ARIC Manuscript Proposal #2641

PC Reviewed: 10/13/15   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a.   **Full Title**: **Decline in lung function and incidence of cardiovascular disease**

1.b. Abbreviated Title: Lung function and cardiovascular disease

2.   **Writing Group**:
Writing group members: Odilson Marcos Silvestre, Amil M. Shah, Wilson Nadruz Junior, Gabriela Querejeta Roca, Brian Claggett, Scott D. Solomon, others welcome

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

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3.   **Timeline**: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4.   **Rationale**:

The physiological decline in lung function usually starts after 25 years of age, with an average loss of 25 ml per year in the forced expiratory volume in one second (FEV_1). Vital capacity levels also progressively decreases during lifetime reaching approximately 75% of its supposed best value.[1] FEV_1 decline over 100 ml per year, which is considered a fast decline, is associated with development of chronic obstructive pulmonary disease (COPD)[2] and individuals with an accelerated decline in FEV_1 have 50% higher risk of all-cause mortality in comparison with patients with slow decline in lung function.[3] Genetic and environmental factors interact to determine the speed of the decline in lung function.[4] Cigarette smoking is the main cause but occupational exposure to organic and inorganic dust, chemical agents, and indoor and outdoor air pollution contribute to the acceleration of pulmonary aging process.[5]

Previous studies consistently showed that reduced baseline levels of forced vital capacity (FVC) and FEV_1 are associated with incidence of cardiovascular disease. For instance, reduced lung function is associated with higher incidence of coronary heart disease,[6] heart failure (HF)[7] and 1.8-fold higher risk of cardiovascular death in comparison with individuals with normal lung function.[8] Impaired vascular reactivity and systemic inflammation have been considered causal mechanisms linking reduced lung function and cardiovascular disease.[9,10] Rapid declines in FEV_1 have been associated with higher levels of systemic inflammation markers, independently of smoking status in young adults with normal lung function.[11] Additionally, lung function deterioration was independently associated with elevated incidence of hypertension, even among subjects with low-normal lung function.[12] These findings support the notion that not only reduced baseline lung function but also higher decline rates in pulmonary function might be associated with increased cardiovascular risk. The association between velocity of decline in lung function and cardiovascular events and incident HF has not been explored.

Aim:

To evaluate the association between changes in lung function and incidence of heart failure, myocardial infarction, and stroke among patients with normal lung function.

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

In subjects with normal lung function, a greater decline in pulmonary function, three years after initial assessment, is associated with an increased risk of incident heart failure, myocardial infarction, and stroke after 20 years of follow-up.

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 methodological limitations or challenges if present).

We will include patients who underwent tests of pulmonary function in Visit 1, and Visit 2. We will perform an analysis of changes in pulmonary function defined by the difference between spirometric parameters between visits 1 and 2, and evaluate its association with incident HF, MI, stroke and death.

We will exclude subjects with prevalent coronary heart disease, stroke and HF in Visit 1 and Visit 2, and participants without information regarding lung function up to Visit 2. We will also exclude subjects with poor performance on spirometry indicated by quality control grades of "F" or "D."

Variables to be evaluated

Exposures variables:

Spirometry is a reliable test, with a coefficient of variation within subjects of about 5%.[13] In the ARIC Study, pulmonary function was obtained at Visits 1 and Visits 2, and Visit 5, and is available in the ARIC Study dataset. The following parameters will be analyzed: forced expiratory volume in one second (FEV_1), in mL; forced vital capacity (FVC), in mL; and forced expiratory flow (FEF) 25%-75%. We will consider the delta between Visit 1 and Visit 2 of each variable, as follows:

1) Difference between the FEV_1 at Visit 1 and Visit 2 (FEV_1 in Visit 2 - FEV_1 in Visit 1)
2) Difference between FVC at Visit 1 and Visit 2 (FVC in Visit 2 – FVC in Visit 1)
3) Difference between FEF25-75 at Visit 1 and Visit 2 (FEF 25-75% in Visit 2 – delta FEF 25-75% in Visit 1)

Outcome variables:

Incident heart failure, myocardial infarction, stroke and all cause mortality.

Other covariates:

- Demographic characteristics (age, race, sex, body mass index, ARIC center)

- Cardiovascular risk factors (arterial hypertension (diagnosis criteria or medication), diabetes mellitus, dislipidemia, alcohol consumption, smoking status)

- Lipid profile, glomerular filtration rate, C-reactive protein.

- Coronary heart disease, stroke

- Baseline parameters: FEV_1, FVC, or FEF 25%-75%

Analytical approach:

Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and first and third quartiles. Changes in lung function will be categorized in quartiles to perform Cox proportional analysis. Comparison among the groups will be performed using ANOVA or Kruskal-Wallis test according to the distribution of continuous variables. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Incident HF, stroke and myocardial infarction will be calculated and presented as events per 1000 person-years at risk. Analysis on the changes in lung function (quartiles of the differences between Visit 1 and Visit 2) for cardiovascular events and death will be performed using Cox proportional hazards model. We will create a univariate and a multivariable model to identify both the unadjusted and adjusted risk of the outcome of interest. We will test for interaction for age and race with decline in lung function to access the effect modification of both, age and race, in the relationship between changes in lung function and cardiovascular outcomes. If sustained by a significant interaction, we will perform a stratified analysis by age and race strata. The multivariable model will include the potential confounders: age, sex, race, body mass index, ARIC center, arterial hypertension, diabetes mellitus, dislipidemia, amount of alcohol consumption, smoking status, LDL cholesterol, glomerular filtration rate, and coronary heart disease. P-values <0.05 will be considered significant.

Limitations:

The 3-year period between the two spirometry tests could be short to detect differences in the lung function. Also, in this study, only the pre-bronchodilator measurements are available, even

though the post-bronchodilator would be the ideal according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[4] Finally, the residual confounding of the relationship between lung function and cardiovascular outcomes could not be completely addressed by multivariate model.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes   __X__ 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? ____ Yes   ____ No
   (This file ICTDER03 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)?

#1376: Agarwal SK, Chambless LE, Folsom A, Bertoni A, Ni H, Russel S, Rosamond WD, Heiss G. Optimal predictors of incident hospitalized heart failure: the ARIC study

#1377: Agarwal SK, Kitzman DW, Loehr L, Punjabi N, Shahar E. Relationship between pulmonary disease, lung function, and incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) study

#2117: Amil M Shah, John Hankinson, Christie Ballantyne, Dalane Kitzman, Sunil Agarwal, Scott D. Solomon. Relationship between pulmonary airflow obstruction, cardiac structure and function, and heart failure risk in a biracial elderly cohort: The ARIC study

#2173: Maria C. Mirabelli, Sunil K. Agarwal, R. Graham Barr, David J. Couper, Aaron R. Folsom, John L. Hankinson, Laura R Loehr, Stephanie J. London. Lung function decline among adults: the Atherosclerosis Risk in Communities Study

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**)* #946)

*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.

References:

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   associated with ageing. *Eur. Respir. J.* **13,** 197–205 (1999).

2. Lange, P. *et al.* Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary

   Disease. *N. Engl. J. Med.* **373,** 111–122 (2015).

3. Mannino, D. M. & Davis, K. J. Lung function decline and outcomes in an elderly population.

   Thorax **61,** 472–477 (2006).

4. GOLD_Report_2015.pdf. at

   <http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015.pdf>

5. Balmes, J. *et al.* American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am. J. Respir. Crit. Care Med.* **167,** 787–797 (2003).

6. Engström, G., Hedblad, B. & Janzon, L. Reduced lung function predicts increased fatality in future cardiac events. A population-based study. *J. Intern. Med.* **260,** 560–567 (2006).

7. Agarwal, S. K. *et al.* Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *Eur. J. Heart Fail.* **14,** 414–422 (2012).

8. Sin, D. D., Wu, L. & Man, S. F. P. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* **127,** 1952–1959 (2005).

9. Sin, D. D. & Man, S. F. P. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* **107,** 1514–1519 (2003).

10. Eickhoff, P. *et al.* Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **178,** 1211–1218 (2008).

11. Hancox, R. J. *et al.* Systemic inflammation and lung function in young adults. *Thorax* **62,** 1064–1068 (2007).

12. Jacobs, D. R. *et al.* Rate of decline of forced vital capacity predicts future arterial hypertension: the Coronary Artery Risk Development in Young Adults Study. *Hypertension* **59,** 219–225 (2012).

13. Laszlo, G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. *Thorax* **61,** 744–746 (2006).