The Prevalence of Age-related Maculopathy in the Rotterdam Study

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Purpose: To determine the prevalence of age-related maculopathy in an elderly population in The Netherlands.

Methods: Fundus photographs of 6251 participants of the Rotterdam Study, a single-center prospective follow-up study in persons 55 to 98 years of age, were reviewed for the presence of drusen, pigmentary abnormalities, and atrophic or neovascular age-related macular degeneration.

Results: The prevalence of at least one drusen of 63 μm or larger increased from 40.8% in persons 55 to 64 years of age to 52.6% in those 85 years of age or older. Similarly, the prevalence of the following abnormalities increased significantly in these age categories: drusen of 125 μm or larger from 4.8% to 17.5%, retinal pigment epithelial hypopigmentations from 3.5% to 9.0%, and increased retinal pigment from 3.7% to 15.3%. Atrophic or neovascular age-related macular degeneration was present in 1.7% of the total population. Atrophic age-related macular degeneration increased from 0.1% in persons 55 to 64 years of age to 3.7% in those 85 years of age or older. Neovascular age-related macular degeneration increased from 0.1% to 7.4% in these age groups. No sex differences were observed for these lesions.

Conclusions: The prevalence of atrophic or neovascular age-related macular degeneration is 1.7%. In those 55 years of age or older, the prevalence increases strongly with age and it is similar in men and women. Neovascular age-related macular degeneration was twice as common as atrophic age-related macular degeneration. These findings suggest that age-related maculopathy may be less common in this European population than in similar populations in the United States.

Ophthalmology 1995;102:205-210

Originally received: June 10, 1994.

Revision accepted: August 31, 1994.

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Presented at the 5th Annual Congress of the Royal College of Ophthalmologists, Guernsey, April 1994.

Supported by the Nestor program for geriatric research in The Netherlands (Ministries of Health and of Education), The Hague, Topcon Europe B.V., Rotterdam, Haagsch Oogheelkundig Fonds, The Hague, Merck, Sharp & Dohme—Chibret Nederland, Haarlem, Stichting Bevordering Volkskracht and Stichting Blindenhulp, The Hague, Rotterdamse Vereniging voor Blindenbelangen, Rotterdam, The Netherlands Society for the Prevention of Blindness, Utrecht, Stichting voor Ooglijders, Rotterdam, and Stichting Roos, Rotterdam, The Netherlands.

The term *age-related maculopathy* (ARM) is used for a variety of abnormalities that are observed in the macular area of elderly persons. The late stages, characterized by geographic atrophy and neovascular disease, also called *age-related macular degeneration* (AMD), are major causes of severe visual impairment in the elderly in industrialized countries.¹ Few detailed population-based data are available for comparison, however, especially with

Each author states that she/he has no proprietary interest in the equipment mentioned in this article.

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Table 1. Age- and Sex-specific Percentage of Participation, and of Ophthalmologic Data of Study Participants

	Age (yrs)	No. Eligible	% of Participation (no.)		
			Interview	Ophthalmologic Examination	Gradable Fundus Photographs
Men	55-64	1418	82 (1157)	78 (1099)	73 (1033)
	65-74	1382	82 (1127)	76 (1054)	71 (977)
	75-84	796	72 (573)	63 (505)	57 (456)
	85+	191	66 (126)	47 (89)	38 (73)
	Total	3787	79 (2983)	73 (2747)	67 (2539)
Women	55-64	1802	85 (1540)	81 (1466)	77 (1391)
	65-74	1865	79 (1469)	73 (1354)	69 (1280)
	75-84	1505	71 (1063)	59 (894)	52 (788)
	85+	815	68 (544)	39 (320)	31 (253)
	Total	5987	77 (4616)	67 (4034)	62 (3712)
All	55-64	3220	84 (2697)	80 (2565)	75 (2424)
	65-74	3247	80 (2596)	74 (2408)	70 (2257)
	75-84	2301	71 (1636)	61 (1399)	54 (1244)
	85+	1006	67 (670)	41 (409)	32 (326)
	Total	9774	78 (7599)	69 (6781)	64 (6251)

regard to the oldest age groups.¹⁻⁴ The Rotterdam Study is the first major European study that provides population-based data on ARM obtained by the grading of fundus photographs. This article presents data on the prevalence of ARM in persons 55 years of age or older.

Population and Methods

Study Population

The Rotterdam Study is a single-center prospective follow-up study of the population of persons 55 years of age or older from a suburb of Rotterdam, The Netherlands. The study was approved by the Medical Ethics Committee of the Erasmus University, Rotterdam. Ra-

tionale and design of the study have been described elsewhere.⁵ In brief, the objective of the study is to investigate prevalence, incidence, and determinants of chronic ophthalmologic, neurologic, cardiovascular, and locomotor diseases. The primary ophthalmologic diseases studied in the Rotterdam Study are ARM and glaucoma. Names and addresses of the residents were drawn from the municipal register. In random clusters, potential participants were invited by letter, followed by a telephone call, to make an appointment. All participants gave a written informed consent. Baseline data were obtained during an initial home visit with an interview, followed by a physical examination in the field center. During the home visit, the participants were asked, among other questions, if they had visited an ophthalmologist in the past for reasons other than for

Table 2. Definitions*

Small drusen	Drusen <63 μ m in diameter
Large drusen	Drusen $\geq$ 63 μ m in diameter
Retinal pigment epithelial hypopigmentation	Area of decreased pigmentation not classifiable as drusen or atrophic AMD†
Increased retinal pigment	Clumps of increased brown, gray, or black pigment, $\geq$ 63 μ m†
Atrophic AMD	Well-demarcated area of retinal pigment epithelium atrophy with visible choroidal vessels†
Neovascular AMD	Serous or hemorrhagic retinal pigment epithelial detachment and/or subretinal neovascular membrane and/or subretinal hemorrhage and/or periretinal fibrous scar

AMD = age-related macular degeneration.

* The grading of age-related maculopathy was performed in an area within a radius of 3000 μ m from the foveola.

† Lesions that were considered to be the result of generalized vascular disease, such as diabetic retinopathy or chorioretinitis, or high myopia, trauma, congenital diseases, or photocoagulation for reasons other than for neovascular AMD, were not included in the definition.

Table 3. Interobserver and Intraobserver Agreement in Grading of Changes Related to Age-related Maculopathy

Characteristic	Interobserver Agreement (kappa)	Intraobserver Agreement (kappa)	
		Reader 1	Reader 2
No. of small drusen (0; 1-9; 10+)	0.43	0.36	0.37
No. of large drusen (0; 1-9; 10+)	0.55	0.64	0.73
Predominant size large drusen (63-124 μ m; $\geq$ 125 μ m)	0.46	0.63	0.64
Retinal pigment epithelial hypopigmentation	0.48	0.56	0.70
Increased retinal pigment	0.76	0.76	0.64
Atrophic or neovascular AMD	0.79	0.72	0.72

AMD = age-related macular degeneration.

prescription of glasses. Participants living in nursing homes were examined at their home.

The ophthalmologic examination was performed between March 1990 and July 1993. During this period, 10,191 persons were invited to participate in the study. Of these, 67 had died and 350 could not be reached, resulting in 9774 eligible participants. Of these, 7599 persons (78%) were visited at home and 6781 (69%) participated in the ophthalmologic examination in the field center (Table 1).

Ophthalmologic Examination

Participants of the ophthalmologic study were examined and had fundus photographs taken by one of three investigators. Eyes were dilated with 0.5% tropicamide and 5% phenylephrine. After an average period of 45 minutes, two 35° color photographs (Kodak Ektachrome 64 ASA, Topcon TRV-50VT fundus camera, Tokyo Optical CO

Company Ltd, Tokyo, Japan) centered on the macular area were taken of each eye. After photography, direct and indirect ophthalmoscopy was performed. From 530 persons, fundus photographs could not be obtained due to refusal (5%), technical failure (4%), logistic reasons (5%), and physical problems (86%). In 211 persons, photographs were gradable in one eye only, and in 6040 persons photographs of both eyes were gradable. As a result, gradable fundus photographs of at least one eye were available from 6251 subjects.

Photographic Grading

Photographs were graded using the definitions and grids of the Wisconsin Age-Related Maculopathy Grading System (WARMGS)⁶ by one of three graders. All questionable lesions, and all lesions that were classified as geographic atrophy or neovascular macular degeneration were discussed and adjudicated by two of the authors. Frequent

Table 4. Comparison of Participants and Nonparticipants

	Nonparticipants*	Study Participants			P
		Interview Only	Interview/Ophthalmic Examination	Interview/Ophthalmic Examination/Fundus Photograph	
No.	2175	818	530	6251	
Age (yrs)†					
Mean $\pm$ SE	73.5 $\pm$ 0.2	78.2 $\pm$ 0.3	73.5 $\pm$ 0.5	68.9 $\pm$ 0.1	<0.01
Sex (% women)	63.0	64.8	59.1	59.7	0.03
Visit ophthalmologist† (%)		40.1	42.5	41.3	0.71
Ophthalmoscopy					
Large drusen (%)	—	—	3.6	7.5	0.01
AMD‡ (%)	—	—	1.3	2.4	0.09

SE = standard error; AMD = age-related macular degeneration.

* Eligible to the study but not participating.

† History of visit to ophthalmologist in the past for reasons other than prescription of glasses.

‡ Atrophic or neovascular AMD.

Table 5. Age-specific Prevalence (%) of Large Drusen within Radius 3000 μm from the Fovea of the Worse Eye, Subclassified for Size and Number

Age (yrs)	Size and No. of Predominant Large Drusen					
	63-124 μm		$\geq 125 \mu\text{m}$		Total	
	1-9	10+	1-9	10+	1-9	10+
55-64	33.0	2.7	4.6	0.5	37.6	3.2
65-74	37.2	6.0	6.9	1.4	44.1	7.3
75-84	31.5	9.5	10.1	4.8	41.6	14.4
85+	25.6	8.8	11.4	6.8	37.0	15.6
Total	33.9	5.5	6.8	2.0	40.7	7.5

sessions of simultaneous grading were held to maintain reproducibility. The WARMGS grid was adapted to the magnification of the camera. The slides were examined on a portable stereo viewer with fluorescent back light (Philips PL-S 9 W/84, Philips Ltd, Eindhoven, The Netherlands; 4000° K) with $\times 5$ magnification. Combined with a $\times 2.5$ magnification of the fundus camera, the total magnification was approximately $\times 12.5$.

Definitions of Age-related Maculopathy

In this study, the definitions of the WARMGS were used.⁶ In brief, drusen and pigmentary changes without neovascular disease or geographic atrophy were considered to be signs of early ARM. Neovascular macular degeneration and geographic atrophy were defined by WARMGS as late ARM, and we called these neovascular and atrophic AMD. The grading of ARM was performed within an area 3000 μm from the foveola.

Drusen were graded according to their diameter. Small drusen were defined as drusen smaller than 63 μm . Large drusen were defined as all drusen 63 μm or larger. Instead of estimating the area of drusen, as was done in the WARMGS, we counted the number of drusen. The exact number of small drusen was counted only in a subset of 5152 participants. The exact number of large drusen was counted separately, and the size of the predominant dru-

sen was estimated as 63 to 124 μm , 125 μm , or larger. The number of drusen was subclassified as either none, one to nine, or ten or more drusen. Retinal pigment epithelial hypopigmentation was defined as a local area of decreased pigmentation not classifiable as drusen or atrophic AMD. Increased retinal pigment was defined as any clump of increased brown, gray, or black pigment 63 μm or larger.

Atrophic AMD was defined as any well-demarcated atrophic area of retinal pigment epithelium with visible choroidal vessels and without the presence of neovascular AMD. Neovascular AMD was defined as the presence of a serous or hemorrhagic retinal pigment epithelial detachment and/or a subretinal neovascular membrane and/or a subretinal hemorrhage, and/or a periretinal fibrous scar. Lesions that were considered to be the result of generalized vascular disease, such as diabetic retinopathy or chorioretinitis, or high myopia, trauma, congenital diseases, or photocoagulation for reasons other than for neovascular AMD, were not included in the definition. A summary of definitions is given in Table 2.

Statistical Analysis

We first analyzed the possible effect of nonparticipation in the ophthalmologic study by comparing age, sex, and reason for visiting an ophthalmologist in the past. Differences in ages between participants and nonparticipants were adjusted by direct standardization. For those who participated in the ophthalmologic examination, the possible effect of absent or ungradable fundus photographs on the prevalence estimate was analyzed by comparing funduscopically assessed ARM changes. Equality of means was tested using the Student's *t* test. In a substudy, the reproducibility was examined. Inter- and intraobserver agreement was tested with the kappa statistic. When three answers were possible, weighted kappa was used with weights of 0 for perfect agreement, 1 for one-category disagreement, and 2 for two-category disagreement. The prevalence data in persons were based on the eye with the most severe signs of ARM. If, for example, two eyes of a participant were discrepant with regard to the number of large drusen, the eye with the largest number of large drusen was taken. The prevalence of early ARM was com-

Table 6. Age-specific Prevalence (%) of Pigmentary Abnormalities within Radius 3000 μm from the Fovea of the Worse Eye

Age (yrs)	Retinal Pigment Epithelial Hypopigmentation			Increased Retinal Pigment			Total Pigmentary Abnormalities		
	Men	Women	All	Men	Women	All	Men	Women	All
55-64	4.5	2.7	3.5	4.1	3.4	3.7	5.7	4.0	4.8
65-74	4.8	3.3	4.0	7.2	3.7	5.2	9.0	4.7	6.5
75-84	8.1	5.0	6.1	10.3	8.7	9.3	12.5	9.8	10.8
85+	10.3	8.6	9.0	20.6	13.8	15.3	23.5	15.5	17.3
Total	5.4	3.8	4.4	6.8	5.2	5.9	8.7	6.2	7.2

Table 7. Age- and Sex-specific Prevalence (%) of Atrophic and Neovascular Age-related Macular Degeneration

Age (yrs)	Atrophic AMD			Neovascular AMD			Total AMD		
	Men	Women	All	Men	Women	All	Men	Women	All
55-64	0.2	0.0	0.1	0.1	0.1	0.1	0.3	0.1	0.2
65-74	0.6	0.2	0.4	0.3	0.5	0.4	0.9	0.6	0.8
75-84	1.1	1.4	1.3	2.4	2.4	2.4	3.5	3.8	3.7
85+	2.7	4.0	3.7	6.8	7.5	7.4	9.6	11.5	11.0
Total	0.6	0.6	0.6	0.8	1.2	1.1	1.4	1.9	1.7

AMD = age-related macular degeneration.

puted by 10-year age groups, and for men and women separately. Changes of the prevalence with age were tested using regression analysis and expressed in terms of 10-year prevalence increase with 95% confidence intervals (95% CI). Odds ratios, as an estimate of relative risk, were calculated by means of logistic regression as a measure of strength of the association between ARM and sex with adjustment for age.

Results

Inter- and intraobserver agreement was examined in a sample of 226 photographs with an oversampling for lesions (Table 3). The agreement was moderate to good⁷ for most characteristics. Only the agreement on grading the number of small drusen was fair. The participants of the Rotterdam Study were younger than those who were invited but did not take part (Table 4). Similarly, participants who completed the ophthalmologic examination and fundus photography were younger than those who did not. Nonparticipants were more likely to be women. In participants of the ophthalmologic examination, the prevalence of ophthalmoscopically observed large drusen and atrophic or neovascular AMD was higher in the group with gradable photographs.

Small drusen were very common in all age groups. The prevalence of small drusen decreased with age from 83.1% in persons 55 to 64 years of age to 29.1% in those 85 years of age or older (regression analysis, -16.8% per 10 years;

95% CI, $-18.2, -15.5$). Similarly, the prevalence of one to nine drusen of 63 to 124 μm decreased with age (regression analysis, -6.8% per 10 years; 95% CI, $-7.9, -5.7$) (Table 5). All other subgroups showed a significant increase with age, especially for ten or more drusen of 125 μm or larger (regression analysis, 2.7% per 10 years; 95% CI, $1.8-2.6$). No sex differences were observed for the presence of drusen. Pigmentary abnormalities also were observed more frequently with increasing age (Table 6). Regression analysis showed that the prevalence of retinal pigment epithelial hypopigmentation increased with 1.8% for each 10 years (95% CI, $1.2-2.3$) and by 3.3% per 10 years for increased retinal pigment (95% CI, $2.6-3.9$). Both lesions were found more frequently in men with a relative risk of 1.6 for retinal pigment epithelial hypopigmentations (95% CI, $1.2-2.0$) and 1.5 for increased retinal pigment, respectively (95% CI, $1.2-1.9$).

Atrophic or neovascular AMD was diagnosed in 104 persons (1.7%). The prevalence of atrophic AMD increased from 0.1% in subjects 55 to 64 years of age to 3.7% in persons 85 years of age or older (Table 7). In these age groups, the prevalence of neovascular AMD was 0.1% and 7.4%, respectively. No sex differences were observed for these lesions.

Discussion

In this study, we examined the prevalence of ARM in an elderly population in The Netherlands. The findings can

Table 8. Comparison of the Prevalence of Atrophic or Neovascular Age-related Macular Degeneration in Population-based Studies

Site	Size*	Age Group (yrs)									
		55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94		
Chesapeake Bay ²	769	0.0	—	—	0.6	—	—	4.3	—	—	—
Beaver Dam ⁴	4771	0.1	—	0.6	—	—	1.4	—	—	7.1	—
Rotterdam	6251	—	0.2	—	—	0.8	—	—	3.7	—	11.0

* Number of participants with gradable photographs of at least one eye.

Figure 1. Comparison of the prevalence of age-related macular degeneration (atrophic or neovascular) in population-based studies.

be used for comparison with other populations but only after some methodological issues have been mentioned. The effect of nonresponse to our findings has to be considered because it is likely that nonresponse is related to disease. On fundus examination, persons without gradable fundus photographs had a lower prevalence of large drusen and atrophic or neovascular AMD, which could have led to an overestimation of the prevalence of ARM. This could, however, also be due to increased media opacities in this group. The frequency of visiting an ophthalmologist for reasons other than for needing glasses was not different in participants with and without ophthalmologic examination, suggesting that a selection with regard to disease did not occur. In the oldest age-category, the percentage of people in whom gradable fundus photographs could be obtained was small (Table 1). Therefore, the estimates in this group need to be interpreted with caution.

In this study, the photographs were monoscopic, which could have resulted in an underestimation of the prevalence of neovascular AMD by missing subtle pigment epithelial detachments. In addition, the availability and quality of photographs declined with age due to the increasing prevalence of media opacities and physical impairment of the participants. As a result, subtle macular changes become less visible with increasing age. The inverse relation between small drusen and age could have resulted from this problem. Likewise, other changes such as small clumps of retinal pigment and small areas of atrophy could have been underestimated in the older age-groups. This problem will be identical for all studies grading fundus photographs.

Comparison with other population-based studies, notably of atrophic and neovascular AMD, is best done with the Chesapeake Bay Study and the Beaver Dam Eye Study.^{2,4} Both studies used similar methods of case as-

certainment and assessment of the prevalence of ARM. Other studies used different methods, which makes comparison more difficult.^{1,3} We made no attempt to define early ARM as a bounded entity because the criteria for such a definition are still very arbitrary. For comparison, the separate abnormalities are used. With respect to the early stages of ARM, the prevalence of any drusen 63 μ m or larger is higher in the current study than in the Chesapeake Bay and Beaver Dam studies. Small differences in grading and photographic techniques, particularly camera magnification and adaptation of the grid, could have caused the discrepancy, although a real difference also may be present. Assuming that the methodology is responsible for the difference, any drusen 125 μ m or larger would be a more appropriate, although still arbitrary, cutoff point for large drusen in this study. The prevalence of increased retinal pigment in men was similar to that in the Chesapeake Bay Study but approximately three times lower than in the Beaver Dam Study. The reason for this is not clear. Our observation that increased retinal pigment is more common in men was observed in the Beaver Dam Study only in subjects younger than 65 years of age. In people older than 75 years of age, the Beaver Dam Eye Study reported a higher risk of pigmentary changes in women.

In Table 8 and Figure 1, a comparison is made between the age-specific prevalence of atrophic or neovascular AMD in the Rotterdam Study and two population-based studies conducted in the United States.^{2,4} The current study shows the lowest estimates. It is conceivable that part of the difference may have resulted from the use of nonstereoscopic photographs in the current study. A real difference, however, also must be considered. The excess risk of neovascular AMD in women 75 to 84 years of age that was reported in the Beaver Dam Eye Study⁴ and the Framingham Eye Study,¹ was not observed in the current study.

In conclusion, the results of this study suggest that ARM may be less common in this European population than in similar populations in the United States.

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