BMC Gastroenterology

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Causal relationships between neuropsychiatric disorders and nonalcoholic fatty liver disease: A bidirectional Mendelian randomization study

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Abstract

Background Increasing evidences suggest that nonalcoholic fatty liver disease (NAFLD) is associated with neuropsychiatric disorders. Nevertheless, whether there were causal associations between them remained vague. A causal association between neuropsychiatric disorders and NAFLD was investigated in this study.

Methods We assessed the published genome-wide association study summary statistics for NAFLD, seven mental disorder-related diseases and six central nervous system dysfunction-related diseases. The causal relationships were first assessed using two-sample and multivariable Mendelian randomization (MR). Then, sensitivity analyses were performed, followed by a reverse MR analysis to determine whether reverse causality is possible. Finally, we performed replication analyses and combined the findings from the above studies.

Results Our meta-analysis results showed NAFLD significantly increased the risk of anxiety disorders (OR = 1.016, 95% CI = 1.010–1.021, *P* value < 0.0001). In addition, major depressive disorder was the potential risk factor for NAFLD (OR = 1.233, 95% CI = 1.063–1.430, *P* value = 0.006). Multivariable MR analysis showed that the causal effect of major depressive disorder on NAFLD remained significant after considering body mass index, but the association disappeared after adjusting for the effect of waist circumference. Furthermore, other neuropsychiatric disorders and NAFLD were not found to be causally related.

Conclusions These results implied causal relationships of NAFLD with anxiety disorders and Major Depressive Disorder. This study highlighted the need to recognize and understand the connection between neuropsychiatric disorders and NAFLD to prevent the development of related diseases.

Keywords Nonalcoholic fatty liver disease, Major depressive disorder; Anxiety disorders, Mendelian randomization

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Introduction

Nonalcoholic fatty liver disease (NAFLD), known as metabolic dysfunction-associated steatotic liver disease (MASLD) [1], affects approximately one in four adults worldwide [2]. And because of its high prevalence, it is currently the liver-related disease with the greatest increase in mortality worldwide [3]. It is related to a higher risk of complications such as end-stage liver disease, hepatocellular carcinoma and cirrhosis in patients with NAFLD [4]. At the same time, mental disorders also carry a high risk of mortality and may worsen over time and are estimated to account for nearly 21.2–32.4% of years lived with disability globally [5]. Related studies have shown that, globally, the greatest risk factor for years lived with disability is neurological and mental health disorders [6]. Therefore, the prevention and treatment of neuropsychiatric disorders and NAFLD are substantial problems warranting attention in clinical work.

Related studies have also suggested that NAFLD can directly affect brain structure through the liver-brain axis [7, 8]. NAFLD has a common pathogenesis with neurological and psychiatric diseases, which are jointly caused by inflammation and oxidative stress pathways [9, 10]. Hence, it is necessary to recognize the interaction between NAFLD and neuropsychiatric disorders. Researchers have discovered a potential connection between them in recent years. In terms of central nervous system disorders, dementia is a neurodegenerative disorder of cognitive dysfunction [11], and Alzheimer's disease is the most common form of dementia [12]. NAFLD contains toxic components that cannot be cleared by the liver, and these may further affect brain function [13]. Several studies have already associated NAFLD with cognitive dysfunction [14, 15]. In terms of mental disorders, a 3-year prospective study hinted that metabolic liver disease including NAFLD is more prevalent in schizophrenia patients [16]; a retrospective cross-sectional study showed that NAFLD patients often have depression and anxiety disorders [17]. However, these associations between NAFLD and neuropsychiatric disorders may in part be affected by confounding or selection bias inherent in conventional observational researches. Furthermore, whether NAFLD is causal or reverse causal in neuropsychiatric disorders remains controversial. Therefore, any potential causal relationship still requires further investigation.

In this context, Mendelian randomization (MR) is a statistical method for assessing exposure factors' causal relationship with disease outcomes [18]. Because genetic variation is completely random during gamete formation and genotypes do not change with disease progression, in MR analysis, the measure of genetic variation, such as a single nucleotide polymorphism (SNP) can be used as an instrument of exposure (IV) or a modifiable risk factor for diseases. Since genetic variation is relatively less susceptible to measurement errors and biases, causal inferences about exposure-outcomes can be strengthened. As a result, causal relationships are explored extensively by MR. Here, we selected seven mental disorder-related diseases and six central nervous system dysfunction-related diseases, performing Two-sample MR to comprehensively assess the association of the risk of NAFLD with those diseases in discovery stage. Multivariate MR was followed immediately to adjust for the potential effects of body mass index (BMI) and waist circumference on the causal relationships. Finally, we performed replication analyses and combined the findings from the above MR studies. In order to examine the inverse effect of NAFLD on neuropsychiatric disorders, we performed a reverse MR analysis (Fig. 1). This study was performed in accordance with the STROBE-MR guidelines (**Additional file 1: Table S1**).

Methods

Data sources

The data source for our analysis was primarily European populations, which avoided potential bias due to population stratification (Additional file 1: Table S2). Because the data used in the study were published, no ethical approval or informed consent was required. In discovery phase, genetic associations for NAFLD were examined using GWAS, involving 8,434 cases and 770,180 controls [19]. Obtaining a replication phase with data from several leading European tertiary liver centers, which involved 1,483 NAFLD patients and 17,781 control individuals [20]. Schizophrenia is a highly heritable disease with GWAS analysis of 33,640 patients and 43,456 control individuals from the Psychiatric Genomics Consortium (PGC) [21]. Data on bipolar disorder, characterized by severe swings in mood and behavior, were obtained from a meta-analysis of 41,917 patients and 371,549 control individuals [22]. Posttraumatic stress disorder is a common disease in a stressful state after exposure to extreme, life-threatening trauma, and the GWAS data used for its analysis came from the PGC analysis of 23,212 patients and 151,447 control individuals [23]. GWAS data for Major Depressive Disorder (MDD) were also derived from the UK Biobank and PGC (excluding 23andme) analysis of 170,756 patients and 329,443 control individuals [24]. In the International Parkinson's Disease Genomics Consortium, we retrieved a GWAS date included 33,674 patients and 449,056 control individuals [25]. Genetic variants in Alzheimer's disease (AD) were acquired from a large GWAS included 39,106 patients of European ancestry and 46,828 control individuals of European ancestry [26]. Neurodegenerative diseases such

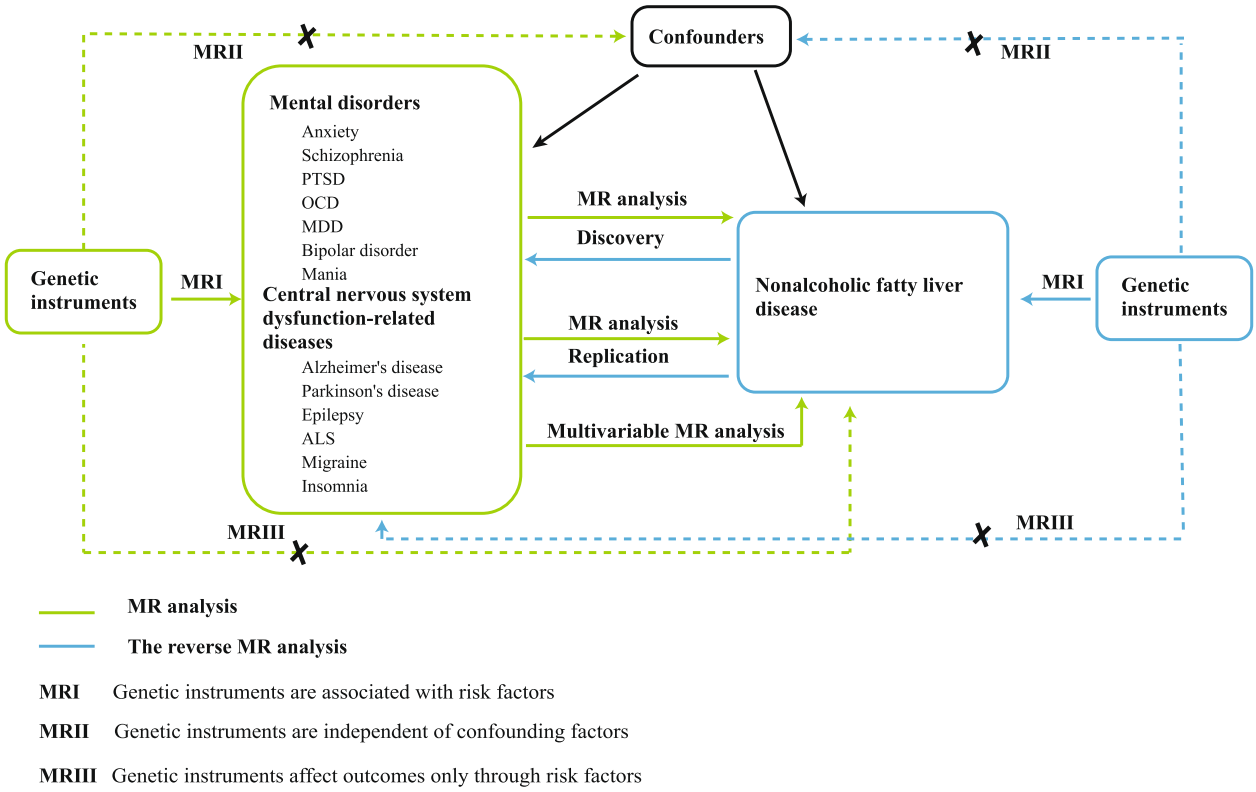

Fig. 1 Design of the bidirectional two-sample Mendelian randomization study. The three core assumptions were as follows: (MRI) relevance assumption; (MRII) independence assumption; and (MRIII) exclusion restriction. PTSD, posttraumatic stress disorder; OCD, obsessive–compulsive disorder; MDD, Major Depressive Disorder; ALS, amyotrophic lateral sclerosis

as amyotrophic lateral sclerosis can be fatal, and GWAS data were obtained by analyzing 27,205 patients and 110,881 control individuals [27]. The data we selected for epilepsy included 4,382 cases and 453,928 controls [28]. Data on migraine used for analysis included 1,488 cases and 454,860 controls [29]. The study provided us with analytical data on insomnia, encompassing 345,022 cases and 108,357 controls [30]. Mania is clinically manifested by increased speech, disturbed thinking, and elevated mood [31]. Genetic associations for anxiety disorders and mania were obtained by analyzing 29,129 patients and 6,455 control individuals and 7,988 cases and 18,667 controls from UK Biobank (http://www.nealelab.is/uk-biobank), respectively. Obsessive–compulsive disorder is characterized by repetitive behaviors that individuals feel compelled to engage in due to unwanted personal thoughts [32], the GWAS from the FinnGen Biobank were analyzed, including 1,059 patients and 198,110 control individuals (https://r9.finngen.fi/).

Selection of instrumental variables

In order to satisfy the three core MR assumptions, we performed strict filtering steps to control the quality of genetic IVs. 1) We extracted SNPs strongly associated with neuropsychiatric disorders from published GWAS databases and took $P < 5 \times 10^{-8}$ as the initial filter criteria. However, except for AD, schizophrenia, bipolar disorder, MDD, amyotrophic lateral sclerosis, Parkinson's disease and insomnia, SNPs were absent or too few with P values less than 5×10^{-8}. Therefore, to select eligible instrumental variables, we expanded the threshold to $< 5 \times 10^{-6}$. SNPs strongly associated with NAFLD for reverse MR analysis are displayed in Additional file 1: Table S3 and S4. 2) SNPs in linkage disequilibrium (LD) were excluded from exposure experiments to ensure the instruments were independent ($r^2 < 0.001$, aggregation window = 10,000 kb). 3) To maintain consistency of the SNPs serving as IVs across the different analyses, we only used variants available for all traits examined and did not replace missing variants with proxies. 4) The F statistic was applied to quantify the intensity of the genetic tool, whose calculation of $(\text{beta/se})^2$ greater than 10 was regarded sufficient [33]. Finally, exposure-associated SNPs were extracted from each result.

MR analysis

In the current study, we applied inverse variance weighting (IVW), the weighted median method and the

MR–Egger method for analysis, and the multiplicative random-effects IVW method was the primary method, followed by sensitivity analysis. In IVW, the Wald estimates associated with the individual SNPs are combined to estimate the causal relationship of exposure on the outcome. It is a weighted regression that transforms the MR estimates into SNP-outcome effects on SNP-exposure effects [34]. MR–Egger is found on the InSIDE assumption, and the outcome coefficients are linearly weighted regressions on the exposure coefficients, which can also detect small study biases [35]. We can calculate the weighted median estimate of Wald ratio by using the weighted median method that does not require the InSIDE assumption. The analysis of invalid instrumental variables provides 50% of the information, but it can also provide the outcome of causal effect detection [36]. If the results of the IVW method are significant ($P<0.05$), even if the results of other methods are not significant, on the basis of no pleiotropic effects and heterogeneity, as long as there are same trends in the beta values of other methods, it is also acceptable and considered a positive result [37]. Multivariable MR (MVMR) can discern the effects of various interrelated factors, suggesting that these factors operate in concert. Consequently, each association identified by MVMR is regarded as a "direct" or "independent" causal link [38]. Thus, we conducted MVMR analysis to adjust for the genetic association of the instruments with BMI and waist circumference.

Sensitivity analysis

MR–Egger regression was performed to assess whether there was a potential pleiotropic effect, and the intercept item can assess the horizontal pleiotropic effect of its direction; $P<0.05$ indicates that there is a potential horizontal pleiotropic effect [39]. The MR pleiotropic residuals and outliers (MR-PRESSO) global test can also be used for horizontal pleiotropic detection. $P>0.05$ indicates that there is no level pleiotropy, and pleiotropy refers to genetic variation, which may impact the causal effects [40]. The MR-PRESSO outlier test corrects for pleiotropy by removing outliers, while the outlier test involves at least 50% valid variables, has balanced pleiotropy, and depends on instrument exposure and multiple effects [41]. Heterogeneity was analyzed by applying Rucker's Q test (MR–Egger regression) and Cochran's Q test (MR-IVW), mainly Cochran's Q test, with $P<0.05$. Moreover, I^2 was used to quantify heterogeneity (take 0 when I^2 is negative). Multiplicity or other causes of heterogeneity were mainly explored with the Q test [42]. Then, the MR-robust adjusted spectral score (MR-RAPS) method was applied to further verify the causality (estimated causal effect) and detect the stability of the analysis, that is, the presence of pleiotropic effects (estimated overdispersion variance trend toward 0 or a P value >0.05 indicates the absence of horizontal pleiotropic effects) [43]. MR-RAPS can provide unbiased, as well as reliable results, even with weak instrumental variables [44]. What's more, to ensure that the results were robust and consistent, we used leave-one-out analysis [34]. Applying IVW (fixed-effects) to further verify the solidity of the results. In the visual analysis, heterogeneity can be represented by scatter plots, and horizontal pleiotropic effects can be represented by forest plots and funnel plots. Finally, the fixed-effect meta-analysis was performed to assess the integrated causality between NAFLD and neuropsychiatric disorders from MR results of the discovery and replication phases [45, 46]. We chose the results of the meta-analysis as the final causality [47].

Statistical analysis

The association between genetically predicted neuropsychiatric disorders and NAFLD was signaled as the odds ratio (OR) and its 95% confidence interval (95%CI). MR analyses were conducted using R (version 4.3.1) and the "TwoSampleMR", "MR-PRESSO", "MVMR"and "MR.RAPS" software packages. Bonferroni correction was applying to adjust the data because of multiple comparisons. When the observed $P<4.17\times10^{-3}$ (0.05/12), associations were deemed statistically significant evidence of causality. P values between 4.17×10^{-3} and 0.05 were considered suggestive evidence of potential causality.

Result

Instrumental variable selection

In the discovery stage of mental disorders, we extracted 9 SNPs for anxiety disorders, 75 for schizophrenia, 17 for posttraumatic stress disorder, 10 SNPs for obsessive–compulsive disorder, 50 for MDD, 44 SNPs for bipolar disorder, and 13 for mania. For central nervous system disorders, 50 SNPs for AD, 23 SNPs for Parkinson's disease, 11 for epilepsy, 11 SNPs for amyotrophic lateral sclerosis, 14 for migraine and 43 for insomnia were extracted. There was no weak instrumental variable based on the F-statistics, which were all greater than 10. In the replication phase, the same manipulation was performed and sufficiently powerful instrumental variables were extracted. Next, so as to analyze the inverse effect of NAFLD (exposure) on neuropsychiatric disorders (outcome), we included 4 SNPs with a median F value of 59.450 (discovery) and 4 SNPs with a median F value of 49.071 (replication), indicating sufficient heritability. Detailed information on the instrumental variables, such as beta, SE, and P values, can be found in Additional file 1: Tables S3 and S4.

Discovery results

Genetics predict neuropsychiatric disorders on NAFLD

A potential positive causal effect of MDD on NAFLD was demonstrated (OR = 1.210, 95% CI = 1.031–1.420, *P* value = 0.020) (Table 1). the "leave one out" analysis (Additional file 2: Supplementary Figure S5), the IVW fixed-effects model (OR = 1.210, 95% CI = 1.020–1.436) (Additional file 1: Table S11) and the effect size of MR.RAPS, also suggested the same results. The MR–Egger regression test (intercept *P* = 0.214) and the MR-PRESSO global test (*P* value = 0.696) did not reveal pleiotropy. Meanwhile, no unusual outliers were detected. Cochran's Q test (*P* value = 0.716) revealed no evidence of heterogeneity (Additional file 1: Table S5).

In addition, we found that insomnia potentially elevated the risk of NAFLD (OR = 1.865, 95% CI = 1.044–3.333, *P* value = 0.035) (Table 1), the IVW fixed-effects model (OR = 1.865, 95% CI = 1.090–3.192) (Additional file 1: Table S11) also indicated the same trend. Additionally, sensitivity analyses revealed no evidence of pleiotropy (intercepts *P* = 0.085) or heterogeneity (*P* value = 0.212).

Genetics predict NAFLD on neuropsychiatric disorders

In reverse MR, the random-effects IVW model showed potential evidence that NAFLD increased the risk of anxiety disorders (OR = 1.024, 95% CI = 1.001–1.046, *P* value = 0.034) (Table 1). Several other methods, including the "leave one out" analysis (Additional file 2: Supplementary Figure S14), the IVW fixed-effects model (OR = 1.024, 95% CI = 1.006–1.042) (Additional file 1: Table S11) and the effect size of MR.RAPS, also suggested the same causal trend. The MR–Egger regression test did not indicate horizontal pleiotropic effects (intercept *P* = 0.857), the MR-PRESSO global test (*P* value = 0.421) also did not suggest pleiotropic results, and no abnormal outliers were detected. At the same time, MR-RAPS (overdispersion variance *P* value = 0.704) also indicated that no pleiotropy was present. Cochran's Q test (*P* value = 0.219) showed no heterogeneity (Additional file 1: Table S6).

Potential negative associations were found between NAFLD and PTSD (OR = 0.943, 95% CI = 0.892–0.996, *P* value = 0.036) (Table 1). Effect size values for several other methods, including MR.RAPS, also suggested the same causal trend. Sensitivity analyses also failed to observe evidence of any level of pleiotropy (intercepts *P* = 0.690) or heterogeneity (*P* value = 0.782).

Some degree of heterogeneity was present (*P* value = 0.024) in the causal effect of NAFLD on AD. However, there were no pleiotropy and outliers (Additional file 1: Table S6). Therefore, we believed that this result was feasible.

Given the frequent occurrence of obesity in patients with NAFLD, after adjusting for genetically predicted BMI and waist circumference, we performed MVMR for anxiety disorders, schizophrenia, MDD, bipolar disorder, AD and insomnia. Our results showed that MMD remained a potential risk factor for NAFLD after adjusting for genetically predicted BMI (OR = 1.334, 95% CI = 1.054–1.687, *P* value = 0.016), which confirmed the robustness of the results. However, once we accounted for waist circumference, the causal connection between MDD and NAFLD disappeared, indicating that this relationship might be influenced by waist circumference. Additionally, there was no significant link between insomnia and NAFLD, suggesting that BMI and waist circumference might influence this association. For the other diseases, no connections were observed either. (Additional file 1: Table S7).

Replication results

In reverse MR, the random-effects IVW model showed significant evidence that NAFLD increased the risk of anxiety disorders (OR = 1.015, 95% CI = 1.010–1.021, *P* value = 9.24×10^{-9}) (Table 2). The "leave one out" analysis (Additional file 2: Supplementary Figure S40) and fixed-effects model (Additional file 1: Table S11) demonstrated the robustness of the results (OR = 1.015, 95% CI = 1.007–1.024). Furthermore, sensitivity analyses also didn't observe evidence of any level of pleiotropy (intercepts *P* = 0.415) or heterogeneity (*P* value = 0.763).

Some degree of heterogeneity was present (*P* value = 0.013) in the causal effect of NAFLD on MDD. There was also some degree of heterogeneity in the causal effect of NAFLD on Bipolar Disorder and insomnia, as indicated by a *P*-values of 0.017 and 0.002. However, there were no pleiotropy and outliers (Additional file 1: Table S9). Hence, we considered this outcome to be achievable.

Combined results from the *meta*-analysis

Pooled analysis suggested that MDD was the potential risk factor for NAFLD (OR = 1.233, 95% CI = 1.063–1.430, *P* value = 0.006) (Fig. 2 and Additional file 1: Table S10). The fixed-effect model of MDD suggested the same results (OR = 1.241, 95% CI = 1.064–1.447, *P* value = 0.006). Meta-analysis also showed significant evidence that NAFLD increased the risk of anxiety disorders (OR = 1.016, 95% CI = 1.010–1.021, *P* value < 0.0001) (Fig. 3), and fixed-effects model (Additional file 1: Table S11) demonstrated the robustness of the results (OR = 1.017, 95% CI = 1.009–1.024, *P* value < 0.0001).

In addition, there was no causal connection between NAFLD and other neuropsychiatric disorders (all *P* values > 0.05), nor was any level of pleiotropy or

Table 1 The causal effects of NAFLD with the risk of neuropsychiatric disorders in discovery stage

Exposure/ Outcome	Methods	OR	95%CI	Beta	SE	*P*-value
Anxiety/NAFLD	IVW	1.124	0.479, 2.639	1.17E-01	0.44	0.789
	MR Egger	2.160	0.267, 17.441	7.70E-01	1.066	0.493
	Weighted median	1.124	0.373, 3.386	1.17E-01	0.56	0.835
Schizophrenia/ NAFLD	IVW	1.013	0.957, 1.072	1.28E-02	0.03	0.658
	MR Egger	1.271	0.994, 1.625	2.40–01	0.13	0.059
	Weighted median	0.992	0.918, 1.072	-8.11E-03	0.04	0.838
PTSD/NAFLD	IVW	0.994	0.899, 1.099	-6.17E-03	0.05	0.906
	MR Egger	0.989	0.747, 1.308	-1.15E-02	0.14	0.937
	Weighted median	1.018	0.883, 1.174	1.82E-02	0.07	0.802
OCD/NAFLD	IVW	0.999	0.967, 1.032	-1.04E-03	0.02	0.950
	MR Egger	1.036	0.875, 1.227	3.75E-02	0.09	0.689
	Weighted median	1.020	0.963, 1.080	1.94E-02	0.03	0.506
MDD/NAFLD	IVW	1.210	1.031, 1.420	1.91E-01	0.08	**0.020**
	MR Egger	2.256	0.843, 6.039	8.14E-01	0.50	0.112
	Weighted median	1.242	0.983, 1.570	2.17E-01	0.12	0.069
Bipolar disorder/NAFLD	IVW	0.931	0.860, 1.008	-7.16E-02	0.04	0.077
	MR Egger	0.887	0.591, 1.332	-1.19E-01	0.21	0.567
	Weighted median	0.919	0.819, 1.031	-8.44E-02	0.06	0.150
Mania/NAFLD	IVW	1.109	0.747, 1.648	1.04E-01	0.20	0.607
	MR Egger	2.109	0.663, 6.707	7.46E-01	0.59	0.232
	Weighted median	1.161	0.617, 2.184	1.49E-01	0.32	0.645
Alzheimer's disease/NAFLD	IVW	0.964	0.910, 1.021	-3.68E-02	0.03	0.213
	MR Egger	0.985	0.889, 1.092	-1.51E-02	0.05	0.775
	Weighted median	0.981	0.899, 1.071	-1.88E-02	0.04	0.674
Parkinson's disease/NAFLD	IVW	1.027	0.967, 1.090	2.63E-02	0.03	0.390
	MR Egger	0.964	0.830, 1.120	-3.65E-02	0.08	0.638
	Weighted median	1.010	0.938, 1.087	9.80E-03	0.04	0.794
Epilepsy/NAFLD	IVW	1.001	0.924, 1.085	9.49E-04	0.04	0.982
	MR Egger	0.920	0.803, 1.054	-8.37E-02	0.07	0.259
	Weighted median	0.947	0.855, 1.049	-5.47E-02	0.05	0.295
ALS/NAFLD	IVW	1.031	0.895, 1.189	3.09E-02	0.07	0.670
	MR Egger	1.215	0.833, 1.772	1.95E-01	0.19	0.339
	Weighted median	1.094	0.928, 1.290	9.02E-02	0.08	0.283
Migraine/NAFLD	IVW	0.987	0.953, 1.022	-4.77E-02	0.02	0.462
	MR Egger	1.008	0.905, 1.123	7.71E-03	0.06	0.891
	Weighted median	0.987	0.942, 1.034	-7.36E-03	0.02	0.585
Insomnia/NAFLD	IVW	1.865	1.044, 3.333	6.23E-01	0.30	**0.035**
	MR Egger	9.869	1.426, 68.288	2.289E-0	0.98	0.025
	Weighted median	1.787	0.798, 4.006	5.81E-01	0.41	0.158
NAFLD/Anxiety	IVW	1.024	1.001, 1.046	2.35E-02	1.11E-02	**0.034**
	MR Egger	1.002	0.942, 1.065	2.97E-03	3.31E-02	0.464
	Weighted median	1.022	1.002, 1.044	2.25E-02	1.06E-02	0.033
NAFLD/ Schizophrenia	IVW	0.978	0.880, 1.087	-2.19E-02	0.05	0.684
	MR Egger	0.857	0.670, 1.097	-1.54E-01	0.12	0.345
	Weighted median	0.960	0.883, 1.042	-4.12E-02	0.04	0.328
NAFLD/PTSD	IVW	0.943	0.892, 0.996	-5.88E-02	0.03	**0.036**
	MR Egger	0.990	0.790, 1.240	-1.03E-02	0.12	0.937
	Weighted median	0.957	0.863, 1.060	-4.43E-02	0.05	0.397

Table 1 (continued)

Exposure/ Outcome	Methods	OR	95%CI	Beta	SE	*P*-value
NAFLD/OCD	IVW	0.907	0.666, 1.236	-9.76E-02	0.16	0.536
	MR Egger	0.719	0.304, 1.701	-3.30E-01	0.44	0.531
	Weighted median	1.012	0.720, 1.422	1.14E-02	0.17	0.947
NAFLD/MDD	IVW	0.987	0.956, 1.018	-1.35E-02	0.02	0.405
	MR Egger	0.956	0.880, 1.038	-4.54E-02	0.04	0.394
	Weighted median	0.996	0.965, 1.028	-4.38E-03	0.02	0.790
NAFLD/Bipolar disorder	IVW	0.961	0.917, 1.008	-3.92E-02	0.02	0.103
	MR Egger	0.989	0.857, 1.141	-1.14E-02	0.07	0.890
	Weighted median	0.962	0.900, 1.028	-3.90E-02	0.03	0.250
NAFLD/Mania	IVW	1.001	0.972, 1.031	7.15E-04	1.50E-02	0.962
	MR Egger	1.024	0.944, 1.111	2.39E-02	4.14E-02	0.622
	Weighted median	1.001	0.972, 1.030	8.28E-04	1.46E-02	0.954
NAFLD/ Alzheimer's disease	IVW	0.978	0.881, 1.086	-2.21E-02	5.34E-02	0.679
	MR Egger	0.976	0.681, 1.398	-2.47E-02	1.84E-01	0.915
	Weighted median	0.952	0.894, 1.015	-4.85E-02	3.25E-02	0.135
NAFLD/ Parkinson's disease	IVW	0.957	0.884, 1.037	-4.35E-02	0.04	0.287
	MR Egger	0.997	0.769, 1.293	-2.80E-03	0.13	0.985
	Weighted median	0.958	0.850, 1.079	-4.31E-02	0.06	0.478
NAFLD/Epilepsy	IVW	0.935	0.858, 1.019	-6.72E-02	0.04	0.124
	MR Egger	1.085	0.828, 1.423	8.19E-02	0.14	0.613
	Weighted median	0.957	0.847, 1.081	-4.39E-02	0.06	0.480
NAFLD/ALS	IVW	0.939	0.876, 1.007	-6.27E-02	0.04	0.077
	MR Egger	0.952	0.877, 1.034	-4.89E-02	0.04	0.246
	Weighted median	0.981	0.918, 1.049	-1.88E-02	3.38E-02	0.579
NAFLD/Migraine	IVW	1.140	0.867, 1.497	1.31E-01	0.14	0.349
	MR Egger	1.411	0.661, 3.011	3.44E-01	0.39	0.467
	Weighted median	1.164	0.893, 1.518	1.52E-01	0.14	0.261
NAFLD/Insomnia	IVW	1.002	0.974, 1.032	2.43E-03	0.01	0.869
	MR Egger	0.974	0.903, 1.052	-2.54E-02	0.04	0.582
	Weighted median	0.995	0.983, 1.008	-4.61E-03	6.50E-03	0.478

SNP Single nucleotide polymorphism, *IVW* Inverse-variance weighted, *OR* Odds ratio, *CI* Confidence interval, *q-value P*-value corrected for False Discovery Rate, *PTSD* Post-traumatic stress disorder, *OCD* Obsessive–compulsive disorder, *MDD* Major Depressive Disorder, *ALS* Amyotrophic lateral sclerosis, *NAFLD* nonalcoholic fatty liver disease

heterogeneity observed (Additional file 1: Tables S5, S6, S8, S9). The visual analyses of the discovery (Additional file 2: Supplementary Figures S1-S26) and replication (Additional file 2: Supplementary Figures S27-S52) stages can be found in Supplementary materials.

Discussion

This bidirectional Mendelian randomization study leveraged genetic data from a large number of published GWASs to explore a bidirectional hypothetical causal association between NAFLD and neuropsychiatric disorders. From a genetic perspective, our results revealed that MDD was the potential risk factor for NAFLD, and NAFLD also increased significantly the risk of anxiety disorders.

Anxiety disorders are common in Western populations [48]. A study comparing 19,871 NAFLD patients with 19,871 matched control individuals found that new-onset anxiety disorders was linked to NAFLD even after multiple complications were controlled [48]. In a cross-sectional study conducted in the United States, depression and anxiety symptoms were evaluated using scale scores in 567 patients diagnosed with NAFLD through biopsy [49], 45% and 25% of the patients had subclinical and clinical anxiety symptoms, respectively, indicating that anxiety disorders is one of the common symptoms of NAFLD and that it is related to advanced

Table 2 The causal effects of NAFLD with the risk of neuropsychiatric disorders in replication stage

Exposure/ Outcome	Methods	OR	95%CI	Beta	SE	*P*-value
Anxiety/NAFLD	IVW	0.980	0.074, 12.891	-2.05E-02	1.31	0.988
	MR Egger	62.883	0.140, 28,329.898	4.141E-00	3.12	0.226
	Weighted median	1.748	0.076, 40.042	5.58E-01	1.60	0.727
Schizophrenia/ NAFLD	IVW	1.032	0.935, 1.137	3.10E-02	0.05	0.534
	MR Egger	1.072	0.614, 1.871	6.92E-02	0.28	0.808
	Weighted median	1.017	0.892, 1.159	1.67E-02	0.07	0.802
PTSD/NAFLD	IVW	0.978	0.914, 1.047	-2.20E-02	0.03	0.526
	MR Egger	0.880	0.474, 1.634	-1.28E-01	0.32	0.690
	Weighted median	0.987	0.917, 1.062	-1.32E-02	0.04	0.724
OCD/NAFLD	IVW	1.034	0.893, 1.196	3.33E-02	0.07	0.656
	MR Egger	1.057	0.657, 1.700	5.55E-02	0.24	0.825
	Weighted median	1.101	0.913, 1.328	9.62E-02	0.10	0.314
MDD/NAFLD	IVW	1.380	0.931, 2.045	3.22E-01	0.20	0.108
	MR Egger	1.731	0.313, 9.569	5.49E-01	0.87	0.532
	Weighted median	1.643	0.965, 2.795	4.96E-01	0.27	0.067
Bipolar disorder/NAFLD	IVW	1.019	0.966, 1.076	1.93E-02	0.03	0.485
	MR Egger	1.273	0.789, 2.054	2.42E-01	0.24	0.327
	Weighted median	1.018	0.946, 1.096	1.81E-02	0.04	0.630
Mania/NAFLD	IVW	0.523	0.238, 1.152	-6.47E-01	0.40	0.108
	MR Egger	1.458	0.098, 21.786	3.77E-01	1.38	0.791
	Weighted median	0.785	0.235, 2.617	-2.42E-01	0.61	0.694
Alzheimer's disease/NAFLD	IVW	0.990	0.934, 1.050	-9.93E-03	0.03	0.739
	MR Egger	1.085	0.863, 1.364	8.15E-02	0.12	0.489
	Weighted median	0.990	0.929, 1.054	-1.04E-02	0.03	0.745
Parkinson's disease/NAFLD	IVW	0.989	0.924, 1.059	-1.06E-02	0.03	0.761
	MR Egger	1.002	0.906, 1.108	1.62E-03	0.05	0.975
	Weighted median	0.984	0.910, 1.064	-1.61E-02	0.04	0.685
Epilepsy/NAFLD	IVW	0.897	0.773, 1.042	-1.08E-01	0.08	0.156
	MR Egger	0.881	0.687, 1.129	-1.27E-01	0.13	0.340
	Weighted median	0.955	0.794, 1.148	-4.64E-02	0.09	0.623
ALS/NAFLD	IVW	1.073	0.856, 1.345	7.07E-02	0.12	0.539
	MR Egger	0.783	0.444, 1.378	-2.45E-01	0.29	0.416
	Weighted median	1.089	0.788, 1.505	8.54E-02	0.16	0.605
Migraine/NAFLD	IVW	0.931	0.824, 1.051	-7.16E-02	0.06	0.248
	MR Egger	0.881	0.638, 1.218	1.26E-01	0.17	0.458
	Weighted median	0.920	0.780, 1.085	-8.38E-02	0.08	0.320
Insomnia/NAFLD	IVW	0.947	0.598, 1.497	-5.49E-02	0.23	0.814
	MR Egger	1.888	0.019, 189.369	6.36E-01	2.35	0.788
	Weighted median	0.918	0.568, 1.483	-8.61E-02	0.24	0.725
NAFLD/Anxiety	IVW	1.015	1.010, 1.021	1.54E-02	2.68E-03	**9.24E-09**
	MR Egger	1.003	0.979, 1.028	3.27E-03	1.26E-02	0.819
	Weighted median	1.014	1.004, 1.024	1.39E-02	5.08E-03	6.20E-03
NAFLD/ Schizophrenia	IVW	0.998	0.949, 1.049	-2.08E-03	0.03	0.935
	MR Egger	0.916	0.807, 1.039	-8.78E-02	0.06	0.305
	Weighted median	0.995	0.956, 1.037	-4.63E-03	0.02	0.824
NAFLD/PTSD	IVW	0.992	0.942, 1.043	-8.49E-03	0.03	0.744
	MR Egger	0.944	0.799, 1.115	-5.75E-02	0.09	0.569
	Weighted median	0.989	0.941, 1.040	-1.08E-02	0.03	0.672
NAFLD/OCD	IVW	0.919	0.788, 1.071	-8.48E-02	0.08	0.277

Table 2 (continued)

Exposure/ Outcome	Methods	OR	95%CI	Beta	SE	*P*-value
	MR Egger	1.041	0.628, 1.725	4.05E-02	0.26	0.890
	Weighted median	0.972	0.838, 1.127	-2.88E-02	0.08	0.703
NAFLD/MDD	IVW	1.001	0.977, 1.025	7.88E-04	0.01	0.949
	MR Egger	0.963	0.903, 1.026	-3.79E-02	0.03	0.364
	Weighted median	1.002	0.987, 1.017	2.19E-03	0.01	0.773
NAFLD/Bipolar disorder	IVW	0.995	0.946, 1.046	-5.36E-03	0.03	0.835
	MR Egger	0.937	0.800, 1.097	-6.53E-02	0.08	0.502
	Weighted median	0.990	0.959, 1.023	-9.63E-03	0.02	0.557
NAFLD/Mania	IVW	1.006	0.997, 1.016	6.50E-03	4.77E-03	0.173
	MR Egger	1.001	0.9671.036	9.45E-04	1.75E-02	0.962
	Weighted median	1.002	0.989, 1.016	2.05E-03	6.85E-03	0.764
NAFLD/ Alzheimer's disease	IVW	0.993	0.956, 1.031	-7.28E-03	0.02	0.704
	MR Egger	0.946	0.846, 1.059	-5.52E-02	0.06	0.437
	Weighted median	0.993	0.965, 1.022	-7.26E-03	0.01	0.622
NAFLD/ Parkinson's disease	IVW	0.961	0.908, 1.017	-3.94E-02	0.03	0.172
	MR Egger	1.058	0.915, 1.223	5.63E-02	0.07	0.526
	Weighted median	0.978	0.922, 1.037	-2.25E-02	0.03	0.451
NAFLD/Epilepsy	IVW	1.003	0.969, 1.039	3.46E-03	0.02	0.847
	MR Egger	0.958	0.833, 1.103	-4.27E-02	0.07	0.612
	Weighted median	0.990	0.938, 1.044	-1.05E-02	0.03	0.701
NAFLD/ALS	IVW	0.984	0.948, 1.021	-1.59E-02	0.02	0.399
	MR Egger	0.946	0.841, 1.064	-5.60E-02	0.06	0.450
	Weighted median	0.986	0.948, 1.026	-1.38E-02	0.02	0.492
NAFLD/Migraine	IVW	1.101	0.966, 1.254	9.60E-02	0.07	0.149
	MR Egger	0.866	0.630, 1.190	-1.44E-01	0.16	0.469
	Weighted median	1.053	0.929, 1.193	5.15E-02	0.06	0.420
NAFLD/Insomnia	IVW	0.998	0.989, 1.007	-2.10E-03	4.61E-03	0.650
	MR Egger	0.990	0.961, 1.021	-9.86E-03	0.02	0.588
	Weighted median	0.995	0.990, 1.000	-5.00E-03	2.71E-03	0.065

SNP Single nucleotide polymorphism, *IVW* Inverse-variance weighted, *OR* Odds ratio, *CI* Confidence interval, *q-value P*-value corrected for False Discovery Rate, *PTSD* Post-traumatic stress disorder, *OCD* Obsessive–compulsive disorder, *MDD* Major Depressive Disorder, *ALS* Amyotrophic lateral sclerosis, *NAFLD* nonalcoholic fatty liver disease

NAFLD. On the other hand, to some extent, NAFLD may progress to nonalcoholic steatohepatitis (NASH) [50]. A smaller study involving 36 NASH patients and 36 control individuals without liver disease after cholecystectomy revealed that NASH increased the risk of anxiety disorders than the control group. It was also found that anxiety disorders was related to more serious changes in liver histological characteristics [51]. This is consistent with the evidence that NAFLD increased significantly the risk of anxiety disorders observed in our MR study.

MDD is a common recurrent mental illness that leads to decreased quality of life and increased mortality in the relevant population [52]. After adjusting for genetically predicted BMI, our findings indicated that MDD continued to be a potential risk factor for NAFLD. However, after adjusting for waist circumference, the association disappeared. This suggested that multiple factors impact the relationship between them, and future research should further explore the offset effects of these factors. In patients with depression, biological disturbances related to obesity are linked to a prolonged course of the disease and negative reactions to conventional antidepressant therapies [53]. Meantime, many studies have found a high prevalence of MDD in patients with NAFLD [54, 55]. A study found that NAFLD patients with MDD had more severe histological liver steatosis and higher NAFLD activity scores compared with NAFLD patients without MDD [56]. Pathologically, MDD is associated with a severe hepatocellular balloon [49], which is one

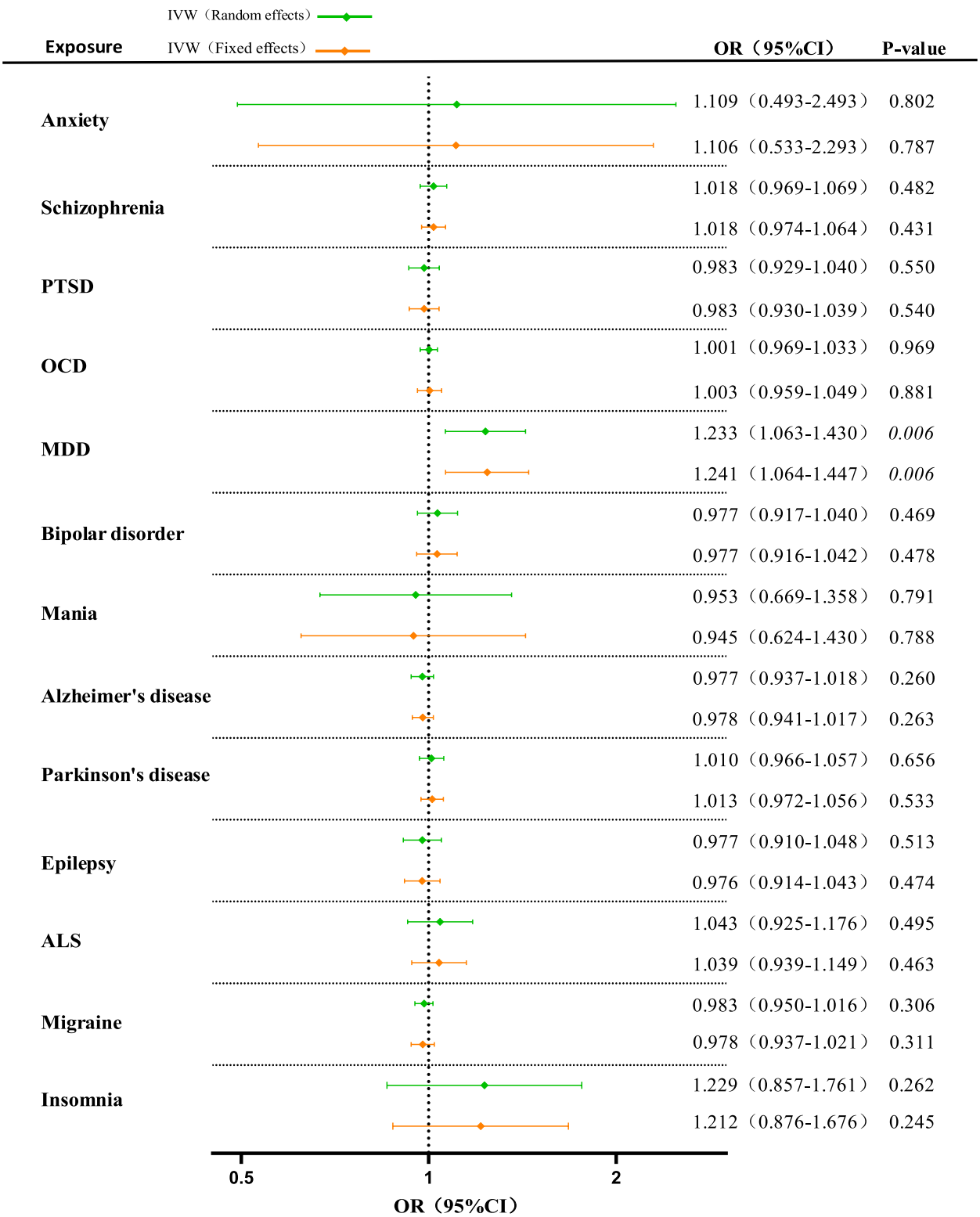

Fig. 2 The effects of neuropsychiatric disorders on NAFLD were estimated by Meta-analysis using IVW. OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted method; PTSD, posttraumatic stress disorder; OCD, obsessive–compulsive disorder; MDD, Major Depressive Disorder; ALS, amyotrophic lateral sclerosis

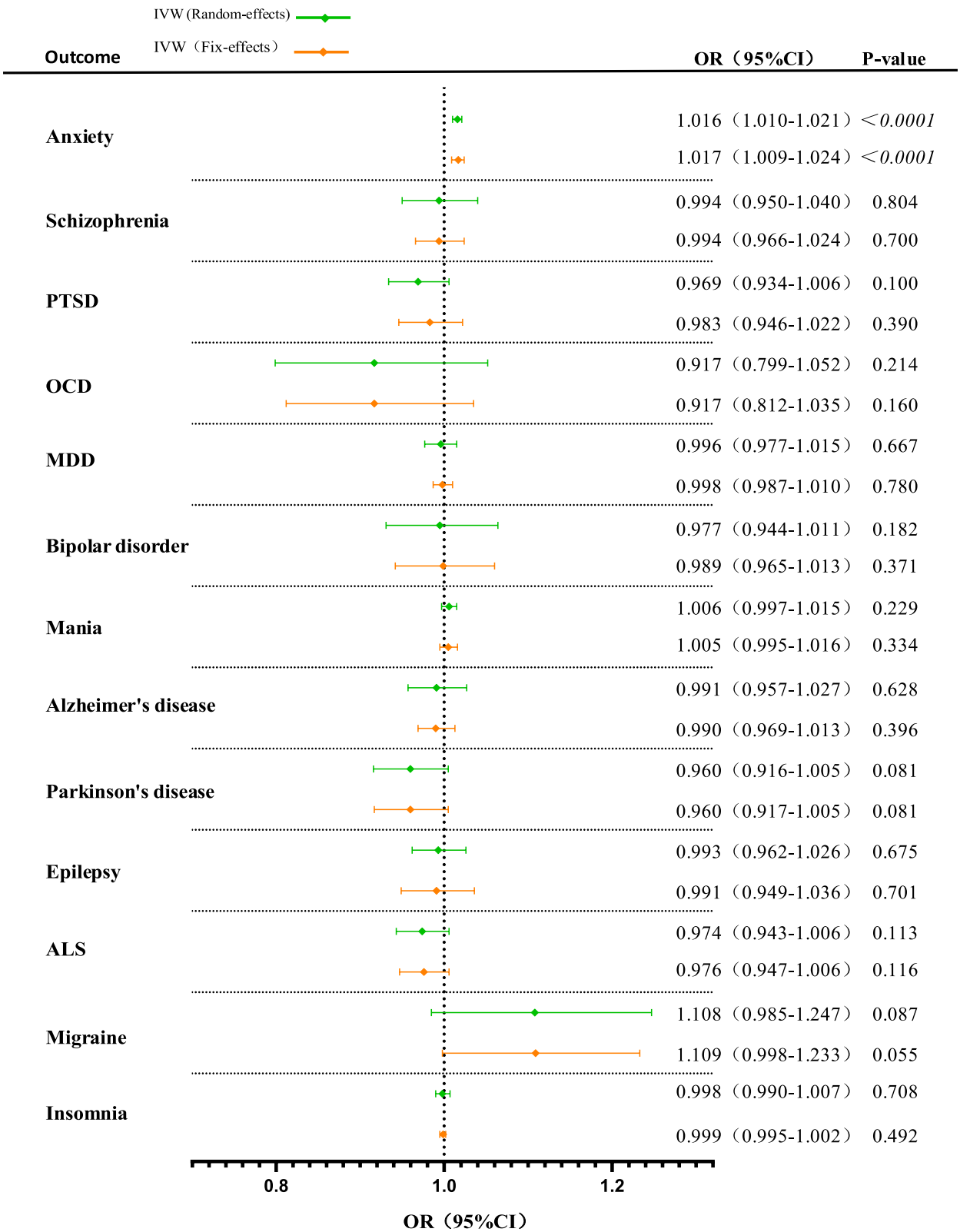

Fig. 3 The effects of NAFLD on neuropsychiatric disorders were estimated by Meta-analysis using IVW. OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted method; PTSD, posttraumatic stress disorder; OCD, obsessive–compulsive disorder; MDD, Major Depressive Disorder; ALS, amyotrophic lateral sclerosis

of the characteristics of NAFLD [57]. In another aspect, the rising levels of inflammatory markers in depressed patients, such as intercytotin-6, C-reactive protein and tumor necrosis factor α [58], provide another reasonable explanation for the association with NAFLD. Meta-analyzing the results of nine longitudinal studies showed that depression was an independent risk factor for diabetes [59]. Moreover, depression triggers activity in the HPA axis and the sympathetic nervous system, which leads to the secretion of the stress hormone cortisol. Elevated cortisol levels promote the breakdown of fats and the release of free fatty acids into the bloodstream. Concurrently, cortisol suppresses insulin production and reduces the body's sensitivity to insulin [60]. Meantime, insulin resistance is tightly related to NAFLD. Insulin resistance may also lead to damage to the mitochondrial fatty acid β-oxidation pathway, increasing free fatty acids and other lipids in the body. This may lead to endothelial dysfunction, resulting in a proinflammatory state in the body [61], and increasing the incidence of NAFLD.

Our MR results found no causal relationship between NAFLD and AD, which goes against the previous studies. However, these studies were basically cross-sectional studies, and the longitudinal associations between them should still be supported by further research data. At the same time, there are also many studies showing that there is no significant direct correlation between NAFLD and AD [62, 63]. As mentioned above, differences in the mean ages of the study population and the cognitive level tests used are also responsible. And the severity of liver fibrosis with disease progression (rather than NAFLD itself) may be associated with cognitive dysfunction [64, 65]. Numerous studies also emphasize the influence of fibrosis severity on the development of diseases such as cardiovascular dysfunction [66] and stroke [67]).

The results of this study contradict previous observational studies that reported a link between schizophrenia and NAFLD. Similarly, it has been reported that there may be a causal link between bipolar disorder and NAFLD [68], but this is not consistent with our results. The results may be affected by the confusion or selection bias inherent in traditional observational studies, such as differences in diet structure, lifestyle and genetic susceptibility of different populations. The connection between NAFLD and these factors may be caused by lots of factors rather than simply the disease itself. For example, a research explained that the use of atypical antipsychotic drugs for the treatment of schizophrenia and other diseases will produce many metabolic and endocrine-related side effects, like insulin resistance, dyslipidemia and systemic inflammation, which will increased the risk of NAFLD [69]. And antidepressants have been shown to be associated with hyperglycemia [70]. As a study showed that MDD was not associated with an increased risk of any cardiovascular disease, and the use of antidepressants increased the risk of multiple cardiovascular diseases [71]. In young male patients, different drug doses and combinations are also risk factors for NAFLD [72]. Although glucose homeostasis is altered before the onset of schizophrenia [73], these only suggest that both have a similar pathogenesis. The possible potential causal relationships between them still need to be further explored.

Schizophrenia and AD, similar in many clinical and pathophysiological features, may accelerate brain aging by promoting neuroinflammation [74] and show similarities in white matter damage patterns [75]. Therefore, the causal link between them and NAFLD may also share similarities, which is consistent with our findings.

In discovery stage, we found that insomnia was a risk factor for NAFLD, while the results of the meta-analysis indicated no causal relationship between them. In the MVMR analysis, there was still no significant association between them. Therefore, the connection between them should still be further evaluated. Insomnia is usually defined by asking "Do you have trouble falling asleep or staying asleep?" [76] Multiple studies indicated that short sleep duration may cause an increase in insulin resistance [77], a significant decrease in antioxidant activity and significantly higher levels of lipid peroxidation [78]. Furthermore, the concentrations of gamma glutamyl transpeptidase and 8-hydroxydeoxyguanosine are often elevated in the serum of NAFLD patients, suggesting that oxidative stress may have occurred [79]. However, a study found that the incidence of insomnia did not seem to be significantly different in NAFLD patients compared to the general population, and the severity of inflammation-related histology may not play a critical role in the pathogenesis of insomnia in NAFLD patients [80]. In conclusion, there may be no direct causal relationship between insomnia and NAFLD, and the association between them may result from a combination of multiple factors.

A cross-sectional study suggested that there was no significant relationship between NAFLD and migraine [81], which is consistent with our results. Although a study has found that there may be a causal relationship [82], we believe that the sample size used is too small and the appropriate control cases are not used, so the causal relationship between them still needs further studies to verify.

Alternatively, socioeconomic status consists mainly of income and education level, the genetic liability of which may play a role in the outcome of mental and physical health. Intelligence can be seen as an individual's innate mental capacity, whereas education reflects the process of socialization from birth through adulthood, with income being an outcome of this process [83]. A study showed that higher income levels are effective in reducing

the incidence of psychiatric disorders, and that a higher genetic liability for education may increase the occurrence of mental health problems independently of salary change [84]. On the other hand, higher education can reduce the occurrence of NAFLD, and the income level is independent of it [85]. Hence, the link between NAFLD and neuropsychiatric disorders within socioeconomic contexts requires deeper investigation, and upcoming public health initiatives could gain from the careful utilization of research on social environments and genetics.

The main strength of our study was that the MR design avoids the confusion or selection bias common in traditional observational studies and supports a robust causal relationships between exposure and results. Besides, our study used aggregate data from large genetic databases, which made our research assumptions more accurate. The use of multiple sensitivity analyses combined with "leave one out" analysis enabled the testing of the stability of key results and provided additional reliable evidence. In addition, this was a MVMR and bidirectional causal-association study that expands the evidence on the relationships between neuropsychiatric disorders and NAFLD. Finally, this analysis had guiding recommendations for future studies on MASLD.

However, our research also had some limitations. First, the population studied was exclusively of European descent; therefore, further studies should be encouraged to verify these results in other populations. Second, although the sensitivity analysis did not reveal any evidence of multiple effects that may affect the results, the potential for horizontal pleiotropic effects couldn't be completely excluded. Third, we chose some disease-related instruments with a relatively loose threshold of 5×10^{-6}, which was considered to be a reasonable threshold [86, 87], but it will affect the statistical efficacy of causal estimation to some extent. Furthermore, since some databases are not publicly available, databases such as MMD and insomnia were not the largest used in our study. Moreover, given that the data analysis should be all European populations, our database for schizophrenia analysis was not the largest. Finally, in studies, exposure and outcome were not only likely to have potentially duplicate participants, but it was also difficult to predict the extent to which the sample overlap. However, in this study, the use of sufficiently powerful tool variables (F statistics > 10) could minimize the potential deviation caused by sample overlap [33].

In summary, our study implied causal relationships of NAFLD with MDD and anxiety disorders. For other related diseases, more genetic instruments and larger GWAS data are needed to verify the results. On the other hand, our study further verified the bidirectional causality between NAFLD and neuropsychiatric disorders.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
OR	Odds ratio
CI	Confidence interval
MR	Mendelian randomization;
MVMR	Multivariable Mendelian randomization
SNP	Single nucleotide polymorphism
IV	Instrumental variable
GWAS	Genome-wide association study
IVW	Inverse-variance weighted
PGC	Psychiatric Genomics Consortium
AD	Alzheimer's disease
PTSD	Post-traumatic stress disorder
MDD	Major Depressive Disorder
OCD	Obsessive-compulsive disorder
ALS	Amyotrophic lateral sclerosis
BMI	Body mass index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03386-6.

Additional file 1: Table S10. Meta-analysis in the multiplicative random-effects IVW method.

Additional file 2: Supplementary Figure S1. Forest plot (A), Leave-one-out plot (B), scatter plot (C) and funnel plot (D) of the causal effect of anxiety on NAFLD.

Acknowledgements
We would like to thank the UK Biobank consortia, FinnGen consortia, IPDGC consortia, PGC consortia and European tertiary liver centers for contributing data.

Author contributions
L. Xu conceived the study design. S. Wang and H. Gao performed the statistical analysis. S. Wang and H. Gao wrote the manuscript. T. Qian and P. Lin reviewed the manuscript. S. Wang and H. Gao contributed equally to this work. All authors approved the submitted draft.

Funding
This work was supported by the Ningbo Top Medical and Health Research Program (No. 2023020612), the Ningbo Leading Medical & Healthy Discipline Project (2022-S04), and the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. 2022KY315). Ningbo Science and Technology Public Welfare project (No. 2023S133). The Ningbo City Medical Science and Technology project (No. 2019Y71).

Availability of data and materials
All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 6 February 2024 Accepted: 26 August 2024
Published online: 04 September 2024

References

1. Song SJ, Lai JC, Wong GL, Wong VW, Yip TC. Can we use old NAFLD data under the new MASLD definition? J Hepatol. 2024;80(2):e54–e56.
2. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397(10290):2212–24.
3. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatology (Baltimore, MD). 2020;72(5):1605–16.
4. W M. The Diagnostic Evaluation of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH). Gastroenterology & Hepatology International Journal. 2019;4(2):1–14.
5. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis Lancet Psychiatry. 2015;2(8):718–25.
6. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS ONE. 2015;10(2).
7. Jakhmola-Mani R, Islam A, Katare DP. Liver-Brain Axis in Sporadic Alzheimer's Disease: Role of Ten Signature Genes in a Mouse Model. CNS Neurol Disord: Drug Targets. 2021;20(9):871–85.
8. Hadjihambi A, Konstantinou C, Klohs J, Monsorno K, Le Guennec A, Donnelly C, et al. Partial MCT1 invalidation protects against diet-induced non-alcoholic fatty liver disease and the associated brain dysfunction. J Hepatol. 2023;78(1):180–90.
9. Caldwell SH, Swerdlow RH, Khan EM, Iezzoni JC, Hespenheide EE, Parks JK, et al. Mitochondrial abnormalities in non-alcoholic steatohepatitis. J Hepatol. 1999;31(3):430–4.
10. Milaneschi Y, Lamers F, Berk M, Penninx B. Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. Biol Psychiat. 2020;88(5):369–80.
11. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia. 2011;7(3):263–9.
12. Alzheimer's disease facts and figures. Alzheimer's Dementia. 2021;17(3):327–406.
13. Kabir MT, Uddin MS, Zaman S, Begum Y, Ashraf GM, Bin-Jumah MN, et al. Molecular Mechanisms of Metal Toxicity in the Pathogenesis of Alzheimer's Disease. Mol Neurobiol. 2021;58(1):1–20.
14. Seo SW, Gottesman RF, Clark JM, Hernaez R, Chang Y, Kim C, et al. Nonalcoholic fatty liver disease is associated with cognitive function in adults. Neurology. 2016;86(12):1136–42.
15. Elliott C, Frith J, Day CP, Jones DE, Newton JL. Functional impairment in alcoholic liver disease and non-alcoholic fatty liver disease is significant and persists over 3 years of follow-up. Dig Dis Sci. 2013;58(8):2383–91.
16. Galiano Rus S, Ortiz García de la Foz V, Arias-Loste MT, Iruzubieta P, Gómez-Revuelta M, Juncal-Ruiz M, et al. Elevated risk of liver steatosis in first-episode psychosis patients: Results from a 3-year prospective study. Schizophrenia research. 2022;246:30–8.
17. Choi JM, Chung GE, Kang SJ, Kwak MS, Yang JI, Park B, et al. Association Between Anxiety and Depression and Nonalcoholic Fatty Liver Disease. Front Med (Lausanne). 2020;7.
18. Sekula P, Del Greco MF, Pattaro C, Kottgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. J Am Soc Nephrol. 2016;27(11):3253–65.
19. Anstee QM, Darlay R, Cockell S, Meroni M, Govaere O, Tiniakos D, et al. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort☆. J Hepatol. 2020;73(3):505–15.
20. Namjou B, Lingren T, Huang Y, Parameswaran S, Cobb BL, Stanaway IB, et al. GWAS and enrichment analyses of non-alcoholic fatty liver disease identify new trait-associated genes and pathways across eMERGE Network. BMC Med. 2019;17(1):135.
21. Consortium SWGotPG. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–7.
22. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53(6):817–29.
23. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nat Commun. 2019;10(1):4558.
24. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. The Lancet. 2013;381(9875):1371–9.
25. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. The Lancet Neurology. 2019;18(12):1091–102.
26. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet. 2019;51(3):414–30.
27. van Rheenen W, van der Spek RAA, Bakker MK, van Vugt J, Hop PJ, Zwamborn RAJ, et al. Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. Nat Genet. 2021;53(12):1636–48.
28. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 2021;53(10):1415–24.
29. Jiang L, Zheng Z, Fang H, Yang J. A generalized linear mixed model association tool for biobank-scale data. Nat Genet. 2021;53(11):1616–21.
30. Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, et al. Biological and clinical insights from genetics of insomnia symptoms. Nat Genet. 2019;51(3):387–93.
31. Martino DJ, Valerio MP, Parker G. The structure of mania: An overview of factorial analysis studies. Eur Psychiatry. 2020;63(1):e10.
32. Goodman WK, Storch EA, Sheth SA. Harmonizing the Neurobiology and Treatment of Obsessive-Compulsive Disorder. Am J Psychiatry. 2021;178(1):17–29.
33. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40(3):740–52.
34. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. eLife. 2018;7:e34408.
35. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25.
36. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol. 2016;40(4):304–14.
37. Wang S, Zhu H, Pan L, Zhang M, Wan X, Xu H, et al. Systemic inflammatory regulators and risk of acute-on-chronic liver failure: A bidirectional mendelian-randomization study. Front Cell Dev Biol. 2023;11:1125233.
38. Sanderson E. Multivariable Mendelian Randomization and Mediation. Cold Spring Harb Perspect Med. 2021;11(2):a038984.
39. Shu MJ, Li JR, Zhu YC, Shen H. Migraine and Ischemic Stroke: A Mendelian Randomization Study. Neurol Ther. 2022;11(1):237–46.
40. He J, Luo X, Xin H, Lai Q, Zhou Y, Bai Y. The Effects of Fatty Acids on Inflammatory Bowel Disease: A Two-Sample Mendelian Randomization Study. Nutrients. 2022;14(14):2883.
41. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.
42. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Stat Med. 2015;34(21):2926–40.
43. Zhang J. Mendelian Randomization Study Implies Causal Linkage Between Telomere Length and Juvenile Idiopathic Arthritis in a European Population. J Inflamm Res. 2022;15:977–86.
44. Zhao Q, Chen Y, Wang J, Small DS. Powerful three-sample genome-wide design and robust statistical inference in summary-data Mendelian randomization. Int J Epidemiol. 2019;48(5):1478–92.
45. Niu W, Gu M. Adding Mendelian randomization to a meta-analysis-a burgeoning opportunity. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2016;37(2):1527–9.
46. Freuer D, Meisinger C. Association between inflammatory bowel disease and Parkinson's disease: A Mendelian randomization study. NPJ Parkinson's disease. 2022;8(1):55.
47. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med. 2012;31(29):3805–20.

48. Labenz C, Huber Y, Michel M, Nagel M, Galle PR, Kostev K, et al. Nonalcoholic Fatty Liver Disease Increases the Risk of Anxiety and Depression. Hepatology Communications. 2020;4(9):1293–301.
49. Youssef NA, Abdelmalek MF, Binks M, Guy CD, Omenetti A, Smith AD, et al. Associations of depression, anxiety and antidepressants with histological severity of nonalcoholic fatty liver disease. Liver Int. 2013;33(7):1062–70.
50. Cohen JC, Horton JD, Hobbs HH. Human Fatty Liver Disease: Old Questions and New Insights. Science. 2011;332(6037):1519–23.
51. Elwing JE, Lustman PJ, Wang HL, Clouse RE. Depression, Anxiety, and Nonalcoholic Steatohepatitis. Psychosom Med. 2006;68(4):563–9.
52. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545–602.
53. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatry. 2019;24(1):18–33.
54. Kim D, Yoo ER, Li AA, Tighe SP, Cholankeril G, Harrison SA, et al. Depression is associated with non-alcoholic fatty liver disease among adults in the United States. Aliment Pharmacol Ther. 2019;50(5):590–8.
55. Ng CH, Xiao J, Chew NWS, Chin YH, Chan KE, Quek J, et al. Depression in non-alcoholic fatty liver disease is associated with an increased risk of complications and mortality. Front Med (Lausanne). 2022;9.
56. Tomeno W, Kawashima K, Yoneda M, Saito S, Ogawa Y, Honda Y, et al. Non-alcoholic fatty liver disease comorbid with major depressive disorder: The pathological features and poor therapeutic efficacy. J Gastroenterol Hepatol. 2015;30(6):1009–14.
57. Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol. 2021;56(11):951–63.
58. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry. 2019;9(1):127.
59. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis Diabetologia. 2006;49(5):837–45.
60. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obesity reviews : an official journal of the International Association for the Study of Obesity. 2001;2(2):73–86.
61. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of Insulin Resistance in Nonalcoholic Fatty Liver Disease. Hepatology (Baltimore, MD). 2019;70(2):711–24.
62. Shang Y, Nasr P, Ekstedt M, Widman L, Stål P, Hultcrantz R, et al. Non-alcoholic fatty liver disease does not increase dementia risk although histology data might improve risk prediction. JHEP reports : innovation in hepatology. 2021;3(2).
63. Huang H, Liu Z, Xie J, Xu C. NAFLD does not increase the risk of incident dementia: A prospective study and meta-analysis. J Psychiatr Res. 2023;161:435–40.
64. Weinstein G, Davis-Plourde K, Himali JJ, Zelber-Sagi S, Beiser AS, Seshadri S. Non-alcoholic fatty liver disease, liver fibrosis score and cognitive function in middle-aged adults: The Framingham Study. Liver international : official journal of the International Association for the Study of the Liver. 2019;39(9):1713–21.
65. Solfrizzi V, Scafato E, Custodero C, Loparco F, Ciavarella A, Panza F, et al. Liver fibrosis score, physical frailty, and the risk of dementia in older adults: The Italian Longitudinal Study on Aging. Alzheimer's & dementia (New York, N Y). 2020;6(1): e12065.
66. Long MT, Wang N, Larson MG, Mitchell GF, Palmisano J, Vasan RS, et al. Nonalcoholic fatty liver disease and vascular function: cross-sectional analysis in the Framingham heart study. Arterioscler Thromb Vasc Biol. 2015;35(5):1284–91.
67. Kim SU, Song D, Heo JH, Yoo J, Kim BK, Park JY, et al. Liver fibrosis assessed with transient elastography is an independent risk factor for ischemic stroke. Atherosclerosis. 2017;260:156–62.
68. Godin O, Leboyer M, Belzeaux R, Bellivier F, Loftus J, Courtet P, et al. Non-alcoholic fatty liver disease in a sample of individuals with bipolar disorders: results from the FACE-BD cohort. Acta Psychiatr Scand. 2020;143(1):82–91.
69. May M, Barlow D, Ibrahim R, Houseknecht KL. Mechanisms Underlying Antipsychotic-Induced NAFLD and Iron Dysregulation: A Multi-Omic Approach. Biomedicines. 2022;10(6):1225.
70. Renn BN, Feliciano L, Segal DL. The bidirectional relationship of depression and diabetes: a systematic review. Clin Psychol Rev. 2011;31(8):1239–46.
71. Cao H, Baranova A, Zhao Q, Zhang F. Bidirectional associations between mental disorders, antidepressants and cardiovascular disease. BMJ Ment Health. 2024;27(1):e300975.
72. Yan J, Hou C, Liang Y. The prevalence and risk factors of young male schizophrenics with non-alcoholic fatty liver disease. Neuropsychiatr Dis Treat. 2017;13:1493–8.
73. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. JAMA Psychiat. 2017;74(3):261–9.
74. Wrigglesworth J, Ward P, Harding IH, Nilaweera D, Wu Z, Woods RL, et al. Factors associated with brain ageing - a systematic review. BMC Neurol. 2021;21(1):312.
75. Baranova A, Zhao Q, Cao H, Chandhoke V, Zhang F. Causal influences of neuropsychiatric disorders on Alzheimer's disease. Transl Psychiatry. 2024;14(1):114.
76. Roth T. Insomnia: definition, prevalence, etiology, and consequences. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2007;3(5 Suppl):S7-10.
77. Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen KW, et al. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. J Clin Endocrinol Metab. 2010;95(6):2963–8.
78. Gulec M, Ozkol H, Selvi Y, Tuluce Y, Aydin A, Besiroglu L, et al. Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 2012;37(2):247–51.
79. Irie M, Sohda T, Iwata K, Kunimoto H, Fukunaga A, Kuno S, et al. Levels of the oxidative stress marker γ-glutamyltranspeptidase at different stages of nonalcoholic fatty liver disease. J Int Med Res. 2012;40(3):924–33.
80. Taketani H, Sumida Y, Tanaka S, Imajo K, Yoneda M, Hyogo H, et al. The association of insomnia with gastroesophageal reflux symptoms in biopsy-proven nonalcoholic fatty liver disease. J Gastroenterol. 2014;49(7):1163–74.
81. Martami F, Ghorbani Z, Abolhasani M, Togha M, Meysamie A, Sharifi A, et al. Comorbidity of gastrointestinal disorders, migraine, and tension-type headache: a cross-sectional study in Iran. Neurol Sci. 2018;39(1):63–70.
82. Celikbilek A, Celikbilek M, Okur A, Dogan S, Borekci E, Kozan M, et al. Non-alcoholic fatty liver disease in patients with migraine. Neurol Sci. 2014;35(10):1573–8.
83. Andreu-Bernabeu Á, González-Peñas J, Arango C, Díaz-Caneja CM. Socioeconomic status and severe mental disorders: a bidirectional multivariable Mendelian randomisation study. BMJ Ment Health. 2023;26(1):e300821.
84. Howe LJ, Tudball M, Davey Smith G, Davies NM. Interpreting Mendelian-randomization estimates of the effects of categorical exposures such as disease status and educational attainment. Int J Epidemiol. 2022;51(3):948–57.
85. Vilar-Gomez E, Nephew LD, Vuppalanchi R, Gawrieh S, Mladenovic A, Pike F, et al. High-quality diet, physical activity, and college education are associated with low risk of NAFLD among the US population. Hepatology (Baltimore, MD). 2022;75(6):1491–506.
86. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–65.
87. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of Naturally Random Allocation to Lower Low-Density Lipoprotein Cholesterol on the Risk of Coronary Heart Disease Mediated by Polymorphisms in NPC1L1, HMGCR, or Both. J Am Coll Cardiol. 2015;65(15):1552–61.

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