ARIC Manuscript Proposal #4139

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1.a. Full Title: Lung Function and Cardiovascular Disease: Attributable Risk

b. Abbreviated Title (Length 26 characters): Lung Function and CVD

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

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3. Timeline: Manuscript submission by June 2023.

4. Rationale:

Cardiovascular disease (CVD) is frequently observed in patients with lung disease. Subjects with chronic obstructive pulmonary disease (COPD) have a 2 to 5 fold higher risk of coronary artery disease (CAD), even after adjustment for shared risk factors such as age and cigarette smoking.(1, 2) Although data for other chronic respiratory diseases is limited, arrhythmias are reported in about 20%, congestive heart failure in 4% to 26%, and CAD in 3% to 68% of patients with interstitial lung diseases, depending on disease severity.(3) Active asthma is also associated with a greater risk of myocardial infarction.(4) These associations may be due to systemic inflammation and an enhanced atherosclerotic milieu.

Impairments in lung function have also been consistently associated with CVD risk. Results from the Lung Health Study showed that adjusted cardiovascular mortality increases by 28% for every 10% reduction in FEV_1.(5) Although FEV_1 is not part of the traditional Framingham study (or the more recent ASCVD) risk factors for CAD, the Renfrew and Paisley prospective population study reported that approximately 25% of the attributable risk for death due to CAD is due to low FEV_1,(6) placing reduced lung function very high in the list of cardiovascular risk factors. The PURE-BREATH study investigators estimated that FEV_1 impairment (even in the clinically normal range) ranked second only to hypertension in attributable risk for incident cardiovascular events, and that all levels of impaired FEV_1 contributed significantly to cardiovascular mortality.(7) They found however that the contribution of mildly to moderately impaired FEV_1% (within the clinically normal range but up to 2 standard deviations from the population mean, adjusted for demographics) was several times larger than that of severe FEV_1% impairment (in the abnormal range). This may be due to the fact that those with more severe disease are dying from respiratory causes rather than cardiovascular causes. Despite these observations, traditional risk classification schemes for CVD do not include respiratory disease or lung function as risk factors, likely due to lack of awareness. This may also be due to counterintuitive findings (e.g., stronger CVD associations with mild versus severe lung function impairment), which did not support a mechanistic role, as well as other limitations in study design.

In this proposal, we aim to estimate the population attributable risk (PAR) of spirometry-defined lung function (FEV_1 %predicted, FVC %predicted and FEV_1/FVC) with respect to 10-year risk of incident CAD, incident CVD, and cardiovascular mortality in a large, population-based sample of US adults. We will address a number of the limitations of prior studies, including (1) adjustment for major confounders (e.g., smoking, hyperlipidemia) that were frequently missing from prior models; (2) modeling of CVD and respiratory mortality as competing risks, which was not performed in prior studies; (3) differentiation of different patterns of lung function impairment (e.g., obstructive versus restrictive), which was wholly missing from the prior literature; and (4) consideration of variation in PAR over the lifecourse. Our findings on the relative importance of lung function impairment on CVD risk will

improve our understanding of the population burden of chronic respiratory diseases and may better inform cardiovascular risk prediction.

5. Main Hypothesis/Study Questions:

- What is the population attributable risk (PAR) of lung function with respect to incident CAD?
- What is the PAR of lung function with respect to CVD mortality? We will stratify lung disease by presence of airflow obstruction ($FEV_1/FVC<0.70$) and restrictive ventilatory defect ($FEV_1/FVC\geq0.70$ and FVC<80% predicted).

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 nine cohorts with longitudinal 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 (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)

The total pooled sample includes 55,013 adults with at least one valid measure of FEV_1/FVC, all of whom have follow-up for all-cause and CVD mortality.

Most of the required data has already been harmonized and pooled at Columbia University, where the proposed analyses will be performed.

Exposures:

- Primary exposure: FEV_1 %predicted (Quartiles), stratified by presence of obstruction/restriction
- Secondary exposures
    - FVC %predicted and FEV_1/FVC

Endpoints:

- Primary endpoint: Incident CAD events as defined in the first 10 years of follow-up (myocardial infarction, percutaneous coronary revascularization, coronary artery bypass grafting, cardiac-specific mortality)
- Secondary endpoints
    - Incident diagnosis of cardiovascular disease (CAD plus peripheral arterial disease, congestive heart failure, and stroke)
    - CVD mortality

Covariates:

- Socio-demographics: age, sex, race/ethnicity, educational attainment

- Anthropometric: height, weight, BMI
- Smoking: smoking status (ever/never), pack-years
- Medical history: diabetes mellitus, hypertension, hyperlipidemia, family history of CAD
- Medications: statins, ACE inhibitors, Angiotensin receptor blockers, beta blockers, aspirin, inhalers

Analysis Plan

We will utilize baseline measures of the primary risk exposures (BMI, pack-years of smoking, and presence or absence of hypertension, diabetes mellitus, hyperlipidemia and cigarette smoking status). We will calculate the cumulative incidence function as

$$h_{c,CIF}(t) = h_{0c,CIF}(exp)[\sum_{i=1}^{P} \gamma_i X_i]$$

Where c is the event type and t is time.

We will then calculate PAR for each risk exposure as

$$PAR = \frac{P(F)(RR-1)}{1+P(F)(RR-1)}.$$

Where P is the prevalence of the risk factor, and RR the hazards derived from the Fine and Gray model.

We will categorize lung function %predicted into quartiles, stratified by presence of obstruction/restriction in separate models. The primary end point will be new-onset CAD within 10 years from the baseline visit. At each visit, we will estimate the PAR of each primary risk exposure (hypertension, diabetes mellitus, obesity, hyperlipidemia, cigarette smoking status, and lung function quartile) for the 10-year incidence of CAD. At each time point, we will exclude those with known CAD and CVD. We will perform all PAR calculations using the prevalence of primary exposure at each visit, and assess multivariable-adjusted hazards ratio estimate for 10 years after each exam using the Fine and Gray hazards models for competing risks (causes of death other than cardiovascular). The hazards models will include FEV_1 quartiles, demographics, the above mentioned risk factors for CAD, and study center. PAR proportion will be calculated using PAR % = Pd*[(HR-1)/HR], where Pd is the proportion of total cases in the population arising from the given exposure category and HR is the adjusted hazards ratio for the given exposure category. A 2-sided alpha of 0.05 will be considered statistically significant.

We anticipate that some risk exposure will be more pertinent in different age brackets and so we will perform these analyses for each decade of life from age 30 to 80. For each decade, we will tabulate the PARs and rank them accordingly. We will also stratify age groups by event counts given that young adults are likely to have a very low frequency of events.

Scoring system:

In the cohorts in which laboratory data are available (for example serum lipids), we will divide the pooled cohort into derivation and validation cohorts. Using regression models for prediction, we will derive a new score that incorporates lung function and compare outcomes for this score with the Framingham Score and ASCVD Risk Score for MI or death. C statistics will be calculated and compared for these scores.

Summary/conclusion: Calculating PAR across a wide age range will enable us to rank risk factors in terms of importance for CAD/CVD. If lung function turns out to be an important risk exposure, this will highlight the importance of chronic lung disease in CAD/CVD.

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/aricproposals/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)? None that are similar to the one proposed.

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.

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