Incidence and Progression Rates of Age-Related Maculopathy: The Rotterdam Study

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Purpose. To describe the incidence rate of age-related macular degeneration (AMD) and the progression rates of early stages of age-related maculopathy (ARM), and to study the hierarchy of fundus features that determine progression.

Methods. A group of 4953 subjects aged 55 years and older living in Rotterdam, The Netherlands, was studied at baseline and at 2-year follow-up to determine the incidence of neovascular and atrophic AMD. A subgroup of 1244 subjects was studied for progression of early stages of ARM. Fundus transparencies were graded for features of ARM using the International Classification System. ARM was stratified in four exclusive stages, according to type of drusen and presence of pigmentary irregularities.

Results. The overall 2-year cumulative incidence of AMD was 0.2%, increasing to 1.8% in subjects of 85 years and older. Of those in the early stages, one fourth showed progression to a more severe stage. The most important predictors for progression were more than 10% of macular area covered by drusen (odds ratio [OR] 5.7, 95% confidence interval [CI] 2.9–11.3), presence of depigmentation (OR 4.0, 95% CI 2.5–6.4), and hyperpigmentation (OR 3.4, 95% CI 2.1–5.4).

Conclusions. The incidence of AMD appears to be lower in The Netherlands than in the United States. Progression of early ARM stages occurs in a distinct pattern at a stable rate, with a large area of drusen and presence of pigmentary changes as the most important predictors. (*Invest Ophthalmol Vis Sci.* 2001; 42:2237–2241)

Many studies have contributed to the current knowledge that age-related maculopathy (ARM) is a frequent eye disorder in the elderly.[1–3] Its end stages, referred to as age-related macular degeneration (AMD), have been shown to be the most important cause of irreversible blindness in the Western world.[4–6] The epidemiologic designs of the population-based studies that provided these data have been mostly cross-sectional, allowing for data on disease prevalence and prevalence associations. In etiologic research, however, incidence is preferred over prevalence, because this represents the actual disease occurrence. Incidence data for ARM would improve the knowledge on the origin, early development, and progression of this disease. At present, these data are still scarce.[7,8]

The purpose of this study was to describe the incidence and progression rates of ARM in the population-based Rotterdam Study in The Netherlands. We studied the incidence of AMD in the entire cohort and investigated progression of early ARM features in specific subgroups. Furthermore, we sought to assess the prognostic value of the various fundus features that are associated with ARM.

Materials and Methods

Population

The Rotterdam Study is a population-based prospective cohort study conducted in a suburb of Rotterdam, The Netherlands, in which chronic ophthalmologic, neurologic, cardiovascular, and locomotor disorders are investigated. Methods used to identify and describe the population have appeared in previous reports.[2,9] The study protocol was approved by the medical ethics committee of Erasmus University, and the research was in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after explanation of the nature of the study. Baseline interviews and screening examinations took place from 1990 to mid-1993 and follow-up examinations from mid-1993 to the end of 1994.

Of 10,275 subjects aged 55 years and older living in Ommoord (a suburb of Rotterdam), 7,983 (78%) agreed to participate in the baseline phase of the entire study. The eye examination became part of the Rotterdam Study after the initial phase, therefore a smaller portion (n = 6872) was eligible for ophthalmic study. Gradable fundus transparencies were available on 6418 (93%) subjects, in 105 (1.6%) of whom atrophic or neovascular AMD was diagnosed. This resulted in a cohort of 6313 subjects potentially at risk for incident AMD.

Procedures and Definitions

The screening for presence of ARM followed the same protocol at baseline and at follow-up. The procedures have been described in detail elsewhere.[2,9] During the screening eye examination, 35° color transparencies were taken of the macular area (model TRV-50VT fundus camera; Topcon Optical Co., Tokyo, Japan). The diagnosis of ARM features was based on grading of fundus transparencies according to the International Classification System,[10] in which all features of maculopathy related to age are named ARM and its late stages (i.e., atrophic or neovascular macular degeneration) are named AMD. At baseline, fundus transparencies of the entire cohort were graded in a detailed manner to identify all features of ARM in the macular grid area (radius, 3000 μm). At follow-up, all fundus transparencies of the entire cohort were graded for presence of AMD using side-by-side grading with the transparencies of the baseline phase. Inter- and intragrader agreement on each fundus feature was regularly assessed, and consensus training

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Table 1. Stratification of ARM in Exclusive Stages of Severity

Stage	Criteria	At Baseline	At Follow-up	Selected for Detailed Grading
No ARM	No ARM features or only drusen ≤63 μm	4038	3238	365
1a	Soft, distinct drusen	1485	1160	348
1b	Pigmentary irregularities	307	217	193
2a	Soft, indistinct, or reticular drusen	191	133	133
2b	Soft, distinct drusen with pigmentary irregularities	209	158	158
3	Soft, indistinct, or reticular drusen with pigmentary irregularities	83	47	47
4	Atrophic or neovascular macular degeneration (AMD)	105	56	0

Data are the number of subjects at each stage.

was initiated when κ values were below 0.6. All photographs showing AMD and all uncertain diagnoses were adjudicated by senior investigators (PTVMdeJ, CCWK, JRV).

To assess the incidence and progression rates of early ARM features, ARM at baseline was stratified in four exclusive stages of disease (Table 1). On the basis of previous findings,[7,8,11,12] we assumed more macular disease and a higher risk of development of AMD with each successive stage of early ARM. Stratification was based on the eye with the most severe stage. ARM stages 1a and 1b were considered one stage of clinical severity, as were stages 2a and 2b. For reasons of feasibility and efficiency, only a randomly selected subset of subjects with no ARM or ARM stage 1a at baseline underwent detailed grading of early ARM features at follow-up. For the remaining stages, the entire group of subjects with gradable fundus transparencies underwent detailed grading at follow-up. All detailed grading at follow-up was performed using side-by-side grading with the transparencies from baseline.

Incidence of an ARM lesion was defined as absence of this particular lesion within the grid area of either eye at baseline and presence of this lesion in at least one eye at follow-up. Progression of ARM was defined as a worsening to the next or a higher stage of ARM; no progression was defined as no change or a decrease in stage.

Statistical Methods

Subjects with AMD at baseline were excluded from the incidence and progression analyses. The age-specific incidence rates of AMD were obtained per 10-year age categories by dividing the number of incident cases by the number of person-years per age category. The latter was calculated by summing each participant's contribution of follow-up time per age category. Confidence intervals of incidence rates were calculated with the exact method. Age at onset of incident AMD was set at the midpoint between age at baseline and age at follow-up. Cumulative incidences were calculated from the incidence rates with the formula

$$CI_t = 1 - e^{-IR*t}$$

where CI is the cumulative incidence over a period of t years, IR is the incidence rate, and e is the constant 2.71828, which is the base of the natural logarithm. Incidence of AMD in the contralateral eye of subjects with unilateral AMD at baseline was analyzed in a separate analysis.

Progression of early ARM stages was studied by logistic regression analysis with age, gender, baseline stage of ARM and duration of the follow-up period fixed in the model. In an initial analysis with these fixed factors, the predictive powers of drusen size and location, proportion of macular grid area covered by drusen, most frequent drusen size, largest drusen size, drusen confluence, presence and area of hyperpigmentation, and presence and area of depigmentation were assessed. Statistical interaction between macular area of drusen and hyper- or depigmentation, between hyper- and depigmentation, as well as between area of drusen and drusen confluence, was studied by entering the product term of these factors in the model. Determinants or product terms with a significant odds ratio (OR) were entered in a subsequent multivariate analysis to determine the independence and magnitude of prognostic factors.

Results

Incidence of AMD

Of the 6313 subjects at risk for incident AMD, 326 subjects died before follow-up. Of the remaining 5987 subjects, 5445 (91%) responded to the 2-year follow-up phase of the Rotterdam Study, and 5095 (85%) participated in the rescreening eye examination. Gradable fundus transparencies of at least one eye were present in 4953 subjects (83%), and these subjects were included in the incidence analyses. They significantly differed from other eligible subjects in age, gender, smoking status, and vascular status (Table 2). After adjustment for age, those alive and nonparticipating at follow-up did not differ by stage of ARM at baseline, nor were those who were deceased at the time of follow-up different in ARM stage at baseline from those participating (latter data not shown). Thus, there was no significant selection of those included in the incidence analysis on the basis of disease.

After an average follow-up period of 2.0 ± 0.6 years (SD), incident AMD was identified in 12 participants. Of those, four had atrophic AMD and eight had neovascular AMD. Given a total of 9849 person-years, the overall incidence rate of AMD was 1.2 per 1000 person-years (2-year cumulative incidence 0.24%). The incidence rate increased with age (Table 3). Figure 1 shows the age-specific incidence rates in the Rotterdam Study in comparison with two other population-based incidence studies.[7,8]

Table 2. Baseline Characteristics of Subjects at Risk of Incident ARM

	In Analysis* (n = 4953)	Not in Analysis† (n = 1034)	P‡
Age at baseline			<0.001
55–64 y	43.3	28.5	
65–74 y	38.1	32.9	
75–84 y	16.2	29.7	
85+ y	2.5	8.9	
Gender (women)	58.5	61.3	0.07
Institutionalized	3.0	10.3	<0.001
ARM stage at baseline			0.24
1	27.8	29.3	
2	5.9	7.5	
3	0.9	2.4	
Smoking			0.01
Currently	20.4	23.1	
Formerly	42.3	35.5	
Hypertension	27.7	35.6	0.02
Atherosclerosis	14.2	24.7	<0.001

Data are percentages of eligible subjects alive at the 2-year follow-up. Total alive was 5987.

* Subjects with gradable fundus transparencies.

† Nonparticipants alive at follow-up, and subjects with ungradable fundus transparencies.

‡ Adjusted for age and gender, when appropriate.

TABLE 3. Age-Specific Incidence Rates per 1000 Person-Years, and 2-Year Cumulative Incidences of AMD in the Rotterdam Study

Age Category (y)	Person-Years	*n*	Incidence Rate	95% CI	2-Year Cumulative Incidence (%)
55–64	3546	0	0	0–1.0	0
65–74	4011	3	0.75	0.15–2.2	0.15
75–84	1952	6	3.07	1.1–6.7	0.61
85+	340	3	8.80	1.8–25.8	1.75
Total	9849	12	1.22	0.6–2.1	0.24

Overall, there were no statistically significant gender differences in incidence rates of AMD. Among the 2080 men, the overall incidence rate was 1.00 per 1000 person-years (2-year cumulative incidence 0.2%), whereas among the 2873 women, the overall incidence rate was 1.37 per 1000 person-years (2-year incidence 0.2%, $P = 0.99$, adjusted for age and follow-up time).

Incident AMD was strongly associated with stage of ARM at baseline. Neither ARM stage 0 nor stage 1 progressed to incident AMD. ARM stage 2 progressed in two subjects to incident atrophic AMD and in five to incident neovascular AMD. For this stage, the overall incidence rate of AMD was 14.0 per 1000 person-years (2-year cumulative incidence 3%), ranging from 0 per 1000 person years in subjects under 65 years to 25.7 per 1000 person-years (2-year incidence 5.0%) in subjects aged 85 years and older. Stage 3 at baseline progressed in two subjects to incident atrophic AMD and in three to incident neovascular AMD. For stage 3, the total incidence rate of AMD was 48.2 per 1000 person-years (2-year incidence 9%), and the age category in which this occurred was less than 85 years.

Of the 31 subjects with AMD in only one eye at baseline, incident AMD had developed in the second eye in three subjects with atrophic AMD and in three subjects with neovascular AMD, by the 2-year follow-up. This resulted in an incidence rate of 170.6 per 1000 person-years (2-year cumulative incidence 28.9%) for involvement of the second eye. In the three subjects with unilateral atrophic AMD at baseline, the same type of AMD developed in the second eye. Neovascular AMD developed in the second eye of two of the three subjects with neovascular AMD, and atrophic AMD developed in the fellow eye of the remaining subject. The baseline ARM stages of the second eye were stages 2 (three subjects) and 3 (three subjects).

Progression of Early Stages

Of the 1244 subjects who were included in the early ARM progression analyses, disease in 316 progressed to a more severe stage of ARM. For the total cohort, this implied a 2-year cumulative progression rate of 21.5%. Table 4 shows the incidence rates of the various stages of ARM at follow-up. Age was associated with progression: Adjusted for gender, follow-up time, and baseline stage of ARM, the OR of progression for age per year was 1.04 (95% [CI] 1.01–1.06). Gender was not associated with progression: The OR for women versus men was 0.90 (95% CI 0.62–1.31; adjusted for age, follow-up time and baseline stage of ARM).

In the (univariate) analysis of prognostic factors, macular area covered by drusen, presence and area of hyperpigmentation, presence and area of depigmentation, number of small drusen (<63 μm), and drusen confluence were significantly associated with progression (data not shown). In the multivariate analysis with the significant factors in the model, all factors remained statistically significant. A large area of drusen was the most important predictor of ARM progression: The OR for more than 10% of macular area covered by drusen was 5.7 (95% CI 2.9–11.3; Table 5). The other important independent predictors were presence of depigmentation, hyperpigmentation, 10 or more small drusen, and at least 10% drusen confluence. Patients with large areas of depigmentation were at a higher risk of progression than those with smaller areas (OR for area $\geq$175 μm versus area <175 μm, 2.3; 95% CI 1.5–3.5). Areas of hyperpigmentation larger than 125 μm did not have higher ORs than areas of 125 μm or smaller, indicating that larger areas of hyperpigmentation were not significantly of additional prognostic value. We found no evidence for statistical interaction between area of drusen and pigmentary irregularities, between hyper- and depigmentation, or between area and confluence of drusen (data not shown).

DISCUSSION

In the Rotterdam Study, the incidence rate of AMD was 1.2 per 1000 persons per year for subjects aged 55 years and over. The incidence rate of AMD showed a strong relation with age and increased to 8.8 per 1000 persons per year for those aged 85 years and older. The incidence of AMD in the contralateral eye of subjects already affected by unilateral AMD was 170.6 per 1000 persons per year. The most predictive stage for development of incident AMD was ARM stage 3, which comprises the presence of either soft, indistinct drusen or soft drusen with pigmentary irregularities. Progression of early stages of ARM occurred in a very distinct pattern at a rate of 25% in 2 years. The most important predictors for progression were more than 10% of macular area covered by drusen, presence of depigmentation, and presence of hyperpigmentation.

A good estimate of the incidence of AMD requires the follow-up of many subjects over a long period, because the occurrence of this clinical end stage is relatively infrequent. A large study population with a significant number of elderly is one of the strengths of the Rotterdam Study. However, the length of the follow-up period was not long, and the number of subjects in whom incident AMD developed was low. This resulted in wide confidence intervals around the estimated incidence rates. The short follow-up period was a benefit, however, for the study of the progression of early ARM stages.

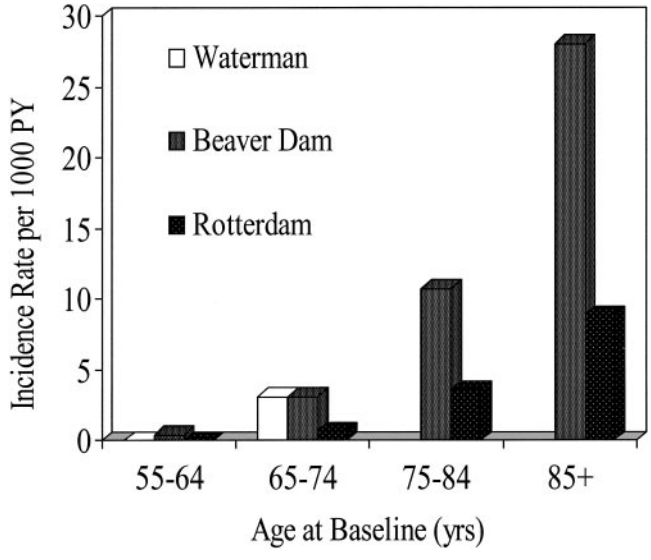

FIGURE 1. Comparison of the estimated age-specific incidence rates of AMD in The Rotterdam Study with the estimated incidence rates in the Waterman Study,[7] and in the Beaver Dam Eye Study.[8]

TABLE 4. Incidence Rates of Stages of ARM per 1000 Person-Years Based on 2-Year Follow-up

		Stage at Follow-up			
Baseline Stage	**Person-Years**	**1**	**2**	**3**	**4**
0	638.99	136.2 (24)	3.1 (1)	0	0
1	936.85		139.8 (24)	10.7 (2)	0
2	498.34			148.5 (26)	14.0 (3)
3	103.74				48.2 (9)

Two-year cumulative incidence, expressed as a percentage, is shown in parentheses.

This enabled us to register small changes and to determine a pattern of progression, which may add to the understanding of the natural course of this disease.

Loss to follow-up was a concern in this study as it is in all cohort studies. Nonparticipation in the second round was mainly due to death and nonresponse to the entire study, not to the eye examination itself. Comparison of participating and nonparticipating subjects showed that the latter group was older and had more vascular disease; however, the groups did not significantly differ in stage of ARM at baseline. Thus, selection bias regarding ARM disease status due to loss to follow-up appears to be limited in our study.

The age-specific incidences of AMD appeared to be lower in the Rotterdam Study than in the Waterman Study[7] and Beaver Dam Eye Study[8] (Fig. 1). The US studies took place in different parts of the US, but showed incidences within the same range. Although a longer follow-up period is needed to confirm the incidences, the difference appears to be considerable, is consistent over the age-groups, and is in agreement with earlier reports indicating global differences in the occurrence of AMD. Comparison of prevalence data from the Beaver Dam Eye Study, the Blue Mountain Eye Study, and the Rotterdam Study show that the prevalence of AMD is highest in the US and lowest in The Netherlands.[1–3] The three studies used very similar methods of diagnosis based on fundus photography, which makes it less likely that the differences were a result of observation bias. Known risk factors such as smoking and cardiovascular disease did not explain the differences,[13] and it remains a key point of interest to identify the environmental and genetic factors that are accountable.

The 2-year cumulative incidence of AMD in the fellow eye in subjects with unilateral AMD was 29% in the entire study, and the type of AMD was not necessarily concordant with the first eye. The Beaver Dam Eye Study found a 5-year incidence of 22% for the second eye,[8] considerably lower than the Rotterdam Study. The lower maximum age at baseline in the Beaver Dam study may account for this difference. Our data are in line with clinic-based studies reporting the rate of fellow eye involvement. The majority of these studies focused on patients with neovascular AMD, and estimates for annual second eye incidence mostly ranged from 4% to 15%.[11,14–19] All prevalence figures in these studies were crude prevalences, because numbers were mostly too small for any stratification. Therefore, comparison of these prevalences is hampered by differences in age, duration of disease, and diagnosis. Long-time follow-up of large, well-defined study groups is needed to provide valid and precise estimates and to enable more profound comparisons.

TABLE 5. Independent Prognostic Fundus Features for Progression of ARM

Fundus Feature	**OR (95% CI)***
Total drusen area ≥10% of grid	5.7 (2.9–11.3)
Presence of depigmentation	4.0 (2.5, 6.4)
Presence of hyperpigmentation	3.4 (2.1, 5.4)
≥10 Small drusen (≤63 μm)	2.5 (1.5, 4.1)
≥10% Drusen confluence	2.5 (1.7, 3.8)

* Based on a model that included these factors and age, baseline stage of ARM, and duration of follow-up period.

An important objective of this study was to describe the progression of early features of ARM. It has long been known that soft drusen and pigmentary changes are precursor lesions that increase the risk of geographic atrophy and neovascular macular degeneration.[7,8,11–21] After appearing, drusen and pigmentary changes may regress and disappear, but this may be a result of appearance of more severe lesions.[7,8] In the Rotterdam Study, we did not focus on individual fundus lesions. To enhance clinical relevance, we preferred to study progression of ARM in exclusive stages of disease. We stratified early features of ARM in three stages based on type of drusen and presence of pigmentary changes, the factors that have been shown to be strong predictors for the development of AMD.[7,8,11,12] The ranking of the stages proved to be in accordance with clinical severity: the risk of AMD increased from virtually no risk for stages 0 and 1, to a 2-year risk of 3% and 9% for stages 2 and 3, respectively. An interesting finding was that progression was predominantly to only one more advanced stage at a rate of approximately one-fourth of the cohort per 2 years for the earliest stages (Table 4). Progression from stage 3 to 4 was slower and occurred at a rate of 9% in 2 years. In some subjects, maculopathy progressed fast and skipped a stage, but no subjects skipped more than one stage in the 2 years of follow-up. Although future studies are awaited to confirm these data, our findings add to the view that development of ARM is not a random chain of events, but rather seems to follow a well-defined pattern at a stable rate.

In accordance with Klein et al.,[8] we found that a large area of the macula covered by drusen and pigmentary irregularities were important predictors of ARM progression, independent of stage of disease. Other predictors were number of small drusen and drusen confluence. The number of intermediate (64–124 μm) and large (≥125 μm) drusen did not have additional predictive power, neither did location of drusen. Although small drusen (≤63 μm) are not considered an ARM feature in the International Classification System, our data indicate that more than 10 small drusen are predictive of ARM progression, independent of other features. This is consistent with findings from the Waterman Study[7] and the Beaver Dam Eye Study,[8] both of which reported that presence of many small drusen increases the risk of large and soft indistinct drusen, but not of AMD.

From our results and those of others we conclude that progression of early ARM appears to follow a distinct pattern. A large number of small, hard drusen or isolated pigmentary changes may indicate the very early start of ARM. Then soft drusen emerge. Subsequently, at a stable rate, multiple drusen of various sizes appear and become confluent, the total area increases, and some of the drusen become soft and indistinct.

The appearance of pigmentary changes at this stage, especially large areas of depigmentation, then further increases the risk of AMD. Subretinal neovascularization or development of geographic atrophy denote the end stage of ARM.

In conclusion, the incidence of AMD in the Rotterdam Study was 1.2 per 1000 subjects per year. Our data provide further evidence that ARM is a progressive disease with a distinct temporal sequence of events ultimately resulting in AMD.

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