Pulmonary Disease and Age-Related Macular Degeneration

The Beaver Dam Eye Study

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Objective: To examine the association of pulmonary symptoms, disease, and function with the incidence of age-related macular degeneration (AMD).

Design: Population-based cohort study of persons aged 43 to 86 years at baseline (N = 4926), of whom 3779 participated in 1 or more follow-up examinations.

Methods: Stereoscopic photographs of the macula were graded to determine the presence of AMD. Existence of emphysema, asthma, and respiratory symptoms was determined from subjects’ medical history questionnaires; the peak expiratory flow rate was measured using a Mini-Wright Peak Flow Meter (Clement Clarke International, Harlow, England). Discrete logistic hazard and logistic regression models were used.

Main Outcome Measures: Incidence and progression of AMD.

Results: While controlling for age, sex, and other factors, a history of emphysema at baseline was found to be associated with the 15-year cumulative incidence of increased retinal pigment (odds ratio, 2.08; 95% confidence interval, 1.06-4.06), retinal pigment epithelium depigmentation (2.40; 1.23-4.67), and exudative AMD (3.65; 1.24-10.73). Mild pulmonary symptoms were associated with the 5-year incidence of exudative AMD (odds ratio, 3.83; 95% confidence interval, 1.39-10.58), and the fourth (ie, highest) quartile of pulmonary expiratory flow rate showed a protective effect for progression of AMD among women (0.36; 0.15-0.86).

Conclusion: Independent of smoking, a history of emphysema and respiratory symptoms and function are modestly but inconsistently associated with the incidence and progression of AMD.


There are few epidemiological data regarding pulmonary disease and age-related macular degeneration (AMD). In the Framingham Eye Study, decreased vital capacity and a history of lung infection were associated with AMD. On the other hand, a history of lung infection was not associated with AMD in 2 case-control studies. In the Beaver Dam Eye Study, a history of emphysema at baseline, independent of smoking history, was associated with the 10-year cumulative incidence of retinal pigment epithelium (RPE) abnormalities and exudative AMD. In the present study, we extend these findings to the 15-year follow-up examination with more incident cases of late AMD and include new observations regarding the relationship of a history of asthma, pulmonary symptoms, and peak expiratory flow rate (PEFR) to incident and progressed AMD.

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METHODS

POPULATION

Methods used to identify and describe the population have appeared in previous reports. In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were aged 43 to 84 years. Of 5924 eligible individuals, 4926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Ninety-nine percent of the population was white. Between March 1, 1993, and June 14, 1995, 3722 participated in the 5-year follow-up examination. Between March 1, 1998, and June 9, 2000, 2962 participated in the second follow-up examination. Between March 31, 2003, and April 30, 2005, 2375 participated in the third follow-up examination. Comparisons between participants and nonparticipants at the baseline, 5-, 10-, and 15-year follow-up examination.
PROCEDURES AND DEFINITIONS

Similar procedures, used at the baseline and follow-up examinations, have been described in detail elsewhere.10-17 Informed consent was obtained from each participant at the beginning of the examination. At baseline and follow-up examinations, stereoscopic 30° color fundus photographs centered on the macula were taken (Diabetic Retinopathy Study standard field 2). The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions associated with AMD.12,13 Grading procedures, lesion descriptions, and detailed definitions for the presence and severity of specific lesions have appeared elsewhere.14-16 Early AMD was defined by the presence of either soft indistinct drusen or the presence of any type of drusen associated with RPE depigmentation or increased retinal pigment. Incidence of early and late AMD and component lesions were defined by their presence at follow-up in either eye when absent at the previous examination. For each eye, a 6-level severity scale for AMD has been defined.18 In brief, the first level on the scale is equivalent to having no AMD; the next 3 levels on the scale involve lesions that define early AMD of increasing severity (by type, size, area of drusen, and presence of pig-mentary abnormalities), and the last 2 levels involve lesions that define late AMD. Progression for a participant was defined as an increase in the AMD severity in either eye by 2 steps or more from level 1 through 3, and by 1 step or more from level 4 or level 5 in the following AMD severity scale:

Level 1: No drusen, hard drusen, or soft drusen (<125 µm in diameter) only, regardless of area of involvement, and no pigmentary abnormality (increased retinal pigment or RPE depigmentation);

Level 2: Hard drusen or soft drusen (<125 µm in diameter), regardless of area of involvement, with increased retinal pigment but no RPE depigmentation or soft drusen (>125 µm in diameter) with drusen area less than 196 350 µm² (equiva- lent to a circle with a diameter of 500 µm) and no pigmentary abnormalities;

Level 3: Soft drusen (≥125 µm in diameter) with drusen area less than 196 350 µm² and RPE depigmentation or soft drusen (>125 µm in diameter) with drusen area 196 350 µm² or more and with or without increased retinal pigment but without RPE depigmentation;

Level 4: Soft drusen (≥125 µm in diameter) with drusen area 196 350 µm² or more and RPE depigmentation with or without increased retinal pigment;

Level 5: Geographic atrophy without exudative macular degeneration; and

Level 6: Exudative macular degeneration with or without geographic atrophy.

Casual blood specimens were obtained. White blood cell and platelet counts were determined by using a Coulter counter method. The PEFR was first measured at the 10-year follow-up using the Mini-Wright Peak Flow Meter (Clement Clarke International, Harlow, England) 3 times. The best value (ie, greatest flow rate) was used.19

The medical history questionnaire used at all examinations included the question, “Has a doctor ever told you that you had emphysema?” The questionnaire first obtained information regarding a history of asthma at the 5-year follow-up examination. History of other respiratory symptoms (eg, coughing, phlegm, or chest wheezing or whistling) was collected at the 10-year follow-up examination. From these questions, we defined a 3-level respiratory symptom variable. Severe symptoms were defined as any of the following: (1) coughing on most mornings and days or evenings, lasting at least 3 months a year; (2) bringing up phlegm on most mornings and days or evenings, lasting at least 3 months a year; (3) wheezing or whistling from the chest on most days or evenings; (4) history of having attacks of shortness of breath with wheezing; or (5) history of emphysema. If severe respiratory symptoms were not present, then mild respiratory symptoms were defined as any of the following: (1) coughing in the morning or during the day in the winter; (2) bringing up phlegm from the chest in the morning or during the day in the winter; or (3) wheezing or whistling from the chest. If none of these symptoms were present and all information was collected, then the participant was considered to have no respiratory symptoms.

Cigarette smoking status was determined as follows: a participant was classified as a nonsmoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime; as an ex-smoker if he/she had smoked more than this number of cigarettes in his/her lifetime but had stopped smoking before the examination; and as a current smoker if he/she had not stopped smoking. Pack-years smoked was defined as the average number of cigarettes smoked per day divided by 20, multiplied by the number of years smoked. A current heavy drinker was defined as a person consuming 4 or more servings of alcoholic beverages daily; a former heavy drinker had consumed 4 or more servings daily in the past but not in the previous year; and a non-heavy drinker had never consumed 4 or more servings daily on a regular basis. Current vitamin use was defined in 3 levels: no use; use of multivitamins; or use of other single or combinations of vitamins (eg, vitamin B complex).

STATISTICAL METHODS

For these analyses, we examined the relationships of emphysema status to the 13-year cumulative incidence of early AMD and to the specific AMD lesions defining it, exudative AMD, pure geographic atrophy, and cumulative progression of AMD. Also examined were the relationship of history of asthma at the 5-year follow-up examination to the 10-year cumulative incidence and progression of AMD and of PEFR and other respiratory symptoms at the 10-year follow-up examination to the 5-year incidence of AMD. Data were analyzed using SAS statistical software, version 9 (SAS Institute Inc, Cary, North Carolina). Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from discrete logistic hazard models (logistic regression for 5-year incidence).20 These analytical approaches allowed those persons who were right-censored (ie, not seen after the 5- or 10-year examination because of death or nonparticipation) to contribute information to the estimates.21

Analyses first controlled for age in 4 categories of 10-year bands and sex. We considered smoking history, white blood cell count, body mass index, and vitamin use as potential confounders in multivariate analyses. White blood cell count was not measured at the third follow-up examination, so we could not control for this variable in those models. We controlled additionally for history of respiratory symptoms in the analysis of PEFR. Furthermore, since the distribution of PEFR was very different between men and women, we chose to stratify these models by sex.
The 5-year incidence from the start of each examination phase is shown in Table 1. Incidence of AMD was similar in men and women and increased with age.15-17

EMPHYSEMA AND INCIDENCE OF AMD

At baseline, 74 of 3525 participants (2.2%) at risk for incidence or progression of AMD had a history of emphysema. Prevalence of emphysema increased with age in men but not women (data not shown). While controlling for age, those with a history of emphysema at baseline were more likely to smoke and have more pack-years smoked and to have a higher white blood cell count, lower body mass index, and a history of cardiovascular disease than those without a history of emphysema (data not shown). There were no statistically significant differences in hyper- tension status, systolic blood pressure, serum total and high-density lipoprotein cholesterol levels, serum albumin levels, and AMD status between those with and without a history of emphysema at baseline (data not shown).

While controlling for age and sex, history of emphysema was associated with the 15-year cumulative incidence of increased retinal pigment, RPE depigmentation, and exudative AMD but not the incidence of early AMD or its progression (Table 2). In multivariate analyses, controlling additionally for smoking history, body mass index, white blood cell count, and vitamin use did not affect these associations (Table 2). Additionally, controlling for an interaction between smoking and white blood cell count at baseline did not affect these associations (data not shown). Similar associations were found using time-dependent covariate analyses (data not shown). There were no significant interactions between emphysema and age, sex, or smoking and the incidence of any of the AMD outcomes (data not shown). Controlling further for baseline AMD severity, the association between increased retinal pigment and RPE depigmentation remained (data not shown), while the association with a history of emphysema at baseline and the 15-year incidence of exudative AMD was attenuated and no longer statistically significant (OR, 2.48; 95% CI, 0.74-8.33; P = .14).

ASTHMA AND INCIDENCE OF AMD

History of asthma was first recorded at the 5-year follow-up. Asthma was present in 163 of 2660 participants (6.1%) at risk for incidence and progression of AMD and decreased with age in men but not women (data not shown). At the 5-year follow-up examination, while controlling for age, a history of asthma was significantly associated with being female and with having a higher white blood cell count, a higher serum high-density lipoprotein cholesterol level, and a history of emphysema but not with smoking status, pack-years smoked, body mass index, systolic blood pressure, hypertension, history of cardiovascular disease, and AMD status (data not shown). While adjusting for age and sex, a history of asthma was not related to the 10-year cumulative incidence or progression of any of the AMD end points (data not shown).

Table 1. Incidence and Progression of AMD and Its Lesions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline to First Follow-up</th>
<th>First Follow-up</th>
<th>Second Follow-up</th>
<th>Second Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early AMD</td>
<td>1600/116 (7.3)</td>
<td>1207/81 (6.7)</td>
<td>968/62 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1228/84 (6.8)</td>
<td>884/41 (4.6)</td>
<td>692/36 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2828/200 (7.1)</td>
<td>2091/122 (5.8)</td>
<td>1660/98 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>1687/102 (6.1)</td>
<td>1273/73 (5.7)</td>
<td>1039/81 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1325/77 (5.8)</td>
<td>979/47 (4.9)</td>
<td>750/44 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3022/179 (5.9)</td>
<td>2243/120 (5.4)</td>
<td>1789/125 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Increased retinal pigment</td>
<td>1756/62 (4.7)</td>
<td>1322/64 (4.8)</td>
<td>1045/38 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1364/62 (4.6)</td>
<td>977/40 (4.1)</td>
<td>736/27 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3110/144 (4.6)</td>
<td>2299/104 (4.5)</td>
<td>1781/65 (3.7)</td>
<td></td>
</tr>
<tr>
<td>RPE depigmentation</td>
<td>1861/67 (3.1)</td>
<td>1403/51 (3.6)</td>
<td>1112/37 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1431/44 (3.1)</td>
<td>1033/28 (2.9)</td>
<td>776/16 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3292/101 (3.1)</td>
<td>2436/80 (3.3)</td>
<td>1888/55 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Exudative AMD</td>
<td>1970/17 (0.9)</td>
<td>1507/13 (0.9)</td>
<td>1213/16 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1537/4 (0.3)</td>
<td>1143/7 (0.6)</td>
<td>874/7 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3507/21 (0.6)</td>
<td>2650/20 (0.8)</td>
<td>2087/23 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>1958/7 (0.4)</td>
<td>1493/5 (0.3)</td>
<td>1187/12 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1535/4 (0.3)</td>
<td>1131/7 (0.6)</td>
<td>859/5 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3493/11 (0.3)</td>
<td>2824/12 (0.5)</td>
<td>2046/17 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Progression of AMD</td>
<td>1997/96 (4.9)</td>
<td>1455/64 (5.8)</td>
<td>1121/60 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1538/51 (3.3)</td>
<td>1108/37 (3.3)</td>
<td>832/38 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3509/147 (4.2)</td>
<td>2563/121 (4.7)</td>
<td>1953/98 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; RPE, retinal pigment epithelium.

For the dates and number of participants for each follow-up examination, see the “Population” subsection of the “Methods” section.

RESULTS

INCIDENCE OF AMD

The 5-year incidence from the start of each examination phase is shown in Table 1. Incidence of AMD was similar in men and women and increased with age.15-17
associated with the 5-year incidence of exudative AMD and progression of AMD (Table 3). While further controlling for history of smoking, vitamin use, and body mass index, the relationship with incident exudative AMD remained, while that with progressed AMD was no longer statistically significant. After adding baseline AMD severity to the model, the association of mild pulmonary symptoms with the 5-year incidence of exudative AMD remained statistically significant (OR, 2.98; 95% CI, 1.00-8.81; \( P = .05 \)). There were no associations of severe respiratory symptoms with the 5-year incidence of AMD.

### PEFR AND INCIDENCE OF AMD

The PEFR was first measured at the 10-year follow-up examination. Mean PEFR was higher in men than women and decreased with age (data not shown). While controlling for age and sex, poorer PEFR at the 10-year examination was statistically significantly associated with smoking status, pack-years smoked, a history of asthma, emphysema, respiratory symptom severity, hypertension, and waist to hip ratio, but was not associated with body mass index (data not shown).

There were no significant relationships between PEFR defined continuously with the incidence of progression of AMD (Table 4). However, comparing the fourth (ie, highest) quartile of PEFR vs all other quartiles showed that men with the highest PEFR had a lower incidence of early AMD after controlling for age and other factors. Among women, while controlling for age and other factors, those with the highest PEFR were less likely to have AMD progression.

### COMMENT

We hypothesized that a history of decreased pulmonary function, respiratory symptoms, and respiratory diseases such as emphysema and asthma would be associated with increased risk of incident AMD. This was based on the Framingham Eye Study that found higher frequency of AMD in persons with reduced vital capacity and our earlier finding that history of emphysema was associated with the 10-year incidence of exudative AMD.\(^1\)\(^4\)

We speculated that this would be a result of systemic inflammation and/or decreased systemic oxygenation associated with emphysema. Although a history of emphy-

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**Table 2. History of Emphysema at Baseline and 15-Year Incidence and Progression of AMD**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>( P ) Value</th>
<th>Multivariate Adjusted(^a) OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early AMD</td>
<td>1.12 (0.53-2.39)</td>
<td>.76</td>
<td>1.02 (0.48-2.19)</td>
<td>.95</td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>1.28 (0.63-2.60)</td>
<td>.50</td>
<td>1.14 (0.56-2.33)</td>
<td>.73</td>
</tr>
<tr>
<td>Increased retinal pigment</td>
<td>2.29 (1.13-4.27)</td>
<td>.02</td>
<td>2.08 (1.06-4.06)</td>
<td>.03</td>
</tr>
<tr>
<td>RPE depigmentation</td>
<td>2.55 (1.33-4.91)</td>
<td>.01</td>
<td>2.40 (1.23-4.67)</td>
<td>.01</td>
</tr>
<tr>
<td>Exudative AMD</td>
<td>3.37 (1.18-9.67)</td>
<td>.02</td>
<td>3.65 (1.24-10.73)</td>
<td>.02</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>1.06 (0.14-7.94)</td>
<td>.95</td>
<td>1.41 (0.18-10.91)</td>
<td>.74</td>
</tr>
<tr>
<td>Progression of AMD</td>
<td>1.70 (0.93-3.10)</td>
<td>.09</td>
<td>1.57 (0.85-2.90)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio; RPE, retinal pigment epithelium.

\(^a\) Controlling for age, sex, history of smoking, body mass index, and white blood cell count at baseline.

**Table 3. History of Respiratory Symptoms at 10-Year Follow-up and 5-Year Incidence and Progression of AMD**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Respiratory Symptoms Level(^a)</th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>( P ) Value</th>
<th>Multivariate Adjusted(^b) OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early AMD</td>
<td>Mild vs none</td>
<td>0.92 (0.52-1.62)</td>
<td>.76</td>
<td>0.81 (0.44-1.49)</td>
<td>.50</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>1.26 (0.77-2.07)</td>
<td>.35</td>
<td>1.26 (0.75-2.10)</td>
<td>.39</td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>Mild vs none</td>
<td>0.85 (0.50-1.44)</td>
<td>.56</td>
<td>0.78 (0.45-1.35)</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>1.52 (0.99-2.34)</td>
<td>.06</td>
<td>1.43 (0.91-2.25)</td>
<td>.12</td>
</tr>
<tr>
<td>Increased retinal pigment</td>
<td>Mild vs none</td>
<td>1.13 (0.59-2.13)</td>
<td>.72</td>
<td>1.10 (0.56-2.14)</td>
<td>.38</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>1.08 (0.57-2.08)</td>
<td>.81</td>
<td>1.06 (0.54-2.09)</td>
<td>.87</td>
</tr>
<tr>
<td>RPE depigmentation</td>
<td>Mild vs none</td>
<td>0.94 (0.44-1.99)</td>
<td>.86</td>
<td>0.83 (0.37-1.84)</td>
<td>.64</td>
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<tr>
<td></td>
<td>Severe vs none</td>
<td>1.64 (0.85-3.14)</td>
<td>.14</td>
<td>1.56 (0.79-3.11)</td>
<td>.20</td>
</tr>
<tr>
<td>Exudative AMD</td>
<td>Mild vs none</td>
<td>3.63 (1.38-9.52)</td>
<td>.01</td>
<td>3.83 (1.39-10.58)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>2.21 (0.76-6.43)</td>
<td>.15</td>
<td>2.23 (0.72-6.88)</td>
<td>.16</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>Mild vs none</td>
<td>2.22 (0.75-6.59)</td>
<td>.15</td>
<td>1.58 (0.49-5.14)</td>
<td>.45</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>1.21 (0.31-4.65)</td>
<td>.78</td>
<td>0.96 (0.24-3.83)</td>
<td>.95</td>
</tr>
<tr>
<td>Progression of AMD</td>
<td>Mild vs none</td>
<td>1.72 (1.12-2.66)</td>
<td>.01</td>
<td>1.53 (0.97-2.40)</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>Severe vs none</td>
<td>1.44 (0.92-2.26)</td>
<td>.11</td>
<td>1.29 (0.81-2.07)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio; RPE, retinal pigment epithelium.

\(^a\) For a description of the respiratory symptoms categories, see the “Procedures and Definitions” subsection of the “Methods” section.

\(^b\) Controlling for age, sex, smoking history, body mass index, and vitamin use at the 10-year examination.
Hypoxia was associated with pigmentary abnormalities and exudative AMD, we did not find a relationship to either incidence of early AMD, geographic atrophy, or progression of AMD. To our knowledge, there are no other studies from population-based studies examining the relationship of history of emphysema, asthma, and other comorbid conditions, women younger than 75 years with poorer PEFs were more likely to have signs of prevalent early AMD (OR per 50 L/min decrease, 1.11; 95% CI, 0.99-1.25; P = .07) and late AMD (OR, 1.79; 95% CI, 1.13-2.82; P = .01). This relationship was not found in older women or in men. The relationship between PEF and incidence and progression of early AMD in men and women, respectively, may also be a source of chronic inflammation resulting in higher risk of AMD. There is evidence suggesting that both systemic and ocular inflammation and abnormal complement activation are involved in the pathogenesis of AMD.24-33 Signs of chronic inflammation in the choroid of donor eyes with AMD have been found, and retinal drusen have been shown to contain inflammatory and immune-mediated molecules, including components of the complement cascade.26-33 However, epidemiological data from large population-based studies have not consistently shown a relationship between systemic inflammation and the incidence of AMD, and it is not certain that systemic inflammation explains the relationship of pulmonary disease and AMD.4,34-36

We previously reported that, independent of smoking and other comorbid conditions, women younger than 75 years with poorer PEFs were more likely to have signs of prevalent early AMD (OR per 50 L/min decrease, 1.11; 95% CI, 0.99-1.25; P = .07) and late AMD (OR, 1.79; 95% CI, 1.13-2.82; P = .01). This relationship was not found in older women or in men. The relationship between PEF and incidence and progression of early AMD in men and women, respectively, may also be a source of chronic inflammation resulting in higher risk of AMD. There is evidence suggesting that both systemic and ocular inflammation and abnormal complement activation are involved in the pathogenesis of AMD.24-33 Signs of chronic inflammation in the choroid of donor eyes with AMD have been found, and retinal drusen have been shown to contain inflammatory and immune-mediated molecules, including components of the complement cascade.26-33 However, epidemiological data from large population-based studies have not consistently shown a relationship between systemic inflammation and the incidence of AMD, and it is not certain that systemic inflammation explains the relationship of pulmonary disease and AMD.4,34-36

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reflect biological aging in addition to a specific pulmonary disease process.\(^{35,30}\) There are many strengths to this study, including its high participation rate, length of follow-up, and use of standardized protocols to measure AMD end points. However, any conclusions or explanations regarding associations or lack of them, described herein, must be made with caution for a number of reasons. First, the concomitant low frequency of some risk factors (eg, emphysema) and of the incidence of some lesions (eg, pure geographic atrophy) limits our ability to detect, or reject, meaningful relationships. Second, some findings (eg, mild pulmonary symptoms and the 5-year incidence of neovascular AMD) that may be of potential biological significance may be entirely due to chance, given the large number of associations examined. Third, it is also possible that we failed to find significant relationships between some risk factors and AMD because participants with these factors (eg, emphysema) who developed AMD did not live to participate in the follow-up examinations. However, nonparticipation owing to death is probably unlikely to bias our findings because AMD had not been shown to be associated with mortality in the Beaver Dam cohort.\(^{40}\) Of course, death is likely to have diminished our number, and, therefore, our power to detect important relationships. Fourth, there may be misclassification of pulmonary disease and its symptoms. This might be expected to bias the results to the null. Fifth, there may be uncontrolled confounding. Although we have found relationships of emphysema to be independent of smoking, we were not able to control for inhalation, type of cigarette smoked (eg, filter or tar and nicotine content), and exposure to passive smoking that might have affected the relationships.

In summary, the data from Beaver Dam show modest but inconsistent associations of emphysema and symptoms of pulmonary disease with the incidence of AMD, independent of smoking and other risk factors. Further study is needed to understand whether these relationships reflect inflammation or hypoxia in persons with these conditions.

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REFERENCES


The Faces Behind the Eponyms

If you ever wondered what Anton Elschnig, Karl Stargardt, Alfred Vogt, and 80 other great ophthalmologists looked like, there is a Web site with their portraits and short biographies.1 Each of their names has been immortalized by one or more names of diseases, signs, or ophthalmic instruments. Vitelliform macular degeneration is named after Friedrich Best, who studied macular degeneration in Germany. Hans Goldmann developed and refined numerous ophthalmic instruments, including the slitlamp, bowl perimeter, gonioscopes, and applanation tonometer. Robert Marcus Gunn and Douglas Moray Cooper Lamb Argyll Robertson both were Scottish ophthalmologists who described special conditions affecting the pupil. David Cogan, a 20th century American ophthalmologist and editor-in-chief of the Archives from 1960 to 1906, has a disease, a syndrome, and a sign named after him. Yoshio Harada, a Japanese ophthalmologist, along with Yuki Koyanagi and Vogt, described a rare autoimmune multisystem disorder that bears their names. Giovanni Battista Morgagni (Figure) is the earliest scientist in the group, whose name we use to describe a hypermature cataract with a brown nucleus that sinks within liquefied cortex.

Finally, we should mention that Hans Reiter, a Nazi supporter and member of the SS (Schutzstaffel), imprisoned at Nuremberg from 1945 to 1947 for medical experiments on concentration camp prisoners, is no longer associated with the classic triad of conjunctivitis, urethritis, and arthritis. In 2003, rheumatology journal editors agreed to expunge the term Reiter syndrome from the literature, replacing it with reactive arthritis.2 He was a Nazi war criminal and, to preserve the ethics and humanity of our profession, should be remembered only for his involvement in heinous atrocities.

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