

ARIC Manuscript Proposal # 1552

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Priority: 2
Priority: _____

1. a. Full Title: Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities Study

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

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

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3. Timeline:

We expect to have a well-advanced draft of the manuscript by the end of October. To achieve this aim, we plan to start statistical analysis immediately upon approval of the proposal and start drafting of the manuscript soon after.

4. Rationale:

Dementia is a major public health problem in the US, which will continue increasing as the population ages.¹ The limited effectiveness of available treatments for dementia highlights the need of a preventive approach to this neurodegenerative disorder. Different studies have shown that cardiovascular risk factors are associated with a higher risk of developing both Alzheimer's disease and vascular dementia, the two most frequent types of dementia. Poor lung function is considered also a potential cardiovascular risk factor, given its association with different cardiovascular outcomes [Schroeder Am J Epidemiol 2003, Hozawa Chest 2006]. In fact, a few studies have found a higher risk of dementia or lower cognitive function among individuals with worse pulmonary function. However, most of these studies have been cross-sectional, conducted in small population, or included only white samples [Chyou Am J Epidemiol 1996, Schaub J Geront Med Sci 2000, Guo Neurobiol Aging 2007, Alonso J Neurol Sci 2009]. No previous studies have examined this association a sizeable population of African-Americans, who have a higher risk of dementia.

Different mechanisms could explain the association of lung function with cognitive decline and dementia. For example, it has been shown that reduced oxygen supply could increase levels of amyloid precursor protein and beta-amyloid [REF 2]. It has been also shown that reduced lung function is associated with a pro-inflammatory state that could, eventually, lead to a higher risk of dementia [Engstrom Circulation 2002, Thyagarajan Chest 2009]. Finally, in the ARIC study, reduced lung function has been associated with MRI-detected cerebral subclinical abnormalities [Liao Chest 1999]. Medical studies have also shown that decreased oxygen supply due to reduced lung function causes hypoxia that possibly leads to hypoperfusion of the brain leading to potential brain injury.

Exploring the association between lung function and cognitive decline/dementia might provide new insights into the mechanisms involved in the association between determinants of lung function (such as smoking or physical activity) and dementia, as well as highlight a new avenue for the prevention of this neurological disorders.

5. Main Hypothesis/Study Questions:

We propose to evaluate the association of lung function (FEV₁, FVC, FEV₁/FVC, predicted FEV₁ and predicted FVC) measured in midlife patients (ages 47-68) with cognitive decline and risk of dementia hospitalization in the ARIC study. We hypothesize that:

1. Individuals with reduced lung function will be more likely to experience cognitive decline between ARIC visits 2 and 4.
2. Individuals with reduced lung function will have a higher risk of dementia hospitalization.
3. These associations will be present both in Whites and African-Americans.
4. Associations will be stronger when lung function was measured at a younger age.
5. The association of the FEV₁/FVC ratio as an important measure of obstructive lung disease will show reduced lung function leading to a higher risk of dementia hospitalization.

Finally, as a secondary hypothesis, we will explore the association of lung function with cognitive function change measured four times in the subset of ARIC participants enrolled in the ARIC Brain MRI study.

The hypothesized associations are assumed to be independent of the other confounders such as smoking.

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 population

We will include all ARIC study patients who attended visit 2 and did not meet any of the following exclusion criteria: no consent to collaborate in genetic research, previous pulmonary disease, history of myocardial infarction, stroke or heart failure, missing values for covariates or any of the pulmonary variables of interest (Spirometry, FEV₁, FVC), and, for the dementia hospitalization analysis, those scoring below gender and race-specific percentile 5th in any of the cognitive tests administered (delayed word recall, digit span substitution, word fluency).

Exposures

Information on pulmonary risk factors and other variables will be obtained from study questionnaires and physical exams. We will consider the following variables measured at visit 2: age at baseline, sex, race, education (visit 1; less than high school, high school graduate but no college degree, college degree), occupation (visit 1; 9 categories: managerial/professional specialty, technical/sales/administrative support, service, farming/forestry/fishing, precision production/craft/repair, operator/fabricator/laborer, homemaker, retired, missing), field center, hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), smoking (current, past, never), pack-years of smoking, body mass index (<20, 20-<25, 25-<30, ≥30), history of pulmonary diseases (COPD, asthma) and APOE genotype.

Outcome Ascertainment

Our analysis will focus on two different outcomes. First, we will assess cognitive decline as the change in cognitive score tests (DWR, DSS, WF) between visit 2 and visit 4. Second, we will ascertain hospitalizations through December 2005 in individuals who attended visit 2. We will define this event as the presence of an ICD-9 or -10 code for dementia in a hospital discharge or dementia considered as the primary cause of death (using ICD-9 or ICD-10 codes). Although dementia was not assessed specifically at baseline, the study characteristics precluded the inclusion of participants with significant cognitive impairment suggesting that most of the cases detected will be incident cases.

Statistical analysis

FEV₁ and FVC measured at visit 2 will be used as estimates of lung function. We will classify individuals by quartiles of these variables. The association of lung function with cognitive decline will be tested with linear general models with change in each cognitive score between visit 2 and 4 as main outcome variables. For dementia hospitalizations, we will use Cox proportional hazards model with time from visit 2 to index hospitalization or end of follow-up as main outcome. Initial models will be adjusted for age, gender, and race. Subsequently, we will

adjust for other covariates potentially confounding the association: smoking (never, past, current; pack-years of smoking), education, occupation, APOE genotype, study center, body mass index, and other cardiovascular risk factors (diabetes, hypercholesterolemia, systolic blood pressure, use of BP lowering drugs). Because smoking is a major confounder of this association, we will additionally conduct analyses stratified by smoking status. Finally, we will explore cognitive changes in the ARIC MRI study participants using multivariate, random-effects linear models.

Limitations

The main limitation is classification of dementia. It is known that dementia is not a disease usually requiring hospitalization. Although we will make use of the ICD 9 or ICD 10 codes, it is difficult to classification the exact type of dementia the patient develops, i.e. Alzheimer's disease, vascular, or decreased lung function associated. The focus of this analysis will be center on the development of dementia in general. An additional major limitation is confounding by smoking. We will try to address this problem conducting an analysis stratified by smoking status.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
 ☒ 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.csc.unc.edu/ARIC/search.php>

☒ 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)? None

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ☐ 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)* 1999.01 _____)

*ancillary studies are listed by number at <http://www.cscce.unc.edu/aric/forms/>

12. 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.

References:

1. A Hovestadt, J M Bogaard, J D Meerwaldt, F G van der Meché and J Stigt. Pulmonary Function in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 1989;52;329-333 doi:10.1136/jnnp.52.3.329
2. Peers C. et al. Hypoxia and Alzheimer's disease. *The Journal of Quality Research in Dementia*, Issue 4. 2009 Available Online: http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=382&pageNumber=2
3. Whitmer RA. et al. Midlife Cardiovascular Risk Factors and Risk of Dementia in Late Life. *Neurology*. 2005 Jan 25; 64(2):277-81.
4. Hozawa A, et al. Lung Function and Ischemic Stroke Incidence. *Chest*. 2006 December;130; 1642-1649
5. Duanping L. et al. Lower Pulmonary Function and Cerebral Subclinical Abnormalities Detected by MRI. *Chest* 1999 July;116; 150-156
6. Schaub R. et al Ventilatory Capacity and Risk for Dementia. *Journal of Gerontology:MEDICAL SCIENCES February* 2000, Vol. 55A, No. 11, M677-M683
7. Schroeder E. et al. Lung Function and Incident Coronary Heart Disease: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol* June 2003;158:1171-1181
8. Bharat T. et al. Association of Circulating Adhesion Molecules with Lung Function. *Chest* 2009 February;135;1481-1487;
9. Alvaro A. et al. Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the Seven Countries Study. *Journal of the Neurological Sciences* 280 (2009) 79-83
10. Chyou P. et al. Pulmonary Function Measures as Predicators and Correlates of Cognitive Function in Later Life. *Am J Epidemiol* Vol. 143, No. 8, 1996
11. Engstrom G. et al. Lung Function and Cardiovascular Risk: Relationship with Inflammation-Sensitive Plasma Proteins. *Circulation* 2002;106;2555-2560
12. Guo X. et al, Midlife respiratory function and Incidence of Alzheimer's disease: A 29-year longitudinal study in women. *Neurobiology of Aging* 28 (2007) 343-350