Severity of Age-Related Macular Degeneration in 1 Eye and the Incidence and Progression of Age-Related Macular Degeneration in the Fellow Eye

The Beaver Dam Eye Study

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IMPORTANCE Previous studies regarding the severity of age-related macular degeneration (AMD) in 1 eye and its prognostic implications for the fellow eye have focused on the incidence of neovascular AMD in the fellow eye of participants with neovascular AMD in the other eye. It is unclear to what extent the severity of AMD in 1 eye affects the incidence, progression, and regression of AMD in its fellow eye across the entire range of AMD severity.

OBJECTIVE To investigate the effect of the severity of AMD in 1 eye on the incidence, progression, and regression of AMD in the fellow eye.

DESIGN, SETTING AND PARTICIPANTS The Beaver Dam Eye Study is a longitudinal population-based study of age-related eye diseases conducted in the city and township of Beaver Dam, Wisconsin. Examinations were performed every 5 years over a 20-year period (from the baseline examination in 1988-1990 to 2008-2010). Study participants (n = 4379) were 43 to 86 years of age at the baseline examination. At baseline and in up to 4 subsequent examinations, retinal photographs were taken.

MAIN OUTCOMES AND MEASURES Incidence, progression, and regression of AMD (assessed by use of the Wisconsin Age-Related Maculopathy Grading System on retinal photographs and adjusted for age, sex, and the Y402H polymorphism in the complement factor H gene on chromosome 1q) and mortality.

RESULTS More severe AMD in 1 eye was associated with increased incidence of AMD and accelerated progression in its fellow eye (levels 1-2: hazard ratio [HR], 4.90 [95% CI, 4.26-5.63]; levels 2-3: HR, 2.09 [95% CI, 1.42-3.06]; levels 3-4: HR, 2.38 [95% CI, 1.74-3.25]; levels 4-5: HR, 2.46 [95% CI, 1.65-3.66]). Less severe AMD in 1 eye was associated with less progression of AMD in its fellow eye (levels 2-3: HR, 0.42 [95% CI, 0.33-0.55]; levels 3-4: HR, 0.50 [95% CI, 0.34-0.83]). We estimate that 51% of participants who develop any AMD always maintain AMD severity states within 1 step of each other between eyes; 90% of participants stay within 2 steps.

CONCLUSIONS AND RELEVANCE Using multistate models, we show that AMD severity in 1 eye tracks AMD severity in its fellow eye.

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Age-related macular degeneration (AMD) is thought to be a symmetric disease in that its presence, incidence, and progression of lesions defining it are not significantly different between eyes, although one eye may precede the other in progression. This results in asymmetry between eyes for both early and late AMD. Most studies that have examined the prognostic implications of risk based on knowing the severity of AMD in one eye have focused on using signs of neovascular AMD in that eye to estimate the risk of developing neovascular AMD in the fellow eye. These estimates have been made using data from clinical trials and cohort studies. Understanding of the course of AMD and the risk of early AMD progressing based on either the worse or better eye may help in determining how often patients who are at risk of progression of AMD should be seen. The purpose of our study is to investigate the effect of the severity of AMD in one eye on incidence, progression, and regression of AMD in the fellow eye using multistate models (MSMs) in the Beaver Dam Eye Study (BDES).

Methods

Population

The methods used to identify the study population have been described previously. The characteristics of the study population at each examination and the reasons for nonparticipation have also been described elsewhere.

Procedures and Definitions

Similar procedures were used at all examinations. Data were collected with institutional review board approval from the University of Wisconsin–Madison, written informed consent was obtained from each participant at each examination, and the study adhered to the tenets of the Declaration of Helsinki. Participants were not financially compensated at any examination. Pertinent parts of the examination consisted of taking stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and taking a nonstereoscopic color photograph (Diabetic Retinopathy Study standard field 2) and macula (Diabetic Retinopathy Study standard field 2) and macula. Similar procedures were used at all examinations. Data procedures and Definitions

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Grading procedures have been described previously. Information on gradability has also been published elsewhere. In this study, AMD status in each eye was classified using a 5-step severity scale. Participants were classified as to severity level based on the worse eye.

Information on alleles for the Y402H polymorphism for the complement factor H (CFH) gene was available for 4479 of the 4973 participants (90%). The distributions of other characteristics for these participants did not differ from the rest of the population (data not shown).

Vital status was monitored by reading the obituaries in local newspapers and by making annual contacts by telephone. Persons not known to have died but who could not be contacted had their survival time entered as their last contact date.

Statistical Analysis

Incidence, progression, and regression of AMD and mortality were modeled using MSMs in continuous time for panel data. Traditional survival analysis is a special case of an MSM in which (1) there are 2 possible states (alive or dead), (2) there is a single possible transition between states (alive to dead), and (3) the process is under continuous observation (ie, if the participant is not lost to follow-up, the current state is always known [continuous observation]). The MSM generalizes traditional survival analysis models to incorporate multiple disease states (AMD severity as well as death) and to accommodate panel data in which the state is only observed at a finite series of times (scheduled visits with fundus photographs).

We identified 26 mutually exclusive and exhaustive states representing the current status of each participant at a given age. Here, eyes were classified as being in 1 of the 5 levels on the BDES AMD severity scale:

- **No AMD (level 1).** Hard drusen or small soft drusen (<125 μm in diameter) only, regardless of area of involvement, and no pigmented abnormalities (defined as increased retinal pigment or depigmentation of the retinal pigment epithelium).
- **Mildly severe early AMD (level 2).** Hard drusen or small soft drusen (<125 μm in diameter), regardless of area of involvement, with any pigmented abnormality or soft drusen (≥125 μm in diameter) with a drusen area of less than 196 350 μm² (equivalent to a circle with a diameter of 500 μm) and no pigmentary abnormalities.
- **Moderately severe early AMD (level 3).** Soft drusen (≥125 μm in diameter) with a drusen area of less than 196 350 μm² (equivalent to a circle with a diameter of 500 μm) and with any pigmentary abnormality or soft drusen (≥125 μm in diameter) with a drusen area of 196 350 μm² or greater (equivalent to a circle with a diameter of 500 μm) with or without increased retinal pigment but no depigmentation of the retinal pigment epithelium.
- **Severe early AMD (level 4).** Soft drusen (≥125 μm in diameter) with a drusen area of 196 350 μm² or greater (equivalent to a circle with a diameter of 500 μm) and depigmentation of the retinal pigment epithelium, with or without increased retinal pigment.

- **Late AMD (level 5).** Pure geographic atrophy in the absence of exudative macular degeneration or exudative macular degeneration with or without geographic atrophy.

Participants were classified as being in 1 of 25 AMD states (AMD severity in the right eye, AMD severity in the left eye) or dead. Figure 1 illustrates the underlying MSM at the participant level. For each eye, instantaneous transitions (the next state to which the individual moves and the time of the change) were allowed between adjacent AMD states with 1 exception, namely that regression from late AMD (level 5) to severe early AMD (level 4) was not allowed. We assumed that an eye could not instantaneously worsen (or improve) by multiple steps (eg, 1 eye could not move from level 1 to level 3 without being in level 2 for some length of time) and that both eyes could not instantaneously worsen (or improve) at the same instant of time. These assumptions apply to the underlying continuously observed process.
Transitions are governed by 25 intensities, one for each possible instantaneous transition between states (represented by arrows in Figure 1), which represent the hazard (instantaneous risk) of moving between states at the participant level. These intensities reflect 7 fundamental transitions between AMD states in a single eye modified by the AMD status of the fellow eye (20 total transitions) and the transition to death modified by the AMD state in the better eye (5 total transitions). The dependence of transition intensities on age, sex, CFH Y402H genotype, and AMD severity in the fellow eye was specified using log-linear regression models. Age was entered as a linear term and updated annually. Sex and CFH Y402H genotype were entered using indicator variables. Covariate effects on transitions within the AMD scale were unconstrained. Covariate effects on transitions to death were constrained to be equal (ie, independent of current AMD level in either eye). For transitions within the AMD scale, AMD severity in the fellow eye (categorized as worse, same, or better) was entered using indicator variables. For transitions to death, AMD severity in the better eye was included as a covariate.

The MSM incorporates all available information on the history of disease progression into likelihood calculations. Current AMD state is observed at intermittent study follow-up visits; transition times and numbers of intermediate transitions are unobserved. Death times are available, but AMD state at death is unknown. If participants are alive at the end of follow-up, the final AMD state is unknown. At study visits, the exact...
AMD state may be unknown if photographs from 1 or both eyes were ungradable.

Analyses were conducted in R using the MSM package. Covariate effects on transition intensities are summarized as hazard ratios (HRs). We estimated 5-year transition probabilities to each AMD state (and death), adjusted to the sex and CFH Y402H genotype distribution at the first BDES visit, for specified subgroups based on age, current AMD severity, and AMD severity in the fellow eye.

Results

Of the 4973 participants seen at any study visit, 494 were excluded for missing the CFH Y402H genotype, and an additional 100 were excluded for ungradable AMD status at all visits; 4779 participants contributed data from 12 640 BDES follow-up visits (up to 4 per participant). Table 1 displays characteristics of the cohort at the start of each interval by AMD level. Participants with more severe AMD in the primary or fellow eye were older and more likely to be female, to have CFH Y402H genotype CT or CC, and to be seen at later visits.

Table 2 shows observed transitions between consecutive BDES visits. The second column presents transitions for the 16 948 BDES visits for which participants had no AMD (level 1) in the primary eye and no AMD in the fellow eye. With regard to the consecutive BDES visits, the primary eyes of participants in 12 849 follow-up BDES visits (76%) were still free of AMD, the primary eyes of participants in 465 BDES visits (3%) progressed to minimally severe early AMD (level 2), the primary eyes of participants in 250 BDES visits (1%) progressed to level 3, the primary eyes of participants in 18 BDES visits (0.1%) progressed to level 4, and the primary eyes of participants in 13 BDES visits (0.1%) progressed to late AMD. The participants in 2013 BDES visits (12%) died. In 725 of 16 948 BDES visits (4%), participants were seen with no information, and in 598 of 16 948 BDES visits (4%) participants were not seen.

In a given eye, progression was more common, and regression less common, if the severity in the fellow eye was worse (progression: 4% if same vs 16% if worse for level 1, 14% if better vs 25% if same vs 31% if worse for level 2, 12% vs 27% vs 38% for level 3, 15% vs 26% vs 28% for level 4; regression: 4% if same vs 16% if worse for level 1, 14% if same vs 1% if worse for level 4). Few participants were not seen at the next scheduled visit, and the proportion not seen did not vary with AMD severity.

Covariate Effects on Transition Intensities

Covariate effects from the MSMs are presented in Table 3. There was no evidence of interactions between AMD severity in the fellow eye and age (P = .18), sex (P = .21), or CFH Y402H genotype (P = .15).

More severe AMD in 1 eye was associated with an increased incidence of AMD and accelerated progression in its fellow eye (from level 1 to level 2: HR, 4.90 [95% CI, 4.26-5.63]; from level 2 to level 3: HR, 2.09 [95% CI, 1.42-3.06]; from

Table 1. Characteristics of the Cohort by Current AMD Status at the Beginning of the BDES Follow-up Intervals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (10)</td>
<td>68 (10)</td>
<td>71 (10)</td>
<td>73 (10)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>Male sex</td>
<td>7288 (43)</td>
<td>801 (48)</td>
<td>626 (48)</td>
<td>220 (44)</td>
<td>119 (44)</td>
</tr>
<tr>
<td>BDES visit</td>
<td>6302 (17)</td>
<td>547 (15)</td>
<td>442 (15)</td>
<td>176 (15)</td>
<td>160 (15)</td>
</tr>
<tr>
<td>CFH Y402H genotype</td>
<td>6964 (10)</td>
<td>652 (10)</td>
<td>508 (10)</td>
<td>172 (10)</td>
<td>106 (10)</td>
</tr>
<tr>
<td>Abbreviations: AMD, age-related macular degeneration; BDES, Beaver Dam Eye Study; level 1, no AMD; level 2, minimally severe early AMD; level 3, moderately severe early AMD; level 4, severe early AMD; and level 5, late AMD.</td>
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level 3 to level 4: HR, 2.38 [95% CI, 1.74-3.25]; from level 4 to level 5: HR, 2.46 [95% CI, 1.65-3.66]). Less severe AMD in 1 eye was associated with a lesser incidence of progression of AMD in its fellow eye (from level 2 to level 3: HR, 0.42 [95% CI, 0.33-0.55]; from level 3 to level 4: HR, 0.50 [95% CI, 0.34-0.83]).

Older age was associated with increased incidence of AMD, accelerated progression and accelerated regression of AMD, and increased mortality. Being male was associated with increased mortality but not with increased AMD incidence, accelerated progression, or accelerated regression. 

To quantify the extent to which AMD severity in 1 eye tracks AMD severity in the fellow eye, we simulated realizations of AMD history for individuals free of AMD at 45 years of age. To simulate assuming no effect of the fellow eye on AMD incidence, progression, and/or regression. The incidence of any AMD (through age 100 years) adjusted to the sex and CFH Y402H genotype at the first BDES visit was 50% in both sets of simulations. When accounting for fellow eye AMD status, we found that 51% of participants who developed any AMD always maintained AMD states in their 2 eyes within 1 step of each other; 90% of participants stayed within 2 steps. Conversely, without the influence of the fellow eye, only 31% stayed within 1 step, and 64% stayed within 2 steps.

**Discussion**

In a cohort that was observed for 20 years, we showed that AMD severity in 1 eye largely tracks AMD severity in the fellow eye at all stages of the disease (with a <10% chance of lifetime oc-
These transitions for participants with asymmetric disease. This information may be helpful to clinicians in assessing the prognosis of the better eye. For example, over 5 years, an eye free of AMD is 2.4 to 3.5 times as likely to develop incidence, progression, or regression of AMD. In our study, late AMD in both eyes is associated with a 28% increase in overall mortality compared with no AMD in at least 1 eye. This is qualitatively consistent with our prior findings, which found late AMD in at least 1 eye to be associated with a 37% increase in overall mortality compared with no AMD in both eyes, despite the differences in the reference and exposed categories. These differences suggest that there may be a role for the fellow eye’s AMD severity in the association with mortality. Owing to the small number of participants with late AMD, we have a limited ability to investigate this question.

This information may be helpful to clinicians in assessing the prognosis of the better eye. For example, over 5 years, an eye free of AMD is 2.4 to 3.5 times as likely to develop incident AMD if the fellow eye has AMD than if the fellow eye is also free of AMD. In a clinical trial setting, it provides estimates for samplesize calculation for trials of eye-specific interventions for participants with asymmetric disease.

The estimates of late AMD were based solely on grading of stereoscopic 30° color fundus photographs. It is likely that those seen in participant-level MSMs. Age and CFH genotypes CC and CT are associated with increased incidence and accelerated progression of AMD, whereas sex is not associated with incidence, progression, or regression of AMD. In our study, late AMD in both eyes is associated with a 28% increase in overall mortality compared with no AMD in at least 1 eye. This is qualitatively consistent with our prior findings, which found late AMD in at least 1 eye to be associated with a 37% increase in overall mortality compared with no AMD in both eyes, despite the differences in the reference and exposed categories. These differences suggest that there may be a role for the fellow eye’s AMD severity in the association with mortality. Owing to the small number of participants with late AMD, we have a limited ability to investigate this question.

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new imaging technologies such as spectral domain optical coherence tomography, fundus autofluorescence, and infrared imaging will, in the future, be incorporated into new classification schemes that may provide different estimates of disease. The MSM described herein will be applicable to the assessment of risk of AMD progression using these newer, more detailed classification systems.

We are currently working to extend these models to account for the potential misclassification of AMD assessed by use of fundus photographs. Based on our previous findings, the major substantive impact of the failure to directly incorporate misclassification into the MSM is likely to be an overestimate of the rate of AMD regression, but the qualitative findings for covariate effects, including the fellow eye’s AMD severity, are unlikely to change. As such, the rates of AMD regression presented here should be interpreted with caution.

Conclusions

In summary, we provide an approach using MSMs to model the incidence, progression, and regression of AMD at the eye level rather than the participant level. We have considered a small number of determinants of AMD to illustrate the modeling approach; extensions of the model to incorporate additional covariates are conceptually straightforward, if computationally

Figure 2. Five-Year Transition Probabilities to Age-Related Macular Degeneration (AMD) States and Death

The size of squares represents the 5-year transition probability for the specified initial AMD state, the fellow eye’s AMD state, and age in the Beaver Dam Eye Study, adjusted to the sex and complement factor H Y402H genotype distribution at the baseline examination. D indicates death.
challenging. This modeling approach will provide greater insight into the effect of genetic and environmental factors on the course of AMD; it will also facilitate the inclusion of eye-level covariates as exposures, confounders, and mediators. The general modeling approach described here will be applicable to other AMD severity scales.24,25

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Drafting of the manuscript: Gangnon.

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REFERENCES