

The Pathogenic Role of Inflammation in Idiopathic Intracranial Hypertension: An Assessment Based on Genetic Evidence

Dinglang Chen^{2,†}, Yuhao Yuan^{3,†}, Shengnan Wang^{1,*}

¹ Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

² Department of Cardiothoracic and Thyroid Surgery, Wuming Hospital, Guangxi Medical University, Nanning, China

³ Department of Forensic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

***Correspondence:** Shengnan Wang, Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

E-Mail: 903970942@qq.com

Abstract

Background: The etiology of idiopathic intracranial hypertension (IIH) remains poorly understood, because it is a complex disorder involving multiple factors. Observational studies have indicated a possible association between inflammation and IIH. To investigate this relationship, we employed Mendelian randomization (MR) analysis to assess the causal link between inflammatory regulators and IIH.

Materials and methods: We used genome-wide association study (GWAS) data on 41 inflammatory regulators from 8293 European individuals. Summary statistics for IIH were obtained from the FinnGen consortium R9 release, comprising 102 cases and 205,799 controls. Single nucleotide polymorphisms (SNPs) strongly associated with the exposure traits were selected as instrumental variables. Potential confounding factors, such as obesity, were evaluated and excluded using the PhenoScanner database. The primary method for estimating causal effects was the inverse variance weighted (IVW) approach.

Results: Lower levels of vascular endothelial growth factor (VEGF) and interleukin-10 (IL-10) were associated with an increased risk of IIH (odds ratio [OR] = 0.683, 95% confidence interval [CI] = 0.495–0.943, $P = 0.021$; and OR = 0.560, 95% CI = 0.351–0.903, $P = 0.017$, respectively, at a nominal significance threshold of $P < 0.05$). Notably, these associations did not remain statistically significant after correction for multiple testing (Bonferroni-adjusted threshold $P < 0.05/41 [\approx 0.0012]$).

Discussion: These nominally significant findings suggest that VEGF and IL-10 may be involved in IIH pathogenesis. VEGF regulates cerebrovascular permeability and cerebrospinal fluid dynamics, and its reduction may disrupt intracranial pressure homeostasis; decreased IL-10 may impair anti-inflammatory defense and induce intracranial inflammatory imbalance. However, the loss of significance after multiple testing correction indicates the current evidence is preliminary and likely limited by the small IIH case sample size.

Conclusion: Our findings suggest that genetically predicted lower levels of VEGF and IL-10 are nominally associated with increased IIH risk, providing preliminary genetic evidence for a potential role of inflammatory

[†] These two authors contributed equally and share first authorship.

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modulation in the pathogenesis of IIH. Further research in larger cohorts is warranted to validate these findings and clarify the underlying molecular mechanisms.

Keywords: idiopathic intracranial hypertension; Mendelian randomization; inflammatory regulators; vascular endothelial growth factor; interleukin-10

Introduction

Idiopathic intracranial hypertension (IIH) is a complex, multifactorial disorder characterized by elevated intracranial pressure in the absence of structural brain lesions or other identifiable causes, with normal cerebrospinal fluid (CSF) composition^[1]. It predominantly affects women of reproductive age and is strongly associated with obesity^[2]. With rising global obesity rates, the incidence of IIH has increased progressively—from 1.0 per 100,000 individuals in 1990–2001 to 2.4 per 100,000 in 2002–2014^[2,3]. The clinical severity of IIH is substantial. It often presents with debilitating persistent headaches and progressive visual decline, significantly impairing patients' quality of life and daily functioning^[4,5]. Notably, over 80% of patients experience considerable visual impairment, with a substantial risk of permanent vision loss if the condition is not managed effectively^[6]. This visual morbidity, coupled with the chronic nature of headaches, represents a significant and often under-recognized disease burden. Furthermore, due to the non-specific nature of its symptoms, IIH is frequently misdiagnosed or diagnosis is delayed, which can exacerbate long-term visual outcomes and increase healthcare costs^[7,8]. Current treatment strategies primarily aim to lower intracranial pressure and include weight loss, pharmacotherapy (e.g., acetazolamide and topiramate), and surgical interventions^[9–11]. However, these approaches are largely symptomatic, not disease-specific, and robust evidence supporting their long-term efficacy remains limited^[12]. They often address the consequences of elevated pressure rather than the underlying pathophysiological drivers of the disease^[4]. The lack of targeted therapies underscores the critical need to elucidate the fundamental mechanisms of IIH. Identifying specific causative factors is a vital step toward developing novel, more effective treatments that can prevent irreversible neurological damage.

Growing evidence highlights a close link between IIH and a pro-inflammatory state^[13]. Patients with IIH show markedly elevated CSF levels of the chemokine C-C motif chemokine ligand 2 (CCL2), along with increased serum concentrations of monocyte chemotactic protein 2 (MCP2), monocyte chemotactic protein 3 (MCP3), interleukin (IL)-1 α , and leptin^[14]. These findings support immune system activation and inflammatory activity in IIH. Independent studies have also reported altered expression of microRNAs related to pro-inflammatory responses in both CSF and serum of patients with IIH^[15], providing molecular evidence for central nervous system and systemic inflammation. Moreover, elevated levels of IL-2 and IL-17 in the CSF of IIH patients further underscore the potential role of inflammation in this condition^[16]. Despite these compelling associations, a major gap remains: observational studies cannot establish causality due to inherent limitations such as reverse causation and unmeasured confounding. It is unclear whether inflammation is a cause, a consequence, or merely an epiphenomenon of IIH. This uncertainty hinders the translation of these findings into actionable therapeutic targets.

Mendelian randomization (MR) employs genetic variants as instrumental variables (IVs) to emulate a “natural experiment,” allowing for causal inference between exposures and outcomes while minimizing reverse causation and confounding^[17–19]. Our study addresses this gap by performing a bidirectional MR analysis to investigate the causal relationship between circulating inflammatory regulators and IIH. Establishing a causal link is of paramount importance, as it would shift inflammation from a correlative finding to a potential modifiable pathogenic mechanism. This could pave the way for repurposing existing anti-inflammatory agents or developing new ones specifically for IIH, ultimately aiming to preserve vision and improve patient outcomes. Our results reveal a significant causal association of

vascular endothelial growth factor (VEGF) and IL-10 with IIH, offering new insights into its etiology.

Methods

Study assumption

MR analysis is predicated on three assumptions^[17], as shown in Fig. 1: (1) exposure is linked to genetic variation; (2) the presence of genetic diversity is not affected by any factors that may cause confusion; and (3) genetic diversity only affects the outcome through exposure.

Data sources and selection of instrumental variables

Table 1 provides a summary of data from 41 inflammatory regulatory factors included in the genome-wide association studies (GWASs), including sample sizes and entry codes for the studies. All single nucleotide polymorphisms (SNPs) were derived from a study involving 8293 individuals of European descent. Summary statistics for IIH were acquired from the FinnGen consortium R9 release data. The phenotype “IIH” was adopted in the current study. The GWAS comprised 205,901 Finnish women who were adults. It involved 102 individuals with the condition being studied and 205,799 individuals without the condition. During the analysis, adjustments were made for sex, age, the first 10 principal components, and genotyping batch^[20,21].

We specifically selected SNPs that exhibited a strong correlation with exposure at a genome-wide

significance level ($P < 5 \times 10^{-6}$)^[22]. In order to guarantee the independence of instruments and the precision of causal impacts, we excluded SNPs with linkage disequilibrium (LD; $r^2 > 0.001$, clumping window = 10,000 kb)^[23]. Additionally, we excluded palindromic variants after verifying that allele frequency information was harmonized across exposure and outcome datasets to ensure consistent strand orientation. Furthermore, we excluded weak IVs with an F -statistic less than 10^[24]. We calculated the joint proportion of variance explained (R^2) by IVs for each inflammatory regulator using the formula $R^2 = F/(F + N - 2)$, where F is the F -statistic of each SNP and $N = 8293$ is the exposure sample size. Fourth, we used the PhenoScanner database (phenoscaner.medschl.cam.ac.uk/phenoscaner, accessed on 12 December, 2022) to rule out SNPs related to confounding factors, such as obesity. Ultimately, we chose SNPs that were highly correlated with all 41 factors that regulate inflammation as IVs (Table S1).

Statistical analysis

To examine the causal relationship between exposure and outcome, we utilized inverse variance weighted (IVW) regression analysis, which is the primary analytical approach in MR studies and has the greatest statistical efficiency. A nominal significance level of $P < 0.05$ was adopted as the primary threshold for discovery. Given the evaluation of 41 inflammatory regulators, we acknowledge that this threshold does not account for multiple testing; therefore, results should be interpreted as exploratory and require replication in larger cohorts. The underlying principle of this approach is based on the

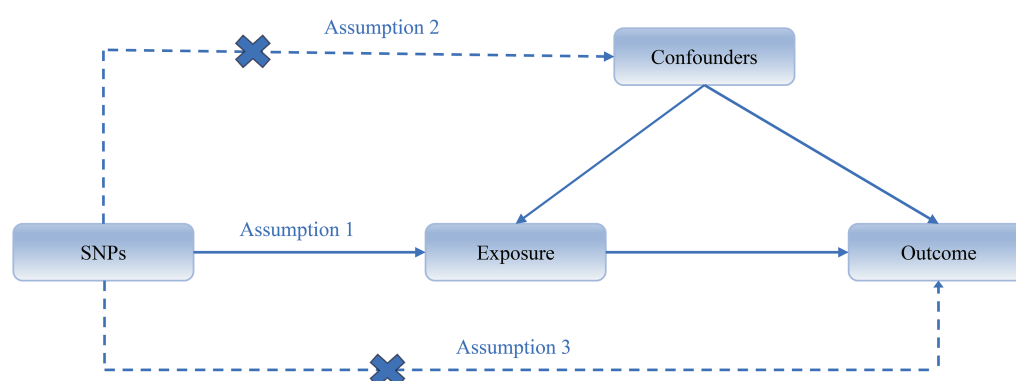


Figure 1: Study assumption of the MR analysis.

Table 1: Summary of data on 41 inflammatory regulatory factors included in GWAS.

Inflammatory regulatory factors	Abbreviation	Sample size	Number
Eotaxin 1	CCL11	8153	GCST004460
Basic fibroblast growth factor	bFGF	7565	GCST004459
Colony stimulating factor 3	CSF3	7904	GCST004458
C–X–C motif chemokine ligand 1	CXCL 1	3505	GCST004457
Interferon-gamma	IFN- γ	7701	GCST004456
Interleukin-2	IL-2	3475	GCST004455
Interleukin-2 receptor α	IL-2 RA	3677	GCST004454
Interleukin-4	IL-4	8124	GCST004453
Interleukin-5	IL-5	3364	GCST004452
Interleukin-7	IL-7	3409	GCST004451
Interleukin-9	IL-9	3634	GCST004450
Hepatocyte growth factor	HGF	8292	GCST004449
Interleukin-1 β	IL-1 β	3309	GCST004448
Interleukin-1 receptor antagonist	IL-RA	3638	GCST004447
Interleukin-6	IL-6	8189	GCST004446
C–X–C motif chemokine ligand 8	CXCL 8	3526	GCST004445
Cytokine synthesis inhibitory factor	CSIF	7681	GCST004444
Interleukin-13	IL-13	3557	GCST004443
Interleukin-17	IL-17	7760	GCST004442
Interferon gamma inducing factor	IGIF	3636	GCST004441
Interferon gamma induced protein 10	IP10	3685	GCST004440
Interleukin-12 p70	IL-12 p70	8270	GCST004439
C–C motif chemokine ligand 2	CCL2	8293	GCST004438
C–C motif chemokine ligand 7	CCL7	843	GCST004437
Colony stimulating factor 1	CSF1	840	GCST004436
C–X–C motif chemokine ligand 9	CXCL9	3685	GCST004435
C–C motif chemokine ligand 3	CCL3	3522	GCST004434
C–C motif chemokine ligand 4	CCL4	8243	GCST004433
Platelet derived growth factor BB	PDGF-BB	8293	GCST004432
C–C motif chemokine ligand 5	CCL5	3421	GCST004431
Interleukin-16	IL-16	3483	GCST004430
Stem cell factor	SCF	8290	GCST004429
Stem cell growth factor β	SCGF β	3682	GCST004428
C–X–C motif chemokine ligand 12	CXCL12	5998	GCST004427
Tumor necrosis factor- α	TNF α	3454	GCST004426
Tumor necrosis factor- β	TNF β	1559	GCST004425
Tumor necrosis factor ligand superfamily member 10	TNFSF10	8186	GCST004424
Macrophage migration inhibitory factor	MIF	3492	GCST004423
Vascular permeability factor	VPF	7118	GCST004422
β nerve growth factor	β -NGF	3531	GCST004421
C–C motif chemokine ligand 27	CCL27	3631	GCST004420

presumption that all IVs are efficient. To validate the consistency of effect estimates, we also employed weighted median and MR-Egger analysis methods as supplementary approaches, considering the possible existence of pleiotropy^[24]. The weighted median method assumes that most IVs are effective, displaying higher tolerance to outliers but sensitivity to the addition and removal of IVs^[25]. The MR-Egger analysis method assumes all IVs are invalid, enabling the generation of credible effect estimates in the presence of pleiotropy; however, it is sensitive to outliers and has lower efficiency^[26]. Furthermore, the presence of potential variation and pleiotropy was evaluated using Cochran's Q test and the MR-Egger intercept (significance was determined at $P < 0.05$)^[27,28]. To examine and eliminate anomalies, we utilized Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO)^[29–31]. To evaluate the reliability of the findings, the leave-one-out technique was employed.

Results

After careful examination, we discovered genetic variations closely linked to 41 factors that regulate inflammation ($P < 5 \times 10^{-6}$). Subsequently, we performed an MR analysis to investigate the influence of these inflammation regulatory factors on IIH. Table 2 displays the primary findings of the MR analysis, while Table S1 provides supplementary results. According to the IVW analysis, higher levels of VEGF and IL-10 were linked to a decreased likelihood of IIH (OR = 0.683, 95% CI = 0.495–0.943, $P = 0.021$; OR = 0.560, 95% CI = 0.351–0.903, $P = 0.017$, respectively) as shown in Table 2. The consistency of these findings was supported by the weighted median method, which yielded similar effect estimates for both VEGF (OR = 0.665, 95% CI = 0.463–0.955, $P = 0.027$) and IL-10 (OR = 0.487, 95% CI = 0.272–0.868, $P = 0.015$). The MR-Egger method produced directionally concordant

Table 2: Major MR analysis results on the causal relationship between inflammatory regulatory factors and IIH.

Systemic inflammatory regulators	Analytical method	Numbers of SNPs	β	OR (95% CI)	P value	P value for heterogeneity test	P value for MR-Egger intercept	P value for MR-PRESSO
Vascular endothelial growth factor	Inverse variance weighted	10	−0.381	0.683 (0.495–0.943)	0.021	0.830	0.885	0.679
	MR-Egger	10	−0.413	0.661 (0.386–1.133)	0.171	0.889		
	Weighted median	10	−0.408	0.665 (0.463–0.955)	0.027			
Interleukin-10	Inverse variance weighted	11	−0.575	0.560 (0.351–0.903)	0.017	0.877	0.383	0.657
	MR-Egger	11	−0.988	0.370 (0.137–1.013)	0.085	0.836		
	Weighted median	11	−0.720	0.487 (0.272–0.868)	0.015			
Interleukin-13	Inverse variance weighted	9	−0.233	0.792 (0.507–1.236)	0.304	0.434	0.023	0.130
	MR-Egger	9	−1.000	0.368 (0.195–0.692)	0.014	0.070		
	Weighted median	9	−0.371	0.689 (0.458–1.038)	0.074			
Interleukin-7	Inverse variance weighted	9	−0.369	0.691 (0.462–1.032)	0.071	0.250	0.772	0.333
	MR-Egger	9	−0.520	0.594 (0.204–1.733)	0.369	0.324		
	Weighted median	9	−0.475	0.622 (0.388–0.998)	0.049			

but wider confidence intervals (VEGF: OR = 0.661, 95% CI = 0.386–1.133, $P = 0.171$; IL-10: OR = 0.370, 95% CI = 0.137–1.013, $P = 0.085$), with point estimates crossing or approaching the null, likely reflecting the reduced statistical efficiency of this method. The overall consistency in direction of effect across all three MR approaches strengthens confidence in the causal estimates derived from the primary IVW analysis. In addition, there was no evidence of potential heterogeneity and pleiotropy based on Cochran's Q test and MR-Egger intercept ($P > 0.05$; Table 2 and Fig. S1). Furthermore, the results were shown to be robust by the leave-one-out analysis (Fig. S2). Figs. S1, S3, and S4 contain funnel plots, forest plots, and leave-one-out plots for the MR analysis of VEGF and IL-10, respectively.

Moreover, the MR-Egger method suggested a causal relationship between IL-13 and IIH (OR = 0.368, 95% CI = 0.195–0.692, $P = 0.014$). However, the intercept from the MR-Egger method indicated the presence of pleiotropy, casting doubt on the reliability of this result. The weighted median technique proposed a possible causal link between IL-7 and IIH (OR = 0.622, 95% CI = 0.388–0.988, $P = 0.049$). However, the IVW analysis did not provide evidence for the presence of a causal relationship (OR = 0.691, 95% CI = 0.462–1.032, $P = 0.071$). Hence, our conclusion is that there is no evident causal connection between IL-7 and IIH.

In addition, utilizing the identical approach, we chose SNPs that are closely linked to IIH as IVs, yet we did not discover any evidence of IIH impacting factors that regulate inflammation.

Discussion

Through bidirectional MR analysis, we identified that elevated circulating levels of VEGF and IL-10 may be associated with a reduced risk of developing IIH. To our knowledge, this is the first MR study to investigate the causal relationship between inflammatory mediators and IIH. While previous observational studies struggled to fully account for confounding by obesity, our analysis controlled for this key factor at the genetic level, providing more robust causal evidence. Despite the limited number of IIH cases ($n = 102$), our *post hoc* power analysis confirmed that the strong IVs ($F > 20$ for most SNPs)

yielded sufficient statistical power ($> 99\%$) to detect the observed effect sizes for VEGF and IL-10. However, weaker causal effects (OR closer to 1) may remain undetected due to the small case cohort. Additionally, while we used PhenoScanner to exclude SNPs associated with obesity, we acknowledge that multivariable MR analysis incorporating body mass index (BMI) as a covariate would provide stronger evidence that these cytokines are independent risk factors rather than proxies for adiposity. Future studies with larger IIH GWAS datasets should incorporate such multivariable approaches.

It should be noted that the GWAS exposure trait analyzed in this study was vascular permeability factor (VPF), which is functionally equivalent to VEGF-A. Throughout this discussion, we use “VEGF” to refer broadly to this signaling pathway, consistent with the established literature. VEGF is a key regulator of angiogenesis, lymphangiogenesis, and vascular permeability. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF)^[32]. VEGF-C, expressed in lymphatic endothelial cells, stimulates lymphatic vessel formation via VEGFR3 activation^[33]. Our findings suggest that higher VEGF levels may lower IIH risk. The link between VEGF and IIH has been scarcely studied. We hypothesize that increased circulating VEGF could reduce IIH risk by enhancing CSF drainage. Supporting this, intracisternal injection of VEGF-C in rats upregulated VEGFR3 expression and increased CSF drainage^[34]. Similarly, in mice with chronic *Toxoplasma*-induced brain edema, VEGF-C promoted meningeal lymphatic vessel growth and facilitated CSF outflow^[35]. However, the interplay between lifestyle factors (e.g., diet, physical activity) and genetic predisposition to VEGF levels may further modulate IIH risk. For instance, obesity—a major IIH risk factor—is known to alter VEGF expression and systemic inflammation, potentially affecting both vascular permeability and CSF dynamics. Our MR design genetically fixed the effect of obesity, but residual confounding through obesity-related behaviors (e.g., dietary patterns) cannot be fully excluded. Future studies integrating longitudinal lifestyle data, polygenic risk scores, and dynamic brain imaging (e.g., CSF flow metrics) are needed to dissect how environmental and genetic factors jointly influence the VEGF–CSF drainage axis. Such multi-layered approaches could uncover novel intervention targets at

the intersection of vascular plasticity, energy homeostasis, and brain hydrodynamics. However, it is important to recognize that VEGF also increases vascular permeability—a function that could theoretically exacerbate intracranial pressure by promoting fluid extravasation across the blood-brain barrier^[36]. The net protective effect observed in our MR analysis may therefore reflect a balance between enhanced CSF drainage and the potential risks of increased vascular permeability. This interpretation is derived from population-level average causal estimates, and the precise molecular mechanisms require validation in experimental models. These insights position VEGF as a potential therapeutic target for IIH, warranting further investigation.

IL-10 is a pivotal anti-inflammatory cytokine in the central nervous system. Produced by microglia upon Toll-like receptor activation, IL-10 binding triggers the JAK-STAT signaling pathway, modulating antigen presentation to T cells^[37–39]. Furthermore, IL-10 facilitates the transformation of microglial cells into the M2 phenotype, inhibiting the generation of inflammatory cytokines and aiding in the resolution of inflammation and restoration of tissue^[40,41]. To summarize, IL-10 has a crucial function in controlling the inflammatory responses within the central nervous system and facilitating the protection of neurons. Previous studies have suggested that IL-10 may accelerate the clearance of hematoma after brain hemorrhage, leading to improved neurological function^[42,43]. Reduced levels of IL-10 exacerbate inflammation and contribute to the progression of Alzheimer's disease (AD)^[44]. In ischemic stroke models, IL-10 has been shown to reduce infarct size^[45,46]. According to our study, insufficient amounts of IL-10 could heighten the likelihood of IIH, which aligns with the pro-inflammatory hypothesis of IIH: reduced anti-inflammatory signaling (IL-10) may predispose individuals to a neuroinflammatory state that contributes to disease development^[47,48]. While previous studies have found elevated levels of IL-10 in the serum of IIH patients, it is essential to note that these findings are from cross-sectional studies, making it unclear whether the increased IL-10 is a result or a cause of IIH^[49]. Our MR results suggest that low IL-10 is causal, and the observed elevation in cross-sectional studies may reflect a compensatory response to ongoing inflammation. Future research is needed to further explore the relationship

between IL-10 and IIH. The treatment of IIH may benefit from focusing on the regulation of inflammation, which could potentially become a new and innovative therapeutic strategy. Beyond inflammatory mechanisms, it is worth considering that IIH patients frequently exhibit psychiatric comorbidities such as depression and anxiety, which may share overlapping neurobiological pathways with the inflammatory processes investigated here. Recent studies have identified genetic links between physical activity and mental health through neural pathways^[50], demonstrated that neurodevelopmental risk factors contribute to the comorbidity between internalizing and externalizing disorders via cell-specific gene expression patterns^[51], and revealed that cortical thickness asymmetries are associated with psychiatric risk^[52]. These findings suggest that physiological stressors—including altered inflammatory signaling—may affect brain structure and mental health through shared mechanisms. Integrating our MR results within this broader neurobiological framework highlights the potential for inflammatory regulators to influence both the physical and psychiatric dimensions of IIH.

The existing research on the relationship between inflammatory regulatory factors and IIH is limited, with most studies being observational in nature. MR analysis provides a means to simulate randomized controlled trials in a natural setting, mitigating bias through the random segregation of alleles at conception. Compared with observational studies, MR analysis helps avoid reverse causation. During our analysis using MR, we investigated the connection between 41 factors that regulate inflammation and IIH. We noticed a possible link between decreased levels of VEGF and IL-10 and the occurrence of IIH. This study has several limitations. First, the limited number of IIH cases ($n = 102$) in the FinnGen dataset reduces statistical power to detect modest causal effects and increases the risk of winner's curse, potentially inflating effect estimates. Replication in larger, independent IIH cohorts is essential. Second, our study evaluated 41 inflammatory regulators using a nominal significance threshold of $P < 0.05$ without correction for multiple testing; the reported associations should therefore be regarded as exploratory. Third, while we used PhenoScanner to exclude SNPs associated with obesity, we were unable to perform multivariable MR adjusting for BMI due to the limited sample size of

the IIH GWAS, which precludes robust estimation in a multivariable framework. As larger IIH GWAS datasets become available, future studies should employ multivariable MR to definitively disentangle the effects of inflammatory cytokines from those of adiposity. Although we employed SNPs closely associated with lifelong exposures as IVs to investigate causality, it is important to note that the implications for clinical treatment effects may not be directly applicable^[53]. Furthermore, our research solely concentrated on the individuals of European ancestry, and additional verification of these findings is necessary in other ancestral populations^[50,52,54].

To summarize, our study illuminates a possible cause-and-effect connection between VEGF, IL-10, and IIH, providing valuable insights into the development of IIH. However, the complex interplay between inflammation and IIH necessitates further in-depth exploration to reconcile our findings with the known vascular and inflammatory physiology of the disease, including experimental studies that examine both the protective and detrimental pathways of these molecules. Given the limited sample size of the IIH GWAS, our reverse MR analysis (testing the effect of IIH on inflammatory regulators) had insufficient statistical power, and the null findings should be interpreted cautiously rather than as definitive evidence of unidirectionality. Future studies with larger IIH cohorts should re-evaluate the bidirectional relationship to confirm and extend these findings.

Author contributions

In the preparation of this research manuscript, the contributions of the authors were distinct and complementary. Data analysis was conducted by Dinglang Chen and Yuhao Yuan. Figures were created and results were interpreted by Dinglang Chen. Shengnan Wang edited the manuscript. The manuscript's final version was approved by all authors.

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Ethics statement

This study is a secondary analysis of publicly available

genome-wide association study (GWAS) summary statistics; no new data were collected from human participants. The summary statistics for the 41 inflammatory regulators were derived from a published GWAS of 8293 European individuals, and the idiopathic intracranial hypertension (IIH) summary statistics were obtained from the FinnGen consortium (release R9). Each contributing study obtained the appropriate ethical approval and written informed consent from its participants, as detailed in the original publications. No additional ethical approval was required, and the analysis was conducted in accordance with the Declaration of Helsinki.

Data availability statement

GWAS data related to IIH can be accessed at Risteys (risteys.finregistry.fi/endpoints/G6_BENINTRAHYP). For GWAS data associated with inflammation regulatory factors, information can be obtained by searching for the accession number on the GWAS Catalog server ([ebi.ac.uk/gwas/](https://europe.ebi.ac.uk/gwas/)). The accession numbers are provided in Table 1. No application number is required to access these datasets.

AI statement

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, or writing of this manuscript.

Conflicts of interest

The researchers confirm that the investigation was conducted without any business or monetary affiliations that could be seen as possible conflicts of interest.

Supplemental materials

Electronic supplementary material is available in the online version of this article at doi.org/10.2738/NPR.2026.0002 and is accessible for authorized users.

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