The Prevalence of Age-Related Maculopathy in Iceland

Reykjavik Eye Study

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Objective: To examine the age- and sex-specific prevalence of age-related maculopathy (ARM) and age-related macular degeneration (AMD) in citizens of Reykjavik, Iceland, who were 50 years and older.

Design: Random sample, cross sectional.

Materials and Methods: Response rate was 75.8%. The presence and severity of various characteristics of drusen and pigmentary changes that are typical of ARM and AMD were determined by grading stereoscopic color fundus photographs, using the international classification and grading system for ARM and AMD.

Results: We were able to evaluate 1021 right-eye and 1020 left-eye macular photographs. There was no statistically significant difference between right and left eyes. In people aged 50 to 59 years, 4.8% of participants (95% confidence interval [CI], 2.6-7.0) were found to have intermediate soft drusen measuring 63 to 125 µm in either eye; 1.2% (95% CI, 0.0-2.3) had large soft distinct drusen larger than 125 µm; and 0.6% (95% CI, 0.0-1.4) had large soft, crystalline, or semisolid drusen. The same figures for those 80 years and older were 18.2% (95% CI, 9.8-26.6), 10.9% (95% CI, 4.0-17.8), and 25.5% (95% CI, 18.4-32.6), respectively. Geographic atrophy was found in either eye in 9.2% of those participants 70 years and older (95% CI, 5.6-12.7), and exudative macular degeneration was found in 2.3% of participants 70 years and older (95% CI, 0.5-4.1).

Conclusion: Geographic atrophy was found to be more common in our study than in other population-based studies.

tion. The participants were citizens of Reykjavik 50 years and older who were randomly sampled using the national population census. The sample included 6.4% of the Reykjavik population for each year of birth and for both sexes. The examination took place in 1996. Of those 1635 randomly sampled, 1579 could be contacted and were eligible. Of these, 1045 elected to participate, 461 were men and 584 were women, at a response rate of 75.8%. All were white. They were examined at the University Eye Department in Reykjavik. All were required to answer a questionnaire regarding lifestyle, such as outdoor exposure, alcohol and smoking habits, health, disease, previous surgery, and medication, including eye medication.

EXAMINATION

All participants went through a standard examination protocol including keratoreflectometry (ARK 900; Nidek Co Ltd, Gamagori, Japan), air puff tonometry (NT 2000; Nidek Co Ltd), Scheimpflug photography of the anterior segment (EAS 1000; Nidek Co Ltd), and visual acuity measurements. The pupils were maximally dilated with tropicamide 1% and phenylephrine 10%. We then performed slitlamp biomicroscopy of the fundi using (30°) (3Dx/NM; Nidek Co Ltd). This was done by a single trained ophthalmic photographer. The 35-mm slide transparencies were put into a frame and analyzed using the pocket stereoscope (Cartographic Engineering Ltd, Hampshire, England). The grading of the photographs was based on the international classification system by Bird et al., which again, is based on the Wisconsin grading system. The grading was carried out in the Moorfields Eye Hospital Reading Centre (London, England).

Each patient’s unique identification number was displayed on the photographs. Image quality was graded from 1 to 6. A grade of “1” was awarded when the photograph was in perfect stereo with sharp focus; “2,” for good stereo and good focus; “3,” for acceptable stereo and focus; “4,” for poor stereo and focus, but with main features, such as end-stage AMD still gradable; “5,” for no stereo, thus not gradable; “6,” for good stereo and focus, but with the photograph not centered properly on the macula; and “0,” for a missing image. Grades 5, 6, and 9 were disregarded when analyzing the results of the detailed grading.

GRADING METHODS

The protocol of the International ARM Group was followed with minor modifications. We used a standard grid for ARM classification for the 30° fundus camera, with central, middle, and outer circles, the radii of which were 500 µm, 1500 µm, and 3000 µm, corresponding with zones 1, II, and III in results, respectively. Spokes then split the circles into upper, lower, temporal, and nasal zones. Sets of the 3 circles and spokes were printed on clear plastic as well as 5 circles measuring 63 µm, 125 µm, 175 µm, 250 µm, and 500 µm, respectively, to estimate the size of drusen and pigmentary abnormalities. These were developed according to the published guidelines. To phenotype ARM and AMD precisely in this population, all abnormalities were graded in all 3 zones including drusen, pigment changes, and end-stage AMD. For the physical development of the grid, AutoCAD Software (Autodesk Inc, San Rafael, Calif) was used and the images were reproduced as 3 × 3 slides for easy use with stereo images. In estimating the lesion size or area, the grading circles were placed on one side of the slide (one member of the stereoscopic pair) and viewed through the stereo viewer, which was placed on a standard fluorescent viewing box. Intergrader reliability was assessed on a random subsample of gradeable eyes. This report includes only lesions of ARM present within the grid. The type, size, and number of drusen in each zone was established, as well as hyperpigmentation and hypopigmentation.

All images were graded by 2 trained ophthalmic graders, and 30% of the images were graded by the ophthalmologist trained in grading, without having access to previous grades, age, sex, and clinical information regarding the participants. Fourteen days later, an ophthalmologist trained in grading (T.P.) individually viewed all images and created the final grade based on the results of the previous gradings. In case of disagreement between the graders, one of the authors (A.C.B.) adjudicated the results, and his grading was taken as final. Ten percent of the photographs were randomly selected and regraded by the ophthalmologist after another 14 days, and thus, an audit final grade was created. These grades were compared with the original final gradings to check for internal consistency. If there was a difference between the original and the audit final gradings, the adjudicator’s (A.C.B.) decision was taken as the absolute final. Using Microsoft Access (Microsoft Corp, Redmond, Wash), we developed a database containing all information on grading, identity of graders, data entry persons, and date the photographs were graded. The data were checked for inconsistency at the end of the study by an independent observer who had not been involved in the original data entry process. There was a less than 0.5% error in the data entry process, whereby none of these errors would have affected the validity of the results.

We present the results separately, for hard drusen, early ARM, and AMD. The number of hard drusen smaller than 63 µm was established for each zone.

DEFINITION OF EARLY ARM

Grading of early ARM included the presence of soft, indistinct, or reticular drusen (>63 µm) within the grid, and/or presence of retinal pigment epithelial abnormalities measuring 63 µm or greater within the grid.

DEFINITION OF AMD

The late stages of ARM were defined to include geographic atrophy and exudative macular degeneration — the lesions termed AMD by the International ARM study group. Geographic atrophy was defined as a discrete area of the retinal depigmentation characterized by the sharp border and presence of the visible choroidal vessels at least equaling the size of circle one (zone 1). Exudative AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, presence of subretinal or subpigment epithelium hemorrhage, or subretinal fibrous scar.
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Table 1 presents the number of gradable photographs (grades 1-4), as well as percentages of hard drusen and early ARM by patient age and sex. There were slightly higher numbers of gradable photographs for women than for men, reflecting the higher participation rate of women. The results for both sexes are remarkably similar. In either eye, the prevalence of hard drusen smaller than 63 \( \mu \)m decreased from 85.3% in people 50 to 59 years old to 37.1% (95% confidence intervals (CI) of 25.5-48.8) in those 80 years and older (Table 3). EARLY ARM

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indistinct drusen larger than 125 µm were, however, predominantly seen in zone II. Results for left eyes were similar. In people 50 to 59 years old, 4.8% (95% CI, 2.6-7.0) of participants were found to have intermediate soft drusen measuring 63 to 125 µm in either eye; 1.2% (95% CI, 0.0-2.3) had large soft distinct drusen larger than 125 µm; and 0.6% (95% CI, 0.0-1.4) had large soft crystaline (calcified) or semisolid drusen larger than 125 µm. The same figures for those 80 years and older were 18.2% (95% CI, 9.8-26.6), 10.9% (95% CI, 4.0-17.8), and 25.5% (95% CI, 18.4-32.6), respectively (Table 4).

When both sexes were combined, the prevalence of hypopigmentation 63 µm or larger in at least one eye was 1.2% (95% CI, 0.0-2.4) in people 50 to 59 years old, and 20.0% (95% CI, 9.1-30.9) in those 80 years and older (Table 5). The most common form of hyperpigmentation was punctate (67%), followed by “linear” (24%), a term used if the pigment seemed to form a line. Hyperpigmentation was not counted for each and every drusen; if, however, it was large enough to be taken into account, it was counted as punctate. Hyperpigmentation was found in zone II in 74% of cases, in zone I in 34%, and in zone III in 8%. There was no statistically significant difference between the frequency of hyperpigmentation and hypopigmentation between the sexes (P=.13).

**AGE-RELATED MACULAR DEGENERATION**

Exudative macular degeneration was found in 6 persons—3 women and 3 men, and in 3 right eyes and 3 left eyes. Their mean age was 84 years (range, 77-88 years). One of these, an 86-year-old woman, had exudative macu-
lary degeneration in the right eye and geographic atrophy in the left eye, and an 84-year-old woman and an 88-year-old man had geographic atrophy in the right eye and exudative macular degeneration in the left eye. Thus, half of those with exudative macular degeneration in one eye had geographic atrophy in the other eye. No one had definite exudative macular degeneration in both eyes, though 1 of the 3 had a questionable membrane in the second eye. Further, 3 eyes had questionable neovascular AMD, 2 of them with definite geographic atrophy in the same eye. The prevalence for those 70 years and older was 2.3% (95% CI, 0.5-4.1), and 9.8% for those 80 years and older (Table 6). The exudative lesions were generally large, including all zones (I-III) in 4 instances, and zones I and II, and zone II only in the fifth and sixth person, respectively.

### GEOGRAPHIC ATROPHY

Twenty-nine persons had definite geographic atrophy in either eye (18 women and 11 men). The age range for geographic atrophy was 52 to 87 years (mean, 77 years). Only 1 person younger than 60 years was found to have geographic atrophy. Sixteen persons had geographic atrophy in the right eye, and 23 were affected in the left eye. In the right eye, zone I was affected in 14 instances (87.5%), and zone II was affected 12 instances (75.0%); whereas zone III was affected in 6 instances and was always affected in conjunction with zones I and II. The results in the left eyes were similar. The prevalence for geographic atrophy in both sexes combined was 0.3% for 50- to 59-year-old patients, 1.2% for 60- to 69-year-old patients, 5.3% for those 70 to 79 years old, and 25.0% for those 80 years and older. It therefore seems that geographic atrophy starts at an earlier age than exudative macular degeneration, and both increase rapidly after age 80 years (Table 6). Geographic atrophy was found in either eye of 9.2% of those 70 years and older (95% CI, 5.6-12.7).

Considering the advanced (AMD) types together, the prevalence increases from 5.8% in patients in their 70s, to 30.8% in those 80 years and older.

Thirty-nine right eyes were without gradable photographs — 4, 6, 18, and 11 in persons 50 to 59 years old, 60 to 69 years old, 70 to 79 years old, and 80 years and older, respectively. The most common cause for ungradable photographs was poor focus or stereo in 74.4%.

The results of the slitlamp grading of these 39 eyes were similar to the results of the graded images, considering the same age groups. Advanced AMD, namely geographic atrophy, was only found in one right eye (that of a 92-year-old woman) among the 39 slitlamp-graded eyes. The results for the left eyes were similar.

We did a genealogical analysis using the deCODE genetics genealogical data base. All those with geographic atrophy were found to have a common ancestor 6 generations back, whereas more than 10 generations were required for those with exudative disease, with the last being similar to a random sample of the Icelandic population.

### Table 6. Age- and Sex-Specific Percent Prevalence of AMD in Either Eye

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Men, No. (%)</th>
<th>Women, No. (%)</th>
<th>Combined, No. (%)</th>
<th>Men, No. (%)</th>
<th>Women, No. (%)</th>
<th>Combined, No. (%)</th>
<th>Men, No. (%)</th>
<th>Women, No. (%)</th>
<th>Combined, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>4 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>60-69</td>
<td>2 (1.5)</td>
<td>1 (0.6)</td>
<td>3 (1.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>70-79</td>
<td>4 (4.0)</td>
<td>7 (6.5)</td>
<td>11 (5.3)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>5 (5.1)</td>
<td>7 (6.5)</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>5 (21.7)</td>
<td>8 (27.6)</td>
<td>13 (25.0)</td>
<td>2 (8.7)</td>
<td>3 (10.7)</td>
<td>5 (9.8)</td>
<td>6 (21.7)</td>
<td>9 (34.5)</td>
<td>15 (30.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11 (2.7)</td>
<td>18 (3.5)</td>
<td>29 (3.2)</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
<td>6 (0.7)</td>
<td>13 (2.9)</td>
<td>19 (3.9)</td>
<td>32 (3.5)</td>
</tr>
</tbody>
</table>

Abbreviation: AMD, age-related macular degeneration.

* N = 1022.
ties. In the present study, we found an age-related increase per year from 50 years of age for intermediate soft drusen measuring 63 to 125 µm (OR=1.08; 95% CI, 1.04-1.11; P < .001), soft distinct drusen larger than 125 µm (OR=1.08; 95% CI, 1.04-1.13; P < .001), and soft indistinct drusen larger than 125 µm (OR=1.13; 95% CI, 1.08-1.19; P < .001), with the biggest rise with increasing age for the last abnormality mentioned. Conversely, we found a decrease in the prevalence of small drusen measuring less than 63 µm with increasing age, which was also observed in the Beaver Dam Eye Study.13 14 These drusen are not necessarily expected to contribute to the development of AMD, though they may in some instances break down, to later cluster, and eventually form larger more confluent drusen.15

Intermediate soft drusen 63 to 125 µm in size, and large distinct drusen larger than 125 µm affect zone I and zone II with similar frequency, whereas zone II is most frequently affected (60%) by large indistinct drusen larger than 125 µm. These large indistinct drusen seem to spare fixation to some extent until late stages. Vinding17 found rising frequency of pigmentary changes with increasing age in Denmark, which is also in agreement with our findings. Like our group, this Danish study found geographic atrophy to be more common than the exudative type; however, they did not use exactly the same criteria as we did. Both hypopigmentation (83%) and hyperpigmentation (74%) are most commonly found in zone II, followed by zone I.

Since zone I has the highest concentration of macular pigment, it may be relatively resistant to early retinal pigmentary abnormalities. In the more advanced form (namely, geographic atrophy), this relative resistance appears to collapse since in geographic atrophy, zone I alone or with zone II are affected in more than 80% of instances. In the Beaver Dam Eye Study,14 for those 75 years and older, the prevalence of geographic atrophy was 3.5%, and 6.7% for exudative macular degeneration. The same figures for the present study are 13.5% and 4.5%, respectively. While our results for exudative macular degeneration are somewhat lower than those of the Beaver Dam Eye Study,14 they are slightly higher than the results from the Rotterdam Eye Study18 and the Blue Mountain Eye Study,4 with all studies analyzing populations either living in or derived from Northern Europe to a great extent, and all using the same criteria. The prevalence of geographic atrophy is, however, much higher in the present study than in the 3 previously mentioned studies. It is of interest that the ratio for neovascular vs geographic AMD was found to be approximately 2:1 in the Beaver Dam Eye Study,14 the Rotterdam Eye Study,18 and the Blue Mountain Eye Study.4 Conversely, in a previous article from Eastern Iceland, Jonasson and Thordarson1 found geographic atrophy cases to outnumber those of the exudative type by 3:1 for those 73 years and older.1 However, this last study used the Framingham Eye Study criteria, including a visual criterion.19 In the present study of southwest Iceland, considering those 75 years and older, geographic atrophy in Iceland is again found to outnumber the exudative type by a ratio of 3:1.

Bilaterality of geographic atrophy, as well as the increased prevalence of choroidal neovascularization found in the present study, are in agreement with the findings of Sunness et al.20 At the Department of Ophthalmology at the University of Iceland, we have had centralized laser and fluorescein angiography facilities for the entire country for more than 20 years. All those found to have exudative macular degeneration had angiograms confirming the diagnosis. The differential diagnosis of geographic atrophy, atrophy secondary to macular lasers, and/or atrophy secondary to exudative macular degeneration may sometimes be difficult. We therefore went through the laser register to exclude possible laser scars as cases of pseudogeographic atrophy, and also looked up all those cases of geographic atrophy to find out if they had ever had fluorescein angiography for exudative disease. Neither of these possibilities was the case in instances of atrophy.

In this study, all participants with geographic atrophy had a common ancestor 6 generations back, whereas we would, on average, require 10 to 12 generations for a common ancestor from a random sample of Icelanders. These results suggest that the participants with geographic atrophy may be more related than would be expected from a random sample, supporting the findings of a genetic component suggested by Klein et al21 and Weeks et al.22 It also supports the findings of a previous Icelandic twin study23 and a British twin study,24 both suggesting a genetic component to AMD. Those with exudative AMD did not, however, appear to be more related than would be expected from a random sample. This last result should be interpreted with caution however, since the numbers for exudative AMD are small.

Oxidative damage to the retina may be involved in the pathogenesis of AMD, and antioxidants and zinc supplements have been found to delay vision loss and progression of the disease.25 The Icelandic population is relatively well nourished. According to the United Nations Food and Agriculture Organization, no European nation eats more fish per capita than Icelanders,26 while their consumption of green vegetables and fruits is relatively low by European standards,27 which possibly results in relatively low levels of vitamin A. Daily intake of multivitamins and cod liver oil is, however, known to be very common among elderly Icelanders.28 Intake of zinc is similar to other Northern European populations.27 Smoking, which has been implicated as a risk factor for AMD, was relatively uncommon among those 70 years and older in our study, and fish was usually consumed several times a week.7,8

The main conclusion of this study is that the phenotype of ARM and AMD is different in different communities, or at least Iceland is different than most other Northern European communities. This difference is expressed by the higher prevalence of geographic atrophy in Iceland than it is in similar populations. Our genealogical analysis suggests that those affected are more related than would be expected from a random sample from this population.
REFERENCES


