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Risk of age-related macular degeneration according to the chronic kidney disease and proteinuria in Korea: a 10-year nationwide cohort study

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The association between chronic kidney disease (CKD) and the risk of age-related macular degeneration (AMD) is unclear. Our study aimed to evaluate this relationship considering the potential impact of proteinuria. This retrospective cohort study used a large representative population sample from the Korean National Health Insurance Service database (2009–2019) of individuals who participated in a national health screening program in 2009. CKD was determined by estimated glomerular filtration rate (eGFR). Proteinuria was assessed using dipstick urinalysis. AMD was identified according to International Classification Disease, Tenth Revision, codes in claims data. The Cox regression hazards model was used to estimate the association between CKD and risk of AMD. Among 4,005,946 participants, 400,189 (10.0%) had CKD. There was no significant association between CKD and AMD, but a positive relationship was identified between proteinuria and AMD. In stratification analysis with age and sex, the risk of AMD was more evident in younger (< 65 years) than older individuals (*P*-interaction < 0.001) and in men than women (*P*-interaction < 0.001). A positive association between proteinuria and AMD risk was observed and was prominent in younger males.

Keywords Age-related macular degeneration, Chronic kidney disease, Glomerular filtration rate, Proteinuria

The association between renal disease and blindness was first reported by Richard Bright in 1836,[1] marking a significant milestone in our understanding of the intricate relationship between the kidney and the eye. Over the years, extensive research has revealed that these two organs share not only anatomical similarities, but also developmental, physiological, and pathogenic pathways[2]. Notably, the glomerulus, a vital component of the kidney, and the choroid, a crucial part of the eye, possess vascular networks that exhibit striking structural resemblance. Moreover, a range of oculo-renal syndromes, including von Hippel–Lindau syndrome and Alport syndrome, with genetic links has been identified, further highlighting the connection between these two organs[3].

Chronic kidney disease (CKD) is a major public health problem increasing rapidly around the world, and much of this increasing burden is expected to occur in Asia[4]. CKD has been consistently linked to various eye disorders, including retinopathy, glaucoma, and cataract[5]. Age-related macular degeneration (AMD), an important cause of blindness[6–8], has also been investigated in relation to CKD[9,10]. However, a meta-analysis of 12 observational studies investigating CKD and AMD yielded inconclusive results due to statistical and methodological heterogeneity[11]. In addition, results have been inconsistent among individual studies[5,9–12].

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Although current CKD diagnosis in clinical practice largely relies on reduced estimated glomerular filtration rate (eGFR), proteinuria per se is a marker of structural kidney damage even in patients with normal eGFRs. Patients with proteinuria possess a greater risk of progressive kidney failure compared to those without proteinuria[13]. Thus, the current CKD guideline includes not only eGFR-based criteria, but also albuminuria criteria[14]. Interestingly, Nitsch suggested proteinuria rather than eGFR as a main factor independently related to AMD[15]. Given that overt proteinuria indicates the presence of glomerular disease, which may share a pathology with AMD, an association between proteinuric kidney disease and AMD can be hypothesized. However, there is little information about the relationship between proteinuria and AMD except for a single case–control study.

Our study aimed to provide a comprehensive analysis of the relationship between CKD and AMD, considering the potential impact of proteinuria, ultimately seeking to improve the understanding of the interplay between these two conditions.

Methods

Study setting and data source

In Korea, the National Health Insurance Service (NHIS) provides mandatory universal medical insurance to around 97% of the population, while the remaining 3% are Medicaid beneficiaries. The NHIS maintains a comprehensive database that contains demographic information (like age, sex, disability, and income) and health claims data, such as clinical visit date, prescription, and diagnosis according to International Classification of Disease, Tenth Revision (ICD-10) codes based on medical bills for reimbursement[16].

The biennial NHIS health screening program includes anthropometric measurements (such as blood pressure and body mass index), laboratory tests (such as fasting glucose and serum lipid levels), and a self-administered questionnaire on medical history and lifestyle behaviors (such as smoking, drinking, and physical activity)[17]. Fasting serum glucose, lipid levels, and hemoglobin were measured after an overnight fast. Urine samples were collected randomly during the early morning following an overnight fast. Detailed information on lifestyle was obtained by self-questionnaire.

Given its comprehensive linkage of demographic, mortality, health claims, and health screening data, the mentioned population-based nationwide NHIS database is widely used in epidemiological studies[18].

Study population

This retrospective cohort study included 4,471,011 individuals ≥ 50 years of age who participated in a national health screening program in 2009. Subjects who had any missing data ($n = 253,148$), end-stage renal disease diagnosis at baseline ($n = 10,673$), or AMD diagnosis at baseline ($n = 154,131$) were excluded. We applied a one-year lag time to reduce the effect of reverse causality ($n = 47,113$). A total of 4,005,946 participants was included for the final analysis (Fig. 1).

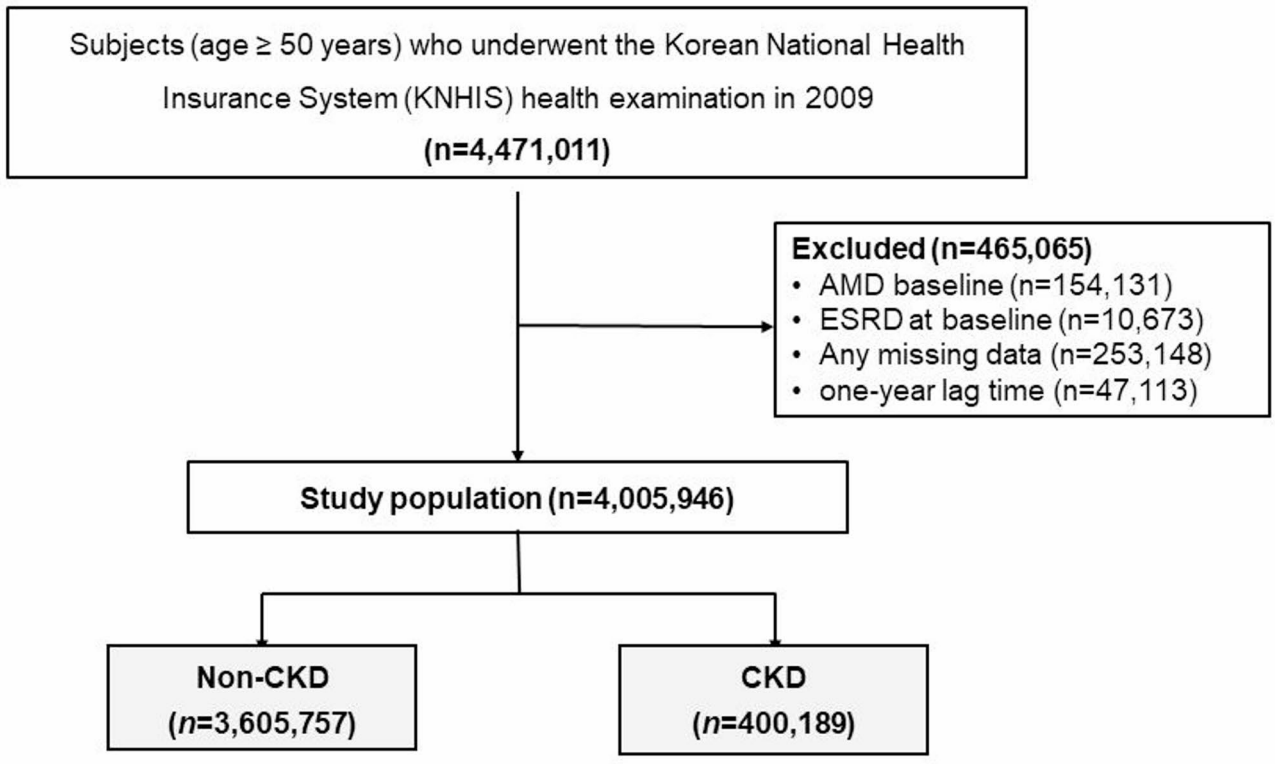

Fig. 1. Flow chart of the study population. AMD age-related macular degeneration, ESRD end-stage renal disease, CKD chronic kidney disease.

The Institutional Review Board of Soongsil University approved this study (SSU-202007-HR-236-01), this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was waived in this study by the Institutional Review Board of Soongsil University, Seoul, South Korea. Informed consent was waived by the Institutional Review Board of Soongsil University because the data in the NHIS were anonymized and de-identified.

Definitions of CKD and proteinuria

The NHIS had been using the Modification of Diet in Renal Disease (MDRD) equation for CKD screening[19,20].

$$eGFR(mL/min/1.73\,m2) = 175 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \ \ (female \times 0.742)$$

CKD was defined as eGFR < 60 mL/min/1.73 m^2which measures the filtering efficiency of the kidneys.

Separately, proteinuria was assessed using dipstick urinalysis. The levels of proteinuria were categorized as negative (−), trace (±), 1+, 2+, 3+, and 4+, corresponding to urinary protein levels of undetectable, 10 mg/dL, 30 mg/dL, 100 mg/dL, 300 mg/dL, and 1000 mg/dL or greater, respectively.

Study outcomes and follow-up

The endpoints of the study were incident AMD. Newly diagnosed AMD was operationally defined based on claim records collected within 1 year before the health screening examination. AMD was identified based on ICD-10 code H35.3, in consideration of previous studies[21–23]. All participants were followed from the index date of the health screening examination in 2009 and were censored on the date of AMD occurrence, death, or at the end of the study period (December 31, 2019).

Covariates

In Korea, insurance premium levels are determined based on income. Household income was categorized based on the lowest 25 percentile of health insurance premium level. Comorbidities were defined based on the medical claims data before screening according to ICD-10 codes and relevant medication use (hypertension, I10–I13 and I15; diabetes mellitus, E11–E14; dyslipidemia, E78). The Charlson comorbidity index (CCI) was calculated based on the diagnosis code[24]. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Smoking status was classified as non-smoker, ex-smoker, or current smoker. Alcohol consumption was categorized as none, mild (< 30 g/day), or heavy (≥ 30 g/day). Regular physical activity was defined as strenuous exercise performed at least three times a week for ≥ 20 min per session or moderate physical activity performed at least five times per week for > 30 min.

Statistical analysis

The comparison of baseline characteristics based on the presence of CKD and proteinuria was conducted using the chi-square test for categorical variables or the *t* test for continuous variables. The hazard ratio (HR) for AMD accompanying 95% CI was calculated using Cox regression analysis. We used Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazard models. We adjusted for multiple confounding factors, mainly the shared common risk factors for CKD and AMD[9,11,25]. Model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was further adjusted for income, smoking, alcohol consumption, regular physical activity, and BMI; and model 4 was further adjusted for hypertension, diabetes mellitus, dyslipidemia, and CCI. Kaplan–Meier curves were used to illustrate the cumulative incidence probabilities of AMD. Furthermore, to assess the potential effect modification by age, we examined sex, comorbidities, and BMI through stratified analysis. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among the participants, 400,189 (10.0%) had CKD and were more likely to be older, female, non-smokers, and non-drinkers. They also had a greater prevalence of comorbid conditions such as hypertension, diabetes, and dyslipidemia, as well as higher CCI scores, compared to the non-CKD group (Table 1).

When comparing the groups with proteinuria to the group without proteinuria, the former groups tended to be older, with the exception of the 4 + proteinuria group, which comprised the youngest patients (mean ± standard deviation, 52.0 ± 8.6 years). The total proteinuria group also demonstrated a higher likelihood of unfavorable traits, such as current smoking and/or heavy drinking, and a higher prevalence of comorbidities. These findings were accompanied by elevated measurements of BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, lipid levels, and CCI scores, all of which increased as the severity of proteinuria increased (Table 2).

Risk of AMD according to CKD and proteinuria

During the mean follow-up period of 8.6 years, 468,838 AMD events were reported. The CKD group was associated with a higher risk of AMD (unadjusted HR 1.26, 95% confidence interval [CI] 1.25–1.27) than the non-CKD group based on eGFR. However, the increased risk was attenuated after adjustment for confounding factors (Model 2, adjusted HR [aHR] 1.02, 95% CI 1.01–1.02; Model 3, aHR 1.01, 95% CI 1.00–1.02; Model 4, aHR 0.99, 95% CI 0.98–1.00). Notably, a positive relationship was identified between proteinuria and AMD (trace, aHR 1.01, 95% CI 1.00–1.03; 1+, aHR 1.04, 95% CI 1.02–1.06; 2+, aHR 1.13, 95% CI 1.10–1.16; 3+, aHR 1.17, 95% CI 1.10–1.23; and 4+, aHR 1.32, 95% CI 1.17–1.48) (Table 3; Fig. 2). Kaplan–Meier analysis also demonstrated a significant trend in the risk of AMD according to severity of proteinuria (Fig. 3).

Variables	Non-CKD (eGFR ≥ 60 mL/min/1.73 m^2)	CKD (eGFR < 60 mL/min/1.73 m^2)	*P*-value
Total subject, No. (%)	3,605,757 (90.0)	400,189 (10.0)	
Mean age (years)	59.9 ± 8.0	64.9 ± 9.0	< 0.001
Sex, male, No. (%)	1,775,735 (49.3)	168,172 (42.0)	< 0.001
Income, lowest 25%, No. (%)	785,089 (21.8)	77,847 (19.5)	< 0.001
Place of residence, urban, No. (%)	1,635,615 (45.4)	186,778 (46.7)	< 0.001
Smoking, No. (%)			< 0.001
Never smoker	2,376,045 (65.9)	285,738 (71.4)	
Ex-smoker	573,337 (15.9)	62,516 (15.6)	
Current smoker	656,375 (18.2)	51,935 (13.0)	
Alcohol consumption, No. (%)			< 0.001
Non	2,300,353 (63.8)	292,533 (73.1)	
Mild	1,062,781 (29.5)	92,346 (23.1)	
Heavy	242,623 (6.7)	15,310 (3.8)	
Physical activity, regular, No. (%)	769,221 (21.3)	82,325 (20.6)	< 0.001
Comorbidity, No. (%)			
Hypertension	1,586,236 (44.0)	244,467 (61.1)	< 0.001
Diabetes mellitus	513,474 (14.2)	87,436 (21.9)	< 0.001
Dyslipidemia	980,969 (27.2)	146,662 (36.7)	< 0.001
Charlson comorbidity index	1.2 ± 1.3	1.6 ± 1.5	< 0.001
Anthropometric			
Body mass index (kg/m^2)	24.1 ± 3.0	24.4 ± 3.1	< 0.001
Waist circumference (cm)	82.1 ± 8.3	83.4 ± 8.5	< 0.001
Systolic BP (mmHg)	126.3 ± 15.7	128.3 ± 16.3	< 0.001
Diastolic BP (mmHg)	77.9 ± 10.2	78.2 ± 10.3	< 0.001
Laboratory findings (mg/dL)			
Glucose, fasting	101.6 ± 26.6	105.7 ± 31.9	< 0.001
Total cholesterol	201.1 ± 37.9	202.2 ± 40.7	< 0.001
Triglycerides*	120.2 (120.1–120.2)	132.3 (132.1–132.6)	< 0.001
HDL-C	55.2 ± 26.8	58.9 ± 57.2	< 0.001
LDL-C	119.1 ± 39.4	119.4 ± 40.0	< 0.001

Table 1. Baseline characteristics of the study population according to the presence of CKD. Values are expressed as mean ± standard deviation or number (%). *Values presented as geometric mean (95% confidence interval). *CKD* chronic kidney disease, *AMD* age-related macular degeneration, *BP* blood pressure, *GFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol.

Stratified analysis

When stratified by age, the risk of AMD in individuals with higher proteinuria was more prominent in younger individuals (< 65 years) than older individuals (*P*-interaction < 0.001). Also, the risk of AMD was more evident in men than women (*P*-interaction < 0.001). However, there was no significant difference in the relationship between proteinuria and the risk of AMD according to the presence of comorbidities (*P*-interaction = 0.1403) or obesity (*P*-interaction = 0.4475) (Table 4).

Discussion

The present study demonstrated a risk of AMD according to the CKD and proteinuria using a large population-based nationwide sample. There was an association between CKD and the risk of AMD with a fixed, narrow confidence interval, indicating highly accurate estimates. However, it became no longer significant after adjusting for multiple confounding factors, such as hypertension, diabetes, and dyslipidemia. Remarkably, a clear positive relationship according to the degree of proteinuria was noted even after adjusting for the shared common risk factors of CKD and AMD. When performing a stratified analysis, the association between proteinuria and AMD was more prominent among younger and male individuals.

There are several possible mechanisms that could explain our findings. First, epidemiological studies have demonstrated that the kidneys and eyes are genetically and epigenetically connected[2,3]. Since they share common developmental processes, the two exhibit an anatomical resemblance to glomerular-like vascular structures[2] and likely will be similarly affected. For example, in dense deposit disease, also known as membranoproliferative glomerulonephritis (MPGN), which affects both the kidneys and eyes, immune system proteins attack and adhere to the glomerular basement membrane in thick patches called dense deposits. Over time, these deposits interfere with the kidney's ability to filter fluids, and the individual experiences kidney failure. Also, deposits in the eye appear as drusen, which are a hallmark of AMD and result in breakdown of the blood–retinal barrier

Variables	Negative	Proteinuria					*P*-value
		Trace	1+	2+	3+	4+	
Total subject, No. (%)	3,773,524 (94.2)	101,106 (2.5)	85,785 (2.1)	34,351 (0.9)	9323 (0.2)	1857 (0.0)	
Mean age (years)	60.4 ± 8.2	61.0 ± 8.6	61.6 ± 8.6	62.1 ± 8.7	62.3 ± 8.3	52.0 ± 8.6	< 0.001
Sex, male, No. (%)	1,819,947 (48.2)	52,553 (52.0)	45,772 (53.4)	19,156 (55.8)	5406 (58.0)	1073 (57.8)	< 0.001
Income, lowest 25%, No. (%)	813,639 (21.6)	20,655 (20.4)	18,535 (21.6)	7609 (22.2)	2088 (22.4)	410 (22.1)	< 0.001
Place of residence, urban, No. (%)	1,712,532 (45.4)	48,842 (48.3)	40,445 (47.2)	15,655 (45.6)	4164 (44.7)	755 (40.7)	< 0.001
Smoking, No. (%)							
Non-smoker	2,516,801 (66.7)	63,955 (63.3)	53,382 (62.2)	20,964 (61.0)	5526 (59.3)	1155 (62.2)	< 0.001
Ex-smoker	594,663 (15.8)	17,575 (17.4)	15,242 (17.8)	6279 (18.3)	1781 (19.1)	313 (16.9)	
Current smoker	662,060 (17.5)	19,576 (19.4)	17,161 (20.0)	7108 (20.7)	2016 (21.6)	389 (21.0)	
Alcohol consumption, No. (%)							
Non	2,446,482 (64.8)	63,408 (62.7)	53,771 (62.7)	21,918 (63.8)	6049 (64.9)	1258 (67.7)	< 0.001
Mild	1,087,857 (28.8)	30,040 (29.7)	24,859 (29.0)	9437 (27.5)	2489 (26.7)	445 (24.0)	
Heavy	239,185 (6.3)	7658 (7.6)	7155 (8.3)	2996 (8.7)	785 (8.4)	154 (8.3)	
Physical activity, regular, No. (%)	802,360 (21.3)	21,860 (21.6)	17,924 (20.9)	7182 (20.9)	1821 (19.5)	399 (21.5)	< 0.001
Comorbidity, No. (%)							
Hypertension	1,688,167 (44.7)	55,535 (54.9)	53,935 (62.9)	24,365 (70.9)	7230 (77.6)	1471 (79.2)	< 0.001
Diabetes mellitus	533,497 (14.1)	22,872 (22.6)	26,001 (30.3)	13,325 (38.8)	4305 (46.2)	910 (49.0)	< 0.001
Dyslipidemia	1,042,842 (27.6)	33,426 (33.1)	31,469 (36.7)	14,358 (41.8)	4585 (49.2)	951 (51.2)	< 0.001
Anthropometric							
Body mass index (kg/m^2)	24.1 ± 3.0	24.3 ± 3.2	24.6 ± 3.3	24.8 ± 3.4	24.9 ± 3.5	24.8 ± 3.5	< 0.001
Waist circumference (cm)	82.1 ± 8.3	83.2 ± 8.6	84.1 ± 8.7	84.9 ± 8.9	85.4 ± 9.0	85.3 ± 9.2	< 0.001
Systolic BP (mmHg)	126.2 ± 15.7	128.4 ± 16.6	130.4 ± 17.3	132.4 ± 18.0	134.8 ± 18.9	24.9 ± 3.5	< 0.001
Diastolic BP (mmHg)	77.8 ± 10.1	78.9 ± 10.6	79.7 ± 10.9	80.5 ± 11.2	81.4 ± 11.5	82.2 ± 11.8	< 0.001
Laboratory findings (mg/dL)							< 0.001
Glucose, fasting	101.3 ± 26.1	107.9 ± 33.5	113.9 ± 40.6	119.7 ± 46.1	125.3 ± 51.9	127.8 ± 52.6	< 0.001
Total cholesterol	201.1 ± 38.0	202.3 ± 40.0	202.6 ± 41.8	202.9 ± 43.6	207.5 ± 49.2	210.2 ± 52.5	< 0.001
Triglycerides*	120.7 (120.7–120.8)	125.2 (124.7–125.6)	132.7 (132.2–133.2)	141.3 (140.5–142.2)	151.4 (149.7–153.2)	157.4 (153.3–161.5)	< 0.001
HDL-C	55.7 ± 31.4	55.1 ± 30.7	53.9 ± 23.9	53.0 ± 25.7	52.6 ± 25.9	52.3 ± 25.3	< 0.001
LDL-C	119.1 ± 39.3	119.2 ± 39.1	118.1 ± 42.2	117.3 ± 42.9	119.4 ± 44.7	121.6 ± 50.4	< 0.001
Charlson comorbidity index	1.2 ± 1.3	1.4 ± 1.4	1.6 ± 1.5	1.8 ± 1.6	2.0 ± 1.7	2.1 ± 1.7	< 0.001

Table 2. Baseline characteristics of the study population according to the level of proteinuria. Values are expressed as mean ± standard deviation or number (%). *Values presented as geometric mean (95% confidence interval). *AMD* age-related macular degeneration, *BP* blood pressure, *GFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol.

	Subject No. (%)	AMD Case	Duration	IR	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Presence of CKD								
Non-CKD (≥ 60 mL/min/1.73 m^2)	3,605,757 (90.0)	414,778	31,219,634	13.3	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
CKD (< 30 mL/min/1.73 m^2)	400,189 (10.0)	54,060	3,279,691	16.5	1.26 (1.25–1.27)	1.02 (1.01–1.02)	1.01 (1.00–1.02)	0.99 (0.98–1.00)
Proteinuria								
Negative	3,773,524 (94.2)	439,916	32,569,671	13.5	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Trace	101,106 (2.5)	12,144	857,137	14.2	1.06 (1.04–1.07)	1.04 (1.02–1.06)	1.04 (1.02–1.06)	1.01 (1.00–1.03)
1+	85,785 (2.1)	10,656	710,808	15.0	1.12 (1.10–1.15)	1.08 (1.06–1.10)	1.08 (1.06–1.10)	1.04 (1.02–1.06)
2+	34,351 (0.9)	4,597	275,501	16.7	1.26 (1.23–1.30)	1.20 (1.17–1.24)	1.20 (1.17–1.24)	1.13 (1.10–1.16)
3+	9,323 (0.2)	1,247	72,296	17.2	1.32 (1.25–1.40)	1.26 (1.19–1.34)	1.26 (1.19–1.33)	1.17 (1.10–1.23)
4+	1,857 (0.0)	278	13,913	20.0	1.55 (1.38–1.75)	1.44 (1.28–1.62)	1.43 (1.27–1.61)	1.32 (1.17–1.48)

Table 3. Risk of AMD according to the presence of CKD and proteinuria. *AMD* age-related macular degeneration, *eGFR* estimated glomerular filtration rate, *IR* incidence rate, *HR* hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval. Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: Model 2 + income, smoking, alcohol consumption, regular physical activity, and body mass index; Model 4: Model 3 + hypertension, diabetes mellitus, dyslipidemia, and Charlson comorbidity index.

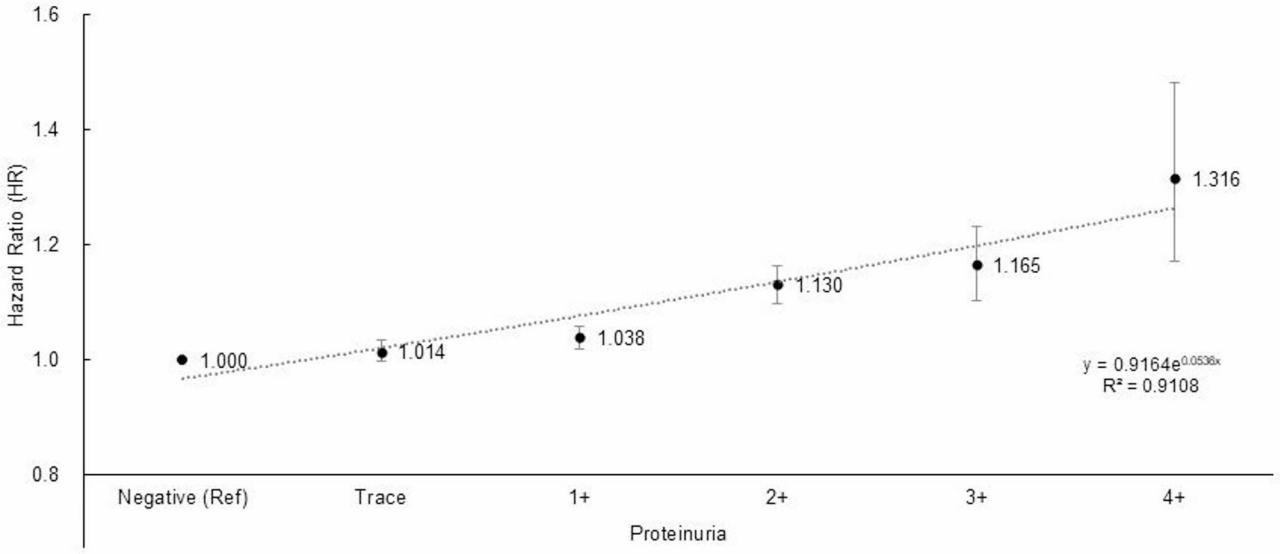

Fig. 2. Dose-dependent association between proteinuria and risk of age-related macular degeneration.

by interfering with the retinal pigment epithelium (RPE). Macular changes from drusen-like deposits with RPE alteration could facilitate the onset of choroidal neovascularization, an advanced form of AMD[26,27]. In addition, potentially underlying this renal–ocular association, mutations have been found in the complement factor H (CFH) gene. CFH is expressed in the RPE and is critical for normal retinal development[28]. Previous studies have revealed that its absence is linked to AMD[29,30], and urinary CFH is an indicator of renal damage[31,32]. When renal function declines, mutated CFH is excreted into the urine and can cause AMD.

Second, there is a plausible hypothesis of common pathogenic pathways between CKD and AMD. For example, the renin–angiotensin–aldosterone system (RAAS), which regulates blood volume and systemic vascular resistance, is found in both the kidneys and various ocular tissues. Proteinuria is associated with activation of the RAAS[33], which contracts glomerular afferent arterioles to aggravate renal ischemia and reduce glomerular filtration function[34]. Interestingly, a local RAAS and its component have been detected in many structures of the human eye, with possible roles in aqueous humor dynamics and intraocular pressure, as well as retinal vascular implications in concert with AMD in hypertension and diabetes[35]. RAAS hyperactivity promotes an inflammatory condition that causes macrophage infiltration resulting in ocular choroidal neovascularization, which is one of the most important characteristics of wet AMD[36]. In stratified analysis, the association between proteinuria and AMD risk was remarkable in younger individuals and men. AMD is an age-related disease with higher probability of occurrence in older than younger people. Thus, younger subjects with proteinuria might have a strong genetic predisposition or an association with systemic diseases of the kidney. The high AMD risk in young people is consistent with findings from a Taiwanese nationwide population-based study[37]. Interestingly, the onset age of cuticular drusen, which is a subtype marked by extracellular deposits in AMD and a well-known association with MPGN type 2, is generally younger than that for other age-related drusen[38,39].

The effect of proteinuria on AMD risk was prominent in males. A previous study demonstrated that the relationship between proteinuria and AMD was prominent only in men but was limited by measurement errors in women[15]. Furthermore, several studies have suggested that AMD progression might follow different processes in women than men due to the protective effect of estrogen, which may lead to favorable alterations in serum lipid levels and may exert antioxidant properties[40]. Thus, further evaluation is required to enhance our understanding of the complex relationship between proteinuria and AMD development among the sexes.

While our study showed a clear positive correlation between proteinuria with AMD, we found no significant association between eGFR determined by creatinine measurement and AMD (**Supplementary Table 1**). This is consistent with previous studies that serum creatinine was not associated with AMD in the Korean population[41] and another recent study of the 'Asian Eye Epidemiology Consortium' reporting that CKD defined by eGFR was associated with only late AMD, but not with early AMD[42]. This might be because eGFR is temporary and highly time-sensitive[43]. On the other hand, proteinuria reflects progressive renal injury and is a better and earlier marker of local kidney inflammation and increased complement production[44].

Clinical implications

The finding that CKD could elevate the risk of AMD is important for the clinical management of patients with CKD. Strict management of common shared risk factors of CKD and AMD, such as hypertension, diabetes, and dyslipidemia, should be recommended. In addition, subjects who reported proteinuria in their health examination should be considered as having a risk of development of AMD, as well as the risk of renal disease. Since proteinuria is a modifiable risk factor of renal disease, the use of a renin–angiotensin system (RAS) inhibitor, such as an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, could help to protect patients from AMD. In addition, SGLT2 inhibitors[45] and non-steroidal Mineralocorticoid Receptor

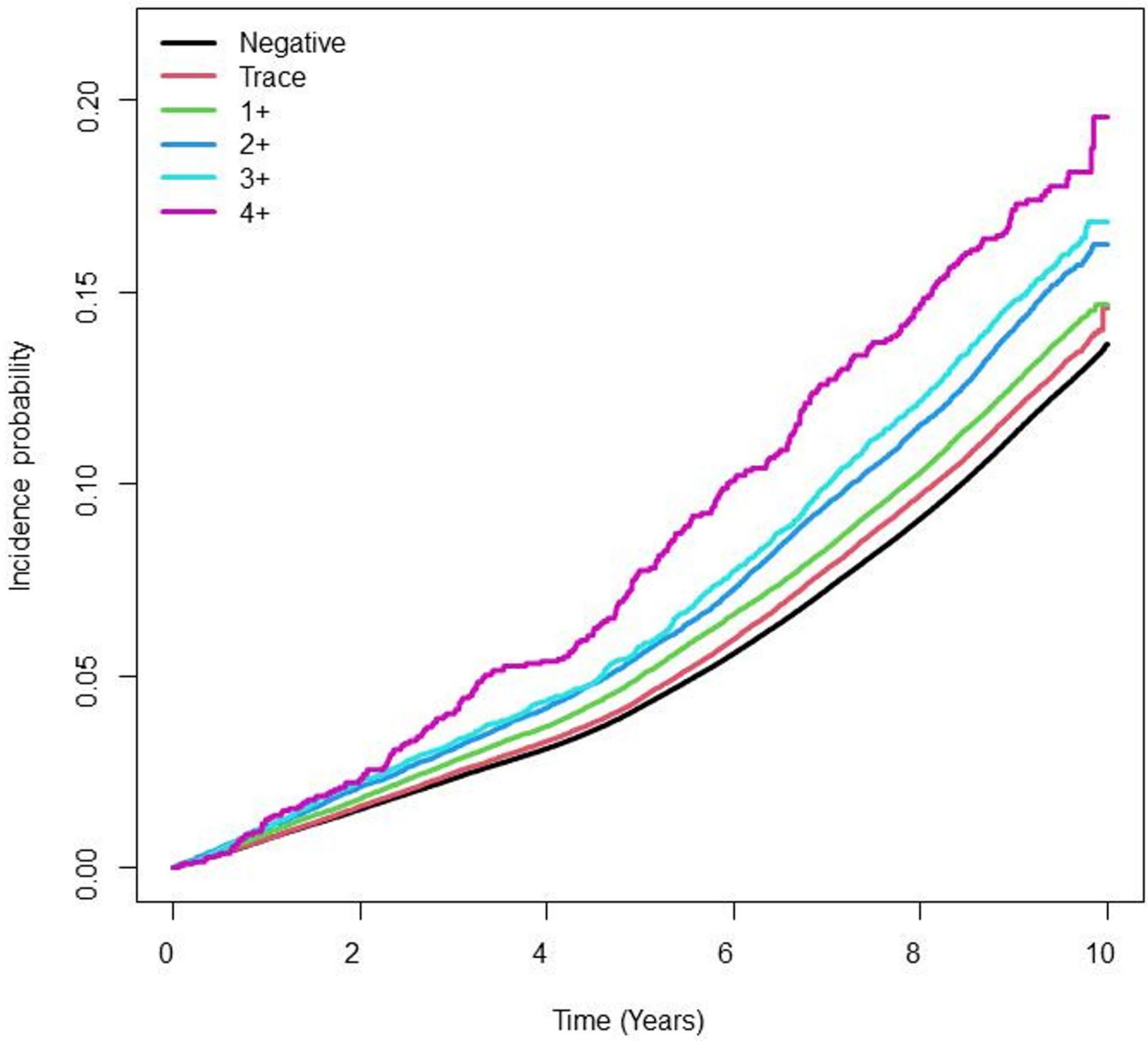

Fig. 3. Cumulative incidence of age-related macular degeneration by degree of proteinuria.

antagonists[46] can decrease proteinuria. Previous studies suggested[47,48] that the utilization of RAS inhibitors could protect against AMD in hypertensive patients and retinal vascular diseases such as retinopathy in at-risk patients with diabetes. Further basic or translational research may reveal the pathophysiology and underlying mechanisms between proteinuria and AMD.

Study limitations

There are several potential limitations in this study. First, selection bias may be present because individuals who undergo health screening examinations tend to have healthier lifestyles than the general population. Second, AMD was defined based on the H35.3 ICD-10 diagnostic code using medical claims data, and there is a greater chance for a false-positive diagnosis compared to that of an ophthalmologic examination. H35.3 includes not only AMD, but also non-AMD such as macular cyst, hole and toxic maculopathy. The association between CKD and non-AMD included in H35.3 was not well established. Thus, the results might be underestimated because non-AMD unrelated to CKD were also included as study outcomes. Besides, AMD can be underdiagnosed due to patients not seeking healthcare services, which may lead to underestimation of the results. Furthermore, Dry and wet types of AMD could not be separated because the medical claim code did not include that distinction. Further analysis with distinction of dry and wet AMD is needed to demonstrate the clear impact of CKD on the development of AMD. Third, considering AMD is a degenerative disease, the duration of our study may not be sufficient to fully elucidate its association with CKD. Fourth, proteinuria was categorized based on the dipstick method, which can be influenced by various factors. For example, dehydration, exercise, and infection could cause false positives, while dilute urine and non-albumin proteins could cause false negatives[49]. Thus,

Variable	Proteinuria	Subject No. (%)	AMD case.	Duration	IR	aHR (95% CI)	*P* for interaction
Age (years)							
< 65	Negative	2,672,696	264,222	23,814,433	11.1	1 (ref.)	< 0.0001
	Trace	68,593	7054	606,593	11.6	1.03 (1.01–1.06)	
	1+	55,516	5969	484,933	12.3	1.06 (1.03–1.08)	
	2+	21,443	2577	183,425	14.0	1.18 (1.13–1.22)	
	3+	5784	754	48,042	15.7	1.28 (1.20–1.38)	
	4+	1092	155	8891	17.4	1.43 (1.22–1.68)	
65–74	Negative	883,369	148,160	7,227,038	20.5	1 (ref.)	
	Trace	25,187	4223	201,256	21.0	1.00 (0.97–1.03)	
	1+	23,213	3869	180,376	21.4	1.01 (0.98–1.05)	
	2+	9866	1666	73,371	22.7	1.06 (1.01–1.11)	
	3+	2729	408	19,500	20.9	0.98 (0.89–1.08)	
	4+	559	97	3862	25.1	1.16 (0.95–1.42)	
≥ 75	Negative	217,459	27,534	1,528,200	18.0	1 (ref.)	
	Trace	7326	867	49,288	17.6	0.96 (0.89–1.02)	
	1+	7056	818	45,499	18.0	0.98 (0.91–1.05)	
	2+	3042	354	18,706	18.9	1.03 (0.93–1.15)	
	3+	810	85	4755	17.9	1.00 (0.81–1.24)	
	4+	206	26	1160	22.4	1.22 (0.83–1.79)	
Sex							
Male	Negative	1,819,947	184,679	15,545,567	11.9	1 (ref.)	< 0.0001
	Trace	52,553	5627	440,727	12.8	1.03 (1.00–1.06)	
	1+	45,772	5213	372,960	14.0	1.08 (1.05–1.11)	
	2+	19,156	2405	149,727	16.1	1.20 (1.15–1.25)	
	3+	5406	700	40,598	17.2	1.27 (1.18–1.37)	
	4+	1073	148	7763	19.1	1.40 (1.19–1.64)	
Female	Negative	1,953,577	255,237	17,024,103	15.0	1 (ref.)	
	Trace	48,553	6517	416,410	15.7	0.99 (0.97–1.01)	
	1+	40,013	5443	337,848	16.1	0.99 (0.96–1.01)	
	2+	15,195	2192	125,774	17.4	1.03 (0.99–1.08)	
	3+	3917	547	31,699	17.3	1.01 (0.93–1.10)	
	4+	784	130	6149	21.1	1.19 (1.00–1.41)	
Comorbidity							
No comorbidity	Negative	1,528,995	155,012	13,454,106	11.5	1 (ref.)	0.1403
	Trace	30,480	3043	266,248	11.4	1.00 (0.96–1.03)	
	1+	19,961	2006	172,566	11.6	1.00 (0.96–1.04)	
	2+	5717	596	48,981	12.1	1.03 (0.95–1.12)	
	3+	1067	110	9067	12.1	1.02 (0.85–1.23)	
	4+	182	21	1523	13.8	1.19 (0.78–1.83)	
Any comorbidity	Negative	2,244,529	284,904	19,115,564	14.9	1 (ref.)	
	Trace	70,626	9101	590,889	15.4	1.01 (0.99–1.03)	
	1+	65,824	8650	538,241	16.1	1.04 (1.01–1.06)	
	2+	28,634	4001	226,520	17.7	1.13 (1.09–1.16)	
	3+	8256	1137	63,229	18.0	1.16 (1.09–1.23)	
	4+	1675	257	12,389	20.7	1.30 (1.15–1.47)	
Obesity							
Non-obesity	Negative	2,403,941	277,535	20,644,020	13.4	1 (ref.)	0.4475
(BMI < 25 kg/m^2)	Trace	60,305	7119	506,654	14.1	1.01 (0.98–1.03)	
	1+	48,431	5919	394,880	15.0	1.03 (1.01–1.06)	
	2+	18,704	2492	146,283	17.0	1.13 (1.09–1.18)	
	3+	4944	639	37,020	17.3	1.14 (1.05–1.23)	
	4+	991	157	7081	22.2	1.41 (1.20–1.64)	
Obesity	Negative	1,369,583	162,381	11,925,651	13.6	1 (ref.)	
Continued							

Variable	Proteinuria	Subject No. (%)	AMD case.	Duration	IR	aHR (95% CI)	*P* for interaction
(BMI ≥ 25 kg/m^2)	Trace	40,801	5025	350,483	14.3	1.01 (0.98–1.04)	
	1+	37,354	4737	315,928	15.0	1.02 (0.99–1.05)	
	2+	15,647	2105	129,218	16.3	1.09 (1.04–1.14)	
	3+	4379	608	35,277	17.2	1.14 (1.06–1.24)	
	4+	866	121	6832	17.7	1.16 (0.97–1.39)	

Table 4. Association between proteinuria and the risk of AMD stratified by age, sex, comorbidity, and obesity. *AMD* age-related macular degeneration, *BMI* body mass index, *IR* incidence rate, *aHR* adjusted hazard ratio, *CI* confidence interval. Adjusted for age, sex, income, smoking, alcohol consumption, regular physical activity, body mass index, hypertension, diabetes mellitus, dyslipidemia, and Charlson comorbidity index.

careful consideration is required to interpret the results, and future studies using albumin creatinine ratios or 24-h urine albumin levels are warranted to validate the dose-dependent relationship. Fifth, the impact of other eye diseases was not considered. For example, cataract surgery might accelerate the progression of AMD, particularly for the Asians[50]. To date, cataract and glaucoma are not direct risk factors for the development of AMD[51,52]but there might be interfering effects since they share common risk factors, such as age, smoking and family history. In addition, AMD can be overdiagnosed due to patients seeking healthcare services for the other eye diseases. Also, there might be residual confounding variables, such as environmental and nutritional factors which was unavailable. Sixth, we could not consider the effect of RAS-related medication use, which might affect the relationship between proteinuria and AMD risk. Finally, this study could not determine causal inference due to its observational nature. Further mechanistic studies are needed to confirm our findings.

Conclusion

The present study findings enhance our understanding of the relationship between the eyes and kidneys. In young, male patients with persistent high-grade proteinuria, an ophthalmic examination could be helpful. Future translational and prospective research are needed to validate our results and determine the underlying mechanisms.

Data availability

The data that support the findings of this study are available from the Korean National Health Insurance Service (KNHIS) and were used under license for the current study (http://nhiss.nhis.or.kr). Restrictions apply to their availability (data are not publicly available). Data are available from the authors with permission from the KNHIS upon reasonable request to corresponding authors (Shin and Han).

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Conception and design: Park, Han, Kim, Lee, Jang, Yoon, Lim, Shin; Analysis and interpretation: Park, Han, Kim, Lee, Jang, Yoon, Lim, Shin; Data collection: Park, Han, Kim, Shin; Overall responsibility: Han, Shin.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The Institutional Review Board of Soongsil University approved this study (SSU-202007-HR-236-01), this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was waived in this study by the Institutional Review Board of Soongsil University, Seoul, South Korea. Informed consent was waived by the Institutional Review Board of Soongsil University because the data in the NHIS-NSC were anonymized and de-identified.

Additional information

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