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Factors Associated with Age-related Macular Degeneration: The Korea National Health and Nutrition Examination Survey 2008-2012

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Purpose: To evaluate the associations between early/late age-related macular degeneration (AMD) and systemic and ocular parameters using national population-based data.

Methods: From 2008 to 2012, a total of 16,897 participants of the Korea National Health and Nutrition Examination Survey underwent ophthalmologic examinations by the Korean Ophthalmological Society. Cases of early and late (neovascular and geographic atrophy) AMD were identified using digital fundus images. Risk factors were identified using logistic regression.

Results: Age-standardized prevalence of early and late AMD among subjects aged 40 years and older was 5.5% and 0.6%, respectively. Increasing age was the most significant risk factor for both early and late AMD (adjusted odds ratio [aOR]: 1.09, 95% confidence interval [CI]; 1.07–1.10; aOR: 1.14, 95% CI: 1.10–1.19, respectively). Patients who slept, on average, more than nine hours per day (aOR: 0.68, 95% CI: 0.47–1.00) and who were in the lowest quintile ($\leq$ 38.21 g/dL) of high-density lipoprotein (HDL) cholesterol (aOR: 0.68, 95% CI: 0.51–0.92) were significantly associated with a lower prevalence of early AMD. Increasing spherical equivalent (SE) [aOR: 0.53 of the first quintile of SE $\leq$ -1.38 diopters (D), 95% CI: 0.35–0.78; aOR: 1.41 of the fifth quintile of SE $\geq$ +0.69 D, 95% CI: 1.07–1.86] was associated with a higher prevalence of early AMD. Lower quartile of systolic blood pressure ($\leq$ 110.0 mmHg) was associated with a lower prevalence of neovascular AMD (aOR: 0.25, 95% CI: 0.09–0.67).

Conclusions: Aging was the most significant risk factor for both early and late AMD. Lower level of HDL cholesterol, longer duration of sleep, and myopia had protective associations with early AMD, while lower systolic blood pressure had a protective association with neovascular AMD.

Keywords: Age-related macular degeneration; Epidemiology; Risk factor

Introduction

There are currently insufficient data to determine whether the prevalence and incidence of age-related macular degeneration (AMD) differ among different ethnic groups at varying or within the same geographic locations [1]. The Baltimore Eye Survey showed that more severe forms of early AMD and late AMD are more prevalent in whites compared to blacks [2]. However, the National Health and Nutrition Survey (NHANES) III reported that, among subjects aged 40 to 59 years, the prevalence of AMD was actually higher in blacks than in whites [3]. Furthermore, AMD was generally thought to be less frequently found in Asian populations, based on earlier hospital-based observational studies, but a recent systematic review reported that the pooled prevalence estimates of early and late AMD were 6.8% and 0.56%, respectively, in Asian populations aged 40 to 79 years, which are comparable to those of the 8.8% and 0.59% found in corresponding prevalence estimates in white populations [4]. However, the epidemiological study of AMD in Asians is still limited, and prevalence data vary among Asian countries or even within the same country [5-9]. In addition, age and smoking have been found to be significant risk factors for AMD [5,6,8-15]. Furthermore, studies involving other risk factors such as drinking, hyperopia, hypertension, and cataract have reported conflicting results [5,7,9,11,13,14].

Several previous studies reported the prevalence of early and late AMD in the Korea population using different time periods of the Korea National Health and Nutrition Examination Survey (KNHANES) [16-18]. The prevalence of early and late AMD ranged between 6.0% and 6.7% and between 0.6% and 0.7%, respectively. The purpose of the present study involving 16,897 subjects was to provide updated estimates of the prevalence of AMD in Korean adults ≥40 years old and to evaluate associated ocular and systemic risk factors as determined in the 2008 to 2012 KNHANES.

Materials and Methods

Study design and population

The Korea Centers for Disease Control and Prevention conducted a series of surveys of the KNHANES I, II, III, IV, and V starting in 1998 in order to examine the general health and nutritional status of Koreans. The KNHANES includes three parts: a health interview, a health examination, and a nutrition survey. Ophthalmological interviews and examinations of participants were conducted for this survey, which was administered annually from July 2008 to December 2012. Participation percentages were 74.3% (2008), 79.2% (2009), 77.5% (2010), 76.1% (2011), and 75.9% (2012). Participants who were ≥19 years old received ocular examinations, including slit lamp examination, visual acuity testing, auto refraction, and fundus photography. This study included 16,897 adults who were ≥40 years old. Fig. 1 provides a flow diagram of the study population. This study was reviewed and approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention. All participants provided written informed consent, and the study adhered to the tenets of the Declaration of Helsinki.

Outcome variables

A digital non-mydriatic fundus camera (TRC-NW6S; Topcon, Tokyo, Japan) and a Nikon D-80 digital camera (Nikon, Tokyo, Japan) were used for fundus photography. For each participant, a retinal image was taken for each eye. Each image was graded twice based on International Age-Related Maculopathy Epidemiological Study Group criteria [19]. Nine retina specialists participated in rating the retinal images. Final grades were approved by a senior reading specialist in the Korean Ophthalmological Society (KOS). The inter-rater reliability values for AMD grading (for the right eye and left eye, respectively) were 90.2% and 90.7% in 2008, 92.4% and 93.3% in 2009, 94.1% and 95.0% in 2010, and 96.2% and 96.6% in 2011. Early AMD was defined as the "presence of soft, indistinct drusen or reticular drusen" or the "presence of hard or soft distinct drusen with pigmentary abnormalities." Late AMD includes either geographic atrophy or neovascular AMD. Neovascular AMD includes (1) retinal pigment epithelium detachment, (2) serous detachment of neurosensory retina, (3) subretinal or subretinal pigment epithelium hemorrhage, or (4) fibrous scars. Geographic atrophy includes the presence of round, sharply edged areas of retinal pigment epithelium (RPE) hypopigmentation that are ≥175 μm in diameter. If AMD severity was found to vary between both eyes, the subject was given a higher grade. To determine the prevalence of early AMD and late AMD, 39 subjects with early AMD in one eye and late AMD in another eye were designated as having late AMD.
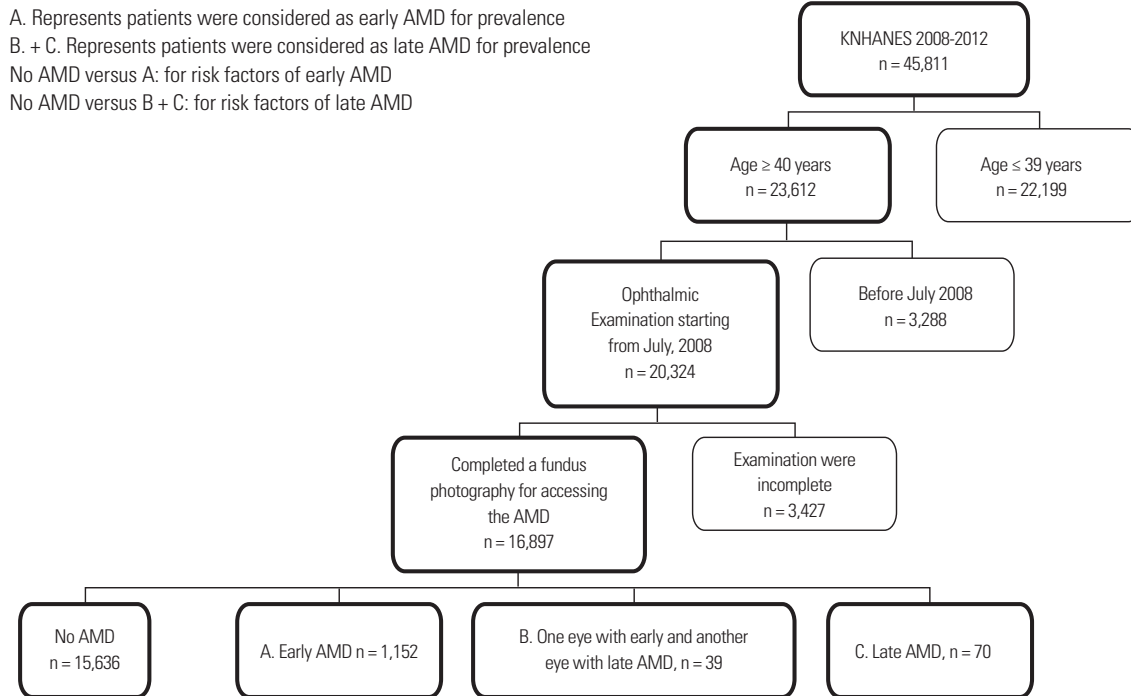
A. Represents patients were considered as early AMD for prevalence
B. + C. Represents patients were considered as late AMD for prevalence
No AMD versus A: for risk factors of early AMD
No AMD versus B + C: for risk factors of late AMD

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                              ┌─────────────────────┐
                              │  KNHANES 2008-2012   │
                              │     n = 45,811       │
                              └──────────┬───────────┘
                        ┌────────────────┴────────────────┐
              ┌─────────────────┐              ┌─────────────────┐
              │  Age ≥ 40 years │              │ Age ≤ 39 years  │
              │   n = 23,612    │              │   n = 22,199    │
              └────────┬────────┘              └─────────────────┘
              ┌────────┴─────────────────────┐
    ┌──────────────────────┐       ┌─────────────────┐
    │     Ophthalmic       │       │ Before July 2008│
    │ Examination starting │       │   n = 3,288     │
    │   from July, 2008    │       └─────────────────┘
    │     n = 20,324       │
    └──────────┬───────────┘
       ┌───────┴──────────────────────┐
  ┌──────────────────────┐   ┌─────────────────┐
  │  Completed a fundus  │   │ Examination were│
  │ photography for      │   │  incomplete     │
  │ accessing the AMD    │   │   n = 3,427     │
  │    n = 16,897        │   └─────────────────┘
  └──────────┬───────────┘
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| No AMD n = 15,636 | A. Early AMD n = 1,152 | B. One eye with early and another eye with late AMD, n = 39 | C. Late AMD, n = 70 |

Figure 1. Flow diagram of the study population. The Korean Ophthalmological Society participated in the Korea National Health and Nutritional Examination Survey (KNHANES) starting in July 2008 and ending in December 2012. AMD = age-related macular degeneration.

Independent variables

Independent variables were divided into four categories: (1) socio-demographic factors, (2) health behavioral risk factors, (3) health examination variables, and (4) eye variables. Binge alcohol users included men who consumed more than seven drinks or women who consumed more than five drinks on a single occasion at least once per month [20]. Lifetime smokers were defined as participants who have smoked 100 or more cigarettes in their lifetime.

All refraction measurements were performed using an autorefractor-keratometer (KR8800; Topcon, Tokyo, Japan) under non-cycloplegic conditions. If it was impossible to attain results with the auto-start mode, an ophthalmologist directly measured the refractive error using the manual mode. If this method also failed due to poor cooperation, severe lens opacity, or corneal opacity, we reported the results as missing. If a subject had no AMD in both eyes or had any AMD in both eyes, the average refractive error of both eyes was chosen as an independent variable. If the subject had AMD in one eye only, the refractive error of the corresponding eye was chosen as an independent variable.

Statistical methods

To determine the age-standardized prevalence of early and late AMD in Korea, prevalence according to age group and sex were estimated using a weight-defined method, based on the guidelines of the KNHANES administered from 2008 to 2012. A three-step multidimensional approach was used to evaluate AMD-associated predictive factors (Fig. 2). First, to identify age-adjusted risk factors associated with early AMD and late AMD, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated using age-adjusted univariable logistic regression analysis (Fig. 2, left column). Second, multivariable logistic regression was used to evaluate risk factors from age-adjusted risk factors ($p < 0.1$), while considering all possible risk factors as either continuous or ordered variables. Some factors were not assessed for five years, so multivariable logistic regression analysis was performed in all cases except for these variables between 2008 and 2012, and additional multivariable logistic regression was performed using these variables for the duration between 2010 and 2011. Statistically significant variables other than high-density lipoprotein (HDL)cholesterol were
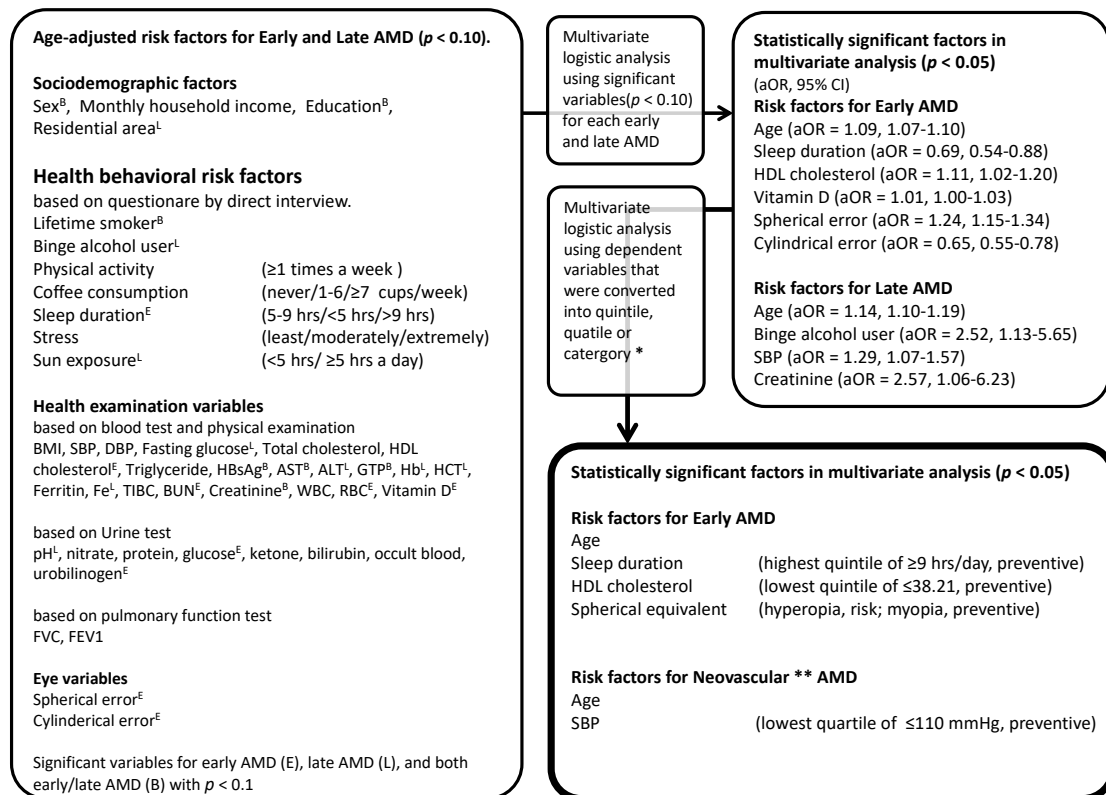
Age-adjusted risk factors for Early and Late AMD (*p* < 0.10).

Sociodemographic factors
Sex[B], Monthly household income, Education[B], Residential area[L]

Health behavioral risk factors
based on questionare by direct interview.
Lifetime smoker[B]
Binge alcohol user[L]
Physical activity (≥1 times a week)
Coffee consumption (never/1-6/≥7 cups/week)
Sleep duration[E] (5-9 hrs/<5 hrs/>9 hrs)
Stress (least/moderately/extremely)
Sun exposure[L] (<5 hrs/ ≥5 hrs a day)

Health examination variables
based on blood test and physical examination
BMI, SBP, DBP, Fasting glucose[L], Total cholesterol, HDL cholesterol[E], Triglyceride, HBsAg[B], AST[B], ALT[L], GTP[B], Hb[L], HCT[L], Ferritin, Fe[L], TIBC, BUN[L], Creatinine[B], WBC, RBC[E], Vitamin D[E]

based on Urine test
pH[L], nitrate, protein, glucose[E], ketone, bilirubin, occult blood, urobilinogen[E]

based on pulmonary function test
FVC, FEV1

Eye variables
Spherical error[E]
Cylinderical error[E]

Significant variables for early AMD (E), late AMD (L), and both early/late AMD (B) with *p* < 0.1

Multivariate logistic analysis using significant variables(*p* < 0.10) for each early and late AMD

Multivariate logistic analysis using dependent variables that were converted into quintile, quatile or catergory *

Statistically significant factors in multivariate analysis (*p* < 0.05)
(aOR, 95% CI)
Risk factors for Early AMD
Age (aOR = 1.09, 1.07-1.10)
Sleep duration (aOR = 0.69, 0.54-0.88)
HDL cholesterol (aOR = 1.11, 1.02-1.20)
Vitamin D (aOR = 1.01, 1.00-1.03)
Spherical error (aOR = 1.24, 1.15-1.34)
Cylindrical error (aOR = 0.65, 0.55-0.78)

Risk factors for Late AMD
Age (aOR = 1.14, 1.10-1.19)
Binge alcohol user (aOR = 2.52, 1.13-5.65)
SBP (aOR = 1.29, 1.07-1.57)
Creatinine (aOR = 2.57, 1.06-6.23)

Statistically significant factors in multivariate analysis (*p* < 0.05)

Risk factors for Early AMD
Age
Sleep duration (highest quintile of ≥9 hrs/day, preventive)
HDL cholesterol (lowest quintile of ≤38.21, preventive)
Spherical equivalent (hyperopia, risk; myopia, preventive)

Risk factors for Neovascular ** AMD
Age
SBP (lowest quartile of ≤110 mmHg, preventive)

Figure 2. Framework of the study. A three-step multidimensional approach was used to evaluate the factors associated with early/late age-related macular degeneration. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; HBsAg = hepatitis B surface antigen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GTP = gamma-glutamyl transpeptidase; Hb = hemoglobin; HCT = hematocrit; TIBC = total iron-binding capacity; BUN = blood urea nitrogen; WBC = white blood cell; RBC = red blood cell; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; aOR = adjusted odds ratio; CI = confidence interval. *Independent variables divided into quintile for early age-related macular degeneration (AMD), and divided into quartile for neovascular AMD due to the number of subjects for each category was not enough to analysis; **Finally, Late AMD was analyzed by dividing neovascular AMD and geographic atrophy, but the prevalence of geographic atrophy was too low to analyze using categorical variables.

the same for early AMD in both the years from 2008 to 2012 and 2010 to 2011 (see Table 1, 2 and Fig. 2, right upper corner). Third, each independent risk factor for early AMD (age, sleep duration, HDL cholesterol, vitamin D, and spherical equivalent) was divided into quintiles or into five ordered categories, followed by the performance of multivariable logistic analysis to determine clinical significance rather than using a simple relationship as a continuous independent variable. Sleep duration was divided into approximate quintiles. Late AMD was analyzed by dividing neovascular AMD and geographic atrophy. Each independent variable (systolic blood pressure and creatine) was divided into quartiles, and multivariable logistic regression was used to confirm the tendency and clinical association with neovascular AMD.

Quartiles, instead of quintiles, for neovascular AMD were used because the number of subjects for each category was not enough for analysis, and mid-second and mid-third quartiles were considered as a single reference group. It was impossible to perform multivariable logistic regression using independent variables as a quartile for geographic atrophy because of the limited number of subjects. Multivariable logistic regression using dependent variables as continuous variables was therefore performed for geographic atrophy. The variable of sex was included for the final model of early and late AMD for adjusting the sex-dependent differences of health examination variables, including HDL cholesterol and creatine. All statistical tests were two-sided at 95% CI and performed using the Stata/MP 14.0 software (StataCorp, College Station, TX, USA).

Table 1. Factors associated with early AMD using survey design-multivariate logistic analysis

Factors	Increase	Early AMD (2008–2012)		Early AMD (2010–2011)	
		aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	1 year	1.09 (1.07–1.10)	<0.01	1.08 (1.07–1.10)	<0.01
Sex	Female	0.79 (0.55–1.13)	0.20	0.77 (0.45–1.34)	0.36
Education	Elementary/middle/high/university or higher	0.95 (0.86–1.05)	0.32	0.88 (0.77–1.00)	0.05
Lifetime smoker	100 cigarettes	0.78 (0.58–1.04)	0.09	0.71 (0.46–1.11)	0.14
Sleep duration	<5 hours/5–8.5 hours/≥9 hours	0.69 (0.54–0.88)	<0.01	0.64 (0.47–0.88)	<0.01
HDL cholesterol	1 g/dL	1.11 (1.02–1.20)	0.01	1.12 (0.99–1.25)	0.07
HBsAg	100 IU/mL	1.00 (1.00–1.01)	0.24	1.00 (0.99–1.02)	0.46
AST	10 IU/L	1.03 (0.98–1.07)	0.22	1.02 (0.92–1.12)	0.76
BUN	1 mg/dL	0.98 (0.96–1.00)	0.06	0.97 (0.94–1.01)	0.11
Creatine	1 mg/dL	0.72 (0.37–1.38)	0.32	0.67 (0.27–1.63)	0.37
RBC	1 Mil/µL	0.82 (0.62–1.08)	0.16	0.80 (0.55–1.17)	0.26
Vitamin D	1 ng/mL	1.01 (1.00–1.03)	0.03	1.02 (1.00–1.03)	0.05
Urine glucose	Positive	0.91 (0.73–1.15)	0.44	1.00 (0.75–1.35)	0.98
Urine urobilinogen	Positive	1.78 (0.91–3.49)	0.09	2.12 (0.98–4.59)	0.06
Spherical equivalent	1 dipoter	1.24 (1.15–1.34)	<0.01	1.21 (1.09–1.34)	<0.01
Cylindrical error	1 dipoter in minus format (more astigmatic)	0.65 (0.55–0.78)	<0.01	0.66 (0.52–0.84)	<0.01
Variable were not conducted for 5 years[*]					
GTP[*]	10 IU/L	Not available		1.02(1.00–1.03)	0.09

AMD = age-related macular degeneration; aOR = adjusted odds ratio; CI = confidence interval; HDL = high density lipoprotein; HBsAg = hepatitis B surface antigen; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; GTP = gamma-glutamyl transpeptidase.
[*]Conducted between 2010 and 2011.

Table 2. Factors associated with late AMD using survey design-multivariate logistic analysis

Factors	Increase	Late AMD (2008–2012)		Late AMD (2010–2011)	
		aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	1 year	1.14 (1.10–1.19)	<0.01	1.17 (1.11–1.23)	<0.01
Sex	Female	2.25 (0.81–6.27)	0.12	2.21 (0.46–10.63)	0.32
Education	Elementary/middle/high/university or higher	1.39 (0.97–2.00)	0.08	1.54 (0.98–2.44)	0.06
Residential area	Rural	0.60 (0.31–1.14)	0.12	0.52 (0.22–1.22)	0.13
Lifetime smoker	Yes	1.91 (0.81–4.54)	0.14	1.42 (0.45–4.46)	0.55
Binge alchohol user	Yes	2.52 (1.13–5.65)	0.02	4.01 (1.35–11.93)	0.01
Sun exposure	≥5 hours/day	0.71 (0.36–1.42)	0.33	0.62 (0.24–1.64)	0.34
SBP	10 mmHg	1.29 (1.07–1.57)	<0.01	1.35 (1.04–1.75)	0.02
Fasting glucose	1 g/dL	0.98 (0.96–1.00)	0.06	0.98 (0.95–1.01)	0.19
HBsAg	100 IU/mL	0.95 (0.87–1.04)	0.24	0.92 (0.84–1.01)	0.10
AST	10 IU/L	1.01 (0.80–1.28)	0.93	1.01 (0.81–1.25)	0.96
ALT	10 IU/L	1.07 (0.93–1.23)	0.37	1.06 (0.75–1.51)	0.74
Hb	1 g/dL	1.78 (0.84–3.75)	0.13	1.43 (0.54–3.78)	0.47
HCT	1%	0.87 (0.64–1.18)	0.36	0.96 (0.66–1.40)	0.84
Creatinine	1 mg/dL	2.57 (1.06–6.23)	0.04	4.06 (1.38–11.93)	0.01
Urine pH	1 pH	1.37 (0.97–1.94)	0.07	1.14 (0.67–1.95)	0.63
Variable were not conducted for 5 years*					
GTP*	1 µg/dL	Not available		1.02 (0.99–1.05)	0.22
Fe (serum)†	10 IU/L	Not available		1.01 (1.00–1.01)	0.13

AMD = age-related macular degeneration; aOR = adjusted odds ratio; CI = confidence interval; SBP = systolic blood pressure; HBsAg = hepatitis B surface antigen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Hb = hemoglobin; HCT = hematocrit; GTP = gamma-glutamyl transpeptidase; Fe = ferritin.
*Conducted between 2010 and 2011; †Conducted between 2010 and 2012.

Table 3. Prevalence* of early and late AMD

	Total	Early AMD		Late AMD		Neovacular AMD		Geographic atrophy	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
≥40									
Overall	16,897	1,152	5.5 (5.1–5.9)	109	0.6 (0.4–0.7)	86	0.5 (0.3–0.6)	25	0.1 (0.1–0.2)
Male	7,107	450	4.6 (4.1–5.2)	61	0.8 (0.5–1.0)	47	0.6 (0.4–0.8)	15	0.2 (0.1–0.3)
Female	9,790	702	6.3 (5.8–6.8)	48	0.4 (0.3–0.6)	39	0.3 (0.2–0.5)	10	0.1 (0.0–0.2)
≥65									
Overall	4,956	695	14.5 (13.3–15.7)	75	1.8 (1.2–2.3)	56	1.2 (0.8–1.7)	21	0.6 (0.3–0.9)
Male	2,024	243	11.8 (10.1–13.5)	38	2.4 (1.4–3.5)	27	1.7 (0.8–2.6)	12	0.8 (0.3–1.4)
Female	2,932	452	16.2 (14.5–18.0)	37	1.3 (0.8–1.8)	29	0.9 (0.5–1.3)	9	0.5 (0.1–0.9)
Age group									
40–49	5,047	58	1.2 (0.8–1.6)	7	0.1 (0.0–0.3)	7	0.1 (0.0–0.3)	0	No observation
50–59	4,787	222	4.5 (3.8–5.1)	16	0.4 (0.2–0.6)	15	0.4 (0.1–0.6)	1	0.0 (0.0–0.1)
60–69	4,010	404	10.2 (9.0–11.4)	32	1.1 (0.6–1.6)	24	0.7 (0.4–1.1)	8	0.4 (0.1–0.7)
70–79	2,624	387	15.3 (13.6–17.0)	40	1.5 (0.8–2.1)	31	1.2 (0.6–1.8)	10	0.4 (0.1–0.6)
≥80	429	81	16.5 (12.5–20.6)	14	3.5 (1.5–5.5)	9	2.3 (0.7–4.0)	6	1.7 (0.1–3.2)

AMD = age-related macular degeneration; CI = confidence interval.
*Complex sample analysis was performed with reference to the weight, stratification variance, and cluster variance, following the statistical guidelines of the Korea Centers for Disease Control and Prevention. Subjects with early AMD in one eye and late AMD in the opposite eye were considered as late AMD.

Results

Baseline characteristics of the study population

The mean age of the 16,897 patients aged 40 years or older was 57.4 years [standard deviation (SD) ± 11.4] years. The percentage of female patients was 57.9%. The age-standardized prevalence of early AMD was 5.5% (95% CI: 5.1−5.9), and the age-standardized prevalence of late AMD was 0.6% (95% CI: 0.4−0.7). Table 3 shows the age-standardized prevalence of early AMD, late AMD, neovascular AMD, and geographic atrophy.

Factors associated with age-related macular degeneration

The independent risk factors associated with early or late AMD in age-adjusted univariable analysis are designated as "B" for both early and late AMD; "E" for early AMD; and "L" for late AMD in the left column of Fig. 2. Table 4 shows the results of age-adjusted logistic regression with aORs and 95% CIs for early and late AMD. See Table 2 for results of multivariable logistic analysis using significant variables (p < 0.1) from age-adjusted logistic regression analysis.

Table 5 shows our final model for early AMD. Age (1 [reference] for 40 to 49 years of age; aOR: 3.29 for 50 to 59 years of age, 95% CI: 2.13−5.09; aOR: 7.94 for 60 to 69 years of age, 95% CI: 5.07−12.45; aOR: 15.07 for 70 to 79 years of age, 95% CI: 9.38−24.19; and aOR: 21.56 for ≥ 80 years of age, 95% CI: 11.10−41.87) was the most significant risk factor for early AMD. Subjects sleeping more than nine hours per day were less likely to have early AMD compared with those who were sleeping between 6.5 hours per day and seven hours per day as a reference group (aOR: 0.67, 95% CI, 0.46−0.99). The lowest level of HDL cholesterol reduced the risk of early AMD in comparison with the mid-third quintile as a reference group (aOR: 0.68, 95% CI: 0.51−0.92). Spherical equivalents (SE) (aOR: 0.53 in the first quintile [SE ≤ -1.38 diopters {D}], 95% CI: 0.35−0.78; aOR: 0.99 in the second quintile [-1.37 D ≤ SE ≤ -0.50 D], 95% CI: 0.71−1.40; 1 [reference] in the third quintile [-0.50 D < SE ≤ 0.00 D];

Table 4. Age-adjusted risk factors for early and late AMD using the survey design

	Increase	Early AMD			Late AMD		
		aOR	95% CI	p-value	aOR	95% CI	p-value
Socio demographic factors							
Sex	Female	1.16	0.99–1.36	0.07	0.49	0.27–0.92	0.03
Monthly household income	1 quintile	1.00	0.94–1.05	0.91	1.16	0.92–1.45	0.20
Education	1 grade[†]	0.90	0.83–0.98	0.02	1.45	1.04–2.02	0.03
Residential area	Rural	0.99	0.83–1.17	0.88	0.37	0.18–0.75	<0.01
Health behavioral factors							
Lifetime smoker	Yes	0.82	0.70–0.96	0.02	2.19	1.14–4.22	0.02
Binge alcohol user	Yes	1.07	0.89–1.30	0.46	2.73	1.36–5.49	<0.01
Physical activity (moderate intensity)	≥1 time/wk	0.94	0.64–1.38	0.75	3.08	0.70–13.43	0.14
Coffee consumption (cups/wk)	1–6/≥ 7	0.99	0.88–1.11	0.88	0.96	0.59–1.58	0.88
Sleep duration (hours/day)	<5/5–8.5/≥9	0.78	0.64–0.95	0.01	0.64	0.29–1.43	0.28
Stress	1 grade[†]	1.06	0.90–1.26	0.49	0.72	0.37–1.39	0.33
Sun exposure	≥5 hours/day	1.11	0.93–1.32	0.26	0.48	0.22–1.02	0.06
Health examination variables							
BMI	1 kg/m^2	1.00	0.97–1.02	0.69	1.00	0.91–1.09	0.92
SBP	10 mmHg	1.00	0.96–1.05	0.86	1.30	1.11–1.51	<0.01
DBP	10 mmHg	1.01	0.94–1.09	0.73	1.32	0.95–1.83	0.10
Blood test							
Fasting glucose	1 g/dL	0.97	0.94–1.01	0.13	0.85	0.72–1.00	0.06
Total cholesterol	1 g/dL	1.00	0.97–1.02	0.64	0.96	0.88–1.05	0.37
HDL cholesterol	1 g/dL	1.12	1.05–1.20	<0.01	1.11	0.80–1.53	0.54
Triglyceride	1 g/dL	0.99	0.98–1.00	0.11	1.00	0.97–1.03	0.95
HBsAg	100 IU/mL	1.01	1.00–1.02	<0.01	0.96	0.92–1.00	0.05
AST	10 IU/L	1.04	1.00–1.08	0.03	1.10	1.05–1.15	<0.01
ALT	10 IU/L	0.99	0.94–1.04	0.65	1.07	1.03–1.10	<0.01
GTP[Π]	10 IU/L	1.02	1.00–1.03	0.01	1.04	1.02–1.06	<0.01
Hb	1 g/dL	0.97	0.91–1.02	0.24	1.28	1.00–1.64	0.05
HCT	1%	0.99	0.97–1.01	0.31	1.09	0.99–1.20	0.07
Ferritin (serum)	1 ng/mL	1.00	1.00–1.00	0.63	1.00	0.99–1.00	0.22
Fe (serum)[§]	1 μg/dL	1.00	1.00–1.00	0.24	1.01	1.00–1.02	<0.01
TIBC[§]	1 μg/dL	1.00	1.00–1.00	0.63	1.00	0.99–1.01	0.92
BUN	1 mg/dL	0.98	0.97–1.00	0.07	1.01	0.95–1.08	0.79
Creatinine	1 mg/dL	0.49	0.33–0.74	<0.01	1.55	1.22–1.96	<0.01
WBC	1 thous/μL	0.96	0.92–1.01	0.14	0.94	0.80–1.12	0.49
RBC	1 Mil/μL	0.83	0.68–1.01	0.07	1.45	0.63–3.32	0.38
Vitamin D	1 ng/mL	1.01	1.00–1.02	0.09	0.99	0.95–1.04	0.66

Table 4. Continued

	Increase	Early AMD			Late AMD		
		aOR	95% CI	p-value	aOR	95% CI	p-value
Urine test							
Urine pH	1 pH	1.07	0.98–1.17	0.13	1.40	1.00–1.94	0.05
Urine nitrate	Positive	1.36	0.87–2.12	0.18	0.43	0.06–3.24	0.42
Urine protein	Positive	1.05	0.86–1.28	0.63	0.81	0.33–2.02	0.65
Urine glucose	Positive	0.84	0.69–1.01	0.07	1.02	0.57–1.81	0.96
Urine ketone	Positive	0.94	0.77–1.15	0.54	1.47	0.84–2.58	0.18
Urine bilirubin	Positive	0.96	0.81–1.12	0.59	0.86	0.48–1.53	0.61
Urine occult blood	Positive	1.00	0.93–1.07	0.93	0.95	0.72–1.27	0.74
Urine urobilinogen	Positive	1.92	0.99–3.72	0.05	1.26	0.17–9.64	0.82
Pulmonary function test							
FVC ratio to normal	1%	0.98	0.86–1.12	0.81	1.07	0.69–1.66	0.77
Forced expiratory volume	1 L	0.98	0.83–1.16	0.82	0.84	0.50–1.43	0.53
Eye variables*							
Spherical equivalent	1 dipoter	1.25	1.18–1.34	<0.01	1.25	0.94–1.68	0.13
Cylindrical error (minus format)	1 dipoter	1.56	1.34–1.82	<0.01	1.72	0.70–4.21	0.24

AMD = age-related macular degeneration; aOR = adjusted odds ratio; CI = confidence interval; wk = weeks; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; HBsAg = hepatitis B surface antigen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GTP = gamma-glutamyl transpeptidase; Hb = hemoglobin; HCT = hematocrit; Fe = ferritin; TIBC = total iron-binding capacity; BUN = blood urea nitrogen; WBC = white blood cell; RBC = red blood cell; FVC = forced vital capacity.
*Patients who received cataract surgery were excluded (n = 1,325). For patients with any AMD in one eye, we used the spherical or cylindrical error of the same eye; for patients with or without any AMD in both eyes, we used the average value between the two eyes; [†]Elementary/middle/high/university or higher; [‡]Least/mod/extremely; [§]Conducted between 2010 and 2012 (n = 11,922); [∏]Conducted between 2010 and 2011 (n = 8,007).

aOR: 1.23 in the fourth quintile [+0.06 D ≤ SE < +0.69 D], 95% CI: 0.91−1.68; and aOR: 1.41 in highest quintile [SE ≥ +0.69 D], 95% CI: 1.07−1.86) were statistically significant using multivariable analysis.

Table 6 shows our final model for neovascular AMD and geographic atrophy. Patients in the first quartile of systolic blood pressure (≤110 mmHg) were less likely to have neovascular AMD compared with patients in the second or third quartile (110.3−133.9 mmHg, reference). Only age was associated with geographic atrophy (aOR: 1.10, 95% CI: 1.05−1.17).

Discussion

Prevalence of age-related macular degeneration

The prevalence of early AMD and late AMD was 5.5% and 0.6%, respectively, in Korean adults aged 40 years or older. A recent meta-analysis suggested that AMD was as common in Asian adults as in Caucasian adults, with prevalence estimates of 6.8% and 0.6% for early and late AMD present in Asian adults aged ≥40 years, respectively [4]. In a Beijing eye study, the prevalence of early AMD was 4.2% in participants aged ≥40 years [21], while in a Singapore−Indian eye study, the prevalence of early AMD was 5.6% [22]. In a separate comparative study completed in Singapore and India, the age-standardized prevalence of early and late AMD was 4.45% and 0.34%, respectively, in Singapore and 5.80% and 0.16% in India [12]. Another study using a multiethnic Asian cohort found that the age-standardized prevalence in subjects aged 40 years and older was similar in three Asian ethnic groups: specifically, Chinese with 7.3%; Malay with 7.7%; and Indian with 5.7% [23]. In the Funagata Study performed in Japan, the age-standardized prevalence of early and late AMD was 4.2% and 0.7%, respectively, in subjects

Table 5. Factors associated with early AMD-multivariable logistic regression analysis using dependent variables as quintile or categorical variables

Variables	Unadjusted OR	Adjusted OR (95% CI)	p-value
Age (years)			
40~49	1 (ref)	1 (ref)	
50~59	3.84	3.06 (2.02–4.64)	<0.01
60~69	9.32	6.68 (4.41–10.12)	<0.01
70~79	14.94	11.84 (7.81–17.97)	<0.01
Over 80	16.70	16.30 (8.73–30.42)	<0.01
Sex			
Male	1 (ref)	1 (ref)	
Female	1.38	1.04 (0.76–1.41)	0.82
Smoking			
Never smoker	1 (ref)	1 (ref)	
Ex-smoker	0.87	0.86 (0.61–1.21)	0.39
≤17.77 PY	0.65	1.05 (0.66–1.66)	0.84
17.85~31.5 PY	0.42	0.71 (0.42–1.18)	0.18
≥31.8 PY	0.79	0.78 (0.50–1.22)	0.28
Sleep duration (quintile approximately)			
≤5 hours	1.58	1.04 (0.79–1.38)	0.76
6 hours	0.98	0.98 (0.76–1.25)	0.87
6.5~7.5 hours	1 (ref)	1 (ref)	
8~8.5 hours	0.90	0.78 (0.60–1.01)	0.06
≥9 hours	1.04	0.68 (0.47–1.00)	0.05
HDL-cholesterol (g/dL, quintile)			
≤38.21	0.75	0.67 (0.50–0.90)	<0.01
38.22~43.44	0.77	0.78 (0.57–1.07)	0.13
43.79~48.70	1 (ref)	1 (ref)	
48.81~56.52	0.72	0.76 (0.56–1.04)	0.09
≥56.83	0.85	0.98 (0.73–1.32)	0.89
Vitamin D (ng/mL, quintile)			
≤13.01	0.91	0.99 (0.74–1.33)	0.96
13.02~16.30	0.87	0.92 (0.69–1.22)	0.57
16.31~19.65	1 (ref)	1 (ref)	
19.66~24.21	1.03	1.02 (0.76–1.36)	0.89
≥24.22	1.31	1.28 (0.98–1.68)	0.07
Spherical equivalent (diopter, quintile)			
≤-1.38	0.53	0.53 (0.35–0.78)	<0.01
-1.37~0.50	0.95	0.99 (0.71–1.40)	0.98
-0.50*~0.00	1 (ref)	1 (ref)	
+0.06~ +0.69*	1.73	1.23 (0.91–1.68)	0.18
≥+0.69	2.97	1.41 (1.07–1.86)	0.02

AMD = age-related macular degeneration; OR = odds ratio; CI = confidence interval; PY = pack year, tertile in current smokers; HDL = high density lipoprotein; ref = reference.
*Not included, 0.50 or 0.69.

Table 6. Factors associated with neovascular AMD and geographic atrophy-multivariate logistic regression analysis using dependent variables as quartile or categorical variables for neovascular AMD and as continuous variables for geographic atrophy due to lack of number

Variables	Unadjusted OR	Adjusted OR (95% CI)	p-value
Neovascular AMD			
Age (years)			
40–49	1 (ref)	1 (ref)	
50–59	2.63	4.67 (1.52–14.36)	<0.01
60–69	5.33	10.48 (3.70–29.72)	<0.01
70–79	8.44	16.23 (5.49–47.93)	<0.01
Over 80	17.57	52.59 (15.21–181.81)	<0.01
Sex			
Male	1 (ref)	1 (ref)	
Female	0.55	0.83 (0.38–1.81)	0.64
Binge alcohol user			
No	1 (ref)	1 (ref)	
Yes	1.32	1.86 (0.89–3.89)	0.10
Systolic blood pressure (mmHg)			
≤110 (1st quartile)	0.14	0.25 (0.09–0.67)	<0.01
110.3–133.9 (2nd–3rd quartile)	1 (ref)	1 (ref)	
≥134 (4th quartile)	1.25	0.83 (0.43–1.59)	0.57
Creatinine (g/dL)			
≤0.7 (1st quartile)	0.59	0.76 (0.35–1.66)	0.49
0.71–0.96 (2nd–3rd quartile)	1 (ref)	1 (ref)	
≥0.97 (4th quartile)	1.49	1.34 (0.65–2.76)	0.44
Geographic atrophy			
Age (1 year increase)	1.11	1.10 (1.05–1.17)	<0.01
Sex (female)	0.61	0.34 (0.10–1.12)	0.08
Binge alcohol user (yes)	0.22	0.35 (0.07–1.71)	0.20
SBP (1 mmHg increase)	1.04	1.02 (0.98–1.06)	0.25
Creatinine (1 g/dL increase)	1.14	0.30 (0.01–10.79)	0.51

AMD = age-related macular degeneration; OR = odds ratio; CI = confidence interval; ref = reference; SBP = systolic blood pressure.

aged 35 years and older [8]. In the Hadan Eye Study performed in a rural Chinese population, the age-standardized prevalence among subjects aged 50 years and older for early and late AMD was 4.7% and 0.2%, respectively [23]. In the present study, the prevalence of early AMD was 8.6% in subjects aged 50 years and older (data not shown). Overall, in Asia, the prevalence of early AMD was 4.2% to 7.7%, and that of late AMD was 0.34% to 0.7% in Asian adults aged ≥40 years.

Risk factors for early age-related macular degeneration

Age
Increasing age strongly correlated with increasing prevalence of early AMD. Adjusted ORs for early and late AMD were 1.09 (95% CI: 1.07−1.10) and 1.14 (95% CI: 1.10−1.19), respectively, for each year increase in patients aged 40 years and older (Fig. 2; see Table 1, 2). At 10-year intervals, the prevalence of early AMD increased gradually (1.2% in the 40s, 4.5% in the 50s, 10.2% in the 60s, 15.3% in the 70s, and 16.5% in the 80s), whereas the prevalence of late AMD increased rather abruptly in subjects aged 80 years and older, especially in those with geographic atrophy (0.0% in the 50s, 0.4% in the 60s, 0.4% in the 70s, and 1.7% in the 80s or older) (Table 3). These findings suggest that development of geographic atrophy is associated with the cumulative effects of senile changes and may progress rapidly after 80 years of age. However, no clear explanation for this trend has yet been determined [24,25].

Refractive error
Regarding an association between refraction error and AMD, previous studies have been inconsistent. The Singapore Indian Eye Study [26], the Los Angeles Latino Eye Study (LALES) [27], and other studies [23] have reported that eyes that were more myopic were associated with a lower prevalence of AMD, while the Singapore Malay Eye Study [28], the Rotterdam Study [29], the Age-Related Eye Disease Study [10], the France-DMLA Study [30], the Blue Mountains Eye Study [31], and others [32,33] found a correlation between hyperopic eyes and a higher prevalence of early AMD. Additionally, LALES [27], and the Singapore

Indian Eye Study [34], reported that there was no association between hyperopia and early AMD, though there was an association between myopia and a lower prevalence of early AMD. The Blue Mountains Eye Study [35] and the Beaver Dam Eye Study [36] reported no association between refractive error and early AMD. However, care must be taken in interpreting these previous studies because the definition of refractive error was different in cut values.

The present study found that myopia correlated with a lower prevalence of early AMD but not with late AMD (Table 5). Currently, there is no confirmed reason for an association between AMD and refractive error. However, potential causes for this association could include differences in vitreous body properties, the prevalence of posterior vitreous detachment [37], hemodynamic factors [33], or differences in the intraocular concentration of cytokines between myopic eyes and hyperopic eyes [38]. Differences in hemodynamic factors could be partly explained by the character of the sclera in hyperopic eyes. Hyperopic eyes are generally smaller and have thicker sclera [39]. Some experimental results obtained using laser Doppler flow measurements showed an increased choroidal resistance in AMD [10]. Flow measurements may decrease during the exchange of metabolic products across the RPE, resulting in drusen formation [28],

Sleep duration and HDL cholesterol
The proportions of subjects with sleep times less than five hours per day or nine or more hours per day increased at older ages (data not shown). Thus, age may be a confounding factor in characterizing a possible association between sleep hours and AMD prevalence. Even after age was controlled, multivariable logistic regression showed that subjects who slept nine or more hours per day (highest approximate quintile) were less likely to have early AMD (aOR: 0.68, 95% CI: 0.46−0.99, Table 5). However, there was no association between sleep duration and late AMD.

For analysis of blood test results, we chose to use quintiles for independent variables rather than raw values. Increasing HDL cholesterol was associated with increasing early AMD (aOR: 1.11, 95% CI: 1.02−1.20 in Table 1). However, when patients were divided into quintiles, the lowest quintile (≤38.21 g/dL) of HDL cholesterol was associated with a lower prevalence of early AMD (aOR: 0.68, 95% CI: 0.51−0.92), while the highest quintile of HDL cholesterol was not associ-

ated with a higher prevalence of early AMD (Table 5). There has been controversy over whether HDL cholesterol levels are associated with early AMD [40-42]. Although logistic regression using HDL cholesterol showed a positive association between HDL cholesterol level and prevalence of AMD, an alternative conclusion could be that lower levels of HDL cholesterol had a protective effect rather than higher levels. Based upon these observations, further study is warranted on the role of HDL cholesterol in AMD.

Risk factors for late age-related macular degeneration

Neovascular age-related macular degeneration
Multivariable logistic regression showed that increasing age was associated with a higher prevalence of neovascular AMD, while low systolic blood pressure was associated with a lower prevalence of neovascular AMD (Table 6). Various measures of hypertension or blood pressure have been associated with AMD [34,43]. Our findings suggest that low systolic blood pressure (≤110 mmHg) had a protective effect on the development of neovascular AMD rather than higher blood pressure.

Geographic atrophy
Among continuous variables including age, binge alcohol use, systolic blood pressure, and creatine, multivariable logistic regression analysis showed that only increasing age was associated with geographic atrophy (Table 6). However, the total number of patients associated with geographic atrophy was too small for further analysis, and more cumulative data are needed to obtain further conclusions.

Since this was a cross-sectional study, it was limited in that the temporal cause-and-effect relationships could not be definitively established. More detailed analysis according to severity of AMD (e.g., intermediate AMD) was impossible, as the original data provided classified variables of early, late, and neovascular AMD and geographic atrophy. In addition, early AMD was identified using non-mydriatic fundus photography, which may have resulted in potential misdiagnosis. In addition, participants were required to be able to visit the mobile laboratory to undergo their examinations. Therefore, in some cases, even if certain people were selected as target subjects, their examinations may not have actually been completed, leading to selection bias. The association between smoking and AMD is well-known. In the present study, a significant association was observed in univariate analysis, while smoking was excluded from the final model in multivariate analysis. Other variables may be considered more important than smoking, due to the analysis of various independent variables. On one hand, this may have been caused by some uncontrolled confounding factors, such as sun exposure. In addition, personal biases or recall biases could not be completely eliminated from the data.

In conclusion, age-standardized prevalence of early AMD and late AMD among subjects aged 40 years and older was 5.5% (95% CI: 5.1−5.9) and 0.6% (95% CI: 0.4−0.7), respectively. This study confirmed that increasing age was the most important risk factor for any AMD. Longer sleep duration (nine or more hours per day), low serum level of HDL cholesterol (≤ 38.21 g/dL), and myopia (SE ≤ -1.38 D) were associated with a lower prevalence of early AMD, while hyperopia (SE > +0.69 D) was associated with a higher prevalence of early AMD. Low systolic pressure (≤110 mmHg) was associated with a lower prevalence of neovascular AMD, but higher systolic pressure (≥ 134 mmHg) was not associated with increased neovascular AMD. There were no significant risk factors for geographic atrophy except increasing age.

Authorship statement
The authors alone are responsible for the content and writing of this paper.

Conflicts of interest
The authors declare no conflicts of interest relevant to this article.

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