Journal of Pain Research

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ORIGINAL RESEARCH

Associations Between Circulating Inflammatory Cytokines and Neuropathic Pain: A Two-Sample Mendelian Randomization Study

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Purpose: Several recent observational studies have reported that the circulating inflammatory cytokine composition is associated with neuropathic pain. However, the causal effect of 41 circulating inflammatory cytokines on neuropathic pain is unknown.

Patients and Methods: A two-sample Mendelian randomization study was performed using summary statistics for a genome-wide association study (GWAS) of circulating inflammatory cytokines conducted within three Finnish cohorts (YFS and FINRISK 1997 and 2002, n=8,293). The summary statistics of neuropathic pain were obtained from the GWAS dataset (800 patients and 195,047 controls). Inverse variance weighting, weighted median weighting, MR–Egger regression, simple weighting, and weighted weighting were used to examine the causal associations between inflammatory cytokines and neuropathic pain. Sensitivity analyses, including the Cochran Q test, Egger intercept test, and leave-one-out analysis, were performed to verify the robustness of the MR results.

Results: Inverse variance weighted estimates suggested that *G-CSF* (OR=0.57, 95% CI=0.39–0.83, *P*=3.4e−03), *IL-16* (OR=0.73, 95% CI=0.55–0.96, *P*=2.7e−02), and *IL-1β* (OR=0.57, 95% CI=0.33–0.99, *P*=4.4e−02) had protective effects on neuropathic pain. In addition, *IP-10* (OR=1.36, 95% CI=1.06–1.74, *P*=1.5e−02) was suggested to be associated with neuropathic pain. No significant heterogeneity of instrumental variables or horizontal pleiotropy was found.

Conclusion: This two-sample Mendelian randomization study revealed that *G-CSF, IL-16, IL-1β, and IP-10* were causally associated with neuropathic pain. This knowledge could guide future research in developing more effective treatments for neuropathic pain, potentially leading to better pain management options for patients.

Keywords: neuropathic pain, inflammatory cytokines, Mendelian randomization, genome-wide association study, pain management

Introduction

Neuropathic pain (NeP) is a complex and often chronic condition that results from nerve damage and significantly impacts quality of life.[1,2] The impact of NeP on patients' quality of life is substantial, imposing a significant economic burden on both society and individuals.[3] Despite its prevalence, the biological mechanisms underlying neuropathic pain are poorly understood, hindering effective treatment development. A growing body of research suggests the potential role of inflammatory cytokines in the pathogenesis of neuropathic pain.[4–6] Taken together, the intricate nature of NeP, its widespread prevalence, and its significant impact on both individual lives and societal economics underscore the importance and urgency of disease prevention strategies.

The intricate nature of the etiology of neuropathic pain continues to challenge the medical community, although recent advancements have emphasized the significant role of inflammatory processes, particularly the involvement of inflammatory cytokines.[7] After nerve injury, inflammatory responses can lead to the onset and persistence of neuropathic pain. Inflammatory cytokines such as TNF- α, IL-1 β, and IL-6 play important roles in the pathophysiological process of

Received: 12 September 2024
Accepted: 12 March 2025
Published: 24 March 2025

neuropathic pain.[7,8] These cytokines, which are critical for mediating immune responses, have emerged as focal points in understanding the pathophysiological mechanisms of NeP. Current research suggests that these signaling proteins potentially contribute to the sensitization that characterizes this pain state.[9] Observational studies have further emphasized this, indicating a correlation between cytokine levels and the severity of neuropathic symptoms, pointing toward an intricate interplay of inflammatory factors and neural pathways.[10] However, establishing a causal relationship has been challenging due to limitations in traditional observational studies, such as confounding factors and reverse causation.[11]

This study aimed to address these challenges using Mendelian randomization, a method that leverages genetic variants as instrumental variables to infer causal relationships between risk factors and clinical outcomes.[12] Mendelian randomization offers a more robust approach than conventional observational studies by minimizing confounding factors. This is achieved through the random allocation of alleles at conception, mirroring the principles of a randomized controlled trial. Additionally, this method reduces the likelihood of reverse causation, as genetic variants are established at birth and therefore precede the development of neuropathic pain.[13]

In this work, we employed a two-sample Mendelian randomization strategy, an advanced form of MR, to determine the causal relationship between 41 inflammatory cytokines and NeP. This approach leverages data from extensive genome-wide association studies (GWASs), providing a more expansive genomic landscape to inform our analysis.[11] Specifically, we aimed to discern whether the genetic factors that influence cytokine levels also play a role in susceptibility to or severity of NeP.

Material and Methods

This MR analysis included GWAS summary statistics that have already been published. The ethics committee at each institutional review board authorized all participants' written informed consent in separate studies. No additional ethical approval or informed consent was needed. The STROBE-MR checklist has been checked and uploaded as supplementary data.[14]

MR Assumptions

There are three core assumptions of MR analysis, namely, relevance, independence, and exclusion restriction.[15] It is assumed that the selected genetic variants are related to the risk factor (relevance) but not to any confounders in the risk factor–outcome association (independence) and that they are not connected with the outcome via any pathways other than the risk factor for interest (exclusion restriction). Here, in this bidirectional study, two GWASs were utilized to select genetically significant SNPs for 41 inflammatory cytokines and NeP (Figure 1).

Study Design and Data Sources

Our research utilized a two-sample Mendelian randomization (MR) approach, a powerful tool that leverages genetic variants as instrumental variables. This design is particularly advantageous because it minimizes potential confounders, offering more robust evidence of causality than traditional observational studies can provide. The primary objective was to ascertain the causal relationship between circulating inflammatory cytokines and the onset or severity of neuropathic pain.

With respect to our data, we performed a genome-wide association study (GWAS). The summary statistics for circulating inflammatory cytokines were extracted from studies conducted within three distinct Finnish cohorts: YFS, FINRISK 1997, and FINRISK 2002. Together, these cohorts encompassed a total of 8,293 individuals, providing a rich and diverse dataset for our analyses. On the other hand, the data concerning neuropathic pain were sourced from a separate GWAS dataset (https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_TRINEU/). This dataset was notably extensive, comprising 800 patients with neuropathic pain and a substantial control group of 195,047 individuals. The sheer size of this control group was instrumental in enhancing the statistical power of our study, thereby increasing the reliability and validity of our findings. There was no overlap in population selection between the exposure group and the outcome group.

Instrumental Variable Selection

To ensure the reliability of these instruments, we implemented a stringent criterion, considering only single nucleotide polymorphisms (SNPs) that reached a genome-wide significance level ($P<5\times10^{-8}$) as valid instrumental variables. Given the scarcity of SNPs for certain cytokines when used as exposures, a higher cutoff ($P<5\times10^{-6}$) was applied.

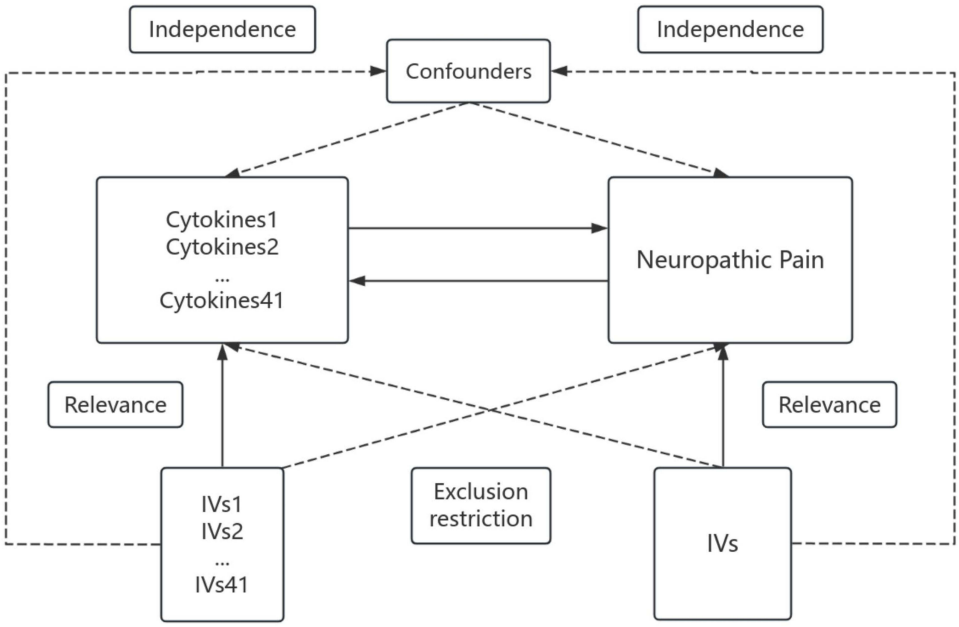

Figure 1 Schematic of the study design in this bidirectional Mendelian randomization (MR) analysis. Significant instrumental variables were selected for 41 inflammatory cytokines and neuropathic pain, and the bidirectional causalities were then explored. Three basic assumptions of MR analysis were illustrated in this causal directed acyclic graph, namely, relevance, Independence, and exclusion restrictions.

Subsequently, to mitigate linkage disequilibrium, we clumped these SNPs (kb=10,000, r^2=0.001). Palindromic SNPs were excluded because their alignment direction for exposure and outcome in the GWASs of systemic inflammatory regulators could not be reliably determined. The proportion of variance in exposure was subsequently calculated using the R^2 value of each SNP, and the instrument strength was estimated using the F-statistic to avoid weak instrument bias.[16,17] Finally, we substituted the SNPs that were unavailable in the outcome summary with proxy SNPs (R^2>0.9) from LDlink (https://ldlink.nci.nih.gov/).[18]

Statistical Analysis

Our analysis employed a multifaceted approach utilizing various MR methods to assess the causal association between inflammatory cytokines and neuropathic pain. The inverse variance weighted (IVW) method combines causal estimates from each SNP, weighting them by their precision; however, it assumes that all genetic variants are valid instrumental variables, an assumption that may not hold in practice.[19] Thus, other robust methods that do not require all genetic variants to be valid IVs were also employed to give consistent estimates of a causal parameter. The weighted median approach was more robust than the other methods, providing a consistent estimate even if up to half of the weight came from invalid SNPs.[20] The MR–Egger method was particularly useful in cases of potential pleiotropy, offering a causal estimate that was corrected for such instances.[21] Additionally, the simple mode and weighted mode methods prioritized the most consistent SNP-specific causal estimates. To further bolster the reliability of our findings, we conducted a series of sensitivity analyses. Cochrans' Q test was employed to assess any heterogeneity among the different instrumental variables. The Egger intercept test was crucial in detecting directional horizontal pleiotropy, a scenario where genetic variants might affect the outcome through pathways other than the exposure pathway. Leave-one-out analysis was instrumental in evaluating the influence of individual SNPs on the overall results. Finally, we performed reverse Mendelian randomization and Steiger tests to verify the causal relationship between inflammatory factors and NeP.

The major assessment for each regulator among all the approaches listed above was chosen in accordance with the recommended strategy, which would consider three fundamental assumptions, NOME and InSIDE.[22] Should MR-PRESSO identify any outlier SNPs, these outliers will be initially excluded. Subsequently, the remaining instrumental variables (IVs) will undergo further evaluation to determine the appropriate statistical strategy. Once the recommended

approach has been established, sensitivity analyses for causal relationships will be conducted concurrently, employing additional analytical techniques. We applied a Bonferroni correction to account for the number of systemic inflammatory regulators assessed ($P<0.0012$; Bonferroni correction with 41 tests).

The culmination of our research was the visual representation of our findings. We employed two distinct visualization tools for this purpose. The circular heatmap was invaluable in offering a comprehensive view of the relationships between multiple inflammatory cytokines and neuropathic pain. The tool highlights patterns and intensities of associations in a visually intuitive manner. On the other hand, the MR forest plot provided a more detailed perspective, revealing the causal effect estimates for each inflammatory cytokine, complete with their respective confidence intervals. This approach allowed for easy comparison and interpretation of the data, increasing the accessibility of the results to both experts and laypersons. All the statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). MR analyses were performed using TwoSampleMR and MR-PRESSO (version 0.5.6).[23] The study was not preregistered on any platform.

Ethics Approval and Consent to Participate

This research has been conducted using published studies and consortia providing publicly available summary statistics. All original studies have been approved by the corresponding ethical review board, and the participants have provided informed consent (FINRISK 1997: Ethical Committee of National Public Health Institute, Statement 38/96.30.10.1996; FINRISK 2002: Helsinki University Hospital, Ethical Committee of Epidemiology and Public Health, Statement 87/2001; YFS: The study protocol was reviewed and approved by Ethics Committees of each of the participating universities (medical schools of Helsinki, Turku, Tampere, Kuopio, and Oulu); finn-b-G6_TRINEU: North West Centre for Research Ethics Committee, 11/NW/0382). In addition, no individual-level data was used in this study. Therefore, no new ethical review board approval was required. According to the 2017 International Ethical Guidelines for Health-related Research Involving Humans (Council for International Organizations of Medical Sciences, CIOMS), studies using publicly available data that ensure participant anonymity may be exempt from Institutional Review Board (IRB) approval.[24] Additionally, per Chinese national legislation guidelines ("Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, Article 32, Items 1 and 2"), this research is not subject to further ethics committee review.[25]

Results

Of the forty-one systemic inflammatory regulators examined, nine had three or more valid genetic variants when the genome-wide significance cutoff was set at $P<5\times10^{-8}$. For the remaining cytokines, a higher threshold ($P<5\times10^{-6}$) was applied to ensure that enough SNPs were present for subsequent MR analysis. All the F-statistic values of the SNPs surpassed 10, suggesting a low likelihood of significant weak instrument bias (Supplementary Tables S1–S3).

According to the selection criteria of IVs, a total of 745 SNPs were used as IVs for 41 circulating inflammatory cytokines. As shown in Table 1, five inflammatory cytokines, namely, *G-CSF, IL-16, IL-1β, IL-2, and IP-10*, were shown to be associated with neuropathic pain in at least one MR analysis. In our quest to understand the intricate relationship between circulating inflammatory cytokines and neuropathic pain, our Mendelian randomization analysis revealed

Table 1 MR Result of Causal Correlations of 41 Inflammatory Cytokines on Neuropathic Pain (NP)

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
Chemokines						
CTACK	Inverse variance weighted	13	0.080	0.103	0.436	1.083(0.886–1.324)
	MR Egger	13	0.152	0.191	0.442	1.164(0.801–1.693)
	Weighted median	13	0.125	0.149	0.400	1.134(0.846–1.519)
	Simple mode	13	0.282	0.223	0.230	1.325(0.856–2.05)
	Weighted mode	13	0.184	0.159	0.269	1.202(0.88–1.641)

(*Continued*)

Table 1 (Continued).

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
EOTAXIN	Inverse variance weighted	15	−0.196	0.124	0.115	0.822(0.644–1.049)
	MR Egger	15	−0.320	0.276	0.267	0.726(0.423–1.247)
	Weighted median	15	−0.240	0.172	0.162	0.787(0.562–1.101)
	Simple mode	15	−0.268	0.316	0.411	0.765(0.412–1.421)
	Weighted mode	15	−0.209	0.192	0.293	0.811(0.557–1.181)
GROA	Inverse variance weighted	11	0.012	0.092	0.898	1.012(0.845–1.212)
	MR Egger	11	−0.171	0.223	0.463	0.843(0.544–1.305)
	Weighted median	11	−0.063	0.111	0.572	0.939(0.755–1.168)
	Simple mode	11	−0.050	0.223	0.827	0.951(0.614–1.474)
	Weighted mode	11	−0.098	0.115	0.414	0.906(0.723–1.136)
IP-10	Inverse variance weighted	11	0.306	0.126	**0.015**	1.358(1.06–1.739)
	MR Egger	11	0.435	0.271	0.142	1.545(0.909–2.628)
	Weighted median	11	0.231	0.170	0.173	1.26(0.903–1.757)
	Simple mode	11	0.173	0.301	0.578	1.189(0.659–2.145)
	Weighted mode	11	0.168	0.272	0.550	1.183(0.694–2.018)
MCP-1-MCAF	Inverse variance weighted	14	0.022	0.147	0.880	1.022(0.766–1.364)
	MR Egger	14	0.644	0.316	0.064	1.904(1.025–3.54)
	Weighted median	14	0.134	0.185	0.470	1.143(0.796–1.642)
	Simple mode	14	0.399	0.284	0.185	1.49(0.853–2.601)
	Weighted mode	14	0.173	0.226	0.459	1.188(0.763–1.852)
MCP-3	Inverse variance weighted	6	0.095	0.100	0.344	1.1(0.903–1.339)
	MR Egger	6	0.102	0.294	0.746	1.107(0.623–1.969)
	Weighted median	6	−0.019	0.131	0.887	0.982(0.759–1.27)
	Simple mode	6	−0.064	0.213	0.776	0.938(0.618–1.424)
	Weighted mode	6	−0.066	0.218	0.773	0.936(0.611–1.434)
MIG	Inverse variance weighted	13	0.202	0.111	0.070	1.224(0.984–1.523)
	MR Egger	13	0.208	0.246	0.414	1.232(0.761–1.993)
	Weighted median	13	0.264	0.151	0.081	1.302(0.968–1.75)
	Simple mode	13	0.306	0.251	0.246	1.358(0.831–2.22)
	Weighted mode	13	0.302	0.234	0.221	1.353(0.856–2.138)
MIP-1A	Inverse variance weighted	4	−0.005	0.228	0.983	0.995(0.637–1.556)
	MR Egger	4	−0.920	0.627	0.280	0.398(0.117–1.361)
	Weighted median	4	0.207	0.275	0.452	1.23(0.717–2.111)
	Simple mode	4	0.285	0.403	0.531	1.33(0.603–2.932)
	Weighted mode	4	0.282	0.416	0.546	1.326(0.587–2.997)
MIP-1B	Inverse variance weighted	19	0.060	0.070	0.392	1.062(0.925–1.219)
	MR Egger	19	0.003	0.111	0.976	1.003(0.808–1.246)
	Weighted median	19	0.027	0.091	0.767	1.027(0.859–1.229)
	Simple mode	19	−0.017	0.164	0.920	0.983(0.713–1.357)
	Weighted mode	19	0.023	0.078	0.772	1.023(0.878–1.193)
RANTES	Inverse variance weighted	10	0.185	0.184	0.315	1.204(0.839–1.727)
	MR Egger	10	0.170	0.488	0.736	1.186(0.455–3.087)
	Weighted median	10	0.200	0.199	0.315	1.222(0.827–1.805)
	Simple mode	10	0.274	0.349	0.453	1.315(0.663–2.606)
	Weighted mode	10	0.211	0.318	0.524	1.235(0.662–2.304)
SDF-1A	Inverse variance weighted	8	0.373	0.238	0.117	1.452(0.911–2.315)
	MR Egger	8	−0.301	0.441	0.520	0.74(0.312–1.757)
	Weighted median	8	0.219	0.286	0.443	1.245(0.711–2.18)
	Simple mode	8	0.020	0.504	0.970	1.02(0.38–2.737)
	Weighted mode	8	0.046	0.453	0.923	1.047(0.43–2.545)

(*Continued*)

https://doi.org/10.2147/JPR.S495896

Table 1 (Continued).

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
Growth factors						
B-NGF	Inverse variance weighted	4	−0.197	0.221	0.373	0.821(0.532–1.267)
	MR Egger	4	1.512	1.140	0.316	4.534(0.485–42.386)
	Weighted median	4	−0.338	0.240	0.159	0.713(0.446–1.142)
	Simple mode	4	−0.400	0.360	0.347	0.67(0.331–1.357)
	Weighted mode	4	−0.389	0.308	0.296	0.678(0.37–1.24)
FGF-BASIC	Inverse variance weighted	7	−0.081	0.278	0.770	0.922(0.535–1.59)
	MR Egger	7	−0.794	0.658	0.282	0.452(0.124–1.643)
	Weighted median	7	−0.237	0.317	0.454	0.789(0.424–1.469)
	Simple mode	7	−0.617	0.502	0.265	0.539(0.202–1.442)
	Weighted mode	7	−0.497	0.469	0.330	0.608(0.242–1.525)
G-CSF	Inverse variance weighted	9	−0.562	0.192	0.003	0.57(0.391–0.831)
	MR Egger	9	−0.702	0.320	0.065	0.496(0.264–0.929)
	Weighted median	9	−0.356	0.280	0.204	0.701(0.405–1.213)
	Simple mode	9	−0.309	0.429	0.492	0.734(0.317–1.703)
	Weighted mode	9	−0.304	0.381	0.448	0.738(0.349–1.558)
HGF	Inverse variance weighted	9	−0.235	0.216	0.276	0.79(0.518–1.207)
	MR Egger	9	−0.306	0.522	0.576	0.736(0.264–2.049)
	Weighted median	9	−0.350	0.279	0.209	0.705(0.408–1.217)
	Simple mode	9	−0.566	0.493	0.284	0.568(0.216–1.492)
	Weighted mode	9	−0.414	0.500	0.431	0.661(0.248–1.761)
M-CSF	Inverse variance weighted	11	−0.010	0.109	0.929	0.99(0.8–1.226)
	MR Egger	11	−0.132	0.230	0.580	0.876(0.559–1.374)
	Weighted median	11	0.052	0.145	0.718	1.054(0.793–1.399)
	Simple mode	11	0.076	0.258	0.775	1.079(0.65–1.79)
	Weighted mode	11	0.081	0.241	0.745	1.084(0.676–1.737)
PDGF-BB	Inverse variance weighted	14	−0.109	0.123	0.374	0.896(0.704–1.141)
	MR Egger	14	0.089	0.246	0.724	1.093(0.675–1.77)
	Weighted median	14	−0.061	0.161	0.704	0.941(0.685–1.291)
	Simple mode	14	−0.123	0.265	0.651	0.884(0.526–1.487)
	Weighted mode	14	−0.090	0.172	0.608	0.914(0.652–1.279)
SCF	Inverse variance weighted	11	0.142	0.194	0.464	1.153(0.788–1.688)
	MR Egger	11	0.390	0.491	0.447	1.478(0.564–3.872)
	Weighted median	11	0.000	0.242	0.999	1(0.622–1.607)
	Simple mode	11	0.052	0.366	0.890	1.053(0.514–2.157)
	Weighted mode	11	0.036	0.377	0.926	1.037(0.495–2.169)
SCGF-B	Inverse variance weighted	18	0.046	0.098	0.639	1.047(0.864–1.27)
	MR Egger	18	0.021	0.189	0.912	1.021(0.706–1.478)
	Weighted median	18	−0.046	0.126	0.713	0.955(0.746–1.222)
	Simple mode	18	−0.070	0.230	0.765	0.932(0.593–1.465)
	Weighted mode	18	−0.026	0.192	0.894	0.974(0.669–1.419)
VEGF	Inverse variance weighted	15	−0.014	0.083	0.870	0.986(0.838–1.161)
	MR Egger	15	−0.007	0.136	0.957	0.993(0.761–1.295)
	Weighted median	15	0.008	0.101	0.936	1.008(0.826–1.23)
	Simple mode	15	−0.050	0.239	0.838	0.951(0.595–1.521)
	Weighted mode	15	0.001	0.105	0.990	1.001(0.815–1.23)

(*Continued*)

Table 1 (Continued).

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
Interleukins						
IL-10	Inverse variance weighted	14	0.007	0.124	0.954	1.007(0.79–1.285)
	MR Egger	14	0.046	0.269	0.868	1.047(0.618–1.774)
	Weighted median	14	0.018	0.158	0.908	1.018(0.748–1.387)
	Simple mode	14	0.018	0.255	0.943	1.019(0.618–1.679)
	Weighted mode	14	0.023	0.171	0.897	1.023(0.732–1.429)
IL-12-P70	Inverse variance weighted	14	0.026	0.113	0.818	1.026(0.823–1.28)
	MR Egger	14	−0.116	0.200	0.575	0.891(0.602–1.319)
	Weighted median	14	0.009	0.131	0.948	1.009(0.78–1.305)
	Simple mode	14	−0.064	0.282	0.825	0.938(0.539–1.632)
	Weighted mode	14	0.008	0.125	0.951	1.008(0.788–1.289)
IL-13	Inverse variance weighted	13	−0.063	0.083	0.446	0.939(0.798–1.104)
	MR Egger	13	0.053	0.160	0.745	1.055(0.771–1.444)
	Weighted median	13	−0.004	0.112	0.970	0.996(0.799–1.241)
	Simple mode	13	−0.167	0.224	0.470	0.846(0.546–1.312)
	Weighted mode	13	−0.011	0.118	0.927	0.989(0.784–1.248)
IL-16	Inverse variance weighted	9	−0.317	0.144	**0.027**	0.728(0.549–0.965)
	MR Egger	9	−0.039	0.225	0.867	0.962(0.618–1.495)
	Weighted median	9	−0.232	0.142	0.101	0.793(0.6–1.047)
	Simple mode	9	−0.435	0.323	0.214	0.647(0.344–1.218)
	Weighted mode	9	−0.189	0.162	0.278	0.828(0.602–1.138)
IL-17	Inverse variance weighted	11	0.159	0.213	0.454	1.173(0.773–1.78)
	MR Egger	11	0.105	0.449	0.820	1.111(0.46–2.681)
	Weighted median	11	0.361	0.231	0.119	1.434(0.911–2.257)
	Simple mode	11	0.352	0.367	0.360	1.422(0.692–2.921)
	Weighted mode	11	0.415	0.290	0.183	1.514(0.858–2.672)
IL-18	Inverse variance weighted	12	−0.079	0.094	0.402	0.924(0.769–1.111)
	MR Egger	12	−0.122	0.214	0.581	0.885(0.582–1.347)
	Weighted median	12	−0.103	0.119	0.388	0.902(0.714–1.14)
	Simple mode	12	−0.114	0.165	0.506	0.893(0.646–1.234)
	Weighted mode	12	−0.103	0.160	0.533	0.902(0.66–1.234)
IL-1β	Inverse variance weighted	3	−0.560	0.279	**0.044**	0.571(0.331–0.986)
	MR Egger	3	−0.691	0.693	0.501	0.501(0.129–1.95)
	Weighted median	3	−0.541	0.320	0.091	0.582(0.311–1.09)
	Simple mode	3	−0.482	0.405	0.356	0.618(0.279–1.366)
	Weighted mode	3	−0.488	0.386	0.334	0.614(0.288–1.308)
IL-1RA	Inverse variance weighted	10	−0.196	0.135	0.145	0.822(0.631–1.07)
	MR Egger	10	−0.372	0.335	0.299	0.689(0.357–1.33)
	Weighted median	10	−0.216	0.178	0.226	0.806(0.568–1.143)
	Simple mode	10	−0.215	0.269	0.444	0.806(0.476–1.365)
	Weighted mode	10	−0.246	0.265	0.376	0.782(0.465–1.313)
IL-2	Inverse variance weighted	8	0.002	0.199	0.994	1.002(0.679–1.478)
	MR Egger	8	−0.746	0.273	**0.034**	0.474(0.278–0.809)
	Weighted median	8	−0.115	0.202	0.571	0.892(0.6–1.326)
	Simple mode	8	−0.128	0.366	0.737	0.88(0.43–1.803)
	Weighted mode	8	−0.261	0.243	0.319	0.77(0.478–1.241)

(*Continued*)

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Table 1 (Continued).

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
IL-2RA	Inverse variance weighted	8	−0.045	0.141	0.751	0.956(0.726–1.26)
	MR Egger	8	0.009	0.232	0.972	1.009(0.64–1.589)
	Weighted median	8	−0.048	0.142	0.736	0.953(0.722–1.259)
	Simple mode	8	−0.234	0.294	0.453	0.792(0.445–1.408)
	Weighted mode	8	−0.067	0.155	0.678	0.935(0.69–1.268)
IL-4	Inverse variance weighted	14	0.172	0.182	0.347	1.187(0.83–1.698)
	MR Egger	14	0.644	0.363	0.101	1.904(0.936–3.875)
	Weighted median	14	0.158	0.241	0.512	1.171(0.731–1.876)
	Simple mode	14	0.179	0.440	0.690	1.196(0.505–2.836)
	Weighted mode	14	0.171	0.418	0.689	1.186(0.523–2.691)
IL-5	Inverse variance weighted	8	0.166	0.140	0.235	1.18(0.898–1.552)
	MR Egger	8	0.064	0.323	0.850	1.066(0.566–2.006)
	Weighted median	8	0.161	0.182	0.377	1.175(0.822–1.679)
	Simple mode	8	0.308	0.252	0.261	1.361(0.83–2.23)
	Weighted mode	8	0.164	0.243	0.520	1.179(0.733–1.896)
IL-6	Inverse variance weighted	11	−0.009	0.189	0.961	0.991(0.684–1.434)
	MR Egger	11	−0.310	0.424	0.484	0.734(0.32–1.684)
	Weighted median	11	0.120	0.257	0.641	1.127(0.681–1.865)
	Simple mode	11	0.180	0.445	0.695	1.197(0.5–2.864)
	Weighted mode	11	0.164	0.436	0.715	1.178(0.501–2.768)
IL-7	Inverse variance weighted	11	0.045	0.097	0.643	1.046(0.865–1.264)
	MR Egger	11	−0.006	0.213	0.978	0.994(0.654–1.509)
	Weighted median	11	0.018	0.136	0.892	1.019(0.78–1.33)
	Simple mode	11	0.032	0.203	0.877	1.033(0.694–1.538)
	Weighted mode	11	0.019	0.149	0.900	1.019(0.762–1.364)
IL-8	Inverse variance weighted	8	−0.093	0.151	0.535	0.911(0.678–1.224)
	MR Egger	8	0.105	0.278	0.718	1.111(0.644–1.917)
	Weighted median	8	−0.019	0.197	0.922	0.981(0.666–1.444)
	Simple mode	8	0.071	0.297	0.818	1.074(0.6–1.922)
	Weighted mode	8	0.036	0.268	0.897	1.037(0.613–1.754)
IL-9	Inverse variance weighted	6	−0.214	0.194	0.270	0.807(0.552–1.181)
	MR Egger	6	−0.347	0.509	0.533	0.707(0.26–1.918)
	Weighted median	6	−0.153	0.253	0.545	0.858(0.523–1.409)
	Simple mode	6	−0.099	0.350	0.789	0.906(0.456–1.798)
	Weighted mode	6	−0.054	0.353	0.885	0.947(0.474–1.894)
Others						
IFN-G	Inverse variance weighted	12	−0.110	0.217	0.613	0.896(0.586–1.371)
	MR Egger	12	−0.807	0.427	0.088	0.446(0.193–1.031)
	Weighted median	12	−0.009	0.253	0.973	0.991(0.604–1.627)
	Simple mode	12	0.019	0.441	0.966	1.019(0.43–2.418)
	Weighted mode	12	−0.030	0.468	0.950	0.971(0.388–2.43)
MIF	Inverse variance weighted	10	−0.219	0.137	0.108	0.803(0.615–1.05)
	MR Egger	10	0.063	0.284	0.831	1.065(0.61–1.859)
	Weighted median	10	−0.180	0.185	0.329	0.835(0.581–1.2)
	Simple mode	10	−0.209	0.273	0.464	0.811(0.475–1.385)
	Weighted mode	10	−0.189	0.254	0.475	0.828(0.504–1.36)

(*Continued*)

Table 1 (Continued).

Exposure	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
TNF-α	Inverse variance weighted	4	0.078	0.203	0.703	1.081(0.726–1.609)
	MR Egger	4	−0.096	0.320	0.792	0.908(0.485–1.701)
	Weighted median	4	0.131	0.250	0.600	1.14(0.699–1.859)
	Simple mode	4	0.235	0.344	0.544	1.265(0.644–2.481)
	Weighted mode	4	0.255	0.347	0.516	1.29(0.654–2.547)
TNF-β	Inverse variance weighted	5	0.147	0.197	0.454	1.159(0.788–1.704)
	MR Egger	5	0.327	0.377	0.450	1.386(0.662–2.901)
	Weighted median	5	0.006	0.163	0.973	1.006(0.731–1.383)
	Simple mode	5	−0.096	0.226	0.692	0.908(0.583–1.415)
	Weighted mode	5	−0.036	0.182	0.852	0.965(0.675–1.378)
TRAIL	Inverse variance weighted	14	−0.068	0.088	0.444	0.935(0.786–1.111)
	MR Egger	14	−0.017	0.112	0.882	0.983(0.789–1.225)
	Weighted median	14	−0.076	0.114	0.504	0.926(0.741–1.159)
	Simple mode	14	−0.021	0.173	0.905	0.979(0.697–1.375)
	Weighted mode	14	−0.031	0.116	0.790	0.969(0.772–1.216)

Note: The bold font in the table indicates $P < 0.05$, which means statistically significance.

several significant findings. By leveraging the inverse variance weighted (IVW) method, we were able to delve into the associations and unearth the roles of various inflammatory cytokines in relation to neuropathic pain.

One of the most striking findings was the protective effect of *G-CSF* on neuropathic pain (OR=0.57, 95% CI=0.39–0.83; *P*=3.4e−03). In simpler terms, these numbers suggest that individuals with elevated levels of *G-CSF* might experience a decreased risk of developing neuropathic pain (Figure 2A and 3). This protective effect not only is statistically significant but also hints at potential therapeutic avenues.

IL-16, another inflammatory cytokine, was shown to be associated with the protective effect of *G-CSF* (OR=0.73, 95% CI=0.55–0.96; *P*=2.7e−02). These findings further reinforce the hypothesis that certain inflammatory cytokines, when present at higher concentrations, might play pivotal roles in mitigating the onset or severity of neuropathic pain (Figure 2B and 3).

IL-1β, yet another cytokine in our study, paralleled the findings of *G-CSF* and *IL-16*. This treatment had a protective effect (OR =0.57, 95% CI=0.33–0.99, *P*=4.4e−02). These trifecta of cytokines, which all indicate a protective effect, underscore the potential complexities and interplay involved in the inflammatory response related to neuropathic pain (Figure 2C and 3).

However, not all cytokines followed this protective trend. *IP-10*, for instance, deviated from this pattern. Our analysis indicated that *IP-10* might be associated with an increased risk of neuropathic pain (OR=1.36, 95% CI=1.06–1.74; *P*= 1.5e−02). This finding suggests a potential cautionary role for *IP-10*, indicating that elevated levels of this cytokine might be linked to increased susceptibility to neuropathic pain (Figure 2D and 3). The results showing suggestive associations were considered significant ($P < 0.05$) before correction but did not maintain significance after multiple-comparison adjustment ($P < 0.0012$, Bonferroni correction with 41 tests).[26] Since this was an exploratory study, we did not correct for multiple testing.

Given the profound implications of our primary findings, we deemed it crucial to validate these results through a series of sensitivity analyses. These analyses aimed to test the robustness and reliability of our primary results. Funnel plots of the Mendelian randomization analyses for *G-CSF, IL-16, IL-1β, and IP-10* in patients with neuropathic pain are shown in Figure 4. There were not potential outliers of the IVs of *G-CSF, IL-16, IL-1β, IP-10* that were present on visual inspection in leave-one-out plots (Figure 5). The Cochran Q test, a measure used to assess heterogeneity among different instrumental variables, did not indicate any significant discrepancies (Supplementary Table S4), and no outlier SNPs were detected with the MR-PRESSO method (Supplementary Table S5). Similarly, the Egger intercept test, which was designed to detect potential horizontal pleiotropy (Supplementary Table S6), and the leave-one-out analysis (Figure 5),

https://doi.org/10.2147/JPR.S495896

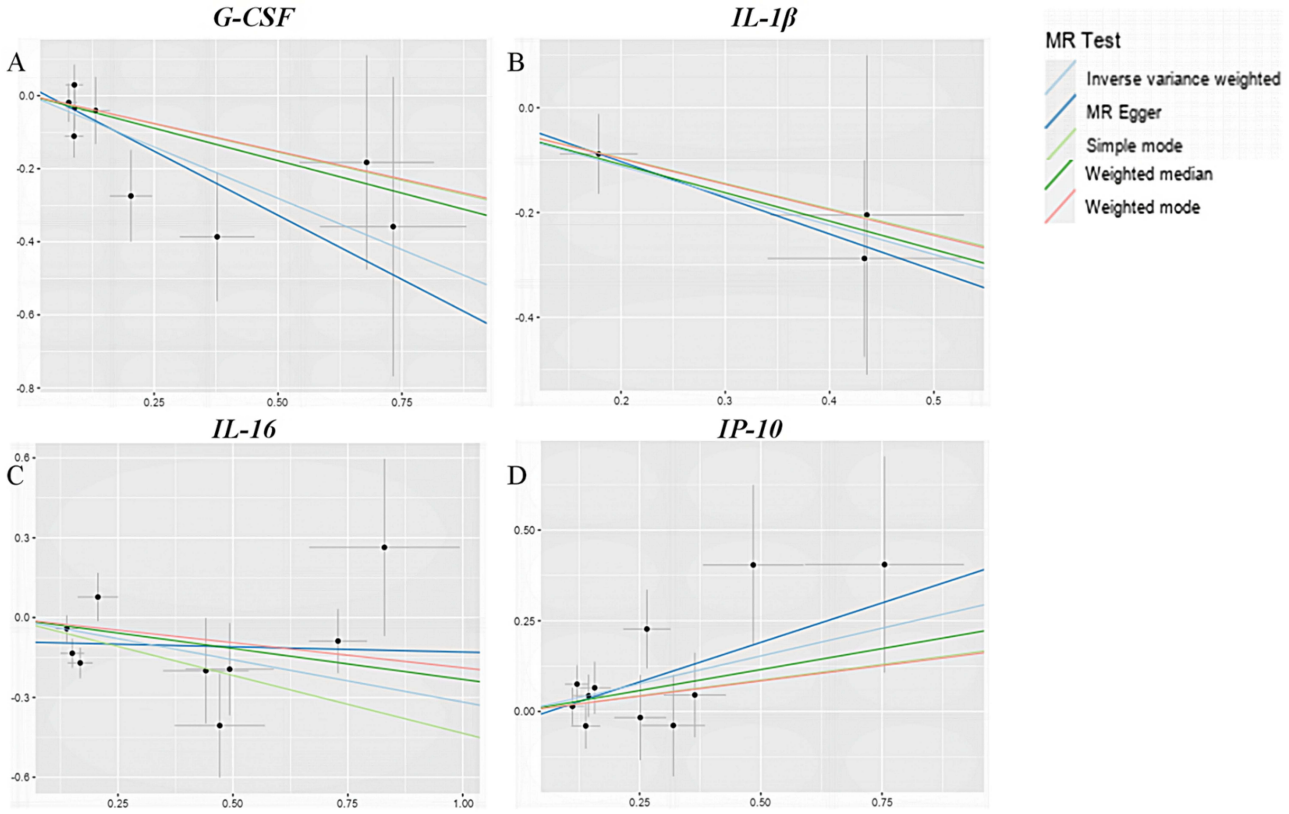

Figure 2 Scatter plots of Mendelian randomization (MR) analyses. (**A–D**) Individual inverse variance (IV) associations with cytokine risk are displayed versus individual IV associations with NeP in black dots. The 95% CI of odd ratio for each IV is shown by vertical and horizontal lines. The slope of the lines represents the estimated causal effect of the MR methods.

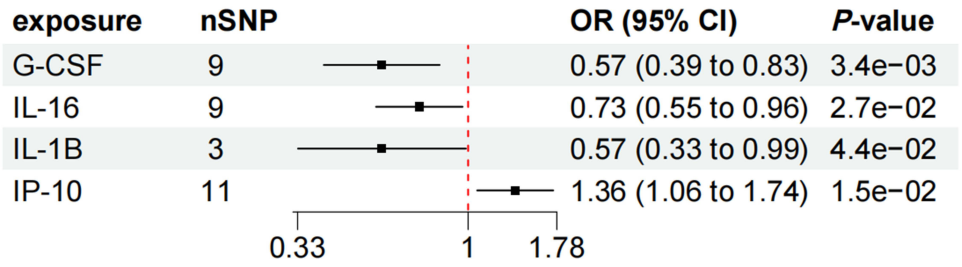

Figure 3 The results of Mendelian randomization (MR) analyses.

which evaluates the influence of individual SNPs on the overall results, both corroborated our primary findings. The Steiger test showed that *IL-16* was upstream of the outcome (P= 0.012; Supplementary Table S7). However, the influence of NeP on 41 inflammatory cytokines, according to the result of IVW (Table 2), was proven that there was no reverse causal association between Nep and *G-CSF* (P=0.541), *IL-16* (P=0.794), *IL-1β* (P=0.940), *IP-10* (P=0.593).

To further elucidate and visually represent our findings, we employed tools such as the circular heatmap (Figure 6) and the MR forest plot (Figure 7). With its vibrant color gradients, the heatmap provides a panoramic view of the relationships between multiple inflammatory cytokines and neuropathic pain. On the other hand, the MR forest plot provided a more granular perspective, detailing the causal effect estimates for each cytokine, complete with their respective confidence intervals.

In conclusion, our results shed light on the multifaceted relationships between inflammatory cytokines and neuropathic pain, suggesting potential avenues for future research and therapeutic interventions.

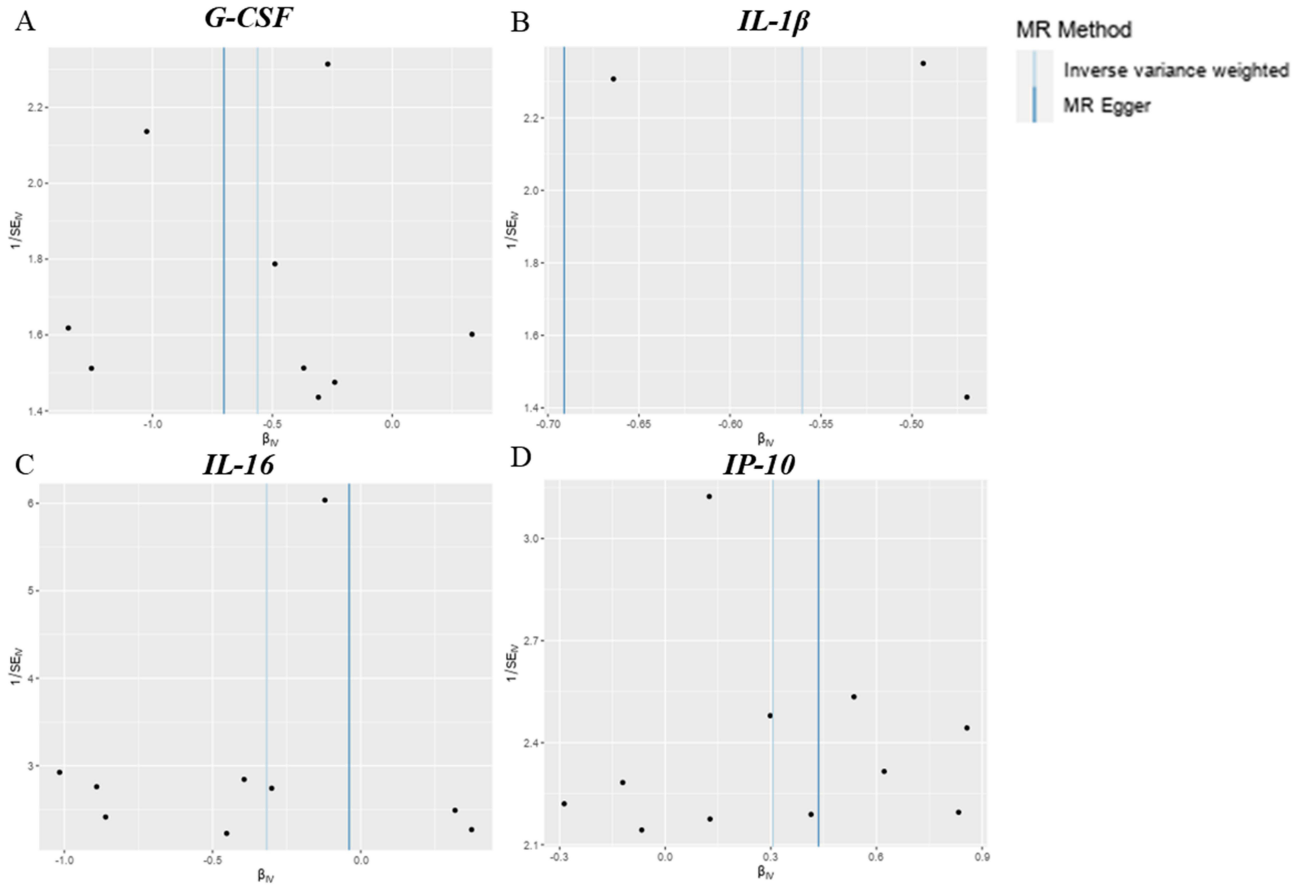

Figure 4 Funnel plots of Mendelian randomization (MR) analyses. (**A**–**D**) The funnel plots show the inverse variance weighted MR estimate of each cytokine single-nucleotide polymorphism with NeP versus 1/standard error (1/SEIV).

Discussion

In this two-sample MR analysis, we first investigated the causative relationships of 41 biomarkers, including growth factor, interleukin, and chemokine levels, and evaluated NeP as the outcome. The relationship between circulating inflammatory cytokines and NeP has been a focal point of numerous studies, with the overarching goal of understanding the underlying mechanisms and identifying potential therapeutic targets. Our Mendelian randomization study shed light on this intricate relationship, suggesting a causal association between specific inflammatory cytokines and NeP. These findings not only corroborate the literature but also provide novel insights that could pave the way for future research and therapeutic interventions.

The protective effects observed for *G-CSF, IL-16*, and *IL-1β* in our study align with the broader understanding of the role of inflammatory cytokines in various diseases. Granulocyte colony stimulating factor (G-CSF) is known for its role in promoting the growth of white blood cells and may have implications in modulating pain pathways, potentially offering protective mechanisms against neuropathic pain.[27] Ming-Feng Liao et al demonstrated that *G-CSF* can relieve neuropathic pain through animal experiments.[28] Additionally, in a Phase I and IIa clinical trial, *G-CSF* was shown to relieve neuropathic pain in patients with compression myelopathy.[29] Although there have been few studies on *G-CSF* in NeP, its underlying function in the formation of NeP should be investigated, and exploratory research utilizing more comprehensive data should be conducted to elucidate the link between *G-CSF* levels and NeP.

IL-1β (interleukin-1 beta), a cytokine known for its role in inflammatory processes, can influence the neuropathic pain pathway, either by exacerbating or alleviating pain symptoms. Mingzhu Li et al showed that *IL-1β* participates in preventing and treating oxaliplatin-induced neuropathic pain.[30] Conversely, in an observational study, increased *IL-1β* release seemed to be a particular phenomenon in patients with NeP.[31] In our study, we found that *IL-1β* has a protective effect against neuropathic pain. More research should be conducted to verify this relationship and elucidate the underlying mechanisms involved.

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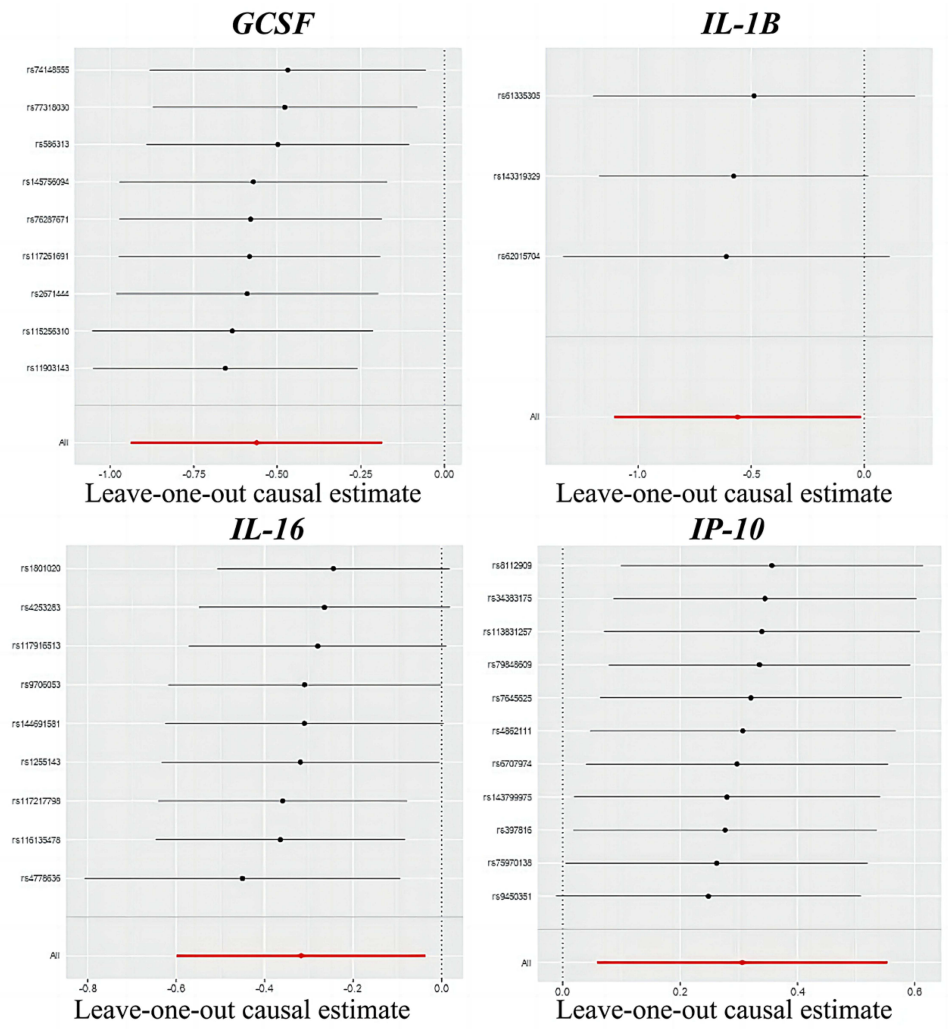

Figure 5 Leave-one-out causal estimate of Mendelian randomization (MR) analyses.

IL-16 (interleukin-16) is an immunomodulatory chemokine that signals through CD4+ T cells, monocytes, macrophages, and dendritic cells.[32] However, the role of IL-16 in NeP is uncertain. In our research, we discovered that IL-16 plays a defensive role in mitigating neuropathic pain. Further investigations are warranted to confirm this link and to clarify the underlying processes involved. For instance, a Mendelian randomization analysis by Bouras et al revealed associations between specific inflammatory biomarkers and the risk of several cancers.[33] Similarly, Li et al explored the causal effects of inflammatory cytokines on the risk of ischemic stroke.[34] These observations contribute to the

Table 2 MR Result of Causal Correlations of Neuropathic Pain (NP) on 41 Inflammatory Cytokines

Outcome	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
Chemokines						
CTACK	Inverse variance weighted	6	0.066	0.041	0.111	1.068(0.985–1.159)
	MR Egger	6	0.017	0.094	0.869	1.017(0.845–1.223)
	Weighted median	6	0.085	0.052	0.103	1.088(0.983–1.205)
	Simple mode	6	0.107	0.073	0.204	1.113(0.964–1.284)
	Weighted mode	6	0.107	0.077	0.223	1.113(0.957–1.293)

(*Continued*)

Table 2 (Continued).

Outcome	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
EOTAXIN	Inverse variance weighted	6	−0.054	0.039	0.163	0.947(0.878–1.022)
	MR Egger	6	−0.054	0.099	0.615	0.948(0.781–1.15)
	Weighted median	6	−0.02	0.037	0.595	0.981(0.912–1.054)
	Simple mode	6	−0.008	0.055	0.888	0.992(0.89–1.105)
	Weighted mode	6	−0.014	0.051	0.792	0.986(0.892–1.09)
GROA	Inverse variance weighted	6	0.031	0.051	0.54	1.032(0.934–1.14)
	MR Egger	6	0.02	0.129	0.882	1.021(0.793–1.314)
	Weighted median	6	0.035	0.056	0.527	1.036(0.929–1.156)
	Simple mode	6	0.054	0.075	0.503	1.055(0.912–1.222)
	Weighted mode	6	0.046	0.073	0.557	1.047(0.907–1.209)
IP_10	Inverse variance weighted	6	−0.029	0.054	0.593	0.971(0.874–1.08)
	MR Egger	6	0.108	0.114	0.399	1.114(0.89–1.393)
	Weighted median	6	−0.048	0.057	0.396	0.953(0.852–1.065)
	Simple mode	6	−0.06	0.087	0.519	0.942(0.794–1.116)
	Weighted mode	6	−0.053	0.08	0.533	0.948(0.811–1.108)
MCP-1-MCAF	Inverse variance weighted	6	0.006	0.028	0.84	1.006(0.953–1.062)
	MR Egger	6	0.006	0.063	0.923	1.006(0.89–1.138)
	Weighted median	6	0.008	0.034	0.814	1.008(0.943–1.078)
	Simple mode	6	0.01	0.047	0.84	1.01(0.92–1.109)
	Weighted mode	6	0.008	0.048	0.88	1.008(0.918–1.107)
MCP-3	Inverse variance weighted	4	0.002	0.088	0.979	1.002(0.844–1.191)
	MR Egger	4	−0.012	0.218	0.962	0.988(0.644–1.516)
	Weighted median	4	0.005	0.109	0.961	1.005(0.813–1.244)
	Simple mode	4	−0.062	0.155	0.717	0.94(0.693–1.274)
	Weighted mode	4	0.028	0.151	0.864	1.028(0.765–1.382)
MIG	Inverse variance weighted	6	0.029	0.041	0.489	1.029(0.949–1.116)
	MR Egger	6	0.092	0.094	0.381	1.097(0.912–1.319)
	Weighted median	6	0.034	0.054	0.536	1.034(0.93–1.151)
	Simple mode	6	0.041	0.08	0.626	1.042(0.891–1.219)
	Weighted mode	6	−0.02	0.08	0.808	0.98(0.838–1.146)
MIP-1α	Inverse variance weighted	6	0.033	0.043	0.445	1.033(0.95–1.124)
	MR Egger	6	−0.078	0.096	0.46	0.925(0.767–1.116)
	Weighted median	6	0.013	0.058	0.822	1.013(0.905–1.134)
	Simple mode	6	−0.035	0.089	0.707	0.965(0.811–1.148)
	Weighted mode	6	−0.02	0.092	0.836	0.98(0.819–1.174)
MIP-1β	Inverse variance weighted	6	−0.041	0.034	0.236	0.96(0.897–1.027)
	MR Egger	6	0.018	0.081	0.832	1.019(0.869–1.194)
	Weighted median	6	−0.065	0.036	0.068	0.937(0.874–1.005)
	Simple mode	6	−0.084	0.055	0.191	0.92(0.825–1.025)
	Weighted mode	6	−0.085	0.056	0.189	0.919(0.824–1.025)
RANTES	Inverse variance weighted	6	0.026	0.043	0.544	1.026(0.944–1.117)
	MR Egger	6	0.044	0.097	0.678	1.044(0.863–1.264)
	Weighted median	6	0.039	0.054	0.479	1.039(0.934–1.156)
	Simple mode	6	0.035	0.082	0.692	1.035(0.881–1.217)
	Weighted mode	6	0.046	0.082	0.6	1.047(0.892–1.229)
SDF-1α	Inverse variance weighted	6	0.002	0.029	0.931	1.002(0.948–1.06)
	MR Egger	6	−0.091	0.065	0.231	0.913(0.804–1.036)
	Weighted median	6	−0.004	0.038	0.925	0.996(0.925–1.073)
	Simple mode	6	−0.025	0.063	0.706	0.975(0.862–1.103)
	Weighted mode	6	−0.04	0.066	0.575	0.961(0.845–1.094)

(*Continued*)

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Table 2 (Continued).

Outcome	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
Growth factors						
B-NGF	Inverse variance weighted	6	0.027	0.046	0.558	1.028(0.938–1.125)
	MR Egger	6	0.032	0.118	0.802	1.032(0.819–1.3)
	Weighted median	6	0.021	0.052	0.69	1.021(0.923–1.129)
	Simple mode	6	0.013	0.083	0.883	1.013(0.86–1.193)
	Weighted mode	6	0.014	0.076	0.859	1.014(0.874–1.177)
G-CSF	Inverse variance weighted	6	−0.017	0.028	0.541	0.983(0.93–1.039)
	MR Egger	6	−0.069	0.064	0.341	0.933(0.823–1.058)
	Weighted median	6	−0.028	0.036	0.448	0.973(0.906–1.045)
	Simple mode	6	−0.031	0.053	0.582	0.969(0.873–1.076)
	Weighted mode	6	−0.037	0.051	0.494	0.963(0.872–1.064)
HGF	Inverse variance weighted	6	−0.021	0.032	0.503	0.979(0.92–1.042)
	MR Egger	6	−0.054	0.078	0.526	0.947(0.813–1.104)
	Weighted median	6	0.001	0.036	0.979	1.001(0.933–1.074)
	Simple mode	6	0.002	0.048	0.961	1.002(0.913–1.101)
	Weighted mode	6	0.002	0.045	0.959	1.002(0.917–1.096)
FGF-BASIC	Inverse variance weighted	6	−0.033	0.029	0.252	0.967(0.914–1.024)
	MR Egger	6	−0.052	0.065	0.471	0.949(0.835–1.079)
	Weighted median	6	−0.03	0.036	0.409	0.97(0.904–1.042)
	Simple mode	6	−0.019	0.05	0.721	0.981(0.89–1.082)
	Weighted mode	6	−0.021	0.046	0.673	0.98(0.895–1.072)
M-CSF	Inverse variance weighted	6	0.01	0.051	0.848	1.01(0.914–1.116)
	MR Egger	6	0.163	0.116	0.232	1.177(0.938–1.475)
	Weighted median	6	−0.006	0.065	0.922	0.994(0.876–1.128)
	Simple mode	6	0.006	0.099	0.956	1.006(0.828–1.222)
	Weighted mode	6	−0.004	0.096	0.968	0.996(0.825–1.202)
PDGF-BB	Inverse variance weighted	6	−0.008	0.028	0.769	0.992(0.94–1.047)
	MR Egger	6	−0.006	0.063	0.932	0.994(0.879–1.124)
	Weighted median	6	−0.008	0.035	0.812	0.992(0.927–1.061)
	Simple mode	6	0.005	0.047	0.922	1.005(0.917–1.101)
	Weighted mode	6	−0.03	0.046	0.543	0.971(0.887–1.062)
SCF	Inverse variance weighted	6	0.054	0.044	0.22	1.055(0.968–1.15)
	MR Egger	6	−0.012	0.105	0.916	0.988(0.804–1.215)
	Weighted median	6	0.029	0.04	0.457	1.03(0.953–1.113)
	Simple mode	6	−0.038	0.088	0.685	0.963(0.811–1.144)
	Weighted mode	6	−0.032	0.079	0.698	0.968(0.829–1.13)
SCGF-β	Inverse variance weighted	6	0.017	0.041	0.684	1.017(0.938–1.103)
	MR Egger	6	−0.048	0.094	0.637	0.953(0.793–1.146)
	Weighted median	6	0.011	0.052	0.829	1.011(0.914–1.119)
	Simple mode	6	−0.041	0.075	0.602	0.959(0.829–1.11)
	Weighted mode	6	−0.041	0.082	0.636	0.959(0.816–1.128)
VEGF	Inverse variance weighted	6	−0.07	0.042	0.098	0.932(0.858–1.013)
	MR Egger	6	−0.161	0.094	0.162	0.851(0.708–1.024)
	Weighted median	6	−0.06	0.043	0.16	0.942(0.866–1.024)
	Simple mode	6	−0.123	0.082	0.197	0.885(0.753–1.04)
	Weighted mode	6	−0.128	0.088	0.208	0.88(0.74–1.047)
Interleukins						
IL-10	Inverse variance weighted	6	−0.084	0.029	0.003	0.919(0.869–0.972)
	MR Egger	6	−0.14	0.066	0.101	0.87(0.765–0.989)

(*Continued*)

Table 2 (Continued).

Outcome	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
	Weighted median	6	−0.056	0.038	0.136	0.945(0.877–1.018)
	Simple mode	6	−0.066	0.051	0.253	0.936(0.847–1.035)
	Weighted mode	6	−0.051	0.049	0.349	0.951(0.864–1.046)
IL-12-P70	Inverse variance weighted	6	−0.072	0.028	0.01	0.931(0.882–0.983)
	MR Egger	6	−0.104	0.063	0.172	0.901(0.797–1.019)
	Weighted median	6	−0.077	0.034	0.025	0.926(0.866–0.99)
	Simple mode	6	−0.083	0.047	0.135	0.92(0.839–1.008)
	Weighted mode	6	−0.084	0.047	0.131	0.919(0.839–1.007)
IL-13	Inverse variance weighted	6	−0.029	0.053	0.58	0.971(0.875–1.078)
	MR Egger	6	−0.201	0.095	0.102	0.818(0.678–0.986)
	Weighted median	6	0.018	0.061	0.768	1.018(0.903–1.148)
	Simple mode	6	−0.141	0.103	0.227	0.868(0.71–1.062)
	Weighted mode	6	0.034	0.094	0.731	1.035(0.861–1.243)
IL-16	Inverse variance weighted	6	0.012	0.047	0.794	1.012(0.923–1.11)
	MR Egger	6	0.06	0.116	0.635	1.061(0.845–1.333)
	Weighted median	6	−0.023	0.055	0.684	0.978(0.877–1.09)
	Simple mode	6	−0.037	0.08	0.664	0.964(0.825–1.127)
	Weighted mode	6	−0.037	0.071	0.626	0.964(0.839–1.107)
IL-17	Inverse variance weighted	6	−0.032	0.028	0.255	0.968(0.915–1.024)
	MR Egger	6	−0.053	0.065	0.457	0.948(0.835–1.076)
	Weighted median	6	−0.032	0.035	0.359	0.969(0.905–1.037)
	Simple mode	6	−0.038	0.052	0.494	0.963(0.87–1.065)
	Weighted mode	6	−0.03	0.046	0.546	0.971(0.887–1.062)
IL-18	Inverse variance weighted	6	−0.04	0.042	0.336	0.961(0.886–1.042)
	MR Egger	6	−0.069	0.095	0.507	0.934(0.776–1.124)
	Weighted median	6	−0.017	0.049	0.726	0.983(0.892–1.083)
	Simple mode	6	0.002	0.076	0.984	1.002(0.863–1.162)
	Weighted mode	6	−0.005	0.071	0.946	0.995(0.865–1.144)
IL-1B	Inverse variance weighted	6	−0.003	0.044	0.94	0.997(0.915–1.086)
	MR Egger	6	−0.13	0.099	0.259	0.878(0.723–1.066)
	Weighted median	6	−0.007	0.059	0.907	0.993(0.885–1.115)
	Simple mode	6	−0.002	0.088	0.983	0.998(0.839–1.187)
	Weighted mode	6	−0.009	0.085	0.92	0.991(0.839–1.17)
IL-1RA	Inverse variance weighted	6	−0.039	0.042	0.35	0.962(0.886–1.044)
	MR Egger	6	−0.06	0.095	0.561	0.942(0.783–1.134)
	Weighted median	6	−0.016	0.051	0.758	0.984(0.89–1.088)
	Simple mode	6	−0.007	0.071	0.924	0.993(0.864–1.142)
	Weighted mode	6	−0.008	0.064	0.901	0.992(0.876–1.123)
IL-2	Inverse variance weighted	6	−0.036	0.043	0.399	0.965(0.887–1.049)
	MR Egger	6	−0.181	0.097	0.135	0.834(0.69–1.009)
	Weighted median	6	−0.036	0.055	0.51	0.964(0.866–1.074)
	Simple mode	6	−0.051	0.09	0.593	0.95(0.797–1.133)
	Weighted mode	6	−0.038	0.088	0.685	0.963(0.81–1.144)
IL-2RA	Inverse variance weighted	6	0.051	0.047	0.27	1.053(0.961–1.153)
	MR Egger	6	−0.086	0.094	0.41	0.917(0.763–1.103)
	Weighted median	6	0.074	0.057	0.188	1.077(0.964–1.204)
	Simple mode	6	0.115	0.101	0.307	1.122(0.92–1.369)
	Weighted mode	6	0.127	0.1	0.258	1.136(0.934–1.382)
IL-4	Inverse variance weighted	6	−0.035	0.028	0.21	0.966(0.914–1.02)
	MR Egger	6	−0.062	0.063	0.381	0.939(0.83–1.064)

(*Continued*)

https://doi.org/10.2147/JPR.S495896

Table 2 (Continued).

Outcome	Methods	nSNP	Beta	SE	*P*	OR (95% CI)
	Weighted median	6	−0.02	0.034	0.557	0.98(0.916–1.048)
	Simple mode	6	−0.017	0.043	0.708	0.983(0.904–1.069)
	Weighted mode	6	−0.016	0.044	0.737	0.985(0.903–1.073)
IL-5	Inverse variance weighted	6	−0.009	0.043	0.833	0.991(0.911–1.078)
	MR Egger	6	−0.02	0.098	0.852	0.981(0.809–1.189)
	Weighted median	6	−0.006	0.053	0.913	0.994(0.897–1.102)
	Simple mode	6	0.02	0.082	0.814	1.021(0.869–1.199)
	Weighted mode	6	0.02	0.082	0.814	1.021(0.869–1.199)
IL-6	Inverse variance weighted	6	−0.059	0.028	0.035	0.943(0.893–0.996)
	MR Egger	6	−0.081	0.063	0.27	0.923(0.815–1.044)
	Weighted median	6	−0.042	0.034	0.219	0.959(0.896–1.025)
	Simple mode	6	−0.04	0.043	0.391	0.961(0.884–1.045)
	Weighted mode	6	−0.04	0.04	0.358	0.96(0.888–1.039)
IL-7	Inverse variance weighted	6	−0.042	0.048	0.381	0.959(0.874–1.053)
	MR Egger	6	−0.11	0.115	0.392	0.896(0.716–1.122)
	Weighted median	6	−0.037	0.055	0.504	0.964(0.866–1.074)
	Simple mode	6	−0.036	0.08	0.669	0.964(0.824–1.128)
	Weighted mode	6	−0.033	0.075	0.677	0.967(0.835–1.121)
IL-8	Inverse variance weighted	6	0.029	0.042	0.485	1.03(0.948–1.118)
	MR Egger	6	−0.079	0.096	0.453	0.924(0.766–1.114)
	Weighted median	6	0.024	0.054	0.656	1.024(0.922–1.138)
	Simple mode	6	0.003	0.079	0.971	1.003(0.86–1.17)
	Weighted mode	6	−0.001	0.079	0.99	0.999(0.855–1.167)
IL-9	Inverse variance weighted	6	0.002	0.042	0.964	1.002(0.923–1.087)
	MR Egger	6	−0.07	0.094	0.5	0.932(0.775–1.122)
	Weighted median	6	0.005	0.051	0.927	1.005(0.909–1.111)
	Simple mode	6	0.011	0.068	0.877	1.011(0.885–1.156)
	Weighted mode	6	0.015	0.063	0.822	1.015(0.897–1.149)
Others						
IFN-G	Inverse variance weighted	6	−0.057	0.029	0.045	0.944(0.893–0.999)
	MR Egger	6	−0.074	0.065	0.316	0.928(0.817–1.055)
	Weighted median	6	−0.051	0.036	0.154	0.95(0.885–1.02)
	Simple mode	6	−0.04	0.053	0.485	0.961(0.867–1.066)
	Weighted mode	6	−0.043	0.048	0.413	0.958(0.873–1.052)
TNF-A	Inverse variance weighted	6	0.019	0.043	0.664	1.019(0.937–1.108)
	MR Egger	6	−0.165	0.097	0.164	0.848(0.701–1.025)
	Weighted median	6	−0.035	0.054	0.519	0.966(0.868–1.074)
	Simple mode	6	−0.043	0.076	0.598	0.958(0.826–1.112)
	Weighted mode	6	−0.041	0.078	0.625	0.96(0.824–1.119)
MIF	Inverse variance weighted	6	−0.035	0.051	0.5	0.966(0.874–1.068)
	MR Egger	6	−0.043	0.13	0.757	0.958(0.743–1.235)
	Weighted median	6	−0.017	0.058	0.766	0.983(0.877–1.102)
	Simple mode	6	−0.019	0.082	0.827	0.981(0.837–1.151)
	Weighted mode	6	−0.022	0.077	0.785	0.978(0.841–1.137)
TRAIL	Inverse variance weighted	6	0.043	0.028	0.118	1.044(0.989–1.103)
	MR Egger	6	0.061	0.063	0.387	1.063(0.939–1.203)
	Weighted median	6	0.022	0.036	0.538	1.023(0.953–1.098)
	Simple mode	6	0.021	0.049	0.687	1.021(0.927–1.125)
	Weighted mode	6	0.02	0.046	0.682	1.02(0.932–1.116)

Note: The bold font in the table indicates $P < 0.05$, which means statistically significance.

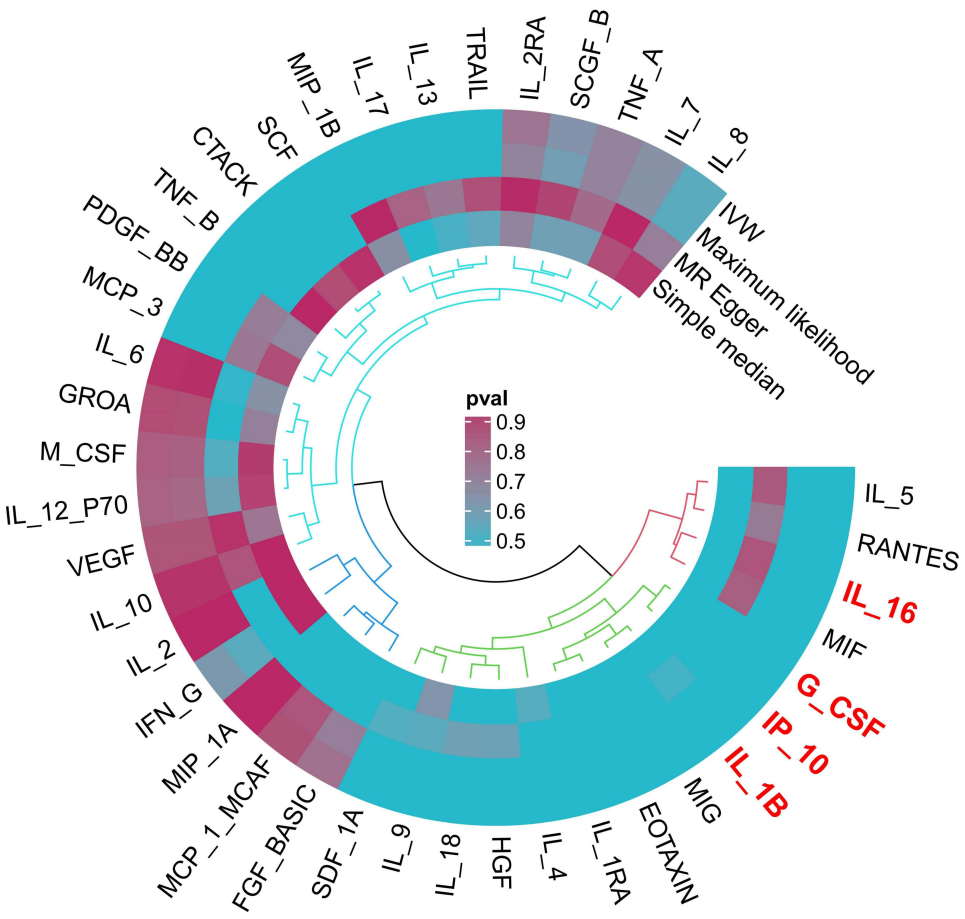

Figure 6 The circular heatmap. With its vibrant color gradients, the heatmap provides a panoramic view of the relationships between multiple inflammatory cytokines and neuropathic pain.

broader understanding of how inflammatory cytokines, often associated with various diseases, can have specific implications in the context of neuropathic pain. These studies underscore the multifaceted roles of inflammatory cytokines in health and disease.

Interestingly, our findings regarding the protective effects of certain cytokines against neuropathic pain are in line with recent studies that have investigated the role of inflammatory cytokines in other diseases. For instance, Guan et al conducted a Mendelian randomization study exploring the causal correlations between inflammatory cytokines and hypertensive disorders during pregnancy.[35] Their study suggested that certain cytokines, such as interleukin-9 (*IL-9*) and macrophage migration inhibitory factor (*MIF*), might reduce HDP risk, while others could be involved in HDP development.

Furthermore, the role of inflammatory cytokines in the context of infectious diseases, such as COVID-19, has been a topic of recent interest. Wang et al conducted a Mendelian randomization analysis to identify the causal effects of COVID-19 on 41 cytokines.[36] Their findings indicated that certain cytokines are promoted by COVID-19, while others are inhibited, emphasizing the complex interplay between viral infections and the host inflammatory response.

Interferon-γ (IFN-γ)-induced protein 10 (*IP-10* or *CXCL-10*) is a chemokine involved in trafficking immune cells to inflammatory sites.[37] The increased risk associated with *IP-10*, as observed in our study, is particularly intriguing. These findings underscore the need for a deeper understanding of the role of *IP-10* in the pathogenesis of neuropathic pain. Dong and Ubogu highlighted the association between proinflammatory cytokines and chronic neuropathic pain in traumatic and inflammatory neuropathies.[10] Their observations suggest that early expression of specific proinflammatory cytokines might predict the development of chronic nociception.

https://doi.org/10.2147/JPR.S495896

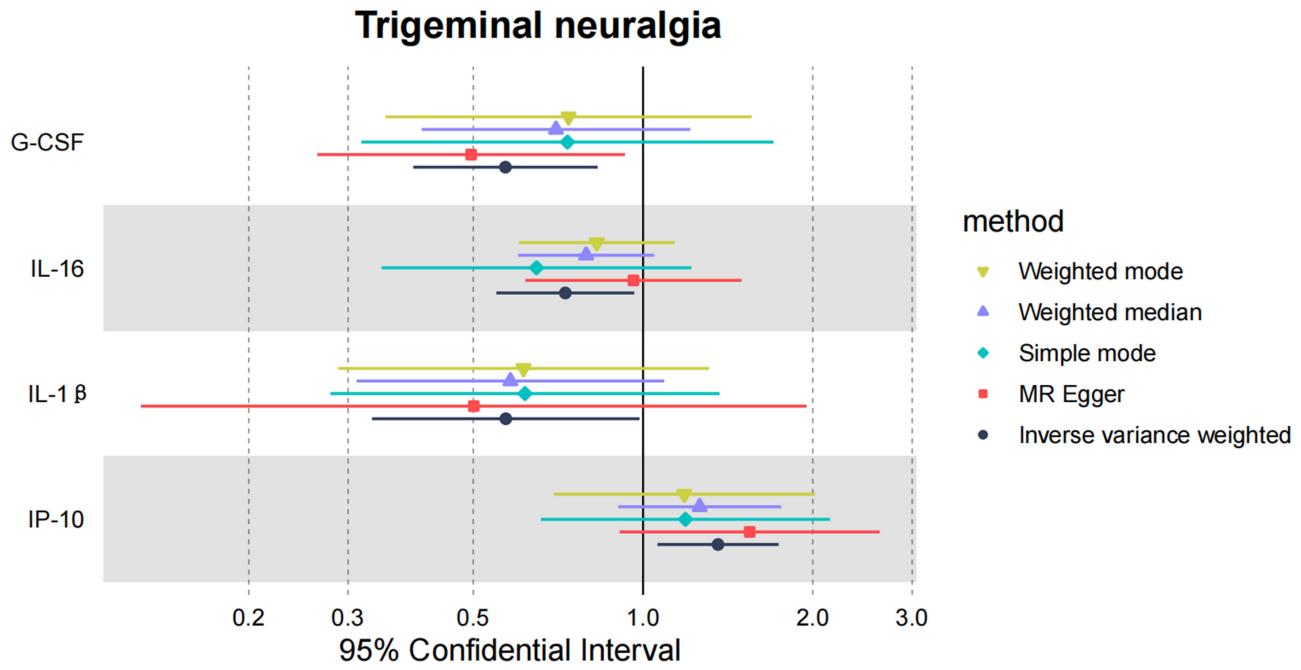

Figure 7 The MR Forest plot. MR forest plot provided a more granular perspective, detailing the causal effect estimates for each cytokine, complete with their respective confidence intervals.

This study involved inaugural Mendelian randomization analysis to explore the causal link between NeP and 41 inflammatory cytokines. Nevertheless, it is important to acknowledge its limitations. First, constraints in the MR analysis meant that the second and third assumptions were not thoroughly tested, which could introduce bias. Second, our data were sourced from two extensive GWASs, but a lack of detailed demographic and clinical data precluded subgroup analyses. Third, the study may have an ethnic bias, as participants were predominantly of European descent; this cautions against generalizing the findings to other ethnic groups. Moreover, given the heterogeneity of neuropathic pain, with cytokine profiles varying across subpopulations due to factors like pain etiology and comorbidities, the findings may not fully represent the diversity observed in specific patient groups,[38] Other molecules that are not cytokines, so far little investigated in neuropathic pain, may have a more causal role in neuropathic pain.[39] However, further research is needed to validate our findings and explore their potential applications in clinical diagnosis and treatment strategies.

Conclusion

In conclusion, our study has added to the growing body of evidence highlighting the pivotal role of inflammatory cytokines in NeP. As the field continues to evolve, it is crucial to integrate findings from various studies to develop a comprehensive understanding of the underlying mechanisms and identify potential therapeutic targets.

Acknowledgments

The authors express their gratitude to the participants and investigators of the FinnGen study. The authors also sincerely thank related investigators for sharing the GWAS summary statistics included in this study.

Funding

(1) Fujian Provincial Health Commission Young and Middle-Aged Talents Training Project (Grant Number: 2020GGB043). (2) Joint Funds for the Innovation of Science and Technology, Fujian Province (Grant Number: 2023Y9390).

Disclosure

The authors declare that they have no competing interests.

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