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Population-Based Prevalence and 5-Year Change of Soft Drusen, Pseudodrusen, and Pachydrusen in a Japanese Population

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Purpose: To elucidate the prevalence of soft drusen, pseudodrusen, and pachydrusen and their 5-year changes in a Japanese population.

Design: Longitudinal population-based cohort study conducted from 2013 through 2017.

Participants: Residents 40 years of age or older.

Methods: Nonmydriatic color fundus photographs were used to grade drusen subtypes and retinal pigment epithelium (RPE) abnormalities according to the Three Continent Age-Related Macular Degeneration Consortium. The 5-year changes of each drusen were investigated.

Main Outcome Measures: The prevalence of each drusen subtype and the 5-year changes of each drusen.

Results: Among 1731 participants, 1660 participants had gradable photographs that were assessed. The age-adjusted prevalence of soft drusen, pachydrusen, and pseudodrusen was 4.3% (95% confidence interval [CI], 3.2%−5.8%), 7.7% (95% CI, 6.2%−9.7%), and 2.8% (95% CI, 1.7%−4.2%), respectively. Pachydrusen accounted for 82.0% (n = 50) of the extramacular drusen (n = 61). Pigment abnormalities were seen in 28.3% and 8.3% of eyes with soft drusen and pachydrusen, respectively ($P < 0.0001$). Longitudinal changes were investigated in 1444 participants with follow-up examinations, which showed an increase in size in 8.3% and 3.7% and regression in 1.7% and 5.5% for eyes with soft drusen and pachydrusen, respectively. No participants demonstrated RPE atrophy after pachydrusen regression.

Conclusions: The prevalence of pachydrusen was higher than that of soft drusen and pseudodrusen combined. Pachydrusen may regress over time and typically is not associated with RPE atrophy as detected using color fundus photographs. *Ophthalmology Science 2021;1:100081*

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Drusen are a hallmark of early age-related macular degeneration (AMD).[1,2] Longitudinal studies have reported that soft drusen generally increase in size over time and subsequently regress.[1] Regression of soft drusen is associated with the subsequent degeneration and atrophy of the retinal pigment epithelium (RPE) and photoreceptors.[1,3] Pseudodrusen also confer a high risk of late AMD,[4−7] and outer retinal atrophy may develop with regression. Additionally, soft drusen and pseudodrusen are associated with a high risk of progression to neovascular AMD.[1,2,8]

Recently, considerable attention has been paid to pachydrusen,[9] which are a peculiar form of drusen-like deposits[10] that are frequently found in eyes with exudative maculopathies in elderly Asians.[11−16] Pachydrusen are larger than 125 μm in diameter and are characterized by distinct contours, show a scattered pattern of distribution throughout the posterior pole, and are not associated with overlying pigment that may have been diagnosed as soft distinct drusen.[9,17] Essentially, the diagnosis is made through color fundus photography,[9] and OCT, fluorescein angiography, and indocyanine green angiography may aid in diagnosis.[12,14,15] Pachydrusen are increasingly reported in the fellow eyes of patients with unilateral exudative AMD[13−15] and dry AMD[11] and in eyes with central serous chorioretinopathy.[12] Moreover, pachydrusen are associated with an increased choroidal thickness, which may result in an increased risk of developing type 1 choroidal neovascularization or polypoidal choroidal vasculopathy.[10,14,17]

Increasingly, pachydrusen have been recognized to be structurally and morphologically distinct from soft drusen and pseudodrusen, although consensus diagnostic criteria have not yet been reached. Moreover, their epidemiologic significance is uncertain. The prevalence of pachydrusen in the general population is unknown, and no population studies have investigated the natural history of eyes with pachydrusen. Hence, whether they actually progress over time and confer a risk for exudative maculopathies

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developing, such as polypoidal choroidal vasculopathy and RPE atrophy in the general population, is not clear. In this regard, it is worth mentioning that only when they were present with pigment abnormalities are distinct drusen considered to constitute early AMD in major epidemiologic studies.[18–20] To address these issues, we investigated the prevalence of soft drusen, pseudodrusen, and pachydrusen and their 5-year changes in a cohort study conducted in Hokkaido, in northern Japan.

Methods

Study Design

Data from the Rumoi Cohort Study were used for this study. The study was conducted following the tenets of the Declaration of Helsinki, and it was approved by the institutional research board of Asahikawa Medical University (approval no., 858). Written informed consent was obtained from all participants.

Participants

The details regarding the Rumoi Cohort Study were reported previously.[21] Briefly, Rumoi is a seaside rural city in Hokkaido prefecture located in northern Japan. Participants were recruited using the town bulletin, posters, and direct phone calls to businesses and public offices located in the city. Among the 15 373 residents, 1731 people 40 years of age or older (based on the Rumoi city resident register as of January 2015) were recruited for the study. This equated to 11% of the residents 40 years of age or older. Color fundus photographs (CFPs) and physical examinations were obtained at the Rumoi health station.

Baseline examinations were performed from January 2013 through March 2015. Additionally, 1444 of the original participants (83.4%) took part in at least 1 annual follow-up examination conducted from 2013 through 2017. History of physician-diagnosed disease and medication use were recorded during the examinations. All items were assessed by physicians, public health nurses, or registered nurses. A digital nonstereo retinal camera (model AFC-230; Nidek, Aichi, Japan) was used to record the CFPs.

Age-Related Macular Degeneration Grading

Grading was based on the Three Continent AMD Consortium,[22] which was developed by harmonizing the grading systems used by the population-based Rotterdam Study, the Beaver Dam Eye Study, the Los Angeles Latino Eye Study, and the Blue Mountains Eye Study.[18,19,23,24] The Three Continent AMD Consortium was developed for epidemiologic studies and does not distinguish between early and intermediate AMD; hence, it is a 3-category scale (no AMD, early AMD, and late AMD). Exclusion criteria were defined as follows: participants with poor-quality CFPs of both eyes and eyes with other conditions that would interfere with the precise grading of AMD. Each image was graded for drusen, pigment abnormalities, and late AMD. Drusen size within the macula grid was determined using the standard circles (a 3000-μm radius centered on the fovea). The Three Continent Consortium severity scale[22] defines early AMD as the presence of small to intermediate drusen ($<$ 125 μm in diameter) with any pigmentary abnormality, large drusen (soft distinct or soft indistinct drusen with a diameter of $\geq$ 125 μm), retinal pigment abnormalities (hyperpigmentation or hypopigmentation) in the absence of late AMD, or a combination thereof. Late AMD was defined as the presence of exudative AMD or geographic atrophy (GA). Exudative AMD was defined as RPE detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhage, and subretinal fibrous scarring. Geographic atrophy was defined as sharply edged, roughly round or oval areas of RPE hypopigmentation with clearly visible choroidal vessels.

Assessment of Drusen Subtypes and Pigmentary Changes

Drusen subtypes were determined on the basis of CFPs using the same criteria according to published definitions.[2,9] Figure 1 shows representative photographs for each drusen. In 22 eyes, more than 1 drusen subtype was observed. Similar to previous studies,[13,14] eyes with both pseudodrusen and soft drusen were classified into the pseudodrusen group and those with both soft drusen and pachydrusen were classified into the soft drusen group. Pigmentary changes were defined as depigmentation or hyperpigmentation with a size larger than one-eighth of the disc diameter.[10]

All grades were assigned by 2 independent ophthalmologists (M.S.-A. and Y.Y.) who were unaware of the participants' information. Our definition was discussed among the graders after the first grading of 200 cases to improve the accuracy and repeatability.[25] In total, 100 eyes were selected to evaluate intergrader agreement, and the resultant κ score was 0.65, 0.70, 0.69, 0.40, and 0.66 for soft drusen, pachydrusen, pseudodrusen, pigment abnormality, and late AMD, respectively. Any disagreement was resolved either by open adjudication or another retinal specialist (S.O.).

Drusen Changes over Time

Using a side-by-side evaluation of the CFPs between visits, we assessed changes of drusen over time, focusing on the individual drusen size, drusen area as estimated by the closest circle area, and RPE atrophy.[26–28] Eyes in which the individual or total drusen area increased in size or eyes in which RPE atrophy developed were categorized into the "increase in size" group. Eyes that showed partial or complete regression of individual drusen or a decreased area of total drusen were categorized into the "regression" group. If none of these changes were observed, eyes were categorized into the "stable" group. Two ophthalmologists assessed the images independently, and any disagreement was resolved by open adjudication. For the stratified analysis, we categorized the eyes on the basis of the total drusen area size; for this purpose, we used the O2 circle, which is defined as a circle with a diameter of 650 μm.[22,29]

Statistical Analysis

We conducted a per-eye analysis for signs of early AMD and per-individual analysis for signs of late AMD, similar to previous studies.[30,31] Briefly, we used the right eye of the participant for drusen classification. The left eye was used when the right eye was ungradable for any of the aforementioned reasons. For late AMD, both eyes were used for the analysis to avoid underestimation. Additionally, we used both eyes of all participants and investigated the drusen prevalence per individual and the symmetricity of the drusen subtypes.

Age- and gender-specific prevalence of soft drusen, pachydrusen, pseudodrusen, RPE abnormalities, and early and late AMD were calculated. Using the direct method with reference to the Rumoi population figures published on the official homepage in Rumoi city, the age-adjusted standardized prevalence was assessed after determining crude prevalence. The Cochran–Armitage test was used to analyze the age trend, whereas the Cochran–Mantel–Haenszel test was used to evaluate differences

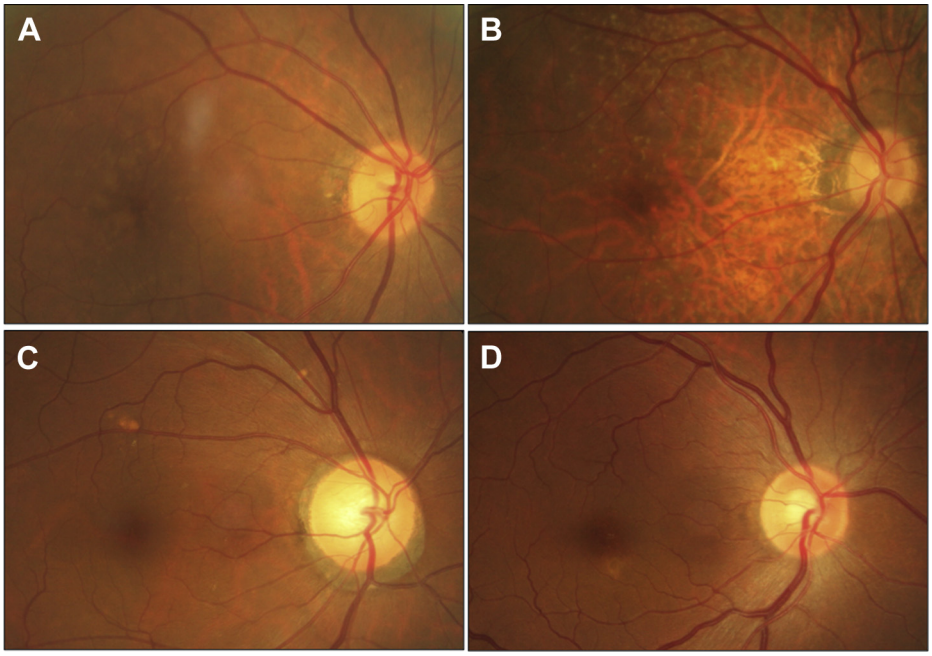

Figure 1. Representative color fundus photographs (CFPs) of each drusen subtype and pigment abnormality. **A**, Soft drusen. The CFP shows round or ovoid deposits with a poorly defined border; they can be tightly packed and confluent in the center of the macula. **B**, Pseudodrusen. The CFP shows whitish deposits scattered with irregular outer contours that do not involve the central macula and a characteristic reticular pattern. **C**, Pachydrusen. The CFP shows yellow-white deposits, which have an ovoid or more complex and well-defined irregular outer border compared with soft drusen and are present in isolated or scattered patterns anywhere in the temporal vascular arcades. **D**, Pigment abnormalities. The CFP shows hyperpigmentation at the center of the macula.

in terms of sex. The unadjusted *P* value was assessed using the Wilcoxon rank-sum test and Fisher exact test. Using logistic regression analysis, the *P* value adjusted for age and sex was assessed. Differences in the demographic characteristics between participants with gradable and ungradable CFPs also were assessed. For all analyses, R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Australia) and EZR (Jichi Medical University, Saitama, Japan), a graphical user interface for R, were used.[32] For this study, $P < 0.05$ was considered statistically significant.

Results

Characteristics of Participants

Among the 1731 participants in this study, 37 who were diagnosed as undeterminable from the CFPs and 34 with ungradable CFPs of both eyes were excluded. The most common causes of ungradable photographs were insufficient light caused by miosis and marked opacity of the medium. A total of 1660 participants were assessed, 1444 (83.4%) of whom took part in the annual follow-up examination during the 5-year follow-up period (Supplemental Fig 1). The mean age of the ungradable participants was older than that of the gradable participants ($P < 0.001$; Supplemental Tables 1 and 2). The numbers of participants examined at each annual visit were 1660, 1444, 1269, 1071, and 826 at years 1, 2, 3, 4, and 5, respectively.

Prevalence of Age-Related Macular Degeneration

Of the 1660 participants, 194 (11.7%) had early AMD. Participants with early AMD were older than those without early AMD (mean age, 63.8 and 56.8 years, respectively; $P < 0.001$). The background characteristics of the participants are presented in Table 1 and Supplemental Table 3. The age-adjusted prevalence of late AMD was 0.06% (95% confidence interval [CI], 0.001%−0.6%) in this population. Notably, a 68-year-old man was found to have unilateral GA. Of the examined eyes, none showed exudative AMD. However, 10 eyes showed subretinal fibrosis that was not associated with medium or large drusen.

Prevalence of Age-Related Macular Degeneration Lesions and Drusen Subtypes

Among the 1660 participants, 60, 109, and 25 showed soft drusen, pachydrusen, and pseudodrusen, respectively. Eight participants showed both pseudodrusen and soft drusen, and 14 participants showed both soft drusen and pachydrusen. No eyes showed both pseudodrusen and pachydrusen.

The age-adjusted prevalences of soft drusen, pachydrusen, reticular pseudodrusen, and pigment abnormalities were 4.3% (95% CI, 3.2%−5.8%), 7.7% (95% CI, 6.2%−9.7%), 2.8% (95% CI, 1.7%−4.2%), and 2.7% (95% CI, 1.8%−4.0%), respectively. Increasing age was associated

Table 1. Participants' Baseline Characteristics

Characteristic	Total (n = 1660)	Early Age-Related Macular Degeneration		Unadjusted P Value
		Present (n = 194)	*Absent (n = 1466)*	
Age (yrs)	57.6 ± 10.9	63.8 ± 9.7	56.8 ± 10.8	<0.001*
Male sex	57.5 (955)	58.2 (113)	57.4 (842)	0.877†
BMI (kg/m^2)	24.2 ± 3.8	23.8 ± 3.4	24.2 ± 3.8	0.185*
Diabetes mellitus	6.5 (107)	5.2 (10)	6.6 (97)	0.534†
Hypertension	20.2 (335)	25.3 (49)	19.5 (286)	0.070†

BMI = body mass index.
Data are presented as mean ± standard deviation or percentage (no.). Results from multivariate regression analysis are shown in Supplemental Table 1.
*Wilcoxon rank-sum test.
†Fisher exact test.

with all drusen subtypes and pigment abnormalities ($P < 0.05$ for all, Cochran−Armitage test). The prevalence of soft drusen and pigment abnormalities in men was significantly higher than that in women (4.3% vs. 2.7% [$P = 0.024$] and 2.7% vs. 1.6% [$P = 0.044$], respectively), whereas reticular pseudodrusen was less frequent in men (0.6% vs. 2.7% [$P = 0.046$]). No gender preponderance was found for pachydrusen. Furthermore, 61 eyes harbored drusen exclusively located in the extramacular regions. Pachydrusen accounted for most of the drusen located in the extramacular region; that is, soft drusen, pachydrusen, and reticular pseudodrusen accounted for 6.6%, 82.0%, and 11.5%, respectively (Table 2).

The percentage of eyes with a smaller total drusen area (overall drusen area less than the O2 circle) was 50% (n = 30) and 67% (n = 73) for soft drusen and pachydrusen, respectively ($P < 0.0001$). Additionally, concomitant pigment abnormalities were seen in 28.3% (n = 17) and 8.3% (n = 9) of eyes with soft drusen and pachydrusen, respectively.

As per individual analysis, 86, 140, and 27 participants demonstrated soft drusen, pachydrusen, and pseudodrusen, respectively (Supplemental Table 4). Among those in whom both eyes were gradable (n = 1599), 241 participants (15.1%) demonstrated soft drusen, pseudodrusen, pachydrusen, or a combination thereof in either eye. Furthermore, among the participants who showed soft drusen, pseudodrusen, pachydrusen, or a combination thereof in either eye, 164 participants (68.0%) were affected unilaterally, whereas 77 participants (32.0%) were affected bilaterally. When soft drusen, pseudodrusen, pachydrusen, or a combination thereof were found in both eyes, the drusen subtypes were the same in both eyes in 66 participants (85.7%); in particular, pseudodrusen (n = 22) were bilateral in all participants. Of the participants who harbored soft drusen or pachydrusen in either eye (n = 55), 44 showed the same drusen subtype in the fellow eye (80.0%; Supplemental Table 5).

Longitudinal Changes of Drusen

At least 1 follow-up examination was available for 194 eyes with soft drusen (n = 60), pachydrusen (n = 109), and pseudodrusen (n = 25). Each drusen type indicated different dynamic changes; an increase in size was noted in 8.3%, 3.7%, and 8.0%, and regression was noted in 1.7%, 5.5%, and 0% of eyes with soft drusen, pachydrusen, and pseudodrusen, respectively. No changes were found in the drusen subtype; pachydrusen remained as pachydrusen and never evolved into soft drusen, and vice versa.

A larger drusen area was numerically associated with the increased size of soft drusen; 3.3% of eyes with a smaller soft drusen area experienced an increase in size compared with 13.3% of eyes with a larger soft drusen area. By contrast, an increase in size was noted in 4.1% of eyes with a small pachydrusen area compared with 2.8% of eyes with a large pachydrusen area. Among the 4 eyes that demonstrated pachydrusen progression, coalescence was observed only in 1 eye (Supplementary Fig 2), whereas the individual drusen increased in size in the other 3 eyes. Moreover, regression was noted in 4.1% and 8.3% of eyes with a small and large pachydrusen area, respectively. No participants demonstrated RPE atrophy after regression of pachydrusen. Notably, pseudodrusen did not regress in this cohort during the follow-up period (Table 3). Additionally, no eyes in the cohort with early AMD progressed to late AMD within the 5-year follow-up period. Figure 2 shows the representative changes of the eyes with soft drusen and pachydrusen. The 5-year incidence of soft drusen during follow-up was 1.5% (21 participants) and 2.7% (39 participants) per eye and individual analysis, respectively. No participants demonstrated pachydrusen or pseudodrusen de novo during the 5-year follow-up period.

Discussion

In this study, we investigated the prevalence of each drusen subtype, early AMD, and late AMD. We also investigated the longitudinal changes of these extracellular deposits and disclosed important differences between pachydrusen and soft drusen. The prevalence of early AMD in Asia varies from 1.4% to 37.9%, and this variation is attributable to the different classifications used in different studies.[33] The prevalence of pachydrusen in a general population has not been elucidated. In this cohort, the age-standardized prevalence of pachydrusen was 7.7% and 10% among participants

Table 2. Prevalence of Each Drusen Subtype

	Soft Drusen	Pachydrusen	Pseudodrusen	Pigment Abnormalities	Late Age-Related Macular Degeneration
Crude prevalence					
Age group (yrs)					
40–49 (n = 457)	1.8 (8)	2.2 (10)	0.0 (0)	0.9 (4)	0 (0)
50–59 (n = 479)	2.9 (14)	6.7 (32)	0.2 (1)	1.7 (8)	0 (0)
60–69 (n = 469)	4.7 (22)	8.3 (39)	1.5 (7)	3.2 (15)	0.2 (1)
70+ (n = 255)	6.3 (16)	11.0 (28)	6.7 (17)	3.9 (10)	0 (0)
Total 40+ (n = 1660)	3.6 (60)	6.6 (109)	1.5 (25)	2.2 (37)	0.06 (1)
Total 50+ (n = 1203)	4.3 (52)	8.2 (99)	2.1 (25)	2.7 (33)	0.08 (1)
P value for age trend*	<0.001	<0.001	<0.001	0.002	
Sex					
Male 40 + (n = 955)	4.3 (41)	6.9 (66)	0.6 (6)	2.7 (26)	0.1 (1)
Female 40+ (n = 705)	2.7 (19)	6.1 (43)	2.7 (19)	1.6 (11)	0 (0)
P value between sexes†	0.024	0.160	0.046	0.044	
Extramacular regions only (n = 61)	6.6 (4)	82.0 (50)	11.5 (7)		
Age-adjusted prevalence (yrs)‡					
All 40+	4.3 (3.2–5.8)	7.7 (6.2–9.7)	2.8 (1.7–4.2)	2.7 (1.8–4.0)	0.06 (0.001–0.6)
All 50+	5.0 (3.5–6.8)	9.1 (7.2–11.4)	3.4 (2.2–5.2)	3.1 (2.0–4.7)	0.07 (0.002–0.7)
Men 40+	5.2 (3.5–7.6)	8.4 (6.2–11.3)	1.5 (0.5–3.4)	3.1 (1.9–5.0)	0.11 (0.003–1.2)
Men 50+	6.1 (4.0–9.2)	10.0 (7.2–13.7)	2.0 (0.7–4.4)	3.7 (2.2–6.2)	0.14 (0.004–1.5)
Women 40+	3.3 (1.9–5.5)	7.0 (4.9–9.8)	3.9 (2.3–6.4)	2.1 (1.0–4.1)	0 % (0–1.0)
Women 50+	3.7 (2.1–6.3)	8.2 (5.7–11.5)	4.8 (2.8–7.7)	2.5 (1.1–4.8)	0 % (0–1.2)

Data are presented as percentage (no.) or percentage (95% confidence interval).
*Cochran-Armitage test.
†Cochran-Mantel-Haenszel test.
‡Standardized to the age distribution of the Rumoi city population.

40 years of age and older and 70 years of age and older, respectively. The age-stratified analysis indicated that pachydrusen was more prevalent than soft drusen and pseudodrusen combined, except for participants 70 years of age or older. Thus far, only hospital-based studies have investigated the frequency of pachydrusen, which was 11.7% in White people,[9] 8.4% in Indian people,[11] and 25.5% in Singaporean people[17] among nonexudative AMD. Moreover, pachydrusen reportedly was observed in 27.2% of eyes with central serous chorioretinopathy.[12] No population studies have used the current drusen classification; previously, pachydrusen may have been classified as soft distinct drusen because they typically have distinct borders.[25,34–37] The Singapore Epidemiology of Eye Diseases Study reported a higher prevalence of distinct soft drusen than of indistinct soft drusen and pseudodrusen combined. In Asian populations, the reported prevalence of distinct soft drusen (22.73%, 21.75%, 28.76%, and 23.93% in the Singapore Malay Eye Study, the Singapore Indian Eye Study, the Singapore Chinese Eye Study, and Combined Asian; age-adjusted to Blue Mountains Eye Study) is generally higher than that of soft indistinct or pseudodrusen combined (4.92%, 8.36%, 5.20%, and 6.52% in the Singapore Malay Eye Study, Singapore Indian Eye Study, Singapore Chinese Eye Study, and Combined Asian, respectively).[38] This is in contrast to the Blue Mountains Eye Study, in which the prevalence of soft distinct drusen (6.15%) was lower than that of soft indistinct or pseudodrusen combined (8.32%). Together with our study, it seems rational to consider that the prevalence of pachydrusen is higher than that of soft drusen and pseudodrusen in Asian populations.

Table 3. Longitudinal Changes of Drusen

Variable	Increase in Size	Regression	No Changes	Development of Conditions Other Than Age-Related Macular Degeneration*	No Follow-up Data
Soft drusen (n = 60)	8.3 (5)	1.7 (1)	71.7 (43)	3.3 (2)	15.0 (9)
<O2 circle (n = 30)	3.3 (1)	0 (0)	76.7 (23)	0 (0)	20 (6)
≥O2 circle (n = 30)	13.3 (4)	3.3 (1)	66.7 (20)	6.7 (2)	10 (3)
Pachydrusen (n = 109)	3.7 (4)	5.5 (6)	77.1 (84)	1.8 (2)	11.9 (13)
<O2 circle (n = 73)	4.1 (3)	4.1 (3)	78.1 (57)	2.7 (2)	11.0 (8)
≥O2 circle (n = 36)	2.8 (1)	8.3 (3)	75.0 (27)	0 (0)	13.9 (5)
Pseudodrusen (n = 25)	8.0 (2)	0 (0)	72.0 (18)	8.0 (2)	12.0 (3)

Data are presented as percentage (no.).
*Branch retinal vein occlusion in all 6 eyes.

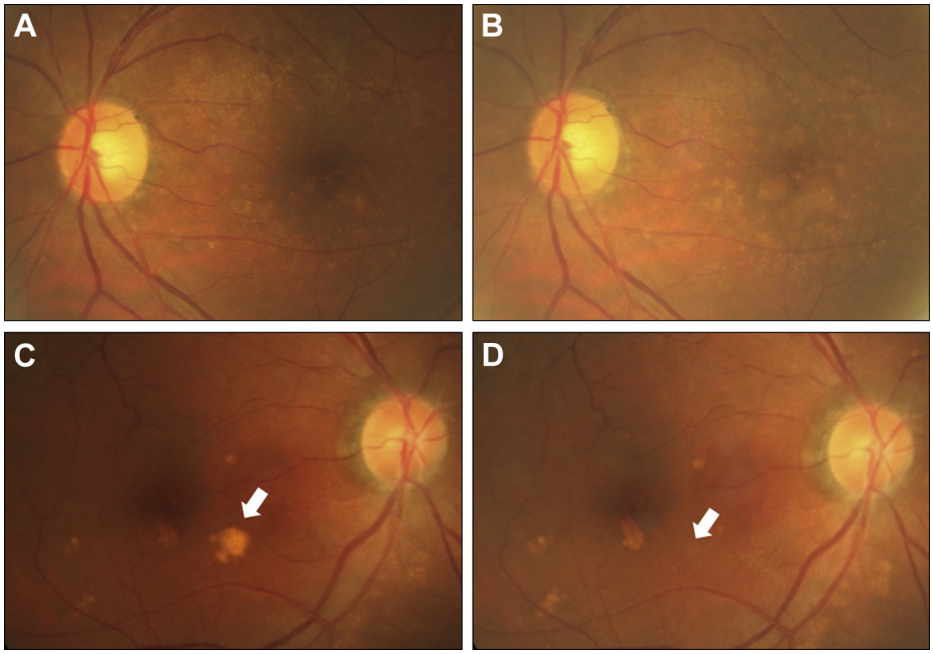

Figure 2. Color fundus photographs showing longitudinal changes of drusen. **A**, **B**, Longitudinal changes of soft drusen (**A**) at baseline, with a total drusen area smaller than an O2 circle, are seen in the macula that (**B**) increased in size during the 5-year follow-up period. **C**, **D**, Longitudinal changes of pachydrusen (**C**) at baseline and (**D**) at year 5. At baseline, a large, irregular, well-defined yellow pachydrusen is seen at the nasal-inferior part of the macula (white arrow). The margin became a little blurred and color became slightly lighter at year 1, and then it disappeared without leaving any signs of retinal pigment epithelium atrophy at year 2. No apparent sign of atrophy is present at the corresponding region at year 5 (white arrow).

The reason for the high prevalence of pachydrusen in Asian populations is not clear. However, it is generally accepted that a thick choroid is associated with pachydrusen,[14,17] and Asians seem to have thick choroids.[39–43] This may explain the relatively high prevalence of pachydrusen in Asians. In this study, a high prevalence of pachydrusen (2.2%) was found even among relatively young participants (between 40 and 49 years of age). Some evidence may support the presence of pachydrusen, which develops over the years, from young adulthood. First, a small, hard macular drusen is relatively common even in 11- to 12-year-old children, with a prevalence of 11%.[44] Furthermore, the study found that increased subfoveal choroidal thickness is associated with the presence of one or more small hard macular drusen and with extramacular drusen. The number of soft, distinct drusen increases with age, beginning in young adulthood.[45] Second, when imaged using multimodal imaging, the shape of the drusen in young adults may be oval or lobular.[46] Although longitudinal studies are necessary, it is tempting to consider that hard drusen, which are present in patients with thick choroids, evolve into pachydrusen.

We also observed the confluence of pachydrusen in 1 eye, further supporting that soft drusen and pachydrusen may behave similarly, at least in part. Nevertheless, this participant showed extrafoveal pachydrusen and was unlikely to demonstrate drusenoid pigment epithelial detachment; hence, we believe that the progression pattern of pachydrusen is different from the behavior of soft drusen. When the symmetricity of the drusen was analyzed, the drusen phenotype seemed to be surprisingly low; this was mainly because drusen were unilateral in approximately two-thirds of the participants. However, when both eyes are affected with either soft drusen, pseudodrusen, or pachydrusen, the drusen subtypes were highly concordant between both eyes. However, we also noted that soft drusen and pachydrusen are not always observed symmetrically. This may provide support that soft drusen and pachydrusen share the same pathogenesis, but further studies are needed to confirm our findings.

In this population-based study, the prevalence of late AMD was extremely low. Geographic atrophy is uncommon in Asian populations compared with Europeans,[47] and the prevalence of GA is extremely low in Japan.[25,48–50] Neovascular AMD was nonexistent in this study; nevertheless, 10 eyes showed subretinal fibrosis without any signs of AMD. We believe that presumed pachychoroid neovasculopathy may have been present among such participants,[16] which could masquerade as neovascular AMD[51] (Supplemental Fig 3).

Our study showed that during the 5-year follow-up, 8.3% of eyes with soft drusen demonstrated progression, whereas only 1.7% of eyes demonstrated regression. An increase in size, which was observed more frequently in eyes with a large drusen area, corroborates previous studies that reported that a large drusen area is associated with an increased risk of AMD progression.[52] By contrast, little is known about the natural history of pachydrusen. Although the association between pachydrusen and pachychoroid-driven macular neovascularization (type I choroidal

neovascularization or polypoidal choroidal vasculopathy) seems strong, the high degree of collinearity between the presence of pachydrusen and thick choroids limits our understanding of their role in the pathogenesis of macular neovascularization. Interestingly, our study indicated that 3.7% of pachydrusen progressed within 5 years, whereas 5.5% of pachydrusen regressed without photographically detectable signs of atrophy. Unexpectedly, regression was observed more frequently in eyes with a larger total pachydrusen area. Moreover, in this study, no RPE atrophy was observed after the regression of pachydrusen. In this regard, note that drusen reportedly regress without residual signs in some eyes.[26,36,52] A small-scale, hospital-based study reported that focal RPE atrophy and overlying outer retinal layer changes may be observed after the regression of pachydrusen, but vision-threatening atrophy or GA develops rarely.[53] Taken together, pachydrusen do not seem to affect RPE directly and may have little pathologic significance on macular diseases.

Study Limitations

This study has several limitations, which are mostly inherent to the study design and limitation of the imaging methods used in this cohort study. First, the participants needed to visit the city health station for the screening examination, which might have introduced selection bias. Participants in this study accounted for 11.3% of the population. The percentage of the total population was 15.6% in their 40s, 16.2% in their 50s, 12.3% in their 60s, and 5.2% in their 70s or older,[21] and the number of participants 70 years and older was smaller than that of other age groups. Considering that the participants who could not commute to the screening station were not included in this study, combined with the fact that patients with AMD tend to have other comorbidities that may impair locomotor function, caution should be paid to the interpretation of the prevalence data because it may be underestimated. Second, the CFPs were obtained through undilated pupils, and 2.0% of the photographs were ungradable. The mean age of the ungradable participants was older than that of the gradable participants ($P < 0.001$, Supplemental Table 1). Additionally, 2.2% of the photographs were excluded because of undeterminable CFPs. Third, only CFPs were used for grading. Because pseudodrusen are identified at lower rates on CFPs than on multimodal imaging,[54] the prevalence of pseudodrusen is likely to have been underestimated. Also, certain types of drusen might have been underdiagnosed. However, this is a common problem in epidemiologic study settings where OCT is not used for retinal examinations. Additionally, small yellow patches appearing on CFPs involve not only drusen or drusen-like deposits, but also exudates, epiretinal membrane, and foveal reflex in young patients. In this study, experienced ophthalmologists, including 2 retinal specialists, graded the photographs, and maximum attention was paid to classifying each druse and differentiating them from other features. More importantly, no standard definition of pachydrusen exists. Indeed, pachydrusen look somewhat distinct from soft drusen, but some gray area exists between the two. Although the agreement between the graders was fair in the present study, OCT may be helpful to distinguish the two lesions, and future studies will require a better classification of extracellular deposits. Additionally, this study did not use the Early Treatment Diabetic Retinopathy Study subgrid to categorize drusen location. Future studies using the Early Treatment Diabetic Retinopathy Study subgrid would be useful for a more detailed analysis. However, we used the standard 3000-μm grid and implicated different distributions of soft drusen, pachydrusen, and pseudodrusen. Fourth, the prevalence and incidence of late AMD were extremely low. Nonattendance may be related to poor vision and late-stage AMD. However, the nonattendance rate was quite low and not age dependent.[21] Moreover, the Japanese may be idiosyncratic among Asians.[48] Finally, our definition of RPE atrophy was depigmentation or hyperpigmentation on CFPs.[55] This study applied a side-by-side analysis of the CFPs to scrutinize minute changes of RPE, and the graders were allowed to change the contrast for better visibility so that minute RPE changes were not missed; however, OCT should be included in future studies to precisely document longitudinal changes of pachydrusen.

In conclusion, the prevalence and longitudinal changes of each drusen were investigated in a population-based study conducted in the northern part of Japan. This study indicated an unexpectedly high prevalence of pachydrusen. A high regression rate of pachydrusen without the development of pigmentary changes or atrophy was also observed. To understand how pachydrusen are involved in the pathogenesis of pachychoroid diseases, future studies are warranted.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CFP** = color fundus photograph; **CI** = confidence interval; **GA** = geographic atrophy; **RPE** = retinal pigment epithelium; **OCT** = optical coherene tomography.

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References

1. Gass JD. Drusen and disciform macular detachment and degeneration. *Arch Ophthalmol*. 1973;90(3):206–217.
2. Khan KN, Mahroo OA, Khan RS, et al. Differentiating drusen: drusen and drusen-like appearances associated with ageing, age-related macular degeneration, inherited eye disease and other pathological processes. *Prog Retin Eye Res*. 2016;53:70–106.
3. Sallo FB, Rechtman E, Peto T, et al. Functional aspects of drusen regression in age-related macular degeneration. *Br J Ophthalmol*. 2009;93(10):1345–1350.
4. Klein R, Meuer SM, Knudtson MD, et al. The epidemiology of retinal reticular drusen. *Am J Ophthalmol*. 2008;145(2):317–326.
5. Schmitz-Valckenberg S, Alten F, Steinberg JS, et al. Reticular drusen associated with geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(9):5009–5015.
6. Pumariega NM, Smith RT, Sohrab MA, et al. A prospective study of reticular macular disease. *Ophthalmology*. 2011;118(8):1619–1625.
7. Sarks J, Arnold J, Ho IV, et al. Evolution of reticular pseudodrusen. *Br J Ophthalmol*. 2011;95(7):979–985.
8. Zhou Q, Daniel E, Maguire MG, et al. Pseudodrusen and incidence of late age-related macular degeneration in fellow eyes in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(7):1530–1540.
9. Spaide RF. Disease expression in nonexudative age-related macular degeneration varies with choroidal thickness. *Retina*. 2018;38(4):708–716.
10. Kang SW, Lee H, Bae K, et al. Investigation of precursor lesions of polypoidal choroidal vasculopathy using contralateral eye findings. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(2):281–291.
11. Singh SR, Oli A, Mohan S, et al. Pachydrusen in Indian population: a hospital-based study. *Indian J Ophthalmol*. 2019;67(3):371–375.
12. Matsumoto H, Mukai R, Morimoto M, et al. Clinical characteristics of pachydrusen in central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(6):1127–1132.
13. Lee J, Kim M, Lee CS, et al. Drusen subtypes and choroidal characteristics in Asian eyes with typical neovascular age-related macular degeneration. *Retina*. 2018;00:1–9.
14. Lee J, Byeon SH. Prevalence and clinical characteristics of pachydrusen in polypoidal choroidal vasculopathy: multimodal image study. *Retina*. 2019;39(4):670–678.
15. Fukuda Y, Sakurada Y, Yoneyama S, et al. Clinical and genetic characteristics of pachydrusen in patients with exudative age-related macular degeneration. *Sci Rep*. 2019;9:11906.
16. Yanagi Y. Pachychoroid disease: a new perspective on exudative maculopathy. *Jpn J Ophthalmol*. 2020;64(4):323–337. https://doi.org/10.1007/s10384-020-00740-5.
17. Cheung CMG, Gan A, Yanagi Y, et al. Association between choroidal thickness and drusen subtypes in age-related macular degeneration. *Ophthalmol Retina*. 2018;2(12):1196–1205.
18. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1995;102(10):1450–1460.
19. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology*. 1995;102(2):205–210.
20. Joachim N, Mitchell P, Rochtchina E, et al. Incidence and progression of reticular drusen in age-related macular degeneration: findings from an older Australian cohort. *Ophthalmology*. 2014;121(4):917–925.
21. Kinouchi R, Ishiko S, Hanada K, et al. A low meat diet increases the risk of open-angle glaucoma in women-the results of population-based, cross-sectional study in Japan. *PLoS One*. 2018;13(10):e0204955.
22. Klein R, Meuer SM, Myers CE, et al. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. *Ophthal Epidemiol*. 2014;21(1):14–23.
23. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*. 1992;99(6):933–943.
24. Varma R, Fraser-Bell S, Tan S, et al. Prevalence of age-related macular degeneration in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology*. 2004;111(7):1288–1297.
25. Obata R, Yanagi Y, Inoue T, et al. Prevalence and factors associated with age-related macular degeneration in a southwestern island population of Japan: the Kumejima Study. *Br J Ophthalmol*. 2018;102(8):1047–1053.
26. Bressler NM, Munoz B, Maguire MG, et al. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities: Waterman Study. *Arch Ophthalmol*. 1995;113(3):301–308.

27. Tikellis G, Robman LD, Dimitrov P, et al. Characteristics of progression of early age-related macular degeneration: the cardiovascular health and age-related maculopathy study. *Eye (Lond)*. 2007;21(2):169−176.
28. Wu Z, Ayton LN, Luu CD, Guymer RH. Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration. *JAMA Ophthalmol*. 2015;133(4):442−448.
29. Klein R, Davis MD, Magli YL, et al. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98(7):1128−1134.
30. Klein R, Klein BE, Jensen SC, et al. Age-related maculopathy in a multiracial United States population: the National Health and Nutrition Examination Survey III. *Ophthalmology*. 1999;106(6):1056−1065.
31. Klein R, Clegg L, Cooper LS, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. *Arch Ophthalmol*. 1999;117(9):1203−1210.
32. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48:452−458.
33. Wong CW, Yanagi Y, Lee WK, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. *Prog Retin Eye Res*. 2016;53:107−139.
34. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-relate maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology*. 2002;109(6):1092−1097.
35. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7−21.
36. Sparrow JM, Dickinson AJ, Duke AM, et al. Seven year follow-up of age-related maculopathy in an elderly British population. *Eye (Lond)*. 1997;11(3):315−324.
37. Cheung CM, Li X, Cheng CY, et al. Prevalence, racial variations, and risk factors of age-related macular degeneration in Singaporean Chinese, Indians, and Malays. *Ophthalmology*. 2014;121(8):1598−1603.
38. Joachim N, Mitchell P, Younan C, et al. Ethnic variation in early age-related macular degeneration lesions between white Australians and Singaporean Asians. *Invest Ophthalmol Vis Sci*. 2014;55(7):4421−4429.
39. Chhablani J, Rao PS, Venkata A, et al. Choroidal thickness profile in healthy Indian subjects. *Indian J Ophthalmol*. 2014;62(11):1060−1063.
40. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. *Invest Ophthalmol Vis Sci*. 2010;51(4):2173−2176.
41. Rahman W, Chen FK, Yeoh J, et al. Repeatability of manual subfoveal choroidal thickness measurements in healthy subjects using the technique of enhanced depth imaging optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52(5):2267−2271.
42. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol*. 2009;147(5):811−815.
43. Ding X, Li J, Zeng J, et al. Choroidal thickness in healthy Chinese subjects. *Invest Ophthalmol Vis Sci*. 2011;52(13):9555−9560.
44. Munch IC, Li XQ, Ahmad SSM, et al. Small hard macular drusen and associations in 11- to 12-year-old children in the Copenhagen Child Cohort 2000 Eye Study. *Invest Ophthalmol Vis Sci*. 2019;60(5):1454−1460.
45. Munch IC, Sander B, Kessel L, et al. Heredity of small hard drusen in twins aged 20−46 years. *Invest Ophthalmol Vis Sci*. 2007;48(2):833−838.
46. Pedersen HR, Gilson SJ, Dubra A, et al. Multimodal imaging of small hard retinal drusen in young healthy adults. *Br J Ophthalmol*. 2018;102(1):146−152.
47. Friedman DS, O'Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122(4):564−572.
48. Hyungtaek Rim T, Ryo K, Tham YC, et al. Prevalence and pattern of geographic atrophy in Asia: the Asian Eye Epidemiology Consortium. *Ophthalmology*. 2020;127:1371−1381.
49. Nakata I, Yamashiro K, Nakanishi H, et al. Prevalence and characteristics of age-related macular degeneration in the Japanese population: the Nagahama Study. *Am J Ophthalmol*. 2013;156(5):1002−1009.
50. Kawasaki R, Wang JJ, Ji GJ, et al. Prevalence and risk factors for age-related macular degeneration in an adult Japanese population: the Funagata Study. *Ophthalmology*. 2008;115(8):1376−1381.
51. Miyake M, Ooto S, Yamashiro K, et al. Pachychoroid neovasculopathy and age-related macular degeneration. *Sci Rep*. 2015;5:16204.
52. Klein R, Klein BE, Tomany SC, et al. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 2002;109(10):1767−1779.
53. Lee JH, Kim JY, Jung BJ, Lee WK. Focal disruptions in ellipsoid zone and interdigitation zone on spectral-domain optical coherence tomography in pachychoroid pigment epitheliopathy. *Retina*. 2019;39(8):1562−1570.
54. Rabiolo A, Sacconi R, Cicinelli MV, et al. Spotlight on reticular pseudodrusen. *Clin Ophthalmol*. 2017;11:1707−1718.
55. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clin Trials*. 1999;20(6):573−600.