의학석사 학위논문

Nationwide Estimates of Prevalences and Risk Factors for Age-Related Macular Degeneration

한국인에서 나이관련황반변성의 유병률 및 위험인자에 대한 연구

2014년 7월

서울대학교 대학원

의학과 안과학

박 상 준

A thesis of the Master's degree

한국인에서 나이관련황반변성의 유병률 및 위험인자에 대한 연구

Nationwide Estimates of Prevalences and Risk Factors for Age-Related Macular Degeneration

July 2014

The Department of Ophthalmology,

Seoul National University

College of Medicine

Sang Jun Park

Nationwide Estimates of Prevalences and Risk Factors for Age-Related Macular Degeneration

지도교수 박 규 형

이 논문을 의학석사 학위논문으로 제출함

2014년 4월

서울대학교 대학원

의학과 안과학

박 상 준

박상준의 의학석사 학위논문을 인준함

2014년 7월

위 원 장 김 태 우 (인)

부위원장 박 규 형 (인)

위 원 현 준 영 (인)

ABSTRACT

Introduction: Age-related macular degeneration is the leading causes of blindness in the world. Age-related macular degeneration is responsible for over 3 million blind people in the world. As a consequence of population aging, the prevalence and absolute number of age-related macular degeneration has sharply increased. Numerous studies have investigated the epidemiology of age-related macular degeneration over the past 30 years largely in Caucasians, but scarcely in Asians. In addition, epidemiologic studies representing a nationwide population have been scarce even in Caucasian populations.

Methods: The present study was designed as a cross-sectional study using the Korean National Health and Nutrition Examination Survey, which is a complex, stratified, multistage, probability-cluster survey. All the analyses were conducted using the participants aged 40-or-over years of the Korean National Health and Nutrition Examination Survey. First, the prevalence and risk factors of age-related macular degeneration were estimated. Age-related macular degeneration was determined by fundus photograph using a standardized protocol. Age-related macular degeneration risk factor analyses were conducted using logistic regression analyses. Second, the associations between age-related macular degeneration and five heavy metallic elements

(lead, mercury, cadmium, manganese, and zinc) were investigated. Blood levels of lead, mercury, cadmium, manganese, and zinc were measured, and associations were estimated using logistic regression analyses. In addition, the distributions of the five metallic elements in blood were analyzed, and the same set of logistic regression analyses estimating the association between age-related macular degeneration and logarithmic-transformed blood levels of the five metallic elements were also conducted.

Results: First, the prevalence and risk factors of age-related macular degeneration were estimated. The prevalence of age-related macular degeneration was 6.62% (95% confidence interval [CI], 6.15%-7.09%) in the Korean population; 6.02% (95% CI, 5.56%-6.48%) of early AMD and 0.60% (95% CI, 0.45%-0.75%) of late age-related macular degeneration. The prevalence of early age-related macular degeneration in women (6.73%; 95% CI, 6.11%-7.35%) was higher than that in men (5.25%;95% CI, 4.61%-5.89%, $p<0.001$) and the prevalence of late age-related macular degeneration in women (0.37%; 95% CI, 0.22%-0.52%) was lower than that in men (0.85%; 95% CI, 0.59%-1.12%, $p<0.001$). However, in multiple logistic regression analyses, the prevalences of both early and late age-related macular degeneration had no association with sex, house income, residence, sun exposure, and systemic comorbidities including hypertension, diabetes mellitus, and cardiovascular diseases. Early age-related macular degeneration had positive associations with older age groups ($p<0.001$), lower education

(p=0.027), occupation (p<0.001), anemia (p=0.027), HBsAg carrier status (p<0.001), non-overweight (body mass index [BMI], p=0.032; waist circumference, p=0.041 in separate analyses), and higher serum high-density lipoprotein (HDL) level (p=0.046), but not with smoking status (p=0.668). Late age-related macular degeneration had positive associations with age groups (p<0.001), current smokers (p=0.022) and lower BMI (p=0.037). Second, the associations between age-related macular degeneration and five heavy metallic elements (lead, mercury, cadmium, manganese, and zinc) were investigated. Lead was positively associated with both early age-related macular degeneration and late age-related macular degeneration in all logistic regression analyses. Mercury and cadmium also had a positive association with late age-related macular degeneration in all logistic regression analyses, but not with early age-related macular degeneration. On the contrary, manganese and zinc had an inverse association with late age-related macular degeneration in all logistic regression analyses. Manganese and zinc were not associated with early age-related macular degeneration. Using logarithmic-transformed blood levels for each metallic element, the logistic regression analyses showed similar results compared to those of the LRAs using non-transformed blood levels, despite the skewed distribution of these metallic elements in the blood.

Conclusions: The present study investigated the nationally-representative estimates of prevalences and risk factors for age-related macular degeneration.

The results suggest that there are 1.21 million individuals with early age-related macular degeneration and 121,000 individuals with late AMD in Korea and there are 9.4 million individuals with cataract and 1.7 million individuals with cataract surgery in Korea. Non-overweight and higher-HDL, generally assumed as positive health indicators, as well as anemia and hepatitis B infection had harmful associations with age-related macular degeneration. These results imply a possible different pathophysiology of age-related macular degeneration in Asians compared to that of Caucasians. In addition, the present study showed that the toxic metals including lead, mercury, and cadmium may negatively influence late AMD, while essential heavy metals including manganese and zinc may favorably influence late age-related macular degeneration. Moreover, lead may widely affect the pathogenesis of both early and late age-related macular degeneration.

Keywords: Age-related macular generation, prevalence, risk factor, heavy metals

Student Number: 2009-23509

CONTENTS

Abstract i

Contents v

List of tables and figures vi

General Introduction 1

Chapter 1 2

Age-related Macular Degeneration: Prevalence and Risk Factors from Korean National Health and Nutrition Examination Survey, 2008-2011

Introduction 3

Material and Methods 5

Results 11

Discussion 38

Chapter 2 45

Five Heavy Metallic Elements and Age-Related Macular Degeneration: Korean National Health and Nutrition Examination Survey, 2008–2011

Introduction 46

Material and Methods 49

Results 54

Discussion 62

References 68

Abstract in Korean 87

LIST OF TABLES AND FIGURES

Chapter 1

Table 1-1 14
Table 1-2 16
Table 1-3 17
Table 1-4 20
Table 1-5 23
Table 1-6 26
Table 1-7 29
Table 1-8 32
Table 1-9 35
Table 1-10 36
Figure 1-1 37

Chapter 2

Table 2-1 56
Table 2-2 58
Table 2-3 59
Table 2-4 60
Figure 1-1 61

GENERAL INTRODUCTION

Age-related macular degeneration is the leading causes of blindness in the world, both in industrialized countries and developing countries. Age-related macular degeneration is responsible for over 3 million blind people in the world[1]. As a consequence of population aging, the prevalence and absolute number of age-related macular degeneration has sharply increased. Age-related macular degeneration is the major socioeconomic and public health burden, [3, 4] estimating prevalences and clinical risk factors of these conditions are important for establishing public health plan, identifying modifiable risk factors, and minimizing public health burden. Numerous studies have investigated the epidemiology of age-related macular degeneration and cataract/cataract surgery over the past 30 years largely in Caucasians, but scarcely in Asians. In addition, epidemiologic studies representing a nationwide population have been scarce even in Caucasian populations.

Korea is one of newly industrialized countries in Asia and one of the most populous countries in the world. As the issue of an aging population has dawned on Korea as in other industrialized countries, several nationwide, government-led surveys have been conducted. The Korea National Health and Nutritional Examination Survey (KNHANES) is one of these national surveys initiated in 1998 and represents the entire Korean population of about 50 million. Using the database of the KNHANES, we estimated the prevalences and risk factors of age-related macular degeneration

CHAPTER 1

Age-related Macular Degeneration:

Prevalence and Risk Factors

from

Korean National Health and Nutrition

Examination Survey, 2008-2011

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries and responsible for over 3 million blind people in the world.[1] As a consequence of population ageing, the prevalence and absolute number of AMD is likely to increase and the health expenditure for AMD has sharply increased.[3] Numerous studies have investigated the epidemiology of AMD over the past 30 years largely in Caucasians, and recently in Asians. It has been generally assumed that AMD is less frequent in Asians than in Caucasians however, recent studies have shown conflicting results.[5] A recent meta-analysis reported that early AMD signs were less common in Asians compared to that in Caucasians, while the prevalence of late AMD was comparable.[6] On the contrary, in other studies, late AMD prevalence was lower in Asians than that in Caucasians, while early AMD prevalence was comparable.[7] In addition, proportions of late AMD subtypes might be different between Asians and Caucasians as well as overall AMD prevalence; polypoidal choroidal vasculopathy (PCV), a distinct subtype of wet AMD, accounts for 50% of wet AMD in Asian populations while only 8-13% in the Caucasian population.[8] Hence, a reliable, large population-based study is needed to investigate the difference in prevalence and risk factors for AMD between East Asians and Caucasians. However, despite the socioeconomic importance and burden of AMD, epidemiologic studies representing a nationwide population have been scarce. There have been prevalence studies from only the United States (US), based on the National Health and Nutrition

Examination Survey, and to date, no study conducted in the Asian population.[9]

Korea is one of the newly industrialized countries in Asia and one of the most populous countries in the world. As the issue of an ageing population has dawned on Korea as in other industrialized countries, several nationwide, government-led surveys have been conducted. The Korea National Health and Nutrition Examination Survey (KNHANES) is one of these national surveys initiated in 1998 and represents the whole Korean population of about 50 million. Using the data of the KNHANES from 2008 to 2011, we estimated the prevalence and risk factors of AMD and investigated racial/ethnic differences in AMD epidemiology.

MATERIALS AND METHODS

Study Design and Population

The KNHANES is an ongoing, population-based, cross-sectional survey in South Korea conducted by the Korea Centers for Disease Control and Prevention and the Korean Ministry of Health and Welfare. The present study analyzed the data of the 2008-2011 KNHANES. The detailed design of the KNHANES has been described elsewhere.[10] In brief, the 2008-2011 KNHANES annually selected 4600 households in 200 enumeration districts (2008-2009, KNHANES IV) and 3840 households in 192 enumeration districts (2010-2011, KNHANES V), which represented the civilian, non-institutionalized Korean population using rolling sampling designs involving a complex, stratified, multistage, probability-cluster survey. The quoted design, not a simple random sample, is widely used in health surveys to sample a fraction of a large finite population while accounting for its size and characteristics. In this design, sampling is always multistage, using strata (separate sampling from population subgroups), cluster (considering possibility of group of observations), and weight (considering over sampling or under sampling).[11] In KNHANES, both each 1-year data and integrated data of 2008-2011 surveys represents the whole population of Korea. Response rates were 77.8%, 82.8%, 81.9%, and 80.4% in 2008, 2009, 2010, and 2011, respectively. A total of 16108 eligible subjects (6952 men and 9157 women) aged ≥40 years participated during the 4-year study period. The

participants having gradable fundus photograph of at least 1 eye were included in the present study.

The institutional review board of the Seoul National Bundang Hospital (SNUBH) approved the present study (IRB No: X-1211/177-903), which was conducted in accordance with the Declaration of Helsinki.

Data Collection

The KNHANES consisted of three components: Health Interview Survey, Health Examination Survey, and Nutrition Survey. The detail of data collection has been published elsewhere.[10, 12] We used the data from the first two surveys; data regarding medical histories, socioeconomic status using a set of structured questionnaires, anthropometry investigation, blood test, and ophthalmic survey. Fundus photographs were taken with a non-mydriatic fundus camera (TRC-NW6S, Topcon, Japan). Patients were defined as having early AMD if the fundus photograph met one of the two criteria: 1) the presence of soft indistinct drusen or reticular drusen, or 2) the presence of hard or soft distinct drusen with pigmentary abnormalities (increased pigmentation or hypopigmentation of the retinal pigment epithelium) in the absence of signs of late AMD. Late AMD included the presence of signs of wet AMD or geographic atrophy (GA). Wet AMD was defined as retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, and subretinal fibrous scars. Geographic atrophy was defined as a circular discrete area (of 175 microns in diameter) of retinal depigmentation with visible choroidal vessels, in the absence of signs

of wet AMD. Each fundus photograph was graded twice (a preliminary grade and a detailed grade) using the grading protocol of the International Age-related Maculopathy Epidemiological Study Group.[13] Detailed grading was done later by 9 retina specialists who were masked to the patients' characteristics and entrusted by the Korean Ophthalmologic Society. Final grading was based on the detailed grading, and any discrepancies between the preliminary and detailed grading was resolved by 1 reading specialist.[12] The inter-rater reliability for AMD grading was 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% (right eye and left eye, respectively) in 2011, respectively (https://knhanes.cdc.go.kr/knhanes/sub04/sub04_03_02.do?classType=8, accessed in 2014-01-06). The quality of the ophthalmic survey and fundus photograph readings were verified by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society.[10]

Variable Definitions and Statistical Analysis

The variables analyzed in this study were defined and categorized as follows. The first category among the categories of each variable defined below was selected as a reference in logistic regression analysis (LRA). Participants were divided into 4 age groups: 40-49, 50-59, 60-69, and ≥70. Smoking status was defined as never-smoker, ex-smoker, and current-smoker. House income status was divided into two groups; participants with >50 % house income and those with ≤50 % house income according to equivalized gross household income in each year. Education status was divided into two groups;

participants with at least a high school degree and those who had graduated from middle school or less. Occupation was categorized as white collars (managers, professionals, clerks, service/sales workers), blue collars (agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and simple labor), and inoccupation (unemployed, retired, students, and housewives). Residence was categorized into urban and rural areas based on the address of participants. Sun-exposure status was divided into two groups; participants with an average of <5 hours/day and those of ≥5 hours/day. Co-morbidities were categorized into participants without history of co-morbidities and those with history of co-morbidities. Participants were categorized into two groups by body mass index (BMI), the ratio of weight (kg) to height^2 (m^2): those with BMI <25 kg/m^2 and those with BMI ≥25 kg/m^2. Waist circumference (WC) was measured to nearest 0.1 cm at the narrowest point between lower borders of the rib cage and iliac crest after normal expiration. Participants were divided into two groups: those with WC <90 cm in men or <80 in women and those with WC ≥90 cm in men or ≥80 cm in women. Hemoglobin, hematocrit, and red blood cells (RBCs) were measured by XE-2100D (Sysmex, Japan) and participants with hemoglobin level <13 g/dL in men and <12 g/dL in women were designated as anemia. Mean corpuscular volume (MCV) was calculated by dividing the hematocrit (%) by the number of RBCs (millions/μL), and then multiplying it with 10. Using calculated MCV, participants diagnosed as anemia were sub-categorized as microcytic anemia (MCV<80), normocytic anemia (80≤MCV<100), and macrocytic anemia (MCV≥100). Methods of

other blood tests were as followings: hepatitis B surface antigen (HBsAg, electrochemiluminescence immunoassay, E-170, Roche, Germany), lipoproteins (total cholesterol, triglyceride [TG], and high-density lipoprotein [HDL]) (enzymatic cholesterol assay, Automatic Analyzer 7600, Hitachi, Japan), blood urea nitrogen (BUN) (kinetic ultraviolet assay), creatinine (colorimetric method), and vitamin D (radioimmunoassay, 1470 Wizard gamma-counter, PerkinElmer, Finland). Data regarding HDL collected in 2011 is not yet released on the ground of quality control because the measuring method of HDL was changed in 2011.

The data were analyzed with SAS, version 9.2 (SAS Institute, North Carolina) using proc survey procedures, which can properly analyze the presented data using the variable of strata, cluster, and weight; we used the KNHANES sample weight adjusted for oversampling, non-response, and the Korean Population in 2008-2011.[14] The standard errors of estimates were calculated. P values <0.050 were considered statistically significant. The comparison of participants included and excluded from the study was conducted. The prevalence of AMD and AMD subgroups were estimated. Simple LRAs were conducted to investigate the associations between AMD prevalence and a set of variables. After that, the age-groups-, sex-, and smoking-status-adjusted (ASS-adjusted) LRAs were performed. Covariates that had a p value <0.100 in each ASS-adjusted LRA were chosen for multiple LRAs of each subtype of AMD. Age groups, sex, and smoking status were always included in multiple LRAs regardless of p values. Variables, which significantly correlated with each other (e.g. dyslipidemia and lipoproteins, BMI and WC), were not

simultaneously included in multiple LRAs; we chose the most significant covariate amongst correlated variables for multivariable models or, if significances of correlated variables were similar to each other, we conducted multiple LRAs in separate ways using each variable. When HDL, collected only in 2008-2010, had a p value <0.100 in ASS-adjusted LRA and was included in multiple LRA, the multiple LRA was conducted separately based on the analyses of 2008-2010 data using the proper sample weight for 3-year analyses. Lastly, a multiple LRA was re-conducted using the variable of sub-categorized anemia instead of the anemia variable when anemia had a significant association in that multiple LRA. We calculated odds ratio (OR) and 95% confidence interval (CI) values in all LRAs.

RESULTS

Of the 16109 participants, 14352 subjects had gradable fundus photograph of at least 1 eye (right eye in 13842 and left eye in 13778) and comparisons between participants with and without gradable fundus photographs for AMD is demonstrated in **Table 1**.

Prevalence of Age-related Macular Degeneration

The prevalence of overall AMD was 6.62% (95% CI, 6.15%-7.09%); 6.02% (95% CI, 5.56%-6.48%) of early AMD and 0.60% (95% CI, 0.45%-0.75%) of late AMD (0.48% [95% CI, 0.34%-0.62%] for wet AMD and 0.12% [95% CI, 0.06%-0.18%] for GA). The prevalence of early AMD in women (6.73%; 95% CI, 6.11%-7.35%) was higher than that in men (5.25%; 95% CI, 4.61%-5.89%, $p<0.001$), whereas the prevalence of late AMD in women (0.37%; 95% CI, 0.22%-0.52%) was lower than that in men (0.85%; 95% CI, 0.59%-1.12%, $p<0.001$) and either in the prevalence of wet AMD (0.67% [95% CI, 0.42%-0.91%] in men and 0.31% [95% CI, 0.16%-0.45%]in women, $p<0.001$)and GA (0.19% [95% CI, 0.08%-0.30%] in men and 0.06% [0.01%-0.12%] in women, $p<0.001$). (**Table 2 and Figure 1**) However, the LRAs revealed that the prevalence of early and late AMD did not differed by sex.

Risk Factors of Age-related Macular Degeneration

Results of age-groups-, sex-, and smoking-status-adjusted LRAs are provided in **Table 3** (early AMD), **Table 4** (early AMD using the 2008-2010 data),

Table 5 (late AMD), **Table 6** (wet AMD), and **Table 7** (GA). **Table 8** also provide results of simple LRA for each subgroup of AMD, and the results of simple LRA for early AMD and late AMD are provided separately in **Table 8**.

Multiple LRAs for Early AMD

The variables with a p value <0.100 in ASS-adjusted LRAs for early AMD were age group, house income, education, occupation, diabetes mellitus (DM), dyslipidemia, BMI, WC, anemia, HBsAg carrier, TG, HDL, and creatinine. Multiple LRAs were conducted in three ways, Model 1 (using BMI instead of WC), Model 2 (using WC instead of BMI), and Model 3 (using HDL and analyzing the 2008-2010 data). Early AMD had similar results in Model 1 and Model 2, and had positive associations with older age groups (p<0.001), lower education (p=0.027), occupation (p<0.001), anemia (0.027), HBsAg carrier (<0.001), lower BMI (p=0.032), and smaller WC (0.041). (**Table 3**) In Model 3, results of the 3-year data, early AMD also had a similar result: older age groups (p<0.001), lower education (p=0.007), occupation (p=0.024), anemia (p=0.035), HBsAg carrier (p<0.001), and higher HDL level (p=0.046). (**Table 4**) In multiple LRAs using the variable of sub-categorized anemia instead of anemia, early AMD had a positive association with normocytic anemia (p=0.008), but no association with either microcytic or macrocytic anemia. (**Table 9**)

Multiple LRAs for Late AMD

The variables with a p-value <0.100 in ASS-adjusted LRAs for late AMD were age group, smoking status, and BMI. In multiple LRA, late AMD had positive associations with older age groups (p<0.001), current smokers (p=0.022), and lower BMI (0.037). (**Table 5**) Multiple LRAs in subgroups of late AMD were provided in supplement tables (**Table 6 and Table 7**).

Table 1. Comparisons of participants included and excluded from analyses regarding prevalence and risk factors of age-related macular degeneration among participants aged 40 years or over in Korean National Health and Nutrition Examination Survey during 4-year study period (2008 to 2011).

Characteristics	Included Participants	Excluded Participants	p Value
No. (weighted %)	14352 (90.01)	1757 (9.99)	
Age, weighted mean (SE)	54.95 (0.16)	62.87 (0.52)	<0.001
Sex, No. (weighted %)			0.900
Male	6156 (48.03)	796 (48.23)	
Female	8196 (51.97)	961 (51.77)	
Smoking, No. (weighted %)			0.039
Never-smoker	8410 (54.70)	897 (50.92)	
Ex-smoker	3089 (22.35)	425 (25.42)	
Current smoker	2674 (22.95)	340 (23.66)	
House Income, No. (weighted %)			<0.001
>50%	7058 (53.39)	628 (41.05)	
≤50%	7090 (46.61)	1092 (58.95)	
Education, No. (weighted %)			<0.001
≥High school	6611 (52.71)	527 (39.06)	
≤Middle school	7561 (47.28)	1131 (60.94)	
Occupation, No. (weighted %)			<0.001
White collar	1913 (16.42)	117 (9.23)	
Blue collar	6540 (48.77)	612 (38.21)	
Inoccupation	5701 (34.80)	928 (52.56)	
Residence, No. (weighted %)			0.575
Urban	10324 (75.45)	1207 (74.35)	
Rural	4028 (24.55)	550 (25.65)	
Sun exposure, No. (weighted %)			
<5 hours/day			
≥5 hours/day			
Hypertension, No. (weighted %)	4306 (26.62)	675 (36.25)	<0.001
DM, No. (weighted %)	1616 (10.03)	232 (13.34)	0.002
Dyslipidemia, No. (weighted %)	1932 (12.31)	193 (11.37)	0.351
Stroke, No. (weighted %)	398 (2.14)	84 (4.26)	<0.001

MI or IHD, No. (weighted %)	511 (2.93)	75 (4.00)	0.026
OA or RA, No. (weighted %)	3303 (19.48)	494 (25.12)	<0.001
Pulmonary Tb, No. (weighted %)	1051 (7.09)	133 (7.94)	0.355
Asthma, No. (weighted %)	723 (4.61)	107 (5.70)	0.105
Thyroid disease, No. (weighted %)	683 (4.32)	59 (2.95)	0.012
Body mass index, No. (weighted %)			0.749
<25	9359 (64.88)	1147 (64.38)	
≥25	4958 (35.12)	587 (35.62)	
Waist Circumference, No. (weighted %)			0.386
Normal	8206 (59.63)	976 (58.26)	
≥90cm (men)	6095 (40.37)	751 (41.74)	
≥80cm(women)			
Anemia, No. (weighted %)			<0.001
Yes	1332 (8.98)	215 (12.50)	
No	12309 (91.02)	1302 (87.50)	
HBsAg carrier, No. (weighted %)	503 (3.93)	47 (3.21)	0.280

DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, WC = waist circumference, HBsAg = hepatitis B surface antigen

Table 2. Weighted prevalences and frequencies of age-related macular degeneration (AMD) in Korean population during the study period (2008-2011).

	No AMD	Age-related Macular Degeneration				
		All AMD	Early AMD	Late AMD		
				All Late AMD	Wet AMD	GA
Age, weighted mean (SE)	54.25 (0.16)	64.73 (0.43)	64.71 (0.43)	64.99 (1.69)	63.6 (1.9)	70.5 (3.1)
Overall, weighted % (95% CI)	93.38 (92.91-93.85)	6.62 (6.15-7.09)	6.02 (5.56-6.48)	0.60 (0.45-0.75)	0.48 (0.34-0.62)	0.12 (0.06-0.18)
frequency	13223	1129	1034	95	72	23
Age groups						
40-49, weighted % (95% CI)	98.38 (97.94-98.82)	1.62 (1.18-2.06)	1.44 (1.03-1.86)	0.18 (0.03-0.33)	0.18 (0.03-0.33)	0
frequency	4168	64	57	7	7	0
50-59, weighted % (95% CI)	94.84 (94.05-95.62)	5.16 (4.38-5.95)	4.75 (4.00-5.51)	0.41 (0.14-0.69)	0.37 (0.11-0.63)	0.05 (0.00-0.14)
frequency	3758	205	192	13	12	1
60-69, weighted % (95% CI)	88.32 (86.96-89.67)	11.68 (10.33-13.04)	10.65 (9.36-11.94)	1.03 (0.55-1.52)	0.83 (0.39-1.28)	0.20 (0.00-0.40)
frequency	3038	386	358	28	22	6
≥70, weighted % (95% CI)	82.04 (80.20-83.88)	17.96 (16.12-19.80)	16.26 (14.46-18.07)	1.70 (1.17-2.23)	1.15 (0.69-1.60)	0.55 (0.25-0.86)
frequency	2259	474	427	47	31	16

GA = geographic atrophy, SE = standard error, CI = confidence interval

Table 3. Characteristics of normal and early age-related macular degeneration (AMD) participants and associations between early AMD and potential risk factors using logistic regression analysis.

	No AMD	**Early AMD**	**Adjusted** (Age group, sex, and smoking status)		**Multivariable Model*** (using all variables with p<0.100 in Adjusted analysis)			
					Model 1		**Model 2**	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age groups			p trend	<0.001	p trend	<0.001	p trend	<0.001
40-49	4168 (41.17)	57 (9.36)	1 (reference)		1 (reference)		1 (reference)	
50-59	3758 (30.71)	192 (23.88)	3.42 (2.43-4.82)	<0.001	2.99 (2.02-4.12)	<0.001	3.02 (2.04-4.47)	<0.001
60-69	3038 (16.36)	358 (30.61)	8.29 (5.99-11.48)	<0.001	6.34 (4.33-9.30)	<0.001	6.43 (4.37-9.45)	<0.001
≥70	2259 (11.75)	427 (36.16)	13.52 (9.88-18.50)	<0.001	9.59 (6.57-14.00)	<0.001	9.86 (6.73-14.44)	<0.001
Sex								
Men	5670 (48.30)	428 (41.89)	1 (reference)		1 (reference)		1 (reference)	
Women	7553 (51.70)	606 (58.11)	1.05 (0.81-1.37)	0.718	0.88 (0.63-1.22)	0.431	0.93 (0.66-1.30)	0.662
Smoking			p trend	0.670	p trend	0.623	p trend	0.668
Never	7740 (54.49)	633 (60.08)	1 (reference)		1 (reference)		1 (reference)	
Ex	2833 (22.29)	224 (22.37)	0.88 (0.66-1.17)	0.378	0.88 (0.65-1.18)	0.387	0.88 (0.65-1.19)	0.409
Current	2487 (23.23)	162 (17.56)	0.94 (0.69-1.28)	0.684	0.87 (0.62-1.22)	0.428	0.87 (0.62-1.22)	0.432
House income								
>50%	6696 (54.58)	331 (36.10)	1 (reference)		1 (reference)		1 (reference)	
≤50%	6342 (45.42)	685 (63.90)	1.25 (1.05-1.50)	0.015	1.10 (0.91-1.33)	0.344	1.11 (0.91-1.34)	0.310
Education								
≥High school	6327 (54.52)	250 (25.74)	1 (reference)		1 (reference)		1 (reference)	
≤Middle school	6733 (45.48)	768 (74.26)	1.49 (1.19-1.86)	0.001	1.33 (1.03-1.70)	0.027	1.32 (1.03-1.69)	0.027
Occupation			p trend	<0.001	p trend	<0.001	p trend	<0.001
White collar	3589 (32.21)	101 (11.04)	1 (reference)		1 (reference)		1 (reference)	
Blue collar	4338 (34.33)	386 (39.66)	2.00 (1.54-2.58)	<0.001	1.82 (1.37-2.41)	<0.001	1.82 (1.37-2.42)	<0.001
Inoccupation	5117 (32.75)	530 (49.30)	1.62 (1.24-2.12)	0.001	1.58 (1.19-2.10)	0.002	1.60 (1.20-2.13)	0.001
Residence					N/A		N/A	
Urban	9588 (75.94)	674 (68.35)	1 (reference)					
Rural	3635 (24.06)	260 (31.65)	1.12 (0.95-1.34)	0.182				

Sun exposure					N/A		N/A	
<5 hours/day	9794 (77.63)	713 (72.29)	1 (reference)					
≥5 hours/day	3313 (22.37)	314 (27.71)	1.07 (0.89-1.28)	0.485				
Hypertension	3838 (25.59)	421 (41.38)	1.07 (0.91-1.27)	0.410	N/A		N/A	
DM	1479 (9.89)	130 (12.40)	0.78 (0.62-0.99)	0.039	0.82 (0.63-1.07)	0.144	0.83 (0.64-1.08)	0.161
Dyslipidemia	1784 (12.33)	134 (12.23)	0.77 (0.59-0.99)	0.043	0.85 (0.64-1.13)	0.254	0.85 (0.64-1.13)	0.256
Stroke	354 (2.09)	40 (3.71)	0.99 (0.64-1.52)	0.949	N/A		N/A	
MI or IHD	453 (2.77)	54 (5.12)	1.11 (0.76-1.62)	0.593	N/A		N/A	
OA or RA	2939 (18.63)	340 (32.64)	1.14 (0.94-1.39)	0.191	N/A		N/A	
Pulmonary Tb	956 (7.01)	81 (7.74)	0.92 (0.68-1.25)	0.580	N/A		N/A	
Asthma	651 (4.53)	65 (5.74)	0.85 (0.62-1.16)	0.296	N/A		N/A	
Thyroid disease	631 (4.36)	50 (3.88)	0.81 (0.58-1.15)	0.235	N/A		N/A	
BMI							N/A	
<25	8565 (64.48)	727 (69.64)	1 (reference)		1 (reference)			
≥25	4625 (35.52)	307 (30.36)	0.79 (0.66-0.95)	0.013	0.81 (0.67-0.98)	0.032		
WC					N/A			
Normal	7563 (59.77)	589 (56.80)	1 (reference)				1 (reference)	
≥90cm (men) ≥80cm(women)	5614 (40.23)	442 (43.20)	0.82 (0.69-0.98)	0.033			0.82 (0.68-0.99)	0.040
Anemia (anem)	1197 (8.70)	126 (13.31)	1.39 (1.04-1.86)	0.025	1.39 (1.04-1.87)	0.027	1.39 (1.04-1.86)	0.028
HBsAg carrier	446 (3.82)	52 (5.79)	1.91 (1.33-2.75)	0.001	1.98 (1.38-2.85)	<0.001	1.96 (1.36-2.83)	<0.001
***Serum levels*>**	No (mean)	No (mean)	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value
Total Chol (mg/dL)	12667 (193.40)	958 (192.57)	1.00 (1.00-1.00)	0.538	N/A		N/A	
TG (mg/dL)	12667 (148.18)	958 (137.78)	1.00 (1.00-1.00)	0.078	N/A		N/A	
HDL (mg/dL)	9189 (51.28)	626 (51.16)	1.01 (1.00-1.02)	0.057	N/A		N/A	
BUN (mg/dL)	12667 (14.9)	958 (15.68)	0.99 (0.98-1.01)	0.277	N/A		N/A	
Cr (mg/dL)	12665 (0.84)	958 (0.83)	0.61 (0.38-0.98)	0.042	0.77 (0.50-1.19)	0.243	0.77 (0.49-1.21)	0.255
Vit D (ng/mL)	12667 (19.0)	959 (19.90)	1.01 (1.00-1.02)	0.130	N/A		N/A	

*Variables, which were significantly related to each other, were not included simultaneously in a multiple logistic regression analysis (LRA); multiple LRA in this table were conducted in two ways: model 1 (including BMI [instead of WC] and dyslipidemia [instead of lipoproteins] as a covariate) and model 2 (including included WC [instead of

BMI] and dyslipidemia [instead of lipoproteins] as a covariate).
Unadjusted = unadjusted simple logistic regression analysis, Adjustied = age groups, sex, and smoking status-adjusted logistic regression analysis, OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D

Table 4. Characteristics of normal and early age-related macular degeneration (AMD) participants and associations between early AMD and potential risk factors using logistic regression analysis using the 3-year data (2008 to 2010).

	No AMD	**Early AMD**	**Unadjusted**		**Adjusted** (Age group, sex, and smoking status)		**Multivariable Model** (using all variables with p<0.100 in Adjusted analysis)	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Demographics>								
Age groups			p trend	<0.001	p trend	<0.001	p trend	<0.001
40-49	3151 (41.75)	41 (10.13)	1 (reference)		1 (reference)		1 (reference)	
50-59	2689 (30.57)	124 (23.98)	3.23 (2.15-4.87)	<0.001	3.28 (2.17-4.94)	<0.001	2.80 (1.79-4.38)	<0.001
60-69	2203 (16.37)	236 (30.11)	7.58 (5.11-11.26)	<0.001	7.75 (5.22-11.50)	<0.001	5.87 (3.70-9.31)	<0.001
≥70	1542 (11.30)	274 (35.78)	13.05 (8.94-19.05)	<0.001	13.39 (9.21-19.47)	<0.001	9.94 (6.34-15.59)	<0.001
Sex								
Men	4099 (48.13)	292 (44.62)	1 (reference)		1 (reference)		1 (reference)	
Women	5486 (51.87)	383 (55.38)	1.15 (0.95-1.40)	0.153	0.89 (0.65-1.23)	0.494	0.78 (0.53-1.16)	0.223
Smoking			p trend	0.043	p trend	0.737	p trend	0.885
Never	5662 (54.66)	409 (58.59)	1 (reference)		1 (reference)		1 (reference)	
Ex	1992 (21.74)	157 (23.63)	1.01 (0.80-1.29)	0.910	0.88 (0.62-1.24)	0.457	0.92 (0.64-1.34)	0.681
Current	1849 (23.61)	106 (17.78)	0.70 (0.53-0.94)	0.016	0.88 (0.59-1.31)	0.520	0.90 (0.58-1.39)	0.635
House income							N/A	
>50%	4851 (55.57)	219 (37.64)	1 (reference)		1 (reference)			
≤50%	4589 (44.43)	444 (62.36)	2.07 (1.68-2.55)	<0.001	1.20 (0.96-1.50)	0.117		
Education								
≥High school	4485 (53.85)	153 (24.03)	1 (reference)		1 (reference)		1 (reference)	
≤Middle school	5017 (46.15)	517 (75.97)	3.69 (2.91-4.68)	<0.001	1.70 (1.27-2.27)	<0.001	1.53 (1.13-2.09)	0.007
Occupation			p trend	<0.001	p trend	<0.001	p trend	0.024
White collar	2613 (32.49)	67 (11.54)	1 (reference)		1 (reference)		1 (reference)	
Blue collar	3198 (33.49)	255 (39.05)	3.28 (2.40-4.48)	<0.001	1.90 (1.37-2.63)	<0.001	1.62 (1.15-2.30)	0.007
Inoccupation	3675 (34.23)	247 (49.41)	4.09 (3.00-5.57)	<0.001	1.57 (1.11-2.22)	0.012	1.40 (0.98-1.98)	0.064
Residence							N/A	
Urban	6812 (75.71)	427 (67.18)	1 (reference)		1 (reference)			

Rural	2773 (24.29)	248 (32.82)	1.52 (1.22-1.90)	<0.001	1.18 (0.94-1.48)	0.148		
Sun exposure							N/A	
<5 hours/day	6837 (75.79)	452 (70.85)	1 (reference)		1 (reference)			
≥5 hours/day	2647 (24.21)	218 (29.15)	1.29 (1.05-1.58)	0.016	1.02 (0.83-1.26)	0.848		
Medical History>								
Hypertension	2735 (25.43)	272 (41.60)	2.09 (1.73-2.52)	<0.001	1.14 (0.93-1.39)	0.214	N/A	
DM	1043 (9.63)	91 (13.90)	1.52 (1.15-1.99)	0.003	0.93 (0.70-1.24)	0.631	N/A	
Dyslipidemia	1181 (11.57)	82 (12.10)	1.05 (0.79-1.41)	0.736	0.85 (0.64-1.14)	0.284	N/A	
Stroke	246 (1.93)	27 (3.75)	1.82 (1.14-2.89)	0.012	0.99 (0.62-1.59)	0.975	N/A	
MI or IHD	308 (2.65)	31 (3.94)	1.51 (0.92-2.47)	0.104	0.87 (0.53-1.42)	0.577	N/A	
OA or RA	2175 (19.25)	214 (30.12)	1.81 (1.46-2.24)	<0.001	0.99 (0.78-1.25)	0.929	N/A	
Pulmonary Tb	682 (7.03)	51 (6.68)	0.95 (0.67-1.34)	0.752	0.77 (0.54-1.09)	0.136	N/A	
Asthma	466 (4.39)	37 (5.35)	1.23 (0.84-1.81)	0.291	0.82 (0.55-1.21)	0.312	N/A	
Thyroid disease	440 (4.37)	34 (3.90)	0.89 (0.59-1.34)	0.574	0.85 (0.56-1.31)	0.467	N/A	
Clinical Measures>								
BMI							N/A	
<25	6216 (64.44)	470 (68.37)	1 (reference)		1 (reference)			
≥25	3349 (35.56)	205 (31.63)	0.84 (0.68-1.04)	0.104	0.85 (0.68-1.06)	0.145		
WC								
Normal	5512 (60.35)	376 (54.76)	1 (reference)		1 (reference)		N/A	
≥90cm (men) ≥80cm(women)	4029 (39.65)	296 (45.24)	1.26 (1.02-1.54)	0.029	0.94 (0.75-1.18)	0.612		
Anemia	897 (8.96)	89 (13.77)	1.62 (1.14-2.32)	0.008	1.47 (1.02-2.12)	0.040	1.49 (1.03-2.15)	0.035
HBsAg carrier	329 (3.75)	37 (6.54)	1.80 (1.19-2.71)	0.005	2.23 (1.43-3.46)	<0.001	2.33 (1.51-3.59)	<0.001
Serum levels>	No (mean)	No (mean)	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value
Total Chol (mg/dL)	9189 (192.92)	626 (190.47)	1.00 (1.00-1.00)	0.195	1.00 (1.00-1.00)	0.222	N/A	
TG (mg/dL)	9189 (148.96)	626 (139.10)	1.00 (1.00-1.00)	0.074	1.00 (1.00-1.00)	0.073	N/A	
HDL (mg/dL)	9189 (51.28)	626 (51.16)	1.00 (0.99-1.01)	0.854	1.01 (1.00-1.02)	0.057	1.01 (1.00-1.02)	0.046
BUN (mg/dL)	9189 (14.87)	626 (15.71)	1.04 (1.02-1.06)	<0.001	0.99 (0.98-1.01)	0.512	N/A	
Cr (mg/dL)	9187 (0.83)	626 (0.83)	1.01 (0.70-1.45)	0.970	0.74 (0.44-1.26)	0.273	N/A	

Vit D (ng/mL)	9189 (19.36)	626 (20.44)	1.02 (1.01-1.04)	0.005	1.01 (1.00-1.03)	0.189	N/A

Unadjusted = unadjusted simple logistic regression analysis, Adjustied = age groups, sex, and smoking status-adjusted logistic regression analysis, OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D
$P<0.05$

Table 5. Characteristics of normal and late age-related macular degeneration (AMD) participants and associations between late AMD and potential risk factors using logistic regression analysis.

	No AMD	**Late AMD**	**Adjusted** (Age group, sex, and smoking status)		**Multivariable Model** (using all variables with p<0.100 in Adjusted analysis)	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value
Age groups			p trend	<0.001	p trend	<0.001
40-49	4168 (41.17)	7 (11.79)	1 (reference)		1 (reference)	
50-59	3758 (30.71)	13 (20.75)	3.31 (1.10-9.93)	0.033	3.25 (1.08-9.77)	0.035
60-69	3038 (16.36)	28 (29.67)	9.46 (3.51-25.47)	<0.001	9.37 (3.48-25.23)	<0.001
≥70	2259 (11.75)	47 (37.78)	18.34 (7.44-45.22)	<0.001	16.71 (6.75-41.33)	<0.001
Sex						
Men	5670 (48.30)	58 (67.96)	1 (reference)		1 (reference)	
Women	7553 (51.70)	37 (32.04)	0.62 (0.35-1.10)	0.100	0.63 (0.35-1.13)	0.123
Smoking			p trend	0.050	p trend	0.072
Never	7740 (54.49)	37 (33.37)	1 (reference)		1 (reference)	
Ex	2833 (22.29)	32 (32.97)	1.55 (0.79-3.04)	0.208	1.54 (0.77-3.06)	0.219
Current	2487 (23.23)	25 (33.67)	2.28 (1.18-4.40)	0.015	2.20 (1.12-4.31)	0.022
House income					N/A	
>50%	6696 (54.58)	31 (40.21)	1 (reference)			
≤50%	6342 (45.42)	63 (59.79)	0.92 (0.51-1.66)	0.778		
Education					N/A	
≥High school	6327 (54.52)	34 (43.20)	1 (reference)			
≤Middle school	6733 (45.48)	60 (56.80)	0.65 (0.36-1.17)	0.152		
Occupation			p trend	0.663	N/A	
White collar	3589 (32.21)	10 (14.15)	1 (reference)			
Blue collar	4338 (34.33)	29 (34.71)	1.18 (0.46-3.03)	0.733		
Inoccupation	5117 (32.75)	54 (51.14)	1.43 (0.58-3.50)	0.437		
Residence					N/A	
Urban	9588 (75.94)	62 (71.06)	1 (reference)			
Rural	3635 (24.06)	33 (28.94)	0.85 (0.52-1.41)	0.535		

Sun exposure					N/A	
<5 hours/day	9794 (88.09)	68 (84.48)	1 (reference)			
≥5 hours/day	1283 (11.91)	11 (15.52)	0.83 (0.37-1.86)	0.655		
Hypertension	3838 (25.59)	45 (38.44)	0.97 (0.59-1.57)	0.886	N/A	
DM	1479 (9.89)	7 (8.46)	0.48 (0.18-1.31)	0.153	N/A	
Dyslipidemia	1784 (12.33)	11 (11.69)	0.85 (0.38-1.90)	0.699	N/A	
Stroke	354 (2.09)	4 (3.86)	0.89 (0.31-2.56)	0.833	N/A	
MI or IHD	453 (2.77)	4 (6.22)	1.23 (0.40-3.72)	0.720	N/A	
OA or RA	2939 (18.63)	24 (19.01)	0.71 (0.41-1.22)	0.210	N/A	
Pulmonary Tb	956 (7.01)	14 (12.96)	1.43 (0.73-2.79)	0.295	N/A	
Asthma	651 (4.53)	7 (4.90)	0.70 (0.32-1.54)	0.375	N/A	
Thyroid disease	631 (4.36)	2 (1.03)	0.32 (0.06-1.75)	0.189	N/A	
BMI						
<25	8565 (64.48)	67 (79.29)	1 (reference)		1 (reference)	
≥25	4625 (35.52)	26 (20.71)	0.54 (0.31-0.96)	0.037	0.54 (0.31-0.96)	0.037
WC					N/A	
Normal	7563 (59.77)	54 (66.72)	1 (reference)			
≥90cm (men) ≥80cm(women)	5614 (40.23)	39 (33.28)	0.76 (0.44-1.32)	0.332		
Anemia	1197 (8.70)	9 (10.01)	1.13 (0.50-2.60)	0.766	N/A	
HBsAg carrier	446 (3.82)	5 (4.37)	1.49 (0.51-4.32)	0.467	N/A	
***Serum levels*>**	No (mean)	No (mean)	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value
Total Chol (mg/dL)	12667 (193.40)	88 (197.01)	1.01 (1.00-1.01)	0.216	N/A	
TG (mg/dL)	12667 (148.18)	88 (150.32)	1.00 (1.00-1.00)	0.874	N/A	
HDL (mg/dL)	9189 (51.28)	58 (48.57)	1.00 (0.97-1.02)	0.837	N/A	
BUN (mg/dL)	12667 (14.9)	88 (15.80)	0.99 (0.94-1.04)	0.581	N/A	
Cr (mg/dL)	12665 (0.84)	88 (0.89)	1.07 (0.54-2.11)	0.858	N/A	
Vit D (ng/mL)	12667 (19.0)	88 (19.49)	0.99 (0.95-1.03)	0.552	N/A	

Unadjusted = unadjusted simple logistic regression analysis, Adjustied = age groups, sex, and smoking status-adjusted logistic regression analysis, OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease,

OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D
$P<0.05$

Table 6. Characteristics of normal and wet age-related macular degeneration (AMD) participants and associations between wet AMD and potential risk factors using logistic regression analysis.

	No AMD	**Wet AMD**	**Unadjusted**		**Adjusted** (Age group, sex, and smoking status)		**Multivariable Model** (using all variables with p<0.100 in Adjusted analysis)	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Demographics>								
Age groups			p trend	<0.001	p trend	<0.001	p trend	<0.001
40-49	4168 (41.17)	7 (14.83)	1 (reference)		1 (reference)		1 (reference)	
50-59	3758 (30.71)	12 (23.07)	2.09 (0.70-6.25)	0.189	2.93 (0.96-8.99)	0.060	4.16 (1.31-13.17)	0.015
60-69	3038 (16.36)	22 (30.09)	5.11 (1.89-13.83)	0.001	7.67 (2.76-21.29)	<0.001	11.00 (3.78-31.99)	<0.001
≥70	2259 (11.75)	31 (32.02)	7.56 (3.12-18.37)	<0.001	12.25 (4.85-30.98)	<0.001	18.37 (6.88-49.02)	<0.001
Sex								
Men	5670 (48.30)	43 (66.74)	1 (reference)		1 (reference)		1 (reference)	
Women	7553 (51.70)	29 (33.26)	0.47 (0.26-0.85)	0.013	0.76 (0.40-1.43)	0.391		0.411
Smoking			p trend	0.018	p trend	0.035	p trend	0.069
Never	7740 (54.49)	28 (33.26)	1 (reference)		1 (reference)		1 (reference)	
Ex	2833 (22.29)	23 (31.31)	2.30 (1.13-4.68)	0.021	1.73 (0.79-3.79)	0.172	1.65 (0.71-3.83)	0.247
Current	2487 (23.23)	20 (35.43)	2.50 (1.23-5.09)	0.012	2.67 (1.27-5.60)	0.010	2.53 (1.15-5.54)	0.021
House income				0.075			N/A	
>50%	6696 (54.58)	24 (40.24)	1 (reference)		1 (reference)			
≤50%	6342 (45.42)	47 (59.76)	1.78 (0.94-3.38)		1.00 (0.50-2.00)	0.992		
Education							N/A	
≥High school	6327 (54.52)	26 (45.71)	1 (reference)		1 (reference)			
≤Middle school	6733 (45.48)	45 (54.29)	1.42 (0.78-2.61)	0.252	0.63 (0.33-1.21)	0.163		
Occupation			p trend	0.067	p trend	0.609	N/A	
White collar	3589 (32.21)	8 (16.83)	1 (reference)		1 (reference)			
Blue collar	4338 (34.33)	21 (32.49)	1.83 (0.64-5.22)	0.260	1.01 (0.36-2.84)	0.985		
Inoccupation	5117 (32.75)	41 (50.68)	2.87 (1.09-7.55)	0.033	1.39 (0.53-3.67)	0.506		
Residence							N/A	
Urban	9588 (75.94)	48 (69.87)	1 (reference)		1 (reference)			

Rural	3635 (24.06)	24 (30.13)	1.36 (0.73-2.53)	0.328	0.91 (0.50-1.65)	0.759		
Sun exposure							N/A	
<5 hours/day	9794 (88.09)	51 (85.85)	1 (reference)		1 (reference)			
≥5 hours/day	1283 (11.91)	7 (14.15)	1.22 (0.43-3.44)	0.708	0.80 (0.29-2.16)	0.655		
Medical History>								
Hypertension	3838 (25.59)	32 (34.69)	1.54 (0.86-2.77)	0.145	0.87 (0.48-1.56)	0.638	N/A	
DM	1479 (9.89)	4 (7.33)	0.72 (0.21-2.54)	0.612	0.43 (0.12-1.58)	0.203	N/A	
Dyslipidemia	1784 (12.33)	8 (10.31)	0.82 (0.31-2.12)	0.679	0.73 (0.28-1.89)	0.515	N/A	
Stroke	354 (2.09)	2 (2.33)	1.15 (0.27-4.82)	0.849	0.57 (0.14-2.40)	0.442	N/A	
MI or IHD	453 (2.77)	3 (4.83)	1.78 (0.45-7.02)	0.407	0.99 (0.25-3.94)	0.989	N/A	
OA or RA	2939 (18.63)	17 (17.56)	0.93 (0.49-1.78)	0.827	0.66 (0.34-1.27)	0.210	N/A	
Pulmonary Tb	956 (7.01)	13 (14.53)	2.25 (1.12-4.55)	0.023	1.71 (0.82-3.55)	0.150	N/A	
Asthma	651 (4.53)	6 (5.40)	1.20 (0.50-2.87)	0.677	0.81 (0.34-1.92)	0.633	N/A	
Thyroid disease	631 (4.36)	2 (3.88)	0.29 (0.05-1.54)	0.145	0.40 (0.07-2.19)	0.288	N/A	
Clinical Measures>								
BMI							N/A	
<25	8565 (64.48)	50 (77.38)	1 (reference)		1 (reference)			
≥25	4625 (35.52)	21 (22.62)	0.53 (0.28-1.00)	0.051	0.60 (0.31-1.16)	0.127		
WC							N/A	
Normal	7563 (59.77)	39 (63.45)	1 (reference)		1 (reference)			
≥90cm (men) ≥80cm(women)	5614 (40.23)	32 (36.55)	0.74 (0.44-1.24)	0.257	0.91 (0.48-1.71)	0.765		
Anemia	1197 (8.70)	3 (6.37)	0.72 (0.19-2.63)	0.613	0.73 (0.20-2.65)	0.633	N/A	
HBsAg carrier	446 (3.82)	3 (3.85)	1.01 (0.26-3.93)	0.989	1.25 (0.31-4.98)	0.752	N/A	
Serum levels>	No (mean)	No (mean)	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value
Total Chol (mg/dL)	12667 (193.40)	66 (201.83)	1.01 (1.00-1.02)	0.200	1.01 (1.00-1.02)	0.080	1.01 (1.00-1.02)	0.080
TG (mg/dL)	12667 (148.18)	66 (160.18)	1.00 (1.00-1.00)	0.362	1.00 (1.00-1.00)	0.677	N/A	
HDL (mg/dL)	9189 (51.28)	43 (47.68)	0.98 (0.95-1.00)	0.073	0.99 (0.97-1.02)	0.431	N/A	
BUN (mg/dL)	12667 (14.9)	66 (15.71)	1.03 (1.00-1.07)	0.059	0.99 (0.93-1.05)	0.715	N/A	

Cr (mg/dL)	12665 (0.84)	66 (0.89)	1.49 (1.19-1.86)	<0.001	1.04 (0.46-2.38)	0.926	N/A
Vit D (ng/mL)	12667 (19.0)	66 (19.91)	1.02 (0.98-1.06)	0.355	1.00 (0.96-1.04)	0.964	N/A

Unadjusted = unadjusted simple logistic regression analysis, Adjustied = age groups, sex, and smoking status-adjusted logistic regression analysis, OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D
P<0.05

Table 7. Characteristics of normal and geographic atrophy (GA) participants and associations between GA and potential risk factors using logistic regression analysis.

	No AMD	**GA**	**Unadjusted**		**Adjusted** (Age group, sex, and smoking status)		**Multivariable Model*** (using all variables with p<0.100 in Adjusted analysis)			
							Model 1		**Model 2**	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Demographics>										
Age groups			p trend	<0.001	p trend	<0.001	p trend	<0.001	p trend	<0.001
40-49	4168 (41.17)	0 (0)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
50-59	3758 (30.71)	1 (11.73)	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001
60-69	3038 (16.36)	6 (28.07)	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001
≥70	2259 (11.75)	16 (60.20)	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001	∞ (NE)	<0.001
Sex										
Men	5670 (48.30)	15 (72.71)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Women	7553 (51.70)	8 (27.29)	0.35 (0.13-0.96)	0.041	0.30 (0.10-0.91)	0.033	0.34 (0.10-1.11)	0.073		0.140
Smoking			p trend	0.163	p trend	0.918	p trend	0.610	p trend	0.588
Never	7740 (54.49)	9 (33.78)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Ex	2833 (22.29)	9 (39.16)	2.83 (0.96-8.34)	0.058	1.06 (0.31-3.60)	0.930	0.68 (0.18-2.53)	0.565	0.68 (0.19-2.49)	0.560
Current	2487 (23.23)	5 (27.06)	1.88 (0.52-6.81)	0.337	1.30 (0.35-4.83)	0.698	1.27 (0.32-5.12)	0.736	1.31 (0.33-5.18)	0.702
House income							N/A		N/A	
>50%	6696 (54.58)	7 (40.10)	1 (reference)		1 (reference)					
≤50%	6342 (45.42)	16 (59.90)	1.80 (0.63-5.09)	0.272	0.64 (0.22-1.92)	0.430				
Education							N/A		N/A	
≥High school	6327 (54.52)	8 (33.81)	1 (reference)		1 (reference)					
≤Middle school	6733 (45.48)	15 (66.19)	2.35 (0.86-6.40)	0.096	0.76 (0.21-2.75)	0.672				
Occupation			p trend	0.013	p trend	0.546	N/A		N/A	
White collar	3589 (32.21)	2 (4.32)	1 (reference)		1 (reference)					
Blue collar	4338 (34.33)	8 (42.84)	9.39 (1.66-53.13)	0.011	3.03 (0.42-22.12)	0.274				
Inoccupation	5117 (32.75)	13 (52.85)	11.67 (2.26-60.31)	0.003	2.41 (0.36-16.30)	0.368				
Residence							N/A		N/A	
Urban	9588 (75.94)	14 (75.67)	1 (reference)		1 (reference)					

Rural	3635 (24.06)	9 (24.33)	1.02 (0.41-2.49)	0.974	0.67 (0.28-1.61)	0.375				
Sun exposure							N/A		N/A	
<5 hours/day	9794 (88.09)	17 (79.75)	1 (reference)		1 (reference)					
≥5 hours/day	1283 (11.91)	4 (20.25)	1.88 (0.54-6.49)	0.319	0.94 (0.26-3.44)	0.926				
Medical History>										
Hypertension	3838 (25.59)	13 (52.46)	3.21 (1.22-8.42)	0.018	1.39 (0.57-3.41)	0.474	N/A		N/A	
DM	1479 (9.89)	3 (12.65)	1.32 (0.33-5.25)	0.694	0.67 (0.17-2.68)	0.576	N/A		N/A	
Dyslipidemia	1784 (12.33)	3 (16.86)	1.44 (0.31-6.53)	0.635	1.42 (0.33-6.04)	0.638	N/A		N/A	
Stroke	354 (2.09)	2 (9.62)	5.13 (1.08-24.47)	0.040	1.83 (0.40-8.38)	0.438	N/A		N/A	
MI or IHD	453 (2.77)	1 (11.43)	4.54 (0.59-34.72)	0.145	1.95 (0.27-14.25)	0.512	N/A		N/A	
OA or RA	2939 (18.63)	7 (24.43)	1.41 (0.50-3.97)	0.513	0.92 (0.40-2.10)	0.840	N/A		N/A	
Pulmonary Tb	956 (7.01)	1 (7.09)	1.01 (0.13-7.74)	0.991	0.61 (0.08-4.51)	0.632	N/A		N/A	
Asthma	651 (4.53)	1 (3.00)	0.65 (0.09-4.94)	0.679	0.36 (0.05-2.74)	0.326	N/A		N/A	
Thyroid disease	631 (4.36)	0 (0)	0 (NE)	<0.001	0 (NE)	<0.001	0 (NE)	<0.001	0 (NE)	<0.001
Clinical Measures>										
BMI									N/A	
<25	8565 (64.48)	17 (86.87)	1 (reference)		1 (reference)		1 (reference)			
≥25	4625 (35.52)	5 (13.13)	0.27 (0.09-0.80)	0.018	0.33 (0.12-1.00)	0.051	0.43 (0.14-1.37)	0.153		
WC							N/A			
Normal	7563 (59.77)	15 (79.71)	1 (reference)		1 (reference)				1 (reference)	
≥90cm (men) ≥80cm(women)	5614 (40.23)	7 (20.29)	0.38 (0.14-1.00)	0.050	0.35 (0.13-0.92)	0.033			0.43 (0.15-1.21)	0.109
Anemia	1197 (8.70)	6 (24.20)	3.35 (1.18-9.54)	0.024	2.71 (0.86-8.61)	0.090	2.61 (0.79-8.61)	0.116	2.55 (0.75-8.67)	0.135
HBsAg carrier	446 (3.82)	2 (6.40)	1.72 (0.39-7.63)	0.473	2.85 (0.60-13.56)	0.189	N/A		N/A	
Serum levels>	No (mean)	No (mean)	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value		

Total Chol (mg/dL)	12667 (193.40)	22 (178.44)	0.99 (0.98-1.00)	0.024	0.99 (0.98-1.00)	0.154	N/A	N/A
TG (mg/dL)	12667 (148.18)	22 (111.61)	1.00 (0.99-1.00)	0.185	0.99 (0.98-1.00)	0.181	N/A	N/A
HDL (mg/dL)	9189 (51.28)	15 (52.26)	1.01 (0.94-1.08)	0.871	1.02 (0.96-1.09)	0.464	N/A	N/A
BUN (mg/dL)	12667 (14.9)	22 (16.15)	1.05 (1.00-1.09)	0.032	0.98 (0.88-1.08)	0.626	N/A	N/A
Cr (mg/dL)	12665 (0.84)	22 (0.93)	1.61 (1.28-2.03)	<0.001	1.18 (0.35-3.91)	0.792	N/A	N/A
Vit D (ng/mL)	12667 (19.0)	22 (17.83)	0.97 (0.91-1.05)	0.465	0.95 (0.88-1.02)	0.148	N/A	N/A

*Variables, which were significantly related to each other, were not included simultaneously in a multiple logistic regression analysis (LRA); multiple LRA in this table were conducted in two ways: model 1 (including BMI, instead of WC, as a covariate) and model 2 (including included WC, instead of BMI, as a covariate).
Unadjusted = unadjusted simple logistic regression analysis, Adjustied = age groups, sex, and smoking status-adjusted logistic regression analysis, OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D

Table 8. Results of simple logistic regression analyses (LRAs) between age-related macular degenerations (AMDs, early AMD and late AMD) and potential risk factors. These are supplement results for Table 3 and 5.

	Unadjusted LRA for Early AMD		**Unadjusted LRA for Late AMD**	
	OR (95% CI)	p value	OR (95% CI)	p value
Demographics>				
Age groups	p trend	<0.001	p trend	<0.001
40-49	1 (reference)		1 (reference)	
50-59	3.42 (2.43-4.81)	<0.001	2.36 (0.89-6.89)	0.117
60-69	8.23 (5.95-11.40)	<0.001	6.33 (2.42-16.60)	<0.001
≥70	13.53 (9.88-18.54)	<0.001	11.22 (4.72-26.68)	<0.001
Sex				
Men	1 (reference)		1 (reference)	
Women	1.30 (1.11-1.52)	<0.001	0.44 (0.26-0.75)	0.002
Smoking	p trend	0.004	p trend	0.005
Never	1 (reference)		1 (reference)	
Ex	0.91 (0.75-1.11)	0.348	2.42 (1.32-4.42)	0.004
Current	0.69 (0.55-0.87)	0.001	2.37 (1.27-4.42)	0.007
House income				
>50%	1 (reference)		1 (reference)	
≤50%	2.13 (1.80-2.52)	<0.001	1.79 (1.03-3.10)	0.039
Education				
≥High school	1 (reference)		1 (reference)	
≤Middle school	3.46 (2.89-4.14)	<0.001	1.58 (0.93-2.67)	0.090
Occupation	p trend	<0.001	p trend	0.018
White collar	1 (reference)		1 (reference)	
Blue collar	3.40 (2.65-4.37)	<0.001	2.32 (0.89-6.02)	0.084
Inoccupation	4.26 (3.31-5.47)	<0.001	3.44 (1.41-8.43)	0.007
Residence				
Urban	1 (reference)		1 (reference)	
Rural	1.46 (1.24-1.73)	<0.001	1.29 (0.76-2.17)	0.347

Sun exposure				
<5 hours/day	1 (reference)		1 (reference)	
≥5 hours/day	1.33 (1.12-1.58)	0.001	1.36 (0.60-3.08)	0.463
Medical History>				
Hypertension	2.05 (1.75-2.40)	<0.001	1.82 (1.11-2.97)	0.018
DM	1.29 (1.02-1.63)	0.032	0.84 (0.32-2.21)	0.736
Dyslipidemia	0.99 (0.77-1.27)	0.946	0.94 (0.42-2.11)	0.884
Stroke	1.86 (1.23-2.80)	0.003	1.94 (0.67-5.58)	0.219
MI or IHD	1.90 (1.32-2.72)	<0.001	2.33 (0.77-7.07)	0.134
OA or RA	2.12 (1.77-2.53)	<0.001	1.03 (0.60-1.78)	0.930
Pulmonary Tb	1.11 (0.82-1.50)	0.488	1.98 (1.04-3.76)	0.038
Asthma	1.28 (0.95-1.74)	0.110	1.08 (0.49-2.41)	0.842
Thyroid disease	0.88 (0.64-1.23)	0.468	0.23 (0.04-1.20)	0.081
Clinical Measures>				
BMI				
<25	1 (reference)		1 (reference)	
≥25	0.79 (0.66-0.94)	0.009	0.47 (0.27-0.83)	0.009
WC				
Normal	1 (reference)		1 (reference)	
≥90cm (men) ≥80cm(women)	1.13 (0.96-1.33)	0.148	0.74 (0.44-1.24)	0.257
Anemia	1.61 (1.22-2.23)	0.001	1.17 (0.51-2.68)	0.714
HBsAg carrier	1.55 (1.09-2.19)	0.013	1.15 (0.41-3.26)	0.790
Serum levels>	OR (95% CI) per 1 unit	p value	OR (95% CI) per 1 unit	p value
Total Chol (mg/dL)	1.00 (1.00-1.00)	0.574	1.00 (0.99-1.01)	0.525
TG (mg/dL)	1.00 (1.00-1.00)	0.041	1.00 (1.00-1.00)	0.869
HDL (mg/dL)	1.00 (0.99-1.07)	0.854	0.98 (0.95-1.01)	0.204
BUN (mg/dL)	1.04 (1.02-1.06)	<0.001	1.04 (1.01-1.07)	0.016
Cr (mg/dL)	0.76 (0.50-1.14)	0.179	1.54 (1.25-1.89)	<0.001
Vit D (ng/mL)	1.02 (1.01-1.03)	0.001	1.01 (0.98-1.05)	0.563

OR = odds ratio, CI = confidence interval, Never = never-smoker, Ex = ex-smoker, Current = current-smoker, DM = diabetes mellitus, MI = myocardial infarction, IHD = ischemic heart disease, OA = osteoarthritis, RA = rheumatoid arthritis, Tb = tuberculosis, BMI = body mass index, WC = waist circumference, HBsAg = hepatitis B surface antigen, Total chol = total cholesterol, LDL = low-density lipoprotein, TG = triglyceride, HDL = high-density lipoprotein, BUN = blood urea nitrogen, Cr = creatinine, Vit D = vitamin D

Table 9. The results of multiple models for sub-categorized anemia and early age-related macular degeneration (AMD).

	No AMD	Early AMD	Multiple LRAs					
			Model 1		Model 2		Model 3	
	No (%)	No (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
No anemia	11405 (91.30)	826 (86.69)	1 (reference)		1 (reference)		1 (reference)	
Microcytic anemia	239 (2.00)	8 (1.00)	0.97 (0.41-2.34)	0.953	0.94 (0.39-2.26)	0.888	1.35 (0.52-3.51)	0.537
Normocytic anemia	910 (6.31)	116 (12.01)	1.53 (1.12-2.10)	0.008	1.53 (1.12-2.09)	0.008	1.58 (1.07-2.34)	0.021
Macrocytic anemia	48 (0.39)	4 (0.30)	0.47 (0.16-1.39)	0.174	0.48 (0.16-1.41)	0.179	0.22 (0.03-1.68)	0.144

Participants with anemia were sub-categorized by mean corpuscular volume (MCV) value; microcytic anemia (MCV<80), normocytic anemia (80≤MCV<100), and macrocytic anemia (MCV≥100).
Covariates included in Model 1 are as follow: age groups, sex, smoking status, house income, occupation, diabetes mellitus, dyslipidemia, body mass index, hepatitis B surface antigen carrier, serum creatinine level, and anemia. See also Table 3.
Covariates included in Model 2 are as follow: age groups, sex, smoking status, house income, occupation, diabetes mellitus, dyslipidemia, waist circumference, hepatitis B surface antigen carrier, serum creatinine level, and anemia. See also Table 3.
Covariates included in Model 3 are as follow: age group, sex, smoking status, education, occupation, hepatitis B surface antigen carrier, high-density lipoprotein, and anemia. See also Table 4
Model 3 analyzed the 3-year data from 2008 to 2010.
OR = odds ratio, CI = confidence interval

Table 10. Smoking status among the Korean population in 2008-2011.

		Total	Men	Women
		Frequency (Weighted Percent [%])		
40-49	Never-smoker	2432 (52.01)	278 (14.77)	2154 (90.53)
	Ex-smoker	739 (19.74)	653 (35.22)	86 (3.73)
	Current-smoker	1020 (28.25)	897 (50.01)	123 (5.73)
50-59	Never-smoker	2410 (54.77)	273 (15.72)	2137 (93.07)
	Ex-smoker	747 (21.50)	696 (40.96)	51 (2.40)
	Current-smoker	769 (23.74)	683 (43.31)	86 (4.53)
60-69	Never-smoker	2008 (56.88)	242 (15.30)	1766 (93.78)
	Ex-smoker	848 (26.40)	790 (52.56)	58 (3.18)
	Current-smoker	528 (16.73)	466 (32.14)	62 (3.05)
70-	Never-smoker	1560 (59.67)	177 (14.84)	1383 (87.69)
	Ex-smoker	755 (26.78)	653 (58.87)	102 (7.17)
	Current-smoker	357 (13.55)	274 (26.29)	83 (5.76)
All ages	Never-smoker	8410 (54.70)	970 (15.17)	7440 (91.31)
	Ex-smoker	3089 (22.35)	2792 (42.41)	297 (3.78)
	Current-smoker	2674 (22.95)	2320 (42.43)	354 (4.91)

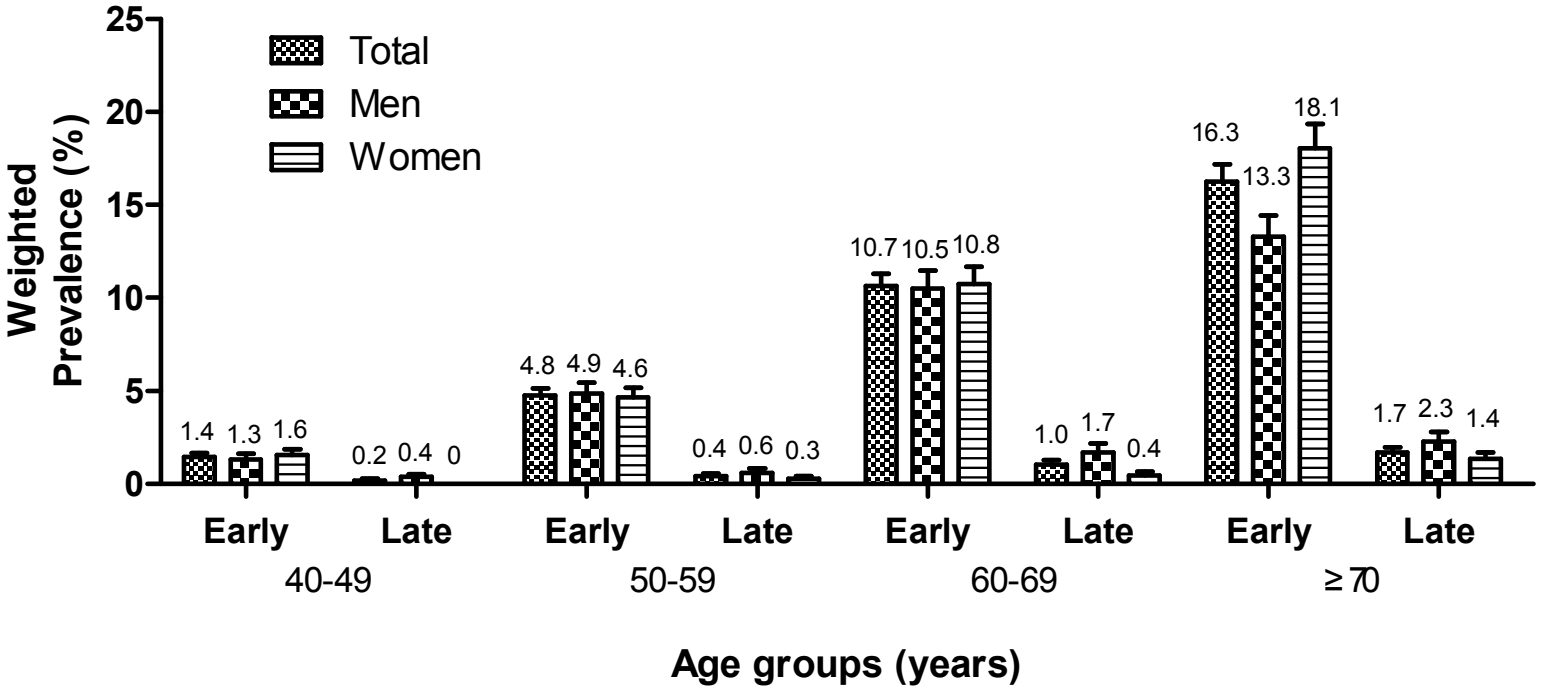

Figure 1. Age- and sex-specific weighted prevalence of early and late age-related macular degeneration in Korea during the 4-year study period (2008-2011).

DISCUSSION

The present study provided detailed data on the prevalence and risk factors of AMD based on the nationwide representing population including 14352 participants aged ≥40 years. The prevalence of early and late AMD in Korea were similar to those of Asian populations from meta-analysis.[6] As with previous studies in Asian populations,[7, 15] not in Caucasian populations,[9, 16] men had a higher prevalence of late AMD than women in the Korean population, which has in part been explained by the male dominance of PCV in Asian men.[6, 17] Some authors explained the higher frequency of PCV cases in Asian populations brings about the higher ratio of wet AMD to GA in Asian populations than that in Caucasian populations.[6] The 4-times-higher prevalence of wet AMD than GA in our study was similar to those in Asian populations and higher than those in Caucasian populations. Another explanation is that it might be related to higher smoking rates in Asian men compared to that in Asian women,[6, 15] which was even observed in our study; over 90% of women had never smoked while about 85% of men had smoked previously or were smoking currently (**Table 10**), and smoking had a positive association with late AMD. Smoking, although a well-defined risk factor of both early and late AMD,[18] was not associated with early AMD in the Korean population. These findings were also observed in the data from the SNUBH AMD Cohort Study, a hospital-based cohort study, including 463 AMD patients and 395 normal controls; smoking had a positive association with wet AMD (N=314, p=0.003) but an inverse association with early AMD

(N=112, p<0.001) in multiple LRAs including age, sex, education, DM, hypertension, cardiovascular disease (CVD), and dyslipidemia as covariates (Park KH, et al. IOVS 2012;53:ARVO E-Abstract 3304).

In our study, increased age was strongly associated with both early and late AMD, but sex did not have any association. Interestingly, higher serum HDL level was positively associated with early AMD. Some studies have reported positive associations between serum HDL level and AMD,[12, 19, 20] while no association[21] or inverse associations[22] have also been reported. Likewise, two genome-wide association studies implied that some alleles associated with increased serum HDL level increase the risk of AMD,[23] while other alleles with inverse association were also reported.[24, 25] Deposition of cholesterol and lipids underneath the retinal pigment epithelium is one of the defining features of drusen that characterizes early AMD,[26, 27] and our study shows HDL may increase the risk of early AMD. Further investigation regarding ethnic differences and genuine associations of HDL-related AMD pathophysiology is needed.

Obesity has been regarded as a risk factor of AMD.[28, 29] However, a study from the Caucasian population reported that the association between obesity and AMD may differ by sex,[30] and some studies were unable to reveal the association even in Asian population, although the study by Chen et al. had a relative small sample size (N=1105).[31] Interestingly, in our study, early AMD was inversely associated with obesity indices in Model 1 and 2, and late AMD was also inversely associated with BMI. These inverse associations with obesity, the obesity paradox, have been also observed in other

diseases.[32] There are several plausible explanations for these inverse associations. First, old age brings about selected populations of non-obese individuals because obese individuals have higher mortality rates than non-obese individuals.[33] Second, ethnic differences may influence the association between obesity and AMD as with different associations reported in other diseases.[34, 35] In addition, participants aged ≥50, born in 1958 or earlier, grew up in a destitute country suffering the Korean War. Since overall diet quality and micronutrients intake are associated with AMD,[36] such impoverished states may affect these associations. The overweight in those aged Koreans may suggest a better general health status with an increased metabolic reservoir.[37]

One of the most distinct variables associated with early AMD was HBsAg. There has been only one epidemiologic study regarding the association between hepatitis B and AMD, which was also conducted in Korea and revealed a positive association.[38] Unlike Caucasians, Hepatitis B infection is still highly prevalent in Asian populations; the prevalence of HBsAg carrier was 3.9% in our study. Hepatitis B virus was detected in subretinal fluids as well as in tears and the aqueous humor,[39-41] and it might increase the risk of uveoretinal pathology and associate cross reactivity with retinal S-antigen which can cause inflammation processes.[38, 42, 43] It may partially explain ethnic differences and the role of chronic inflammation in the pathogenesis of AMD.

Anemia was also associated with early AMD. There has been no study regarding the association between anemia and AMD to date, while a study in

Caucasians reported that hematocrit level had no association with early AMD.[19] The prevalence of anemia in our study was 9.0%, higher than that in developed countries. The pro-inflammatory state of ageing, independent of disease, may be a cause for anemia.[44] Moreover, inflammation is the second most cause of anemia and accounts for one third of anemia in older persons.[45, 46] As inflammation plays an important role in the pathogenesis of AMD, it partially explains the association between anemia and AMD. In addition, genetic susceptibility, namely the complement factor H polymorphism, activates the alternative complement pathway and is known to have associations with several chronic conditions including hemolytic uremic syndrome, microangiopathic hemolytic anemia, and AMD.[47] These inflammatory pathways and their relation to AMD parallel our detailed analysis of the subtypes of anemia, where normocytic anemia was associated with early AMD. Common cause of normocytic anemia includes anemia of chronic diseases, chronic inflammation, and hemolytic anemia (e.g. microangiopathic anemia).[48] However, the concurrence of iron and vitamin B12/folate deficiencies could results in normocytic anemia, which has a usual association with microcytic anemia and macrocytic anemia, respectively.[48] Recent studies suggested that deficiencies in vitamin B12 and/or folate, which are one of the causes of anemia, may increase the risk of AMD incidence.[49, 50] As the KNHANES lacks the information regarding the blood level of vitamin B12/folate, we could not conduct further anemia differentiation. Further investigation is warranted to reveal not only the pathophysiology of

the association between early AMD and anemia but also its differences between Asians and Caucasians.

Education and occupation were associated with early AMD. Although several studies have reported no association between education and AMD,[51] other studies showed inverse associations between education and AMD as in our study,[28] suggesting AMD is affected by behaviors and lifestyles as well as non-amendable risk factors.

Before conducting multiple LRAs, several systemic risk factors were associated with AMDs. But, systemic risk factors − hypertension, DM, and CVDs − were not associated with both early and late AMD in multiple LRAs. The relationships between these systemic risk factors and AMD remain unclear although they have been investigated in numerous studies. In addition, vitamin D was not associated with AMDs, although several studies have reported otherwise.[52] Furthermore, we were unable to reveal the association between sun-exposure and AMD, a conflicting issue in the literature.[53, 54] Further investigation with thorough evaluation of sun-exposure is needed because its measurement in our study depended on only a single question regarding average hours of daily sun-exposure.

The present study has several limitations. First, KNHANES did not include institutionalized individuals, and we excluded participants without any gradable fundus photographs. It may cause not only underestimation of AMD prevalence and affect risk factor analyses but also selection bias in analyzing risk factors of AMD. The results should be interpreted under the consideration of these limitations. Second, although the response rates for the KNHANES

during the study period were relatively high, ranged 77.8–82.8%, and the KNHANES sample weight had adjusted for the responded participants to provide nationally-representative estimates, approximately 20% of the population did not complete the KNHANES through the study period, which might result in the selection bias. This limitation, an inherent bias of the survey, should also be considered when interpreting the results. Third, AMD was graded using only fundus photographs; we could not identify PCV which is more prevalent in Asians.[17] Third, though the largest population-based study including 14,352 participants, the frequencies and prevalence of late AMD and its subtypes were too low to achieve a sufficient statistical power. The KNHANES, a government-led survey for nationally-representative estimates, is not solely designated for evaluating the prevalence and risk factors of late AMD, resulting in low statistical power for evaluating late AMD. This is an inherent limitation for the study using pre-existing surveys. Despite lacking sufficient statistical power, these analyses implied that the pathophysiology and risk factors of wet AMD and GA are somewhat different from each other.

Recently, Cho et al. also reported the prevalence and risk factor of AMD in Korea using the 2-year KNHANES database.[10] However, compared to the recent study by Cho et al, our study analyzed all available databases in the KNHANES, the 4-year data of KNHANES, resulting having the larger sample size. In addition, we investigated the prevalences and risk factors with more detailed stratification of AMD, and conducted a rigorous study in providing all possible information (e.g. frequencies for each covariate), handling the

missing values (e.g. HDL), and in-depth analyzing the risk factors (e.g. subtype analysis of anemia).

In conclusion, the prevalence of AMD was 6.62% in the Korean population aged ≥40 years; 6.02% of early AMD and 0.60% of late AMD, suggesting 1.21 million individuals with early AMD and 121,000 individuals with late AMD in Korea. In addition, we revealed novel risk factors for AMD; non-overweight and higher HDL, generally assumed as positive health indicators, as well as anemia and hepatitis B infection. Maintaining good health indicators such as not being overweight or having higher HDL levels may not be enough to prevent the occurrence of AMD. Correction of possible low grade inflammatory conditions may be recommended taking into account the harmful associations of anemia and hepatitis B infection with AMD. This also implies a possible different pathophysiology of AMD in Asians compared to that of Caucasians.

CHAPTER 2

Five Heavy Metallic Elements and Age-Related Macular Degeneration : Korean National Health and Nutrition Examination Survey, 2008–2011

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries and has blinded over 3 million people worldwide.[1] The socioeconomic costs for AMD have sharply increased in countries with an increasing aging population.[3] Numerous studies have sought to determine risk factors for AMD, and there is some evidence that heavy metallic elements might play a role in the development and progression of AMD. In early 2000, the Age-Related Eye Disease Study (AREDS) raised the issue of an association between AMD and heavy metallic elements, finding that consumption of a high level of zinc (and antioxidants) can reduce the risk of developing advanced AMD.[55] Zinc is an essential metallic element, not only in antioxidant/anti-inflammatory pathways, but also in the immune system and for enzyme function,[56-58] and many studies have investigated the association and protective mechanisms of zinc on AMD. Cadmium has also drawn considerable attention as some studies showed that cadmium might play a role in AMD pathogenesis, especially in a smoking population.[59-61] Recent evidence suggests that the association between cadmium and AMD exists because cadmium increases oxidative stress and produces inflammatory cytokines.[62, 63] In addition, zinc and cadmium, both bivalent cation metallic elements, share numerous binding sites for biomolecules (e.g. metallothionein) and several intracellular metabolic pathways (e.g. MAPK pathways).[64-66] Alteration of these mechanisms and pathways may play a role in the pathogenesis of AMD. Other metallic elements (e.g. manganese, lead, and mercury) are also known to be associated

with these biomolecules and intracellular pathways, suggesting an association with AMD similar to zinc and cadmium. In addition, several studies have implied that lead and mercury, well-known toxic metallic elements that can cause devastating health-related morbidities, might be causally involved in AMD pathogenesis as well as in other ocular pathologies.[59, 67-74]

To date, however, there has been no population-based study investigating the association between AMD and blood levels of heavy metallic elements. Such a study could provide insights into the causal relationship between AMD and heavy metallic elements and help verify the assumptions derived from the experimental research. A number of researchers have reported an association between heavy metallic elements and other diseases of aging, including hypertension, peripheral artery disease, cognitive decline, and cataracts, which are quite prevalent in the general population.[68, 75-77] On the contrary, AMD has a relatively low prevalence in the general population, 6.0% for early AMD and 0.6% for late AMD in a Korean population aged ≥40 years (Chapter 1). A large-scale epidemiologic study with reliable ophthalmologic examination is required to determine the association between AMD and heavy metallic elements. Recently, we reported the prevalence and risk factors of AMD in Korea using the Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2001 (Chapter 1). The KNHANES is a large, population-based, government-led survey that can produce nationally representative estimates. The 2008–2011 KNHANES measured blood levels of heavy metallic elements as well as conducted detailed ophthalmic examinations, including fundus photography and its grading. As a follow-up

study, we evaluated the association between AMD and heavy metallic elements using the same data set as our previous study (Chapter 1).

MATERIALS AND METHODS

The KNHANES is an ongoing, population-based, cross-sectional survey in South Korea conducted by the Korea Centers for Disease Control and Prevention and the Korean Ministry of Health and Welfare. We recently reported the nationally representative estimates for prevalence and risk factors of AMD using the 2008–2011 KNHANES databases analyzing over 16,000 participants aged ≥40 years; the present study also used the same database set for analysis. Briefly, the 2008–2011 KNHANES selected 3,840–4,600 households in 192–200 enumeration districts representing the civilian, non-institutionalized South Korean population; it used a rolling sampling design involving a complex, stratified, multistage, probability-cluster survey. A total of 37,753 subjects participated in the 2008–2011 KNHANES. Blood concentration of heavy metals was measured only in a selected subpopulation, a total of 8,800 participants who can provide nationally representative estimates. The subpopulation for heavy metal measurements consisted of 10 randomly sampled participants in each district with stratification of age and sex from the annual KNHANES databases. Lead, cadmium, and mercury were measured each year (2008–2011), manganese was measured only in 2 years (2008–2009), and zinc was measured only in 1 year (2011). Each of the 5 datasets regarding the heavy metallic elements can produce nationally representative estimates as well. Measuring methods for heavy metal elements were as follows: lead, cadmium, and manganese were measured by graphite

furnace atomic absorption spectrometry (AAnalyst 600, PerkinElmer, Finland); mercury was measured by the gold amalgamation method (DMA-80, Milestone, Italy); and zinc was measured by an inductively coupled plasma/mass spectrometer (ICP-MS, PerkinElmer, US).

AMD grading was performed in subjects aged ≥40 years. Fundus photographs were taken with a non-mydriatic fundus camera (TRC-NW6S, Topcon, Japan). Patients were defined as having early AMD if the fundus photograph met 1 of 2 criteria: (1) the presence of soft, indistinct drusen or reticular drusen, or (2) the presence of hard or soft, distinct drusen with pigmentary abnormalities (increased pigmentation or hypopigmentation of the retinal pigment epithelium) in the absence of signs of late AMD. Late AMD included the presence of signs of wet AMD or geographic atrophy. Wet AMD was defined as retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal or sub-retinal pigment epithelium (RPE) hemorrhages, or subretinal fibrous scars. Geographic atrophy was defined as a circular discrete area (of 175 microns in diameter) of retinal depigmentation with visible choroidal vessels in the absence of signs of wet AMD. Each fundus photograph was graded at least twice using the grading protocol of the International Age-Related Maculopathy Epidemiological Study Group,[13] and all AMD grading was verified by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society.[10] The details of the AMD grading, including the method of resolving discrepancies and inter-rater reliability, have been described previously (Chapter 1). Participants having both a

gradable fundus photograph of at least 1 eye and blood concentration data for heavy metals were included in the present study.

Covariates analyzed in this study were defined and categorized as follows. The participants were divided into 4 age groups: 40–49, 50–59, 60–69, and ≥70 years. Smoking status was defined as never-smoker (someone who has never smoked a cigarette), ex-smoker (someone who smoked in the past but does not smoke cigarettes currently), and current smoker (someone who smokes cigarettes currently). Occupation was categorized as white collar (managers, professionals, clerks, and service/sales workers), blue collar (agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and simple labor), and inoccupation (unemployed, retired, students, and homemakers). Residence was categorized into urban and rural areas on the basis of the address of the participants. Household income status was divided into 2 groups: the subjects with >50% household income and those with ≤50% household income according to the equivalized gross annual household income. Hemoglobin was measured by an XE-2100D (Sysmex, Japan), and participants with a hemoglobin level of <13 g/dL in men and <12 g/dL in women were designated as anemic. Body mass index (BMI) was estimated as the ratio of weight (kg) to height^2 (m^2). Participants were categorized into 2 groups: those with BMI <25 kg/m^2 and those with BMI ≥25 kg/m^2.

Data were analyzed with SAS, version 9.2 (SAS Institute, North Carolina) using PROC SURVEY procedures. Descriptive data were estimated for each

of the 5 metallic elements, including weighted mean and standard error according to AMD grades and covariates stated above. The KNHANES sample weight was then used for heavy metal surveys adjusted for oversampling, non-response, and the Korean Population. The standard errors of estimates were calculated to account for the design of the KNHANES survey. Logistic regression analyses (LRAs) were used to assess associations between AMDs (both early and late AMD) and serum levels of the 5 metallic elements: simple LRAs, Model I (multiple LRAs adjusting for age groups, sex, and smoking-status), and Model II (multiple LRAs adjusting for Model I and potential confounders including occupation, residence, house income, anemia, and BMI). In addition, information is provided regarding the distributions of 5 metallic elements analyzed in the present study, including the non-weighted mean, median, standard deviation, range, coefficient of variation, skewness, and results of the Kolmogorov-Smirnov test (or the Shapiro–Wilk test). Although independent variables in LRA do not have to be normally distributed and many studies have analyzed blood concentrations of heavy metals without transformation,[67] several studies have analyzed blood concentrations of heavy metals after logarithmic transformation because the heavy metal distribution in blood were generally skewed.[78] Hence, the same set of LRAs was conducted using the logarithmic-transformed blood concentration of 5 metallic elements to show the robustness of estimated associations. P values <0.05 were considered statistically significant.

The institutional review board of the Seoul National Bundang Hospital approved the present study (IRB No: X-1211/177-903), which was conducted in accordance with the Declaration of Helsinki.

RESULTS

Of the 8,800 participants, the number of eligible subjects aged ≥40 years was 3,865 (including 243 with early AMD and 11 with late AMD) in 2008–2011 for lead, mercury, and cadmium; 1,625 (including 100 with early AMD and 4 with late AMD) in 2008–2009 for manganese; and 1,107 (including 71 with early AMD and 3 with late AMD) in 2011 for zinc. Mean blood levels of heavy metals according to AMD grades and covariates are provided in **Table 1**.

Lead was positively associated with both early AMD and late AMD in all LRAs, including simple LRA ($p = 0.020$ and $p < 0.001$, respectively), Model I ($p = 0.010$ and $p = 0.012$, respectively), and Model II ($p = 0.009$ and $p = 0.015$, respectively). Mercury and cadmium also had a positive association only with late AMD in all LRAs ($p = 0.004$ and $p < 0.001$, respectively, in simple LRA; $p = 0.015$ and $p = 0.001$, respectively, in Model I; and $p = 0.008$ and $p = 0.001$, respectively, in Model II). On the contrary, manganese and zinc had an inverse association with late AMD in all LRAs ($p = 0.013$ and $p < 0.001$, respectively, in simple LRA; $p = 0.009$ and $p = 0.005$, respectively, in Model I; and $p = 0.022$ and $p = 0.049$, respectively, in Model II). However, mercury, cadmium, manganese, and zinc were not associated with early AMD in all LRAs. Detailed results of each LRA conducted for the 5 elements are provided in **Table 2** and **Figure 1**.

The distributions of the 5 metallic elements in the blood are provided in **Table 3**); all 5 metallic elements showed skewed distributions. The results of LRAs

using logarithmic-transformed blood concentrations were similar to those of LRAs using the non-transformed values stated above. Lead was positively associated with both early AMD and late AMD in all LRAs except the Model I for late AMD. Mercury and cadmium also had a positive association only with late AMD in all LRAs, but had no association with early AMD. In contrast, manganese and zinc had an inverse association with late AMD in all LRAs and no association with early AMD. These results indicate that skewed distributions of heavy metallic elements in blood might not have a significant influence on these association analyses. Detailed results of logarithmic-transformed analyses are provided in **Table 4**.

Table 1. Mean blood levels of five metallic elements according to the grade of age-related macular degeneration (AMD) and the covariates used in multiple logistic regression analyses

	Serum Level of Heavy Metals									
	Lead (μg/dL)		**Mercury (μg/L)**		**Cadmium (μg/L)**		**Manganese (μg/dL)**		**Zinc (μg/dL)**	
	N	Weighted Mean (SE)	N	Weighted Mean (SE)	N	Weighted Mean (SE)	N	Weighted Mean (SE)	N	Weighted Mean (SE)
Total	3865	2.69 (0.03)	3865	5.19 (0.12)	3865	1.33 (0.01)	1625	1.33 (1.89)	1107	133.66 (0.01)
AMD	p trend	p trend	p trend	0.001	p trend	<0.001	p trend	0.004	p trend	<0.001
No AMD	3611	2.67 (0.03)	3611	5.22 (0.12)	3611	1.32 (0.01)	1521	1.33 (0.01)	1033	133.98 (1.84)
Early AMD	243	2.90 (0.11)	243	4.52 (0.28)	243	1.41 (0.05)	100	1.33 (0.04)	71	130.78 (5.31)
Late AMD	11	3.66 (0.57)	11	9.52 (1.69)	11	1.90 (1.13)	4	1.13 (0.06)	3	101.23 (6.30)
Age Groups	p trend	<0.001	p trend	<0.001	p trend	<0.001	p trend	0.049	p trend	<0.001
40-49	1330	2.57 (0.05)	1330	5.38 (0.14)	1330	1.25 (0.02)	564	1.37 (0.02)	378	136.20 (2.12)
50-59	1316	2.83 (0.04)	1316	5.66 (0.20)	1316	1.37 (0.02)	562	1.30 (0.02)	377	135.53 (1.97)
60-69	929	2.76 (0.04)	929	4.98 (0.18)	929	1.36 (0.03)	309	1.30 (0.02)	305	135.92 (2.56)
70-	290	2.63 (0.09)	290	3.90 (0.27)	290	1.42 (0.04)	190	1.33 (0.04)	47	118.92 (4.13)
Sex	p	<0.001	p	<0.001	p	<0.001	p	<0.001	p	<0.001
Men	1918	3.17 (0.04)	1918	6.46 (0.19)	1918	1.20 (0.02)	800	1.25 (0.02)	558	138.84 (2.13)
Women	1947	2.25 (0.02)	1947	4.01 (0.09)	1947	1.45 (0.02)	825	1.41 (0.02)	549	128.69 (2.01)
Smoking Status	p trend	<0.001	p trend	<0.001	p trend	<0.001	p trend		p trend	<0.001
Never-smoker	2099	2.35 (0.03)	2099	4.33 (0.10)	2099	1.35 (0.02)	889	1.39 (0.02)	591	129.17 (1.93)
Ex-smoker	901	2.96 (0.05)	901	5.98 (0.18)	901	1.03 (0.02)	368	1.25 (0.02)	249	138.81 (2.87)
Current-smoker	842	3.27 (0.06)	842	6.48 (0.28)	842	1.56 (0.03)	360	1.27 (0.03)	261	139.02 (2.80)
Occupation[a]	p trend	<0.001	p trend	<0.001	p trend	<0.001	p trend	0.129	p trend	<0.001
White collar	1184	2.62 (0.04)	1184	6.06 (0.17)	1184	1.21 (0.02)	463	1.34 (0.02)	370	134.40 (2.09)
Blue collar	1296	2.98 (0.05)	1296	5.29 (0.23)	1296	1.34 (0.02)	539	1.30 (0.02)	367	139.88 (2.75)
Inoccupation	1354	2.48 (0.04)	1354	4.32 (0.14)	1354	1.41 (0.02)	615	1.35 (0.02)	355	127.08 (2.46)
Residence[b]		0.045		0.258		0.096		0.678		0.483
Urban	2965	2.66 (0.03)	2965	5.09 (0.11)	2965	1.31 (0.02)	1210	1.33 (0.01)	850	132.79 (2.04)

Rural	900	2.79 (0.06)	900	5.54 (0.38)	900	1.37 (0.03)	415	1.32 (0.02)	257	136.23 (4.43)
House income[c]	p	0.254	p	<0.001	p	<0.001	p	0.510	p	0.868
>50%	2028	2.66 (0.04)	2028	5.85 (0.13)	2028	1.27 (0.02)	835	1.34 (0.02)	593	134.06 (2.68)
≤50%	1798	2.72 (0.04)	1798	4.47 (0.16)	1798	1.38 (0.02)	777	1.32 (0.02)	501	133.66 (1.72)
Anemia[d]	p	<0.001	p	<0.001	p	0.005	p	0.002	p	<0.001
No	3553	2.73 (0.03)	3553	5.35 (0.12)	3553	1.31 (0.01)	1490	1.31 (0.01)	1015	134.61 (1.98)
Yes	311	2.32 (0.08)	311	3.52 (0.18)	311	1.47 (0.05)	135	1.52 (0.06)	91	123.83 (2.89)
BMI	p	0.737	p	<0.001	p	0.110	p	0.821	p	0.026
<25 kg/m^2	2491	2.70 (0.03)	2491	4.86 (0.15)	2491	1.34 (0.02)	1059	1.33 (0.02)	712	131.88 (1.97)
≥25 kg/m^2	1362	2.68 (0.05)	1362	5.79 (0.16)	1362	1.30 (0.02)	560	1.33 (0.02)	392	136.71 (2.45)

[a]Occupation was categorized as white collars (managers, professionals, clerks, service/sales workers), blue collars (agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and simple labor), and inoccupation (unemployed, retired, students, and homemakers).
[b]Residence was categorized into urban and rural areas based on the address of the participants.
[c]House income status was divided into two groups; participants with >50% house income and those with ≤50% house income according to equalized gross household income in each year.
[d]Anemia was diagnosed when the hemoglobin level <13 g/dL in men and <12 g/dL in women among participants.
SE = standard error, AMD = age-related macular degeneration, BMI = body mass index

Table 2. Logistic regression analyses (LRAs) between blood levels of five metallic elements and age-related macular degeneration (AMD)

	Early AMD (per unit)					
	Simple LRA		Model I LRA[a]		Model II LRA[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Pb (μg/dL)	1.11 (1.02-1.20)	0.020	1.13 (1.03-1.24)	0.010	1.12 (1.02-1.23)	0.009
Hg (μg/L)	0.95 (0.90-1.00)	0.070	0.98 (0.95-1.03)	0.441	0.99 (0.96-1.03)	0.610
Cd (μg/L)	1.20 (0.99-1.46)	0.067	1.12 (0.88-1.42)	0.366	1.04 (0.81-1.33)	0.481
Mn (μg/dL)	0.99 (0.59-1.66)	0.977	1.14 (0.68-1.89)	0.625	1.06 (0.63-1.77)	0.479
Zn (μg/dL)	1.00 (0.98-1.01)	0.534	1.00 (0.99-1.01)	0.700	1.00 (0.99-1.01)	0.699

	Late AMD (per unit)					
	Simple LRA		Model I LRA[a]		Model II LRA[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Pb (μg/dL)	1.21 (1.09-1.34)	<0.001	1.24 (1.05-1.47)	0.012	1.25 (1.05-1.50)	0.015
Hg (μg/L)	1.03 (1.01-1.05)	0.004	1.03 (1.01-1.06)	0.015	1.03 (1.01-1.06)	0.008
Cd (μg/L)	2.17 (1.71-2.76)	<0.001	2.19 (1.40-3.42)	0.001	2.25 (1.46-4.10)	0.001
Mn (μg/dL)	0.16 (0.04-0.69)	0.013	0.15 (0.04-0.62)	0.009	0.16 (0.03-0.79)	0.022
Zn (μg/dL)	0.94 (0.90-0.97)	<0.001	0.91 (0.86-0.97)	0.005	0.91 (0.85-0.98)	0.049

Table 3. Concentrations and distribution of five heavy metallic elements in blood among the included participants

	Number	Mean	Median	SD	Range	VC	Skewness	Kolmogorov-Smirnov Test (p-value)
Pb (μg/dL)	3865	2.72	2.53	1.32	0.51-26.51	48.57	4.91	<0.01
Hg (μg/L)	3865	5.36	4.27	4.84	0.62-168.49	90.35	11.72	<0.01
Cd (μg/L)	3865	1.34	1.20	0.69	0.02-6.31	51.85	1.52	<0.01
Mn (μg/dL)	1625	1.33	1.28	0.40	0.48-4.62	30.03	1.48	<0.01 (<0.001*)
Zn (μg/dL)	1107	135.81	133.30	28.04	67.80-326.42	20.65	0.96	<0.01 (<0.001*)

SD = standard deviation, VC = variation coefficient
*Results by the Shaprio-Wilk test

Table 4. Logistic regression analyses (LRAs) between logarithmic transformed blood levels of five metallic elements and age-related macular degeneration (AMD).

	Early AMD (per unit)					
	Simple LRA		Model I LRA[a]		Model II LRA[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Pb (μg/dL)	1.72 (1.16-2.55)	0.007	1.86 (1.16-2.99)	0.010	1.89 (1.16-3.08)	0.010
Hg (μg/L)	0.70 (0.50-0.99)	0.043	0.95 (0.69-1.30)	0.753	1.01 (0.72-1.40)	0.972
Cd (μg/L)	1.34 (0.95-1.87)	0.092	1.18 (0.79-1.76)	0.419	1.36 (0.22-8.33)	0.738
Mn (μg/dL)	1.08 (0.49-2.37)	0.845	1.34 (0.59-3.02)	0.480	1.39 (0.62-3.13)	0.424
Zn (μg/dL)	0.53 (0.09-3.14)	0.481	1.38 (0.23-8.09)	0.723	1.13 (0.76-1.69)	0.534

	Late AMD (per unit)					
	Simple LRA		Model I LRA[a]		Model II LRA[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Pb (μg/dL)	4.81 (1.55-14.96)	0.007	4.07 (0.85-19.47)	0.078	4.55 (1.05-19.74)	0.043
Hg (μg/L)	3.92 (2.01-7.63)	<0.001	4.26 (1.95-9.28)	<0.001	5.01 (2.12-11.86)	<0.001
Cd (μg/L)	7.17 (3.76-13.67)	<0.001	8.15 (2.81-23.68)	<0.001	9.76 (3.00-31.69)	<0.001
Mn (μg/dL)	0.18 (0.04-0.77)	0.020	0.20 (0.04-0.89)	0.034	0.11 (0.01-0.98)	0.048
Zn (μg/dL)	0.00 (NA-0.05)	<0.001	NA (NA-0.03)	0.002	NA (NA-1.00)	0.050

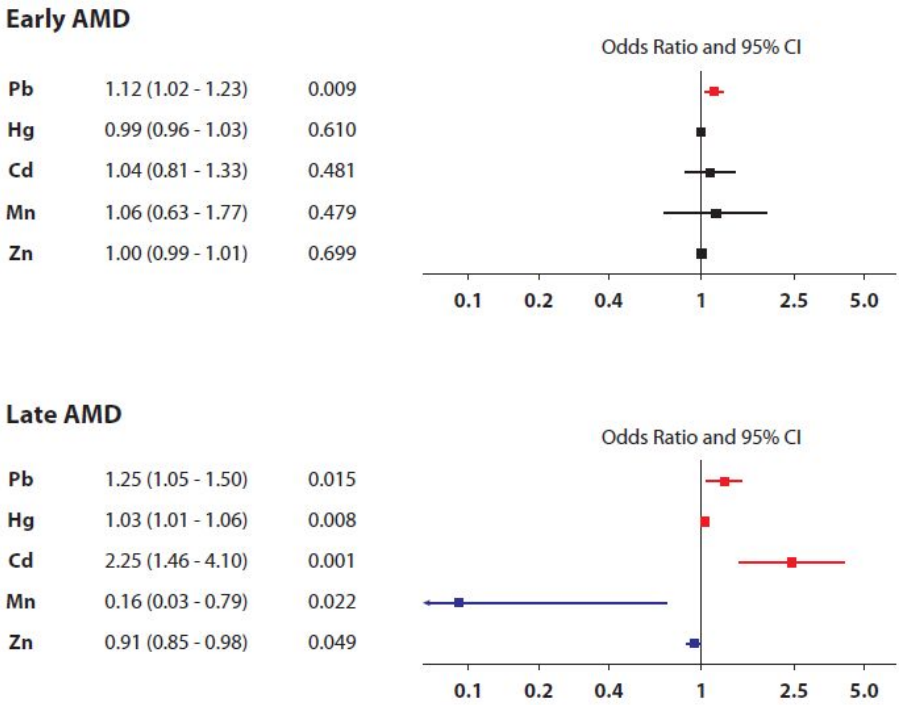

Figure 1. Odds ratios and 95% confidence intervals from the multiple logistic regression analyses (Model II) between blood levels of five metallic elements and age-related macular degeneration (AMD). Red indicates the positive associations and blue indicates the negative associations. Model II included the follow covariates; age groups, sex, smoking status, occupation, residence, house income, anemia, and body mass index.

DISCUSSION

To our knowledge, the present study is the first large, population-based, nationally representative study providing distinct insights into the association between AMD and blood levels of heavy metallic elements. Even large, prominent eye studies, such as the Beaver Dam Eye study,[79, 80] the Blue Mountains Eye study,[81] the Rotterdam study[82], and AREDS,[55] have investigated only the association between AMD and zinc/antioxidant intake, not the blood levels of heavy metallic elements. Although we could not find any relevant reference for population-based studies utilizing a Medline search, there is some evidence that heavy metallic elements might play a role in AMD pathogenesis.[83] The current study showed associations between AMD and essential metallic elements (manganese and zinc) as well as toxic metallic elements (lead, mercury, and cadmium), even after adjusting the relevant covariates. The results of the present study parallel those of previous studies, including in vivo and in vitro experiments and clinical studies, where heavy metallic elements were associated with AMD.

Historically, lead is one of the most well-known toxic metallic elements in the biomedical field. However, studies investigating the association between lead and eye diseases have been scarce, with just one study on cataract formation in men[68] and one on primary open-angle glaucoma in women.[70] In addition to these studies, Erie et al. reported that AMD is associated with excess lead in the neural retina,[69] which is concordant with the present results. Unlike the other metallic elements, lead was associated with both

early and late AMD, suggesting that the toxic mechanism of lead may be different from and more extensive than those of other metallic elements. Future investigation is warranted to determine the toxic mechanism of lead.

Mercury is also a high-impact toxic metallic element; mercurial poisoning is known to have devastating effects on health even with low-level exposure.[84] Although there has been no study suggesting the direct association between mercury intoxication and AMD, toxicity of mercury on the retina has been reported in the literature, including in vitro and in vivo experiments and clinical studies.[59, 71-74, 84-87] In vivo studies using zebrafish showed that methylmercury localizes primarily in the photoreceptor layer and the inner/outer nuclear layers[87] and targets the outer segments of photoreceptor cells.[74] An in vitro study by Bridges et al. suggested that the RPE plays a role in the mercury-associated retinal toxicity by which the RPE mediates transport of both mercury and essential nutrients to the photoreceptor cells.[72] An in vivo study using monkeys also showed that mercury penetrates the blood-retina barrier.[71] Studies have reported visual disturbances, including blindness, with acute methylmercury poisoning, which primarily damages the visual cortex.[84, 88] In addition, studies from Brazil and Russia showed that mercury intoxication could cause visual dysfunction using retinal and cortical electrophysiological techniques.[85, 86]

With developing industrialization, cadmium has increased in the surrounding environment. Recent studies implied that cadmium may play a role in development and progression of AMD, especially in a smoking population.[59-61] Erie et al. also reported that among smokers, AMD

patients had a higher urinary cadmium level compared to non-AMD patients.[62] In the present study, cadmium was associated with late AMD even after adjusting for smoking status, suggesting that cadmium is causally involved in late AMD. Cadmium may facilitate development and/or progression of AMD by increasing oxidative stress, promoting lipid peroxidation, and producing inflammatory cytokines.[62, 63] In addition, cadmium tightly binds to many biomolecules that specialize in handling bivalent cations, including alkaline earth and transition ions (e.g. zinc and manganese), and enclose cationic sites to which these essential metallic ions must bind.[64] Metallothionein is an important intracellular storage protein for zinc, copper, and manganese that decreases with oxidative stress[65]; cadmium may interfere with zinc and manganese binding by competing for the bivalent cation binding sites of metallothionein. Moreover, in the neural retina in men, a correlation between the neural levels of zinc and cadmium was also reported.[61, 89] Hence, the toxicity mechanism of cadmium must be understood with consideration of the mechanisms of other essential metallic elements. Fortunately, we were able to analyze the association between AMD and 2 essential elements of zinc and manganese. As cadmium has a long half-life in the human body, about 10–30 years, and because there is no way to promote cadmium excretion,[57] it may compete with the bivalent cations, zinc and manganese, carrying a significant implication for both the extracellular and intracellular environments.[83]

Zinc is vital for overcoming oxidative stress as well for the immune system and enzymes, and it plays an essential role in retina function.[56-58] The

average zinc level in the neural retina is lower in aged eyes than in young eyes[61]; moreover, it is also lower in the RPE/choroid complex in AMD-affected eyes than in eyes without AMD.[90] The findings of the AREDS ended the discussion of the benefit of zinc on AMD progression,[55] and subsequent studies supported the AREDS results.[82, 91, 92] Recently, Satarug et al. showed that manganese and zinc could prevent the accumulation and possible toxic effects of cadmium in RPE cells.[93] Manganese is also an essential element, although it has possible neurotoxicity at a higher concentration.[94] Manganese reduces uptake as well as accumulation of cadmium because manganese and cadmium exhibit an equal affinity for metal transporter proteins (e.g. a zinc transporter, ZIP14).[95] In addition, Kobayashi et al. suggested that manganese might be a unique metallic element inducing the synthesis of metallothionein, an important intracellular storage protein, through cytokine responses and expression of a zinc transporter, ZIP14.[96] In the present study, both zinc and manganese showed inverse associations with late AMD in the general population, indicating a possible protective effect of zinc and manganese on late AMD.

This study has several limitations. First, KNHANES did not include institutionalized individuals, and participants without any gradable fundus photographs were excluded. In addition, the KNHANES investigated the blood levels of heavy metals only in a subpopulation of participants (8,800 subjects among 37,753 participants); moreover, manganese and zinc were estimated only in 2 years and 1 year out of a 4-year survey, respectively. This obligated the current study to be conducted separately from the previous study.

These issues may cause selection bias and affect the analyses for associations between AMD and these metallic elements. The results should be interpreted under consideration of these limitations. Second, although thousands of participants were included in the present study, the frequencies and prevalence of AMD, especially late AMD for manganese and zinc analyses, were quite low. This is an inherent limitation for a study using pre-existing surveys, and should also be considered when interpreting the results. Third, associations proposed in the present study were estimated from a cross-sectional study and cannot be interpreted as causal relationships. Similarly, we could not explain the pathophysiology regarding the effects of heavy metallic elements on AMD. This is also an inherent limitation of the present study.

Notwithstanding these limitations, the present study also has strong points. First, the results of the present study can be interpreted in the context of the results of our previous study, which reported the prevalence and risk factors of AMD (unpublished data, 2014, Park et al.). Although the present study necessarily included only a subgroup of the KNHANES participants, the references for AMD estimates reported in our previous study were expected to be quite reliable as our previous study analyzed the entire KNHANES database, including over 16,000 eligible participants aged $\geq$40 years. Second, detailed information was provided for 5 heavy metallic elements in the Korean population; this information included not only the mean concentrations according to AMD grades, age groups, sex, and other covariates, but also their distribution in blood (e.g. range, coefficient of variation, and skewness). Previous population-based studies investigating the

association between metallic elements (mostly zinc) and AMD have always depended on intake estimates. It is expected that these findings will provide a reference for follow-up studies. In addition, the estimates were provided using logarithmic-transformed blood levels for each heavy metal as well as those using non-transformed blood levels. The results from 2 sets of LRAs showed similar results, indicating the robustness of the analyses.

In conclusion, this study set out to determine the association between heavy metallic elements and AMD. The results suggest that the toxic heavy metals (lead, mercury, and cadmium) may negatively influence AMD, while essential heavy metals (manganese and zinc) may favorably influence AMD. Environmental and industrial pollution should be highlighted in view of public health and eye diseases. In addition, biomedical researchers should pay more attention to deficiencies of and supplementation with these essential elements.

REFERENCES

1. (2007). World Health Organization. Vision 2020. The Right to Sight: Global initiative for the elimination of avoidable blindness: action plan 2006–2011.
2. Pascolini, D., and Mariotti, S.P. (2012). Global estimates of visual impairment: 2010. Br J Ophthalmol *96*, 614-618.
3. Lee, P.P., Feldman, Z.W., Ostermann, J., Brown, D.S., and Sloan, F.A. (2003). Longitudinal prevalence of major eye diseases. Arch Ophthalmol *121*, 1303-1310.
4. Blindness, C. (2000). Vision 2020: the cataract challenge. Community Eye Health *13*, 17-19.
5. Jager, R.D., Mieler, W.F., and Miller, J.W. (2008). Age-related macular degeneration. N Engl J Med *358*, 2606-2617.
6. Kawasaki, R., Yasuda, M., Song, S.J., Chen, S.-J., Jonas, J.B., Wang, J.J., Mitchell, P., and Wong, T.Y. (2010). The Prevalence of Age-Related Macular Degeneration in Asians: A Systematic Review and Meta-Analysis. Ophthalmology *117*, 921-927.
7. Yang, K., Liang, Y.B., Gao, L.Q., Peng, Y., Shen, R., Duan, X.R., Friedman, D.S., Sun, L.P., Mitchell, P., Wang, N.L., et al. (2011). Prevalence of age-related macular degeneration in a rural Chinese population: the Handan Eye Study. Ophthalmology *118*, 1395-1401.
8. Laude, A., Cackett, P.D., Vithana, E.N., Yeo, I.Y., Wong, D., Koh,

A.H., Wong, T.Y., and Aung, T. (2010). Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease? Prog Retin Eye Res *29*, 19-29.

9. Klein, R., Chou, C.F., Klein, B.E., Zhang, X., Meuer, S.M., and Saaddine, J.B. (2011). Prevalence of age-related macular degeneration in the US population. Arch Ophthalmol *129*, 75-80.

10. Yoon, K.C., Mun, G.H., Kim, S.D., Kim, S.H., Kim, C.Y., Park, K.H., Park, Y.J., Baek, S.H., Song, S.J., Shin, J.P., et al. (2011). Prevalence of eye diseases in South Korea: data from the Korea National Health and Nutrition Examination Survey 2008-2009. Korean J Ophthalmol *25*, 421-433.

11. Oyeyemi, G., Adewara, A., and Adeyemi, R. (2010). Complex survey data analysis: A comparison of SAS, SPSS and STATA. Asian Journal of Math Statistics *3*, 33-39.

12. Cho, B.J., Heo, J.W., Kim, T.W., Ahn, J., and Chung, H. (2013). Prevalence and Risk Factors of Age-Related Macular Degeneration in Korea: The Korean National Health and Nutrition Examination Survey. Invest Ophthalmol Vis Sci.

13. Bird, A.C., Bressler, N.M., Bressler, S.B., Chisholm, I.H., Coscas, G., Davis, M.D., de Jong, P.T., Klaver, C.C., Klein, B.E., Klein, R., et al. (1995). An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol *39*, 367-374.

14. Kim, Y., Park, S., Kim, N.S., and Lee, B.K. (2013). Inappropriate survey design analysis of the Korean National Health and Nutrition Examination Survey may produce biased results. J Prev Med Public Health *46*, 96-104.

15. Kawasaki, R., Wang, J.J., Ji, G.J., Taylor, B., Oizumi, T., Daimon, M., Kato, T., Kawata, S., Kayama, T., Tano, Y., et al. (2008). Prevalence and risk factors for age-related macular degeneration in an adult Japanese population: the Funagata study. Ophthalmology *115*, 1376-1381, 1381 e1371-1372.

16. Klein, R., Klein, B.E.K., and Linton, K.L.P. (1992). Prevalence of age-related maculopathy: The Beaver Dam Eye Study. Ophthalmology *99*, 933-943.

17. Maruko, I., Iida, T., Saito, M., Nagayama, D., and Saito, K. (2007). Clinical characteristics of exudative age-related macular degeneration in Japanese patients. Am J Ophthalmol *144*, 15-22.

18. Christen, W.G., Glynn, R.J., Manson, J.E., Ajani, U.A., and Buring, J.E. (1996). A prospective study of cigarette smoking and risk of age-related macular degeneration in men. JAMA *276*, 1147-1151.

19. Klein, R., Cruickshanks, K.J., Nash, S.D., Krantz, E.M., Nieto, F.J., Huang, G.H., Pankow, J.S., and Klein, B.E. (2010). The prevalence of age-related macular degeneration and associated risk factors. Arch Ophthalmol *128*, 750-758.

20. VanderBeek, B.L., Zacks, D.N., Talwar, N., Nan, B., and Stein, J.D. (2013). Role of statins in the development and progression of age-

related macular degeneration. Retina *33*, 414-422.

21. (1992). Risk factors for neovascular age-related macular degeneration. The Eye Disease Case-Control Study Group. Arch Ophthalmol *110*, 1701-1708.

22. Tan, J.S., Mitchell, P., Smith, W., and Wang, J.J. (2007). Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology *114*, 1143-1150.

23. Chen, W., Stambolian, D., Edwards, A.O., Branham, K.E., Othman, M., Jakobsdottir, J., Tosakulwong, N., Pericak-Vance, M.A., Campochiaro, P.A., Klein, M.L., et al. (2010). Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America *107*, 7401-7406.

24. Reynolds, R., Rosner, B., and Seddon, J.M. (2010). Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degeneration. Ophthalmology *117*, 1989-1995.

25. Zhang, X., Li, M., Wen, F., Zuo, C., Chen, H., Wu, K., and Zeng, R. (2013). Different impact of high-density lipoprotein-related genetic variants on polypoidal choroidal vasculopathy and neovascular age-related macular degeneration in a Chinese Han population. Experimental eye research *108*, 16-22.

26. Mullins, R.F., Russell, S.R., Anderson, D.H., and Hageman, G.S.

(2000). Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB journal : official publication of the Federation of American Societies for Experimental Biology *14*, 835-846.

27. Curcio, C.A., Presley, J.B., Malek, G., Medeiros, N.E., Avery, D.V., and Kruth, H.S. (2005). Esterified and unesterified cholesterol in drusen and basal deposits of eyes with age-related maculopathy. Experimental eye research *81*, 731-741.

28. Age-Related Eye Disease Study Research, G. (2000). Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Ophthalmology *107*, 2224-2232.

29. Hogg, R.E., Woodside, J.V., Gilchrist, S.E., Graydon, R., Fletcher, A.E., Chan, W., Knox, A., Cartmill, B., and Chakravarthy, U. (2008). Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. Ophthalmology *115*, 1046-1052 e1042.

30. Adams, M.K., Simpson, J.A., Aung, K.Z., Makeyeva, G.A., Giles, G.G., English, D.R., Hopper, J., Guymer, R.H., Baird, P.N., and Robman, L.D. (2011). Abdominal obesity and age-related macular degeneration. Am J Epidemiol *173*, 1246-1255.

31. Chen, S.J., Cheng, C.Y., Peng, K.L., Li, A.F., Hsu, W.M., Liu, J.H., and Chou, P. (2008). Prevalence and associated risk factors of age-related macular degeneration in an elderly Chinese population in

Taiwan: the Shihpai Eye Study. Invest Ophthalmol Vis Sci *49*, 3126-3133.

32. Kim, B.J., Lee, S.H., Jung, K.H., Yu, K.H., Lee, B.C., and Roh, J.K. (2012). Dynamics of obesity paradox after stroke, related to time from onset, age, and causes of death. Neurology *79*, 856-863.

33. Allison, D.B., Fontaine, K.R., Manson, J.E., Stevens, J., and VanItallie, T.B. (1999). Annual deaths attributable to obesity in the United States. JAMA *282*, 1530-1538.

34. Gatineau, M., and Mathrani, S. (2011). Obesity and ethnicity. National Obesity Observatory: Oxford.

35. Ma, R.C., and Chan, J.C. (2013). Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Annals of the New York Academy of Sciences *1281*, 64-91.

36. Montgomery, M.P., Kamel, F., Pericak-Vance, M.A., Haines, J.L., Postel, E.A., Agarwal, A., Richards, M., Scott, W.K., and Schmidt, S. (2010). Overall diet quality and age-related macular degeneration. Ophthalmic Epidemiol *17*, 58-65.

37. Oreopoulos, A., Kalantar-Zadeh, K., Sharma, A.M., and Fonarow, G.C. (2009). The obesity paradox in the elderly: potential mechanisms and clinical implications. Clinics in geriatric medicine *25*, 643-659, viii.

38. Roh, M.I., Kim, J.H., Byeon, S.H., Koh, H.J., Lee, S.C., and Kwon, O.W. (2008). Estimated prevalence and risk factor for age-related maculopathy. Yonsei medical journal *49*, 931-941.

39. Friberg, T.R., and Williamson, D. (1983). Hepatitis B surface antigen in human subretinal fluid. Am J Ophthalmol *95*, 712-713.

40. Temel, A., Seber, E., and Gunay, M. (1990). Detection of hepatitis B surface antigen in aqueous humor. Acta Ophthalmol (Copenh) *68*, 205-208.

41. Koksal, I., Cetinkaya, K., and Aker, F. (1992). Hepatitis B surface antigen in tears and aqueous humor. A comparative study of serum hepatitis B surface antigen levels. Ophthalmologica *204*, 19-22.

42. Singh, V.K., Kalra, H.K., Yamaki, K., Abe, T., Donoso, L.A., and Shinohara, T. (1990). Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. Induction of experimental autoimmune uveitis in Lewis rats. Journal of immunology (Baltimore, Md. : 1950) *144*, 1282-1287.

43. Slepova, O.S., Kushnir, V.N., Zaitseva, N.S., Titarenko, Z.D., and Dumbrava, V.A. (1994). [Clinical and immunological signs of retinal lesions and possibilities of their correction by drugs in patients with chronic diffuse liver diseases of viral etiology and carriers of Australia antigen]. Vestnik oftalmologii *110*, 27-29.

44. Roy, C.N. (2010). Anemia of inflammation. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program *2010*, 276-280.

45. Guralnik, J.M., Eisenstaedt, R.S., Ferrucci, L., Klein, H.G., and Woodman, R.C. (2004). Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained

anemia. Blood *104*, 2263-2268.

46. Weiss, G., and Goodnough, L.T. (2005). Anemia of chronic disease. N Engl J Med *352*, 1011-1023.

47. Atkinson, J.P., and Goodship, T.H. (2007). Complement factor H and the hemolytic uremic syndrome. The Journal of experimental medicine *204*, 1245-1248.

48. Tefferi, A. (2003). Anemia in adults: a contemporary approach to diagnosis. Mayo Clinic proceedings *78*, 1274-1280.

49. Rochtchina, E., Wang, J.J., Flood, V.M., and Mitchell, P. (2007). Elevated serum homocysteine, low serum vitamin B12, folate, and age-related macular degeneration: the Blue Mountains Eye Study. Am J Ophthalmol *143*, 344-346.

50. Gopinath, B., Flood, V.M., Rochtchina, E., Wang, J.J., and Mitchell, P. (2013). Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration. The American journal of clinical nutrition *98*, 129-135.

51. You, Q.S., Xu, L., Yang, H., Li, Y.B., Wang, S., Wang, J.D., Zhang, J.S., Wang, Y.X., and Jonas, J.B. (2012). Five-year incidence of age-related macular degeneration: the Beijing Eye Study. Ophthalmology *119*, 2519-2525.

52. Seddon, J.M., Reynolds, R., Shah, H.R., and Rosner, B. (2011). Smoking, dietary betaine, methionine, and vitamin D in monozygotic twins with discordant macular degeneration: epigenetic implications. Ophthalmology *118*, 1386-1394.

53. Pham, T.Q., Rochtchina, E., Mitchell, P., Smith, W., and Wang, J.J. (2009). Sunlight-related factors and the 10-year incidence of age-related maculopathy. Ophthalmic Epidemiol *16*, 136-141.

54. Sui, G.Y., Liu, G.C., Liu, G.Y., Gao, Y.Y., Deng, Y., Wang, W.Y., Tong, S.H., and Wang, L. (2013). Is sunlight exposure a risk factor for age-related macular degeneration? A systematic review and meta-analysis. Br J Ophthalmol *97*, 389-394.

55. Age-Related Eye Disease Study Research, G. (2001). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol *119*, 1417-1436.

56. Ugarte, M., and Osborne, N.N. (2001). Zinc in the retina. Progress in neurobiology *64*, 219-249.

57. Nordberg, G. (2007). Handbook on the toxicology of metals, 3rd Edition, (Amsterdam ; Boston: Academic Press).

58. Prasad, A.S. (2012). Discovery of human zinc deficiency: 50 years later. Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS) *26*, 66-69.

59. Erie, J.C., Butz, J.A., Good, J.A., Erie, E.A., Burritt, M.F., and Cameron, J.D. (2005). Heavy metal concentrations in human eyes. Am J Ophthalmol *139*, 888-893.

60. Wills, N.K., Ramanujam, V.M., Chang, J., Kalariya, N., Lewis, J.R., Weng, T.X., and van Kuijk, F.J. (2008). Cadmium accumulation in the

human retina: effects of age, gender, and cellular toxicity. Experimental eye research *86*, 41-51.

61. Wills, N.K., Ramanujam, V.M., Kalariya, N., Lewis, J.R., and van Kuijk, F.J. (2008). Copper and zinc distribution in the human retina: relationship to cadmium accumulation, age, and gender. Experimental eye research *87*, 80-88.

62. Erie, J.C., Good, J.A., Butz, J.A., Hodge, D.O., and Pulido, J.S. (2007). Urinary cadmium and age-related macular degeneration. Am J Ophthalmol *144*, 414-418.

63. Bertin, G., and Averbeck, D. (2006). Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie *88*, 1549-1559.

64. Moulis, J.M. (2010). Cellular mechanisms of cadmium toxicity related to the homeostasis of essential metals. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine *23*, 877-896.

65. Nicolas, M.G., Fujiki, K., Murayama, K., Suzuki, M.T., Shindo, N., Hotta, Y., Iwata, F., Fujimura, T., Yoshikawa, Y., Cho, F., et al. (1996). Studies on the mechanism of early onset macular degeneration in cynomolgus monkeys. II. Suppression of metallothionein synthesis in the retina in oxidative stress. Experimental eye research *62*, 399-408.

66. Kalariya, N.M., Wills, N.K., Ramana, K.V., Srivastava, S.K., and van Kuijk, F.J. (2009). Cadmium-induced apoptotic death of human retinal pigment epithelial cells is mediated by MAPK pathway.

Experimental eye research *89*, 494-502.

67. Nash, D., Magder, L., Lustberg, M., Sherwin, R.W., Rubin, R.J., Kaufmann, R.B., and Silbergeld, E.K. (2003). Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. Jama *289*, 1523-1532.

68. Schaumberg, D.A., Mendes, F., Balaram, M., Dana, M.R., Sparrow, D., and Hu, H. (2004). Accumulated lead exposure and risk of age-related cataract in men. JAMA *292*, 2750-2754.

69. Erie, J.C., Good, J.A., and Butz, J.A. (2009). Excess lead in the neural retina in age-related macular degeneration. Am J Ophthalmol *148*, 890-894.

70. Yuki, K., Dogru, M., Imamura, Y., Kimura, I., Ohtake, Y., and Tsubota, K. (2009). Lead accumulation as possible risk factor for primary open-angle glaucoma. Biological trace element research *132*, 1-8.

71. Warfvinge, K., and Bruun, A. (2000). Mercury distribution in the squirrel monkey retina after in Utero exposure to mercury vapor. Environmental research *83*, 102-109.

72. Bridges, C.C., Battle, J.R., and Zalups, R.K. (2007). Transport of thiol-conjugates of inorganic mercury in human retinal pigment epithelial cells. Toxicology and applied pharmacology *221*, 251-260.

73. Mela, M., Grotzner, S.R., Legeay, A., Mesmer-Dudons, N., Massabuau, J.C., Ventura, D.F., and de Oliveira Ribeiro, C.A. (2012). Morphological evidence of neurotoxicity in retina after methylmercury exposure. Neurotoxicology *33*, 407-415.

74. Korbas, M., Lai, B., Vogt, S., Gleber, S.C., Karunakaran, C., Pickering, I.J., Krone, P.H., and George, G.N. (2013). Methylmercury Targets Photoreceptor Outer Segments. ACS chemical biology.

75. Vig, E.K., and Hu, H. (2000). Lead toxicity in older adults. Journal of the American Geriatrics Society *48*, 1501-1506.

76. Mecocci, P., Mariani, E., Cornacchiola, V., and Polidori, M.C. (2004). Antioxidants for the treatment of mild cognitive impairment. Neurological research *26*, 598-602.

77. Navas-Acien, A., Silbergeld, E.K., Sharrett, R., Calderon-Aranda, E., Selvin, E., and Guallar, E. (2005). Metals in urine and peripheral arterial disease. Environmental health perspectives *113*, 164-169.

78. Lee, M.S., Park, S.K., Hu, H., and Lee, S. (2011). Cadmium exposure and cardiovascular disease in the 2005 Korea National Health and Nutrition Examination Survey. Environmental research *111*, 171-176.

79. VandenLangenberg, G.M., Mares-Perlman, J.A., Klein, R., Klein, B.E., Brady, W.E., and Palta, M. (1998). Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol *148*, 204-214.

80. Klein, B.E., Knudtson, M.D., Lee, K.E., Reinke, J.O., Danforth, L.G., Wealti, A.M., Moore, E., and Klein, R. (2008). Supplements and age-related eye conditions the beaver dam eye study. Ophthalmology *115*, 1203-1208.

81. Kuzniarz, M., Mitchell, P., Flood, V.M., and Wang, J.J. (2002). Use of

vitamin and zinc supplements and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmic Epidemiol *9*, 283-295.

82. Ho, L., van Leeuwen, R., Witteman, J.C., van Duijn, C.M., Uitterlinden, A.G., Hofman, A., de Jong, P.T., Vingerling, J.R., and Klaver, C.C. (2011). Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and omega-3 fatty acids: the Rotterdam study. Arch Ophthalmol *129*, 758-766.

83. Junemann, A.G., Stopa, P., Michalke, B., Chaudhri, A., Reulbach, U., Huchzermeyer, C., Schlotzer-Schrehardt, U., Kruse, F.E., Zrenner, E., and Rejdak, R. (2013). Levels of aqueous humor trace elements in patients with non-exsudative age-related macular degeneration: a case-control study. PloS one *8*, e56734.

84. Karagas, M.R., Choi, A.L., Oken, E., Horvat, M., Schoeny, R., Kamai, E., Cowell, W., Grandjean, P., and Korrick, S. (2012). Evidence on the human health effects of low-level methylmercury exposure. Environmental health perspectives *120*, 799-806.

85. da Costa, G.M., dos Anjos, L.M., Souza, G.S., Gomes, B.D., Saito, C.A., Pinheiro Mda, C., Ventura, D.F., da Silva Filho, M., and Silveira, L.C. (2008). Mercury toxicity in Amazon gold miners: visual dysfunction assessed by retinal and cortical electrophysiology. Environmental research *107*, 98-107.

86. Iablonskaia, D.A., Mishchenko, T.S., Lakhman, O.L., Rukavishnikov, V.S., and Malyshev, V.V. (2010). [Functional state of vision system under chronic mercury intoxication]. Meditsina truda i

promyshlennaia ekologiia, 40-44.

87. Mela, M., Cambier, S., Mesmer-Dudons, N., Legeay, A., Grotzner, S.R., de Oliveira Ribeiro, C.A., Ventura, D.F., and Massabuau, J.C. (2010). Methylmercury localization in Danio rerio retina after trophic and subchronic exposure: a basis for neurotoxicology. Neurotoxicology *31*, 448-453.

88. Davis, L.E., Kornfeld, M., Mooney, H.S., Fiedler, K.J., Haaland, K.Y., Orrison, W.W., Cernichiari, E., and Clarkson, T.W. (1994). Methylmercury poisoning: long-term clinical, radiological, toxicological, and pathological studies of an affected family. Annals of neurology *35*, 680-688.

89. Wills, N.K., Kalariya, N., Sadagopa Ramanujam, V.M., Lewis, J.R., Haji Abdollahi, S., Husain, A., and van Kuijk, F.J. (2009). Human retinal cadmium accumulation as a factor in the etiology of age-related macular degeneration. Experimental eye research *89*, 79-87.

90. Erie, J.C., Good, J.A., Butz, J.A., and Pulido, J.S. (2009). Reduced zinc and copper in the retinal pigment epithelium and choroid in age-related macular degeneration. Am J Ophthalmol *147*, 276-282 e271.

91. Zeng, S., Hernandez, J., and Mullins, R.F. (2012). Effects of antioxidant components of AREDS vitamins and zinc ions on endothelial cell activation: implications for macular degeneration. Invest Ophthalmol Vis Sci *53*, 1041-1047.

92. Age-Related Eye Disease Study 2 Research, G. (2013). Lutein + zeaxanthin and omega-3 fatty acids for age-related macular

degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA *309*, 2005-2015.

93. Satarug, S., Kikuchi, M., Wisedpanichkij, R., Li, B., Takeda, K., Na-Bangchang, K., Moore, M.R., Hirayama, K., and Shibahara, S. (2008). Prevention of cadmium accumulation in retinal pigment epithelium with manganese and zinc. Experimental eye research *87*, 587-593.

94. Farina, M., Avila, D.S., da Rocha, J.B., and Aschner, M. (2013). Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury. Neurochemistry international *62*, 575-594.

95. He, L., Girijashanker, K., Dalton, T.P., Reed, J., Li, H., Soleimani, M., and Nebert, D.W. (2006). ZIP8, member of the solute-carrier-39 (SLC39) metal-transporter family: characterization of transporter properties. Molecular pharmacology *70*, 171-180.

96. Kobayashi, K., Kuroda, J., Shibata, N., Hasegawa, T., Seko, Y., Satoh, M., Tohyama, C., Takano, H., Imura, N., Sakabe, K., et al. (2007). Induction of metallothionein by manganese is completely dependent on interleukin-6 production. The Journal of pharmacology and experimental therapeutics *320*, 721-727.

97. Kweon, S., Kim, Y., Jang, M.-j., Kim, Y., Kim, K., Choi, S., Chun, C., Khang, Y.-H., and Oh, K. (2014). Data Resource Profile: The Korea National Health and Nutrition Examination Survey (KNHANES). International Journal of Epidemiology *43*, 69-77.

98. Chylack, L.T., Jr., Wolfe, J.K., Singer, D.M., Leske, M.C., Bullimore, M.A., Bailey, I.L., Friend, J., McCarthy, D., and Wu, S.Y. (1993). The

Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol *111*, 831-836.

99. Seah, S.K., Wong, T.Y., Foster, P.J., Ng, T.P., and Johnson, G.J. (2002). Prevalence of lens opacity in Chinese residents of Singapore: the tanjong pagar survey. Ophthalmology *109*, 2058-2064.

100. Congdon, N., Vingerling, J.R., Klein, B.E., West, S., Friedman, D.S., Kempen, J., O'Colmain, B., Wu, S.Y., and Taylor, H.R. (2004). Prevalence of cataract and pseudophakia/aphakia among adults in the United States. Arch Ophthalmol *122*, 487-494.

101. Athanasiov, P.A., Casson, R.J., Sullivan, T., Newland, H.S., Shein, W.K., Muecke, J.S., Selva, D., and Aung, T. (2008). Cataract in rural Myanmar: prevalence and risk factors from the Meiktila Eye Study. Br J Ophthalmol *92*, 1169-1174.

102. Duan, X.R., Liang, Y.B., Wang, N.L., Wong, T.Y., Sun, L.P., Yang, X.H., Tao, Q.S., Yuan, R.Z., and Friedman, D.S. (2013). Prevalence and associations of cataract in a rural Chinese adult population: the Handan Eye Study. Graefes Arch Clin Exp Ophthalmol *251*, 203-212.

103. Mahdi, A.M., Rabiu, M.M., C, E.G., Sivasubramaniam, S., Murthy, G.V., Ezelum, C., and Entekume, G. (2014). Prevalence and risk factors for lens opacities in Nigeria: results of the national blindness and low vision survey. Invest Ophthalmol Vis Sci.

104. Foster, P.J., Wong, T.Y., Machin, D., Johnson, G.J., and Seah, S.K. (2003). Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar

Survey. Br J Ophthalmol *87*, 1112-1120.

105. Chang, J.R., Koo, E., Agron, E., Hallak, J., Clemons, T., Azar, D., Sperduto, R.D., Ferris, F.L., 3rd, and Chew, E.Y. (2011). Risk factors associated with incident cataracts and cataract surgery in the Age-related Eye Disease Study (AREDS): AREDS report number 32. Ophthalmology *118*, 2113-2119.

106. Klein, R., Klein, B.E., Jensen, S.C., Moss, S.E., and Cruickshanks, K.J. (1994). The relation of socioeconomic factors to age-related cataract, maculopathy, and impaired vision. The Beaver Dam Eye Study. Ophthalmology *101*, 1969-1979.

107. Klein, B.E., Klein, R., and Lee, K.E. (1998). Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. Am J Ophthalmol *126*, 782-790.

108. Leske, M.C., Wu, S.Y., Hennis, A., Connell, A.M., Hyman, L., and Schachat, A. (1999). Diabetes, hypertension, and central obesity as cataract risk factors in a black population. The Barbados Eye Study. Ophthalmology *106*, 35-41.

109. Christen, W.G., Glynn, R.J., Manson, J.E., Macfadyen, J., Bubes, V., Schvartz, M., Buring, J.E., Sesso, H.D., and Michael Gaziano, J. (2013). A Multivitamin Supplement and Cataract and Age-Related Macular Degeneration in a Randomized Trial of Male Physicians. Ophthalmology.

110. Tan, J.S., Wang, J.J., and Mitchell, P. (2008). Influence of diabetes

and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. Ophthalmic Epidemiol *15*, 317-327.

111. Anderson, G.F. (1989). Universal health care coverage in Korea. Health affairs (Project Hope) *8*, 24-34.

112. Park, S.J., Choi, N.K., Park, K.H., and Woo, S.J. (2013). Five year nationwide incidence of rhegmatogenous retinal detachment requiring surgery in Korea. PloS one *8*, e80174.

113. Erie, J.C., Baratz, K.H., Hodge, D.O., Schleck, C.D., and Burke, J.P. (2007). Incidence of cataract surgery from 1980 through 2004: 25-year population-based study. Journal of cataract and refractive surgery *33*, 1273-1277.

114. Lansingh, V.C., Resnikoff, S., Tingley-Kelley, K., Nano, M.E., Martens, M., Silva, J.C., Duerksen, R., and Carter, M.J. (2010). Cataract surgery rates in latin america: a four-year longitudinal study of 19 countries. Ophthalmic Epidemiol *17*, 75-81.

115. International Federation of Health Plans. 2012 Comparative Price Report. Available at: http://www.ifhp.com. Accessed March 3, 2014

116. Girdhar, A., Kumar, V., Singh, A., Menon, B., and Vijayan, V.K. (2011). Systemic inflammation and its response to treatment in patients with asthma. Respiratory care *56*, 800-805.

117. Wood, L.G., Baines, K.J., Fu, J., Scott, H.A., and Gibson, P.G. (2012). The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. Chest *142*, 86-93.

118. Prevention, P. (2007). Expert Panel Report 3 (EPR-3): Guidelines for

the Diagnosis and Management of Asthma-Summary Report 2007. The Journal of allergy and clinical immunology *120*, S94.

119. Weatherall, M., Clay, J., James, K., Perrin, K., Shirtcliffe, P., and Beasley, R. (2009). Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. Respirology (Carlton, Vic.) *14*, 983-990.

120. Christen, W.G., Manson, J.E., Glynn, R.J., Ajani, U.A., Schaumberg, D.A., Sperduto, R.D., Buring, J.E., and Hennekens, C.H. (1998). Low-dose aspirin and risk of cataract and subtypes in a randomized trial of U.S. physicians. Ophthalmic Epidemiol *5*, 133-142.

121. Cumming, R.G., and Mitchell, P. (1998). Medications and cataract. The Blue Mountains Eye Study. Ophthalmology *105*, 1751-1758.

122. Rim, T.H., Kim, M.H., Kim, W.C., Kim, T.I., and Kim, E.K. (2014). Cataract subtype risk factors identified from the Korea National Health and Nutrition Examination survey 2008-2010. BMC Ophthalmol *14*, 4.

국문 초록

서론: 나이관련황반변성 및 백내장은 전세계에서 실명의 가장 큰 원인으로 알려져 있으며, 개발도상국과 선진국 모두에서 실명의 가장 큰 원인이다. 나이관련황반변성은 전세계에서 300 만명 이상에서 실명을 초래하는 것으로 알려져 있으며, 백내장은 전세계 실명인구의 약 절반 – 약 2000 만명 –의 원인으로 보고되어왔다. 인구가 노령화되면서 나이관련황반변성의 유병률 및 실제 유병인구는 급속히 증가하고 있으며, 이에 따라 사회경제적인 비용 또한 급격히 증가하고 있다. 지난 30 년간 서양에서는 나이관련황반변성의 역학에 대한 연구가 활발히 이루어져왔으나, 상대적으로 아시아인에서의 이들 질환에 대한 역학 연구는 드물었다. 이에 더하여, 아시아 뿐만 아니라 서양에서도 국가규모의 인구집단을 대표할 수 있는 역학연구는 드물었다.

방법: 본 연구는 국민건강영양조사 자료를 이용한 단면인구이다. 국민건강영양조사는 복합 층화 추출된 건강 및 영양조사로서, 한국인을 대표할 수 있는 인구집단으로 구성되었다. 모든 분석은 40 세 이상의 인구에서 시행되었다. 첫 번째 연구에서는 나이관련황반변성의 유병 및 위험인자를 분석하였다.

나이관련황반변성은 안저 사진을 판독하여 진단하였으며, 로지스틱 회귀분석을 이용하여 위험인자를 분석하였다. 두 번째 연구에서는 나이관련황반변성과 다섯 가지 중금속 (납, 수은, 카드뮴, 망간, 아연)의 상관관계에 대해서 분석하였다. 혈중 중금속 농도를 측정하였으며, 나이관련황반변성과 이들 중금속과의 관계는 로지스틱 회귀분석으로 분석하였다. 이에 더하여, 이들 다섯가지 중금속의 혈중 분포를 분석하였다. 다섯 가지 중금속의 혈중농도가 편위 되어있는 것을 확인하였으며, 이에 중금속 농도를 로그 변환한 후 로지스틱회귀분석을 통하여 같은 분석을 시행하였다.

결과: 첫 번째 연구에서 한국인의 나이관련황반변성의 유병률은 6.62% (95% confidence interval [CI], 6.15%-7.09%) 이었다. 초기 나이관련황반변성의 유병률은 6.02% (95% CI, 5.56%-6.48%)이었으며, 후기 나이관련황반변성의 유병률은 0.60% (95% CI, 0.45%-0.75%)이었다. 초기 나이관련황반변성의 유병률은 여자에서 (6.73%; 95% CI, 6.11%-7.35%) 남자보다 (5.25%; 95% CI, 4.61%-5.89%, $p<0.001$) 유의하게 높았으며, 이와 반대로 후기 나이관련황반변성의 유병률은 여자에서 (0.37%; 95% CI, 0.22%-0.52%) 남자보다 (0.85%; 95% CI, 0.59%-1.12%, $p<0.001$) 유의하게 낮았다. 그러나, 다중회귀분석 결과에서는 초기와 후기 나이관련황반변성 모두 성별과는 관계가 없었다. 또한, 가구소득, 지역, 햇빛노출, 고혈압, 당뇨, 심혈관계

질환등과의 관계도 없었다. 그렇지만, 초기 나이관련황반변성은 고령의 연령층 ($p<0.001$), 낮은 학력수준 ($p=0.027$), 직업 ($p<0.001$), 빈혈 ($p=0.027$), B 형 간염 보균자 ($p<0.001$), 정상 체질량지수 및 허리둘레 (체질량지수, $p=0.032$; 허리둘레, $p=0.046$), 그리고 고밀도지질단백질 ($p=0.046$)과 유의미한 상관관계를 보였다. 흡연과는 유의미한 상관관계를 보이지 않았다. 후기 나이관련황반변성은 고령의 연령층 ($p<0.001$), 현재흡연 ($p=0.022$), 정상 체질량지수 ($p=0.037$)과 유의미한 상관관계를 보였다. 두 번째 연구에서 나이관련황반변성은 다섯 가지 중금속의 혈중농도와 유의미한 상관관계를 관찰할 수 있었다. 독성 중금속인 납, 수은, 카드뮴은 후기 나이관련황반변성과 양의 상관관계를 갖는 것이 관찰되었으며, 이에 비해 필수 중금속인 망간 및 아연은 후기 나이관련황반변성과 음의 상관관계를 갖는 것이 관찰되었다. 납은 초기 나이관련황반변성과도 양의 상관관계가 있었지만, 나머지 중금속들은 초기 나이관련황반변성과의 연관성은 확인할 수 없었다. 다섯 중금속의 혈중 분포를 확인해보면, 편위되어 있는 것을 확인할 수 있었으며, 이에 시행한 로그변환한 중금속의 혈중농도를 이용한 로지스틱 회귀분석에서도 거의 같은 결과를 확인할 수 있었다.

결론: 본 연구에서는 나이관련황반변성과 백내장/백내장 수술의 한국인을 대표할 수 있는 유병률을 산출하였으며, 이들의

위험인자를 분석하였다. 본 연구를 통해 한국에는 약 121 만명의 초기 나이관련황반변성 환자들 및 12 만 여명의 후기 나이관련황반변성 환자들이 있을 것을 추정할 수 있다. 이에 더하여 한국에는 약 940 만명의 백내장에 이환된 사람들이 있으며, 이 들 중 약 170 만명의 사람들은 적어도 한눈에서 백내장 수술을 받았다는 것을 알 수 있다. 기존 연구결과와 달리 정상체중 및 고밀도지질단백질이 나이관련황반변성과 관계가 있는 것으로 밝혀졌으며, 빈혈과 B 형 간염보균자 역시 나이관련황반변성과의 관계가 밝혀졌다. 아시아인의 나이관련황반변성의 병태생리학적 기전이 서양인과는 다를 수도 있음을 시사하는 결과라고 할 수 있다. 또한, 독성 중금속들은 나이관련황반변성에 나쁜 영향을 주는 것으로 생각되며, 반대로 필수 중금속들은 나이관련황반변성에 좋은 영향을 줄 것으로 생각된다. 납은 다른 중금속들과 달리 나이관련황반변성의 초기부터 후기까지 영향을 끼치는 것으로 생각된다.

주요어 : 나이관련황반변성, 유병률, 위험인자, 결정인자, 중금속

학 번 : 2009-23509