Supplementary Materials

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SUPPLEMENTARY METHODS AND RESULTS

Description of study outcomes

Association of SNPs with risk of MASLD (nonalcoholic fatty liver disease) were extracted from a GWAS (GWAS) including 1,483 MASLD cases and 17,781 non-cases of European descent.[1] Notably, this study is largest histopathology-based MASLD GWAS to date recruiting patients from clinics at several leading European tertiary liver centers. Since liver biopsy is still considered the gold standard for diagnosing MASLD, the genetic variations linked to MASLD from this study can be considered more credible than those identified through electronic medical records-based GWAS.

GWAS summary statistics for alcohol-related cirrhosis (ALC) were obtained from a GWAS meta-analysis of 712 cases and 1,466 controls.[2] Cases were defined as patients with clinically diagnosed or biopsy-proven cirrhosis who had consumed alcohol for more than 10 years at least 60 g/d for women and 80 g/d for men. In the control group, no clinical or laboratory evidence of liver disease was present. This was confirmed by a noninvasive assessment of liver fibrosis, in the context of alcohol dependence.

SNP (single nucleotide polymorphism) associations with AIH (autoimmune hepatitis), PBC (primary biliary cirrhosis), and HCC (hepatocellular carcinoma) risk were obtained from GWAS based on UK Biobank including 906 AIH cases and 650,942 controls, 121 PBC cases and 456,227 controls, and 123 HCC cases and 456,225 controls.[3,4] The UK Biobank is a long-term prospective cohort study recruiting about 500,000 individuals aged between 40 and 69 years.

The summary statistics for primary PSC (primary sclerosing cholangitis) were sourced from the largest genome-wide association study of PSC, which comprised 2,871 cases and 12,019 controls of European ancestry.[5] PSC was diagnosed based on clinical, biochemical, cholangiographic and histological criteria, and secondary causes of sclerosing cholangitis were excluded.

Mendelian randomization

MR relies upon three main assumptions: the relevance, the independence, and exclusion-restriction assumption. The relevance assumption is substantiated by the observation that each cis-pQTL exhibits a significant correlation ($P \leq 5 \times 10^{-6}$) with its corresponding protein level. Concerning the independence assumption, instruments are assumed to be unlinked to confounders influencing the exposure and outcome. The potential confounders, such as ancestry, is minimized by restricting the GWAS case and control cohorts to individuals of European descent. Lastly, the exclusion restriction assumption, which posits that the genetic variants affect the outcome only through their impact on the exposure, is reinforced by the use of cis-acting SNPs within 500 kb of the corresponding gene. As different MR methods have different performances under different scenarios and vary in their statistical efficiency, we performed three methods of two-sample MR: inverse-variance weighted, weighted median, and MR-PRESSO. The inverse-variance weighted (IVW) method could give unbiased estimates if all the instruments are valid or there is balanced horizontal pleiotropy. Since cis-variants are less likely to be affected by pleiotropy, we use IVW approach as our primary analysis method. The weighted median method could provide robust estimates when at least 50% of the weight comes from valid instrumental variables[6]. In addition, the MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect and correct for potential outlier SNPs.[7]

Pharmacovigilance study was used to identify drugs with potential hepatotoxicity

We retrieved adverse drug event data from the US Food and Drug Administration's Adverse Event Reporting System (FAERS) compiled from the first quarter of 2004 to the last quarter of 2022 using OpenFDA (https://open.fda.gov/), which is a database for data mining and analysis of adverse drug event data. In the FAERS, adverse events can be specified at different levels of the medical dictionary for regulatory activities (MedDRA) terminology. We employed 9 preferred terms ("drug-induced liver injury", "hepatotoxicity", "acute hepatic failure", "hepatic failure", "liver disorder", "hepatic lesion", "liver function test increased", "transaminases increased", and "hepatic enzyme increased") for collecting relevant cases associated with "drug-induced liver injury".

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We have performed Yates' chi-square test and calculate relative reporting ratio (RRR) from adverse drug event data to determine the relationship between the drug and hepatotoxicity (Supplementary Table 5). In this study, Chi square values >4, number of adverse events of drugs >4, and the lower limit of the 95% confidence interval (CI) of the RRR>2 indicate that the adverse event and the drug is related and can be considered as potentially hepatotoxic agent.