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ORIGINAL RESEARCH

From Mind to Liver: Exploring the Causal Relationship Between Anxiety Disorders and Non-Alcoholic Fatty Liver Disease Through Mendelian Randomization and UK Biobank Validation

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Background: Non-alcoholic Fatty Liver Disease (NAFLD) is highly prevalent and increasingly recognized as a multisystem condition with bidirectional links to the brain–liver axis. While most prior work emphasized "liver-to-brain" effects, whether anxiety disorders increase the risk of Non-alcoholic Fatty Liver Disease remains unclear.

Methods: We employed Mendelian randomization (MR) analysis using Genome-wide association study (GWAS) data to investigate whether genetically predicted anxiety disorders play a causal role in NAFLD risk. We then validated our findings using a prospective cohort of 393,229 participants from the UK Biobank, with a median follow-up of 12.6 years.

Results: Our MR analysis provides suggestive evidence for a potential causal effect of genetically predicted anxiety disorders on NAFLD (odds ratio [OR] = 1.73, 95% confidence interval [CI]: 1.12–2.67, P = 0.013). This finding was further supported by the UK Biobank prospective study, which demonstrated that baseline anxiety was associated with increased incident NAFLD risk even after adjusting for potential confounding factors (hazard ratio [HR] = 1.630, 95% CI: 1.488–1.786, P < 0.001). Notably, participants with anxiety exhibited elevated liver fat content at follow-up magnetic resonance imaging, as assessed through follow-up magnetic resonance imaging, irrespective of gender (P < 0.001).

Conclusion: Our study provides converging evidence from genetic and observational data suggesting that anxiety disorders may be associated with an increased risk of NAFLD onset. This relationship necessitates a reconsideration of both NAFLD management and pharmacotherapy for anxiety disorders, advocating for a shift from a specialized clinical focus to a comprehensive community-level strategy for addressing non-communicable diseases (NCDs).

Keywords: anxiety, nonalcoholic fatty liver disease, Mendelian randomization, UK Biobank, prospective study, liver-brain axis

Introduction

Non-alcoholic fatty liver disease (NAFLD), which afflicts approximately 38% of the global population, posing significant societal challenges, including substantial healthcare costs, economic losses, and reduced quality of life.[1,2] India became the first country to integrate NAFLD into its national non-communicable disease (NCD) program in 2021.[3] As

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a multisystem disorder, NAFLD impacts multiple organ systems beyond the liver.[2,4] The "liver-to-brain" axis is well-established: research suggests that even the early stage NAFLD can affect cognitive performance, brain volume, and increase mental health disorders such as anxiety, depression, bipolar disorder, and schizophrenia-related behaviors.[5–8] A recent UK Biobank study has elucidated negative correlations between liver fibrosis and cognitive function, underscoring the pivotal role of inflammation in the liver-brain axis.[9] However, most studies primarily focused on the "liver-to-brain" direction. Given our current understanding of the liver-brain axis an important question arises: can mental health issues also reciprocally cause liver dysfunction?

The brain constantly communicates with metabolic organs via the endocrine and peripheral nervous systems, playing a central role in metabolic regulation.[10,11] Recent evidence suggests that autonomic nervous system dysfunction, particularly anxiety, may contribute to metabolic dysregulation.[12] Anxiety disorders affect approximately 4–7% of the global population.[13] Observational studies have reported associations between anxiety and metabolic disorders, including obesity, type 2 diabetes, and metabolic syndrome.[14] Regarding NAFLD specifically, cross-sectional studies have yielded conflicting results. Some studies reported higher prevalence of anxiety symptoms among NAFLD patients,[15] while others found no significant association after adjusting for metabolic confounders. Critically, most existing studies have examined the prevalence of anxiety in established NAFLD cohorts, with limited prospective evidence evaluating whether pre-existing anxiety predicts incident NAFLD. Furthermore, observational studies are susceptible to residual confounding and reverse causation, limiting causal inference. It is important to note that anxiety and NAFLD share common risk factors, including obesity, sedentary lifestyle, and metabolic dysfunction.[15] Obesity itself may contribute to anxiety through inflammatory pathways and body image concerns,[16] creating complex bidirectional relationships that require rigorous methodological approaches to disentangle.

Mendelian randomization (MR) employs genetic variants as instrumental variables to explore causal relationships between exposures and outcomes, leveraging the random assortment of alleles at conception to mimic a randomized controlled trial.[17] MR offers several advantages, including minimizing confounding by environmental factors and eliminating reverse causation biases, as genetic variants are fixed at conception and precede disease onset.[18,19] When combined with prospective cohort data, MR can provide complementary evidence to strengthen causal inference.[20]

In this study, we primarily focused on anxiety disorders as the exposure and NAFLD as the outcome in the MR framework, with schizophrenia and bipolar disorder examined as exploratory exposures. We then validated temporality and clinical relevance in the UK Biobank by assessing incident NAFLD among participants with baseline anxiety disorder and by evaluating liver fat content on Dixon MRI. We hypothesized that anxiety disorders may increase the risk of NAFLD through metabolic and neurobiological mechanisms along the brain–liver axis. Clarifying this "mind-to-liver" relationship could inform integrated screening and management strategies bridging mental health and liver care.

Methods

Study Design

We used a mixed methods approach combining two methodologies. In Phase 1, this research employed MR approach, using mental disorders as the exposure and NAFLD as the outcome to examine causality (Figure 1). Bipolar disorder and schizophrenia were examined as secondary exposures for comparison. The MR analysis is based on three core assumptions: relevance, independence, and exclusion restriction.[21] These assumptions require that: (1) genetic variants are robustly associated with the exposure (anxiety disorders); (2) genetic variants are independent of confounders; and (3) genetic variants affect the outcome (NAFLD) only through the exposure, not through alternative pathways.

Then in Phase 2, we conducted a prospective cohort study based on the UK Biobank to validate the MR findings and assess the temporality of the association. The integration of MR analysis with prospective cohort data provides complementary strengths: MR leverages genetic randomization to minimize confounding and reverse causation, while the UK Biobank cohort offers real-world validation with detailed covariate adjustment and outcome ascertainment. The UK Biobank is a prospective cohort study comprising a vast database of 500,000 participants recruited between 2006 and 2010. At recruitment, information on socio-demographic characteristics, lifestyle factors, anthropometry, and biological samples were collected and participants were followed from recruitment until death, loss to follow-up, or end of the study

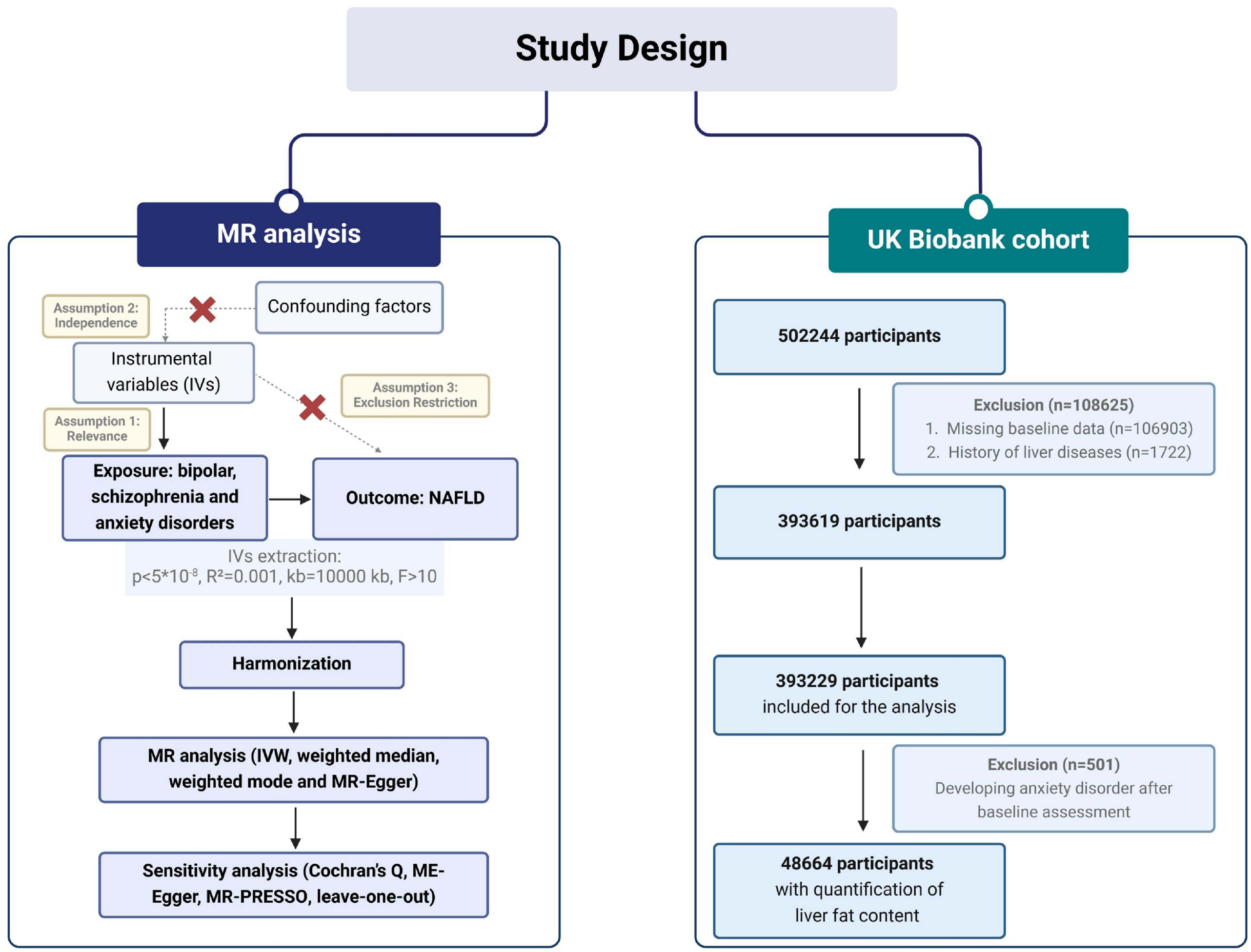

Figure 1 Flow-chart of the Mendelian randomization study and the prospective cohort study from UK Biobank. The study employed a two-phase design. Phase 1: Two-sample Mendelian randomization analysis using GWAS summary statistics to examine the causal effect of anxiety disorders (primary exposure), bipolar disorder, and schizophrenia (secondary exposures) on NAFLD risk. Phase 2: Prospective cohort validation in 393,229 UK Biobank participants, with assessment of incident NAFLD and liver fat content by MRI in a subsample of 48,664 participants.
Abbreviations: NAFLD, non-alcoholic fatty liver disease; GWAS, genome-wide association study; MR, Mendelian randomization; IVs, instrumental variables; SNPs, single nucleotide polymorphisms.

period.[22] After exclusions, 393,229 eligible participants were included for further analysis, among whom 48,664 underwent subsequent Dixon MRI examinations to obtain hepatic fat content (Figure 1). The study received review and approval from the UK Biobank (Project ID: 93118). This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Mendelian Randomization

Data Source

The GWAS data for NAFLD were derived from the FinnGen consortium (R10) (https://www.finngen.fi/fi)., featuring a sample of European ancestry with cases and controls with respective counts of 2568/409,613. NAFLD was defined based on ICD-10 codes (K76.0) and ICD-9 codes (571.8), excluding individuals with excessive alcohol consumption (>20g/day for women, >30g/day for men), viral hepatitis, or other liver diseases. As for the primary exposure, GWAS data for anxiety disorders were obtained from FinnGen R10, comprising 44,663 cases and 301,879 controls. Anxiety disorders were defined using ICD-10 codes F40.0-F40.9 (phobic anxiety disorders) and F41.0-F41.9 (other anxiety disorders). For secondary exposures, data on bipolar disorder[23] and schizophrenia[24] were derived from previously published literature, involving 20,352/31,358 and 1513/66,236 cases/controls respectively. Detailed information on sample characteristics, genotyping platforms, quality control procedures, and disease definitions for all GWAS datasets are shown in Table S1. To minimize the impact of ethnic disparities, all GWAS data utilized in this analysis were sourced exclusively from individuals of European ancestry. The GWAS summary data used are sourced from public databases, thus eliminating the need for additional ethical approval.

Selection of Instrumental Variables

The selection criteria for the instrumental variables (IVs) in this study are as follows: (1) Initially, screen for single nucleotide polymorphisms (SNPs) significantly associated with anxiety disorders (or bipolar disorder/schizophrenia), requiring a $P < 5 * 10^{-8}$ to ensure genome-wide significance;[25] (2) Select SNPs with a minor allele frequency (MAF) > 0.01 to ensure adequate statistical power; (3) Address linkage disequilibrium (LD) among SNPs by ensuring $R^2 < 0.001$ within a 10,000 kb window to ensure independence of genetic instruments;[26] (4) If an IV is not present in the outcome's summary data, a proxy SNP with high LD ($R^2 > 0.8$) is used as a substitute;[27] (5) Calculate the F-value of each SNP using the formula: $F = R^2*(N-2)/(1-R^2)$, to assess the strength of the IVs, ensuring an F- statistic > 10 to avoid weak instrument bias.[28] All selected IVs in our study had F-statistics ranging from 29.66 to 126.93, indicating strong instruments. No multiple comparison correction was applied at the SNP selection stage, as the genome-wide significance threshold ($P < 5 \times 10^{-8}$) is already stringent and widely accepted in MR studies to control for type I error.

Statistical Analysis

Inverse Variance Weighted (IVW) was utilized as the primary method to assess the causal relationship between anxiety disorders and the risk of NAFLD. We evaluate the causal effect by calculating the odds ratio (OR) and its 95% confidence interval (CI).[29] To ensure the robustness of our results, we also implemented MR-Egger,[30] weighted median,[31] and weighted mode methods.[32] The IVW method assumes all genetic variants are valid instruments and provides the most precise estimates when this assumption holds. The MR-Egger method can detect and adjust for directional pleiotropy but has lower statistical power. The weighted median method provides consistent estimates when at least 50% of the weight comes from valid instruments. The weighted mode method identifies the most common causal estimate and is robust to horizontal pleiotropy. All analyses are conducted using the R software environment (version 4.3.0), employing the "TwoSampleMR" package.[33]

Several sensitivity analyses were conducted to ensure the reliability and accuracy of the conclusions drawn from our MR analysis. Cochran's Q test was employed to assess heterogeneity among the IVs using IVW methods.[34] Additionally, MR-Egger regression was utilized to explore the potential impacts of pleiotropy on the estimation results.[30] The MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method was also applied to identify and exclude potential outliers.[35] Furthermore, leave-one-out analysis was conducted to verify the robustness and consistency of the findings by sequentially removing each SNP and recalculating the MR estimate.

UK Biobank Prospective Cohort Study

Diagnosis and Definition

Diagnoses of all diseases were based on International Classification of Diseases (ICD), Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes, listed in Table S2. The primary exposure of this study was a history of anxiety disorder, including anxiety disorder for any reason based on hospitalization records. The onset date of anxiety disorder (ICD-10 code F40.0–9 [phobic anxiety disorders] and F41.0–9 [other anxiety disorders]) was defined as the date of the first diagnosis in all available data sources. To establish temporal precedence, only participants with anxiety diagnosed before the baseline assessment were included as exposed, ensuring that anxiety preceded NAFLD onset. The primary outcome of this study was NAFLD based on hospitalization data and death registry records. NAFLD was defined using ICD-10 codes K76.0 (fatty liver, not elsewhere classified) and ICD-9 code 571.8 (other chronic nonalcoholic liver disease). Participants with a history of excessive alcohol consumption (defined as >14 units/week for women or >21 units/week for men), viral hepatitis (ICD-10 codes B15-B19), or other chronic liver diseases at baseline were excluded. Anxiety disorder was defined using ICD-10 codes F40–F41.

Participants were excluded when meeting any of the following criteria: 1) missing baseline data on key covariates (age, sex, BMI); 2) prevalent NAFLD or other history of liver diseases at baseline; 3) incident (rather than prevalent) anxiety disorder, defined as anxiety diagnosed after baseline assessment. This study is reviewed and approved by UK biobank (Project ID: 93118). According to the UK Biobank's approved access procedures and our institutional guidelines, no additional ethical approval was required for this secondary data analysis. No other ethical approval was required.

Covariates

Based on previous epidemiological studies, covariates included age (continuous variable), gender (female or male), body mass index (BMI) (continuous variable), smoking history (never, previous or current), the frequency of alcohol intake (daily/almost daily, 3–4 times a week, once/twice a week, 1–3 times a month, special occasions only and never), Townsend deprivation index (a marker of socioeconomic status, with higher values indicating greater deprivation), physical activity and the components of the metabolic syndrome (central obesity, high glycaemia/diabetes, high blood pressure/ hypertension). The level of high-density lipoprotein (HDL) cholesterol and triglycerides were also included. The definition of metabolic syndrome references previous studies.[36] Information on medication use, including anxiolytic medications (benzodiazepines and selective serotonin reuptake inhibitors [SSRIs]), was available for a subset of participants from the baseline assessment questionnaire and verbal interview. However, detailed longitudinal medication data were not available for the full cohort. Details about the source of the data were listed in Table S3.

Liver Fat Content

Liver fat content was obtained using the method described in our previous study.[37] Briefly, automatic segmentation of the liver was first performed done by a deep learning-based image segmentation framework (nnUNet), and then the fat content of the liver was calculated from the Dixon MRI images of fat and water sequences. The nnUNet algorithm provides automated, reproducible quantification of hepatic fat fraction with high accuracy (Dice coefficient >0.95 for liver segmentation), reducing potential bias from manual delineation.

Statistical Analysis

Continuous variables were expressed as median (interquartile range) [M (P25, P75)] and compared using the Mann–Whitney *U*-test between groups. Categorical variables were presented as number (percentage) and analyzed using the chi-square test, with Fisher's exact test applied when necessary. The relationship between anxiety and NAFLD was investigated using Cox proportional hazards models, with hazard ratios (HR) calculated, adjusted for covariates in a stepwise manner. Model 1 was adjusted for age and sex; Model 2 additionally adjusted for BMI, smoking, and alcohol intake; Model 3 (fully adjusted model) further adjusted for Townsend deprivation index, physical activity, and metabolic syndrome components (central obesity, high glycaemia/diabetes, hypertension, HDL cholesterol, and triglycerides). The proportional hazards assumption was tested using Schoenfeld residuals. For survival analysis, cumulative risks were estimated using the Kaplan-Meier method and compared using the Log rank test. The impact of anxiety on hepatic fat content was analyzed using multiple linear regression. All analyses were performed using R software version 4.3.2. A two-sided P less than 0.05 was considered statistically significant.

Results

Genetic Liabilities Between Mental Disorders and NAFLD by MR Analysis

We first explored the causal potential relationship between anxiety disorders and the risk of NAFLD using MR analysis. A total of 116 IVs related to anxiety disorders, bipolar disorder, and schizophrenia were selected for further analysis, including 13 IVs for anxiety disorders, 16 IVs for bipolar disorder, and 87 IVs for schizophrenia respectively. All of these IVs had F-statistics greater than 10 (ranging from 29.66 to 126.93), ensuring the reliability of our analysis. For full details on the IVs, including any missing data, the use of proxy SNPs, and exclusions, please refer to Table S4.

IVW results revealed a suggestive genetically predicted causal association between anxiety disorders and NAFLD (OR = 1.73, 95% CI: 1.12–2.67, P=0.013), suggesting that anxiety disorders might be a risk factor for NAFLD. Additionally, the weighted median method supported the IVW findings (OR = 1.88, 95% CI: 1.11–3.17, P=0.018). The MR-Egger method

Table 1 Mendelian Randomization Estimates of the Causal Effect of Anxiety Disorders, Schizophrenia, and Bipolar Disorder on Non-Alcoholic Fatty Liver Disease (NAFLD) Risk

Exposure	Outcome	Significant of SNP	N.SNPs	Methods	OR (95% CI)	P
Anxiety disorders	Nonalcoholic fatty liver disease	$<5*10^{-8}$	11	Inverse variance weighted	1.73 (1.12–2.67)	0.013
Anxiety disorders	Nonalcoholic fatty liver disease	$<5*10^{-8}$	11	MR Egger	0.35 (0.09–1.42)	0.176
Anxiety disorders	Nonalcoholic fatty liver disease	$<5*10^{-8}$	11	Weighted median	1.88 (1.11–3.17)	0.018
Anxiety disorders	Nonalcoholic fatty liver disease	$<5*10^{-8}$	11	Weighted mode	2.03 (0.87–4.71)	0.131
Schizophrenia	Nonalcoholic fatty liver disease	$<5*10^{-8}$	79	Inverse variance weighted	0.99 (0.91–1.08)	0.834
Schizophrenia	Nonalcoholic fatty liver disease	$<5*10^{-8}$	79	MR Egger	1.17 (0.85–1.62)	0.345
Schizophrenia	Nonalcoholic fatty liver disease	$<5*10^{-8}$	79	Weighted median	1.01 (0.90–1.15)	0.819
Schizophrenia	Nonalcoholic fatty liver disease	$<5*10^{-8}$	79	Weighted mode	0.98 (0.74–1.32)	0.918
Bipolar disorder	Nonalcoholic fatty liver disease	$<5*10^{-8}$	12	Inverse variance weighted	1.15 (0.93–1.42)	0.19
Bipolar disorder	Nonalcoholic fatty liver disease	$<5*10^{-8}$	12	MR Egger	2.02 (0.57–7.19)	0.305
Bipolar disorder	Nonalcoholic fatty liver disease	$<5*10^{-8}$	12	Weighted median	1.16 (0.88–1.54)	0.287
Bipolar disorder	Nonalcoholic fatty liver disease	$<5*10^{-8}$	12	Weighted mode	1.18 (0.78–1.77)	0.455

Notes: The inverse variance weighted (IVW) method was used as the primary analysis. P < 0.05 was considered statistically significant.
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

yielded a non-significant result (OR = 0.35, 95% CI: 0.09–1.42, P=0.176), and the weighted mode method also showed a non-significant trend (OR = 2.03, 95% CI: 0.87–4.71, P=0.131) (Table 1). Scatter plots and forest plots indicated the effects of SNPs, as shown in Figure 2A and B. In contrast, schizophrenia or (OR = 0.99, P=0.834) and bipolar disorder (OR = 1.15, P=0.19) showed no significant associations with NAFLD (Table 1, Figure S1 and 2).

Sensitivity analyses, including Cochran's Q test, MR-PRESSO, and leave-one-out analysis, indicated no significant heterogeneity or outlier effects, supporting the robustness of the primary finding (Figure 2, Tables S5 and S6). In contrast, no significant associations were found for genetic liability to schizophrenia (IVW OR = 0.99, 95% CI: 0.91–1.08) or bipolar disorder (IVW OR = 1.15, 95% CI: 0.93–1.42) with NAFLD risk (Table 1, Figures S1 and S2).

Prospective Cohort Study from UK Biobank

The analysis included 393,229 participants from the UK Biobank, of whom 21,065 (5.4%) had a diagnosis of anxiety disorder at baseline. Participants with anxiety were more likely to be female, have a higher BMI, and exhibit a greater prevalence of metabolic abnormalities compared to those without anxiety (Table S7).

Over a median follow-up of 12.6 years, incident NAFLD was significantly more common in participants with baseline anxiety disorder (2.5%) compared to those without (1.2%; P < 0.001). In multivariable Cox proportional hazards models, baseline anxiety was associated with a 63% higher risk of developing NAFLD (hazard ratio [HR] = 1.63, 95% CI: 1.49–1.79, P < 0.001) after adjusting for demographic, lifestyle, and metabolic factors (Figure 3A and B). This association remained stable in sensitivity analyses excluding participants with less than one year of follow-up (Table S8). Furthermore, in a sub-cohort of 48,664 participants with follow-up magnetic resonance imaging, baseline anxiety was associated with significantly higher liver fat content, independent of sex and other covariates ($\beta = 0.004$, P < 0.001) (Figure 3C and Table 2).

Discussion

This study is the first to demonstrate suggestive evidence of a causal effect of anxiety disorders on NAFLD development, specifically on the fat content in the liver, using complementary genetic and prospective cohort approaches. It complements and refines the understanding of the complex, bidirectional relationships between NAFLD and mental disorders, advocating for a shift from a specialized clinical focus to a comprehensive community-level strategy for addressing NCDs.

The intricate communication between the brain and the gastrointestinal tract relies on a complex system that includes the vagus nerve, as well as sympathetic, endocrine, immune, and humoral connections.[38] Recently, the liver has gained attention for its role in the liver-brain axis, which interacts closely with the central nervous system through the autonomic nervous system. The "liver-to-brain" direction has been well-documented. Patients with NAFLD are more likely to

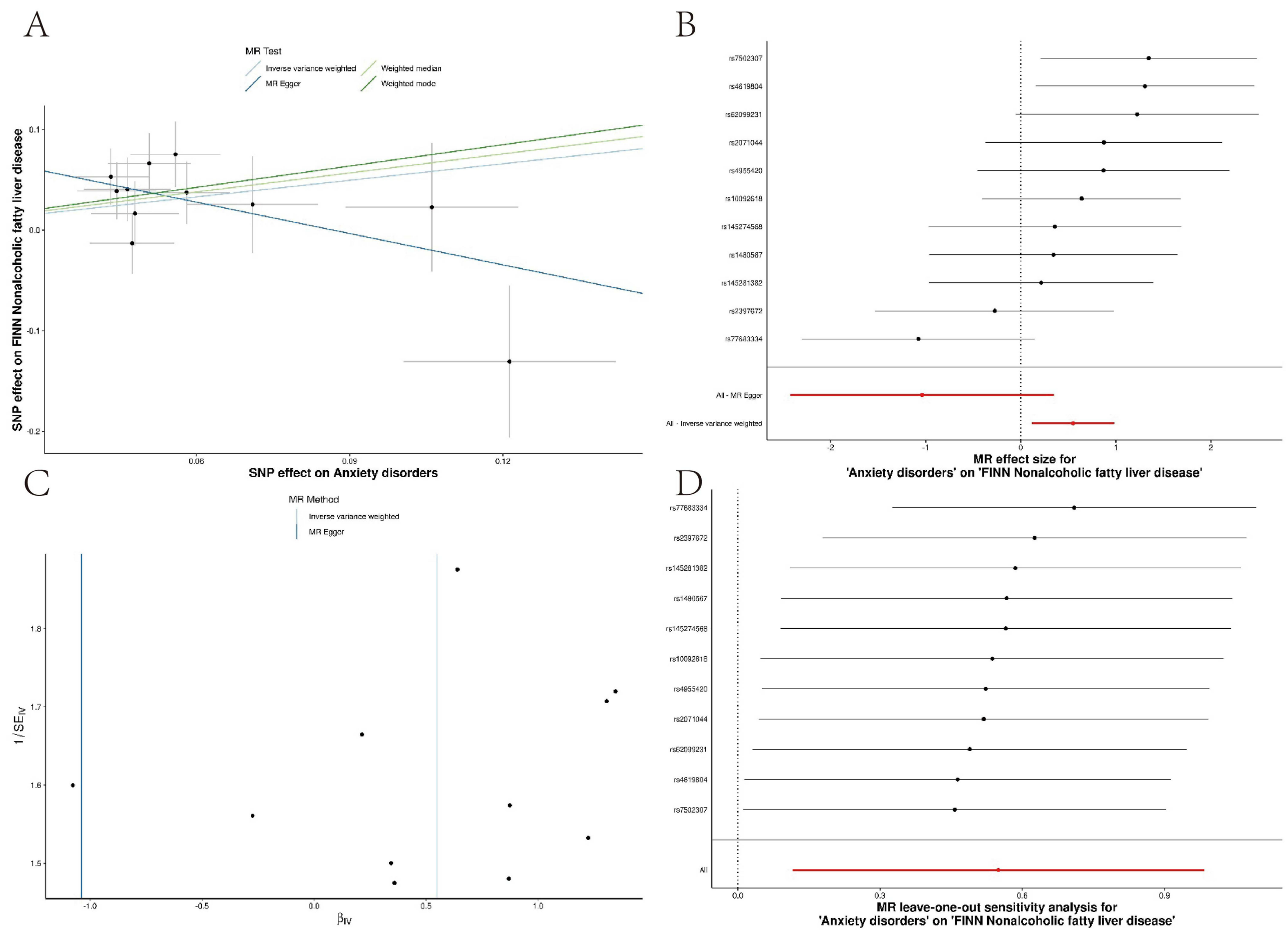

Figure 2 The causal effect of anxiety disorder on NAFLD using MR analysis. (**A**) Scatter plot of the MR analysis of anxiety disorders on NAFLD, showing the SNP-exposure associations (x-axis: effect of SNP on anxiety disorders, measured in log odds ratio) plotted against SNP-outcome associations (y-axis: effect of SNP on NAFLD, measured in log odds ratio). Each point represents a single SNP. Lines represent the causal estimates from different MR methods: IVW (inverse variance weighted, red), MR-Egger (blue), weighted median (green), and weighted mode (Orange). Sample sizes: anxiety disorders GWAS n=346,542 (44,663 cases); NAFLD GWAS n=412,181 (2568 cases). (**B**) Forest plot showing MR effect size and 95% CI for anxiety disorders on NAFLD**, displaying the individual SNP effects and combined estimates from different MR methods. The vertical dashed line indicates the null effect (OR=1.0). (**C**) Funnel plot of the MR analysis of anxiety disorders on NAFLD**, used to assess potential asymmetry suggestive of pleiotropy. Each point represents a single SNP, with the x-axis showing the individual SNP MR estimates and the y-axis showing the inverse of the standard error (precision). The vertical line represents the combined IVW estimate. (**D**) Leave-one-out IVW regression analysis of anxiety disorders on NAFLD**, showing the MR estimate when each SNP is sequentially removed. The consistent estimates across all iterations indicate that no single SNP disproportionately influences the overall result, confirming the robustness of the findings.

Abbreviations: CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

exhibit autonomic dysfunction,[39,40] and extensive research has demonstrated that even early-stage NAFLD can negatively impact cognitive performance, cerebral function, and mental health, with cross-sectional studies reporting 20–40% prevalence of anxiety and depression among NAFLD patients.[41] A recent UK Biobank study revealed that liver fibrosis was negatively correlated with cognitive function, with inflammation playing a pivotal mediating role.[42] However, the reverse "mind-to-liver" pathway has received considerably less attention. Our study provides novel evidence for this direction, demonstrating that pre-existing anxiety disorders may causally contribute to NAFLD development. The concordance between genetic prediction and prospective observation substantially strengthens the evidence for a causal relationship. Interestingly, we did not observe significant associations between schizophrenia or bipolar disorder and NAFLD in our MR analyses. These null findings may reflect several factors. First, statistical power may be limited, as the GWAS for schizophrenia and bipolar disorder had smaller case numbers compared to anxiety disorders. Second, different psychiatric disorders may influence liver metabolism through distinct pathophysiological mechanisms. Anxiety disorders are characterized by chronic sympathetic overactivity and HPA axis activation that directly impact hepatic metabolism,[43,44] whereas schizophrenia and bipolar disorder have more complex neurobiological underpinnings. Third,

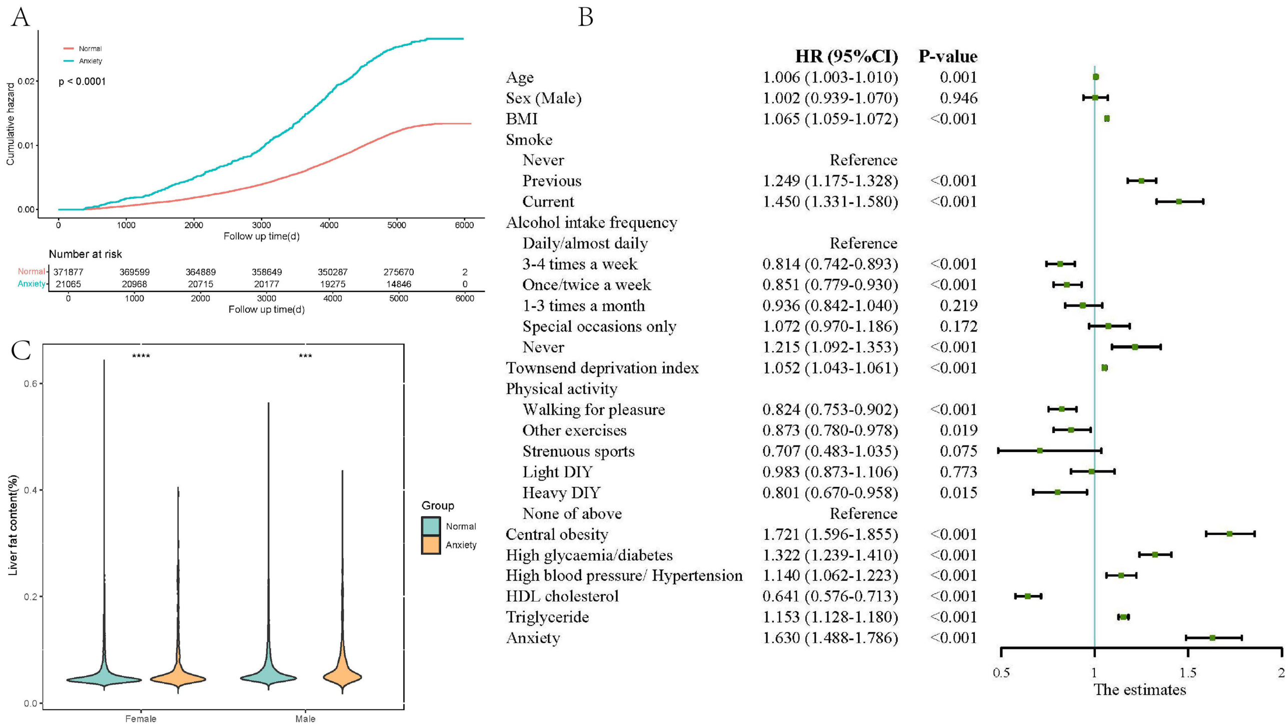

Figure 3 Association between anxiety disorder on NAFLD using UK Biobank cohort. (**A**) Kaplan-Meier estimates of cumulative incidence of NAFLD in participants without anxiety disorders (blue line) versus those with anxiety disorders (red line). Numbers at risk are displayed below the plot at yearly intervals. Log rank test P < 0.001, indicating significantly higher cumulative risk in the anxiety group. Sample size: n=393,229 (21,065 with anxiety disorders, 372,164 without anxiety disorders). (**B**) Cox regression model of the association between anxiety disorders and incident NAFLD. Data presented as hazard ratio (95% CI). Model 1: adjusted for age and sex; Model 2: adjusted for Model 1 covariates plus BMI, smoking, and alcohol intake frequency; Model 3 (fully adjusted): adjusted for Model 2 covariates plus Townsend deprivation index, physical activity, central obesity, high glycaemia/diabetes, high blood pressure/hypertension, HDL cholesterol, and triglyceride. Sample size: n=393,229. Follow-up duration: median 12.6 years (IQR: 11.8–13.4 years). (**C**) Distribution of liver fat content grouped by anxiety disorder status and sex, measured by Dixon MRI. Box plots show median (center line), interquartile range (box), and 1.5×IQR (whiskers). Individual points represent outliers. Sample size: n=48,664 (males: n=22,358; females: n=26,306). Statistical comparisons performed using Mann–Whitney *U*-test. ***P < 0.001, ****P < 0.0001.

Note: Symbols indicate statistical significance levels: ***P < 0.001, ****P < 0.0001.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; IQR, interquartile range; MRI, magnetic resonance imaging.

antipsychotic medications commonly used in these conditions have well-documented metabolic side effects, but these medication effects would not be captured in genetic instruments. The specificity of the anxiety-NAFLD association underscores distinct mechanistic pathways and warrants further investigation.

The multifaceted potential link between anxiety disorders and the increased incidence of NAFLD observed in our study warrants exploration of several plausible mechanisms beyond the autonomic nervous system. From a metabolic perspective, chronic stress associated with anxiety can trigger the release of cortisol, a hormone known to promote visceral fat accumulation and insulin resistance, both pivotal in the pathogenesis of NAFLD.[45–47] Elevated cortisol levels can lead to hepatic lipid accumulation by increasing lipolysis in adipose tissue and enhancing hepatic glucose production, thereby exacerbating hepatic steatosis.[48] In our cohort, participants with anxiety had significantly higher rates of central obesity, diabetes, and hypertension, consistent with chronic HPA axis activation. Notably, the hazard ratio for NAFLD was attenuated when adjusting for these metabolic factors, suggesting partial mediation by HPA axis-related metabolic disturbances. However, the persistent significant association in the fully adjusted model indicates that metabolic factors alone do not fully account for the anxiety-NAFLD relationship. Furthermore, individuals with anxiety disorders often adopt unhealthy coping behaviors that predispose them to NAFLD, such as overeating, particularly high-calorie, high-fat foods, which contribute to obesity and subsequent hepatic fat deposition.[49] Moreover, sleep disturbances, common among those with anxiety, can disrupt circadian rhythms and metabolic homeostasis, further contributing to NAFLD development.[50] In our study, participants with anxiety were more likely to be current smokers, had higher BMI, and reported lower levels of physical activity. When we sequentially adjusted for these behavioral factors, the hazard ratio for

Table 2 Multiple Linear Regression Analysis of the Association Between Anxiety Disorders and Liver Fat Content

	Estimate	Std.Error	t value	Pr(>|t|)
(Intercept)	0.032	0.003	11.892	<0.001
Age	0	0	−12.024	<0.001
Sex (Male)	0.002	0	4.619	<0.001
BMI	0.002	0	31.737	<0.001
Smoke				
Never	Reference			
Previous	0	0	1.079	0.281
Current	0.005	0.001	6.75	<0.001
Alcohol intake frequency				
Daily/almost daily	Reference			
3–4 times a week	−0.003	0.001	−4.982	<0.001
Once/twice a week	−0.003	0.001	−5.892	<0.001
1–3 times a month	−0.004	0.001	−5.047	<0.001
Special occasions only	0	0.001	0.098	0.922
Never	0	0.001	−0.194	0.846
Townsend deprivation index	0	0	1.563	0.118
Physical activity	−0.007	0.001	−6.45	<0.001
Walking for pleasure	−0.006	0.001	−5.716	<0.001
Other exercises	−0.006	0.002	−3.029	0.002
Strenuous sports	−0.003	0.001	−2.271	0.023
Light DIY	−0.004	0.002	−2.667	0.008
Heavy DIY	−0.003	0.001	−4.982	<0.001
None of above	Reference			
Central obesity	0.009	0.001	14.647	<0.001
High glycaemia/diabetes	0.005	0.001	9.006	<0.001
High blood pressure/ Hypertension	0.003	0	6.412	<0.001
HDL cholesterol	−0.007	0.001	−11.205	<0.001
Triglyceride	0.005	0	23.313	<0.001
Anxiety disorders	0.004	0.001	4.15	**<0.001**

Note: The model was adjusted for all listed covariates. Continuous variables (age, BMI, Townsend deprivation index, HDL cholesterol, triglyceride) were centered at their means. The estimate for anxiety disorders indicates that individuals with anxiety had, on average, 0.4% higher liver fat fraction compared to those without anxiety, after adjusting for all other variables. Multiple R2: 0.1407; Adjusted R2: 0.1403; p-value: < 0.001.
Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; DIY, do-it-yourself.

NAFLD was substantially attenuated by approximately 26%, indicating that behavioral and lifestyle factors mediate a significant portion of the anxiety-NAFLD relationship. However, the persistent significant association in Model 3 after full adjustment suggests that biological mechanisms contribute independently beyond lifestyle pathways. Lastly, pharmacological treatments for anxiety disorders, such as certain antidepressants, have been associated with weight gain and metabolic disturbances.[51] Although these medications provide relief from anxiety symptoms, they may inadvertently increase the risk of NAFLD by promoting adverse metabolic effects.[52] In our cohort analyses, the association between baseline anxiety and incident NAFLD remained after adjustment for adiposity, glycaemia, blood pressure, lipids, lifestyle, and deprivation, and anxiety was also associated with higher liver fat content, which is consistent with, but does not prove, a pathway that may be partly independent of measured metabolic risk factors. We did not conduct formal mediation analyses; therefore, the extent to which adiposity, glycaemic traits, sleep, or inflammation mediate the link between anxiety and NAFLD requires further longitudinal and multivariable MR work.

By understanding the underlying mechanisms and clinical implications, several clinical implications emerge. While dietary changes and increased physical activity can prevent disease progression, patient adherence to these lifestyle changes is often poor.[53] Nearly 40% of NAFLD patients who undergo liver transplantation show signs of disease recurrence within five years.[54] These findings highlight the need to examine psychological barriers to diet and exercise to develop more effective treatments and prevent post-transplantation recurrence. Mental health significantly influences attitudes towards diet and exercise. Personality disorders, for example, often negatively impact treatment outcomes.[55] It is crucial to investigate whether anxiety affects the success of weight-loss programs and if these programs need adaptation for anxiety. Addressing underlying anxiety before treating NAFLD may be more effective, as mental health issues can hinder necessary behavioral changes. We suggest that NAFLD patients be screened for anxiety and, if identified, receive appropriate mental health interventions before implementing diet and exercise management strategies.

Recognizing anxiety disorders as a potential risk factor for NAFLD has several important clinical implications. Patients with anxiety disorders may need tailored screening protocols for NAFLD due to their elevated risk profile. Our findings suggest that individuals with anxiety have a 1.63-fold increased risk of developing NAFLD, comparable to other established risk factors. Clinicians managing patients with chronic anxiety disorders should consider periodic assessment of liver function tests and, when appropriate, non-invasive imaging modalities to detect early hepatic steatosis. Lifestyle modifications, such as dietary adjustments and physical activity, are crucial for managing both conditions. A diet rich in omega-3 fatty acids and antioxidants can benefit patients with anxiety by alleviating symptoms and reducing the risk of NAFLD.[56] Pharmacotherapy for anxiety disorders should be carefully selected to minimize metabolic side effects, prioritizing medications with a lower propensity for weight gain and metabolic disruption.[57] Psychological interventions, like cognitive-behavioral therapy, which do not carry metabolic risks, may be recommended as a first-line treatment.[58]

Strengths of our study include the innovative application of MR to explore the causal relationship between anxiety disorders and NAFLD, supported by a large prospective cohort data from UK Biobank for empirical validation. The integration of MR and prospective cohort analyses provides complementary evidence that strengthens causal inference: MR leverages genetic randomization to minimize confounding and eliminate reverse causation, while the UK Biobank cohort offers real-world validation with detailed covariate adjustment and outcome ascertainment. We applied stringent criteria for selecting IVs and conducted extensive sensitivity analyses to enhance the robustness of our findings. Notably, the cohort study provided not only incidence rates but also quantification of liver fat content using automated deep learning-based segmentation (nnUNet), offering, a comprehensive and objective assessment of NAFLD severity. The large sample size and the availability of detailed covariate data allowed for comprehensive adjustment for potential confounders.

However, our investigation has several important limitations. Firstly, a limitation is our MR analysis's reliance on GWAS data from FinnGen for both NAFLD and anxiety disorders. This single-source approach for the anxiety-NAFLD association may introduce population-specific biases or sample overlap, potentially affecting the generalizability of our findings. Although we used different analytical methods and sensitivity analyses to assess robustness, independent replication in diverse datasets is needed to confirm our findings. Secondly, despite rigorous adjustment for confounding factors in the UK Biobank cohort, residual confounding cannot be entirely ruled out. Moreover, the homogeneity of the study populations, predominantly of European ancestry in both MR and prospective studies, limits the generalizability of our findings to other ethnic groups. Third, NAFLD ascertainment in the cohort relied on hospital admission coding and may preferentially capture more severe disease; however, MRI-based liver fat analyses support the main findings on a continuous scale. Fourth, psychotropic medication data were not available in GWAS and were incompletely captured in the cohort, precluding formal adjustment; medications could confound or mediate the association and merit future evaluation. Fifth, although MR-Egger intercepts did not materially deviate from zero, unmeasured horizontal pleiotropy cannot be fully excluded. Sixth, we did not perform multivariable MR, bidirectional MR, or formal mediation analyses; these should be prioritized in future work.

In conclusion, our study provides converging evidence suggesting that anxiety disorders may be causally associated with increased NAFLD risk. These findings highlight the "mind-to-liver" pathway in the bidirectional liver-brain axis and support integrating mental health care with metabolic disease prevention. Further research is needed to elucidate underlying mechanisms, replicate findings in diverse populations, and develop integrated clinical pathways.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study involved secondary analyses of de-identified, publicly available summary-level GWAS and UK Biobank data. According to the Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects (issued by the National Health Commission of China, effective February 18, 2023), Article 32, Items 1 and 2, research using legally and publicly available human data, or data in which individual identities cannot be ascertained, is exempt from ethical review. Therefore, this study was exempt from institutional ethics approval.

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Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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