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REVIEW ARTICLE

Cardiometabolic factors and risk of non-arteritic anterior ischemic optic neuropathy: a systematic review and meta-analysis

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Abstract

Purpose The purpose of this systematic review and meta-analysis of the literature is to evaluate the association between cardiometabolic risk factors (hypertension, diabetes mellitus, hypercholesterolemia/dyslipidemia, HDL cholesterol, LDL cholesterol, lipoprotein(a), and triglycerides) and non-arteritic anterior ischemic optic neuropathy (NAION).

Methods Pertinent publications were identified through a systematic search in PubMed and EMBASE databases, without language restrictions. The pooled odds ratios (OR) and standardized mean differences (SMD), with their 95% confidence intervals (95% CI) were estimated using random effects (DerSimonian Laird) models, as appropriate. A set of subgroup analyses and meta-regression analysis models were performed.

Results Twenty-one studies (including 1560 patients with NAION and 2292 controls), examining the association between NAION and cardiometabolic risk factors, were eligible for the systematic review and meta-analysis. Hypertension (pooled OR = 1.50; 95% CI: 1.16–1.94), diabetes mellitus (pooled OR = 1.71; 95% CI: 1.33–2.21), and hypercholesterolemia/dyslipidemia (pooled OR = 2.00; 95% CI: 1.53–2.62) were associated with NAION. Among the components of dyslipidemia, higher serum triglycerides were associated with NAION, with a medium effect size (SMD = +0.58, 95% CI: +0.12 to +1.04), whereas synthesis of four studies reporting on HDL and LDL cholesterol did not reveal any significant associations. A significant association between NAION and higher serum lipoprotein(a) levels (pooled OR = 2.88; 95%CI: 1.01–8.21) was also noted.

Conclusions This systematic review and meta-analysis found that NAION was associated with cardiometabolic factors, suggesting that vascular dysfunction may be implicated in the pathogenesis of the disease. Our findings may alert health care providers to try modifying these risk factors for NAION prevention.

Key messages

- The pathogenesis of non-arteritic anterior ischemic optic neuropathy (NAION) is considered to be multifactorial, involving mainly hypoperfusion or non-perfusion of the optic nerve head due to anatomic predisposition.
- This systematic review and meta-analysis found that cardiometabolic factors were associated with NAION, suggesting that vascular dysfunction may be also implicated in the pathogenesis of the disease.
- A multidisciplinary approach is needed in patients with NAION, so as to modify risk factors to prevent fellow eye involvement.

Keywords Dyslipidemia · Diabetes mellitus · Hypertension · Non-arteritic anterior ischemic optic neuropathy · Cardiometabolic · Risk factors

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Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy and a relatively common cause of irreversible vision loss in middle-aged and elderly populations [1–3]. The annual incidence of NAION has been estimated to be about 2.3–10.3 per 100,000 individuals [3–6]. Patients with NAION usually present with sudden, painless, and unilateral vision loss, which evolves over several hours to days, accompanied by relative afferent pupillary defect, optic disc edema, and delayed optic atrophy [7, 8]. Visual field defects may also occur in NAION with arcuate or altitudinal inferior visual field defects to be the most common [9].

The exact mechanisms of NAION are not definitively known, but it is considered to be multifactorial [9]. The best evidence suggests that NAION is caused by infarction or circulatory insufficiency in the prelaminar region of the optic nerve head, which is primarily supplied by paraoptic short posterior ciliary arteries circulation [10]. The pathogenesis of NAION mainly involves hypoperfusion or non-perfusion of the optic nerve head, resulting from a small and crowded disc, decreased blood delivery, low blood oxygen carrying capacity, or increased vascular resistance [1, 2, 9–11]. Previous studies have found a variety of potential risk factors for NAION, including anatomic predisposition of a "disc at risk," advanced age, vascular diseases, such as hypertension, diabetes mellitus, dyslipidemia and ischemic heart disease, thromboembolic disorders and hypercoagulable states, nocturnal arterial hypotension, anemia, obstructive sleep apnea, as well as cigarette smoking [11–15].

Known cardiometabolic factors, i.e., hypertension, diabetes mellitus, and dyslipidemia/hypercholesterolemia, gain significant interest and need further investigation since they are common comorbidities, especially in the elderly population [16–18]. Noticeably, nearly half of adults in the USA (108 million or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg or are taking medication for hypertension [17], while diabetes mellitus affects more than 400 million people worldwide [18]. Additionally, the prevalence of dyslipidemia is quite high worldwide; it is estimated to reach 40.5% in Korea, more than 50% in Venezuela, and 51.3–87% in Northern Europe [19–21]. In light of the above, the purpose of this systematic review and meta-analysis was to evaluate the possible associations between cardiometabolic factors, namely hypertension, diabetes mellitus, dyslipidemia/hypercholesterolemia, and risk of NAION.

Methods

Search methods

We conducted a comprehensive search in the PubMed and EMBASE databases to include articles up to November 1, 2020, using the following search algorithm: ("hypertension" OR "diabetes" OR "diabetes mellitus" OR "dyslipidemia" OR "dyslipidaemia" OR "hyperlipidemia" OR "hyperlipidaemia" OR "hypercholesterolemia" OR "hypercholesterolaemia" OR "risk factors") AND ("NAION" OR "non arteritic anterior ischemic optic neuropathy"). Articles and book chapters cited in the reference lists of relevant studies and reviews obtained by this algorithm were reviewed and included when considered appropriate, while the retrieved articles were assessed for eligibility and filtered manually to exclude duplicates. No language restrictions were set.

Eligibility criteria-study selection

All studies included in this systematic review and meta-analysis had to meet the following inclusion criteria: (1) comparative case–control studies examining the association between NAION and cardiometabolic factors, namely hypertension, diabetes mellitus, dyslipidemia/hypercholesterolemia, serum HDL cholesterol, LDL cholesterol, triglycerides and lipoprotein(a); (2) clear definition of NAION cases; (3) sufficient dichotomous or continuous data on cardiometabolic factors. Case–control studies with "inappropriate selection of controls," namely those comparing versus other diseases (associated with cardiometabolic factors) or including matching on the examined cardiometabolic risk factors, therefore not allowing comparisons, were excluded.

Reviews, case reports, and animal studies were excluded from this systematic review. From multiple publications from the same study group, the largest dataset and recent results were chosen. Two reviewers (I.C., D.K.), working independently, performed the selection of studies; in case of disagreement, a consensus with a third reviewer (TNS) followed.

Data collection and risk of bias

Data were independently extracted and reviewed from each study by two reviewers (I.C., D.K.). Any discrepancy between data extractions was resolved by discussion or a third reviewer (TNS). The following data were extracted: first author, year of publication, journal name, country in which the study was conducted, study design, number of patients and controls, patient demographics (mean age, percentage of males), matching factors and data

about hypertension (dichotomous variable), diabetes mellitus (dichotomous), dyslipidemia/hypercholesterolemia (dichotomous or continuous), serum HDL cholesterol/LDL cholesterol/triglycerides/lipoprotein(a) (dichotomous or continuous) in cases and controls. Wherever appropriate, multivariate odds ratios (ORs and 95% confidence intervals, CIs) were preferred over univariate continuous data, to ensure controlling of confounders; similarly, maximally adjusted effect ORs and 95% CIs were preferred, in case of alternative models presented in the individual studies.

Quality assessment was performed using the Newcastle–Ottawa scale for included studies [22]. The scale allocates a maximum of 9 stars assessing selection, comparability, and exposure. Two investigators (I.C., A.C.) rated the quality of studies, and a discussion with a third referee (TNS) was followed in case of disagreement.

Data synthesis and analysis

Based on the frequencies in patients who presented with NAION and controls, pooled OR together with 95% CI was used to assess the association between hypertension, diabetes mellitus, hypercholesterolemia/dyslipidemia, and NAION. Of note, dyslipidemia and hypercholesterolemia were analyzed jointly due to the large overlap between the two conditions. Elaborating on statistical notions, the OR is the ratio of the odds of an event, whereas the risk ratio (relative risk) is the ratio of the risk of an event in two groups. The term "odds" refers to the ratio of the probability that a particular event occurred, divided by the probability that it did not occur [23]. In the context of case–control studies, the odds ratio is the preferable, widely used, effect size [24].

In case of serum triglycerides, HDL cholesterol, and LDL cholesterol, as some studies presented continuous data while other studies presented ORs, dichotomous and continuous data were combined to estimate the pooled standardized mean difference (SMD, Cohen's *d*), using the approach described in the Cochrane Handbook for Systematic Reviews of Interventions version 6.2 [23]. This approach has been presented in detail in the previous works by Chinn [25] and Anzures-Cabrera et al. [26]. This transformation was necessitated for the calculation of SMD in the studies by Nagy et al. (triglycerides) [27] and Zotz et al. (HDL cholesterol, LDL cholesterol, triglycerides) [28]. Cohen's *d* equal to 0.2 is interpreted as "small" effect size, 0.5 as a "medium" effect size, and 0.8 as a "large" effect size.

Between-study heterogeneity and between-study inconsistency were assessed by using Q statistics and by estimating I^2 respectively [29]. I^2 is a statistic describing the percentage of the variability in effect estimates that is due to heterogeneity rather than chance (sampling error); I^2 values above 50% may denote substantial heterogeneity [23]. The random effects (DerSimonian Laird) model was appropriately used to calculate the pooled OR or SMD and their 95% CI. Subgroup analyses by geographical region were performed.

Meta-regression analysis was performed to evaluate potential modifying effects of publication year, mean age, and percentage of males upon the examined associations; meta-regression analysis was performed in case of ten or more synthesized studies, as appropriate [30]. Evidence of publication bias was evaluated by visual inspection of the funnel plot and using Egger's formal statistical test [31], in cases of ten or more studies. For the interpretation of Egger's test, statistical significance was defined as $p < 0.1$. For the optimization of this systematic review and meta-analysis, the guidelines summarized in the PRISMA statement were followed (Online resource 1) [31]. The meta-analysis was conducted using STATA/SE version 13 (STATA Corp., College Station, TX, USA).

Results

Selection and description of studies

The electronic database search identified 1397 abstracts (834 from PubMed and 563 from EMBASE); after the exclusion of duplicates, 1054 abstracts were screened. After reviewing all titles and abstracts, 814 records were excluded as irrelevant. Out of 240 remaining relevant articles, 90 were reviews/letters to the editor, 57 case reports, and 60 did not meet the inclusion criteria, as not being case–control studies or being treatment-related studies. In addition, three studies were excluded because they were based on overlapping populations, namely two articles by Weger et al. [32, 33] were based on the same population, and we included the most recent one with the largest study sample [33]. Moreover, the studies by Asproudis et al. [34], Felekis et al. [35], and Markoula et al. [36] were based on the same population and we included the one with the largest study sample by Felekis et al. [35]. Regarding "inappropriate selection of controls," nine studies were excluded. Specifically, Arda et al. [37], Bilgin et al. [38], Inanc et al. [39], Foster et al. [40], He et al. [41], and Wang et al. [42] recruited controls matched with cases on the examined cardiometabolic risk factors, therefore precluding any comparison; three studies [43–45] encompassed controls with other conditions associated with hypertension and diabetes mellitus, such as cataract [43], restless leg syndrome [44], and psychiatric disorders [45]. Therefore, a total of 21 studies were included in the systematic review and meta-analysis [27, 28, 33, 35, 46–62]. The flowchart describing the successive steps for the selection of eligible articles is presented in Fig. 1.

The study characteristics of the included studies are shown in Table 1, while the definitions of cardiometabolic

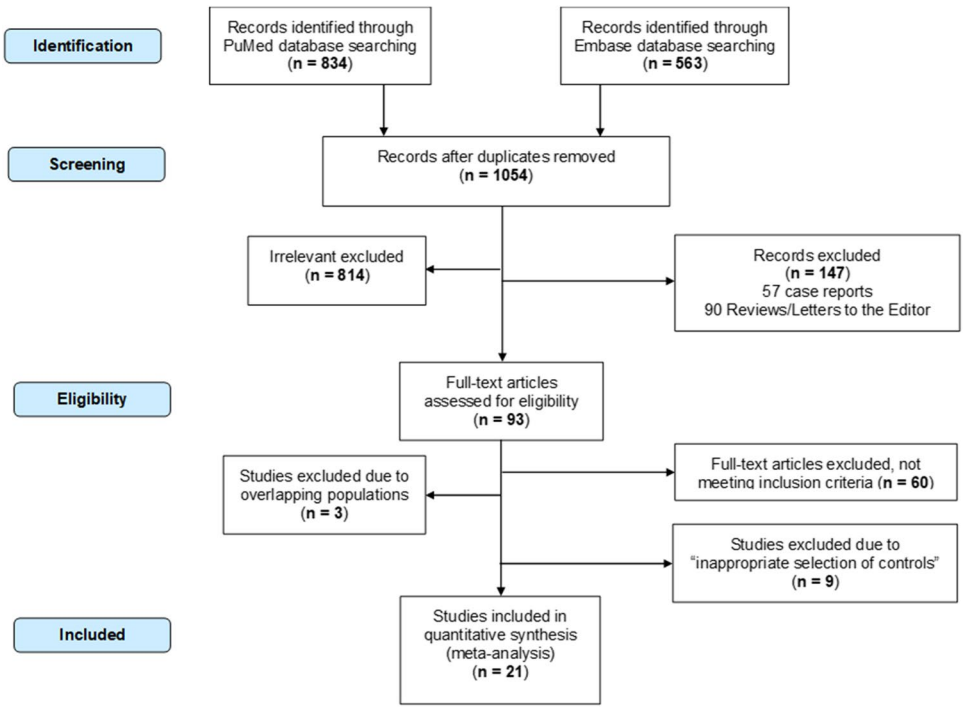


Fig. 1 Flowchart describing the successive steps for the selection of eligible articles

conditions examined in each study are shown in Online resource 2. A total of 1560 participants and 2292 controls were included in these 21 case–control studies, with a sample size ranging from 37 to 400. In these studies, six were conducted in the USA, 11 in Europe/Mediterranean region (Hungary, Germany, Italy, Greece, Spain, Turkey, and Israel), and four in Asia.

As far as an abstraction of data is concerned, in the study by Deramo et al. [49] regarding cholesterol, the OR pertaining to the binary classification of hypercholesterolemia (≥ 240 vs. < 240 mg/dL) was preferred over continuous relevant data. In the study by Pinna et al. [51], the multivariate OR based on the binary classification of hypercholesterolemia (> 220 mg/dL or intake of lipid-lowering agents) was preferred over crude, continuous cholesterol data. In the study by Kesler et al. [54], estimated standard errors from an analysis of variance (ANOVA) were not used and the OR pertaining to dyslipidemia (yes vs. no classification) was retained in the analysis. Regarding lipoprotein(a), in the study by Giambene et al. [53], the multivariate OR pertaining to higher lipoprotein(a) levels was preferred over crude, continuous lipoprotein(a) data; therefore, all eligible studies reported ORs and no analysis on SMDs was necessary.

The quality assessment of the included studies is depicted on the Online resource 3. The vast majority of studies was based on hospital-based controls and did not report the rate of non-responders, whereas details about the assessment of exposure (cardiometabolic factors) were not provided in all studies, except for one.

Results of the meta-analysis

Table 2 presents the results of the meta-analysis; the forest plots are provided in Figs. 2, 3, 4, 5, 6, and 7. We found a significant positive association between NAION and hypertension (pooled OR = 1.50; 95% CI: 1.16–1.94, $p = 0.002$, Fig. 2), that was reproducible in studies performed in Europe/Mediterranean region and East Asia.

Diabetes mellitus (pooled OR = 1.71; 95% CI: 1.33–2.21, $p < 0.001$, Fig. 3) was associated with NAION. The association was replicated in subgroup analyses on studies conducted in East Asia and the USA.

Hypercholesterolemia/dyslipidemia overall (pooled OR = 2.00; 95% CI: 1.53–2.62, $p < 0.001$, Fig. 4) was associated with NAION; the association was reproducible in the subgroup of studies examining hypercholesterolemia (pooled OR = 2.25, 95% CI: 1.62–3.14) and dyslipidemia (pooled OR = 1.58, 95% CI: 1.06–2.36). The correlation was present in all studied geographic regions, namely East Asia, Europe/Mediterranean, and the USA (Online resource 4).

Analyzing the components of dyslipidemia, higher serum triglycerides were associated with NAION, with a significant, medium effect size (SMD, Cohen's $d = +0.58$, 95% CI: + 0.12 to + 1.04, $p = 0.014$, Fig. 5), but with a considerable heterogeneity ($I^2 = 91.4\%$). When the study on East Asians (Cui et al.) [55] was excluded in a post hoc sensitivity analysis, the effect size decreased to a small-to-medium difference that was still significant (SMD, Cohen's $d = +0.38$, 95% CI: + 0.11 to + 0.66, $p = 0.007$, $I^2 = 46.0\%$, Online resource 5).

Table 1 Characteristics of eligible studies

Study (year)	Country	Number of patients with NAION	Number of controls	Matching	Mean age (NAION/controls)	Percentage of males (NAION/controls)	Analyzed factors	Adjustment factors
Kalenak (1991)	USA	45	45	Age, sex	66.7/66.6	46.7/46.7	Hypertension, diabetes	
Jacobson (1997)	USA	51	153	Age, sex	68/NR	59/59	Hypertension, diabetes, hypercholesterolemia	For the analysis on diabetes, hypertension, and BMI—for the analysis of hypertension, diabetes, and BMI
Salomon (1999)	USA	61	90	Age, sex	62/66	74/59	Hypertension, diabetes, hypercholesterolemia	None
Weger (2002)	USA	59	59	Age, sex	69.1/69.7	57.7/57.7	Hypertension, diabetes	
Deramo (2003)	USA	37	74	Age, sex	43/43.2	68/68	hypertension, diabetes, hypercholesterolemia, LDL, HDL, triglycerides	None
Nagy (2006)	Hungary	37	81	Age, sex	65.9/61.6	62.2/65.4	Hypertension, diabetes, cholesterol, triglycerides, Lp(a)	None
Li (2007)	USA	73	73	Age, sex	63.5/63.5	52.1/52.1	Hypertension, diabetes, hypercholesterolemia	
Pinna (2008)	Italy	140	280	Age, sex	63.6/NR	48.6/48.6	Hypertension, diabetes, hypercholesterolemia	G6PD deficiency, hypertension, diabetes, hypercholesterolemia
Kuhli-Hattenbach (2009)	Germany	35	70	Age, sex	49.1/49.8	77.1/74.3	Lp(a)	None
Giambene (2009)	Italy	85	170	Age	65/65	45.9/44.1	Hypertension, diabetes, dyslipidemia, Lp(a)	None
Kesler (2009)	Israel	33	151	Age, sex, BMI	62.5/61.9	60.6/60.3	Hypertension, diabetes, dyslipidemia, HDL, LDL, triglycerides	None
Felekis (2010)	Greece	77	60	Age, sex	63.4/66.3	64.9/53.3	Hypertension, diabetes, hypercholesterolemia	None
Pollat (2015)	Turkey	45	50	Age, sex	60.1/62.7	51.1/50.0	Hypertension, diabetes	None
Cui (2016)	China	360	400	NR	58.5/57.3	58.3/50.5	Hypertension, diabetes, HDL, LDL, triglycerides	Gender, hypertension, diabetes, triglycerides, arteriosclerosis, optic disc parameters
Sahin (2016)	Turkey	46	90	Age	57.3/55.7	50.0/43.3	Hypertension, diabetes	None
Zotz (2016)	Germany	109	109	Age, sex	58.1/57.2	60.6/60.6	Hypercholesterolemia, HDL, LDL, triglycerides, Lp(a)	None
Kim (2017)	Korea	45	45	Age, sex	63.5/62.4	42.2/42.2	Hypertension, diabetes, hypercholesterolemia	None
Chen (2018)	China	71	142	Age, sex	54.9/55.1	66.2/66.2	Hypertension, diabetes	None
Fernandez-Vega (2020)	Spain	72	72	Age, sex	57.4/65.4	51.4/51.4	Hypertension, diabetes, dyslipidemia	None

Table 1 (continued)

Study (year)	Country	Number of patients with NAION	Number of controls	Matching	Mean age (NAION/controls)	Percentage of males (NAION/controls)	Analyzed factors	Adjustment factors
Kocak (2020)	Turkey	41	41	Age, sex	67.1/66.6	41.5/46.3	Hypertension, diabetes, HDL, LDL	None
Nikkhah (2020)	Iran	38	37	Age, sex	62/61	52.6/48.6	Hypertension, diabetes	None

BMI, body mass index; *Lp(a)*, lipoprotein alpha; *NAION*, non-arteritic anterior ischemic optic neuropathy; *NR*, not reported; *USA*, United States of America

On the other hand, synthesis of four studies reporting on HDL cholesterol (SMD, Cohen's $d = +0.03$, 95% CI: −0.29 to +0.34, $p = 0.858$, Fig. 6A) and LDL cholesterol (SMD, Cohen's $d = +0.26$, 95% CI: −0.08 to +0.59, $p = 0.140$, Fig. 6B) did not reveal any significant associations with NAION.

A significant association between NAION and higher serum lipoprotein(a) levels (pooled OR = 2.88; 95%CI: 1.01–8.21, $p = 0.049$, Fig. 7) also became evident; all pertinent studies were derived from Europe/Mediterranean region.

Meta-regression analysis and publication bias

Meta-regression analysis revealed that the association between diabetes mellitus and NAION was more pronounced in studies with a higher percentage of males (exponentiated coefficient = 1.50, 95%CI: 1.06–2.12, $p = 0.024$). On the other hand, publication year and mean age of individual studies did not seem to exert any significant modifying effects (Online resource 6).

Publication bias was evident in the analysis examining hypertension ($p = 0.083$), but not regarding diabetes mellitus ($p = 0.296$) and hypercholesterolemia/dyslipidemia ($p = 0.359$), as it is shown on Table 2.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the association between cardiometabolic factors and NAION. The results showed that cardiometabolic factors, namely hypertension, diabetes mellitus, dyslipidemia, and elevated lipoprotein(a), were significantly associated with NAION, with a 1.5-fold, 1.7-fold, two-fold, and 2.9-fold increase in odds, respectively. Of note, no significant publication bias was present, whereas subgroup analyses revealed no major impact of the geographical area on the documented associations, as a rule.

The underlying mechanisms of the correlations between cardiometabolic factors and NAION remain elusive. Hypertension may compromise the optic nerve perfusion in a similar manner to that seen in disturbances of retinal circulation [63]. Elevated blood pressure leads to intimal thickening, media wall hyperplasia, and hyaline degeneration, accompanied by retinal arteriolar narrowing and sequential impairment in retinal, choroidal, and optic nerve circulation, which can be the triggering factor for NAION [64].

Accordingly, dyslipidemia, including elevated levels of triglycerides and lipoprotein(a), can cause arteriosclerotic changes in the carotid system, affecting retinal vessels as well. Moreover, high lipoprotein(a) may increase thrombophilic risk, being an established risk factor for cardiovascular

Table 2 Results of the meta-analysis regarding cardiometabolic risk factors for non-arteritic anterior optic neuropathy

Variable	Number of studies	Odds ratio (95%CI)	*p*	I^2	Test for heterogeneity	Publication bias Egger's test
Hypertension	19	1.50 (1.16–1.94)	***p* = 0.002**	55.2%	*p* = 0.002	*p* = 0.083
Diabetes mellitus	19	1.71 (1.33 to 2.21)	***p* < 0.001**	38.1%	*p* = 0.047	*p* = 0.027
Hypercholesterolemia/dyslipidemia overall	13	2.00 (1.53 to 2.62)	***p* < 0.001**	35.2%	*p* = 0.108	*p* = 0.359
Studies on hypercholesterolemia	10	2.25 (1.62 to 3.14)	***p* < 0.001**	36.1%	*p* = 0.129	
Studies on dyslipidemia	3	1.58 (1.06 to 2.36)	***p* = 0.026**	16.9%	*p* = 0.300	
Lipoprotein(a)	4	2.88 (1.01 to 8.21)	***p* = 0.049**	71.9%	*p* = 0.014	
		SMD (95%CI)				
High-density lipoprotein (HDL)	3	+0.03 (−0.29 to +0.34)	*p* = 0.858	70%	*p* = 0.019	
Low-density lipoprotein (LDL)	3	+0.26 (−0.08 to +0.59)	*p* = 0.555	71.7%	*p* = 0.014	
Triglycerides	3	+0.58 (+0.12 to +1.04)	***p* = 0.014**	91.4%	*p* < 0.001	

CI, confidence interval; *SMD*, standardized mean difference; bold cells denote statistical significance

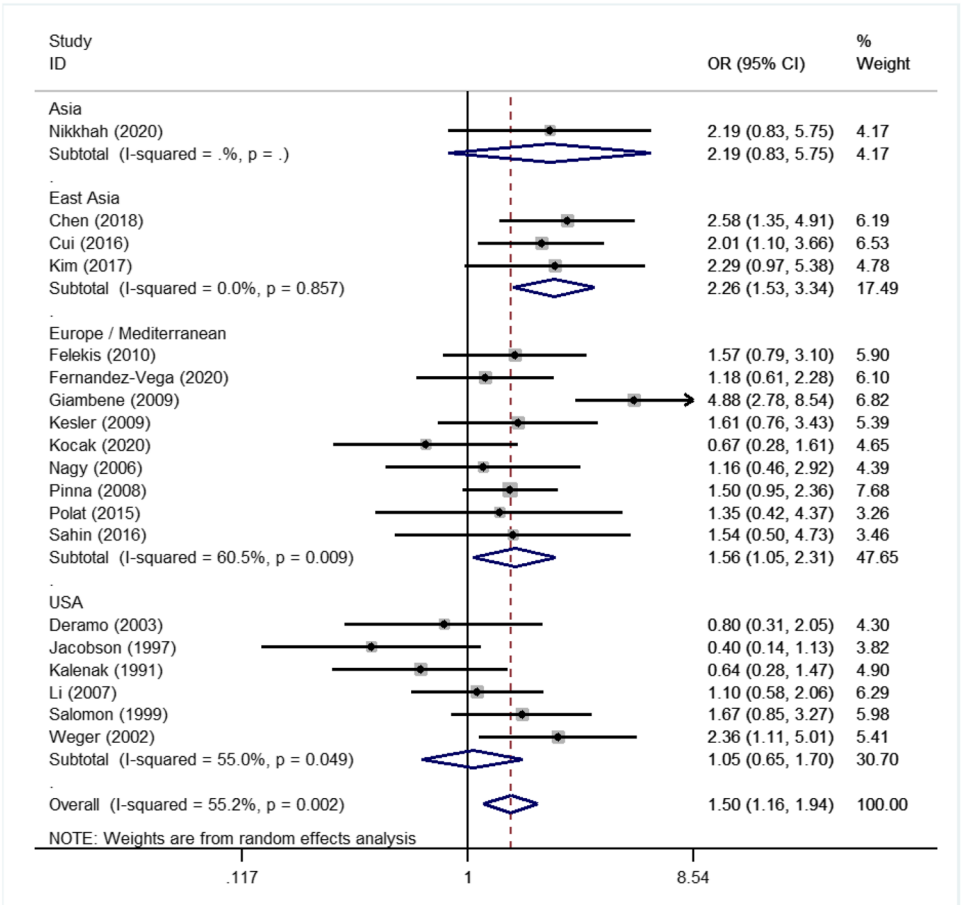


Fig. 2 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and hypertension. Each study is shown by the point estimate of the odds ratio (the size of the square is proportional to the weight of each study) and 95% confidence interval for the odds ratio (extending lines); the pooled odds ratio and 95% confidence interval are shown as diamonds

and cerebrovascular diseases [28]. Hypercholesterolemia/dyslipidemia may have an impact on the circulation of the short posterior ciliary arteries, leading to optic nerve head infarction and consequent NAION [8].

Regarding diabetes mellitus, hyperglycemia may promote several biochemical changes, such as the polyol pathway, advanced glycation end products, activation of protein kinase C, increased oxidative stress, and induction of the inflammation pathway, which lead to structural alterations in retinal vessels' wall [64]. The latter include loss of pericytes, vascular endothelium damage, and thickening of capillaries' basement membrane, resulting in abnormal hemodynamics, capillary occlusion, and non-perfusion [65]. These alterations in diabetes mellitus may predispose for optic nerve's

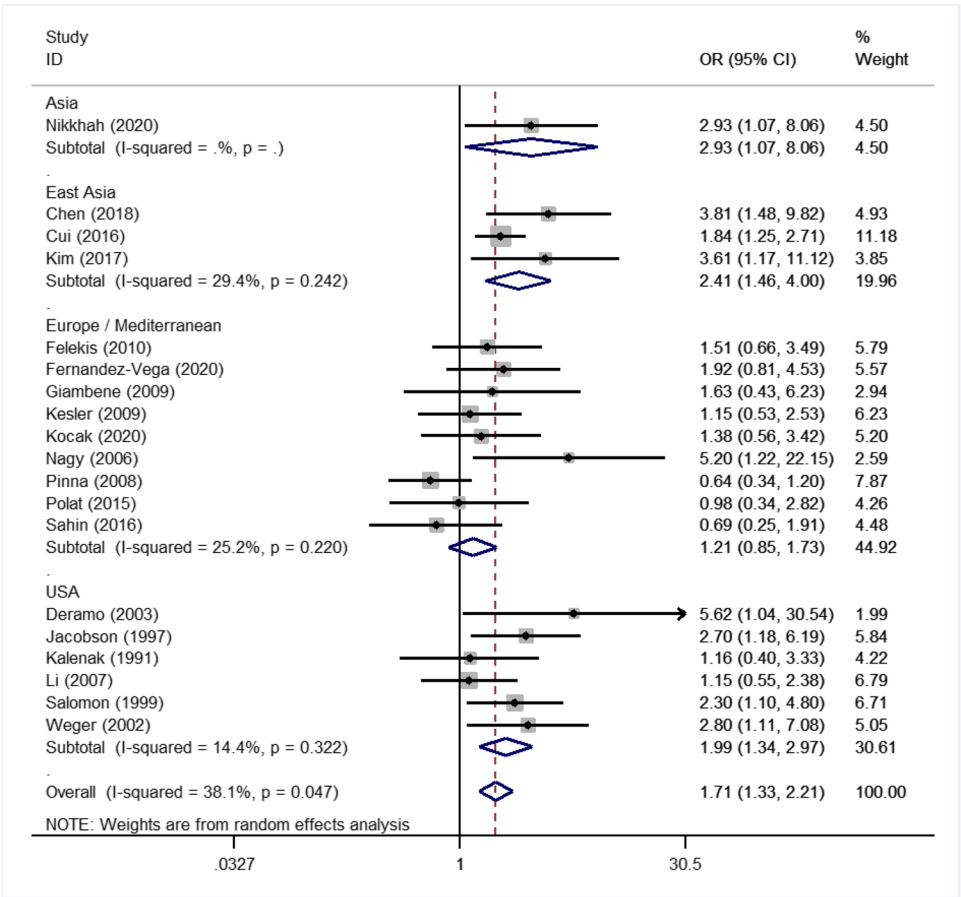


Fig. 3 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and diabetes mellitus. Each study is shown by the point estimate of the odds ratio (the size of the square is proportional to the weight of each study) and 95% confidence interval for the odds ratio (extending lines); the pooled odds ratio and 95% confidence interval are shown as diamonds

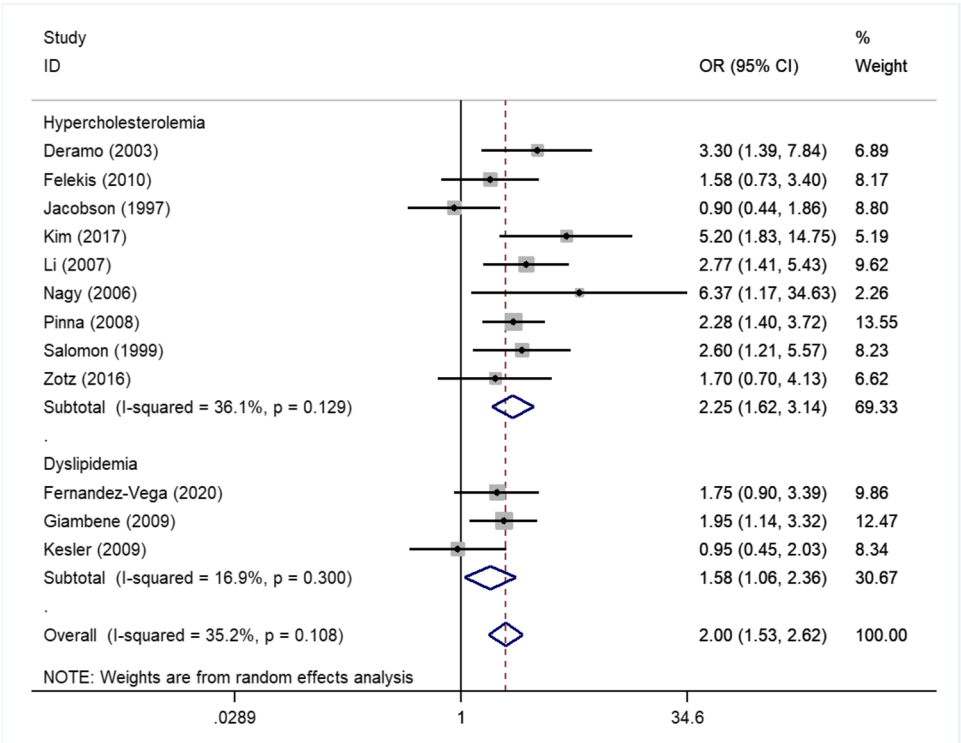
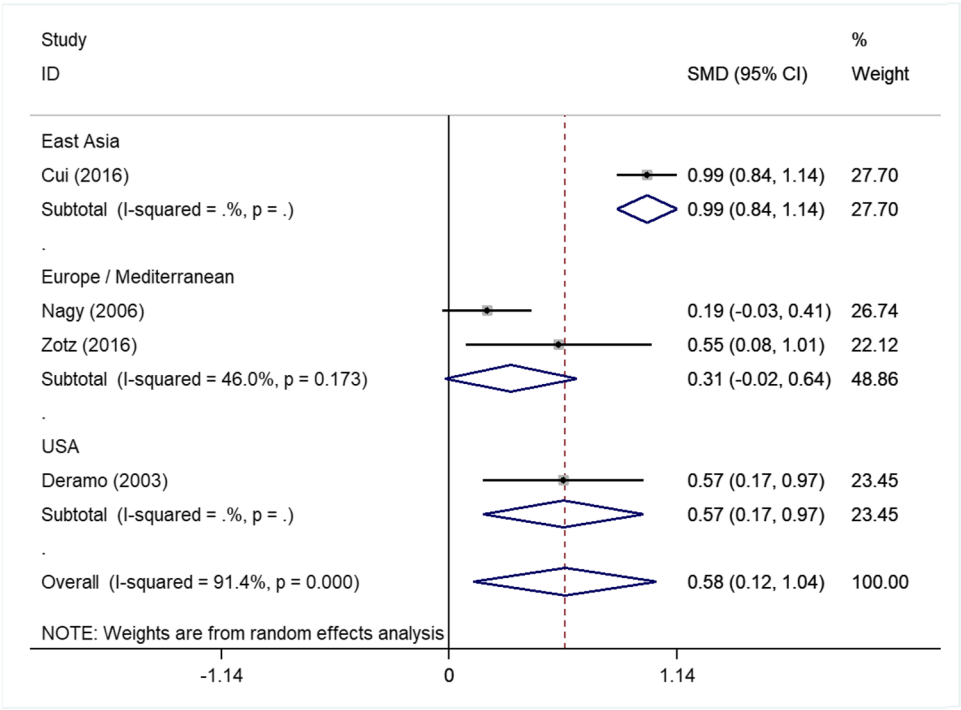


Fig. 4 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and hypercholesterolemia/dyslipidemia. Each study is shown by the point estimate of the odds ratio (the size of the square is proportional to the weight of each study) and 95% confidence interval for the odds ratio (extending lines); the pooled odds ratio and 95% confidence interval are shown as diamonds



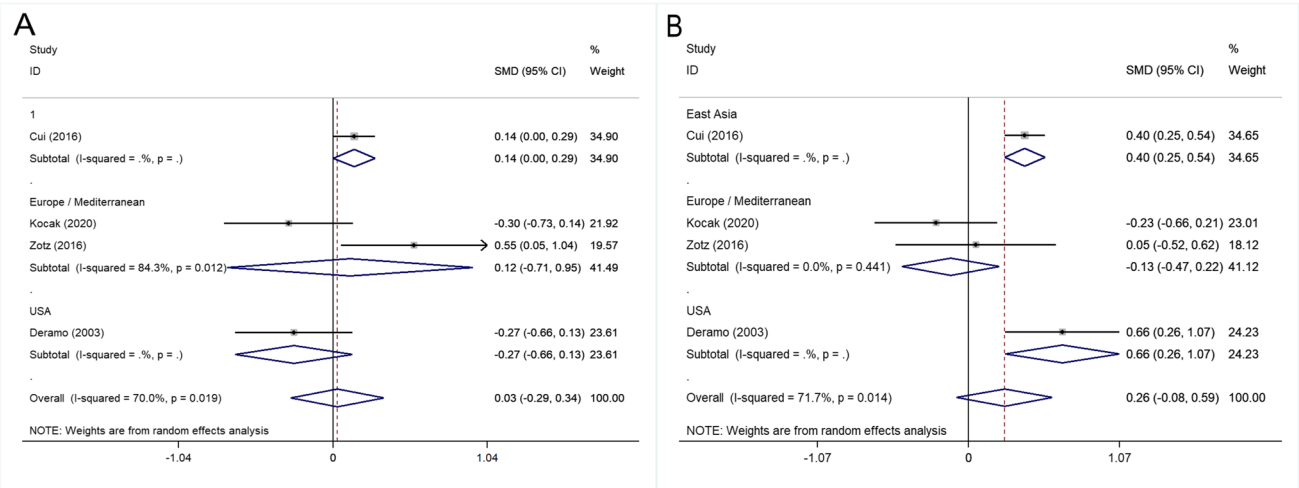


Fig. 5 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and triglycerides

Fig. 6 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and HDL cholesterol (**A**), as well as LDL cholesterol (**B**)

perfusion deficiency and end up to the development of NAION, suggesting that insufficient circulation may be the pathogenic factor [66, 67].

Meta-regression analysis revealed that the association between diabetes mellitus and NAION seemed more pronounced in studies with a higher percentage of males. The mechanisms underlying this pattern remain elusive; however, interactions of diabetes mellitus with hormonal, sex-specific factors have been noted [68, 69].

Regarding the risk of bias, the quality of studies was compromised by the fact that the majority of studies did not report the rate of non-responders and was based on hospital-based controls. Moreover, details about the assessment of exposure were not provided. Nearly half of the studies presented a representative series of cases.

Potential limitations of the current meta-analysis should be taken into account. First, all examined studies adopted a case–control design. Furthermore, the meta-analysis was mainly based on the unadjusted OR, because adjusted OR was not available in most of the included studies; lack of adjustment by other cardiometabolic factors or confounders can lead to the biased estimate of the associations between

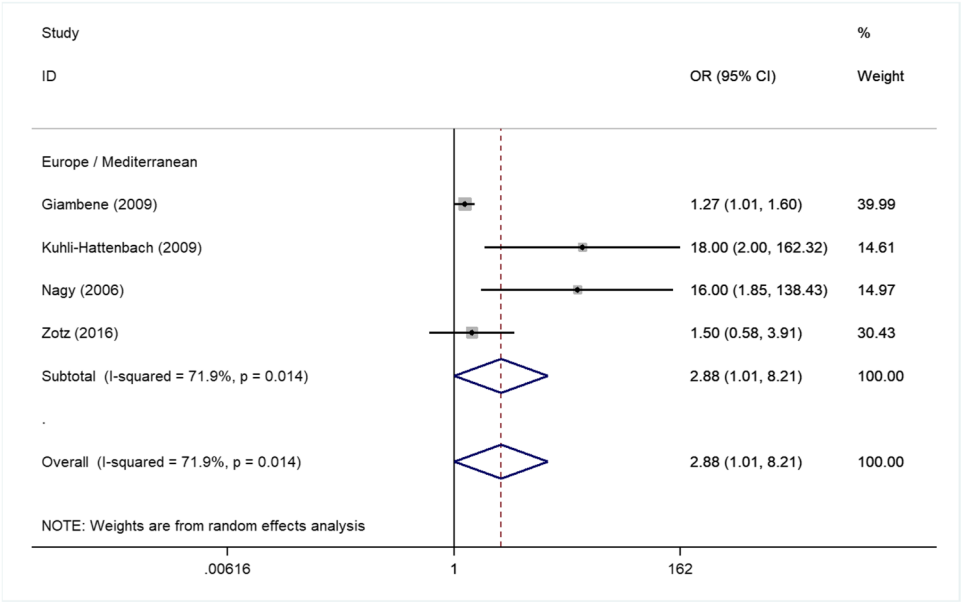


Fig. 7 Forest plot showing the association of non-arteritic anterior ischemic optic neuropathy and lipoprotein

cardiometabolic factors and NAION. Moreover, the paucity of studies reporting on LDL and HDL cholesterol may account for the fact that no significant associations were noted about the aforementioned two components. In addition, despite no language restrictions, only few eligible studies from East Asia were identified, whereas no studies from Latin America, Africa, and Australia/New Zealand were noted. However, to our knowledge, up to the date last searched, this is the first meta-analysis on the associations of NAION with hypertension, hypercholesterolemia/dyslipidemia, serum triglyceride, HDL, LDL cholesterol, and lipoprotein(a), whereas only one meta-analysis on diabetes mellitus [67] had been published.

In conclusion, this systematic review and meta-analysis demonstrate that NAION is significantly associated with cardiometabolic factors, such as hypertension, diabetes mellitus, elevated lipoprotein(a), and dyslipidemia, suggesting that vascular dysfunction may be implicated in the pathogenesis of the disease. Based on our findings, health care providers should pay attention to patients with cardiometabolic factors, being alert of potential visual symptoms indicative of NAION, while they could advise patients to try modifying these risk factors for the prevention of NAION. Prospective studies with large samples are needed to further validate our findings, enhancing the prevention of NAION in vulnerable groups with cardiometabolic risk factors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00417-021-05522-4.

Author contribution I.C., D.K., and T.S. conceived and designed the meta-analysis; I.C., D.K., A.C., and G.M. performed the literature search and collected data; E.P., T.P., and T.S. performed the statistical analysis; I.C. and T.S. drafted the manuscript; I.C., G.T., E.P., T.P., P.T., and T.S. critically revised the manuscript. All authors have read and approved the current version of the manuscript.

Declarations

Ethical approval For this type of study, formal consent is not required.

Conflict of interest The authors declare no competing interests.

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