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Original Research

Association between Lipid-Lowering Drugs and Traumatic Subdural Hemorrhage: A Mendelian Randomization Study

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Abstract

Background: There are current clinical observations that atorvastatin may promote subdural hematoma resorption. We aimed to assess the causal effects of lipid-lowering agents 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*) inhibitors, Proproteinconvertase subtilisin/kexin type 9 (*PCSK9*) inhibitors and Niemann-Pick C1-like protein 1 (*NPC1L1*) inhibitors on traumatic subdural hematomas. **Methods**: We used genetic instruments to proxy lipid-lowering drug exposure, with genetic instruments being genetic variants within or near low-density lipoprotein (LDL cholesterol)-associated drug target genes. These were analyzed by using a two-sample Mendelian randomization (MR) study. **Results**: A causal relationship was found between *HMGCR* inhibitors and traumatic subdural hematoma (Inverse variance weighted (β = –0.7593341 (Odds Ratio (OR) = 0.4679779), $p = 0.008366947 < 0.05$)). However, no causal relationship was found between *PCSK9* inhibitors and *NPC1L1* inhibitors and traumatic subdural hematoma (*PCSK9* inhibitors: Inverse variance weighted (β = 0.23897796 (OR = 1.2699505), p = 0.1126327), *NPC1L1* inhibitors: Inverse variance weighted (β = –0.02118558 (OR = 0.9790373), p = 0.9701686)). Sensitivity analysis of the data revealed good stability of the results. **Conclusions**: This two-sample MR study suggests a potential causal relationship between *HMGCR* inhibition (atorvastatin) and traumatic subdural hemorrhage.

Keywords: lipid-lowering drugs; traumatic subdural hemorrhage; mendelian randomization analysis; cause-and-effect relationship; drug targeting

1. Introduction

Subdural hemorrhage (SDH), also called traumatic subdural hematoma, often occurs following traumatic brain injury [1]. SDH may spread rapidly, causing progressive midline displacement and cerebral hernia, endangering the patient's life [2]. Additionally, it leads to several complications, such as epilepsy, hydrocephalus, and chronic subdural hematoma [3–5]. Subdural hemorrhage occurs most often after craniocerebral injury, and the incidence is approximately 11%–49% [6]. This places a great burden on individuals, families, and society, and economic losses can reach $19,000,000 [6]. Surgical treatment (decompressive craniotomy) is the primary treatment for traumatic subdural hematoma [7]. However, medication plays an important role, especially in patients who are not eligible for surgery. Therefore, finding effective drugs to improve traumatic subdural hematoma is crucial.

By establishing a rat model of subdural hematoma, Wang *et al.* [8] found that atorvastatin could promote the absorption of subdural hematoma in the rat model. Atorvastatin also promotes the absorption of chronic subdural hematoma in human patients [9]. Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase reductase (*HMGCR*) inhibitor, which is the most commonly used class of lipid-lowering drugs. It has several major advantages, such as proven safety, low cost, and multi-potency [10]. Recent studies on atorvastatin have proposed that the mechanism of chronic subdural hemorrhage is stabilizing immature leaky vessel formation in neomembranes [11]. However, the mechanism of traumatic subdural hemorrhage is usually caused by trauma, and Paseban *et al.* [12] found that the combined use of high-dose aspirin, metformin, captopril, and atorvastatin potentiated their antioxidant effects on the brain and hence could improve cognitive function with their neuroprotective effects on the hippocampus. Therefore, we explored the efficacy of lipid-lowering drugs for acute traumatic subdural hemorrhage. However, current clinical studies are often influenced by confounding factors, which significantly impact the investigation of the causal relationship between exposure and outcome. Furthermore, in these studies, the clinical characteristics of patients using statins and those not using statins were quite different. Because of the retrospective nature of observational studies, causal inference is not allowed; however, Mendelian randomization (MR) analysis can over-

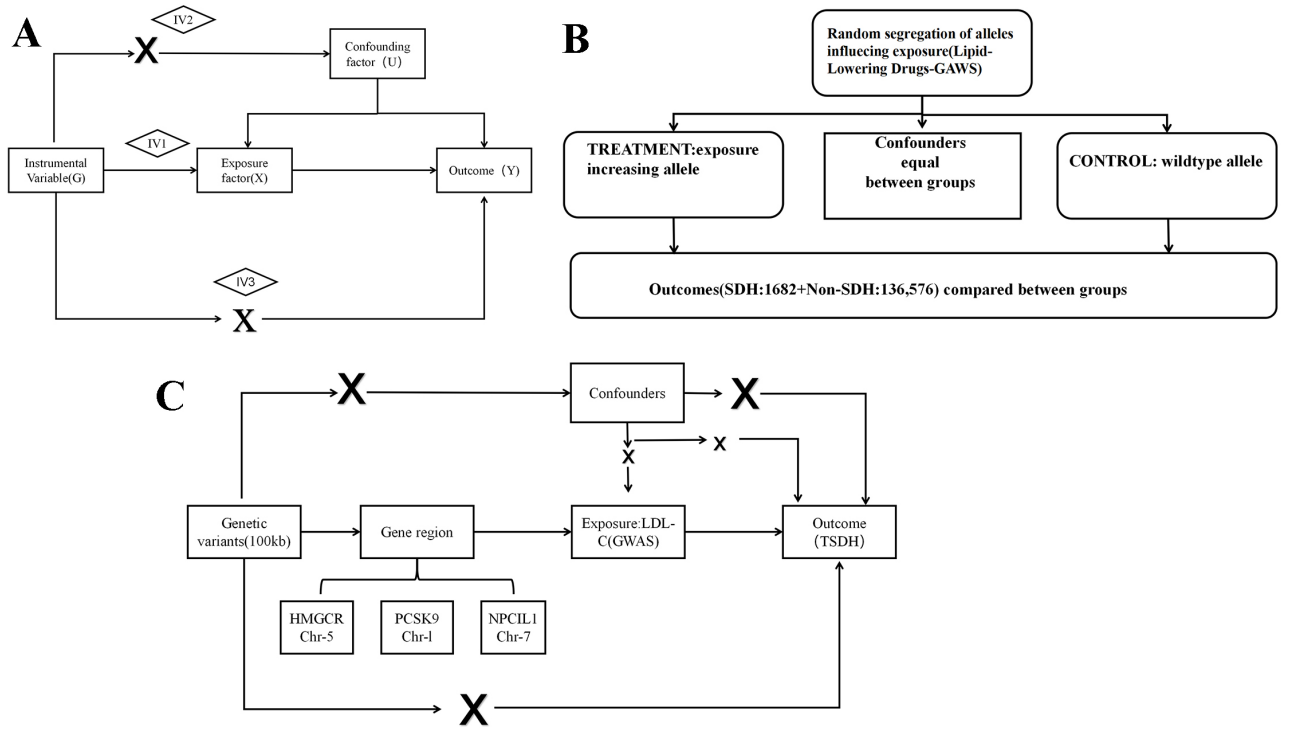

Fig. 1. Principle of Mendelian randomization of drug targeting. (A) Working principle of instrumental variables (genetic variation (G); exposure factor (X); outcome (Y)). (B) Schematic diagram of Mendelian laws of inheritance in Mendelian randomization. (C) Working principle diagram of Mendelian randomization of drug targeting. LDL-C, low-density lipoprotein cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; PCSK9, Proproteinconvertase subtilisin/kexin type 9; NPC1L1, Niemann-Pick C1-like protein 1; SDH, subdural hemorrhage; GWAS, Genome wide association study; TSDH, traumatic subdural hemorrhage.

come the limitations of traditional observational studies. Therefore, we aimed to explore the relationship between lipid-lowering agents and traumatic subdural hematoma using MR.

MR uses a genetic variation to infer causation between exposure and outcome, thereby assessing whether an observational association is consistent with a causal effect [13]. It is based on the principle of random gamete division and combination in genetic variation to simulate the random assignment process of research objects [14]. Therefore, we used this property to explore the causal relationship between common lipid-lowering drugs and traumatic subdural hematoma.

2. Materials and Methods

2.1 Mendelian Randomization

MR is a statistical method used to estimate the causal effect of an exposure factor on an outcome variable. There are two fundamental principles of Mendelian randomization:

The first is instrumental variable: This is a method derived from econometrics. It is a classical statistical method used to address endogeneity issues and is one of the most commonly used empirical analysis methods in research. The purpose is to identify the causal relationship between the exposure and outcome variables using the exogeneity assumption of instrumental variables (Fig. 1A).

The second is Mendelian genetics law: Based on the random allocation principle followed by alleles during gamete formation, the genotype can be used as an instrumental variable for the intermediate phenotype under investigation to infer its causal association with the disease status. The estimated effect is not influenced by confounding factors or reverse causation. For this reason, MR is often referred to as a "nature-created randomized controlled trial" [15] (Fig. 1B).

Therefore, MR is a causal inference method based on genetic variation. Its basic principle is to use genetic variants that are randomly allocated in nature to investigate the impact of phenotypes on diseases. In other words, Mendelian randomization is a randomized controlled trial conducted on a population using Mendelian genetics law.

In this study, we introduced the concept of drug targeting. We used single nucleotide polymorphisms (SNPs) associated with low-density lipoprotein cholesterol (LDL-C) reduction at or near the *HMGCR*, Proproteinconvertase subtilisin/kexin type 9 (*PCSK9*), and Niemann-Pick C1-like protein 1 (*NPC1L1*) loci as instrumental variables for statins, *PCSK9* inhibitors, and ezetimibe, respectively. The outcome phenotype chosen is the occurrence of traumatic subdural hemorrhage [16] (Fig. 1C).

2.2 Data Sources

Sources of LDL-C data: LDL-C Genome wide association study (GWAS) data comprising 2,437,752 individual data points of European ancestry (GWAS ID: ieu-a-300) were collected from an open GWAS database (https://gwas.mrcieu.ac.uk/) [17].

Data sources for traumatic subdural hematoma: The inclusion criteria were ICD-10 code S065 in the Hospital Discharge Registry or Cause of Death Registry and complete GAWS data. Those with incomplete GAWS data were not included in the study. The GWAS data, consisting of the experimental (1682) and control (136,576) groups, were obtained from the FinnGen database (https://www.finngen.fi/fi). All groups were Europeans (GWAS ID: finn-b-ST19_TRAUMAT_SUBDU_HAEMORRHAGE) [18]. The baseline clinical characteristics of the cohort are shown in Table 1.

Table 1. Patient clinical baseline.

	All	Female	Male
Number of individuals	1682	550	1132
Unadjusted prevalence (%)	0.78	0.45	1.2
Mean age at first event (years)	65.23	67	64.37
Case fatality at 5 years (%)	18.91	19.82	18.46
Median number of events per individual	1	1	2
Recurrence at 6 months (%)	43.88	35.82	47.79

2.3 Instrumental Variable Selection

According to Mendel's randomization theory, instrumental variables must satisfy the following three assumptions:

Correlation hypothesis: Instrumental variables must be strongly correlated with exposure factors;

Independence hypothesis: Instrumental variables are independent of confounding factors affecting expose-outcome;

Exclusivity hypothesis: Instrumental variables can only influence the occurrence of results through "exposure" factors but not through other means.

Based on a study by Ference *et al.* [19], we selected *HMGCR*, *PCSK9*, and *NPC1L1* inhibitors as the three major common lipid-lowering drugs targeting genes.

To identify potential instrumental variables as substitutes for these drugs, we used the screening method proposed by Huang *et al.* [20].

(1) SNPs minor allele frequency (MAF) >1%; (2) Low linkage imbalance ($r^2 < 0.30$); (3) Correlation with LDL-C ($p < 5.0 \times 10^{-8}$); and (4) Located within 100 kb of the drug target region.

The instrumental variables that could replace the target drug were obtained by satisfying these four conditions.

2.4 Two-Sample MR Analysis

The R software (Lucent Technologies, Jasmine Hill, NJ, USA) package "TwoSampleMR (version 0.5.6, https://github.com/MRCIEU/TwoSampleMR/releases/tag/v0.5.6)" was used for MR data analysis, employing methods such as inverse-variance weighting, MR Egger, weighted median, simple model, and weighted model. Inverse-weighted variance analysis was used to determine the causal relationship between exposure factors and results [21–23]. Statistical significance was set at $p < 0.05$, and the Bate value (Odds Ratio, OR) was used to determine the protective or promoting effects.

2.5 Sensitivity Analysis: Heterogeneity Analysis

MR Egger and inverse variance weighted functions in Cochran Q were used to assess heterogeneity among the study samples, and $p > 0.05$ indicates non-heterogeneity. The results were obtained by using the "mr_heterogene" function in the R package "TwoSampleMR", and the "MR-PRESS" function was used to detect and remove outliers if identified. Subsequently, we performed another heterogeneity analysis.

2.6 Sensitivity Analysis: Horizontal Multi-Effect Analysis

The horizontal pleiotropy was analyzed using the "mr_pleiotropy test" function of the R package with the same name, and $p > 0.05$ indicates the absence of horizontal pleiotropy.

All statistical analyses were performed using the "TwoSampleMR" (version 0.5.6) package in the statistical program R (version 4.1.1) (Lucent Technologies) [24].

3. Results

3.1 Instrumental Variables

Table 2 lists the desired SNPs obtained by satisfying the four major conditions for drug-targeted MR. Seven SNPs (rs10066707, rs10515198, rs12659791, rs12916, rs3804231, rs3857388, and rs72633962) were identified from drug-targeting genes with *HMGCR* inhibitors (**Supplementary Table 1**). Twelve SNPs (rs10493176, rs11206510, rs11206514, rs11583974, rs11591147, rs12067569, rs2479394, rs2479409, rs2495495, rs4927193, rs572512 and rs58513) were obtained from drug-targeting genes with *PCSK9* inhibitors (**Supplementary Table 2**). Three SNPs (rs2073547, rs217386, and rs7791240) were obtained from drug-targeting genes with *NPC1L1* inhibitors (**Supplementary Table 3**).

3.2 Two-Sample MR Analysis

3.2.1 HMGCR Inhibitors

The two-sample analysis yielded the following results: Inverse variance weighted (β = –0.7593341 [OR = 0.4679779], p = 0.008366947), MR Egger (β = –0.6874875

Table 2. Information of genetic instruments.

Exposure	Gene ID	Description	Gene region	Genetic variants associated with LDL cholesterol level
HMGCR inhibitors	3156	3-hydroxy-3-methylglutaryl-CoA reductase	Chr5 75336529-75362116	(1) SNPs (MAF >1%) (2) low linkage disequilibrium ($r^2 < 0.30$) (3) associated with LDL cholesterol ($p < 5.0 \times 10^{-8}$) (4) located within ±100 kb windows from *HMGCR* region
PCSK9 inhibitors	255738	proprotein convertase subtilisin/kexin type 9	Chr1 55039548-5506485	(1) SNPs (MAF >1%) (2) low linkage disequilibrium ($r^2 < 0.30$) (3) associated with LDL cholesterol ($p < 5.0 \times 10^{-8}$) (4) located within ±100 kb windows from *PCSK9* region
NPC1L1 inhibitors	29881	NPC1 like intracellular cholesterol transporter 1	Chr7 44512535-44541330	(1) SNPs (MAF >1%) (2) low linkage disequilibrium ($r^2 < 0.30$) (3) associated with LDL cholesterol ($p < 5.0 \times 10^{-8}$) (4) located within ±100 kb windows from *NPC1L1* region

SNPs, single nucleotide polymorphisms; MAF, minor allele frequency; LDL, low-density lipoprotein.

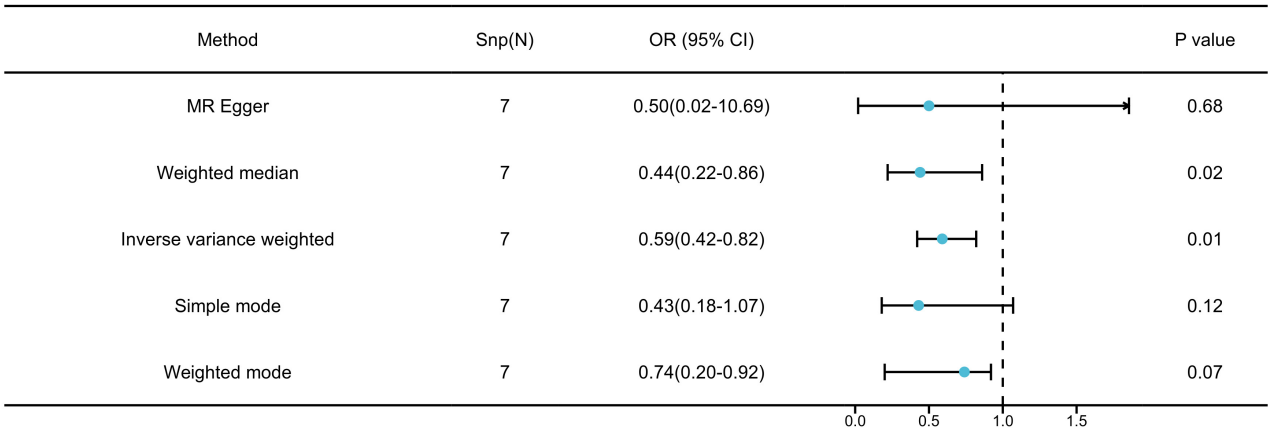

Fig. 2. Forest map of Drug target Mendelian randomization results (Expose: *HMGCR*; Outcome: Traumatic Subdural Hemorrhage). CI, confidence interval; MR, mendelian randomization; OR, odds ratio.

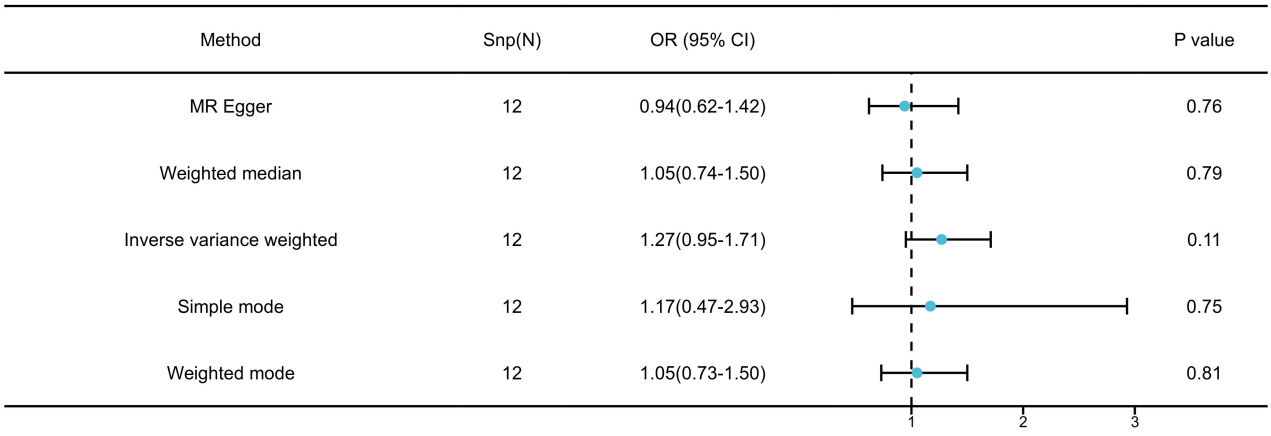

Fig. 3. Forest map of Drug target Mendelian randomization results (Expose: *PCSK9*; Outcome: Traumatic Subdural Hemorrhage).

[OR = 0.5028379], p = 0.677795748), weighted median (β = –0.8308311 [OR = 0.4356870], p = 0.015892642), simple mode (β = –0.8384289 [OR = 0.4323893], p = 0.119123730) and weighted mode (β = –0.8384289 [OR = 0.4323893], p = 0.073815137). Inverse variance weighted results of $p < 0.05$ indicated a causal relationship between

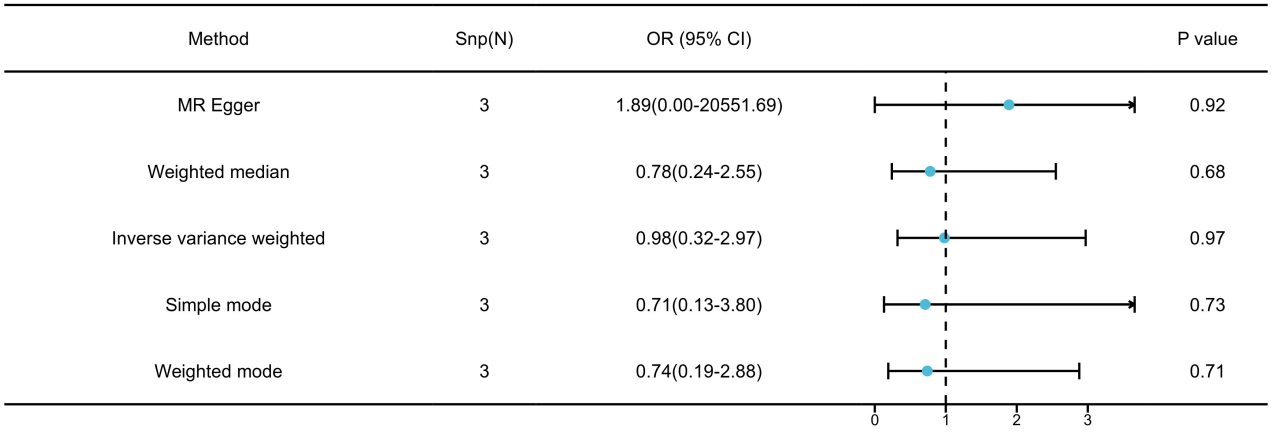

Fig. 4. Forest map of Drug target Mendelian randomization results (Expose: *NPC1L1*; Outcome: Traumatic Subdural Hemorrhage).

statins and traumatic subdural hematoma, and the OR (β) directions of the five statistical results (inverse variance weighted, MR Egger, weighted median, simple model, and weighted model) were consistent, suggesting a protective effect of statins (Fig. 2). The results of this study suggest that the probability of traumatic subdural hemorrhage in patients taking atorvastatin is lower than that in patients not taking atorvastatin. It is suggested that atorvastatin protects against traumatic subdural hemorrhage.

3.2.2 PCSK9 Inhibitors

The two-sample analysis yielded the following results: Inverse variance weighted (β = 0.23897796 [OR = 1.2699505], p = 0.1126327), MR Egger (β = –0.06664885 [OR = 0.9355236], p = 0.7610650), weighted median (β = 0.04823351 [OR = 1.0494157], p = 0.7902609), simple mode (β = 0.15570672 [OR = 1.1684835], p = 0.7464987), and weighted mode (β = 0.04555979 [OR = 1.0466136], p = 0.8099050). All five statistical methods above resulted in $p > 0.05$, indicating that lipid-lowering drugs targeting *PCSK9* inhibitors were not causally related to traumatic subdural hematoma (Fig. 3).

3.2.3 NPC1L1 Inhibitors

The two-sample analysis results are as follows: Inverse variance weighted (β = –0.02118558 [OR = 0.9790373], p = 0.9701686), MR Egger (β = 0.63455320 [OR = 1.8861792], p = 0.9153299), weighted median (β = –0.24655823 [OR = 0.7814859], p = 0.6828022), simple mode (β = –0.34675588 [OR = 0.7069779], p = 0.7251089), and weighted mode (β = –0.29873433 [OR = 0.7417564], p = 0.7083821). All five statistical methods above resulted in $p > 0.05$. Therefore, there is no significant causal relationship between lipid-lowering drugs targeting *NPC1L1* inhibitors and traumatic subdural hematoma (Fig. 4).

3.3 Sensitivity Analysis: Heterogeneity Analysis

The Cochran Q test results are as follows:

HMGCR inhibitors: MR-Egger (p = 0.931067) and inverse variance weighted (p = 0.969446) (Table 3).

PCSK9 inhibitors: MR-Egger (p = 0.7646204) and inverse variance weighted (p = 0.969446) (Table 4).

NPC1L1 inhibitors: MR-Egger (p = 0.2809581) and inverse variance weighted (p = 0.4707652) (Table 5).

These results indicate that our data exhibited no significant heterogeneity and demonstrated good stability, strongly supporting the results of the MR analysis.

3.4 Sensitivity Analysis: Horizontal Multi-Effect Analysis

The horizontal multi-effect analysis results were insignificant, with p = 0.9644335 for *HMGCR* inhibitors (Table 3), p = 0.07044835 for *PCSK9* inhibitors (Table 4), and p = 0.9118129 for *NPC1L1* inhibitors (Table 5). These results indicate the absence of horizontal diversity.

4. Discussion

Traumatic SDH is one of the most fatal craniocerebral disorders, with a mortality rate of 40–80%. Despite surgical interventions, patients may experience fatal outcomes or severe disabilities [25]. Because surgery is the primary treatment modality for traumatic SDH, most research on traumatic SDH has mainly focused on the surgical approach and timing. However, with an aging society, the incidence of traumatic cranial injury increases yearly in older adults and is often accompanied by SDH [26]. The importance of pharmacological treatment is gaining prominence, especially among older adults who frequently have comorbidities and medication history (anticoagulants) that pose significant challenges for surgical treatment. Consequently, the importance of pharmacological treatment is becoming apparent.

Statistics reveal that the average out-of-pocket cost per new drug development is $403 million [27]. Reusing existing drugs is a cost-effective, time-efficient, and conve-

Table 3. Pleiotropy test of drug target (*HMGCR* inhibitors) Mendelian randomization results.

Heterogene-test						Pleiotropy-test		
MR Egger			IVW			MR Egger		
Q	Q_df	Q_*p*val	Q	Q_df	Q_*p*val	intercept	SE	*p*val
1.337112	5	0.931067	1.339308	6	0.969446	–0.004310834	0.09198007	0.9644335

IVW, Inverse variance weighted; SE, Standard Error.

Table 4. Pleiotropy test of drug target (*PCSK9* inhibitors) Mendelian randomization.

Heterogene-test						Pleiotropy-test		
MR Egger			IVW			MR Egger		
Q	Q_df	Q_*p*val	Q	Q_df	Q_*p*val	intercept	SE	*p*val
6.577696	10	0.7646204	10.676316	11	0.4707652	0.04011494	0.01981469	0.07044835

Table 5. Pleiotropy test of drug target (*NPC1L1* inhibitors) Mendelian randomization.

Heterogene-test						Pleiotropy-test		
MR Egger			IVW			MR Egger		
Q	Q_df	Q_*p*val	Q	Q_df	Q_*p*val	intercept	SE	*p*val
1.162450	1	0.2809581	1.185044	2	0.5529310	–0.02829321	0.2029396	0.9118129

nient alternative to research and development. Atorvastatin is one of the most studied drugs, and recent studies have shown that atorvastatin is useful in treating subarachnoid and cerebral hemorrhage [28,29]. Therefore, investigating the effect of lipid-lowering drugs on traumatic SDH is important.

This study revealed that lipid-lowering drugs targeting *HMGCR* inhibitors, such as atorvastatin, exhibit a causal and protective effect against traumatic SDH. In contrast, the analysis of lipid-lowering with *PCSK9* and *NPC1L1* inhibitors as pharmacogenetic targets associated with causality was not supported by the results. These results align with recent studies on brain hemorrhage and lipid metabolism, in which the lipid-lowering effect of statins was not associated with cerebral hemorrhage. However, statins can play a role in improving the prognosis of cerebral hemorrhage [30,31]. This statement seems contradictory, as Li *et al*. [31] found that atorvastatin plays an important role in eliminating SDH and improving neurological recovery in a rat model. These mechanisms may improve neurological recovery and anti-inflammatory effects after cerebrovascular disease by reducing the expression of nitric oxide synthase and myeloperoxidase in the brain tissue surrounding the hematoma after cerebral hemorrhage [32].

In this MR study, we used *HMGCR*-mediated genetic variants associated with LDL-C to represent statin exposure. The MR analysis suggested that *HMGCR* inhibitors have a protective role in traumatic SDH. The meninges are known to protect and support brain tissue. Especially when the head is subjected to external forces, the meninges can play a protective role, but with the increase of age, the meninges are more and more closely adhered to the skull, and the protection of the meninges is weakened with the increase of skull adhesion. It has been reported that taking atorvastatin can improve tissue adhesion [33]. Therefore, atorvastatin may improve the adhesion between the meninges and the skull, improve the protective function of the meninges and further reduce the incidence of traumatic subdural hemorrhage. Secondly, atorvastatin also specifically improves the effect of neuroinflammation [34], which can reduce the secondary injury of traumatic subdural hemorrhage. This study suggests the need for additional observational, mechanistic, and randomized controlled studies in different populations to examine their potential for treating traumatic SDH. We recommend that patients with traumatic SDH who are currently prescribed or initiating statin therapy should continue their treatment. Statins may be a priority drug in future clinical trials for treating SDH.

This study had several limitations. First, the population in this study was limited to Europeans, lacking ethnical diversity. Our subsequent study will encompass a broader population. Second, the aggregated data used in this study does not adequately support further data analysis. Third, this study did not analyze the complete lipid profile. Finally, this study did not include any *in vivo* experiments, and the underlying mechanism of statin protection in traumatic subdural hemorrhage was not thoroughly investigated. Therefore, future studies should further explore and elucidate the mechanism behind the potential protective effects of statins in this context.

5. Conclusions

This MR study suggests a causal relationship between *HMGCR* inhibition and traumatic SDH. More clinical trials are needed to determine whether statins protect against trau-

matic subdural hematomas and further studies are needed to explore the underlying mechanisms.

Abbreviations

SDH, subdural hemorrhage; MR, Mendelian randomization; LDL-C, low-density lipoprotein cholesterol; HGMCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; SNP, single nucleotide polymorphism.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LFW and KQC designed the research study. HL, HSH and YTC analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2304076.

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