Ten-Year Progression From Intermediate to Exudative Age-Related Macular Degeneration and Risk Factors: Bundang AMD Cohort Study Report 1

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• PURPOSE: This study investigated the 10-year incidence of progression from intermediate to exudative age-related macular degeneration (AMD) and identified genetic and environmental factors influencing that progression in the Korean population.
• DESIGN: Retrospective, observational cohort study.
• METHODS: In total, 632 eyes of 418 patients (age: ≥50 years) with intermediate AMD were enrolled. The incidence of exudative AMD was assessed from color fundus photographs and optical coherence tomography images obtained at baseline and during annual visits. Data regarding lifestyle variables and dietary habits were acquired through comprehensive questionnaires. Genotyping data concerning 3 single nucleotide polymorphisms (SNPs), rs800292 and rs1061170 in the CFH gene and rs10490924 in *ARMS2* were also analyzed. The cumulative incidence of exudative changes was estimated using Kaplan-Meier analysis. Associated influential factors were evaluated using univariate and multivariate Cox regression models.
• RESULTS: The mean follow-up period was 3.99 ± 2.85 years. The cumulative incidence of progression to exudative AMD was 5.6%, 14.8%, and 28.4% at 2, 5, and 10 years, respectively. Multivariate Cox analysis showed that age (hazard ratio [HR]: 1.041; $P = .0393$), family history of AMD (HR: 3.175; $P = .0184$), and preexisting exudative AMD in the fellow eye (HR: 3.186; $P = 5.31 \times 10^{-5}$) were positively associated with exudative changes. Regular intake of green tea (HR: 0.632; $P = .0475$) was associated with a decrease in exudative changes. The *ARMS2* SNP rs10490924 (HR: 1.482; $P = .0185$) showed a significant association with AMD progression.
• CONCLUSIONS: The annual progression rate from intermediate to exudative AMD in the Korean population is approximately 2.8%, which is comparable with that for whites. Intake of green tea may be a modifiable protective factor against exudative changes. (Am J Ophthalmol 2021;224:228–237. © 2020 Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS A leading cause of blindness among adults ≥50 years of age worldwide.[1–7] Similar to the prevalence in Western populations, the prevalence of AMD in Asians continues to increase, and the socioeconomic burden associated with AMD is soon expected to become significant.[8,9] However, most AMD studies have been conducted predominantly in white subjects, and studies in Asian populations are limited by conflicting results.[8,10–14] The Age-Related Eye Disease Study (AREDS), a major clinical trial that recently reported 10-year follow-up data, revealed the natural history and progression rate of AMD, risk factors for advanced AMD, and effects of antioxidants.[15–19] However, 96% of participants in that trial were whites, and <1% were Asians. Similarly, the Age, Gene/Environment Susceptibility Study (AGES), the Beaver Dam Eye Study, the Rotterdam Eye Study, and the Blue Mountain Eye Study were also studies of populations of European ancestry.[1,20–22] Although those large-scale studies have reported the outcomes of AMD progression in whites, it is not reasonable to assume that similar results would be obtained for Asian subjects. AMD is a multifactorial disorder triggered by multiple genes in combination with lifestyle and environmental factors. That suggests the presence of ethnic and regional differences in the development and progression of AMD. Therefore, a comprehensive analysis covering genetic and environmental factors is required. Clinical manifestations of AMD in Asians are, in fact, known to be somewhat different from those in whites, including a lower frequency of bilaterality, a relative lack of drusen in the affected and fellow eyes, and a high frequency of polypoidal choroidal vasculopathy.[9] Recently, it was reported that an East Asian-specific polymorphism in the *CEPT* gene, Asp442Gly (rs2303790), is associated with an increase in the risk and incidence of AMD in East Asians and may have a distinct genetic signature.[23] That observation

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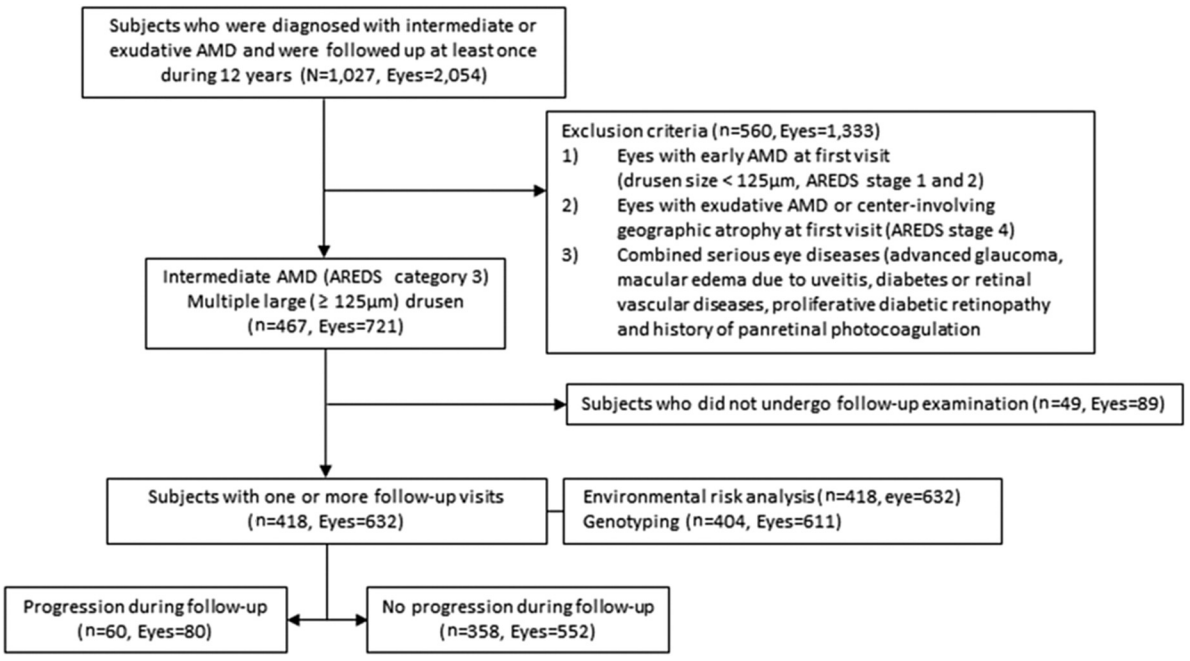


FIGURE 1. Flow chart illustrates the number of subjects and eyes with age-related macular degeneration who participated in the study and the reasons for exclusion.

suggests that there may be differences between the triggers and patterns for AMD progression in Asians and those in whites.[24] Although several studies on the prevalence of AMD in Asians have been reported, there is no well-established study of the long-term rate of progression from intermediate to exudative AMD and the associated influential factors in Asian populations.

The aims of the present study were to investigate the 10-year incidence of progression from intermediate to exudative AMD and to comprehensively analyze genetic and environmental factors influencing exudative changes in the Korean population.

METHODS

• **STUDY DESIGN:** This retrospective, observational cohort study was conducted at Seoul National University Bundang Hospital. Institutional Review Board approval was obtained (IRB no: B-1701-377-103), and all participants provided written informed consent. In this cohort, a total of 1,027 participants ≥50 years of age, newly diagnosed with both intermediate AMD and exudative AMD between October 1, 2003, and December 31, 2016, were enrolled (Figure 1). In this study, only the patients with diagnoses of intermediate AMD at the initial visit were sorted and analyzed. The diagnosis of intermediate AMD was based on the international AMD classification[25] and patients eligible for AREDS category 3 were enrolled, based particularly on the presence of multiple large (≥125-μm) drusen on the macula with or without pigmentation changes and the absence of pre-existing signs of central geographic atrophy and exudative AMD. The exclusion criteria are shown in Figure 1. Progression to geographic atrophy during the follow-up period was not excluded.

• **INTERVIEWS AND EXAMINATIONS:** Questionnaires were administered to collect information regarding influential factors (Table 1, Supplemental Table S1). At the first visit, all patients underwent general physical examinations including body mass index (BMI), blood pressure measurements, and a comprehensive ophthalmologic examination including assessment of best-corrected visual acuity, manifest refraction, and intraocular pressure, slit-lamp biomicroscopy, fundus examination, color fundus photography, and optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Measurements of best-corrected visual acuity, color fundus photography, and OCT were usually performed at 6- to 12-month intervals in the absence of visual symptoms.

• **EVALUATION OF AMD PROGRESSION:** In case of subjective or objective visual deterioration or suspicion of exudative changes in fundus examination or photography, fluorescein angiography, indocyanine green angiography (Heidelberg retina angiography; Heidelberg Engineering), and OCT were performed to confirm the progression to exudative AMD. Progression from intermediate to exudative AMD was defined by evidence of choroidal neovascularization (CNV) associated with nondrusenoid retinal

TABLE 1. Baseline Characteristics of Patients With AMD (N = 418)

Characteristics	n (%)	Characteristics	n (%)
Age, years		DM	93 (22.2)
50-60	24 (5.7)	DM medication	89 (21.3)
61-70	130 (31.1)	Uncontrolled	4 (4.5)
71-80	219 (52.4)	Diet and exercise	6 (6.7)
81-90	45 (10.8)	Oral medication	73 (82.0)
Sex		Insulin	5 (5.6)
Males	139 (33.3)	Insulin + oral medication	1 (1.1)
Females	279 (66.7)	Hypertension	242 (57.9)
Body mass index, kg/m^2		Hypertension control	
<18.5	24 (5.7)	Well controlled	232 (95.9)
18.5-24.9	288 (68.9)	Uncontrolled	10 (4.1)
>25	98 (23.4)	Cardiovascular disease	65 (15.6)
Family history of AMD		Ischemic vascular disease	38 (58.5)
Yes	15 (3.6)	Other vascular disease	27 (41.5)
No	285 (68.2)	Dyslipidemia	104 (24.9)
Unknown	118 (28.2)	Smoking status	
Education level		Never smoked	293 (70.1)
Elementary school or less	89 (21.3)	Former smoker	97 (23.2)
Middle school graduates	50 (12.0)	Current smoker	23 (5.5)
High school graduates	139 (33.3)	Smoking duration, pack-years	29.2
Bachelor's degree or higher	136 (32.5)	Consistent lutein supplement use	267 (63.9)
Refusal to answer	4 (1.0)	Alcohol consumption	75 (17.9)
Past occupation		Less than 3 days/week	40 (53.3)
Unemployed	98 (23.4)	More than 3 days/week	17 (22.6)
Indoor	215 (51.4)	Daily	18 (24.0)
Outdoor	55 (13.2)		
Indoor + outdoor	44 (10.5)		
Refusal to answer	6 (1.4)		

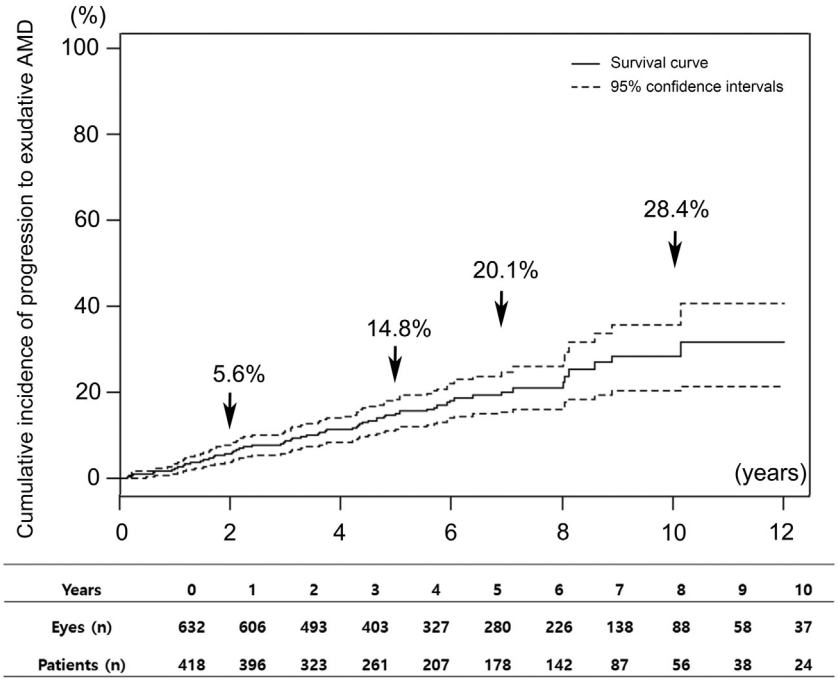
AMD = age-related macular degeneration; DM = diabetes mellitus.

pigment epithelial detachment, serous sensory retinal detachment, subretinal hemorrhage, or subretinal exudation.[16,26] Idiopathic CNV and any secondary CNVs due to myopic degeneration, angioid streak, and ocular histoplasmosis syndrome were excluded.

• **ENVIRONMENTAL FACTOR DEFINITIONS:** Risk factors for AMD progression that were previously reported in studies involving white populations were evaluated in this study (Table 1, Supplemental Table S1).[26] Oral supplements followed AREDS and AREDS2 formulas mainly including lutein, zeaxanthin, β-carotene, vitamins C and E, zinc, and copper, but the dosages and composition of supplements could not be unified due to the retrospective design. Participants' dietary patterns were also assessed with regard to the consumption of meat, vegetables, fish, nuts, coffee, and green tea. Types of meat were not investigated separately.

• **GENOTYPING:** Genotyping was performed in all except 13 patients whose DNA samples were either lost or of low DNA quality. Patients' DNA was obtained from peripheral blood using a DNA extraction kit (QIAamp DNA Maxi kit, Qiagen, Hilden, Germany). Multiplex polymerase chain reaction using a single base extension technique was performed for single-nucleotide polymorphism (SNP) genotyping using the iPLEX Gold kit and MassARRAY software (Sequenom, San Diego, California, USA). Three SNPs known to be major risk alleles for AMD in Koreans, namely the *CFH* SNPs rs800292 and rs1061170 SNPs and the *ARMS2* SNP rs10490924, were analyzed.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SPSS version 24.0 software (SPSS Inc, Chicago, Illinois, USA) and R software (R Foundation, Vienna, Austria). The analyses were performed on a per-eye basis rather than per-patient. Because the eyes were analyzed independently, AREDS criteria that calculated the risk of the opposite eye could not be applied. The 10-year cumulative incidence of progression from intermediate to exudative AMD was calculated using Kaplan-Meier survival analysis. The per-eye analysis of this study has the limitation of intereye correlation that can affect the *P* value. To



Years	0	1	2	3	4	5	6	7	8	9	10
Eyes (n)	632	606	493	403	327	280	226	138	88	58	37
Patients (n)	418	396	323	261	207	178	142	87	56	38	24

FIGURE 2. The cumulative incidence of progression from intermediate to exudative AMD over 12 years. The table shows the numbers of patients and eyes followed in each year. AMD = age-related macular degeneration.

adjust for this, data clustering was performed by patient and univariate and multivariate Cox regression analyses. Univariate analysis of environmental and genetic factors associated with progression to exudative AMD was performed using a log-rank test and Cox proportional hazard model. A Cox regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors influencing progression to exudative AMD over time. To calculate genetic risk of exudative changes, 3 SNPs were treated as 3-level variables. To decrease random error from multiple testing, corrected *P* values were calculated with Bonferroni corrections. Multivariate Cox regression analyses were performed for significant factors with a *P* value of $<.05$ in univariate analyses. Multivariate analyses were performed with and without SNPs to avoid the effect of neutralization. Two SNPs, which were significant only without Bonferroni correction, were included in the multivariate analysis; this was because the Bonferroni method is often too conservative as the tests may be highly positively correlated.[27] Hormone replacement therapy (HRT) was excluded in multivariate Cox analysis. When HRT for women is included, there is a statistical limitation that the entire male data are treated as a missing value.

RESULTS

• **DEMOGRAPHIC DATA:** The baseline characteristics of participants are described in Table 1. In total, 632 eyes of 418 patients with intermediate AMD were enrolled (mean age: 72.3 ± 7.0 years; 279 women vs. 139 men). Among these participants, 106 had exudative AMD in the fellow eye at the time of registration. Follow-up participants were observed at each period (Figure 2); 15 individuals reported a family history of AMD. The mean BMI was 23.04 ± 2.80 kg/m^2, and it was within the normal range in 68.9% patients. Half the patients (n = 215 [51.4%]) had had an indoor occupation in the past. The prevalence of hypertension was relatively high (n = 242 [57.9%]) compared with that of diabetes mellitus (DM) (n = 93 [22.2%]) and hyperlipidemia (n = 104 [24.9%]). Only 5.5% of patients (n = 23) were current smokers, and 70.1% patients (n = 293) did not have a history of smoking. Oral lutein supplements were used by 63.9% of patients (n = 267). Most patients regularly consumed vegetables and fruits, and 10.9% consumed green tea every day (Supplemental Table S1).

• **RATE OF PROGRESSION TO EXUDATIVE AMD:** Of 632 eyes, 415 (65.7%), 233 (36.8%), 110 (17.4%), and 33 (5.2%) had no exudative changes at 2-, 5- 7-, and 10-year follow-up visits, respectively; 80 eyes (12.7%) developed exudative AMD over the 10-year follow-up period. The mean follow-up period was 3.99 ± 2.85 years. The cumulative incidence of progression to exudative AMD was 5.6%, 14.8%, 20.1%, and 28.4% at 2, 5, 7, and 10 years, respectively (Figure 2). The annual progression rate was approximately 2.8%.

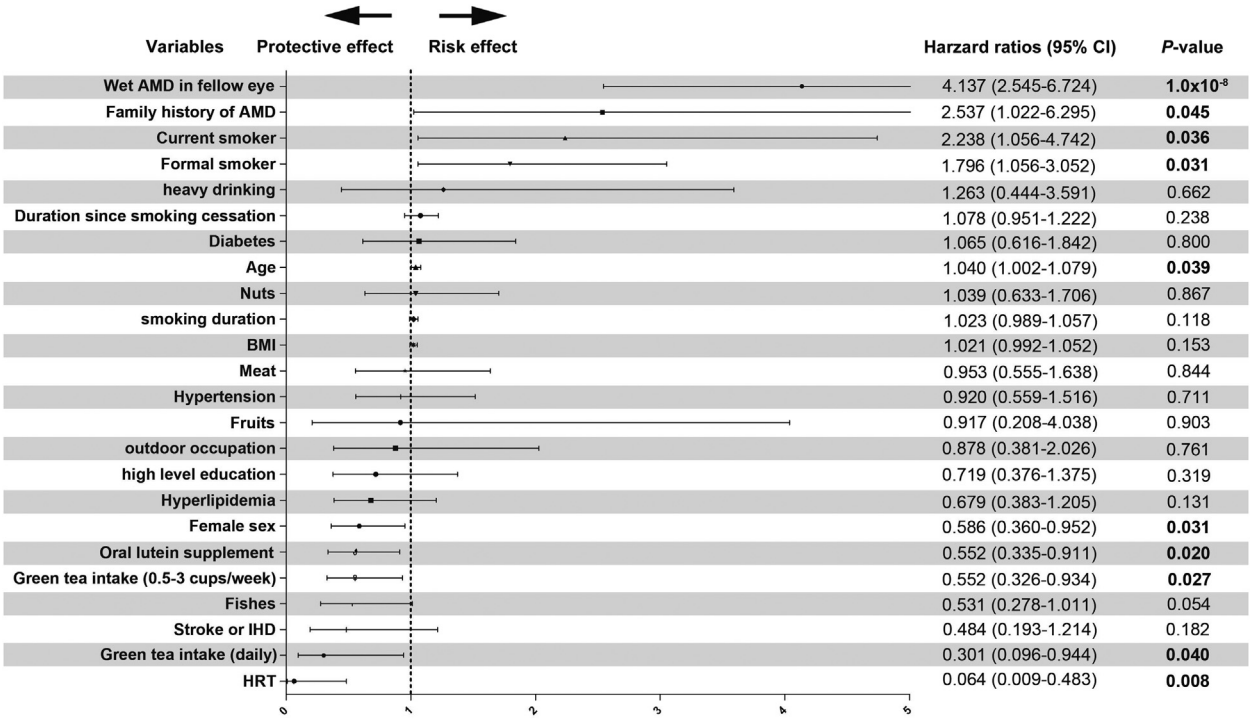


FIGURE 3. Forest plot of factors and their hazard ratios associated with progression from intermediate to exudative AMD in univariate Cox model. AMD = age-related macular degeneration; BMI = body mass index; IHD = ischemic heart disease; HRT = hormone replacement therapy.

• FACTORS INFLUENCING EXUDATIVE CHANGES: Univariate Cox regression analysis with clustering by each patient showed that age (HR: 1.040; 95% CI: 1.002 to 1.079; $P = .039$); male sex (HR: 1.706; 95% CI: 1.050 to 2.778; $P = .031$); family history of AMD (HR: 2.537; 95% CI: 1.022 to 6.295; $P = .045$); pre-existing exudative AMD in the fellow eye (HR: 4.137; 95% CI: 2.545 to 6.724; $P = 1.0 \times 10^{-8}$); former smoking (HR: 1.796; 95% CI: 1.056 to 3.052; $P = .031$); and current smoking (HR: 2.238; 95% CI: 1.056 to 4.742; $P = .036$) increased the risk of progression to exudative AMD (Figures 3 and 4, Supplemental Table S2). Regular use of oral lutein supplements (HR: 0.552; 95% CI: 0.335 to 0.911; $P = .020$); daily green tea intake (HR: 0.301; 95% CI: 0.096 to 0.944; $P = .040$); and HRT (HR: 0.064; 95% CI: 0.009 to 0.483; $P = .008$) showed a protective effect on progression of AMD. The Cox HR for exudative changes decreased with an increase in the consumption of green tea. However, exudative changes were not associated with BMI, education, past occupation, dietary pattern, and systemic comorbidities, including hypertension, DM, hyperlipidemia, cardiovascular disease, and stroke. In univariate analyses without Bonferroni correction, the *CFH* SNP rs1061170 and *ARMS2* SNP rs10490924 were significant risk factors for AMD progression, but those SNPs showed no significant association after Bonferroni correction (Table 2). Clustering by each patient and multivariate Cox regression analysis were performed as shown in Table 3. Multivariate analysis of environmental factors revealed that age (HR: 1.041; 95% CI: 1.002 to 1.081; $P = .0393$); pre-existing exudative AMD in the fellow eye (HR: 3.186; 95% CI: 1.817 to 5.590; $P = 5.31 \times 10^{-5}$); and family history of AMD (HR: 3.175; 95% CI: 1.215-8.299; $P = .0184$) were risk factors for AMD progression, whereas regular intake of green tea (HR: 0.632; 95% CI: 0.402 to 0.995; $P = .0475$) showed protective effects. In the multivariate analysis including the *CFH* SNP rs1061170 and the *ARMS2* SNP rs10490924, and *ARMS2* rs10490924 (HR: 1.482; 95% CI: 1.068 to 2.055; $P = .0185$) were significantly associated with AMD progression, but age was not statistically significant.

DISCUSSION

THIS IS THE FIRST STUDY TO INVESTIGATE THE 10-YEAR INCIdence of progression from intermediate to exudative AMD and determine the associated protective and risk factors in a relatively large number of Korean patients. The annual rates of progression to advanced AMD were reported to be 2.5%-10%, 2.2%-6.2%, and 4% in the AREDS, Blue Mountain Eye Study, and Beaver Dam Eye Study, respectively.[1,17,22,28] In the AGES cohort, the rate of exudative progression was approximately 2.3% per year.[1] Assuming

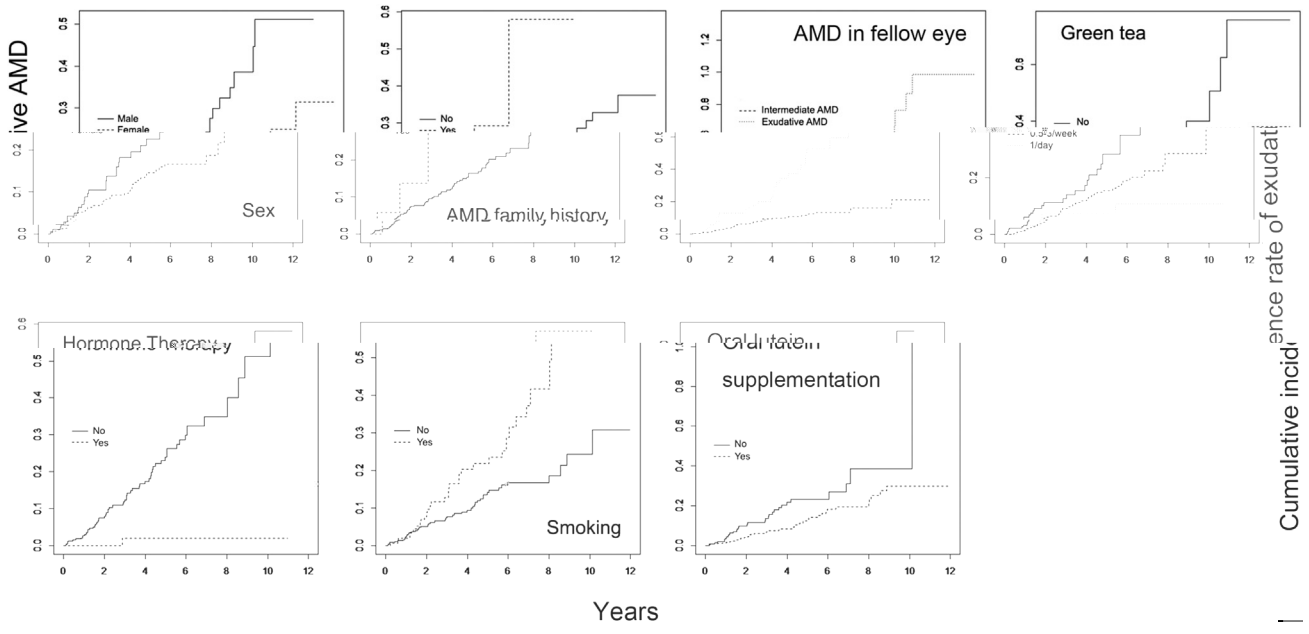


FIGURE 4. Graphs show the rate of progression from intermediate to exudative AMD according to individual risk factors. AMD = age-related macular degeneration; HRT = hormone replacement therapy.

TABLE 2. SNPs Associated With Progression From Intermediate to Exudative AMD

Variable	Eyes (n)	Exudative Change (n)	Reference Allele	Risk Allele	HR (95% CI)	Corrected *P* Value with Clustering (Bonferroni)
CFH rs800292			G	G	1.349 (0.903-2.015)	0.1430 (0.4290)
AA	105	15				
AG	258	22				
GG	242	40				
CFH rs1061170			T	C	1.711 (1.040-2.816)	**0.0347** (0.1041)
TT	492	57				
CT	93	17				
CC	5	1				
ARMS2 rs10490924			G	T	1.524 (1.058-2.194)	**0.0235** (0.0705)
GG	112	12				
GT	221	20				
TT	270	45				

AMD = age-related macular degeneration; CI = confidence interval; HR = hazard ratio; rs = SNP accession identifier; SNP = single nucleotide polymorphism. Bold letters indicate statistical significance (*P* Values <0.05).

that geographic atrophy and exudative AMD each account for approximately half of advanced AMD cases, the rate of progression from intermediate to exudative AMD in whites is estimated to be 2%-5% per year.[1,29,30] However, at 0.43% and 0.88%-1.52% in the Hisayama study by Yasuda and associates[31] and the Singaporean Malays study by Cheung and associates,[32] respectively, the rates in Asians were lower than those in whites. However, recent studies of Asian subjects have shown that the prevalence of AMD, especially exudative AMD, is not lower than that of whites.[8,12,33] As those previous studies analyzed person-person progression, their results could not be compared directly to the present per-eye results. Nevertheless, present finding of an annual progression rate of 2.8% suggests that the rate of progression from intermediate to exudative AMD can be higher than the previously estimated values for Asians and comparable to those for whites.

Our results provide information concerning the associations of demographic, behavioral, medical, and genetic factors with progression from intermediate to exudative AMD. Pre-existing exudative AMD in the fellow eye was found to be the strongest risk factor for progression to

TABLE 3. Findings of Multivariate Cox Regression Analysis for Factors Influencing Progression From Intermediate to Exudative AMD

	Genetic Factor (-)			Genetic Factor (+)		
Variable	HR	95% CI	*P* Value (Clustering)	HR	95% CI	*P* Value (Clustering)
Age	1.041	1.002-1.081	0.0393	1.030	0.991-1.071	.1329
Female sex	0.872	0.436-1.744	0.6978	0.903	0.443-1.840	.7787
Wet AMD in fellow eye	3.186	1.817-5.590	**5.31×10^{-5}**	3.037	1.691-5.453	**.0002**
Family history of AMD	3.175	1.215-8.299	**0.0184**	3.333	1.328-8.365	**.0103**
Smoking	1.276	0.796-2.046	0.3109	1.327	0.837-2.103	.2289
Regular intake of lutein supplement	0.618	0.367-1.041	0.0704	0.605	0.353-1.034	.0662
Regular intake of green tea	0.632	0.402-0.995	**0.0475**	0.556	0.341-0.905	**.0181**
CFH rs1061170	–	–	–	1.617	0.982-2.664	.0591
ARMS2 rs10490924	–	–	–	1.482	1.068-2.055	**.0185**

AMD = age-related macular degeneration; CI = confidence interval; HR = hazard ratio; rs = single nucleotide polymorphism accession identifier. Bold letters indicate statistical significance (*P* Values <0.05).

exudative AMD in this study. A recent AREDS report showed that the 10-year rates of progression to advanced AMD in eyes with medium drusen at baseline were 26.4% and 4.3% when the fellow eye did and did not have pre-existing advanced AMD, respectively,[19] suggesting that pre-existing exudative AMD in the fellow eye is a major risk factor for Asian as well as white patients. In the present cohort, a family history of AMD was also significantly associated with a 3-fold increase in HR for AMD progression. A positive family history is a known risk factor for AMD, although the risk estimates vary among studies, and the reliability of a self-reported family history is unclear.[34]

The occurrence of AMD is associated with various risk factors, including age and smoking.[9] In this study, age was clearly associated with AMD progression. Smoking has been determined to be a strong and consistent risk factor for AMD in numerous studies.[35–39] It can affect the macular luteal pigment, increase oxidative stress, and impair the choroidal microcirculation.[26] Although multivariate analysis in this study showed no correlation between smoking and exudative changes, in univariate analysis, current smoking was a prominent risk factor for exudative changes, and an increased risk of AMD progression remained even in former smokers.

Dietary habits vary among regions and countries, so an investigation of the association between diet and AMD in Asians is necessary to understand the environmental impact on AMD progression. Among several dietary factors, green tea consumption more than once every 2 weeks significantly inhibited exudative progression, whereas daily intake considerably slowed the progression. In the present multivariate analysis, green tea intake was the only significant protective factor for exudative changes. Regular use of oral lutein supplements has also been shown to inhibit AMD progression in univariate analysis, but intake of green tea had a greater protective effect than oral lutein supplements in this study. However, due to the retrospective nature of this study, the type and dosage of supplements cannot be unified. Moreover, the baseline intake rate of lutein was high in our cohort (64%), and the AREDS/AREDS2 formula supplements were recommended for all subjects after cohort enrollment. Thus, oral lutein supplementation cannot be considered less effective than green tea intake in inhibiting AMD progression, but green tea intake is likely to further inhibit AMD progression even if lutein is being consumed. Green tea is rich in flavonoids, which are promising phytochemicals with antioxidant, anti-inflammatory, and antiangiogenic properties.[40] Epigallocatechin gallate, the most abundant and potent antioxidant in green tea extracts, prevented the degeneration of ARPE19 cells in a cell culture model of ultraviolet B (UVB)-induced apoptosis and photoreceptor cells in an animal model of photoreceptor degeneration.[41,42] Most studies of the correlation between AMD and green tea intake were performed in animal models. To the authors' knowledge, this is the only population-based study to show the clinical significance of green tea consumption in patients with AMD.

Intriguingly, HRT showed a significant protective effect on exudative AMD progression. Several studies have reported that exposure to estrogen due to HRT is associated with a lower prevalence of AMD and other retinal diseases,[43] which could be attributed to the secondary protective effect of HRT against cardiovascular diseases in postmenopausal women.[44,45] These findings need to be validated in further studies on Asian subjects.

Genetic variants associated with AMD have been reported in multiple ethnic groups. However, recent studies suggest that AMD-associated variants identified in whites may not be applicable to Asian populations.[46–48] *ARMS2/HTRA1* and *CFH* are major susceptibility genes for AMD in both white and Asian populations. The *ARMS2* (rs10490924) and *HTRA1* (rs11200638) SNPs are more strongly associated with AMD in Asian populations than are other variants found in whites. The

CFH SNP rs1061170 is also a major risk allele for AMD in whites, although it is not frequently found in Asians. A previous study showed that both the TT genotype of the *ARMS2* SNP rs10490924 and the GG genotype of the *CFH* SNP rs800292 increased the risk for development of exudative AMD.[49] In the present cohort, *CFH* SNP rs1061170 and *ARMS2* SNP rs10490924 were significant risk factors for progression of AMD in univariate analyses without Bonferroni correction; however, those 2 SNPs showed no significant association after Bonferroni correction, and only *ARMS2* SNP rs10490924 was significantly associated with AMD progression in multivariate analysis. Considering that the risk of the *CFH* SNP rs1061170 allele was low and that of the *ARMS2* SNP rs10490924 was very high in the present cohort, as it is in other Asian populations, the number of cases might be insufficient to demonstrate statistical significance.

The retrospective, observational design is a major limitation of this study. The association of the baseline factors was analyzed, including diet and AREDS/AREDS2 supplements, with the exudative outcome, but the effect of the factors during the observation period could not be evaluated. This might have affected the association with baseline factors. Because it was recommended that all subjects take AREDS/AREDS2 supplements after enrollment, the protective effect of green tea on exudative change can be an independent additive, one to AREDS/AREDS2 supplements. In addition, the mean follow-up period was not as long as 3.99 years, depending on the follow-up loss and different enrollment point for each patient. The type of green tea or other kinds of tea were not considered. Also, the AREDS simplified scale was not considered because the risk factors were calculated per-eye not per-person. Although this may serve as a limitation, it may be helpful to calculate the independent risk for each eye and use it as real-world data. HRT was not included in multivariate analysis because only females receive HRT, and the number of patients receiving HRT was small; thus, including HRT could have led to statistical errors. Nevertheless, this study analyzed real-world, large-scale data over a 10-year period, so the results are expected to be of great significance for determining the actual progression pattern and treatment direction for AMD in Asian patients. This study targeted eyes with typical intermediate AMD showing multiple drusen on the macula. Although polypoidal choroidal vasculopathy can develop from typical intermediate AMD, it often occurs in patients with relatively few drusen. Therefore, it can be classified under the pachychoroid disease spectrum, which shows a somewhat different natural course from that of typical AMD.[50,51] As a result, it was included and analyzed in patients with multiple drusen only. Our findings suggested that exudative changes in typical intermediate AMD occur to an extent in Asians that is similar to that in whites.

In summary, the present study is the only large-scale cohort study revealing the long-term rate of progression from intermediate to exudative AMD in Koreans. Risk factors for exudative changes included a family history of AMD, pre-existing exudative AMD in the fellow eye, and the *ARMS2* SNP rs10490924. Asian diet habits, such as intake of green tea, may be modifiable protective factors against exudative changes. These findings provide new insights into the treatment and prevention of AMD in Asian populations.

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