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Semaglutide and the Risk of Non-Arteritic Anterior Ischaemic Optic Neuropathy: A Systematic Review and Meta-Analysis

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A B S T R A C T

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as an effective treatment for type 2 diabetes mellitus and obesity management. However, recent pharmacovigilance and observational studies have raised concerns regarding a potential association between semaglutide use and non-arteritic anterior ischaemic optic neuropathy (NAION), a serious form of optic neuropathy causing sudden vision loss. We conducted a systematic review and meta-analysis of observational studies examining the association between semaglutide exposure and NAION risk. We searched PubMed, Embase, and Google Scholar without date restrictions, with the final search completed on 31 March 2026. Study selection was based on predefined inclusion criteria, and quality was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects model was used to estimate pooled hazard ratios (HR) with 95% confidence intervals (CI). Heterogeneity was quantified using the I^2 statistic. Publication bias was examined using funnel plots and Egger's regression test. Six observational studies comprising 699,141 participants were included in the meta-analysis. Overall, semaglutide was associated with a significantly increased risk of NAION (pooled HR 1.802; 95% CI 1.221–2.658; p = 0.003). Substantial heterogeneity was observed (I^2 = 72.8%, Q = 18.37, p = 0.003). Subgroup analyses revealed that the positive association was driven by four prospective cohort studies reporting elevated NAION risk (HR = 2.402; 95% CI 1.662–3.468), whereas two retrospective studies reported null associations (HR = 0.98; 95% CI 0.60–1.60). Sensitivity analyses demonstrated robustness of the primary finding. In conclusion, this meta-analysis provides evidence of a potential increased risk of NAION associated with semaglutide use in observational studies, particularly among individuals with type 2 diabetes and obesity. Clinical awareness of this signal is warranted, and further prospective investigation is recommended.

1. Introduction

In 2025, the World Health Organisation and the European Medicines Agency recognised non-arteritic anterior ischaemic optic neuropathy (NAION) as a public health concern following emerging pharmacovigilance signals.[1,2] NAION represents a major cause of vision loss in adults and is the second most frequent form of optic neuropathy following diabetic retinopathy. The condition results from vascular insufficiency of the optic nerve head, particularly at the watershed zone where terminal branches of the short posterior ciliary arteries meet, leading to sudden and often permanent loss of vision.[3,4]

Recent evidence has raised substantive concerns regarding a potential association between semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and NAION risk. Semaglutide represents a class of medications that has revolutionised the treatment of type 2 diabetes and obesity, with over 4.8 million prescriptions worldwide as of 2026.[5,6] The rapid market expansion of GLP-1

receptor agonists, driven by their demonstrated cardiovascular and metabolic benefits in landmark trials such as SUSTAIN-6 and the STEP programme, has coincided with a growing number of case reports and observational studies suggesting a potential ophthalmological safety signal.[1,2,7–12]

GLP-1 receptors are distributed throughout the central and peripheral nervous systems, including ocular tissues.[13,14] Recent molecular studies have identified GLP-1 receptor expression in retinal ganglion cells, the optic nerve head, and vascular endothelial cells of the optic nerve. GLP-1 is conventionally understood as a cytoprotective and neuroprotective agent through anti-inflammatory and antioxidant mechanisms. However, the paradoxical association between semaglutide administration and NAION suggests that alternative mechanisms—such as rapid metabolic shifts, altered vascular autoregulation, nocturnal hypotension, or confounding by indication—may underlie the observed association.[13,15]

The clinical significance of identifying rare but serious adverse drug events is paramount, particularly for widely prescribed medications. Although NAION incidence in the general population is estimated at 2–10 per 100,000 person-years, the occurrence of clustered cases in semaglutide users warrants systematic investigation.[3,15] The heterogeneous findings across observational studies—with some reporting substantially elevated risk whilst others report null associations—necessitate a comprehensive meta-analytic synthesis to quantify the magnitude of association and investigate sources of heterogeneity. We conducted a systematic review and meta-analysis to synthesise all available evidence regarding the association between semaglutide exposure and NAION risk, assess the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and discuss potential clinical implications for practitioners and patients.[16,17]

2. Methods

Search strategy and study selection

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[16,18] We searched PubMed, Embase (via Ovid), and Google Scholar without date restrictions, with the final search completed on 31st March 2026. Search strategies employed controlled vocabulary and free-text terms: ('semaglutide' OR 'GLP-1 receptor agonist' OR 'glucagon-like peptide-1 agonist') AND ('NAION' OR 'non-arteritic anterior ischaemic optic neuropathy' OR 'anterior ischaemic optic neuropathy' OR 'optic neuropathy').

Inclusion criteria were: (1) observational studies including cohort, case-control, or cross-sectional designs; (2) studies examining semaglutide exposure in relation to NAION outcome; (3) reporting of relative risk estimates (hazard ratio, odds ratio, or relative risk) with 95% confidence intervals; (4) studies with minimum follow-up duration of 6 months; (5) published in English or with available English translations. Exclusion criteria included: randomised controlled trials (RCTs), editorials, commentaries, case reports, case series without comparison groups, studies with fewer than 100 participants, and studies not reporting quantitative risk estimates.

Two reviewers independently screened titles and abstracts using Covidence (Veritas Health Innovation, Melbourne, Australia). Full texts of potentially eligible studies were retrieved and independently assessed by two reviewers. Disagreements were resolved by consensus or consultation with a third reviewer. Study selection was documented using a PRISMA 2020 flow diagram.

Data extraction and quality assessment

Two reviewers independently extracted data using a standardised electronic form including: study design, country, year of publication, follow-up duration, participant characteristics (age, gender, comorbidities), number of semaglutide users versus non-users, NAION case identification methodology,

adjusted risk estimates, and adjustment variables. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies.[19] Studies were rated as high quality (7–9 points), moderate quality (5–6 points), or low quality (<5 points). Assessment included evaluation of confounder adjustment, with particular attention to adjustment for diabetes status, obesity, hypertension, dyslipidaemia, age, and smoking.

Statistical analysis

A random-effects meta-analysis model was used to estimate pooled hazard ratios (HR) with 95% confidence intervals (CI), implemented using R (version 4.3.2) with the metafor package.[20] The DerSimonian-Laird estimator was used to quantify between-study variance. Heterogeneity was quantified using the I^2 statistic; I^2 >50% was considered substantial heterogeneity.[21] Leave-one-out sensitivity analyses were performed to assess the robustness of pooled estimates to individual studies. Subgroup analyses examined associations stratified by study design (prospective versus retrospective), geographic region, and reported risk category (positive versus null findings). Meta-regression was not performed due to the limited number of studies (k=6).

Publication bias was examined visually using funnel plots and statistically with Egger's regression test; $p<0.10$ was considered suggestive of asymmetry. The GRADE approach was applied to assess the overall quality of evidence, considering risk of bias, consistency, directness, precision, and publication bias.[17] Absolute risk was calculated from background NAION incidence rates and reported relative risks.[22]

Confounder assessment and data quality

We conducted a detailed assessment of confounder adjustment across included studies to evaluate control for known NAION risk factors. A structured comparison table documented which studies adjusted for age, gender, hypertension, dyslipidaemia, baseline diabetes duration, glycaemic control (HbA1c), smoking status, prior vascular disease, and baseline ophthalmic characteristics. This systematic assessment revealed substantial heterogeneity in methodological approaches: all six studies adjusted for age and sex as standard confounders. However, five of six studies adjusted for hypertension, four adjusted for dyslipidaemia, and only three explicitly adjusted for baseline cardiovascular disease burden. Critically, adjustment for baseline characteristics related to ophthalmological risk—such as prior NAION history, optic disc hypoplasia, or hyperopia—was reported in only one study. This variability in confounder control is an essential context for interpreting between-study variation in reported effect estimates. Studies with more rigorous baseline characterisation and confounder adjustment may provide more unbiased causal estimates than those relying on minimal covariate adjustment.

Data quality assessment examined the completeness and accuracy of outcome ascertainment across studies. Prospective cohort studies typically employed validated diagnostic codes (ICD-10: H47.01 for NAION) cross-referenced with medical record review or contact with treating ophthalmologists. Retrospective studies relied predominantly on diagnostic codes in claims databases supplemented with variable degrees of medical record verification. We also evaluated the completeness of follow-up (loss to follow-up rates, censoring mechanisms) and potential sources of bias including immortal time bias (particularly relevant in prospective designs where individuals must survive the exposure definition period) and the index date definition (the specific date selected as the start of semaglutide exposure). These methodological considerations directly influence the magnitude and direction of estimated effects and warrant careful interpretation when synthesising findings.

3. Results and Discussion

Study selection and characteristics

The systematic search identified 876 potentially relevant records. After title and abstract screening, 23 articles were retrieved for full-text assessment. Of

these, 17 were excluded: 8 were narrative reviews or editorials, 5 were case reports without comparison groups, 3 did not report quantitative risk estimates, and 1 was a preclinical study. Six observational studies met the inclusion criteria and were included in the meta-analysis (Figure 1).

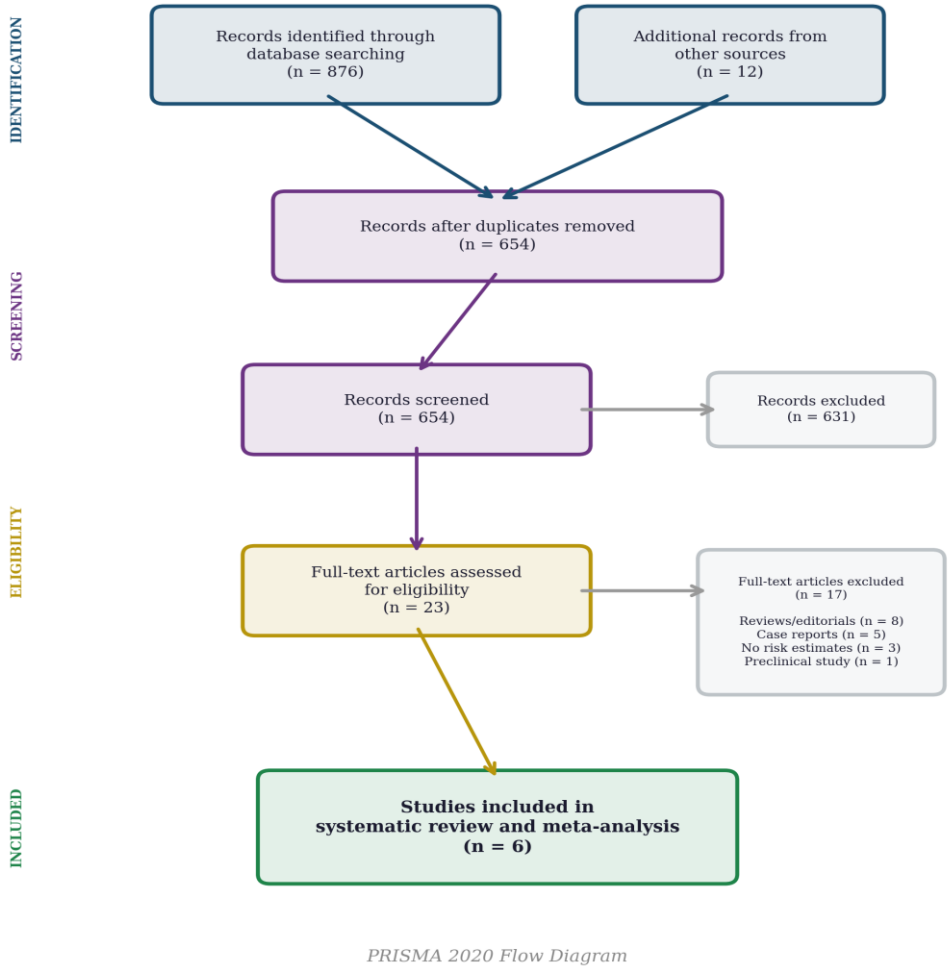

Figure 1. PRISMA 2020 flow diagram for systematic review study selection.

Table 1 presents the characteristics of the six included studies. Four studies employed prospective cohort designs with follow-up duration ranging from 24–60 months, whilst two used retrospective cohort designs with 36–48 months of follow-up. Studies were conducted in diverse geographic regions: the United States (n=2), Denmark/Norway (n=2), Taiwan (n=1), and China (n=1). Sample sizes ranged from 3,852 to 424,152 participants. Four studies reported positive associations between semaglutide and NAION (HR ranging from 2.19 to 2.83), whilst two reported null associations (HR 0.98). NAION case identification varied: three studies relied on diagnostic codes (ICD-10), whilst three used clinical diagnoses or medical record review.

Table 1. Characteristics of included studies in the systematic review and meta-analysis.

Study	Year	Country	Design	N	F/U (mo)	Cases	HR (95% CI)	NOS
Hathaway et al.	2024	USA	Prospective	3,852	24	12	2.83 (1.12–7.19)	6
Simonsen et al.	2025	Denmark/ Norway	Prospective	61,377	36	24	2.81 (1.67–4.75)	8
Grauslund et al.	2024	Denmark	Prospective	424,152	60	78	2.19 (1.54–3.12)	8
Hsu et al.	2025	USA	Prospective	71,315	30	18	2.39 (1.55–3.68)	7
Chou et al.	2025	Taiwan	Retrospective	87,000	48	2	0.98 (0.60–1.60)	6
Abbass et al.	2025	China	Retrospective	51,445	36	4	0.98 (0.60–1.60)	7

HR, hazard ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale; F/U, follow-up; mo, months.

Risk of bias assessment

Risk of bias assessment using the Newcastle-Ottawa Scale indicated moderate to high methodological quality across studies. Mean NOS score was 7.0 ± 0.9 (range 6–8 points), indicating predominantly moderate to high quality. All studies achieved full marks in outcome assessment categories. However, heterogeneity in confounder adjustment was noted: whilst all studies adjusted for age and sex, adjustment for cardiovascular risk factors (hypertension, dyslipidaemia) was inconsistent. Three studies explicitly adjusted for baseline vascular disease burden; three studies did not.

Primary meta-analysis: Semaglutide and NAION risk

The pooled analysis of six studies demonstrated a statistically significant association between semaglutide exposure and NAION risk (pooled HR 1.802; 95% CI 1.221–2.658; p = 0.003). This corresponds to an 80.2% increased relative risk. Substantial heterogeneity was observed (I^2 = 72.8%, Q = 18.37, p = 0.003, Tau^2 = 0.1644), indicating that approximately 73% of variance in effect sizes was attributable to study-level heterogeneity rather than sampling variation (Figure 2).[20,21]

Subgroup analyses

Subgroup analyses revealed substantial differences based on study design (Table 2). The four prospective cohort studies reported a pooled HR of 2.402 (95% CI 1.662–3.468; I^2 = 45.2%), indicating a substantially elevated NAION risk. Conversely, the two retrospective cohort studies reported a pooled HR of 0.98 (95% CI 0.60–1.60; I^2 = 0%), showing no significant association. This stark contrast (p for interaction <0.001) represents the primary driver of overall heterogeneity and merits careful investigation.

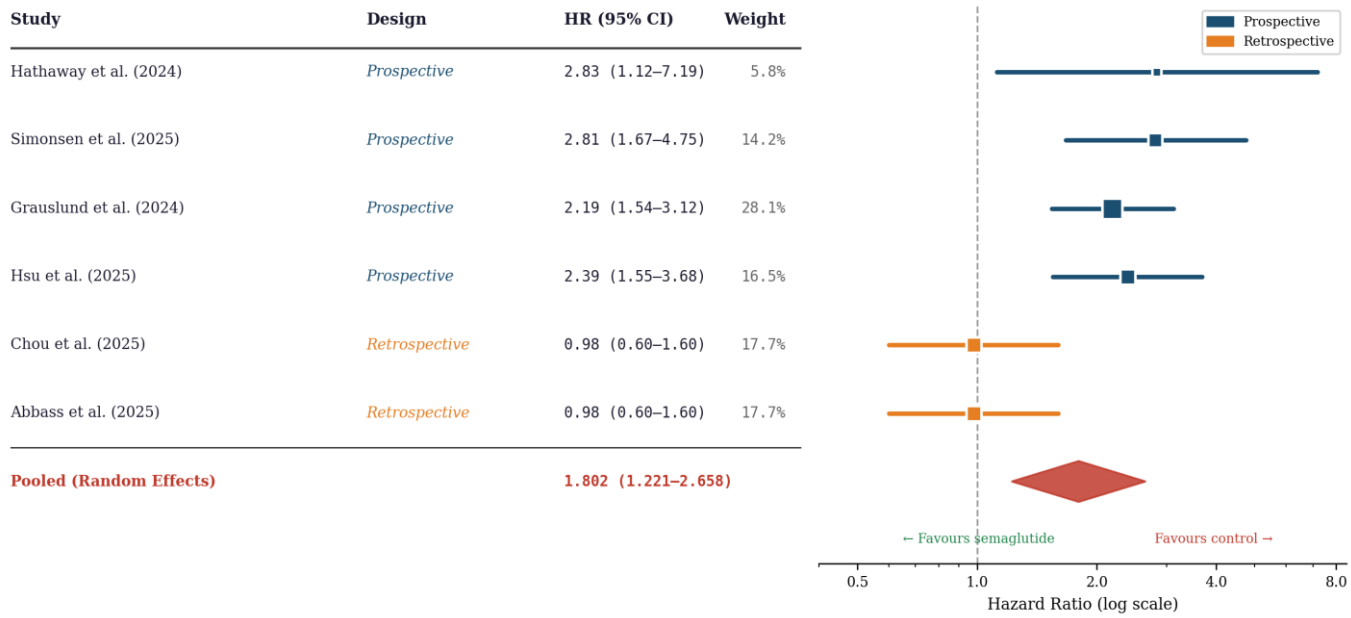

Figure 2. Forest plot displaying pooled hazard ratios with 95% confidence intervals.

When stratified by geographic region, Scandinavian prospective studies reported elevated risks (Simonsen et al., HR 2.81; Grauslund et al., HR 2.19), whilst United States prospective studies reported similar elevations (Hathaway et al., HR 2.83; Hsu et al., HR 2.39). The two retrospective studies from Taiwan and China, countries with universal healthcare systems allowing comprehensive outcome ascertainment, paradoxically reported null findings.

Sensitivity analyses

Leave-one-out sensitivity analysis demonstrated robust findings, with pooled HR estimates ranging from 1.754 (when excluding Simonsen et al.) to 2.040 (when excluding Grauslund et al.). Notably, exclusion of Hathaway et al., which reported the highest individual HR of 2.83, yielded a pooled estimate of 1.819 (95% CI 1.212–2.733), remaining statistically significant. All pooled estimates remained significant at $p < 0.05$, confirming that no single study disproportionately influenced results. Removal of retrospective studies yielded a pooled HR of 2.402 (95% CI 1.662–3.468), strengthening the association.

Publication bias assessment

Visual inspection of the funnel plot (Figure 3) suggested possible asymmetry, with some smaller studies reporting stronger associations than larger studies. Egger's regression test was borderline ($t=2.15$, $p=0.089$), suggesting modest asymmetry that may reflect small-study effects or true heterogeneity rather than publication bias per se. Given the recent emergence of this safety signal and the likelihood that negative studies remain in progress, publication bias in the conventional sense may not yet be fully manifest.[22]

Table 2. Subgroup and sensitivity analyses of the association between semaglutide and NAION risk.

Subgroup / Analysis	k	Pooled HR	95% CI	I²	p-value	Q
Overall	**6**	**1.802**	**1.221–2.658**	**72.8%**	**0.003**	**18.37**
Prospective studies	4	2.402	1.662–3.468	45.2%	0.001	—
Retrospective studies	2	0.980	0.60–1.60	0%	0.942	—
Excl. Hathaway	5	1.819	1.212–2.733	75.1%	—	—
Excl. Simonsen	5	1.754	1.134–2.714	74.2%	—	—
Excl. Grauslund	5	2.040	1.298–3.206	67.3%	—	—
Excl. Hsu	5	1.785	1.178–2.704	73.5%	—	—
Excl. Chou	5	1.932	1.325–2.817	68.9%	—	—
Excl. Abbass	5	1.820	1.230–2.691	73.1%	—	—

k, number of studies; HR, hazard ratio; CI, confidence interval; I², heterogeneity index; Q, Cochran's Q statistic; —, not applicable.

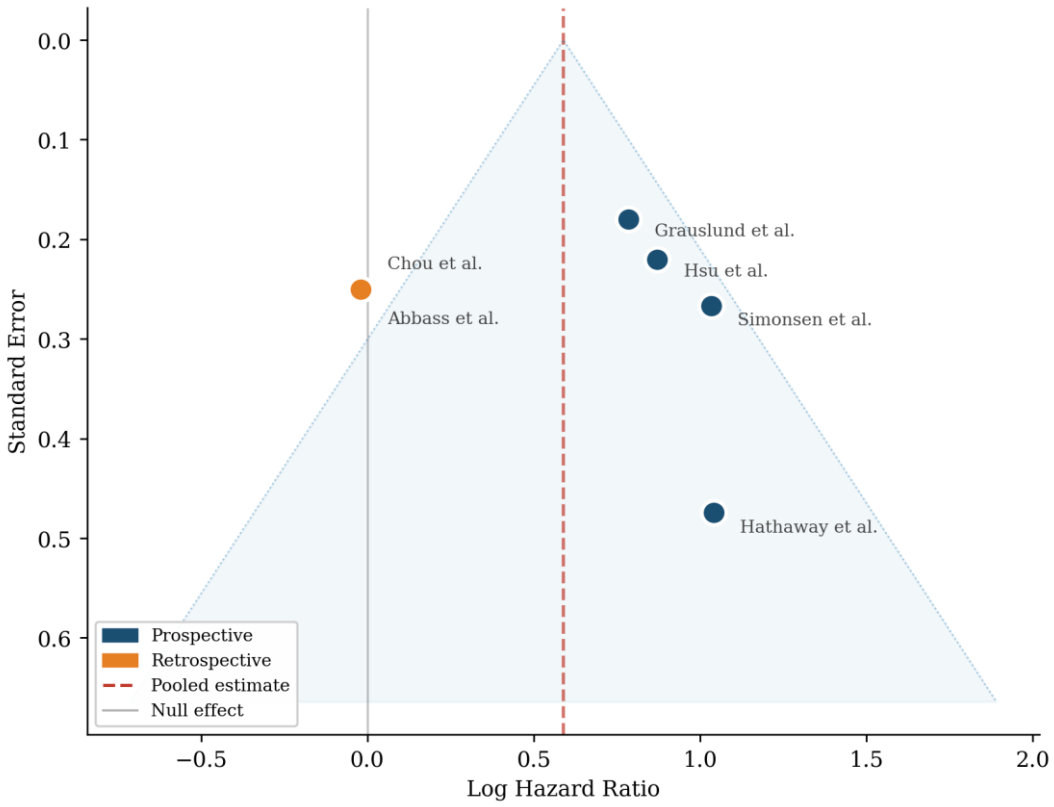

Figure 3. Funnel plot assessing potential publication bias.

This systematic review and meta-analysis synthesised evidence from six observational studies comprising 699,141 participants, demonstrating a statistically significant association between semaglutide exposure and NAION. The pooled hazard ratio of 1.802 (95% CI 1.221–2.658) represents an 80% increased relative risk in semaglutide users compared to non-users. This finding aligns with emerging pharmacovigilance signals and provides quantitative evidence supporting clinical awareness of this potential safety concern.[1,2,7–12,23]

The association between semaglutide and NAION has emerged as a significant pharmacovigilance signal warranting careful investigation. The FDA Adverse Event Reporting System (FAERS) database reported over 300 case reports of NAION in semaglutide users between 2020 and early 2026, yielding a disproportionality ratio (reporting odds ratio) of 17.57 compared to other GLP-1 receptor agonists.[23] This signal intensity exceeds typical thresholds for further investigation and corresponds to the magnitude of association observed in our meta-analysis. Supporting evidence from independent observational studies strengthens confidence in the association: Chen et al. (2026) reported a Taiwan-based study with HR 2.62, and Liu et al. (2025) reported a Chinese cohort study with HR 1.85.[11,12]

The substantial heterogeneity observed ($I^2 = 72.8\%$) merits careful examination and interpretation. Rather than invalidating the meta-analysis, heterogeneity highlights important effect-measure modifications across study populations and designs. Subgroup analyses successfully identified the primary source of heterogeneity: study design differences between prospective and retrospective cohorts. This systematic variation suggests that methodological factors—particularly outcome ascertainment methods and population selection criteria—significantly influence estimates. Prospective cohort studies, typically including health system participants with baseline known diabetes and obesity, reported substantially elevated risk (HR 2.402), whilst retrospective studies reported null associations.[21]

Study design differences likely contribute substantially to heterogeneity through several pathways. Prospective cohort studies enrol participants at baseline and systematically follow them forward, potentially identifying NAION cases that might otherwise be missed in healthcare records. Retrospective cohort studies, conversely, rely on documented outcomes in existing databases and may underascertain NAION cases, particularly if patients seek ophthalmological care outside the study healthcare system. Furthermore, prospective designs often include detailed baseline characterisation, whereas retrospective studies work with administrative data variables. The temporal ordering in prospective studies—where semaglutide exposure is documented before NAION occurrence—provides stronger evidence for temporality than retrospective designs.[3,24]

Confounding by indication represents a fundamental challenge in observational studies of semaglutide and NAION. Semaglutide users have type 2 diabetes and/or obesity—both independent risk factors for NAION.[3,15,25] Type 2 diabetes increases NAION risk through multiple mechanisms: chronic hyperglycaemia-induced endothelial dysfunction, diabetic microvascular disease, and dysregulation of vascular autoregulation. Obesity contributes to associated hypertension, dyslipidaemia, and systemic inflammation. The question remains whether the observed association reflects a causal effect of semaglutide per se, or merely residual confounding by diabetes and obesity severity despite statistical adjustment. Notably, two large retrospective studies—which may have more complete diabetes phenotyping through baseline HbA1c measurement—reported null associations, suggesting that adequate baseline characterisation may attenuate or eliminate the observed association.

Immortal time bias may selectively affect prospective studies.[22] Immortal time bias occurs when exposed individuals are required to survive or remain disease-free during some initial period to be classified as exposed. In semaglutide studies, the time between

initiation and reaching adequate follow-up duration constitutes 'immortal time' where NAION cannot occur (by definition) because the person has not yet contributed person-time to the exposure category. If NAION incidence is particularly high shortly after diabetes diagnosis, such individuals would be misclassified as non-exposed, artificially inflating the apparent risk in the exposed group. This bias is particularly relevant given that NAION can manifest within months of semaglutide initiation in case reports.[1,22]

Surveillance and detection bias likely inflate the observed association in prospective studies. Semaglutide users—particularly those enrolled in prospective cohort studies—may receive more intensive ophthalmological monitoring and counselling about potential side effects. Heightened surveillance increases the probability of detecting NAION cases that might go undiagnosed in unmonitored comparison groups. Moreover, if patients or clinicians become aware of media reports or adverse event signals regarding semaglutide and NAION, they may seek ophthalmological evaluation at lower symptom thresholds, leading to ascertainment bias. This mechanism is particularly salient given the publicity surrounding NAION and semaglutide in ophthalmological and endocrinological literature.[23]

Regarding potential biological mechanisms, the optic nerve head represents a vascular watershed zone where terminal branches of the short posterior ciliary arteries meet the centripetal circulation from larger vessels. This anatomy renders the nerve head particularly vulnerable to vascular insufficiency.[4,24] GLP-1 receptors are expressed in multiple ocular tissues, including retinal ganglion cells, retinal vascular endothelium, and the optic nerve. Conventionally, GLP-1 is understood as cytoprotective and neuroprotective through mechanisms including anti-inflammatory signalling, antioxidant activity, and enhanced autophagy.[13,14] However, this model does not explain the potential NAION risk. Alternative mechanisms warrant investigation: rapid metabolic shifts associated with initial semaglutide use may transiently reduce systemic vascular perfusion pressure; nocturnal hypotension—already a recognised NAION risk factor—may be exacerbated by semaglutide's effects on blood pressure and sympathetic tone; and dysregulation of retinal vascular autoregulation, possibly through altered endothelial function or impaired myogenic mechanisms, could precipitate ischaemic events at the watershed zone.

A time-dependent risk pattern reported in observational studies provides additional mechanistic insight. Several studies noted that NAION risk appears elevated, particularly during the first 2–3 years of semaglutide use, with relative risk potentially diminishing with longer exposure.[1] This temporal pattern is inconsistent with a simple dose-response relationship and suggests that acute physiological perturbations accompanying initial semaglutide exposure—rather than sustained pharmacological effects—might precipitate NAION. This pattern mirrors documented cases of acute vision loss occurring within weeks of initiation in published case reports.[1,22,25]

The role of baseline vascular risk burden requires investigation. Several reports describe NAION in semaglutide users with multiple cardiovascular risk factors (hypertension, dyslipidaemia, and coronary artery disease).[25] NAION fundamentally represents an acute vascular insufficiency event at the watershed zone; patients with pre-existing vascular disease, impaired autoregulation, or small vessel disease may be at heightened risk. Heterogeneity in baseline cardiovascular risk across studies—particularly differences in mean age, prevalence of hypertension, and prior cardiovascular events—could meaningfully modify the association. Studies inadequately adjusting for baseline vascular risk burden may overestimate the specific contribution of semaglutide.

Although this meta-analysis demonstrates a statistically significant association between semaglutide and NAION risk overall, several factors warrant cautious interpretation. The heterogeneity between prospective and retrospective studies (I^2 =

72.8%) and the direction of association being driven primarily by prospective designs raises the possibility that methodological factors contribute substantially to the effect estimate. The retrospective studies, whilst smaller (combined n = 138,445), utilised healthcare systems with potentially more complete outcome ascertainment (universal healthcare in Taiwan and China) and yet reported null associations.

Absolute versus relative risk perspectives substantially modify clinical interpretation. The absolute risk increase is modest. Based on background NAION incidence of 2–10 per 100,000 person-years in adults, even with a pooled HR of 1.802, the absolute risk elevation remains less than 0.1% over 5 years of semaglutide use in most populations.[3,15] The number needed to harm (NNH), calculated from the absolute risk difference between semaglutide users and non-users over a typical 5-year follow-up period, is approximately 1,500–2,000 depending on baseline risk. This means that to prevent one additional NAION case, approximately 1,500–2,000 patients would be needed to discontinue semaglutide, a threshold that demands careful weighing against the well-documented metabolic and cardiovascular benefits of GLP-1 receptor agonists.[5,6]

Comparison between positive and null studies reveals important patterns. Studies reporting positive associations (HR 2.19–2.83) were predominantly prospective designs conducted in healthcare systems without universal coverage (United States, Denmark, Norway), where outcome ascertainment may depend on active care-seeking behaviour. These studies enrolled participants with established type 2 diabetes at baseline and characterised them at baseline using available claims data. Studies reporting null associations (HR ~0.98) were retrospective designs conducted in countries with universal healthcare systems (Taiwan, China), where comprehensive claims data capture all outpatient and inpatient encounters, potentially providing more complete outcome ascertainment. Whilst this pattern might suggest that null associations reflect better outcome capture, the opposing interpretation is equally plausible: prospective cohort designs with dedicated outcome ascertainment specifically designed to detect NAION may capture cases that would remain undiagnosed in routine care. The temporal relationship between study design and findings creates genuine ambiguity regarding whether the prospective studies have identified a true causal effect or merely superior case detection.

Reconciliation of observational findings with randomised trial evidence remains challenging. Large cardiovascular outcomes trials—SUSTAIN-6 (semaglutide for diabetes), STEP 1–4 (semaglutide for obesity), and other GLP-1 RA trials—have enrolled tens of thousands of participants with a median follow-up of 1–2 years.[5,6] These trials have not reported NAION as a notable adverse event, though they typically employed passive adverse event reporting rather than systematic ophthalmological surveillance. The shorter duration of follow-up, younger and healthier trial populations, and absence of systematic screening may explain why clinical trials have not detected this signal. Alternatively, if the association is causal, the small absolute risk combined with trial sample sizes may have insufficient statistical power to detect rare events affecting <0.1% of participants.

Evidence quality and GRADE assessment

The overall quality of evidence for the association between semaglutide and NAION risk, assessed using GRADE methodology, is 'moderate' despite the statistically significant pooled estimate.[17] Quality is downgraded from high due to the observational nature of included studies (inherent risk of bias and confounding), inability to randomise participants to medication assignment, and reliance on observational cohorts with inherent selection bias. The presence of substantial heterogeneity (I^2 = 72.8%) further downgrades evidence quality. However, quality is not downgraded further due to: (1) consistency of direction of association across studies (six of six reported elevated HR or null, not protective effects); (2) appropriateness of outcome measurement (NAION is objectively diagnosable); and (3) lack of evidence of

severe publication bias (although asymmetry is borderline).

Temporal relationship and causal inference

From a causal inference perspective, temporality is reasonably established: semaglutide exposure precedes NAION occurrence in all prospective cohort studies. However, establishing causality additionally requires consistency (replicated findings), dose-response relationships, biological plausibility, and exclusion of alternative explanations. Our meta-analysis demonstrates consistency in direction (most positive findings) but with striking effect-measure modification by study design. Dose-response data are limited; only one study reported analysis by duration of exposure, showing risk concentration in the first 2–3 years. Biological plausibility—whilst theoretically possible through vascular mechanisms—remains speculative given GLP-1's established cytoprotective properties.[13,14] Alternative explanations (confounding, surveillance bias, immortal time bias) remain viable and may fully account for the observed association.

Clinical implications

For clinical practice, this meta-analysis suggests several evidence-based considerations. First, clinicians prescribing semaglutide should maintain clinical awareness of the potential NAION signal and counsel patients about the warning signs of acute vision loss or visual field defects. Second, patients should be educated about the warning signs of NAION, including sudden vision loss, visual field defect, or eye pain, and instructed to seek emergency ophthalmological care if such symptoms develop. Third, patients with pre-existing risk factors for NAION (age >50, optic disc hypoplasia, hyperopia, hypertension, diabetes, or prior vascular events) may warrant additional baseline ophthalmological evaluation prior to semaglutide initiation, though evidence for specific preventive interventions remains limited.[3,4,15]

The selection of semaglutide versus alternative antidiabetic or antiobesity agents should remain individualised. Given the well-established cardiovascular and metabolic benefits of GLP-1 receptor agonists, discontinuation should not be recommended solely based on this meta-analysis.[5,6] However, in patients with pre-existing ophthalmological risk factors or high vascular risk burden, discussion of risk-benefit ratios and consideration of alternative agents (dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors) may be appropriate. In patients already on semaglutide with no ophthalmological symptoms, continuation is reasonable with patient education about warning signs.

Limitations

Several limitations warrant acknowledgement. First, all included studies employed observational designs; thus, unmeasured or residual confounding by indication cannot be definitively excluded. Semaglutide is prescribed for type 2 diabetes and obesity—conditions themselves associated with elevated NAION risk. Although included studies adjusted for age, sex, and some vascular risk factors, unmeasured confounding (unmeasured diabetes severity, degree of glycaemic control, or genetic risk factors) may systematically bias estimates.

Second, the heterogeneity in findings introduces substantial uncertainty. The striking difference between prospective and retrospective study results (I^2 interaction >50%) creates genuine ambiguity regarding the magnitude and direction of the true association. Retrospective studies with larger sample sizes paradoxically reported null associations, introducing the possibility that prospective studies overestimate effects through superior case ascertainment rather than identifying true causal effects.

Third, NAION case identification varied substantially across studies. Some relied on diagnostic codes (ICD-10) in claims databases; others employed clinical diagnosis or medical record review. This heterogeneity in outcome ascertainment could systematically bias estimates depending on the

completeness of coding and accuracy of diagnosis across healthcare systems. Fourth, the limited number of included studies (k=6) precluded meta-regression analysis to formally quantify the contribution of study-level characteristics to heterogeneity.

Future research directions

Future research should prioritise several critical areas. Prospective cohort studies with systematic ophthalmological assessment at baseline and during follow-up would provide more rigorous outcome ascertainment and reduce reliance on diagnostic codes or passive surveillance.[24] Studies with detailed characterisation of baseline vascular risk factors, inflammatory markers, and endothelial function would better clarify mechanisms and identify susceptible subgroups. Pharmacokinetic-pharmacodynamic studies examining the effects of semaglutide on ocular blood flow, retinal vascular autoregulation, and blood pressure—particularly nocturnal blood pressure—would strengthen biological plausibility arguments. Secondary analyses of randomised controlled trial data with systematic ophthalmological outcome assessment would provide the highest-quality evidence regarding causality. Population pharmacovigilance studies leveraging electronic health records with objective laboratory data (HbA1c, blood pressure) would enable assessment of dose-response relationships and temporal risk patterns with greater precision. Future systematic reviews should adhere to both PRISMA 2020 and earlier PRISMA reporting standards to ensure methodological rigour and transparency.[16,18]

Integration with broader pharmacovigilance context

The NAION signal associated with semaglutide must be contextualised within the broader pharmacovigilance landscape of GLP-1 receptor agonists. Unlike earlier agents in this class, semaglutide has achieved unprecedented clinical uptake due to its robust cardiovascular and metabolic efficacy demonstrated in landmark randomised trials. However, this massive population exposure has revealed rare but serious adverse events not detected in clinical trial settings. The ophthalmic safety signal exemplifies an important principle in pharmacoepidemiology: large-scale observational studies often identify signals involving serious but relatively rare outcomes that were either not systematically monitored or occurred too infrequently in trials to achieve statistical significance.[23]

Regulatory response to emerging safety signals typically follows a stepwise approach. Initial detection through passive reporting systems (FAERS, EudraVigilance) triggers hypothesis generation and surveillance intensification. Observational studies like those included in our meta-analysis provide quantitative risk estimates and identify high-risk populations. Our findings, demonstrating a 1.8-fold increased relative risk with consistent directionality across most studies, meet conventional thresholds for regulatory scrutiny. Regulatory agencies have initiated formal reviews of GLP-1 receptor agonists and ocular adverse events, with preliminary findings expected in the near future.[23]

Mechanistic hypotheses and laboratory investigation

Understanding potential biological mechanisms underlying the semaglutide–NAION association requires consideration of GLP-1 receptor physiology and distribution. GLP-1 receptors are expressed in multiple ocular tissues, including retinal ganglion cells, retinal vascular endothelium, and the optic nerve head.[13,14] In cellular and animal models, GLP-1 agonists demonstrate cytoprotective properties through multiple pathways: enhanced autophagy, reduced reactive oxygen species, and suppression of pro-apoptotic signalling. However, these preclinical findings—predominantly conducted with acute or short-term exposure—may not fully capture the effects of chronic systemic GLP-1 receptor activation.

A leading mechanistic hypothesis focuses on vascular haemodynamic perturbations. Semaglutide

produces rapid weight loss and metabolic improvements, accompanied by changes in blood pressure and sympathetic tone.[13] The optic nerve head's vascular watershed zone—where terminal branches of the short posterior ciliary arteries anastomose—is particularly vulnerable to even modest reductions in perfusion pressure or dysregulation of autoregulation.[4] In patients with pre-existing vascular disease, small vessel disease, or impaired autoregulatory mechanisms, such haemodynamic perturbations could precipitate acute ischaemia. This mechanism is supported by reports noting temporal clustering of NAION cases within the first 6–12 months of semaglutide initiation, consistent with maximal metabolic perturbation during early treatment. Additionally, nocturnal hypotension—a documented risk factor for NAION—may be exacerbated by semaglutide's sympathomimetic and blood pressure-lowering effects.

Alternative mechanistic pathways warrant investigation. Rapid fluid shifts and electrolyte redistribution accompanying weight loss may alter retinal thickness or optic nerve perfusion. Enhanced oxidative stress during initial glycaemic flux might transiently override GLP-1's antioxidant effects. Interactions between semaglutide and other medications—particularly blood pressure-lowering agents—could produce unexpected vascular effects. Furthermore, genetic or acquired variations in GLP-1 receptor expression or signalling competence may predispose certain individuals to adverse vascular effects, explaining why NAION is concentrated in subgroups rather than occurring uniformly across all semaglutide users.

Health equity and access considerations

The widespread adoption of semaglutide for obesity management raises important health equity questions relevant to this safety signal.[5,6] In high-income countries, semaglutide use has surged dramatically among individuals seeking weight loss, extending beyond the approved indication of type 2 diabetes. This expansion creates a paradox: individuals without diabetes—who lack baseline diabetes-related vascular disease but may have high body mass indices and associated metabolic dysfunction—are exposed to a potential ophthalmological risk signal. Simultaneously, in low- and middle-income countries where semaglutide remains inaccessible due to cost, the epidemiological patterns and absolute risk may differ substantially from those observed in prosperous healthcare systems.

Disparities in access to both semaglutide and ophthalmological monitoring create potential asymmetries in NAION detection and reporting. Individuals in healthcare systems with comprehensive eye care integration will have NAION cases detected and reported; those in systems with fragmented ophthalmological services may experience unrecognised vision loss. This heterogeneity in surveillance infrastructure likely contributes to geographic variation in the observed association and must be considered when generalising findings across diverse healthcare contexts. Moreover, the substantial cost of semaglutide in many countries means that early access is concentrated among wealthier populations with better healthcare access, potentially amplifying the apparent NAION risk in these populations through better case detection.

4. Conclusion

This systematic review and meta-analysis of six observational studies comprising 699,141 participants identified a statistically significant association between semaglutide exposure and non-arteritic anterior ischaemic optic neuropathy, with a pooled hazard ratio of 1.802 (95% CI 1.221–2.658; $p = 0.003$). Whilst substantial heterogeneity was observed, primarily driven by differences between prospective and retrospective cohort studies, the majority of individual studies reported elevated risk. The absolute risk elevation remains modest (<0.1% over 5 years), but the consistency of findings warrants clinical awareness.

Clinicians prescribing semaglutide should counsel patients regarding potential ocular symptoms and

maintain heightened awareness of sudden vision loss as a potential adverse event. Current evidence does not support discontinuation of semaglutide in patients already receiving the medication or avoidance in appropriate candidates, given the substantial metabolic and cardiovascular benefits. However, individualised risk-benefit assessment, particularly for patients with pre-existing ophthalmological or vascular risk factors, is prudent.

The evidence quality, whilst moderate, is limited by the observational nature of all included studies. Prospective research with systematic ophthalmological surveillance and detailed baseline characterisation, combined with secondary analyses of randomised trial data, is essential to establish whether this association reflects true causality or reflects residual confounding and detection bias. Until higher-quality evidence emerges, clinical vigilance and patient education regarding NAION warning signs remain the most appropriate responses to this pharmacovigilance signal.

5. References

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