ARIC Manuscript Proposal #3798

PC Reviewed: 3/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lung function as a predictor of cognitive decline and dementia risk in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lung function, cognitive decline, and dementia

2. Writing Group:

Writing group members: Beverly Gwen Windham, Kevin Sullivan, Michael Griswold, Pamela L. Lutsey, Srishti Shrestha, Stephanie J. London, Thomas H. Mosley, Xiaoqian Zhu (in an alphabetical order, others welcome)

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

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3. Timeline: Analysis will start immediately following proposal approval

4. Rationale:

Later-life cognitive impairment is associated with substantial public health and financial burden which is likely to increase with the aging of the population [1, 2]. With no foreseeable cure or disease-modifying interventions for severe forms of cognitive impairment including dementia, research on modifiable risk factors of cognitive decline may have important public health implications.

Prior studies have linked subtle changes in lung function measures as well as clinical pulmonary diseases with adverse neurocognitive outcomes including dementia [3-6]. Although a handful of studies have shown consistent links between suboptimal lung function and dementia [4], findings have been inconclusive for cognitive decline [7-12]. Further, the majority of prior studies evaluating cognitive change had short follow-up times, likely inadequate to capture cognitive decline, and they also did not account for cohort attrition that may have biased their findings (that is specifically applicable to those studies that recruited older participants) [7]. Given that reduced lung function in adulthood may be partially preventable, elucidating the association between lung function and cognition and underlying mechanisms may have significant implication for dementia prevention.

Systemic inflammatory processes underlying reduced lung function and chronic hypoxia-mediated neuropathological alterations have been suggested as potential mechanisms for the association between lung function and cognitive impairment, although evidence is not very conclusive [13-15]. Some indirect support for the association also comes from several imaging studies that have found associations between lung function measures, lung diseases and a range of neuropathological changes including reduced brain volume, white matter integrity, microbleeds, and infarcts [16-20]. A shared underlying pathology between pulmonary and cardiovascular conditions has also been suggested as a potential explanation, although, in some studies, associations for both cognitive outcomes and neuropathological outcomes persisted even after adjusting for cardiovascular conditions. While it is difficult to disentangle whether the association between lung function and cognitive decline/dementia risk is due to such common etiology, or simply confounded by vascular or other risk factors, well-designed epidemiological investigations considering subclinical vascular markers may shed light on the issue.

The Atherosclerosis Risk in Communities Study (ARIC) is a prospective cohort of community dwelling adults with over 30 years of follow up. In addition to its strengths including large sample size and long-term follow-up, with repeated lung function measures (assessed at enrollment (visit 1), visit 2, and visit 5) and cognitive assessments (visit 2 through visit 7) and rich vascular risk factors data, the ARIC study is particularly well-suited to examining lung function in relation to cognitive decline and dementia risk. Previously, two prospective investigations on lung function and neurocognitive outcomes were conducted using ARIC data [10, 21]. In one investigation, poor lung function, measured at visit 2, was associated with poor cognitive status at the same visit but not with 6-year cognitive decline in the entire cohort, or with 16 year-decline in a subset of participants with additional cognitive assessments (n=904); the study found elevated dementia hospitalization among those with reduced lung function [10]. Another investigation (with a median follow up of 23 years) reported a modest, non-statistically significant, risk of dementia for some lung function measures (visit 1); it, however, found somewhat stronger odds of dementia and mild cognitive impairment when analysis was restricted to adjudicated neurocognitive outcomes [21]. Both studies found elevated dementia among individuals with certain lung diseases. Since then, the ARIC has performed more cognitive examinations (with 20 more years of cohort-wide follow up data from additional three

investigations as compared to the prior report [10]) and has accumulated additional dementia cases (with six more years of follow up data compared to prior dementia report [21]). With extended follow up data, we propose to conduct an updated analysis to examine visit 2 lung function status in relation to incident dementia and cognitive decline in ARIC participants. We will also examine heterogeneity in lung function-cognitive decline/dementia associations by smoking, *APOE ε4* status, and history of cardiovascular diseases.

5. Main Hypothesis/Study Questions:

Our study aims are:
1) To examine associations between visit 2 lung function measures and incident dementia in ARIC
2) To examine associations between visit 2 lung function measures and cognitive decline in ARIC

We hypothesize that poor lung function measures are associated with elevated dementia risk and cognitive decline.

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: Prospective

Exposure: We will use forced expiratory volume at 1 sec (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio (values generated by spirometry) as our lung function measures. We will model lung function measures as continuous variables. We will also consider obstructive and restrictive lung diseases as defined in a prior ARIC study [21]. Specifically, obstructive lung disease will be defined as FEV1/FVC < limits of normal (LLN) and restrictive lung disease will be defined as FEV1/FVC≥LLN and FVC < LLN). Age-, race-and sex-specific LLN values will be calculated using equations proposed by Hankinson et al. [22]. Further, based on respiratory symptoms (cough, wheeze, phlegm) reported at visit 2 examination, those deemed as "normal" will be classified as "normal without respiratory symptoms" and "normal with respiratory symptoms".

Outcome:
1) Aim 1: Dementia through visit 7
2) Aims 2 and 3: Cognitive test scores (Delayed Word Recall Test, Digit Symbol Substitution test, Word Fluency Tests) and global cognition at visits 2, 3, 4, 5, 6, 7

Other baseline covariates:

Potential confounders, identified via directed acyclic graph, include age, sex, race, center/state, height (predictor of lung function), smoking status, waist-to-hip ratio (instead of body mass index to avoid collinearity with height), education, physical activity, diabetes, total cholesterol, hypertension, heart diseases, *APOE ε4*, and air pollution/traffic density. We will also consider

adjusting for fibrinogen/c-reactive protein, markers of inflammation associated with both cardiovascular and pulmonary diseases.

Statistical analysis:
Aim 1: We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the association between index visit (visit 2) lung function measures and incident dementia adjusting for potential confounders. We will examine proportional hazards assumptions by using log-log survival plots, goodness of fit test based on Schoenfeld residuals, and testing significance of interaction terms between exposures and time in the Cox model. We will examine effect modification in lung function-dementia associations by smoking status, *APOE ε4* status, and history of cardiovascular diseases.

We will consider several secondary/sensitivity analyses: (1) we will repeat analysis using visit 1 lung function measures to examine potential reverse causation bias; (2) we will use Fine and Gray sub-distribution hazard models to account for death as a competing risk for dementia [23]; (3) we will use multinomial models with a 4-category outcome – normal cognition, mild cognitive impairment (MCI), dementia and death, defined using adjudicated dementia status and surveillance through visit 7 as an alternative statistical approach to further examine dementia accounting for competing death effects.

Aim 2: We will use generalized linear mixed models with random slopes and random intercepts to examine the association between index visit 2 lung function measures and cognitive decline adjusting for potential confounders. Non-linearity in cognitive decline trajectories will be inspected and non-linear functions such as linear splines for the time scale will be incorporated in the model if needed. We will examine effect modification similar to Aim 1.

The generalized linear mixed models work under the assumption that missingness is at random and may yield biased parameter estimates when such assumption does not hold. To address potential bias from cohort attrition, we will perform sensitivity analysis using shared parameter models to account for unobserved cognitive decline among those who were censored either due to death or dementia over the course of follow up [24]. Briefly, a longitudinal mixed submodel, examining cognitive changes over time, and two survival submodels, one for dementia and one for death, will be simultaneously modeled, connected through shared latent characteristics (random effects). Given that the shared parameter model connects Aims 1 & 2, it may be adopted as the main analysis model for both aims if deemed appropriate.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)?

Pathan, S.S., et al., *Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study.* Eur J Neurol, 2011. **18**(6): p. 888-98.
Lutsey, P.L., et al., *Impaired Lung Function, Lung Disease, and Risk of Incident Dementia.* Am J Respir Crit Care Med, 2019. **199**(11): p. 1385-1396.
Liao, D., et al., *Lower pulmonary function and cerebral subclinical abnormalities detected by MRI: the Atherosclerosis Risk in Communities study.* Chest, 1999. **116**(1): p. 150-6.

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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