Medicine, Health and Clinical Practice

October 2026 | Volume 1, Issue 3

Hypertension as a Common Cause of Ulcerative Colitis, Intracerebral Hemorrhage, and Major Depressive Disorder: A Causal Inference Study Integrating Cross-Sectional Analysis, Bidirectional Mendelian Randomization, and Drug-Target Genetic Proxies

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Abstract | Patients with intracerebral hemorrhage (ICH) are often observed to have comorbid ulcerative colitis (UC), but whether this reflects a direct causal relationship or confounding by a common cause remains unclear. We aimed to evaluate the causal network among UC, ICH, hypertension, and major depressive disorder (MDD), testing two competing explanations: a shared common cause and a medication-related effect. We conducted a descriptive, hypothesis-generating cross-sectional analysis using NHANES 2009–2010 data to assess phenotypic associations. Bidirectional two-sample Mendelian randomization (MR) served as the primary causal inference tool using GWAS summary data from multiple consortia, with inverse variance weighting (IVW) as the primary estimator and meta-analysis across databases. Drug-target MR was further conducted using genetic proxies for antihypertensive drug targets, with FDR correction applied. In the descriptive NHANES analysis, hypertension and UC were phenotypically associated in the unadjusted model but not after covariate adjustment, limited by small UC event numbers. Bidirectional MR showed significant causal signals from genetically predicted hypertension to UC, ICH, and MDD, although ICH estimates were imprecise due to potential weak instrument bias. MDD showed a statistically significant but clinically limited positive signal for hypertension. No causal association was detected between UC and ICH. Drug-target MR suggested nominally significant, hypothesis-generating signals: CACNB2 proxies were associated with lower UC risk; ADRB1 and CACNA1D with lower ICH risk; and SLC12A2 and CACNA1D with higher MDD risk. These signals lacked colocalization validation and did not uniformly survive FDR correction. Genetic evidence is consistent with hypertension as a shared causal risk factor for UC, ICH, and MDD, rather than a direct causal pathway between UC and ICH. The clinical co-occurrence of UC and ICH is thus more likely confounded by hypertension. Although genetic proxies for antihypertensive drug targets did not increase UC or ICH risk, they were associated with increased MDD risk. Mental health monitoring should be integrated into hypertension management. Drug-target findings remain exploratory and require validation through colocalization analysis and clinical trials.

Keywords | Intracerebral hemorrhage; Ulcerative colitis; Mendelian randomization; Hypertension; Major depressive disorder; Drug targets

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https://doi.org/10.68070/ht80xp30

Introduction

Essential hypertension is a common cardiovascular disease characterized by a persistent increase in blood pressure without an identifiable cause [1]. As a major risk factor for cardiovascular and cerebrovascular events, hypertension is widely recognized to be associated with spontaneous intracerebral hemorrhage (ICH). ICH refers to bleeding within the brain parenchyma caused by spontaneous rupture of cerebral vessels in the absence of trauma and is one of the most severe types of stroke [2,3]. However, apart from hypertension, other potential risk factors for ICH remain unclear. Ulcerative colitis (UC), a chronic inflammatory bowel disease characterized by persistent inflammation of the colonic mucosa [4], has been associated with stroke overall [5,6], a pathophysiological pathway described by the "gut–brain axis" hypothesis. However, whether UC has a causal association with ICH and hypertension at the genetic level, and whether this association is independent of hypertension, still lacks systematic evidence.

Major depressive disorder (MDD) is characterized mainly by persistent depressed mood and diminished interest or pleasure [7]. Its pathogenesis involves interactions among genetic susceptibility, neurobiological changes, and environmental stress [8]. Patients with MDD show alterations in cerebral blood flow, neurotransmitters, and even neural structure [9,10]. Whether these changes are causally linked to ICH, hypertension, and UC remains to be examined within a genetic framework.

Clinically, patients with ICH are often observed to have comorbid UC [11-14]. Song et al. [15] used IIBDGC and ISGC data and reported a protective causal signal from UC to ICH (IVW OR 0.83, 95% CI 0.71–0.96). However, in the replication stage using FinnGen data, the IVW method did not establish a causal link between UC and ICH (OR 0.83, 95% CI 0.65–1.05). Although a meta-analysis of the two datasets still supported a protective association (OR 0.83, 0.72–0.93), the high sensitivity of this signal to database selection itself requires caution. Meanwhile, observational studies have repeatedly reported an increased risk of hemorrhagic stroke in patients with UC; for example, a Swedish national cohort reported a hazard ratio of approximately 1.50 for hemorrhagic stroke within 1–5 years after UC discharge [16]. The coexistence of a positive phenotypic association and a protective or null genetic signal raises an unresolved question: is the co-occurrence of UC and ICH driven by a third variable that increases the risk of both?

Hypertension is a plausible candidate for this hypothesis. In this manuscript, we use common cause in the specific sense of a shared upstream causal risk factor that increases the risk of both UC and ICH. This is distinct from two other causal structures that are often invoked in observational epidemiology: (i) confounding by a common cause, in which a third variable causes both the exposure and the outcome and induces a non-causal association if not adjusted; and (ii) collider stratification, in which conditioning on a common effect of exposure and outcome induces a spurious association. The MR design estimates the total causal effect of genetically predicted hypertension on each outcome without conditioning on hypertension, and therefore directly tests whether hypertension acts as a shared causal risk factor rather than as a confounder or collider. The co-occurrence of hypertension and UC has been reported in observational data such as NHANES, but cross-sectional designs cannot exclude confounding or reverse causation. More importantly, few previous studies have simultaneously estimated the causal effects of hypertension on UC and ICH within the same genetic framework and compared them with the direct UC–ICH pathway. If hypertension causally increases the risk of both UC and ICH, then in analyses not conditioned on hypertension, the phenotypic association between UC and ICH (or the weak signal in MR) may reflect collider stratification or confounding by a common cause rather than a direct causal effect.

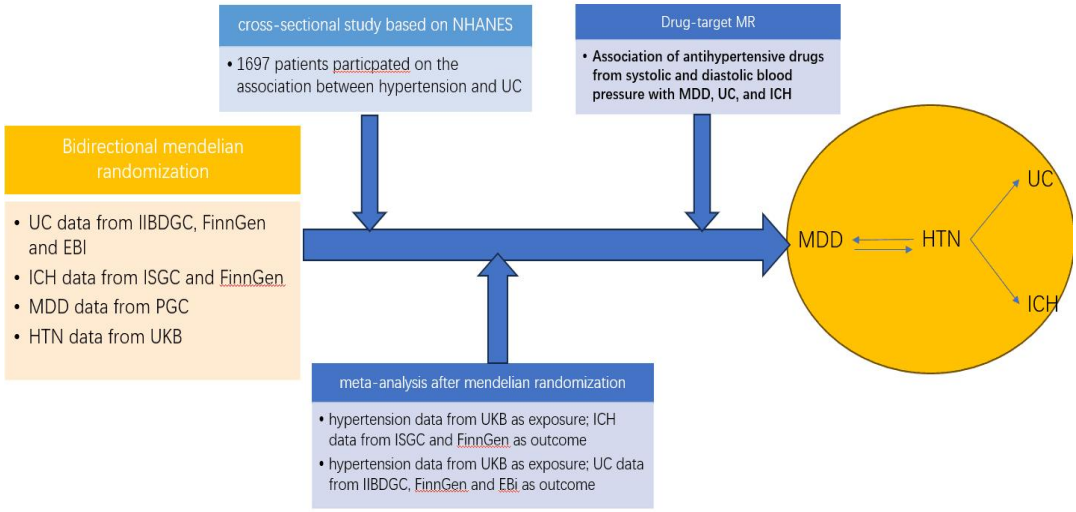
In addition, whether antihypertensive drugs alter the risk of UC, ICH, or MDD while lowering blood pressure needs to be incorporated into the causal inference framework. Traditional observational pharmacoepidemiology is highly susceptible to confounding by indication in this context. In contrast, drug-target MR uses genetic variants in drug target genes as proxy instruments and can simulate the effect of lifelong drug exposure on outcomes at the genetic level [17]. Drug-target MR by Fan and Zhao in European and East Asian populations suggested that antihypertensive drugs do not have a protective effect on mental disorders and may even carry potential harms [18]. However, that study did not cover UC or

https://doi.org/10.68070/ht80xp30

ICH, nor did it interpret the common-cause role of hypertension and drug-target effects within the same network.

Based on these gaps, this study proposes three sequential hypotheses: (1) whether there is a genetic causal association between UC and ICH that is independent of hypertension; (2) whether hypertension causally increases the risk of both UC and ICH, thereby confounding the phenotypic association between them; and (3) whether genetic proxies for antihypertensive drug target genes alter the risk of UC, ICH, or MDD. The study design uses NHANES cross-sectional analysis as the phenotypic starting point, bidirectional MR as the primary causal inference tool, multi-database meta-analysis to improve the robustness of estimates [19], and drug-target MR to test the "medication" hypothesis (Figure 1).

Figue 1. Study flow diagram. Mendelian randomization (MR) analysis serves as the primary framework, complemented by observational analysis, meta-analysis, and drug-target MR.



1 Data and Methods

1.1 NHANES Cross-Sectional Association Analysis

1.1.1 Study Design and Data Source

NHANES is conducted by the National Center for Health Statistics of the United States and uses a complex, multistage probability sampling design. It combines interview, questionnaire, examination, and laboratory data to represent the health and nutritional status of the noninstitutionalized US civilian population [20]. This study used data from the 2009–2010 cycle. The 2-year MEC examination weight WTMEC2YR was used, with SDMVSTRA as the stratification variable and SDMVPSU as the primary sampling unit. Specifying weights, strata, and PSUs simultaneously is a prerequisite for obtaining valid standard errors; "weighting" alone without specifying design variables would systematically underestimate variance [20].

1.1.2 Participants and Variable Definitions

After excluding individuals who refused to answer or were lost to follow-up, a total of 1,697 participants were included in the analysis. UC and hypertension were both derived from self-reported questionnaires. UC was defined as answering "yes" to "Has a doctor or other health professional ever told you that you had ulcerative colitis?" Hypertension was defined as answering "yes" to "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" Covariates included age, sex, race/ethnicity, education, marital status, family income-to-poverty ratio, BMI, diabetes, smoking, alcohol use, blood glucose, albumin, and C-reactive protein (CRP). Missing data for covariates were handled by complete-case analysis. Participants with missing UC or hypertension status

were excluded. Descriptive statistics are shown in Table 1.

Table. 1. Descriptive statistics of all variables

Variable	No UC	UC	*P* value
Hypertension (%)			0.013
Yes	29.13	52.00	
No	70.87	48.00	
Sex (%)			0.110
Male	55.98	40.00	
Female	44.02	60.00	
Age (median)	45	53	0.004
Race/ethnicity (%)			0.411
Mexican American	16.09	28.00	
Other Hispanic	8.73	12.00	
Non-Hispanic White	53.89	44.00	
Non-Hispanic Black	17.11	16.00	
Other race (including multiracial)	4.19	0.00	
Education (%)			—
Less than high school	30.62	40.00	
High school or equivalent	27.09	4.00	
More than high school	42.28	56.00	
Marital status (%)			0.016
Married/living with partner	61.24	52.00	
Widowed/divorced/separated	21.83	44.00	
Never married	16.93	4.00	
PIR (mean)	2.23	2.33	0.763

https://doi.org/10.68070/ht80xp30

Table 1.(continue) Descriptive statistics of all variables

Variable	No UC	UC	*P* value
BMI (mean)	29.13	29.13	0.999
Diabetes (%)			0.030
Yes	10.47	24.00	
No	89.53	76.00	
Smoking (%)			0.147
Yes	54.55	40.00	
No	45.45	60.00	
Heavy alcohol use (%)			0.933
Yes	87.44	88.00	
No	12.56	12.00	
Blood glucose (mg/dL, mean)	100.74	92.32	0.257
Albumin (g/dL, mean)	4.27	4.11	0.021
CRP (mg/L, mean)	0.45	0.64	0.289

2.1.3 Survey-Weighted Logistic Regression

All inferential analyses were performed in R 4.3.1. The survey package was used to define the sampling design, and regression models were fitted using svyglm(). Three models were constructed: Model 1 was unadjusted; Model 2 adjusted for age, sex, race/ethnicity, and BMI; Model 3 further adjusted for diabetes, smoking, alcohol use, blood glucose, and CRP on the basis of Model 2. Given the limited number of UC events, adding six additional covariates in Model 3 carries a risk of overfitting. Therefore, Model 3 was defined as an exploratory analysis, and its non-significant results should not be interpreted as evidence against a phenotypic association between hypertension and UC. Events per variable (EPV) were reported, and Model 2 was used as the primary adjusted model. Two-sided $p < 0.05$ was considered statistically significant. The NHANES analysis was positioned as a descriptive, hypothesis-generating component of the study. Its purpose was to document the phenotypic association between hypertension and UC in a representative US sample and to motivate the subsequent genetic causal analyses, not to provide independent causal evidence. Given the small number of UC events, all adjusted estimates should be interpreted as exploratory.

2.2 Bidirectional Two-Sample Mendelian Randomization

2.2.1 GWAS Data for the Four Diseases

Data sources and sample sizes are shown in Table 2. UC data were obtained from FinnGen, EBI, and IIBDGC; ICH data from FinnGen and ISGC; MDD data from PGC; and hypertension data from UK Biobank.

Table 2. Basic information on the GWAS data for the four diseases

Trait	Consortium	Cases	Controls	Total
UC	FinnGen	5,931	405,386	411,317
UC	EBI	5,371	412,561	417,932
UC	IIBDGC	6,968	20,464	27,432
ICH	FinnGen	4,056	371,717	375,773
ICH	ISGC	1,545	1,481	3,026
MDD	PGC	246,363	561,190	807,553
Hypertension	UK Biobank	54,358	408,652	463,010

UC, ulcerative colitis; ICH, intracerebral hemorrhage; MDD, major depressive disorder.

2.2.2 Instrumental Variable Selection and Weak Instrument Assessment

For all traits except ICH, the instrumental variable selection threshold was $p < 5 \times 10^{-8}$, with linkage disequilibrium parameters of $r^2 = 0.001$ and a window of 10,000 kb. Because the number of genome-wide significant SNPs available for ICH was limited, instrumental variables for ICH were selected at $p < 5 \times 10^{-6}$. For each exposure–outcome combination, F statistics and their minimum values were calculated and reported; F > 10 is the conventional threshold for excluding severe weak instrument bias [21]. For the relaxed-threshold ICH results, a threshold sensitivity analysis was performed using the available $p < 5 \times 10^{-8}$ SNP subset to examine whether the direction and magnitude of the effect changed substantially.

2.2.3 MR Analysis and Assumption Assessment

Exposure and outcome data were harmonized using the harmonise_data() function in the TwoSampleMR package, with the default action = 2 setting, which aligns effect alleles and excludes palindromic SNPs with intermediate allele frequencies. MR Egger, weighted median, and IVW were used as the main methods. IVW was used as the primary causal estimate, and weighted median and MR Egger were used as robustness references [22,23]. The MR Egger intercept was used to test for directional horizontal pleiotropy [23]; MR-PRESSO was used to detect and correct for outlying instrumental variables [24]; Cochran's Q was used to assess heterogeneity [25]; and leave-one-out analysis was used to assess the influence of individual SNPs on the overall estimate. Bidirectional MR was performed between every pair of UC, ICH, hypertension, and MDD. In bidirectional MR, "significant" does not necessarily mean symmetric causal importance: the effect sizes of forward and reverse estimates can differ by orders of magnitude. Interpretation must therefore place statistical significance within a framework of clinical interpretability of effect size [26]. The causal structure assumed in this study is that genetically predicted hypertension has a direct causal effect on UC, ICH, and MDD, and that UC and ICH are not causally related to each other. Under this structure, the observed phenotypic association between UC and ICH in observational data arises because hypertension is a shared cause of both outcomes. This corresponds to confounding by a shared upstream cause in observational analyses, not to collider stratification. The bidirectional MR between UC and ICH tests whether a direct causal edge exists; the MR from hypertension to UC and ICH tests whether the shared-cause pathway is present.

2.3 Meta-Analysis of MR Estimates Across Multiple Databases

MR estimates for the same exposure–outcome combination across different consortia were combined using meta-analysis. Pooled ORs, 95% CIs, Cochran's

https://doi.org/10.68070/ht80xp30

Q, I^2, and tau^2 were reported for both random-effects and fixed-effects models [19,25]. The random-effects model used the DerSimonian–Laird estimator for tau^2. Given the small number of estimates (two for ICH and three for UC), tau^2 estimates are unstable, and the meta-analysis should be regarded as a descriptive summary of directional consistency rather than a precise pooled effect. The included studies were not independent samples, and sample overlap may exist among consortia. Moreover, with only two estimates for ICH and three for UC, the estimate of τ^2 is unstable. Therefore, the meta-analysis was positioned as a summary description of robustness across multiple databases rather than as a second, independent source of causal evidence.

2.4 Drug-Target MR (Genetic Proxy Analysis)

SNPs located within ±100 kb of antihypertensive drug target genes and genome-wide significantly associated with blood pressure were selected from SBP and DBP GWAS as genetic proxy instrumental variables (IEU Open GWAS: ieu-b-38/ieu-b-39). Drug target genes were derived from five drug classes: ACEIs, ARBs, β-blockers, calcium channel blockers, and thiazide diuretics, yielding a total of 20 target genes. Instrumental variables included only common SNPs with minor allele frequency > 1% and $r^2 < 0.3$ with each other. The $r^2 < 0.3$ threshold was chosen because drug target gene regions often contain relatively few genome-wide significant SNPs, and a stricter clumping threshold would leave insufficient instruments for several target genes. This relaxed threshold is consistent with previous drug-target MR studies [17,18]. The number of SNPs used as instruments for each target gene is shown in Figure 6.

This design estimates the association between genetically proxied changes in target gene function and outcomes, not the randomized effect of actual drug intervention [17,18]. Benjamini–Hochberg FDR correction was applied to the P values from drug-target MR (20 target genes × 4 outcomes). Results with $q < 0.05$ after FDR correction were considered statistically robust; nominally significant results that did not pass FDR correction were reported as suggestive signals. Colocalization analysis is a key step for distinguishing a drug-target causal effect from LD contamination or horizontal pleiotropy: PPH4 > 0.8 suggests a shared causal variant, whereas high PPH3 suggests LD confounding. Colocalization was not systematically performed in this study, so the drug-target results were positioned as hypothesis-generating evidence. All MR analyses were performed in R 4.3.1 using the TwoSampleMR package [27].

3 Results

3.1 Survey-Weighted Logistic Regression in NHANES

In the unadjusted model, hypertension was significantly associated with UC (OR 2.64, 95% CI 1.19–5.82, P = 0.016). After adjustment for demographic factors in Model 2, the OR attenuated to 1.81 (0.76–4.31, P = 0.182). After further adjustment in Model 3, the OR was 1.94 (0.75–5.04, P = 0.175) (Table 3). Given approximately 25 UC events, the events per variable (EPV) were clearly below the conventional threshold of 10 in all adjusted models (Model 1: 1 predictor; Model 2: 4 predictors; Model 3: 9 predictors). The EPV for Model 3 was particularly insufficient, and the EPV for Model 2 was also below 10; therefore, all adjusted estimates should be regarded as exploratory and descriptive rather than inferential. The wide confidence interval reflects imprecision rather than definitive evidence of "no association." The appropriate interpretation of the NHANES analysis is that hypertension and UC are associated at the phenotypic level, but the cross-sectional design cannot distinguish whether this association is causal, confounded by common factors, or due to reverse causation.

Table 3. Survey-weighted logistic regression based on NHANES data

	Model 1		**Model 2**		**Model 3**	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
No hypertension	ref		ref		ref	

Table 3.(continue) Survey-weighted logistic regression based on NHANES data

	Model 1		Model 2		Model 3	
Hypertension	2.64 (1.19–5.82)	0.016	1.81 (0.76–4.31)	0.182	1.94 (0.75–5.04)	0.175

Model 1, unadjusted; Model 2, adjusted for age, sex, race/ethnicity, and BMI; Model 3, Model 2 plus diabetes, smoking, alcohol use, blood glucose, and CRP. Model 3 was an exploratory analysis (insufficient EPV). The total number of UC events was approximately 25; therefore, all adjusted estimates are descriptive and should not be interpreted as independent causal evidence.

3.2 Bidirectional Causal Estimates Among the Four Diseases

Table 4 summarizes the statistically significant results obtained by IVW in bidirectional MR. All reported results passed heterogeneity tests, MR-Egger pleiotropy tests, MR-PRESSO outlier tests, and leave-one-out sensitivity analyses; detailed sensitivity results are available from the corresponding author upon reasonable request. The direction and significance of the primary estimates were not materially altered by these sensitivity analyses.

Table 4. Significant causal estimates from bidirectional two-sample MR (IVW method)

Exposure (Consortium)	Outcome (Consortium)	nSNP	OR (95% CI)	*P*
Hypertension (UKB)	ICH (FinnGen)	67	12.593 (2.913–54.446)	0.001
Hypertension (UKB)	ICH (ISGC)	42	132.362 (4.503–3890.745)	0.005
Hypertension (UKB)	MDD (PGC)	67	1.429 (1.012–2.017)	0.043
Hypertension (UKB)	UC (EBI)	68	4.114 (1.365–12.394)	0.012
Hypertension (UKB)	UC (FinnGen)	67	3.868 (1.106–13.523)	0.034
MDD (PGC)	Hypertension (UKB)	45	1.027 (1.016–1.039)	<0.001

ICH, intracerebral hemorrhage; UC, ulcerative colitis; MDD, major depressive disorder.

The OR for hypertension → ICH was 12.59 in FinnGen and 132.36 in ISGC. The ISGC ICH GWAS contained only 1,481 controls, and the ICH instrumental variables used a relaxed threshold of $p < 5 \times 10^{-6}$. Weak instrument bias and extremely imprecise variance estimates can both cause order-of-magnitude inflation of the OR [21]. These two estimates should be interpreted as directionally consistent positive causal signals, and their numerical values do not carry interpretable effect-size meaning. A threshold sensitivity analysis using the available genome-wide significant ($p < 5 \times 10^{-8}$) SNP subset for ICH was performed. The direction of the estimate was consistent with the main analysis, although the confidence interval remained wide; this indicates that the directional signal was robust to the instrument threshold, but the magnitude remained imprecise. The OR for hypertension → UC ranged from 3.87 to 4.11, which is highly consistent with the meta-analysis result (OR 3.68, 1.78–7.60) and is more biologically interpretable in magnitude.

The OR for MDD → hypertension was 1.027 (1.016–1.039). Statistical significance in a sample of more than 800,000 individuals is not unexpected, but the meaning is only that each unit increase in genetically predicted MDD risk is associated with approximately a 2.7% increase in hypertension risk. The OR for hypertension → MDD was 1.429 (1.012–2.017), more than an order of magnitude larger. In the combined observational and genetic analysis by Xu et al., the causal evidence for depression → hypertension was stronger (genetically predicted depression OR approximately 1.27), whereas the reverse genetic evidence for

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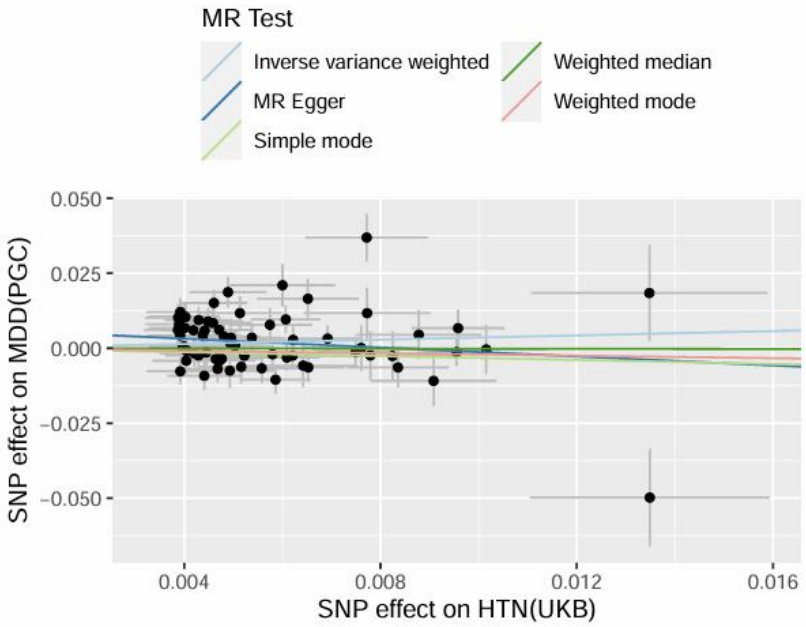
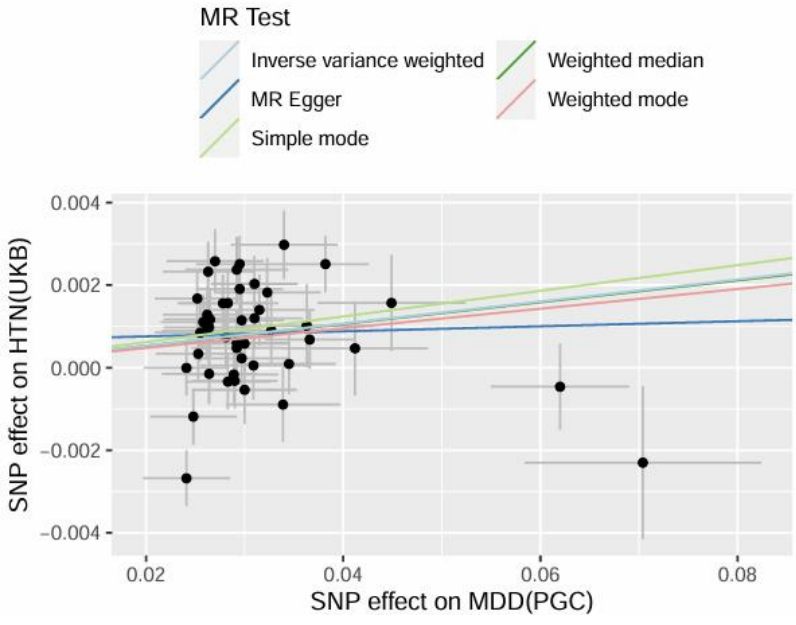
hypertension→depression was insufficient [28]. Taken together, the effect size of hypertension→MDD is clinically interpretable, whereas MDD→hypertension is statistically significant but of limited clinical significance. The term "bidirectional causal association" obscures this asymmetry.

No statistically significant IVW causal estimate was detected between UC and ICH in any direction or any database combination. This negative finding contrasts with the "initial positive, replication negative" pattern of Song et al. [15], and its interpretation is discussed in Section 4.2. Figure 2 shows the scatter regression with hypertension as exposure and MDD as outcome; Figure 3 shows the scatter regression with MDD as exposure and hypertension as outcome.

Figue 2. Scatter regression plot with hypertension as the exposure and major depressive disorder (MDD) as the outcome.



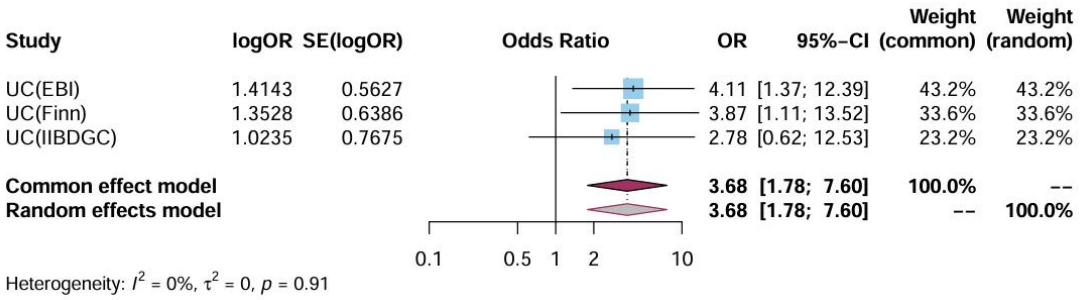
Figue 3. Scatter regression plot with major depressive disorder (MDD) as the exposure and hypertension as the outcome.



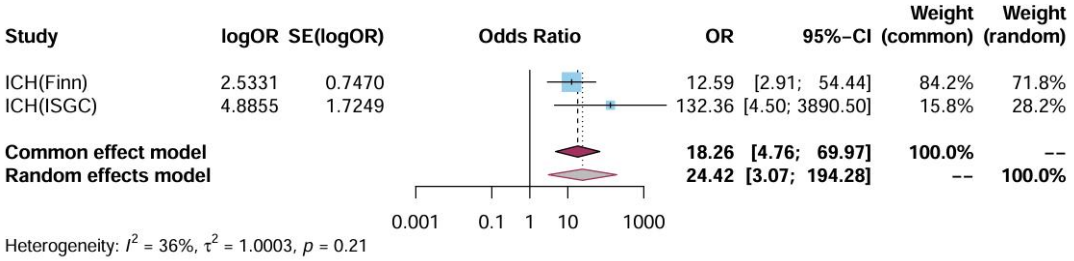
3.3 Meta-Analysis of MR Estimates Across Multiple Databases

For hypertension → ICH, two estimates from FinnGen and ISGC were included (Figure 4). The random-effects pooled OR was 24.42 (95% CI 3.07–194.28), and the fixed-effects pooled OR was 18.26 (4.76–69.97). Both models pointed to a positive pooled effect, but the confidence interval widths differed substantially. With only two estimates, τ^2 is unstable, and the wide interval of the random-effects model more faithfully reflects the uncertainty of the current evidence [25]. The directional conclusion is robust, but the specific pooled OR should not be assigned a precise effect-size meaning. For hypertension → UC, three estimates from EBI, FinnGen, and IIBDGC were included (Figure 5). The random-effects pooled OR was 3.68 (95% CI 1.78–7.60), with lower heterogeneity than the ICH analysis. This is the strongest genetic evidence in this study for "hypertension as a risk factor for UC." Meta-analysis of the UC → ICH direction did not detect a significant pooled effect.

Figue 4. Meta-analysis of Mendelian randomization (MR) estimates with hypertension as the exposure and intracerebral hemorrhage (ICH) as the outcome across different populations.



Figue 5. Meta-analysis of Mendelian randomization (MR) estimates with hypertension as the exposure and ulcerative colitis (UC) as the outcome across different populations.



3.4 Genetic Proxy Analysis of Antihypertensive Drug Targets

The results of MR analyses using genetic proxies for drug target genes as exposures are shown below (Figures 6). The number of instrumental SNPs for each target gene is shown in Figure 6. After Benjamini–Hochberg FDR correction across 20 target genes × 4 outcomes, the drug-target findings should be interpreted as hypothesis-generating: colocalization was not performed, and the number of SNPs for several targets was limited. Nominally significant results that did not pass FDR correction are explicitly described as suggestive signals.

Genetic proxies for CACNB2 (in the SBP-lowering direction) were associated with a lower risk of UC (OR 0.955, 95% CI 0.932–0.977), consistent with its biological identity as a calcium channel blocker target [29]. This finding is hypothesis-generating because colocalization was not performed. This estimate reflects the association between genetically proxied reduced CACNB2 function and UC, not the effect of clinical use of calcium channel blockers.

Genetic proxies for ADRB1 (OR 0.944, 0.896–0.994) and CACNA1D (OR 0.921, 0.859–0.987)

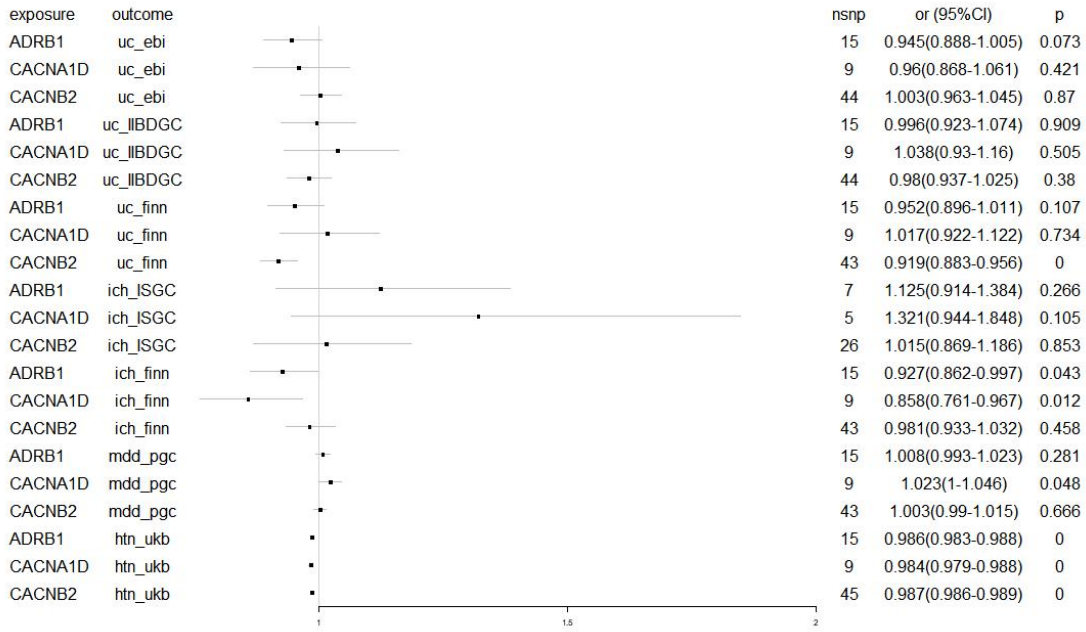
https://doi.org/10.68070/ht80xp30

were associated with a lower risk of ICH. These signals are hypothesis-generating and require colocalization and independent replication before any clinical interpretation. ADRB1 is a target of β-blockers [30]; CACNA1D is one of the targets of calcium channel blockers [31]. The directions of both signals are consistent with the expectation that blood pressure-lowering targets may reduce ICH risk, but the level of evidence is limited by the lack of colocalization validation and the imprecision of instruments with few SNPs.

Genetic proxies for SLC12A2 (a loop diuretic target) and CACNA1D were associated with a higher risk of MDD, consistent with the conclusion of Fan and Zhao that antihypertensive drugs have no protective effect on mental disorders [18] and with the drug-target MR report by Yang et al. [32]. Published drug-target MR studies of SLC12A2 have focused on IBD. Their SMR analysis suggested that higher SLC12A2 expression is a risk factor for ulcerative pancolitis, and that bumetanide inhibition of SLC12A2 can improve tight junctions and inflammation in vitro [33]. However, that study did not provide direct genetic evidence linking SLC12A2 to MDD. Therefore, the signal of "SLC12A2 inhibition→increased MDD risk" is strictly hypothesis-generating. Because colocalization was not performed and these findings did not uniformly survive FDR correction, this result cannot be translated into a clinical recommendation to avoid loop diuretics in patients at risk of MDD; it requires independent colocalization analysis and replication for validation.

A drug-target MR plus pharmacovigilance study covering common drugs and psychiatric disorders listed ADRB1 as a target associated with psychiatric risk (OR approximately 1.42, FDR-corrected significant) [34]. In this study, ADRB1 showed a protective association with ICH. Different outcomes (ICH vs. psychiatric disorders) are the most direct explanation, but contributions from instrumental variable selection and population differences cannot be excluded.

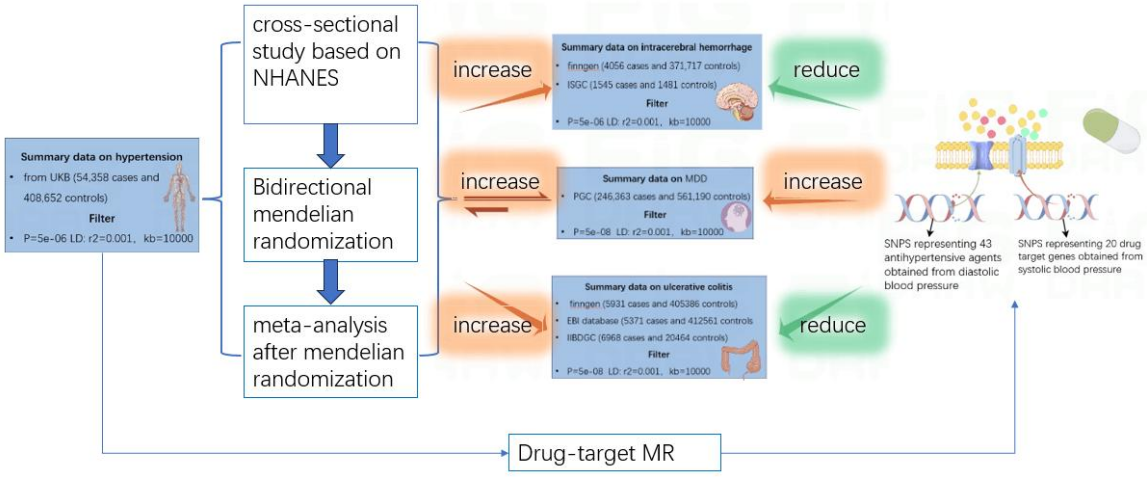
Figue 6. Drug-target Mendelian randomization (MR) analysis of antihypertensive drug genes across different databases.



3.5 Summary of the Causal Network

The mechanistic network is shown in Figure 7. Hypertension occupies the central position and points simultaneously to UC, ICH, and MDD. MDD has a statistically significant but very small reverse signal to hypertension. No detectable direct causal edge exists between UC and ICH, and their clinical co-occurrence is explained by the common-cause pathway through hypertension. At the drug-target level, genetic proxies for CACNB2, ADRB1, and CACNA1D did not show an increased risk of UC or ICH, and some showed protective suggestive signals. Genetic proxies for SLC12A2 and CACNA1D were associated with an increased risk of MDD, representing a signal requiring caution in the "medication" dimension.

Figue 7. Causal network mechanism diagram of hypertension, intracerebral hemorrhage (ICH), ulcerative colitis (UC), and major depressive disorder (MDD), integrating NHANES cross-sectional analysis, bidirectional MR, meta-analysis, and drug-target MR.



4 Discussion

4.1 Common Cause Hypothesis: Hypertension Causally Increases the Risk of Both UC and ICH

Multi-database MR estimates for hypertension → UC were directionally consistent across three UC GWAS, with a pooled OR of 3.68 (1.78–7.60) and acceptable heterogeneity. Hypertension → ICH was directionally consistent in FinnGen and ISGC, and the meta-analysis also pointed to a positive effect. The directional consistency of these two causal edges is the core supporting evidence for the "hypertension as a common cause" hypothesis. The phenotypic association between hypertension and UC in NHANES attenuated and became non-significant after adjustment, but covariate adjustment in a cross-sectional design simultaneously removes mediating components that may lie on the causal pathway, and insufficient EPV limits the inferential power of the adjusted estimate. MR uses genetic variants as instrumental variables and is in principle not affected by these postnatal confounders and mediators [22,26].

The hypertension → UC pathway may involve systemic low-grade inflammation, endothelial dysfunction, alterations in intestinal microcirculation, and regulation of intestinal mucosal immunity by the renin–angiotensin–aldosterone system [10]. The hypertension → ICH pathway is more direct: chronic elevation of blood pressure leads to hyaline degeneration of arteriolar walls and the formation of microaneurysms [2,3]. These two pathways converge at the node of hypertension, and there is no need to postulate a direct causal edge between UC and ICH. Some studies have suggested that UC may reversely increase the risk of hypertension [35]; this study did not confirm this, suggesting that the reverse pathway between the two may be mediated by multiple intermediaries.

4.2 Causal Association Hypothesis: Dialogue Between the Negative UC–ICH Result and Song et al.

This study did not detect a statistically significant causal association between UC and ICH, whereas Song et al. reported a protective effect of UC on ICH in the

https://doi.org/10.68070/ht80xp30

initial stage (IVW OR 0.83, 0.71–0.96). However, in the FinnGen replication stage, the IVW method failed to establish a causal link (OR 0.83, 95% CI 0.65–1.05). Although the meta-analysis of the two datasets still supported a protective association (OR 0.83, 0.72–0.93), the stability of this signal depends precisely on whether the replication stage is included. The study by Song et al. itself shows a pattern of initial positive, replication negative, and meta-analysis barely maintaining protection, rather than a stable positive conclusion. The failure of this study to replicate the initial protective signal may be related to differences in instrumental variable selection parameters, outcome data sources, and weight allocation in the meta-analysis. Neither the initial protective signal nor the negative result of this study supports a causal interpretation that "UC directly causes ICH."

Placing this genetic picture alongside observational epidemiology provides a more complete explanation. The Swedish cohort reported an increased risk of hemorrhagic stroke after UC discharge [16], and an IBD–stroke meta-analysis also reported a positive association (RR = 1.19, 95% CI 1.14–1.24) [5]. The contradiction between the positive phenotypic association and the protective or null genetic signal is consistent with confounding by a shared upstream cause: patients with UC often carry a higher burden of hypertension, have more frequent medical contacts, and have a worse overall vascular risk profile. These factors simultaneously increase the risk of ICH, thereby inducing a UC–ICH association in observational designs without requiring UC itself to have a direct pathogenic effect on cerebral vessels. This structure is distinct from collider stratification, which would require conditioning on a common effect of UC and ICH; no such conditioning is present in the observational literature or in our MR design.

4.3 Medication Hypothesis: Signals and Boundaries of Drug-Target Genetic Proxies

The inferential target of drug-target MR is genetically proxied target gene function, not clinical drug exposure [17]. Therefore, the conclusions in this section are all phrased as genetic evidence suggests rather than "the drug is effective or harmful".

Genetic proxies for CACNB2, ADRB1, and CACNA1D did not show an increased risk of UC or ICH, and some targets showed protective suggestive signals. This result directionally supports the view that antihypertensive treatment targeting these targets will not bring additional harm through the UC or ICH pathway, but it does not constitute evidence that calcium channel blockers or β-blockers can treat UC or ICH. Positive signals from drug-target MR must undergo colocalization (PPH4 > 0.8) and independent cohort replication before entering clinical translation discussions. Colocalization was not performed in this study, so these signals can only be positioned as hypothesis-generating.

Genetic proxies for SLC12A2 and CACNA1D were associated with an increased risk of MDD, consistent with the conclusions of Fan and Zhao and Yang et al. [18,32]. However, the mechanism of SLC12A2→MDD is far from established: existing SLC12A2 MR studies have focused on IBD and have not involved MDD [33]. The electrolyte or neurotransmitter hypothesis linking SLC12A2 inhibition to increased MDD risk is a pharmacological speculation and requires independent colocalization analysis, eQTL-informed MR, and clinical trial adverse event monitoring for validation. The discrepancy between the protective association of ADRB1 with ICH (OR 0.944) and the increased risk direction in drug–psychiatric disorder MR (OR approximately 1.42) [34] is most likely explained by different outcomes. In the absence of independent replication for the same outcome, this should not be used as a basis for clinical drug selection. Importantly, none of the drug-target findings in this study should be translated into clinical recommendations about specific antihypertensive drug classes. The signals for CACNB2, ADRB1, CACNA1D, and SLC12A2 are hypothesis-generating, did not undergo colocalization analysis, and are based on genetic proxies that simulate lifelong minimal exposure rather than clinical drug intervention. They cannot support conclusions such as calcium channel blockers reduce UC risk or β-blockers reduce ICH risk.

4.4 Cautious Implications for Clinical Decision-Making

The hierarchy of evidence in this study is clear. The causal signals for hypertension→UC and hypertension→ICH are supported by directional consistency across multiple databases and meta-analysis, representing moderate-strength genetic evidence. The asymmetric signals between

hypertension → MDD and MDD → hypertension suggest that mental health should be included in the management of patients with hypertension, but this should be described as "a predominantly positive signal from hypertension → MDD" rather than a symmetric "bidirectional causal" relationship. Drug-target signals are hypothesis-generating and cannot be translated into clinical recommendations that a certain class of drugs can reduce the risk of UC or ICH or that a certain class of drugs should be avoided in patients at high risk of MDD. The actionable implication is limited to the following: in the long-term management of hypertension, synchronous monitoring of UC, ICH, and MDD risk is reasonable; drug selection should be based on a comprehensive assessment of blood pressure control, comorbidities, and mental health history. Depression in patients with hypertension may worsen blood pressure control, and genetic proxies for some drug targets are associated with an increased risk of MDD. This suggests that MDD monitoring and treatment in patients with hypertension deserve the same attention as blood pressure management.

4.5 Limitations

First, the NHANES sample size and number of events were limited, and the EPV in Model 3 was insufficient to support inferential interpretation of adjusted estimates. The cross-sectional design cannot exclude reverse causation or residual confounding. Formal post-hoc power calculations for the MR analyses were not performed because reliable estimates of variance explained by the instruments were not available for all exposure–outcome pairs; this is acknowledged as a further limitation. Second, UK Biobank as a source of hypertension exposure has selection bias (response rate approximately 5.5%, and participants are significantly healthier). If selection depends on both exposure and outcome, collider bias can be induced [36]. Third, the relaxed threshold of $p < 5 \times 10^{-6}$ for ICH instrumental variables makes weak instrument bias non-negligible. A threshold sensitivity analysis using the genome-wide significant SNP subset was performed, and the direction of the estimate was consistent with the main analysis; however, this analysis cannot completely eliminate weak instrument bias [21]. Fourth, colocalization was not performed for drug-target MR, so PPH4 cannot be used to distinguish "shared causal variants" from "LD contamination," and some target genes have a limited number of instrumental variable SNPs. Fifth, the consortium samples in the meta-analysis overlap, and with only two estimates for ICH and three for UC, τ^2 is unstable. Meta-analysis results should be regarded as a robustness description rather than independent causal evidence [19,25]. Sixth, all analyses were restricted to populations of European ancestry, and extrapolation requires caution. Seventh, genetic proxies in drug-target MR simulate lifelong minimal exposure, which is fundamentally different from clinical drug dose, duration, and adherence, and cannot be equated with clinical trial conclusions [17,18].

5 Conclusion and Clinical Implications

Genetic evidence is consistent with hypertension as a shared causal risk factor for UC, ICH, and MDD. The NHANES cross-sectional analysis was descriptive and hypothesis-generating and did not provide independent causal evidence. The clinical co-occurrence of UC and ICH does not receive support for a direct causal pathway within the genetic framework. A more parsimonious explanation is confounding of their association by hypertension as a shared risk factor. MDD and hypertension have a statistically significant but highly asymmetric association: the effect size of hypertension → MDD is clinically interpretable, whereas the effect of MDD → hypertension, although significant, is extremely small. Genetic proxies for drug targets do not suggest that antihypertensive drug targets increase the risk of UC or ICH, and some targets show protective suggestive signals. However, genetic proxies for SLC12A2 and CACNA1D are associated with an increased risk of MDD. This signal is directionally consistent with published drug-target MR evidence [18,32] but is hypothesis-generating and cannot serve as a basis for changing clinical medication.

For clinical practice, this study supports synchronous attention to UC, ICH, and MDD risk in the long-term management of hypertension, rather than viewing hypertension solely as a matter of blood pressure values. For the methodological community, when observational associations and MR signals are inconsistent, common cause should be tested as a priority hypothesis alongside direct causation, rather than defaulting to interpreting a negative MR result as

https://doi.org/10.68070/ht80xp30

no association. Future studies should perform colocalization analysis for drug-target MR in independent populations, include non-European ancestry data, and incorporate mediating pathways in the hypertension–UC–ICH–MDD network into a multivariable MR framework.

Author contributions

Zhentao Li: Writing–review & editing, Writing–original draft, Visualization, Investigation. Guowei Liu: Writing–review & editing, Writing–original draft, Visualization, Investigation. Qiushuang Ran: Writing–review & editing, Investigation. Saisai Zhao: Writing–review & editing, Investigation. Haibei Dong: Writing–review & editing, Supervision, Funding acquisition, Project administration. Jilei Tang: Writing–review & editing, Supervision, Conceptualization, Funding acquisition, Project administration.

Ethics approval and consent to participate

This study is a secondary analysis of publicly available, de-identified data from the National Health and Nutrition Examination Survey (NHANES) 2009–2010 cycle, conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention. The NHANES protocol was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent at enrollment. No additional ethical approval was required for this secondary analysis of de-identified public data. All GWAS summary statistics used in this study were derived from publicly available secondary databases that obtained ethical approval during original data collection (FinnGen: Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa, HUS/990/2017; UK Biobank: North West Multi-Centre Research Ethics Committee, REC 21/NW/0157). Ethical approval was waived because the study used de-identified, publicly available data.

Data availability

The NHANES 2009–2010 data are publicly available from the National Center for Health Statistics at https://www.cdc.gov/nchs/nhanes/. GWAS summary statistics were obtained from the following sources: ulcerative colitis from FinnGen (https://www.finngen.fi/), the EBI GWAS Catalog, and the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC; summary statistics available via https://gwas.mrcieu.ac.uk/); intracerebral hemorrhage from FinnGen (https://www.finngen.fi/) and the International Stroke Genetics Consortium (ISGC; https://www.strokegenetics.com/ or the Cerebrovascular Disease Knowledge Portal, https://www.cerebrovascularportal.org/); major depressive disorder from the Psychiatric Genomics Consortium (PGC; https://pgc.unc.edu/for-researchers/download-results/); and hypertension from UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). All summary-level data are publicly accessible or available through application to the respective consortium or repository.

Acknowledgements

This work was supported by the CAPTRA-STAR Scientific Research Fund Project (KY202502041), the Open Fund of Anhui Engineering Laboratory for Conservation and Sustainable Utilization of Traditional Chinese Medicine Resources (TCMRPSU-2022-11), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Conflict of interest

The authors declare that they have no conflict of interest.

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