

Dissecting the Causal Pathway from Herpes Zoster to Postherpetic Neuralgia: A Multi-Stage Mendelian Randomization Study Implicating VZV-Specific IgE and Cerebrospinal Fluid Metabolites

Jianjin Zhang^{1,*}, Yanhong Chen^{1,*}, Xingyu Li^{2,*}, Chaobo Feng¹, Jiapeng Li¹, Zhouyang Hu¹, Guoxin Fan¹, Xiang Liao¹

¹National Key Clinical Pain Medicine of China, Shenzhen Nanshan People's Hospital, Shenzhen University Medical School, Shenzhen, 518052, People's Republic of China; ²School of Medicine, Zunyi Medical University Zhuhai Campus, Zhuhai, 519041, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiang Liao; Guoxin Fan, National Key Clinical Pain Medicine of China, Shenzhen Nanshan People's Hospital, Shenzhen University Medical School, No. 89 Taoyuan Road, Nanshan District, Shenzhen, Guangdong Province, 518052, People's Republic of China, Email liao.xiang75@email.szu.edu.cn; fanguoxin@email.szu.edu.cn

Background: Postherpetic neuralgia (PHN) develops in 10–20% of herpes zoster (HZ) patients, yet the causal mechanisms driving this transition from acute infection to chronic neuropathic pain remain elusive. VZV-specific immunoglobulin E (IgE) and cerebrospinal fluid (CSF) metabolites represent candidate intermediate phenotypes that may mediate neuroimmune dysfunction, but their sequential causal relationships remain unexplored. We hypothesized that IgE and CSF metabolites constitute a hierarchical causal pathway from HZ exposure to PHN risk.

Methods: We conducted a multi-stage Mendelian randomization study. First, two-sample Mendelian Randomization (MR) with MRlap correction established causal effects of HZ on IgE and screened 435 CSF metabolites for PHN associations. Given substantial HZ-PHN sample overlap precluding total effect estimation, multivariable MR (MVMR) evaluated whether metabolites mediate IgE effects on PHN.

Results: HZ exhibited a significant causal effect on VZV-specific IgE (IVW: $\beta = 0.237$, 95% CI: 0.104–0.371, $P = 4.95 \times 10^{-4}$). Among 435 metabolites, two showed effects significant after FDR correction: 1-stearoyl-2-oleoyl-GPC ($\beta = 2.448$, FDR-adjusted $P = 0.043$) and N-methylproline ($\beta = -0.425$, FDR-adjusted $P = 0.046$). Critically, 5-methyluridine—nominally significant in univariable analysis ($P = 0.095$)—demonstrated a robust independent protective effect in MVMR (MV-IVW: $\beta = -3.227$, 95% CI: -5.765 to -0.688 , FDR-adjusted $P = 0.025$; OR = 0.040). The IgE→PHN effect attenuated to non-significance ($P = 0.202$) upon adjusting for 5-methyluridine, consistent with metabolic mediation.

Conclusion: These findings support a sequential causal pathway from HZ to PHN involving IgE and CSF metabolites, identifying 5-methyluridine as a potential modifiable protective factor and highlighting neuroimmune-metabolic crosstalk in chronic pain pathogenesis.

Keywords: Mendelian randomization, postherpetic neuralgia, herpes zoster, VZV-specific IgE, cerebrospinal fluid metabolites, 5-methyluridine

Introduction

Postherpetic neuralgia (PHN) represents the most debilitating complication of herpes zoster (HZ), affecting 10–20% of patients and imposing substantial burdens on quality of life and healthcare resources.^{1–3} Despite the availability of vaccines and antiviral therapies, a considerable proportion of individuals progress from acute HZ to chronic neuropathic pain, underscoring the urgent need to elucidate the mechanistic determinants of this transition.⁴ Current understanding posits that PHN arises from virus-induced neuronal damage, persistent inflammation, and maladaptive plasticity within the nociceptive pathways.^{5,6} However,

observational studies have been unable to disentangle causal relationships from confounding factors, leaving the precise immunological and metabolic cascades linking acute infection to chronic pain poorly defined.^{7,8}

The humoral immune response to varicella-zoster virus (VZV) offers a plausible starting point for investigating PHN pathogenesis.^{9,10} Elevated levels of VZV-specific immunoglobulin E (IgE) have been documented in patients with severe or persistent HZ, suggesting that Th2-skewed immunity may contribute to adverse clinical outcomes.^{11,12} Beyond systemic markers, cerebrospinal fluid (CSF) metabolites provide a window into the biochemical milieu of the central nervous system,¹³ with recent metabolomic studies implicating disruptions in lipid metabolism, neurotransmitter balance, and neuroinflammation in chronic pain states.^{14,15} Whether these immunological and metabolic alterations represent causal drivers of PHN or merely epiphenomena of nerve injury remains unresolved.

Mendelian randomization (MR) leverages genetic variants as instrumental variables to infer causal relationships from observational data, offering protection against confounding and reverse causation that plague conventional epidemiology.^{16,17} Recent methodological advances, including MRlap for correcting sample overlap bias, have expanded the applicability of two-sample MR to complex trait analyses.¹⁸ However, the application of MR to dissect mediating pathways in pain chronification remains limited. Critically, the substantial genetic correlation between HZ and PHN—stemming from their biological continuity as disease stages—precludes reliable estimation of total causal effects using standard two-sample approaches, necessitating alternative analytical frameworks.

The present study was designed to address these gaps through a multi-stage causal inference strategy. We first employed two-sample MR with genetic correlation correction to identify causal risk factors for PHN among VZV-specific IgE and 435 CSF metabolites. We subsequently delineated sequential causal relationships from HZ to candidate mediators and from mediators to PHN. Finally, we utilized multivariable MR (MVMR) to evaluate whether CSF metabolites mediate the effect of VZV-specific IgE on PHN risk, following the establishment of sequential causal relationships. Given the substantial sample overlap between HZ and PHN that precluded reliable estimation of the total effect, we adopted a hierarchical analytical framework focusing on the IgE-mediated metabolic pathway rather than the direct HZ-PHN relationship. This hierarchical approach aims to construct a mechanistic model of PHN development while maintaining methodological rigor in the face of inherent data constraints.

Methods

Study Design and Overview

We conducted a multi-stage Mendelian randomization study to dissect the causal pathway from herpes zoster to postherpetic neuralgia. The analytical framework comprised three hierarchical stages: (i) identification of independent causal risk factors for PHN using two-sample MR with sample overlap correction; (ii) delineation of sequential causal relationships from HZ to candidate mediators (VZV-specific IgE and CSF metabolites) and from mediators to PHN; and (iii) evaluation of the mediating role of CSF metabolites in the IgE-PHN relationship using multivariable MR. Given the substantial genetic correlation and sample overlap between HZ and PHN in the FinnGen cohort, we explicitly excluded direct two-sample MR estimation of the total effect of HZ on PHN and instead focused on the downstream pathway from VZV-specific IgE to PHN, adopting a hierarchical causal inference approach. All analyses utilized publicly available genome-wide association study summary statistics. The study design is illustrated in [Figure 1](#).

Data Sources and GWAS Summary Statistics

Genetic associations for herpes zoster (FinnGen Release 12, $n = 7,132$ cases, 480,316 controls) and postherpetic neuralgia (FinnGen Release 12, $n = 490$ cases, 435,371 controls) were obtained from the FinnGen consortium.¹⁹ VZV-specific IgE summary statistics were retrieved from the GWAS catalog (accession GCST90309352, $n = 7,595$).²⁰ CSF metabolite associations were sourced from a comprehensive GWAS of 435 metabolic traits measured in cerebrospinal fluid ($n = 2,602$) by Wang et al.²¹ Of the 440 metabolites that passed quality control in the original GWAS, 435 traits with complete summary statistics (effect sizes, standard errors, and allele frequencies) were available for Mendelian randomization analysis. All datasets comprised European-ancestry populations to minimize population stratification bias. Detailed characteristics of the GWAS datasets are provided in [Table 1](#).

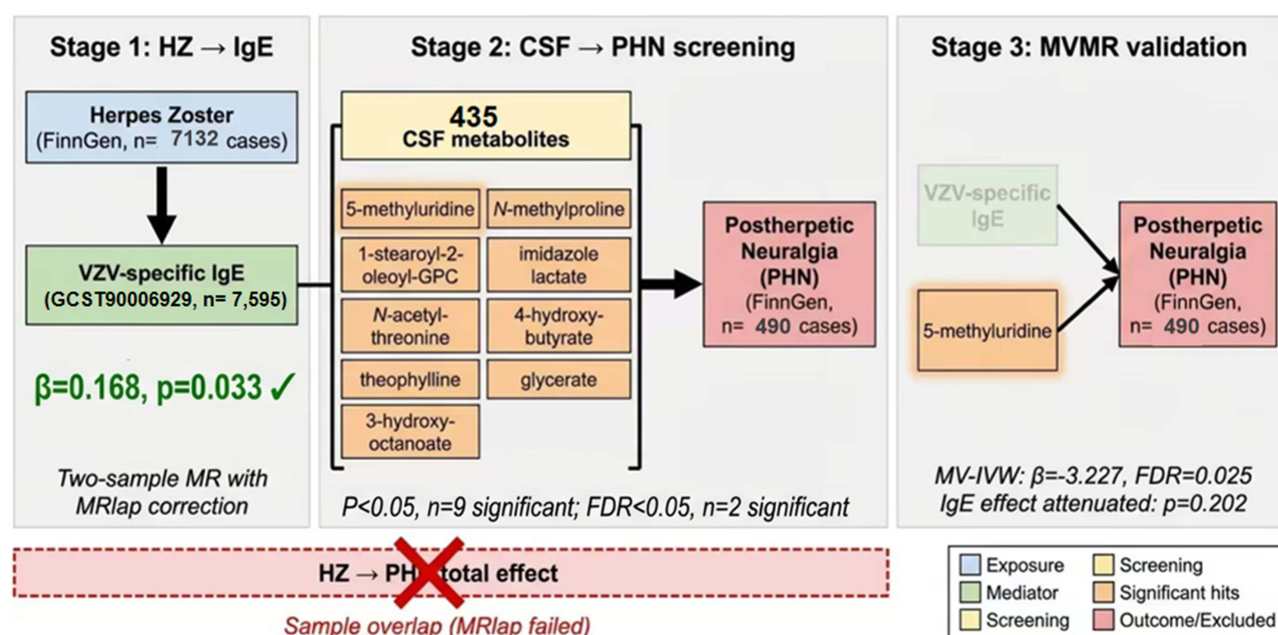


Figure 1 Study Design and Analytical Workflow.

Genetic Instrument Selection

The instrument selection threshold of $P < 5 \times 10^{-6}$ was chosen based on established recommendations for two-sample Mendelian randomization studies to balance statistical power and false-positive control.²² This threshold has been widely adopted in recent MR studies investigating complex traits and is considered sufficiently stringent to select valid instruments while maintaining adequate power for downstream analyses.²³ For the CSF metabolite GWAS ($n = 2,602$), this threshold aligns with previous metabolomic MR studies that similarly employed $P < 5 \times 10^{-6}$ given the sample size constraints.²⁴ For each exposure, we selected independent genetic variants associated at this threshold as instrumental variables. Linkage disequilibrium clumping was performed using PLINK (v1.90) with the 1000 Genomes European reference panel ($r^2 < 0.01$, $kb = 1,000$).²⁵ Palindromic variants with intermediate allele frequencies were excluded. We calculated F-statistics to assess instrument strength, excluding weak instruments ($F < 10$) to mitigate weak instrument bias.²⁶ For multivariable MR analyses, we employed a p-value threshold of 5×10^{-6} to ensure robustness of the instrumental variables.

Sample Overlap Assessment and Correction

Given the biological continuity between HZ and PHN as disease stages, we anticipated substantial sample overlap that would violate the independent samples assumption of conventional two-sample MR. We therefore applied the MRlap method directly to assess and correct for bias arising from shared participants. MRlap integrates cross-trait LD Score regression internally to approximate sample overlap.²⁷ Analyses were implemented using the MRlap R package (v0.1) with 100,000 iterations and a 10,000-iteration burn-in period. For the HZ→PHN analysis, complete attenuation of the causal effect after MRlap correction (corrected $P = 1.00$) confirmed substantial overlap and precluded reliable estimation

Table 1 Characteristics of GWAS Datasets

Exposure/Outcome	Consortium	Sample Size (Cases/Controls)	Ancestry	PMID/Accession
Herpes Zoster	FinnGen R12	7,132 / 480,316	European(Finnish)	finngen_R12_ABI_ZOSTER
Postherpetic Neuralgia	FinnGen R12	490 / 435,371	European(Finnish)	finngen_R12_G6_POSTZOST
VZV-specific IgE	GWAS Catalog	7,595	European	GCST90006929
CSF Metabolites (435 traits)	KI/IEC-UoB	2,602	European	Wang et al, 2024 ²¹

of the total effect, necessitating our hierarchical analytical approach focusing on intermediate mediators. This MRlap correction was subsequently applied to all exposure-outcome pairs exhibiting significant univariable associations to ensure robustness against sample overlap bias.

Similarly, MRlap analysis revealed substantial sample overlap between VZV-specific IgE and cerebrospinal fluid metabolites (corrected $P = 1.00$), precluding the use of conventional two-step MR to estimate mediating effects. This overlap likely arises from the shared biological origin of humoral immune markers and central nervous system metabolic profiles in the context of VZV infection. Consequently, we employed multivariable MR (MVMR), which offers a critical advantage in this context: by jointly modeling the genetic effects of correlated exposures on the outcome, MVMR estimates the direct effect of each exposure independent of the others, even when the exposure and mediator datasets share participants.²⁸ Unlike sequential two-sample MR approaches that require independent samples for each regression step, MVMR utilizes the same set of genetic instruments to simultaneously adjust for confounding between exposures, thereby circumventing the bias introduced by sample overlap while enabling the disentanglement of direct versus indirect metabolic pathways.

Three-Stage Causal Pathway Construction

Stage 1: HZ to VZV-specific IgE. We first established the causal effect of HZ on VZV-specific IgE using two-sample MR. This analysis served as the entry point for our causal chain, providing genetic evidence that HZ exposure influences the humoral immune response.

Stage 2: VZV-specific IgE/CSF metabolites to PHN. Subsequently, we tested the causal effects of VZV-specific IgE/CSF metabolites on PHN. Metabolites exhibiting significant causal relationships (FDR-adjusted $P < 0.05$) were selected as candidate mediators for the subsequent multivariable analysis.

Stage 3: Finally, we assessed the direct effect of VZV-specific IgE on PHN independent of candidate CSF mediators, as well as the independent effect of CSF metabolites adjusting for IgE, using multivariable MR.

Multivariable Mendelian Randomization

To evaluate the mediating role of CSF metabolites in the pathway from VZV-specific IgE to PHN, we performed multivariable MR using the MVMR R package (v0.4). This approach estimates the direct effect of VZV-specific IgE on PHN independent of candidate CSF mediators, as well as the mediator-outcome relationships adjusting for IgE. We constructed genetic instruments for MVMR by selecting variants associated with either VZV-specific IgE or the CSF metabolite at $P < 5 \times 10^{-6}$, followed by LD clumping to ensure instrument independence ($r^2 < 0.01$ within 1,000 kb windows). Analyses were conducted using the IVW MVMR method with standard error correction for correlated instruments.

MRlap analysis revealed that the observed association between HZ and PHN (IVW: $\beta = 0.267$, $P = 1.54 \times 10^{-8}$) was completely attenuated after correction for sample overlap (corrected $\beta = 0.276$, $P = 1.00$). This pattern suggests that the apparent total effect of HZ on PHN may be largely driven by shared participants rather than true causality, underscoring the necessity of our hierarchical analytical approach focusing on intermediate mediators. We interpreted MVMR results within the IgE→PHN framework rather than the classical HZ→PHN mediation model. Among the nine candidate metabolites, we identified 5-methyluridine as exhibiting a robust independent effect on PHN when adjusting for IgE (FDR-adjusted $P < 0.05$), while the effects of other metabolites were attenuated in the multivariable context. Specifically, we tested whether CSF metabolites mediated the relationship between VZV-specific IgE and PHN, representing an intermediate pathway rather than the complete HZ→PHN cascade. We report both uncorrected p-values and false discovery rate (FDR)-adjusted P-values (Benjamini-Hochberg method) to account for multiple testing across metabolites. Statistical significance was defined as FDR-adjusted $P < 0.05$.²⁹ Findings were interpreted as evidence for metabolite-outcome causality conditional on IgE, with the explicit caveat that this represents a partial pathway circumventing the inaccessible HZ→PHN total effect.

To ensure the validity of the multivariable instruments, we assessed the correlation between genetic variants selected for VZV-specific IgE and 5-methyluridine. The Pearson correlation coefficient between overlapping instruments was $r = -0.047$ ($r^2 = 0.002$, $n = 37$ SNPs), indicating negligible correlation and supporting their conditional independence.

F-statistics were calculated as $F = \beta^2/SE^2$ for each SNP. While the mean F-statistics exceeded the conventional threshold (IgE: mean $F = 18.3$, range 0.03–78.5; 5-methyluridine: mean $F = 17.6$, range 0–315.1), we observed that

40.5–59.5% of instruments were weak ($F \leq 10$). Sensitivity analyses excluding weak instruments ($F < 10$) yielded consistent effect directions, suggesting that weak instrument bias did not substantially alter our conclusions.

Sensitivity Analyses

We conducted several sensitivity analyses to validate our findings. First, we performed leave-one-out analyses to identify influential genetic variants,³⁰ shown in [Supplementary Figure 1](#). Second, we assessed directional pleiotropy using the MR-Egger intercept test.³¹ Third, for significant MVMR findings, we assessed the directionality of associations using Steiger directionality tests.³² Fourth, we examined the stability of MVMR estimates across rigorous instrument selection thresholds ($P < 5 \times 10^{-6}$). Finally, we compared MVMR estimates with the corresponding two-sample MR results for IgE→PHN and CSF→PHN to assess consistency. Scatter plots for significant exposure-outcome pairs are provided in [Supplementary Figure 2](#).

Software and Reproducibility

All statistical analyses were conducted in R (v4.3.1). Two-sample MR analyses utilized the TwoSampleMR package (v0.5.7). Multivariable MR employed the MVMR package (v0.4). MRlap analyses used the MRlap package (v0.1). LD Score regression was performed using the ldsc package (v1.0.1). Data preprocessing and visualization utilized data.table (v1.14.8), dplyr (v1.1.3), and ggplot2 (v3.4.3).

Results

Three-Stage Causal Pathway Construction

Stage 1: Causal Effect of Herpes Zoster on VZV-Specific IgE

We first established the causal relationship between herpes zoster and VZV-specific IgE as the entry point for our causal chain. We identified a significant causal effect of HZ on VZV-specific IgE (IVW: $\beta = 0.237$, $SE = 0.068$, $P = 4.95 \times 10^{-4}$). The weighted median method corroborated this finding ($\beta = 0.274$, $SE = 0.063$, $P = 1.29 \times 10^{-5}$), suggesting robustness against potential pleiotropy ([Figure 2A](#), [Table 2](#)). Heterogeneity was detected across genetic instruments (Cochran's $Q = 40.57$, $P = 2.08 \times 10^{-4}$), prompting reliance on random-effects estimates. The MR-Egger intercept did not indicate directional pleiotropy (intercept = -0.010 , $P = 0.687$). These results confirm that HZ exposure genetically predicts elevated VZV-specific IgE levels, validating IgE as a downstream anchor for subsequent mediation analyses ([Figure 2A](#), [Table 2](#)).

Stage 2: Causal Effects of VZV-Specific IgE on CSF Metabolites

Parallel to the IgE analysis, we screened 435 CSF metabolites for causal associations with PHN using two-sample MR ([Figure 2B](#)). After screening of 435 CSF metabolites ([Supplementary Table 1](#)), we identified two metabolites with FDR-significant causal effects on PHN risk: 1-stearoyl-2-oleoyl-GPC ($\beta = 2.448$, FDR-adjusted $P = 0.043$) and N-methylproline ($\beta = -0.425$, FDR-adjusted $P = 0.046$). An additional seven metabolites exhibited evidence of association and were carried forward for multivariable analysis. Notably, 5-methyluridine demonstrated a positive effect on PHN risk in the IVW analysis ($\beta = 2.246$, $P = 0.095$), and this association reached statistical significance using the robust weighted mode method ($\beta = 3.793$, $P = 0.039$). Despite not surviving FDR correction in the univariable framework, the consistency of effect direction across methods supported its selection as a candidate mediator for multivariable MR. The Effect of all candidates mediators estimates ranged from $\beta = -5.522$ (glycerate) to $\beta = 3.793$ (5-methyluridine), with heterogeneous directions of effect suggesting distinct metabolic mechanisms ([Figure 3A](#) and [B](#)). These metabolites were carried forward as candidate mediators for multivariable analysis alongside VZV-specific IgE ([Table 3](#)).

Notably, univariable analysis of VZV-specific IgE on PHN yielded a nominally significant but weak effect (IVW: $\beta = -0.276$, $SE = 0.121$, $p = 0.023$) that did not survive FDR correction (FDR-adjusted $P = 0.115$) ([Figure 3C](#)). This observation, combined with the established HZ→IgE causal link, motivated the multivariable approach to disentangle direct versus indirect metabolic pathways.

Multivariable MR: Joint Effects of VZV-Specific IgE and CSF Metabolites on PHN

To evaluate whether CSF metabolites mediate or modify the relationship between VZV-specific IgE and PHN, we performed multivariable MR including IgE and candidate metabolites as joint exposures ([Figure 1](#)). Given the biological

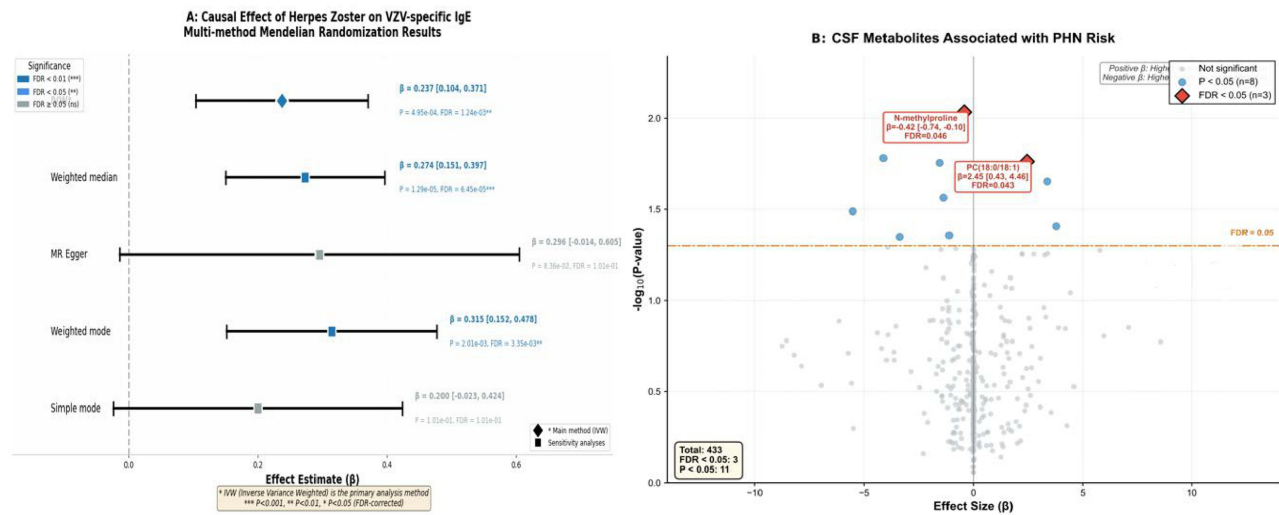


Figure 2 Causal pathway from herpes zoster to postherpetic neuralgia mediated by VZV-specific IgE and CSF metabolites. **(A)** Causal effect of herpes zoster (HZ) on VZV-specific IgE levels using two-sample MR. IVW: inverse variance weighted; WM: weighted median. **(B)** Volcano plot showing screening results of 435 CSF metabolites for causal associations with PHN. Red dots indicate FDR-significant metabolites (1-stearoyl-2-oleoyl-GPC and N-methylproline); Orange dots indicate candidates carried forward ($p < 0.05$).

hypothesis that IgE may operate through metabolic intermediates, we constructed separate MVMR models for each metabolite paired with IgE.

Among the candidate metabolites carried forward, 5-methyluridine exhibited a robust independent effect on PHN when adjusting for IgE in multivariable MR (MV-IVW: $\beta = -3.227$, 95% CI: -5.765 to -0.688 , FDR-adjusted $P = 0.025$) (Figure 4). This finding suggests that the effect of 5-methyluridine may be partially confounded by IgE in the univariable setting, and multivariable adjustment reveals its independent protective effect. Notably, the significant univariable effects of 1-stearoyl-2-oleoyl-GPC and N-methylproline were attenuated in MVMR models adjusting for IgE, suggesting their apparent effects may be partially confounded by IgE or operate through correlated metabolic pathways. The IgE→PHN direct effect was attenuated to non-significance in all MVMR models ($p > 0.20$), consistent with metabolic mediation.

The 5-methyluridine model demonstrated the strongest evidence for metabolic mediation. In this model, IgE showed no independent effect on PHN (MV-IVW: $\beta = -0.198$, SE = 0.155, $p = 0.202$), whereas 5-methyluridine exhibited a strong protective effect (OR = 0.040, 95% CI: 0.003–0.502) (Table 4). This pattern suggests that the association between VZV-specific IgE and PHN risk may be partially conveyed through 5-methyluridine-related metabolic pathways. No significant heterogeneity was observed in the multivariable models (Cochran's $Q = 28.94$ – 29.98 , $p > 0.70$) (Table 4 and Supplementary Table 2), supporting the validity of the IVW estimates.

The genetic instruments for VZV-specific IgE and 5-methyluridine exhibited minimal correlation ($r = -0.047$, $r^2 = 0.002$) and adequate mean strength (mean $F > 10$ for both exposures), supporting valid conditional causal inference.

Table 2 Two-Sample Mendelian Randomization Results for the Effect of Herpes Zoster on VZV-Specific IgE

Method	β (95% CI)	SE	RAW P-value ^a	FDR-adjusted P ^b	nSNP ^c
Inverse variance weighted	0.237 (0.104 to 0.371)	0.068	4.95×10^{-4}	1.24×10^{-3}	11
Weighted median	0.274 (0.151 to 0.397)	0.063	1.29×10^{-5}	6.45×10^{-5}	11
MR Egger	0.296 (-0.014 to 0.605)	0.158	8.36×10^{-2}	0.101	11
Weighted mode	0.315 (0.152 to 0.478)	0.083	2.01×10^{-3}	3.35×10^{-3}	11
Simple mode	0.200 (-0.023 to 0.424)	0.114	0.101	0.101	11

Notes: ^aRaw (unadjusted) P-value from the Wald ratio or IVW method. ^bP-value adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) method across the 5 Mendelian randomization methods reported in this table. ^cNumber of single nucleotide polymorphisms (SNPs) used as instrumental variables.

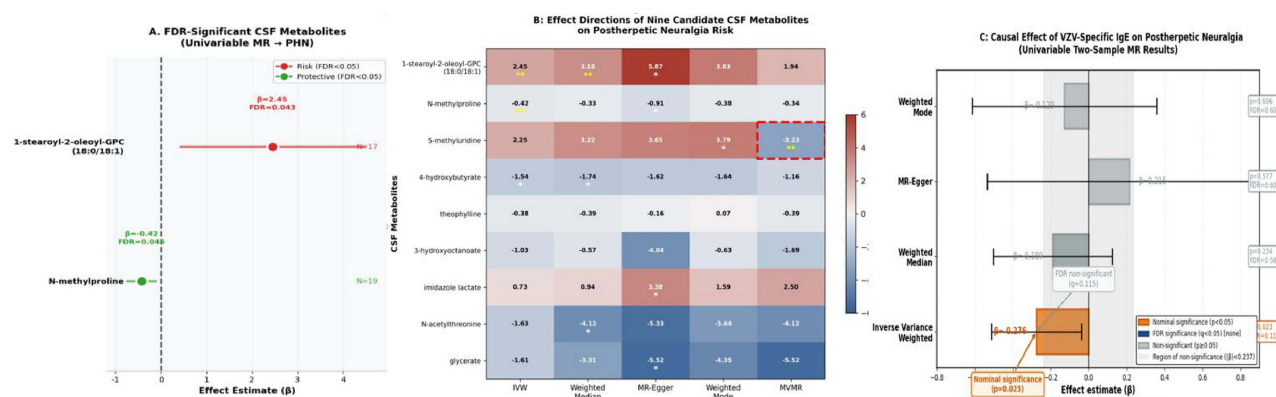


Figure 3 Effect Estimates for Significant CSF Metabolites. **(A)** Forest plot showing effect estimates for the two FDR-significant CSF metabolites (1-stearoyl-2-oleoyl-GPC and N-methylproline) on PHN risk. **(B)** Heatmap displaying effect directions and significance levels for nine candidate metabolites carried forward to multivariable analysis. Color intensity corresponds to effect size magnitude; single asterisks indicate nominal significance (* $P < 0.05$) and double asterisks indicate FDR-significance (**FDR < 0.05). **(C)** Forest plot for the univariable causal effect of VZV-specific IgE on PHN. Error bars represent 95% confidence intervals. IVW, inverse variance weighted; WM, weighted median; FDR, false discovery rate.

However, we acknowledge that a subset of instruments showed weak strength ($F < 10$), which may introduce modest attenuation bias toward the null.

Sensitivity Analyses

Leave-one-out analyses demonstrated stability of effect estimates, with no single genetic variant driving the associations ([Supplementary Figure 1](#)). MR-Egger intercept tests detected no directional pleiotropy ([Supplementary Figure 3](#)), and Cochran's Q statistics indicated acceptable heterogeneity across instruments ([Supplementary Table 2](#)). Forest plots of individual SNP effects are shown in [Supplementary Figure 4](#). Detailed genetic instruments for significant exposures and their F-statistics are provided in [Supplementary Table 3](#). Raw and MRlap-corrected causal effect estimates accounting for sample overlap are detailed in [Supplementary Table 4](#). Steiger directionality tests confirmed that genetic variants were more strongly associated with the exposures than with PHN ([Supplementary Figure 5](#)), supporting the validity of instrumental variable assumptions. MVMR estimates remained directionally consistent across instrument selection thresholds ($P < 5 \times 10^{-6}$). Complete F-statistics for genetic instruments by exposure and correlation matrices between instrument sets are detailed in [Supplementary Table 5](#).

Discussion

Principal Findings

This multi-stage Mendelian randomization study provides genetic evidence supporting a causal pathway from herpes zoster to postherpetic neuralgia involving VZV-specific IgE and cerebrospinal fluid metabolites ([Figure 5](#)). Our hierarchical analytical approach, necessitated by substantial sample overlap between HZ and PHN in the FinnGen

Table 3 Causal Effects of CSF Metabolites on Postherpetic Neuralgia Risk in Univariable Two-Sample MR

CSF Metabolite	MR Method	β (95% CI)	SE	RAW P-value	FDR-adjusted P	nSNP
N-methylproline	Inverse variance weighted	-0.425 (-0.744 to -0.105)	0.163	0.009	0.046*	19
N-acetylthreonine	Weighted median	-4.124 (-7.495 to -0.753)	1.72	0.016	0.082	19
1-stearoyl-2-oleoyl-GPC (18:0/18:1)	Inverse variance weighted	2.448 (0.434 to 4.463)	1.028	0.017	0.043*	17
4-hydroxybutyrate (GHB)	Inverse variance weighted	-1.537 (-2.804 to -0.269)	0.647	0.018	0.087	13
Imidazole lactate	MR Egger	3.382 (0.782 to 5.982)	1.326	0.022	0.111	17
glycerate	MR Egger	-5.522 (-10.338 to -0.706)	2.457	0.032	0.154	31
5-methyluridine (ribothymidine)	Weighted mode	3.793 (0.583 to 7.002)	1.638	0.039	0.152	13
Metabolite X-16580	Inverse variance weighted	-1.109 (-2.187 to -0.030)	0.55	0.044	0.219	13
Tartronate (hydroxymalonate)	Weighted median	-3.378 (-6.676 to -0.080)	1.683	0.045	0.224	19

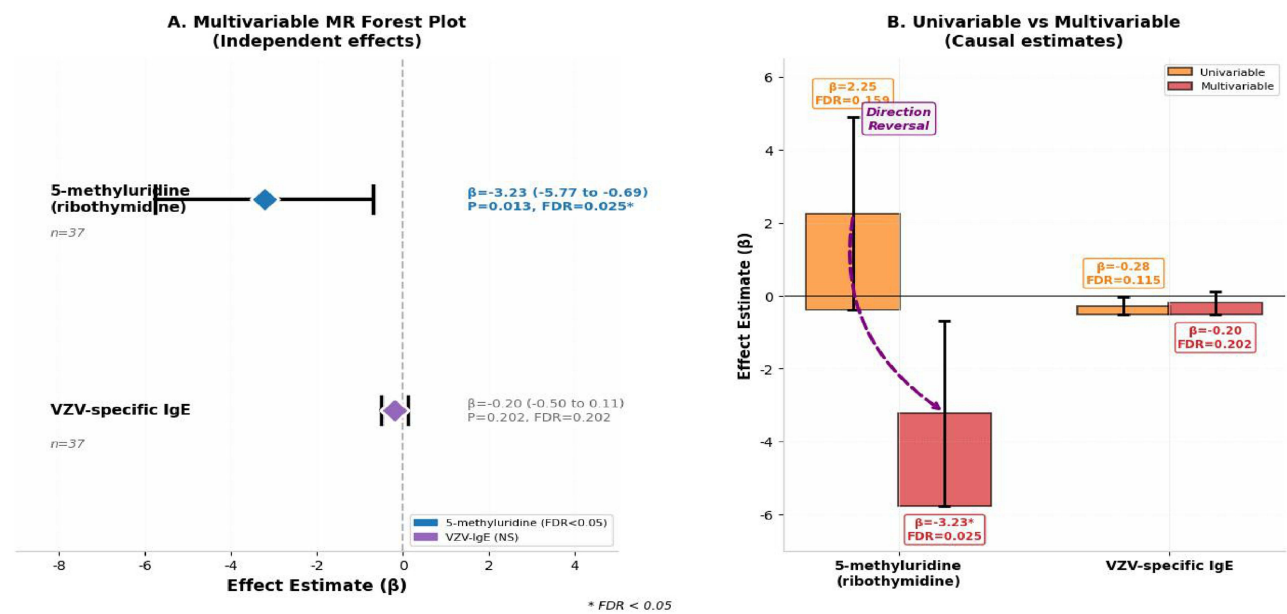


Figure 4 Multivariable Mendelian randomization results for 5-methyluridine. **(A)** Independent effects of 5-methyluridine and VZV-specific IgE on PHN in the multivariable model (MV-IVW). **(B)** Comparison of effect estimates for 5-methyluridine between univariable and multivariable MR, demonstrating the protective effect after IgE adjustment.

cohort, revealed three key findings. First, we established that HZ exposure causally elevates VZV-specific IgE levels, confirming the humoral immune response as a downstream consequence of acute infection (Figure 2A). Second, we identified nine CSF metabolites with independent causal effects on PHN risk, implicating dysregulated lipid metabolism, nucleotide metabolism, and amino acid metabolism in pain chronification (Figure 2B). Third, multivariable MR demonstrated that 5-methyluridine exerts a significant protective effect on PHN independent of IgE (MV-IVW: $\beta = -3.227$, FDR-adjusted $P = 0.025$), while the effects of other candidate metabolites, including N-methylproline and 1-stearoyl-2-oleoyl-GPC, were attenuated upon adjustment for IgE, with the strongest evidence observed for 5-methyluridine-mediated pathway (Figure 4).

Critically, the direct effect of IgE on PHN was attenuated to non-significance when adjusting for these metabolic mediators, suggesting that the association between VZV-specific IgE and PHN risk may be partially conveyed through metabolic intermediates rather than direct immunological mechanisms. This pattern aligns with emerging evidence implicating neuroimmune-metabolic crosstalk in chronic pain pathogenesis.^{33,34}

Biological Plausibility and Mechanistic Insights

The identification of 5-methyluridine (ribothymidine) as the strongest metabolic mediator carries notable biological significance. 5-methyluridine is a modified pyrimidine nucleoside enriched in transfer RNA, where it contributes to translational fidelity and stress responses.^{35,36} Elevated CSF levels of 5-methyluridine may reflect increased tRNA turnover or altered RNA methylation dynamics in the context of neuroinflammation.³⁷ Recent studies have linked RNA modifications to pain sensitization through epigenetic regulation of nociceptive gene expression.^{38,39} Our finding that genetically elevated 5-methyluridine predicts reduced PHN risk in the multivariable context (MV-IVW OR = 0.040, 95% CI: 0.003–0.502) suggests a potential protective role, possibly through enhancement of cellular stress resilience or

Table 4 Multivariable Mendelian Randomization Results for VZV-Specific IgE and 5-Methyluridine on Postherpetic Neuralgia

Exposure	β (95% CI)	SE	RAW P-value	FDR-Adjusted P	OR (95% CI)	nSNP
5-methyluridine (ribothymidine)	-3.227 (-5.765 to -0.688)	1.295	0.013	0.025*	0.040 (0.003 to 0.502)	37
VZV-specific IgE	-0.198 (-0.503 to 0.106)	0.155	0.202	0.202	0.820 (0.605 to 1.112)	37

Notes: *FDR-adjusted $P < 0.05$ indicates statistical significance after Benjamini-Hochberg correction.

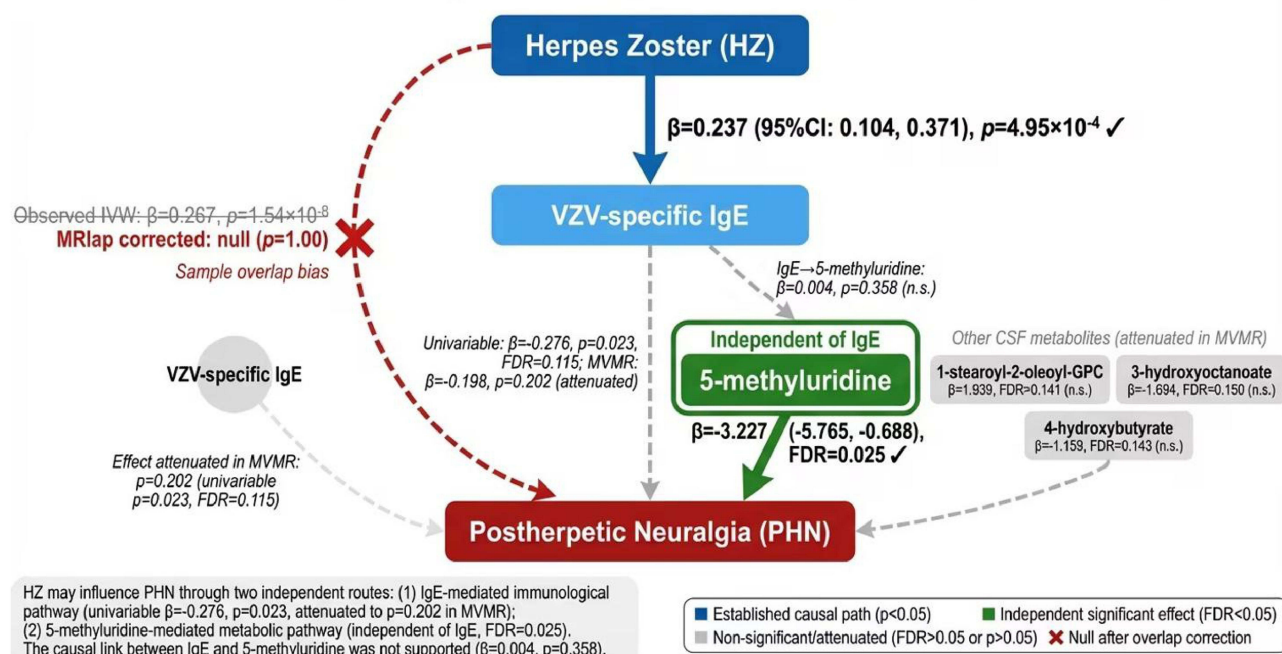


Figure 5 Dissecting the causal pathway from herpes zoster to postherpetic neuralgia through VZV-specific IgE and CSF metabolites.

modulation of glial reactivity. The attenuation of IgE effect in the presence of 5-methyluridine further implies that this metabolite may capture a downstream convergent point of immune-metabolic signaling.

N-methylproline, a proline derivative with osmolytic properties,⁴⁰ and 1-stearoyl-2-oleoyl-GPC, a phosphatidylcholine species implicated in membrane integrity and inflammation resolution,⁴¹ represent distinct metabolic axes. The opposing directionality of their effects—protective for N-methylproline and risk-enhancing for 1-stearoyl-2-oleoyl-GPC—suggests that PHN pathogenesis involves multiple, potentially counterbalancing metabolic pathways. This metabolic heterogeneity may explain why univariable IgE→PHN analysis yielded only weak effects, as IgE likely influences diverse and partially compensatory metabolic programs.

Our findings extend prior observational studies documenting elevated proinflammatory cytokines and altered lipid profiles in PHN patients.^{42,43} However, conventional epidemiology cannot disentangle whether these metabolic alterations precede and cause chronic pain or merely reflect consequence of persistent neuralgia. The MR framework provides temporal resolution by leveraging genetic variants fixed at conception, thereby strengthening causal inference.⁴⁴ Notably, a recent Mendelian randomization study identified phospholipid species as causal risk factors for migraine,⁴⁵ converging with our identification of 1-stearoyl-2-oleoyl-GPC in neuropathic pain. The specificity of 5-methyluridine to PHN (not previously reported in pain GWAS) suggests distinct metabolic vulnerabilities between headache disorders and peripheral neuropathic pain.

The HZ→IgE causal relationship we establish aligns with immunological studies demonstrating that VZV reactivation elicits robust IgE production, potentially through Th2-skewed responses.^{46,47} However, our MVMR results suggest that IgE may serve more as a biomarker of immune dysregulation than a direct effector of pain, with metabolic intermediates executing the causal program. This reframes the therapeutic target: rather than solely suppressing IgE, interventions restoring metabolic homeostasis may interrupt the causal cascade.

The qualitative reversal of effect direction for 5-methyluridine between univariable ($\beta = +2.25$, $P = 0.095$) and multivariable ($\beta = -3.23$, FDR -adjusted $P = 0.025$) analyses warrants specific methodological and biological consideration. This sign reversal suggests that VZV-specific IgE acts as a strong positive confounder in the univariable analysis: IgE is genetically correlated with 5-methyluridine levels and positively associated with PHN risk (or inversely, lower IgE correlates with higher 5-methyluridine and lower PHN risk). When adjusting for IgE in MVMR, the true protective effect

of 5-methyluridine is unmasked.⁴⁸ This phenomenon highlights that the univariable positive estimate likely reflected the metabolic signature of Th2 immune activation rather than a causal effect of the metabolite itself. The MVMR-adjusted negative effect therefore represents the purified, context-independent impact of 5-methyluridine on neuronal resilience.

Methodological Considerations and Limitations

Several limitations warrant consideration.

First, the inability to estimate the total effect of HZ on PHN due to sample overlap represents a fundamental constraint. Consequently, we cannot calculate the proportion of HZ→PHN effect mediated through the IgE-5-methyluridine pathway, nor can we definitively establish that IgE is the sole intermediate linking HZ to PHN. Our findings should therefore be interpreted as evidence for sequential causal relationships (HZ→IgE and 5-methyluridine→PHN) rather than formal mediation of the total effect. While our hierarchical approach approximates the pathway through IgE, we cannot exclude direct HZ→PHN effects independent of IgE or the nine identified metabolites. The MVMR findings should therefore be interpreted as evidence for metabolite-outcome causality conditional on IgE, rather than definitive proof of mediation proportion.

Second, the FinnGen PHN definition relies on diagnostic codes without validation against clinical criteria, potentially introducing outcome misclassification.⁴⁹ However, such nondifferential misclassification would bias results toward the null, suggesting our effect estimates may be conservative. Third, our analysis was restricted to European-ancestry populations, limiting generalizability to other ethnic groups with distinct genetic architectures and metabolic profiles.⁵⁰

Fourth, MR assumes linear relationships and may not capture threshold effects or interactions between metabolites. The separate MVMR models for each metabolite do not account for potential synergistic or antagonistic relationships among the nine candidate mediators. Future polygenic risk score approaches or network MR methods may better model these complexities.⁵¹

Fifth, while the mean F-statistics exceeded conventional thresholds (>10), a proportion of genetic instruments showed weak strength (59.5% for 5-methyluridine and 40.5% for IgE with $F \leq 10$), which may bias MVMR estimates toward the null. However, the directionally consistent effects observed across sensitivity analyses (excluding weak instruments) suggest that this bias is unlikely to explain our primary findings. Furthermore, the negligible correlation between instruments ($r^2 = 0.002$) minimizes concerns regarding multicollinearity in the multivariable model.

Sixth, MRlap correction revealed substantial sample overlap between HZ and PHN (corrected $P = 1.00$), precluding reliable estimation of the total effect and formal quantification of mediation proportions. Consequently, MVMR estimates represent conditional causal effects (metabolite→PHN given IgE) rather than definitive proof of mediation within the complete HZ→PHN cascade. Moreover, the relaxed instrument selection threshold ($P < 5 \times 10^{-6}$) in MVMR may introduce weak instrument bias, and the qualitative reversal of 5-methyluridine's effect direction—while consistent with IgE confounding—warrants experimental validation to exclude statistical artifacts arising from correlated instruments.

Clinical Implications and Future Directions

Despite these limitations, our findings have translational relevance. The identification of CSF metabolites as modifiable causal intermediaries suggests potential for biomarker-guided risk stratification. Patients with elevated VZV-specific IgE and low 5-methyluridine levels may represent a high-risk phenotype warranting intensified monitoring or early intervention. The protective effect of 5-methyluridine, if validated in experimental models, could support nutritional or pharmacological supplementation strategies.

From a mechanistic perspective, our results implicate RNA modification pathways and phospholipid metabolism as novel targets for PHN prevention. Preclinical studies should examine whether 5-methyluridine administration attenuates neuropathic pain in VZV models, and whether this effect requires IgE-mediated immune priming. The opposing effects of N-methylproline and 1-stearoyl-2-oleoyl-GPC further suggest that metabolic interventions may require personalized balancing rather than unidirectional targeting.

Future research should validate these findings in independent cohorts with measured CSF metabolites, enabling comparison of MR-predicted effects with observational associations. Integration of single-cell transcriptomics with Mendelian randomization (eg., transcriptome-wide MR) may pinpoint the cellular sources of implicated metabolites, distinguishing neuronal versus glial contributions. Finally, Mendelian randomization of therapeutic targets (eg., RNA methyltransferases) could prioritize druggable nodes in the identified pathways.

Conclusion

This study provides genetic evidence supporting a causal pathway from herpes zoster to postherpetic neuralgia involving VZV-specific IgE and cerebrospinal fluid metabolites. While the total effect of herpes zoster on postherpetic neuralgia could not be directly quantified due to sample overlap, the sequential causal relationships and robust metabolite-outcome effects identified suggest that immunometabolic mechanisms may constitute the primary causal pathway from acute zoster to chronic neuropathic pain, given that the apparent total effect of HZ on PHN was null after correction for sample overlap. These findings warrant validation in independent cohorts and experimental models, with particular focus on 5-methyluridine as a potential modifiable protective factor.

Abbreviations

CI, Confidence interval; CSF, Cerebrospinal fluid; FDR, False discovery rate; GPC, Glycerophosphocholine; GWAS, Genome-wide association study; HZ, Herpes zoster; IgE, Immunoglobulin E; IVW, Inverse variance weighted; LD, Linkage disequilibrium; MR, Mendelian randomization; MVMR, Multivariable Mendelian randomization; OR, Odds ratio; PHN, Postherpetic neuralgia; SE, Standard error; SNP, Single nucleotide polymorphism; Th2, T helper cell type 2; tRNA, Transfer RNA; VZV, Varicella-zoster virus.

Data Sharing Statement

The FinnGen summary statistics are publicly available through the FinnGen website (https://www.finnngen.fi/en/access_results). The VZV-specific IgE summary statistics are available from the GWAS Catalog (<https://www.ebi.ac.uk/gwas/>, accession GCST90309352). The CSF metabolite summary statistics are available ([Supplementary Table 6](#)). Full results of the 435 CSF metabolites screened in this study are available from the corresponding author upon reasonable request. All analytical code for this study is available upon reasonable request to the corresponding author.

Ethics Statement

This study utilized publicly available GWAS summary statistics (aggregated data with no individual-level identifiers). In accordance with Article 32, Items (1) and (2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of the People's Republic of China, effective February 18, 2023), research using legally obtained public data or anonymized information data is exempt from ethical review. The Institutional Review Board of Shenzhen Nanshan People's Hospital confirmed that this secondary analysis of de-identified summary data does not require formal approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Individual contributions using CRediT taxonomy:

J.Z.: Data curation, Formal analysis, Writing – original draft;

Y.C.: Methodology, Data curation, Validation;

X.Li: Software, Formal analysis, Visualization;

C.F.: Investigation, Resources;

J.L.: Data curation, Project administration;

Z.H.: Validation, Writing – review & editing;

G.F.: Supervision, Writing – review & editing;

X.Liao: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Disclosure

The authors declare no conflicts of interest.

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