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Association between non-arteritic anterior ischaemic optic neuropathy and cardiovascular events: A retrospective, propensity score-matched cohort study using the TriNetX network

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Abstract

Background

The cardiovascular risk following non-arteritic anterior ischaemic optic neuropathy (NAION) remains uncertain.

Objective

To assess 1-year mortality and cardiovascular events after an initial recorded episode of NAION.

Methods

We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. The primary outcome was 1-year all-cause mortality. Secondary outcomes were ischaemic and haemorrhagic stroke, acute myocardial infarction (AMI), heart failure (HF), and atrial fibrillation (AF).

Results

Between 2015 and 2024, 17,217 patients with an initial episode of NAION and 1,503,464 with age-related cataract were identified. Propensity score matching on 59 demographic, clinical, pharmacological, and laboratory covariates yielded 17,208 patients per group with balanced baseline characteristics. At 1 year, NAION was associated with increased all-cause mortality (OR, 1.38; 95% CI, 1.14–1.68; p = 0.001), ischaemic stroke (OR, 3.26; 95% CI, 2.73–3.91; p < 0.001), haemorrhagic stroke (HR, 2.23; 95% CI, 1.51–3.31; p < 0.001), and AMI (HR, 1.33; 95% CI, 1.03–1.73; p = 0.031). No significant association was observed with HF (HR, 1.10; 95% CI, 0.91–1.32; p = 0.324) or AF (HR, 1.11; 95% CI, 0.93–1.33; p = 0.228).

Conclusion

An initial recorded episode of NAION was associated with increased 1-year mortality, stroke, and AMI, but not HF or AF. These findings support considering NAION as a marker of increased short-term cardiovascular risk and prompt cardiovascular assessment.

What is Known

- NAION shares its risk factor profile with atherosclerotic disease.

- Whether NAION is independently associated with ischaemic stroke remains debated.

- Data on haemorrhagic stroke, myocardial infarction and mortality after NAION are scarce.

What this study adds

- In 17,208 propensity-matched pairs (59 covariates, TriNetX), an initial NAION episode was associated with higher 1-year all-cause mortality (OR 1.38), ischaemic stroke (OR 3.26), haemorrhagic stroke (HR 2.23) and acute myocardial infarction (HR 1.33).

Clinical relevance

- NAION may identify patients at increased short-term cardiovascular risk rather than representing an isolated ocular event.

- These findings support timely cardiovascular risk assessment and optimization of modifiable risk factors following NAION.

- The observed excess risk of haemorrhagic stroke warrants caution regarding routine antiplatelet therapy solely on the basis of NAION, in the absence of another cardiovascular indication.

INTRODUCTION

Clinically characterized by a sudden and painless decline in visual acuity, non-arteritic anterior ischaemic optic neuropathy (NAION) is a major neuro-ophthalmological condition resulting from an acute ischaemic injury to the optic nerve head. While its multifaceted pathophysiological mechanisms remain incompletely understood[1], the disease is fundamentally driven by localized hypoperfusion within the microvascular network feeding the optic nerve. Consequently, the visual prognosis generally remains guarded. NAION represents a significant cause of sudden visual impairment worldwide. It is the most frequent acute optic neuropathy in patients over the age of 50 years and the second most prevalent optic nerve pathology overall, following glaucoma. Although epidemiological data in France are limited, global incidence rates of NAION are reported to range from 2.3 to 82 cases per 100,000 person-years[2–7].

The pathophysiology of NAION shares close similarities with systemic vascular diseases[2,8,9]. Its established risk factors heavily overlap with traditional cardiovascular risk factors, including advancing age, male sex, diabetes mellitus, arterial hypertension, dyslipidaemia, and obstructive sleep apnoea syndrome[10–17]. These parameters are well-known contributors to atherosclerotic disease, directly promoting the occurrence of major cardiovascular events.

While the role of NAION as an independent risk factor for the subsequent occurrence of ischaemic stroke remains debated in the literature[5,18], the broader cardiovascular risk profile of patients presenting with NAION is even more uncertain[19]. In particular, there is a lack of robust data to accurately determine whether this initial ocular ischaemic event represents an independent risk factor for other severe systemic outcomes, namely haemorrhagic stroke, acute myocardial infarction (AMI), and all-cause mortality.

In this context, the objective of our study was to evaluate the short-term risk of all-cause mortality and specific cardiovascular events, including ischaemic and haemorrhagic stroke, AMI, atrial fibrillation (AF) and heart failure (HF), in patients who have experienced an initial recorded episode of NAION.

METHODS

Study design and participants

Study design and data source

This was a retrospective, multicentre, propensity score-matched cohort study using the TriNetX health research network. TriNetX is a global federated health research network providing real-time access to anonymized electronic health records (EHRs) of more than 200 million of patients from 181 healthcare organizations (HCOs) worldwide. Extracted data include demographic characteristics, diagnoses (coded according to the International Classification of Diseases, ICD-10), medical procedures, medication prescriptions, and laboratory results. The specific analysis conducted for this study was a "Compare Outcomes Analysis" generated on the platform on 9th July, 2026.

Study population

The study population included all patients aged between 50 and 85 years who received an initial diagnosis of NAION (ICD-10 code H47.01) between 1st January, 2015, and 31st December, 2024.

Exclusion criteria included any diagnosis of arteritic optic neuropathy (giant cell arteritis, ICD-10 code M31.5, or other giant cell arteritides, ICD-10 code M31.6) recorded at any time in the patient's record, whether occurring before or after the index date, as well as any history of major cardiovascular disease prior to the index date.

A history of major cardiovascular disease was defined as prior diagnoses of coronary artery diseases (ICD-10 codes I20-I25), HF (ICD-10 code I50), the presence of cardiac and vascular implants and grafts (ICD-10 code Z95), AF (ICD-10 code I48), haemorrhagic stroke (ICD-10 codes I60-I62), or ischaemic stroke (ICD-10 code I63).

The control group consisted of patients aged between 50 and 85 years who received their first diagnosis of age-related cataract (ICD-10 code H25) during the same period. For both cohorts, the index date was defined as the date of the first qualifying diagnosis (NAION for the target group, and age-related cataract for the control group). The control group was subject to the exact same exclusion criteria as the target group, with the additional exclusion of any diagnosis of NAION recorded at any time (either before or after the index date).

Ethics approval

The study was approved by the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1) and conducted in accordance with the ethical principles of the Declaration of Helsinki[20]. The requirement for informed consent was waived, as this retrospective investigation exclusively analysed de-identified and aggregated data. No protected health information was accessed, and no study-specific interventions were performed.

Outcomes

The primary outcome of this study was all-cause mortality, identified via the TriNetX demographic status "Deceased" or the diagnostic code for ill-defined and unknown cause of mortality (ICD-10 code R99). Secondary outcomes were defined as the incident occurrence of ischaemic stroke (ICD-10 code I63), haemorrhagic stroke (ICD-10 codes I60–I62), AMI (ICD-10 codes I21–I22), HF (ICD-10 code I50), or AF (ICD-10 code I48). The predefined observation window for outcome measurement was strictly set to one year. Specifically, the follow-up period began 1 day after the index date and continued for up to 365 days. Follow-up concluded upon the occurrence of an outcome of interest, death, or the end of this 1-year observation window, whichever occurred first.

Statistical analysis

Baseline demographic and clinical characteristics of the study and control cohorts were described using means and standard deviations for continuous variables, and frequencies (percentages) for categorical variables.

To mitigate the impact of potential confounding factors and selection biases inherent to retrospective observational designs, we performed a rigorous 1:1 propensity score matching (PSM). This technique was employed to balance the baseline characteristics between the NAION group and the age-related cataract control group. The propensity score was estimated for each patient using a multivariate logistic regression model.

The matching process was comprehensive, incorporating a total of 59 distinct covariates to ensure robust adjustment for baseline health status (see Table 2 in the Results section for details). These covariates encompassed demographic characteristics, including age at index, sex, and race or ethnicity (White, Black or African American, Asian, Hispanic or Latino). To thoroughly adjust for baseline clinical status, patients were matched on cardiovascular and metabolic conditions, such as hypertensive diseases (including 2018 deprecated codes), diabetes mellitus, lipidaemia and lipoprotein metabolism disorders, overweight and obesity, other cardiac arrhythmias, and unspecified peripheral vascular disease. Pulmonary, renal, and lifestyle factors were also included, specifically sleep apnoea, specified and unspecified chronic obstructive pulmonary disease, acute kidney failure, chronic kidney disease, tobacco use, history of nicotine dependence, and alcohol-related disorders. Furthermore, the clinical matching criteria incorporated neoplasms, sexual arousal disorders, socioeconomic or psychosocial health hazards, and diagnostic codes indicating the long-term use of aspirin, anticoagulants, antithrombotics/antiplatelets, and insulin.

In addition to medical history, we accounted for specific baseline pharmacological treatments. These included antidiabetic agents (metformin, SGLT2 inhibitors, GLP-1 analogues such as dulaglutide, liraglutide, lixisenatide, semaglutide, tirzepatide, and exenatide, as well as other non-insulin blood glucose-lowering drugs), cardiovascular therapies (beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II inhibitors, diuretics, and amiodarone), lipid-lowering agents (HMG-CoA reductase inhibitors, general antilipemic agents), and specific vasodilators (sildenafil, tadalafil). Finally, baseline physiological measurements and laboratory data were integrated into the propensity score, encompassing systolic and diastolic blood pressure, Body Mass Index (BMI), lipid profiles (total, HDL, and LDL cholesterol, triglycerides), glycaemic control (haemoglobin A1c), and renal function evaluated via the estimated glomerular filtration rate using the MDRD formula.

Patients were matched using a nearest-neighbour greedy matching algorithm. The effectiveness of the PSM was evaluated by assessing the standardized mean differences (SMD) between the groups across all 59 covariates. An SMD < 0.1 was considered indicative of a well-balanced distribution. Before matching, significant imbalances were observed. For instance, the control group was older and had a higher prevalence of diabetes, obesity, and dyslipidaemia, whereas the NAION group presented higher rates of sleep apnoea and chronic kidney diseases. Following the PSM procedure, the matched cohorts comprised 17,208 patients in each group, achieving optimum comparability across the entire set of covariates.

The risk of developing the primary and secondary outcomes over the 1-year follow-up period was compared between the matched cohorts. Risk estimates were calculated and reported as either Odds Ratios (OR) or Hazard Ratios (HR) alongside their 95% Confidence Intervals (CI). When analysing time-to-event data using Cox regression, the validity of reporting the HR relies strictly on the proportional hazards assumption, which was evaluated using the proportionality p-value. If this p-value was statistically significant ($p < 0.05$), indicating that the risk was not constant over time, the OR was used as the preferred and more robust metric. Conversely, if the proportional hazards assumption was met ($p \geq 0.05$), the HR, along with its Log-Rank p-value, was reported. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses. All statistical tests and PSM procedures were conducted directly within the TriNetX Global Collaborative Network analytical interface.

RESULTS

Between 1st January, 2015, and 31st December, 2024, a total of 17,217 patients with an initial incident diagnosis of NAION and 1,503,464 patients with a diagnosis of age-related cataract were identified within the TriNetX Global Collaborative Network (**Figure 1**).

Baseline characteristics of the study population

Before PSM, significant differences in baseline demographic and clinical characteristics were observed between the two cohorts (**Table 1**). The control group exhibited a higher prevalence of several

cardiovascular risk factors and systemic comorbidities, including diabetes mellitus (23.3% vs. 21.1%), dyslipidaemia (32.6% vs. 29.4%), obesity (11.3% vs. 9.4%), tobacco use (2.0% vs. 1.7%), and neoplasms (23.1% vs. 18.8%). Conversely, patients who experienced an initial recorded episode of NAION presented with significantly higher baseline rates of sleep apnoea (8.6% vs. 6.1%) and chronic kidney diseases (7.3% vs. 5.7%).

Table 1 Baseline medical characteristics observed in non-arteritic anterior ischaemic optic neuropathy (NAION) patients compared to patients with cataract.

Characteristic	Age-Related Cataract group (n=1,503,464)	NAION group (n=17,217)	p-value	Std diff.
Demographics				
Age at index (years), mean ± SD	66.5 ± 7.9	65.3 ± 8.8	<0.001	0.143
Male sex, n (%)	601,088 (40.0%)	9,411 (54.7%)	<0.001	0.297
Female sex, n (%)	902,376 (60.0%)	7,806 (45.3%)	<0.001	0.297
White, n (%)	843,826 (56.1%)	12,012 (69.8%)	<0.001	0.285
Black or African American, n (%)	194,578 (12.9%)	1,590 (9.2%)	<0.001	0.118
Hispanic or Latino, n (%)	84,977 (5.7%)	552 (3.2%)	<0.001	0.119
Asian, n (%)	82,291 (5.5%)	460 (2.7%)	<0.001	0.142
Diagnosis & Clinical Status				
Hypertensive diseases (deprecated 2018), n (%)	545,349 (36.3%)	6,213 (36.1%)	0.613	0.004
Hypertensive diseases, n (%)	545,512 (36.3%)	6,228 (36.2%)	0.765	0.002
Personal history of nicotine dependence, n (%)	99,691 (6.6%)	1,259 (7.3%)	<0.001	0.027
Tobacco use, n (%)	30,067 (2.0%)	291 (1.7%)	0.004	0.023
Diabetes mellitus, n (%)	350,506 (23.3%)	3,640 (21.1%)	<0.001	0.052
Disorders of lipoprotein metabolism/lipidaemias, n (%)	490,867 (32.6%)	5,064 (29.4%)	<0.001	0.070
Overweight and obesity, n (%)	169,854 (11.3%)	1,616 (9.4%)	<0.001	0.063
Other cardiac arrhythmias, n (%)	39,578 (2.6%)	432 (2.5%)	0.315	0.008
Alcohol related disorders, n (%)	23,707 (1.6%)	281 (1.6%)	0.563	0.004
Other chronic obstructive pulmonary disease, n (%)	50,972 (3.4%)	511 (3.0%)	0.002	0.024
Chronic obstructive pulmonary disease, unspecified, n (%)	46,180 (3.1%)	478 (2.8%)	0.026	0.018
Chronic kidney disease (CKD), n (%)	71,556 (4.8%)	998 (5.8%)	<0.001	0.046
Acute kidney failure and chronic kidney disease, n (%)	85,215 (5.7%)	1,252 (7.3%)	<0.001	0.065
Sleep apnoea, n (%)	92,230 (6.1%)	1,483 (8.6%)	<0.001	0.095
Haemolytic anaemias, n (%)	6,062 (0.4%)	71 (0.4%)	0.850	0.001

Persons with potential health hazards (socioeconomic), n (%)	21,381 (1.4%)	204 (1.2%)	0.009	0.021
Peripheral vascular disease, unspecified, n (%)	19,555 (1.3%)	232 (1.3%)	0.590	0.004
Neoplasms, n (%)	346,719 (23.1%)	3,236 (18.8%)	<0.001	0.105
Sexual arousal disorders, n (%)	1,446 (0.1%)	22 (0.1%)	0.184	0.009
Long term (current) use of aspirin, n (%)	40,577 (2.7%)	765 (4.4%)	<0.001	0.094
Long term (current) use of anticoagulants, n (%)	13,753 (0.9%)	238 (1.4%)	<0.001	0.044
Long term (current) use of insulin, n (%)	50,254 (3.3%)	710 (4.1%)	<0.001	0.041
Long term (current) use of antithrombotics/antiplatelets, n (%)	2,816 (0.2%)	82 (0.5%)	<0.001	0.050
Medication				
Amiodarone, n (%)	1,182 (0.1%)	82 (0.5%)	<0.001	0.076
Metformin, n (%)	149,854 (10.0%)	1,572 (9.1%)	<0.001	0.028
Dulaglutide, n (%)	13,155 (0.9%)	166 (1.0%)	0.212	0.009
Liraglutide, n (%)	7,917 (0.5%)	121 (0.7%)	0.002	0.023
Lixisenatide, n (%)	423 (0.0%)	10 (0.1%)	0.021	0.014
Semaglutide, n (%)	11,966 (0.8%)	218 (1.3%)	<0.001	0.047
Tirzepatide, n (%)	2,167 (0.1%)	34 (0.2%)	0.067	0.013
GLP-1 analogues, n (%)	29,894 (2.0%)	482 (2.8%)	<0.001	0.053
SGLT2 inhibitors, n (%)	23,245 (1.5%)	279 (1.6%)	0.432	0.006
Beta blockers / related, n (%)	204,211 (13.6%)	3,112 (18.1%)	<0.001	0.123
Calcium channel blockers, n (%)	168,910 (11.2%)	2,168 (12.6%)	<0.001	0.042
Antilipemic agents, n (%)	321,960 (21.4%)	4,357 (25.3%)	<0.001	0.092
Diuretics, n (%)	219,480 (14.6%)	2,573 (14.9%)	0.201	0.010
ACE inhibitors, n (%)	159,429 (10.6%)	2,007 (11.7%)	<0.001	0.033
Angiotensin II inhibitor, n (%)	132,194 (8.8%)	1,593 (9.3%)	0.034	0.016
HMG CoA reductase inhibitors, n (%)	306,560 (20.4%)	4,114 (23.9%)	<0.001	0.084
Blood glucose-lowering drugs (excl. insulins), n (%)	172,828 (11.5%)	1,984 (11.5%)	0.908	0.001

Exenatide, n (%)	12,883 (0.2%)	5 (0.3%)	0.002	0.021
Sildenafil, n (%)	27,038 (1.8%)	303 (1.8%)	0.705	0.003
Tadalafil, n (%)	15,850 (1.1%)	213 (1.2%)	0.020	0.017
Laboratory Results & Vitals				
Cholesterol (Total) [mg/dL], mean ± SD	185.4 ± 44.0	178.1 ± 53.9	<0.001	0.148
Cholesterol in HDL [mg/dL], mean ± SD	50.3 ± 22.3	47.2 ± 21.8	<0.001	0.143
Cholesterol in LDL [mg/dL], mean ± SD	105.2 ± 36.2	101.1 ± 40.3	<0.001	0.105
eGFR (MDRD formula) [mL/min], mean ± SD	77.7 ± 23.1	74.1 ± 24.9	<0.001	0.150
Diastolic Blood Pressure [mmHg], mean ± SD	75.4 ± 10.7	76.4 ± 11.7	<0.001	0.088
Systolic Blood Pressure [mmHg], mean ± SD	131.1 ± 18.0	133.9 ± 19.6	<0.001	0.148
Triglycerides [mg/dL], mean ± SD	132.0 ± 94.6	141.6 ± 115.8	<0.001	0.091
Haemoglobin A1c [%], mean ± SD	6.5 ± 1.6	6.4 ± 1.8	<0.001	0.067
BMI [kg/m2], mean ± SD	29.3 ± 6.7	29.8 ± 6.5	<0.001	0.083

ACE: Angiotensin-Converting Enzyme; BMI: Body Mass Index; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; eGFR: estimated Glomerular Filtration Rate; GLP-1: Glucagon-Like Peptide-1; HDL: High-Density Lipoprotein; HMG-CoA: 3-Hydroxy-3-Methylglutaryl Coenzyme A; LDL: Low-Density Lipoprotein; MDRD: Modification of Diet in Renal Disease; NAION: Non-Arteritic Anterior Ischaemic Optic Neuropathy; SD: Standard Deviation; SGLT2: Sodium-Glucose Cotransporter-2; Std diff.: Standardized Difference.

Propensity score matching analysis

To address these significant baseline imbalances, a rigorous 1:1 PSM procedure was performed utilizing 59 distinct covariates encompassing demographic characteristics, comorbidities, medications, and laboratory values (**Table 2**). Following the matching process, the final study population consisted of two highly comparable groups, each comprising 17,208 patients. The post-matching assessment confirmed optimal balance across all selected variables, ensuring that both cohorts were adequately adjusted for baseline risk factors prior to the survival and risk analyses.

Table 2 Baseline characteristics before and after propensity score (PS) matching

	Before PS matching			After PS matching		
Characteristic	**Age-Related Cataract group (n=1,503,464)**	**NAION group (n=17,217)**	**Std diff.**	**Age-Related Cataract group (n=17,208)**	**NAION group (n=17,208)**	**Std diff.**
Demographics						
Age at Index (years), mean ± SD	66.5 ± 7.9	65.3 ± 8.8	0.143	65.1 ± 8.3	65.3 ± 8.8	0.014
Male sex, n (%)	601,088 (40.0%)	9,411 (54.7%)	0.297	9,387 (54.6%)	9,402 (54.6%)	0.002
Female sex, n (%)	902,376 (60.0%)	7,806 (45.3%)	0.297	7,821 (45.4%)	7,806 (45.4%)	0.002
White, n (%)	843,826 (56.1%)	12,012 (69.8%)	0.285	12,108 (70.4%)	12,003 (69.8%)	0.013
Black or African American, n (%)	194,578 (12.9%)	1,590 (9.2%)	0.118	1,608 (9.3%)	1,590 (9.2%)	0.004
Hispanic or Latino, n (%)	84,977 (5.7%)	552 (3.2%)	0.119	595 (3.5%)	552 (3.2%)	0.014
Asian, n (%)	82,291 (5.5%)	460 (2.7%)	0.142	520 (3.0%)	460 (2.7%)	0.021
Diagnosis & Clinical Status						
Hypertensive diseases (deprecated), n (%)	545,349 (36.3%)	6,213 (36.1%)	0.004	6,398 (37.2%)	6,205 (36.1%)	0.023
Hypertensive diseases, n (%)	545,512 (36.3%)	6,228 (36.2%)	0.002	6,400 (37.2%)	6,220 (36.1%)	0.022
History of nicotine dependence, n (%)	99,691 (6.6%)	1,259 (7.3%)	0.027	1,282 (7.5%)	1,257 (7.3%)	0.006
Tobacco use, n (%)	30,067 (2.0%)	291 (1.7%)	0.023	305 (1.8%)	291 (1.7%)	0.006
Diabetes mellitus, n (%)	350,506 (23.3%)	3,640 (21.1%)	0.052	3,690 (21.4%)	3,638 (21.1%)	0.007
Lipidaemia, n (%)	490,867 (32.6%)	5,064 (29.4%)	0.070	5,337 (31.0%)	5,060 (29.4%)	0.035
Overweight and obesity, n (%)	169,854 (11.3%)	1,616 (9.4%)	0.063	1,600 (9.3%)	1,612 (9.4%)	0.002

Other cardiac arrhythmias, n (%)	39,578 (2.6%)	432 (2.5%)	0.008	420 (2.4%)	432 (2.5%)	0.004
Alcohol related disorders, n (%)	23,707 (1.6%)	281 (1.6%)	0.004	270 (1.6%)	281 (1.6%)	0.005
COPD (other), n (%)	50,972 (3.4%)	511 (3.0%)	0.024	508 (3.0%)	509 (3.0%)	<0.001
COPD (unspecified), n (%)	46,180 (3.1%)	478 (2.8%)	0.018	472 (2.7%)	476 (2.8%)	0.001
Chronic kidney disease (CKD), n (%)	71,556 (4.8%)	998 (5.8%)	0.046	998 (5.8%)	997 (5.8%)	<0.001
Acute kidney failure and CKD, n (%)	85,215 (5.7%)	1,252 (7.3%)	0.065	1,234 (7.2%)	1,247 (7.2%)	0.003
Sleep apnoea, n (%)	92,230 (6.1%)	1,483 (8.6%)	0.095	1,473 (8.6%)	1,479 (8.6%)	0.001
Haemolytic anaemias, n (%)	6,062 (0.4%)	71 (0.4%)	0.001	70 (0.4%)	71 (0.4%)	0.001
Socioeconomic health hazards, n (%)	21,381 (1.4%)	204 (1.2%)	0.021	190 (1.1%)	204 (1.2%)	0.008
Peripheral vascular disease, n (%)	19,555 (1.3%)	232 (1.3%)	0.004	240 (1.4%)	230 (1.3%)	0.005
Neoplasms, n (%)	346,719 (23.1%)	3,236 (18.8%)	0.105	3,275 (19.0%)	3,236 (18.8%)	0.006
Sexual arousal disorders, n (%)	1,446 (0.1%)	22 (0.1%)	0.009	23 (0.1%)	22 (0.1%)	0.002
Long-term use of aspirin, n (%)	40,577 (2.7%)	765 (4.4%)	0.094	753 (4.4%)	761 (4.4%)	0.002
Long-term use of anticoagulants, n (%)	13,753 (0.9%)	238 (1.4%)	0.044	232 (1.3%)	235 (1.4%)	0.002
Long-term use of insulin, n (%)	50,254 (3.3%)	710 (4.1%)	0.041	724 (4.2%)	709 (4.1%)	0.004
Long-term use of antithrombotics, n (%)	2,816 (0.2%)	82 (0.5%)	0.050	82 (0.5%)	79 (0.5%)	0.003
Medication						

Amiodarone, n (%)	1,182 (0.1%)	82 (0.5%)	0.076	95 (0.6%)	73 (0.4%)	0.018
Metformin, n (%)	149,854 (10.0%)	1,572 (9.1%)	0.028	1,621 (9.4%)	1,572 (9.1%)	0.010
Dulaglutide, n (%)	13,155 (0.9%)	166 (1.0%)	0.009	166 (1.0%)	166 (1.0%)	<0.001
Liraglutide, n (%)	7,917 (0.5%)	121 (0.7%)	0.023	110 (0.6%)	121 (0.7%)	0.008
Lixisenatide, n (%)	423 (0.0%)	10 (0.1%)	0.014	10 (0.1%)	10 (0.1%)	<0.001
Semaglutide, n (%)	11,966 (0.8%)	218 (1.3%)	0.047	210 (1.2%)	217 (1.3%)	0.004
Tirzepatide, n (%)	2,167 (0.1%)	34 (0.2%)	0.013	33 (0.2%)	34 (0.2%)	0.001
GLP-1 analogues, n (%)	29,894 (2.0%)	482 (2.8%)	0.053	452 (2.6%)	481 (2.8%)	0.010
SGLT2 inhibitors, n (%)	23,245 (1.5%)	279 (1.6%)	0.006	277 (1.6%)	279 (1.6%)	0.001
Beta blockers / related, n (%)	204,211 (13.6%)	3,112 (18.1%)	0.123	3,076 (17.9%)	3,107 (18.1%)	0.005
Calcium channel blockers, n (%)	168,910 (11.2%)	2,168 (12.6%)	0.042	2,171 (12.6%)	2,164 (12.6%)	0.001
Antilipemic agents, n (%)	321,960 (21.4%)	4,357 (25.3%)	0.092	4,466 (26.0%)	4,349 (25.3%)	0.016
Diuretics, n (%)	219,480 (14.6%)	2,573 (14.9%)	0.010	2,584 (15.0%)	2,569 (14.9%)	0.002
ACE inhibitors, n (%)	159,429 (10.6%)	2,007 (11.7%)	0.033	2,122 (12.3%)	2,005 (11.7%)	0.021
Angiotensin II inhibitor, n (%)	132,194 (8.8%)	1,593 (9.3%)	0.016	1,616 (9.4%)	1,592 (9.3%)	0.005
HMG CoA reductase inhibitors, n (%)	306,560 (20.4%)	4,114 (23.9%)	0.084	4,226 (24.6%)	4,106 (23.9%)	0.016
Blood glucose drugs (excl. insulins), n (%)	172,828 (11.5%)	1,984 (11.5%)	0.001	2,025 (11.8%)	1,982 (11.5%)	0.008
Exenatide, n (%)	12,883 (0.2%)	5 (0.3%)	0.021	9 (0.2%)	5 (0.3%)	0.014
Sildenafil, n (%)	27,038 (1.8%)	303 (1.8%)	0.003	306 (1.8%)	302 (1.8%)	0.002
Tadalafil, n (%)	15,850 (1.1%)	213 (1.2%)	0.017	219 (1.3%)	212 (1.2%)	0.004

Laboratory Results & Vitals						
Cholesterol (Total) [mg/dL], mean ± SD	185.4 ± 44.0	178.1 ± 53.9	0.148	182.0 ± 44.2	178.1 ± 53.9	0.079
Cholesterol in HDL [mg/dL], mean ± SD	50.3 ± 22.3	47.2 ± 21.8	0.143	49.3 ± 22.0	47.2 ± 21.8	0.095
Cholesterol in LDL [mg/dL], mean ± SD	105.2 ± 36.2	101.1 ± 40.3	0.105	102.7 ± 35.9	101.1 ± 40.3	0.039
eGFR (MDRD formula) [mL/min], mean ± SD	77.7 ± 23.1	74.1 ± 24.9	0.150	76.8 ± 23.8	74.2 ± 24.8	0.111
Diastolic Blood Pressure [mmHg], mean ± SD	75.4 ± 10.7	76.4 ± 11.7	0.088	75.8 ± 10.9	76.4 ± 11.7	0.053
Systolic Blood Pressure [mmHg], mean ± SD	131.1 ± 18.0	133.9 ± 19.6	0.148	131.2 ± 18.1	133.9 ± 19.6	0.140
Triglycerides [mg/dL], mean ± SD	132.0 ± 94.6	141.6 ± 115.8	0.091	136.3 ± 89.6	141.6 ± 115.8	0.052
Haemoglobin A1c [%], mean ± SD	6.5 ± 1.6	6.4 ± 1.8	0.067	6.6 ± 1.6	6.4 ± 1.8	0.092
BMI [kg/m2], mean ± SD	29.3 ± 6.7	29.8 ± 6.5	0.083	29.7 ± 6.5	29.8 ± 6.5	0.022
ACE: Angiotensin-Converting Enzyme; BMI: Body Mass Index; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; eGFR: estimated Glomerular Filtration Rate; GLP-1: Glucagon-Like Peptide-1; HDL: High-Density Lipoprotein; HMG-CoA: 3-Hydroxy-3-Methylglutaryl Coenzyme A; LDL: Low-Density Lipoprotein; MDRD: Modification of Diet in Renal Disease; NAION: Non-Arteritic Anterior Ischaemic Optic Neuropathy; PS: Propensity Score; SD: Standard Deviation; SGLT2: Sodium-Glucose Cotransporter-2; Std diff.: Standardized Difference.						

Primary and secondary outcomes

Primary and secondary outcomes at 1-year follow-up are presented in **Table 3**. During the one-year follow-up period, the NAION group showed a significantly higher risk for the primary outcome of all-cause mortality (OR, 1.380; 95% CI, 1.137-1.675; p = 0.001).

Among the secondary outcomes, the risk of ischaemic stroke was markedly elevated in the NAION group (OR, 3.263; 95% CI, 2.725-3.906; $p < 0.001$). For outcomes where the proportional hazards assumption was met ($p > 0.05$), survival analysis revealed a significantly increased risk of haemorrhagic stroke (HR, 2.234; 95% CI, 1.508-3.309; Log-Rank $p < 0.001$) and AMI (HR, 1.334; 95% CI, 1.026-1.733; Log-Rank $p = 0.031$) compared to the matched control group.

There was no significant difference between the two cohorts regarding the occurrence of incident HF (HR, 1.099; 95% CI, 0.911-1.324; Log-Rank $p = 0.324$) or incident AF (HR, 1.114; 95% CI, 0.934-1.328; Log-Rank $p = 0.228$).

Table 3 Primary and secondary outcomes at 1-year follow-up in the matched cohorts

Outcome	Age-Related Cataract group	NAION Group	OR (95% CI)	p-value (OR)	HR (95% CI)	Log-Rank p-value	Proportionality p-value
Primary outcome							
All-cause death	179 (1.0%)	246 (1.4%)	1.380 (1.137 - 1.675)	0.001	1.521 (1.255 - 1.844)	<0.001	0.016
Secondary outcomes							
Cerebral Infarction (Ischaemic)	158 (0.9%)	505 (2.9%)	3.263 (2.725 - 3.906)	<0.001	3.487 (2.917 - 4.169)	<0.001	<0.001
Haemorrhagic Stroke	37 (0.2%)	76 (0.4%)	2.059 (1.389 - 3.051)	<0.001	2.234 (1.508 - 3.309)	<0.001	0.379
Acute myocardial infarction	102 (0.6%)	124 (0.7%)	1.217 (0.936 - 1.583)	0.142	1.334 (1.026 - 1.733)	0.031	0.065
Incident Heart Failure	221 (1.3%)	219 (1.3%)	0.993 (0.822 - 1.198)	0.939	1.099 (0.911 - 1.324)	0.324	0.362
Incident Atrial Fibrillation	247 (1.4%)	250 (1.5%)	1.012 (0.848 - 1.208)	0.893	1.114 (0.934 - 1.328)	0.228	0.540

CI: Confidence Interval; HR: Hazard Ratio; MACE: Major Adverse Cardiovascular Events; NAION: Non-Arteritic Anterior Ischaemic Optic Neuropathy; OR: Odds Ratio.
HRs are reported when the proportional hazards assumption is met (proportionality $p \geq 0.05$); otherwise, ORs are reported. Statistical significance ($p < 0.05$ or Log-Rank $p < 0.05$; 95% CI excluding 1.00).

DISCUSSION

In this large propensity score-matched cohort, an initial recorded episode of NAION was associated with increased 1-year all-cause mortality and higher risks of ischaemic stroke, haemorrhagic stroke, and AMI. In contrast, no significant association was observed with incident AF or HF. These findings suggest that NAION, beyond its established ocular consequences, may identify a population at increased short-term vascular risk.

Increase in all-cause mortality following an initial episode of NAION

An initial recorded episode of NAION was associated with a significantly higher 1-year all-cause mortality risk (OR = 1.380). This result contradicts two landmark studies[21,22], which found no statistically significant overall excess mortality in NAION patients compared to the general population or age-, sex-, and race-matched controls. Guyer *et al.* observed no increase in mortality rates among NAION patients, including those with hypertension. Hayreh *et al.* similarly concluded that there was no excess mortality, even within their subgroup analyses (idiopathic, hypertensive, diabetic, or combined hypertension and diabetes).

We believe that these discrepancies stem from key methodological differences. First, historical single-centre studies lacked statistical power and robust confounder adjustments, whereas we rigorously matched over 17,000 patients across 59 covariates. Second, older tertiary cohorts suffered from attrition bias, missing deceased patients lost to follow-up, while EHR-linked networks such as TriNetX capture mortality seamlessly. Finally, rather than evaluating long-term survival where excess risk dilutes, our study specifically captured an acute, 1-year window of vascular vulnerability in a modern, multimorbid population.

NAION and cerebrovascular disease

The association between NAION and the subsequent occurrence of ischaemic stroke remains debated. We observed that an initial recorded episode of NAION is associated with a significantly higher risk of ischaemic stroke at one year (OR = 3.263). Similarly, Chu *et al.* reported a relative risk of ischaemic stroke of 2.35 at one year, independent of the presence of comorbidities[5]. Other investigations found an overall higher risk (HR = 2.03), which was even more pronounced (HR = 3.35) in patients with systemic comorbidities[3]. A higher probability of cerebral infarction (OR = 2.691) has also been highlighted, with arterial hypertension identified as a predominant risk factor[23]. These modern observations align with historical studies, which showed a highly increased risk of cerebrovascular events in hypertensive patients (RR = 11.48) and in those with idiopathic NAION (RR = 3.70)[21,22]. Finally, recent data from 2026 further corroborated this significant increase in stroke risk, regardless of baseline cardiovascular risk factors[18].

Conversely, other authors did not report any significant association between cerebrovascular disease and NAION in the overall population. For instance, no significant difference was reported regarding the occurrence of symptomatic stroke compared to a control group matched for vascular risk factors, concluding that NAION does not confer an independent risk beyond that related to age and pre-existing risk factors[24]. In agreement, another analysis reported no significant excess risk of stroke after NAION (HR = 1.10) in an adjusted multivariate model[25]. Lastly, earlier research limited this increased risk of cerebrovascular events (SMR = 7.59) exclusively to the subpopulation with concurrent hypertension and diabetes, without identifying a direct link for idiopathic forms[22].

NAION and ischaemic stroke share a common cardiovascular risk profile (atherosclerosis, endothelial dysfunction) and hypoperfusive microangiopathic mechanisms[25,26]. NAION, caused by acute ischemia secondary to hypoperfusion of the microvascular network of the short posterior ciliary arteries, is increasingly considered an ocular manifestation of cerebral small vessel disease (SVD)[5] rather than a thromboembolic mechanism typical of stroke. This hypothesis is further supported by radiological evidence[27], with signs of small vessel ischaemic damage noted on MRI in 88% of patients in a dedicated NAION cohort[7]. This close association with SVD is confirmed by large-scale imaging studies, which demonstrated a significantly increased prevalence of SVD in patients with NAION (68% versus 37% in controls), independent of traditional risk factors[28]. Thus, as systemic microangiopathy alters cerebrovascular reactivity and endothelial autoregulation, the link to ischaemic stroke could rely on an atherothrombotic substrate and chronic hypoperfusion. Infarction of the optic nerve head would therefore constitute an early clinical marker of a broader underlying cerebral vascular fragility.

AF is a frequent aetiology of stroke, which led us to address this diagnosis on two distinct levels. First, we chose to exclude patients with a history of AF due to their high emboligenic risk, as AF strongly promotes thromboembolic events. Second, we assessed the incidence of AF and found no significant difference in its occurrence within the year following a diagnosis of NAION or cataract, even though the incidence of both ischaemic and haemorrhagic strokes was markedly higher in the NAION group. These findings suggest that AF, despite being a well-known thrombogenic risk factor for stroke, did not significantly drive the markedly higher stroke incidence observed in our cohort. This is further supported by the significantly higher risk of haemorrhagic strokes following NAION, whereas AF is classically known to be an aetiology for ischaemic strokes.

An initial episode of NAION is associated with a significantly higher risk of haemorrhagic stroke at one year (HR = 2.234). This aligns with recent multinational data reporting a significantly higher risk of haemorrhagic stroke across all follow-up intervals (with a relative risk of 7.49 at 1 month and 3.20 at 1 year), regardless of baseline comorbidities[5]. Another recent study has similarly demonstrated a statistically significantly higher risk of haemorrhagic stroke in patients with NAION, independent of vascular comorbidities[11].

The association between NAION and haemorrhagic stroke appears less obvious and has historically been underexplored. This relationship was not demonstrated in early studies, likely owing to a lack of statistical power within small or ethnically homogeneous cohorts. For example, earlier research reported no statistically significant difference regarding the risk of haemorrhagic stroke between patients with NAION and controls (aHR = 1.24; p = 0.696), a finding entirely attributed to the very low number of haemorrhagic events in their cohort (e.g., only 6 cases)[3].

Pathophysiologically, linking an ischaemic hypoperfusive condition (NAION) to a cerebral bleed (haemorrhagic stroke) may seem counterintuitive. However, a recent hypothesis suggests that NAION can ultimately be considered an ocular manifestation of cerebral SVD, specifically affecting the optic

nerve in this context[5]. Both entities share common microvascular alterations involving arteriolar perfusion and endothelial autoregulation. CSVD does not merely cause luminal stenosis or hypoperfusion; it leads to a profound structural fragility of the small cerebral vessels through endothelial dysfunction. Given that CSVD is responsible for approximately 80% of non-traumatic intracerebral hemorrhages[29], NAION may serve as a clinical "window" revealing an underlying systemic microvascular fragility that logically predisposes these patients to an increased risk of subsequent haemorrhagic events.

NAION and cardiac outcomes

Although myocardial infarction is a well-established risk factor for the development of NAION[10–14], the incidence of AMI following this neuropathy remains significantly less documented. In our study, we demonstrate that an initial episode of NAION is associated with a significantly higher short-term risk of AMI at one year (HR = 1.334). This aligns with some historical investigations that found a significantly higher incidence of myocardial infarction in patients with idiopathic or hypertension-associated NAION[21]. Conversely, other early studies failed to demonstrate this association, regardless of the patient's baseline metabolic profile[22]. These historical discrepancies can largely be attributed to single-centre recruitment biases and limited statistical power, which are overcome by our large-scale design.

Pathophysiologically, this association is highly coherent, as NAION and AMI share a common atherothrombotic genesis driven by identical systemic risk factors, including advancing age, diabetes, dyslipidaemia, arterial hypertension, and sleep apnoea.

We chose to exclude patients with a history of HF. This decision was motivated not only by the generally poor prognosis of these patients but also by the substantial clinical and coding heterogeneity of this condition, which encompasses everything from HF with preserved ejection fraction in the elderly to various ischaemic and non-ischaemic cardiomyopathies. Such heterogeneity carried the risk of introducing a baseline imbalance in disease severity between the two groups, which might not have been adequately mitigated by PSM alone. Nevertheless, assessing incident cases of HF following a diagnosis of NAION remains highly relevant, given that coronary artery disease is the underlying aetiology in approximately half of all HF cases.

The fact that NAION was associated with a higher risk of AMI, without a concomitant higher risk of incident HF, suggests that the cardiovascular vulnerability linked to this neuropathy is primarily acute and ischaemic in nature. Furthermore, the magnitude of the excess risk observed for AMI is notably lower than that for cerebrovascular events (HR = 1.334 for AMI versus OR = 3.263 for ischaemic stroke and HR = 2.234 for haemorrhagic stroke). This more modest association, combined with our initial exclusion of patients with prevalent HF, likely contributes to the neutral risk regarding chronic pump failure.

Clinical implications

In practice, early screening for subclinical atherosclerosis appears reasonable, including Doppler ultrasound of the supra-aortic trunks, alongside a comprehensive cardiological evaluation to consider myocardial ischemia testing. Although NAION is not yet formally classified as a major cardiovascular event per se due to limited literature, its occurrence should be regarded as an additional cardiovascular risk enhancer that elevates the patient's overall risk profile. Consequently, clinicians should consider targeting lower LDL-C levels and initiating lipid-lowering therapy when appropriate.

Conversely, routine antiplatelet therapy does not appear justified at present. From an ophthalmological standpoint, large retrospective data have demonstrated that aspirin provides little to no long-term benefit in reducing the 5-year risk of NAION recurrence in the contralateral fellow eye[30]. From a systemic perspective, this lack of indication is reinforced by the absence of evidence supporting its efficacy in primary prevention, or in secondary prevention for atherosclerotic lesions <50%[31,32]. Furthermore, the observed excess risk of haemorrhagic stroke warrants caution regarding routine antiplatelet therapy solely on the basis of NAION, in the absence of another cardiovascular indication.

Future prospective studies with extended follow-up periods are needed to evaluate the long-term cardiovascular trajectory of these patients and to establish standardized post-NAION cardiovascular prevention guidelines.

Strength and limitations

This study’s primary strengths lie in leveraging the global TriNetX network to assemble an unprecedented cohort of over 17,000 NAION cases, overcoming the statistical and selection biases of prior single-centre studies. Patients with age-related cataract were specifically selected as the control group to represent an active ophthalmic patient population of comparable age and healthcare utilization, yet free from acute ocular vascular pathology. To minimize confounding NAION as an independent cardiovascular risk factor rather than a metabolic bystander, we performed rigorous 1:1 PSM across 59 covariates[33,34], accounting for clinical history, laboratory values, potential drug triggers[35–39] (GLP-1 agonists, amiodarone, phosphodiesterase inhibitors), and malignant neoplasms.

Several limitations must be acknowledged: reliance on administrative ICD-10 codes carries a risk of diagnostic misclassification, the database lacks detailed ophthalmological metrics (such as visual acuity, OCT findings, or optic disc morphology), and unmeasured lifestyle factors or residual confounding cannot be entirely excluded. Furthermore, our analysis focused strictly on short-term, one-year outcomes without capturing long-term trajectories or the precise clinical severity of secondary vascular events.

CONCLUSION

This large-scale retrospective study highlights that an initial episode of NAION is independently associated with a significantly higher short-term risk of all-cause mortality, all strokes, and AMI. The absence of a significantly higher risk for incident AF or HF suggests that this cardiovascular vulnerability may predominantly involve acute vascular and microvascular pathways. Clinically, these results suggest

that NAION may no longer be viewed solely as an isolated "stroke of the optic nerve" with a guarded visual prognosis, but rather as a potential marker of short-term systemic vascular risk, supporting timely cardiovascular risk assessment and optimization of modifiable risk factors.

Abbreviations

ACE
Angiotensin-Converting Enzyme
AF
Atrial Fibrillation
AMI
Acute Myocardial Infarction
BMI
Body Mass Index
CI
Confidence Interval
CKD
Chronic Kidney Disease
eGFR
estimated Glomerular Filtration Rate
GLP-1
Glucagon-Like Peptide-1
HCOs
Healthcare Organizations
HDL
High-Density Lipoprotein
HF
Heart Failure
HMG-CoA
3-Hydroxy-3-Methylglutaryl Coenzyme A
HR
Hazard Ratio
ICD-10
The 10th revision of the International Classification of Diseases
IQR
Interquartile Range
LDL
Low-Density Lipoprotein
MDRD
Modification of Diet in Renal Disease

MI
Myocardial Infarction
NAION
Non-arteritic anterior ischaemic optic neuropathy
OR
Odds Ratio
PSM
Propensity score matching
SDs
Standard Deviations
SGLT2
Sodium-Glucose Cotransporter-2
Std diff.
Standardized Difference
y.o.
Years old

Declarations

Data availability: The data underlying this article were provided by TriNetX under licence and cannot be shared publicly. Aggregated data are available from the corresponding author on reasonable request.

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Figures

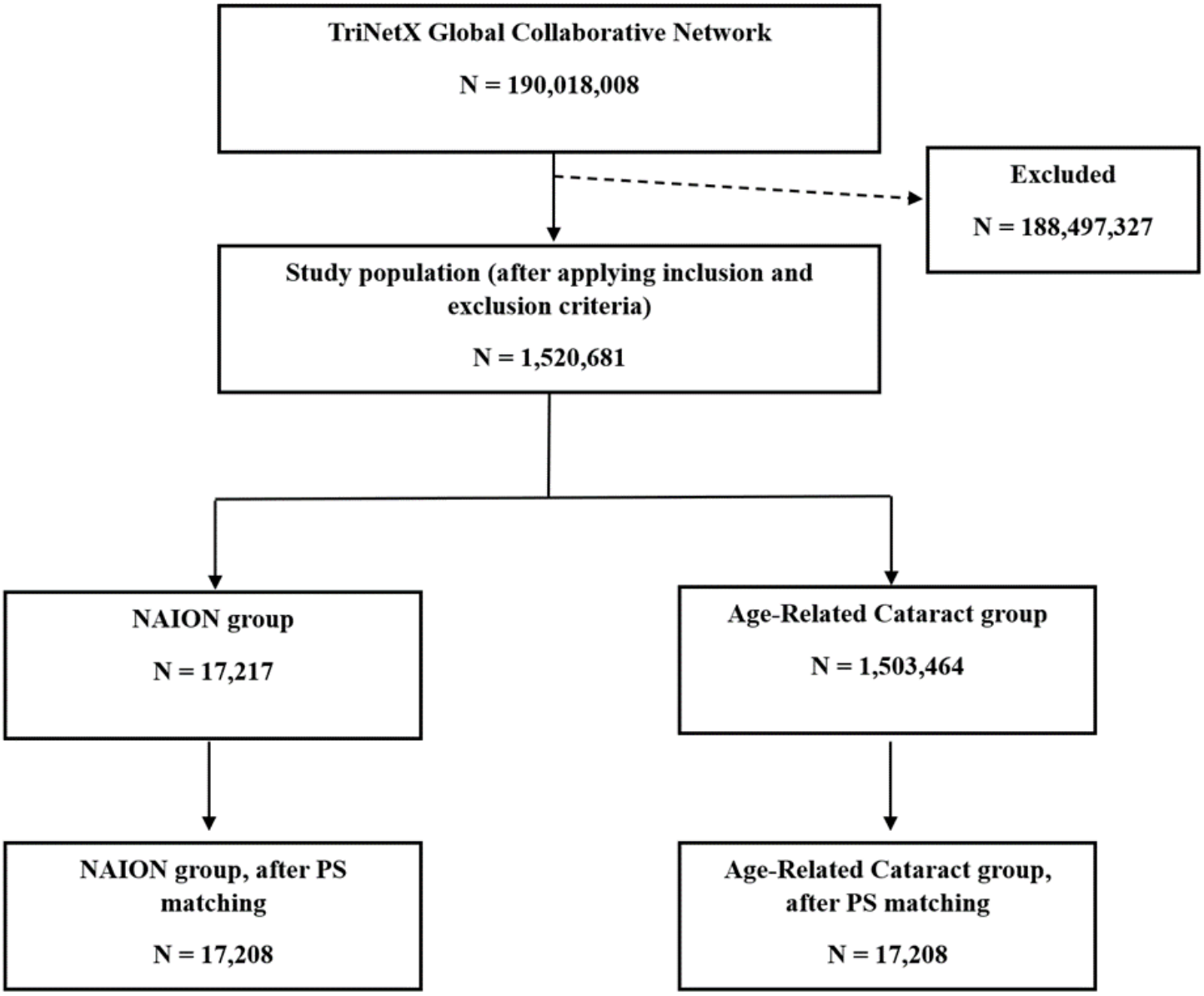


Figure 1

Study flow chart (N: number of patients; NAION: non-arteritic anterior ischaemic optic neuropathy; PS: propensity score.