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Peer Reviewer of *World Journal of Gastrointestinal Surgery*, Deven Juneja, DNB, FNB, EDIC, FCCP, Director, Department of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India. devenjuneja@gmail.com

## AIMS AND SCOPE

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*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Clinical and Translational Research

# Metabolic disorders and hepatitis: Insights from a Mendelian randomization study

Ling-Bo Liang, Xiang-Ping Liu, Ting-Rui Mao, Qiao-Li Su

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## Abstract

***BACKGROUND***

Hepatitis is a systemic disease that often results in various comorbidities. Metabolic disorders, the most common comorbidities in clinical practice, were selected for this study.

***AIM***

To investigate the causal relationship between comorbidities and hepatitis treatment outcomes.

***METHODS***

A total of 23583378 single nucleotide polymorphisms from 1248743 cases and related summaries of genome-wide association studies were obtained from online public databases. A two-sample Mendelian randomization (MR) was performed to investigate causality between exposure [type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension] and outcome (chronic hepatitis B or C infections).

***RESULTS***

The data supported the causal relationship between comorbidities and hepatitis infections, which will affect the severity of hepatitis progression and will also provide a reference for clinical researchers. All three exposures showed a link with progression of both hepatitis B (T2D, $P = 0.851$; hyperlipidemia, $P = 0.596$; and hypertension, $P = 0.346$) and hepatitis C (T2D, $P = 0.298$; hyperlipidemia, $P = 0.141$; and hypertension, $P = 0.035$).

***CONCLUSION***

The results of MR support a possible causal relationship between different ex-

posures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression; however, the potential mechanisms still need to be elucidated.

**Key Words:** Hepatitis; Comorbidity; Type 2 diabetes mellitus; Hyperlipidemia; Hypertension



**Core Tip:** In our study, the randomization model was well defined for the exposures [type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension] and outcomes (chronic hepatitis B and chronic hepatitis C) by two-sample Mendelian randomization (MR) analysis, and they showed capabilities for interaction with chronic hepatitis infection. The results of our MR support a possible causal relationship between different exposures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression.

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## INTRODUCTION

According to the Global Hepatitis Report 2017 by the World Health Organization, more than 1.34 million people died of hepatitis virus infection worldwide in 2015; more than half of the patients died because of progression to cirrhosis and the other half died due to hepatocellular carcinoma[1]. Hepatitis can be caused by infections with different viruses: Hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus. However, only HBV, HCV, and HDV can induce chronic hepatitis, leading to severe cirrhosis and hepatocellular carcinoma[1]. Because chronic hepatitis is mainly caused by HBV and HCV[2], we investigated the comorbidities of these two types in this study.

HBV is a DNA virus, whereas HCV is an RNA virus. HBV can activate severe immune responses in patients and can be removed by the human body in the short term[3]. However, HBV can also induce a chronic form in the long term; approximately 40% of HBV patients progress to cirrhosis[4], which could be attributable to the long half-life of HBV covalently closed circular DNA[5,6]. Meanwhile, other risk factors such as aging[5], other concomitant diseases, or consumption of alcohol, could significantly increase the probability of being diagnosed with cirrhosis, based on the theory of Sagnelli *et al*[7]. Similar to HBV, the chances of progression to cirrhosis and hepatocellular carcinoma among patients with HCV infection also increase with age[8]. Other potential risk factors, such as gastrointestinal diseases of the esophagus, stomach, and duodenum (41.7%), could induce comorbidities with hepatitis[9].

Researchers have recently explored the relationship between hepatitis and related comorbidities. According to Hsu *et al* [10], comorbidities accompanying hepatitis are often caused by hypertension, diabetes, and ischemic heart disease. In addition, circulatory diseases[9], renal diseases, and non-liver cancers can worsen hepatitis progression accompanied by comorbidities[8]. Therefore, in this study, we investigated the role of the following typical comorbidities in influencing hepatitis: Type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension.

As the risk factors and pathology of hepatitis comorbidities vary, analyzing the relationship between clinical treatment and hepatitis progression among different comorbidities becomes challenging. Meanwhile, knowledge in this field is still rather limited; therefore, we employed a Mendelian randomization (MR) protocol to explore this pair of causations. Currently, MR is a widely used research method based on genome-wide association studies (GWAS) and the theory of nucleotide polymorphisms. As a newly developed tool, MR inherits the principles of the equal, random, and independent distribution method, which adopts genetic variants to reveal causal relationships[11,12], thus providing more reliable and authentic results[13,14]. Regarding hepatitis research, MR will help establish the causal linkage between hepatitis comorbidities and disease outcomes. In this study, patients with different comorbidities were regarded as having a functional variation of specific genes, and MR analysis will guide researchers to better understand hepatitis comorbidities and progression.

## MATERIALS AND METHODS

### *Study design*

In this study, a two-sample MR analysis was employed to investigate the causal relationship between comorbidities and hepatitis treatment outcomes. Meanwhile, the inverse variance weighting (IVW) method was applied to determine the causal relationship between exposures and outcomes, where comorbidities were regarded as exposures and indicators from various aspects were regarded as outcomes. Consequently, single nucleotide polymorphisms (SNPs) associated with

**Table 1 Description of included traits**

| Group | Trait | ID | Sample size | Year | Case/control | SNPs |
|---|---|---|---|---|---|---|
| Exposures | T2D | ebi-a-GCST90093109 | 50533 | 2022 | 16677/33856 | 13403040 |
| | Hyperlipidemia | ebi-a-GCST90090994 | 9714 | 2022 | 3310/6404 | 592502 |
| | Hypertension | ebi-a-GCST90038604 | 484598 | 2021 | 129909/354689 | 9587836 |
| Outcomes | CHB | ebi-a-GCST90018804 | 351885 | 2021 | 145/351740 | 19079722 |
| | CHC | ebi-a-GCST90018805 | 352013 | 2021 | 273/351740 | 19074546 |

T2D: Type 2 diabetes mellitus; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; Chronic hepatitis B; CHC: Chronic hepatitis C.

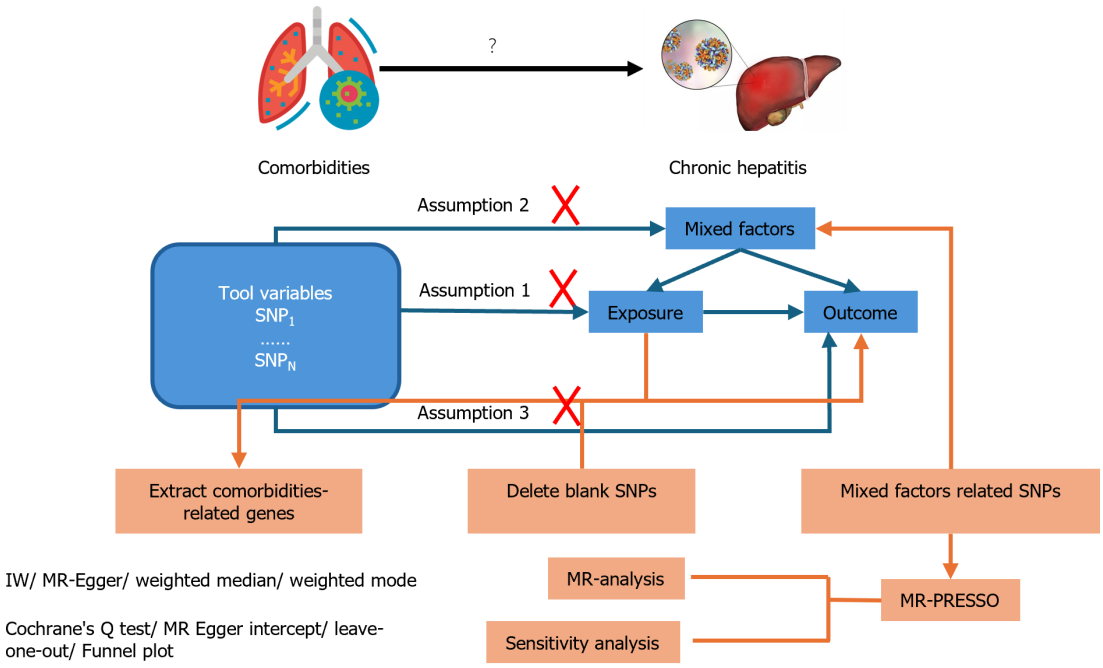



**Figure 1 Mendelian randomization analysis.** MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

hepatitis comorbidities were used as instrumental variables, while their clinical conditions were used as outcome variables. Based on this condition, three important assumptions should be satisfied.

Assumption 1: The selected SNPs should be significantly related to the exposure variable. Assumption 2: SNPs should remain independent of factors that could play a role in exposure and outcomes. Assumption 3: SNPs should not have a direct impact on inducing changes in hepatitis status but can only alter the status *via* comorbidities to exhibit a causal relationship.

Based on the descriptions above, we conducted an MR analysis as depicted in Figure 1.

### *Data of exposure and outcome*

The included SNPs and related GWAS summaries were obtained from the online public databases IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) and FinnGen Biobank (https://r8.finngen.fi/), which provide genetic insights from a well-phenotyped isolated population[15]. Online calculations were performed using the MR-Base platform (http://app.mrbase.org/, version 1.4.3 8a77eb; accessed on 08 January 2024)[11]. In this study, different pairs of exposures and outcomes were formed to examine their relationships, where T2D (total 50,533 samples, 16677 cases/33856 controls), hyperlipidemia (total 9714 samples, 3310 cases/6404 controls), and hypertension (total 484598 samples, 129909 cases/354689 controls) comprised the exposures, and chronic hepatitis B (CHB; total 351885 samples, 145 cases/351740 controls) and chronic hepatitis C (CHC) infections (total 352013 samples, 273 cases/351740 controls). Table 1 lists the characteristics of these pairs. These data were accessed and investigated on 06 January 2024.

### *MR analysis*

MR analysis was deployed to investigate the association between metabolic disorders and chronic hepatitis, which leveraged genetic variants as instrumental variables to infer causal relationships. The MR-base GWAS catalog served as a crucial tool for selecting appropriate SNPs as instrumental variables during the MR analysis. Meanwhile, rigorous criteria

were adopted to ensure the high authenticity of the SNP statistics: *P* value threshold of less than $5 \times 10^{-8}$ and LD Rsq threshold of 0.001.

Meanwhile, we utilized various models to test the theory that comorbidities affect chronic hepatitis. For instance, the IVW method as a commonly used approach in MR analysis, was used to estimate the causal effect between exposure and outcome. Additionally, the MR-Egger model was utilized to detect and correct for potential horizontal pleiotropy with a non-zero *P* value indicating statistical significance ($P < 0.05$). To ensure a convincing conclusion, the Cochrane Q test was applied with the IVW and MR-Egger tests to test for heterogeneity.

To verify the robustness of this MR analysis, sensitivity analyses were conducted by using various MR methods, including MR-Egger regression, weighted median, and weighted mode methods. The weighted mode was examined by leave-one-out analysis, where the impact of each instrumental SNP on exposures and outcomes could be detected. In addition, the odds ratio (OR) and its 95% confidence interval (95%CI) were calculated using the MR results to predict the integrity of the causal relationship between exposure and outcome factors.

Presentation of the results was meticulously executed through the creation of comprehensive visualizations, including forest plots, funnel plots, leave-one-out plots, and scatter plots. These plots provided insights into the effects of each SNP on both exposure and outcome variables, facilitating a deeper understanding of the observed associations.

The statistical analyses were conducted using R (version 4.0.3) and R/TwoSampleMR (https://mrcieu.github.io/TwoSampleMR, version 0.5.5) were used with the online analysis tool for computational efficiency. By employing these rigorous statistical approaches, the study aimed to provide robust evidence regarding the relationship between metabolic disorders and chronic hepatitis, contributing to the broader understanding of disease etiology and potential therapeutic interventions.

## RESULTS

### MR estimates

We chose three typical comorbidities among patients with chronic hepatitis, namely T2D, hyperlipidemia, and hypertension, as exposure factors and found their GWAS summary for detailed MR. In this study, we found that these factors were significantly associated with the progression of chronic hepatitis. As shown in Table 1, the overall SNP exposure was 23583378 and the total sample accounted for 1248743 cases. In the outcome group, the number of patients with hepatitis B and C infections was 418 of 703898 cases. These data were retrieved from public research worldwide and, therefore, present extensive human research.

Detailed data of the two-sample MR are presented in Table 2. All three exposures exhibited a role in promoting the progress of hepatitis: T2D showed a link with hepatitis B progression examined by IVW (OR = 1.01676, 95%CI = 0.854–1.210, $P = 0.851$), as did hyperlipidemia (OR = 0.97827, 95%CI = 0.902–1.061, $P = 0.596$), and hypertension (OR = 1.35243, 95%CI = 0.721–2.535, $P = 0.346$). For the other outcomes of CHC infection, T2D promoted its progression with OR = 0.94825, 95%CI = 0.858–1.048, $P = 0.298$; hyperlipidemia with OR = 0.96140, 95%CI = 0.912–1.013, $P = 0.141$; and hypertension with OR = 0.67301, 95%CI = 0.465–0.973, $P = 0.035$).

Consistent with the findings in Table 2, the effects of the SNPs on exposure and outcomes are illustrated below (Figure 2).

### Sensitivity analyses

As mentioned in the MR section, different statistical models were applied to examine the quality of the analysis. For example, to examine the horizontal pleiotropy of this MR, the MR-Egger intercept was calculated based on the mode with $P > 0.05$, suggesting a correct scientific basis for this analysis. Directional horizontal pleiotropy was drawn in funnel plots (Figure 3), where the data dots were distributed in a symmetrical form. In addition, no heterogeneity was found in this study because the *P* values were greater than 0.05. Meanwhile, the leave-one-out analysis results indicated a significant relationship between different exposures and outcomes (Figures 4 and 5).

## DISCUSSION

Currently, with faster transportation and a changeable lifestyle in modern societies, the probability of a person diagnosed with two or more diseases are increasing[16]. Since the mortality rate for patients with chronic hepatitis remains low, and the situations for the patients carrying an additional disease become complicated, we performed this MR to analyze the potential effects of comorbidities during hepatitis and the disease progression among the patients, and the first category went to cardiovascular disease after we looked up the related findings.

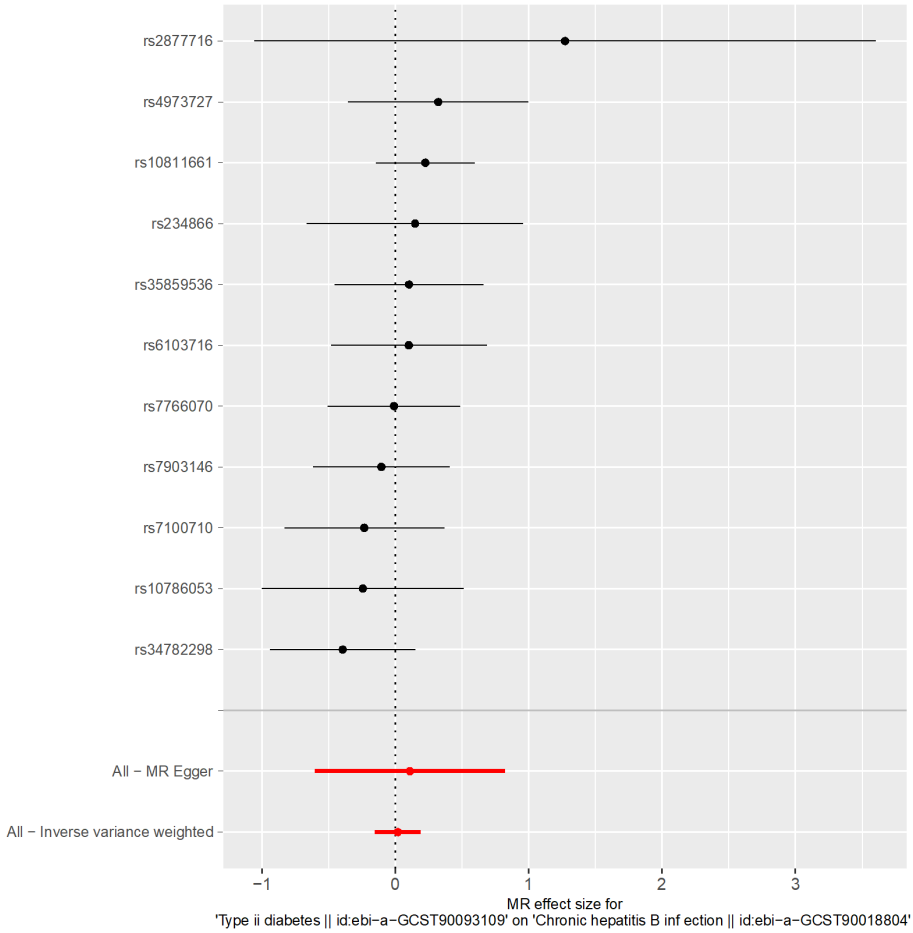
According to our findings, comorbidities associated with metabolic disorders and cardiovascular disease promote the progression of chronic hepatitis. A meta-analysis by Naing *et al*[17], which included 17 studies with 286084 patients demonstrated a strong relationship between T2D and CHC infection. This correlation was first proposed by Allison *et al*[18] in 1994, based on the finding of abnormalities in carbohydrate metabolism, such as glucose intolerance, in cirrhosis. The exact molecular mechanisms remain to be further explored, but MR could help answer this question since the underlying mechanisms are related to genetic specificity[19]. In addition, a meta-analysis found that T2D is associated with hepatitis B infection, and that T2D could promote hepatitis B progression into hepatocellular carcinoma[20]. The pathology remains to be further explored, but studies have indicated that altered microbiome caused by HBV affect both

**Table 2 Mendelian randomization for the association between comorbidities and chronic hepatitis**

| Outcome | Exposure | Number of instruments | Method | OR | 95%CI | *P* value | Heterogeneity | | | Pleiotropy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Q | Q_df | Q p | Intercept | *P* value |
| CHB infection | T2D | 11 | MR Egger | 1.11338 | 0.546-2.271 | 0.774 | 6.861 | 9 | 0.6516 | -0.011 | 0.803 |
| | | | Weighted median | 1.08022 | 0.860-1.357 | 0.504 | - | - | - | | |
| | | | IVW | 1.01676 | 0.854-1.210 | 0.851 | 6.927 | 10 | 0.7323 | | |
| | | | Weighted mode | 1.10321 | 0.815-1.493 | 0.576 | - | - | - | | |
| | Hyperlipidemia | 5 | MR Egger | 1.00996 | 0.804-1.269 | 0.938 | 3.888 | 3 | 0.2738 | -0.013 | 0.784 |
| | | | Weighted median | 1.00910 | 0.918-1.110 | 0.857 | - | - | - | | |
| | | | IVW | 0.97827 | 0.902-1.061 | 0.596 | 4.004 | 4 | 0.4055 | | |
| | | | Weighted mode | 1.01660 | 0.912-1.133 | 0.765 | - | - | - | | |
| | Hypertension | 277 | MR Egger | 1.845401 | 0.350-9.728 | 0.471 | 279.1 | 258 | 0.1751 | -0.0028 | 0.693 |
| | | | Weighted median | 1.56894 | 0.604-4.077 | 0.346 | - | - | - | | |
| | | | IVW | 1.35243 | 0.721-2.535 | 0.346 | 279.3 | 259 | 0.1846 | | |
| | | | Weighted mode | 1.81921 | 0.519-6.379 | 0.359 | - | - | - | | |
| CHC infection | T2D | 11 | MR Egger | 1.13338 | 0.744-1.726 | 0.574 | 9.143 | 9 | 0.4242 | -0.022 | 0.414 |
| | | | Weighted median | 0.94250 | 0.825-1.077 | 0.391 | - | - | - | | |
| | | | IVW | 0.94825 | 0.858-1.048 | 0.298 | 9.887 | 10 | 0.4504 | | |
| | | | Weighted mode | 0.94916 | 0.810-1.112 | 0.550 | - | - | - | | |
| | Hyperlipidemia | 5 | MR Egger | 0.89288 | 0.793-1.005 | 0.158 | 3.222 | 3 | 0.3587 | 0.03 | 0.274 |
| | | | Weighted median | 0.94627 | 0.898-0.997 | 0.038 | - | - | - | | |
| | | | IVW | 0.96140 | 0.912-1.013 | 0.141 | 5.134 | 4 | 0.2738 | | |
| | | | Weighted mode | 0.94262 | 0.891-0.998 | 0.108 | - | - | - | | |
| | Hypertension | 260 | MR Egger | 0.59067 | 0.223-1.566 | 0.291 | 289.5 | 258 | 0.08644 | 0.0012 | 0.777 |
| | | | Weighted median | 0.69088 | 0.391-1.220 | 0.206 | - | - | - | | |
| | | | Inverse variance weighted | 0.67301 | 0.465-0.973 | 0.035 | 289.6 | 259 | 0.09284 | | |
| | | | Weighted mode | 0.83477 | 0.408-1.707 | 0.617 | - | - | - | | |

MR: Mendelian randomization; IVW: Inverse variance weighting; T2D: Type 2 diabetes mellitus; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C.

**A**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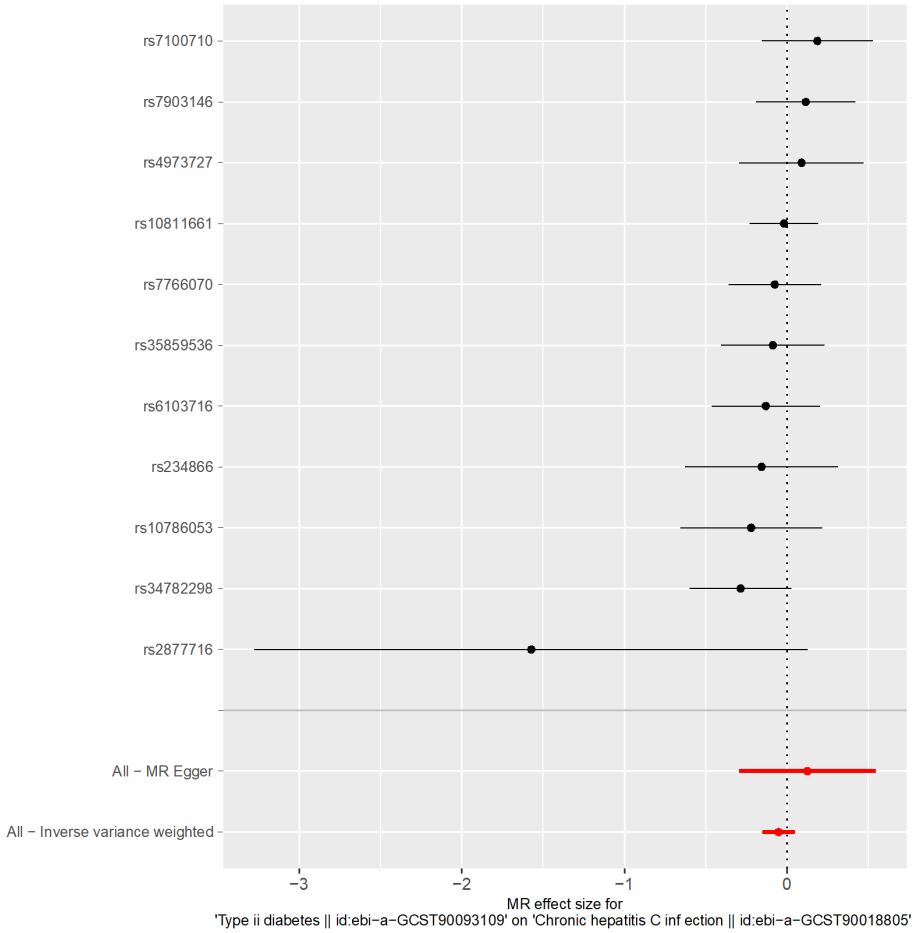
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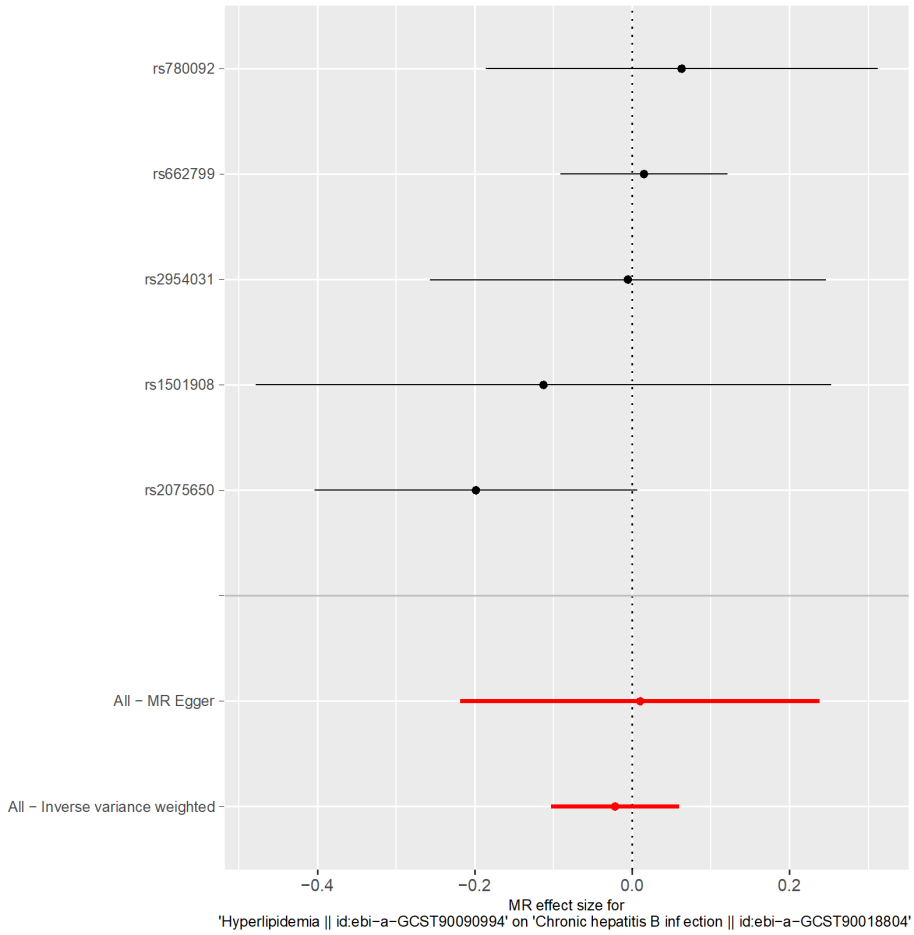
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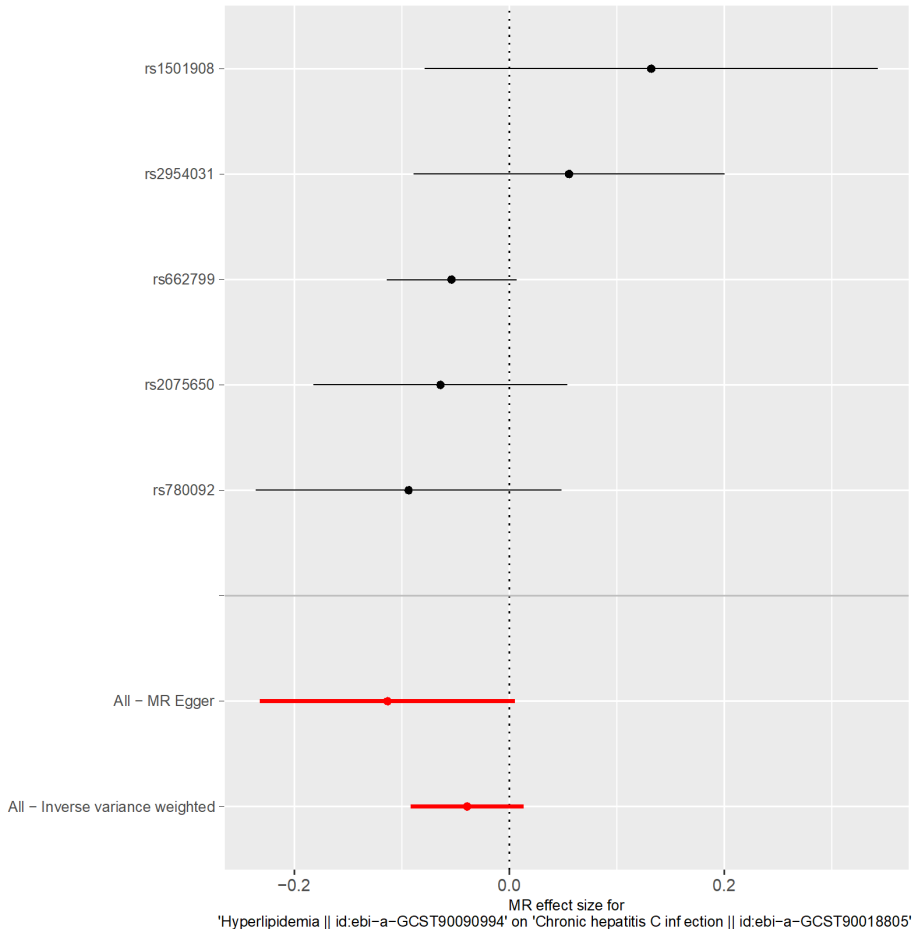
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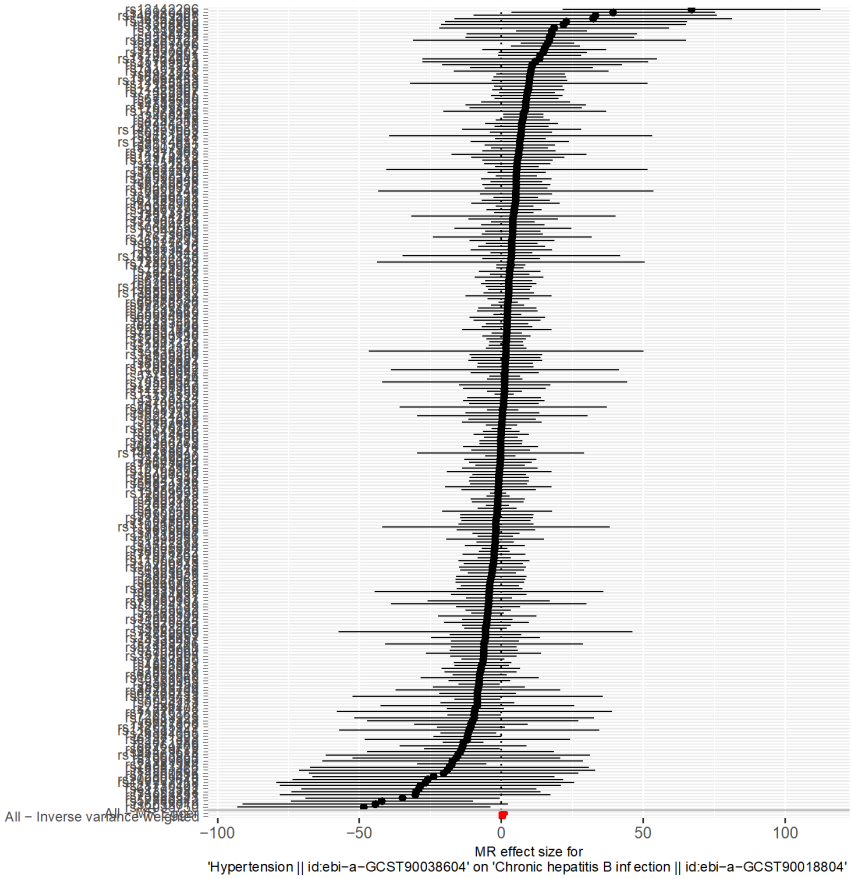


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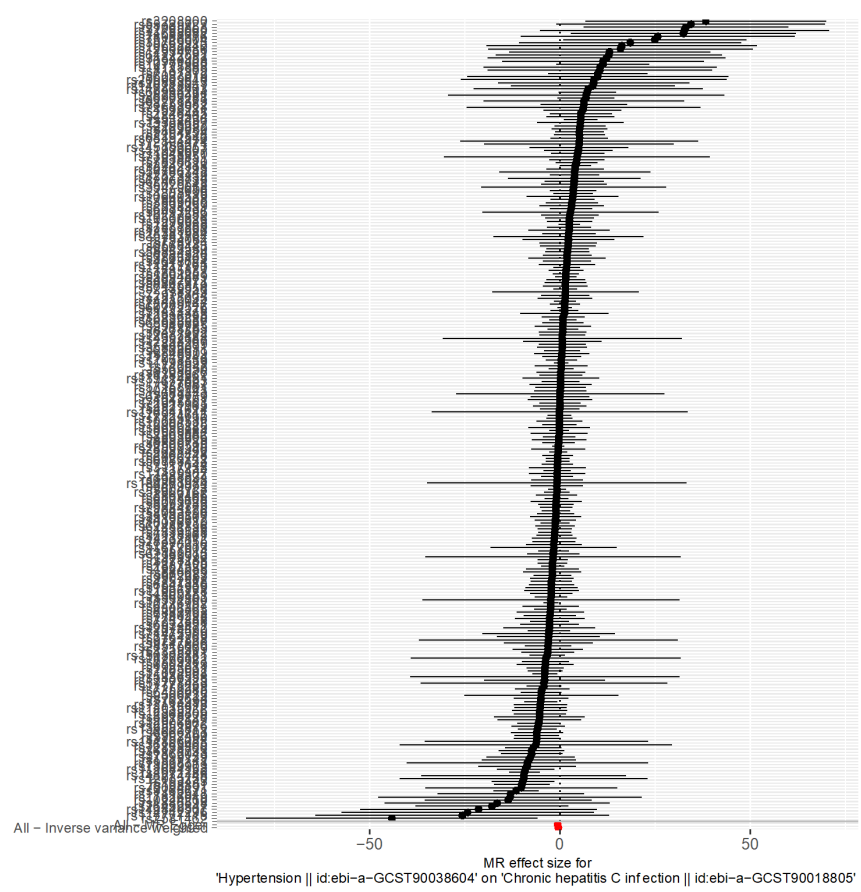


**Figure 2 Forest plot of the comorbidities.** A and B: type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

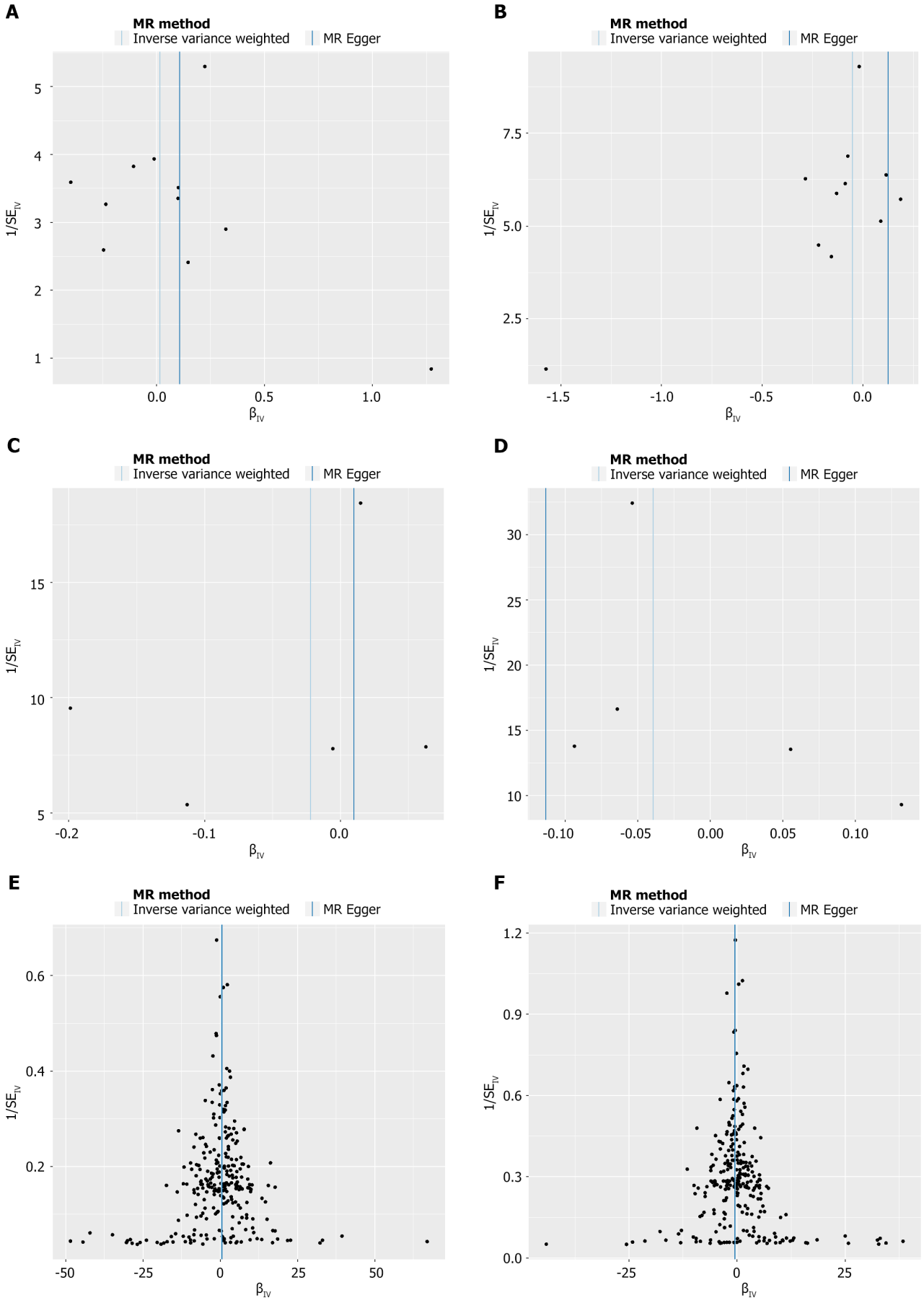


**Figure 3 Funnel plot of the comorbidities.** A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

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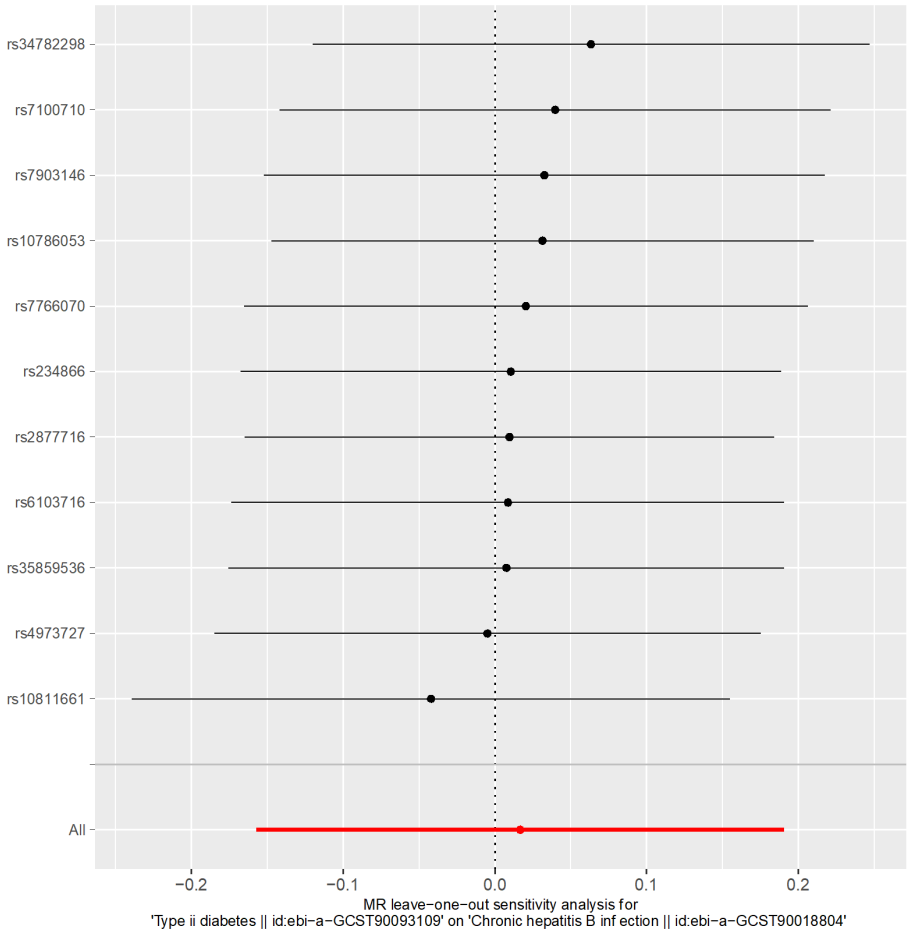
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All
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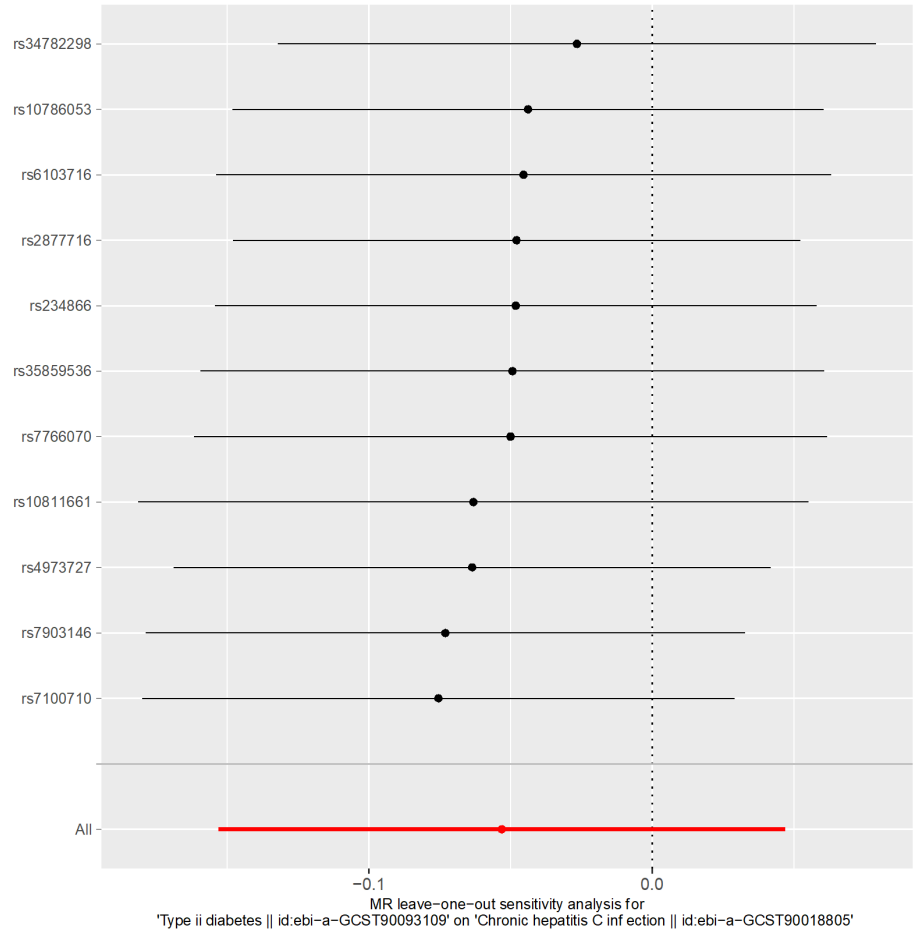
**B**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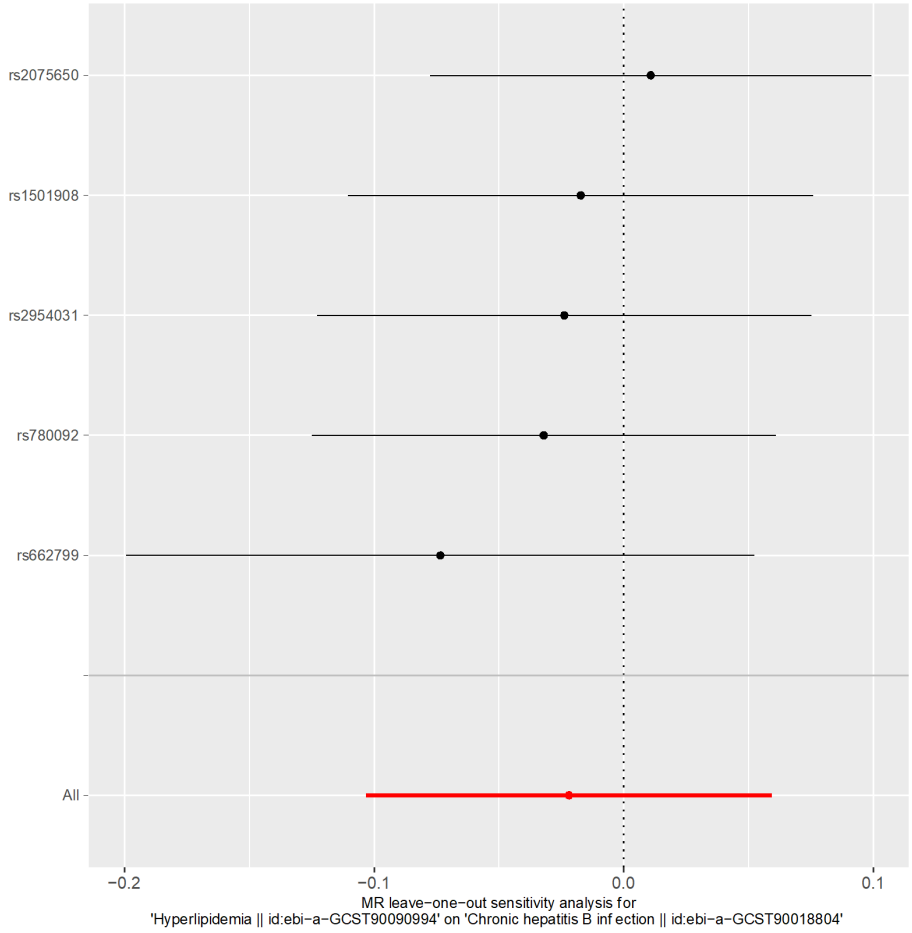
MR leave−one−out sensitivity analysis for
'Type ii diabetes || id:ebi−a−GCST90093109' on 'Chronic hepatitis C inf ection || id:ebi−a−GCST90018805'

**C**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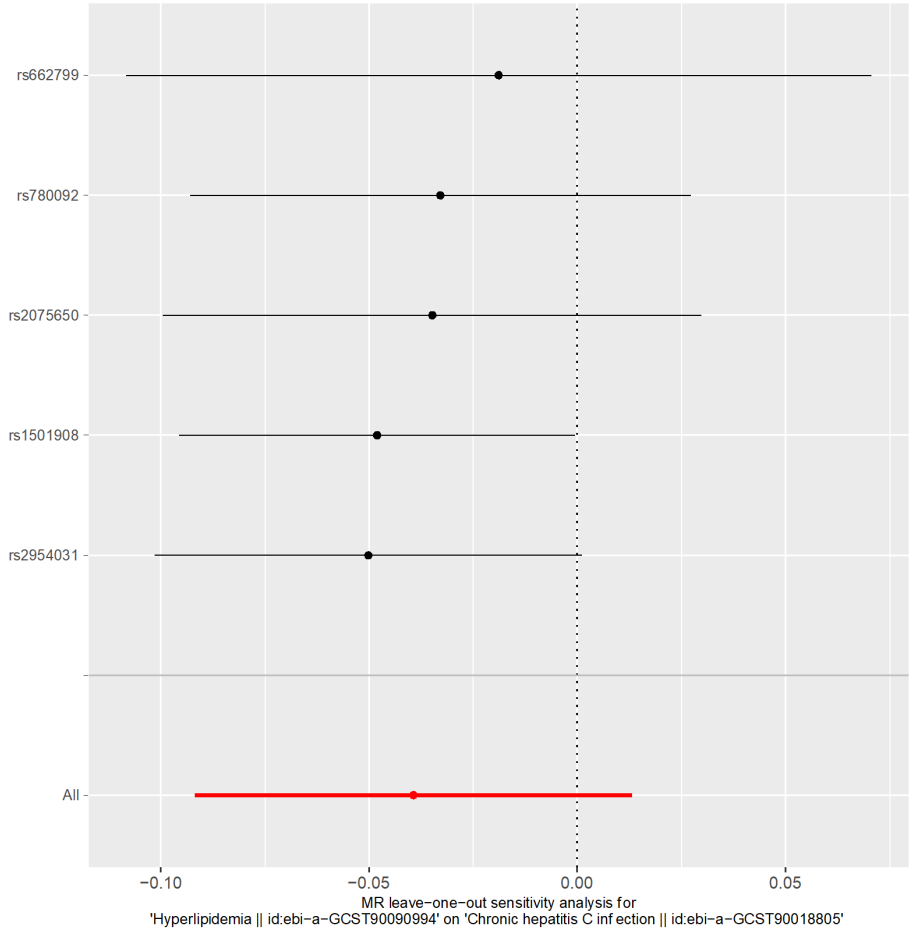
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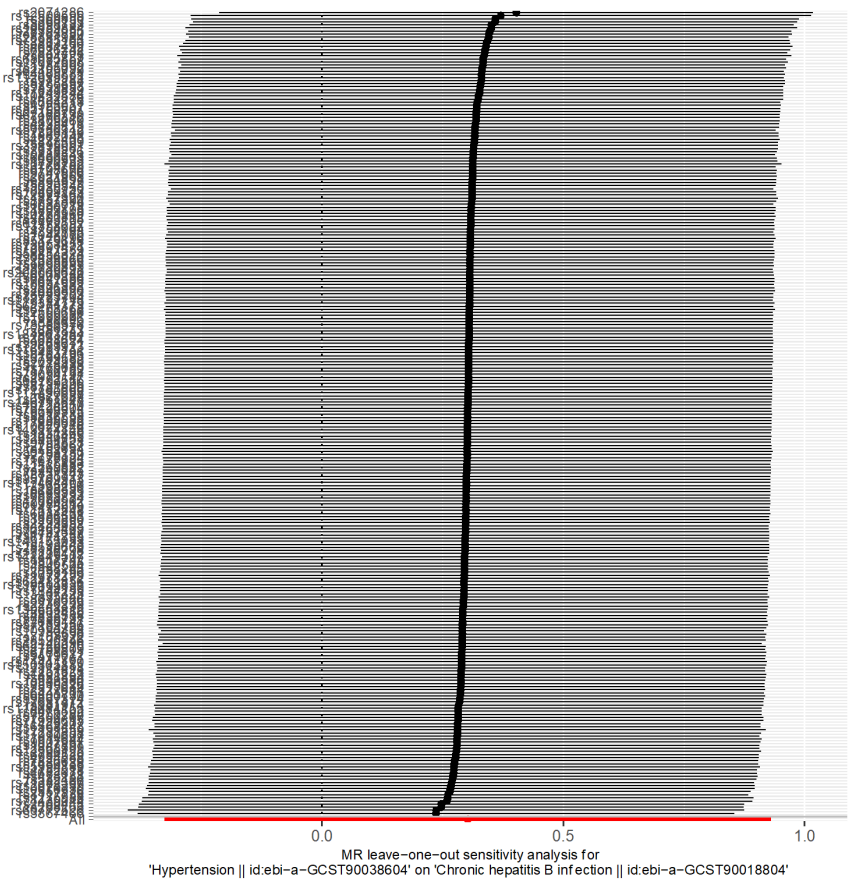
**E**

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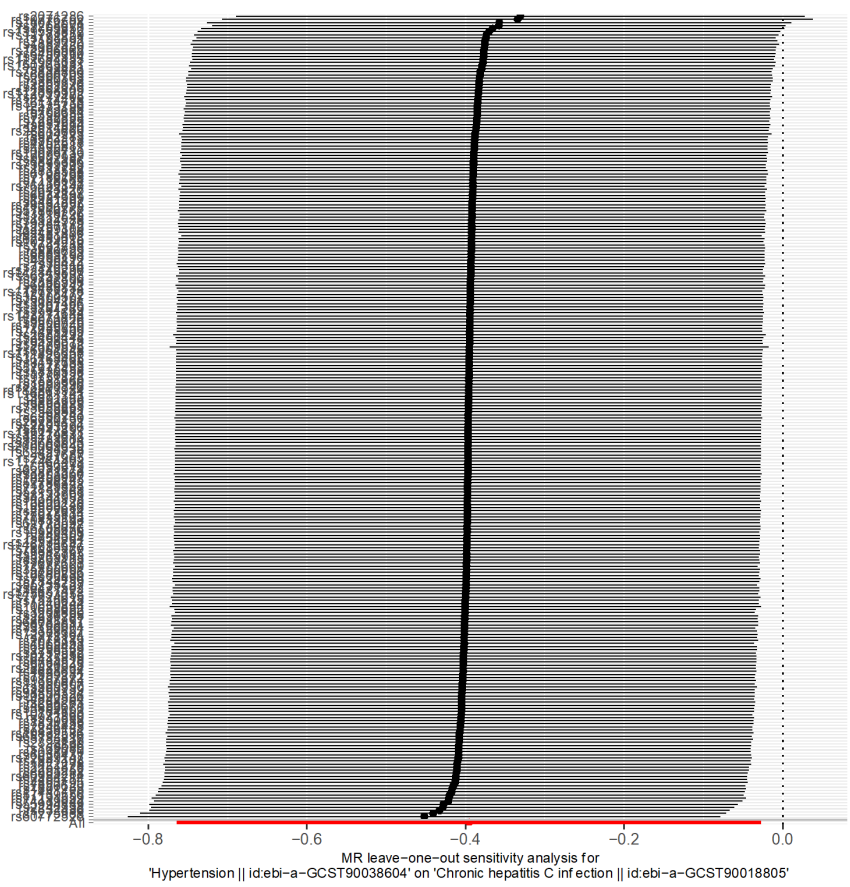


**Figure 4 Leave one-out plot of the comorbidities.** A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

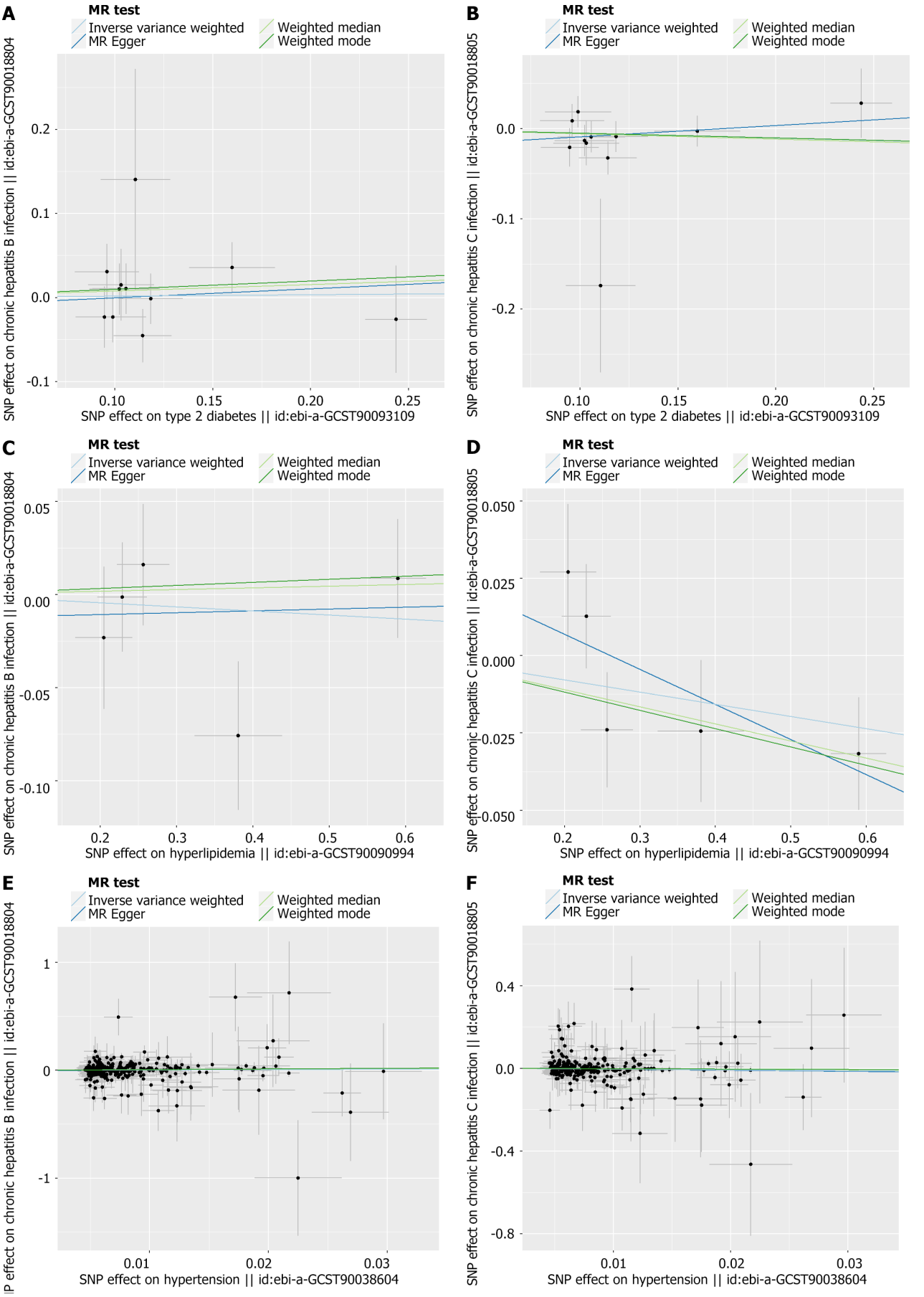


**Figure 5 Scatter plot of the comorbidities.** A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

lipid and glucose metabolism, thus increasing the severity of the chronic hepatitis infection until non-alcoholic fatty liver disease (NAFLD) develops[21]. Multiple studies have revealed that parenteral viral hepatitis can affect insulin resistance in the body, thus increasing the severity of hepatitis progression in patients[22]. Hepatitis infection with comorbid T2D eventually progresses to NAFLD[21,23], hepatic steatosis[24], hepatocarcinoma, and fibrosis[25].

Hyperlipidemia is also a frequently observed comorbidity of chronic hepatitis infections in clinical practice[26]. According to a cohort study of 1927 patients from 2005 to 2015, hyperlipidemia was correlated with hepatitis progression into hepatocarcinoma without cirrhosis[27]. Meanwhile, a new type of HBV infection, occult HBV (HBV DNA-positive, but HBV surface antigen-negative), is more likely to occur in patients with hyperlipidemia[28]. The molecular mechanisms by which hyperlipidemia interacts with hepatitis remain unknown; however, an interesting phenomenon between hyperlipidemia and HBV infection has been reported. Statins, which were originally used to treat hyperlipidemia, have been widely used in clinical hepatitis treatment, and they could reduce the risks of progression to cirrhosis [29] and hepatocarcinoma[30,31].

Hypertension, which shares most instrumental SNPs with hepatitis, exhibits a strong association with hepatitis B and C infections. In clinical research, hypertension has been reported to be a risk factor for HCV patients with severe progression[32], and the overall effect in patients (*e.g.*, ascites) with both hypertension and HCV is dependent on the severity of liver damage[33]. However, if patients receive antihypertensive treatment, they present with a mild viral syndrome upon exposure to HBV infection[34]. Researchers have attempted to explain this relationship, and one recent finding is that among patients with hypertension, the estimated glomerular filtration rate (eGFR) is lower in patients with HCV than those without HCV infection[35]. eGFR and other pathways may link hepatitis progression to hypertension; however, further research is required to support this theory.

In our study, the randomization model was well defined for the exposures (T2D, hyperlipidemia, and hypertension) and outcomes (CHB and CHC) by two-sample MR analysis, and they showed capabilities for interaction with chronic hepatitis infection; however, this study lacks clinical experimental data and other supporting materials to strengthen this theory. However, this shortage does not hinder this finding from being further explored, and as the next step in continued research, in-depth research on both clinical and molecular levels will be conducted to determine the exact molecular mechanisms and pathology of this linkage.

## CONCLUSION

The results of our MR support a possible causal relationship between different exposures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression; however, the potential mechanisms still need to be elucidated, and more supported data should come together to support the theory that these common comorbidities will surely affect the clinical treatment of chronic hepatitis infections.

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## FOOTNOTES

**Author contributions:** Su QL and Liang LB and Mao TR designed and performed the experiments; Liang LB and Liu XP provided support for data analysis and writing the manuscript; Su QL provided the supervision, resources, discussion, design and peer review process; all the authors have seen and approved the manuscript.

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