



Original Article

Causal relationship and mediating role between depression and cognitive performance



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ABSTRACT

Background: Recent studies have increasingly emphasized the robust correlation between depression and cognitive function. However, it remains unclear whether this relationship is causal or merely coincidental. To address this uncertainty, we conducted two-sample bidirectional Mendelian randomization (MR) analyses to investigate the connection between depression and cognitive performance.

Methods: We sourced genome-wide association study (GWAS) data for depression ($N_{\text{SNPs}}=21,306,230$) from the FinnGen (R10) and for cognitive performance ($N_{\text{SNPs}}=10,049,954$) from the IEU GWAS database. Causal effects employed methodologies such as Inverse variance weighted (IVW), weighted median, MR Egger, simple mode and weighted mode. Two-step analysis determined the contribution of the mediator variable to the outcomes. To determine stability and reliability, sensitivity analyses were performed that included an assessment of heterogeneity, horizontal pleiotropy, and the leave-one-out techniques.

Results: This MR analysis identified 8 independent significant SNPs associated with depression and 81 SNPs linked to cognitive performance. Our findings revealed that depression increases the risk of developing deteriorating cognitive performance (IVW β , -0.11; 95 % confidence interval (CI), -0.18 – -0.05; P_{IVW} value= 5.97E-04). Conversely, cognitive performance decline could also predispose individuals to depression [odds ratio (OR)_{IVW}, 0.85; 95 % CI, 0.76 – 0.95; P_{IVW} value=0.004]. Multivariate MR analysis confirmed the robustness of this bidirectional association. A two-step MR mediation analysis indicated that the pathway from depression to cognitive performance is mediated by pain, with a mediation effect size of -0.022 and a mediation ratio of 28.95 %. The pathway from cognitive performance to depression is mediated by frailty, with a mediation effect value of -0.028, representing 22.40 % of the mediation proportion.

Conclusion: A two-way causal relationship between depression and cognitive performance, with pain and frailty being mediating factors, respectively. Future research should prioritize mechanistic studies, targeted interventions, and personalized approaches to disentangle and mitigate the bidirectional effects of depression and cognitive performance.

1. Introduction

Depression is the most common psychological disorder and has always been among the top three leading causes of disability worldwide [1,2]. It can seriously disrupt daily activities, hinder social interaction and overall physical health, and be accompanied by adverse symptoms

such as changes in appetite, sleep problems and even suicidal tendencies [3,4]. So far, the substantial prevalence and severity of depression have exerted a considerable strain on healthcare systems and hindered socioeconomic progress. Therefore, clarifying the underlying nature of its effects could aid in devising effective preventive measures. Previous studies indicates that depression arises from an interplay of various

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elements such as genetic predispositions, biological processes, environmental influences, and psychological conditions [5–7]. Apart from the acknowledged risks of depression, like family background and demographic characteristics, the connection between depression and cognitive performance has drawn extensive concern in recent years [8,9].

Cognitive performance refers to the series of psychological activities and abilities related to intelligence, including the acquisition, storage, processing, and application of knowledge [10]. It involves multiple aspects, such as perception, attention, memory, imagination, and decision-making, and is also the foundation for communication, problem-solving and creating new things [11,12]. Numerous studies have shown that education level, nutritional status and other factors can all affect cognitive performance [13,14]. Increasing evidence emphasizes the link between peripheral lipoprotein levels and cognitive ability [15]. Mirza et al. indicated that 80 ~ 90 % of clinical depression patients exhibit cognitive performance problems during depressive episodes [16]. On the contrary, a cross-sectional study on elderly depression has shown that it is associated with higher perceived social support, but not with other executive processes or cognitive domains [17]. Therefore, the relationship between depression and cognitive performance is ambiguous.

An observational cohort study suggests that veterans should be considered a high-risk group for cognitive impairment, especially those with chronic comorbidities of depression [18]. Although depression and cognitive impairment often coexist, observational studies cannot provide direct evidence of causal relationships. Previous studies analyzing only 90 elderly patients with depression have shown the negative correlation between the severity of depression symptoms and cognitive performance, but it is worth noting that residual confounding factors are still inevitable [19]. In addition, the China Health and Retirement Longitudinal Study (CHARLS) study of 4771 patients found that a close correlation between severe depression and cognitive decline, but due to the lack of follow-up data, its causal relationship cannot be confirmed [20]. Hence, alternative strategies to fortify causal inference can elucidate whether such experiments might be requisite.

Mendelian randomization (MR) is an alternative method for inferring the potential causal relationship between depression and cognitive performance by utilizing genetic variants as instrumental variables [21–23]. Given the random allocation of genetic variants at an early life stage, their correlation with subsequent lifestyle choices and extraneous environmental influences pertinent to disease progression is absent, thereby significantly reducing concerns regarding confounding and reverse causality [24]. MR studies could help determine whether there was a true causal relationship between depression and cognitive performance, rather than just a correlation [25]. The stability and randomness of genetic factors make the results more reliable and convincing. Furthermore, genome-wide association studies (GWAS) have delineated a multitude of genetic variants implicated in a spectrum of intricate diseases, propelling the utilization of MR methodologies to an advanced level of applicability [26,27]. MR methods provide a powerful tool for understanding the complex relationship between depression and cognitive performance, help uncover underlying causal mechanisms, and provide a scientific basis for relevant prevention and treatment strategies.

In this study, we applied a two-sample bidirectional MR analysis to assess the potential causal relationship of depression and cognitive performance. Given that physical conditions such as pain, frailty and inflammatory factors are crucial in preventing and managing depression and cognitive performance, we conducted a two-step MR analysis to investigate the mediating pathways of related phenotypes.

2. Materials and methods

2.1. Two-sample MR study design

Two-sample MR analysis usually refers to the statistical method in genetic research that compares the genetic data of two independent sam-

ple populations, using single nucleotide polymorphism (SNP) as a risk factor tool [28,29]. Compared to single sample MR, two-sample MR utilizes data derived from independent and non-overlapping data, making this method more robust and effective [30]. The MR method relies on three core assumptions in the supplementary Method. Overview diagram of this bidirectional dual sample MR study shows the research process and screening criteria in Fig. 1. Firstly, we utilized two-sample to determine the bidirectional MR association between depression and cognitive performance. We employed a multivariate MR method to further evaluate if there remains a bidirectional causal relationship between depression and cognitive performance after controlling for confounders. Ultimately, a two-step multivariate analytical approach was employed to assess mediating variables, like pain and frailty, which exert a causal effect within the mediating pathways between relative depression and cognitive performance.

2.2. Data sources

The datasets involved in the present research were all publicly available, and all original studies have obtained ethical approval. The data source, sample size details, and data download link are detailed in Supplementary Table 1. Show more data and more detailed descriptions in the method of Supplementary Method.

2.3. Depression

Summary statistics for depression were primarily retrieved from the FinnGen (R10 release) database of depression in the European population, which included a total of 47,696 cases and 359,290 controls (median age was 41.7 years old and 67.9 % were female). Depression was unipolar depression, an emotional disorder that involves one or more severe episodes of psychological depression, each lasting two weeks or more, without any intervention episodes of mania or hypomania. Diagnosis of the selected cases was based on standardized diagnostic tools and was assessed by a trained interviewer, clinician-administered checklist, or medical record review, all of which met the ICD-9 or ICD-10 classification criteria.

2.4. Cognitive performance

The database of the MRC Integrated Epidemiological Unit (IEU GWAS) includes a summary estimate of genetic associations for cognitive performance ($N_{\text{cases}}=257,841$, $N_{\text{SNPs}} = 10,049,954$), which is evaluated based on the scores of participants in language cognitive ability tests. A lower score represents worse cognitive performance, and a higher score is associated with better cognitive performance. In the 2019 meta-analysis, this dataset was first reported, indicating 225 SNPs significantly associated with cognitive performance, and the data increased the reliability of multi gene scores by 7–10 % through joint analysis [31]. When diagnosing cognitive function in the IEU GWAS datasets, the relevant diagnostic criteria specified in the ICD-10 classification system must be strictly followed.

2.5. Instrumental variables selection

In conducting MR analysis, adherence to three cardinal assumptions – correlation, independence, and exclusion restriction – is mandatory. Selected SNPs with a significance threshold of $P < 5 \times 10^{-6}$ were subjected to an independence evaluation via the PLINK clumping feature integrated within the Two-sample MR software. A stringent criterion of an R^2 value less than 0.001 and a window size of 10,000 kilobases was applied during the clumping procedure, employing the 1000 Genomes European datasets as the reference panel for this analysis [32]. In the presence of linkage disequilibrium (LD) among the SNPs, only the SNP exhibiting the most significant P value would be retained for further analysis. The susceptibility of the retained SNPs to weak instrument bias was assessed using the F statistic.

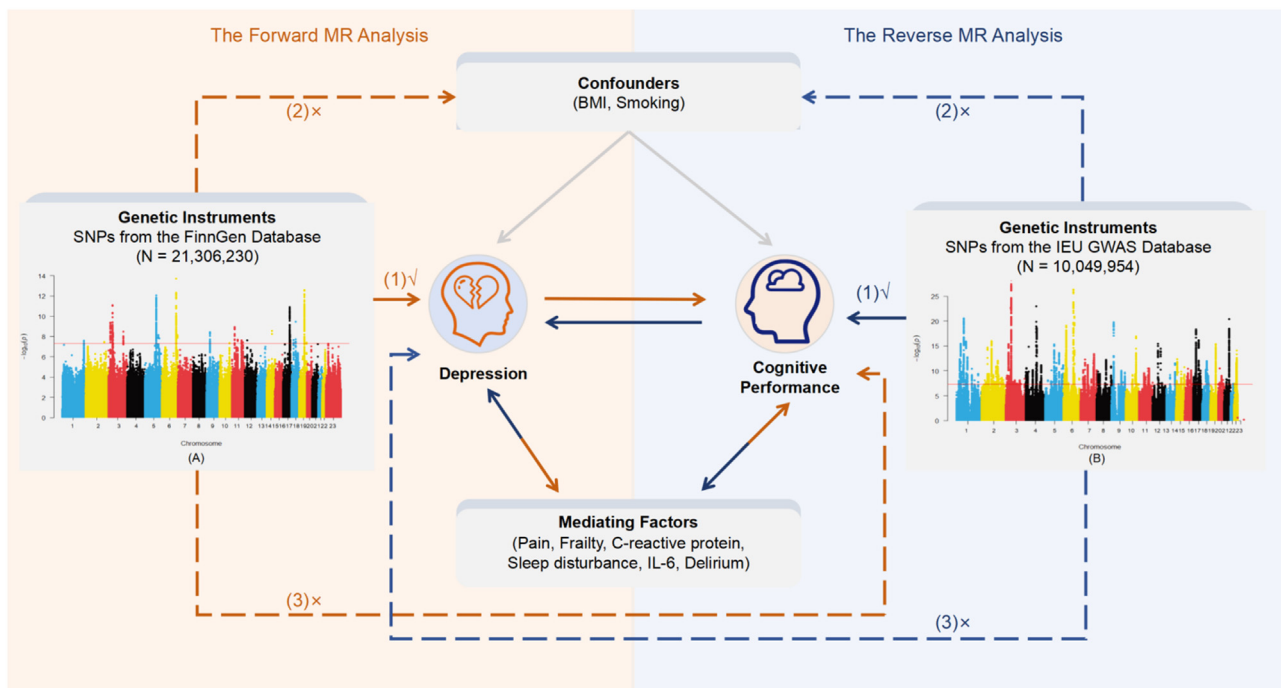


Fig. 1. Overview plots of Mendelian randomization (MR) study. The dotted lines represent the three hypotheses studied by MR. The red line represents positive MR for depression to cognitive performance, and the blue line represents reverse MR for cognitive performance to depression. (A) Manhattan plot of all SNP of depression gene data ($N_{\text{SNP}}=21,306,230$). (B) Manhattan plot of all SNP of cognitive performance gene data ($N_{\text{SNP}}=10,049,954$). The horizontal axis represents chromosomes, and the vertical axis represents the correlation strength of each gene locus. The red horizontal line represents the genome-wide significance threshold (P value $< 5 \times 10^{-8}$). BMI, Body mass index; MR, Mendelian randomization; IVW, Inverse-variance weighted; SNP, Single nucleotide polymorphisms, UVMR, Univariate Mendelian research; MVMR, Multivariate Mendelian research.

2.6. Confounder analysis

To evaluate whether the selected SNPs were associated with confounders ($P < 1 \times 10^{-5}$) within the relationship between depression and cognitive performance [33]. While MR is inherently designed to bypass confounders, in reality, there may still exist certain genetic variants that are not purely driven by causal mechanisms but rather correlated through alternative pathways (such as pleiotropy) [34]. Confounders multivariate MR (MVMR) analysis generally refers to the simultaneous consideration of multiple genetic variants as instrumental variables to analyze the relationship between these genetic variants and exposure and outcomes (defined as: β) [35]. The inverse-variance weighted (IVW) method was considered a determinant method and was supplemented by the MR Egger test.

2.7. Two-step MR analysis

Two-step MR analysis lies that the purpose of the first step is to determine whether genetic variations actually affect the outcome by influencing the mediator variables (defined as: β_1), and the second step is to quantify the causal contribution of the mediator variables to the outcome (defined as: β_2) [36]. We determined potential mediator factors that may be associated with the exposure, based on previously published articles, clinical research experience, and review articles, including pain, frailty, sleep disturbance and delirium. If there is evidence that depression affects the mediator, which in turn affects cognitive performance, we will employ the “product of coefficients” ($\beta_1 * \beta_2$) to evaluate the indirect effect of the potential mediator. In general, we can use $\beta_1 * \beta_2$ as a mediating effect from exposure to outcome. The standard error of the indirect effect is derived using the Delta method.

2.8. Statistical analysis

Univariate MR (UVMR) used five different methods to explore the genetic association between depression and cognitive performance: IVW,

weighted median, MR Egger regression, simple mode and weighted mode [37]. Because all SNPs used in the IVW hypothesis analysis are valid, it can produce the most accurate estimates. We assessed heterogeneity due to different genetic variants in the fixed-effect IVW method by using Cochran's Q test, with significant heterogeneity if the P value was less than 0.05. In this case, a multiplicative random-effects model based on the IVW method will be employed to estimate the impact of this genetic variation. The funnel plot revealed heterogeneity through asymmetry. Furthermore, the MR Egger regression intercept served as a means to examine the possibility of horizontal pleiotropy, where any departure from zero (with a P value below 0.05) suggested directional pleiotropic effects. To ensure the robustness of the findings, a leave-one-out (LOO) method was employed to investigate whether the overall outcome was primarily influenced by a single genetic variant. Statistical analyses were completely performed using R (version 4.4.1) and the Two-sample MR (version 0.5.7), Mendelian Randomization (version 0.8.0), and MR PRESSO (version 1.0) packages. All statistical tests were two tailed, and $\alpha = 0.05$ was considered as the significant level.

3. Results

3.1. Characteristics of selected genetic variants

Fig. 1 showed the overview of the design of this bidirectional two-sample Mendelian study. Manhattan plots illustrated the fluctuating data in the depression and cognitive performance datasets and highlight the SNPs that are strongly correlated. The sample size of depression data from the FinnGen database was 47,696, the SNP data was 21,306,230, the sample size of cognitive performance data was 257,841, and the SNP data was 10,049,954. Supplementary Fig. 1 was a flowchart of the research methodology, including the SNP data screening process and the sensitivity analysis method for MR. Based on predetermined assumptions and screening criteria, 8 SNPs for forward MR depression to cognitive performance and 81 SNPs for reverse MR cognitive performance to

Table 1
Bidirectional univariate Mendelian analysis of depression and cognitive performance.

Methods	No. of SNPs	MR analysis		Heterogeneity test		MR Egger intercept
		β /OR (95 % CI)	P value	Cochran's Q	P value	P value
Depression on cognitive performance						
IVW	8	-0.11 (-0.18 to -0.05)	5.97E-04	13.63	0.06	0.345
Weighted median	8	-0.08 (-0.15 to -0.02)	0.014			
MR Egger	8	0.08 (-0.30 to 0.46)	0.684			
Simple mode	8	-0.04 (-0.15 to 0.08)	0.539			
Weighted mode	8	-0.06 (-0.15 to 0.04)	0.301			
Cognitive performance on depression						
IVW	81	0.85 (0.76 to 0.95)	0.004	146.46	0.547	0.662
Weighted median	81	0.91 (0.80 to 1.04)	0.169			
MR Egger	81	0.95 (0.58 to 1.56)	0.834			
Simple mode	81	0.87 (0.61 to 1.26)	0.47			
Weighted mode	81	0.98 (0.71 to 1.36)	0.902			

OR, Odds ratio; MR, Mendelian randomization; IVW, Inverse-variance weighted; SNP, Single nucleotide polymorphisms.

depression were identified, listed in Supplementary Table 2 and Table 3, respectively.

3.2. Univariable MR analysis

3.2.1. Casual effect of depression on cognitive performance

UVMR analysis to explore the bidirectional causal relationship between depression and cognitive performance were shown in Table 1. The IVW method was used as the main method to find that depression can increase the risk of cognitive performance deterioration (β , -0.11; 95 % CI, -0.18 to -0.05; P value = 5.97E-04). However, among the remaining four alternative methods, only the weighted median method showed significant results similar to those of the IVW method (β , -0.08; 95 % CI, -0.15 to -0.02; P value = 0.014). As a supplement to the research, we validated the robust results using the depression validation, which also confirmed the causal relationship between depression and cognitive performance using the IVW method (β , -0.09; 95 % CI, -0.15 to -0.03; P value = 0.003, Supplementary Table 4). The instrumental variables for bidirectional Mendelian studies that validate the datasets were all presented in Supplementary Tables 5 and 6. Scatter plot shows a clear linear relationship, indicating a causal relationship between the selected genetic variation and the exposure or outcome (Fig. 2A). No evidence supported the existence of heterogeneity in the association between depression and cognitive performance ($Q = 13.63$, P value = 0.060). Funnel plot showed that there was no clear direct association between genetic variation and the outcome variables, which supported the validity of the Mendelian randomization analysis (Fig. 2B). MR Egger regression intercept term showed that there was no obvious directional pleiotropy between the SNPs of the two datasets (P value = 0.345). The LOO analysis results show that no SNP drives the entire effect (Supplementary Fig. 2A). The forest plot shows the effect size of each SNP on depression in the forward MR (Fig. 2C).

3.2.2. Casual effect of cognitive performance on depression

The cognitive performance was presented as an exposure factor, and 81 SNPs were finally selected for single-factor MR analysis (Table 1). The IVW method showed that the risk of developing depression decreased as the cognitive performance score increased (OR, 0.85; 95 % CI, 0.76 to 0.95; P value = 0.004). Scatter plot of the 5 lines in the scatter plot corresponded to the MR effect estimated by the 5 methods, and the IVW method is statistically significant (Fig. 2D). Funnel plots also suggested no heterogeneity in the association between cognitive performance and depression (Fig. 2E). Similar results were found in the depression validation datasets (OR, 0.90; 95 % CI, 0.84 to 0.97; P value = 0.003), which provided evidence for the robustness of the results from the IVW approach (Supplementary Table 4). The LOO plot illustrated the overall effect of cognitive manifestations to depression without a single SNP

(Supplementary Fig. 2B). The forest plot showed the effect size of each SNP on depression in the reverse MR (Supplementary Fig. 2C).

3.3. Multivariable MR analysis

3.3.1. Evaluation of the assumptions of forward MR

UVMR analysis demonstrated that Body Mass Index (BMI) and smoking were confounding factors for depression and cognitive performance (Supplementary Table 7). After adjusting for BMI and smoking, depression was associated with deterioration in cognitive performance (adjusted BMI: β_{IVW} , -0.05; 95 % CI, -0.08 to -0.02; P_{IVW} value=0.001; adjusted smoking: β_{IVW} , -0.03; 95 % CI, -0.07 to -0.01; P_{IVW} value = 0.003, Table 2). The trends of the MR Egger method were consistent with that of IVW method.

3.3.2. Evaluation of the assumptions of reverse MR

After adjusting for BMI and smoking, deterioration in cognitive performance was also associated with the development of depression (adjusted BMI: OR_{IVW}, 0.91; 95 % CI, 0.85 to 0.98; P_{IVW} value = 0.009; adjusted smoking: OR_{IVW}, 0.88; 95 % CI, 0.79 to 0.98; P_{IVW} value=0.023; Table 2). There was no heterogeneity between these two multivariate correction results. MR Egger intercept analysis found no evidence of directional pleiotropy. Supplement Fig. 3 showed scatter and funnel plots of confounding variables of the bidirectional Mendelian analysis. The instrumental variables of the bidirectional Mendelian study of confounding factors were all shown in Supplementary Tables 8–11.

3.4. Mediation analysis

3.4.1. Filter for mediating variables

UVMR analysis to verify whether the variables were mediators of depression and cognitive performance showed that only pain and frailty met the criteria for mediating factors (Supplementary Table 12). C-reactive protein, sleep disturbance, IL-6 and delirium showed no significant causality for cognitive function and depression MR (IVW: P value > 0.05). Univariate analysis found a positive correlation between depression and pain (IVW: OR, 1.04; 95 % CI, 1.02 to 1.06; P value<0.001), and the same findings were found in the weighted median, simple mode, and weighted mode methods (Fig. 3A). Pain was further identified as a risk factor for the development of cognitive decline (IVW: β , -0.21; 95 % CI, -0.39 to -0.03; P value = 0.023, Fig. 3B). In reverse MR studies, deterioration in cognitive performance was found to be a risk factor for frailty (IVW: β , -0.11; 95 % CI, -0.17 to -0.05; P value <0.001, Fig. 3C). Further research found that frailty is a risk factor for depression (IVW: OR, 1.76; 95 % CI, 1.30 to 2.38; P value <0.001, Fig. 3D). Multivariate analysis showed that there were significant statistical differences in pain and frailty in forward and reverse MR studies, respectively (Table 3).

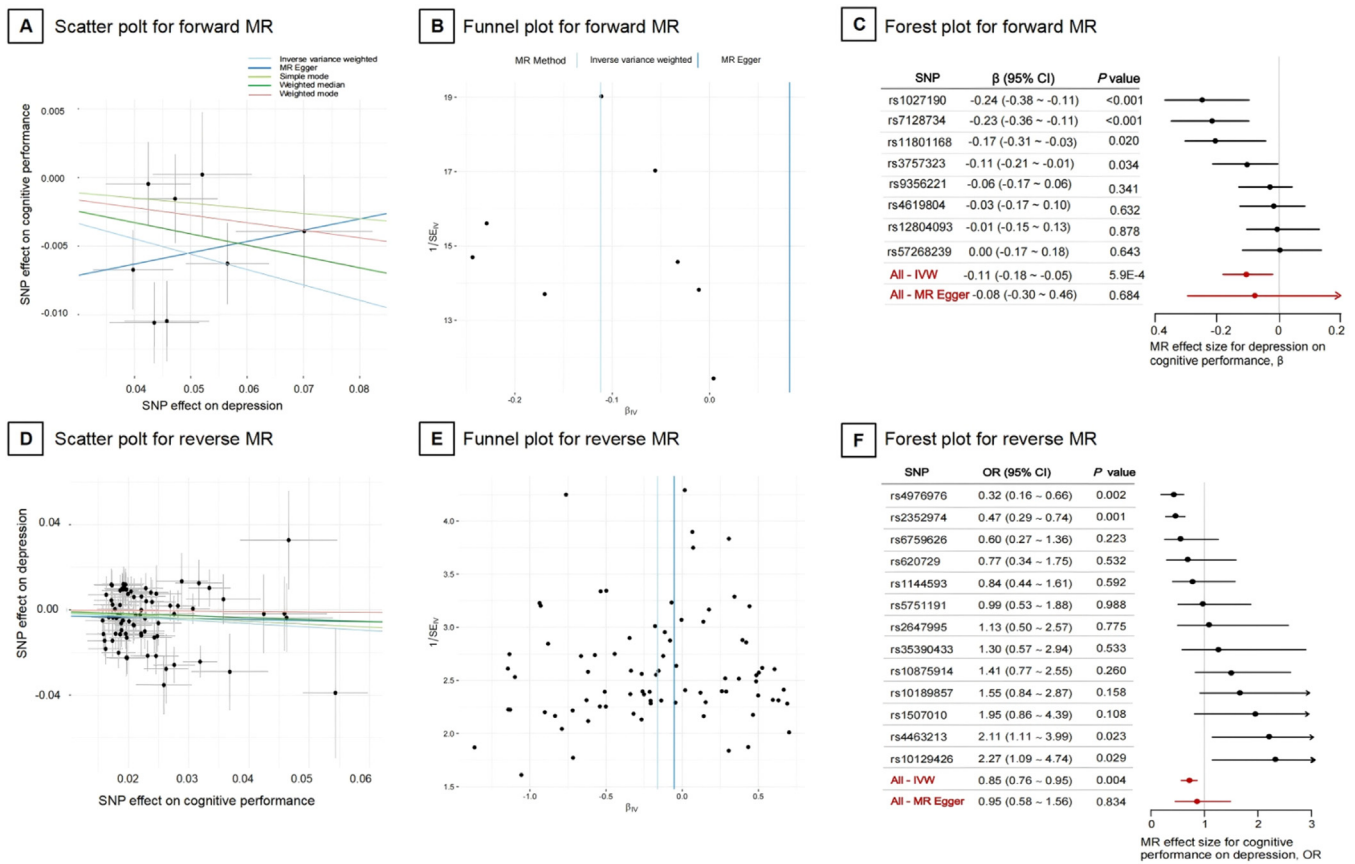


Fig. 2. Mendelian randomization plots for the relationship of depression with cognitive performance. (A) Scatter plot of SNP effects on depression versus cognitive performance, with the slope of each line corresponding to the estimated MR effect per method. The data are expressed as raw β values with 95 % confidence interval. (B) Funnel plot showed that the SNPs were symmetric, indicating that there was not heterogeneity in the association between depression versus cognitive performance. (C) Forest plot of causal effects of depression versus cognitive performance. Forest plot of all 8 individual and combined SNP MR-estimated effect sizes. (D) Scatter plot of SNP effects on cognitive performance versus depression, with the slope of each line corresponding to the estimated MR effect per method. (E) Funnel plot showed that the SNPs were symmetric, indicating that there was not heterogeneity in the association between depression versus cognitive performance. (F) This forest plot was a collection of 13 SNPs (partial) selected and presented in a pattern from 81 SNPs, all of which are presented in the Supplementary materials. MR, Mendelian randomization. Abbreviations: OR, Odds ratio. CI, Confidence interval. IVW, Inverse variance weighted.

Table 2
Bidirectional multivariate Mendelian analysis of adjusted BMI and smoking.

Exposure	Outcome	Methods	No. of SNPs	MR analysis		Heterogeneity test		MR Egger intercept
				β /OR (95 % CI)	P value	Cochran's Q	P value	P value
Depression	Cognitive performance	IVW						
		BMI	615	-0.05 (-0.08 to -0.02)	0.001	2453.83	0.586	0.571
		Smoking	206	-0.03 (-0.07 to -0.01)	0.003	781.4	0.472	0.804
		MR Egger						
Cognitive performance	Depression	BMI	615	-0.05 (-0.08 to -0.02)	0.001			
		Smoking	206	-0.19 (-0.30 to -0.12)	0.006			
		IVW						
		BMI	317	0.91 (0.85 to 0.98)	0.009	623.78	0.678	0.36
		Smoking	214	0.88 (0.79 to 0.98)	0.023	500.31	0.375	0.135
		MR Egger						
		BMI	317	0.91 (0.85 to 0.98)	0.007			
		Smoking	214	0.87 (0.78 to 0.97)	0.015			

OR, Odds ratio; BMI, Body mass index; MR, Mendelian randomization; IVW, Inverse-variance weighted; SNP, Single nucleotide polymorphisms.

3.4.2. Mediation effect and proportion

UVMR effect size of depression on pain (β_1 , 0.038), and we had a multivariate MR effect size of pain on cognitive function (β_2 , -0.584) when controlling depression. The mediating effect size was (β' , -0.022), accounting for 28.95 %. The univariate MR effect size of cognitive function on frailty (β_1 , -0.110), and the multivariate MR effect size of frailty

on depression (β_2 , 0.257) when controlling for cognitive function. The mediating effect size was (β' , -0.028), accounting for 22.40 % (Supplementary Table 13). Pain was a mediating factor in the positive MR study, and there were statistically significant differences in β , β_1 , β_2 , and β' (Fig. 3E). And frailty was a mediating factor in reverse MR studies, and there were statistically significant differences in β , β_1 , β_2 , and

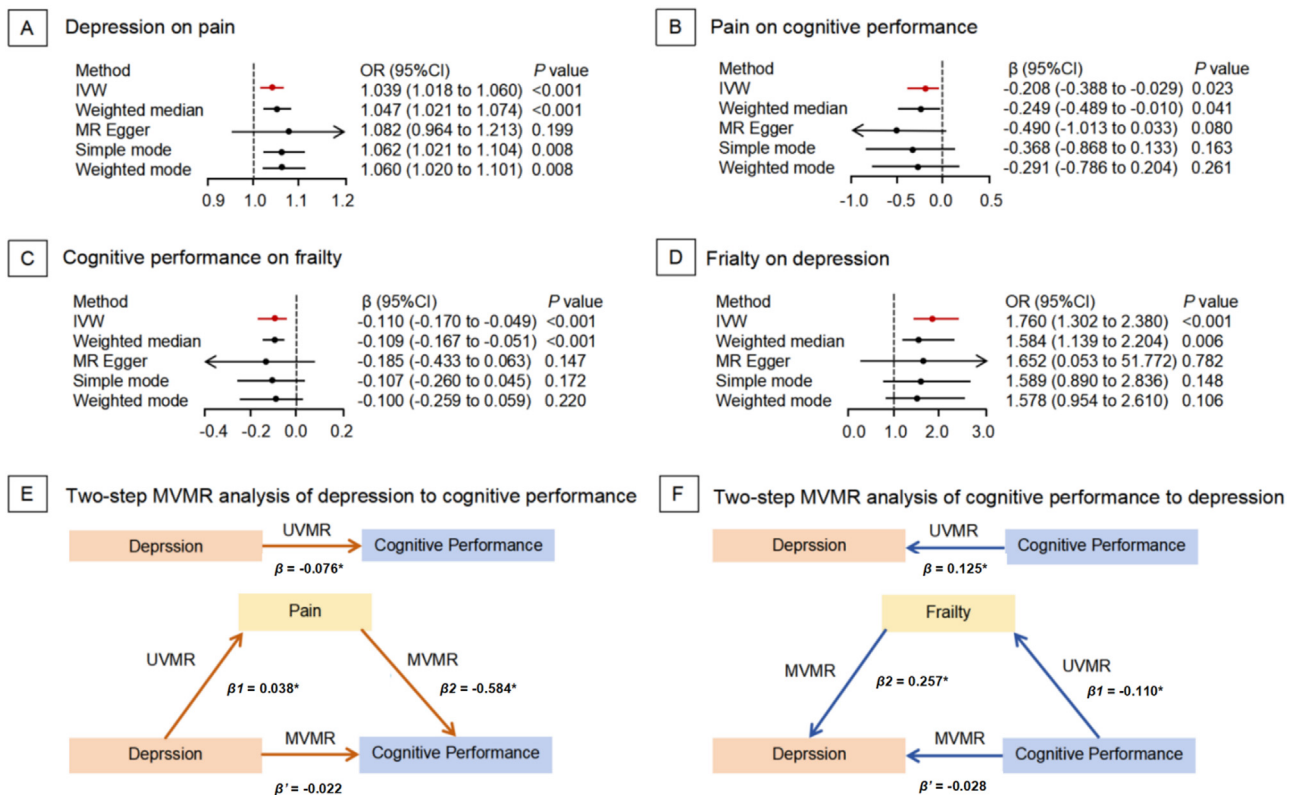


Fig. 3. Bidirectional mediation analysis of depression and cognitive performance via potential mediators. (A) Forest plot of univariate Mendelian analysis of depression to pain. (B) Forest plot of univariate Mendelian analysis of pain to cognitive performance. (C) Forest plot of univariate Mendelian analysis of cognitive performance to frailty. (D) Forest plot of univariate Mendelian analysis of frailty to depression. (E) Two-step MVMR MR analysis framework of depression to cognitive performance. (F) Two-step MVMR MR analysis framework of cognitive performance to depression. The error bars represent 95 % CIs. All statistical tests were two-sided. P value < 0.05 was considered significant. OR, Odds ratio; MR, Mendelian randomization; IVW, Inverse-variance weighted; UVMR, Univariate Mendelian randomization; MVMR, Multivariate Mendelian randomization.

Table 3
Multivariate Mendelian analysis of mediation variables (frailty and pain) for exposure and outcome.

Exposure Methods	No. of SNPs	β /OR (95 % CI)	P value	Heterogeneity test Cochran's Q P value	MR Egger intercept P value
Depression on cognitive performance					
Pain					
IVW	107	-0.584 (-0.868 to -0.301)	0.001	347.893 0.685	0.729
MR Egger		-0.631 (-1.018 to -0.243)	<0.001		
Cognitive performance on depression					
Frailty					
IVW	341	0.257 (0.110 to 0.404)	0.001	704.389 0.853	0.437
MR Egger		0.316 (0.108 to 0.523)	0.003		

β' (Fig. 3F). The instrumental variables of the bidirectional Mendelian study of mediating factors were all shown in Supplementary Tables 14–19.

4. Discussion

In this two-sample MR study, we found in forward MR studies that depression increases the risk of deterioration in cognitive performance. Reverse analysis provides evidence that reduced deterioration in cognitive performance was also associated with depression. After adjusting for BMI and smoking covariates, these associations persisted. The mediation analysis of two-step MR showed that pain was the main mediator of depression on cognitive performance, with a mediating effect ratio of 29.0 %. Frailty was a partial mediator of depression on cognitive performance, with a mediating effect ratio of 22.4 %. These findings may inform prevention strategies and interventions for depression and cognitive impairment.

4.1. Potential causal effects of depression on cognitive performance

The findings from our MR study provide novel insights into the causal relationship between depression and cognitive performance. We found in the forward MR study that depression increases the risk of deteriorating cognitive performance. Decades of research have shown that the cognitive factor of depression provides strong support in many ways [38,39]. Early research focused on demonstrating that the content of thoughts in depressed and non-depressed people was different. Existing surveys generally agree that one of the characteristics of depression is negative thought patterns and biases in attention, interpretation, and memory. A meta-analysis of studies showed that patients with depression showed more pronounced moderate cognitive impairment in executive function, memory, and attention than in the normal control group [40]. Reppermund et al.'s study found that cognitive impairment is often impaired in patients with depression, and these impairments persist even after psycho-pathological symptoms have resolved [41].

4.2. An exploratory analysis of the mediating factors of depression on cognitive performance

The impact of depression on cognitive performance is multi-factorial and multi-layered. Pain is a mediator between depression and deterioration in cognitive performance. Patients with depression often exhibit a chronic inflammatory state that may affect multiple areas of the brain, including areas of pain processing, through the release of inflammatory mediators, such as cytokines. Inflammatory mediators can affect neuronal function, synaptic plasticity, and neuronal-to-neuron communication, leading to increased pain perception or a decrease in pain threshold [42]. Pain may also affect cognitive function by affecting areas of the brain that regulate emotions, such as the prefrontal cortex, and areas of cognitive control, such as the hippocampus and anterior cingulate cortex [43]. Furthermore, both pain and depression can affect the brain's neuroplasticity, the brain's ability to adapt and change its structure and function. Long-term depressive states and pain may affect cognitive function by affecting the growth of neurons, the formation and remodeling of synapses, and the connections between neurons [44]. This effect may be one of the key mechanisms by which depression leads to cognitive impairment. Many studies have found that patients with depression exhibit abnormalities in pain perception tests, such as increased sensitivity to pain or decreased pain threshold. In addition, cognitive function test results in patients with depression also showed significant differences compared to healthy controls, particularly in the areas of attention, executive function, and memory. So, while depression is often seen as a key affective illness, we are gradually understanding that depression is often accompanied by significant cognitive dysfunction that is important for clinical treatment.

A 12-year follow-up study of the Whitehall II study found that C-reactive protein and interleukin-6 predicted cognitive symptoms of depression [45]. People with depression often have sleep disturbances, such as insomnia or excessive sleepiness. Sleep is essential for consolidating memory and cognitive function, and not getting enough or too much sleep can impair cognitive performance [46]. However, in the context of limited sample size, the C-reactive protein, interleukin-6, and sleep disturbances identified in this MR study do not satisfy the conditions for mediators. Future studies may continue to explore more mediators of depression and cognitive performance.

4.3. Potential causal effects of cognitive performance on depression

In reverse MR studies, we found that deterioration in cognitive performance increased the risk of depression. A systematic review and meta-analysis of longitudinal datasets found an association between deterioration in cognitive function and subsequent depression [47]. Deficits in cognitive functions such as executive function, working memory, and attention can impair an individual's ability to cope with stress, making it more difficult to effectively solve problems or regulate emotions, increasing feelings of helplessness and the accumulation of negative emotions [48]. Cognitive biases can motivate individuals to pay more attention to negative information and make pessimistic interpretations, forming and maintaining cognitive patterns of depression.

In addition, dysfunction of the prefrontal cortex and limbic system may affect both cognitive control and emotion regulation, forming a vicious circle [49,50]. Long-term cognitive stress may damage hippocampal and prefrontal structures through HPA axis dysregulation and neurotrophic factors such as BDNF. This neurological impairment further reduces cognitive flexibility and creates a predisposition to depression [51,52].

4.4. An exploratory analysis of cognitive performance as mediators of depression

Frailty, characterized by a decline in multiple physiological systems, including cognitive function, serves as a critical mediator in the asso-

ciation between cognitive performance and depression due to several interrelated factors. Frailty is a multidimensional concept often used to describe an individual's physical, psychological, and social state of decline [53]. It involves the decline of physical function, cognitive ability and self-care ability caused by aging, chronic diseases, malnutrition and other factors [54]. Firstly, deterioration in cognitive performance can make individuals encounter difficulties in their daily lives, such as difficulty in completing daily tasks and a decline in self-care abilities. This vulnerability to cognitive challenges may exacerbate the risk of depression by impairing an individual's ability to cope with stress and maintain social connections [55]. Secondly, frailty is linked to altered neurobiological pathways, such as increased inflammation and oxidative stress, which are known to contribute to both cognitive decline and the development of depressive symptoms. These pathways may mediate the relationship between cognitive performance and depression by affecting brain function and mood regulation. Frailty is often associated with cognitive impairment, which can lead to difficulties in processing information and maintaining attention. Furthermore, cognitive impairment may affect an individual's ability to communicate and interact with others, leading to a narrowing of social circles and reduced social support, which in turn increases the risk of frailty and depression [56]. Therefore, this finding provides a scientific basis for intervening in frailty to reduce the risk of depression in patients with cognitive impairment.

4.5. Advantages of MR analysis

MR studies provided an effective way to explore the causal relationship between depression and cognitive performance, reducing bias and controlling for confounders. On the one hand, in traditional epidemiological studies, the observed associations may be influenced by a variety of confounding factors. MR could reduce or control for the effects of these confounders by using genetic variation as an "instrumental variable", providing a more accurate estimate of causal effects. On the other hand, these findings may provide clues for the development of new treatment strategies and interventions, particularly for patients who do not respond well to existing treatments. It is important to consider the implications of these results in the context of clinical practice. If depression indeed causally influences cognitive performance, then early detection and intervention for depression could potentially mitigate cognitive decline. This has significant ramifications for the management of depression, particularly in populations where cognitive impairment is a concern, such as the individuals with a history of pain or frailty state.

4.6. Limitations

There are limitations to this study. Firstly, due to limitations in the database structure, confounding factors such as history of invasive surgery, age, and income that may be associated with depression and cognitive performance were not included in this study. Future prospective cohort studies were designed to include potential confounders related to cognitive performance and depression to improve the validity of the study. Future research also should continue to explore neurobiological mediators such as inflammation, neuroplasticity, and HPA axis dysfunction to elucidate how depression impairs cognitive performance and vice versa. Secondly, MR analyses reflect lifetime effects and may lack temporal dynamics to identify critical developmental windows. Through multicenter, large-scale longitudinal cohort studies, systematically investigate the temporal relationship between depressive symptoms and cognitive functions (particularly executive function and working memory), and identify critical intervention windows (such as adolescence, perinatal period, or old age). Thirdly, GWASs used in this study were derived from large samples, but phenotypic measures in these samples may be heterogeneous. The assessment of depression relies primarily on self-report, but this report does not specify the intensity or duration of depression. Future studies should adopt a multimodal assessment

approach, integrating objective cognitive measures (such as computerized tests and neuroimaging data) with subjective reporting to minimize measurement bias. Examine brain network connections by fMRI to determine the neural correlation of bidirectional relationships. By integrating neuroscientific, genetic, and clinical perspectives, we can develop more effective strategies to improve mental and cognitive health simultaneously.

5. Conclusions

Depression exerts a detrimental effect on cognitive performance, while impaired cognitive performance exacerbates depression. This bidirectional association suggests that interventions targeting cognitive enhancement may alleviate depressive symptoms, and conversely, depression mitigation strategies could improve cognitive function. Future research should prioritize mechanistic studies, targeted interventions, and personalized approaches to disentangle and mitigate the bidirectional effects of depression and cognitive performance.

Ethics approval and consent to participate

Informed consent and ethical approval are not required for Mendelian randomization studies.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xinyu Hao: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **Fuyang Cao:** Methodology, Conceptualization. **Ziyao Xu:** Data curation, Conceptualization. **Shaohua You:** Methodology, Data curation. **Tianyue Mi:** Software, Resources, Data curation, Conceptualization. **Lei Wang:** Resources, Methodology, Data curation. **Yongxin Guo:** Methodology, Investigation. **Zhuoning Zhang:** Resources, Investigation. **Jiangbei Cao:** Software, Resources. **Jingsheng Lou:** Validation, Supervision. **Yanhong Liu:** Resources, Methodology. **Xianyang Chen:** Supervision, Data curation. **Zhikang Zhou:** Software, Resources. **Weidong Mi:** Writing – original draft, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Li Tong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Data availability

Corresponding authors can be contacted to request access to the datasets used or analyzed in this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100196.

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