Deciphering the interplay between inflammatory factors and brain structural features in epilepsy

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Abstract

Introduction: The aim of the study was to evaluate potential causal links among circulating inflammatory factors, deep learning–derived brain structural phenotypes (unimodal deep imaging phenotypes – UDIPs), and epilepsy using Mendelian randomization (MR).

Material and methods: We used genome-wide association study (GWAS) summary statistics for 512 UDIPs derived from whole-brain MRI, 91 circulating inflammatory factors, and epilepsy. Two-sample MR was used to systematically estimate: (i) the effects of inflammatory factors on epilepsy, (ii) the effects of inflammatory factors on UDIPs, and (iii) the effects of UDIPs on epilepsy. We further applied two-step MR to explore whether UDIPs may mediate the associations between inflammatory factors and epilepsy. Robustness was assessed using heterogeneity tests, pleiotropy evaluation, and sensitivity analyses.

Results: Several inflammatory factors showed significant associations with epilepsy risk. Genetically predicted higher levels of CCL23, CXCL11, FGF5, GDNF, and VEGFA were associated with increased epilepsy risk, whereas higher levels of LIFR and OPG were associated with reduced risk. MR analyses also identified multiple T1- and T2-weighted UDIP dimensions associated with epilepsy in opposite directions, indicating heterogeneous structural signatures linked to epilepsy liability (e.g., T1 dimension 76 showed a positive association, while other dimensions were inversely associated). Two-step MR suggested that, for selected pathways, UDIPs may partly explain the associations between inflammatory factors and epilepsy, consistent with partial mediation. These findings were broadly consistent across heterogeneity, pleiotropy, and sensitivity analyses.

Conclusions: These findings implicate specific inflammatory factors and MRI-derived structural phenotypes in epilepsy susceptibility and suggest that brain structural features may partly lie on pathways linking inflammation to epilepsy, providing potential insights for biomarker discovery and therapeutic prioritization.

Key words: epilepsy, inflammatory factors, brain structural features, Mendelian randomization, unsupervised deep learning–derived imaging phenotypes.

Introduction

Epilepsy is a prevalent neurological disorder affecting an estimated 50 million people worldwide, with marked geographic and population-level heterogeneity in incidence and prevalence [1, 2]. Despite major ad-

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vances in diagnosis and treatment, a substantial proportion of patients remain refractory to conventional antiseizure medications, leading to persistent morbidity and a considerable healthcare burden [1, 3]. Recent progress in neuroimaging and genomics has opened new avenues for earlier detection, deeper mechanistic insight, and the development of personalized therapeutic strategies in epilepsy [4]. In particular, magnetic resonance imaging (MRI) is integral to the clinical evaluation of epilepsy, with strong utility for detecting structural lesions and assisting in seizure-focus localization [4–6]. In parallel, therapeutic development has increasingly moved toward precision medicine, prioritizing targeted approaches tailored to epilepsy subtypes and individual patient characteristics [7].

In recent years, circulating inflammatory factors – often used as peripheral indicators of inflammatory activity – have become a major focus in efforts to clarify epilepsy pathophysiology [8–10]. Accumulating evidence suggests that neuroinflammatory processes contribute to epilepsy onset and progression, and that specific circulating mediators, including C-C motif chemokine ligand 23 (CCL23) and vascular endothelial growth factor A (VEGFA), are associated with epilepsy-related risk and disease features [11–13]. In parallel, the application of deep learning to neuroimaging has created new opportunities to interrogate epilepsy-related brain changes beyond conventional MRI readouts. In particular, unsupervised deep learning methods can derive high-dimensional MRI phenotypes that capture subtle patterns of brain structure and tissue properties, enabling the identification of imaging signatures linked to epilepsy [14, 15]. Such imaging-derived features may relate to clinical phenotypes and provide a potential bridge between peripheral inflammatory signals and brain structural alterations relevant to epilepsy.

Although the individual contributions of circulating inflammatory factors and brain MRI measures to epilepsy have been increasingly described, the interplay between these domains – and their causal relevance to epilepsy risk – remains incompletely understood [16]. Mendelian randomization (MR) leverages germline genetic variants as instrumental variables to strengthen causal inference, thereby reducing bias from confounding and limiting reverse causation. In this study, we therefore applied MR to systematically examine the genetically proxied causal relationships among circulating inflammatory factors, deep learning–derived brain MRI phenotypes, and epilepsy. We further used two-step MR to investigate whether brain imaging phenotypes may partially mediate the effects of inflammatory factors on epilepsy risk. Together, this integrative framework provides additional mechanistic insight into epilepsy pathogenesis and may inform future biomarker development and precision therapeutic strategies.

Material and methods

Data sources

We used genome-wide association study (GWAS) summary statistics for 512 unsupervised deep learning–derived imaging phenotypes (UDIPs) to investigate potential causal relationships among circulating inflammatory factors, brain structure, and epilepsy [17]. UDIPs are high-dimensional MRI-derived traits generated by an unsupervised deep learning framework applied to high-quality whole-brain MRI. These phenotypes summarize multiregional variation in brain structure and demonstrate relatively high SNP-based heritability. Compared with conventional imaging-derived phenotypes that rely on predefined regional parcellations and extensive preprocessing, UDIPs require less complex preprocessing and integrate information across multiple brain regions, enabling a more holistic characterization than single-region analyses.

GWAS summary statistics for 91 circulating inflammatory cytokines were obtained from Zhao *et al*. (2023), which included 14,824 individuals of European ancestry [18]. Circulating cytokine levels were quantified using the Olink Target Inflammation panel and analyzed in conjunction with genome-wide genotypes.

Summary statistics for epilepsy were sourced from the FinnGen consortium (Release R12), including 15,645 cases and 374,605 controls. The dataset is publicly available at: https://r12.finngen.fi/.

Overall, our MR framework addressed three primary questions: 1) whether genetically predicted UDIP-derived brain MRI phenotypes influence epilepsy risk; 2) whether genetically predicted circulating inflammatory factors influence epilepsy risk; and 3) whether genetically predicted circulating inflammatory factors influence UDIP-derived brain MRI phenotypes.

Instrumental variable selection

Single-nucleotide polymorphisms (SNPs) were selected as instrumental variables based on an association threshold of $p < 1 \times 10^{-5}$ with the exposure. To reduce bias from linkage disequilibrium (LD), we performed LD clumping using a 10,000 kb window and $r^2 = 0.001$, retaining the most significant variant in each LD block. Palindromic SNPs were handled by inferring the positive-strand alleles where possible, thereby minimizing unnecessary SNP exclusion and preserving statistical power. For each instrument, we calculated the

proportion of exposure variance explained (R^2) and assessed instrument strength using the *F*-statistic; SNPs with $F < 10$ were excluded to limit weak-instrument bias [19, 20].

Statistical analysis

We used two-sample MR (TSMR) to estimate the causal effects of genetically proxied exposures on epilepsy. The inverse-variance weighted (IVW) approach served as the primary analysis [19]. Under the standard MR assumptions (relevance, independence, and exclusion restriction), IVW provides efficient and consistent causal estimates by meta-analyzing SNP-specific Wald ratios. Because the assumption that all variants are valid instruments may be violated in practice (e.g., due to pleiotropy), we performed complementary analyses using the weighted median (WM) estimator and MR-Egger regression to assess the robustness of the findings [21, 22].

The WM method yields consistent estimates provided that at least 50% of the total instrument weight derives from valid instruments, and is less sensitive to outlying variants than IVW, particularly when heterogeneity is present. MR-Egger regression relaxes the assumption of no directional pleiotropy by including an intercept term; under the Instrument Strength Independent of Direct Effect (InSIDE) assumption, MR-Egger can provide an unbiased causal estimate even when horizontal pleiotropy exists. However, MR-Egger typically has lower statistical power and wider confidence intervals than IVW.

To assess the robustness of our findings, we conducted a series of sensitivity analyses. Cochran's Q statistic was used to evaluate heterogeneity across SNP-specific estimates [23]. When heterogeneity was detected, we applied an IVW random-effects model to account for between-variant heterogeneity. Horizontal pleiotropy was examined using the MR-Egger intercept test, where a non-zero intercept suggests directional pleiotropy. We additionally used MR-PRESSO to identify potential outlier variants and to provide outlier-corrected causal estimates [24]. Finally, leave-one-out analyses were performed by iteratively removing each SNP to determine whether any single variant disproportionately influenced the overall result [25].

All analyses were conducted in R (version 4.4.1) using the TwoSampleMR package (version 0.6.8) and the MR-PRESSO package (version 1.0).

Mediation analysis

We applied a TSMR framework to decompose the total effect of circulating inflammatory cytokines on epilepsy into direct and indirect (mediated) components via UDIPs [26–28]. In this framework, the exposure (cytokine level) influences the mediator (UDIP), which in turn affects the outcome (epilepsy). TSMR assumes no exposure–mediator interaction and relies on the standard MR assumptions for each step.

Specifically, we first estimated the total effect of each circulating inflammatory cytokine on epilepsy using univariable MR (β_1). We then obtained two additional causal estimates: (i) the effect of the mediator (UDIP) on epilepsy (β_2), and (ii) the effect of the exposure (circulating inflammatory cytokine) on the mediator (α). The indirect (mediated) effect was calculated using the product-of-coefficients approach ($\alpha \times \beta_2$). The proportion mediated was computed as the ratio of the indirect effect to the total effect: $(\alpha \times \beta_2)/\beta_1$.

Ethical approval and participant consent

All data analyzed in this study were obtained from publicly available GWAS summary statistics. Each contributing GWAS received approval from the relevant institutional ethics committees, and all participants (or their legal representatives, where applicable) provided written informed consent. Because only de-identified, aggregate-level data were used, no additional ethical approval or participant consent was required for the present analyses.

Results

Genetic instruments for exposures

The number of SNPs selected as instrumental variables varied across traits. For the 91 circulating inflammatory cytokines, the number of instruments ranged from 13 to 54 (median 32). For the 512 UDIPs, instrument counts ranged from 13 to 88 (median 35). For epilepsy, 42 SNPs were used as instruments (Supplementary Tables SI–SIII). All retained instruments had F-statistics > 10, indicating adequate instrument strength and reducing concerns about weak-instrument bias.

Genetic causal associations between circulating inflammatory cytokines and epilepsy

Using the IVW framework to evaluate the causal effects of circulating inflammatory cytokines on epilepsy risk, we identified several cytokines with statistically significant associations. Genetically predicted higher levels of C-C motif chemokine ligand 23 (CCL23), C-X-C motif chemokine ligand 11 (CXCL11), fibroblast growth factor 5 (FGF5), glial cell line-derived neurotrophic factor (GDNF), and vascular endothelial growth factor A (VEGFA) were associated with an increased risk of epilepsy,

whereas higher leukemia inhibitory factor receptor (LIFR) and osteoprotegerin (OPG) were associated with a reduced risk. Among these, VEGFA showed the strongest association with epilepsy (OR = 1.079, 95% CI: 1.035–1.125, p = 0.0003) (Figure 1; Supplementary Table SIV).

In the reverse-direction analysis, IVW results indicated that genetic liability to epilepsy was associated with lower circulating levels of interleukin-10 receptor subunit alpha (IL-10RA), interleukin-20 (IL-20), neurturin (NRTN), and sirtuin-2 (SIRT2), with the largest decrease observed for IL-10RA (OR = 0.900, 95% CI: 0.836–0.969, p = 0.005) (Figure 2; Supplementary Table SIV).

Sensitivity analyses supported the robustness of these findings. MR-Egger intercept and MR-PRESSO analyses provided no evidence of directional horizontal pleiotropy (p > 0.05), and funnel plots showed no obvious asymmetry (Supplementary Table SV; Supplementary Figure S1). After outlier assessment/correction, Cochran's Q tests suggested no significant heterogeneity across SNP-specific estimates (p > 0.05) (Supplementary Table SVI). In addition, leave-one-out analyses demonstrated that sequential removal of individual SNPs did not materially alter the overall estimates, indicating that the associations were not driven by any single instrument (Supplementary Figure S2).

Genetic causal associations between UDIPs and epilepsy

To evaluate the causal effects of UDIP-derived brain MRI phenotypes on epilepsy risk, we performed IVW Mendelian randomization across 512 UDIPs. In total, 13 UDIPs showed positive associations with epilepsy risk, including five T1-weighted UDIPs (dimensions 18, 38, 49, 67, 76) and eight T2-weighted UDIPs (dimensions 15, 35, 41, 42, 49, 72, 99, 105). Conversely, 17 UDIPs were inversely associated with epilepsy, including nine T1-weighted UDIPs (dimensions 7, 14, 16, 46, 50, 56, 104, 120, 125) and eight T2-weighted UDIPs (dimensions 12, 13, 55, 58, 81, 91, 96, 99). Among all UDIPs, T1 dimension 76 exhibited the strongest association with epilepsy risk (OR = 1.001, 95% CI: 1.0004–1.0018, p = 0.003) (Figure 3; Supplementary Table SVII).

In the reverse-direction analyses (epilepsy → UDIPs), genetic liability to epilepsy was associated with lower levels of several UDIP dimensions from T1-weighted MRI (dimensions 32, 34, 39) and T2-weighted MRI (dimensions 30, 54, 70, 113, 123). In contrast, epilepsy liability was positively associated with multiple UDIP dimensions across both modalities (dimensions 8, 18, 38, 39, 49, 59, 68, 76, 80, 96, 113, 126, 40) (Figure 4; Supplementary Table SVII).

Notably, we observed bidirectional MR evidence between epilepsy and several T1-weighted UDIP dimensions (dimensions 18, 38, and 49), suggesting potential reciprocal relationships or shared underlying biology for these specific imaging-derived traits.

Sensitivity analyses supported the robustness of these findings. MR-Egger and MR-PRESSO tests did not indicate significant directional horizontal pleiotropy (p > 0.05) (Supplementary Table SVIII), and funnel plots showed no obvious asymmetry (Supplementary Figure S3). Cochran's Q statistics suggested no substantial heterogeneity across SNP-specific estimates (p > 0.05) (Supplementary Table SIX). Finally, leave-one-out analyses did not identify influential single variants that materially altered the overall estimates (Supplementary Figure S4).

Exposure	Method	nsnp	HR (95% CI)	*P*-value
C-C motif chemokine 23 levels	Inverse variance weighted	30	1.08 (1.02 to 1.13)	0.0039
C-X-C motif chemokine 11 levels	Inverse variance weighted	38	1.07 (1.01 to 1.14)	0.0279
Fibroblast growth factor 5 levels	Inverse variance weighted	32	1.04 (1.00 to 1.08)	0.0378
Glial cell line-derived neurotrophic factor levels	Inverse variance weighted	24	1.07 (1.00 to 1.14)	0.0494
Leukemia inhibitory factor receptor levels	Inverse variance weighted	27	0.92 (0.87 to 0.98)	0.0145
Osteoprotegerin levels	Inverse variance weighted	27	0.93 (0.87 to 1.00)	0.0403
Vascular endothelial growth factor A levels	Inverse variance weighted	33	1.08 (1.04 to 1.13)	0.0003



Figure 1. Forest plot of the genetic effects of circulating inflammatory cytokines on epilepsy

Outcome	Method	nsnp	HR (95% CI)	*P*-value
Interleukin-10 receptor subunit alpha levels	Inverse variance weighted	40	0.90 (0.84 to 0.97)	0.0051
Interleukin-20 levels	Inverse variance weighted	40	0.93 (0.87 to 1.00)	0.0356
Neurturin levels	Inverse variance weighted	40	0.92 (0.86 to 0.99)	0.0231
SIR2-like protein 2 levels	Inverse variance weighted	39	0.94 (0.88 to 1.00)	0.0489



Figure 2. Forest plot of the genetic effects of epilepsy on circulating inflammatory cytokines

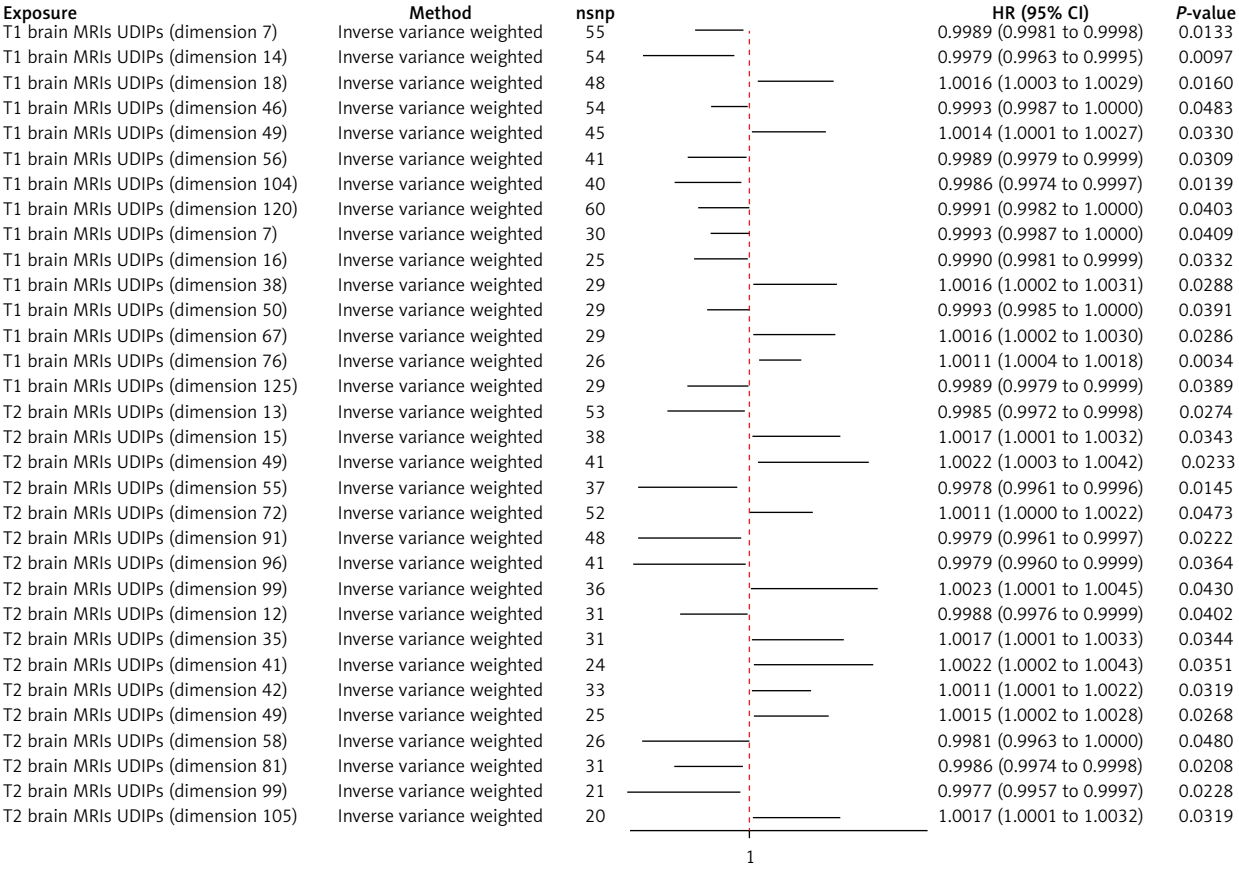


Figure 3. Forest plot of the genetic effects of unsupervised deep learning–derived imaging phenotypes on epilepsy

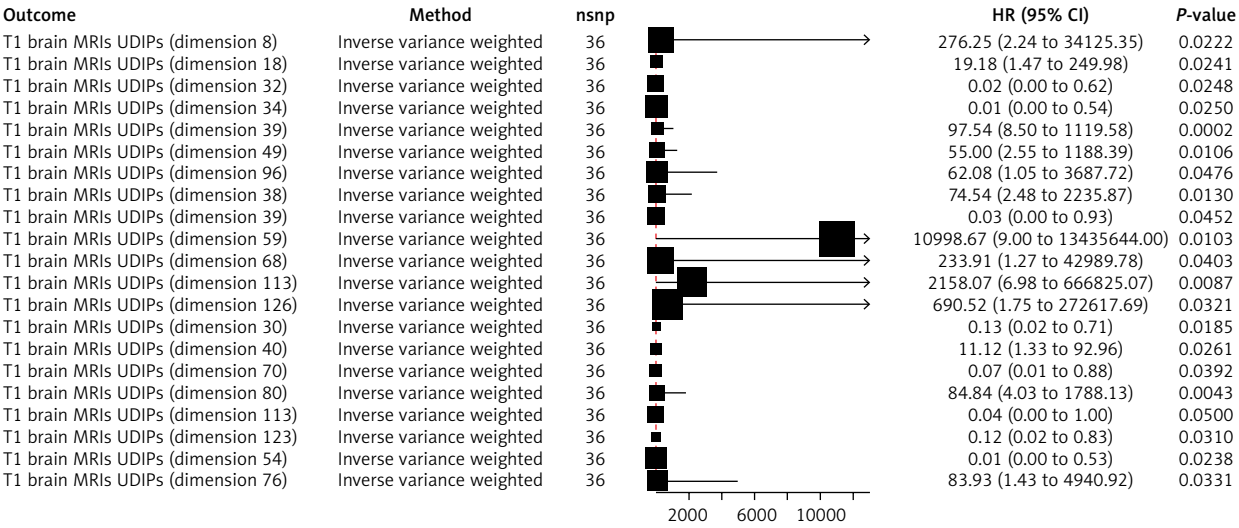


Figure 4. Forest plot of the genetic effects of epilepsy on unsupervised deep learning–derived imaging phenotypes

Mediation analysis of candidate UDIPs

In the TSMR analysis (Figure 5), we identified eight UDIPs that showed evidence of involvement in cytokine–UDIP–epilepsy pathways (Table I). Genetically predicted CCL23 levels were inversely associated with T1-weighted UDIP dimension 14 (β = –4.263, 95% CI: –6.230 to –2.297) and T2-weighted UDIP dimension 96 (β = –1.956, 95% CI: –3.660 to –0.252). Higher CCL23 levels were associated with increased epilepsy risk (OR = 1.076, 95% CI: 1.024–1.130), whereas both T1 dimension 14 and T2 dimension 96 were inversely associated with epilepsy (OR = 0.998, 95% CI: 0.996–0.999; and OR = 0.998, 95% CI: 0.996–1.000, respectively).

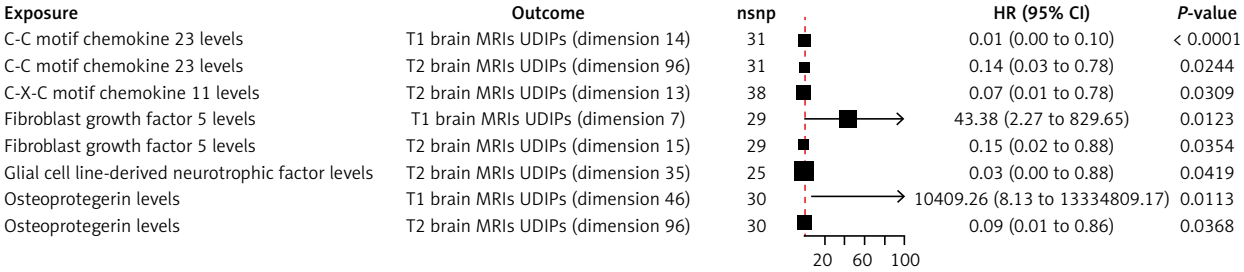


Figure 5. Forest plot of the genetic effects of circulating inflammatory cytokines on unsupervised deep learning–derived imaging phenotypes

Table I. Two-step Mendelian randomization analyses of potential mediation between circulating inflammatory cytokines, unsupervised deep learning–derived imaging phenotypes, and epilepsy

Exposure	Outcome	Method	nsnp	β	*SE*	*P*-value	Lower CI	Upper CI	Mediated (%)
C-C motif chemokine 23 levels	T1 brain MRIs unsupervised deep learning–derived imaging phenotypes (dimension 14)	Inverse variance weighted	31	–4.264	1.003	2.145×10^{-05}	–6.23	–2.30	12.30
C-C motif chemokine 23 levels	T2 brain MRIs unsupervised deep learning–derived imaging phenotypes (dimension 96)	Inverse variance weighted	31	–1.956	0.869	0.024	–3.66	–0.25	5.59
C-X-C motif chemokine 11 levels	T2 brain MRIs unsupervised deep learning–derived imaging phenotypes (dimension 13)	Inverse variance weighted	38	–2.631	1.219	0.031	–5.02	–0.24	5.79
Osteoprotegerin levels	T1 brain MRIs unsupervised deep learning–derived Imaging Phenotypes (dimension 46)	Inverse variance weighted	30	9.250	3.651	0.011	2.10	16.41	8.81

Genetically predicted CXCL11 levels were associated with a decrease in T2-weighted UDIP dimension 13 (β = –2.631, 95% CI: –5.019 to –0.242). Higher CXCL11 levels were associated with higher epilepsy risk (OR = 1.071, 95% CI: 1.007–1.138), while T2 dimension 13 was inversely associated with epilepsy (OR = 0.998, 95% CI: 0.997–1.000).

For osteoprotegerin (OPG), genetically predicted levels were inversely associated with T2-weighted UDIP dimension 96 (β = –2.431, 95% CI: –4.714 to –0.149) and positively associated with T1-weighted UDIP dimension 46 (β = 9.250, 95% CI: 2.095–16.406). Higher OPG levels were associated with a reduced risk of epilepsy (OR = 0.933, 95% CI: 0.872–0.997), and T1 dimension 46 was also inversely associated with epilepsy (OR = 0.999, 95% CI: 0.999–1.000).

Genetically predicted GDNF levels were inversely associated with T2-weighted UDIP dimension 35 (β = –3.357, 95% CI: –6.592 to –0.122). Higher GDNF levels were associated with increased epilepsy risk (OR = 1.067, 95% CI: 1.000–1.139), and T2 dimension 35 was positively associated with epilepsy (OR = 1.002, 95% CI: 1.000–1.003).

For FGF5, genetically predicted levels were inversely associated with T2-weighted UDIP dimension 15 (β = –1.924, 95% CI: –3.717 to –0.131) and positively associated with T1-weighted UDIP dimension 7 (β = 3.770, 95% CI: 0.819–6.721). Higher FGF5 levels were associated with higher epilepsy risk (OR = 1.041, 95% CI: 1.002–1.081). In turn, T2 dimension 15 was positively associated with epilepsy (OR = 1.001, 95% CI: 1.000–1.003), whereas T1 dimension 7 was inversely associated with epilepsy (OR = 0.999, 95% CI: 0.998–1.000).

Finally, in the mediation assessment, when the estimated indirect effect ($\alpha \times \beta_2$) was in the opposite direction to the total effect, we did not

interpret the UDIP as a potential mediator in that pathway. Accordingly, T2 dimension 96 was not considered to mediate the association between OPG and epilepsy. Similarly, T2 dimension 35 was not considered a mediator of the GDNF–epilepsy association, and T2 dimension 15 and T1 dimension 7 were not considered mediators of the FGF5–epilepsy association (Supplementary Tables SX–SXII, Supplementary Figures S5–S10).

Discussion

In this study, we applied Mendelian randomization to delineate the genetic architecture linking circulating inflammatory factors, deep learning–derived brain MRI phenotypes (UDIPs), and epilepsy. We identified significant associations between several inflammatory factors and epilepsy, with VEGFA showing the most prominent risk-increasing association (OR = 1.079, p = 0.0003). In parallel, multiple T1- and T2-weighted UDIP dimensions were associated with epilepsy in both directions, indicating heterogeneous structural signatures underlying epilepsy susceptibility. Among these, T1-weighted UDIP dimension 76 demonstrated the strongest positive association with epilepsy risk (OR = 1.001, p = 0.003). Two-step MR further suggested that, for selected cytokines, part of the association with epilepsy may operate through UDIP-related brain structural features. However, mediation was not consistently supported across all examined pathways, highlighting potential heterogeneity in mechanisms and/or limited power for specific mediator models.

Inflammatory signaling is increasingly recognized as a central component of epilepsy pathophysiology. Accumulating evidence indicates that inflammation is not merely a downstream consequence of seizures, but can also contribute to epileptogenesis and disease progression [29, 30]. Seizures can trigger broad neuroinflammatory responses that may, in turn, promote epileptogenesis by increasing neuronal excitability, disrupting the BBB, and activating glial cells, thereby establishing a self-reinforcing cycle of inflammation and network hyperexcitability [31–33]. Against this background, clarifying the role of circulating inflammatory factors is important for mechanistic insight, biomarker discovery, and therapeutic prioritization. In our MR analyses, genetically predicted higher levels of CCL23, CXCL11, FGF5, GDNF, and VEGFA were associated with an increased odds of epilepsy, whereas higher LIFR and OPG were associated with lower odds of epilepsy, further supporting an association between inflammatory pathways and epilepsy susceptibility.

Several of the identified factors have biologically plausible links to seizure-related brain changes. VEGFA, a key regulator of angiogenesis and vascular remodeling, also participates in neurodevelopment and repair processes. In epilepsy, VEGFA signaling may relate to cerebrovascular remodeling, inflammatory activation, and alterations in neuronal excitability. Notably, elevated VEGFA has been reported to increase BBB permeability, potentially destabilizing the brain microenvironment and facilitating seizures [34]. In experimental models, Jeong *et al*. showed that VEGFA can aggravate clinical phenotypes by enhancing vascular permeability and activating glial cells [35]. In addition, chemokines such as CCL23 and CXCL11 are critical for immune-cell recruitment and neuroimmune signaling [36–38]. Prior studies suggest that chemokines contribute to epilepsy through neuroimmune activation and inflammatory amplification at seizure foci [39, 40]. Excessive chemokine activity may promote immune-cell accumulation, intensify local inflammation, exacerbate neuronal injury, and increase seizure propensity [41]. Consistent with these observations, our findings support associations between genetically predicted CCL23 and CXCL11 levels and epilepsy risk, aligning with a model in which heightened chemokine signaling sustains inflammatory microenvironments permissive to seizures. Finally, FGF5 and GDNF are often discussed in the context of neuroprotection and tissue repair [42, 43]. GDNF promotes neuronal survival and functional recovery and has been widely studied in epilepsy-related neurobiology [43, 44]. Although some experimental work suggests that increasing GDNF may reduce seizure severity – potentially via synaptic plasticity modulation – its effects likely depend on timing, brain region, and cellular context [45]. FGF5 may also influence epilepsy-related processes indirectly through glial proliferation and tissue remodeling after injury [46]. Taken together, these observations highlight that inflammatory and trophic signaling pathways may exert complex, context-dependent effects in epilepsy, underscoring the need for mechanistic and longitudinal studies to clarify when and where these factors are pathogenic versus compensatory.

The interplay between inflammatory signaling and brain structure is also likely to be relevant to epilepsy pathogenesis. Circulating inflammatory mediators may reshape the brain microenvironment – particularly via effects on glial activation and BBB integrity – thereby indirectly influencing seizure susceptibility and disease progression [47]. Chronic inflammatory stimulation can activate microglia and astrocytes and promote a reactive state that enhances network excitability and lowers seizure thresholds. Consistent with this, glial activation and BBB dysfunction have been implicated as key components of epileptogenesis [48, 49]. Moreover, peripheral inflammatory

factors may be linked to epilepsy through their associations with MRI-derived brain phenotypes, providing a potential bridge between systemic inflammation and structural brain alterations [49, 50]. In our mediation framework, we observed evidence that selected inflammatory factors may be associated with epilepsy through UDIP-defined structural features. For example, genetically predicted CCL23 levels were inversely associated with a T1-weighted UDIP dimension (dimension 14) that was itself inversely associated with epilepsy, suggesting that CCL23-related inflammatory signaling may relate to epilepsy partly through structural phenotypes captured by UDIPs. Similarly, CXCL11 and GDNF showed associations with specific T2-weighted UDIP dimensions, supporting the concept that inflammatory and trophic pathways may converge on brain structural features relevant to epilepsy vulnerability. Taken together, our findings support a model in which inflammatory factors may contribute to epilepsy through both direct and indirect mechanisms, potentially involving neuroimmune activation, BBB perturbation, glial reactivity, and downstream structural brain changes. Factors such as VEGFA, CCL23, CXCL11, FGF5, and GDNF emerge as candidates for further investigation, although their roles may be context dependent and may reflect a mixture of pathogenic and compensatory processes. Future studies should map UDIP dimensions to interpretable neuroanatomical substrates, validate these associations in independent multi-ancestry cohorts, and integrate longitudinal imaging and experimental data to clarify mechanistic pathways and evaluate translational potential for risk stratification and targeted intervention.

Integrating advanced neuroimaging – particularly deep learning–derived MRI phenotypes such as UDIPs – may provide new opportunities for epilepsy risk stratification and the development of personalized management strategies. With continued improvements in MRI acquisition and the rapid maturation of representation-learning approaches, UDIPs have emerged as a promising framework for capturing subtle, distributed patterns of brain structure that may not be apparent using conventional region-based measures. Increasing efforts have therefore focused on leveraging these high-dimensional imaging signatures to improve early detection, refine phenotypic characterization, and potentially support monitoring of treatment response in epilepsy. Methodologically, UDIPs are designed to learn latent features directly from MRI data, enabling extraction of potentially biologically informative variation that can be difficult to capture with traditional, predefined parcellation-based pipelines. In our analyses, several UDIP dimensions showed evidence of bidirectional MR associations with epilepsy, suggesting a more complex relationship than a purely one-way causal pathway. In particular, T1-weighted UDIP dimensions 18, 38, and 49 demonstrated bidirectional genetic associations with epilepsy, consistent with the possibility that these imaging features may reflect both (i) structural phenotypes that contribute to epilepsy susceptibility and (ii) downstream brain changes associated with epilepsy liability or disease-related processes. This bidirectionality highlights the potential value of such features as candidate risk markers while also emphasizing that some imaging signatures may represent disease-related remodeling rather than solely antecedent causes.

Our analyses also extend prior work by linking circulating inflammatory factors to MRI-derived brain phenotypes, reinforcing the concept that inflammation may contribute to epilepsy through pathways that involve structural brain alterations. Using the TSMR framework, we identified several cytokines – most notably CCL23, CXCL11, and GDNF – that were associated with specific T1- and T2-weighted UDIP dimensions, with corresponding associations between those UDIPs and epilepsy risk. Together, these results provide genetic evidence consistent with the hypothesis that inflammatory signaling may be related to brain structural characteristics captured by UDIPs and thereby be associated with epilepsy susceptibility. At the same time, our mediation results suggest that such imaging features do not uniformly explain cytokine–epilepsy associations across all pathways, underscoring mechanistic heterogeneity and the likelihood of multiple, parallel routes linking inflammation to epilepsy. Nonetheless, the observed cytokine–UDIP–epilepsy relationships are concordant with experimental and clinical observations that inflammatory mediators can remodel the brain microenvironment and contribute to epileptogenesis. Future studies should focus on mapping UDIP dimensions to interpretable neuroanatomical and microstructural substrates, integrating longitudinal imaging and inflammatory profiling, and testing causal mechanisms in experimental models. Such work would clarify how specific inflammatory pathways may relate to structural brain changes and could support the development of precision medicine strategies for epilepsy prevention and treatment.

The principal strengths of this study include the use of Mendelian randomization, which leverages genetic instruments to interrogate potential causal relationships among circulating inflammatory factors, UDIP-derived brain MRI phenotypes, and epilepsy. By design, this framework can mitigate confounding and reduces the risk of reverse causation that often limits conventional observational analyses. A further strength is the

incorporation of unsupervised deep learning–derived imaging phenotypes (UDIPs), which capture distributed, high-dimensional structural information from MRI and may be more sensitive to subtle brain alterations than traditional region-based measures. In addition, the two-step MR mediation framework enabled us to explore whether brain structural phenotypes may lie on pathways linking inflammatory factors to epilepsy, thereby providing a more integrated view of disease biology. Finally, the use of large-scale GWAS summary statistics improved statistical power and supports the reliability of the genetic associations identified.

Several limitations warrant consideration. First, the underlying GWAS datasets were largely derived from specific ancestral groups (predominantly European), which may limit generalizability and introduce population-specific effects; replication in diverse ancestries is therefore essential. Second, although we performed extensive sensitivity analyses to probe pleiotropy and heterogeneity, MR remains dependent on instrument validity and cannot fully exclude residual violations of MR assumptions. Third, while high-dimensional UDIPs increase sensitivity, they also reduce interpretability, as the biological and neuroanatomical substrates of individual UDIP dimensions are not always straightforward. Finally, we lacked direct multicenter clinical validation and longitudinal phenotyping, which will be important for assessing clinical utility and temporal ordering. Future studies should validate these findings across independent and multi-ancestry cohorts, improve UDIP interpretability through neuroanatomical mapping, and integrate longitudinal imaging and clinical data to strengthen translational relevance.

In conclusion, this study systematically evaluated the genetic associations between circulating inflammatory factors, MRI-derived brain structural features (UDIPs), and epilepsy. Our findings support a role for inflammation and structural brain alterations in epilepsy susceptibility, providing a genetic epidemiological framework that may inform earlier risk stratification and offer mechanistic insights. Limitations include potential population bias, model complexity, and the absence of multicenter clinical validation; future work should validate these associations across diverse ancestries and independent cohorts, refine imaging-feature interpretability, and integrate broader clinical and longitudinal datasets to inform precision diagnosis and treatment of epilepsy.

Data availability

There are restrictions to the availability of data from the FinnGen consortium (R12 release, https://r12.finngen.fi/) and GWAS Catalog (https://www.ebi.ac.uk/).

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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