The Risk and Natural Course of Age-Related Maculopathy

Follow-up at 6½ Years in the Rotterdam Study

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Objectives: To evaluate the natural course of age-related maculopathy (ARM) and to assess the incidence and absolute risk of its final stage, age-related macular degeneration (AMD).

Methods: In a population-based prospective cohort study of 6418 persons 55 years and older, we studied the incidence and natural course of ARM. Subjects underwent identical examinations, including stereoscopic fundus photography, at baseline and at 2.0 and 6½ years’ follow-up. Age-related maculopathy was graded according to the International Classification and Grading System for ARM and AMD, and stratified into 5 exclusive stages. Incidence was expressed in rates and 5-year absolute risks.

Results: At follow-up, 47 new cases of AMD were identified, with a ratio of neovascular-atrophic AMD of 1.4:1. The 5-year risk of AMD increased with more severe stages to 28.0% for subjects 55 years and older with indistinct drusen and pigmentary irregularities (stage 3). Age, but not sex, independently increased this risk to a maximum of 42.0% for subjects with stage 3 ARM who were 80 years and older. Individual ARM fundus signs that predicted best the development of AMD were 10 or more large drusen (>125 µm) and 10% or more of the grid area covered by drusen. Subjects who developed atrophic AMD showed no significant (P=.25) differences in baseline fundus signs and natural course compared with subjects who developed neovascular AMD.

Conclusions: We provided the absolute risk of AMD as a function of age and early ARM fundus signs, and showed that both are prominent independent risk factors. The progression of ARM stages follows, after the appearance of the first soft drusen, a distinct course at a gradual pace that accelerates with increasing age.

Arch Ophthalmol. 2003;121:519-526

Since the first epidemiological report1 on age-related maculopathy (ARM) in 1977, its high prevalence among individuals 65 years and older in Western societies has been well documented.2-5 The reported prevalences in those aged 65 to 75 years range from 9%4 to 25%,2 depending on the definition of ARM, geographic location, and ethnicity of the population. In contrast to prevalence, few data are available on the incidence and natural course of this disease. Most studies on ARM frequency either were cross-sectional or included patients with unicoval end-stage disease who were recruited from clinics. With these designs, it was not possible to examine the rate at which early stages of ARM develop and the speed with which they progress to end-stage disease, also called age-related macular degeneration (AMD).

In an earlier report,6 the initial 2-year incidence rates of AMD were provided and an ARM staging system to stratify the clinical severity of ARM was proposed. Since then, we have prolonged the study period and added significantly to our number of incident ARM outcomes. In the present article, we provide the results from 6½ years of follow-up with the following objectives: to validate our previous AMD incidence estimates, to determine the long-term progression and natural course of ARM, and to assess the absolute risk of AMD as a function of age and the presence and type of early ARM fundus signs.

STUDY POPULATION

Information on the identification and description of the baseline study population has appeared in previous reports.5,6 Briefly, the Rotterdam Study is a population-based prospective cohort study of all inhabitants 55 years and older of a suburb of Rotterdam. Common cardiovascular, locomotor, neurologic, and ophthalmologic diseases of elderly persons are investigated. The medical ethics committee of
Of the initial cohort of 10,275 eligible individuals, 7,983 (77.7%) participated in the baseline interview of the Rotterdam Study. Because the ophthalmologic part of the study became operational after the screening of participants had started, a smaller portion (n = 6,780) participated in the ophthalmic examination. At baseline, gradable fundus transparencies were available for 6,418 participants. Persons with prevalent atrophic or neovascular AMD (n = 106) were excluded from the assessment of AMD incidence, resulting in a cohort of 6,312 subjects at risk for incident AMD. Prevalent early ARM was present in 476 (7.5%) of the participants, leaving a cohort of 5,836 subjects at risk for incident early ARM. Data for all eligible subjects who participated in at least 1 follow-up examination were entered into the incidence analyses.

### DIAGNOSIS OF ARM

In addition to a standard eye examination, stereoscopic 35° color photographs were taken centered on the fovea (Topcon TRV-50VT fundus camera; Topcon Corporation, Tokyo, Japan). The fundus transparencies were graded with \( \times 12.5 \) magnification according to the International Classification and Grading System for ARM and AMD. In this system, all ARM signs within a standard grid (diameter, 6,000 µm) around the fovea are recorded. The fundus signs that were graded included the following: number of drusen (0, <10, 10-19, and \( \geq 20 \), both within and outside the grid) for each of these sizes (<63, \( \geq 63 \) to <125, and \( \geq 125 \) µm), largest and most frequent drusen size (<63, <125, <175, or \( \geq 175 \) µm or reticular), confluence of drusen (none, <10%, 10-25%, or \( \geq 25% \)), most severe drusen type (hard, soft, distinct, and <125 µm; soft, distinct, and \( \geq 125 \) µm; soft indistinct, or reticular), grid area occupied by the drusen (<1%, 1-10%, 10-25%, or \( \geq 25% \) for the central, inner, and outer circles), increased pigmentation (none or <125, <175, or \( \geq 175 \) µm) and hypopigmentation (none, <175 µm, \( \geq 175 \) µm, or less than or more than area of central circle) of the retinal pigment epithelium (RPE), atrophic AMD, and neovascular AMD.

Graders first graded the follow-up transparencies, after which they were compared with those taken at baseline. The grading procedures and definitions, as well as the graders, were identical at baseline and at follow-up. Graders were trained according to the Wisconsin ARM grading system. Consensus sessions, and between-grader comparisons, were performed regularly. Weighted \( k \) values ranged from 0.69 for hard drusen (<63 µm) to 0.88 for drusen area. All photographs with possible AMD and all uncertain diagnoses were adjudicated by 3 of us (C.C.W.K., J.R.V., and P.T.V.M.d.J.). In addition, all transparencies of incident AMD were adjudicated by the principal investigators of the Beaver Dam Eye Study and the Blue Mountains Eye Study.

### DEFINITIONS

Atrophic AMD was defined as any sharply demarcated round or oval area of apparent absence of the RPE, larger than 175 µm, with visible choroidal vessels and no neovascular AMD. Neovascular AMD was defined as the presence of a serous or a hemorrhagic RPE detachment and/or a subretinal neovascular membrane and/or a subretinal hemorrhage and/or a peri retinal fibrous scar. Lesions that were considered to be the result of generalized disease, such as diabetic retinopathy, chorio retinitis, high myopia, trauma, congenital diseases, or photo coagulation, for reasons other than for neovascular AMD were excluded from ARM grading.

We defined early ARM as the presence of either soft distinct drusen (\( \geq 63 \) µm) with hyperpigmentation and/or hypo pigmentation of the RPE or soft indistinct or reticular drusen.
with or without pigmentary irregularities. To study the progression of ARM, and to enhance the clinical application, we stratified the range of ARM fundus signs into 5 mutually exclusive stages. Definitions and photographic examples of these stages are given in Table 1 and Figure 1, respectively. Stages 2 and 3 correspond with early ARM; stage 4 is equal to AMD.

The incidence of early ARM and of AMD was defined as the absence of this diagnosis in both eyes at baseline and the presence of the diagnosis in at least 1 eye at follow-up. For the risk analysis of individual fundus signs, subjects with unilateral AMD at baseline were included, using the unaffected eye.

DATA ANALYSIS

The age-specific incidence rates of early ARM and AMD were obtained per 5-year age category by dividing the number of incident cases by the number of person-years within that age category. The number of person-years was calculated by adding each person’s contribution of follow-up time to the successive age categories. So, one subject could contribute person-years to different age categories. We assumed that early ARM or AMD started at the date of the first examination at which this diagnosis was made. Consequently, follow-up time ended on the date of screening. Confidence intervals (CIs) of incidence rates were calculated with Poisson SEs. The cumulative incidence (actual risk per period) was derived from the incidence rate using the following exponential formula:

$$CI(t) = 1 - e^{-IR \cdot t}$$

where CI(t) is the cumulative incidence over a period of t years, IR is the incidence rate, and e is the constant 2.71828, the base of the natural logarithm.

The predictive power of individual fundus signs for the incidence of AMD was calculated by a data set of 1 eye per subject, so that an affected eye was included from persons with incident AMD and a randomly selected right or left eye from all other subjects. Unaffected eyes of participants with unilateral AMD at baseline were also included. Subsequently, the incidences of atrophic and neovascular AMD were calculated for each type of fundus sign or combination of features.

An analysis of covariance adjusted for age and sex, when appropriate, was used to compare the baseline characteristics of participants and nonparticipants. All statistical analyses were performed with SPSS for Windows (SPSS Inc, Chicago, Ill.).

Table 2. Baseline Characteristics of Participants in the First and Second Follow-up Examinations

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>First Follow-up Examination</th>
<th>Second Follow-up Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died (n = 359)</td>
<td>Refused to Participate, Ungradable Photographs, or Lost to Follow-up (n = 1085)</td>
<td>Participated (n = 4974)</td>
</tr>
<tr>
<td>Died (n = 1308)</td>
<td>Refused to Participate, Ungradable Photographs, or Lost to Follow-up (n = 1474)</td>
<td>Participated (n = 3636)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y†</th>
<th>55-64</th>
<th>65-74</th>
<th>75-84</th>
<th>≥85</th>
<th>Female sex</th>
<th>Institutionalized</th>
<th>Hypertension</th>
<th>Smoking</th>
<th>Stage of ARM‡</th>
<th>Current</th>
<th>Former</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>55-64</td>
<td>65-74</td>
<td>75-84</td>
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<td>Female sex</td>
<td>Institutionalized</td>
<td>Hypertension</td>
<td>Smoking</td>
<td>Stage of ARM‡</td>
<td>Current</td>
<td>Former</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Total Person-years</th>
<th>No. of Cases Atrophic AMD</th>
<th>Incidence (95% CI) per 1000 Person-years</th>
<th>5-y Risk</th>
<th>No. of Cases Neovascular AMD</th>
<th>Incidence (95% CI) per 1000 Person-years</th>
<th>5-y Risk</th>
<th>No. of Cases Total AMD</th>
<th>Incidence (95% CI) per 1000 Person-years</th>
<th>5-y Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>2240</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-64</td>
<td>6218</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>65-69</td>
<td>6602</td>
<td>3</td>
<td>0.5 (0.2-1.4)</td>
<td>0.2</td>
<td>2</td>
<td>0.3 (0.1-1.2)</td>
<td>0.2</td>
<td>19</td>
<td>1.0 (0.7-1.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>70-74</td>
<td>5460</td>
<td>3</td>
<td>0.6 (0.2-1.7)</td>
<td>0.3</td>
<td>7</td>
<td>1.3 (0.6-2.7)</td>
<td>0.6</td>
<td>17</td>
<td>4.7 (3.6-6.2)</td>
<td>1.7</td>
</tr>
<tr>
<td>75-79</td>
<td>3578</td>
<td>5</td>
<td>1.4 (0.6-3.4)</td>
<td>0.7</td>
<td>9</td>
<td>2.5 (1.3-4.8)</td>
<td>1.3</td>
<td>25</td>
<td>7.0 (4.9-11.2)</td>
<td>1.9</td>
</tr>
<tr>
<td>≥80</td>
<td>2494</td>
<td>8</td>
<td>3.2 (1.6-6.4)</td>
<td>1.6</td>
<td>9</td>
<td>3.6 (1.9-6.9)</td>
<td>1.8</td>
<td>31</td>
<td>7.8 (5.2-11.0)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

| Total  | 26 592            | 19                        | 0.7 (0.5-1.1)                            | 0.4     | 28                          | 1.1 (0.7-1.5)                            | 0.5     | 47                    | 1.8 (1.3-2.4)                            | 0.9     |

Abbreviations: ARM, age-related maculopathy. AMD, age-related macular degeneration; CI, confidence interval.

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(Reprinted) Arch Ophthalmol. 121(4):521-528, April 2003
The mean time between baseline and the first follow-up was 2.0 (median, 2.0; SD, 0.6) years, and between baseline and the second follow-up was 6½ (median, 6.4; SD, 0.4) years. Of 6418 participants with gradable photographs at baseline, 358 (5.6%) died before the first follow-up examination and another 951 (14.8%) died before the second follow-up examination. Of those alive at the first screening (n=6060), 52 (0.9%) were lost to follow-up, 987 (16.3%) refused to participate, and 13 (0.2%) had ungradable photographs. Of those alive at the second follow-up (n=5109), 27 (0.5%) were lost to follow-up, 343 (6.7%) refused to participate, and 51 (1.0%) had ungradable photographs. A comparison of general characteristics between participants and nonparticipants is provided in Table 2. Compared with participants, persons who were alive but were not included in the analyses were on average older, included more women, were more often residents in a nursing home, included more current smokers, and had a higher frequency of systemic hypertension (P<.001 for all). The difference in baseline prevalence of early ARM was considerable, but did not reach statistical significance (P<.06).

During 26592 person-years of follow-up, 47 subjects with incident AMD were identified, resulting in an overall incidence rate of 1.8 per 1000 person-years. The ratio of neovascular AMD–atrophic AMD was 1.4:1 (27 cases of pure neovascular AMD, 19 cases of pure atrophic AMD, and 1 mixed case). The age-specific incidence rates of atrophic, neovascular, and total AMD are shown in Table 3 and Figure 2. The rate of total AMD varied from 0 for those aged 55 to 59 years to 6.8 per 1000 person-years for those 80 years or older. The corresponding 5-year risks were 0% and 3.4%, respectively. This increase over age was exponential when expressed on a logarithmic scale (data not shown). The incidence of neovascular AMD was somewhat higher than that of atrophic AMD, especially in the older groups.

In the cohort without early ARM at baseline, 413 subjects with newly developed early ARM at follow-up were identified. The incidence rate of early ARM increased with age, ranging from 1.4 per 1000 person-years (5-year risk, 0.7%) for those aged 55 to 59 years to 6.8 per 1000 person-years for those 80 years or older. The corresponding 5-year risks were 0% and 3.4%, respectively. This increase over age was exponential when expressed on a logarithmic scale (data not shown). The incidence of neovascular AMD was somewhat higher than that of atrophic AMD, especially in the older groups.

The rate of total AMD varied from 0 for those aged 55 to 59 years to 42.0% for those 80 years and older (Table 4).

### RISK OF AMD AS A FUNCTION OF EARLY FUNDUS SIGNS

From Table 5, the absolute 5-year risk of AMD for an individual can be seen, stratified by stage of early ARM and age. For subjects with stage 0 ARM, the overall risk of AMD within a 5-year period was virtually absent, irrespective of age. For subjects with stage 1 ARM, the overall 5-year risk was 0.9%. However, this risk varied with age from 0.5% for those aged 60 to 69 years to 2.4% for those 80 years and older. Subjects with stage 2 ARM had an overall risk of 7.8%, which increased to 11.9% if they were 80 years or older. Finally, subjects with stage 3 ARM had an overall 5-year risk of 28.0%, varying from 17.3% for those aged 60 to 69 years to 42.0% for those 80 years and older.

### RISK OF ARM AS A FUNCTION OF SEX

The crude incidence rate of AMD was 2.0 per 1000 person-years among men and 1.6 per 1000 person-years among women. This difference did not reach statistical significance when corrected for age (rate ratio, 0.7; 95% CI, 0.4-1.2 [women vs men]), nor was there a significant differ-

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**Table 4. Age-Specific Incidence of Early ARM**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Total Person-years</th>
<th>No. of Cases</th>
<th>Incidence (95% CI) per 1000 Person-years</th>
<th>5-y Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>2179</td>
<td>3</td>
<td>1.4 (0.4-4.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>60-64</td>
<td>6085</td>
<td>32</td>
<td>5.3 (3.7-7.4)</td>
<td>2.6</td>
</tr>
<tr>
<td>65-69</td>
<td>6376</td>
<td>69</td>
<td>10.8 (8.6-13.7)</td>
<td>5.3</td>
</tr>
<tr>
<td>70-74</td>
<td>5102</td>
<td>97</td>
<td>19.0 (15.6-23.2)</td>
<td>9.1</td>
</tr>
<tr>
<td>75-79</td>
<td>3212</td>
<td>102</td>
<td>31.8 (26.2-38.6)</td>
<td>14.7</td>
</tr>
<tr>
<td>≥80</td>
<td>2159</td>
<td>110</td>
<td>51.0 (42.3-61.4)</td>
<td>22.5</td>
</tr>
<tr>
<td>Total</td>
<td>25,113</td>
<td>413</td>
<td>16.4 (14.9-18.1)</td>
<td>7.9</td>
</tr>
</tbody>
</table>

**Table 5. The 5-Year Absolute Risk of AMD as a Function of Stage of ARM and Age**

<table>
<thead>
<tr>
<th>Stage of ARM</th>
<th>60-69</th>
<th>70-79</th>
<th>≥80</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>1.1</td>
<td>2.4</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>9.2</td>
<td>11.9</td>
<td>7.8</td>
</tr>
<tr>
<td>3</td>
<td>17.5</td>
<td>22.5</td>
<td>42.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Total</td>
<td>0.2</td>
<td>1.3</td>
<td>3.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Abbreviations: ARM, age-related maculopathy; CI, confidence interval.
*Early ARM is defined as the presence of other soft distinct drusen with pigmentary irregularities or soft indistinct or reticular drusen (equal to ARM stage 2 plus stage 3).
ence in type of AMD (P = .38 for atrophic and neovascular AMD). The sex-specific rates for early ARM were 17.1 per 1000 person-years for men and 16.0 per 1000 person-years for women (rate ratio, 0.8; 95% CI, 0.7-1.0 [women vs men, adjusted for age]). In addition, the progression of ARM was not different for women vs men, when adjusted for age (odds ratio, 1.0; 95% CI, 0.9-1.2).

NATURAL COURSE OF ARM

The natural course of ARM is visualized in Figures 3, 4, and 5. Figure 3 projects for 3 age categories the distribution of the 5 ARM stages at baseline and after 2.0 and 6½ years of follow-up. A slow but constant progression in ARM severity can be seen with advancing age and with time. Likewise, the risk of each stage of ARM increased with age (Figure 4). This age-dependent increase in risk is similar for all stages, but the absolute risks differed between stages. In Figure 5, the change of each ARM stage at baseline separately is shown for the 2 follow-up examinations at 2.0 and 6½ years. It demonstrates that ARM evolved stage after stage, with only few subjects skipping 1 stage during a short 2-year period. The proportion of subjects who changed to a lower stage of ARM, and seemed to regress, was low, with a maximum of 8% (n=69) for the change from stage 1 to stage 0 within 2 years. At the second follow-up, 64 (93%) of

Figure 3. Distribution of the 5 stages of age-related maculopathy (ARM) at baseline (0) and after 2.0 and 6½ years of follow-up, for 3 age categories separately. Definitions of the ARM stages are given in Table 1.

Figure 4. Age-specific incidence in at least 1 eye of the stages of age-related maculopathy (ARM) as used in the Rotterdam Study, expressed as 5-year risk. Definitions of the ARM stages are given in Table 1.

Figure 5. Change over time of the stages of age-related maculopathy (ARM). In the first column, the total prevalence of each stage at baseline (0) is set at 100%. The second and third columns represent the relative proportions of the ARM stages as they emerged from this baseline stage at the first and second follow-up examinations, after a mean interval of 2.0 and 6½ years, respectively. Definitions of the ARM stages are given in Table 1. A, Stage 0. B, Stage 1. C, Stage 2. D, Stage 3.
these subjects with presumed regression had returned to their baseline stage. The percentage of subjects who developed AMD during a 6\(\frac{1}{2}\)-year period was negligible for stages 0 and 1.

Next, we studied whether the advancement to atrophic and neovascular AMD resulted from differences in early fundus signs. Figure 6 shows the distribution of the stages of age-related maculopathy (ARM) before the incidence of atrophic (A) and neovascular (B) age-related macular degeneration. In the third column, the total number of incident cases at the second follow-up is set at 100%. The first and second columns represent the relative proportions of the ARM stages as they were seen at the baseline and first follow-up examinations, with a mean interval of 6\(\frac{1}{2}\) and 4\(\frac{1}{2}\) years, respectively. Definitions of the ARM stages are given in Table 1.

Figure 6. Distribution of the stages of age-related maculopathy (ARM) before the incidence of atrophic (A) and neovascular (B) age-related macular degeneration. In the third column, the total number of incident cases at the second follow-up is set at 100%. The first and second columns represent the relative proportions of the ARM stages as they were seen at the baseline and first follow-up examinations, with a mean interval of 6\(\frac{1}{2}\) and 4\(\frac{1}{2}\) years, respectively. Definitions of the ARM stages are given in Table 1.

Of 56 subjects who had prevalent uniocular AMD at baseline, 25 participated in the first follow-up examination and 7 participated in the first and the second follow-up examinations. In addition, 3 of the 9 subjects with inci-
dent unioocular AMD at the first follow-up examination participated in the second follow-up examination. In this subcohort of 35 persons with unioocular AMD (21 with neovascular AMD and 14 with atrophic AMD), 9 developed AMD in the second eye. This resulted in an incidence rate of 97.8 per 1000 person-years, or a 5-year cumulative incidence of 38.7% (95% CI, 22.5%-60.9%). The type of AMD in the first eye was strongly related to the type of AMD in the second eye. All 5 subjects with unioocular neovascular AMD developed the same type of AMD in the other eye, as did 3 of the 4 subjects with unioocular atrophic AMD, resulting in 89% concordance between fellow eyes.

We studied the incidence and progression of ARM in a large population-based cohort in the Netherlands during a 61/2-year period. Our data demonstrate that the overall 5-year risk of atrophic or neovascular AMD in subjects 55 years and older is 0.9%, and the risk of early ARM is 7.9%. The incidence of AMD strongly depended on age and stage of ARM, reaching a maximum 5-year risk of 42.0% for persons 80 years or older who were seen with soft indistinct drusen and pigmentary abnormalities. Sex was not an independent predictor of disease incidence or progression. The natural progression of ARM seemed to follow a distinct course, which we expressed as the succession of exclusive stages of disease with increasing risk of AMD. There were no significant differences in the early ARM fundus signs preceding atrophic or neovascular AMD.

Our study has merits and drawbacks. The design of the Rotterdam Study offered us the opportunity to investigate the development of ARM over a long period with many elderly people unaffected by the disease at baseline. The 3 successive examinations with short intervals enabled us to describe the stepwise progression of ARM. We minimized the potential for misclassification by the grading of fundus transparencies in a standard well-established procedure by the same well-trained graders. Moreover, the principal investigators of 2 other cohort studies that use the same grading method were approached to confirm the diagnosis of incident AMD.

Among the potential biases of a prospective cohort study is selective unavailability for follow-up. In our study, the percentage of subjects who were alive but did not participate in both follow-up examinations was 23.3% of the total cohort. This group was on average older, lived more often in a nursing home, and included more persons who smoked and had systemic hypertension. Moreover, nonparticipants had more severe stages of early ARM at baseline. This indicates that participants in the follow-up study were at a lower risk of developing AMD compared with the total eligible cohort, and that we have underestimated the incidence of AMD. Comparing the age-specific prevalence of ARM at baseline and at the second follow-up, we indeed found lower numbers for AMD in those older than 80 years, but not for early ARM. This effect could be explained by selective nonparticipation of subjects with clinically significant AMD (ie, visual impairment). Considering the prevalence difference, the incidence in those 80 years and older may have been up to 2 times higher. There was no prevalence difference in those aged 70 to 79 years.

To provide meaningful risk estimates for clinical practice, and for comparisons of our data with those of others, we converted the incidence rates to 5-year cumulative risks. For this conversion, 3 assumptions need to be satisfied: a closed cohort, a small ratio of events per time to the population at risk, and no competing risk.9 The first 2 criteria were fulfilled in our study, but the third criterion was not. Because only participants in the eye examination were included in the analyses, and participation is conditional on being alive, the considerable competing risk of death was not taken into account. For this reason, the actual 5-year risk of AMD, which is most frequent at the oldest age, will be higher than that observed in our study. So, the 5-year risks of AMD are conditional on staying alive.

How do our data compare with those of others? In line with former findings, the incidence of AMD seems to be lower in the Rotterdam Study than in the Beaver Dam Eye Study.10 The 5-year incidence of late ARM for persons aged 65 to 74 years was 1.3% in the US cohort, compared with 0.6% in our population. However, the design of the studies and the calculation of incidences are different, and a comparison is, therefore, vulnerable to distortion. When we applied the same method and determined the age-specific incidence proportion in our cohort, the differences were less dramatic, but the incidence in the Beaver Dam cohort was still higher than in the Rotterdam cohort (for those aged 65-74 years, the incidence was 1.3% in Beaver Dam and 1.2% in Rotterdam; for those ≥75 years, the incidence was 5.4% in Beaver Dam and 2.4% in Rotterdam).2,11 Because the diagnostic procedures and definitions were similar, this difference seems to be real.

Comparing the progression rate from early ARM to AMD is also hampered by differences in ARM definition, time of follow-up, and age composition of the cohort.11,12 Recently, the results of the Age-Related Eye Disease Study (AREDS),13 evaluating the effect of supplementation with vitamins C and E, beta carotene,
and zinc on progression of ARM, were published. The design of this multicenter clinical trial enabled an interesting comparison with our data, for subjects with clearly defined categories of ARM were enrolled and followed up for an average of 6.3 years. The AREDS AMD category 2, indicating intermediate drusen (≥63 to <125 µm) with or without pigment abnormalities, is close to our stage 1, while the AREDS AMD category 3, indicating extensive intermediate or large drusen with or without pigment abnormalities, may be considered similar to our ARM stages 2 and 3 combined. The probability of progression of AMD category 2 to advanced AMD was 2.0% after 7 years in the placebo group of the AREDS, while progression to AMD was 0.9% for those with stage 1 ARM in our study. The probability of advanced AMD in subjects with category 3 was 26.8% in the AREDS, while this risk for subjects with stage 2 or 3 ARM was 9.7% in the Rotterdam Study. The incidence of second eye involvement in subjects with uniconal AMD at baseline was 55.1% in the AREDS and 38.7% in the Rotterdam Study. These comparisons were not adjusted for age. Nevertheless, taking all considerations into account, comparison with the Beaver Dam Eye Study data and the AREDS findings seems to suggest that the progression and incidence rate of ARM are higher in a US compared with a European population. In an earlier report,\textsuperscript{14} it was shown that known risk factors, such as smoking and cardiovascular disease, could not explain the observed frequency difference. The elucidation of genetic and environmental factors that are accountable remains a challenge for the future.

We described the natural course of ARM by mutually exclusive stages with an increasing risk of AMD. This exercise confirmed the previous thinking that drusen evolve from hard to soft distinct, and from soft distinct to soft indistinct. They increase in number, size, and confluence to form irregular plaques. Retinal pigment epithelial depigmentation and hyperpigmentation appearing at this stage significantly enhance the risk of AMD. Deducing from our data, the type of AMD does not result from a significant difference in the course of early fundus signs, although extensive areas of drusen seem to have a slight predilection for the development of geographic atrophy. However, the number of incident cases of atrophic or neovascular AMD was low and, therefore, the power to detect a statistically significant difference in baseline fundus signs may have been insufficient. The observed regression in ARM stage is most likely misclassification due to variability in photographic quality as a consequence of increasing media opacities. An argument supporting this explanation is the fact that most subjects with regression returned to the stage diagnosed at baseline at the next follow-up. However, a genuine temporary regression cannot be excluded.

In conclusion, the long-term follow-up of this large population-based cohort enabled us to estimate the absolute risk of AMD as a function of age and fundus signs. These data can be used effectively in the clinical care of patients, the design of clinical trials and other research objectives, and the establishment of risk profiles and strategies for future eye cases. Most of all, they give insight into the natural course of this disease.

Submitted for publication June 11, 2002; final revision received December 9, 2002; accepted December 19, 2002.

We thank Ada Hooghart and Corina Brussee for their extensive assistance in data collection and photograting; Jacqueline Assink, MD, PhD, Raan Ramrattan, MD, and Petra Borger, MD, for their help in the ophthalmologic examinations; and the principal investigators of the Beaver Dam Eye Study (Ronald Klein, MD, MPH) and the Blue Mountains Eye Study (Paul Mitchell, MD, PhD) for their adjudication of the diagnosis of incident AMD.

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REFERENCES

This study was supported by the M. Manasaki Fellowship of the University of Crete, Crete, Greece (Dr Papadaki).
This study was presented in part at the 11th Aegean Cornea Meeting, Heraklion, Crete, July 1, 2000.

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REFERENCES


Correction

Error in Acknowledgments. In the Epidemiology feature titled “The Risk and Natural Course of Age-Related Maculopathy,” published in the April issue of the ARCHIVES (2003;121:519-526), there were omissions from the acknowledgments.

In addition to those mentioned in the acknowledgments paragraph, the authors wish to acknowledge the contributions of the following institutions: Optimix Foundation, Amsterdam; Netherlands Organization for Scientific Research (NWO), The Hague; The Netherlands Society for the Prevention of Blindness, Doorn; Blindenhulp Foundation, The Hague; Rotterdamse Blindenbelangen Foundation, Rotterdam; OOG Foundation, The Hague; Topcon Europe BV, Capelle aan de IJssel; and The Edward and Marianne Blaauw Foundation, Amsterdam; the Netherlands.