Journal of Translational Medicine

RESEARCH

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# Explore genetic susceptibility association between viral infections and Guillain-Barré syndrome risk using two-sample Mendelian randomization

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## Abstract

**Background** Numerous observational studies have indicated that patients with Guillain-Barré syndrome (GBS) frequently had infections with various pathogens before the onset of the disease, particularly several viral infections. Some of these infections are linked to specific clinical and immunological subgroups of GBS, suggesting a potential correlation between viral infections and the development of GBS. However, observational studies have several limitations, including the presence of confounding factors.

**Method** We explored the potential correlation between HIV, SARS-CoV-2, varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, hepatitis B virus, and influenza virus with GBS using a two-sample Mendelian randomization approach. The data was derived from published summary statistics from genome-wide association studies (GWAS). After removing linkage disequilibrium, selecting strong instrumental variables and addressing confounding factors, we would conduct a two-sample Mendelian randomization analysis along with sensitivity testing and the MR-Steiger directional test.

**Result** HIV may have a causal association with GBS (IVW: $p=0.010$, OR [95% CI] 1.240 [1.052–1.463]), while no such relationship exists with COVID-19 (IVW: $p=0.275$, OR [95% CI] 0.831[0.596–1.159]), varicella (IVW: $p=0.543$, OR [95% CI] 0.919 [0.701–1.206]), herpes zoster (IVW: $p=0.563$, OR [95% CI] 0.941 [0.766–1.156]), HSV (IVW: $p=0.280$, OR [95% CI] 1.244 [0.837–1.851]), EBV (IVW: $p=0.218$, OR [95% CI] 0.883 [0.724–1.076]), HBV (IVW: $p=0.179$, OR [95% CI] 1.072 [0.969–1.187]), or influenza virus (IVW: $p=0.917$, OR [95% CI] 0.971 [0.553–1.703]). We did not find any abnormal SNPs, pleiotropy, or heterogeneity, nor is there any reverse causation.

**Conclusion** Our study results indicate a causal relationship between HIV and GBS, providing new research directions for the etiology of GBS.

**Keywords** Guillain-Barré Syndrome, Viral Infections, Mendelian randomization analysis, Genetic susceptibility

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## Introduction

Guillain-Barré Syndrome (GBS) emerges as a significant cause for acute paralysis, often presenting with inflammatory cell infiltration, demyelination, and axonal damage within the peripheral nervous system (PNS) [1, 2]. The crude incidence of GBS has been reported to fluctuate from 0.81 to 1.89 cases per 100,000 person-years, with a median incidence of 1.11, and it has been observed to be rising exponentially [3]. GBS often occurs as a post-infectious, immune-mediated nerve injury, with two-thirds of patients reporting prodromal gastrointestinal or respiratory symptoms. Campylobacter jejuni, the most commonly identified pathogenic trigger, is responsible for GBS in approximately 1 out of every 1000 cases [4]. GBS is also believed to have a genetic predisposition, although specific genetic risk loci have not yet been clearly defined [5]. Despite an incomplete understanding of the precise causes of GBS, it is believed that genetics, environmental factors, and their interactions play a significant role in its development.

Recent studies suggest that certain viral infections, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Varicella-zoster virus (VZV), may potentially contribute to the development of GBS. However, findings from different studies have been inconsistent. Meta-analysis indicated an association and para-infectious nature between COVID-19, caused by SARS-CoV-2, and GBS [6, 7]. In contrast, another research did not find a similar strong causal link [8]. Studies indicate a heightened risk of neurological and psychiatric complications among COVID-19 patients when compared to those with influenza or other respiratory diseases. Particularly striking is the revelation that individuals with pre-existing chronic neurological conditions face greater mortality from COVID-19 than neurologically healthy counterparts [9]. VZV causes varicella (chickenpox) as a primary infection, following which it becomes latent in peripheral ganglia, and can reactivate many years later to produce herpes zoster [10]. While there are numerous reported cases in the literature of GBS occurring following VZV reactivation [11], this neurological syndrome is believed to rarely follow an episode of herpes zoster [12]. The scarcity of published cases, coupled with the fact that both GBS and herpes zoster are relatively common conditions, complicates the definitive attribution of a clear association between the two, as it may be coincidental.

However, the relationships between certain viral infections and GBS have remained unclear. Observational studies are frequently hindered by challenges such as confounding influences and the complexities of reverse causality. These factors have made it difficult to assess the causal relationship between them. Therefore, there is an urgent need for a comprehensive study with a rigorous approach to definitively establish the causal relationship between viral infections and GBS.

Genome-wide association studies offer insights into genetic determinants associated with diverse diseases. Mendelian randomization (MR), based on these studies, constitutes a valuable technique for causal inference [13], minimizing the influence of confounders through genetic variables' unique properties at conception, thereby avoiding some limitations of observational studies [14]. This study employed two-sample MR to assess the genetic susceptibility association of various viruses including Human Immunodeficiency Virus (HIV), SARS-CoV-2(COVID-19), varicella-zoster virus (VZV) (varicella, herpes zoster), herpes simplex virus (HSV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and influenza virus on GBS.

## Methods

### Exposure GWAS dataset

In this research, the following exposure variables and dataset had been meticulously curated to delineate our study's scope:

HIV exposure was explored using the finn-b_AB1_HIV dataset from the FinnGen database [15], which included 357 cases, 218,435 controls, and a comprehensive set of 16,380,466 SNPs.

COVID-19 was examined through the ebi-a-GCST011081 dataset provided by the COVID-19 Host Genetics Initiative [16], comprising 9986 cases, 1,877,672 controls, and 8,107,040 SNPs, sourced from GWAS.

Varicella (VZV) was investigated with the finn-b-AB1_VARICELLA dataset from the latest FinnGen, encompassing 710 cases, 211,856 controls, and 16,380,433 SNPs.

Herpes zoster (VZV) was studied using the ebi-a-GCST90018941 dataset from GWAS, which contained 522 cases, 351,740 controls, and 19,078,292 SNPs.

HSV was analyzed with the finn-b_AB1_HERPES_SIMPLEX dataset from the FinnGen database, consisting of 1,595 cases, 211,856 controls, and 16,380,457 SNPs.

EBV was assessed using the finn-b-AB1_EBV dataset from FinnGen (release 9), which included 1,238 cases, 213,666 controls, and 16,380,461 SNPs.

HBV was investigated with the ebi-a-GCST90018804 dataset from GWAS, containing 145 cases, 351,740 controls, and 19,079,722 SNPs [17].

Influenza virus exposure was evaluated using the finn-b_J10_INFLUENZA dataset from the latest

FinnGen, with 4262 cases, 188,868 controls, and 16,380,378 SNPs.

Each dataset was chosen to provide a robust foundation for the analysis of the respective viral exposures in relation to the study's objectives.

#### Outcome GWAS dataset

The data for GBS as an outcome were sourced from the Finnish database, which includes 213 cases and 215,718 controls, with a total of 16,380,463 SNPs, all from individuals of European descent.

#### Instrument identification

Instrumental variables need to satisfy the following three assumptions: SNPs must be strongly associated with the exposure factor (objective criterion: $p < 5 \times 10$^-8), independent of confounding factors, and not directly associated with the outcome [18]. Given that only a small proportion of the SNPs for the exposure factor under study meet the condition of strong association with the outcome, we had adjusted the p-value to $p < 5 \times 10$^-6. Meanwhile, to avoid instruments with linkage disequilibrium and to exclude non-random associations between certain genes and specific traits, we set the parameters to $r^2 = 0.001$ and kb = 10,000. We further refined our analysis by computing the variance and employing F-statistics to evaluate the robustness of the genetic instrument utilized in our study. Instruments with an F-statistic greater than 10 were defined as strong instruments [19]. Finally, we used the LDlink tool (https://ldlink.nih.gov/) of the National Institutes of Health to exclude confounders-related SNPs and determine the final instrumental variables.

#### Two-sample MR analysis

In the R computing environment, we performed MR analysis employing the TwoSampleMR package, which coordinated and integrated the exposure and outcome datasets. The analysis employed five methods of two-sample MR analysis: MR-Egger regression [20], Weighted median estimator [21], Inverse Variance Weighted (IVW), weighted mode [22], and Simple mode. Previous studies had shown that the IVW method was not affected by horizontal pleiotropy, which in turn minimizes the impact of confounding factors and providing unbiased estimates [23]. As a result, we primarily relied on the IVW method to determine positive outcomes, while utilizing other methods for supplementary validation. Then evaluated the effect size using the β value, odds ratio (OR), and 95% confidence interval (CI).

The second step was the outlier test. We applied MR-PRESSO to detect any outliers that may indicate pleiotropic bias in the reported results [24]. If outliers are present, they needed to be manually removed and then MR analysis should be conducted again.

The third step was sensitivity analysis, which aimed to test whether the results of MR analysis were reliable, mainly including heterogeneity test (Cochran's Q test) ($p < 0.05$ indicates heterogeneity), pleiotropy test (Egger Intercept test) ($p < 0.05$, indicating that there is pleiotropy in the data), single SNP test and retention one method analysis.

Finally, we conducted the MR-Steiger directional test to determine whether there is a reverse causal relationship between the exposure and the outcome. The above steps about the two sample MR are detailed in the flowchart below (Fig. 1).

## Result

Our study identified a significant causal link between HIV infection and the occurrence of GBS, indicating that HIV increases the risk of GBS (IVW: $p = 0.010$, OR [95% CI] 1.240 [1.052–1.463]). However, no causal relationship was found between GBS and COVID-19 (IVW: $p = 0.275$, OR[95% CI] 0.831[0.596–1.159]), varicella (IVW: $p = 0.543$, OR [95% CI] 0.919 [0.701–1.206]), herpes zoster (IVW: $p = 0.563$, OR [95% CI] 0.941 [0.766–1.156]), herpes simplex (IVW: $p = 0.280$, OR [95% CI] 1.244 [0.837–1.851]), Epstein-Barr virus (EBV) (IVW: $p = 0.218$, OR [95% CI] 0.883 [0.724–1.076]), hepatitis B virus (HBV) (IVW: $p = 0.179$, OR [95% CI] 1.072 [0.969–1.187]), or influenza virus (IVW: $p = 0.917$, OR [95% CI] 0.971 [0.553–1.703]). The results of MR Egger, Weighted Median, Simple Mode, and Weighted Mode analyses are consistent with the directionality of IVW, all indicating that there is no causal relationship with GBS (Figs. 2, 3).

For HIV, the MR-PRESSO analysis did not identify any potential SNP outliers. At this point, MR Egger's $p$ (Q-statistic) = 0.190, and IVW's $p$ (Q-statistic) = 0.253, indicating a lack of heterogeneity. Furthermore, the MR-Egger analysis showed no evidence of horizontal pleiotropy (intercept = − 0.045, $p = 0.715$). The leave-one-out analysis reinforced the robustness of the results, as all SNP p-values were found to be greater than 0, indicating that the causal relationship between HIV and GBS is deemed reliable. For COVID-19, varicella, herpes zoster, HSV, EBV, HBV, and influenza virus, no abnormal SNPs were identified, and there was no indication of heterogeneity or horizontal pleiotropy (Table 1). All of these have confirmed the absence of a causal relationship. Meanwhile, the results of the MR-Steiger directional test indicate that there is no reverse causal relationship between all viral infections and GBS (Table 2).

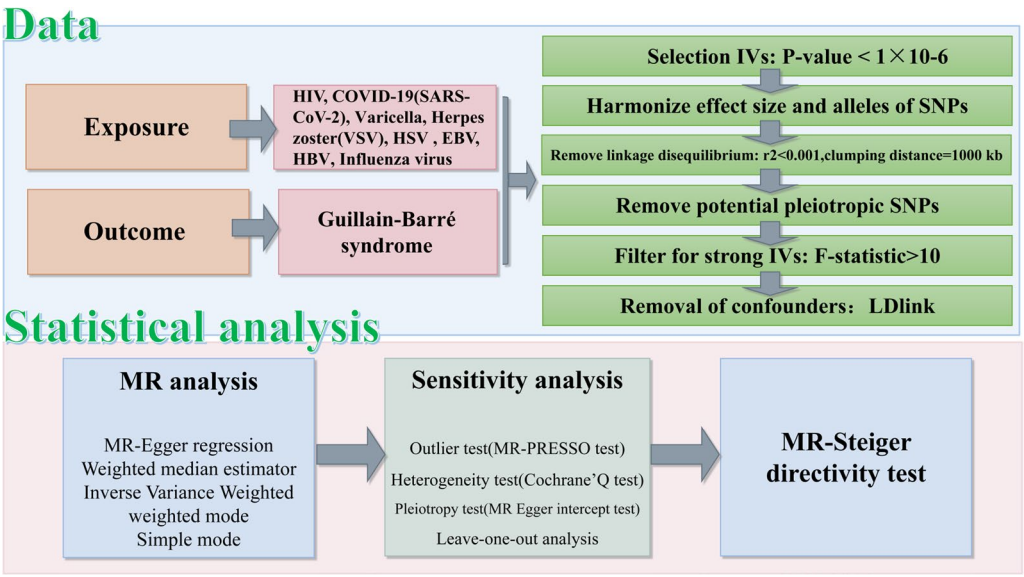


**Fig. 1** Flowchart of two-sample Mendelian randomization

## Discussion

GBS is typically regarded as an autoimmune disease that sporadically affects the nerves, often following an infection. Nonetheless, a small number of familial cases have been documented, indicating potential genetic susceptibility in conjunction with environmental triggers in the development of GBS [25, 26]. Our study revealed a significant causal association between HIV and GBS, while the remaining viral infections did not exhibit such a causal relationship. As far as we know, this is the first MR analysis to establish a causal link between viral infection and GBS, and the results are less vulnerable to reverse causality and confounding bias than those found in many earlier traditional observational studies.

The disruption of immune tolerance drives a response to autoantigens, this inability to distinguish between self and non-self allows the observed autoimmune response [27]. The HIV tropism for the central nervous system (CNS) is established within the first weeks, the potential mechanisms might encompass aspects of cell-mediated immunity, such as macrophage-induced demyelination and the perivascular infiltration by T lymphocytes [28]. Autoantibody-mediated autoimmune responses driven by molecular mimicry may also be a mechanism [29, 30]. At the same time, it may also be related to the release of NETs by neutrophils caused by HIV virus infection and the promotion of the interaction between TRL7 and TRL9 [31, 32]. Previous studies have demonstrated GBS is a HIV-driven disease whose clinical expression depends on the susceptibility of the host, the intensity and quality of the antiretroviral induced immune response, and the nature and characteristics of the HIV [33]. In this study, MR analysis performed between HIV and GBS only demonstrated a significant effect with IVW (P value < 0.05), but the OR values of the five methods were all in the same direction, suggesting that presence of SNPs linked to increased susceptibility to HIV increases the risk of GBS and further reinforce genetic susceptibility in the pathogenesis of GBS. Although the genetic basis of GBS remains uncertain, our MR results has revealed genetic mechanisms associated with HIV deserve much more attention. For suspected cases of GBS, HIV screening should be included in the initial blood tests due to the favorable impact of antiretroviral therapy on the progression of this neurological complication [34].

During the SARS-CoV-2 outbreak, there have been increasing reports of an association between COVID-19 and immune-mediated GBS [35–37], but the retrospective epidemiological and prospective cohort study does not support a significant causal link between COVID-19 infection and GBS [8]. Our MR analysis showed that COVID-19 doesn't increase the risk of GBS (IVW: p = 0.275, OR [95% CI] 0.831 [0.596–1.159]), further reinforcing the perspective that there is no association between COVID-19 and GBS. SARS-CoV-2 infection has been associated with an increased likelihood of GBS, possibly due to the induction of antiganglioside antibodies leading to GBS [38], or through the virus interfering with the host's self-tolerance of antigens via molecular mimicry [39]. Similar to this, there have been case reports or systematic reviews suggesting VZV, HSV, EBV, HBV, and the influenza virus association with GBS, our research

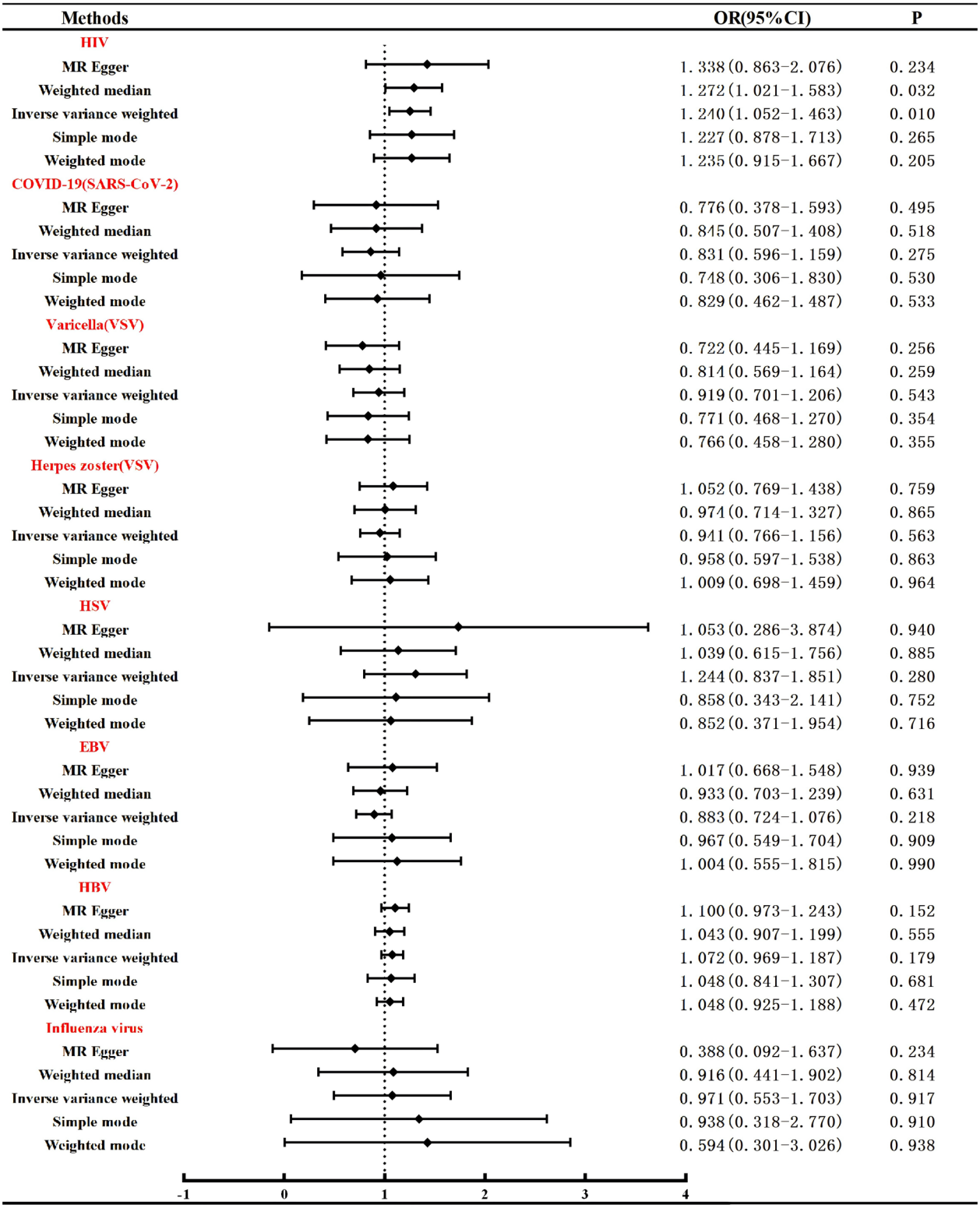


**Fig. 2** Forest plot of MR analysis result

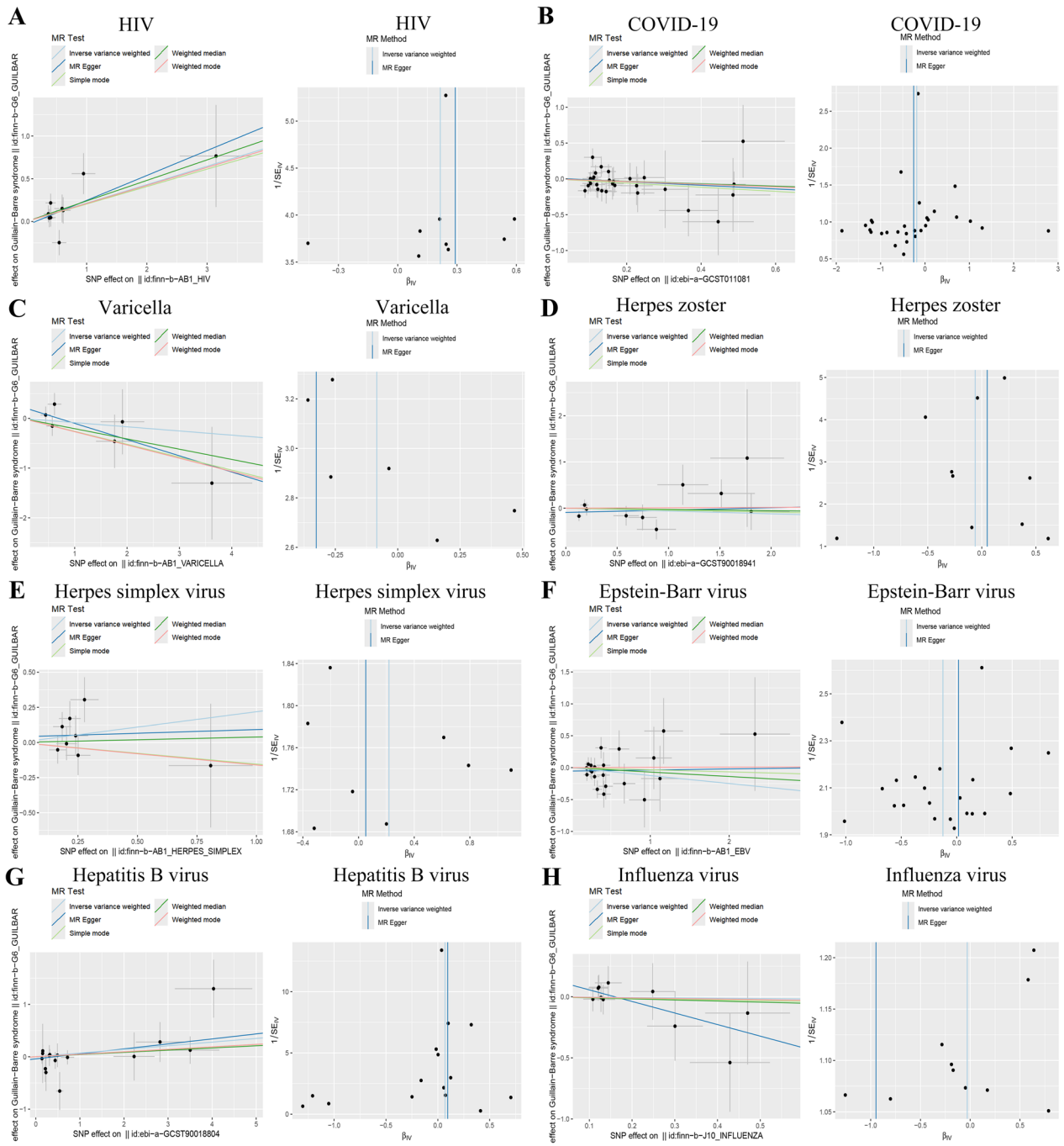


**Fig. 3** Scatter and funnel plots display associations of Guillain-Barré syndrome with eight viral infections. **A** HIV with GBS, **B** COVID-19 with GBS, **C** Varicella with GBS, **D** Herpes zoster with GBS, **E** HSV with GBS, **F** EBV with GBS, **G** HBV with GBS, **H** Influenza virus with GBS

findings indicate that there is no causal relationship between these viral infections and GBS (varicella (IVW: p = 0.543, OR [95% CI] 0.919 [0.701–1.206]), herpes zoster (IVW: p = 0.563, OR [95% CI] 0.941 [0.766–1.156]), HSV (IVW: p = 0.280, OR [95% CI] 1.244 [0.837–1.851]), Epstein-Barr virus (EBV) (IVW: p = 0.218, OR [95% CI] 0.883 [0.724–1.076]), HBV (IVW: p = 0.179, OR [95% CI] 1.072 [0.969–1.187]), or influenza virus (IVW: p = 0.917, OR [95% CI] 0.971 [0.553–1.703])). These studies, primarily based on case reports and observational research, have inherent limitations, such as small sample sizes and potential confounding factors. Additionally, it has been

**Table 1** Sensitivity analyses results

| Exposures | MR-PRESSO global test *p*_value | Heterogeneity | | | | Horizontal pleiotropy | | Leave_one_out test All SNPs *p*_value |
|---|---|---|---|---|---|---|---|---|
| | | MR egger | | Inverse variance weighted | | MR egger | | |
| | | Cochran'Q | *p*_value | Cochran'Q | *p*_value | Egger intercept | *p*_value | |
| HIV | 0.310 | 9.969 | 0.190 | 10.174 | 0.253 | − 0.045 | 0.715 | 0.023 |
| COVID-19 (SARS-CoV-2) | 0.797 | 21.724 | 0.751 | 28.000 | 0.792 | 0.012 | 0.834 | 0.275 |
| Varicella (VZV) | 0.487 | 2.708 | 0.608 | 4.122 | 0.532 | 0.227 | 0.300 | 0.543 |
| Herpes zoster (VZV) | 0.240 | 9.860 | 0.275 | 11.152 | 0.265 | − 0.092 | 0.336 | 0.603 |
| HSV | 0.515 | 6.437 | 0.376 | 6.512 | 0.481 | 0.040 | 0.800 | 0.280 |
| EBV | 0.380 | 21.481 | 0.369 | 22.090 | 0.394 | − 0.053 | 0.460 | 0.229 |
| HBV | 0.781 | 10.243 | 0.674 | 10.769 | 0.704 | − 0.040 | 0.481 | 0.179 |
| Influenza | 0.889 | 2.634 | 0.955 | 4.471 | 0.878 | 0.151 | 0.212 | 0.917 |

**Table 2** The results of the MR-Steiger directional test

| Exposures | HIV | COVID-19 (SARS-CoV-2) | Varicella (VZV) | Herpes zoster (VZV) | HSV | EBV | HBV | Influenza |
|---|---|---|---|---|---|---|---|---|
| steiger p_val | 4.29E-13 | 1.40E-08 | 1.09E-14 | 3.92E-11 | 1.03E-13 | 4.28E-36 | 2.34E-40 | 9.36E-22 |

observed that infections typically occur prior to the onset of GBS [40], but a temporal association per se does not necessarily imply a causal association. This is especially true for herpes zoster, because VZV infection persists throughout an individual's lifetime. Further basic and clinical research is needed to potentially transform the absence of evidence into actual evidence of absence.

As previously mentioned, MR enables the identification of genetic susceptibility at the genetic level, significantly minimizing the influence of confounding factors. However, our study has some limitations. Our study's reliance on sample data exclusively from individuals of European descent limits the broader applicability of our results to diverse populations. Therefore, future research should include more diverse populations to establish whether a causal relationship exists between these viral infections and GBS.

## Conclusion

While the genetic basis of GBS remains uncertain, our MR results indicate that there is a genetic susceptibility association between HIV infection and GBS, which deserves more attention. Additionally, our findings did not establish a causal relationship between GBS and infections from SARS-CoV-2, VZV, HSV, EBV, HBV, and the influenza virus. This approach helps mitigate the interference of confounding factors and reverse causality to some extent, but it also has certain limitations. In the future, we will expand the study population and conduct necessary clinical trials to further validate our conclusions.

### Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| EBV | Epstein-Barr virus |
| GBS | Guillain-Barré syndrome |
| HBV | Hepatitis B virus |
| HIV | Human immunodeficiency virus |
| HSV | Herpes simplex virus |
| IVW | Inverse variance weighted |
| MR | Mendelian randomization |
| OR | Odds ratio |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SNPs | Specifically single nucleotide polymorphisms |
| VZV | Varicella-zoster virus |

### Acknowledgements

We would like to thank the researchers and participants of all GWAS from which the summary statistics datasets were used in this study.

### Author contributions

All co-authors have made substantial and intellectual contributions to the work and approved the submitted article. Zhi-Yun Lian and Yuan-Jie Liu conceived and designed the research. Material preparation and data collection were performed by Qing-Xiang Kong, Yan Liu, Lu-Lu Jiang. Data analysis, interpretation and visualization were performed by Qing-Xiang Kong, Zhao-Kun Gao, Yuan-Jie Liu. The manuscript was written by Qing-Xiang Kong, Yuan-Jie Liu and Zhi-Yun Lian revised it critically for important intellectual content. All authors confirm that they had full access to all the data in the study and accept the responsibility to submit for publication.

### Funding

The study was financially supported by the "Xinglin Scholars" discipline talent research improvement program of Chengdu University of Traditional Chinese Medicine [Grant Numbers: YYZX20180052].

### Availability of data and materials

The used GWAS data were publicly available and their origins were described appropriately in the manuscript (https://gwas.mrcieu.ac.uk). The detailed

information and codes required to reanalyze the data in this work are available from the corresponding authors upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
The used data were publicly available and approved by their corresponding institutions. An ethics approval for the current work is not required. No animal subjects were used in this work.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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Received: 22 August 2024 Accepted: 25 September 2024
Published online: 02 October 2024

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