ARIC Manuscript Proposal #2214

PC Reviewed: 9/10/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title:
Variation in Forced Vital Capacity with Body Mass Index: A Comparison of Obstructive and Restrictive Lung Disease

b. Abbreviated Title (Length 26 characters):
BMI affects FVC in COPD vs. ILD

2. Writing Group:
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3. **Timeline**: Begin immediately.

4. **Rationale**:

   Body mass index (BMI) has important, described effects on lung function. For example, investigations in healthy individuals with normal pulmonary function tests (PFTs) demonstrate that there is a negative, linear correlation between increasing BMI and decreasing total lung capacity (TLC), vital capacity (VC), and residual volume (RV) (Jones et al, 2006). An exponential relationship exists between increasing BMI and decreasing expiratory reserve volume (ERV) (Littleton, 2011). An association between ideal body weight (IBW) and forced vital capacity (FVC) has been examined in one prior study, a subset of the Lung Health Study (Wise et al, 1998). In this sub-study, currently smoking men and women, ages 35-60, were randomized to a smoking cessation intervention. Participants had evidence of mild-moderate obstruction on PFTs. There was a linear decrease in FVC with increasing IBW beyond roughly 90%, and a non-significant increase up to that point. BMI was not specifically examined.

   FVC is of particular interest in the case of interstitial lung disease (ILD), where it is an important predictor of clinical outcome and survival, and a change in FVC is recommended as a clinical endpoint in pharmaceutical trials by the Food and Drug Administration (Schwartz et al, 1994; ATS Consensus Statement; Karini-Shah, S-000). While the significance of FVC in ILD is widely-recognized, the forced expiratory volume in 1 second (FEV$_1$) is the currently preferred clinical predictor in obstructive lung disease. Studies evaluating FVC comprehensively as a clinical predictor in obstructive lung disease are lacking.

   We propose that FVC will be associated with BMI. This is proposed to occur through a mechanism of altered elastic load via changes in chest wall and abdominal adipose tissue load, causing variation in achieved maximal inspiration. Deconditioning, prevalent at the extremes of weight, may also contribute to reductions in FVC. We predict that FVC will be lower at the extremes of weight, and that there will be an optimal BMI at which FVC is maximized. This is based on preliminary analyses in the longitudinal ILD cohort that will be used as a comparison. We propose to explore BMI as a correlate of FVC in opposing classifications of lung disease, restrictive (ILD) and obstructive (COPD). We seek to replicate and affirm the results of Wise et al in an additional population, and compare the results to those in an ILD population from another longitudinal dataset to which we have access. If there is a similar association, this study will inform clinician counseling and future intervention trials in ILD, aimed at improving the ideal weight of individuals in this population, and prompt further investigation into the relationship between FVC and clinical outcomes in COPD.

5. **Main Hypothesis/Study Questions**:

   We hypothesize FVC will demonstrate a similar association with BMI in both obstructive and restrictive lung disease.
To test this hypothesis, we propose to conduct analyses to answer the following questions:

1. What is the association between BMI and FVC in patients with physician-diagnosed restrictive lung disease (ILD)? Does this association differ by age, sex, and race? (analysis conducted in a separate cohort).
2. What is the relationship between BMI and FVC in patients with PFT-defined obstructive lung disease (COPD)? (exploratory: What is the association between BMI and FVC in patients with reported, doctor-diagnosed obstructive lung disease (COPD)?) Does this relationship differ by age, race, and sex?
3. How does the association between BMI and FVC differ in patients with restrictive (ILD) versus obstructive (COPD) lung disease?

If our hypothesis is correct, then this paper should identify a similar association between BMI and FVC in both obstructive and restrictive lung disease. The importance of this outcome in ILD is clear, given FVC is used clinically as a predictor of ILD outcomes. Though FVC is not a primary clinical predictor of COPD outcomes, those with a combined obstructive-restrictive phenotype (COPD/ILD, and therefore a low FVC combined with obstruction) have been documented to have a particularly grave prognosis (Cottin et al., 2005). A link between BMI and FVC in these distinct populations, may prompt trials of BMI manipulation in both populations with a goal of improving clinical outcomes.

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).

We propose to analyze data on all ARIC participants with complete data on COPD status and pulmonary function.

COPD will be defined at visit 1 via either reported doctor-diagnosis of emphysema or chronic bronchitis, and in a separate analysis via the Global Initiative for Chronic Obstructive Lung Disease criteria (FEV1/FVC ratio <0.7 and FEV1 <80%), with an estimated prevalence of 11.1% (n=1,321, as described in Kan et al., 2007). All data points where FVC and BMI are available (visits 1, 2, and any available data from visit 5) will be examined first at each visit in, cross-sectional analyses and then in a longitudinal, mixed model to examine the association between percent-predicted FVC and BMI. We will adjust for medication use (steroid [inhaled and systemic], beta-agonist, anticholinergic), smoking status, and socioeconomic status in this model. We will further explore the relationship between BMI and raw FVC values, adjusted for age, race, gender, medication use, smoking status, and socioeconomic status. We will include interaction terms to explore effect modification, specifically between BMI, race, and gender.

The outcomes will be compared to the findings in a longitudinal ILD cohort currently undergoing analysis.
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”? 
      __x__ 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/search.php
   __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)?

Published papers:

Mannino DM, Doherty DE, Buist AS. Global Initiative on Obstructive Lung Disease 
(GOLD) classification of lung disease and mortality: findings from the Atherosclerosis 

Function in Adults with Type 2 Diabetes: The Atherosclerosis Risk in Communities 

Proposals:

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 http://www.csc.c.unc.edu/ari/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
     shows you which journals automatically upload articles to Pubmed central.

References:

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