ARIC Manuscript Proposal #4018

PC Reviewed: 3/8/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lung function and brain MRI outcomes in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lung function and brain neuropathology

2. Writing Group:

Writing group members: Beverly Gwen Windham, Jeannette Simino, Kevin Sullivan, Michael Griswold, Pamela L. Lutsey, Rebecca Gottesman, 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]**

First author: Srishti Shrestha
Address: University of Mississippi Medical Center
2500 N State St, Jackson, MS 39216

Phone: (601)815-1967 Fax:
E-mail: sshrestha1@umc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Thomas Mosley
Address: University of Mississippi Medical Center
2500 N State St, Jackson, MS 39216

Phone: (601)984-4467 Fax:
E-mail: tmosley@umc.edu

3. Timeline: Analysis will start immediately following proposal approval

4. Rationale:

A growing body of literature suggests a potential link between lung function measures and adverse neurological outcomes including cognitive decline, dementia, and stroke [1-7]. While systemic inflammation, chronic hypoxia, and shared underlying pathology between pulmonary and cardiovascular functions have been implicated for such associations [5, 8-10], potential mechanisms are less understood. Brain imaging studies can improve the understanding of underlying neurodegenerative and cerebrovascular disease processes associated with poor lung function and provide more cogent evidence for the associations with dementia and stroke. A few studies have evaluated lung function measures and brain neuropathological changes including reduced brain volumes [11, 12], white matter abnormalities (including lesions and hyperintensities) [12-18], white matter integrity [19], microbleeds [20], and infarcts [14, 16, 17], although findings have not been consistent [11, 17, 21]. With a majority of the studies examining white matter abnormalities, other brain pathologies remain minimally explored. Further, only a few of these had larger sample sizes and focused on general populations, with others based on health care seeking individuals or smaller clinical populations.

Using 30 years of follow up data from the Atherosclerosis Risk in Communities (ARIC) Study, we recently found that better lung function measures at visit 2 were associated with reduced dementia risk and attenuation in cognitive decline over time (manuscript proposal # 3798). Previously, in the ARIC study, two investigations had explored associations between lung function measures and brain MRI markers. Specifically, in a select sample of participants (n=1917), lower forced expiratory volume at 1 sec (FEV_1) and forced vital capacity (FVC), assessed at visits 1 and 2, were associated with higher prevalence of subclinical cerebral infarction and white matter lesions at visit 3 [14]. Later, another investigation conducted after 10-year follow up of these participants (n=1112) found that higher FEV_1 was associated with slower 10-year progression of ventricular size worsening, but was not associated with other brain MRI changes examined [21]. At visit 5, the ARIC Study conducted more comprehensive brain MRI exams that include volumetric measures, infarcts, microbleeds, white matter hyper-intensities, and white matter microstructural integrity. Here, we propose comprehensive analyses of brain MRI findings assessed at visit 5 in relation to lung function measured at mid-life (visit 2) and late-life (visit 5). As a secondary aim, we will also consider evaluating if these brain MRI markers mediate association between lung function and cognitive decline.

5. Main Hypothesis/Study Questions:

Primary Aim: To examine associations of visit 2 and visit 5 lung function measures with brain MRI markers assessed at visit 5.

Hypothesis: We hypothesize that poor lung function measures are associated with adverse brain neuropathology (specifically, smaller brain volumes; higher levels of infarcts, microbleeds, white matter hyperintensities, and poor white matter microstructural integrity).

Secondary Aim: To examine if brain MRI markers mediate the association between lung function and future cognitive decline.

Hypothesis: We hypothesize that brain MRI markers partially mediate the association between lung function and visit 5 to visit 7 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:
Cross-temporal (visit 2 lung function and visit 5 brain MRI) and cross-sectional (visit 5 lung function and visit 5 brain MRI)

Exposure:
We will use FEV_1, FVC and FEV_1/FVC ratio (values generated by spirometry) as our lung function measures. We will model lung function measures as continuous variables. We will also consider using clinically defined diseases based on these spirometry measures using reference equations from the Global Lung Function Initiative. We will examine both visit 2 and visit 5 lung function measures as they reflect measures at mid- and later-life.

Outcome:
Primary Aim: Outcomes (measured at visit 5) include white matter hyper-intensity (WMH) volume, cortical and lacunar infarcts, cerebral microbleeds, white matter microstructural integrity (i.e. fractional anisotropy and mean diffusivity as measured by diffusion tensor imaging, and based on both the Lobar-22 and Johns Hopkins University Atlases), and brain volumes (total and regional). We will also consider longitudinal changes in these brain MRI markers once follow up data are available.

Secondary Aim: Global cognition at visits 5, 6, 7

Other baseline covariates:
Potential covariates for adjustment include age (and age squared), sex, race, center/state, height (predictor of lung function), smoking status including pack-years, 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 estimated total intracranial volume. We will also consider adjusting for fibrinogen/c-reactive protein, markers of inflammation associated with both cardiovascular and pulmonary diseases. Except for time invariant covariates (obtained at visit 1) and estimated total intracranial volume (obtained at visit 5), we will use visit 2 covariates for analysis examining visit 2 lung function and visit 5 covariates for analysis examining visit 5 lung function.

Statistical analysis:
Primary aim: We will use generalized linear models to examine the associations of lung function measures with brain MRI outcomes, adjusting for potential confounders; models will be selected based on the distribution of the outcome of interest (i.e., WMH volumes, white matter microstructural integrity, cortical or lacunar infarcts, cerebral microbleeds, brain volumes). In a previous analysis examining lung function and cognitive decline, we observed interaction

between FEV_1 and FVC (manuscript proposal # 3798) suggesting cognitive declines depended on varying levels of both measures. We will also examine potential interaction between them with brain MRI markers. Given that only a subsample of original cohort participated in ARIC at visit 5 due to death or other causes, we will conduct sensitivity analysis by incorporating inverse probability weights or multiple imputation (as appropriate) for cohort attrition.

Additionally, we will perform other sensitivity analyses by (i) incorporating sampling weights to account for sampling approach used to select participants for MRI; (ii) excluding participants with prevalent dementia and all stroke; and (iii) excluding participants with morphological abnormalities of the brain, lung cancer, and lung surgery; and (iv) restricting analysis to never smokers.

Secondary aim: The mediation analysis will be performed for those brain MRI markers that are associated with both lung function measures and visit 5 to visit 7 cognitive declines. Briefly, we will consider using Generalized Structural Equation Modeling (GSEM) techniques to identify mediation pathways and obtain direct and indirect effect estimates, adjusting for potential confounders.

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. (ARIC Manuscript Proposal # 1552)

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. (ARIC Manuscript proposal #2942)

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.

Knopman DS, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology. 2011;76(22):1879-85.

ARIC Manuscript proposal # 3798: Lung function as a predictor of cognitive decline and dementia risk in 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)* _____ _____ _____)

*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.

References

1. Gilsanz, P., et al., *Early Midlife Pulmonary Function and Dementia Risk.* Alzheimer Dis Assoc Disord, 2018. **32**(4): p. 270-275.

2. Russ, T.C., M. Kivimaki, and G.D. Batty, *Respiratory Disease and Lower Pulmonary Function as Risk Factors for Dementia: A Systematic Review With Meta-analysis.* Chest, 2020. **157**(6): p. 1538-1558.
3. Guo, X., et al., *Midlife respiratory function and Incidence of Alzheimer's disease: a 29-year longitudinal study in women.* Neurobiol Aging, 2007. **28**(3): p. 343-50.
4. Qiao, H., et al., *Poor lung function accelerates cognitive decline in middle-aged and older adults: Evidence from the English Longitudinal Study of Ageing.* Arch Gerontol Geriatr, 2020. **90**: p. 104129.
5. Lahousse, L., et al., *Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review.* Respir Med, 2015. **109**(11): p. 1371-80.
6. Portegies, M.L., et al., *Chronic Obstructive Pulmonary Disease and the Risk of Stroke. The Rotterdam Study.* Am J Respir Crit Care Med, 2016. **193**(3): p. 251-8.
7. Silvestre, O.M., et al., *Declining Lung Function and Cardiovascular Risk: The ARIC Study.* J Am Coll Cardiol, 2018. **72**(10): p. 1109-1122.
8. Gibson, G.E., et al., *Brain dysfunction in mild to moderate hypoxia.* Am J Med, 1981. **70**(6): p. 1247-54.
9. Row, B.W., *Intermittent hypoxia and cognitive function: implications from chronic animal models.* Adv Exp Med Biol, 2007. **618**: p. 51-67.
10. Dodd, J.W., *Lung disease as a determinant of cognitive decline and dementia.* Alzheimers Res Ther, 2015. **7**(1): p. 32.
11. Sachdev, P.S., et al., *Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample.* Dement Geriatr Cogn Disord, 2006. **21**(5-6): p. 300-8.
12. Wang, J., et al., *Pulmonary function is associated with cognitive decline and structural brain differences.* Alzheimers Dement, 2021.
13. Longstreth, W.T., Jr., et al., *Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study.* Stroke, 1996. **27**(8): p. 1274-82.
14. 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.
15. Murray, A.D., et al., *Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people.* Radiology, 2005. **237**(1): p. 251-7.
16. Kim, Y., et al., *Reduced forced vital capacity is associated with cerebral small vessel disease burden in cognitively normal individuals.* Neuroimage Clin, 2020. **25**: p. 102140.
17. Guo, X., et al., *Midlife respiratory function related to white matter lesions and lacunar infarcts in late life: the Prospective Population Study of Women in Gothenburg, Sweden.* Stroke, 2006. **37**(7): p. 1658-62.
18. Takamatsu, K., K. Park, and A. Yokoyama, *Association between airflow limitation and leukoaraiosis of the brain.* Respir Investig, 2021. **59**(3): p. 320-326.
19. Dodd, J.W., et al., *Brain structure and function in chronic obstructive pulmonary disease: a multimodal cranial magnetic resonance imaging study.* Am J Respir Crit Care Med, 2012. **186**(3): p. 240-5.
20. Lahousse, L., et al., *Chronic obstructive pulmonary disease and cerebral microbleeds. The Rotterdam Study.* Am J Respir Crit Care Med, 2013. **188**(7): p. 783-8.
21. Knopman, D.S., et al., *Vascular risk factors and longitudinal changes on brain MRI: the ARIC study.* Neurology, 2011. **76**(22): p. 1879-85.