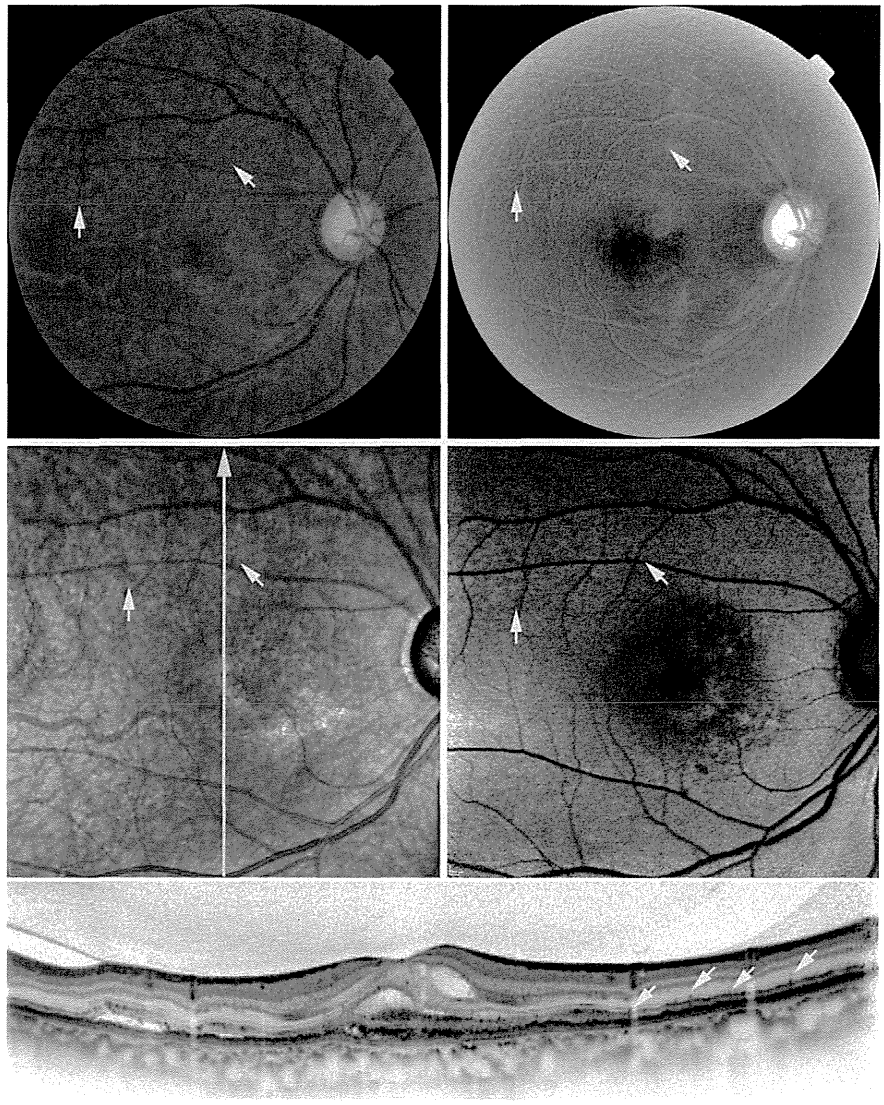

FIGURE 2. Images of a patient with neovascular age-related macular degeneration and reticular pseudodrusen. (Top row, left) Color fundus photography. (Top row, right) Blue channel of contrast-enhanced color fundus photography. (Second row, left) Infrared reflectance imaging. (Second row, right) Fundus autofluorescence imaging. (Bottom) Spectral-domain optical coherence tomography (vertical B-scan thorough the fovea in the direction of the green arrow in Second row, left). Reticular pattern is visible in each imaging (arrows), but it may be difficult to make a diagnosis of reticular pseudodrusen using only 1 imaging method.

bilateral CNV may have had reticular pseudodrusen before CNV development.

In conclusion, reticular pseudodrusen was found in 14% of patients with newly diagnosed late AMD using multimodal imaging. About half of the patients with reticular pseudodrusen had bilateral late AMD. Moreover, there was an association between reticular pseudodrusen and the *ARMS2* gene. Further epidemiologic or genetic studies will deepen our understanding of the clinical significance of reticular pseudodrusen.

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Biosketch

Naoko Ueda-Arakawa, MD, graduated from Kyoto University, Faculty of Medicine. She completed her residency program at Kyoto University Hospital and a fellowship at Osaka Red Cross Hospital, Osaka, Japan. She is now in a PhD program in the Department of Ophthalmology and Visual Sciences at Kyoto University under the supervisor of Professor Nagahisa Yoshimura. Her main interest is imaging analysis of macular diseases.

SUPPLEMENTAL TABLE. Prevalence of Reticular Pseudodrusen in Patients Over 70 Years of Age

	No. of Patients	No. of Patients With Reticular Pseudodrusen	Prevalence (%)
Typical AMD	67	8	11.9
PCV	53	2	3.8
RAP	11	10	90.9
Geographic atrophy	7	5	71.4
Combined[a]	8	3	37.5

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation.

[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (4 typical AMD and PCV, 1 typical AMD and RAP, 1 typical AMD and geographic atrophy, 1 geographic atrophy and RAP, and 1 geographic atrophy and PCV).

Reduction of Retinal Sensitivity in Eyes With Reticular Pseudodrusen

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• PURPOSE: To evaluate the effect of macular reticular pseudodrusen on retinal function using multiple imaging methods.
• DESIGN: Prospective cross-sectional study.
• METHODS: Thirteen eyes with reticular pseudodrusen, but without any other macular abnormality or glaucoma, and 20 normal eyes were evaluated. All subjects underwent color fundus photography, infrared reflectance (IR), fundus autofluorescence (FAF), and microperimetry.
• RESULTS: The similarity in the number of reticular pseudodrusen was evaluated through inter-observer intraclass correlation coefficients, which ranged from 0.852-0.944. IR could detect reticular pseudodrusen within the center circle area in 12 eyes, whereas blue-channel fundus photography and FAF could only detect these lesions in 1 and 3 eyes, respectively. The number of reticular pseudodrusen correlated among the different imaging modalities ($P < .001$ for all) for all areas of the macula, except the center. The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes ($P < .001$ for all). The number of reticular pseudodrusen correlated with retinal sensitivity in all areas by IR imaging ($P = .003$, $P < .001$, $P = .003$ for center, inner ring, outer ring, respectively), in the inner and outer rings by blue-channel fundus photography ($P < .001$ for both), and in the inner and outer rings by FAF ($P < .001$ and $P = .001$, respectively).
• CONCLUSIONS: Although multiple imaging modalities are capable of quantifying reticular pseudodrusen, IR appears to have the best ability to do so as compared to blue-channel photography and FAF. The distribution and number of reticular pseudodrusen lesions are closely associated with retinal sensitivity. (Am J Ophthalmol 2013;156:1184–1191. © 2013 by Elsevier Inc. All rights reserved.)

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RETICULAR PSEUDODRUSEN WERE FIRST IDENTIFIED as distinctive yellowish patterns in the macula of patients with age-related macular degeneration (AMD) by using blue-light fundus photography.[1] Arnold and associates described a yellowish interlacing network of oval or roundish lesions, termed reticular pseudodrusen, with a diameter of 125-250 μm that were detected in red-free fundus photography.[2] Recently, reticular pseudodrusen have been recognized as an additional distinctive morphologic feature of AMD.[3] Several reports have suggested that reticular pseudodrusen are associated with a high risk of progression to late-stage AMD.[4–8]

The development of new imaging methods, such as confocal scanning-laser ophthalmoscopy (SLO) and spectral-domain optical coherence tomography (SDOCT), has led to the determination of the exact location of reticular pseudodrusen and to additional insight into its pathogenesis.[8–21] Using SDOCT, several researchers have suggested that the hyperreflective material above the retinal pigment epithelium (RPE) may alter photoreceptor structures in eyes with reticular pseudodrusen,[9,15] implying that reticular pseudodrusen may have an influence on retinal function. However, understanding of the relationship between reticular pseudodrusen and retinal function has been limited, and further investigation for comprehending such relationship is required.

The purpose of this study was to evaluate the effect of the presence of macular reticular pseudodrusen on retinal function by using multiple imaging methods, including fundus photography, infrared reflectance (IR), fundus autofluorescence (FAF), and fundus-monitoring microperimetry (MP). Although several terminologies have been used to describe this clinical feature,[2,9,14] we use the term "reticular pseudodrusen" according to the nomenclature promoted by Arnold and associates.[2]

METHODS

ALL OF THE STUDY INVESTIGATIONS ADHERED TO THE tenets of the Declaration of Helsinki, and this study was approved by the Institutional Review Board and the Ethics Committee of Kyoto University Graduate School of Medicine. The nature of the study, the implications of participating in this research study, and its possible consequences were explained to the study candidates, after

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which a written informed consent was obtained from all participants.

• PARTICIPANTS: Candidates in this prospective cross-sectional study were patients with reticular pseudodrusen, but without any other macular abnormality or glaucoma, who visited the Kyoto University Hospital, Kyoto, Japan, between February 2011 and March 2013, as well as healthy volunteers.

All of the patient eyes had already been classified as having reticular pseudodrusen on the basis of the appearance of reticular patterns in at least 2 imaging modalities, including the blue-channel images obtained using color fundus photography, IR, FAF, indocyanine green angiography, and SDOCT.[8,16] Eyes with conventional drusen (hard/soft drusen), cuticular drusen, pigment epithelial detachment, serous retinal detachment, choroidal neovascularization (ie, neovasucular AMD, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation), or geographic atrophy were excluded from this study. Eyes with other macular abnormalities (ie, pathologic myopia, idiopathic choroidal neovascularization, angioid streaks, other secondary choroidal neovascularization, central serous chorioretinopathy, epiretinal membranes, or retinal arterial macroaneurysms) or any history or signs of retinal surgery, including laser treatment, were also excluded from this study.

• MULTIMODAL IMAGING METHODS: All subjects underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), determination of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a noncontact lens, color fundus photography, IR, FAF, and MP during the same visit.

Color fundus photographs (field, 40 degrees) were obtained digitally using a Topcon TRC NW6S nonmydriatic retinal camera (Topcon, Tokyo, Japan) after medical dilation of the pupil (phenylephrine, 0.5% and tropicamide, 0.5%). To examine the blue-channel images, ImageJ software (National Institutes of Health, Bethesda, Maryland, USA) was used to display the individual color channels (red, green, and blue) of the photographs. Adjustment was performed automatically by using the ImageJ software before grading. IR and FAF images were acquired using a confocal SLO (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The IR images were obtained using a light stimulus at a wavelength of 820 nm. The FAF images were obtained using an excitation light with a wavelength of 488 nm and a barrier filter beginning at 500 nm. The field of view was set to 30 × 30 degrees, centered on the macula. Adjustment of brightness and contrast for IR and FAF images was performed automatically by using the ImageJ software before grading.

The quality of each image was evaluated by an experienced observer and only eyes with adequate image quality from each imaging modality were included.

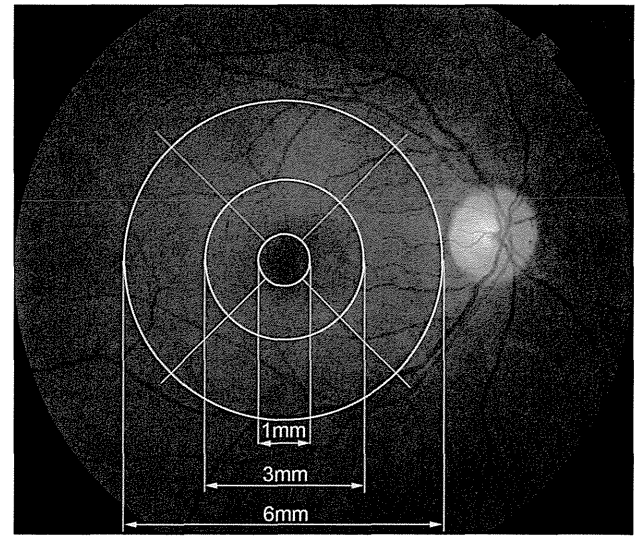


FIGURE 1. Early Treatment Diabetic Retinopathy Study sector. Delineation of the 9 macular sectors, according to the Early Treatment Diabetic Retinopathy Study (ETDRS), within which we measured the number of reticular pseudodrusen.

• QUANTIFICATION OF THE RETICULAR PSEUDODRUSEN: In the blue-channel contrast-enhanced color fundus photography, the reticular pattern was identified as light flecks.[2] Reticular IR was defined as a group of hyporeflectant or halo-like (hyperreflectant lesions surrounded by hyporeflective rings) lesions against a background of mild hyperreflectance.[14] Reticular autofluorescence was defined as a group of hypofluorescent or halo-like lesions against a background of mildly elevated AF.[11,13] The number of flecks in the blue-channel fundus photography images, hyporeflectant or halo-like lesions on IR, and hypoautofluorescent or halo-like lesions on FAF in 9 separate macular areas (based on the Early Treatment Diabetic Retinopathy Study [ETDRS] sectors [Figure 1]) were determined by 2 experienced observers using a cell-count tool built into ImageJ. The center of the fovea was determined to be the center of the foveal avascular zone on each image, before grading. The numbers of each lesion were determined as the mean of the number determined by the 2 graders; if the values reported were significantly different between the graders, a third grader was invited to determine the number of lesions and the value closest to that determined by the third grader was selected.

• MICROPERIMETRY: We used fundus-monitoring MP to measure retinal sensitivity. MP-1 software (NIDEK, Padova, Italy) was set to automatically track eye movements and to evaluate every acquired frame for shifts in the directions of the x and y axes of the fundus, with respect to a reference image obtained by an infrared camera at the beginning of the examination.

We used a 4-2-staircase strategy with Goldmann size III stimuli against a white background with an illumination of

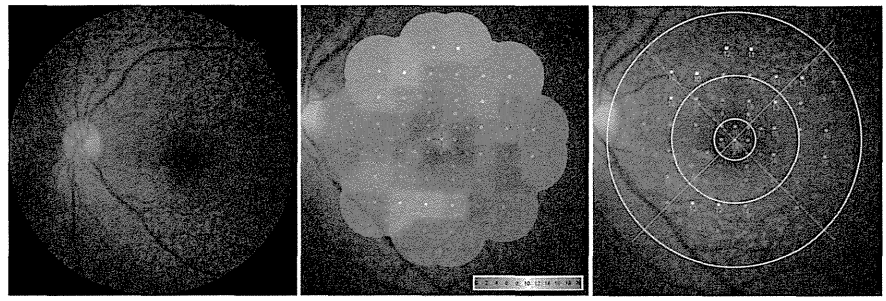


FIGURE 2. Reticular pseudodrusen and retinal sensitivity in the macula. Images of the left eye of a 55-year-old woman with reticular pseudodrusen but without any macular abnormalities. Her Snellen-equivalent best-corrected visual acuity was 20/15. (Left) Color fundus photography shows numerous reticular pseudodrusen. (Middle) Colored map image of microperimetry. Green indicates normal, and yellow indicates decreased retinal sensitivity. (Right) Retinal sensitivity map image merged with the ETDRS scale. Retinal sensitivity is decreased in the area with reticular pseudodrusen.

1.27 cd/m^2 to examine 57 stimulus locations covering the central 20 degrees (designed to probe photopic vision). Differential luminance, defined as the difference between the stimulus luminance and the background luminance, was 127 cd/m^2 at 0-dB stimulation, and the maximum stimulus attenuation was 20 dB; the stimulus duration was 200 ms. The mean retinal sensitivity was calculated in 9 separate areas, based on ETDRS sectors, within the macula (Figure 2). Retinal sensitivity on the border between sectors was included in the counterclockwise sector.

• STATISTICAL ANALYSES: BCVA, measured using the Landolt chart, was expressed as the Snellen equivalent or the logarithm of the minimal angle of resolution (logMAR). For inter-observer measurements, 2-way mixed, average measure intraclass correlation coefficients (ICC [3, K]) were obtained. For comparing the variables among areas, the Bonferroni correction was used. We calculated the Pearson product moment correlation coefficient to determine associations between mean retinal sensitivity and the number of reticular pseudodrusen in each sector. All statistical evaluations were performed in SPSS v.17 (SPSS, Chicago, Illinois, USA). Significance was defined as $P < .05$.

RESULTS

FIFTEEN CONSECUTIVE EYES WITH RETICULAR PSEUDODRUsen but without any other macular abnormality or glaucoma were examined. Among them, 2 eyes were excluded because of the poor image quality. Thus 13 eyes from 10 patients were included in this study. Twenty normal eyes in 20 subjects were included as control. The ages of the subjects ranged from 55-86 years (mean ± SD, 71.6 ± 9.4 years) for patients with reticular pseudodrusen and from 65-79 years (mean ± SD, 70.2 ± 4.8 years) for normal volunteers ($P = .200$).

TABLE 1. Reproducibility of the Determination of the Number of Reticular Pseudodrusen in the Macula Using Different Imaging Modalities

	Inter-observer Intraclass Correlation Coefficients		
Imaging	Center	Inner Ring[b]	Outer Ring[b]
Fundus photography[a]	0.919	0.852	0.854
IR	0.930	0.939	0.944
FAF	0.906	0.923	0.920

FAF = fundus autofluorescence; IR = infrared reflectance.
[a]Blue channel of fundus photography.
[b]Center, central fovea (1 mm); Inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

The BCVA of patients with reticular pseudodrusen ranged from 20/32-20/12 (mean logMAR = −0.04 ± 0.10), and 11 eyes (85%) had BCVA ≥ 20/20. The spherical equivalent refractive error ranged from −1.25 to +1.75 diopter.

The reproducibility of the determination of the number of reticular pseudodrusen (the light flecks in blue-channel fundus photographs, the hyporeflectant or halo-like lesions in IR images, and the hypofluorescent or halo-like lesions in FAF images) was evaluated through an inter-observer ICC; the ICC ranged from 0.852-0.944. The ICCs of each region, obtained by each imaging method, are shown in Table 1 and the Supplemental Table (available at AJO.com) (using log values).

The mean numbers of reticular pseudodrusen in each macular ETDRS sector are shown in Table 2. Reticular pseudodrusen were most frequently detected in the superior area by each modality (Figure 3). In the outer ring, the reticular pseudodrusen were found in greater numbers in the superior side than in the temporal side ($P = .039$, $P = .020$, and $P < .001$ for blue-channel fundus photography, IR, and FAF, respectively, with Bonferroni correction), the inferior side ($P = .081$, $P = .044$, and $P = .001$ for blue-channel fundus photography, IR, and FAF,

TABLE 2. Mean Number of Reticular Pseudodrusen in Macular Early Treatment Diabetic Retinopathy Study Sectors Using Different Imaging Modalities

Imaging	Center[b]	Inner Ring[b]				Outer Ring[b]				Whole Macula
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	
Fundus photography[a]	1.8 ± 5.7	30.0 ± 21.4	24.9 ± 28.6	18.0 ± 16.1	16.4 ± 20.8	103.3 ± 65.2	42.4 ± 52.2	34.3 ± 44.7	35.6 ± 45.0	306.7 ± 270.2
IR	12.9 ± 11.5	42.2 ± 17.2	27.0 ± 21.0	29.8 ± 21.9	30.0 ± 25.4	92.5 ± 41.1	47.5 ± 43.6	44.3 ± 38.3	42.9 ± 40.7	369.3 ± 219.1
FAF	0.5 ± 1.0	20.1 ± 13.4	17.3 ± 13.1	18.5 ± 15.4	16.2 ± 14.5	78.1 ± 28.3	32.7 ± 26.9	18.5 ± 15.5	30.4 ± 29.0	247.7 ± 132.6

FAF = fundus autofluorescence; IR = infrared reflectance.
Values are mean ± standard deviation.
[a]Blue channel of fundus photography.
[b]Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

respectively, with Bonferroni correction), or the nasal side ($P = .034$, $P = .026$, and $P = .001$ for blue-channel fundus photography, IR, and FAF, respectively, with Bonferroni correction). IR could reveal reticular pseudodrusen within the center circle area (1 mm diameter) in 12 eyes (92%), whereas blue-channel fundus photography and FAF could only detect their presence in 1 (8%) or 3 eyes (23%), respectively ($P < .001$, χ^2 test; Figure 3, Table 2). The number of reticular pseudodrusen correlated among the different imaging modalities ($P < .001$ for all), except for the center area (Figure 3, Table 3).

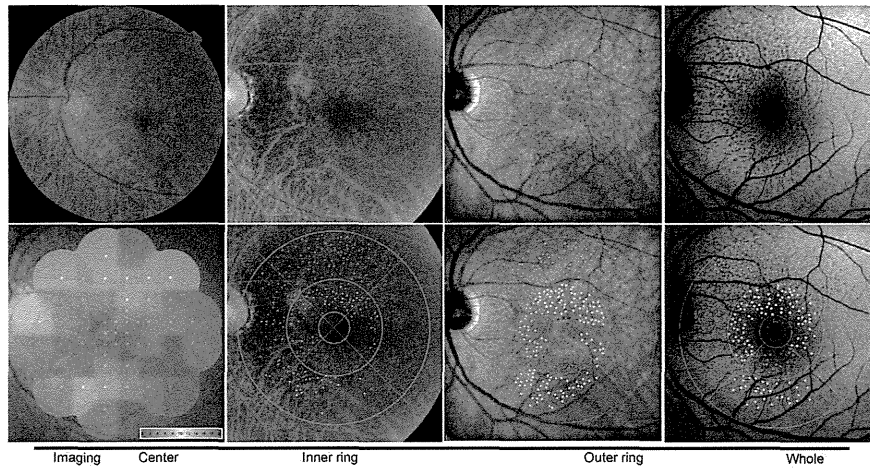
Table 4 shows the mean retinal sensitivity in each ETDRS sector. In normal eyes, the mean retinal sensitivity was >16.0 dB in each ETDRS sector, though it was slightly lower in the superior area of the outer ring (Table 4). The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes ($P < .001$ for all). In eyes with reticular pseudodrusen, the mean retinal sensitivity of the whole macula was 12.9 ± 3.9 dB, but the mean retinal sensitivity in the superior side was significantly lower compared with the inferior side ($P = .001$, with Bonferroni correction), the temporal side ($P = .006$, with Bonferroni correction), and the nasal side ($P = .020$, with Bonferroni correction) of the outer ring (Figures 2 and 3).

The extent of the effect of decreased sensitivity was identical to reticular pseudodrusen distribution. The reduction in retinal sensitivity was most severe in the superior area of the outer ring (48.5% reduction as compared with the controls) in eyes with reticular pseudodrusen, whereas it was least in the central area (20.7% reduction as compared with the controls) (Table 4).

The number of reticular pseudodrusen correlated with the retinal sensitivity determined in each area by IR imaging ($P = .003$, $P < .001$, and $P = .003$ for center, inner ring, and outer ring, respectively), in the inner and outer rings in blue-channel fundus photographs ($P < .001$ for both), and in the inner and outer rings by FAF ($P < .001$ and $P = .001$, respectively; Figure 3, Table 5). Thus, the lesion number did not correlate significantly with sensitivity in the central sector for FAF and blue-channel fundus photographs, but did for IR images.

DISCUSSION

RETICULAR PSEUDODRUSEN HAVE TRADITIONALLY BEEN identified with blue-light fundus photography. However, recent studies have suggested that additional imaging modalities, such as IR, FAF, indocyanine green angiography imaging, and SDOCT, would facilitate the identification of these interlacing networks.[4,5,8–10,13–17] Using SDOCT, Zweifel and associates suggested the hyperreflective material could be graded by the thickness of the accumulation above the RPE and their



Imaging	Center	Inner ring				Outer ring				Whole
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	Macula
Fundus photography	0	36	27	23	14	78	26	39	16	259
IR	5	46	40	35	31	91	54	67	35	404
FAF	3	38	28	34	21	102	32	62	26	346

FIGURE 3. Quantification of reticular pseudodrusen using multimodal imaging and relationship with retinal sensitivity in the macula. Images of the left eye of a 74-year-old man with reticular pseudodrusen but without any macular abnormalities. His Snellen-equivalent best-corrected visual acuity was 20/15. (Upper row, left) Color fundus photography shows numerous reticular pseudodrusen. (Upper row, middle-left) On the blue-channel of contrast-enhanced color fundus photography, the reticular pattern is identified as light flecks. (Upper row, middle-right) On infrared reflectance (IR) imaging, reticular pseudodrusen are identified as a group of hyporeflectant lesions or halo-like lesions against a background of mild hyperreflectance. (Upper row, right) In fundus autofluorescence (FAF) imaging, reticular pseudodrusen are identified as a group of hypofluorescent lesions or halo-like lesions against a background of mildly elevated FAF. (Lower row, left) Microperimetry (MP) results. Retinal sensitivity is decreased in the superior, nasal, and inferior sides of the fovea. (Lower row, middle and right) Reticular pseudodrusen labeling results of the blue-channel of fundus photography (Lower row, middle-left), IR (Lower row, middle-right), and FAF (Lower row, right). Note that reticular pseudodrusen are frequently seen in the area where retinal sensitivity is decreased in MP. The color coding for the spots was used to show each area of the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. (Bottom) Table shows the number of reticular pseudodrusen in macular ETDRS sectors using each imaging modality.

TABLE 3. Correlation of the Observed Number of Reticular Pseudodrusen in the Macula, Using the Different Imaging Modalities

Imaging	Area[b]	IR	Fundus photography[a]
Fundus photography[a]	Center	.343 (0.336)	
	Inner ring	**<.001** (0.798)	
	Outer ring	**<.001** (0.834)	
FAF	Center	.617 (0.153)	**.007** (0.784)
	Inner ring	**<.001** (0.667)	**<.001** (0.544)
	Outer ring	**<.001** (0.882)	**<.001** (0.737)

FAF = fundus autofluorescence; IR = infrared reflectance.

Data presented as *P* value (correlation coefficient). Bold indicates statistical significance.

[a]Blue channel of fundus photography.

[b]Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

breakthrough into the inner and outer segment junction (IS/OS) of the photoreceptor, in later stages.[9] Querques and associates analyzed the progression of reticular pseudodrusen using SDOCT and found that the hyperreflective material faded because of reabsorption and migration within the inner retinal layers during the last stage of the disease.[15] These reports suggest that the subretinal material above the RPE in eyes with reticular pseudodrusen may alter photoreceptor structure. In the current study, we investigated how the distribution of reticular pseudodrusen affected retinal sensitivity by using multiple imaging modalities.

Several studies have revealed that reticular pseudodrusen lesions are seen most frequently in and near the superior arcades.[14,16] Consistent with these reports, the current study showed that these lesions were most frequently detected in the superior portion of the outer macula by all of the modalities. In addition, IR could detect reticular pseudodrusen within the center circle area in most eyes,

TABLE 4. Mean Retinal Sensitivity in Normal Eyes vs Eyes With Reticular Pseudodrusen in the Macular Early Treatment Diabetic Retinopathy Study Sectors

	Center[b]	Inner Ring[b]				Outer Ring[b]				Whole Macula
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	
Normal (n = 20)	17.9 ± 1.9	18.1 ± 1.3	19.0 ± 1.3	18.9 ± 1.3	18.7 ± 1.4	16.3 ± 1.5	18.6 ± 1.1	17.8 ± 1.5	18.1 ± 1.2	18.2 ± 1.1
RPD (n = 13)	14.2 ± 3.3	11.5 ± 4.9	14.9 ± 3.5	14.8 ± 3.4	14.1 ± 2.8	8.4 ± 3.7	13.6 ± 2.8	12.2 ± 3.4	12.7 ± 2.7	12.9 ± 3.9
RPD/normal (%)	79.3	63.5	78.4	78.3	75.4	51.5	73.1	68.5	69.3	70.9
P^a	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**	**< .001**

FAF = fundus autofluorescence; IR = infrared reflectance; RPD = reticular pseudodrusen.
Values are mean ± standard deviation (dB) unless otherwise indicated. Bold indicates statistical significance.
[a] *t* test.
[b] Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

whereas blue-channel fundus photography and FAF could detect these lesions in the center circles of only a few eyes, similar to the results of Smith and associates.[14] These authors reported that the region associated with the lesions, as detected by IR, was the central, 1-mm-diameter zone in 52% of affected eyes; FAF and color fundus images never found lesions in the central zone.[14] In most eyes, the central macula is observed to be dark by blue-channel fundus photography and FAF, using SLO. Thus, the evaluation of reticular pseudodrusen, near the fovea, is difficult when using these imaging methods. These results suggest thatIR imaging is necessary for the visualization and quantification of reticular pseudodrusen in the central macula.

The number of reticular pseudodrusen correlated well among the different imaging modalities, except for those in the center area. However, more reticular pseudodrusen were also detected by IR even in the inner and outer ring sectors. These results suggest that the flecks observed by fundus photography and the hypofluorescent lesions observed by FAF and IR reflect identical reticular pseudodrusen lesions, although the sensitivity for detecting the lesions is different among the methods. In fact, several researchers have reported that IR imaging has superior sensitivity compared with that of blue-channel fundus photography.[9,14,16] Compared with IR, blue-channel fundus photography and FAF imaging may be hampered to a greater extent by media opacity because of the short wavelengths being used, giving these modalities a lower sensitivity of detecting the lesions than IR.

The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes. The mean retinal sensitivity in the superior side, where reticular pseudodrusen lesions were most frequently seen, was significantly lower than that for any other side. In addition, the number of reticular pseudodrusen correlated with the detected retinal sensitivity in each area, by each imaging modality. All these results suggest that the distribution and number of reticular pseudodrusen lesions are closely associated with the reduction of retinal sensitivity. Recently, Curcio and associates reported on the morphology, prevalence, and topography of subretinal drusenoid deposits (SDD), a candidate histologic correlate of reticular pseudodrusen, in donor eyes with nonneovascular AMD.[22] In 1 specimen from their study, photoreceptor morphology was disrupted by SDD formations, manifest as outer segment shortening and loss of inner segment deflection.[22] Migration of subretinal material into neurosensory retina has been reported histologically.[23] These results suggest that reticular pseudodrusen may cause damage to the adjacent photoreceptors, resulting in a reduction of retinal sensitivity. Thus, ophthalmologists should be aware that reticular pseudodrusen not only are a risk factor for late AMD,[4–8] but may also cause retinal dysfunction.

To date, there have been few reports about the relationship between reticular pseudodrusen and retinal function. Recently, Alten and associates evaluated the effect of reticular pseudodrusen on retinal function by multifocal

TABLE 5. Correlation of the Number of Reticular Pseudodrusen With Macular Retinal Sensitivity, Using the Different Imaging Modalities

Imaging	Area[b]	Correlation Coefficient	P[c]
Fundus photography[a]	Center	−0.437	.206
	Inner ring	−0.632	**<.001**
	Outer ring	−0.496	**<.001**
IR	Center	−0.760	**.003**
	Inner ring	−0.619	**<.001**
	Outer ring	−0.409	**.003**
FAF	Center	−0.246	.418
	Inner ring	−0.532	**<.001**
	Outer ring	−0.465	**.001**

FAF = fundus autofluorescence; IR = infrared reflectance.
Bold indicates statistical significance.
[a]Blue channel of fundus photography.
[b]Center = central fovea (1 mm); inner ring = 1-3 mm from the central fovea; outer ring = 3-6 mm from the central fovea.
[c]*P* value using Pearson correlation coefficient.

electroretinography (mfERG) in 19 eyes.[24] They reported that mfERG measurements did not show a definite influence of these lesions on electrophysiological activity in the areas affected exclusively by reticular pseudodrusen,[23] inconsistent with the current study. One possible explanation for the discrepancy may be that the main mfERG signals are derived from cones, and reticular pseudodrusen are present primarily in the outer macula, where cones are sparse and rods are abundant. Curcio and associates proposed a hypothesis that rods may play an important role as a pathophysiological stimulus for the formation of SDD.[22] Thus rods, rather than cones, may have a close relationship with retinal sensitivity reduction in eyes with reticular pseudodrusen.

The effects of conventional drusen on visual function are controversial.[25,26] There was no decrease in the sensitivity of eyes with soft drusen over the drusen in one study; however, the results of another study were different. Iwama and associates[26] reported that mean retinal sensitivity was lower (61.8%-82.6%) than that of the intact retina in areas with confluent soft drusen. In the present study, we have shown that mean retinal sensitivity was lower (51.5%-79.3%) than that in normal controls in the entire macular area of eyes with reticular pseudodrusen.

Our study has several limitations. First, this study included a relatively small sample size, which also involves binocular cases accordingly, mostly because of practical limitations associated with the rarity of "pure" reticular pseudodrusen; most eyes with reticular pseudodrusen (90% of patients in our institution) also demonstrate other macular abnormalities such as soft drusen, choroidal neovascularization, or geographic atrophy.[8] Second, MP-1 can only test more central regions, and therefore cannot be used to evaluate peripheral areas. Reticular pseudodrusen was observed outside the vascular arcades and on the nasal side of the disc. Thus, further investigation of the wider areas is required. Third, reticular pseudodrusen are sometimes branching or confluent;[19] thus, the number of reticular pseudodrusen might have been underestimated, and the quantification might be rather subjective. However, reticular pseudodrusen were identified with a more punctate appearance within the macular area, compared with outside the macula. In addition, the inter-observer reproducibility was high in the current study. Fourth, because this was a cross-sectional study, we might have overlooked stage 4 reticular pseudodrusen (fading of the subretinal material because of reabsorption and migration within the inner retinal layers), reported by Querques and associates.[15] Longitudinal studies are needed to evaluate the last stage of reticular pseudodrusen development.

In conclusion, we have shown that the number of reticular pseudodrusen is related to retinal sensitivity, based on different types of imaging. In the future, longitudinal studies need to be conducted to learn more about the involvement of reticular pseudodrusen pathogenesis on retinal function. Cumulatively, such studies should facilitate improved management of this disease.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. This research was supported in part by the Grant-in-Aid for Scientific Research (21791679) from the Japan Society for the Promotion of Science (JSPS), Tokyo, Japan. Author contributions: conception and design (S.O.); analysis and interpretation (S.O., A.A.E.); writing the article (S.O.); critical revision of the article (S.O., N.Y.); final approval of the article (S.O., A.A.E., N.U.A., A.O., H.T., K.Y., A.T., N.Y.); data collection (S.O., A.A.E.); provision of materials (N.U.A., A.O., H.T., K.Y., A.T., N.Y.); statistical expertise (S.O.); obtaining funding (S.O.); literature search (S.O., N.U.A.).

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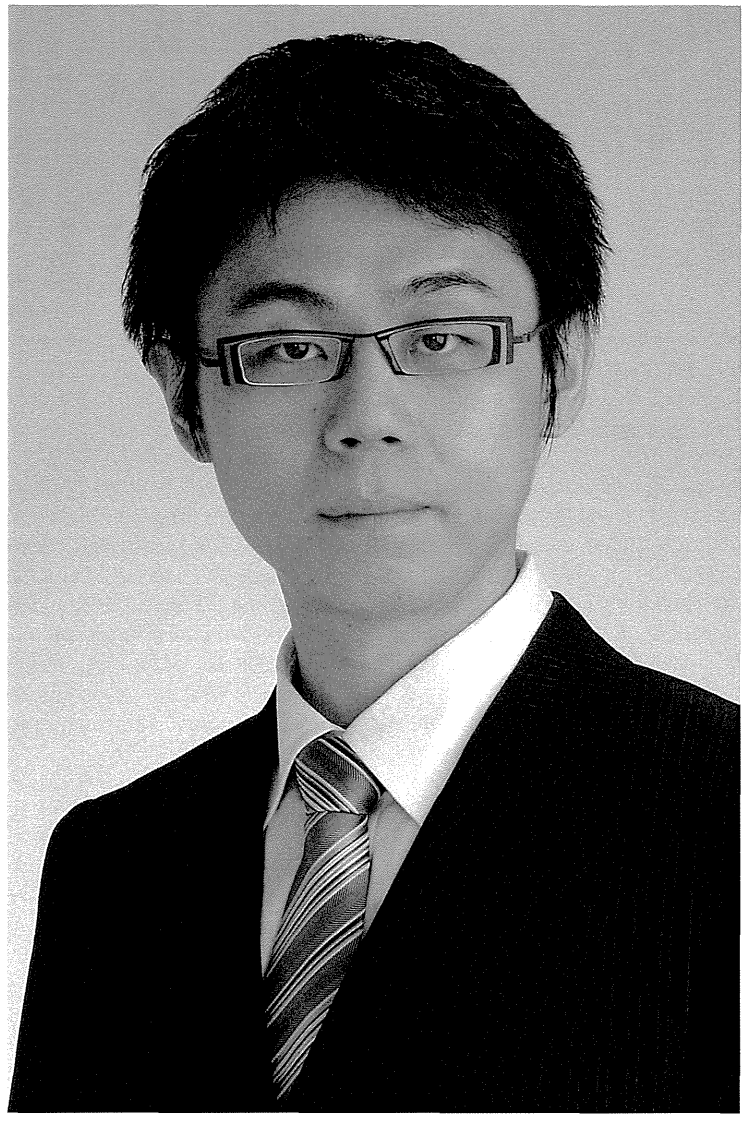

Biosketch

Sotaro Ooto MD, PhD, joined the Faculty of Medicine of Kyoto University and completed a medical course. He completed his residency in ophthalmology in 2001, after which he joined Kyoto University Graduate School of Medicine, where he worked on stem cell research. He became an assistant professor of Kyoto University Graduate School of Medicine in 2008, and he has been working as a member of the Macular Service and conducting studies on retinal imaging.

SUPPLEMENTAL TABLE. Reproducibility of the Determination of the Log Value of the Number of Reticular Pseudodrusen in the Macula Using Different Imaging Modalities

	Inter-observer Intraclass Correlation Coefficients		
Imaging	Center	Inner Ring[b]	Outer Ring[b]
Fundus photography[a]	0.946	0.839	0.845
IR	0.921	0.919	0.939
FAF	0.937	0.941	0.917

FAF = fundus autofluorescence; IR = infrared reflectance.
[a]Blue channel of fundus photography.
[b]Center, central fovea (1 mm); Inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

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

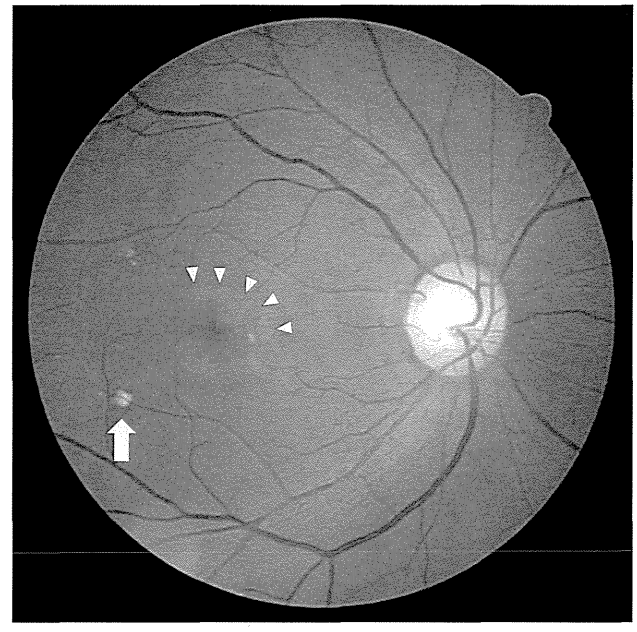

FIGURE 1. Fundus photograph of a 64-year-old Japanese woman with a large drusen (white arrow) and retinal pigment epithelial abnormalities (arrowheads).

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

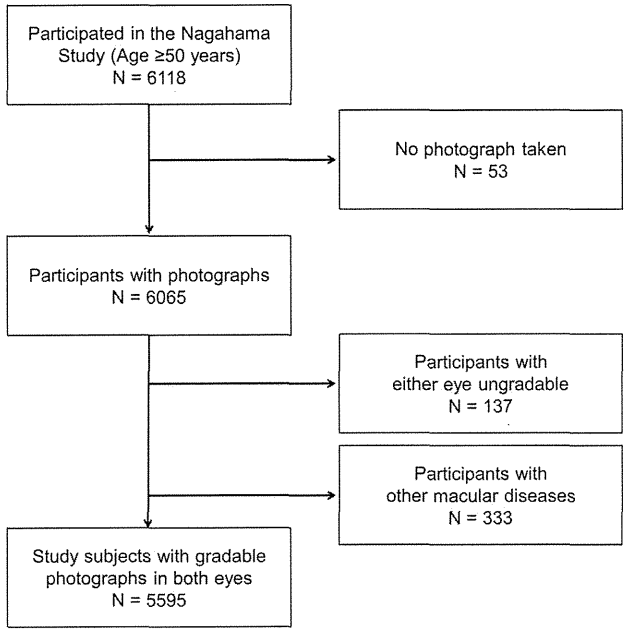

FIGURE 2. Flowchart describing participants from the Nagahama Study who were included and excluded from the analysis for age-related macular degeneration in the Japanese population. Of the 6065 subjects aged ≥50 years, 5595 (92.3%) had gradable fundus photographs in both eyes.

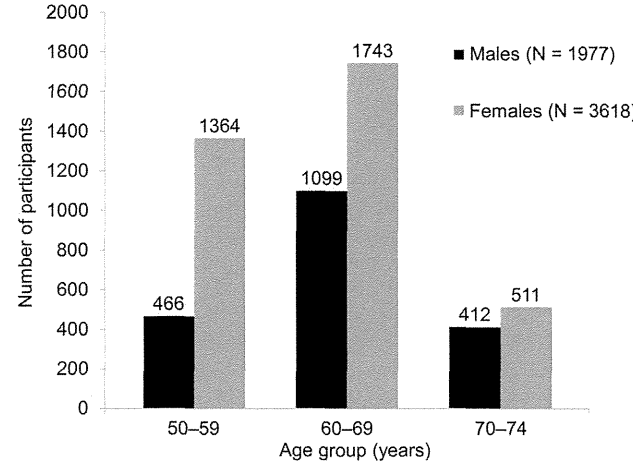

FIGURE 3. Age and sex distribution of the study subjects for age-related macular degeneration in the Japanese population (n = 5595).

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]