Prevalence and Characteristics of Age-Related Macular Degeneration in the Japanese Population: The Nagahama Study

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• PURPOSE: To estimate the age- and sex-specific prevalence of early age-related macular degeneration (AMD; drusen and retinal pigment abnormalities) and late AMD (exudative AMD and geographic atrophy) in the Japanese population.

• DESIGN: Community-based, cross-sectional study.

• METHODS: The study was held in Nagahama, Japan, and included 6065 Japanese individuals (aged ≥50 years) recruited in 2008-2010. We graded fundus photographs of both eyes for the AMD phenotype based on drusen size, the presence of retinal pigment abnormalities, and late AMD. The associations between smoking and AMD phenotypes were also evaluated.

• RESULTS: We assessed 5595 subjects (women, 65%) with a gradable macular condition. Early and late AMD prevalence increased from 16.1% and 0.27% at 50-59 years to 31.2% and 0.98%, respectively, at 70-74 years and was predominant in male subjects in each age group. Smoking was associated with both early and late AMD stages and retinal pigment abnormalities ($P < .0001$), but not with drusen ($P = .305$). The prevalence of retinal pigment abnormalities was significantly higher in men ($P < .0001$), which was associated with high rates of cigarette smoking. We found no sex difference for the prevalence of large drusen ($P = .264$).

• CONCLUSIONS: The prevalence of early AMD among adult Japanese persons was similar to the rates in white populations. The prevalence of late AMD in Japanese people aged <70 years was similar to that observed in white populations, whereas that in Japanese people aged ≥70 years was relatively lower. (Am J Ophthalmol 2013;156:1002–1009. © 2013 by Elsevier Inc. All rights reserved.)

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AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of visual impairment in the elderly and is the most common cause of blindness in developed countries.[1] The stages of AMD are categorized as early, in which visual symptoms are inconspicuous,[2] and late, in which severe vision loss is typical. Early AMD is characterized by drusen or by pigment abnormalities of the retinal pigment epithelium (RPE) in the macula, without visible choroidal vessels.[1] The presence or absence of these 2 features is characteristic of AMD and is highly associated with the development of late AMD, especially when the status of both eyes is considered.[3]

To date, the introduction of anti–vascular endothelial growth factor (VEGF) intravitreal injections has offered remarkable clinical benefits for patients with late AMD.[4] However, because these benefits are associated with an increased financial burden of providing care for these patients,[5] determining the precise incidence of AMD and identifying its risk factors are still required in order to develop preventive measures for this disease. In fact, an increasing number of studies have reported the epidemiology of AMD in different racial/ethnic groups over the last 10 years.[6–8] However, although the state of health, food intake, nutritional intake, and lifestyle of the Japanese people have been changing,[9] only 2 small cohorts, the Hisayama study[10] (1998), with 1486 participants aged ≥50 years, and the Funagata study[11] (2000-2002), with 1246 participants aged ≥50 years, have evaluated the prevalence of AMD in the Japanese population.

These 2 population-based studies (the Hisayama study and Funagata study) arrived at similar conclusions regarding the prevalence of late AMD: late AMD is less common among Japanese people (with a reported overall prevalence of 0.87% and 0.6%, respectively) than among white subjects.[10,11] However, these 2 studies arrived at different conclusions regarding the prevalence of early AMD in Japanese. Although the Hisayama study suggested a lower prevalence of early AMD in the Japanese,[10] the Funagata study indicated that the prevalence of early AMD is similar to that reported in the Blue Mountains Eye Study (BMES).[11] A recent meta-analysis in 4 Asian populations reported that the prevalence of early AMD in Asians is lower than that in white populations.[12] It is well known that polypoidal choroidal vasculopathy (PCV) has a higher

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prevalence as a subtype of AMD in Asians than in whites.[13] Therefore, these results showing a lower prevalence of early AMD in Asians were convincing because previous studies reported a lower prevalence of drusen in PCV.[14–16] However, a subsequent clinical study suggested that drusen is not an uncommon feature of PCV.[17–19] Because the small number of participants in previous Japanese studies limits meaningful comparisons of the prevalence between the Japanese and other populations, a study with a larger number of participants is required to estimate the precise prevalence of AMD in the Japanese.

Nagahama is a regional mid-sized city located in the central region of the main island of Japan. The municipality has a population of approximately 126 000 (2010 Japan census). The aim of the present study was to describe the age- and sex-specific prevalence of early and late AMD in a general adult population of Nagahama, Japan.

METHODS

THE NAGAHAMA PROSPECTIVE GENOME COHORT FOR THE Comprehensive Human Bioscience, hereinafter referred to as the Nagahama Study, is a community-based prospective cohort study that aims to determine the prevalence and risk factors of various diseases in a community. At baseline, all participants underwent automatic refractometry (Autorefractor ARK-530; Nidek, Tokyo, Japan), axial length measurement (IOL Master; Carl Zeiss, Jena, Germany), and fundus photography using a digital retinal camera (CR-DG10; Canon, Tokyo, Japan) in a darkened room. For this study, residents of Nagahama City who satisfied the following criteria were recruited as participants and were examined between November 2008 and November 2010: (1) age ≥30 years and ≤74 years; (2) ability to participate on one's own; (3) no significant problems communicating in Japanese; (4) no current serious diseases/symptoms or health issues; and (5) voluntarily decided to participate in this study. Information regarding recruitment was provided through newsletters/homepages of government and citizen organizations, newspaper flyers, and brochures. The goal for the number of participants was set at 10 000 (approximately 15% of the population; age, 30-74 years). All procedures in this study adhered to the tenets of the Declaration of Helsinki. The Kyoto University Graduate School and Faculty of Medicine Ethics Committee, the Ad Hoc Review Board of the Nagahama Cohort Project, and the Nagahama Municipal Review Board of Personal Information Protection approved all protocols and informed consent procedures.

Overall, 6118 healthy Japanese individuals aged ≥50 years participated in the Nagahama Study. In the present study, we evaluated subjects who had nonmydriatic fundus photographs of both eyes showing sufficient quality for grading lesions (Figure 1). Participants with other retinal diseases that would disturb the precise grading for

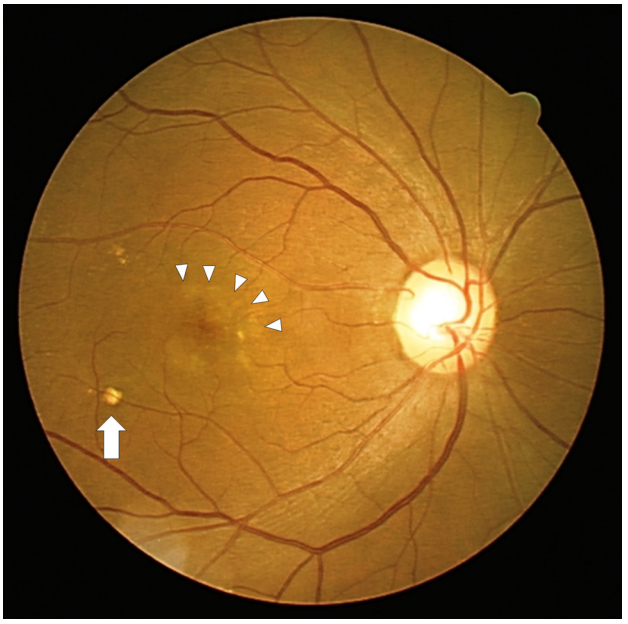

FIGURE 1. Fundus photograph of a 64-year-old Japanese woman with a large drusen (white arrow) and retinal pigment epithelial abnormalities (arrowheads).

macular lesions (such as diabetic retinopathy, retinal vein occlusion, and epiretinal membrane) were excluded from the analysis. Two independent ophthalmologists (I.N. and Y.A. or M.M.) graded each image twice for drusen, RPE abnormalities (hyperpigmentation or hypopigmentation), and late AMD (exudative AMD and geographic atrophy) according to the simplified severity scale for age-related macular degeneration in the Age-Related Eye Disease Study (AREDS).[3] We used the maximum drusen size within the grid (a 3000-μm radius centered on the fovea) at baseline to assess drusen phenotypes. Drusen size was determined using standard circles with diameters corresponding to 63, 125, and 250 μm. Reticular drusen, which were enhanced with the blue channel of the color photograph,[20–22] were considered as soft drusen for the purpose of the analysis.[23] Before grading was initiated for all subjects, intergrader and intragrader agreements were assessed on a random subset of images of 80 eyes of 40 participants. In this initial assessment, the level of agreement between the graders was 1.0 for the presence of late AMD and the agreements between the presence of retinal pigment changes and of drusen size were 0.75 and 0.85-0.90, respectively (crude agreement ratios). The senior reviewers (K.Y. and N.Y.) discussed the cases in which the 2 independent ophthalmologists disagreed and made the final diagnosis. After an agreement had been reached regarding the diagnosis, each photograph was graded twice for all subjects. The level of overall agreement between the grading ophthalmologists was more than 0.94 for most features.

Early AMD was defined by the presence of large drusen (soft distinct and soft indistinct drusen of ≥125 μm in

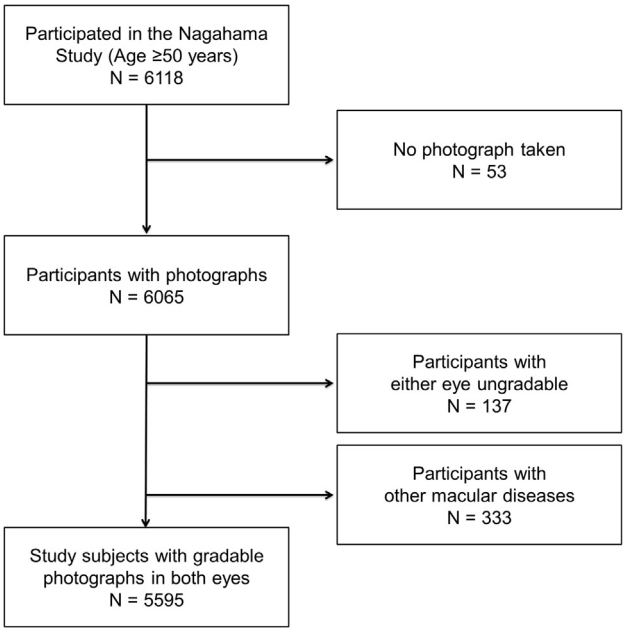

FIGURE 2. Flowchart describing participants from the Nagahama Study who were included and excluded from the analysis for age-related macular degeneration in the Japanese population. Of the 6065 subjects aged ≥50 years, 5595 (92.3%) had gradable fundus photographs in both eyes.

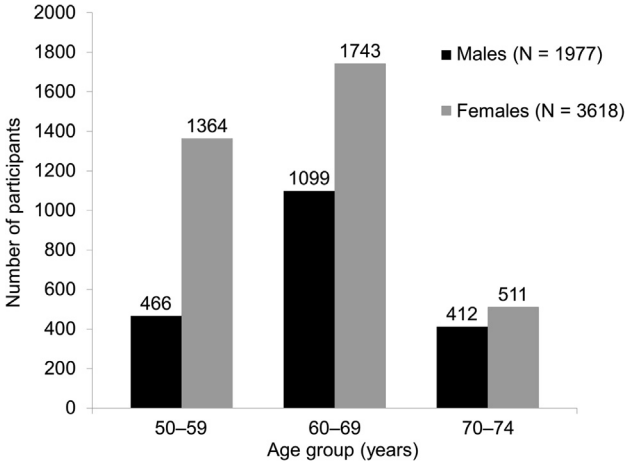

FIGURE 3. Age and sex distribution of the study subjects for age-related macular degeneration in the Japanese population (n = 5595).

diameter) or RPE pigment abnormalities within the grid in the absence of late AMD in either eye.[10,24] Late AMD was defined as the presence of exudative AMD or geographic atrophy (GA). Signs of exudative AMD were retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, and subretinal fibrous scars. GA was defined as a circular discrete area (of at least 175 μm in diameter) of retinal depigmentation with visible choroidal vessels in the absence of exudative AMD.

Information on smoking status was obtained via a self-reported questionnaire. To assess the association between the effect of cigarette smoking and the development of AMD in detail, we used 2 methods of analysis: (1) total cigarette amount using the Brinkman index, which was calculated by the daily number of cigarettes × years of smoking[25]; and (2) smoking status, in which the subjects were categorized as never smokers (had smoked less than 100 cigarettes in the past) and ever smokers (had smoked more than 100 cigarettes in the past).

We assessed the age- and sex-specific prevalence of early AMD and late AMD, including the phenotypes of AMD lesions. The age- and sex-adjusted standardized incidences of AMD were calculated using the direct method with reference to the World Health Organization standard population in 2010. We used analysis of variance or the χ^2 test to compare demographic characteristics. *P* values less than .05 were considered statistically significant.

RESULTS

FUNDUS PHOTOGRAPHS WERE AVAILABLE FOR 6065 subjects aged ≥50 years, and 5595 of these subjects (92.3%) had photographs that were gradable for AMD lesions in both eyes (Figures 2 and 3). Photographs were not taken for 53 participants because of significant media opacities, poor fixation, and/or poor participant cooperation/refusal. Photographs were ungradable in either eye (n = 137) because of media opacities (such as asteroid hyalosis of the vitreous) or poor camera focus. We excluded 333 participants with other macular disease, such as diabetic retinopathy, from the analysis. Thus, a total of 523 participants who had missing or ungradable photographs or who had macular conditions that were inadequate were excluded from this analysis. The participants with gradable photographs (n = 5595) who were included in the analyses were younger (mean age, 62.5 ± 6.5 years) than those excluded from the analysis (65.9 ± 5.9 years; $P < .0001$). However, no differences were found in sex between those with gradable and ungradable photographs ($P = .588$). Thus, the following prevalence data are from 5595 participants with gradable photographs in both eyes.

The summary of the prevalence of phenotypes of AMD in the Nagahama cohort is shown in Table 1. In the study cohort of participants aged ≥50 years, the prevalence of soft drusen (defined as drusen of >63 μm) was 39.4% (39.2%, standardized) and that of large drusen (defined as drusen of ≥125 μm) was 17.4% (17.5%, standardized). Overall, 22.3% of all subjects had early AMD in at least 1 eye, and the prevalence increased from 16.1% in subjects aged 50-59 years to 31.2% in subjects aged ≥70 years. The overall prevalence of late AMD was 0.52% (0.58%, standardized), which increased from 0.27% in subjects aged 50-59 years to 0.98% in subjects aged 70-74 years.

TABLE 1. Prevalence of Age-Related Macular Degeneration in the Japanese Population

	50-59 Years N = 1830	60-69 Years N = 2842	70-74 Years N = 923	Total N = 5595	Overall Standardized Prevalence[a] (95% CI)
Either eye, n (%)					
Early AMD	294 (16.1)	665 (23.4)	288 (31.2)	1247 (22.3)	22.8 (21.7-24.0)
Late AMD	5 (0.27)	15 (0.53)	9 (0.98)	29 (0.52)	0.58 (0.36-0.80)
Soft drusen	561 (30.7)	1173 (41.3)	468 (50.7)	2202 (39.4)	39.2 (37.9-40.5)
Large drusen	216 (11.8)	516 (18.2)	239 (25.9)	971 (17.4)	17.5 (16.5-18.5)
Pigment abnormality	98 (5.4)	222 (7.8)	71 (7.7)	391 (7.0)	7.6 (6.8-8.3)
Bilateral, n (%)					
Early AMD	57 (3.1)	171 (6.0)	101 (10.9)	329 (5.9)	6.1 (5.5-6.8)
Late AMD	0 (0.00)	3 (0.11)	1 (0.11)	4 (0.07)	0.09 (0.00-0.18)
Soft drusen	61 (3.3)	141 (5.0)	67 (7.3)	269 (4.8)	4.6 (4.0-5.1)
Large drusen	45 (2.5)	127 (4.5)	87 (9.4)	259 (4.6)	4.8 (4.2-5.3)
Pigment abnormality	10 (0.5)	32 (1.1)	22 (2.4)	64 (1.1)	1.3 (1.0-1.7)

AMD = age-related macular degeneration; CI = confidence interval.
[a]The prevalence was standardized to the World Health Organization standard population.

TABLE 2. Prevalence of the Phenotype of Age-Related Macular Degeneration in Japanese According to Sex

	Male N = 1977	Female N = 3618	*P* Value
Early AMD	491 (24.8)	756 (20.9)	.0007
Late AMD	16 (0.81)	13 (0.36)	.025
Soft drusen	765 (38.7)	1437 (39.7)	.454
Large drusen	357 (18.1)	614 (17.0)	.305
Pigment abnormality	192 (9.7)	199 (5.5)	<.0001

AMD = age-related macular degeneration.
Prevalence shown as n (%).

We found similar tendencies regarding age dependence in other features of AMD (soft drusen, large drusen, and pigment abnormalities). Whereas 10.7% of drusen subjects had pigment abnormalities, 60.4% of subjects with pigment abnormalities also had drusen. We found that subjects with larger drusen tended to have pigment abnormalities ($P < .0001$). Reticular pseudodrusen were present in 38 participants (0.68%), including those that were outside of the grid; 17 cases, including a case with late AMD, were within the grid. The prevalence of reticular pseudodrusen was significantly higher among women ($P = .011$), with women accounting for 32 of the 38 subjects (84.2%) with reticular pseudodrusen.

AMD was present in both eyes in 333 of the 1276 participants (20.7%) with any AMD. The overall prevalence of bilateral early AMD was 5.9% (6.1%, standardized), and this value increased from 3.1% in subjects aged 50-59 years to 10.9% in subjects aged ≥70 years. Bilateral late AMD was present in 4 of the 29 participants (13.8%) with any late AMD.

The prevalence of AMD according to sex is shown in Table 2. The prevalence of early and late AMD was significantly higher in men than in women ($P = .0007$ and $P = .025$, respectively). The subtype analysis revealed that the prevalence of RPE abnormalities was significantly higher in men than in women ($P < .0001$). This tendency was found in all age groups ($P = .0001$ in subjects aged 50-59 years and $P = .0002$ in those aged 60-69 years), although this association failed to reach significance in subjects aged ≥70 years ($P = .0694$). The incidences of soft and large drusen were not significantly different according to sex ($P = .454$ and $P = .305$, respectively).

Finally, we evaluated the association between cigarette smoking and the development of AMD (Table 3). The total amount of cigarette smoking was significantly associated with the development of early and late AMD ($P = .0153$ and $P = .0402$, respectively). Particularly, subjects with a Brinkman index greater than 500 had a significantly higher risk for the incidence of early and late AMD ($P = .011$ and $P = .042$, respectively, Supplemental Table 1, available at AJO.com). Never smokers were less likely to have early and late AMD, although these associations did not reach statistical significance ($P = .120$ and $P = .159$, respectively). In the subgroup phenotype analysis, we found strong associations between the presence of RPE abnormalities and both the total amount ($P < .0001$) and status ($P = .0003$) of cigarette smoking. However, these significant associations diminished when we divided the cohort by sex ($P > .05$, Supplemental Table 2, available at AJO.com). We found no significant association between cigarette smoking and the incidence of soft or large drusen ($P > .05$).

DISCUSSION

ALTHOUGH A RECENT META-ANALYSIS IN 4 ASIAN POPULATIONS suggested that the prevalence of early AMD signs

TABLE 3. Association Between Smoking Status and the Phenotype of Age-Related Macular Degeneration in Japanese

	Brinkman Index[a]			Smoking Status, N (%)		
	N	Mean	*P* Value	Ever (N = 1853)	Never (N = 3742)	*P* Value
No AMD	4319	169.9 ± 344.3		1405 (75.8)	2914 (77.9)	
Early AMD	1247	197.2 ± 368.9	.0153	435 (23.5)	812 (21.7)	.120
Late AMD	29	301.9 ± 462.2	.0402	13 (0.70)	16 (0.42)	.159
Soft drusen			.939			.069
Absent	3393	177.0 ± 348.8		1155 (62.3)	2238 (59.8)	
Present	2202	176.2 ± 354.0		698 (37.7)	1504 (40.2)	
Large drusen			.305			.798
Absent	4624	174.5 ± 348.7		1528 (82.5)	3096 (82.7)	
Present	971	187.2 ± 360.7		325 (17.5)	646 (17.3)	
Pigment abnormality			<.0001			.0003
Absent	5204	171.6 ± 346.4		1691 (91.3)	3513 (93.9)	
Present	391	243.9 ± 399.9		162 (8.7)	229 (6.1)	

AMD = age-related macular degeneration.
[a]The Brinkman index was calculated by the daily number of cigarettes × years.

TABLE 4. Age-Specific Prevalence of Large Drusen (≥125 μm) in Various Populations

	Nagahama[a]	Los Angeles[23]	Singapore[7]	Blue Mountains[28]	Beaver Dam[29]	Baltimore[27]
Number of Participants	6065	6357	3280	3632	4752	1843
Ethnicity	Japanese	Latino	Malay	White	White	Black
Years Study Conducted	2008-2010	2000-2003	2004-2006	1992-1994	1988-1990	1985-1988
Age, y						
50-59 (95% CI)	11.9 (10.2-13.6)	13.6	38.3	1.9	6.8	4.7
60-69 (95% CI)	18.1 (16.6-19.5)	19.3	48.1	5.2	15.8	8.4
70-79 (95% CI)	25.9 (23.1-28.7)[b]	26.3	46.3	11.6	27.8	7.9
Sex						
Male (95% CI)	15.4 (13.6-17.3)	19.7	43.8	4.3	-	-
Female (95% CI)	16.4 (15.2-17.6)	14.9	34.5	5.5	-	-

CI = confidence interval.
[a]The prevalence was standardized to the World Health Organization standard population.
[b]The last age group is 70-74 years.

were lower in Asians than in white populations,[12] a wide consensus regarding the prevalence of AMD in Asians has not been established. Several factors make it difficult to compare the prevalences reported in various studies: the differences in photographic and grading techniques, the definition of early AMD, and the age groups used when reporting age-specific rates. Because the prevalence of AMD is strongly related to age and because the age distributions of different populations are not similar, it is important to compare age-specific rates rather than the overall prevalence. However, the details regarding the age-specific rates of the prevalence of AMD have not been reported in the Japanese population because of the small sample sizes of previous studies.[10,11] Thus, the present study should be more reliable than previous studies for comparing the prevalence of AMD in the Japanese population with that in other populations because it includes the age-specific rates of AMD.

Large drusen is an important component of early AMD that has been shown in many longitudinal studies to be predictive of incident late AMD.[3,26] Because the definition of large drusen (≥125 μm) has been defined similarly and measured in all of the populations, we chose to look at large drusen as a manifestation of intermediate AMD in various populations (Table 4). In this comparison, the age-specific prevalence of large drusen in the Japanese was comparable to that reported in white populations and higher than that reported in the black population among persons aged ≥50 years.[27] Of particular interest, our study found high rates of large drusen in all Japanese age groups, which is comparable to the reported prevalence in the Los Angeles Latino eye study (LALES).[23]

TABLE 5. Age-Specific Prevalence of Late Age-Related Macular Degeneration in Various Populations

	Nagahama[a]	Hisayama[10]	Los Angeles[23]	Singapore[7]	Blue Mountains[28]	Beaver Dam[29]	Baltimore[27]	Barbados[30]
N	6065	1486	6357	3280	3632	4752	1843	3444
Ethnicity	Japanese	Japanese	Latino	Malay	White	White	Black	Black
Years	2008-2010	1998	2000-2003	2004-2006	1992-1994	1988-1990	1985-1988	1988-1992
Age, y								
50-59 (95% CI)	0.39 (0.02-0.77)	0.45	0.22	0.21	0.0	0.2	0.35	0.7
60-69 (95% CI)	0.53 (0.26-0.80)	0.88	0.26	0.39	0.5	0.8	0.42	0.4
70-79 (95% CI)	0.99 (0.35-1.63)[b]	0.51	1.50	2.49	2.6	3.7	0.00	1.0
Sex								
Male (95% CI)	0.73 (0.28-1.18)	1.2	0.53	0.46	1.3	1.2	-	0.36
Female (95% CI)	0.30 (0.13-0.48)	0.34	0.38	0.22	2.4	1.9	-	0.89

CI = confidence interval.
[a]The prevalence was standardized to the World Health Organization standard population.
[b]The last age group is 70-74 years.

The lesions of late AMD have been defined and graded similarly in most population studies. The age-specific prevalence of late AMD in various populations is shown in Table 5. Although the small number of cases in each study limits these comparisons, the age-specific prevalence of late AMD in Japanese subjects aged <70 years was comparable with that reported in other populations.[7,10,23,27–30] However, the age-specific prevalence of late AMD in subjects aged 70-79 years was relatively lower than that in the other populations. Caution should be exercised when interpreting our data for the oldest age group because we evaluated subjects aged 70-74 years, which would underestimate the prevalence of AMD in elderly Japanese people. However, considering that a recent meta-analysis in whites reported the predicted late AMD prevalence at 70 and 75 years as 1.4% and 2.8%, respectively, the current study suggests that the prevalence of late AMD is lower in elderly Japanese than in elderly whites.[31] This difference among age groups might be linked to the exceptional change in circumstances in Japan that would lead to potential differences in the lifestyles of these groups; for example, participants aged 66 or younger were born after the end of World War II.

In the present study, the prevalence of early and late AMD was higher in men than in women ($P = .0007$ and $P = .025$, respectively). These results are consistent with those of previous studies in Asian populations, which reported a higher prevalence of AMD among men than among women.[7,11,32,33] Although it is speculated that the reason for this disparity is the higher smoking rate in Asian men compared to women, these sex differences remained in this study even after adjusting for smoking status ($P = .0128$). A similar association was found in LALES.[23] The reason for the higher prevalence of AMD in Japanese men is unclear. A previous genetic study in Japanese subjects[34] may provide insight into this observation because this study suggested that sex had the greatest effect on the development of PCV. In this study, we found sex differences in the prevalence of RPE abnormalities in all age groups. Similar results have been consistently found in Asians[7,10,11] but not in whites.[28,29] Given that RPE atrophy was a prevailing finding in the fellow eyes of patients with PCV,[35] this difference between Asians and whites regarding the background of RPE abnormalities may be associated with the higher prevalence of the particular phenotype of AMD, such as PCV, in Asian populations. In contrast, we did not find a sex difference in the prevalence of drusen. These results are consistent with those of many studies in white populations[6,28,36,37] but are inconsistent with those of previous Japanese studies[11,24] that reported a sex difference in the prevalence of drusen.

Cigarette smoking is a consistently identified risk factor for AMD.[38–40] Although several previous reports confirmed a link between current smoking and AMD in the Japanese,[10,32] this association has not been studied in detail. In this study, we showed that smoking is associated with the development of both early and late AMD in the Japanese, and this is particularly dependent on the total amount of cigarettes smoked. This observed association for smoking is consistent with many previous studies that reported a dose-response effect in whites.[36,39,40] In addition, a strong association between smoking and RPE pigment abnormalities has been revealed. This association is consistent with the Beaver Dam Eye Study, which suggested that smoking is associated with the incidence and progression of RPE pigment abnormalities.[39] However, because this association failed to reach significance when we divided the subjects by sex, it must be evaluated in a larger cohort to conclude whether an association exists between smoking and pigment abnormalities. In contrast to late AMD, the association between cigarette smoking and drusen remains controversial because of the limited number of previous studies. In the present study, we did not find any association between smoking and the incidence of drusen, which is consistent with the result of the LALES.[41]

One of the potential limitations of our study is that it included a low percentage of the overall population, which may have introduced selection bias. It is speculated that women who did not work full time were more likely to participate, resulting in the high female-to-male ratio of this study. Because this study recruited persons who were able to participate on their own, the participants may have been highly health conscious. Further, people working in government and citizen organizations may have been more likely to participate in this study. Finally, people who could not read or move on their own would have experienced difficulty participating in this study, and this bias may have resulted in an underestimated prevalence of late AMD in the Japanese population. However, because the symptoms of early AMD are usually not obvious[2] and would not affect study participation, the magnitude of the selection bias on early AMD prevalence should be negligible. Another limitation was the lack of a detailed evaluation for the subtypes of late AMD (ie, PCV) because of the limited examination in our cohort. A study in which further ophthalmic examinations are performed in the general population is required to identify the prevalence and rate of AMD subtypes in the Japanese population.

Previous reports revealed that early signs of AMD are strong predictors of subsequent advanced stage. The reported 5-year-risk estimates for the development of advanced AMD for each of the scores from 0 to 4 are 0.4%, 3.1%, 11.8%, 25.9%, and 47.3%, respectively.[3] In our study, 1.2% of men aged 70-74 years had a score of 4. If our data are generalizable to all Japanese people, we anticipate that an increased number of Japanese individuals, particularly men, will have late AMD (see Supplemental Figure, available at AJO.com). Applying the reported estimates to our data indicates that a total of 3.1% of men aged 70-74 years may develop advanced AMD in 5 years.

In summary, our study involving >6000 participants aged ≥50 years provides the first evidence of the age-specific prevalence and detailed characteristics of phenotypes of AMD in the Japanese population. We found that the rates of early AMD in the Japanese population are comparable to those of white populations and that the rates of late AMD were comparable to those of white populations aged <70 years but were relatively lower in those aged ≥70 years. Further, we found a male-dominant prevalence of RPE pigment abnormalities associated with cigarette smoking. In the Nagahama study, follow-up examination will be carried out 5 years after the baseline survey. Further studies with longitudinal progression of phenotypes of AMD are needed to estimate the relative risk of developing late AMD in the Japanese.

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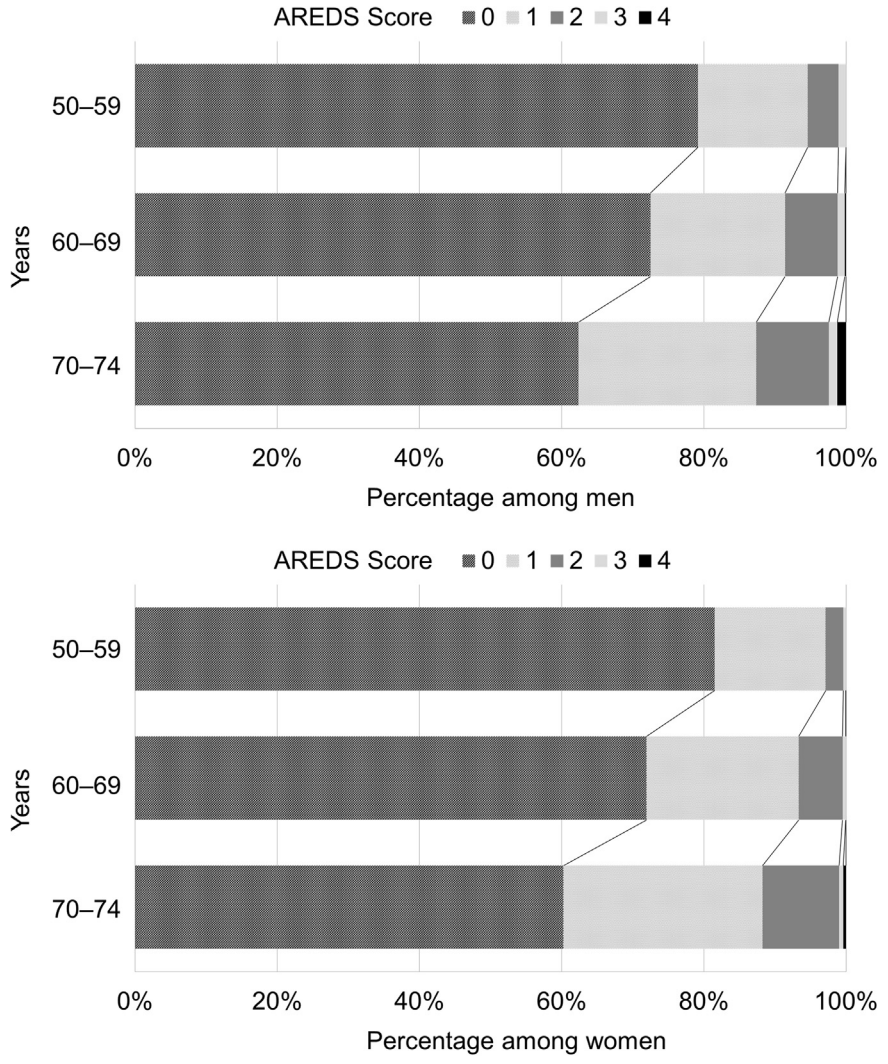

SUPPLEMENTAL FIGURE. Percentages of persons with a risk score for the development of late age-related macular degeneration among men (Top) and women (Bottom) in the Japanese population. Each risk score was calculated by following the severity scale for age-related macular degeneration in the Age-Related Eye Disease Study (AREDS).[3]

SUPPLEMENTAL TABLE 1. Association Between the Brinkman Index and the Risk of Age-Related Macular Degeneration in Japanese

	Brinkman Index[a]			
	Under 500	Over 500	*P* Value	OR (95% CI)
Early AMD	21.7%	25.5%	.011	1.24 (1.05–1.45)
Late AMD	0.43%	0.97%	.042	2.27 (1.03–5.00)

AMD = age-related macular degeneration; CI = confidence interval; OR = odds ratio.

[a]The Brinkman index was calculated by the daily number of cigarettes × years.

SUPPLEMENTAL TABLE 2. Association Between the Brinkman Index and the Phenotype of Age-Related Macular Degeneration in Japanese by Sex

	Male			Female		
	N	Mean BI[a]	*P* Value	N	Mean BI[a]	*P* Value
Total	1977	466.0 ± 451.3		3618	18.6 ± 91.3	
No AMD	1470	461.3 ± 449.6		2849	19.6 ± 94.9	
Early AMD	491	478.7 ± 454.1	.459	756	14.4 ± 76.0	.165
Late AMD	16	511.9 ± 533.7	.655	13	43.5 ± 106.3	.365
Soft drusen			.402			.216
Absent	1212	459.3 ± 447.6		2181	20.1 ± 95.5	
Present	765	476.8 ± 457.1		1437	16.3 ± 84.6	
Large drusen			.414			.260
Absent	1620	462.1 ± 450.8		3004	19.3 ± 94.6	
Present	357	483.7 ± 453.7		614	14.8 ± 73.1	
Pigment abnormality			.500			.145
Absent	1785	463.8 ± 451.3		3419	19.1 ± 92.2	
Present	192	486.9 ± 451.7		199	9.4 ± 74.6	

AMD = age-related macular degeneration; BI = Brinkman index.

[a]The Brinkman index was calculated by the daily number of cigarettes × years.