ARIC Manuscript Proposal #3480

PC Reviewed: 10/8/19          Status: _____          Priority: 2
SC Reviewed: __________       Status: _____          Priority: _____

1.a. Full Title: Associations between metabolic syndrome and incident COPD: The NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters): Associations between metabolic syndrome and incident 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. _PB____ [please confirm with your initials electronically or in writing]
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:
Metabolic syndrome (MetS), which affects about one-third of the US population,¹ is defined by a cluster of metabolic risk factors including abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein (HDL) cholesterol levels.² MetS has been previously associated with increased risks of cardiovascular disease, type-II diabetes, chronic kidney disease, and all-cause mortality.³⁻⁶ Whether MetS also increases the risk of developing chronic pulmonary obstructive disease (COPD), the third leading cause of death,⁷ remains uncertain.

MetS is a commonly encountered co-morbidity in patients with COPD, among whom it has been associated with increased risk of COPD exacerbations.⁸⁻¹⁰ MetS has also been suggested as a risk factor or risk modifier for asthma.¹¹⁻¹⁴ Several cross-sectional studies have demonstrated associations between MetS and reduced lung function, particularly with a restrictive ventilatory pattern,¹⁵⁻²⁴ yet this prior literature is limited by the large number of potential confounders and the potential for reverse causation. Moreover, much of the prior literature has been characterized by inconsistent definitions of MetS¹³,¹⁹ and use of predominantly European or Asian population cohorts, limiting the generalizability of the findings to an increasingly multi-ethnic US population.¹⁵,¹⁶,¹⁸⁻²²,²⁵
Identifying associations between MetS and incident COPD could improve COPD risk stratification and warrant clinical trials of MetS therapies for primary prevention of COPD. Indeed, there is evidence to suggest that MetS or components thereof may promote COPD via inflammatory pathways as well as physiological mechanisms.\textsuperscript{26-28} We therefore propose what we believe to be the first large, US general population-based study to test if MetS is associated with accelerated lung function decline, incident airflow limitation, and incident clinical respiratory events. Using gold-standard metabolic and lung function data that were harmonized and pooled by the NHLBI Pooled Cohorts Study,\textsuperscript{29} we will furthermore test whether associations between MetS and incident COPD differ according to obesity, age, sex, race/ethnicity, smoking history, and the presence of cardiovascular comorbidities.

5. Main Hypothesis/Study Questions:

1. Among adults without COPD, we hypothesize that MetS will be associated with:
   a. Accelerated lung function decline
   b. Incident airflow limitation
   c. Incident COPD-related clinical respiratory events
2. These associations will be modified by smoking status and prevalent cardiovascular comorbidities.

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).

Data

Sample

We propose to use data from nine cohorts that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study:\textsuperscript{29}

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. Multi-Ethnic Study of Atherosclerosis (MESA)
9. Strong Heart Study (SHS)
For the primary analyses of MetS, we will exclude all participants with the following baseline characteristics:

- Prevalent airflow limitation, defined as FEV1/FVC < 0.73
- Prevalent restrictive lung disease, defined as FEV1/FVC < 0.70 and FVC < 80%
- Prevalent chronic lower respiratory disease (CLRD), defined by self-reported COPD, chronic bronchitis, emphysema, or asthma, or inhaler therapy.

**Exposure**

MetS will be defined using the National Institutes of Health guidelines, which define metabolic syndrome as having three or more of the following:

1. A large waistline – a waist measurement of ≥35 inches for women or ≥ 40 inches for men
2. A high triglyceride level – a triglyceride level of ≥ 150 mg/dL or being on medicine to treat high triglycerides
3. A low HDL cholesterol level – an HDL cholesterol level of < 50 mg/dL for women and < 40 mg/dL for men; or, being on medicine to treat low HDL cholesterol
4. High blood pressure – a blood pressure of ≥130/85 mmHg; or, taking medicine to treat high blood pressure
5. High fasting blood sugar – a fasting blood sugar level of ≥ 100 mg/dL; or, taking medicine to treat high blood sugar

**Endpoints**

- Lung function: we will use spirometry data meeting contemporary ATS/ERS quality standards that has been harmonized and pooled by the NHLBI Pooled Cohorts Study
  - FEV1 decline
  - FVC decline
  - FEV1/FVC decline
  - Incident airflow limitation
  - Incident restrictive lung disease

- Incident clinical respiratory events: hospitalizations and deaths will be classified by adjudication and/or administrative definitions
  - CLRD-related events: 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.
  - Severe CLRD events: 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.
  - Both CLRD-related and severe CLRD events will be further stratified into COPD- and asthma-related events and severe COPD and asthma events, respectively.
  - Respiratory deaths were defined by adjudication or administrative criteria (ICD-10, J1-J99)

**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
• Comorbidities: cardiovascular disease, chronic kidney disease
• Medication use: oral hypoglycemics, insulin, anti-hypertensives, statins, niacin, fibrates, antiplatelets, etc.

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 MetS status as well as by cohort.
• Associations between MetS 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.32
• Associations between MetS and incident airflow limitation and 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 MetS will be assessed via logistic regression (i.e., ROC curves, c-statistics) and the net reclassification index. The competing risks of COPD events, asthma events, and non-CLRD mortality will be analyzed in competing risks regression.
• 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 components of MetS.
• In secondary analyses, models will be repeated with MetS as the exposure among participants with prevalent airflow limitation, restrictive lung disease and/or clinical CLRD, as well as among those with/without prevalent cardiovascular disease.

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? _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)?

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. 
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