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Causal relationship between genetically predicted mental disorders and frailty: a bidirectional and multivariable mendelian randomization study

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Abstract

Background In observational studies, frailty has been strongly associated with mental disorders. However, the mechanisms underlying the association between frailty and mental disorders remain unclear.

Methods We conducted a two-sample Mendelian randomization (MR) study to assess the causal relationship between frailty, as measured by the frailty index (FI), and ten common mental disorders. The datasets involved European ancestry individuals and included measurements of the FI (N = 175,226), schizophrenia (SCZ; N = 320,404), major depressive disorder (MDD; N = 143,265), bipolar disorder (N = 337,199), insomnia (N = 462,341), obsessive–compulsive disorder (N = 33,925), anxiety disorders (N = 463,010), autism spectrum disorder (N = 46,351), anorexia nervosa (N = 14,477), opioid-related mental and behavioral disorders (N = 215,650), and mental and behavioral disorders due to use of other stimulants including caffeine (N = 215,570).

Results Two-sample MR analyses were performed using inverse variance weighting followed by various sensitivity and validation analyses. Genetically predicted SCZ (odds ratio [OR] = 1.019, 95% confidence interval [CI] 1.005–1.033) and MDD (OR = 1.211, 95% CI 1.092–1.343) had significant causal effects on FI. In the reverse MR analysis, we discovered that MDD was significantly and causally affected by FI (OR = 1.290, 95% CI 1.133–1.469). No causal links were identified between the FI and the other eight common mental disorders. In the Multivariable MR, the estimated MDD effect on FI is comparable to the univariate IVW estimate (OR = 1.298; 95% CI, 1.175 to 1.435), while the estimated SCZ effect on FI fails to be significant compared to the univariate estimate. The results of the sensitivity and validation analyses confirmed stabilization.

Conclusions Our study found evidence of a causal relationship between SCZ, MDD, and frailty and explored the underlying mechanisms.

Keywords Mental disorders, Schizophrenia, Major depressive disorder, Frailty, Mendelian randomization, Causality

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Introduction

As awareness of health has increased in recent years, frailty, which may have a variety of adverse outcomes, has received considerable attention [1]. The definition of frailty was first proposed by Fried et al.(2001) [2]. It is considered as a group of syndromes characterized by impaired stress tolerance due to decreased muscle, nutritional deficiencies, hormonal changes, and increased inflammation leading to decreased function of different organs. Frailty dimensions can represent an assessment of biological rather than physiological age, which in turn allows for a valid estimation of an individual's health status [3]. As the global population ages, the prevalence of frailty is likely to increase [4]. Ma, L et al. [5] recently selected 5,844 elderly participants from seven cities based on well-established clustering, stratification, and random selection statistical sampling techniques and found a 9.9% prevalence of frailty. According to a 21-cohort survey involving 61,500 participants, 10.7% of community-dwelling older adults were frail [6]. In addition to being associated with different study population characteristics, however, the prevalence of frailty varies widely across studies, ranging from 4.0% to 59.1% [7], which may also be due to differences in how it is measured. To our knowledge, a number of frailty assessments are available, although the two most commonly used are the frailty phenotype (FP) [2] and the frailty index (FI) [8]. FP refers to a clinical syndrome. Specifically, at least three of the following five manifestations need to be present at the same time: fatigue, weakness, slow walking speed, unintentional weight loss, and low physical activity. Investigations into the frailty phenotype have been extensive and have involved numerous disciplines such as dentistry [9], infectious diseases [10], and cardiovascular [11]. Nonetheless, the presentation of FP may overlap with clinical symptoms of other chronic diseases such as depression, which may lead to misinterpretation of the respondent's condition. The FI is based on the deficit accumulation model and operationalized as the proportion of deficits present in an individual out of the total number of age-related health variables considered. In addition, throughout a person's life expectancy, deficit accumulation is thought to be a stochastic process. Thus, FI lessens the impact of the previously mentioned overlapping symptoms. With the widespread use of stable and reliable FI, further research on frailty has been conducted.

Evidence from epidemiological studies suggests a strong correlation between mental disorders and physical frailty [12–14]. Borges et al. [15] investigated 315 elderly outpatients (mean age 72.1 years, 68.3% female) participating in a cohort study and found that the prevalence of frailty was 14.5%, 46.5%, and 65.1% in those who were nondepressed, subthreshold depressed, and severely depressed, respectively. When the results of the study were validated using the FI-36 index, the prevalence of frailty was found to be 10.2%, 20.9%, and 30.2%, respectively. Although the data obtained varied, the overall trend was consistent. Studies confirming insomnia [16], schizophrenia (SCZ) [17], bipolar disorder [BD] [18], and frailty have produced conclusions similar to those above. In addition, a systematic review that included 20 cross-sectional studies and one longitudinal study from 1,272 references retrieved also found that frail older adults were more likely to exhibit symptoms of anxiety [19]. When the Belgian Bone Club investigated the epidemiology of osteoporosis in frail individuals, patients with anorexia nervosa (AN) were included in the study [20]. Frailty-related analyses have also been addressed in substance abuse research [21]. However, the relationship between autism spectrum disorders (ASD), obsessive–compulsive disorder (OCD), and frailty has been scarcely explored. Interestingly, emerging evidence shows that the conclusions of some previous studies are partial, and mental disorders and frailty could have a bidirectional association [2, 22]. Other researchers have raised concerns about frailty for current young and middle-aged adults [23]. Nevertheless, given that most reviews are cross-sectional epidemiological studies or short-term follow-up studies, it is difficult to conclude the causal relationship between frailty and mental disorders.

With the rapid development of genomics, Mendelian randomization (MR) analysis is widely used in various medical fields [24–26]. The instrumental variables obtained by the MR method are single nucleotides that are closely associated with clinical phenotypes. The influence of confounding and reverse causal associations on study conclusions in observational studies is effectively avoided by using the simulation of random assignment in human genetic processes [27]. Therefore, it is plausible that MR analysis was used to verify the causal association between mental disorders and frailty. Recently, Ni Sang et al. [28] designed and analyzed the causal association between depression and frailty risk using the MR method. However, considering the evident association of frailty with multiple psychiatric disorders and the effective reduction of clinical symptom overlap at assessment by FI, an MR study of the causal association between various common mental disorders and frailty is still needed.

In the present study, instrumental variables obtained from large genetic data significantly associated with ten common mental disorders (SCZ [29], major depressive disorder [MDD] [30], BD (https://gwas.mrcieu.ac.uk/datasets/ukb-a-525/), insomnia [ISN] (https://gwas.mrcieu.ac.uk/datasets/ukb-b-3957/), anxiety disorder [AD] (https://gwas.mrcieu.ac.uk/datasets/ukb-b-11311/),

ASD (https://gwas.mrcieu.ac.uk/datasets/ieu-a-1185/), OCD (https://gwas.mrcieu.ac.uk/datasets/ieu-a-1189/), AN [31], opioid-related mental and behavioral disorders [MBDO] (https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_OPIOIDS/), and mental and behavioral disorders due to use of other stimulants [MBDS] (https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_STIMUL/)) were used to analyze the underlying association with frailty in a two-sample MR. Then, the inverse MR was used to detect the association between the two at the genetic level. Finally, multivariate MR was used to explore the direct effect of mental disorders on FI [32]. The purpose of this study was to provide an accurate and comprehensive assessment of the causal association between mental disorders and frailty from a genetic perspective.

Methods

Study design

An overview of the MR framework is shown in Fig. 1. To comprehensively assess the causal association between the ten common psychiatric disorders and frailty, a two-sample MR analysis was first performed (e.g., MR analysis of the causal association from the ten psychiatric disorders to frailty), and the reverse analysis was then performed (from frailty to the ten mental disorders) (Fig. 2). All publicly available summary statistics of the GWAS data used for the analysis were downloaded and obtained from the Psychiatric Genomics Consortium (PGC), Neale lab, UK biobank, and Integrative Epidemiology Unit (IEU). Therefore, no additional ethical approval or informed consent was required. This study followed the STROBE-MR guidelines [33].

Data source for frailty

Summary statistics for the frailty phenotypic measure of frailty were obtained from a recent meta-analysis of a genome-wide association study (GWAS) in the UK Biobank and TwinGene, Sweden, which included 175,226 participants of European ancestry [34] (Table 1). FI is a continuous measure, expressed as the proportion of the combined total of all age-related health deficits with more than 40 components, covering a wide range of physical and mental health domains [8]. FI, as a proxy for overall health, has been validated as a strong predictor of many adverse health outcomes and has been demonstrated to be more appropriate than other measures for assessing frailty at younger ages [35–37].

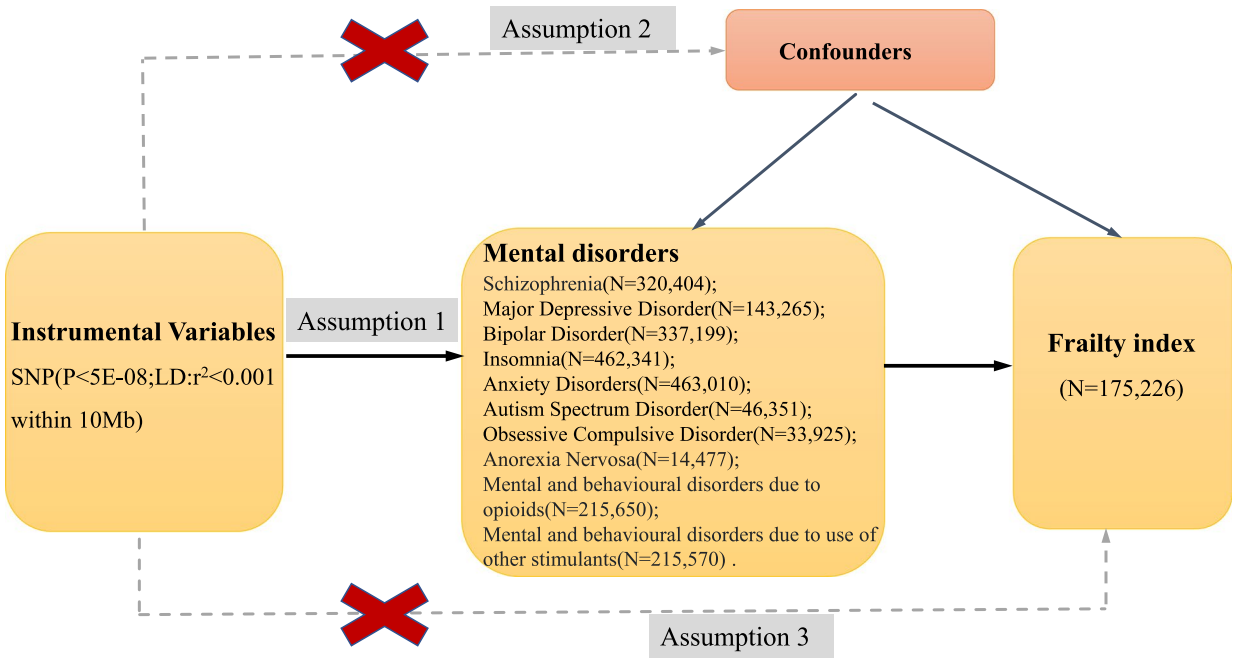

Fig. 1 Diagram for Mendelian randomization (MR). MR was developed on the premise of three assumptions. First, SNPs designated as instrumental variables (IVs) should be extremely connected to exposure (Assumption 1). Second, SNPs selected as IVs are required to be independent of confounders (Assumption 2). Third, rather than being directly correlated, IVs and FI (outcome) only have a relationship through mental disorders (exposure) (Assumption 3)

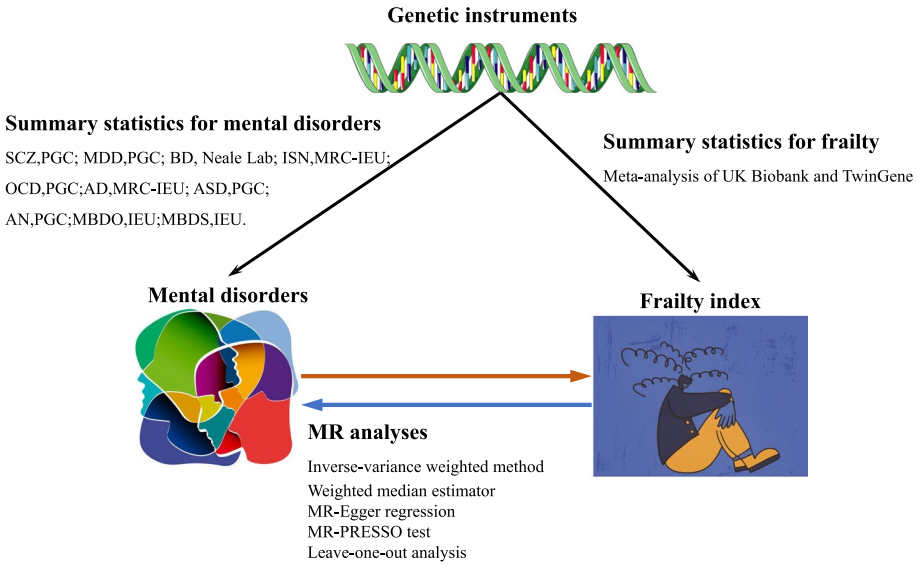

Fig. 2 Study design of the associations between mental disorders and FI. First, we genetically assessed the causal associations between frailty and ten common mental disorders by 2-sample MR; we then assessed the causal associations between the two aforementioned by reverse MR. Multiple sensitivity analyses confirmed the robustness of the findings

Table 1 The GWAS summary data used in the MR study

Phenotype	Consortium/ author	Year	Participants	SNP(N)	Age	N_IVs	URL/PMID
Exposure/Outcome							
SCZ	PGC/ Trubetskoy V	2022	320,404 (Ncase:76,755)	7,585,078	-	206	https://gwas.mrcieu.ac.uk/datasets/ieu-b-5099/; 35,396,580
MDD	PGC/Wray	2018	143,265 (Ncase:45,591)	1,048,575	-	19*	https://doi.org/10.6084/m9.figshare.21655784; 29,700,475
BD	Neale lab/ UK-B	2017	337,199 (Ncase:303)	10,894,596	44–69	27*	https://gwas.mrcieu.ac.uk/datasets/ukb-a-525/
ISN	MRC-IEU/ UK-B/ Ben Elsworth	2018	462,341	9,851,867	44–69	42	https://gwas.mrcieu.ac.uk/datasets/ukb-b-3957/
AD	MRC-IEU/ UK-B/ Ben Elsworth	2018	463,010 (Ncase:1,523)	9,851,867	44–69	0	https://gwas.mrcieu.ac.uk/datasets/ukb-b-11311/
ASD	PGC	2017	46,351 (Ncase:18,382)	9,112,386	-	16*	https://gwas.mrcieu.ac.uk/datasets/ieu-a-1185/
OCD	PGC	2017	33,925 (Ncase:26,888)	8,409,517	-	2*	https://gwas.mrcieu.ac.uk/datasets/ieu-a-1189/
AN	PGC/Duncan	2017	14,477 (Ncase:3,495)	10,641,224		5*	https://gwas.mrcieu.ac.uk/datasets/ieu-a-1186/; 28,494,655
MBDO	IEU	2021	215,650 (Ncase:651)	16,380,458	20–80	1*	https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_OPIOIDS/
MBDS	IEU	2021	215,570 (Ncase:571)	16,380,435	20–80	1*	https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_STIMUL/
Outcome/Exposure							
FI	Atkins JL	2021	175,226 (Female:90,396)	7,589,717	41–87	15	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90020053/; 34,431,594

Abbreviations: SCZ schizophrenia, *MDD* major depressive disorder, *BD* bipolar disorder, *ISN* insomnia, *OCD* obsessive compulsive disorder, *AD* anxiety disorders, *ASD* autism spectrum disorder, *AN* anorexia nervosa, *MBDO* opioid-related mental and behavioral disorders, *MBDS* mental and behavioral disorders due to use of other stimulants, including caffeine, *FI* frailty index, *PGC* Psychiatric Genomics Consortium, *IEU* integrative epidemiology unit, *N_IVs* number of instrumental variables,

* the P threshold is 1e-6

Selection of genetic instruments

We selected genetic instruments for ten common psychiatric disorders from the largest GWAS meta-analysis involving European ancestry individuals conducted by PGC, Neale lab, UK biobank, and IEU (Table 1). Independent IVs were obtained after aggregation based on the 1000 Genomes Project linkage disequilibrium (LD) structure ($r^2 < 0.001$ within 10 Mb). Overlapping proxy SNPs in LD ($r^2 = 0.8$) were used when SNPs did not appear in the summary statistics of the corresponding psychiatric phenotype. SNPs that were strongly linked to the current study outcome ($p < 5e\text{-}08$) were also excluded from the IVs before MR analysis was performed. To obtain sufficient IVs for analysis, the P threshold is adjustable to 1e-06.

IVs for the FI were obtained from large GWAS data for 175,226 participants from the UK and Sweden. In addition, we screened IVs for FI at a strict genome-wide statistical significance ($p < 5e\text{-}08$) (Table S10).

Statistical analysis

To better adjust for significant heterogeneity among SNP effects, the multiplicative random effects model in the inverse variance weighting (IVW) approach was applied in this study as the main analysis in a bidirectional MR study [38]. In the multivariate setting, the covariance between the SNP effects for each exposure was fixed at zero. The weighted mean of SNP effects is provided in the IVW approach, where the intercept is constrained to zero [38]. However, assuming that instrumental SNPs show horizontal pleiotropy, the results may be biased, which is a major source of bias in MR settings. Accordingly, univariate IVW estimates were compared with a range of other well-established MR methods to strengthen the robustness of the findings, including weighted median [39], simple model [40], weighted model [41], and MR-Egger regression [39]. To avoid the effect of reverse causal association, we also performed a two-sample reverse directional MR analysis. Based on evidence that SCZ is genetically significantly linked to MDD [30], we analyzed estimates of the immediate effect of the other mental disorder on FI by adjusting one mental disorder in multivariable MR (MVMR). Selecting random effects or fixed effects based on heterogeneity in the univariable MR (UVMR), we performed the IVW MR method in MVMR.

Complementary analysis

To further check the robustness of the results, the Cochran Q statistic was used to check for evidence of heterogeneity (a potential indicator of pleiotropy) in the IVW estimator. The MR Egger intercept test was conducted to detect the presence of directional pleiotropy [39]. Leave-one-out analyses were performed to assess whether the overall estimate was driven by a single SNP. MR-pleiotropy residual sum and outlier (MR-PRESSO) were employed to detect outliers and all MR analyses were repeated after deleting these outlier SNPs. The R^2 values explaining the exposure variance and the F-statistic for each SNP were calculated by linear regression analysis of the IVs. F-statistics greater than 10 indicate that the IV is strong and that there is only a marginal amount of bias is attributable to sample overlap [42]. In the sensitivity analyses of MVMR, MVMR-Egger, MVMR-Lasso, and MVMR-Median were applied.

The TwoSampleMR (version 0.5.7), MendelianRandomization (version 0.7.0), and MRPRESSO (version 1.0.0) packages in R software (version 4.2.3) were used for the analysis [40]. Significant correlations were required to meet the following requirements: the MR estimates exceeded standard statistical significance ($p < 0.05$), the direction of the effect in the sensitivity analyses was generally consistent, and the MR-Egger intercept showed a limited effect of horizontal pleiotropy.

Results

Details of the GWAS database for the ten common psychiatric disorders used in this study and publicly available GWAS data from UK Biobank and TwinGene are presented in Table 1. Based on the screening criteria for IVs, we separately identified key SNPs significantly associated with each of the GWAS phenotypes for the ten psychiatric disorders and frailty, which were subsequently used as independent IVs (TableS1-10). In the two-sample MR study, a statistically significant bidirectional causal relationship was found between the genetic prediction of MDD and FI (MR: odds ratio [OR] = 1.211, 95% confidence interval [CI] 1.092–1.343, $p = 2.90e\text{–}04$; reverse MR: OR = 1.290, 95% CI 1.133–1.469, $p = 1.17e\text{–}04$). Genetically predicted SCZ had a significant causal effect on FI (OR = 1.019, 95% CI 1.005–1.033, $p = 0.007$), while no significant causal effect of FI on SCZ was found. Nevertheless, no statistically significant causal association was found between BD, ISN, AD, ASD, OCD, AN, MBDO, MBDS, and FI.

Genetically predicted SCZ on FI in univariate MR

According to the selection criteria of genetic instruments in this study, 206 SNPs significantly linked to SCZ were identified (Table S1). The IVW approach shows the causal effect of genetically predicted SCZ on FI (OR = 1.019, 95% CI 1.005–1.033, $p = 0.007$) (Table S11, Figure S1, and Fig. 3). The sensitivity analysis showed heterogeneity in the estimated effect of SCZ on FI ($p < 0.05$), but not horizontal pleiotropy ($p > 0.05$) (Table 2). To control for the effect of heterogeneity

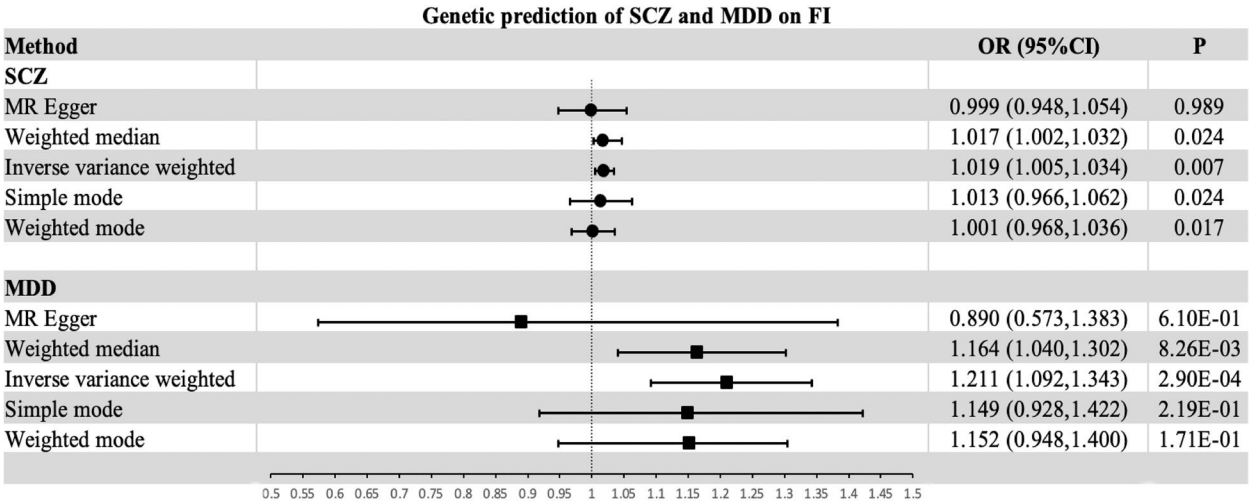

Fig. 3 Effect of genetic risk of SCZ and MDD on FI using various methods. Abbreviations: SCZ, schizophrenia; MDD, major depressive disorder; FI, frailty index; MR, mendelian randomization

Table 2 Association of genetically predicted psychiatric disorders and FI in the sensitivity analysis

Exposure	Outcome	N_IVs	IVW Q statistic	Q_*P* value	MR-Egger intercept	Egger_P value	No. of outlier detected by MR-PRESSO
SCZ	FI	206	460.34	6.91e-24	0.0012	0.458	10
MDD	FI	19	33.29	1.53e-02	0.0072	0.177	1
FI	SCZ	15	63.82	2.48e-08	-0.0353	0.118	3
FI	MDD	15	17.78	1.23e-01	0.0067	0.648	-

Abbreviations: IVW Inverse variance weighting, *MR-PRESSO* Mendelian Randomization-Pleiotropy RESidual Sum and Outlier, *SCZ* schizophrenia, *MDD* major depressive disorder, *FI* frailty index, *N_IVs* number of instrumental variables

on the study, we used a random effects model for the MR analysis. The F-statistics, which were calculated by obtaining the IV of SCZ, were 35.34–135.13, indicating that the intensity of the obtained IVs was good (Table S12). The leave-one-out analysis showed that the estimated effects were relatively stable after excluding any single SNP (Figure S2). The scatterplot and funnel plot demonstrated that the results of the IVW method are robust (Figures S3 and S4). In assessing the causal association between SCZ and FI, the MR-PRESSO test identified ten outliers (Table 2). The causal estimates generated from the MR-PRESSO and MR-PRESSO correction approaches, which eliminate outliers, produced consistent findings (Table S13). Nevertheless, the IVW approach detected no causal association between FI and genetic liability to SCZ in the inverse MR analysis ($p = 0.370$) (Table S13). Heterogeneity was also present in the estimated effect of FI on SCZ ($p < 0.05$), but no horizontal pleiotropy was detected ($p > 0.05$) (Table 2). The F-statistics calculated from the IVs of FI were 39.71–85.38 (Table S14). The MR-PRESSO test found three outliers in the evaluation of FI and genetic liability to SCZ (Table 2).

Genetically predicted MDD and FI in univariate MR

A total of 19 SNPs were eligible for IVs and were substantially associated with MDD (Table S2). Using the IVW approach, genetically determined MDD had a significant effect on FI (OR = 1.211, 95% CI 1.092–1.343, $p = 2.90e{-}04$) (Table S11, Figure S5, and Fig. 3). Similarly, heterogeneity was present in the genetic estimation of the effect of MDD on FI ($p < 0.05$), but no horizontal pleiotropy was detected ($p > 0.05$) (Table 2). Meanwhile, the random effects model was chosen to reduce the effect of heterogeneity. The F-statistics of the IVs obtained, which were closely related to MDD and had good intensity, were 24.03–37.36 (Table S15). From the leave-one-out analysis, it was evident that the estimated overall effect was relatively robust after removing any one SNP (Figure S6). Both scatter plot and funnel plot show that the results of the IVW method are reliable (Figures S7 and S8). In terms of

genetically predicting the effect of MDD on FI, no outliers were found by MR-PRESSO (Table 2). In addition, in the reverse MR analysis, we found a causal effect of FI on MDD (OR = 1.290, 95% CI 1.133–1.469, $p = 1.17e{-}04$) (Table S11 and Figure S9). Heterogeneity in the causal effects of FI on MDD was similarly observed ($p < 0.05$), while no horizontal pleiotropy was identified ($p > 0.05$). The leave-one-out method further confirms the robustness of the results (Figure S10). The scatter plot and funnel plot both confirmed the robustness of the results derived from the IVW method (Figures S11 and S12). No outliers were found in the MR-PRESSO analysis (Table S13).

Genetically predicted MDD and SCZ on FI in Multivariable MR

Given that MDD and SCZ are genetically associated with each other, we conducted MVMR to estimate the direct effect of the other mental disorder (e.g., MDD) on FI in the context of controlling one of these mental disorders (e.g., SCZ). In the MVMR analysis, we extracted 19 SNPs significantly associated with MDD and 303 SNPs associated with SCZ that met the criteria for IVs ($p = 1e{-}06$). Information on instrumental variables for MDD and SCZ used for MVMR is presented separately in Tables S16 and S17. In MVMR, the estimated effect of MDD on FI is equivalent to the univariate IVW estimate (Multivariable IVW OR = 1.298; 95% CI, 1.175 to 1.435; $p = 2.88e{-}07$) (Fig. 4). However, comparing the univariate IVW estimates, the estimated effect of SCZ on FI was not statistically significant ($p > 0.05$) (Fig. 4). MVMR-Egger intercept analyses showed no horizontal pleiotropy ($p = 0.800$) (Table S18). In sensitivity analyses, MVMR-Lasso and MVMR-Median analyses provide evidence that the study findings are reliable and robust (Table S18).

Discussion

Although several observational studies have explored frailty and mental disorders (e.g., INS, AD, MDD, SCZ), conclusions have been mixed and it is difficult to determine a causal association between the two. Therefore, the present MR study aimed to assess the causal relationship between ten common mental disorders and frailty. The findings demonstrated that genetically predicted SCZ and MDD are causally associated with increased FI, whereas no causal association was found between the other eight mental disorders and the FI. In contrast, no causal associations between the FI and ten common mental disorders were found in the reverse MR analysis.

Our findings suggested that the genetic liability to SCZ may causally increase the FI. SCZ is a common, chronic, and severe mental disorder. The majority of SCZ patients struggle to achieve full remission, which places an intense financial strain on families and communities, and intensifies care-related challenges [43]. It is not surprising that a proportion of people with SCZ are hospitalized for long periods of time [44]. As a result, the health status of these patients is all the more alarming. According to a systematic review, the life expectancy of schizophrenia patients is 10–20 years less than the average [45]. A sufficient and plausible explanation is that patients with SCZ are more susceptible to aging compared to the general population [46]. Accumulating evidence of ineffective self-care, chronic unhealthy lifestyle habits (e.g., inadequate diet, physical inactivity, and excessive smoking), and cardiotoxicity (e.g., clozapine) and metabolic disturbances (e.g., olanzapine) associated with continued use of second-generation antipsychotics tend to plague SCZ patients [47–51]. In fact, these problems contribute dramatically to the premature frailty and mortality of people with SCZ. Ming-Tsun Tsai et al. [52] investigated 561 individuals with chronic SCZ at baseline and carried out a follow-up at 18 months. The findings

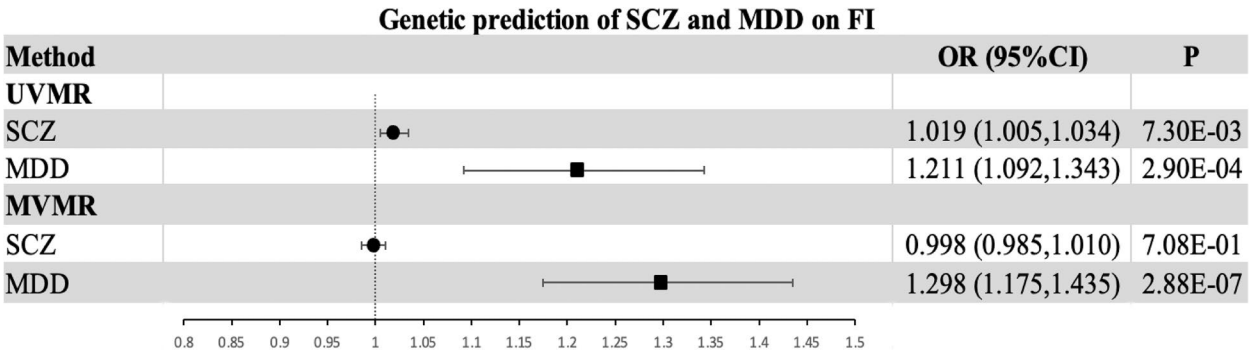

Fig. 4 Effect of genetic risk of SCZ and MDD on FI in UVMR and MVMR. Abbreviations: SCZ, schizophrenia; MDD, major depressive disorder; FI, frailty index; UVMR, univariable mendelian randomization; MVMR, multivariable mendelian randomization

revealed that frailty was remarkably frequent in chronic SCZ patients and was substantially linked with the likelihood of adverse clinical events. A retrospective cohort study of treatment-resistant SCZ also provides novel evidence for these observations [13]. In addition, the accelerated aging hypothesis in SCZ was proposed in 2008 [53] and is based on the assumption that, compared to the general population, SCZ patients tend to experience the physiological changes of aging at a younger age. In a human plasma multi-omics investigation, Campeau et al. [54] discovered that both the diagnosis of SCZ and age had a substantial impact on the plasma proteome of the participants studied. Premature aging in SCZ is widely associated with marked dysregulation of inflammatory and metabolic system components. In further research, individuals with SCZ have been demonstrated to frequently have substantial reductions in brain capacity, cognitive performance, bone density, and leukocyte telomere length [55–58]. In brief, the susceptibility of SCZ patients to frailty and aging may be explained by a combination of external variables and premature internal functioning. Emerging genetic evidence further substantiates this theory [59]. However, a recent study has not established a causal link between schizophrenia and frailty [60]. Even a comprehensive analysis utilizing UK Biobank data yielded no positive findings [61]. Therefore, emerging evidence regarding the relationship between SCZ and FI needs to be supplemented by preclinical and clinical studies.

In addition to SCZ, the genetic liability to MDD distinctly increased the risk of frailty in the current study. According to the World Health Organization, MDD is the primary cause of mental and physical impairment worldwide [62]. Globally, more than 264 million people currently suffer from MDD [63]. Depression is also commonplace among the elderly, with a frequency of 10%–20% [64]. Epidemiological evidence demonstrates that frailty is also frequently observed in the elderly population, with a prevalence similar to that of depression [5]. Both frailty and depression are also characterized by similar clinical symptoms, such as deficiency in daily activities, poor self-care, and loss of interest [65]. In addition, adverse medical outcomes including unintentional weight loss, falls, disability, hospitalization, and even death are intimately associated with depression and frailty [66–68]. In this regard, it is not difficult to recognize that the criteria for determining depression and frailty are highly overlapping as well as disparate and that the relationship between depression and frailty is essential since they both have pronounced health consequences for the elderly population, with widely differing treatment strategies [69–71]. A recent distinctive study further elaborated on the fact that frailty occurs more frequently in people with depression from a gender perspective [71]. Furthermore, a systematic review and meta-analysis of a cohort of 84,351 older adults aged 65 years and older showed that older adults with depression were more susceptible to frailty than those without depression [72]. Yan Liu, et al. [73], on the other hand, also validated the previously mentioned assertion by using data model fitting to explore the association between depression and frailty. Notably, both emerging and accumulating evidence provide further support for our findings [14, 66, 74–76]. The causal association between depression and frailty may be due to several explanations. First, in contrast to frailty, depression usually appears at an earlier age. Second, mood swings, low motivation, reduced sleep, a sedentary lifestyle, and social isolation associated with late-life depression often contribute to frailty [77]. Third, more severe late-life depression is related to a higher prevalence of frailty [78]. Moreover, bereavement, cognitive impairment, and multiple illnesses that characterize later life inevitably exacerbate frailty [79]. Furthermore, the somatic burden of chronic antidepressants combined with sleeping medications further intensifies this issue [80]. Finally, a portion of common pathophysiological pathways may also exist. The above facts can be explained, at least in part, by overlapping mechanisms, such as inflammatory events, oxidative stress, mitochondrial dysfunction, and variability in the response of the hypothalamic–pituitary–adrenal axis to elevated cortisol levels [81, 82]. Obviously, future research will further elucidate the pathological mechanisms underlying the association between depression and frailty.

While a proportion of observational studies provide evidence for a relationship between common mental disorders and frailty, genetically predicting nine other common mental disorders failed to detect a causal association with frailty, as did reverse analyses of MR [12, 14, 18]. On the other hand, the results of MR inverse analysis found a significant and causal relationship between FI and MDD. It was pointed out in a clinical study ($N=5,303$) that a bidirectional association exists between depression and frailty [2]. A systematic review and meta-analysis of 24 studies also indicated an interaction between depression and frailty [83]. The evidence for a bidirectional association between depression and frailty was strengthened by the multivariate MR analysis of Ni Sang et al. [28]. Both the frailty phenotype and the frailty index have been genetically found to be bi-directionally associated with depression [84]. These findings, initially based on GWAS data for depression from the UK Biobank, were further corroborated by GWAS data from the FinnGen database [59]. The pathologic mechanisms underlying the interaction between frailty and depression may also be similar.

However, a systematic review and meta-analysis involving 84,531 older adults found no evidence of a significant effect of frailty on depression [72]. Notably, Morin RT et al. have indicated that the severity of depression in older adults is unrelated to frailty [85]. Hence, given that frailty is a syndrome of aging that involves multi-system impairment, further research involving the pathomechanisms of mental disorders and frailty is needed.

Accumulating evidence demonstrates that MDD and SCZ, although two common mental disorders are inextricably connected [86]. Symptomatologically, there are many similarities between the lack of motivation and reduced activity exhibited by depression and the negative symptoms of SCZ [87]. In terms of clinical diagnosis, evidence that the relationship is not simply a dichotomy is the listing of schizoaffective disorder and post-schizophrenic depression [88, 89]. With regard to health hazards, they cause serious consequences such as impairment of social functioning, disruption of interpersonal relationships, and even impact on personal or public safety [90–92]. In pathological mechanisms, both are closely associated with neurotransmitters [93]. Likewise, emerging Meta-analyses have shown that genetic prediction of MDD is remarkably associated with SCZ [30]. Various indications show that the two mental disorders are associated to some extent and may involve co-morbidities. MVMR provides a better understanding of the direct impact of the two mental disorders on FI. In the MVMR, independent of SCZ, no significant variation in the effect of MDD on FI was observed. However, by adjusting MDD, the impact of SCZ on FI is greatly diminished. Our findings challenge Kraepelin's dichotomous model of major mental disorders [94]. On the basis of this belief in the existence of a "natural" disease entity, Kraepelin divided the major mental disorders according to early-onset dementia or SCZ versus manic-depressive psychosis or bipolar disorder and mood disorders. The syndrome of the Kraepelin dichotomy is characterized by its mutual exclusivity and stability over time. In clinical work, however, it is not difficult to find a large cluster of intermediate symptoms between the dichotomies, such as depressive episodes with psychotic symptoms [95]. A systematic review of 39 clinical studies spanning nearly 40 years showed a trend towards greater diagnostic stability in SCZ over time [96], whereas the results of another review on the overall stability of mood disorder diagnoses across the lifespan hints at a high degree of variability in the diagnostic stability of affective disorders [97]. In adjusted MDD, evidence of a non-significant effect of SCZ on FI at the genetic level strengthens the basis for the overlap of some pathologic mechanisms between the two psychiatric disorders. In terms of phenotypic analysis, a single symptom such as depressed mood, delusions, or irritability is combined in different permutations to give an anxiety-depression syndrome or a hallucinatory-delusional syndrome. Not surprisingly, the composition of the syndromes is characterized by symptom intersection. It is also not difficult to explain the overlap of symptoms between MDD and SCZ. From the point of view of pathological mechanisms, both may involve dysregulation of the dopamine system [98]. The theory is that interneuron dysfunction in SCZ leads to dysregulation of the dopamine system and occurs in other mental disorders as well. Once the interneurons are abnormal, a disruption of rhythmic activity and coherence in exaggerated brain regions may develop. There is evidence that interneurons are especially susceptible to oxidative stress-induced damage during early postnatal development, prior to the formation of the protective perineuronal network [99]. Considering the shared susceptibility of both disorders to stress sensitivity, it is plausible that exacerbated stress responses and exposure during adolescence, resulting in damage to the parvalbumin neurons, may play a role in the development of SCZ. If an individual is protected from mental stress during the peri-adolescent period of parvalbumin susceptibility, they may become prone to developing depression later in life when exposed to stronger stress responses [98].

The association between frailty and psychiatric disorders extends beyond SCZ and MDD to include other conditions, such as insomnia and remains a focal point of ongoing clinical research. The majority of previous discussions between insomnia and frailty have focused on the elderly population. A meta-analysis of insomnia and frailty in older adults showed that the two were independently associated [100]. Previous studies show that older adults who sleep for longer or shorter periods of time, insufficient daytime sleep, and poor sleep quality are more likely to be frail [101, 102]. On the other hand, frail older adults are also prone to insomnia [103]. Recent genetic analyses have found that the two are related and share genes [104]. However, our study did not find positive results, which may be due to different selection criteria for IVs. The relationship between insomnia and frailty needs to be corroborated by more high-level research evidence.

Our study did not identify a genetic association between anxiety disorders and frailty. However, a systematic review of 25 studies involving 2,499 patients reported a high prevalence of frailty in individuals with severe mental illnesses, including anxiety disorders [105]. Furthermore, anxiety has been independently associated with frailty in studies of postmenopausal women [106]. Longitudinal data from the UK Biobank, encompassing up to 500,000 participants, confirmed a significant association between anxiety disorders and frailty

[18]. This finding was confirmed by research on genetic analysis [60, 107]. Additionally, bidirectional associations between genetically determined anxiety and frailty have been observed [59]. Mixed results may stem from factors such as confounding variables in observational studies and variations in genetic data sources used in MR studies. The application of the larger GWAS data on anxiety disorders enables us to remain confident in our findings.

Frailty is notably prevalent in patients with bipolar disorder, a major psychiatric condition [105]. Analysis of UK Biobank data further supports the association between bipolar disorder and frailty [18]. The association between genetic susceptibility to bipolar disorder and frailty has also been established [108]. A bidirectional association between affective disorders and frailty has also been reported [59]. In contrast, some studies have found no evidence of a genetic predisposition to bipolar disorder and frailty [60]. The same is true for our study. These conflicting findings highlight the need to consider confounding factors and the potential impact of differing genetic susceptibility across populations.

The remaining five psychiatric disorders (ASD, OCD, AN, MBDO, and MBDS) have limited research related to frailty, and our study did not find enough IVs for these conditions. Even after adjusting the selection criteria for IVs ($P=1^{*}10^{-6}$), only ASD received a sufficiently large number of IVs, whereas still no positive results were found. With deeper research, their association may be able to be dialed in.

Our research has several important implications and strengths. We obtained IVs for each of the ten common mental disorders from a large GWAS database and analyzed bidirectional causality between mental disorders and frailty using MR methods to reduce the risk of reverse causality bias and the effect of confounders. In addition, frailty, as a reversible variable, gives health and community workers more space for prevention and improvement [109]. Nevertheless, our research also has some limitations. First, given that the GWAS of the IVs obtained in this study were of European ancestry, the findings should be generalized to other races with caution. Second, due to the failure to obtain a sufficient number of IVs, some mental disorders (e.g., OCD) could not be analyzed in the MR analysis. An updated and larger GWAS is needed to polish the study. Third, although our study employed bidirectional MR analyses, the mechanisms underlying the association between mental disorders and frailty are complex. The interference of confounding factors still cannot be completely avoided [110], and research findings should be interpreted with caution. Fourth, overlapping samples of common psychiatric disorders and FI potentially biased MR estimates. Since overlapping samples may reduce the effective sample size, the efficacy of the statistical test is reduced. Finally, the FI, in comparison with the frailty phenotype, is comprehensive and robust. However, its application is limited at present, especially in low-income countries [111].

Conclusion

In conclusion, from a genetic perspective, the current MR analyses provide further evidence for a causal relationship between SCZ, MDD, and frailty and explore the underlying pathologic mechanisms for the aforementioned associations.

Abbreviations

AD	Anxiety disorder
AN	Anorexia nervosa
ASD	Autism spectrum disorder
BD	Bipolar disorder
FI	Frailty index
FP	Frailty phenotype
GWAS	Genome-wide association study
IEU	Integrative Epidemiology Unit
ISN	Insomnia
IVs	Instrumental variables
IVW	Inverse variance weighting
MBDS	Mental and behavioral disorders due to use of other stimulants
MBDO	Opioid-related mental and behavioral disorders
MDD	Major depressive disorder
MR	Mendelian randomization
MR-PRESSO	MR-pleiotropy residual sum and outlier
MVMR	Multivariable Mendelian randomization
OCD	Obsessive compulsive disorder
PGC	Psychiatric Genomics Consortium
SCZ	Schizophrenia
SNPs	Single nucleotide polymorphisms
UVMR	Univariable mendelian randomization

Supplementary Information

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Supplementary Material 1: Supplementary material for this paper is Tables S1 – 15.

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Authors' contributions

Y.R. F., W.X. S., and X.B. Z. contributed to the conception and design of the study. S.J. T. and X.H. W. organized the database and carried out the statistical analyses. W.X. S. wrote the first draft of the manuscript. P. S. and J. C. wrote parts of the manuscript. All authors participated in revising the manuscript, and read and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This MR study was conducted based on publicly available summary statistics from a large genome-wide association study (GWAS) and all participants provided written informed consent.

Competing interests
The authors declare no competing interests.

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