

# Glucagon-like Peptide-1 Receptor Agonists and Risk of Nonarteritic Anterior Ischemic Optic Neuropathy

## Systematic Review and Meta-Analysis

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## Abstract

### Background and Objectives

Recent observational studies have reported conflicting evidence regarding an association between glucagon-like peptide-1 receptor agonists (GLP-1RAs), particularly semaglutide, and nonarteritic anterior ischemic optic neuropathy (NAION). We aimed to synthesize the pooled evidence assessing the association between GLP-1RA use and NAION risk.

### Methods

Embase, Medline, and Cochrane CENTRAL databases were searched from inception to April 5, 2025. Observational studies and randomized controlled trials comparing NAION risk in GLP-1RA users with non-GLP-1RA users were included. Title/abstract and full-text screening were conducted in duplicate by 2 independent reviewers. Discrepancies were resolved through discussion or adjudication by a third reviewer. Risk of bias was assessed using the Risk of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool, and the certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation framework. Pooled relative risks (RRs) were estimated using Bayesian random-effects models, incorporating half-normal, between-study, and weakly informative priors. The RR with 95% credible interval (CrI) was computed to analyze the development of NAION associated with GLP-1RA exposure.

### Results

Five studies were included in the primary analysis, encompassing 1,593,554 patients (682,456 semaglutide users and 911,098 non-GLP-1RA users). Semaglutide use was associated with a high probability of increased risk of NAION compared with non-GLP-1RA use (RR: 2.52, 95% CrI [1.56, 4.72],  $I^2$ : 57.8%,  $P(\text{RR} > 1)$ : 99.9%). This association was particularly pronounced among patients with diabetes (RR: 2.41, 95% CrI [1.57, 4.10],  $I^2$ : 47.2%,  $P(\text{RR} > 1)$ : 99.9%). The overall incidence of NAION across 5 studies and 7 comparisons, encompassing 1,460,760 patients (semaglutide: 1,108,542; dulaglutide: 326,282; and exenatide: 25,936) and 272 NAION events (semaglutide: 198; dulaglutide: 54; and exenatide: 20) was 85 cases per 100,000 GLP-1RA users (95% CrI [29, 263],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%). The incidence of NAION across 1,108,542 semaglutide users was 118 cases per 100,000 (95% CrI [32, 451],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%). Leave-one-out sensitivity analyses consistently supported these findings.

### Discussion

Low-to-moderate certainty evidence indicates that semaglutide significantly increases risk of NAION relative to non-GLP-1RAs, particularly among patients with diabetes. These findings warrant further investigation and should inform clinical risk-benefit discussions.

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## Glossary

**CrI** = credible interval; **GLP-1RAs** = glucagon-like peptide-1 receptor agonists; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HR** = hazard ratio; **NAION** = nonarteritic anterior ischemic optic neuropathy; **ROB** = risk of bias; **RR** = relative risk; **T2DM** = type 2 diabetes mellitus.

## Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) is the leading cause of acute optic neuropathy in those older than 50 years, with an annual incidence of 2.3–10.2 per 100,000 individuals in the United States.<sup>1,2</sup> NAION is characterized by acute, painless, and typically unilateral vision loss alongside hyperemic optic disc edema and a relative afferent pupillary defect.<sup>2</sup> NAION often leads to severe visual morbidity and permanent vision loss.<sup>3</sup>

Risk factors for NAION include hypertension, type 2 diabetes mellitus (T2DM), obstructive sleep apnea, and small optic cup-to-disc ratio.<sup>1</sup> Contemporary investigations implicated glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as semaglutide, dulaglutide, exenatide, and tirzepatide as risk factors for NAION.<sup>4–11</sup> GLP-1RAs, widely used for T2DM and obesity, are a class of medications that mimic the physiologic effects of GLP-1 hormone, delaying gastric emptying, reducing appetite, and food intake.<sup>7,12–14</sup>

Seven observational studies have been performed examining the association between GLP-1RAs and NAION.<sup>5–11</sup> Some studies report a harmful association,<sup>8–11</sup> whereas others suggest a protective<sup>5</sup> or no association.<sup>6,7</sup> This systematic review and meta-analysis aimed to consolidate available evidence and quantify whether there is an association between GLP-1RA exposure and NAION development.

## Methods

This study was prospectively registered on PROSPERO (CRD420251032448). Institutional ethics approval was waived because this work relied on published primary research. We abided by the tenets of the Declaration of Helsinki.

### Search Strategy and Study Selection

A systematic, librarian-informed search was completed for Embase, Medline, and Cochrane Library databases from inception to April 5, 2025 (eTable 1). All observational studies and randomized controlled trials with more than 500 patients that investigated NAION risk with GLP-1RA use were included. Reference lists of relevant articles were manually reviewed. Gray literature and non-English studies were excluded. Studies were uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia) for title and abstract screening (by T.D. and I.B.), full-text screening (T.D., I.B., and F.B.), and data extraction (T.D. and L.A.) by paired independent reviewers.

To account for the presence of nonmutually exclusive comparisons within individual studies, we applied a protocol to avoid double counting of patient data. In cases of multiple GLP-1RA exposure cohorts (i.e., comparisons to different control groups or across cohort populations) or overlapping data sources (i.e., TriNetX or Danish Registries), we included only the comparison or study with the largest sample size in the analysis. Studies were also included for analysis if they provided mutually exclusive comparisons with the other larger studies included. For subgroup analysis, the cohort selected from each included study was based on the sample that best represented the subgroup population rather than the one with largest sample size.

### Data Collection and Risk of Bias Assessment

From each article, we collected information regarding study characteristics (i.e., region, journal, year, study design, and financial support), patient characteristics (i.e., cohort demographics, indication, comorbidities, dose, and duration), exposure (GLP-1RA and control), and outcomes (i.e., NAION incidence, HRs, RRs, and follow-up time). Risk of bias (ROB) assessment was completed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to evaluate the quality of evidence of included studies. Data extraction, ROB, and GRADE assessments were completed in duplicate by 2 independent reviewers (T.D., F.B., L.A., or D.M.). Conflicts at any stage were resolved through discussion and arbitration by a third study author (B.T.) if necessary.

### Data Synthesis and Statistical Analysis

The primary outcome measure was the comparative risk ratio (RR) with 95% credible interval (CrI) for the development of NAION associated with GLP-1RA exposure. As NAION is a rare event with an overall incidence of 0.54 per 100,000, RR was approximated using the hazard ratio (HR) in cases where RRs were not reported.<sup>2,15</sup> This assumption is valid only under rare disease conditions, in which the outcome of interest remains infrequent at the end of follow-up, as is the case with NAION.<sup>15,16</sup>

All statistical analysis were conducted using R (Version 4.4.3), with the bayesmeta, and brms packages for Bayesian meta-analysis. Bayesian meta-analysis was chosen over frequentist methods, owing to the small number of included studies and sparsity of data. For all studies that provided comparative effect size, we performed a Bayesian random-effects meta-analysis using half-normal priors (scale = 0.5) for between-study heterogeneity and weakly informative normal priors

(mean = 0, SD = 4) for overall effect size. Study reported estimates were naturally log-transformed and the corresponding standard errors were derived from the 95% CI interval bounds. Pooled RRs and associated 95% CrIs were derived through back transformation of posterior distributions. The posterior probability, which indicates the likelihood that the true RR exceeded 1, denoted as  $P(RR > 1)$ , was also computed.

For the secondary analysis, we calculated the pooled incidence of NAION, expressed per 100,000 patients, with corresponding 95% CrIs across the included studies. This was performed using a Bayesian random-effects meta-analysis with a normal prior (mean = -4, SD = 2) to model the pooled incidence estimate on the logit scale, and half-normal prior (scale = 0.5) for between-study heterogeneity. The resulting posterior estimates and associated 95% CrIs were transformed back to the original proportion scale. The posterior probability which indicates the likelihood that the incidence proportion was greater than zero,  $P(\text{incidence} > 0)$ , was also computed.

In rare events, between-study heterogeneity and average treatment effect are optimally modeled with weakly informative priors such as the half-normal.<sup>17,18</sup> Weakly informative priors incorporate minimal prior information to ensure broad coverage of all realistic values while excluding implausible values, particularly useful in cases of data sparsity.<sup>18</sup> Half-normal prior distributions are based on the expectation that most studies have low-to-moderate heterogeneity but allow for larger values when supported by data. By contrast, half-Cauchy and half-t priors place greater weight on larger values of between-study variance, accommodating substantial or extreme heterogeneity.<sup>18,19</sup>

To evaluate the robustness of pooled estimates, we conducted sensitivity analyses using alternative prior distributions for between-study heterogeneity, specifically a half-Cauchy distribution (scale = 0.5) and a half-t distribution (degrees of freedom = 3, scale = 0.5). Despite the rarity of NAION, the studies included had large sample sizes, which minimized the influence of alternative priors in pooled incidence estimates; therefore, sensitivity analyses with alternative priors were only performed for comparative estimates which are more susceptible to prior choice. To further validate the robustness of the main comparative estimates, additional sensitivity analyses were performed where (1) all TriNetX studies were included or (2) each TriNetX study was substituted for Hsu et al. included in the main comparative analysis. Leave-one-out analyses were performed for all outcomes derived from 3 or more studies. Subgroup analyses were performed according to GLP-1RA indication (i.e., diabetes and obesity) and comparator group (i.e., SGLT2 inhibitors and other GLP-1RA). Incidence analyses of NAION, both overall and in the diabetic subgroup, were performed for any GLP-1RA and semaglutide alone. To assess potential publication bias and small-study effects, funnel plots were generated, and Bayesian random-effects meta-regression models were applied using Gaussian

or binomial likelihoods with weakly informative priors. Statistical heterogeneity was quantified using the posterior median of the  $I^2$  statistic and interpreted as follows: 0%–25% (low), 25%–50% (moderate), 50%–75% (substantial), and >75% (considerable heterogeneity).<sup>20</sup>

## Standard Protocol Approvals, Registrations, and Patient Consents

This study was exempt from institutional review board approval (under article 2.4 of the Tri-Council Policy Statement) because the data were extracted in its entirety from published primary research. The dissemination of results will not identify any individual or generate new forms of identifiable information.

## Data Availability

Data will be made available for research purposes on reasonable request to corresponding author through email.

## Results

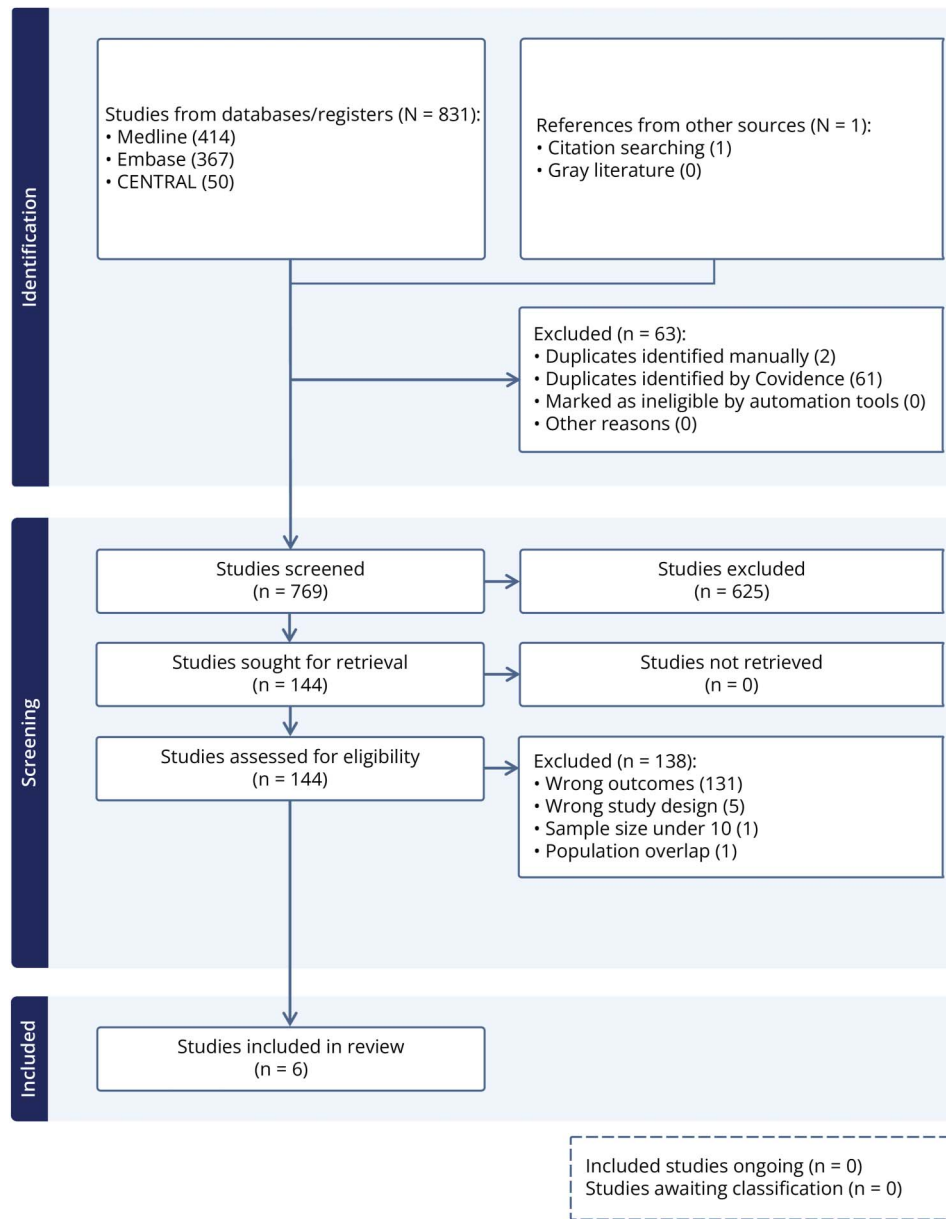
### Search Results and Study Characteristics

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram. From 831 studies, 769 underwent title/abstract screening after deduplication, and 144 underwent full-text screening. Seven observational studies met the inclusion criteria; however 3 used overlapping TriNetX data.<sup>5,7,10</sup> Chou et al.<sup>7</sup> was excluded given its comparatively lower-powered and non-mutually exclusive analyses. Abbas et al. was excluded from overall and diabetes subgroup analysis given its lower powered analyses and overlap in patient population; but included for the obesity subgroup analysis as none of the other TriNetX studies reported comparative or incidence information for an obesity subgroup. Ultimately, 6 retrospective cohort studies were included in the meta-analysis.<sup>5,6,8-11</sup>

The characteristics and covariates adjusted for within each study are summarized in eTable 2. Among included studies, United States (US) was most represented (n = 4, 66.7%),<sup>5,6,9,10</sup> followed by Denmark<sup>8</sup> (n = 1, 16.7%) and Denmark-Norway (n = 1, 16.7%).<sup>11</sup> The latter study involved Danish and Norwegian cohorts, although only the Norwegian cohort was included in the comparative analysis to avoid potential overlap in population.<sup>8,11</sup> Across studies, patients were monitored for a median of 5.0 years (IQR 0.75 years), with follow-up durations ranging from 3 to 5 years. Across all studies, the most powered GLP-1RA cohort with the largest sample size was the semaglutide cohort and therefore used for all comparative analyses to effectively mitigate potential overlap within the control group.

ROBINS-I assessments are presented in eTable 3. All studies had “moderate” ROB, primarily because of concerns related to confounding and outcome reporting.<sup>5,6,8-11</sup> Certainty of evidence was rated as low or moderate, owing to limitations in study design and imprecision. Certainty of evidence was

**Figure 1** PRISMA Flowchart



upgraded for large effect size ( $RR > 2$ ) and maintaining increased risk estimates despite residual confounding from healthy user bias (eTable 4).<sup>8-11</sup>

### Overall Analysis of GLP-1RA Use and NAION Risk

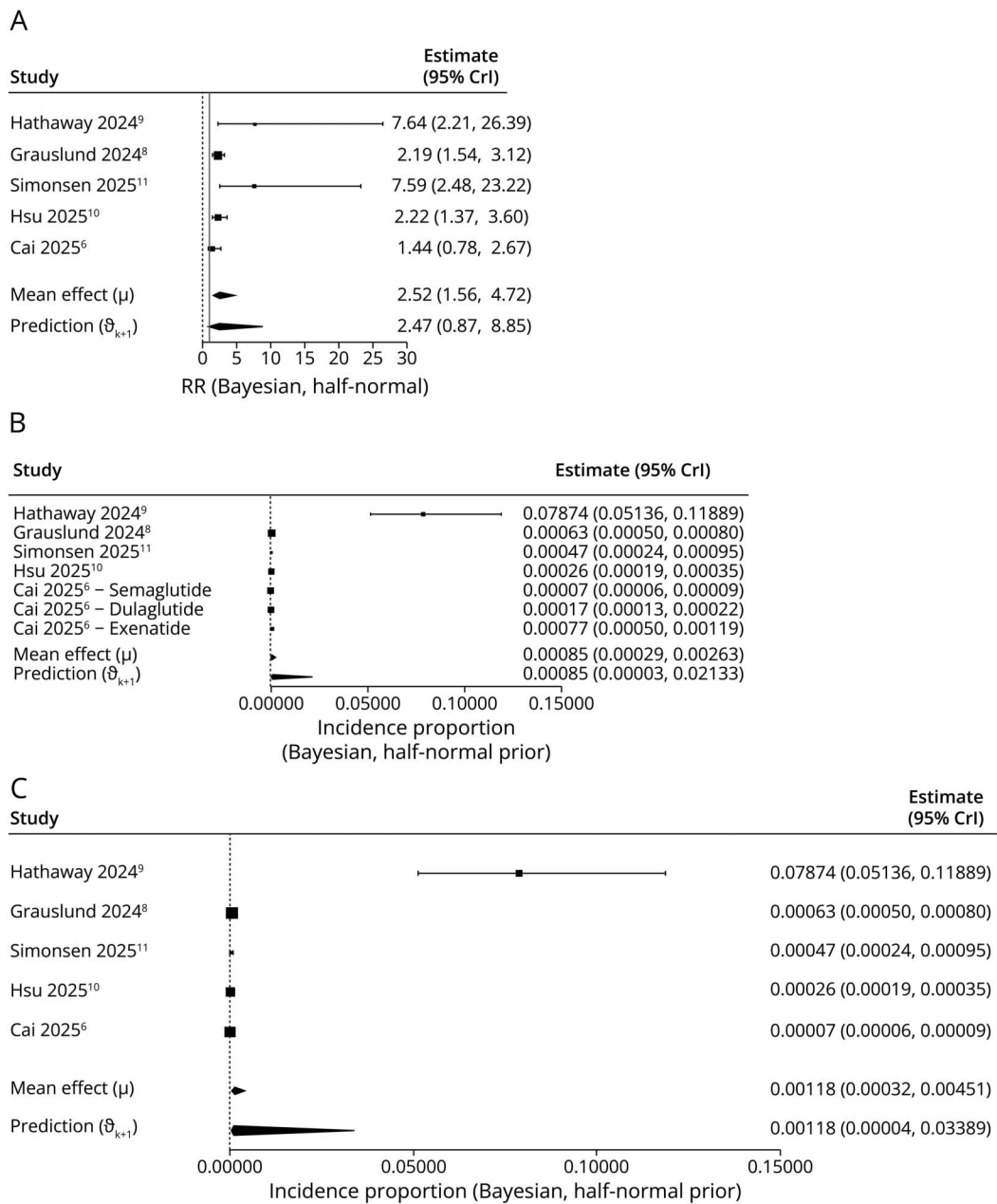
Each study supplied most-adjusted estimates of semaglutide use, involving 1,593,554 patients (682,456 semaglutide users and 911,098 non-GLP-1RA users). Four studies reported 330 NAION cases (140 semaglutide users and 190 non-GLP-1RA users). One study provided effect estimates (95% CIs) without event counts.<sup>6</sup>

Overall, there was strong evidence of elevated NAION risk in semaglutide users compared with non-GLP-1RA users ( $RR$ :

2.52, 95% CrI [1.56, 4.72],  $I^2$ : 57.8%,  $P(RR > 1)$ : 99.9%, Figure 2A). Sensitivity analysis yielded consistent results across half-Cauchy and half-t priors, with each iteration of leave-one-out analyses producing pooled  $RR$ s ranging from 2.24 to 3.05. All lower limits of 95% CrIs remained above null (eTable 5). The funnel plot seemed symmetric, and Bayesian meta-regression showed no evidence of small-study effects (slope: 1.86, 95% CrI [-0.74, 4.30]) or publication bias (eFigure 1).

Proportion of NAION events after any GLP-1RA use was detailed in 5 studies accounting for 7 comparisons, with one study providing 3 distinct proportions for each GLP-1RA (semaglutide, dulaglutide, and exenatide). In total, there were 1,460,760 GLP-1RA users (semaglutide: 1,108,542;

**Figure 2** Forest Plots of GLP-1RA Use and NAION



(A) Main comparative analysis. (B) Main analysis of incidence proportion. (C) Semaglutide subgroup NAION incidence. GLP-1RAs = glucagon-like peptide-1 receptor agonists; NAION = nonarteritic anterior ischemic optic neuropathy.

dulaglutide: 326,282; and exenatide: 25,936) and 272 NAION events (semaglutide: 198; dulaglutide: 54; and exenatide: 20). The pooled incidence was approximately 85 cases per 100,000 patients (95% CrI [29, 263],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%, Figure 2B). Sensitivity analysis yielded consistent results with each iteration of leave-one-out analyses producing pooled incidence proportions ranging from approximately 31 to 109 cases per 100,000 patients, with all lower bounds above null (eTable 6). The funnel plot was visually symmetric, and Bayesian meta-regression showed no evidence of small-study effects (slope: 0.28, 95% CrI [-3.48, 4.13]) or publication bias (eFigure 1).

Proportion of NAION events after semaglutide use was detailed in 5 studies, consisting of 1,108,542 semaglutide users and 198 NAION events. The pooled incidence was approximately 118 cases per 100,000 patients (95% CrI [32, 451],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%, Figure 2C). Sensitivity analysis yielded consistent results with each iteration of leave-one-out analyses producing pooled incidence proportions ranging from approximately 29 to 196 cases per 100,000 patients, with all lower bounds above null (eTable 7). The funnel plot was visually symmetric, and Bayesian meta-regression showed no evidence of small-

study effects (slope: 0.23, 95% CrI [-3.63, 4.14]) or publication bias (eFigure 1).

## Semaglutide Use and NAION Risk in Subgroup of Patients With Diabetes

Each study supplied most-adjusted effect estimates for semaglutide use among the subgroup of patients with diabetes, encompassing a total of 1,593,344 individuals (682,371 semaglutide users and 910,973 non-GLP-1RA users). Four studies reported 330 NAION events (137 semaglutide users and 193 non-GLP-1RA users). One study did not provide diabetic cohort event counts but provided effect estimates with 95% CIs.<sup>6</sup>

Among those with diabetes, there was strong evidence of elevated NAION risk in semaglutide users compared with non-GLP-1RA users (RR: 2.41, 95% CrI [1.57, 4.10],  $I^2$ : 47.2%,  $P(\text{RR} > 1)$ : 99.9%, Figure 3A). Sensitivity analysis yielded consistent results with half-Cauchy and half-t priors, and across each iteration of leave-one-out analyses producing pooled RRs ranging from 2.19 to 2.79. All lower limits of 95% CrIs were above null with consistent effect size magnitudes (eTable 8). The funnel plot seemed symmetric, and Bayesian meta-regression revealed no evidence of small-study effects (slope: 1.54, 95% CrI [-1.03, 3.95]) or publication bias (eFigure 2).

Proportion of NAION events after any GLP-1RA use was detailed in 5 studies accounting for 7 comparisons, with one study providing 3 distinct proportions corresponding to different GLP-1RAs (semaglutide, dulaglutide, and exenatide). In total, there were 1,460,675 GLP-1RA users (semaglutide: 1,108,457; dulaglutide: 326,282; and exenatide: 25,936) and 269 NAION events (semaglutide: 195; dulaglutide: 54; and exenatide: 20). Overall, the pooled incidence was approximately 89 cases per 100,000 patients (95% CrI [29, 280],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%, Figure 3B). The corresponding funnel plot was visually symmetric, and Bayesian meta-regression showed no evidence of small-study effects (slope: 0.38, 95% CrI [-3.50, 4.13]) or publication bias (eFigure 2). The incidence of NAION among semaglutide users with diabetes was detailed in 5 studies, comprising 1,108,457 semaglutide users and 195 NAION events. Overall, the estimated incidence was 125 cases per 100,000 semaglutide users (95% CrI [33, 489],  $I^2$ : 98.8%,  $P(\text{incidence} > 0.00001)$ : 100%, Figure 3C). The corresponding funnel plot was visually symmetric, and Bayesian meta-regression showed no conclusive evidence of small-study effects (slope: 0.17, 95% CrI [-3.92, 4.00]) or publication bias (eFigure 2). All incidence proportion leave-one-out analyses yielded consistent results producing pooled incidence proportions, with all lower bounds above null (eTables 9 and 10).

## Semaglutide-Associated NAION Risk in Obesity and Comparator Subgroups

### Obesity Subgroup

Two studies supplied most-adjusted effect estimates for semaglutide use among the subgroup of patients with obesity,

encompassing a total of 116,613 patients (58,254 semaglutide users and 58,359 non-GLP-1RA users) and 74 NAION events (43 semaglutide users and 31 non-GLP-1RA users).<sup>5,9</sup> Overall, there was moderately elevated risk of NAION in semaglutide users compared with non-GLP-1RA users (RR: 1.77, 95% CrI [0.55, 6.96],  $I^2$ : 66.2%,  $P(\text{RR} > 1)$ : 85.4%, Figure 4A).

The incidence of NAION in semaglutide users with obesity was detailed in 2 studies, comprising 58,254 patients and 43 NAION events.<sup>5,9</sup> Overall, the pooled incidence proportion was 712 cases per 100,000 semaglutide users (95% CrI [126, 4,065],  $I^2$ : 97.4%,  $P(\text{incidence} > 0.00001)$ : 100%, Figure 4B).

## Semaglutide vs Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) and Other GLP-1RAs

Two studies provided estimates comparing semaglutide with SGLT2i use, including a total of 947,995 patients (444,691 semaglutide users and 503,304 SGLT2i users).<sup>6,11</sup> One study reported 64 NAION events (32 semaglutide users and 32 SGLT2i users).<sup>11</sup> One study provided effect estimates with 95% CIs, but did not provide the number of NAION events.<sup>6</sup> Overall, there was moderate evidence of elevated NAION risk in semaglutide users compared with SGLT2i users (RR: 2.07, 95% CrI [0.91, 4.51],  $I^2$ : 57.8%,  $P(\text{RR} > 1)$ : 87.2%, Figure 5A). Two studies reported estimates between semaglutide and other GLP-1RAs, encompassing 865,756 patients (432,878 semaglutide users and 432,878 other GLP-1RA users).<sup>6,10</sup> Overall, there was moderate evidence of increased NAION risk among semaglutide users compared with nonsemaglutide GLP-1RA users (RR: 1.61, 95% CrI [0.63, 3.76],  $I^2$ : 65.0%,  $P(\text{RR} > 1)$ : 88.3%, Figure 5B).

Across all comparative outcomes, sensitivity analyses using half-Cauchy and half-t priors yielded consistent results. Publication bias and leave-one-out analyses could not be performed because of limited studies in each subgroup (eFigures 3-4).

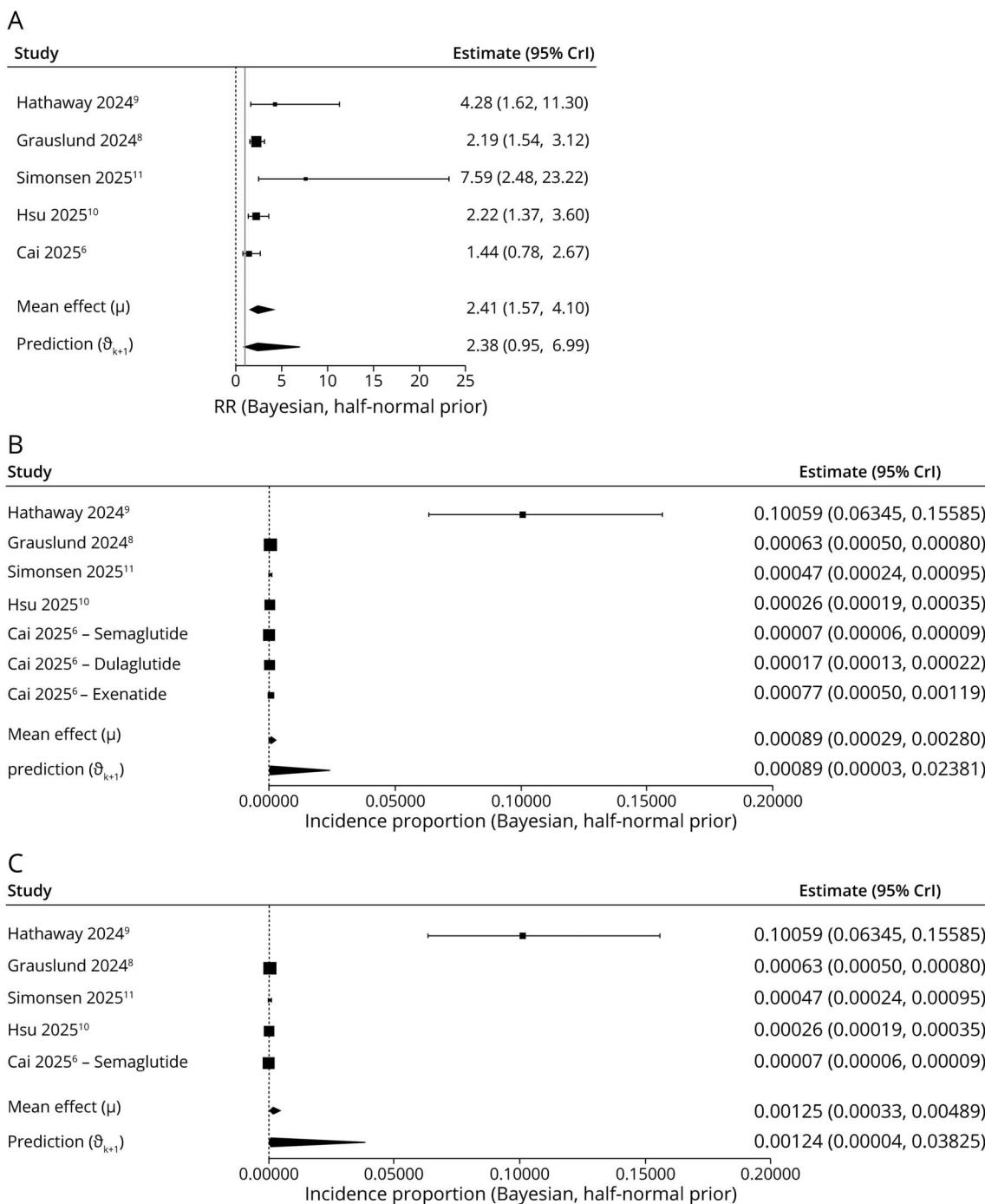
## Sensitivity Analyses With TriNetX Studies

To validate the robustness of our main analysis, multiple sensitivity analyses were conducted including: (1) all TriNetX studies (RR: 1.91, 95% CrI [1.09, 3.56],  $I^2$ : 87.2%,  $P(\text{RR} > 1)$ : 98.9%, eFigure 5A), (2) Abbass et al. 2025 in place of Hsu et al. 2025 (RR: 2.13, 95% CrI [1.01, 4.90],  $I^2$ : 88.6%,  $P(\text{RR} > 1)$ : 98.0%, eFigure 5B), and (3) Chou et al. 2025 in place of Hsu et al. 2025 (RR: 2.27, 95% CrI [1.25, 4.73],  $I^2$ : 77.3%,  $P(\text{RR} > 1)$ : 99.6%, eFigure 5C). Overall, these sensitivity analyses consistently showed that there was strong evidence of elevated NAION risk in semaglutide users compared with non-GLP-1RA users.

## Discussion

Our results show semaglutide use was associated with a 152% higher risk of NAION relative to those who used non-GLP-

**Figure 3** Forest Plots of GLP-1RA Use and NAION in Patients With Diabetes

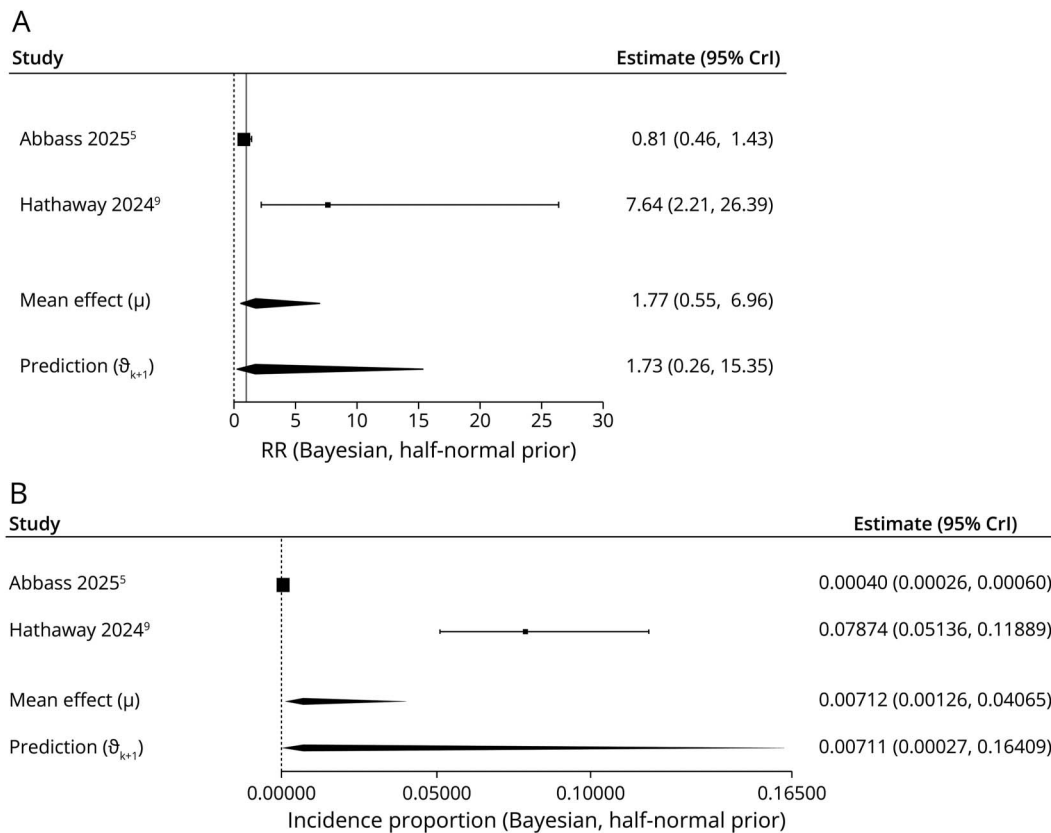


(A) Main comparative analysis of diabetic semaglutide users and NAION risk. (B) Main analysis of GLP-1RA users and incidence of NAION. (C) Main analysis of semaglutide users and incidence of NAION. GLP-1RAs = glucagon-like peptide-1 receptor agonists; NAION = nonarteritic anterior ischemic optic neuropathy.

IRAs. The secondary analysis showed elevated observed NAION incidence in those using GLP-1RAs (i.e., semaglutide, dulaglutide, exenatide), with notably increased incidence among semaglutide users. Comparative subgroup analysis by indication yielded 2.41 times and 1.77 times higher observed risk of NAION compared with non-GLP-1RA users within the diabetes and obesity cohorts, respectively. In the overall and

diabetes subgroup analysis, the likelihood of RR >1 was 99.9%, indicating very strong observed evidence of elevated NAION risk associated with semaglutide use. In the obesity subgroup and compared with specific agents, semaglutide was associated with moderate likelihood of elevated NAION risk. The highest RR of 7.64 was observed in Hathaway et al., whereas the lowest RR of 0.7 was observed in Abbas et al.

**Figure 4** Forest Plots of GLP-1RA Use and NAION in Patients With Obesity



(A) Main comparative analysis of semaglutide and NAION risk in patients with obesity. (B) Main analysis of semaglutide users and incidence of NAION in patients with obesity. GLP-1RAs = glucagon-like peptide-1 receptor agonists; NAION = nonarteritic anterior ischemic optic neuropathy.

Contemporary literature suggests the annual incidence of NAION ranges from 2.3 to 10.2 cases per 100,000 semaglutide users. Our study highlighted a greater pooled incidence of NAION with 118 cases per 100,000 semaglutide users and 85 cases per 100,000 users of any GLP-1RA. The elevated pooled estimate may reflect variations across study populations, outcome assessment, follow-up durations, or study design validity not precluding selection bias particularly among less powered studies.<sup>9,11</sup>

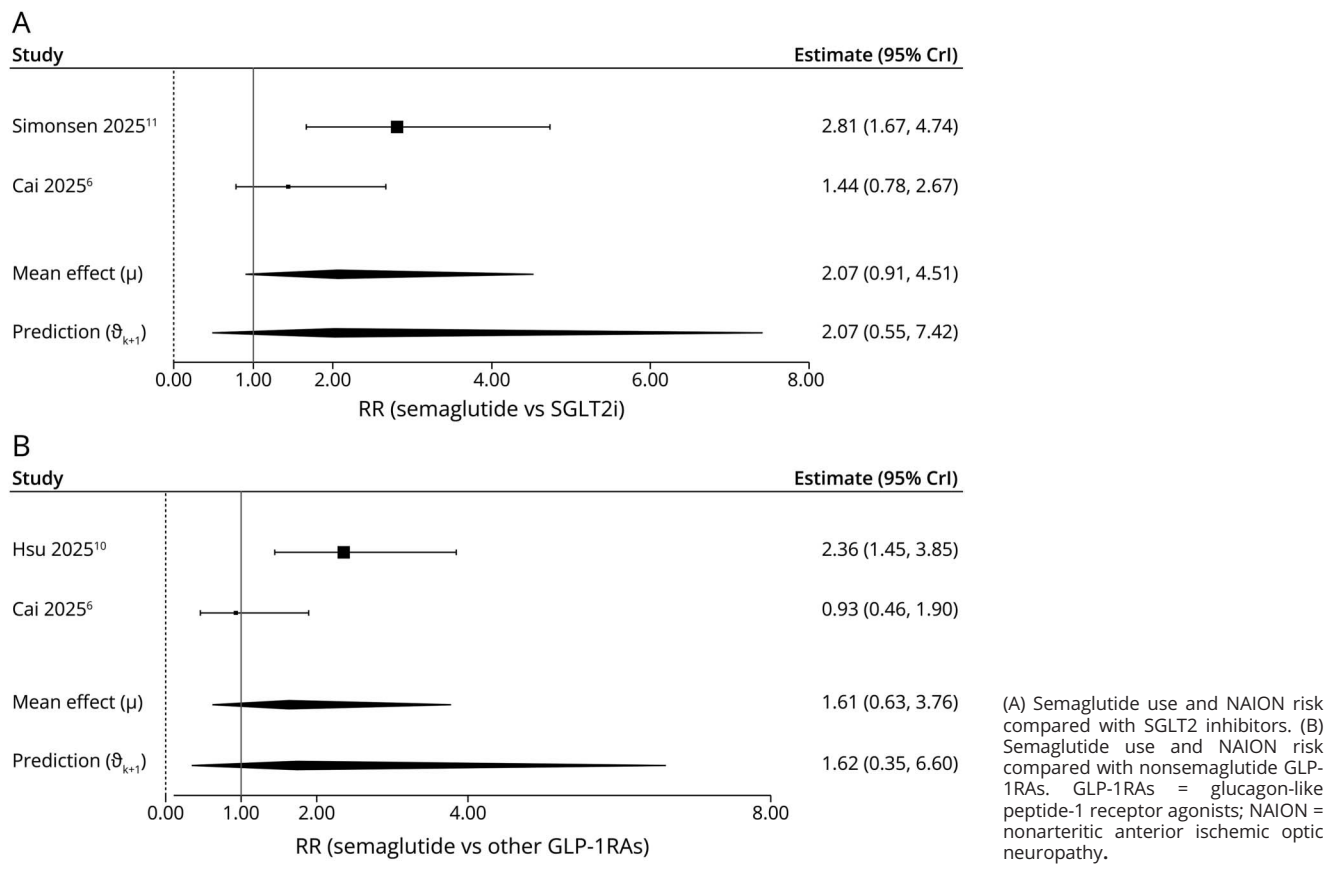
Given the observed association of semaglutide use with a 141% higher risk of NAION and incidence of 125 cases per 100,000 semaglutide users with diabetes, clinicians may consider exercising heightened caution when prescribing semaglutide to individuals with known optic nerve vulnerability. In scenarios where alternative agents such as SGLT2 inhibitors may be clinically appropriate, these should be considered, given their comparatively lower risk profile observed in this analysis. Physicians should counsel patients initiating semaglutide therapy to be vigilant for early symptoms of NAION, including sudden, painless vision loss, and to seek prompt ophthalmic evaluation if such symptoms occur.

Although the mechanism linking GLP-1RAs to NAION is unclear, one hypothesis proposes that modulation of

hemodynamics due to GLP-1RA activity may cause systemic hypotension, reducing perfusion to the optic nerve head.<sup>6</sup> Animal and human studies suggest GLP-1RAs inhibit angiotensin II signaling, suppress sodium reabsorption, and increase natriuresis to reduce systemic blood pressure.<sup>21-24</sup> These findings are compatible with the hypothesis that GLP-1RA-induced hypotension may predispose susceptible individuals to optic nerve ischemia through chronic hypoperfusion.<sup>6</sup> In addition, among diabetic patients with autonomic neuropathy, GLP-1RA effects on the angiotensin II axis may impair baroreflex responses and amplify susceptibility to hypoperfusion.<sup>25</sup> Clinically relevant hypotension may also result indirectly from weight loss without sufficient down-titration of antihypertensive medications.<sup>26,27</sup> These mechanisms may further increase the risk of optic nerve head hypoperfusion.

This study has several strengths. We used a systematic and comprehensive search strategy to identify all relevant literature and synthesize the most current and reliable estimates of the association between GLP-1RAs such as semaglutide and NAION. Bayesian-inference methods were used, which yields more stable and credible estimates, particularly valuable in the case of rare outcomes like NAION where data are sparse. Sensitivity analyses also yielded consistent risk estimates, demonstrating the robustness of our findings. This study also

**Figure 5** Forest Plots of Semaglutide Use and NAION Risk Compared With Other Agents



has multiple limitations. First, only 5 studies were included, all of which were observational, and thus inherently at risk of residual confounding. Our results should therefore be interpreted as hypothesis generating. Second, included studies varied in cohort composition (e.g., semaglutide indication, or comparator). Not all available cohorts could be incorporated into the meta-analysis because of potential overlap in populations. In addition, all included studies were from the United States, Denmark, or Norway which predominantly have White populations, further limiting the generalizability of our findings.

Biological plausibility must also be interpreted cautiously. Although GLP-1RAs mediate angiotensin II inhibition and may theoretically contribute to optic nerve hypoperfusion, it may also be plausible that they reduce ischemic risk through their beneficial effects on blood pressure, weight reduction, glycemic control, and other cardiovascular outcomes.<sup>28-31</sup> The potential for residual confounding remains. Across studies, disease duration and severity were not consistently assessed, which can drive confounding by indication as those with poorly controlled metabolic disease have greater probability of receiving GLP-1RAs and developing NAION.<sup>28</sup> Furthermore, GLP-1RAs take time to reach maximum efficiency, thus early follow-up may reflect disproportionate

contributions from baseline vascular risk factors rather than treatment-mediated risk.<sup>28</sup> The observed associations may also be influenced by failure to address other confounders including optic nerve anatomy, health behaviors, and changes to baseline covariates.<sup>28</sup> These factors highlight the need for prospective research which controls for confounding from vascular and ophthalmic risk factors appropriately.

Furthermore, our study could not comprehensively capture the broader benefits of GLP-1RAs. GLP-1RAs may improve overall vision health through enhancing glycemic control and lowering HbA1c, reducing risk of glaucoma and retinal vascular occlusion, as well as the progression of cataracts and diabetic retinopathy.<sup>32</sup> These conditions are prevalent and the magnitude of benefit they receive from GLP-1RAs may outweigh the rare risk of NAION. Moreover, GLP-1RAs have proven systemic benefits including a reduction in all-cause mortality. Large randomized controlled trials including the SUSTAIN6, SELECT, and PIONEER-6 trials found semaglutide conferred a reduced incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in those with T2DM or obesity.<sup>29-31</sup> This work cannot fully elucidate the net effect of GLP-1RA on long-term overall visual prognosis. Therefore, the findings of this study should be interpreted as hypothesis generating. Future works should

investigate longitudinal visual acuity outcomes and all-cause mortality among those taking GLP-1RAs compared with those who do not, to better elucidate the risk-benefit profile of these drugs in patients with diabetes and obesity.

There is low-to-moderate certainty evidence that semaglutide is associated with NAION incidence relative to non-GLP-1RA medications, especially among patients with diabetes. This analysis underscores the need for increased awareness regarding semaglutide-associated NAION risk and supports the implementation of more vigilant monitoring practices, particularly among those with baseline elevated risk of vascular disease. Further rigorously designed research that sufficiently controls for confounders is necessary to validate these findings.

## Author Contributions

T. Dhivagaran: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. F. Butt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. L. Arunasalam: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. I. Bae: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Mikhail: drafting/revision of the manuscript for content, including medical writing for content. B.K. Tao: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J.S. Xie: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Balas: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Popovic: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. E. Margolin: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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