ARIC Manuscript Proposal #2942

PC Reviewed: 02/14/2017 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Impaired lung function, lung disease, and risk of incident dementia: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Pamela L Lutsey, Nemin Chen, Kamakshi Lakshminarayan, Rebecca Gottesman, Thomas Mosley, David Knopman, Maria Mirabelli, Alvaro Alonso. Other interested investigators are welcome to join.

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

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3. Timeline: Analyses to begin immediately; pen draft anticipated completion summer 2017.

4. Rationale:

Dementia and mild cognitive impairment (MCI) are major causes of disability and dependency among older people. According to the WHO, 47.5 million of people have dementia worldwide and there are 7.7 million new cases every year.[1] Consequently, identification of potentially modifiable risk factors for dementia and MCI remains a research priority.

Growing evidence suggests that impaired lung function may be linked to greater risk of dementia.[2,3] Evidence exists for lung impairment as assessed by objective measures such as low forced expiratory volume in 1 second (FEV_1), forced vital capacity (FEV) and the ratio of FEV_1/FVC, as well as clinically recognized chronic obstructive pulmonary disease (COPD), asthma or chronic bronchitis. Patients with COPD suffer from systemic manifestations of the disease,[4] and growing evidence suggests that these comorbidities are independent of smoking and traditional risk factors.[5-7] Two studies have reported that diagnosis with COPD is associated with an approximately 80% higher risk of developing MCI over 5 years,[8] and MCI or dementia over 25 years,[9] respectively. Furthermore, in the shorter study a dose-response relationship was observed according to COPD duration and risk of MCI.[8] Clinical history of COPD has also been associated with decreasing cognitive performance over time.[10]

Some of the most important previous work exploring the relation between objectively measured impaired lung function and cognitive status comes from a prior ARIC publication. In this paper, impaired lung function was associated cross-sectionally with poorer performance in baseline cognitive assessments, and with increased risk of dementia hospitalization.[11] However, no association was found between lung function and cognitive decline over approximately 6 years of follow-up (between ARIC visits 2 and 4). Limitations of this previous analysis include short intervals between cognitive assessments in the cohort and insensitivity of the dementia definition used. Notably, in a separate ARIC publication we recently demonstrated that associations between sleep characteristics and incident dementia were stronger when using carefully adjudicated outcome definitions than when using a dementia definition which was likely less sensitive.[12] Several other studies,[13-15] though not all,[2] have also shown impaired lung function to be associated with worsening cognitive ability.

Mechanistically, impaired lung function could influence dementia and MCI risk through several pathways, largely mediated through chronic hypoxemia.[2,16] These include systemic inflammation, oxidative stress, physiological stress (e.g. sympathetic nervous system activation), and cerebral arterial stiffness and small-vessel damage.[2,16] Impaired lung function has also been linked to incident stroke, independent of smoking.[17,18] Hypoxemia within the context of obstructive sleep apnea has also been associated with greater risk of dementia.[19]

Herein we propose to explore the associations of lung function and lung disease with incidence of dementia and MCI based on a longer follow-up period than the previous publication, and with more precise event adjudication.

5. Main Hypothesis/Study Questions:

We hypothesize that:

1. Individuals with poorer lung function, as assessed by objective measures at visit 1 (i.e. FEV_1, FVC and FEV_1/FVC), will be more likely to develop dementia* and MCI during follow-up.
2. Self-reported COPD, asthma, emphysema and chronic bronchitis at baseline will be associated with greater risk of incident dementia* and MCI.
3. Participants with COPD or restrictive lung disease,[20] will be more likely to develop dementia* and MCI during follow-up.

*See “outcomes” section for dementia definitions.

Given the importance of smoking to lung function, *a priori* we plan to conduct analyses stratified by smoking status. Additionally, we will explore interactions by age, gender, race and APOE genotype subgroups.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with s

Primary Exposures

1) FEV_1 and FVC were objectively measured at visit 1. FEV_1/FVC is calculated.

2) Self-reported diagnoses of asthma, chronic bronchitis and emphysema were queried at visit 1. Self-reported COPD will be defined as the presence of self-reported diagnosis of either chronic bronchitis or emphysema.

3) We will also classify participants into 4 mutually exclusive groups,[20] as has been previously done in ARIC,[21] on the basis of both objective measures and self-reported information (approximate N's are provided in parentheses):
   - 'COPD': FEV_1/FVC below the lower limit of normal [LLN], (N ~ 2499)
   - 'Restrictive lung disease': FEV_1/FVC ≥ LLN and FVC < LLN, (N ~ 847)
   - 'Respiratory symptoms with normal spirometic results' (without RLD or COPD), (N ~ 1892)
   - 'Normal' (without respiratory symptoms, RLD, or COPD), (N ~ 9162)

Secondary Exposures

We may also explore using ICD codes to identify incident lung disease (particularly COPD). This information would enhance the baseline self-reported information (#2, above), and could be used as a time-varying exposure in the analysis.

Covariates & Potential Effect Modifiers

Covariate information will come from visit 1. Variables we anticipate using are as follows: age, sex, education, race, center, cigarette smoking, pack-years of smoking, physical activity, body mass index, height, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent CHD, stroke, heart failure and APOE genotype.

Outcomes

Outcomes of interested will be defined according to the methodology previously utilized in ARIC.[22] We anticipate using the following outcomes:

- Incident dementia from visit 1 to 2013 will be defined by combining all available information: visit 5 assessment, TICSm, hospitalization codes.
- Visit 5 syndromic adjudicated events: Dementia or MCI, dementia, MCI.
- V5 adjudicated etiologic events: Dementia or MCI due to AD etiology, or due to vascular etiology.

Statistical analysis

We will remain in contact with the ARIC NCS Analysis Committee to ensure that the most current analysis recommendations are employed. Participant characteristics will be described according to categories (most likely quintiles) of FEV_1 and the 4 category exposure variable.

For the incidence analyses, Cox proportional hazards regression will be used. Follow-up time will begin on the date of the visit 1 exam, and will accrue until a dementia hospitalization ICD code, loss-to-follow-up, death, December 31, 2013, or the visit 5 exam date. The proportional hazards assumption will be checked by plotting of log(-log) survival curves and testing the interaction between the exposures and time.

For analyses of the association between visit 1 lung function and risk of the neurocognitive study adjudicated outcomes we will use using relative risk regression using SAS Proc Genmod with a Poisson distribution and a log link.[23] For these analyses selection bias may have occurred as a result of differential participation and survival to visit 5. As such, we will use inverse probability weighting (IPW)[24,25] to adjust for attrition due to either death or failure to attend the follow-up neurocognitive exam (censoring).

A series of nested models will be used. Final decisions about modeling will take place during the analysis. Preliminarily, we envision our models as follows:

- Model 1 will adjust for age, sex, education and race-center (5-level variable).
- Model 2 will additionally adjust cigarette smoking and pack-years of smoking.
- Model 3 will further adjust for physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent coronary heart disease, heart failure, stroke and APOE genotype.

Interactions will be explored by age, gender, race and APOE genotype subgroups. Additionally, because of the importance of smoking on lung health, we will additionally conduct analyses stratified by smoking status. Lastly, we may include lung disease (particularly COPD) in the model as a time-dependent exposure.

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? __X__ Yes ____ 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)?

#1552: Pathan (student), Alonso (senior): Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities Study

#2134: Lutsey: Abnormal sleep characteristics and risk of incident mild cognitive impairment and dementia: The Atherosclerosis Risk in Communities Study (ARIC)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* 2008.06 (NCS))
___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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