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Are Lung Disease and Function Related to Age-related Macular Degeneration?

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Abstract

Purpose—To describe the relationship of lung disease and function with early age-related macular degeneration (AMD) in a population-based study.

Design—A population-based, cross-sectional study of 12,596 middle-aged participants from the Atherosclerosis Risk in Communities Study.

Methods—Lung function was assessed by spirometry. Physician diagnosis of asthma and lung disease was ascertained from a standardized questionnaire. AMD signs were graded from fundus photographs according to the Wisconsin grading protocol.

Results—Of our study population, 587 (4.7%) had early AMD, 638 (5.1%) had asthma and 581 (4.6%) had lung disease. After adjusting for age, gender, smoking and hypertension, each litre increase in predicted forced expiratory volume in one second (FEV₁) (odds ratio [OR]: 1.27; 95% confidence interval [CI]: 0.89, 1.80), forced vital capacity (FVC) (OR 1.18; 95% CI: 0.93, 1.51) and peak expiratory flow rate (OR 1.12; 95% CI: 0.95, 1.33) were not significantly associated with early AMD. FEV₁/FVC ratio (second quartile OR 1.61; 95% CI 0.88–2.93, third quartile OR 1.65; CI 0.90–3.03, fourth quartile OR 1.28; 95% CI 0.68–2.40) was not significantly associated with early AMD. Similarly, asthma (OR 1.06; 95% CI: 0.86, 1.27) and other lung diseases (OR 1.08; 95% CI: 0.90, 1.29) were not associated with early AMD.

Conclusion—Our data do not support a cross-sectional association between lung disease and risk of early AMD.

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in the United States, affecting more than 8 million Americans.¹ Despite ongoing research, the pathogenesis of AMD remains incompletely understood. Cigarette smoking is a modifiable risk factor that has been consistently associated with AMD.² Aside from age, smoking, and genetic factors, few risk factors have been found to be associated with this condition in epidemiological studies.^{1–7}

Two population-based studies reported poorer lung function and a history of chronic lung disease (e.g., emphysema) to be associated with the risk of AMD. Over three decades ago, the Framingham Eye Study⁸ first observed a significant association between decreased vital capacity and a history of lung infection with prevalent cases of AMD. Two subsequent case-control studies^{9–10} failed to replicate this relationship. More recently, the Beaver Dam Eye Study¹¹ provided new data demonstrating that participants with emphysema at baseline were more likely to develop retinal pigment epithelial (RPE) depigmentation, a sign of early AMD (odds ratio 2.5; $p=0.006$), and late AMD (odds ratio 3.0, $p=0.04$) over a 15-year period. In addition, a history of mild respiratory symptoms, such as cough, phlegm and wheezing, was associated with the 5-year incidence of exudative AMD and progression of AMD.¹¹ These associations were shown to be independent of smoking and other risk factors.¹¹ Furthermore, in an earlier cross-sectional study, Klein *et al*¹² reported poorer lung function to be associated with the prevalence of AMD. These findings suggest that lung disease and poorer lung function could contribute to AMD risk, possibly via mechanisms related to inflammation and hypoxia.^{11–12}

In the ARIC study, we examined the cross-sectional relationship between lung disease or function and early AMD in a large population-based sample of white and African Americans in the United States.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a population-based study of 15,792 persons aged 45–64 years selected from four United States communities.^{13–15} Of the baseline participants, 14,346 returned to the second examination (1990–92) and 12,887 to the third examination (1993–95). At second examination, participants had lung function assessed using a spirometry; predicted force-expiratory volume in one second (FEV₁)(L), predicted force vital capacity (FVC)(L), predicted peak expiratory flow rate (PEFR)(L) and percentage predicted FEV₁/FVC ratio (%)^{16–18}. Lung disease variables were collected through physician-administered questionnaires; asthma and lung disease (defined as chronic bronchitis, emphysema, or spirometrically detected COPD), according to the Global Initiative on Obstructive Lung Disease (GOLD)¹⁹ classification.

At the third examination, early AMD was recorded using retinal photography^{13–15} included soft drusen, pigmentary change or both. Potential confounders included age, gender, race, smoking, hypertension and centre.

Study Number

Our study was based on the 12,887 ARIC participants who returned for the third examination, excluding 291 participants, leaving 12,596 participants in the current study. Exclusion criteria included race neither white nor African-American (213), incomplete data for lung function assessment (29), ungradable retinal photographs (32) and late AMD (17).

Late AMD was excluded as an outcome as the numbers available were too small for meaningful analyses.

Retinal Photography and AMD Grading

The assessment of AMD in the ARIC study has been previously reported.^{13–15} In brief, a 45-degree non-mydratic retinal photograph centered on the region of the optic disc and the macula of one randomly selected eye was taken after 5 minutes of dark adaptation. Graders, masked to the subject's identity, evaluated the photographs for AMD based on a simplified version of the Wisconsin AMD grading system.^{13–15} The presence of soft drusen, retinal pigment epithelium (RPE) depigmentation, increased retinal pigment, pure geographic atrophy, and signs of exudative macular degeneration were determined. Soft drusen was defined as those having a diameter larger than 63 μ m. Early AMD was defined as the presence of either soft drusen alone, RPE depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or RPE depigmentation in the absence of late AMD.^{13–15} Late AMD was defined as the presence of exudative AMD or pure geographic atrophy.^{13–15} Quality control procedures, based on repeated assessment of 520 photographs, showed weighted kappa values of 0.67 to 0.81 for intra-grader and 0.55 to 0.92 for inter-grader comparisons.^{13–15}

Lung Function Assessment

Lung function was measured according to a standard protocol, with the use of a Collins Survey II volume-displacement spirometer (Warren E. Collins, Braintree, Mass).²⁰ The technicians were trained and certified, and their performance was closely monitored by the staff of the pulmonary-function reading center. During at least five forced expirations, the technician attempted to obtain three acceptable spirograms at least two of which had similar results (within 5 percent) for forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). At the reading centre, the technician observing the volume-time spirometry would correlate these findings with the acceptability and reproducibility of the spirometry as indicated by the computer program. The largest FEV₁ and the largest FVC on any of the acceptable tests were used.²⁰ Sex-specific predicted values for FEV₁ and FVC, adjusted for age and height, were computed from Crapo's equations.²¹ For African-Americans, equation-derived predicted FEV₁ and FVC were multiplied by 0.88.^{22,23}

Definition of Other Variables

At baseline and second visits, all participants had comprehensive examinations to assess cardiovascular risk factors.^{13–15} Blood pressure was computed from the average of the second and third readings using a standardized Hawksley random-zero instrument.^{13–15} Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication. Cigarette smoking status was obtained from standardized questionnaires with the following questions; (1) Have you ever smoked cigarettes? (2) Do you now smoke cigarettes? Persons were categorized as current smokers if they answered yes to question 1 and 2, former smokers if they answered yes to question 1 and never smokers if they answered no to question 1. Never and former smokers were further classified as exposed to environmental tobacco smoke if they reported being in close contact with smokers for more than 1 hour per week.^{13–15}

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (CIs) were reported for the association between lung function [predicted FEV₁/FVC ratio (%), predicted FEV₁(L), predicted FVC(L) and predicted PEF(L)] and lung disease (physician diagnosed asthma or lung disease) and early AMD. Lung function and disease exposures were analysed for the

entire cohort first. Interaction with gender was explored using the likelihood ratio test. Two models were created; Model 1 adjusted for age and gender and Model 2 further adjusted for race, smoking, hypertension and study site. Interaction with race for the association across predicted FEV₁/FVC ratio quartiles and early AMD was tested in both models. The analyses was further stratified by race due to an interaction between race and lung function variables on the odds of AMD and the purposeful oversampling of blacks in the study design. Two models were created; Model 1 adjusted for age and gender and Model 2 further adjusted for smoking, hypertension and study site. Stata IC version 10.0 (Texas Corp.) was used for all analyses.

RESULTS

Table 1 shows the baseline demographic characteristics of the ARIC study sample by age, with a cut-off at 57 years. There were significantly larger proportions of male and female and African-Americans in the younger age group. Younger participants were also more likely to be current smokers. The mean FEV₁/FVC ratio was higher among younger study participants ($p < 0.001$). The prevalence of lung disease early AMD and hypertension was higher within the older age group ($p < 0.001$).

The mean percentage predicted FEV₁/FVC ratio for the entire cohort follows a bimodal distribution (African-Americans: left normal curve and White-Americans: right normal curve), with a distinct distribution cut-off at approximately 75.0%. [FIGURE 1]

Table 2 shows an association between predicted FEV₁/FVC ratio and early AMD in both models for the entire cohort (p for likelihood ratio test 0.001 and 0.05). After adjusting for age and sex, there is a strong association between predicted FEV₁/FVC ratio and early AMD (OR second quartile 1.49, 95% CI 1.14–1.94, $p = 0.004$ OR third quartile 1.54, 95% CI 1.18–2.00, $p = 0.001$). Attenuation of this association (OR second quartile 1.61, 95% CI 0.88–2.93, $p = 0.12$ OR third quartile 1.65, 95% CI 0.90–3.03, $p = 0.10$) is noted after further adjusting for race, centre, smoking and hypertension, indicating confounding. Race is most likely the strongest confounder, whereby center could well represent a proxy for race. In addition, individual predicted lung function measures of FEV₁, FVC and PEFR were not significantly associated with early AMD. Similarly, there was no association between physician-diagnosed lung disease (OR 1.08, 95% CI 0.90–1.29) and physician-diagnosed asthma (OR 1.06, 95% CI 0.86–1.27) with early AMD for the entire cohort. There was no association between all measures of lung function and disease and early AMD among blacks and whites respectively, after adjusting for confounders.[data not shown]

DISCUSSION

The ARIC study provided a unique opportunity to examine the association of AMD with measures of lung function and disease in a large, bi-ethnic cohort. Our data do not support a strong association between lung disease and early AMD.

Literature regarding the relationship between lung disease and AMD is limited. It has been proposed that poor lung function (and lung disease as a proxy for poor lung function) could accelerate the development and progression of AMD, via mechanisms related to systemic hypoxia, inflammation, and complement activation.^{24–26} For example, both airway inflammation and oxidative stress play an important role in the pathogenesis of chronic obstructive pulmonary disease.^{27–30} Similarly, these two processes are believed to contribute to AMD development.^{24–30} In support of this notion are prospective data from the Framingham Eye Study⁸ and the Beaver Dam Eye study.¹¹ In 2008, the Beaver Dam Eye Study¹¹ showed that a self-reported history of emphysema at baseline was positively

associated with the 15-year incidence of RPE 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, $p=0.04$), independent of smoking and other risk factors.

However, our current study offers no evidence for an independent cross-sectional association between early AMD and measures of lung function and disease.³¹ This could be related to differences in study design (cross-sectional vs. prospective) and population (generally younger participants with lower prevalence of AMD and smokers), which make direct comparison of our results with previous studies difficult. Nonetheless, our findings are similar to another cross-sectional study (the Multi-Ethnic Study of Atherosclerosis).³¹

The strengths of our study include a large bi-ethnic, population-based sample, and standardized assessment of lung function and AMD signs. Limitations should also be noted. First, the cross-sectional design of the study limited our ability to determine the temporal relationship between lung disease and AMD. Second, although we did not find an association, the large number of analyses minimises a type 2 error. Third, the number of participants with late AMD was small due to the relatively young cohort. Thus, it remains undetermined whether lung disease is associated with late AMD. Finally, selective mortality and non-participation were biases that may have limited our findings. However, we believe this was minimised by the good participation rate throughout the study period.

In summary, our data offer no evidence for an independent association between early AMD signs and measures of lung function and disease. Although our findings are not directly comparable to previous prospective studies, these findings do not support an association between lung disease and AMD.

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FIGURE.
The distribution of mean percentage predicted FEV1/FVC ratio in the Atherosclerosis Risk in Communities Study

Table 1

Demographic Characteristics, Lung Function and Disease and Early Age-Related Macular Degeneration Prevalence by Age in the Atherosclerosis Risk in Communities Study

	Age (46–57yrs) N=6801	Age (58–70yrs) N=5795	P
Gender, No. (%)			
Female	3953 (56.4)	3053 (43.6)	<0.001
Male	2848 (51.0)	2742 (49.0)	
Race, No. (%)			
African-American	1736 (25.5)	1101 (19.0)	<0.001
White-American	5065 (74.5)	4694 (81.0)	
Smoking status, No. (%)			
Never smoker	2814 (41.4)	2323 (40.1)	<0.001
Ex-smoker	2436 (35.9)	2408 (41.6)	
Current smoker	1540 (22.7)	1058 (18.3)	
Hypertension, No. (%)			
Yes	1961 (28.9)	2288 (39.7)	<0.001
No	4819 (71.1)	3482 (60.4)	
Asthma, No. (%)			
Yes	349 (5.2)	289 (5.0)	0.80
No	6424 (94.7)	5495 (94.9)	
Lung disease, No. (%)			
Yes	250 (3.7)	331 (5.7)	<0.001
No	6522 (96.2)	5445 (94.1)	
Early AMD, No. (%)			
Yes	231 (3.5)	356 (6.3)	<0.001
No	6456 (96.6)	5295 (93.7)	
FEV1/FVC ratio %, Mean (SD)	77.6 (4.4)	76.4 (3.9)	<0.001

* *p*-value based on chi-square (for categorical variables) and t-test (for continuous variables)

Table 2

Prevalence and Association of Lung Disease and Function with Early Age-Related Macular Degeneration in the Atherosclerosis Risk in Communities Study

	Participant number (prevalance of early AMD, %)	Age-Gender- Adjusted OR (95% CI) [*]	<i>p</i>	Multivariate- Adjusted OR (95% CI) [†]	<i>p</i>
++ FEV1/FVC ratio (%)			**0.001		**0.05
First quartile	3146 (3.9)	1.0		1.0	
Second quartile	3156 (6.3)	1.49 (1.14–1.94)	0.004	1.61 (0.88–2.93)	0.12
Third quartile	3139 (5.2)	1.54 (1.18–2.00)	0.001	1.65 (0.90–3.03)	0.10
Fourth quartile	3139 (3.2)	1.19 (0.88–1.60)	0.24	1.28 (0.68–2.40)	0.45
Physician-diagnosed asthma					
Absent	11919 (4.6)	1.0		1.0	
Present	638 (5.2)	1.07 (0.89–1.28)	0.49	1.06 (0.86–1.27)	0.55
Physician-diagnosed lung disease					
Absent	11967 (4.6)	1.0		1.0	
Present	581 (6.0)	1.10 (0.92–1.32)	0.28	1.08 (0.90–1.29)	0.40
Predicted FEV1 ⁺ , (L)	12580 (4.7)	1.43 (1.05–1.96)	0.02	1.27 (0.89–1.80)	0.18
Predicted FVC [^] , (L)	12580 (4.7)	1.28 (1.02–1.60)	0.03	1.18 (0.93–1.51)	0.18
Predicted FVC [^] , (L)	12580 (4.7)	1.20 (1.03–1.39)	0.02	1.12 (0.95–1.33)	0.19

* Odds ratio (95% confidence interval) adjusted for age and gender

[†] Further adjustment for race, centre, smoking, and hypertension

** p-value for likelihood ratio test

⁺⁺ FEV1/FVC ratio (%), First quartile (64.5–73.3), Second quartile (73.4–78.4), Third quartile (78.5–79.7), Fourth quartile (79.8–85.9).

⁺ FEV1, forced expiratory volume in 1 second

[^] FVC, forced vital capacity

^{^^} PEFR, peak expiratory flow rate