Original Investigation

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

Ronald E. Gangnon, PhD; Kristine E. Lee, MS; Barbara E. K. Klein, MD, MPH; Sudha K. Iyengar, PhD; Theru A. Sivakumaran, PhD; Ronald Klein, MD, MPH

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.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ronald Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Room 417, Wisconsin Alumni Research Foundation, 610 N Walnut St, Madison, WI 53726 (kleinr@epi .ophth.wisc.edu).

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 1 eye may precede the other in progression.[1,2] This results in asymmetry between eyes for both early and late AMD.[3-5] Most studies that have examined the prognostic implications of risk based on knowing the severity of AMD in 1 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.[2,6,7] 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 1 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.[8-13] The characteristics of the study population at each examination and the reasons for nonparticipation have also been described elsewhere.[9-13]

Procedures and Definitions

Similar procedures were used at all examinations.[2,14-18] 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 fundus photograph temporal to but including the fovea of each eye.

Grading procedures have been described previously.[1,14,15] Information on gradability has also been published elsewhere.[2,15,16,19,20] In this study, AMD status in each eye was classified using a 5-step severity scale.[21] 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 pigmentary abnormalities (defined as increased retinal pigment or depigmentation of the retinal pigment epithelium).

Minimally severe early AMD (level 2). Hard drusen or small soft drusen (<125 µm in diameter), regardless of area of involvement, with any pigmentary 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.
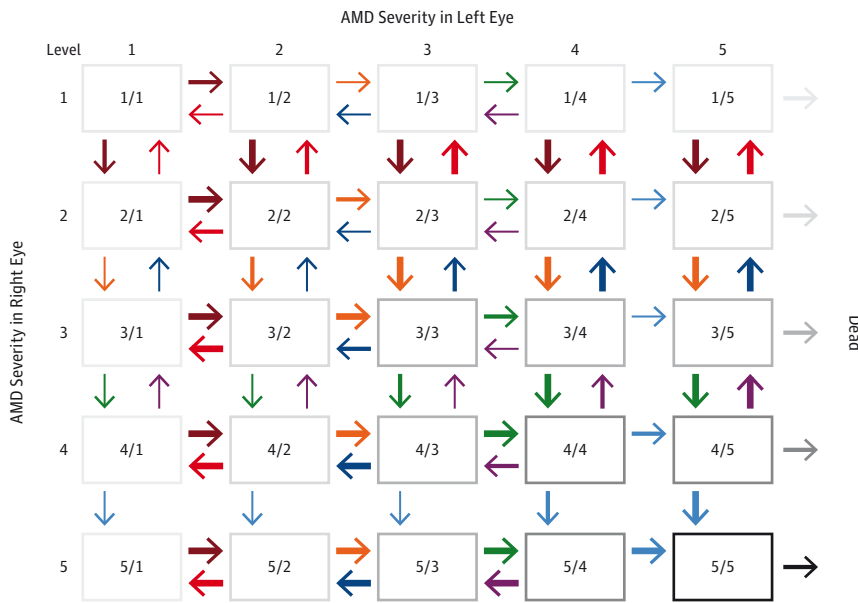
Moderately severe early AMD (level 3). Soft drusen (≥125 µm in diameter) with a drusen area of less than 196 350 µm² (equivalent to a circle with a diameter of 500 µm) and with any pigmentary abnormality or soft drusen (≥125 µm in diameter) with a drusen area of 196 350 µm² or greater (equivalent to 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 simultaneously worsen (or improve) at the same instant of time. These assumptions apply to the underlying continuously observed process.

Figure 1. Transition Diagram for Age-Related Macular Degeneration (AMD) Severity and Death

The arrows indicate possible instantaneous transitions. The colors identify instantaneous transitions in a single eye, whereas the different widths of the arrows identify the intensity of the modifying effect of AMD severity in the fellow eye. The different shades of gray distinguish AMD severity in the better eye.

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

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

	AMD Severity in Primary Eye												
	Level 1		Level 2			Level 3			Level 4			Level 5	
	AMD Severity in Fellow Eye												
Characteristic	Same, Level 1 (n = 16 948)	Worse, Levels 2-5 (n = 1671)	Better, Level 1 (n = 1296)	Same, Level 2 (n = 456)	Worse, Levels 3-5 (n = 273)	Better, Levels 1-2 (n = 544)	Same, Level 3 (n = 578)	Worse, Levels 4-5 (n = 156)	Better, Levels 1-3 (n = 185)	Same, Level 4 (n = 130)	Worse, Level 5 (n = 68)	Better, Levels 1-4 (n = 143)	Same, Level 5 (n = 256)
Age, mean (SD), y	63 (10)	68 (10)	67 (10)	71 (10)	73 (10)	71 (10)	75 (9)	77 (9)	76 (9)	77 (9)	79 (8)	78 (8)	82 (7)
Male sex	7288 (43)	801 (48)	626 (48)	220 (48)	119 (44)	254 (47)	206 (36)	46 (29)	57 (31)	50 (38)	28 (41)	57 (40)	78 (30)
BDES visit													
First	6302 (37)	547 (33)	442 (34)	176 (39)	79 (29)	160 (29)	174 (30)	37 (24)	37 (20)	20 (15)	12 (18)	36 (25)	66 (26)
Second	4370 (26)	486 (29)	380 (29)	128 (28)	79 (29)	161 (30)	156 (27)	46 (29)	50 (27)	28 (22)	16 (24)	36 (25)	50 (20)
Third	3448 (20)	369 (22)	274 (21)	84 (18)	61 (22)	130 (24)	134 (23)	39 (25)	50 (27)	40 (31)	22 (32)	37 (26)	56 (22)
Fourth	2828 (17)	269 (16)	200 (15)	68 (15)	54 (20)	93 (17)	114 (20)	34 (22)	48 (26)	42 (32)	18 (26)	34 (24)	84 (33)
CFH Y402H genotype													
TT	6964 (41)	652 (39)	508 (39)	172 (38)	106 (39)	212 (39)	150 (26)	33 (21)	54 (29)	24 (18)	9 (13)	26 (18)	24 (22)
CT	7806 (46)	811 (49)	634 (49)	218 (48)	136 (50)	258 (47)	292 (51)	88 (56)	98 (53)	80 (62)	46 (68)	91 (64)	154 (60)
CC	2178 (13)	208 (12)	154 (12)	66 (14)	31 (11)	74 (14)	136 (24)	35 (22)	33 (18)	26 (20)	13 (19)	26 (18)	78 (30)

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.

[a] Data are No. (%) of visits, unless otherwise indicated.

AMD state may be unknown if photographs from 1 or both eyes were ungradable.

Analyses were conducted in R[15] using the MSM package.[14] 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; 4379 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: 14% vs 5% vs 4% for level 2, 16% vs 8% vs 1% for level 3, 13% 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 2. Observed State Transitions During Consecutive Visit Intervals[a]

AMD Severity at End of Interval	AMD Severity in Primary Eye at Beginning of Interval												
	Level 1		Level 2			Level 3			Level 4			Level 5	
	AMD Severity in Fellow Eye at Beginning of Interval												
	Same, Level 1 (n = 16 948)	Worse, Levels 2-5 (n = 1671)	Better, Level 1 (n = 1296)	Same, Level 2 (n = 456)	Worse, Levels 3-5 (n = 273)	Better, Levels 1-2 (n = 544)	Same, Level 3 (n = 578)	Worse, Levels 4-5 (n = 156)	Better, Levels 1-3 (n = 185)	Same, Level 4 (n = 130)	Worse, Level 5 (n = 68)	Better, Levels 1-4 (n = 143)	Same, Level 5 (n = 256)
Level 1	12849 (76)	961 (58)	181 (14)	23 (5)	12 (4)	12 (2)	11 (2)	0 (0)	0 (0)	0 (0)	0 (0)		
Level 2	465 (3)	125 (7)	620 (48)	173 (38)	64 (23)	76 (14)	34 (6)	2 (1)	9 (5)	0 (0)	1 (1)		
Level 3	250 (1)	120 (7)	144 (11)	87 (19)	59 (22)	211 (39)	205 (35)	36 (23)	15 (8)	1 (1)	0 (0)		
Level 4	18 (0)	8 (0)	25 (2)	20 (4)	18 (7)	47 (9)	101 (17)	39 (25)	57 (31)	51 (39)	10 (15)		
Level 5	13 (0)	10 (1)	7 (1)	5 (1)	8 (3)	17 (3)	54 (9)	21 (13)	27 (15)	34 (26)	19 (28)	78 (55)	105 (41)
Seen (ungradable)	725 (4)	86 (5)	51 (4)	24 (5)	85 (31)	25 (5)	25 (4)	3 (2)	10 (5)	6 (5)	3 (4)	10 (7)	23 (9)
Not seen	598 (4)	60 (4)	48 (4)	10 (2)	10 (4)	20 (4)	14 (2)	6 (4)	6 (3)	4 (3)	3 (4)	5 (3)	8 (3)
Dead	2030 (12)	301 (18)	220 (17)	114 (25)	17 (6)	136 (25)	134 (23)	49 (31)	61 (33)	34 (26)	32 (47)	50 (35)	120 (47)

Abbreviations: AMD, age-related macular degeneration; 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.

[a] Data are No. (%) of visits.

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. *CFH* Y402H genotype CC was associated, relative to genotype TT, with increased incidence of AMD and accelerated progression but not with accelerated regression or increased mortality. Late AMD in both eyes was associated with increased mortality relative to no AMD, although earlier stages of AMD were not associated with increased mortality.

Five-Year Transition Probabilities by Age and AMD Severity in the Fellow Eye

Five-year transition probabilities by age and AMD severity in the fellow eye are displayed in **Figure 2**. These probabilities are adjusted to the sex and *CFH* Y402H genotype distribution at the first BDES visit. For eyes free of AMD in participants who were 50 years of age, the incidence of any AMD in that eye by 55 years of age was higher if AMD was present in the fellow eye (7% vs 2%). A similar effect of AMD severity in the fellow eye was seen in participants who were 70 years of age (21% vs 6%) and in participants who were 90 years of age (24% vs 10%). For an eye with AMD at level 2 in a participant who was 50 years of age, regression to no AMD by 55 years of age was less common as AMD severity in the fellow eye changed from better to same to worse (14% vs 12% vs 11%); progression to level 3 or

higher was more common as AMD severity in the fellow eye changed from better to same to worse (11% vs 25% vs 40%). Similar relationships were seen in participants who were 70 years of age (regression: 17% vs 12% vs 9%; progression: 23% vs 44% vs 57%) and in participants who were 90 years of age (regression: 6% vs 3% vs 2%; progression: 21% vs 29% vs 31%). Patterns are similar for eyes with AMD at level 3 or level 4.

Simulated Realizations of AMD History for Individuals Free of AMD at 45 Years of Age

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 1000 participants (for each sex and *CFH* genotype combination) free of AMD at 45 years of age from the estimated MSM. For comparison, we performed an identical simulation 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-

Table 3. Estimated Covariate Effects on Transition Intensities or Hazards

Covariate	Hazard Ratio (95% CI)							
	Incidence or Progression				Regression			
	Level 1 to Level 2	Level 2 to Level 3	Level 3 to Level 4	Level 4 to Level 5	Level 2 to Level 1	Level 3 to Level 2	Level 4 to Level 3	Mortality[a]
Age (per 5 y)	1.40 (1.35-1.45)	1.28 (1.20-1.38)	1.11 (1.04-1.19)	1.22 (1.11-1.33)	1.12 (1.05-1.20)	1.17 (1.03-1.33)	0.87 (0.69-1.10)	1.67 (1.63-1.71)
Male sex	0.89 (0.78-1.01)	0.69 (0.55-0.87)	0.79 (0.62-1.01)	1.06 (0.79-1.42)	0.80 (0.62-1.03)	0.81 (0.54-1.21)	0.33 (0.12-0.90)	1.55 (1.42-1.68)
CFH Y402H genotype								
TT	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
CT	1.34 (1.17-1.54)	1.23 (0.94-1.60)	1.26 (0.95-1.68)	1.31 (0.90-1.91)	0.92 (0.70-1.19)	0.84 (0.53-1.31)	0.62 (0.25-1.55)	0.95 (0.86-1.04)
CC	1.94 (1.62-2.33)	1.63 (1.18-2.25)	1.07 (0.75-1.52)	1.57 (1.01-2.46)	1.08 (0.72-1.62)	0.57 (0.30-1.10)	0.62 (0.20-1.93)	0.99 (0.87-1.13)
AMD severity in fellow eye								
Better		0.42 (0.33-0.55)	0.50 (0.34-0.73)	0.88 (0.55-1.42)	1.03 (0.67-1.57)	2.00 (1.12-3.58)	8.97 (1.01-80.10)	
Same	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
Worse	4.90 (4.26-5.63)	2.09 (1.42-3.06)	2.38 (1.74-3.25)	2.46 (1.65-3.66)	1.00 (0.51-1.93)	1.56 (0.82-2.97)	1.23 (0.07-20.40)	
AMD severity in better eye								
Level 1								1 [Reference]
Level 2								0.98 (0.63-1.52)
Level 3								1.03 (0.76-1.40)
Level 4								1.14 (0.77-1.68)
Level 5								1.28 (1.03-1.58)

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio; 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.

[a] From any AMD to death.

currence of asymmetry >2 steps). Our model demonstrated the effect of 1 eye on the incidence and progression of AMD in its fellow eye across the entire continuum of AMD severity.

The MSM used in our study is advantageous because it models the course of AMD at the eye level rather than at the participant level used in previous work.[22,23] The higher resolution of the state space (25 left eye/right eye AMD states rather than 5 worse eye AMD states) allows us to better exploit all of the available information from both eyes rather than artificially integrating them into a single participant-level measure. The model can also easily incorporate eye-level covariates in addition to participant-level covariates. In addition, it can more usefully exploit the information from participants with gradable photographs of 1 eye and ungradable photographs of the fellow eye. The disadvantages of the MSM are the large computational burden involved in model fitting, which grows quickly along with the number of states, and the sparseness of information regarding some transitions, which, for example, requires the categorization of the fellow eye's AMD severity as worse, same, or better instead of using the exact severity level.

The estimated effects of participant-level covariates (age, sex, and *CFH* genotype) on incidence, progression, and regression of AMD are qualitatively and quantitatively similar to those seen in participant-level MSMs.[22,23] 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,[22] 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 of progression of the better (worse) eye that can be used for sample size 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

Figure 2. Five-Year Transition Probabilities to Age-Related Macular Degeneration (AMD) States and Death
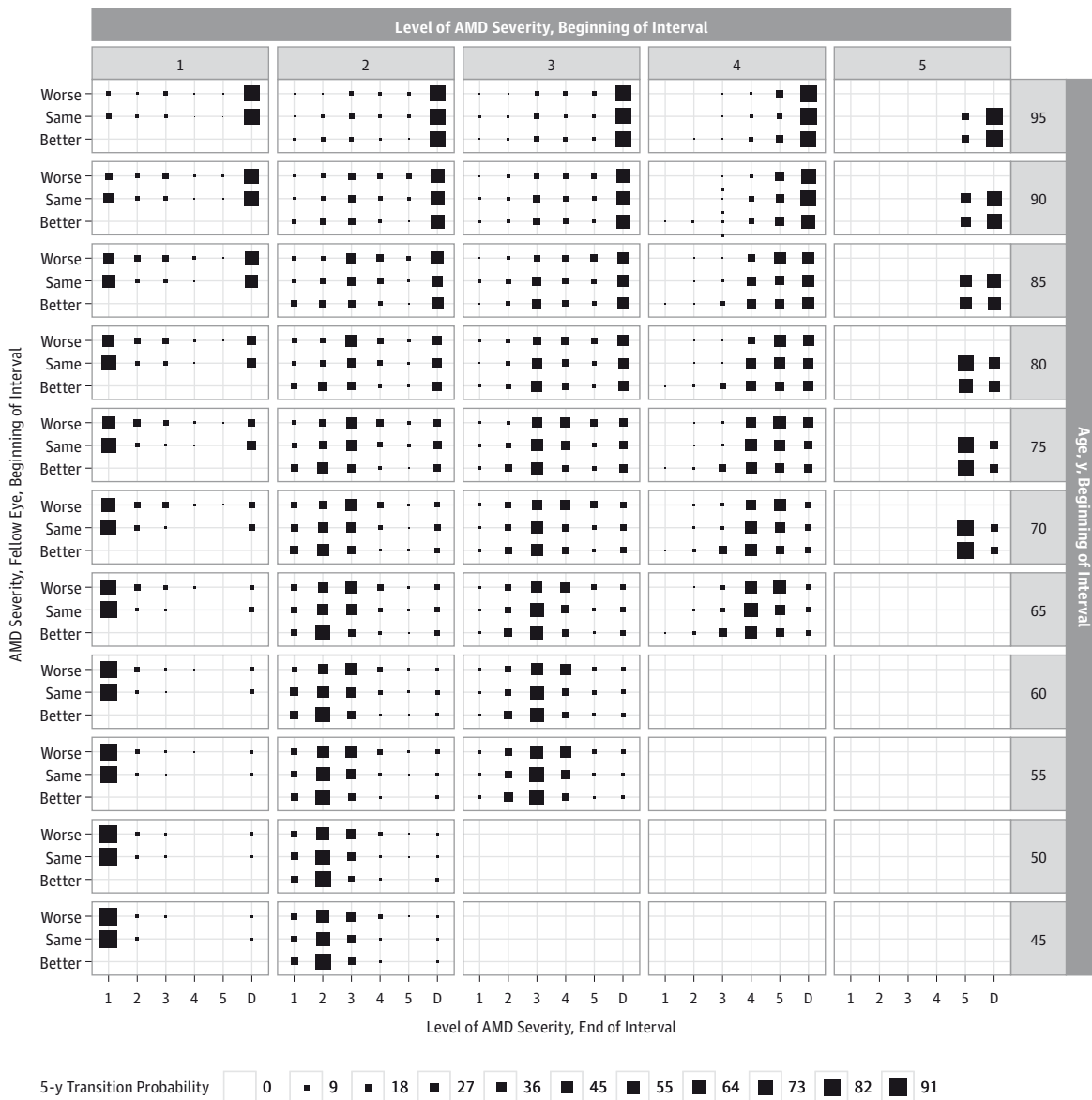
The size of squares represents the 5-year transition probability for the specified initial AMD state, the fellow eye's AMD state, and age in the Beaver Dam Eye Study, adjusted to the sex and complement factor H Y402H genotype distribution at the baseline examination. D indicates death.

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,[23] 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

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]

REFERENCES

1. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99(6):933-943.

2. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7-21.

3. Keilhauer CN, Fritsche LG, Weber BH. Age-related macular degeneration with discordant late stage phenotypes in monozygotic twins. *Ophthalmic Genet*. 2011;32(4):237-244.

4. Mann SS, Rutishauser-Arnold Y, Peto T, et al. The symmetry of phenotype between eyes of patients with early and late bilateral age-related macular degeneration (AMD). *Graefes Arch Clin Exp Ophthalmol*. 2011;249(2):209-214.

5. Nunes RP, Gregori G, Yehoshua Z, et al. Predicting the progression of geographic atrophy in age-related macular degeneration with SD-OCT en face imaging of the outer retina. *Ophthalmic Surg Lasers Imaging Retina*. 2013;44(4):344-359.

6. Marques JP, Costa M, Melo P, et al. Ocular risk factors for exudative AMD: a novel semiautomated grading system. *ISRN Ophthalmol*. 2013;2013:464218.

7. Pieramici DJ, Bressler SB. Age-related macular degeneration and risk factors for the development of choroidal neovascularization in the fellow eye. *Curr Opin Ophthalmol*. 1998;9(3):38-46.

8. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98(8):1310-1315.

9. Klein R, Klein BEK. *The Beaver Dam Eye Study: Manual of Operations (Revised)*. Springfield, VA: National Technical Information Service; 1991. Technical Report/Accession No. PB91-149823.

10. Klein R, Klein BEK. *The Beaver Dam Eye Study II: Manual of Operations*. Springfield, VA: National Technical Information Service; 1995. Technical Report/Accession No. PB95-273827.

11. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population: the Beaver Dam Eye Study. *Ophthalmology*. 1996;103(8):1169-1178.

12. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. *Ophthalmology*. 2001;108(10):1757-1766.

13. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;142(4):539-549.

14. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Software*. 2011;38(8):1-28. http://www.jstatsoft.org/v38/i08. Accessed September 10, 2014.

15. *R: a language and environment for statistical computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2008.

16. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology*. 2002;109(10):1767-1779.

17. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98(7):1128-1134.

18. Klein R, Davis MD, Magli YL, Segal P, Klein BEK, Hubbard L. *The Wisconsin Age-Related Maculopathy Grading System*. Springfield, VA: National Technical Information Service; 1991. Technical Report/Accession No. PB91-184267.

19. Klein R, Klein BE, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology*. 2007;114 (2):253-262.

20. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Boca Raton, FL: Chapman and Hall/CRC; 1993.

21. Knudtson MD, Klein BE, Klein R. Age-related eye disease, visual impairment, and survival: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2006;124 (2):243-249.

22. Gangnon RE, Lee KE, Klein BE, Iyengar SK, Sivakumaran TA, Klein R. Effect of the Y402H variant in the complement factor H gene on the incidence and progression of age-related macular degeneration: results from multistate models applied to the Beaver Dam Eye Study. *Arch Ophthalmol*. 2012;130(9):1169-1176.

23. Gangnon RE, Lee KE, Klein BE, Iyengar SK, Sivakumaran TA, Klein R. Misclassification can explain most apparent regression of age-related macular degeneration: results from multistate models with misclassification. *Invest Ophthalmol Vis Sci*. 2014;55(3):1780-1786.

24. Ferris FL, Davis MD, Clemons TE, et al; Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol*. 2005;123(11):1570-1574.

25. Ferris FL III, Wilkinson CP, Bird A, et al; Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844-851.