

ARIC Manuscript Proposal # 1220r

PC Reviewed: _3/_13/07
SC Reviewed: _____

Status: _A_
Status: _____

Priority: _2_
Priority: _____

1.a. Full Title: Relationship of Lung Function with Age-related Macular Degeneration and Retinal Vascular Disease

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

2. Writing Group:

Writing group members: Cheung N, Klein R, Folsom A, Wong TY

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NC

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3. Timeline:

Manuscript proposal to Publication's Committee:	Jan 2007
Data analysis completed:	Jun 2007
Completed manuscript to Publication's Committee:	Oct 2007

4. Rationale:

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in the United States.¹ Despite much effort in research, the pathogenesis of AMD remains poorly understood and aside from age, family history and smoking, few risk factors have been found to be consistently associated with this condition in epidemiological studies.^{2,3}

Lung disease has long been found to be associated with early and late signs of AMD.⁴ In the Beaver Dam Eye Study, self-reported history of emphysema at baseline was associated with the 15-year incidence of retinal pigment epithelial depigmentation, a sign of early AMD (OR 2.5, 95% CI 1.3, 4.8), $p=0.006$ and exudative AMD, a sign of late AMD (OR 3.0, 95% CI 1.0, 8.4, $p=0.04$). (Klein R., unpublished data) These associations remained after controlling for smoking and other factors. In that study, a history of respiratory symptoms (cough/phlegm/wheezing), first obtained at the 10-year follow-up, was associated with the 5-year incidence of exudative AMD (OR 3.6, 95% CI 1.4, 9.3, $p=0.01$) and progression of AMD (OR 2.9, 95% CI 1.4, 6.0 $p=0.004$), independent of a history of smoking. Also, while controlling for age, smoking status, and a history of emphysema, peak expiratory flow rate was inversely associated with the 5-year incidence of two signs of early AMD, large drusen (OR 4th vs 1st quartile range 0.4, 95% CI, 0.2, 0.7, $p=0.001$) and soft drusen (OR 0.5, 95% CI 0.3, 0.9, $p=0.01$), and progression of AMD (OR 0.5, 95% CI 0.2, 1.0, $p=0.04$). These findings regarding pulmonary disease and function have been hypothesized to be related to inflammation and/or decreased systemic oxygenation. There have been few other population-based studies that have examined these relationships.

Apart from AMD, lung disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) and poorer lung function have also been associated with systemic diseases, such as stroke,⁵⁻⁷ coronary heart disease⁸ and diabetes,⁹ even after controlling for potential confounders. However, the pathophysiological mechanisms underlying these associations remain unclear. While some investigators proposed that inflammation may contribute to the link between lung and cardiovascular diseases,⁸ microvascular processes, which are known to play important roles in the development of cardiovascular disease,¹⁰⁻¹⁴ have not been investigated, possibly due to the difficulty in studying, directly, the effect of lung disease on the systemic microcirculation. Nevertheless, studies now show that the human retina provides a unique, direct and non-invasive “window” to study the health of systemic microcirculation in vivo.¹⁵ Similar to lung disease and function, microvascular disease, reflected as pathological (retinopathy signs) and physiological (narrower retinal arterioles and wider retinal venules) changes in the retinal vasculature, have been shown to predict a range of cardiovascular and metabolic outcomes, independent of other risk factors.¹⁵⁻²⁶ These studies provide strong evidence that standardized assessment of these retinal vascular changes may offer additional insights into the role of microvascular processes in the development of cardiovascular diseases.

In this study, we propose to investigate the relationships of putative lung disease and functional pulmonary measures with AMD and retinal vascular changes, in view of advancing our understanding of the AMD pathogenesis and the potential microvascular processes involved in the link between lung and cardiovascular diseases.

5. Main Hypothesis/Study Questions:

- (1) Poorer lung function is associated with AMD.
- (2) Presence and severity of pulmonary disease (COPD and asthma) are associated with AMD.

- (3) Poorer lung function is associated with adverse retinal vascular changes (narrower retinal arterioles,^{18,19} wider retinal venules,²³⁻²⁶ retinopathy signs^{17,20,21}).
- (4) Presence and severity of pulmonary disease (COPD and asthma) are associated with adverse retinal vascular changes (narrower retinal arterioles, wider retinal venules, retinopathy signs).

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).

- A.** Study sample: all ARIC cohort members, who participated in the eye examinations (at **Visit 3**) and had gradable fundus photographs for (1) AMD signs and (2) retinal vascular variables, with pulmonary data collected at **Visit 1 and 2**.
- B.** Exposure variables:
 - i. Lung function data: forced expiratory volume in one second (FEV1 in liters), forced vital capacity (in liters) and FEV1/FVC ratio measured at ARIC **Visit 1 and 2**.^{5,8,9,27}
 - ii. Lung disease/symptom data (**Visit 1, 2 and 3**): Asthma (self-reported or doctor diagnosed⁶), COPD (chronic bronchitis, physician-diagnosed emphysema, spirometrically detected COPD,²⁸ and also according to the Global Initiative on Obstructive Lung Disease classification²⁹).
- C.** Outcome variables:
 - i. AMD variables at **Visit 3**: any AMD, early AMD, late AMD and specific AMD lesions (drusen, RPE de-pigmentation, any pigmentary changes)
 - ii. Retinal microvascular variables at **Visit 3**: retinal arteriolar diameter, retinal venular diameter, arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinopathy severity, microaneurysms, retinal hemorrhages, soft (cotton-wool spots) and hard exudates, and macular edema.
- D.** Potential confounders (in addition to age, gender, race/ethnicity and study centers):
 - i. Cardiovascular risk factors at **Visit 1, 2 and 3**: BMI, hypertension, blood pressure, diabetes, cigarette smoking and pack-years of smoking, anti-hypertensive medications use, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, fasting glucose, creatinine (at Visit 1, 2, 4), HbA1c (at Visit 2).
 - ii. Educational attainment and income.
 - iii. Occupational exposure to dust, fumes and smoke.
 - iv. Environmental tobacco smoke exposure.
 - v. Air population data from the US Environmental Protection Agency's Aerometric Information Retrieval System.²⁷
 - vi. Medication use (beta-blocker, bronchodilator, multivitamin)
 - vii. Markers of inflammation (e.g., white cell count, fibrinogen) and endothelial dysfunction (e.g., Von Willibrand factor).
- E.** Plan of analysis:
 - i. We will examine associations of various lung measures with AMD (and its lesions) and retinal vascular changes in the total sample and in each race/ethnic group.
 - ii. We will examine interactions of various lung measures and race/ethnicity and other potential effect modifiers (e.g., smoking) for signs of AMD and other retinal vascular signs.

- iii. For these analyses, we will examine the relationships of the various risk factors of interest (e.g., lung function, COPD, asthma) with each of the specific AMD lesions (e.g., drusen, pigmentary abnormalities) and the prevalence of two endpoints of disease severity, early and late AMD. Similarly, this will also be done to examine the relationship with retinal vascular changes (e.g., retinopathy, retinopathy severity, retinal arteriolar and venular calibers). Some risk factors will be treated as continuous variables and others as categorical variables in multivariate models. We will first examine each variable in age- and gender-adjusted logistic models by outcome. Final models will then be built. Appropriate interaction terms will be added into regression models to evaluate interactions.
- iv. Analyses of the associations for AMD and retinal vascular changes (Visit 3) will be based on lung function data determined at Visit 1 and 2. We will use Visit 2 data first and will also try averaging continuous measures of lung function from both Visit 1 and 2, and treat these analyses as cross-sectional. We are aware that there may be changes between the different exams, but anticipate the changes to be small, because of the short interval between the exams (e.g., Visit 2 and 3) and to have little impact on our results. We will, however, address these issues in details in the Discussion if required (e.g., if use of data from Visit 1 is necessary).

7.a. Will the data be used for non-CVD analysis in this manuscript? No

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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? No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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.csc.unc.edu/ARIC/search.php> Yes

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)?

Schroeder EB, Welch VL, Couper D, et al. Lung function and incident coronary heart disease. The Atherosclerosis Risk in Communities Study. Am J Epidemiology 2003;158:1171-1181).

We are aware of no ARIC manuscripts or proposals related to lung function/disease and and retinal signs/disease.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 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 at <http://www.csc.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.

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