Risk of Stroke After Nonarteritic Anterior Ischemic Optic Neuropathy

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• PURPOSE: To determine whether nonarteritic ischemic optic neuropathy (NAION) raises the risk of subsequent stroke in the general population.
• DESIGN: Population-based, retrospective cohort study.
• METHODS: SETTING: Nationwide, population-based, retrospective cohort study. PATIENTS: Of 1 025 340 beneficiaries in the National Health Insurance Service–National Sample Cohort database (2002-2013), we included 400 952 eligible individuals in the analysis. OBSERVATIONS: To determine the effect of incident NAION on the occurrence of subsequent stroke, we used time-varying covariate Cox regression models. Model 1 included only incident NAION as a time-varying covariate. Model 2 included Model 1 and defined demographics. Model 3 included Model 2, comorbidity, co-medication, and Charlson index score. MAIN OUTCOME MEASURES: Effect (hazard ratio [HR]) of NAION on stroke development.
• RESULTS: Of 400 952 eligible individuals, 1125 patients developed NAION and 16 998 patients suffered from stroke. NAION was not associated with an increased risk of subsequent stroke in Model 1, with HR of 1.31 (95% confidence interval [CI], 0.89-1.92). This was consistent, after adjusting for demographics and/or confounding factors, in Model 2 (HR = 1.19, 95% CI, 0.81-1.75) and Model 3 (HR = 1.10, 95% CI, 0.75-1.62).
• CONCLUSIONS: Our results suggest that NAION per se is not associated with a subsequent risk of stroke in the general population. (Am J Ophthalmol 2019;200:123–129. © 2019 Elsevier Inc. All rights reserved.)

STROKE IS THE MAJOR GLOBAL LEADING CAUSE OF disability.[1] In order to prevent stroke, identification of predictive factors as well as modification of risk factors is essential.[2,3] Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common optic neuropathy among adults over 40-50 years of age.[4,5] The pathogenesis of NAION remains elusive; however, it may be different from that of stroke, because stroke is caused by thromboembolism, whereas NAION is mostly caused by arterial hypoperfusion of the posterior ciliary artery supplying the optic nerve head.[6] The association of NAION and stroke is controversial. Hayreh and associates[4] reported that the risk of cerebrovascular disease did not increase in 406 patients with NAION, but increased only in NAION patients with both diabetes mellitus and arterial hypertension. Hasanreisoglu and associates[7] reported that the incidence of stroke after NAION did not increase when comparing the calculated anticipated risk with the Framingham and United Kingdom Prospective Diabetes Study data. In contrast, Guyer and associates[8] reported that the incidence of subsequent development of cerebrovascular disease was significantly higher in "idiopathic" AION, especially in women over 65 years of age. Lee and associates[9] also reported a 3.35 times greater risk of ischemic stroke in NAION patients with comorbidities. Therefore, further investigation is warranted to determine the impact of NAION on future development of stroke. Herein, we performed a nationwide population-based cohort study to investigate the association of NAION with stroke using the Korean National Health Insurance Service (NHIS) database.

METHODS

• STUDY POPULATION: We used the NHIS-National Sample Cohort (NSC) database for this study. The NHIS is a single, compulsory medical insurance program in South Korea that started in 1977 and achieved universal coverage by 1989.[10–12] Therefore, the NHIS contains all information regarding healthcare utilization in Korea. The NHIS-NSC database consists of a random sample of 1 025 340 Korean residents, equivalent to approximately 2.2% of the Korean population in 2002. The database contains 12 years of claims (from 2002 to 2013) for diagnoses, procedures, prescription records, demographic information, direct medical costs, and mortality, without any duplications or omissions.[12] The diagnosis was coded according to the International Classification of Diseases, 10th edition. The validation study showed an overall positive predictive value of the diagnosis as 83.4% by comparing the diagnoses between the database and the patients' medical record.[13] Detailed information regarding the

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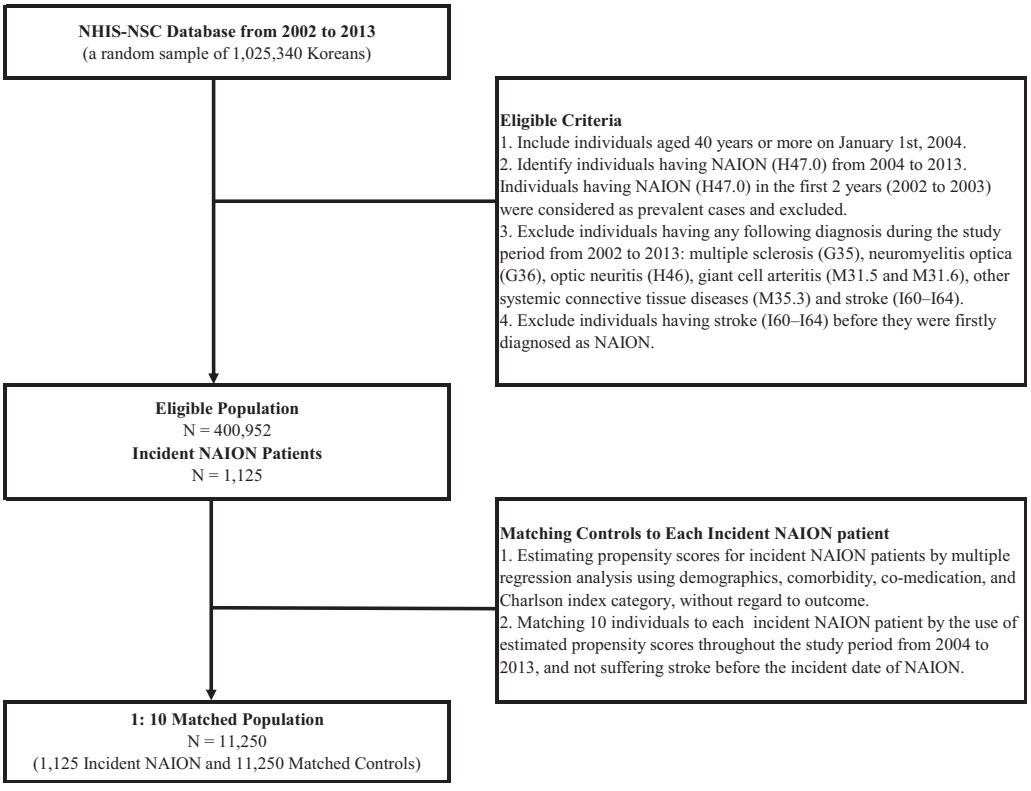

FIGURE. Flow chart illustrating eligibility criteria. NAION = nonarteritic anterior ischemic optic neuropathy.

NHIS and database has been reported elsewhere.[2,3,12,14–19] The database is open to any researcher whose study protocols are approved by the official review committee. This study was approved by the institutional review board of the Seoul National University Bundang Hospital (X-1808-484-904) and the study complied with the guidelines of the Declaration of Helsinki.

• **COHORT DEFINITION:** Using the NHIS-NSC database, we defined the fixed cohort to investigate the association between NAION and subsequent development of stroke, which started on January 1, 2004, and ended on December 31, 2013. Of the 1 025 340 individuals, we included individuals aged 40 years or more on January 1, 2004. We excluded those having NAION (H47.0), multiple sclerosis (G35), acute disseminated demyelination diseases (G36), optic neuritis (H46), giant cell arteritis (M31.5 and M31.6), other systemic connective tissue diseases (M35.3), and stroke (I60-I64) before entering the cohort on January 1, 2004. Eventually, 400 952 individuals entered the cohort.

• **DEFINITION OF NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY AND CONFOUNDERS:** We identified the incidence of NAION by the use of diagnostic codes (H47.0) among the defined cohort. For statistical analysis, we defined age, sex, residential region, household income, comorbidity, and co-medication as possible confounders of the association between NAION and stroke. We defined the presence of comorbidities and the use of co-medications according to previous diagnoses and previous prescriptions up to 2 years before entering the index date. We calculated the modified Charlson comorbidity index by the use of previous diagnosis within 1 year before the index date.[11,20] Defined comorbidities were hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, congestive heart failure, peripheral artery disease, cancer, tuberculosis, and chronic kidney diseases. Defined information on co-medication included the use of low-dose acetylsalicylic acid, platelet aggregation inhibitors, warfarin, heparin, antithrombotic agents, antihypertensive agents, oral hypoglycemic agents, and insulin.

• **STATISTICAL ANALYSIS:** We defined the outcome as the time to first hospital admission with stroke (I60, I61, I62, I63, and I64) after entering the cohort. We defined censoring only when patients died or at the end of follow-up on December 31, 2013. To determine the effect of incident NAION on the development of stroke, we used time-varying covariate Cox regression models: Model 1 included only incident NAION as a time-varying covariate; Model 2 included Model 1 and defined demographic information; and Model 3 included Model 2, comorbidity, co-medication, and the Charlson index score. We plotted Kaplan-Meier curves for stroke according to the presence

TABLE 1. Demographics and Characteristics of the Eligible Population Included in the Analysis and Those of Incident Nonarteritic Anterior Ischemic Optic Neuropathy and Stroke

	Eligible Population, N (%)	NAION, N (%)	Stroke, N (%)
Total number (%)	400 952 (100)	1125 (100)	16 998 (100)
Demographics			
Sex			
Female	209 420 (52.2)	593 (52.7)	8426 (49.6)
Male	191 532 (47.8)	532 (47.3)	8572 (50.4)
Age group at diagnosis (years)			
40-59	273 761 (68.3)	733 (65.2)	5522 (32.5)
60-79	112 876 (28.2)	375 (33.3)	9941 (58.5)
80+	14 315 (3.6)	17 (1.5)	1535 (9.0)
Residential area			
Seoul and Incheon	102 177 (25.5)	367 (32.6)	3441 (20.2)
Gyeonggi and Gangwon	91 898 (22.9)	197 (17.5)	3621 (21.3)
Busan, Daegu, Ulsan, and Gyeongsang	113 410 (28.3)	371 (33.0)	5322 (31.3)
Daejeon, Sejong, and Chungcheong	41 731 (10.4)	88 (7.8)	2028 (12.0)
Gwangju, Jeola, and Jeju	51 736 (12.9)	102 (9.1)	2586 (15.2)
Household income			
Low income	129 521 (32.3)	286 (25.4)	6073 (35.7)
Middle income	150 578 (37.6)	410 (36.4)	6084 (35.8)
High income	120 853 (30.1)	429 (38.1)	4841 (28.5)
Comorbidity	.		
Hypertension	80 790 (20.2)	311 (27.6)	7014 (41.3)
Diabetes mellitus	47 321 (11.8)	213 (18.9)	3744 (22.0)
Dyslipidemia	44 570 (11.1)	176 (15.6)	2664 (15.7)
Ischemic heart disease	23 706 (5.9)	89 (7.9)	1965 (11.6)
Congestive heart failure	10 042 (2.5)	37 (3.3)	1063 (6.3)
Atrial fibrillation	2876 (0.7)	16 (1.4)	385 (2.3)
Peripheral arterial disease	13 652 (3.4)	47 (4.2)	1126 (6.6)
Chronic kidney disease	1396 (0.4)	7 (0.6)	150 (0.9)
Cancer	14 978 (3.7)	48 (4.3)	795 (4.8)
Tuberculosis	6367 (1.6)	35 (3.1)	389 (2.3)
Co-medication			
Antihypertensive agents	36 383 (9.1)	138 (12.3)	3219 (18.9)
Antiplatelet agents	5476 (1.4)	23 (2.0)	583 (3.4)
Anticoagulant agents	643 (0.2)	4 (0.4)	91 (0.5)
Hypoglycemic agents	12 694 (3.2)	58 (5.2)	1317 (7.8)

NAION = nonarteritic anterior ischemic optic neuropathy.

of NAION, which was estimated with the time-varying covariate Cox regression analysis of Model 1.

We performed a sensitivity analysis by the use of propensity score–based matching in the defined cohort. We estimated propensity scores for individuals in the cohort on the basis of cohort entering date, without regard to outcome, by multiple logistic regression analysis using age category, sex, residential region, household income, comorbidity, co-medication, and Charlson index category. We assessed the model discrimination with C-statistics. We identified 1968 patients in the cohort suffering NAION by the use of diagnostic codes mentioned above throughout the study period. We matched 10 controls among individuals without NAION to each identified NAION patient by the use of optimal matching with the estimated propensity score. We compared the baseline characteristics between patients suffering NAION and their matched controls in reference to the cohort entering date. We defined the same outcome stated above, which was the time to first hospital admission with stroke (I60, I61, I62, I63, and I64) after entering the cohort. We also defined censoring when patients died or at the end of follow-up. Then, we did the set of analyses including Cox regression models (Models 1, 2, and 3) and Kaplan-Meier curves as stated above. We used SAS software version 9.3 (SAS Inc, Cary, North Carolina, USA) and R programming version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) for all analyses. *P* values less than .05 were considered statistically significant.

TABLE 2. Results of Time-varying Cox Regression Models for Incident Stroke in the Eligible Population

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3[a] HR (95% CI)
Time-varying covariate			
NAION	1.31 (0.89-1.92)	1.19 (0.81-1.75)	1.10 (0.75-1.62)
Demographics			
Sex			
Male	N/A	1 (reference)	1 (reference)
Female	N/A	0.73 (0.71-0.75)	0.71 (0.69-0.73)
Age group at diagnosis (years)			
40-59	N/A	1 (reference)	1 (reference)
60-79	N/A	4.98 (4.81-5.14)	4.04 (3.91-4.19)
80+	N/A	10.01 (9.45-10.60)	8.10 (7.63-8.59)
Residential area			
Seoul and Incheon	N/A	1 (reference)	1 (reference)
Gyeonggi and Gangwon	N/A	1.14 (1.08-1.19)	1.13 (1.08-1.19)
Busan, Daegu, Ulsan, and Gyeongsang	N/A	1.32 (1.27-1.38)	1.37 (1.32-1.43)
Daejeon, Sejong, and Chungcheong	N/A	1.25 (1.19-1.32)	1.27 (1.21-1.35)
Gwangju, Jeola, and Jeju	N/A	1.25 (1.19-1.32)	1.29 (1.23-1.36)
Household income			
Low income	N/A	1 (reference)	1 (reference)
Middle income	N/A	0.95 (0.92-0.99)	0.92 (0.88-0.95)
High income	N/A	0.91 (0.88-0.95)	0.85 (0.82-0.89)
Comorbidity			
Hypertension	N/A	N/A	1.82 (1.75-1.90)
Diabetes mellitus	N/A	N/A	1.23 (1.18-1.29)
Dyslipidemia	N/A	N/A	0.88 (0.84-0.92)
Ischemic heart disease	N/A	N/A	1.08 (1.02-1.14)
Congestive heart failure	N/A	N/A	1.15 (1.08-1.23)
Atrial fibrillation	N/A	N/A	1.60 (1.43-1.79)
Peripheral arterial disease	N/A	N/A	1.12 (1.05-1.19)
Chronic kidney disease	N/A	N/A	1.62 (1.37-1.92)
Cancer	N/A	N/A	0.94 (0.87-1.03)
Tuberculosis	N/A	N/A	1.05 (0.94-1.16)
Co-medication			
Antihypertensive agents	N/A	N/A	0.91 (0.86-0.95)
Antiplatelet agents	N/A	N/A	1.07 (0.98-1.17)
Anticoagulant agents	N/A	N/A	1.38 (1.10-1.72)
Hypoglycemic agents	N/A	N/A	1.31 (1.23-1.41)

CI = confidence interval; HR = hazard ratio; N/A = not applicable; NAION = nonarteritic anterior ischemic optic neuropathy.
[a]Model 3 included Charlson comorbidity index in the analysis.

RESULTS

THE FLOW CHART (FIGURE) ILLUSTRATES STUDY INCLUSION according to the eligibility criteria. Of 400 952 eligible individuals (209 420 women, 52.2%), 1125 patients (593 women, 52.7%) suffered from NAION and 16 998 patients (8426 women, 49.6%) had stroke. Among those who suffered from NAION during the study period, 26 patients (2.3%) newly developed stroke after the incidence of NAION. Table 1 summarizes the characteristics of individuals in the cohort. Kaplan-Meier curves showed no significant difference in the incident probability of stroke development among those with NAION compared to the general population ($P = .169$, log-rank test) (Supplemental Figure; Supplemental Material available at AJO.com). Cox regression analysis also showed that the incidence of NAION was associated with an increased risk of subsequent stroke in Model 1 (hazard ratio [HR] = 1.31; 95% confidence interval [CI], 0.89-1.92). The results of Models 2 and 3 also showed consistent results when addressing for demographics, covariates, and co-medications (HR = 1.19; 95% CI, 0.81-1.75 in Model 2, and HR = 1.10; 95% CI, 0.75-1.62 in Model 3). Individuals suffering from hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure, atrial fibrillation, peripheral arterial disease, and chronic kidney

TABLE 3. Results of Time-varying Cox Regression Models for Incident Stroke in the Propensity Score-based Matched Cohort as a Sensitivity Analysis

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3[a] HR (95% CI)
Time-varying covariate			
NAION	1.25 (0.84-1.86)	1.13 (0.76-1.69)	1.11 (0.74-1.65)
Demographics			
Sex			
Male	N/A	1 (reference)	1 (reference)
Female	N/A	0.67 (0.56-0.79)	0.65 (0.55-0.77)
Age group (years)			
40-59	N/A	1 (reference)	1 (reference)
60-79	N/A	4.90 (4.08-5.88)	3.83 (3.16-4.64)
80+		16.22 (10.65-24.70)	10.63 (6.85-16.50)
Residential area			
Seoul and Incheon	N/A	1 (reference)	1 (reference)
Gyeonggi and Gangwon	N/A	1.19 (0.94-1.53)	1.20 (0.94-1.54)
Busan, Daegu, Ulsan, and Gyeongsang	N/A	1.24 (1.00-1.53)	1.28 (1.03-1.59)
Daejeon, Sejong, and Chungcheong	N/A	1.29 (0.93-1.77)	1.27 (0.92-1.76)
Gwangju, Jeola, and Jeju	N/A	1.02 (0.75-1.38)	1.11 (0.81-1.51)
Household income			
Low income	N/A	1 (reference)	1 (reference)
Middle income	N/A	0.90 (0.74-1.11)	0.89 (0.72-1.09)
High income	N/A	0.76 (0.61-0.94)	0.71 (0.57-0.88)
Comorbidity			
Hypertension	N/A	N/A	2.13 (1.72-2.64)
Diabetes mellitus	N/A	N/A	1.10 (0.87-1.40)
Dyslipidemia			0.87 (0.68-1.11)
Ischemic heart disease	N/A	N/A	0.78 (0.58-1.06)
Congestive heart failure	N/A	N/A	1.15 (0.77-1.72)
Atrial fibrillation	N/A	N/A	2.59 (1.67-4.01)
Peripheral arterial disease	N/A	N/A	1.30 (0.94-1.81)
Chronic kidney disease	N/A	N/A	1.44 (0.64-3.24)
Cancer	N/A	N/A	0.79 (0.49-1.29)
Tuberculosis	N/A	N/A	1.34 (0.89-2.00)
Co-medication			
Antihypertensive agents	N/A	N/A	0.86 (0.67-1.09)
Antiplatelet agents	N/A	N/A	1.10 (0.69-1.75)
Anticoagulant agents	N/A	N/A	1.30 (0.07-1.25)
Hypoglycemic agents	N/A	N/A	1.61 (0.16-2.22)

CI = confidence interval; HR = hazard ratio; N/A = not applicable; NAION = nonarteritic anterior ischemic optic neuropathy.
[a]Model 3 included Charlson comorbidity index in the analysis.

disease had an increased risk of stroke development in Model 3 (Table 2).

The Supplemental Table (Supplemental Material available at AJO.com) shows the characteristics of individuals with NAION and their propensity score–based matched controls for the sensitivity analyses. The demographics, comorbidity, and the use of co-medication were comparable between subjects with NAION and their matched controls when they entered the cohort on January 1, 2004. All three models in the sensitivity analysis showed that the incidence of NAION was not associated with an increased risk of subsequent stroke, as observed in the main analyses (HR = 1.25; 95% CI, 0.84-1.86 in Model 1; HR = 1.13; 95% CI, 0.76-1.69 in Model 2; and HR = 1.11; 95% CI, 0.74-1.65 in Model 3) (Table 3).

DISCUSSION

WE FOUND THAT NAION PER SE IS NOT ASSOCIATED WITH A subsequent risk of stroke when confounders were properly addressed, using a nationwide, population-based database

consisting of approximately 1 million individuals, both in the main analysis and the sensitivity analysis.

Stroke and NAION share common risk factors,[4–9,21] and this puzzled researchers who had investigated the risk of stroke in patients suffering NAION. Previous studies have shown inconsistent results regarding the risk of stroke after NAION. Certain associations of NAION and subsequent stroke have been reported in patients with hypertension or diabetes mellitus.[4,8] However, in those without hypertension or diabetes, NAION does not seem to increase the risk of stroke in most of the studies.[4,7,8] Lee and associates[9] revealed that the risk of ischemic stroke was higher among the subjects with NAION than those without NAION, only in the subgroup with comorbidities and not in the subgroup without comorbidities.[9] Similarly, in our study, NAION did not increase the risk of stroke in subjects without systemic hypertension or diabetes mellitus.[4,7,8] Hayreh assumed that common vascular changes in NAION and stroke, as well as antihypertensive medication, may play a role in the development of stroke after NAION,[6,22] and concluded that "there is no direct association between NAION and stroke."[23]

Stroke is one of the most devastating diseases, causing morbidity and mortality. Intensive risk factor control is important for prevention of stroke.[24,25] In this population-based nationwide cohort study, we revealed no greater risk of stroke among 1125 patients who developed NAION. Our results support the theory that different pathogenic mechanisms are responsible for the development of NAION and of stroke.[6] While stroke is commonly caused by embolic occlusion of the cerebral artery associated with carotid artery diseases, emboli rarely occlude the posterior ciliary arteries.[6] Further evidence of different underlying mechanisms for NAION vs stroke includes the fact that aspirin reduces the risk of stroke but fails to reduce the risk of NAION recurrence.[26] Thrombophilia is also known as a risk factor for stroke, but not for NAION.[21]

The major limitation of this study is that the NHIS-NSC database does not include information regarding metabolic profiles, physical activity, body mass index, alcohol consumption, or smoking affecting the risk of stroke. That limitation notwithstanding, this study has several strengths. Firstly, we used a nationwide, general population–based database, enabling the identification of all incident NAION patients and minimizing a selection bias. As we included 0.4 million individuals in the analysis over the 10-year study period, this provided an adequate statistical power to evaluate the association of NAION with stroke. We carefully defined all demographics, covariates, and co-medications in the analyses that might be confounders in the Cox regression analyses. In addition, we also conducted the sensitivity analysis thoroughly by the use of propensity score–based matching, which showed robust conclusions in agreement with the main analyses.

In conclusion, our nationwide, general population–based cohort study found no greater risk of stroke after the incidence of NAION compared to controls without NAION, suggesting different etiologic mechanisms of NAION and stroke.

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REFERENCES

1. Katan M, Luft A. Global burden of stroke. *Semin Neurol* 2018;38(2):208–211.
2. Park SJ, Choi NK, Yang BR, et al. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology* 2015;122(11):2336–2643.e2.
3. Park SJ, Choi NK, Yang BR, et al. Risk of stroke in retinal vein occlusion. *Neurology* 2015;85(18):1578–1584.
4. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1994;118(6):766–780.
5. Xu L, Wang Y, Jonas JB. Incidence of nonarteritic anterior ischemic optic neuropathy in adult Chinese: the Beijing Eye Study. *Eur J Ophthalmol* 2007;17(3):459–460.
6. Hayreh SS. Ischemic optic neuropathy. *Prog Retin Eye Res* 2009;28(1):34–62.
7. Hasanreisoglu M, Robenshtok E, Ezrahi D, Stiebel-Kalish H. Do patients with non-arteritic ischemic optic neuritis have increased risk for cardiovascular and cerebrovascular events? *Neuroepidemiology* 2013;40(3):220–224.
8. Guyer DR, Miller NR, Auer CL, Fine SL. The risk of cerebrovascular and cardiovascular disease in patients with anterior ischemic optic neuropathy. *Arch Ophthalmol* 1985;103(8):1136–1142.
9. Lee YC, Wang JH, Huang TL, Tsai RK. Increased risk of stroke in patients with nonarteritic anterior ischemic optic neuropathy: a nationwide retrospective cohort study. *Am J Ophthalmol* 2016;170:183–189.
10. Kwon S. Payment system reform for health care providers in Korea. *Health Policy Plan* 2003;18(1):84–92.
11. Shin JY, Park MJ, Lee SH, et al. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. *BMJ* 2015;351:h3517.

12. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;46(2):e15.
13. Park BJ, Sung JH, Park KD, Seo SW, Kim SW. Report of the evaluation for validity of discharged diagnoses in Korean Health Insurance database. Seoul: Seoul National University College of Medicine; 2003:19–52.
14. Park SJ, Choi NK, Park KH, Woo SJ. Five year nationwide incidence of rhegmatogenous retinal detachment requiring surgery in Korea. *PLoS One* 2013;8(11):e80174.
15. Park SJ, Choi NK, Park KH, Woo SJ. Nationwide incidence of clinically diagnosed retinal vein occlusion in Korea, 2008 through 2011: preponderance of women and the impact of aging. *Ophthalmology* 2014;121(6):1274–1280.
16. Park SJ, Choi NK, Seo KH, et al. Nationwide incidence of clinically diagnosed central retinal artery occlusion in Korea, 2008 to 2011. *Ophthalmology* 2014;121(10):1933–1938.
17. Park SJ, Choi NK, Seo KH, et al. Retinal vein occlusion and pregnancy, pre-eclampsia, and eclampsia: the results from a nationwide, population-based study using the national claim database. *PLoS One* 2015;10(3):e0120067.
18. Park SJ, Kwon KE, Choi NK, et al. Prevalence and incidence of exudative age-related macular degeneration in South Korea: a nationwide population-based study. *Ophthalmology* 2015;122(10):2063–2070.e1.
19. Park SJ, Cho SC, Choi NK, et al. Age, sex, and time-specific trends in surgical approaches for rhegmatogenous retinal detachment: a nationwide, population-based study using the National Claim Registry. *Retina* 2017;37(12):2326–2333.
20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43(11):1130–1139.
21. Salomon O, Huna-Baron R, Kurtz S, et al. Analysis of prothrombotic and vascular risk factors in patients with nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 1999;106(4):739–742.
22. Hayreh SS. Role of nocturnal arterial hypotension in nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol* 2017;37(3):350–351.
23. Hayreh SS. Increased risk of stroke in patients with nonarteritic anterior ischemic optic neuropathy: a nationwide retrospective cohort study. *Am J Ophthalmol* 2017;175:213–214.
24. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2095–2128.
25. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197–2223.
26. Beck RW, Hayreh SS, Podhajsky PA, et al. Aspirin therapy in nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997;123(2):212–217.