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Demographic, Systemic, and Ocular Factors Associated with Nonarteritic Anterior Ischemic Optic Neuropathy

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Objective: Nonarteritic anterior ischemic optic neuropathy (NAION) is a devastating ocular condition causing permanent vision loss. Little is known about risk factors for developing this disease. We assessed demographic, systemic, and ocular factors associated with NAION.

Design: Retrospective longitudinal cohort study.

Participants: Beneficiaries between 40 and 75 years old without NAION at baseline enrolled in a large U.S. managed care network.

Methods: Enrollees were monitored continuously for ≥2 years between 2001 and 2014 to identify those newly diagnosed with NAION (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 377.41). All persons were under ophthalmic surveillance and all cases had ≥1 confirmatory ICD-9-CM code for NAION during follow-up.

Main Outcome Measures: Multivariable Cox regression modeling was used to generate hazard ratios (HRs) with 95% confidence intervals (CIs) to describe the statistical relationship between selected demographic characteristics, systemic and ocular conditions, and the hazard of developing NAION.

Results: Of 1 381 477 eligible enrollees, 977 (0.1%) developed NAION during a mean ± standard deviation (SD) follow-up of 7.8±3.1 years. The mean ± SD age for NAION cases at the index date was 64.0±9.2 years vs. 58.4±9.4 years for the remainder of the beneficiaries. After adjustment for confounding factors, each additional year older was associated with a 2% increased hazard of NAION (HR = 1.02; 95% CI: 1.01−1.03). Female subjects had a 36% decreased hazard of developing NAION (HR = 0.64; 95% CI: 0.55−0.74) compared with male subjects. Compared with whites, Latinos had a 46% decreased hazard of developing NAION (HR = 0.54; 95% CI: 0.36−0.82), whereas African ancestry was not significantly associated with NAION (HR = 0.91; 95% CI: 0.72−1.15). Systemic diseases associated with NAION included hypertension (HR = 1.62; 95% CI: 1.26−2.07) and hypercoagulable states (HR = 2.46; 95% CI: 1.51−4.00). Although diabetes mellitus (DM) was not significantly associated with NAION compared with those without DM ($P = 0.45$), patients with end-organ involvement from DM had a 27% increased hazard of NAION relative to those with uncomplicated DM (HR = 1.27; 95% CI: 1.01−1.59). Ocular diseases associated with NAION were age-related macular degeneration (HR = 1.29; 95% CI: 1.08−1.54) and retinal vein occlusion (HR = 3.94; 95% CI: 3.11−4.99).

Conclusions: Our study identified several modifiable risk factors that may be associated with NAION. Should future studies confirm these findings, they may offer opportunities to prevent or treat this debilitating condition. *Ophthalmology 2016;123:2446-2455 © 2016 by the American Academy of Ophthalmology*

See Editorial on page 2442.
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Ischemic optic neuropathy (ION) is believed to result from vascular insufficiency of the optic nerve and is typically divided into anterior and posterior forms depending on which portion of the nerve is affected, with anterior ION accounting for more than 90% of cases.[1] Anterior ION can be due to an arteritic process, such as giant cell arteritis,[2] but is much more commonly associated with a noninflammatory, nonvasculitic process that is referred to as nonarteritic anterior ION (NAION). NAION has an estimated annual incidence of 2.3−10.2 per 100 000 persons in the United States, making it the most common acute optic neuropathy among individuals older than 50 years of age.[3,4]

The underlying pathophysiology of NAION is unknown but is presumed to be vascular in etiology, although mechanical theories have also been postulated.[5] Past studies have identified vascular risk factors associated with NAION, such as systemic hypertension,[6−9] hyperlipidemia,[9−11] diabetes mellitus (DM),[6−8,12,13] and smoking.[10,14,15] However, data regarding the relation between these and other potential risk factors and new-onset NAION are lacking.

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Because the incidence of NAION is low, prior studies were not adequately powered to study potential risk factors for new-onset NAION. To overcome this challenge, we evaluated a cohort of over 1 million enrollees in a managed care network to evaluate social and demographic factors, as well as ocular and systemic conditions, in relation to the development of NAION. Identifying such factors may help us better understand NAION pathophysiology and lead to potential preventive or therapeutic targets for this visually debilitating condition.

Methods

Data Source

The Clinformatics DataMart database (OptumInsight, Eden Prairie, MN) contains detailed claim data on all beneficiaries in a nationwide U.S. managed care network. The data set analyzed contains all individuals with 1 or more International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes for eye-related diagnoses (360−379.9), or ≥1 Current Procedural Terminology code for any eye-related visits or diagnostic or therapeutic procedures (65091−68899 or 92002−92499) from January 1, 2001, through December 31, 2014. We had access to all medical claims for ocular and nonocular conditions, as well as to sociodemographic information for each enrollee. This database has been used previously to identify novel determinants for other ocular diseases.[16−18]

Participants and Sample Selection

Individuals were included in the analysis if they met the following criteria: age 40−75 years at plan entry and continuous enrollment in the medical plan for ≥2 years. We required at least 1 eye examination by an ophthalmologist or optometrist during a 2-year look-back period and at least 1 eye examination during follow-up to give all enrollees at least 2 opportunities to get diagnosed with NAION. Beneficiaries were identified with NAION if they had 1 or more billing records with the ICD-9-CM code 377.41 along with at least 1 confirmatory diagnosis of this condition on a separate date. Individuals were excluded if they had 1 or more preexisting diagnosis of NAION during the first 2 years they were enrolled in the plan to exclude nonincident cases. To help ensure that conditions that can mimic NAION were not being included, enrollees were excluded if there was any record of giant cell arteritis (ICD-9-CM code 446.5) or optic neuritis (code 377.30), or if they underwent lumbar spine surgery during the study period, because ischemic optic neuropathy can be associated with this procedure[19] (Fig 1).

Analyses

SAS software, version 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses. Participant characteristics were summarized for the entire sample using means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables.

Multivariable Cox regression modeling with delayed entry was used to estimate the hazard of developing NAION. The first 2 years an enrollee was in the plan was considered a look-back period. Enrollees were required to have at least 1 visit to an eye care provider during this 2-year look-back period to afford all enrollees at least 1 opportunity to receive a NAION diagnosis and exclude those with preexisting NAION (nonincident cases). All beneficiaries were followed from the index date (2 years after plan entry) until they were either first diagnosed with NAION or censored. Censoring occurred at the date of their last eye examination, as this was theoretically their last opportunity to be diagnosed with NAION by an eye care provider. Best subset selection was used to identify which covariates to include in the multivariable model.[20] All variables listed in Table 1 were considered. Covariates considered were sociodemographic characteristics (age, sex, race, education level, income, urban/rural residence); number of visits to an eye care provider; the following ocular comorbidities: macular degeneration, open-angle glaucoma, and retinal vein occlusion; the following medical comorbidities: DM, systemic hypertension, hyperlipidemia, myocardial infarction, congestive heart failure, hypercoagulable state, anemia, coagulopathy or bleeding diathesis, sleep apnea, deep vein thrombosis/pulmonary embolism, and depression; and the Charlson comorbidity index, which is a measure of overall health[21] (Table S1, available at www.aaojournal.org). These conditions were selected based on past studies that reported associations with NAION. Individuals with DM and systemic hypertension were each stratified into 2 groups based on ICD-9-CM billing codes: those without end-organ damage from these conditions, which we considered to be "uncomplicated" cases, and those with end-organ damage (i.e., neuropathy, nephropathy), which we considered to be "complicated" cases. For all analyses, P values <0.05 were considered statistically significant.

Because the data source was deidentified, the University of Michigan Institutional Review Board approved this work as a nonregulated study.

Results

During the study period, 977 of 1 381 477 eligible enrollees (0.1%) were newly diagnosed with NAION (Table 1). The mean ± SD age at the index date was 64.0±9.2 years for the group that developed NAION and 58.4±9.4 years for the group that did not develop NAION ($P < 0.0001$). Most newly diagnosed NAION patients presented during the sixth or seventh decade of life (Fig 2). The average time in the plan for those patients was longer than for enrollees who did not develop NAION: 7.8±3.1 vs. 6.0±2.8 years ($P < 0.0001$). Table 1 provides demographic characteristics for all eligible study participants as well as data on systemic and ocular comorbidities among enrollees with and without NAION. Overall, a greater proportion of patients with NAION had each of the medical and ocular comorbidities considered. The group with NAION had a mean Charlson Comorbidity Index score that was higher than for those who did not develop NAION (6.4±4.2 vs. 3.4±3.3; $P < 0.0001$), indicating worse overall health (Table 1).

Sociodemographic Factors

In multivariable analysis, after adjustment for potential confounding factors, for each additional year of life, the hazard of getting diagnosed with NAION increased by 2% (adjusted hazard ratio [HR] = 1.02; 95% confidence interval [CI]: 1.01−1.03; $P = 0.003$) (Table 2). Compared with whites, Latinos had a 46% decreased hazard of developing NAION (adjusted HR = 0.54; 95% CI: 0.36−0.83; $P = 0.004$). There was no significant difference in the hazard of receiving a NAION diagnosis when comparing blacks or Asians to whites. Female subjects had a 36% decreased hazard of developing NAION (adjusted HR = 0.64; 95% CI: 0.55−0.74) compared with male subjects. There was no significant difference in the hazard of receiving a NAION diagnosis based on income ($P > 0.17$ for all comparisons) (Table 2).

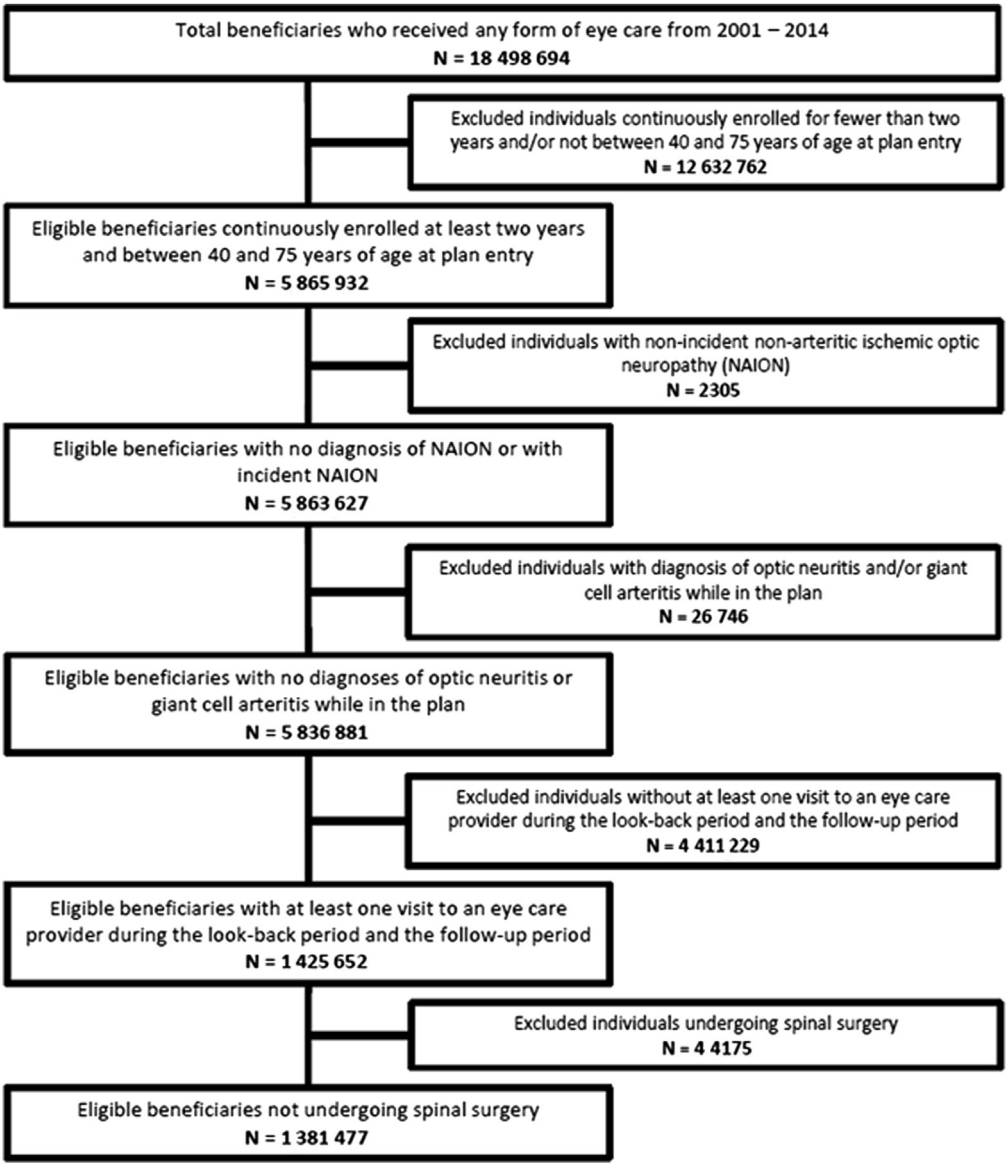

Figure 1. Sample selection algorithm.

Diabetes/Systemic Hypertension

Persons with uncomplicated hypertension had a 62% increased hazard of getting diagnosed with NAION (adjusted HR = 1.62; 95% CI: 1.26−2.07; $P = 0.0001$), whereas those with hypertension complicated by end-organ damage had a 79% increased hazard of NAION (adjusted HR = 1.79; 95% CI: 1.34−2.37; $P < 0.0001$) relative to individuals without systemic hypertension. There was no statistically significant difference in the hazard of getting diagnosed with NAION among those with uncomplicated vs. complicated hypertension ($P = 0.27$). There was no significant difference in the hazard of NAION among persons with uncomplicated DM ($P = 0.13$) or complicated DM ($P = 0.44$) compared with those without DM. However, persons with DM complicated by end-organ damage had a 27% increased hazard of receiving a NAION diagnosis relative to those with uncomplicated DM ($P = 0.04$).

Other Vascular Conditions

Persons with hypercoagulable states (defined as abnormalities in clotting, such as the antiphospholipid syndrome, protein S deficiency, protein C deficiency, and thrombophilia secondary to conditions such as cancer; see Table S1 [available at www.aaojournal.org] for corresponding ICD-9 codes) had a 146% increased hazard of getting diagnosed with NAION (adjusted HR = 2.46; 95% CI: 1.51−4.00). There was no statistically significant difference in the hazard of NAION among persons with myocardial infarction ($P = 0.16$) or deep vein thrombosis/pulmonary embolism ($P = 0.08$) compared with those without these conditions. Other conditions such as congestive heart failure, hyperlipidemia, anemia, and coagulopathy with bleeding tendency were considered in the best subset selection process but were not included in the final multivariable model.

Table 1. Patient Characteristics by Nonarteritic Ischemic Optic Neuropathy

Variable	Value	NAION			P Value	Age-Adjusted P Value
		No	*Yes*	*Total*		
Total patients, N (row %)		1 380 500 (99.9)	977 (0.1)	1 381 477		
Age at index date, yrs		58.4 (9.4)	64.0 (9.2)	58.4 (9.4)	<0.0001	—
Time in plan, yrs		6.0 (2.8)	7.8 (3.1)	6.0 (2.8)	<0.0001	<0.0001
Eye visits		6.5 (6.5)	14.6 (11.1)	6.5 (6.5)	<0.0001	<0.0001
Charlson index		3.4 (3.3)	6.4 (4.2)	3.4 (3.3)	<0.0001	<0.0001
Sex	Male	557 761 (40.4)	529 (54.1)	558 290 (40.4)	<0.0001	<0.0001
	Female	822 739 (59.6)	448 (45.9)	823 187 (59.6)		
Race (N_{miss} = 103 281)	White	1 048 123 (82.1)	763 (82.8)	1 048 886 (82.1)	0.0002	0.006
	Black	120 197 (9.4)	111 (12.1)	120 308 (9.4)		
	Latino	75 328 (5.9)	32 (3.5)	75 360 (5.9)		
	Asian	33 627 (2.6)	15 (1.6)	33 642 (2.6)		
Education (N_{miss} = 48 395)	Less than high school	5536 (0.4)	2 (0.2)	5538 (0.4)	<0.0001	0.0008
	High school diploma	350 739 (26.3)	304 (32.0)	351 043 (26.3)		
	Some college	699 277 (52.5)	508 (53.5)	699 785 (52.5)		
	Bachelor's degree or higher	276 581 (20.8)	135 (14.2)	276 716 (20.8)		
Income (N_{miss} = 401 942)	<$40K	164 311 (16.8)	216 (28.1)	164 527 (16.8)	<0.0001	0.0002
	$40K–59K	143 068 (14.6)	143 (18.6)	143 211 (14.6)		
	$60K–99K	259 909 (26.6)	204 (26.5)	260 113 (26.6)		
	≥$100K	411 477 (42.0)	207 (26.9)	411 684 (42.0)		
Urban/rural (N_{miss} = 11 478)	Urban	1 198 987 (87.6)	812 (84.1)	1 199 799 (87.6)	0.004	0.02
	Large rural	84 079 (6.1)	75 (7.8)	84 154 (6.1)		
	Small rural	85 967 (6.3)	79 (8.2)	86 046 (6.3)		
Diabetes	None	950 034 (68.8)	495 (50.7)	950 529 (68.8)	<0.0001	<0.0001
	Uncomplicated	233 223 (16.9)	179 (18.3)	233 402 (16.9)		
	Complicated	197 243 (14.3)	303 (31.0)	197 546 (14.3)		
Hypertension	None	498 739 (36.1)	118 (12.1)	498 857 (36.1)	<0.0001	<0.0001
	Uncomplicated	691 378 (50.1)	536 (54.9)	691 914 (50.1)		
	Complicated	190 383 (13.8)	323 (33.1)	190 706 (13.8)		
Anemia		161 782 (11.7)	215 (22.0)	161 997 (11.7)	<0.0001	<0.0001
Coagulopathy		75 896 (5.5)	119 (12.2)	76 015 (5.5)	<0.0001	<0.0001
Myocardial infarction		80 482 (5.8)	168 (17.2)	80 650 (5.8)	<0.0001	<0.0001
Congestive heart failure		140 023 (10.1)	255 (26.1)	140 278 (10.2)	<0.0001	<0.0001
Depression		129 030 (9.3)	118 (12.1)	129 148 (9.3)	0.003	0.0002
Hyperlipidemia		1 026 099 (74.3)	874 (89.5)	1 026 973 (74.3)	<0.0001	<0.0001
Sleep apnea		178 489 (12.9)	190 (19.4)	178 679 (12.9)	<0.0001	<0.0001
Age-related macular degeneration		130 602 (9.5)	250 (25.6)	130 852 (9.5)	<0.0001	<0.0001
Open-angle glaucoma		145 422 (10.5)	218 (22.3)	145 640 (10.5)	<0.0001	<0.0001
Hypercoagulable state		8493 (0.6)	22 (2.3)	8515 (0.6)	<0.0001	<0.0001
Retinal vein occlusion		17 244 (1.2)	107 (11.0)	17 351 (1.3)	<0.0001	<0.0001
Deep vein thrombosis/pulmonary embolism		41 820 (3.0)	58 (5.9)	41 878 (3.0)	<0.0001	0.003

NAION = nonarteritic ischemic optic neuropathy; N_{miss} = number with missing data.
Continuous variables comparison tested using 2-sample *t* tests. Age-adjusted testing from linear regression with variable as outcome, with age and NAION as covariates. Categorical variables comparison tested using chi-square tests. Age-adjusted testing from logistic regression with variable as outcome, with age and NAION as covariates.
Data are n (column %) or mean (standard deviation).

Ocular Conditions

Those with retinal venous occlusive disease had a hazard of getting diagnosed with NAION almost 4 times that of enrollees without this condition (adjusted HR = 3.97; 95% CI: 3.13–5.03). Age-related macular degeneration was associated with an increased hazard of getting diagnosed with NAION (HR = 1.29; 95% CI: 10.8–1.53), but open-angle glaucoma was not (HR = 1.11; 95% CI: 0.92–1.34).

Overall Health

Persons with higher Charlson index scores had an increased hazard of getting diagnosed with NAION (adjusted HR = 1.06; 95% CI: 1.04–1.09; $P < 0.0001$). Every 1-unit increase in the Charlson index score was associated with a 6% increased risk of NAION.

Discussion

In this cohort of over 1 million eligible enrollees, we found that older age, male sex, and white race were associated with an increased risk of receiving a NAION diagnosis. Furthermore, persons with systemic hypertension (with or without end-organ damage), hypercoagulable states, retinal venous occlusive disease, and age-related macular

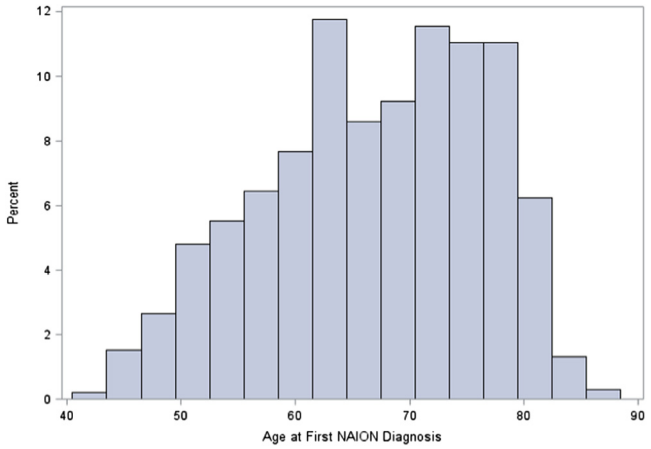

Figure 2. Histogram of age at first diagnosis of nonarteritic anterior ischemic optic neuropathy (NAION).

degeneration also had an increased risk of getting diagnosed with NAION.

Table 2. Cox Proportional Hazards Model Predicting Hazard of Nonarteritic Ischemic Optic Neuropathy

Covariate	Value	HR (95% CI)	*P* Value
Age at index date		1.02 (1.01–1.03)	0.004
Sex	Male	REF	
	Female	0.64 (0.55–0.74)	<0.0001
Race	White	REF	
	Black	0.91 (0.72–1.15)	0.44
	Latino	0.54 (0.36–0.82)	0.004
	Asian	0.80 (0.46–1.38)	0.42
Income	<$40K	REF	
	$40K–59K	0.99 (0.80–1.23)	0.93
	$60K–99K	0.99 (0.80–1.21)	0.89
	≥$100K	0.85 (0.68–1.07)	0.18
Urban/rural	Urban	REF	
	Large rural	1.56 (1.20–2.03)	0.0009
	Small rural	1.30 (0.99–1.72)	0.06
Myocardial infarction		1.17 (0.94–1.45)	0.16
Diabetes	None	REF	
	Uncomplicated	0.85 (0.69–1.05)	0.13
	Complicated	1.08 (0.88–1.33)	0.45
Hypertension	None	REF	
	Uncomplicated	1.62 (1.26–2.07)	0.0001
	Complicated	1.78 (1.34–2.37)	<0.0001
Age-related macular degeneration		1.29 (1.08–1.54)	0.004
Open-angle glaucoma		1.11 (0.92–1.34)	0.27
Hypercoagulative state		2.46 (1.51–4.00)	0.0003
Retinal vein occlusion		3.94 (3.11–4.99)	<0.0001
Deep vein thrombosis/ pulmonary embolism		0.76 (0.55–1.04)	0.09
Number of eye visits		1.02 (1.01–1.02)	<0.0001
Charlson index		1.06 (1.04–1.09)	<0.0001

CI = confidence interval; HR = hazard ratio; REF = reference category. Covariates considered are listed in the Methods. Any covariates not present in Table 2 were excluded because they did not survive the best subset analysis, including sleep apnea. Open-angle glaucoma was forced into the model because it is the most common chronic optic neuropathy.

Demographics

The mean age at onset of NAION in our analysis was 64 years, which is similar to that of past studies, which ranged from 57 to 65 years.[3,6,8,15] We also found an increase in NAION risk with each additional year of age.

Most studies have demonstrated no sex predisposition for NAION,[3,6,8,15] although 1 large case-control study found male subjects to be more likely to develop NAION.[13] We also found that men were more likely to get diagnosed with NAION. Similarly, stroke incidence rates are 1.25 times greater among men than women,[22] suggesting a potential hormonal role in the pathophysiology of NAION.

The Ischemic Optic Neuropathy Decompression Trial Study Group found a much higher incidence of NAION among white individuals compared with black or Hispanic individuals.[15] Specifically, of 420 patients with NAION, only 1.7% were black and 2.6% were Latino; 94.8% of patients were white. After adjusting for potential confounders, we found no significant difference between the hazard of receiving a NAION diagnosis among blacks and Asians compared with whites. However, Latinos had a 46% decreased hazard of getting diagnosed with NAION compared with whites. The reduced risk of getting diagnosed with NAION among Latinos may be due to genetic factors.[3] Although cultural and language barriers may have limited Latinos' access to medical care,[23] all enrollees in our analysis had the same health insurance, and each of them had 2 or more visits to eye care providers. We also adjusted for the number of eye care provider visits in our analyses. So it is doubtful that the lower hazard we observed among Latinos was due to a lack of access to or utilization of eye care services.

Systemic Vascular Risk Factors

NAION is thought to be a consequence of decreased optic nerve head perfusion that is presumed to result from microvascular occlusion. Table 3 summarizes past studies that have demonstrated vascular risk factors, such as hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, and hypercholesterolemia, associated with NAION.[6–9,11–13,24]

Hypertension. Similar to past work, we found a considerably higher risk of NAION among persons with uncomplicated as well as complicated hypertension compared with normotensive enrollees. Systemic hypertension is an important risk factor for ischemic cerebrovascular accidents and this may be due to a decrease in endothelium-dependent, flow-mediated vasodilation.[25–27] Interestingly, decreased flow-mediated vasodilation has also been reported in persons with NAION.[28]

Diabetes Mellitus. Several studies have shown a positive association between DM and NAION.[11–13,29] In contrast, our study did not find DM to be a risk factor for NAION; however, we did identify that those with diabetes-related end-organ damage were more likely to develop NAION compared with those with uncomplicated diabetes. Unlike many prior studies, in this analysis we adjusted for an array of different conditions, including systemic hypertension and

Table 3. Review of Published Systemic Diseases Associated with Nonarteritic Anterior Ischemic Optic Neuropathy

Publication	Patients with NAION	Design; Control Group(s); Statistical Method	Vascular Risk Factors Associated	Nonvascular Risk Factors Associated	Risk Factors Tested and Not Associated	Comments
Repka et al, 1983[8]	169	Prospective; control groups: Framingham, US population; univariate	• Hypertension (young 36%; old 42% [control: young 21%, old 38%]) • Diabetes (young 20%; old 9% [control: young 6%, old 8%])	—	• Heart disease • Cerebrovascular disease	Associations in younger groups only (age 45–64) and not in the older age group (>65 years)
Guyer et al, 1985[6]	200	Retrospective chart review, contacted patients and PCPs for health information; control groups: Rochester (MN) Epidemiologic Project or Hypertension Detection and Follow-up Program; univariate	• Hypertension (42.5%) • Diabetes (17.5%) • Cardiac disease (33.0%) • Cerebrovascular disease (9.5%)	—	—	Hypertension not associated in older age group (>65 years). Diabetes associated in all groups.
Hayreh et al, 1994[7]	406	Prospective; control group: US Public Health surveys; univariate	• Hypertension (55.2%) • Diabetes (35.5%) • Cerebrovascular disease (6.7% - significant only in 45- to 64-year age group) • Ischemic heart disease (15.5%; not significant in youngest age group)	• GI ulcer (8.4%) • Thyroid disease (7.4%; not significant in youngest age group) • COPD (5.7%; significant only in 45- to 64-year age group)	• Migraine	Patients (12.6%) had both hypertension and diabetes; these patients were significantly more likely to go on to develop cerebrovascular disease. Hypertension and diabetes were significant in all age groups.
Jacobson et al, 1997[12]	51	Case-control study; two separate control groups: MESA and case-controls (51 randomly selected); univariate and multivariate regression analyses.	• Hypertension (OR = 0.4 multivariate) • Diabetes (OR = 2.7 multivariate, MESA controls)	-	• Hypertension (OR = 0.7 univariate case-controls) • Diabetes (OR = 1.9 univariate case-controls) • Body mass index • Hypercholesterolemia • Coronary artery disease • COPD	Associations for diabetes and hypertension (inverse) were found using the MESA controls in a multivariate analysis, but not when analyzed with case-controls.
Salomon et al, 1999[11]	61	Retrospective case-control study; univariate and multivariate regression analyses.	• Diabetes (32.8%, univariate) • Ischemic heart disease (32.8%, univariate) • Hypercholesterolemia (36.1%, univariate)	-	• Hypertension (44.3%) • Arrhythmia • Stroke	Control group comprised of patients with unspecified, nonvascular eye problems.

(*Continued*)

Table 3. (Continued.)

Publication	Patients with NAION	Design; Control Group(s); Statistical Method	Vascular Risk Factors Associated	Nonvascular Risk Factors Associated	Risk Factors Tested and Not Associated	Comments
Palombi et al, 2006[24]	27	Prospective; no control group; univariate	• Obstructive sleep apnea (88.9%)	—	—	Systemic diseases not analyzed: Hypertension (59%) Diabetes (37%) Dyslipidemia (44%) Atherosclerotic lesions of carotids (30% of 23)
Giambene et al, 2009[9]	85	Prospective; age-matched and sex-matched controls; univariate	• Hypertension (60.0%) • Dyslipidemia (48.2%)	—	• Diabetes (4.7%) • Sleep apnea	Also found association by multivariate regression that there is increased homocysteine and lipoprotein(a) and lower vitamin B6 (thrombophilic markers)
Lee et al, 2011[13]	319	Retrospective; Cox regression analysis; matched control group (25 515 persons in each group)	• Diabetes (HR = 1.43 unadjusted; HR = 1.40 adjusted)	• Male (HR = 1.32)	• Charlson index • Lipidemia • Ischemic heart disease • Hypertension • Stroke • Chronic heart failure • Black race • Other race • Blindness or low vision • Age-related macular degeneration • Cataract • Diabetic retinopathy	Medicare sample (age ≥65 only) of patients with diabetes and control group without.

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; HR = hazard ratio; MESA = Marshfield Epidemiologic Study Area; NAION = nonarteritic anterior ischemic optic neuropathy; OR = odds ratio; PCP = primary care provider.
Only studies making statistical comparisons are included.

hyperlipidemia, which are known to be strongly associated with DM and, if not accounted for, could confound the relationship between diabetes and NAION. Moreover, because patients with diabetes are recommended to undergo annual eye examinations to check for retinopathy, we accounted for the frequency of eye care provider visits to minimize the effect of surveillance bias. Nevertheless, given the conflicting findings between our results and past work, and our inability to account for glycemic control, body mass index, duration of disease, and treatment of diabetes, additional research is required to better delineate the relation between diabetes and NAION.

Hypercoagulable State. We found a strong positive association between hypercoagulable state and NAION. This result raises the intriguing possibility that oral antiplatelet therapy or other anticoagulants might reduce the risk of NAION. In 1 case-control study, the use of aspirin at doses of 75−325 mg daily did not improve visual outcome in NAION,[30] but 2 retrospective studies reported a lower risk of fellow eye involvement in NAION patients who initiated therapy with aspirin.[31,32]

Ocular Conditions

We are unaware of past studies reporting simultaneous development of retinal venous occlusive disease and NAION, but papillophlebitis (disc edema and accompanying extensive retinal venous hemorrhage) is actually a well-described entity in the setting of NAION.[33] Perhaps more careful stratification of patients who develop retinal vein occlusions by disc appearance might be useful for future research. For example, it might be interesting to know whether retinal vein occlusion accompanied by disc edema tends to occur in persons with smaller optic discs, and whether visual outcomes after retinal vein occlusion vary depending on the optic disc appearance. There is one case report of consecutive retinal occlusive disease and NAION in a patient taking sildenafil,[34] but if the association between retinal occlusive disease and NAION is as strong as that reported here, we would expect to find a greater number of such cases. Perhaps the association between retinal vein occlusion and NAION is related to the fact that hypertension increases the risk of both conditions.[6−9,35,36] We also found a positive association between macular degeneration and NAION, and perhaps this association has a genetic basis. Alternatively, because many patients with age-related macular degeneration have frequent eye examinations, perhaps our finding is due to surveillance bias.

Study Limitations

It is possible that some of the persons diagnosed with NAION in our study may have been misdiagnosed or miscoded with this condition. We minimized the possibility of false-positive discovery of NAION by requiring a confirmatory diagnosis on a separate visit. Furthermore, we excluded persons with conditions that can mimic NAION, such as optic neuritis and giant cell arteritis. Though we are unaware of any study that has validated the accuracy of ICD-9 codes for NAION, it is notable that the incidence of NAION in our study is similar to that reported in the literature (i.e., 0.1% over ~10 years).[3,4] Regardless, NAION misclassification would likely bias our findings to the null. A second limitation is our inability to control for important ocular characteristics not available in this database, such as cup-to-disc ratio, optic nerve head size, and refractive error. Third, we did not adjust for selected systemic medications that have been reported to be associated with NAION, or lifestyle factors such as cigarette smoking, body mass index, or alcohol consumption. Finally, all patients had commercial health insurance, and caution should be taken when applying our findings to those with other forms of insurance.

A known risk factor for NAION is a small optic disc.[37] We were not able to assess any disc features in this study. When optic nerve head parameters were previously examined in African Americans, Hispanics, Asians, and white subjects, people of African descent had the largest discs.[38] African ancestry was not related to NAION risk in our study. In the same study by Tsai et al,[38] people of Hispanic ethnicity had disc sizes intermediate between whites and blacks. It is unclear whether this feature or some other factor contributed to the inverse relation between Hispanic ethnicity and NAION in our study.

This study highlights several key factors associated with NAION, including hypertension and hypercoagulable states, supporting the hypothesis that NAION results from vascular occlusion that might be similar to the pathophysiology of small-vessel lacunar infarct. Interestingly, the incidence of the latter condition similarly increases with age and hypertension, and is more commonly seen in male patients.[39] This raises the question of whether antihypertensive medications, or aspirin,[40] can be used in high-risk patients to decrease their risk of developing NAION. Additionally, those of Latino ancestry and female sex were found to have a lower risk of developing NAION, suggesting there are additional genetic, environmental, or hormonal factors that may play an important role in NAION. Subsequent studies are needed to better understand how these vascular, genetic, and hormonal factors interact to cause NAION so that effective treatment strategies can be developed.

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Abbreviations and Acronyms:
CI = confidence interval; **DM** = diabetes mellitus; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, 9th Revision, Clinical Modification; **ION** = ischemic optic neuropathy; **NAION** = nonarteritic anterior ischemic optic neuropathy; **SD** = standard deviation.

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