1. Title:
   a. Full Title:
      • Associations between longitudinal lung function and the incidence of heart failure in the general population: The NHLBI Pooled Cohorts Study
   b. Abbreviated Title:
      • Lung function and HF

2. Writing Group:
   a. Writing Group Members:
      • Christina Eckhardt, Columbia University, New York, NY, USA, che9039@nyp.org
      • Pallavi Balte, Columbia University, New York, NY, USA, ppb2119@cumc.columbia.edu
      • Michael Cuttica, Northwestern University, Chicago, IL, USA, micuttic@nm.org
      • Pat Cassano, Cornell University, Ithaca, NY, USA, pac6@cornell.edu
      • Paolo Chaves, Florida International University, Miami, FL, pdehendo@fiu.edu
      • David Couper, University of North Carolina, Chapel Hill, NC, david_couper@unc.edu
      • Aaron Folsom, University of Minnesota, Minneapolis, MN, USA, folso001@umn.edu
      • David Jacobs, University of Minnesota, Minneapolis, MN, USA, jacob004@umn.edu
      • Ravi Kalhan, Northwestern University, Chicago, IL, USA, RKalhan@nm.org
      • Richard Kronmal, University of Washington, Seattle, WA, USA, kronmal@u.washington.edu
      • Leslie Lange, University of Colorado, Denver, CO, USA, leslie.lange@ucdenver.edu
      • R Graham Barr, Columbia University, New York, NY, USA, rgb9@cumc.columbia.edu
      • Laura Loehr, University of North Carolina, Chapel Hill, NC, USA, lloehr@email.unc.edu
      • Stephanie London, NIH/NIEHS, Research Triangle Park, NC, USA, london2@niehs.nih.gov
      • Anne Newman, University of Pittsburgh, Pittsburgh, PA, USA, NewmanA@edc.pitt.edu
      • George O’Connor, Boston University, Boston, MA, USA, goconnor@bu.edu
      • Joseph Schwartz, Columbia University, New York, NY, jes2226@cumc.columbia.edu
      • Lewis Smith, Northwestern University, Chicago, IL, USA, lsmith@northwestern.edu
      • Wendy White, Tougaloo College, Tougaloo, MS, USA, wendywhite2001@yahoo.com
      • Sachin Yende, University of Pittsburgh, Pittsburgh, PA, USA, Yendes@upmc.edu
      • Elizabeth C Oelsner, Columbia University, New York, NY, USA, eco7@cumc.columbia.edu
   
      b. I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

   c. First Author:
      • Name: Christina Eckhardt
      • Address: 630 West 168th Street, PH 9E-105, New York, NY 10032
      • Phone: 919-630-0059
      • Fax: 212-305-9349
      • E-mail: Che9039@nyp.org
d. **ARIC author:**

- To be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
- Name: Elizabeth Oelsner
- Address: 630 West 168th Street, PH 9E-105, New York, NY 10032
- Phone: 917-880-7099
- Fax: 212-305-9349
- E-mail: eco7@cumc.columbia.edu

3. **Timeline:**

   a. We plan to begin drafting the manuscript after obtaining proposal approval with a goal to submit a pen draft by 7/2018.

4. **Rationale:**

   Chronic obstructive pulmonary disease (COPD) affects approximately 400 million people worldwide and is the fourth leading cause of death globally and in the United States (1-2). COPD often coexists with heart failure (HF), which is prevalent in over 20% of patients with COPD (3-6). To some extent, the frequent comorbidity of HF with COPD may be due to shared risk factors such as smoking (7). However, there is evidence to suggest that COPD may contribute to cardiac dysfunction via inflammatory pathways (8) as well as physiological mechanisms (9).

   Obstructive respiratory physiology, defined as airflow limitation on spirometry that does not fully reverse (10), has been associated with impaired left ventricular (LV) filling, reduced LV stroke volume, and decreased cardiac output (11). Hyperinflation, which is common in obstructive lung diseases, has been associated with increased LV mass, which predicts incident heart failure and cardiovascular mortality (12). Restrictive physiology, which is characterized by low forced vital capacity (FVC) without airflow obstruction (13), has been associated with LV hypertrophy and diastolic dysfunction (14). Hence, in addition to supporting HF risk stratification, establishing associations between lung function and risk of incident HF with reduced ejection fraction (HFrEF) and/or heart failure with preserved ejection (HFpEF) may facilitate our understanding of mechanisms underlying COPD/HF comorbidty, which may be relevant to HF prediction and prevention.

   Although numerous prior studies have explored associations between lung function and incident clinical HF, the results have been inconsistent, and knowledge gaps remain. The Framingham Study found that low FVC was associated with incident HF, resulting in the inclusion of FVC in the Framingham Risk Score for HF prediction (15-16). However, subsequent studies found that, rather than FVC, low forced expiratory volume in one second (FEV1) was more associated with incident HF (17-18). Still other studies found that both FVC and FEV1 were linearly associated with HF (19). Meanwhile, associations with FEV1/FVC, an index of airflow limitation, have generally been null (20), and associations between longitudinal change in FEV1, FVC, and FEV1/FVC and incident HF are lacking. Discrepancies between previous results may be due to uncontrolled confounding by factors such as smoking or age (21). Furthermore, prior results may not be generalizable to the contemporary, multiethnic, increasingly overweight, and predominantly non- or light-smoking US population.

   We therefore propose to test the associations between longitudinal lung function and incident clinical HF in the NHLBI Pooled Cohorts Study, which has harmonized and pooled lung function, HF, and other relevant covariate data collected over the last 35 years in nine US population-based cohorts (23). This large, highly characterized, multiethnic, general population sample will allow adjustment for a large number of potential confounders, including inflammatory biomarkers. It will also provide adequate statistical power to perform
key stratified analyses according to age, birth cohort, sex, race/ethnicity, smoking intensity and duration, major comorbidities, and medication use.

5. Main Hypothesis/Study Questions:
   a. In adults without clinical cardiovascular disease:
      • Is airflow limitation predictive of incident heart failure? We will test associations with baseline FEV1 and FEV1/FVC; baseline airflow limitation, defined as FEV1/FVC < lower limit of normal (LLN); and rate of decline in FEV1 and FEV1/FVC.
      • Is restrictive ventilatory physiology predictive of incident heart failure? We will test associations with baseline FVC; baseline restriction defined as FVC < 80% and FEV1/FVC > LLN; and decline in FVC.
      • Do associations differ by HFrEF versus HFpEF?
      • To what extent are these associations modified and/or confounded by age, sex, race/ethnicity, smoking history, hypertension, diabetes, hyperlipidemia, obesity, medications, inflammatory biomarkers, and study/birth cohort?

6. Design and Analysis
   a. Data
      • We propose to use data from nine cohorts that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study (23):
         1. Atherosclerosis Risk in Communities (ARIC) Study
         2. Cardiovascular Health Study (CHS)
         3. Coronary Artery Risk Development in Young Adults (CARDIA)
         4. Framingham Offspring Study (FHS-O)
         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)
      • Excluding participants with prevalent cardiovascular disease (self-reported prior myocardial infarction or heart failure, 2,132), we expect to analyze 50,982 adults contributing 96,268 spirometry measures meeting 2005 ATS/ERS standards, and over 425,00 person-years of follow-up for incident HF.
      • The composition of the sample is anticipated to be 55.5% white participants, 45.5% non-white participants, 50% never-smokers, and 20.8% current smokers.
         1. Exposures
            a. Baseline lung function
               i. FEV1, FVC, FEV1/FVC
               ii. Airflow limitation: FEV1/FVC < lower-limit-of-normal (LLN) (24)
               iii. Restriction: FEV1/FVC > LLN and FVC < 80 percent-predicted
            b. Decline in lung function (in cohorts with 2+ lung function measures): we will explore options for modeling lung function decline including analyzing the difference between first and last values divided by years elapsed, and the difference between the first and second values divided by years elapsed.
         2. Endpoints
            a. Physician-adjudicated incident heart failure
            b. HFrEF versus HFpEF, as available in selected cohorts
         3. Covariates
            a. Socio-demographics: age, sex, race/ethnicity
            b. Anthropometric: time-varying height, weight, BMI, systolic blood pressure, diastolic blood pressure
            c. Smoking: smoking status, pack-years, time-varying cigarettes per day
d. Medical history: hypertension, diabetes, renal failure, anti-hypertensives, ACEi/ARB, statins, inhalers

e. Serum measures: HDL, LDL, total cholesterol, eGFR, NT-proBNP (where available), C-reactive protein, fibrinogen

f. Cohort: study cohort, birth year

4. Most of the necessary data have already been obtained, harmonized and pooled under approved study protocols relating to other hypotheses.

b. Analytic Plan

• Participant characteristics will be tabulated by baseline lung function as well as by cohort.
• Associations between baseline lung function and incident heart failure will be analyzed via Cox proportional hazards models in the following manner:
  1. Time-to-event will be defined as biological age at event, with left-truncation for age at study entry
  2. Study cohort will be treated as a stratum term
  3. FEV1, FVC and FEV1/FVC will be examined separately
  4. Baseline lung function will be sequentially adjusted for potential confounders and precision variables
• The contribution of longitudinal lung function will be tested by the addition of lung function decline (e.g., FEV1last-FEV1first/years elapsed) to the above-mentioned models for baseline lung function. As an alternative approach, survival models using time-varying lung function will be explored.
• As alternatives to the Cox proportional hazards models, negative binomial models will be tested to estimate differences in absolute risks of incident HF. Competing risk models including coronary heart disease (CHD) mortality and non-CHD mortality will also be explored
• Prognostic significance of baseline and longitudinal lung function will be quantified via c-statistics.
• Effect modification will be assessed by interaction terms and in stratified models.
• Models will be repeated for HFrEF and HFpEF in cohorts where these endpoints can be defined. In models for one type of HF, we will compare the results treating the other type of HF as censored, versus a competing risks model.

7. a. Will the data be used for non-CVD analysis in this manuscript?
   • 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?
      • N/A

8. a. Will the DNA data be used in this manuscript?
   • No
   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”?
      • N/A

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/search.php
   a. Yes

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
   • ARIC Lung

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.

   1. 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.cscg.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. References:

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