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Exploring the role of interleukin-6 receptor blockade in epilepsy and associated neuropsychiatric conditions through a mendelian randomization study

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Abstract

BACKGROUND

The interplay between inflammation, immune dysregulation, and the onset of neurological disorders, including epilepsy, has become increasingly recognized. Interleukin (IL)-6, a pro-inflammatory cytokine, is suspected to not only mediate traditional inflammatory pathways but also contribute to neuroinflammatory responses that could underpin neuropsychiatric symptoms and broader psychiatric disorders in epilepsy patients. The role of IL-6 receptor (*IL6R*) blockade presents an intriguing target for therapeutic intervention due to its potential to attenuate these processes.

AIM

To explore the potential of *IL6R* blockade in reducing the risk of epilepsy and investigate whether this pathway might also influence associated psychiatric and neuropsychiatric conditions due to neuroinflammation.

METHODS

Mendelian randomization (MR) analysis employing single nucleotide polymorphisms (SNPs) in the vicinity of the *IL6R* gene (total individuals = 408225) was used to evaluate the putative causal relationship between *IL6R* blockade and epilepsy (total cases/controls = 12891/312803), focal epilepsy (cases/controls = 7526/399290), and generalized epilepsy (cases/controls = 1413/399287). SNP weights were determined by their effect on C-reactive protein (CRP) levels and integrated using inverse variance-weighted meta-analysis as surrogates for *IL6R* effects. To address potential outlier and pleiotropic influences, sensitivity analyses were conducted employing a variety of MR methods under different modeling

assumptions.

RESULTS

The genetic simulation targeting *IL6R* blockade revealed a modest but significant reduction in overall epilepsy risk [inverse variance weighting: Odds ratio (OR): 0.827; 95% confidence interval (CI): 0.685-1.000; $P = 0.05$]. Subtype analysis showed variability, with no significant effect observed in generalized, focal, or specific childhood and juvenile epilepsy forms. Beyond the primary inflammatory marker CRP, the findings also suggested potential non-inflammatory pathways mediated by IL-6 signaling contributing to the neurobiological landscape of epilepsy, hinting at possible links to neuroinflammation, psychiatric symptoms, and associated mental disorders.

CONCLUSION

The investigation underscored a tentative causal relationship between *IL6R* blockade and decreased epilepsy incidence, likely mediated *via* complex neuroinflammatory pathways. These results encouraged further in-depth studies involving larger cohorts and multifaceted psychiatric assessments to corroborate these findings and more thoroughly delineate the neuro-psychiatric implications of IL-6 signaling in epilepsy. The exploration of *IL6R* blockade could herald a novel therapeutic avenue not just for seizure management but also for addressing the broader psychiatric and cognitive disturbances often associated with epilepsy.

Key Words: Epilepsy; Interleukin-6 receptor blockade; Mendelian randomization; Neuroinflammation; Psychiatric disorders

Core Tip: This study employed mendelian randomization to explore the potential neuroprotective role of interleukin (IL)-6 receptor blockade in epilepsy, highlighting how it may decrease the incidence of epilepsy by addressing neuro-inflammatory and possibly non-inflammatory pathways. While the results shown a modest reduction in epilepsy risk, they vary across epileptic subtypes and suggested complex interactions with neuropsychiatric conditions. The findings underscored the necessity for further comprehensive investigations to understand the multifaceted effects of IL-6 signaling on both epilepsy and related psychiatric disorders, potentially paving the way for innovative therapeutic strategies that encompass neurological and psychiatric care in epilepsy management.

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INTRODUCTION

Epilepsy is a complex neurological disorder that affects approximately 1% of the global population and represents a significant public health challenge[1]. It is characterized not only by recurrent seizures but also encompasses a wide range of psychological and cognitive impairments that adversely affect the quality of life of affected individuals. Understanding the multifaceted nature of epilepsy, encompassing the underlying biological mechanisms, especially neuroinflammation, and associated psychiatric symptoms and disorders is critical for developing comprehensive therapeutic strategies.

Existing treatment approaches primarily target the symptomatic management of neuronal hyperactivity[2]. Despite the emergence of various antiseizure medications, a considerable proportion, approximately one-third, of individuals with epilepsy experience drug-resistant epilepsy[3]. Thus, identifying new therapeutic targets is of crucial for treating epilepsy and improving patient outcomes.

The relationship between epilepsy and psychiatric conditions such as depression, anxiety, and psychosis is well-established[1]. This comorbidity is not solely a consequence of living with a chronic debilitating disease, but rather may also reflect shared pathophysiological pathways, particularly neuroinflammation. Interleukin (IL)-6, a cytokine with both pro-inflammatory and anti-inflammatory properties, is one such molecule that has been linked to the neuroinflammatory processes thought to underlie both epilepsy and several psychiatric conditions. IL-6 is a pivotal cytokine involved in the innate immune response[4] that collaborates with various pathophysiological processes, collectively contributing to adverse outcomes[5]. Indeed, mounting evidence points to elevated IL-6 levels as a potential bridge linking neuroinflammatory responses to neuropsychiatric symptoms. Such inflammation might not only play a role in the genesis and propagation of epileptic seizures but also impact mood and cognitive functions, contributing to the prevalence of mental health disorders in individuals with epilepsy. Additionally, elevated levels of IL-6 have been implicated in other neuropsychiatric conditions, including major depressive disorder and schizophrenia, underlining the cytokine's broad impact on neurobiological functions and psychiatric health.

IL-6 signals through its receptor, *IL6R*, which exists in both membrane-bound and soluble forms, which adds complexity to its biological activities. The interactions of IL-6 with *IL6R* initiate signaling pathways that can lead to the activation of inflammatory responses. The blockade of *IL6R*, inhibiting these pathways, presents a promising therapeutic target. Not only might such an intervention reduce epileptic activity by mitigating brain inflammation, but it may also ameliorate psychiatric symptoms associated with this condition. IL-6 induced inflammation indirectly by creating a complex with a soluble receptor, thereby activating glycoprotein (gp) 130 (*gp130*) on the cell surface[6]. This trans-signaling pathway provided a distinctive mechanism for IL-6 to manifest its inflammatory effects[7-9]. In the study by Wang *et al*[10], high-sensitivity C-reactive protein (hsCRP) was identified as a potential biomarker for epilepsy, with elevated levels observed in the serum of patients with convulsive status epilepticus, indicating its association with the disease's onset and progression. In the IL-6 signaling pathway, CRP was not directly involved but is associated with the inflammatory response that IL-6 mediates[11]. CRP levels are known to increase in the presence of inflammation, which can be triggered by IL-6 through both classical and trans signaling pathways[12]. Thus, the relationship between IL-6 and CRP is thus one of parallelism, where IL-6 signaling contributes to the inflammatory state that leads to elevated CRP levels, serving as a marker of systemic inflammation[13].

Moreover, psychiatric disorders themselves can exacerbate epileptic seizures, creating a cycle that can further impair the patient's quality of life. Studies has been suggested that managing systemic inflammation could potentially aid in the treatment of both seizure activity and psychiatric symptoms in epileptic patients. The inhibitors of IL-6, such as tocilizumab and sarilumab, already used in other inflammatory conditions, might thus offer dual benefits, controlling seizures and alleviating psychiatric symptoms by reducing neuroinflammation[14]. Given the favorable outcomes observed, IL-6 receptor antibodies (IL6RAs) are now recognized as a standard treatment option for this particular patient cohort[15]. These medications can mitigate various forms of IL-6 signaling, resulting in decreases in CRP and other downstream inflammatory markers[16,17]. Inflammation is implicated in structural brain changes that contribute to neuropsychiatric disorders, affecting microglial and astrocytic function, disrupting synaptic pruning, and subsequently influencing gray matter volume[18]. The role of IL-6 in psychiatric disorders was supported by its known impact on the central nervous system (CNS). Elevated IL-6 levels can disrupt the blood-brain barrier, influence synaptic function, and affect brain regions responsible for mood regulation such as the prefrontal cortex and amygdala[19,20]. Consequently, targeting IL-6 in epilepsy might not only address the primary neurological impacts but also the secondary psychological effects, potentially improving overall patient management.

The relationship between the IL-6 signaling pathway and epilepsy warrants further investigation. An increase in proinflammatory cytokines, including IL-6, has been reported subsequent to seizures, indicating a possible involvement in the inflammatory processes related to the condition[21-23]. Moreover, the observed neuroprotective effects of IL-6 inhibition during status epilepticus support the notion that IL-6 may play a role in the neuroinflammatory response associated with epilepsy[11]. Additionally, nutritional strategies such as the ketogenic diet, which can modulate the levels of IL-6 and other inflammatory markers. These strategies may offer a means to mitigate inflammation and maintain the integrity of the intestinal microbiome, potentially impacting the management of epilepsy[24,25]. Elucidating the precise mechanisms through which IL-6 and associated cytokines engage with the CNS and influence the frequency or severity of seizures may inform the development of targeted therapeutic approaches that address the inflammatory aspects of epilepsy.

The utilization of *IL6R* variants in mendelian randomization (MR) studies provides opportunities for a more profound comprehension of *IL6R*'s involvement in both health and disease[26]. This approach holded the potential to foster the development of novel and enhanced treatment modalities. Moreover, this approach offered a functional proxy for IL6RA therapy[12]. Based on this background, we hypothesize that *IL6R* blockade may play a role in epilepsy. In order to scrutinize this hypothesis, we undertook a two-sample MR study to assess the plausible effects of *IL6R* blockade on epilepsy. By exploring these interactions, this study aimed to elucidate the broader implications of IL-6 signaling in epilepsy. Furthermore, it seemed to evaluate its potential as a target for novel therapeutic approaches that address both neurological and psychiatric aspects of the disease.

MATERIALS AND METHODS

Design of study

In our two-sample MR study, we selected genetic instrumental variables (IVs) for the *IL6R* that are robustly associated with its expression levels, ensuring their validity as proxies for *IL6R* modulation. We assessed these IVs to confirm their lack of association with potential confounders, thereby maintaining the integrity of our analysis. Our study is predicated on the assumption that these IVs influence the risk of epilepsy solely through the *IL6R* pathway, with no pleiotropic effects. To safeguard against any unmeasured confounding, we conducted sensitivity analyses, which supported the reliability of our findings. This approach has allowed us to draw more precise conclusions regarding the potential impact of *IL6R* blockade on epilepsy, contributing valuable insights into the therapeutic potential of targeting this pathway in the management of the disease.

Included populations

Our primary outcomes were based on information from the FinnGen R10, a comprehensive prospective cohort study carried out in Finland[27]. For secondary outcomes, we employed data from a Genome-wide mega-analysis conducted by International League Against Epilepsy Consortium on Complex Epilepsies[28]. All relevant outcome data are encapsulated in Table 1. Epilepsies are categorized based on the manifestation of ictal symptoms into two primary

Table 1 Incorporate genome-wide association study summary information for the outcomes included in the study

Trait	Data source	Case/control	Ancestry
Epilepsy	Finngen_R10	12891/312803	European
Generalized epilepsy	Finngen_R10	1413/399287	European
Focal epilepsy	Finngen_R10	7526/399290	European
Epilepsy	Ieu-b-8	15212/29677	Mixed
Generalized epilepsy	Ieu-b-9	3769/29677	Mixed
Focal epilepsy	Ieu-b-10	9671/29677	Mixed
Juvenile absence epilepsy	Ieu-b-12	415/29677	Mixed
Juvenile myoclonic epilepsy	Ieu-b-17	1181/29677	Mixed
Childhood absence epilepsy	Ieu-b-13	793/29677	Mixed

groups: Those that are generalized from onset and those that are partial, also referred to as focal[29]. Idiopathic generalized epilepsies are exemplified by absence epilepsies[30]. The occurrence of childhood absence epilepsy and juvenile absence epilepsy is notably associated with specific age[31]. Juvenile myoclonic epilepsy (JME) is characterized by the presence of myoclonic jerks, which predominantly affect the shoulders and arms in a bilateral fashion[32].

Definition of instruments of IL6R

We referenced a recent study that conducted a meta-analysis of the genome-wide association study (GWAS) on hsCRP. This investigation incorporated 522681 European individuals from the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium and the United Kingdom Biobank. Based on the findings of this study, *IL6R* was chosen as the research tool[33]. We opted for a genetic instrument to simulate the effects of anti-*IL6R* monoclonal antibodies, blocking *IL6R* signaling by inhibiting both IL6 classical and IL6 trans-signaling pathways[34,35].

According to previous literature[34-36], the establishment of the *cisIL6R* instrument involved selecting variants in *IL6R* with $r^2 < 0.1$ and within a 300kb range. Additionally, these variants were weighted based on their impact on hsCRP.

Definition of instruments of CRP

To investigated the causal relationship between CRP and epilepsy, we extracted variants related to cis-acting CRP (cisCRP) from previous studies[37]. Notably, the pathways through which these variants regulate CRP levels may be independent of downstream IL6 signaling[12].

Definition of instruments of gp130

The significance of *gp130* lies in its role as another crucial component of the *IL6R*. Notably, *gp130* is not only present within *IL6R* but also in other cytokine receptors. While researchers acknowledge the impact of *gp130* variants on specific phenotypes, they emphasize that this influence has not been studied as extensively as *IL6R* variants[38]. To explore the role of *gp130* further, the study utilized a large GWAS dataset on plasma protein levels (DECODE cohort, $n = 35287$) and the TwoSampleMR method to develop tools for investigating *gp130* plasma protein levels. The researchers selected single nucleotide polymorphisms (SNPs) from this dataset that were associated with *gp130* levels and mutually independent ($r^2 < 0.1$), ensuring these SNPs were within 300kb of the *gp130* gene. Subsequently, these SNPs were used to analyze the associations between infection outcomes and *gp130*. The paragraph concludes by noting that MR analysis was separately conducted for each epileptic outcome.

Statistical analysis

In the present study, a two-sample MR analysis was undertaken, employing harmonized SNPs for each distinct outcome. MR estimates were derived from individual SNPs. Afterward, the data was subjected to meta-analysis using inverse variance weighting (IVW) with first-order weights. The TwoSampleMR package (version 0.5.7) in R (version 4.2.2) was used for the analysis. Data were presented as odds ratio (OR) with 95% confidence interval (CI).

To summarize the associations between various genetic variants and specific epilepsy outcomes, we conducted fixed-effects meta-analyses for each outcome. The R package meta was employed to generate summary estimates for each epilepsy condition (version 7.0-0).

Ethics

Ethical review and approval are not required as the research data are sourced from publicly available datasets.

Table 2 Inverse variance weighting meta-analysis of mendelian randomization estimates for interleukin-6 receptor blockade in epilepsy

Trait	OR (95%CI)	*P* value	Case/control
Epilepsy	0.827 (0.685-1.000)	0.050	28103/342480
Generalized epilepsy	0.822 (0.532-1.272)	0.380	5182/428964
Focal epilepsy	0.834 (0.648-1.075)	0.161	17197/428967
Juvenile absence epilepsy	0.987 (0.941-1.036)	0.609	415/29677
Juvenile myoclonic epilepsy	0.967 (0.896-1.044)	0.393	1181/29677
Childhood absence epilepsy	0.984 (0.923-1.049)	0.616	793/29677

OR: Odds ratio; CI: Confidential interval.

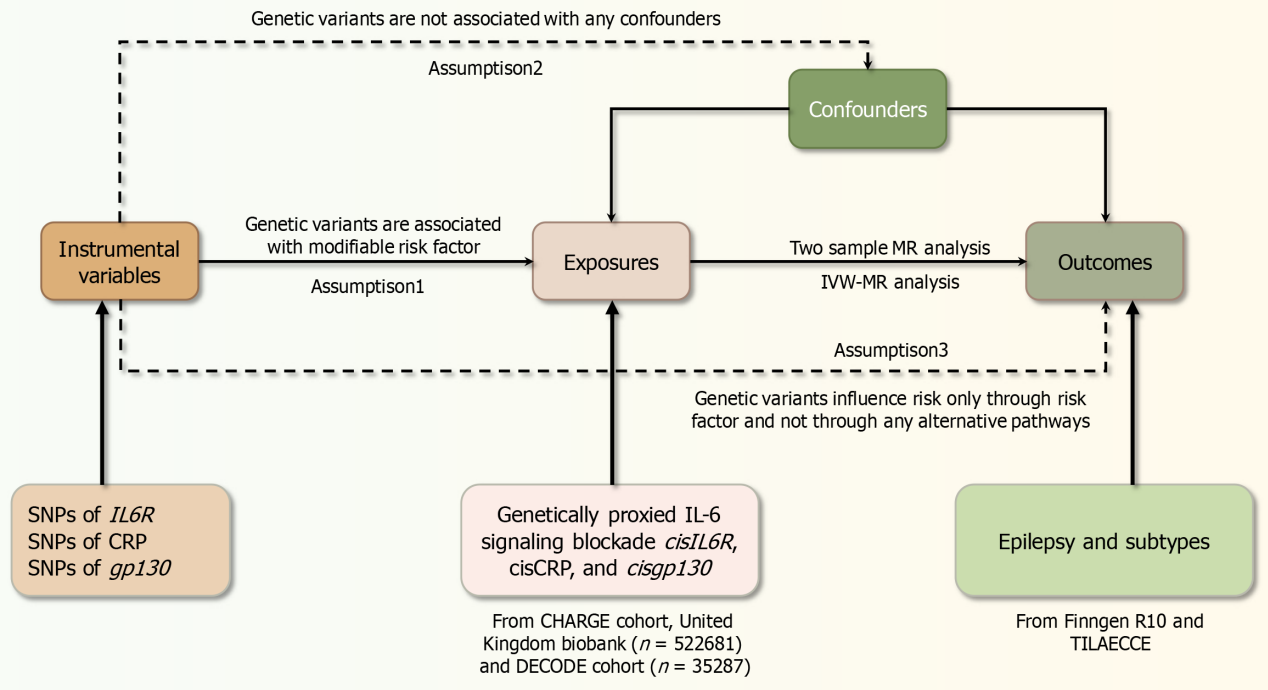

Figure 1 Summary of the study design employed in our mendelian randomization investigation. IL: Interleukin; MR: Mendelian randomization; IVW: Inverse variance weighting; SNP: Single nucleotide polymorphism; *IL6R*: IL-6 receptor; CRP: C-reactive protein; cis: Cis-acting; *gp130*: Glycoprotein 130.

RESULTS

MR based on cisIL6R instrument

The study methodology is schematically represented in Figure 1, delineating the key steps and processes employed in our research. Here, MR analysis found a potential protective effect of genetically predicted inhibition of the *IL6R* pathway on epilepsy risk (OR: 0.827, 95%CI: 0.685-1.000, P = 0.05; Figure 2A and Table 2). Genetically proxied *IL6R* blockade demonstrated no significant effect on generalized epilepsy (OR: 0.823, 95%CI: 0.532-1.2720, P = 0.380; Figure 2B), focal epilepsy (OR: 0.835, 95%CI: 0.648-1.075, P = 0.161; Figure 2C), juvenile absence epilepsy (OR: 0.988, 95%CI: 0.941-1.036, P = 0.610; Figure 2D), childhood absence epilepsy (OR: 0.984, 95%CI: 0.923-1.048, P = 0.616; Figure 2D), and JME (OR: 0.967, 95%CI: 0.896-1.044, P = 0.393; Figure 2D).

MR based on cisCRP and gp130 instrument

We conducted IVW MR analyses using the instrumental variable derived from cisCRP. Our results, as illustrated in Figure 3A-C, revealed no statistically significant association between genetically predicted CRP levels and the risk of epilepsy or most of its subtypes. However, a notable exception was observed for juvenile clonic epilepsy (OR: 1.040, 95%CI: 1.002-1.079, P = 0.038), as depicted in Figure 3D. This study challenged the assumption that CRP is the sole mediator of IL-6's influence on epilepsy and suggested further investigation into other potential mechanisms. Despite investigating *gp130* due to its potential role in inflammation and seizure activity, we did not identify any statistically significant links between *gp130* and the risk of developing epilepsy or its various subtypes (Figure 4).

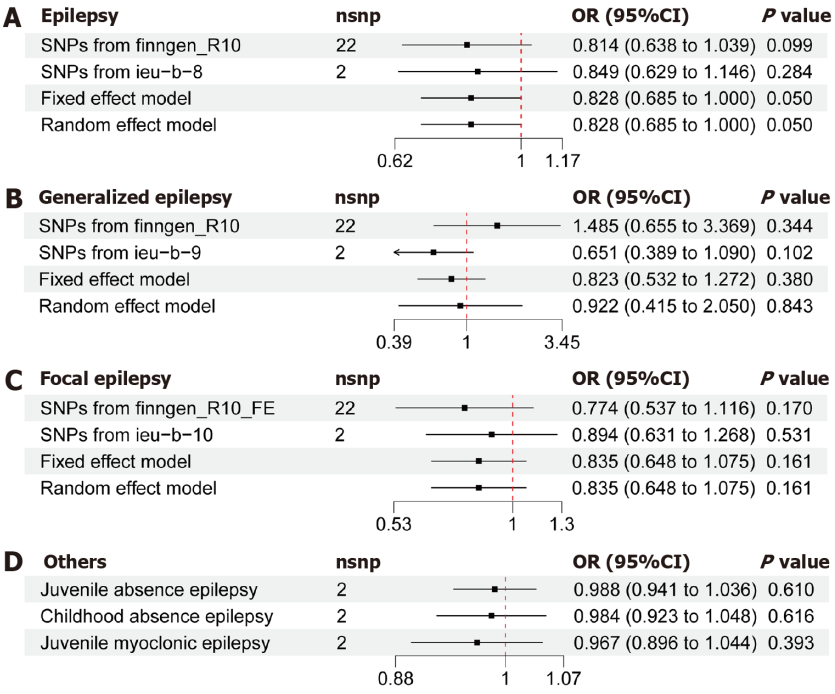

Figure 2 Correlation between genetically mediated inhibition of interleukin 6 signaling and the risk of epilepsy. A: Forest plot displaying mendelian randomization (MR) effect estimates and 95% confidence intervals (CI) for the genetic proxied blockade effect of interleukin (IL)-6 receptor (*IL6R*) on epilepsy; B: Forest plot displaying MR effect estimates and 95%CI for the genetic proxied blockade effect of *IL6R* on generalized epilepsy; C: Forest plot displaying MR effect estimates and 95%CI for the genetic proxied blockade effect of *IL6R* on focal epilepsy; D: Forest plot displaying MR effect estimates and 95%CI for the genetic proxied blockade effect of *IL6R* on juvenile absence epilepsy, childhood absence epilepsy, and juvenile myoclonic epilepsy. SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence intervals.

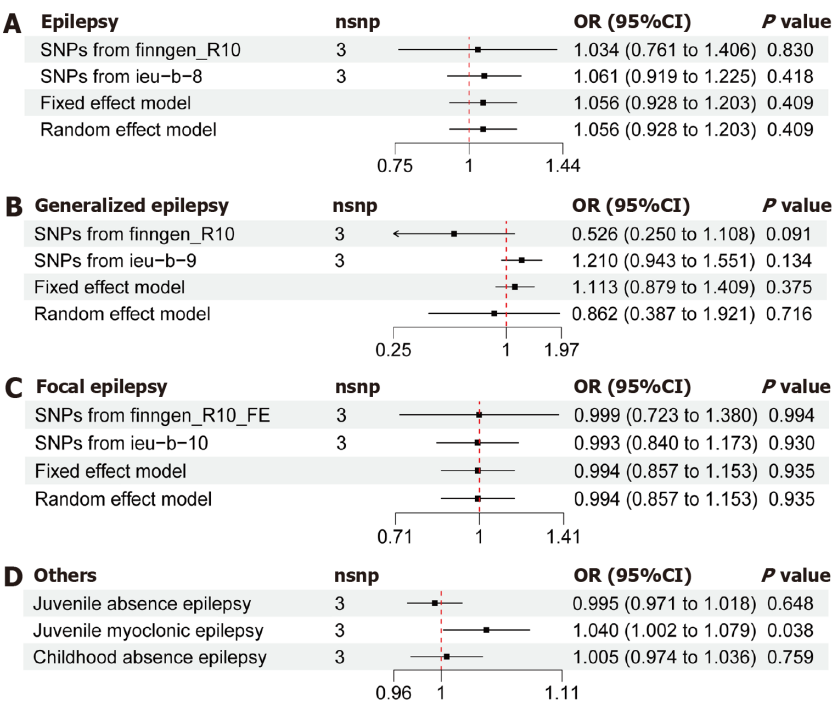

Figure 3 Correlation between genetically mediated C-reactive protein levels and the risk of epilepsy. A: Forest plot illustrating mendelian randomization (MR) effect estimates and 95% confidence intervals (CI) for the genetically mediated C-reactive protein (CRP) levels' impact on epilepsy; B: Forest plot displaying MR effect estimates and 95%CI for the genetically mediated CRP levels' impact on generalized epilepsy; C: Forest plot displaying MR effect estimates and 95%CI for the genetically mediated CRP levels' impact on focal epilepsy; D: Forest plot displaying MR effect estimates and 95%CI for the genetically mediated CRP levels' impact on juvenile absence epilepsy, childhood absence epilepsy, and juvenile myoclonic epilepsy. SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence intervals.

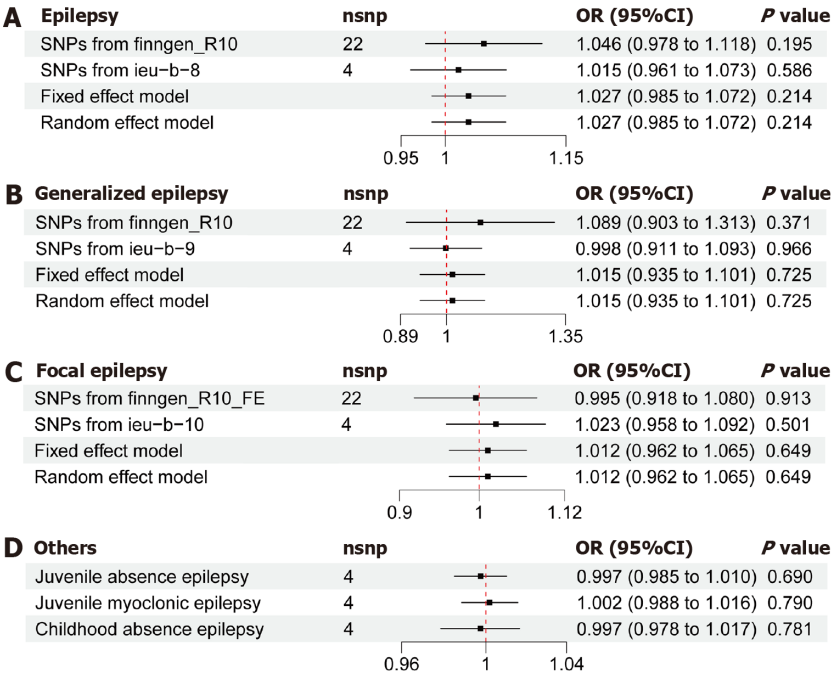

Figure 4 Correlation between genetically mediated glycoprotein 130 levels and the risk of epilepsy. A: Forest plot illustrating mendelian randomization (MR) effect estimates and 95% confidence intervals (CI) for the impact of genetically mediated plasma protein levels of glycoprotein (gp) 130 on epilepsy; B: Forest plot displaying MR effect estimates and 95%CI for the impact of genetically mediated plasma protein levels of *gp130* on generalized epilepsy; C: Forest plot displaying MR effect estimates and 95%CI for the impact of genetically mediated plasma protein levels of *gp130* on focal epilepsy; D: Forest plot displaying MR effect estimates and 95%CI for the impact of genetically mediated plasma protein levels of *gp130* on juvenile absence epilepsy, childhood absence epilepsy, and juvenile myoclonic epilepsy. SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence intervals.

DISCUSSION

This study utilized the MR approach to investigate the role of *IL6R* blockade in epilepsy risk, extending to potential impacts on psychiatric and neuropsychiatric conditions through neuroinflammatory pathways. In this investigation, a two-sample MR approach was employed to scrutinize the correlation between inhibition of IL-6 signaling and epilepsy. To evaluate the causal impact, a proxy of gene was constructed to serve as an instrument to block IL-6 signaling. This instrument correlated with decreased CRP, a downstream product of the classical IL-6 signaling cascade. Our research suggested a potential link between decreased activity of the IL-6 signaling pathway and a lower risk of developing epilepsy. Despite this promising direction, our analysis acrossed epilepsy subtypes yielded no significant findings, highlighted the nuanced nature of *IL6R*'s role in disease pathology.

Our study suggested that inhibiting CRP was unlikely to significantly reduce epilepsy risk. While CRP was a well-established downstream marker of IL-6 signaling, our findings indicated a more nuanced relationship. Specifically, the observed association with epilepsy risk appeared to be more directly driven by specific *IL6R* variants and their impact on the signaling pathway, rather than by changes in CRP levels themselves. Furthermore, our results shown that although *gp130* can inhibit a specific type of IL-6 signaling, it could not prevent the development of different forms of epilepsy. One possible explanation is that the low F-statistic values (< 10) of the selected SNPs indicate weak instruments, which may limit our ability to detect a true association between the exposure and outcome. Another interpretation is that the physiological concentration of *gp130* may not effectively inhibit the IL6 signaling pathway due to the swift assembly and disintegration of the complex of IL-6/sIL-6R[39]. The application of MR methods might not accurately assess the inhibitory role of *gp130* across signaling pathways.

As far as we know, our research was the first to offer tentative evidence for a causal relationship between reduced activity of the IL-6 signaling pathway due to genetic factors and the development of epilepsy (Figure 5). Adding to the mounting body of evidence, our research aligned with past experiments, supported the notion that IL-6 signaling might have causally contributed to epilepsy. Prior research had identified the key immune-related gene *IL6R* as playing a role in the development of epilepsy[40]. Leo *et al*'s study delved into the potential role of IL-6 in childhood absence epilepsy, a form of epilepsy characterized by absence seizures without convulsions[41]. They investigated the impact of tocilizumab (TCZ), a drug known for inhibiting IL-6 signaling, on absence seizures and associated symptoms in Wistar Albino Glaxo from Rijswijk rats, a model for this specific epilepsy condition. The study revealed that chronic TCZ treatment significantly mitigated the occurrence of absence seizures in adult rats, and this effect persisted even after discontinuation of treatment, indicating potential long-term benefits[41]. Compared to the general population, those with autism spectrum disorder (ASD) face a greater risk of developing epilepsy[42]. Both conditions coincide with increased levels of blood-borne immune factors, notably IL-6[42]. Bäckström *et al*[43] found that the intervention using *IL6R* Ain mice lacking the synapsin 2 gene could alleviate ASD-like behavior and result in epileptic seizures. This study is situated within an emerging framework that sees epilepsy not just as a neurological condition but as a disorder potentially

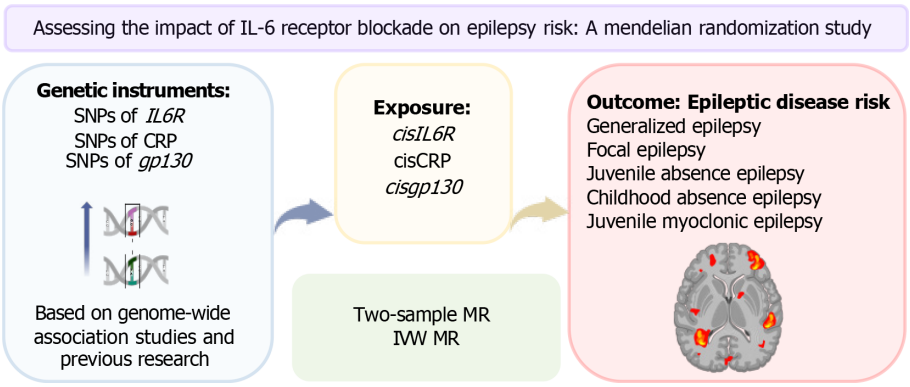

Figure 5 Graphic summary of this study. IL: Interleukin; SNP: Single nucleotide polymorphism; CRP: C-reactive protein; MR: Mendelian randomization; IVW: Inverse variance weighting; *gp130*: Glycoprotein 130; cis: Cis-acting; *IL6R*: IL-6 receptor.

influenced by systemic inflammatory processes. By targeting the IL-6 signaling pathway, we delved into the underexplored intersection between inflammation, immune response, and neurological disease, opening new avenues for therapeutic intervention and patient management. Our findings, contextualized within the broader landscape of neuroimmune interactions, underscore the intricate balance between genetic predispositions, cytokine signaling, and the manifestation of epilepsy and its psychiatric comorbidities.

The Mendelian study on *IL6R* and epilepsy is subject to the following limitations: (1) The employed method (MR) relies on assumptions that may not always be fully met, necessitating future confirmation through randomized controlled trials to establish causal relationships; (2) Limited evidence for alternative pathways: While the study focuses on the IL-6 pathway, it does not exclude the possibility of other factors influencing the risk of chronic pain. However, currently, there is no evidence indicating the existence of alternative pathways; (3) Unidentified confounding factors: The analysis may overlook unknown variables that could affect genetic variation and the risk of pain; and (4) Unclear specificity of mechanisms: Despite identifying *IL6R* as a key factor, the precise localization of the exact mechanisms within this pathway remains challenging due to the focus on specific gene variants.

CONCLUSION

Our analysis presented initial evidence suggesting that blockade of the *IL6R* pathway, as indicated through MR using a *cisIL6R* instrument, might contribute to a reduced risk of epilepsy on a broad level. This finding highlighted the potential of *IL6R* inhibition as a protective factor against epilepsy, mediated by complex neuroinflammatory mechanisms. However, the lack of significant effects on specific epilepsy subtypes, and the absence of a definitive causal relationship identified through CRP and *gp130* markers underscored the intricate interplay between IL-6 signaling and the pathogenesis of epilepsy. The study opened the door for comprehensive future research to validate these findings, explore the neuropsychiatric implications of IL-6 signaling in epilepsy, and investigate *IL6R* blockade as a novel therapeutic strategy. Such endeavors should aim for larger cohort sizes, incorporating multifaceted psychiatric assessments to fully elucidate the roles of inflammation and immune dysregulation in epilepsy and its associated neuropsychiatric comorbidities. Through bridging the gap between genetic predispositions and clinical manifestations, we can move closer to a holistic understanding of epilepsy and its complex relationship with the immune system, potentially paving the way for innovative treatment avenues that address both seizure management and the broader psychiatric disturbances frequently accompanying epilepsy.

FOOTNOTES

Author contributions: Yu YM, Jin GH, Wang L and Zhan F drafted the initial manuscript, analyzed the data, and interpreted the results; Yu YM, Jin GH, Zhong C, Qian H, and Zhan F designed the study, analyzed the data, and critically revised the manuscript; All authors read and approved the final manuscript.

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