EPIDEMIOLOGY

Association between frailty and depression: A bidirectional Mendelian randomization study

Ming-Gang Deng[1]*†, Fang Liu[2]†, Yuehui Liang[2], Kai Wang[3], Jia-Qi Nie[2]‡, Jiewei Liu[1]*

Frailty and depression were linked in observational studies, but the causality remains ambiguous. We intended to explore it using Mendelian randomization (MR). We obtained frailty genome-wide association study (GWAS) data from UK Biobank and TwinGen meta-analysis, and depression GWAS data from Psychiatric Genomics Consortium (PGC) and FinnGen (respectively recorded as PD and FD). We performed univariable and multivariable-adjusted MR with adjustments for body mass index (BMI) and physical activity (PA). Frailty was significantly associated with elevated risks of PD (OR, 1.860; 95% CI, 1.439 to 2.405; $P < 0.001$) and FD (OR, 1.745; 95% CI, 1.193 to 2.552; $P = 0.004$), and depression was meanwhile a susceptible factor for frailty (PD: β, 0.146; 95% CI, 0.086 to 0.201; $P < 0.001$; and FD: β, 0.112; 95% CI, 0.051 to 0.174; $P < 0.001$). This association was robust after adjustments for BMI or PA. Our study provides evidence of the bidirectional causal association between frailty and depression from genetic perspectives.

INTRODUCTION

Frailty is a state of vulnerability to poor resolution of homeostasis following stress, which increases the risk of adverse outcomes including falls, disability, long-term care, and death (*1*). Understanding the potential association between frailty and frailty-related diseases would likely benefit frail patients to seek individualized management and early interventions.

Depression is the most common mental health illness, characterized by long-lasting low mood, anxious feelings, cognitive impairment, and somatic symptoms (*2*, *3*). If left uncontrolled, depression can lead to suicide, increasing the mortality risk (*4*, *5*). To date, depression substantially burdens health care and the social economy because of the high prevalence and severity of symptoms.

Numerous epidemiological studies have found associations between frailty and depression. For example, a retrospective study of 411 patients in the Geriatric Clinic of "Dr. C. I. Parhon" Hospital found that frailty was positively associated with depression (*6*). A cross-sectional study of 80 patients showed depression was associated with the presence of frailty among patients with chronic kidney disease on hemodialysis (*7*). In addition, a cohort study of 1602 Germans observed over 1.5 years found that frailty increased with the increasing occurrence of depression (*8*). Furthermore, a meta-analysis of 14 observational studies (10 cross-sectional and 4 cohorts), including 84,351 community-dwelling older adults, confirmed that depression in older adults was associated with frailty (*9*). However, the exact causal relationship between frailty and depression remains unclear.

Mendelian randomization (MR) is a useful tool to identify the causal effect of the exposure on the outcome (*10*). MR uses genetic variations as instrumental variants and relies on equally, randomly, and independently distributed genetic variants during meiosis, which effectively avoids the influence of confounding and reverse causes (*11*). Genome-wide association studies (GWASs) have identified thousands of genetic variations related to various complex diseases, which has pushed the widespread use of MR to a higher stage (*12*). On the basis of the knowledge above, here, we adopted a bidirectional MR analysis by using recent large-scale GWASs to investigate the causal relationship between frailty and depression.

RESULTS

Genetic correlation

The results of linkage disequilibrium score regression (LDSC) indicated that frailty had a moderate genetic correlation with Psychiatric Genomics Consortium (PGC) depression (PD), and FinnGen depression (FD), the r_g values were 0.617 [standard error (SE) = 0.0367 and $P = 2.47 \times 10^{-63}$], and 0.548 (SE = 0.0334 and $P = 2.05 \times 10^{-60}$), respectively.

Characteristics of selected genetic variants

According to the predetermined criteria, a total of 13, 33, and 15 single-nucleotide polymorphisms (SNPs) associated with frailty, PD, and FD were selected and presented in tables S1 and S2, respectively. The total proportions of variance (R^2) in the frailty, PD, and FD explained by their corresponding SNPs were about 0.239, 1.745, and 1.548%, respectively. The F statistics were all greater than 10, indicating a relatively low risk of weak instrument bias in MR analyses.

Univariable MR analysis

Casual effect of frailty on depression

The results of univariable MR analysis to explore the causal effect of frailty on depression were presented in Fig. 1. MR-Egger regression intercept term indicated no obvious directional pleiotropy existing among the SNPs in two datasets, the P values were both greater than 0.05. No obvious heterogeneity was detected in genetic variants associated with frailty and PD (Cochran's $Q = 17.33$ and $P = 0.137$), whereas obvious heterogeneity was found in genetic variants related

[1]Department of Psychiatry, Wuhan Mental Health Center, Wuhan, China. [2]School of Public Health, Wuhan University, Wuhan 430071, China. [3]Department of Public Health, Wuhan Fourth Hospital, Wuhan 430033, China.
*Corresponding author. Email: deng.minggang@outlook.com (M.G.D.); liujiewei@hust.edu.cn (J.L.)
†These authors contributed equally to this work.
‡Present address: Xiaogan Center for Disease Control and Prevention, Xiaogan, Hubei 432000, China.

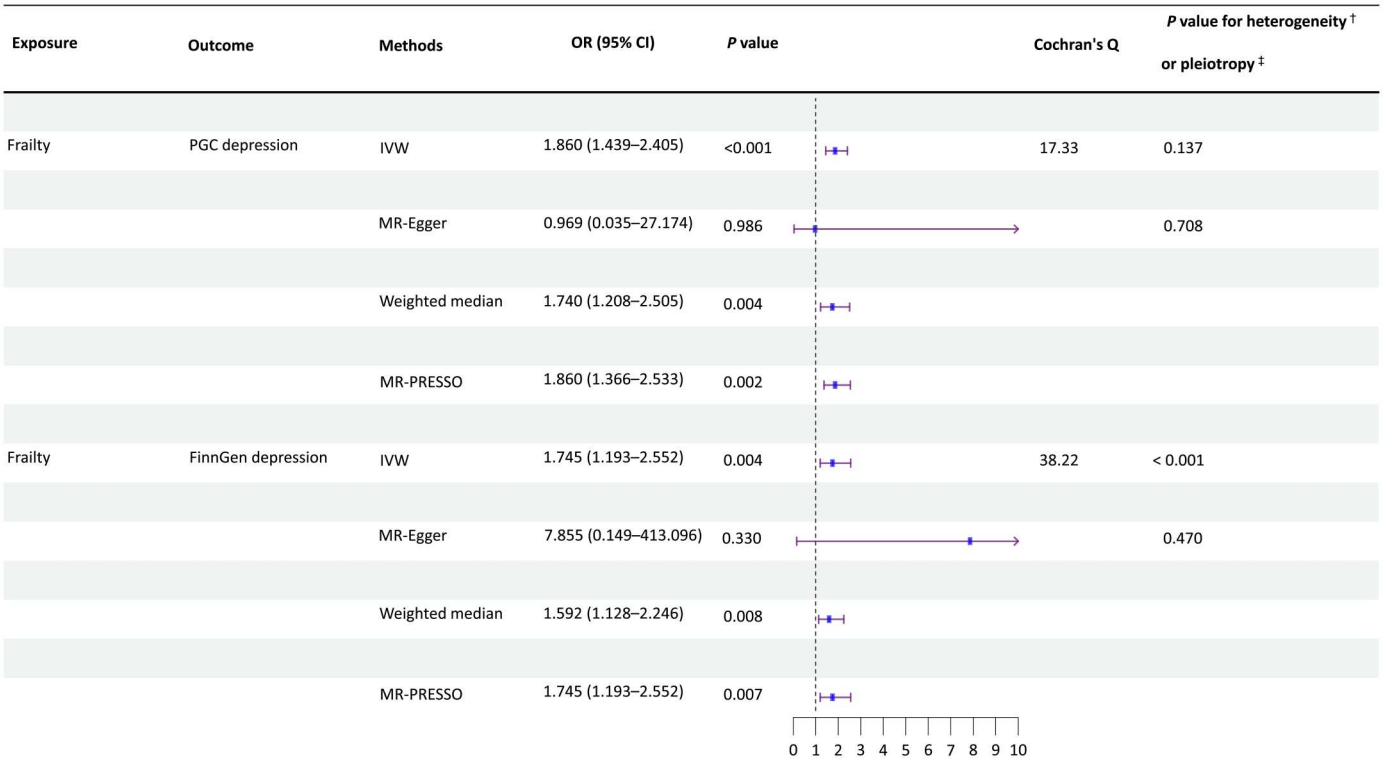

Fig. 1. Univariate MR estimates of frailty on depression. †*P* value for heterogeneity based on Cochran's *Q* statistic. ‡*P* value or pleiotropy based on MR-Egger regression intercept.

to frailty and FD (Cochran's $Q = 38.22$ and $P < 0.001$). Therefore, the inverse variance weighted (IVW) method under fixed and random effect was used to evaluate the causal associations of frailty on PD and FD, respectively. The IVW method demonstrated that genetically predicted higher frailty index was related to the elevated risk of PD [odds ratio (OR), 1.860; 95% confidence interval (CI), 1.439 to 2.405; $P < 0.001$], and the replication in the FinnGen dataset presented a similar association (OR, 1.745; 95% CI, 1.193 to 2.552; $P = 0.004$). Compared to the findings from the supplemented methods, weighted median and MR-PRESSO (Pleiotropy RESidual Sum and Outlier) both demonstrated the risk effect of frailty on PD and FD and provided evidence of the stability of results from the IVW method.

The scatter plots of SNP potential effects on frailty versus depression were demonstrated in fig. S1, with the slope of each representing the evaluated effect size per method. The individual and combined effects of frailty on depression were illustrated in Fig. 2. Among the 13 SNPs, three SNPs (rs1363103, rs2396766, and rs8089807) and six SNPs (rs10891490, rs12739243, rs1363103, rs4952693, rs583514, and rs8089807) were respectively related to increased risks of PD and FD, while the others were not. The result of the leave-one-out (LOO) analysis was presented in fig. S2, where no single SNP was driving the whole effect.

Casual effect of depression on frailty

With genetic liability for PD and FD as the exposures, the results of reverse MR analyses were demonstrated in Table 1. The random-effect IVW methods provided evidence of the causal effect of PD on a higher frailty index (β, 0.143; 95% CI, 0.086 to 0.201; $P < 0.001$). Even though obvious directional pleiotropy among PD-associated instrument variants was identified by the MR-Egger intercept ($P = 0.013$), this causal association was supported by the weighted median (β, 0.166; 95% CI, 0.106 to 0.226; $P < 0.001$) and MR-PRESSO (β, 0.143; 95% CI, 0.086 to 0.201; $P < 0.001$) methods. Similarly, the replication results in the FinnGen data were consistent with the above findings, which were backed up by the IVW (β, 0.112; 95% CI, 0.051 to 0.174; $P < 0.001$), weighted median (β, 0.106; 95% CI, 0.041 to 0.17; $P = 0.001$), and MR-PRESSO (β, 0.112; 95% CI, 0.051 to 0.174; $P = 0.003$) methods.

The scatter plots of SNP potential effects on depression versus frailty were demonstrated in fig. S3. The forest plots illustrating individual and combined effects of PD and FD on frailty were illustrated in Figs. 3 and 4, respectively. A total of 15 (rs10149470, rs10950398, rs10959913, rs11663393, rs1226412, rs12552, rs12666117, rs1432639, rs1806153, rs2005864, rs247910, rs5758265, rs7198928, rs7856424, and rs8025231) of 33 SNPs related to PD and 5 (rs1027190, rs4619804, rs4923546, rs62099231, and rs6876567) of 15 SNPs related to FD were positively related to the frailty index, while the others were not, and consistent with the LOO analyses as illustrated in fig. S4, the whole effects were not driven by a single genetic variant.

Multivariable MR analysis

The results of multivariable MR (MVMR) adjusted for body mass index (BMI) and physical activity (PA) to explore the bidirectional causal relationship between frailty and depression were presented in Table 2. After adjusting for BMI, which was the major confounding

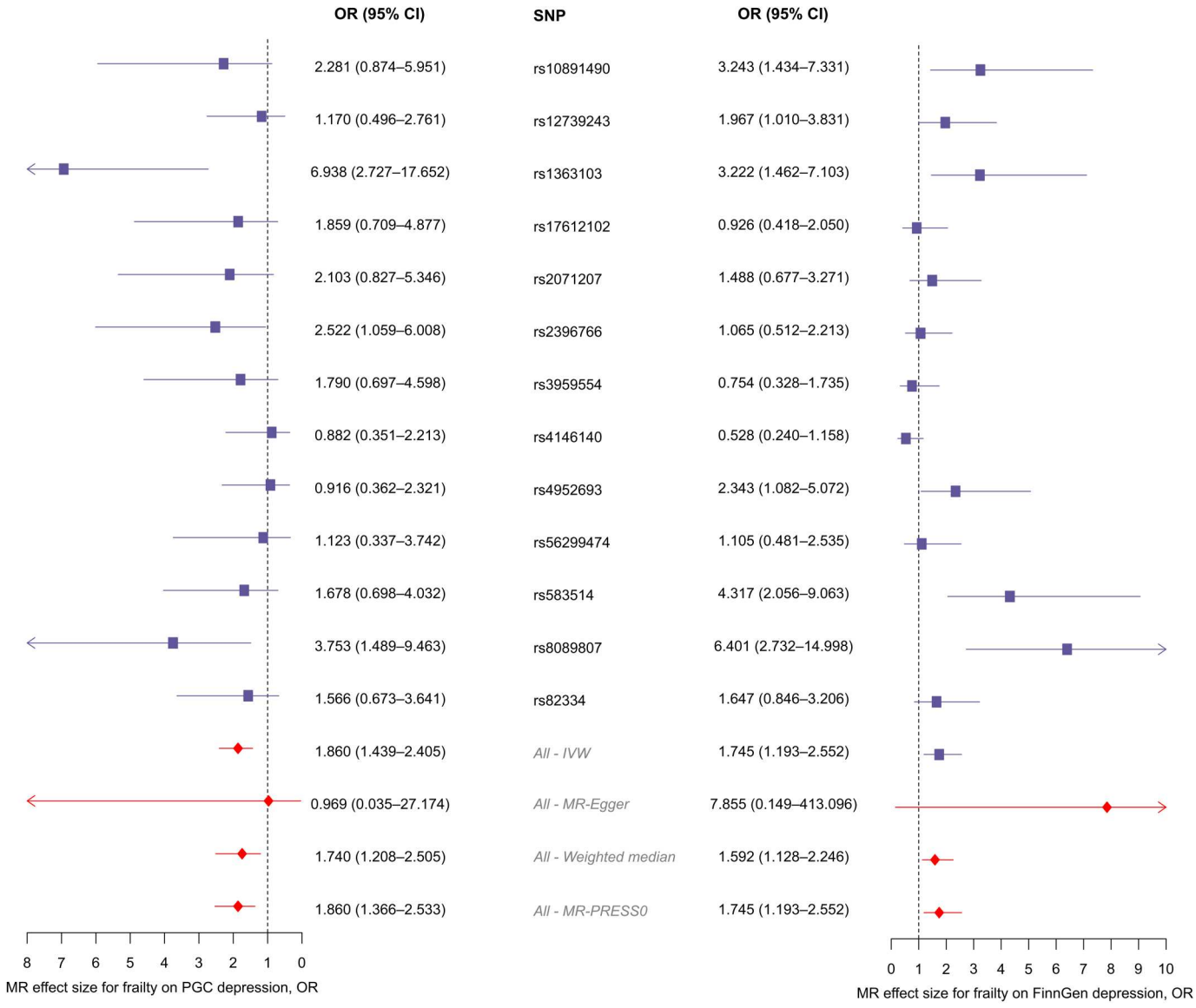

Fig. 2. Forest plot of the individual and combined effect of frailty on PD (left) and FD (right). Data were presented as OR and 95% CI.

factor in the association between frailty and depression (tables S1 and S2), the IVW method indicated that higher frailty index was still associated with elevated risks of PD (OR, 1.639; 95% CI, 1.326 to 2.024; $P = 4.70 \times 10^{-06}$) and FD (OR, 1.459; 95% CI, 1.195 to 1.782; $P = 2.12 \times 10^{-04}$). Reversely, depressed people were also more likely to have a higher frailty index (PD: β, 0.146; 95% CI, 0.086 to 0.201; $P < 0.001$; and FD: β, 0.112; 95% CI, 0.051 to 0.174; $P < 0.001$). Sensitivity analyses conducted by supplemented approaches also supported this bidirectional causal relationship, and this bidirectional causal association was still stable when adjusting for PA.

Evaluation of the assumptions of MR

First, for the relevance assumption, we selected frailty- and depression-associated SNPs from GWAS with large sample sizes, the genome-wide significance was set with a strict threshold at $P < 5 \times 10^{-08}$, and the F statistics for each SNP were all greater than 10, thus making the selected SNPs robustly associated with exposures and unlikely to result in weak instrument bias. In addition, for the independence assumption, we used the PhenoScanner V2 tool to assess whether the SNPs were associated with confounders or risk factors in frailty and depression (*13*), and we found that the selected SNPs were generally associated with BMI at $P < 1 \times 10^{-05}$. In addition, PA was confirmed to help prevent depression by previous MR research and was an easily modifiable lifestyle (*14*). Thus, we furthermore performed MVMR to adjust for BMI and PA, and the results were still robust. Last, for the exclusion assumption, we clumped SNPs at a restricted standard to prune for linkage disequilibrium (LD) to make the SNPs independent of each other. Although horizontal pleiotropy was detected among PD-associated SNPs by the MR-Egger regression intercept, its lower limit of 95% CI was 0.001, which was very close to zero, and the causal inference

Table 1. Univariate MR estimates of depression on frailty.

Exposure	Outcome	Methods	β (95% CI)	*P* value	Cochran's *Q*	*P* value for heterogeneity* or pleiotropy†
PD	Frailty	IVW	0.143 (0.086–0.201)	<0.001	86.16	< 0.001
		MR-Egger	−0.016 (−0.153–0.121)	0.816		0.013
		Weighted median	0.166 (0.106–0.226)	<0.001		
		MR-PRESSO	0.143 (0.086–0.201)	<0.001		
FD	Frailty	IVW	0.112 (0.051–0.174)	<0.001	36.89	0.001
		MR-Egger	−0.001 (−0.567–0.565)	0.998		0.693
		Weighted median	0.106 (0.041–0.17)	0.001		
		MR-PRESSO	0.112 (0.051–0.174)	0.003		

*P value for heterogeneity based on Cochran's Q statistic. †P value or pleiotropy based on MR-Egger regression intercept.

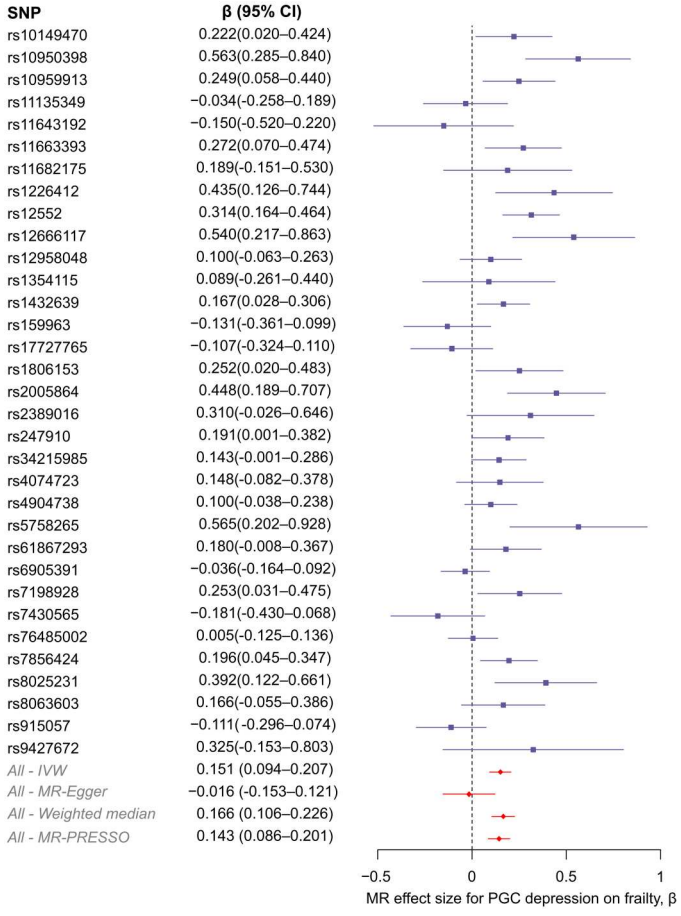

Fig. 3. Forest plot of the individual and combined effect of PD on frailty. Data were presented as β and 95% CI.

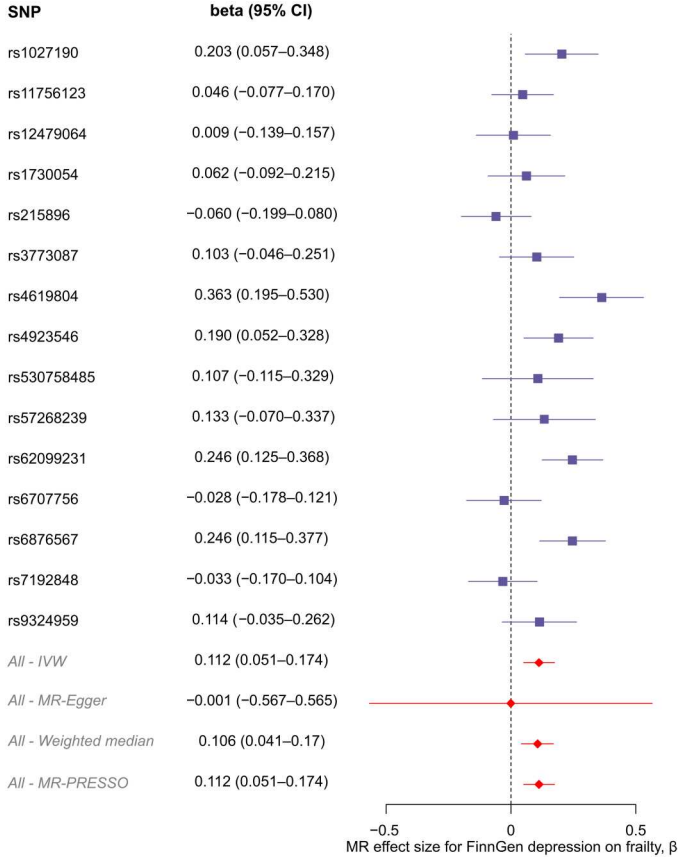

Fig. 4. Forest plot of the individual and combined effect of FD on frailty. Data were presented as β and 95% CI.

Table 2. MVMR estimates between frailty and depression. a, adjusted for BMI; b, adjusted for PA.

Exposure	Outcome	Methods	β/OR (95% CI)	*P* value
Frailty	PD	IVW		
		a	1.639 (1.326–2.024)	4.70E−06
		b	1.680 (1.269–2.228)	2.98E−04
		MR-Egger		
		a	1.654 (1.232–2.219)	8.09E−04
		b	1.692 (1.269–2.257)	3.43E−04
		Weighted median		
		a	1.713 (1.336–2.195)	2.20E−05
		b	1.679 (1.149–2.455)	7.63E−03
		MR-PRESOO		
		a	1.639 (1.326–2.024)	6.01E−06
		b	1.681 (1.269–2.227)	2.13E−03
Frailty	FD	IVW		
		a	1.459 (1.195–1.782)	2.12E−04
		b	1.786 (1.288–2.477)	5.12E−04
		MR-Egger		
		a	1.556 (1.176–2.059)	1.97E−03
		b	1.818 (1.293–2.555)	5.82E−04
		Weighted median		
		a	1.536 (1.231–1.916)	1.41E−04
		b	1.735 (1.250–2.411)	9.99E−04
		MR-PRESOO		
		a	1.460 (1.195–1.783)	2.38E−04
		b	1.786 (1.288–2.478)	2.54E−03
PD	Frailty	IVW		
		a	0.079 (0.045–0.113)	6.23E−06
		b	0.126 (0.061–0.19)	1.37E−04
		MR-Egger		
		a	0.105 (0.051–0.159)	1.47E−04
		b	0.049 (−0.083–0.181)	4.66E−01
		Weighted median		
		a	0.080 (0.043–0.117)	1.78E−05
		b	0.178 (0.113–0.243)	9.15E−08
		MR-PRESOO		
		a	0.079 (0.045–0.113)	7.84E−06
		b	0.126 (0.061–0.190)	5.50E−04
FD	Frailty	IVW		
		a	0.083 (0.045–0.122)	2.03E−05
		b	0.117 (0.040–0.194)	2.75E−03
		MR-Egger		
		a	0.082 (0.044–0.120)	2.08E−05
		b	0.065 (−0.122–0.251)	4.98E−01
		Weighted median		
		a	0.076 (0.034–0.117)	3.47E−04
		b	0.117 (0.038–0.195)	3.50E−03
		MR-PRESOO		
		a	0.083 (0.045–0.122)	2.45E−05
		b	0.117 (0.040–0.194)	7.78E−03

by the IVW method was corroborated by the weighted median and MR-PRESSO approaches, which were robust to horizontal pleiotropy. Accordingly, the causal estimates may unlikely be biased by this marginal significant horizontal pleiotropy.

DISCUSSION

In this bidirectional MR study, we found that frailty had a positive causal effect on the presence of depression. On the other hand, reverse direction analyses provided evidence that depression was also positively associated with frailty. After adjusting for covariates such as BMI and PA, the above associations still existed.

Currently, many epidemiological studies have explored the association between frailty and depression. For example, in a cross-sectional analysis of 382 participants, Jung *et al.* (*15*) reported that taking the participants with no depression as a reference, depressed individuals had an increased risk of having frailty (OR, 5.25; 95% CI, 2.55 to 10.83). McAdams-DeMarco *et al.* (*16*) found depression was strongly associated with frailty in a cohort study comprising 663 kidney transplantation recipients. Moreover, two longitudinal studies that included 4852 older adults found that frailty at baseline increased the risk of incident depression by about 90% (*17*, *18*). In line with the preceding reports, we observed a bidirectional causal association between frailty and depression using a bidirectional MR study. However, more randomized clinical trials were needed to confirm this hypothesis.

Several potential reasons may explain the bidirectional causal association between frailty and depression. On the one hand, frailty could cause adverse outcomes such as falls, higher medical costs, and less social interaction, which subsequently lead to anxiety, and ultimately result in depression (*19*, *20*). On the other hand, depression could lead to poor nutritional status, sleep disturbance, and emotional disorders, which may seriously affect physical health and cause frailty (*21*–*23*). In addition, depression is associated with cognitive impairment, which may also lead to the appearance of frailty (*24*, *25*). Furthermore, growing evidence also supported the bidirectional causal association between frailty and depression could be partially explained by shared risk factors and pathophysiological pathways, such as chronic inflammation, oxidative stress, mitochondrial dysfunction, and hypothalamic adrenal axis dysregulation (*26*–*32*). From the genetic perspective, our LDSC analyses indicated a moderate genetic correlation between frailty index and depression, the genetic correlation coefficients were 0.617 (frailty index and PD) and 0.548 (frailty index and FD), respectively. In addition, the original frailty GWAS summary statistics reported 14 genome-wide significant risk loci and two loci also showed significant association with depression/depressive symptoms (*33*). The lead SNP of the first locus is rs1363103 ($P = 2.2 \times 10^{-08}$), and the neatest gene is a lincRNA, while the *NCAM1* gene is the nearest gene of the second locus (lead SNP rs10891490, $P = 2.0 \times 10^{-08}$). These convergently support the comorbidity between frailty and depression and the substantial shared genetics between these two traits. However, at present, the etiological model of the bidirectional causal association between frailty and depression is very complex and cannot be explained for one or several reasons. Therefore, further research to explore the specific mechanism of a bidirectional causal association between frailty and depression is necessary.

It is worth noting that both frailty and depression are associated with a series of deleterious results such as decreased quality of life and increased use of health care services (*34*, *35*). Coexisting frailty and depression even led to accelerated cognitive impairment, disability, and death (*36*). Therefore, providing timely psychological comfort and psychological guidance to frail patients or screening depressed patients for frailty are both necessary.

The present study had the following advantages. First, we explored the bidirectional causal association of frailty and depression by using a bidirectional MR design, which was less susceptible to the effects of confounders, reverse causation, and exposures nondifferentially (*37*). Second, sensitivity analyses such as MR-Egger, weighted median, and MR-PRESSO were performed to ensure the consistency and robustness of the results, and the application of MVMR with the confounding factors being adjusted making the inference of bidirectional causal relationships between frailty and depression more reliable. Last, two independent depression-associated GWAS datasets were obtained from PGC and FinnGen, and the results were consistent in these two populations, which further confirmed our findings. Despite these strengths, our findings should be interpreted in the context of some limitations. For example, the study population included in the present analyses was the European population. Hence, our findings could not be generalized to other populations. In addition, although the bidirectional causal effect between frailty and depression was demonstrated, whether designing and planning interventions targeting shared risk factors of frailty and depression may better manage patients should be further assessed in a future trial.

In conclusion, this study supported a bidirectional causal association between frailty and depression. On the basis of our findings, it is reasonable to consider promoting routine frailty screening in depression patients. In addition, proper management of depression is also essential for downregulating the risk of frailty.

METHODS AND MATERIALS

Study design

This study was designed as a bidirectional two-sample MR research, and an overview was illustrated in Fig. 5. To assure the causal inference derived from MR analyses be valid, the instrumental variables (SNPs) should satisfy three core assumptions: (i) The relevance assumption implied that genetic variants should be robustly associated with the exposure phenotype, (ii) the independence assumption indicated instrumental variants should not be associated with confounding, and (iii) the exclusion-restriction assumption was that the causal pathway should be through the exposure of interest (*38*). The MR analyses were performed in two directions with frailty (i) as exposure: to evaluate if people with higher frailty index were more susceptible to depression, and (ii) as outcome: to assess whether depressed individuals were more fragile.

Data sources

The datasets involved in the present research were all publicly available and ethical approvals were gained in all original papers.

Frailty-related SNPs were provided by a large GWAS meta-analysis compromising European participants from UK Biobank (n = 164,610, aged 60 to 70 years old, and 51.3% females) and TwinGene (n = 10,616, aged 41 to 87 years old, and 52.5% females) by Atkins *et al.* (*33*). They measured frailty by the frailty index, which was based

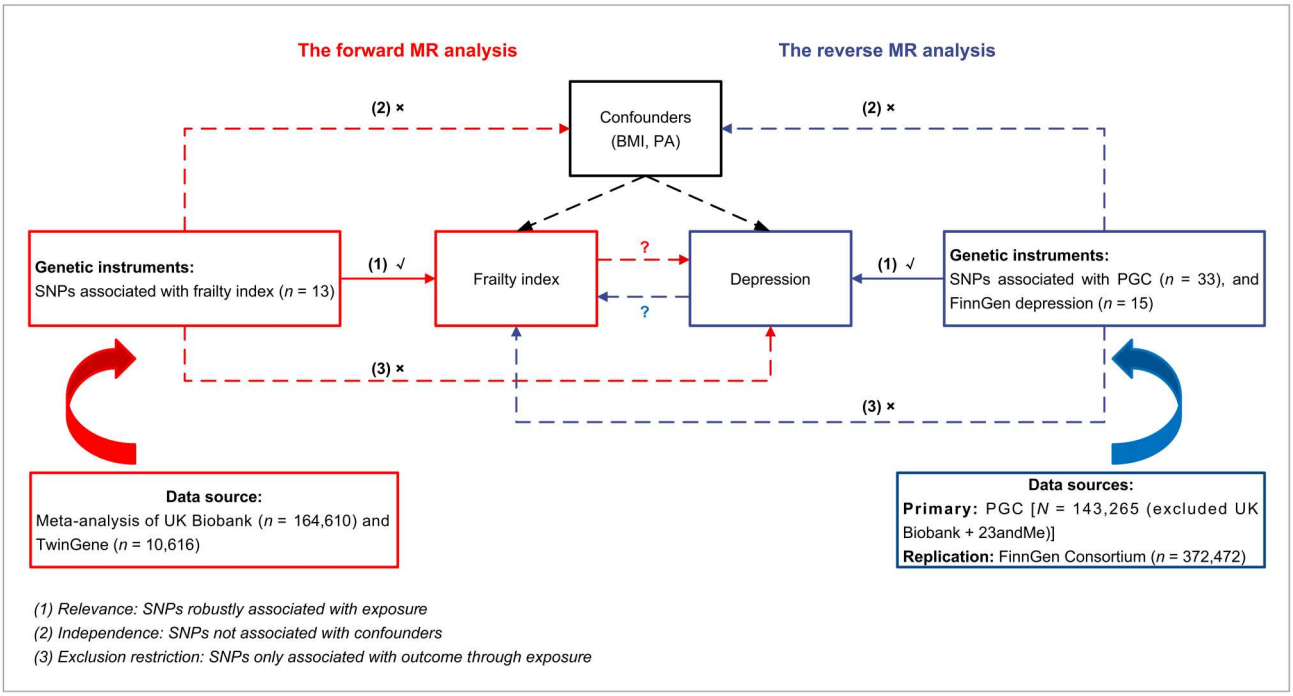

Fig. 5. Overview of this bidirectional MR study design.

on the accumulation of 49 health deficits during the life course (*33*) and has been well-validated and widely used in clinical practice (*39*, *40*).

Summary statistics for depression were primarily retrieved from the recent GWAS of major depression in the European population from PGC, which included a total of 135,458 cases and 344,901 controls (*41*). The enrolled cases were diagnosed via structured diagnostic tools from assessments by trained interviewers, clinician-administered checklists, or medical record reviews, which were required to satisfy the DSM-IV, ICD-9, or ICD-10 criteria (*41*). Considering the large sample overlap between frailty and depression, we excluded the participants from UK Biobank (n = 29,740), and the samples from 23andMe (n = 307,354) were meanwhile removed due to general access constraints. This elimination resulted in a GWAS meta-analytic subsample of 143,265 (45,591 cases and 97,674 controls). To evaluate the MR inference stability, another set of summary-level statistics on depression was obtained from the FinnGen consortium database (R9 release) (*42*), which included 43,280 cases and 329,192 controls. The diagnosis of depression in the FinnGen dataset should meet the corresponding criteria in ICD-9 or ICD-10. The median age of the FinnGen sample was about 41.50 years old, and females accounted for a percentage of about 55.89%.

Instrumental variables selection

SNPs robustly associated with exposures were initially screened at genome-wide significance ($P < 5 \times 10^{-08}$). Then, the identified SNPs were clumped for LD using PLINK v1.9 (*43*) with a strict cutoff of clumping R^2 = 0.001 within a window of 10,000 kb, and LD was estimated with the European samples from the 1000 Genome Project as reference (*44*). If there was an LD effect among SNPs, then the SNP with the lowest P value was retained. To assess whether the retained SNPs may suffer from weak instrument bias or not, the F statistic was used and calculated as in the previous study (*45*), and those with an F statistic smaller than 10 were considered weak instruments and excluded (*46*). After harmonization of exposure and outcome datasets with palindromic and weak instrumental variants being removed, the remained SNPs were used to conduct MR analysis. SNPs for the exposure if unavailable in the outcome datasets would be replaced by suitable proxy SNPs that minimum LD R^2 = 0.8 and minor allele frequency threshold = 0.3, where available. In addition, we used the PhenoScanner V2, which was an expanded tool for searching human genotype-phenotype associations (*13*), to assess whether the selected SNPs were associated with confounders ($P < 1 \times 10^{-05}$) in the relationship between frailty and depression. If confounders were detected, these confounders would be adjusted in further analyses.

Statistical analysis

LDSC, which allows assessment of SNP-based genetic heritability correlation between two traits (*47*), was preliminarily adopted to evaluate the genetic correlation (r_g) between frailty and depression, with European ancestry samples from the 1000 Genomes Project being the reference panel (*44*).

The MR analysis was primarily performed by the IVW approach, which assumes the absence of average pleiotropic effect, and in this case, is the most efficient method (*48*). Cochran's Q statistic was first computed to evaluate the heterogeneity induced by different genetic variants in the fixed-effect IVW method, with a P value <0.05 indicating the presence of heterogeneity. If so, then the effect would be estimated using the IVW method under multiplicative random effect.

Several other well-established and horizontal pleiotropy robust methods including MR-Egger, weighted median, and MR-

PRESSO were performed to compare with the results of the IVW method, as they may be biased when genetic variants exhibit horizontal pleiotropy. Besides, the MR-Egger regression intercept term was used to assess the possible presence of horizontal pleiotropy, where deviation from zero (P value <0.05) indicates directional pleiotropy (*49*). To evaluate the stability of results, the LOO analysis was conducted to assess if the overall effect was driven by a single SNP.

In addition, MVMR, which is an extension of MR that uses genetic variants associated with multiple, potentially related exposures (*50*), can detect the causal effects of multiple risk factors jointly (*51*). In this study, we adjusted BMI in the MVMR analyses, as it was identified as a notable confounding factor by PhenoScanner V2 (tables S1 and S2). Moreover, PA was also included in the MVMR analysis, since it has been confirmed to help prevent depression by previous MR research (*14*) and was an easily modifiable lifestyle. Similar to the univariable MR analysis, the IVW method was treated as the determinant method, supplemented by MR-Egger, weighted median, and MR-PRESSO.

The statistical analyses were completely performed in R software (version 4.3.0, R Foundation for Statistical Computing) with ldscr (version 0.1.0), TwoSampleMR (version 0.5.7), MendelianRandomization (version 0.8.0), and MR-PRESSO (version 1.0) packages. Effect estimates were reported in β values with 95% CI where the outcome was frailty index and were converted to OR where the outcome was depression. All statistical tests were two tailed, and α = 0.05 was considered as the significant level.

Supplementary Materials

This PDF file includes:

Figs. S1 to S4

Tables S1 and S2

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