of 50 years.

We will also conduct sensitivity analyses, using a fixed FEV1/FVC ratio <0.7 and low FEV1 (FEV1% predicted <80%) with normal FEV1/FVC ratio.

5. Outcomes

We will estimate the association between the various proposed diagnostic criteria of Early COPD above and the following respiratory endpoints:

***5.1 COPD-related hospitalization*:** This includes any hospitalization adjudicated as primarily or secondarily attributable to COPD, or, if adjudication was lacking, those with COPD included as a primary or contributing discharge diagnosis.[15,16]

5.2 COPD-related event: We will also use a composite outcome of COPD-related hospitalization and COPD-related mortality.[15]

5.3 Respiratory mortality: Respiratory disease–related deaths will be defined by adjudication or administrative criteria (ICD-10: J1-J99).[15,16]

***5.4 All-cause mortality*:** All-cause mortality was ascertained via follow-up calls and supplemented by the National Death Index.[15,16]

6. Covariates

We anticipate that the following covariates will be used:

- Socio-demographics: age, sex, race/ethnicity, educational attainment
- Anthropometric: height, weight, BMI
- Smoking: smoking status, cigarettes per day, pack-years, pipe use, cigar use[17]
- Comorbidities: asthma

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7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _x___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

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 https://sites.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.