ARIC Manuscript Proposal # 3097

PC Reviewed: 1/9/18	**Status: _____**	**Priority: 2**
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1.a. Full Title: Identification of Ideal FEV1/FVC threshold To Diagnose Airflow Obstruction

b. Abbreviated Title (Length 26 characters): Ideal FEV1/FVC threshold for Airflow Obstruction

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 December 2018.

4. Rationale:

The demonstration of airflow obstruction on spirometry is essential and necessary for the diagnosis of chronic obstructive pulmonary disease (COPD). Current guidelines define COPD as a ratio of the forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) less than a fixed threshold of 0.70. However, this definition remains controversial. A commonly used alternative is to define airflow obstruction as an FEV1/FVC less than the Lower Limit of Normal (LLN), or the fifth percentile, as derived from population-based normative data adjusted for age, sex and ethnicity.(1) The question of which threshold defines airflow obstruction has major implications both for patient care and public health, since the prevalence of airflow obstruction can vary by as much as 33% depending on which threshold is selected.(2)

A number of recent studies have tested whether using a fixed threshold versus a LLN threshold makes any difference for diagnosis and for prediction of respiratory outcomes.(3) A series of studies in the prior decade suggested that the fixed threshold did not measure up to the LLN, arguing that, due to "normal" age-related decline in lung function, the fixed threshold resulted under-diagnosis of airflow obstruction in younger adults and over-diagnosis – and overtreatment – in older adults.(3) However, these studies used the LLN as the gold standard and were therefore inherently biased. More recent studies have used a "neutral" gold standard, and pitted the thresholds against each other using computed tomography (CT) measures of structural lung disease, respiratory morbidity, and mortality as meaningful parameters. These studies showed that participants in the "intermediate zone", disease positive by fixed threshold but not by LLN, have a greater degree of structural disease on CT,(3, 4) higher respiratory morbidity,(5) greater frequency of exacerbations,(5) and higher mortality on follow-up compared to subjects with normal lung function by both criteria.(6, 7) These findings suggested the fixed threshold might detect some subjects with respiratory morbidity who are not detected by the LLN.

Furthermore, there remains a lack of consensus regarding how to set either type of threshold. The 0.70 fixed threshold, although appealing in its simplicity for both clinical and research applications, is based on expert recommendations and not on evidence. Reference equations for the LLN may not be equally valid in all populations or specific race/ethnic groups. Hence, evidence-based guidelines for defining airflow obstruction in the general population are urgently needed to inform COPD guidelines as well as epidemiologic and public health research.

We therefore propose to evaluate different thresholds for the FEV1/FVC with respect to major clinical outcomes in a large, population-based sample of US adults. We will test a range of fixed thresholds and several different approaches to defining the LLN with regards to risk of hospitalization for

COPD; respiratory mortality; and all-cause mortality. The incidence of respiratory symptoms, such as dyspnea and chronic bronchitis, will also be examined. Similar to the cutoffs derived for fasting blood sugar, for which morbidity is considerably higher at >126 mg/dl, we hypothesize that there will be a "J-point" in the curve associating the FEV1/FVC threshold with clinical outcomes. We thereby aim to identify the FEV1/FVC threshold that demonstrates the optimal sensitivity and specificity for COPD morbidity and mortality.

5. Main Hypothesis/Study Questions:

- What is the optimal fixed threshold for FEV1/FVC with respect to predicting clinical outcomes? What is the sensitivity and specificity of the optimal threshold(s)?
- How do the performance characteristics of this optimal fixed threshold compare to 0.70 and those for the LLN threshold using NHANES, GLI, or other approaches?
- Does the optimal threshold vary by age, gender, or race/ethnicity?

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 FEV1/FVC, all of whom have follow-up for all-cause mortality. A subset of at least 29,356 have follow-up for COPD and asthma hospitalizations and respiratory 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: FEV1/FVC < fixed threshold (various fixed thresholds will be tested, as detailed below in the analysis plan)
- Secondary exposures
    - FEV1/FVC percent-predicted based upon NHANES III reference equations and GLI reference equations.(8, 9)
    - FEV1/FVC plus FEV1<80% predicted based upon NHANES III equations.(8)

Endpoints:

- Primary endpoint: composite of first COPD hospitalization and respiratory mortality (defined below)
- Secondary endpoints
    - COPD hospitalization: hospitalizations adjudicated or administratively coded as caused by COPD, chronic bronchitis, or emphysema (ICD-9 490-492, 496, 506.4; ICD-10 J40-J44). Events will be sub-classified by code position (primary diagnosis code or underlying cause of death versus any code position) (10).
    - Respiratory mortality
    - All-cause mortality
    - Respiratory morbidity
        - Incidence of self-reported respiratory symptoms including dyspnea, wheeze, cough.
        - Incidence of self-reported physician diagnosis of COPD or asthma.

Covariates:

- Socio-demographics: age, sex, race/ethnicity, educational attainment
- Anthropometric: height, weight, BMI
- Smoking: smoking status, cigarettes per day, pack-years
- Medical history: history of COPD, asthma, coronary artery disease, diabetes, hypertension
- Medications: inhalers, oral steroids
- Quality of life questionnaires
- Other exposures: occupational history/exposures, air pollution exposure (as available)

Analysis Plan

- The main time-varying exposure of interest will be presence/absence of airflow obstruction, as defined by FEV1/FVC < [threshold].
- We will test survival models with time-varying covariates in order to estimate the hazard of [endpoint] according to the time-varying exposure.
- Time-to-event will be biological age at event, with left truncation at age at study entry.
- The main model will be adjusted for time-varying age at spirometry, time-varying smoking status and pack-years, time-varying weight and height, sex, and race/ethnicity, with source cohort treated as a stratum term. More highly adjusted models will include educational attainment, comorbidities, symptoms, and medication use.
- To identify the [threshold] with the best performance characteristics with respect to predicting the [endpoint]
    - We will fit separate Cox regression models while varying the [threshold] in 0.05 decrements below a ratio of 0.80. The first FEV1/FVC cut-point below 0.80 that yields a statistically significant increase in the risk of mortality will be termed ‘‘critical’’ threshold. Separate analyses will also be performed in decrements of 0.01. We will plot the resulting adjusted hazards for mortality on the Y-axis and [threshold] on the X-axis, and examine whether there is a “J” point at which the risk is considerably higher, which will be termed the “inflection” threshold.
    - We will also generate time-dependent incident/dynamic Receiver Operating Characteristics (ROC) curves to define the incident sensitivity and dynamic

specificity of the time-varying predictor at different times, as well as plotting incident/dynamic area under the curve (AUC), allowing calculation of time-averaged summaries akin to familiar global concordance measures ("c-statistics").(12) The point with the greatest AUC will be defined as the "optimal" threshold.

- We will compare results for the "critical," "inflection," and "optimal" fixed thresholds to the current fixed threshold used by COPD guidelines (0.70) and those using FEV1/FVC < LLN (comparing NHANES III vs GLI equations) and a combination of FEV1/FVC and FEV1<80%predicted
- Differences according to secondary endpoints and participant characteristics will be evaluated in stratified models according to age group (<45, 45-65, 65+), sex, race/ethnicity, body mass index (<30, 30+), and analyses will also be repeated in the subsets with/without respiratory symptoms, smoking history, and clinical diagnoses of asthma.

Methodology comments: We propose a time varying analysis of FEV1/FVC to account for age related changes in lung function and mortality risk, as well as to improve over previous study designs that incorporated cross sectional risk estimates.

Summary/conclusion: In this time-varying analysis, we plan to establish an optimal fixed threshold for FEV1/FVC based upon prediction of clinically meaningful outcomes in a large, multi-ethnic, population-based sample of US adults with gold-standard, longitudinal data. The proposed work will improve upon previous models of cross-sectional association studies of threshold and outcomes, and could potentially confirm the current threshold (0.70) or identify a new age-independent threshold.

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/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)? 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 at http://www.cscc.unc.edu/aric/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 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.