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SHORT COMMUNICATION

# Causal relationships between cathepsins and psychiatric disorders: A Mendelian randomization study

**Zhao Hui Yang[1], Ao Wang[2], and Ke Yi[1,2]***

[1]Department of Orthopedics, Hubei Provincial Key Laboratory of Occurrence and Intervention of Rheumatic Diseases / Hubei Provincial Clinical Research Center for Nephrology, Minda Hospital of Hubei Minzu University, Hubei Minzu University, Enshi, Hubei, China

[2]Key Laboratory of Obstetrics and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

## Abstract

**Introduction:** Observational epidemiological studies investigating the association between cathepsins and psychiatric disorders have reported inconsistent results.
**Objectives:** The objective of this study was to evaluate the potential causal effects of cathepsins on psychiatric disorders using Mendelian randomization (MR) analysis.
**Methods:** A two-sample MR analysis was conducted using single-nucleotide polymorphisms as instrumental variables to examine the effects of cathepsins on psychiatric disorders. The study assessed both the individual and combined impacts of various cathepsins through univariable and multivariable MR analyses. Statistical techniques included the inverse-variance weighted method, along with supplementary approaches such as MR-egger regression, to ensure a comprehensive assessment.
**Results:** Univariable MR analysis demonstrated a significant correlation between cathepsin G and bipolar disorder, as well as between cathepsin S and depression. In addition, multivariate MR analysis further confirmed that elevated levels of cathepsin G were significantly linked to an increased risk of bipolar disorder, while elevated levels of cathepsin S were linked to a higher risk of depression – even after adjusting for the effects of other cathepsins. Reverse MR and sensitivity analyses supported the robustness of these findings.
**Conclusion:** This study suggests that cathepsin G and S are casually associated with an increased risk of bipolar disorder and depression, respectively. However, due to the limitations of the MR approach, including pleiotropic effects, these associations should be considered with caution.

***Keywords:*** Causal effect; Cathepsins; Mendelian randomization; Psychiatric disorders; Risk

***Corresponding author:**
Ke Yi
(yike@scu.edu.cn)

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## 1. Introduction

Psychiatric disorders – encompassing conditions such as depression, anxiety, bipolar disorder, and schizophrenia – represent a global health challenge.[1-3] According to the World Health Organization, hundreds of millions of people worldwide suffer from these conditions, leading to significant personal, social, and economic burdens.[4-7] The impact of psychiatric disorders extends beyond the individual level, as they influence families, communities, and societies at large through diminished productivity, social isolation, and increased healthcare costs.[8-10] Numerous genetic, environmental, and social factors

contribute to the complex epidemiology of psychiatric disorders.[11-15] Despite advances in understanding their biological underpinnings and improving treatment modalities, the prevalence of these conditions remains high, emphasizing the urgent need for continued research into their etiology and interventions.[16-18]

Cathepsins – a family of lysosomal proteases – play a pivotal role in various biological processes, including protein degradation, apoptosis, and autophagy.[19-21] These enzymes participate in the intracellular breakdown of proteins within lysosomes to maintain cellular homeostasis and regulate internal processes.[22,23] Beyond their fundamental roles in cellular maintenance, cathepsins have been implicated in the pathogenesis of numerous diseases, such as cancer, cardiovascular conditions, and neurodegenerative disorders.[24-26] The association between their enzymatic activity and disease mechanisms highlights a complex interplay.

Previous studies have demonstrated that cathepsins may affect brain function and mental health by regulating neuroplasticity, inflammation, and stress response pathways.[27,28] Moon *et al.*[29] reported that cathepsin B regulates the expression of brain-derived neurotrophic factor in adult hippocampus progenitor cells through a mechanism dependent on the multifunctional protein P11, ultimately affecting hippocampus-related memory function. In addition, Zhang *et al.*[30] reported that high expression of cathepsin C aggravated neuroinflammation involved in behavioral and neurochemical disorders in a mouse model of depression. The axonal growth of cultured cortical and spinal neurons was markedly enhanced by cathepsin L.[31] In addition, cathepsin B and L can increase the level of the perlecan C-terminal fragment LG3, which mediates astrocyte proliferation and neuroprotection.[32]

The existing literature on the association between cathepsins and psychiatric disorders has notable limitations. Although many observational studies have highlighted potential connections, they are insufficient to establish causality due to inherent biases and confounding factors. This lack of causal evidence presents a significant challenge for developing targeted therapeutic strategies involving cathepsins in psychiatric disorders. This study aims to address this gap by employing Mendelian randomization (MR), a method that uses genetic variants as instrumental variables (IVs) for risk factors to establish causal relationships.[33] The central research question is whether cathepsins exert a direct causal effect on the development of psychiatric disorders. It is hypothesized that genetic variations influencing cathepsin activity are causally associated with the risk of developing these mental health conditions.

The strength of MR lies in its ability to emulate randomized controlled trials, thereby overcoming the limitations of observational studies. By utilizing genetic data, MR analysis can provide more conclusive evidence on whether cathepsins have a direct impact on the development of mental illnesses. This method not only advances our understanding of the etiological role of cathepsins in these conditions but may also guide future therapeutic interventions.

## 2. Materials and methods

### 2.1. Study design

In this study, a two-sample MR analysis was conducted to evaluate the association between cathepsins and psychiatric disorders, using single-nucleotide polymorphisms (SNPs) as IVs.[34] To ensure the validity and accuracy of the results, three core assumptions must be met throughout the process.[35] First, the selected IVs must have a direct association with cathepsins. Second, the IVs should be independent of any confounding factors that may influence both the exposure and the outcome. Third, the IVs must impact psychiatric disorders exclusively through their effect on cathepsin levels (Figure 1).

Univariable MR analysis was employed to investigate the potential association between specific cathepsins and psychiatric disorders. In contrast, multivariable MR (MVMR) analysis was used to evaluate the independent effects of interrelated cathepsins on psychiatric disorders. Both analyses aimed to clarify the relationship between cathepsins and psychiatric disorders. Ethical approval and informed consent were obtained for this study.

Genetic instruments for cathepsins were extracted from the INTERVAL study, which included 3,301 European participants (Table S1).[36] Data on psychiatric disorders were obtained from the genome-wide association study database (https://gwas.mrcieu.ac.uk/). This database provided data for nine psychiatric outcomes – including schizophrenia, bipolar disorder, depression, anorexia nervosa, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, anxiety disorders, panic disorder, and obsessive-compulsive disorder (Table S2).

### 2.2. Statistical analysis

The fixed-effect inverse-variance weighted (IVW) method was employed as the primary approach for MR analysis. Random-effects modeling was applied in cases where potential heterogeneity among the selected SNPs was present.[37] Moreover, four other methods – MR-egger, weighted median, weighted mode, and simple mode – were employed to comprehensively assess the potential relationships. While these methods offer a comprehensive

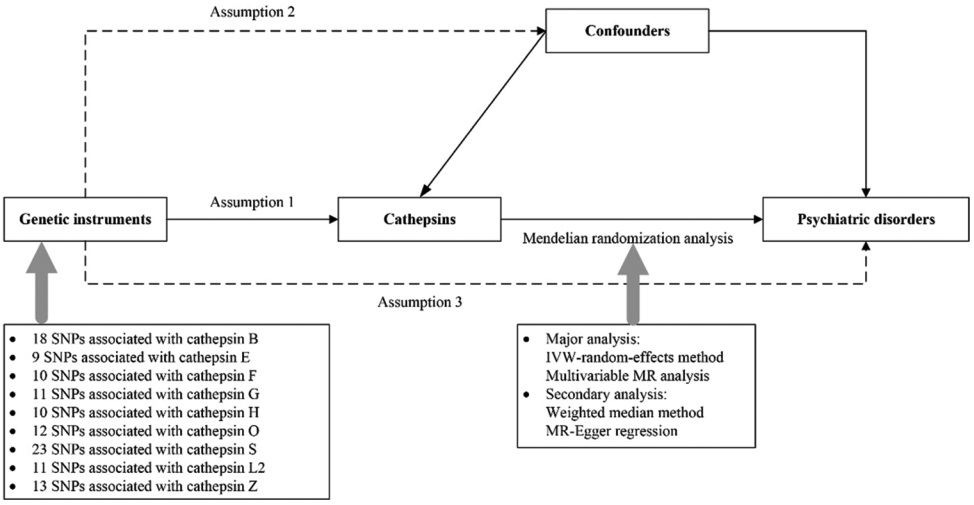


**Figure 1.** Overview of the Mendelian randomization design
Abbreviations: IVW: Inverse-variance weighted; MR: Mendelian randomization; SNP: Single-nucleotide polymorphism.

evaluation, it is important to note that their statistical power may be lower compared to the IVW test. Furthermore, Cochran's *Q* statistic and the MR-egger intercept analysis were used to evaluate heterogeneity and horizontal pleiotropy, respectively.

### 2.3. Genetic instrument selection

In the univariable MR analysis, independent SNPs associated with cathepsins were selected using linkage disequilibrium clumping with a threshold of $r^2 = 0.001$ and a window size of 10 MB. Specifically, genome-wide significant SNPs ($p<5 \times 10^{-6}$) linked to each trait were prioritized to reduce redundancy. Furthermore, a MVMR analysis was conducted based on the IVW method to estimate the direct effects of cathepsins on nine psychiatric disorders individually.

### 2.4. Sensitivity analyses

To ensure the reliability and accuracy of the identified causal effects of cathepsins on psychiatric disorders, a comprehensive set of sensitivity analyses was conducted. Potential heterogeneity in the data was evaluated using Cochran's *Q* statistic,[38] while horizontal pleiotropy was examined using the MR-egger intercept analysis.[39] A leave-one-out analysis was also performed to determine whether any single SNP had a major impact on the results by systematically excluding SNPs individually. In addition, reverse MR analyses were conducted to investigate potential reverse causal relationships between cathepsins and psychiatric disorders. All analyses were performed using R (version 4.2.0, The R Foundation for Statistical Computing, Austria) and RStudio (version 2022.02.2, RStudio, PBC, USA), employing the R packages "TwoSampleMR" and "MR-PRESSO."

## 3. Results

### 3.1. Univariable MR analysis

Following the exclusion of SNPs associated with potential confounders, the final IVs identified for each cathepsin are as follows: cathepsin B (18), cathepsin E (9), cathepsin F (10), cathepsin G (11), cathepsin H (10), cathepsin O (12), cathepsin S (23), cathepsin L2 (11), and cathepsin Z (13).

Instrumental heterogeneity for cathepsin E associated with autism spectrum disorder was identified using Cochran's *Q* test ($p<0.05$; Table S3), and the MR analysis was subsequently performed using a random-effects model.

The IVW method demonstrates a significant association between cathepsin G and increased bipolar disorder risk (odds ratio [OR] = 1.097; 95% confidence interval [CI] = 1.004 – 1.197; $p=0.040$). In addition, Cathepsin S shows a significant association with an increased risk of depression (OR = 1.025; 95% CI = 1.003 – 1.047; $p=0.025$). Furthermore, cathepsin Z demonstrates a significant association with a reduced risk of anorexia nervosa (OR = 0.878; 95% CI = 0.790 – 0.976; $p=0.015$) (Figure 2 and Table S4).

Reverse MR analysis was conducted to explore the potential causal effects of psychiatric disorders on cathepsins. The findings show no evidence of a reverse causal relationship between psychiatric disorders and any of the cathepsins (Table S5).

### 3.2. MVMR analysis

In this study, MVMR analysis was employed to investigate the effects of each cathepsin on the risk of psychiatric

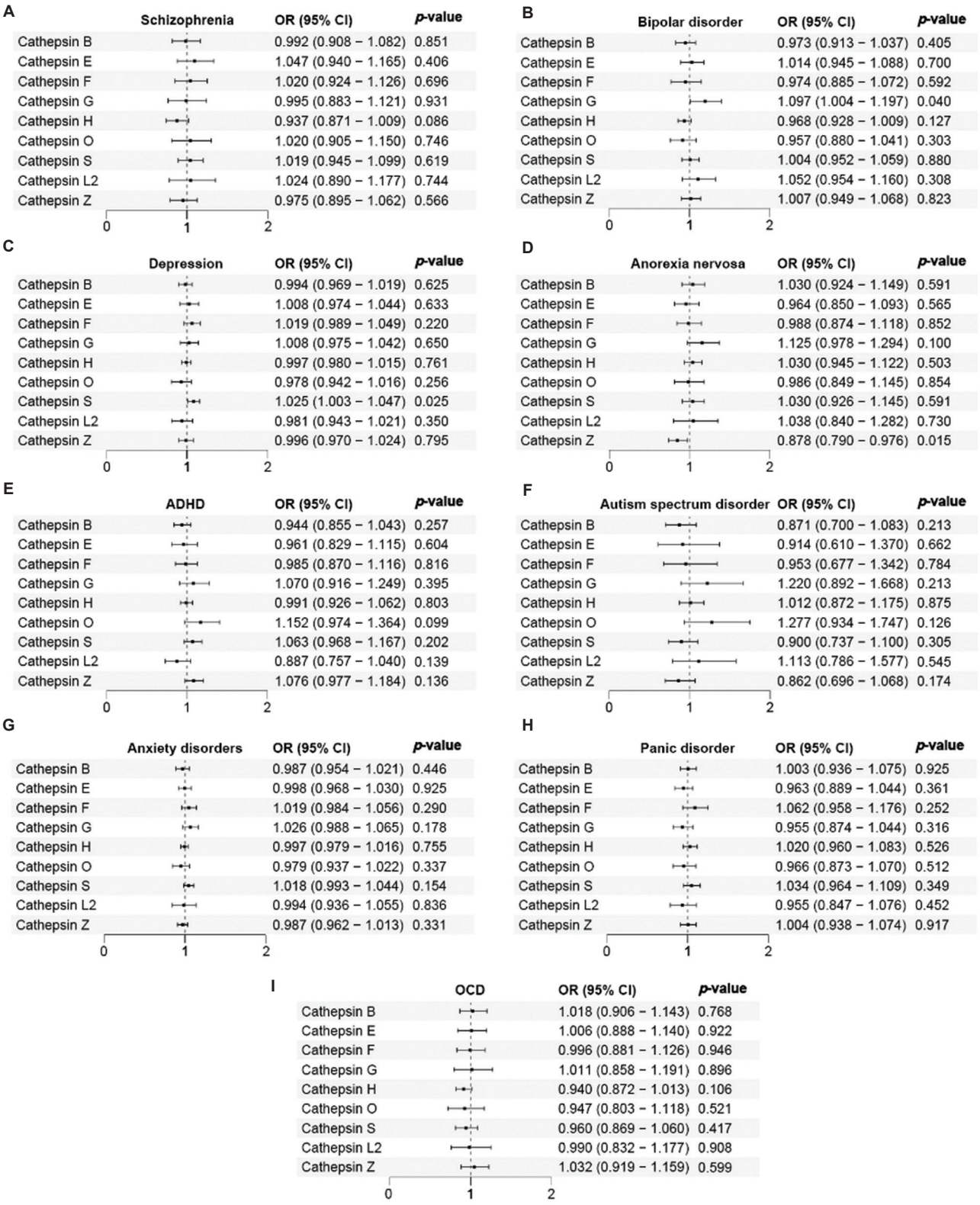


**Figure 2.** Univariable Mendelian randomization results using the inverse-variance weighted method for: (A) Schizophrenia; (B) bipolar disorder; (C) depression; (D) anorexia nervosa; (E) ADHD; (F) autism spectrum disorder; (G) anxiety disorders; (H) panic disorder; and (I) OCD
Abbreviations: ADHD: Attention-deficit hyperactivity disorder; CI: Confidence interval; OCD: Obsessive-compulsive disorder; OR: Odds ratio.

disorders (Table S6). The findings demonstrate that, even after adjusting for other cathepsin types, elevated levels of cathepsin G remain significantly associated with an increased risk of bipolar disorder (OR = 1.079; 95% CI = 1.004 – 1.160; *p*=0.038). Similarly, elevated cathepsin S levels continue to show a significant association with an increased risk of depression (OR = 1.028; 95% CI = 1.004 – 1.052; *p*=0.020). However, no significant causal relationship is observed between cathepsin Z and anorexia nervosa after adjusting for other cathepsin types (Figure 3). In addition, the MR-egger intercept analysis, presented in Table S7, indicates no evidence of horizontal pleiotropy.

## 4. Discussion

The objective of this MR study was to elucidate the causal relationships between different cathepsins and the risk of psychiatric disorders, providing new insights into the biological mechanisms underlying mental health conditions. This study focused on cathepsins – a group of proteases involved in various physiological processes such as immune response and apoptosis – that have been suggested to play a role in psychiatric disorders.

Through rigorous analysis, this study demonstrates a significant association between cathepsins and the risk of psychiatric disorders. Elevated levels of cathepsin G are positively linked to an increased risk of bipolar disorder, while higher levels of cathepsin S are associated with a greater risk of depression. These findings remain robust even after adjusting for potential confounders and considering the possibility of pleiotropy as evidenced by MR-egger intercept analysis. Although the MR-egger intercept is not statistically significant, pleiotropy cannot be completely excluded from the study. Pleiotropic effects – where genetic instruments influence multiple traits – may still introduce bias into causal estimates. Therefore, these findings should be interpreted with caution, acknowledging that unmeasured or unaccounted pleiotropic effects could impact the observed associations. Importantly, the reverse MR analysis shows no evidence of a reverse causal relationship, which strengthens the case for a directional effect of cathepsin levels on the risk of psychiatric disorders.

The findings show a significant inverse association between cathepsin Z and anorexia nervosa in the univariable MR analysis (OR = 0.878; *p*=0.015). However, this association is not significant in the MVMR analysis after adjusting for other cathepsins. Biologically, the effects of cathepsin Z on anorexia nervosa may be mediated by complex biological pathways or external factors not captured in the analysis – such as neurobiological processes or environmental factors such as stress and nutrition. These unmeasured variables could mask the observed effect of cathepsin Z when adjusting for other cathepsins. Statistically, the genetic instruments used may not fully capture the multifaceted role of cathepsin Z, resulting in a weaker causal estimate in the multivariable model.

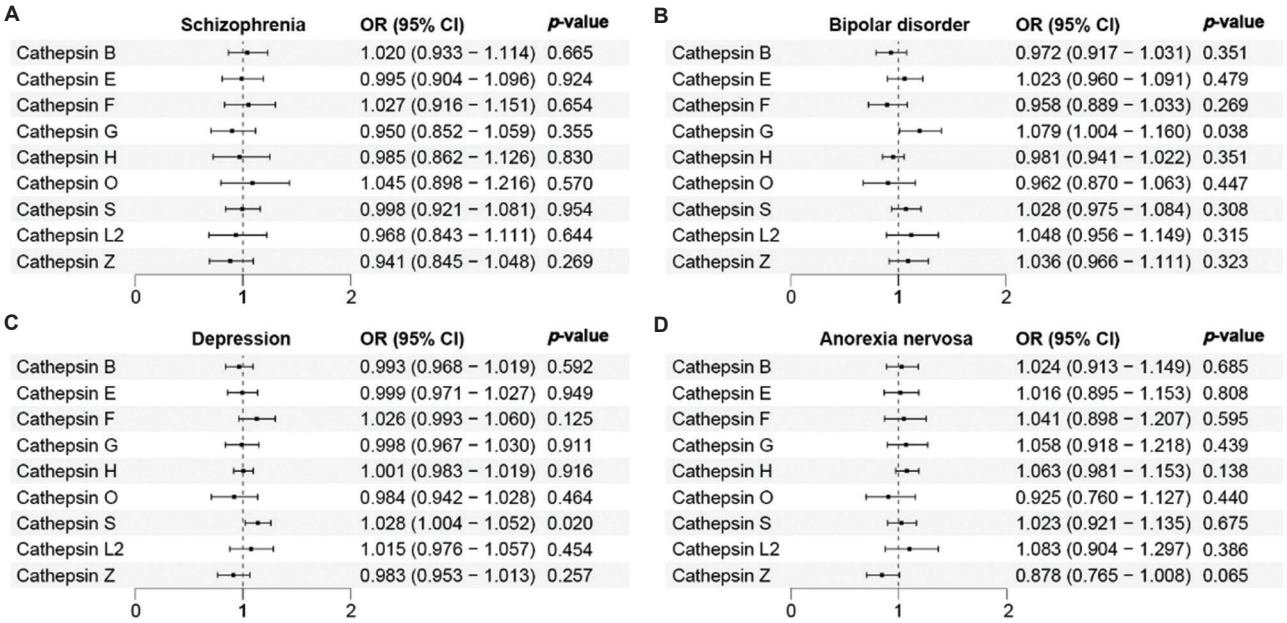


**Figure 3.** Multivariable Mendelian randomization results using the inverse-variance weighted method for: (A) Schizophrenia; (B) bipolar disorder; (C) depression; and (D) anorexia nervosa
Abbreviations: CI: Confidence interval; OR: Odds ratio.

In addition, confounding effects from other cathepsins – many of which share overlapping biological pathways related to neuroinflammation and immune response – may have masked the independent effect of cathepsin Z. This highlights the complexity of these relationships. Future research should aim to refine genetic instruments, incorporate environmental and neurobiological factors, and explore additional pathways to better clarify the role of cathepsin Z in anorexia nervosa.

Further investigation into the underlying biological mechanisms and clinical implications is warranted, given the observed association between elevated cathepsin G levels and increased bipolar disorder risk. Cathepsin G – primarily involved in immune responses and inflammation modulation – may influence bipolar disorder through various pathways. It has been implicated in neuroinflammation, a process increasingly recognized as a contributing factor to the pathophysiology of psychiatric disorders, including bipolar disorder. Elevated levels of cathepsin G may exacerbate neuroinflammatory processes, leading to dysregulation of neurotransmitter systems and neuronal function.[40] Moreover, cathepsin G cleaves neuropeptides, which may affect mood regulation and cognitive function – both commonly impaired in bipolar disorder.[41] Its role in the proteolytic processing of proteins involved in neurodevelopment warrants further investigation into its impact on neuronal connectivity and circuitry implicated in mood disorders. Further clinical studies examining the relationship between cathepsin G and the risk of bipolar disorder may contribute to the identification and development of novel therapeutic targets for psychiatric intervention.

The observed correlation between elevated cathepsin S levels and increased depression risk highlights the intricate relationship between immune regulation and mental health. Cathepsin S – known for its role in modulating immune responses and inflammation – may influence depression pathogenesis through neuroinflammatory mechanisms.[42,43] This relationship highlights the immune system as a promising target for depression prevention and treatment. By focusing on modulating cathepsin S activity, future therapeutic approaches may provide more effective and personalized treatment options for depression, potentially reducing the burden of this mental health condition.

The findings of this study partially align with previous research. Marín-Méndez *et al.*[44] reported no significant association between cathepsin B and either ADHD or bipolar disorder, which is consistent with the present study's results showing no significant correlation between cathepsin B and these disorders. However, the results contrast with those of Wang *et al.*,[45] who highlighted a significant role of cathepsin B in autism-related neurovascular inflammation. Their study utilized an animal model and behavioral assays to evaluate the impact of cathepsin B, which differs significantly from the present genetic MR approach that relies on genetic variants to assess causality.

In addition, no significant association is observed between cathepsin B and autism. Sun *et al.*[46] reported increased depressive-like behaviors in female cathepsin B-deficient mice, providing a behavioral and genetic link. However, their study focused on phenotypic changes in animal models with induced gene knockouts, whereas this study relies on genetic data from human cohorts, which may account for differences in the scope of observed effects. The methodological approach of this study, which focuses on genetic evidence for causality through MR analysis – capable of revealing correlations not apparent in observational or animal model studies – may explain discrepancies with previous research. This study contributes to a deeper understanding of the genetic mechanisms underlying psychiatric disorders and the role of cathepsins, highlighting the complex interplay between genetics and mental health. While these findings provide valuable insights into the potential role of cathepsins in psychiatric disorders, experimental validation through longitudinal studies or controlled experimental models is necessary to confirm these associations and clarify the underlying biological mechanisms.

Notably, this study has several limitations. The MR analyses are based on key assumptions – such as the absence of horizontal pleiotropy – which could affect the validity of the causal inference. Although the MR-Egger intercept analysis is not statistically significant, pleiotropic effects may still exist and potentially confound the results. In particular, if the genetic instruments influence other traits related to psychiatric disorders, the causal estimates may be biased. Despite the use of robust genetic instruments and sensitivity analyses to address these issues, complete elimination of residual confounding remains challenging. Moreover, while this study focused on the genetic effects of cathepsins on the risk of psychiatric disorders and adjusted for other cathepsins through MVMR analysis, it did not consider other factors – including environmental and lifestyle factors. Future studies should incorporate these factors into their analyses to enable a more comprehensive understanding of the causal mechanisms behind the association between cathepsins and psychiatric disorders.

## 5. Conclusion

This MR study highlights the potential associations between specific cathepsins and psychiatric disorders.

Cathepsin G is associated with an increased risk of bipolar disorder, while cathepsin S is linked to a higher risk of depression. However, due to the inherent assumptions of MR and the possibility of pleiotropic effects, these findings should be interpreted with caution. Future research should incorporate longitudinal cohort studies or experimental models to further validate these associations and clarify the underlying biological pathways through which cathepsins may contribute to psychiatric risk.

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## Conflict of interest

The authors declare that they have no conflicts of interest.

## Author contributions

*Conceptualization*: Ke Yi
*Formal analysis:* Zhao Hui Yang, Ao Wang
*Methodology:* Ke Yi
*Writing – original draft*: Zhao Hui Yang, Ao Wang
*Writing – review & editing:* Ke Yi

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. An ethical approval was not necessary as this study was a MR study based on publicly available data from the openGWAS project.

## Consent for publication

Not applicable.

## Availability of data

Original data generated and analyzed during this study are included in this published article or supplementary material. Further inquiries can be directed to the corresponding author.

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