ARIC Manuscript Proposal #2173

PC Reviewed: 7/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lung function decline among adults: the Atherosclerosis Risk in Communities Study

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

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

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3. Timeline:
We expect to submit the manuscript within 12 months of receiving the final visit 5 dataset.

4. Rationale:
Independent of cigarette smoking and known lung disease, pulmonary function has been identified as a predictor of coronary heart disease, heart failure, and mortality (Ebi-Kryston et al. 1989; Lange et al. 1990; Hole et al. 1996; Schunemann et al. 2000; Griffith et al. 2001; Mannino et al. 2003; Schroeder et al. 2003; Schroeder et al. 2005; Mannino and Davis 2006; Agarwal et al. 2012). That the associations are observed in non-smokers suggests non-smoking related effects (Lange et al. 1990; Hole et al. 1996; Schroeder et al. 2003), though the mechanisms by which abnormal lung function is associated with mortality in the absence of established lung disease remain unclear.

Data from the ARIC cohort study provide a unique opportunity to extend our understanding about the progression of lung function throughout adulthood by evaluating 25-year changes in lung function in a large, population-based, longitudinal cohort of African-American and white men and women in the United States. Since 1987, ARIC study participants have responded to extensive health-related questionnaires, completed up to five study examinations, and answered annual follow-up questionnaires. The inclusion of spirometry at visits 1 (1987-1989), 2 (1990-1992), and 5 (2011-2013) enables us to evaluate changes in lung function during the approximately 25 years of ARIC follow-up. Improving our understanding of risk factors for lung function decline can be used to develop additional hypotheses about mechanisms by which metrics of lung function may predict mortality.

5. Main Hypothesis/Study Questions:
There are two main objectives of this proposed paper:
Objective #1: To assess changes in lung function from visit 1 through visit 5.
Objective #2: To evaluate difference in lung function decline across categories of race, smoking status, and history of asthma.

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).

Study Design
The proposed analysis is longitudinal analysis of lung function data collected during visits 1, 2, and 5.

Inclusion/Exclusion Criteria
The eligible study population will include participants who completed spirometry during the visit 1 and visit 5 study examinations. The following exclusion criteria will be applied:
(1) Participants who restricted the use of their data to analysis of cardiovascular outcomes (i.e., RES_OTH="CVD Research")
(2) Race other than black or white

(3) Black participants recruited from suburbs of Minneapolis, Minnesota and from Washington County, Maryland.
(4) Poor performance on spirometry, as indicated by QC grades of "F" or "D."

Lung Function
Variables to describe lung function will be created using measures of lung function collected using spirometry conducted during the study examinations at ARIC visits 1, 2, and 5 (spirometry was not conducted at visits 3 and 4). The measures will be used to assess changes in lung function between visit 1 and 5. For those participants with visit 2 measures, we will consider using the average spirometry values of visits 1 and 2 as baseline measures. The measures are:

- Forced expiratory volume in one second (FEV_1), in mL
- Forced vital capacity (FVC), in mL
- FEV_1/FVC

Covariates
Analysis of spirometry data requires adjustment for age, height, race, and sex. For FVC, additional adjustment for body mass index is often included and will be evaluated for inclusion in our final models. Cigarette smoking status will be evaluated using data collected at visit 1 and updated at follow-up time points. Categories of smoking status, such as lifetime nonsmoker, former smoker with 5 or more years since quitting, former smoker with less than 5 years since quitting, current smoker, and pack-years of smoking will be created using visit 1 and follow-up data. Other covariates to be considered include body mass index and asthma history. Asthma history will be categorized on the basis of two questionnaire items: "Have you ever had asthma?" and "At what age did it start?" As in previous analyses (Mirabelli et al. 2012), individuals who reported having had asthma with onset at or before the age of 16 years will be considered to have childhood asthma. All covariates for which values may change over time (e.g., smoking status, body mass index) will be evaluated for changes between visits 1, 2, and 5 and, where applicable, analyses will incorporate time-dependent variables.

Statistical Methods

For **Objective #1**, changes in lung function from visit 1 through visit 5 will be presented as mean (with standard deviation) annual changes in FEV_1, FVC, and FEV_1/FVC.

For **Objective #2**, differences in lung function decline among African-American and white participants, across categories of smoking status, and by history of asthma will be evaluated using generalized linear mixed models for multivariate repeated and clustered measures. This method will account for the repeated (visits 1, 2, and 5) spirometry measures and for the clustering of participant-level data within ARIC field centers. Specifically, we will use a variation of the generalized linear mixed model $E(Y_x)=\alpha + \Sigma\beta x$. Using FEV_1 as an example in the models shown below, the participant-level model (level 1) will be defined as

$$FEV_{1\mathrm{ij}} = \beta_{0j} + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots + \beta_n x_{nj} \text{ (level 1)},$$

where FEV_{1ij} is the i^{th} FEV_1 measurement for person j, β_{0j} is the random intercept for person j, and β is the effect of participant-level predictor x_{ij}. Level 1 models will include all participant-specific variables, including age, height, and sex. Changes in participant-specific variables (e.g., body mass index) will be incorporated into the participant-level model. The center-level model (level 2) will be defined as

$$\beta_{0j} = \beta_0 + \mu_1 z_1 + \mu_{0j} \text{ (level 2)},$$

where β_0 is the mean of center-level means for FEV_1 (i.e., fixed intercept); μ is the effect of center; $\mu_{0j} \sim N(0, T_{00})$; and T_{00} is between center-variance. The level 2 models will include only the variable for center; correlations between race and center will be evaluated and, if they are determined to be too highly correlated, the modeling strategy to address center-level variables will be revised. If other center-level variables are identified, they will also be included in the level 2 model. The level 2 model, substituted into the level 1 model, results in the final 2-level random intercepts model,

$$FEV_{1ij} = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots + \beta_n x_{nj} + +\mu_1 z_1 + \mu_{0j},$$

where μ is the random intercept term. Associations will be estimated as adjusted absolute changes in FEV_1, in mL, among African-American and white participants, across categories of smoking status, and by asthma history. Similar models will be used to evaluate changes in FVC and the FEV_1/FVC ratio. As the analysis plan is further developed and finalized, these models will be revised, as needed.

Methods to evaluate possible bias due to non-participation in ARIC visit 5 or in the spirometry testing portion of the visit are currently being developed by the ARIC Study Coordinating Center. When these methods are developed, they will be applied to the analyses proposed here in order to draw conclusions about the potential impacts of non-participation on the external validity of our results.

For all analyses, mixed model methods will be applied to take into account repeated measures collected from ARIC participants and the clustering of individuals within study sites. Variation within participants/across time-points and between participants/within study centers will be accounted for by incorporating a random effects intercept term into the regression model, as described above. All other variables will be incorporated as fixed effects. We will evaluate and consider methods for incorporating error in spirometry measurements into our final models.

Limitations

The major limitation to this analysis will be the potential for survival or continued participation in the ARIC study affect our results. Specifically, the ARIC study participants who died before visit 5, who were too ill to participate in visit 5 or who were unable to complete the spirometry protocol may be systematically different from participants who completed spirometry at visit 5. We will evaluate the impact of such as bias on our results; methods (e.g., inverse weighting of the probability of participating in visit 5, conditional on participation in visits 1or 2) to

incorporate additional analysis of the potential bias into our analyses will be considered carefully.

A second limitation will be the potential for comorbidities, household exposures, ambient air quality, and other factors to affect respiratory health. The potential influence of these factors on our findings will be discussed.

A third limitation will be the comparison of spirometry data collected at visits 1 and 2 to data collect at visit 5. In visits 1 and 2, spirometry was conducted using Collins Survey II spirometers and post-bronchodilator spirometry was not performed. Visit 5 data collection was conducted using SensorMedics model 1022 dry-rolling seal volume spirometers and, for a subset of participants with airway obstruction, spirometry was performed after albuterol was administered. We will consider the advantages and disadvantages of using the pre-bronchodilator spirometry data at visit 5, compare pre- and post-bronchodilator data in the subset of participants with pre- and post-bronchodilator spirometry, and evaluate the potential effects of our final analytic decisions. Potential impacts on our results because of these decisions and comparisons will be acknowledged.

A fourth, and minor, limitation to this analysis will be the lack of spirometry data at visits 3 and 4.

7.a. Will the data be used for non-CVD analysis in this manuscript? _YES_

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? _YES_
(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? _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"? _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
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)?

Six manuscripts related to lung function decline have been identified:

1. Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, Heiss G. Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2003; 158(12):1171-81.
2. Schroeder EB, Welch VL, Evans GW, Heiss G. Impaired lung function and subclinical atherosclerosis: The ARIC Study. Atherosclerosis 2005; 180(2):367-73.
3. Yeh H-C, Punjabi NM, Wang N-Y, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2008; 31(4):741-6.
4. Mirabelli MC, London SJ, Charles LE, et al. Occupation and three-year incidence of respiratory symptoms and lung function decline: the ARIC Study. Respir Res 2012; 13(1):24.
5. Imboden M, Bouzigon E, Curjuric I, et al. Genome-wide association study of lung function decline in adults with and without asthma. J Allergy Clin Immunol 2012; 129(5):1218-28.
6. ARIC Manuscript Proposal #1753: "Genome-wide association study of longitudinal change in pulmonary function:meta-analysis in the CHARGE and SpiroMeta Consortia." Co-author Stephanie London has been closely involved in this paper, which uses mixed models to evaluated change in pulmonary function, but does not include data collected at visit 5. This paper has recently been submitted to the American Journal of Respiratory and Critical Care Medicine.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _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.

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Ebi-Kryston KL, Hawthorne VM, Rose G, Shipley MJ, Gillis CR, Hole DJ, Carmen W, Eshleman S, Higgins MW. Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. Int J Epidemiol 1989;18(1):84-88.

Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of Loss of Lung Function in the Elderly. American Journal of Respiratory and Critical Care Medicine 2001;163(1):61-68.

Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 1996;313(7059):711-715; discussion 715-716.

Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Spirometric findings and mortality in never-smokers. J Clin Epidemiol 1990;43(9):867-873.

Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax 2003;58(5):388-393.

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Mirabelli MC, London SJ, Charles LE, Pompeii LA, Wagenknecht LE. Occupation and the prevalence of respiratory health symptoms and conditions: the Atherosclerosis Risk in Communities Study. J Occup Environ Med 2012;54(2):157-165.

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Schunemann HJ, Dorn J, Grant BJ, Winkelstein W, Jr., Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000;118(3):656-664.