



# Design and Baseline Characteristics of the Korean Age-Related Maculopathy Study (KARMS): A Nationwide Multicenter Prospective Observational Study

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**Purpose:** To describe the design and baseline characteristics of the Korean Age-Related Maculopathy Study, a nationwide prospective cohort investigating age-related macular degeneration (AMD) in Koreans.

**Design:** A 5-year prospective observational study conducted across 33 tertiary hospitals and ophthalmology clinics in Korea.

**Participants:** A total of 1159 Korean participants diagnosed with nonexudative or exudative AMD.

**Methods:** Participants aged 50 to 80 years were assigned to the A Study for Intermediate AMD Natural Outcome (ASIANO) arm (nonexudative) or Korean Exudative AMD Treatment Study (KEATS) arm (newly diagnosed exudative AMD). A Study for Intermediate AMD Natural Outcome arm 1 included bilateral intermediate AMD with classic drusen (soft, reticular pseudodrusen, cuticular, or calcified drusen) without advanced AMD. A Study for Intermediate AMD Natural Outcome arm 2 included pachychoroid spectrum disease with unilateral or bilateral findings such as pachydrusen with retinal pigment epithelium undulation, focal attenuation of inner choroidal vessel, and dilated outer choroidal vessels or pigmentary abnormalities corresponding retinal pigment epithelium elevation or disruption in OCT, without significant classic drusen. The KEATS arm comprised active exudative AMD, including typical exudative macular neovascularization, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation. All underwent standardized multimodal imaging at baseline and are followed annually.

**Main Outcome Measures:** Baseline demographic, behavioral, and ocular characteristics across drusen-driven, pachychoroid-driven, and exudative AMD phenotypes.

**Results:** Of the 1409 individuals screened, 1159 were enrolled (ASIANO 1: 551; ASIANO 2: 317; KEATS: 291). A Study for Intermediate AMD Natural Outcome arm 1 participants were older, predominantly female, and universally bilateral; arm 2 participants were younger, more often male, and frequently unilateral. Korean Exudative AMD Treatment Study showed a high proportion of patients with polypoidal choroidal vasculopathy (39.5%, patient-based) and male predominance. Behavioral profiles also differed: the KEATS arm had lower eye-supplement use, higher smoking exposure, and less frequent sunglasses/sun-visor use. Exploratory follow-up analyses suggested differing rates of exudative conversion between ASIANO arm 1 and arm 2.

**Conclusions:** Korean Age-Related Maculopathy Study is the first large-scale, nationally representative prospective cohort in Koreans, distinguishing drusen-driven and pachychoroid-driven maculopathy phenotypes and detailing exudative subtypes. These baseline data provide a foundation for future phenotype-specific progression analyses and management strategies in Asian populations.

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Age-related macular degeneration (AMD) is a progressive degenerative disease of the macula and a leading cause of irreversible central vision loss in older adults.<sup>1</sup> It affects

approximately 200 million people globally, and this number is expected to approach 300 million by 2040, posing a significant public health and socioeconomic

burden worldwide.<sup>2</sup> Large-scale longitudinal studies in Western populations, most notably the Age-Related Eye Disease Study (AREDS) and AREDS 2, have elucidated the natural history of AMD progression and established the protective effects of antioxidant supplementation, particularly in individuals with intermediate AMD.<sup>3–7</sup>

However, these seminal studies were conducted almost exclusively in Caucasian populations, raising concerns about their applicability to Asians. The clinical phenotype of AMD in Asian populations differs significantly from that in Western cohorts. Notably, polypoidal choroidal vasculopathy (PCV) is disproportionately prevalent in Asians, accounting for approximately 33% to 55% of exudative AMD cases, compared to a much lower incidence in Caucasians.<sup>8–10</sup> Moreover, growing evidence suggests that the pachychoroid disease spectrum, encompassing pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and pachychoroid neovascularopathy, plays a significant role in AMD pathogenesis in Asians.<sup>11,12</sup> Pachydrusen, unlike conventional drusen, are associated with increased choroidal thickness and are more frequently observed in Asians than in Western patients.<sup>13</sup> These phenotypic differences imply that AMD classification systems developed in Western populations may fail to capture important features of Asian AMD.

Given the rapidly aging population in Asia and the projected AMD burden of more than 110 million individuals by 2040,<sup>2</sup> there is a critical need to define AMD phenotypes and progression patterns specific to Asians. Yet, to date, few prospective cohort studies in Asian countries have systematically evaluated the natural history, risk factors, and clinical trajectories of AMD subtypes. To address this gap, the Korean Age-Related Maculopathy Study (KARMS) was launched as a nationwide, multicenter, prospective cohort study focused on AMD in Koreans. The study aims to characterize the full spectrum of AMD phenotypes, including typical drusen-driven and pachychoroid-driven forms, and to investigate the relationships between multimodal imaging features and environmental risk factors. Ultimately, this cohort will provide insights into the natural history of AMD in Koreans, including rates of progression to advanced AMD, which may inform ethnicity-specific prediction models and management guidelines.

This report describes the design and baseline characteristics of the KARMS cohort. We detail the study methodology, participant demographics, and cross-sectional ocular findings at enrollment, providing a foundation for future longitudinal analyses on AMD progression in this unique population.

## Methods

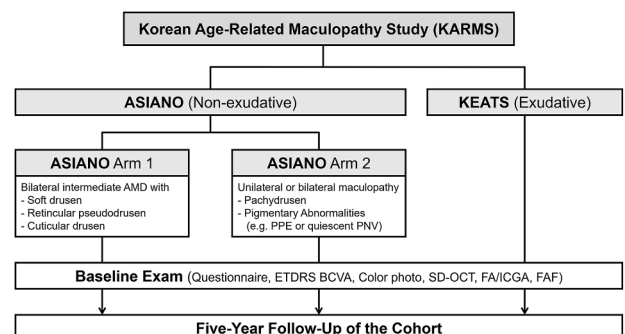
### Study Design and Setting

This study was a nationwide, prospective, multicenter observational cohort study conducted to investigate the clinical characteristics, progression, and treatment outcomes of AMD in Korean patients. Clinical data were collected between August 26, 2015, and March 24, 2023, across 33 tertiary hospitals and clinics in

South Korea, including Samsung Medical Center. The study was originally planned across 32 centers. As the study progressed, 7 additional institutions joined the consortium following the same protocol and regulatory approvals, resulting in 40 participating centers. Of these, 33 centers enrolled eligible participants. The study protocol received ethical approval from the Institutional Review Boards of all participating centers (lead IRB No. SMC-2015-01-109). Each subject provided written informed consent after an explanation of the nature and possible consequences of the study. Participant confidentiality was maintained according to the tenets of the Declaration of Helsinki and local privacy laws. The study was registered in the Clinical Research Information Service (cris.nih.go.kr; registration number KCT0010675). The list of participating institutions is provided in [Supplemental Material 1](#) (available at [www.opthalmologyscience.org](http://www.opthalmologyscience.org)).

### Participants and Cohort Categorization

Eligible participants were Korean adults aged 50 to 80 years who were diagnosed with either nonexudative AMD or exudative AMD. The overall process of subject selection and cohort assignment is illustrated in [Figure 1](#). In brief, participants with nonexudative AMD without evidence of advanced AMD are assigned to A Study for Intermediate AMD Natural Outcome (ASIANO) arm, while those with newly diagnosed exudative AMD, including PCV or retinal angiomatous proliferation (RAP), were assigned to Korean Exudative AMD Treatment Study (KEATS) arm. The ASIANO arm was further subdivided into 2 groups based on clinical phenotypes. A Study for Intermediate AMD Natural Outcome arm 1 included participants with classic bilateral intermediate AMD, defined by the presence of classic drusen (e.g., soft drusen, reticular pseudodrusen [RPD], cuticular drusen, and calcified drusen) without signs of advanced AMD, representing a drusen-driven phenotype. A Study for Intermediate AMD Natural Outcome arm 2 included participants representing unilateral or bilateral pachychoroid-spectrum disease features such as drusen-like deposition (or also called pachydrusen) with retinal pigment epithelium (RPE) undulation, focal attenuation of inner choroidal vessel, and dilated outer choroidal vessels with RPE elevation or disruption, or retinal pigmentary changes with corresponding RPE elevation or disruption on OCT (which represent pachychoroid pigment epitheliopathy or nonexudative pachychoroid neovascularopathy) without significant classic drusen. The detailed inclusion and exclusion criteria are described in [Table 1](#).



**Figure 1.** Flowchart of subject selection. ASIANO = A Study for Intermediate AMD Natural Outcome; BCVA = best-corrected visual acuity; FA = fluorescein Angiography; FAF = fundus autofluorescence; ICGA = indocyanine green angiography; KEATS = Korean Exudative AMD Treatment Study; SD-OCT = spectral-domain OCT.

Table 1. Inclusion and Exclusion Criteria for the ASIANO and KEATS Arms

## ASIANO (A Study for Intermediate AMD Natural Outcome) Arm

## Inclusion criteria

1. Korean men or women aged 50–80 yrs at the time of screening.
2. Diagnosis within the previous 12 mos, as follows:

Arm 1: Bilateral intermediate AMD according to the AREDS protocol by the US National Eye Institute.

Arm 2: Presence of  $\geq 1$  of the following lesions in at least one eye:

- a. Drusen-like deposition (pachydrusen) with RPE elevation (undulation) on spectral-domain OCT (SD-OCT).
- b. Focal attenuation of inner choroidal vessel and dilated outer choroidal vessels with RPE elevation (undulation) on SD-OCT.
- c. Retinal pigmentary change detected on fundus examination or focal irregular fluorescence on fundus autofluorescence imaging, with corresponding RPE elevation (undulation) or RPE disruption on SD-OCT.
  3. Neither eye meets the definition of advanced AMD.
  4. Media clarity sufficient to obtain high-quality color fundus photographs allowing clear visualization of macular lesions.
  5. Willingness to return annually for at least 5 years for follow-up examinations.
  6. Provision of written informed consent after full explanation of the study.

## Exclusion criteria

1. Ocular comorbidities other than intermediate AMD that may affect the vitreoretina or macular structure, including advanced AMD, diabetic retinopathy worse than moderate nonproliferative diabetic retinopathy, macular epiretinal membrane likely to reduce vision, optic atrophy, pathologic myopia, macular hole, retinal vascular disease, choroidal nevus, uveitis, amblyopia, or choroidal neovascularization of etiologies other than AMD.
2. High myopia of  $\leq -6.5$  diopters or axial length  $>26.5$  mm.
3. Ocular media of insufficient clarity to obtain adequate imaging.
4. History of intraocular surgery other than uncomplicated cataract surgery that might influence AMD progression (including vitrectomy).
5. Prior macular laser treatment, photodynamic therapy, or anti-VEGF therapy.
6. Systemic or ocular disease requiring continuous administration of drugs known to be toxic to the retina or optic nerve.
7. Intraocular pressure  $>26$  mmHg, previous glaucoma filtration surgery, or expectation of such surgery.
8. Anticipated inability to complete the follow-up for  $\geq 5$  yrs.
9. Past or current systemic or intraocular antiangiogenic therapy for malignancy or ocular disease.
10. History of allergy to fluorescein or indocyanine green dye.

## KEATS (Korean Exudative AMD Treatment Study) Arm

## Inclusion criteria

1. Korean men or women aged 50–80 years at the time of screening.
2. Newly diagnosed exudative AMD in at least one eye, confirmed by SD-OCT, fluorescein angiography, and indocyanine green angiography as choroidal neovascularization, PCV, or RAP.
3. Media clarity sufficient to obtain high-quality color fundus photographs allowing clear visualization of macular lesions.
4. Willingness to return annually for at least 5 years for follow-up examinations.
5. Provision of written informed consent after full explanation of the study.

## Exclusion criteria

1. Ocular comorbidities other than AMD that may affect the vitreoretinal or macular structure, including diabetic retinopathy worse than moderate nonproliferative diabetic retinopathy, macular epiretinal membrane likely to reduce vision, optic atrophy, pathologic myopia, macular hole, retinal vascular disease, choroidal nevus, uveitis, amblyopia, or choroidal neovascularization of etiologies other than AMD.
2. High myopia of  $\leq -6.5$  diopters or axial length  $>26.5$  mm.
3. Ocular media of insufficient clarity to obtain adequate imaging.
4. History of intraocular surgery other than uncomplicated cataract surgery that might influence AMD progression (including vitrectomy).
5. Systemic or ocular disease requiring continuous administration of drugs known to be toxic to the retina or optic nerve.
6. Intraocular pressure  $>26$  mmHg, previous glaucoma filtration surgery, or expectation of such surgery.
7. Anticipated inability to complete the follow-up for  $\geq 5$  yrs.
8. Past or current systemic or intraocular antiangiogenic therapy for malignancy or ocular disease.
9. History of allergy to fluorescein or indocyanine green dye.

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; ASIANO = A Study for Intermediate AMD Natural Outcome; KEATS = Korean Exudative AMD Treatment Study; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; RPE = retinal pigment epithelium.

## Baseline Examination and Data Collection

All participants underwent a comprehensive ophthalmic evaluation and completed questionnaires at baseline. Examinations included best-corrected visual acuity using ETDRS charts,

intraocular pressure measurement, slit-lamp biomicroscopy, and dilated fundus examination by a retina specialist. Multimodal imaging was performed following a standardized protocol across sites, including color fundus photography, spectral-domain OCT volume scans, fundus autofluorescence, fluorescein angiography,

and indocyanine green angiography. OCT angiography was additionally obtained at available sites but was not part of the core protocol. Questionnaires capturing demographic data, systemic comorbidities, and AMD-related behavioral risk factors were administered at baseline. Annual follow-up visits were scheduled for a 5-year period. Treatment decisions, including the use of anti-VEGF therapy in the KEATS arm or in ASIANO participants who converted to exudative AMD, were made at the discretion of the treating physician. A summary of clinical assessments and questionnaires administered at each visit is presented in Table 2. The full study protocol and materials, including data collection instruments, are available in English translation as supplemental materials (Supplemental Materials 2–4, available at [www.ophtalmologyscience.org](http://www.ophtalmologyscience.org)).

## Multimodal Imaging Interpretation

Imaging characteristics were interpreted by 16 graders (S.H., S.W.K., S.J.K., K.H.P., J.O., Y.-J.C., S.H.B., K.Y.S., J.C., M.S., K.K., D.D.-J.H., Y.-H.P., H.L., E.J.C., and J.L.) to ascertain the existence of soft drusen, RPD, cuticular drusen, pachydrusen (or drusen-like deposits), and pigmentary abnormality. Soft drusen were classified as yellowish-white, elevated deposits exceeding 63  $\mu\text{m}$  in size with indistinct peripheries on color fundus photography,<sup>14</sup> exhibiting confluent formations, and situated beneath the RPE as observed through OCT. Reticular pseudodrusen were distinguished by yellowish interwoven patterns on color fundus photography, hyporeflective regions on infrared reflectance imaging, and corresponding subretinal drusenoid deposits evident on OCT.<sup>15</sup> Cuticular drusen were recognized as numerous small, spherical lesions that manifested hyperfluorescence on fluorescein angiography, displaying a distinct “stars-in-the-sky” configuration.<sup>16</sup> Pachydrusen, alternatively referred to as drusen-like deposits, were delineated as isolated or dispersed yellow-white lesions exceeding 125  $\mu\text{m}$ , characterized by irregular yet well-defined borders, located beneath the RPE as revealed by OCT.<sup>13</sup> Pigmentary abnormality was characterized as regions of hypopigmentation or hyperpigmentation of the RPE within the macular region, as depicted on color fundus photography.<sup>17</sup> In the case of exudative AMD, classification into typical exudative macular neovascularization (MNV), PCV, and RAP was based on the type of MNV and the presence of polypoidal lesions on fluorescein and indocyanine green imaging.<sup>18,19</sup> All image graders were board-certified retinal specialists and academic faculty at tertiary referral centers and applied prespecified, standardized imaging definitions agreed upon prior to study initiation. Each case underwent independent evaluation by 2 specialists; any discrepancies were resolved by adjudication from the principal investigator (S.W.K.).

## Data Analysis

This report focuses on descriptive analysis of baseline characteristics. We summarized demographic variables, systemic risk factors, and behavioral factors by cohort using means ( $\pm$  standard deviation) or proportions as appropriate. For each baseline variable, global 3-group comparisons were performed using multivariable regression models adjusting for age and sex to assess overall differences across ASIANO arm 1, ASIANO arm 2, and KEATS. Linear regression models were used for continuous outcomes and logistic (or multinomial logistic) regression models for categorical outcomes, with global significance assessed using omnibus tests for the group variable. Pairwise comparisons were prespecified and made for (1) ASIANO arm 1 versus ASIANO arm 2, to compare drusen-driven and pachychoroid-driven

phenotypes, and (2) ASIANO (arms 1 and 2 combined) versus KEATS, to contrast nonexudative and exudative AMD. To address multiple testing and control of type I error, false discovery rate control was applied using the Benjamini–Hochberg procedure. All *P* values were interpreted as exploratory rather than confirmatory, consistent with the descriptive aim of this baseline cohort report. Data analysis was performed using R (version 4.3.1; R Foundation for Statistical Computing).

## Results

Of the 1409 individuals screened, 250 were excluded due to screening failure or withdrawal of consent. A total of 1159 Korean participants aged 50 to 80 years were enrolled between August 2015 and March 2023, including 551 in ASIANO arm 1, 317 in ASIANO arm 2, and 291 in the KEATS arm. Figure 2 presents a Venn diagram summarizing the ocular findings that constitute each study arm. In ASIANO arm 1, which included participants with classic bilateral drusen, all eyes exhibited bilateral disease. Among 1102 eyes (from 551 participants), 871 (79.0%) had soft drusen, 554 (49.4%) had RPD, and 238 (21.6%) had cuticular drusen. Soft drusen and RPD were the predominant drusen subtypes in this group, and 36.7% of eyes had both soft drusen and RPD. Calcified drusen were observed in 65 eyes (5.9%), and pigmentary changes were noted in 209 eyes (19.0%). In ASIANO arm 2, among 634 eyes (from 317 participants), 401 eyes (63.2%) had pachydrusen, and 314 eyes (49.5%) showed pigmentary abnormalities. A total of 174 eyes (27.4%) exhibited both pachydrusen and pigmentary changes. Ninety-three patients (29.3%) exhibited unilateral involvement, with no evidence of pachydrusen or pigmentary abnormalities in the fellow eye. In the KEATS arm (315 eyes from 291 patients), the most common subtype was typical exudative AMD, observed in 137 eyes (43.5%, eye-based), followed by PCV in 125 eyes (39.7%), and RAP in 53 eyes (16.8%). At baseline, 24 participants (8.2%, patient-based) in the KEATS arm presented with bilateral exudative AMD.

Table 3 summarizes the baseline demographic and behavioral characteristics of participants in the ASIANO and KEATS arms. Compared to ASIANO arm 2, participants in ASIANO arm 1 were on average more than 6 years older and had a significantly higher proportion of females (77.1% in ASIANO 1 vs. 49.8% in ASIANO 2). Participants in ASIANO arm 1 reported a higher prevalence of current eye supplement use at baseline compared with those in ASIANO arm 2. No other significant differences were observed between the 2 ASIANO arms at baseline. Compared to the ASIANO group, participants in the KEATS arm were older and predominantly male (64.6%). The KEATS arm had the lowest rate of eye supplement use at baseline visit. While total sunlight exposure time at baseline was comparable between groups, the frequency of wearing sunglasses or a sun visor was significantly lower in the KEATS arm than in the ASIANO arm.

Of the 1159 enrolled participants, 485 (41.8%) completed all 6 scheduled visits (V1 to V6). Specifically, 196 of 551 participants in ASIANO arm 1 (35.6%), 139 of 317 in ASIANO arm 2 (43.8%), and 150 of 291 in the

Table 2. Overview of Assessments and Procedures Performed at Each Scheduled Visit

	Visit 1 (Baseline)	Visit 2 (1 Yr)	Visit 3 (2 Yrs)	Visit 4 (3 Yrs)	Visit 5 (4 Yrs)	Visit 6 (5 Yrs)
Informed consent	○					
Inclusion/exclusion criteria met	○					
Demographics/ophthalmic & nonophthalmic medical history	○					○
Physical measurements	○					
Best-corrected visual acuity, refraction, intraocular pressure	○	○	○	○	○	○
Slit-lamp biomicroscopy	○	○	○	○	○	○
Color fundus photo	○	○	○	○	○	○
OCT	○	○	○	○	○	○
Fundus autofluorescence imaging	○	○	○	○	○	○
Fluorescein angiography	○					
Indocyanine green angiography	○					
Questionnaire	○		○			○
Ophthalmic treatment history	○	○	○	○	○	○

KEATS arm (51.5%) completed V6. The remaining participants were lost to follow-up, mainly due to the coronavirus disease 2019 pandemic. Detailed visit completion data are presented in Table 4. Among ASIANO participants who completed 5-year follow-up, descriptive analyses showed a higher proportion of exudative conversion in ASIANO arm

1 compared with ASIANO arm 2. Specifically, 40 of 196 participants in ASIANO arm 1 progressed to exudative AMD over 5 years (20.4%; 95% confidence interval, 14.8–26.0), whereas 7 of 139 participants in ASIANO arm 2 showed exudative conversion (5.0%; 95% confidence interval, 1.4–8.7).

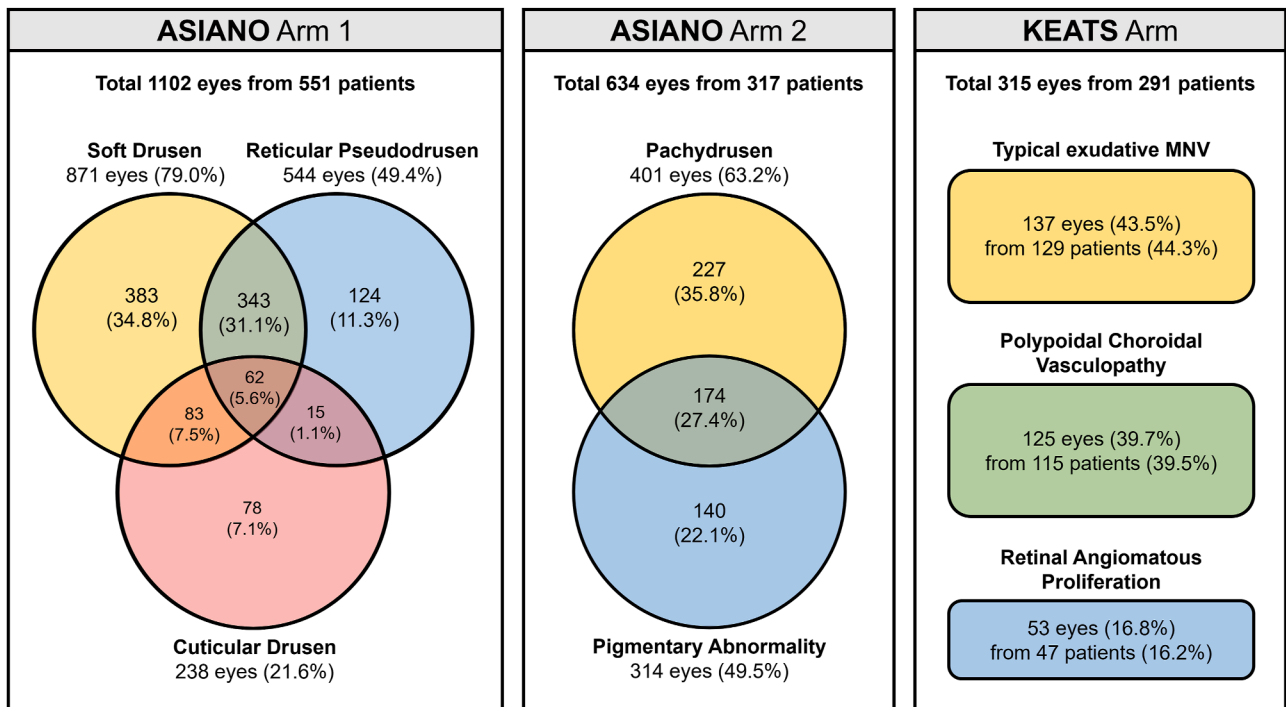


Figure 2. Venn diagram summarizing the eye-based distribution of key ocular findings in each study arm. ASIANO arm 1: soft drusen and reticular pseudodrusen were the predominant findings, with a substantial overlap. ASIANO arm 2: pachydrusen and pigmentary abnormalities were the defining features, frequently co-occurring. Korean Exudative AMD Treatment Study arm: classification of exudative AMD subtypes, including typical exudative macular neovascularization (MNV), polypoidal choroidal vasculopathy, and retinal angiomatous proliferation. AMD = age-related macular degeneration; ASIANO = A Study for Intermediate AMD Natural Outcome; KEATS = Korean Exudative AMD Treatment Study.

Table 3. Baseline Characteristics of Participants in the ASIANO and KEATS Arms

	ASIANO 1	ASIANO 2	KEATS	Global P Value	P Value* (ASIANO 1 vs. 2)	P Value* (ASIANO vs. KEATS)
Number of patients	551	317	291			
Age at baseline, yr						
Average $\pm$ SD	70.7 $\pm$ 6.8	64.0 $\pm$ 7.6	69.4 $\pm$ 7.2	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.010</b>
Sex						
Male	126 (22.9)	159 (50.2)	188 (64.6)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Female	425 (77.1)	158 (49.8)	103 (35.4)			
Systemic comorbidities						
Hypertension	251 (49.2)	104 (33.9)	117 (45.0)	0.581	0.804	0.987
Diabetes mellitus	104 (20.4)	56 (18.2)	43 (16.5)	0.160	0.919	0.220
Dyslipidemia	179 (35.1)	90 (29.3)	62 (23.8)	0.284	1.000	0.273
Stroke	16 (3.1)	6 (2.0)	6 (2.3)	0.573	0.917	0.665
Myocardial infarct	9 (1.8)	6 (2.0)	7 (2.7)	0.866	0.919	0.987
Osteoarthritis	79 (15.5)	34 (11.1)	26 (10.0)	<b>0.005</b>	0.225	0.220
Rheumatoid arthritis	29 (5.7)	3 (1.0)	7 (2.7)	0.654	0.813	0.999
Asthma	23 (4.5)	9 (2.9)	8 (3.1)	<b>0.032</b>	0.225	0.987
Pulmonary tuberculosis	32 (6.3)	23 (7.5)	14 (5.4)	0.897	0.919	0.987
Chronic kidney disease	4 (0.8)	1 (0.3)	2 (0.8)	0.293	1.000	0.293
Depression	25 (4.9)	10 (3.3)	5 (1.9)	0.918	0.919	0.987
Dementia	5 (1.0)	0 (0.0)	0 (0.0)	0.576	0.947	0.562
Any cancer	58 (11.4)	23 (7.5)	25 (9.6)	0.184	1.000	1.000
Previous medicine (>3 mos)						
Aspirin	104 (20.4)	41 (13.4)	50 (19.2)	0.867	0.919	0.999
Anticoagulant	37 (7.3)	20 (6.5)	15 (5.8)	0.497	0.657	0.999
Nutritional supplements						
Eye supplement	279 (54.7)	88 (28.7)	57 (21.9)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Multivitamins	109 (21.4)	71 (23.1)	54 (20.8)	0.445	0.657	0.987
Calcium supplement	60 (11.8)	19 (6.2)	14 (5.4)	0.404	0.657	0.865
Omega-3	98 (19.2)	56 (18.2)	40 (15.4)	0.848	1.000	0.837
Red ginseng	72 (14.1)	41 (13.4)	44 (16.9)	0.200	1.000	0.22
Smoking						
Never	429 (84.1)	190 (61.9)	139 (53.5)	0.218	0.784	0.312
Past	58 (11.4)	79 (25.7)	79 (30.4)			
Current	23 (4.5)	38 (12.4)	42 (16.2)			
Total pack-year	3.4 $\pm$ 11.8	8.2 $\pm$ 16.3	12.0 $\pm$ 18.0	0.098	1.000	0.148
Alcohol						
Never	364 (71.4)	148 (48.2)	114 (43.8)	0.145	0.919	0.174
Past	32 (6.3)	24 (7.8)	40 (15.4)			
Current	114 (22.4)	135 (44.0)	106 (40.8)			
Physical activity						
Inactive	11 (2.2)	4 (1.3)	1 (0.4)	0.843	0.919	0.999
Low activity	125 (24.5)	55 (17.9)	58 (22.3)			
Active	257 (50.4)	149 (48.5)	134 (51.5)			
Highly active	117 (22.9)	99 (32.2)	67 (25.8)			
Screen device uses per day						
Television, min	210.6 $\pm$ 137.9	180.2 $\pm$ 136.2	211.2 $\pm$ 152.3	0.615	1.000	0.562
Computer, min	24.1 $\pm$ 65.1	55.8 $\pm$ 107.9	33.2 $\pm$ 89.3	0.254	0.919	0.273
Mobile phone, min	37.4 $\pm$ 61.0	47.1 $\pm$ 60.6	40.5 $\pm$ 79.6	0.133	0.334	0.912
Total, min	272.1 $\pm$ 160.4	283.1 $\pm$ 172.1	285.0 $\pm$ 201.4	0.895	0.919	0.987
Sunlight exposure						
Minutes per week	49.1 $\pm$ 61.2	51.3 $\pm$ 54.8	63.1 $\pm$ 73.5	0.113	0.386	0.562
Sunglasses use on weekdays						
Rarely	183 (35.9)	136 (44.3)	141 (54.2)	<b>&lt;0.001</b>	0.768	<b>0.002</b>
Occasionally	117 (22.9)	73 (23.8)	57 (21.9)			
Frequently	31 (6.1)	21 (6.8)	18 (6.9)			
Almost always	179 (35.1)	77 (25.1)	44 (16.9)			
Sunglasses use on weekends						
Rarely	186 (36.5)	122 (39.7)	137 (52.7)	<b>&lt;0.001</b>	0.925	<b>0.002</b>

Table 3. (Continued.)

	ASIANO 1	ASIANO 2	KEATS	Global P Value	P Value* (ASIANO 1 vs. 2)	P Value* (ASIANO vs. KEATS)
Occasionally	117 (22.9)	75 (24.4)	56 (21.5)			
Frequently	23 (4.5)	24 (7.8)	20 (7.7)			
Almost always	184 (36.1)	86 (28.0)	47 (18.1)			

ASIANO = A Study for Intermediate AMD Natural Outcome; KEATS = Korean Exudative AMD Treatment Study; SD = standard deviation.

Data are presented as mean  $\pm$  standard deviation for continuous variables and as number (percentage) for categorical variables.

Initial questionnaires were completed by 510 participants in the ASIANO arm 1, 307 in the ASIANO arm 2, and 260 in the KEATS arm; some data were missing due to incomplete responses.

P values were obtained from multivariable regression models adjusted for age and sex and should be interpreted as exploratory.

Bold values indicate statistical significance ( $P < 0.05$ ).

\*P values were additionally adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate method.

## Discussion

This nationwide, prospective, multicenter cohort provides a nationally representative baseline characterization of Korean patients with AMD. Broad geographic sampling across 33 tertiary centers, standardized multimodal imaging, and harmonized phenotype definitions strengthen the external validity of these findings for Korean clinical practice and research.

A key feature of this study is the deliberate separation of age-related maculopathies into drusen-driven (ASIANO arm 1) and pachychoroid-driven (ASIANO arm 2) phenotypes. Participants in ASIANO arm 1 were older, more likely to be female, and universally had bilateral disease, consistent with conventional AMD patterns described in Western studies such as AREDS and AREDS 2.<sup>5,20</sup> In contrast, ASIANO arm 2 included a younger and more male-predominant population, with a higher prevalence of unilateral involvement and minimal classic drusen, aligning with previously reported features of pachychoroid pigment epitheliopathy and pachydrusen in Asian populations.<sup>21</sup> Although pachydrusen and pigmentary abnormality frequently co-occurred, a substantial proportion of eyes exhibited pigmentary abnormality in the absence of pachydrusen. Notably, PCV often presents without background drusen,<sup>22</sup> and eyes with pigmentary abnormality but no significant drusen in the fellow eye have been reported

to carry a higher risk of exudative conversion.<sup>23</sup> Taken together, these findings reinforce the notion that pachychoroid-driven disease represents an independent disease pathway not adequately captured by traditional drusen-centric classification systems. Notably, descriptive 5-year incidence estimates indicate a substantially higher rate of exudative conversion in the drusen-driven group compared with the pachychoroid-driven group. Although these findings are descriptive and based on participants with complete follow-up, and may be influenced by loss to follow-up, they support the biological plausibility that drusen-driven and pachychoroid-driven maculopathies represent distinct disease pathways with different progression risks. More detailed risk estimation will be presented in future longitudinal analyses.

The KEATS arm, comprising newly diagnosed exudative AMD, including PCV and RAP, further highlights the unique distribution of AMD subtypes in the Korean population. The high proportion of PCV (40% of wet AMD) and the marked male predominance are consistent with previous reports from Asian populations,<sup>9</sup> yet contrast with Western cohorts, where typical MNV and female predominance are more common.<sup>10,24</sup> These findings underscore the need for ethnicity-specific models for AMD classification, prognosis, and treatment response prediction.

Baseline cross-sectional comparisons suggested that the KEATS arm had lower rates of eye supplement use and less

Table 4. Visit Completion Status in the ASIANO and KEATS Arms

	Total	ASIANO 1	ASIANO 2	KEATS
Total	1159 (100.0)	551 (100.0)	317 (100.0)	291 (100.0)
Visit 1 only	323 (27.9)	176 (31.9)	85 (26.8)	62 (21.3)
Visit 1 through visit 2	108 (9.3)	54 (9.8)	26 (8.2)	28 (9.6)
Visit 1 through visit 3	94 (8.1)	53 (9.6)	22 (6.9)	19 (6.5)
Visit 1 through visit 4	65 (5.6)	32 (5.8)	15 (4.7)	18 (6.2)
Visit 1 through visit 5	84 (7.2)	40 (7.3)	30 (9.5)	14 (4.8)
Visit 1 through visit 6	485 (41.8)	196 (35.6)	139 (43.8)	150 (51.5)

ASIANO = A Study for Intermediate AMD Natural Outcome; KEATS = Korean Exudative AMD Treatment Study.

The table shows the proportion of enrolled participants who completed each follow-up Visit (Visit 1 through Visit 6) in the ASIANO and KEATS Cohorts.

Of the 1409 individuals screened, 250 were excluded due to screening failure or withdrawal of consent, resulting in a total of 1159 participants enrolled in the study.

frequent use of sunglasses or sun visors despite similar total sunlight exposure time. These differences in behavioral factors should be interpreted cautiously. All behaviors were assessed as self-reported current practices at the baseline visit, and information on the timing of behavior initiation relative to AMD diagnosis was not systematically collected; therefore, reverse causation cannot be excluded. In particular, higher supplement use observed in some groups may reflect behavioral modification following diagnosis or physician counseling rather than underlying etiologic differences. Accordingly, these findings are best viewed as descriptive and hypothesis-generating. Although causality cannot be inferred from these cross-sectional data, the observed patterns highlight potentially modifiable behaviors that warrant further evaluation in longitudinal analyses, including whether improved photoprotection and sustained supplement adherence might be associated with reduced incident exudation or altered treatment needs.<sup>25</sup> These findings also point to actionable opportunities for patient education and risk communication at the clinic level.

A key strength of this study is its conceptual framework that prospectively partitions age-related maculopathies into drusen-driven and pachychoroid-driven phenotypes using prespecified multimodal imaging criteria within a large, nationally representative cohort. This approach challenges the conventional drusen-centric view of AMD. Notably, the pachychoroid-driven phenotype was frequently unilateral and characterized by pigmentary abnormalities in the absence of significant drusen, indicating that pachychoroid-related disease cannot be defined solely by pachydrusen or drusen-like deposits. The observed differences in 5-year exudative conversion between phenotypes further suggest that this classification has potential prognostic relevance, although these findings should be interpreted cautiously given the descriptive and exploratory nature of the analyses. In contrast to prior Asian cohorts largely based on fundus-photography grading,<sup>26–28</sup> KARMS provides harmonized, multimodal phenotyping across a nationwide tertiary-center network, enabling phenotype-specific and ethnicity-informed risk modeling.

Several limitations should be acknowledged. First, the current analysis is based solely on cross-sectional baseline data; longitudinal follow-up will be necessary to determine actual progression rates and validate risk models, and such analyses are planned. Second, because the study began in 2015, OCT angiography was not widely available at baseline. While this did not affect classification into exudative versus nonexudative AMD, it limited our ability to evaluate potentially useful biomarkers such as the presence of

quiescent MNV at enrollment. Accordingly, it was not possible to distinguish pachychoroid pigment epitheliopathy from nonexudative pachychoroid neovascuopathy in ASIANO arm 2. Where available, OCT angiography data may be leveraged in future analyses to further characterize subclinical neovascular features and refine phenotype classification and risk stratification. Third, lifestyle-related factors such as smoking and photoprotection were self-reported, introducing the potential for recall bias. Fourth, the upper age limit of 80 years may limit generalizability to very elderly populations. This criterion was selected to enhance feasibility and reliability of long-term follow-up and to reduce confounding from competing mortality and non-AMD-related visual impairment. Fifth, most importantly, follow-up loss was substantial, with only 41.8% of participants completing all 6 scheduled annual visits. Attrition was particularly concentrated after the first visit, meaning a substantial proportion of patients did not contribute longitudinal data. Much of this loss coincided with the COVID-19 pandemic.<sup>29</sup> This relatively high loss to follow-up rate may introduce selection bias, particularly if follow-up completion is associated with disease severity, treatment burden, or other unmeasured factors, and may limit the generalizability of progression estimates and subgroup comparisons. Differential follow-up completion rates between subgroups (e.g., KEATS vs. ASIANO) further emphasize the need for bias mitigation strategies, such as inverse probability weighting and sensitivity analyses comparing complete-case and weighted models.

Future work will leverage the prospective design to (1) estimate the incidence of exudation and geographic atrophy in ASIANO arm 1 and arm 2; (2) test for effect modification by age, sex, and phenotype; (3) evaluate treatment-response heterogeneity among typical MNV, PCV, and RAP; (4) perform fellow-eye risk stratification; and (5) conduct longitudinal analyses of changes in smoking, photoprotection, and supplement use to clarify whether targeted interventions can modify progression risk.

In conclusion, the KARMS cohort provides nationally representative baseline data characterizing drusen-driven and pachychoroid-driven maculopathies in Koreans. These findings underscore phenotypic heterogeneity and suggest the need for AMD classification systems that reflect ethnic diversity and regional phenotype distribution, while recognizing the descriptive nature of the present analyses. Forthcoming longitudinal analyses from KARMS will further elucidate the natural history of AMD in Asians and help guide phenotype-specific, personalized management approaches.

## Footnotes and Disclosures

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#### Abbreviations and Acronyms:

**AMD** = age-related macular degeneration; **AREDS** = Age-Related Eye Disease Study; **ASIANO** = A Study for Intermediate AMD Natural Outcome; **KARMS** = Korean Age-Related Maculopathy Study; **KEATS** = Korean Exudative AMD Treatment Study; **MNV** = macular neovascularization; **PCV** = polypoidal choroidal vasculopathy; **RAP** = retinal angiomatous proliferation; **RPD** = reticular pseudodrusen; **RPE** = retinal pigment epithelium.

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