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# Risk of allergic diseases in age-related macular degeneration: A nationwide cohort study in South Korea

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## Abstract

**Background:** Premorbid allergic diseases are linked with the development of age-related macular degeneration (AMD), however, the risk of allergic diseases among patients with AMD is largely unknown.

**Objective:** To evaluate the association between AMD with or without visual disability (VD) and the risk of allergic diseases.

**Methods:** A total of 2,744,372 Individuals 50 years or older participated in the Korean National Health Screening Program in 2009 were categorized by presence of AMD and VD. Patients were followed until December 2019, and the prospective association of AMD and related VD with incident allergic diseases cases identified during the study period was investigated using the multivariable-adjusted Cox proportional hazard model.

**Results:** During an average follow-up period of 5.87 years, 1,783,370 individuals were diagnosed with allergic diseases. Moreover, an increased risk of allergic diseases was observed in the group of individuals with AMD as compared to the control group (adjusted HR [aHR], 1.13; 95%CI, 1.11–1.14). The risk of atopic dermatitis or allergic rhinitis was more profound than that of asthma (aHR 1.12 [95%CI 1.07–1.18], aHR 1.13 [95%CI 1.11–1.14], and aHR 1.06 [95%CI 1.04–1.09], respectively). Furthermore, patients affected by AMD with VD were at an increased risk of atopic dermatitis (aHR 1.32, 95%CI 1.12–1.56) than those without VD (aHR 1.11, 95%CI 1.05–1.16) when compared with those in the control group.

**Conclusion:** AMD is associated with an increased risk of developing allergic diseases. Further investigations are required to elucidate the underlying mechanisms.

**Key words:** Nationwide cohort, atopic dermatitis, allergic rhinitis, asthma, age-related macular degeneration, visual disability

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## Introduction

Age-related macular degeneration (AMD) is a major cause of blindness in older adults. The global prevalence of AMD is 8.7%. Moreover, it is estimated that the number of patients with AMD will increase to 288 million by 2040.[1] In the United States (US), approximately 11 million individuals are estimated to have AMD.[2] Meanwhile, in South Korea, the overall prevalence of AMD was estimated at 7.4% among individuals aged ≥ 40 years and 18.7% in those aged ≥ 65 years.[3] AMD can pose a threat to public health and add to socioeconomic burden as the associated visual disability (VD) can lead to significant functional loss, reduced quality of life, and depression.[1,2]

Allergic diseases are characterized by chronic inflammation affecting organs, including the eyes, nose, bronchi, and skin resulting from allergens. Allergic disease afflicts an estimated 10–30% of the US population[4] and is considered the most common chronic disease when combined with comorbid conditions.[5] Owing to the high prevalence of allergic diseases, there is a significant economic burden on the health care system and society.[6]

Although the pathogenesis of AMD is largely ambiguous, the involvement of the complement system in the pathogenesis of both AMD[7,8] and allergic diseases[9-12] has been reported. Therefore, the two diseases may share common inflammatory pathways. However, few studies have investigated the association between AMD and allergic diseases. Some studies that mainly focused on asthma and various respiratory diseases reported conflicting results.[13-16] Two epidemiological studies investigating the association between allergy and AMD in Germany and the Netherlands[17] and Taiwan[18] also showed conflicting outcomes (**Supplemental Table 1**). Moreover, the risk of allergic diseases among patients with AMD has not been reported, and VD has not been considered.

Thus, in the study, we used the data from national registry representative of the entire South Korean population to investigate the association between the risk of allergic diseases in patients according to VD.

## Materials and Methods

### *Data source*

We used data from the National Health Insurance System (NHIS) database of South Korea. As it is mandatory for individuals born in South Korea to be registered in the NHI Program, the NHIS database includes more than 50 million individuals, covering approximately 97% of the South Korean population. Moreover, the database contains reimbursement claims submitted by hospitals and clinics, consists of beneficiaries' demographics, medications, procedures, and disease diagnoses coded according to the International Classification of Disease (ICD), 10$^{th}$ revision.[19]

Furthermore, the NHIS database also covers biennial national health examination information, which provides results for laboratory tests (fasting serum glucose, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein cholesterol, and serum creatinine levels); anthropometric measurements (weight, height, and waist circumference); blood pressure reading; and answers to the self-reported questionnaires on lifestyle choices, including smoking, drinking, and exercise habits.[20] Healthcare providers participating in national health examinations should receive regular certification from the NHIS for quality control. Moreover, the participation rate in the health examinations is currently 70% to 80%.[20] The cohort profile has been described in detail in previous studies.[20,21] In this study, the NHIS database was available from 2002 and onwards.

This study adhered to the Declaration of Helsinki, and the study protocol was reviewed and approved by the Statistical Analysis Institutional Review Board (IRB) and Samsung Medical Center (IRB no. 2022-03-060). The Deliberative Committee of the NHIS approved the use of this database for this study.

### *Study population*

A total of 4,470,729 individuals who were 50 years or older were included in the study and underwent the national health examination in 2009. We excluded those with (1) incomplete data (n = 250,392) or (2) diagnosed with allergic diseases (atopic dermatitis [AD], allergic rhinitis [AR], and asthma) before the health examination date (n = 1,475,965). Ultimately, 2,744,372 individuals were included in the study (**Figure 1**). Among all included individuals, those who had no diagnosis of AMD were classified into the control group.

### *Definitions of age-related macular degeneration and visual disability*

AMD was defined using the ICD-10 code (H353) provided by an ophthalmologist within a year before the health examination date. The definition was also adopted in a previous study on AMD.[22-24] To define VD, we used the national disability registration system of South Korea, which was adopted in 1988, to determine welfare benefits depending on disability type and severity.[25]

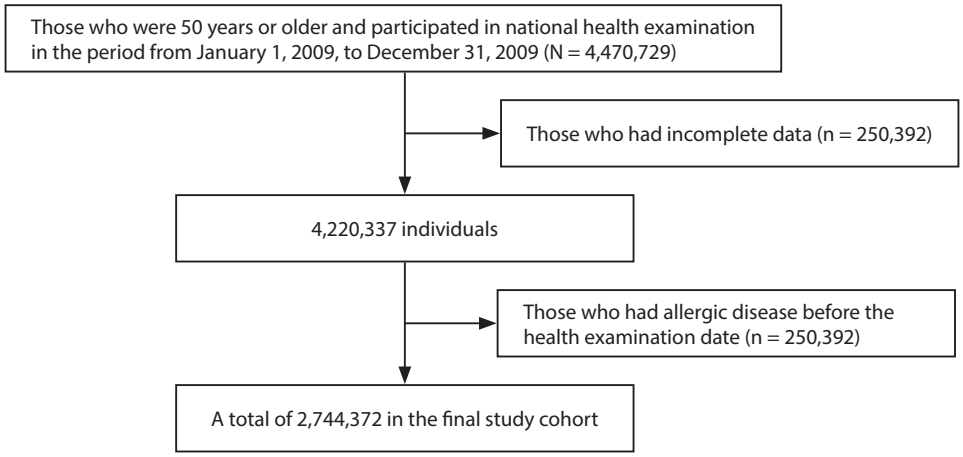


**Figure 1. Research cohort.**

To be registered on the national disability registration system as a patient with VD, a disability diagnosis based on defined criteria made by an ophthalmologist must be submitted (**Supplemental Table 2**).

***Study outcomes***

Primary outcomes included the diagnosis of AD, AR, and asthma during follow-up. In the study, we identified all individuals with allergic diseases using the diagnostic codes for AD (L20), AR (J301–304), or asthma (J45–46) with three or more repeated hospital visits per year. The operational definition was adopted from previous studies.[26,27] Moreover, the study cohort was tracked from the baseline health examination in 2009, until a newly diagnosed allergic condition during the study period, death, censoring (outmigration), or December 31, 2019, whichever occurred first.

***Covariates***

Several variables included as covariates in the statistical analyses were found to be associated with each aforementioned allergic disease in previous studies as follows: hypertension,[28-30] diabetes mellitus,[31,32] dyslipidemia,[33-35] alcohol consumption,[32,36,37] physical activity,[38,39] and the Charlson comorbidity index (CCI).[40] Diabetes mellitus was defined using ICD-10 codes (E10-E14) with a prescription of at least one antidiabetic medication or a fasting blood glucose level of 126 mg/dL. Hypertension was defined as any of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or treatment with an antihypertensive medication that was linked to the arterial hypertension ICD-10 codes (I10–I13 and I15) and resulted in at least one claim in a year. Moreover, dyslipidemia was defined using the ICD-10 code (E78) with at least one prescription of a lipid-lowering drug or a total cholesterol level of 240 mg/dL or more.

Smoking behavior was categorized as "none," "ex," and "current". Individuals who replied in affirmative that "Yes, I am currently smoking" were considered current smokers. However, individuals who responded "no" to the question of current smoking and "yes" to the question "Have you smoked at least 100 cigarettes, five packs, throughout your entire life?" were considered ex-smokers. Participants were inquired about their weekly alcohol consumption, which was calculated by multiplying the frequency of alcohol consumption with the amount of alcohol consumed per occasion. Furthermore, alcohol consumption was classified into four categories: 1) none, 2) light drinkers (less than 15 g/day on average), 3) moderate drinkers (> 15 g/day but less than 30 g/day), and 4) heavy drinkers (> 30 g/day).[41] Regular exercise was defined as strenuous physical activity performed at least five times a week for a minimum of 30 min. The body mass index was determined by dividing the weight in kilograms by the square of the height in meters ($kg/m^2$), whereas abdominal obesity was defined as ≥ 90 cm for men and ≥ 85 cm for women according to the Korean Society for the Study of Obesity.[42] The CCI has been widely adopted as an indicator of composite health status. To calculate CCI, 19 diseases (congestive heart failure, myocardial infarction, peripheral vascular disease, dementia, cerebrovascular disease, connective tissue disease, chronic lung disease, ulcer, chronic liver disease, diabetes, moderate or severe kidney disease, hemiplegia, diabetes with end-organ damage, leukemia, lymphoma, tumor, moderate or severe liver disease, malignant tumor, metastasis, and acquired immunodeficiency syndrome) are included in the index, and each condition is assigned a point from 1 to 6. The points are then summed to produce the index. In the study, the CCI was calculated using ICD-10 codes.[43,44]

### *Statistical analysis*

For descriptive statistics, continuous and categorical variables are presented as means ± standard deviation and number (percentage). Differences between the groups (non-AMD vs. AMD and AMD without VD vs. AMD with VD) were analyzed using independent t-test for continuous variables and $\chi^2$ test or the Fisher's exact test for categorical variables. The Cox proportional hazards analysis was performed to evaluate the risk of AD, AR, and asthma associated with the presence of AMD and VD, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Stratified analyses were performed according to age; sex; and comorbidities (diabetes, hypertension, or dyslipidemia). Moreover, *P*-values for the interactions between variables were also evaluated. Forest plots for HRs and 95% CIs by subgroup were established. All statistical analyses were performed using the SAS statistical package version 9.4 (SAS Institute Inc., Cary, NC, USA), and a value of $p < 0.05$ was considered statistically significant.

## Results

### *Baseline characteristics*

Of the 2,744,372 individuals, 29,166 (1.06%) had AMD at the time of health examination. Compared to individuals without AMD, those with AMD were more likely to be women; older; with lower income; rural inhabitants; non-smokers; non-drinkers; and diagnosed with hypertension, diabetes, or dyslipidemia with statistical significance (**Table 1**).

Of the 29,166 individuals with AMD, 2,135 (7.31%) also had associated VD at the time of health examination. Individuals suffering from AMD with VD were more likely to be men, older, urban inhabitants, with higher income, non-smokers, non-drinkers, and diagnosed with hypertension and diabetes with statistical significance than those without VD (**Supplemental Table 3**).

**Table 1. Baseline characteristics between individuals with/without age-related macular degeneration.**

| Variables | AMD Absent (n = 2,715,206) | AMD Present (n = 29,166) | *p* value |
|---|---|---|---|
| Sex (male) | 1,412,041 (52.0) | 12,963 (44.5) | < 0.01 |
| Age (year) | 60.1 ± 8.2 | 66.8 ± 8.6 | < 0.01 |
| Smoking | | | < 0.01 |
| Non-smoker | 1,738,170 (64.0) | 21,076 (72.3) | |
| Ex-smoker | 440,109 (16.1) | 4,641 (15.9) | |
| Current Smoker | 536,927 (19.8) | 3,449 (11.8) | |
| Alcohol consumption | | | < 0.01 |
| None | 1,686,168 (62.1) | 21,452 (73.6) | |
| Less than 30 g/day | 829,885 (30.6) | 6,424 (22.0) | |
| More than 30 g/day | 199,153 (7.3) | 1,290 (4.4) | |
| Regular exercise† | 568,235 (20.9) | 5,994 (20.6) | 0.12 |
| Income Low* | 586,452 (21.6) | 5,276 (18.1) | < 0.01 |
| Place (urban) | 1,210,246 (44.6) | 11,788 (40.4) | < 0.01 |
| Body-mass index | 24.01 ± 3.0 | 23.9 ± 3.0 | < 0.01 |
| Diabetes | 401,107 (14.8) | 6,504 (22.3) | < 0.01 |
| Hypertension | 1,200,091 (44.2) | 16,864 (57.8) | < 0.01 |
| Dyslipidemia | 714,973 (26.3) | 9,548 (32.7) | < 0.01 |
| Charlson comorbidity index | 1.0 ± 1.2 | 1.6 ± 1.5 | < 0.01 |
| Waist circumference | 82.1 ± 8.3 | 82.5 ± 8.3 | < 0.01 |
| Systolic blood pressure | 126.7 ± 16.0 | 128.4 ± 16.1 | < 0.01 |
| Diastolic blood pressure | 78.2 ± 10.3 | 77.8 ± 10.1 | < 0.01 |
| Fasting blood glucose | 102.3 ± 27.9 | 104.4 ± 29.9 | < 0.01 |

**Table 1. (Continued)**

| Variables | AMD Absent (n = 2,715,206) | AMD Present (n = 29,166) | *p* value |
|---|---|---|---|
| High-density lipoprotein | 55.6 ± 31.4 | 55.3 ± 34.0 | 0.13 |
| Low-density lipoprotein | 118.8 ± 39.4 | 118.4 ± 40.0 | 0.09 |
| Triglyceride | 121.2 (121.2–121.3) | 120.9 (120.4–121.5) | 0.04 |
| Glomerular filtration rate | 83.2 ± 33.6 | 80.3 ± 34.4 | < 0.01 |

**Abbreviations:** AMD, Age-related Macular Degeneration.
Numerical continuous parameters were described as mean ± standard deviation, and categorical parameters were described as total numbers (percentages).
*Individuals with income of less than the lower 20th percentile were defined as low income.
†Regular exercise was defined as strenuous physical activity performed for at least 30 minutes at least five times a week.

***Incidence of AD, AR, and asthma by age-related macular degeneration and presence of visual disability***

Overall, 1,783,370 individuals (64.98%) were diagnosed with AD, AR, or asthma. The number of patients diagnosed with only AD, AR, and asthma was 121,853, 1,694,179, and 518,472, respectively. The cumulative incidence of AD/AR/asthma was significantly higher in the AMD group than that in the non-AMD group (**Figure 2A**). However, no difference was found between the "AMD without VD" and "AMD with VD" groups (**Figure 2B**). The cumulative incidence of each allergic disease is shown in **Supplemental Figure 1**.

In the fully adjusted model, the adjusted HR (aHR) of incident AD/AR/asthma cases were 1.13 (95%CI, 1.11–1.14) in the AMD group compared with the control group. When dividing the AMD group into those with and without VD, the aHRs of incident AD/AR/asthma cases were 1.15 (95%CI, 1.10–1.21) and 1.12 (95%CI, 1.11–1.14) in AMD with and without VD groups, respectively, when compared with that of control group (**Table 2**). When focusing on the risk of each allergic disease separately, the aHR of asthma in the AMD group was 1.06 (95%CI, 1.04–1.09), which was not much different from that of AR [1.13 (95%CI, 1.11–1.14)] and that of AD [1.12 (95%CI 1.07–1.18)].

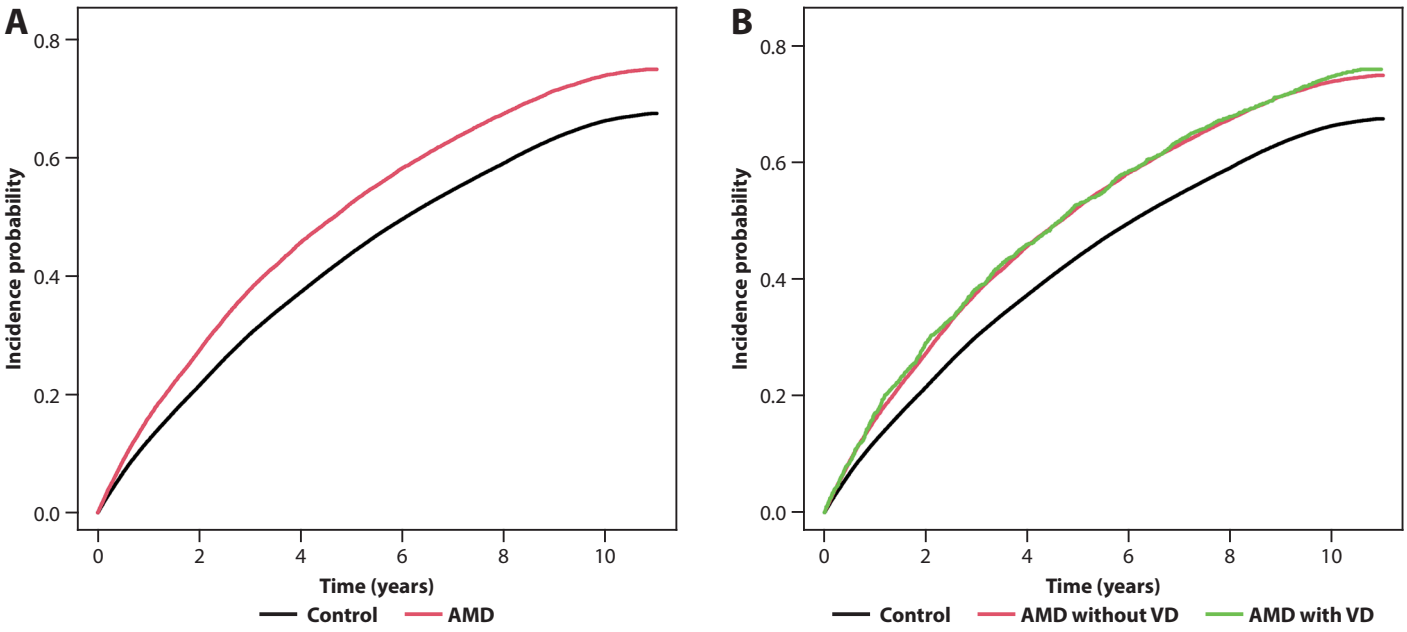


**Figure 2. Cumulative incidence of atopic dermatitis (AD), allergic rhinitis (AR), or asthma according to age-related macular degeneration (AMD) with/without visual disability (VD).**

**Abbreviations:** AD, Atopic dermatitis; AR, Allergic rhinitis; AMD, Age-related macular degeneration; VD, Visual disability.

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**Table 2. Cox regression analysis on risk of atopic dermatitis, allergic rhinitis, and asthma by AMD, and AMD with/without VD.**

| | N | Events | Person-year | IR | Crude (HR with 95%CI) | Model 1* (HR with 95%CI) | Model 2† (HR with 95%CI) | Model 3‡ (HR with 95%CI) |
|---|---|---|---|---|---|---|---|---|
| Atopic dermatitis or Allergic rhinitis or asthma | | | | | | | | |
| Control | 2,715,206 | 1,762,671 | 15,954,755.7 | 110.5 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD | 29,166 | 20,699 | 147,115.6 | 140.7 | 1.26 (1.25, 1.28) | 1.19 (1.17, 1.20) | 1.18 (1.16, 1.20) | 1.13 (1.11, 1.14) |
| Control | 2,715,206 | 1,762,671 | 15,954,755.7 | 110.5 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD without VD | 27,031 | 19,198 | 136,692.2 | 140.4 | 1.26 (1.24, 1.28) | 1.18 (1.17, 1.20) | 1.18 (1.16, 1.19) | 1.12 (1.11, 1.14) |
| AMD with VD | 2,135 | 1,501 | 10,423.4 | 144.0 | 1.29 (1.23, 1.36) | 1.22 (1.16, 1.29) | 1.22 (1.16, 1.28) | 1.15 (1.10, 1.21) |
| Atopic dermatitis | | | | | | | | |
| Control | 2,715,206 | 120,182 | 26,591,197.9 | 4.52 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD | 29,166 | 1,671 | 275333.7 | 6.07 | 1.35 (1.29, 1.42) | 1.18 (1.13, 1.24) | 1.18 (1.13, 1.24) | 1.12 (1.07, 1.18) |
| Control | 2,715,206 | 120,182 | 26591197.9 | 4.52 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD without VD | 27,031 | 1,529 | 255746.8 | 5.98 | 1.33 (1.27, 1.40) | 1.17 (1.11, 1.23) | 1.17 (1.11, 1.23) | 1.11 (1.05, 1.16) |
| AMD with VD | 2,135 | 142 | 19586.8 | 7.25 | 1.64 (1.39, 1.93) | 1.41 (1.20, 1.66) | 1.41 (1.19, 1.66) | 1.32 (1.12, 1.56) |
| Allergic rhinitis | | | | | | | | |
| Control | 2,715,206 | 1,674,722 | 16645861.3 | 100.6 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD | 29,166 | 19,457 | 157079.4 | 123.9 | 1.22 (1.21, 1.24) | 1.18 (1.17, 1.20) | 1.18 (1.16, 1.19) | 1.13 (1.11, 1.14) |
| Control | 2,715,206 | 1,674,722 | 16645861.3 | 100.6 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD without VD | 27,031 | 18,068 | 145808.1 | 123.9 | 1.22 (1.21, 1.24) | 1.18 (1.17, 1.20) | 1.18 (1.16, 1.19) | 1.13 (1.11, 1.14) |
| AMD with VD | 2,135 | 1,389 | 11271.3 | 123.2 | 1.22 (1.15, 1.28) | 1.19 (1.13, 1.26) | 1.19 (1.13, 1.25) | 1.13 (1.07, 1.19) |
| Asthma | | | | | | | | |
| Control | 2,715,206 | 511,338 | 24479823.0 | 20.9 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD | 29,166 | 7,134 | 244989.1 | 29.1 | 1.40 (1.37, 1.43) | 1.13 (1.10, 1.15) | 1.13 (1.10, 1.15) | 1.06 (1.04, 1.09) |
| Control | 2,715,206 | 511,338 | 24479823.0 | 20.9 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| AMD without VD | 27,031 | 6,605 | 227533.0 | 29.0 | 1.40 (1.36, 1.43) | 1.12 (1.10, 1.15) | 1.12 (1.10, 1.15) | 1.06 (1.04, 1.09) |
| AMD with VD | 2,135 | 529 | 17456.1 | 30.3 | 1.46 (1.34, 1.59) | 1.17 (1.08, 1.28) | 1.17 (1.07, 1.27) | 1.10 (1.01, 1.19) |

Hazard ratios (95% CI) were calculated using a Cox proportional hazards model
Statistically significant results are marked with bold
**Abbreviations:** IR, Incidence rate per 1000 persons

***Stratified analyses***

When stratified by sex, the risk of incident AD/AR/asthma cases in AMD was more pronounced in men than that in women (for interaction $p < 0.01$) (**Supplemental Figure 2**). Moreover, when stratified by the presence of chronic diseases (diabetes, hypertension, and dyslipidemia); smoking status; and drinking habits, individuals without chronic disease, past/current smoking, or mild/heavy drinking had a more pronounced risk of AD/AR/asthma in AMD than those without chronic disease, non-smoking, and non-drinking (for interaction $p < 0.01$). When the AMD group was divided into AMD with and without VD groups in the stratified analysis, both groups showed a comparable increased risk of AD/AR/asthma in male individuals, the absence of chronic disease, past/current smoking, or mild/heavy drinking (**Supplemental Figure 3**).

## Discussion

In this longitudinal population-based study of nearly 30,000 patients, we found that AMD was associated with an increased risk of allergic diseases compared to a control group without AMD. Among the allergic diseases, the additional increased risk when accompanied by VD was most profound in AD. The association between AMD and allergic diseases was more prominent when individuals were men; smokers; drinkers; and did not have comorbidities (hypertension, diabetes, and dyslipidemia).

Previous studies evaluating the association between AMD and allergic diseases have mostly focused on asthma. In China, Sun et al.[15] reported that odds ratio (OR) of asthma in neovascular AMD patients was 1.72 (95%CI 1.07–2.76), whereas in the US, Lynch et al.[16] also established a relationship between AMD and asthma (OR 2.34, 95%CI 1.22–4.46). However, Moorthy et al.[14] determined no association exists between AMD and asthma in US patients (OR 1.06, 95%CI 0.86–1.27), and Ristau et al.[17] even discovered a protective effect of allergy in cases of AMD from German and Dutch population (OR 0.75 in German and OR 0.76 in Dutch populations, respectively). After these conflicting results, Shen et al.[18] recently reported that AMD is significantly associated with premorbid allergic diseases (OR 1.54, 95%CI 1.47–1.61) using the largest cohort (10,911 AMD participants). All the aforementioned studies are cross-sectional studies, and the only longitudinal study that showed no significance in the cumulative incidence or progression of AMD among US patients with asthma was conducted by Klein et al.[13] However, the number of participants included in the particular study was relatively small. Additionally, previous studies have reported an increased risk of AMD in patients with allergic diseases.

In the longitudinal study, we reported an increased risk of allergic diseases in patients with AMD using a nationwide cohort. Among allergic diseases, AD and AR showed a similar increase in risk, while the risk of asthma was comparatively lower. The relatively weak association between AMD and asthma may be related to the conflicting results from previous studies conducted on asthmatic patients. Furthermore, in the Taiwanese study,[18] allergic conjunctivitis (OR 2.07, 95%CI 1.94–2.20) and AR (OR 1.32, 95%CI 1.25–1.39) showed an association with AMD, but asthma itself did not demonstrate a significant association. Interestingly, contrary to this study, there was no significant association of AMD with AD itself.

Limited literature confirms the association between AMD, and development of allergic diseases as investigations on allergic diseases among patients with AMD are insufficient. AMD and allergic diseases are multifactorial processes linked by a complex combination of hereditary and environmental factors. However, there are still shared features between the two diseases, and we can hypothesize about the underlying mechanisms based on the pathophysiology of the two diseases.

The complement system plays a complex role in the pathogeneses of AMD and allergic diseases. Recent studies have generated significant interest in the inflammatory underpinnings of AMD pathogenesis.[45] The variation of complement factor H (*CFH*) gene is one of the most popular genetic risk factors in AMD,[8] and the impairment of complement inhibitory activity by CFH contributes to AMD pathogenesis. Other confirmed genes in the complement pathway of AMD also include C2, CFB, C3 and CFI.[46-48] Allergy is an immune-mediated inflammatory response that frequently results in allergic diseases. The complement system plays numerous proinflammatory and immunoregulatory roles in the initiation and regulation of allergic immune responses. Several studies have demonstrated the relationship between the complement system with asthma,[9,10,49] AR,[10] and AD.[50] Interestingly, among the complement-related genes associated with AMD, C2 and CFB genes also have been implicated in pollen allergic sensitization.[51] The involvement of C2 and CFB in both AMD and allergic sensitization suggests a potential shared genetic susceptibility between these conditions, despite their different pathophysiological contexts.

Recent evidence shows elevated plasma levels of IL-4, IL-5, and IL-13 in AMD patients.[52,53] These type 2 immune response cytokines are key mediators in allergic diseases, suggesting a potential mechanistic link between AMD and allergic conditions. Future studies should investigate these cytokines in AMD patients with and without allergic conditions.

Another possible mechanism involves various common risk factors of the two diseases. Firstly, smoking is a strong and consistent risk factor for AMD,[54] with reports suggesting that it may affect the epithelial barrier associated with elevated level of total IgE. Moreover, active smoking may increase the risk of sensitization to allergens, asthma, AR, and AD.[55-57] Secondly, dietary changes, such as decreased fruits and vegetables, which may affect gut microbiota and related metabolites have been linked to the increased prevalence of atopic disorders.[57-59] Similarly, in AMD, a diet rich in healthy nutrient-rich foods, such as fruits, vegetables, legumes, and fish, was associated with a 41% reduced risk of advanced AMD.[60] Lastly, obesity is a systemic risk factor of both AMD[61] and asthma.[62] Obesity can also result in decreased immunological tolerance to allergens.[63]

Interestingly, the risk of AD was higher in AMD patients with VD than in those without VD, whereas the risk of AR or asthma is not. It is not surprising that these differences exist among allergic diseases because of their various clinical phenotypes based on factors related to their pathogenesis, such as genetic, epigenetic, and environmental factors.[64] Furthermore, while AMD is a major cause of visual impairment, the limitations of our dataset prevented us from confirming that AMD was the sole cause of VD in all participants classified as 'AMD with VD'. A subset of individuals may have had VD from other ophthalmic conditions. However, our results demonstrate that the presence of VD in AMD patients, regardless of its specific etiology, is associated with an additional increased risk of AD development. Future studies with more detailed clinical data could help elucidate the specific relationship between AMD-induced VD and allergic disease risk.

A strength of this study was the use of a nationwide population-based dataset that provides a sufficient sample size and statistical power to explore the association between AMD with or without VD and allergic diseases. However, the study had some limitations. First, since patients with non-advanced AMD are generally asymptomatic, a number of patients with AMD might have been misdiagnosed and included in the control group. AMD is associated with the development of allergic diseases, which could result in the null hypothesis. Therefore, the actual association between AMD and allergic diseases may be much stronger than the results of the current study. Second, owing to the difficulty in detecting allergic diseases with diagnostic codes and difficulties faced in accessing healthcare, particularly in AMD patients with VD, allergic diseases might go undiagnosed. Third, the results obtained from the study should be carefully applied to other ethnicities, as this cohort mainly consisted of Koreans. Fourth, our access to diagnostic codes is limited to records from 2002 onwards. Consequently, we are unable to distinguish between individuals diagnosed with allergic conditions prior to 2002 who may not have reported symptoms between 2002 and 2009, and those who developed new allergic conditions after 2009. This limitation may impact our ability to accurately determine the incidence of new allergic conditions in our study population, potentially including some relapsed cases in our incident cases group. Finally, along with the potential misclassification bias described above, the limitations of the study also included unmeasured confounding factors, missing data, and changing eligibility over time.

In conclusion, this study revealed that patients with AMD were more likely to develop allergic diseases, including AD, AR, and asthma. Furthermore, the presence of VD in patients with AMD further increases their risk of developing AD. The findings suggest that the pathogeneses of AMD and other allergic diseases may overlap. Additionally, the modification of systemic risk factors in patients with AMD may help reduce the risk of disease progression and allergic disease development.

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## Conflict of interest

The authors declare that they have no relevant conflicts of interest.

## Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

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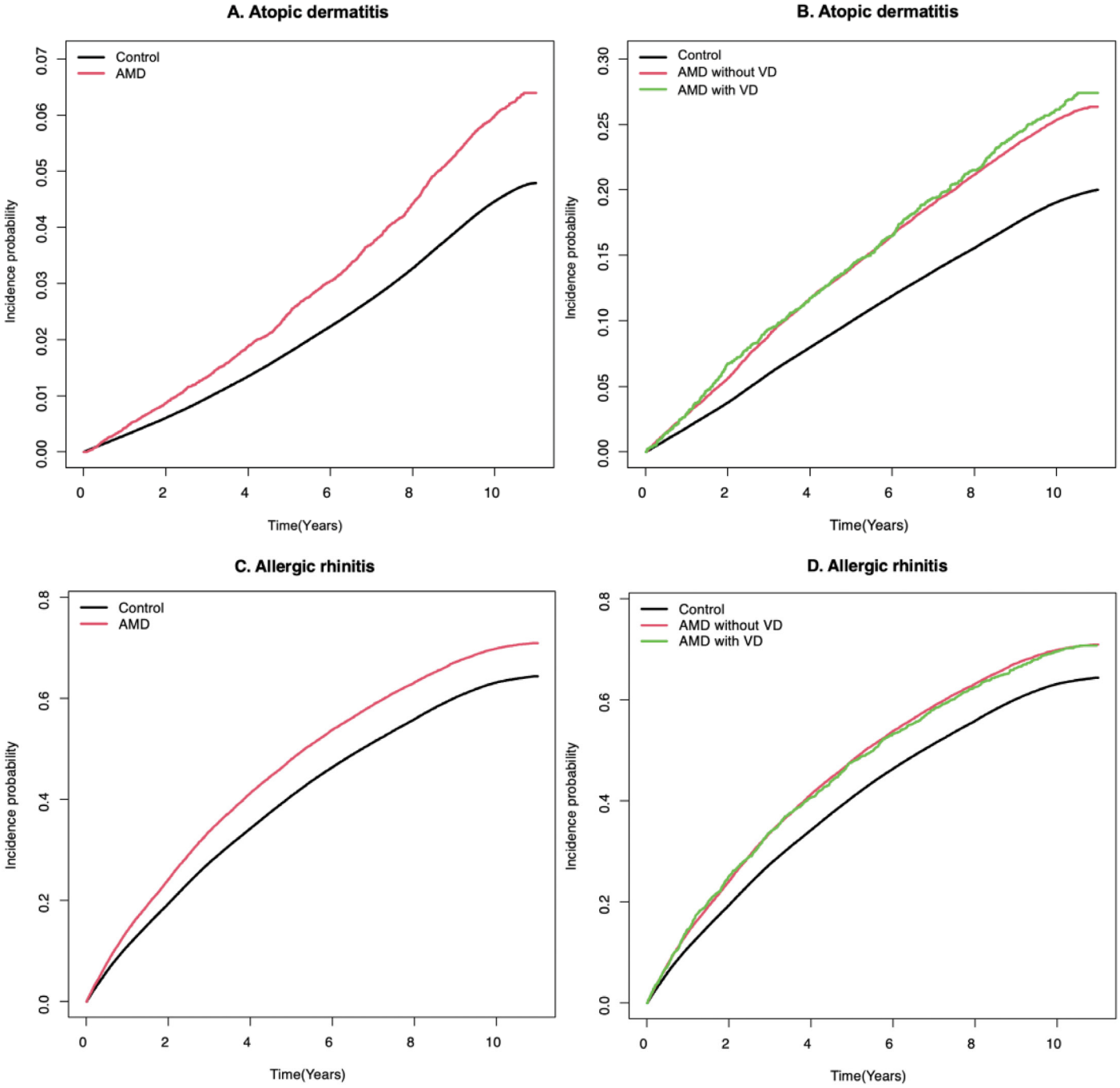


**Figure S1.** Graphs of cumulative incidence probability of (A) Atopic dermatitis (C) Allergic rhinitis, and (E) Asthma grouped by the presence of age-related macular degeneration. Graphs of cumulative incidence probability of (B) Atopic dermatitis, (D) Allergic rhinitis, and (F) Asthma grouped by the presence of age-related macular degeneration with/without visual disability.

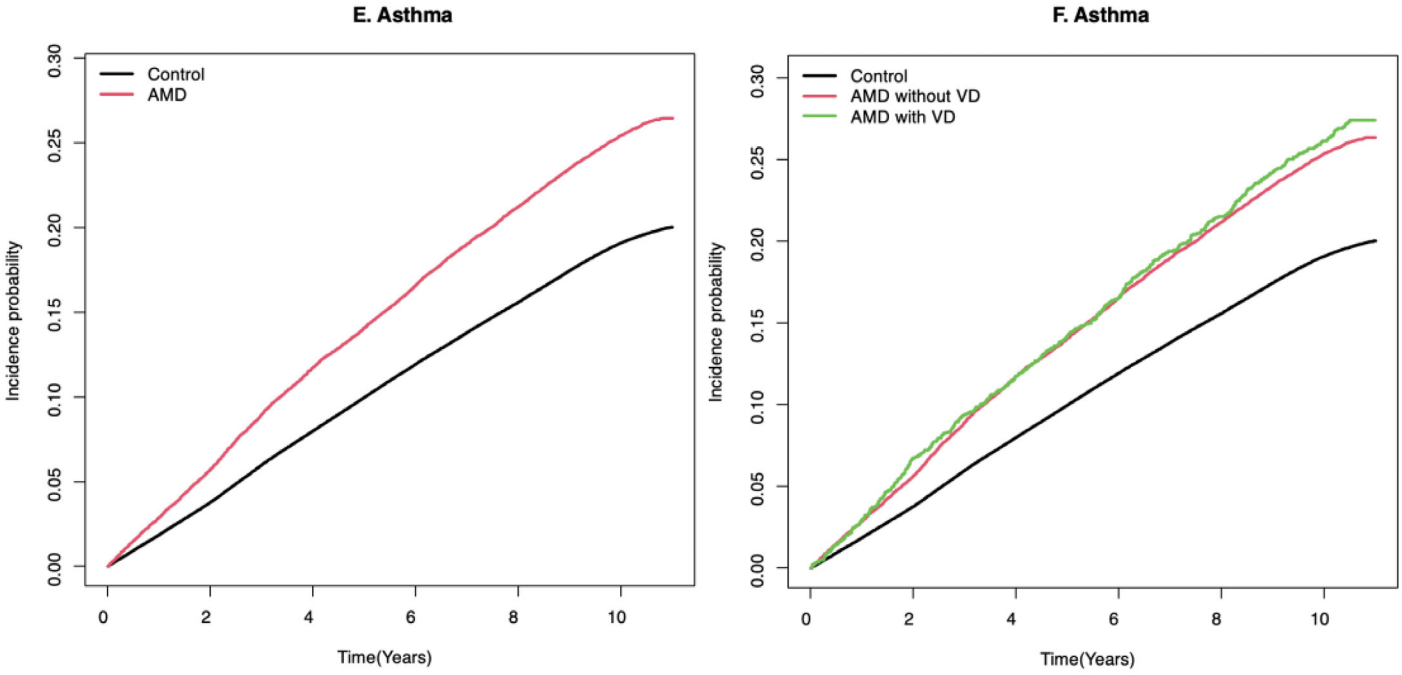


**Figure S1. (Continued)**

| Subgroup | | No. of AD or AR or asthma | HR with 95% CI | P for interaction |
|---|---|---|---|---|
| Male | Control | 853,050 | 1 (ref.) | |
| | AMD | 9,023 | 1.253 (1.227, 1.279) | <0.01 |
| Female | Control | 909,621 | 1 (ref.) | |
| | AMD | 11,676 | 1.043 (1.024, 1.062) | |
| Diabetes or hypertension or dyslipidemia (-) | Control | 716,729 | 1 (ref.) | |
| | AMD | 5,965 | 1.184 (1.154, 1.214) | <0.01 |
| Diabetes or hypertension or dyslipidemia (+) | Control | 1,045,942 | 1 (ref.) | |
| | AMD | 14,734 | 1.103 (1.085, 1.121) | |
| Smoke, Non | Control | 1,172,359 | 1 (ref.) | |
| | AMD | 15,087 | 1.09 (1.073, 1.108) | |
| Smoke, Ex | Control | 282,985 | 1 (ref.) | <0.01 |
| | AMD | 3,273 | 1.178 (1.138, 1.22) | |
| Smoke, Current | Control | 307,327 | 1 (ref.) | |
| | AMD | 2,339 | 1.313 (1.261, 1.368) | |
| Drink, Non | Control | 1,131,295 | 1 (ref.) | |
| | AMD | 15,280 | 1.094 (1.077, 1.112) | |
| Drink, Mild | Control | 515,814 | 1 (ref.) | <0.01 |
| | AMD | 4,562 | 1.229 (1.194, 1.266) | |
| Drink, Heavy | Control | 115,562 | 1 (ref.) | |
| | AMD | 857 | 1.182 (1.105, 1.264) | |



**Figure S2.** Forest plots for subgroup analyses of atopic dermatitis (AD)/allergic rhinitis (AR)/Asthma development by the presence of age-related macular degeneration (AMD). Individuals without AMD were set as a reference group for each subgroup category, and adjusted hazard ratios (95% CIs) were calculated using a Cox proportional hazards model.

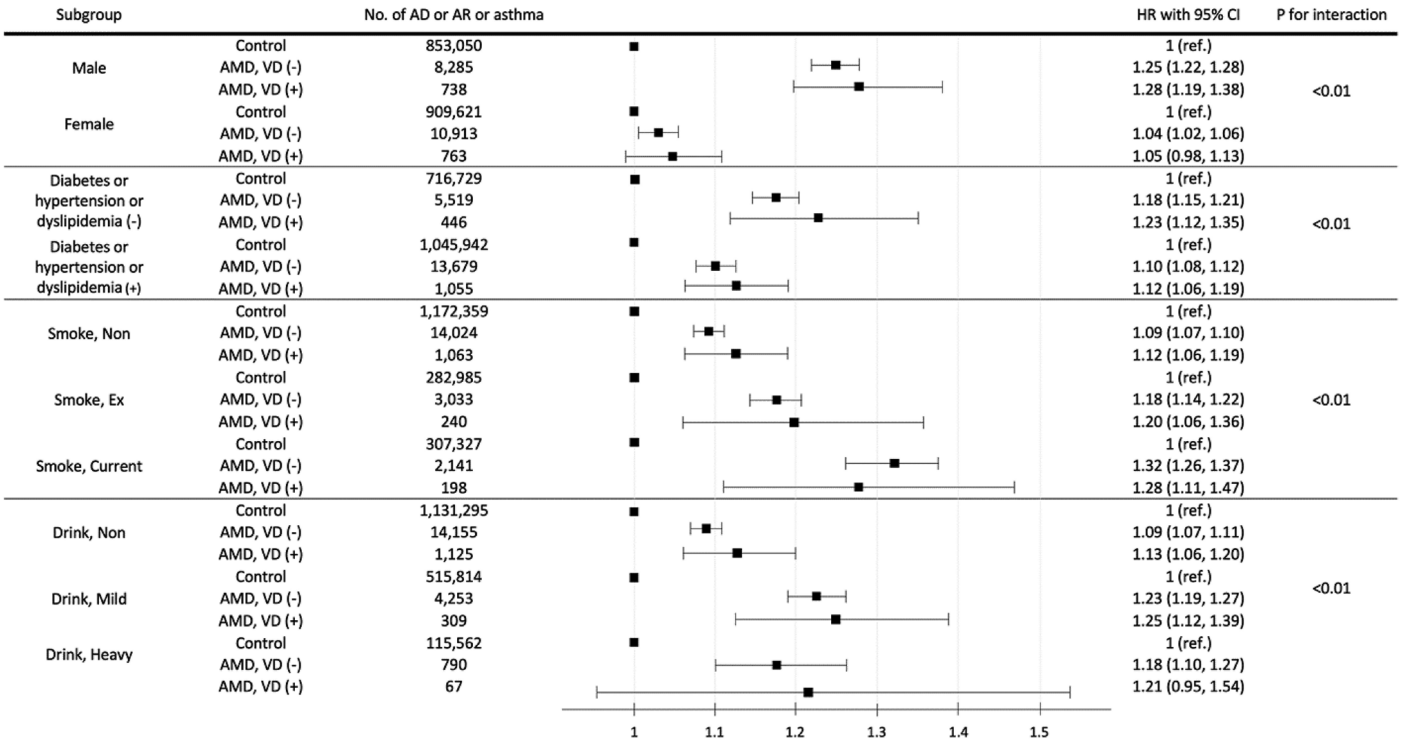


**Figure S3.** Forest plots for subgroup analyses of atopic dermatitis (AD)/allergic rhinitis (AR)/Asthma development by the presence of age-related macular degeneration (AMD) with/without visual disability (VD). Individuals without AMD were set as a reference group for each subgroup category, and adjusted hazard ratios (95% CIs) were calculated using a Cox proportional hazards model.

**Table S1. Summary of prior studies on the association between age-related macular degeneration (AMD) and allergy.**

| Study | Participants, country | No. of Participants | Age (years, mean ± SD) | Follow-up (years) | Adjustment or comparison | Disease or outcome | Exposure | Main finding (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Cross-sectional study | | | | | | | | |
| Moorthy et al. (2011) | AMD, US | 587 | N/A | N/A | Age, sex, ethnicity, study center, smoking, and hypertension | AMD | Physician-diagnosed asthma | OR 1.06 (0.86–1.27) |
| Sun et al. (2012) | AMD, China | 462 | N/A | N/A | No | nAMD | History of Asthma (Self-report) | OR 1.72 (1.07–2.76) |
| Ristau et al. (2013) | AMD, Germany and Netherlands | 864 in German and 938 in Dutch | 76.4 ± 8.8 in German and 75.4 ± 7.7 in Dutch | N/A | Age, sex, use of corticosteroids, and smoking | AMD and late AMD | History of Allergy (Self-report) | AMD<br>OR 0.75 (0.59–0.95) in German<br>OR 0.76 (0.57–0.99) in Dutch<br>Late AMD<br>OR 0.49 (0.35–0.69) in German<br>OR 0.64 (0.46–0.88) in Dutch |
| Lynch et al. (2019) | AMD, US | 157 | N/A | N/A | Age | Early/Intermediate AMD | History of Asthma (review of medical record) | OR 2.34 (1.22–4.46) |
| Shen at al. (2021) | AMD, Taiwan | 10,911 | 67.1 (median) | N/A | Age, sex, urbanization level, occupation category, monthly income, hypertension, diabetes, hyperlipidemia, and obesity | AMD (ICD-9-CM 362.5) | Allergic diseases including allergic conjunctivitis (ICD-9-CM 372.05 and 372.14), allergic rhinitis (ICD-9-CM 477), asthma (ICD-9-CM 493), and atopic dermatitis (ICD-9-CM 691) | OR 1.54 (1.47–1.61) |
| Longitudinal study | | | | | | | | |
| Klein et al. (2008) | Asthma, US | 163 | N/A | 10 | Age, sex | AMD | History of asthma | No significance in cumulative incidence or progression of AMD |

**Abbreviations:** AMD, age-related macular degeneration; CI, confidence interval; nAMD, neovascular age-related macular degeneration.

**Table S2. Criteria for visual disability grading in South Korea.**

| | |
|---|---|
| Grade 1 | Visual acuity of the better eye is less or equal to 20/1000 |
| Grade 2 | Visual acuity of the better eye is less or equal to 20/500 |
| Grade 3 | Visual acuity of the better eye is less or equal to 20/300<br>Or visual field of each eye is less than 5 degrees in any direction |
| Grade 4 | Visual acuity of better eye is less or equal to 20/200<br>Or visual field of each eye is less than 10 degrees in any direction |
| Grade 5 | Visual acuity of the better eye is less or equal to 20/100<br>Or sum of the visual field of both eyes is less than 50% of normal |
| Grade 6 | Visual acuity of the worse eye is less or equal to 20/1000 |

Visual acuity is given based on the Snellen visual acuity system.

**Table S3. Baseline characteristics between subjects with age-related macular degeneration with/without visual disability.**

| | AMD without VD (n = 27,031) | AMD with VD (n = 2,135) | *p*-value |
|---|---|---|---|
| Sex (male) | 11894 (44.0) | 1069 (50.1) | < 0.01 |
| Age (year) | 66.7 ± 8.6 | 67.4 ± 8.4 | < 0.01 |
| Smoking | | | < 0.01 |
| Non-smoker | 19582 (72.4) | 1494 (70.0) | |
| Ex-smoker | 4294 (15.9) | 347 (16.3) | |
| Current Smoker | 3155 (11.7) | 294 (13.8) | |
| Alcohol consumption | | | < 0.01 |
| None | 19859 (73.5) | 1593 (74.6) | |
| Less than 30 g/day | 5983 (22.1) | 441 (20.7) | |
| More than 30 g/day | 1189 (4.4) | 101 (4.7) | |
| Regular exercise† | 5551 (20.5) | 443 (20.8) | 0.28 |
| Income Low* | 4850 (17.9) | 426 (20.0) | < 0.01 |
| Place (urban) | 10919 (40.4) | 869 (40.7) | < 0.01 |
| Body-mass index | 23.9 ± 3.0 | 23.8 ± 3.0 | < 0.01 |
| Diabetes | 15629 (57.8) | 1235 (57.9) | < 0.01 |
| Hypertension | 5997 (22.2) | 507 (23.8) | < 0.01 |
| Dyslipidemia | 8880 (32.9) | 668 (31.3) | < 0.01 |
| Charlson comorbidity index | 1.6 ± 1.5 | 1.6 ± 1.5 | < 0.01 |
| Waist circumference | 82.5 ± 8.3 | 82.9 ± 8.5 | < 0.01 |
| Systolic blood pressure | 128.4 ± 16.0 | 128.2 ± 17.0 | < 0.01 |
| Diastolic blood pressure | 77.8 ± 10.0 | 77.5 ± 10.3 | < 0.01 |
| Fasting blood glucose | 104.4 ± 29.8 | 104.8 ± 31.0 | < 0.01 |
| High-density lipoprotein | 55.4 ± 33.6 | 54.9 ± 39.5 | 0.30 |
| Low-density lipoprotein | 118.5 ± 40.0 | 117.7 ± 40.0 | 0.21 |
| Triglyceride | 120.3 (119.6–121.0) | 121.5 (118.9–124.2) | 0.04 |
| Glomerular filtration rate | 80.4 ± 34.4 | 79.9 ± 34.3 | < 0.01 |

**Abbreviations:** AMD, Age-related Macular Degeneration; VD, Visual disability.
Numerical continuous parameters were described as mean ± standard deviation, and categorical parameters were described as total numbers (percentages).
*Individuals with income of less than the lower 20th percentile were defined as low income.
†Regular exercise was defined as strenuous physical activity performed for at least 30 minutes at least five times a week.