Journal of Biological Regulators and Homeostatic Agents 2025, 39(2), 3334.
https://doi.org/10.54517/jbrha3334

Brief Report

Causal relationships between cathepsins and autoimmune diseases: A mendelian randomization study

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CITATION

Xia Y, Shan D, Yi K. Causal relationships between cathepsins and autoimmune diseases: A mendelian randomization study. Journal of Biological Regulators and Homeostatic Agents. 2025; 39(2): 3334. https://doi.org/10.54517/jbrha3334

ARTICLE INFO

Received: 24 February 2025
Accepted: 19 March 2025
Available online: 27 March 2025

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Abstract: Background: Epidemiological observational studies investigating the association between cathepsins and autoimmune diseases have shown inconsistent results. Hence, we conducted a Mendelian randomization analysis to assess the potential causal impact of cathepsins on these diseases. **Methods:** Employing a two-sample Mendelian randomization analysis, we used single nucleotide polymorphisms as instrumental variables to examine the impact of cathepsins on autoimmune diseases. The research comprised univariable and multivariable Mendelian randomization analyses, focusing on individual and combined effects of cathepsins. Statistical techniques included inverse variance weighted method and supplementary methods like MR-Egger for comprehensive assessment. **Results:** In our Mendelian randomization study, we identified diverse associations between cathepsins and autoimmune diseases. Specifically, cathepsin G was found to significantly increase the risk of myasthenia gravis, while the effects of cathepsin B on rheumatoid arthritis and systemic lupus erythematosus varied. Furthermore, multivariable analysis revealed significant correlations between cathepsins F, G and Z with myasthenia gravis. Importantly, no evidence of reverse causation or horizontal pleiotropy was observed. **Conclusion:** The study establishes a significant causal relationship between cathepsin G and myasthenia gravis risk.

Keywords: cathepsins; autoimmune diseases; risk; causal effect; mendelian randomization

1. Introduction

Autoimmune diseases, characterized by the immune system's aberrant attack on healthy body tissues, pose a significant global health burden [1,2]. These conditions are highly prevalent, affecting millions worldwide and encompassing a diverse range of disorders such as multiple sclerosis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [3–6]. The complexity and chronic nature of these diseases not only present challenges in diagnosis and treatment but also result in substantial socio-economic impacts [7–9]. For instance, rheumatoid arthritis leads to chronic pain, joint deformities, and disability, significantly impacting work productivity and increasing healthcare expenditures. Multiple sclerosis causes neurological degeneration, resulting in progressive disability and a high economic burden due to long-term care. Systemic lupus erythematosus often affects multiple organs, leading to hospitalization, reduced quality of life, and substantial medical costs. The increasing incidence of autoimmune diseases emphasizes the urgent need for deeper understanding and more effective therapeutic strategies [10].

Cathepsins, a family of proteolytic enzymes, are crucial in various biological

processes, including protein degradation, antigen presentation, and cellular homeostasis [11,12]. Classified mainly as cysteine, serine, or aspartic proteases, these enzymes are integral to the lysosomal degradation pathway [13,14]. Their dysfunction, resulting from overexpression or abnormal activity, has been implicated in several pathological conditions, ranging from cancer to neurodegenerative diseases [15–18]. Cathepsins participate in disease progression by degrading extracellular matrix, regulating antigen presentation, and activating inflammatory mediators such as cytokines and chemokines. Cathepsin S promotes synovial inflammation and joint destruction in rheumatoid arthritis, while cathepsin B exacerbates tissue damage in systemic lupus erythematosus by regulating autophagy and apoptosis. Notably, recent research has begun to highlight the potential role of cathepsins in autoimmune diseases [19,20]. Altered cathepsin activity may disrupt immune tolerance, leading to immune system dysfunction and the promotion of autoimmunity. This disruption contributes to the onset and progression of autoimmune conditions [21–23]. For example, cathepsin S is involved in antigen processing, while cathepsin B influences inflammatory processes—both of which are crucial in the pathogenesis of autoimmune diseases [24,25]. This emerging evidence underscores the need for further investigation into the roles of cathepsins in autoimmune disease etiology, providing new insights and potential therapeutic targets.

The existing literature on the association between cathepsins and autoimmune diseases is subject to notable limitations [26–28]. Although predominantly observational studies have provided insights into potential links, they are insufficient in establishing causality due to inherent biases and confounding factors [29–31]. This lack of causal evidence impedes the development of effective therapeutic strategies targeting cathepsins in autoimmune diseases.

Our study aims to bridge this gap by employing Mendelian randomization (MR), a method that utilizes genetic variants as proxies for risk factors to infer causal relationships [32]. The strength of MR lies in its ability to emulate randomized controlled trials, thereby overcoming the limitations of observational studies. By leveraging genetic data, MR analysis can provide more definitive evidence regarding whether cathepsins directly influence the development of autoimmune diseases. This approach not only promises to advance our understanding of the etiological role of cathepsins in these conditions but also has the potential to guide future therapeutic interventions.

2. Materials and methods

2.1. Study design

In this research, we conducted a two-sample Mendelian randomization (MR) analysis to assess the causal link between cathepsins and autoimmune diseases. Single Nucleotide Polymorphisms (SNPs) served as instrumental variables (IVs) [33]. To ensure optimal result accuracy, it's crucial to validate three key hypotheses throughout the entire process [34]. The first step involves confirming that the chosen IVs exhibit a direct association with cathepsins. Secondly, it's essential to establish the IVs' independence from potential confounders impacting both exposure and outcome. Lastly, ensuring that the IVs affect autoimmune diseases solely through their influence

on the risk factor (**Figure 1**).

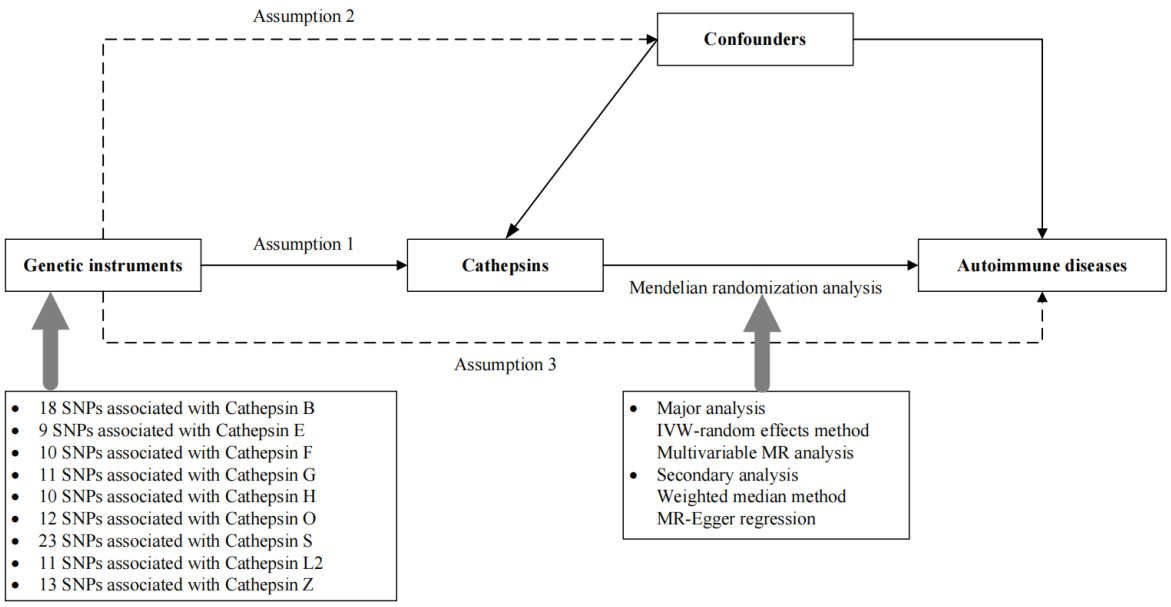


Figure 1. Overview of the MR design.

Note: Abbreviations: MR, mendelian randomization; IVs, instrumental variables; SNPs, single nucleotide polymorphisms; IVW, Inverse variance weighted.

The genetic instruments for cathepsins were derived from publicly available genome-wide association study (GWAS) summary statistics. Specifically, SNPs strongly associated with circulating levels of cathepsins (e.g., Cathepsin B, E, F, G, H, O, S, L2, and Z) were extracted from the INTERVAL study [35], a large-scale proteomic GWAS involving 3301 European participants (Supplementary **Table S1**). For autoimmune disease outcomes, summary-level genetic data were obtained from the FinnGen consortium (Round 9), a population-scale GWAS database integrating genetic and health registry data from over 300,000 Finnish individuals (Supplementary **Table S2**). FinnGen employs GWAS to detect genetic associations with diseases, and its publicly accessible summary statistics are widely utilized in MR analyses.

Our two-sample MR analysis adhered to established guidelines for leveraging pre-existing GWAS data to minimize biases and maximize statistical power. The use of independent GWAS datasets for exposures (cathepsins) and outcomes (autoimmune diseases) aligns with recommendations to avoid sample overlap and ensure validity in causal inference [36]. Notably, while our study did not perform de novo GWAS, the INTERVAL and FinnGen datasets are peer-reviewed, ethically approved resources that have undergone rigorous quality control, including population stratification adjustment, imputation accuracy checks, and significance filtering.

The univariable MR analysis was designed to examine the relationship between individual cathepsins and the risk of specific autoimmune diseases, providing insights into each cathepsin's independent role. In contrast, the multivariable MR analysis sought to assess the combined and individual effects of interrelated cathepsins on autoimmune diseases, offering a more comprehensive view of how these factors interact in disease development. Both approaches were aimed at deepening our

understanding of the causal links between cathepsins and autoimmune diseases.

2.2. Statistical analyses

We used the fixed-effect inverse variance weighted (IVW) method as our primary approach for Mendelian randomization (MR) analysis, which provided a robust estimate of the causal relationship. To ensure comprehensive evaluation, we also applied four additional methods—MR-Egger, weighted median, weighted mode, and simple mode. While these methods offer valuable insights, they generally possess less statistical power than the IVW method. To assess the reliability of our findings, we used Cochran's Q statistic to test for heterogeneity, and if the p-value was less than 0.05, we applied a random-effects model to account for heterogeneity. For potential pleiotropy, we used the MR-Egger intercept test, and if the p-value was less than 0.05, indicating the presence of pleiotropy, we employed the RadialMR method to detect and exclude outlier SNPs, then re-ran the MR-Egger test to verify the results.

2.3. Genetic instrument selection

In the univariable Mendelian randomization (MR) analysis, we isolated independent single nucleotide polymorphisms (SNPs) linked to cathepsins using a stringent threshold for linkage disequilibrium clumping ($r2 = 0.001$) and a window size of 10 megabases to minimize redundancy. We focused on genome-wide significant SNPs ($p < 5 \times 10^{-6}$) associated with each trait to ensure robust instrument selection. Additionally, we conducted multivariable MR using inverse variance weighting to estimate the direct causal impact of cathepsins on a range of autoimmune diseases, including ankylosing spondylitis, asthma, Crohn's disease, hypothyroidism, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and ulcerative colitis, providing a comprehensive understanding of their interrelationships.

2.4. Sensitivity analyses

To ensure the reliability and robustness of the identified causal effect of cathepsins on autoimmune diseases, we conducted an extensive set of sensitivity analyses. First, Cochran's Q statistic was used to evaluate potential heterogeneity within the data, which helps identify whether any variability across the SNPs could affect the results [37]. The MR-Egger intercept analysis was employed to assess horizontal pleiotropy, ensuring that genetic instruments were not influencing multiple traits in an unintended way [38]. We also performed a leave-one-out analysis, systematically removing each SNP to check if any single SNP had a disproportionate influence on the results. In addition, reverse Mendelian randomization (MR) analyses were carried out to explore the potential reverse causal relationship between cathepsins and autoimmune diseases. All statistical analyses were conducted using R (version 4.2.0) and RStudio, with the "TwoSampleMR" and "MR-PRESSO" R packages for performing the MR analyses and detecting outliers.

3. Results

3.1. Univariable mendelian randomization analysis

In our analysis of the impacts of specific cathepsins on autoimmune diseases, we found instrumental heterogeneity in the relationships between cathepsin F and ankylosing spondylitis, cathepsin B and myasthenia gravis, and cathepsin S and systemic lupus erythematosus (Cochran's Q test, $p < 0.05$; Supplementary **Table S3**). To address this, we applied MR-PRESSO to identify and exclude outliers exhibiting significant heterogeneity, which improved the stability of our results. Additionally, leave-one-out analysis demonstrated that removing individual SNPs did not substantially affect the causal estimates, suggesting robustness in our findings (Supplementary **Figures S1–S9**). This confirms the reliability of the identified causal links between cathepsins and autoimmune diseases.

The IVW method revealed a significant association between cathepsin G and an increased risk of myasthenia gravis, with an odds ratio (OR) of 1.452 [95% CI: 1.002–2.106; $p = 0.048$]. Furthermore, cathepsin B was significantly associated with an elevated risk of rheumatoid arthritis, with an OR of 1.072 [95% CI: 1.017–1.131; $p = 0.009$]. Interestingly, cathepsin B was also associated with a reduced risk of systemic lupus erythematosus, showing an OR of 0.794 [95% CI: 0.685–0.921; $p = 0.002$]. These findings, presented in **Figure 2** and Supplementary **Table S4**, provide insights into the diverse roles of cathepsins in autoimmune disease susceptibility.

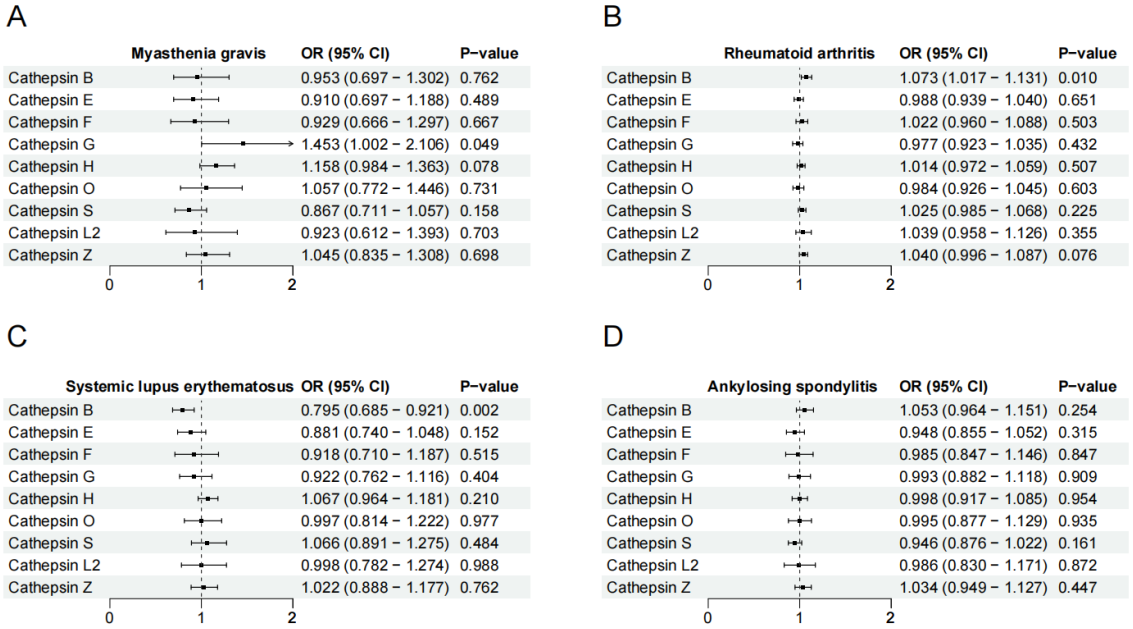


Figure 2. Univariable Mendelian randomization results using the inverse-variance weighted method. **(A)** myasthenia gravis; **(B)** rheumatoid arthritis; **(C)** systemic lupus erythematosus; **(D)** ankylosing spondylitis.

Note: Abbreviations: OR, odds ratio; CI, confidence interval.

We performed a reverse Mendelian randomization (MR) analysis to investigate whether autoimmune diseases could causally influence cathepsins. The results indicated no significant reverse causal relationship between any of the autoimmune diseases and cathepsins. This suggests that the observed associations are more likely driven by the impact of cathepsins on disease risk, as shown in Supplementary **Table S5**.

3.2. Multivariable mendelian randomization analysis

In our study, we utilized multivariable Mendelian randomization (MR) to examine the relationship between various cathepsins and the risk of autoimmune diseases (Supplementary **Table S6**). The results revealed that, after adjusting for other cathepsins, elevated cathepsin G levels remained significantly associated with an increased risk of myasthenia gravis (OR [95% CI] = 1.765 [1.311–2.377]; $p < 0.001$). Furthermore, cathepsin F and cathepsin Z showed distinct associations with the disease. Specifically, higher cathepsin F levels were linked to a reduced risk of myasthenia gravis (OR [95% CI] = 0.715 [0.526–0.973]; $p = 0.033$), while cathepsin Z levels were associated with an increased risk (OR [95% CI] = 1.480 [1.111–1.970]; $p = 0.007$). Interestingly, these associations were not observed in the univariable Mendelian randomization analysis (**Figure 3**). This suggests that adjusting for other cathepsins may reveal hidden relationships that were not apparent in the univariate analysis.

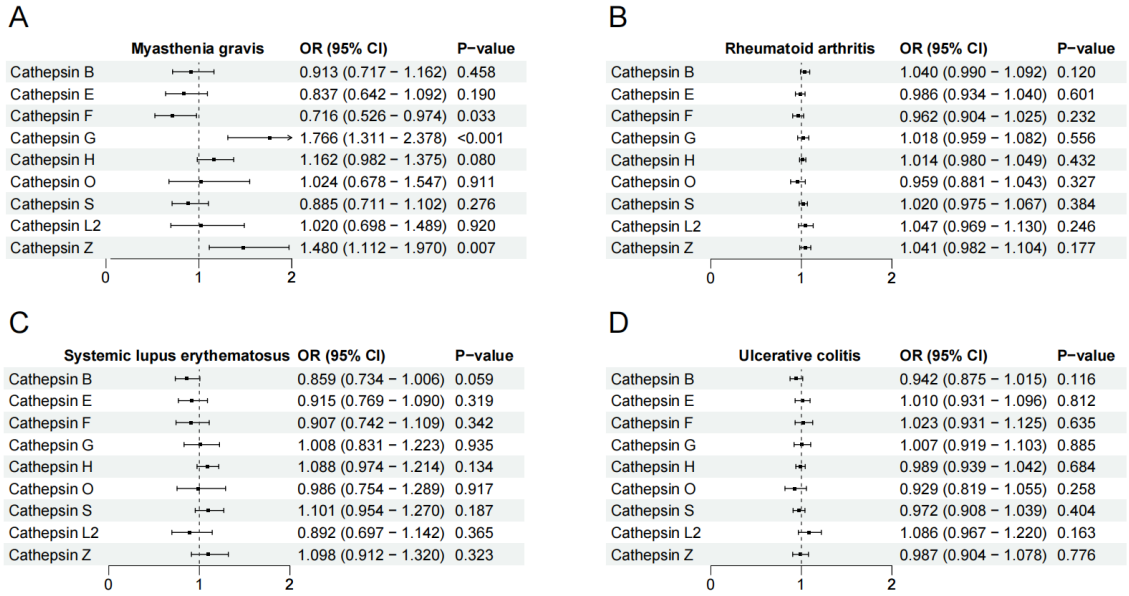


Figure 3. Multivariable Mendelian randomization results using the inverse-variance weighted method. **(A)** myasthenia gravis; **(B)** rheumatoid arthritis; **(C)** systemic lupus erythematosus; **(D)** ulcerative colitis.

Note: Abbreviations: OR, odds ratio; CI, confidence interval.

The study found no significant causal association between cathepsin B and rheumatoid arthritis, nor between cathepsin B and systemic lupus erythematosus, after adjusting for the effects of various other cathepsin types. These findings suggest that the initial observed relationships may be confounded by the intercorrelation of cathepsins. Furthermore, the MR-Egger intercept analysis, outlined in Supplementary **Table S7**, did not provide evidence for horizontal pleiotropy, indicating that the results were not likely biased by genetic variants influencing multiple traits.

4. Discussion

Autoimmune diseases, characterized by the immune system mistakenly attacking the body's own tissues, are intricate and multifaceted [39,40]. Understanding the underlying mechanisms is crucial for developing effective treatments. Current

therapeutic options are often limited and not specifically targeted, leading to a need for more precise interventions [41,42]. Researching cathepsins' role in autoimmune diseases could unveil specific molecular pathways involved in these conditions, offering insights into novel therapeutic targets.

In our study, the primary objective was to elucidate the causal links between cathepsins and the risk of various autoimmune diseases, providing valuable insights into the pathogenesis of these complex conditions. Our key findings revealed a significant association between elevated levels of cathepsin G and an increased risk of myasthenia gravis, a relationship that remained robust even after adjusting for the influence of other cathepsins. Moreover, cathepsin B was found to be significantly associated with an increased risk of rheumatoid arthritis, while it exhibited an inverse relationship with the risk of systemic lupus erythematosus in univariable Mendelian randomization analyses. These results highlight the diverse roles of cathepsins in autoimmune disease susceptibility.

The interpretation of these findings highlights the diverse roles that different cathepsins play in the pathogenesis of autoimmune diseases. Elevated levels of cathepsin G may contribute to the development of myasthenia gravis, suggesting its potential role as a biomarker or therapeutic target. On the other hand, cathepsin B appears to have varying effects depending on the disease, with a significant association with an increased risk of rheumatoid arthritis yet a protective role in systemic lupus erythematosus. These results underscore the complexity of autoimmune diseases and the need for further research into the molecular mechanisms involved. Understanding these relationships could lead to more targeted and personalized treatment approaches, providing novel opportunities for therapeutic intervention in autoimmune disease management.

The potential biological mechanisms linking cathepsins to various autoimmune diseases are multifactorial and complex, reflecting the broad range of roles these enzymes play in the immune system and in tissue homeostasis. Cathepsins, as lysosomal proteases, are crucial in protein degradation, antigen presentation, and immune modulation, with their dysregulation contributing to autoimmune disease pathogenesis.

One key mechanism involves cathepsins' role in antigen processing and presentation, a fundamental process in the immune system. Cathepsin G, for instance, has been implicated in modulating the immune response by affecting antigen processing, leading to an aberrant immune reaction that can contribute to autoimmune diseases [43]. This is particularly relevant in the context of autoimmune diseases such as rheumatoid arthritis, where the immune system erroneously targets the body's own tissues, triggering inflammation and joint damage [44]. Cathepsin G has been shown to influence the activation of T cells and dendritic cells, potentially exacerbating autoimmune responses [19].

In addition to antigen presentation, cathepsins also play significant roles in tissue remodeling and the breakdown of extracellular matrix components, a process that is often dysregulated in autoimmune diseases [45]. For example, in RA, cathepsins K, S, and G are involved in joint inflammation and destruction by degrading collagen and other extracellular matrix proteins [46,47]. This not only leads to the physical damage of joints but also promotes the production of pro-inflammatory cytokines, further

driving the inflammatory cycle.

Beyond their protease activity, cathepsins also influence immune cell function and cytokine production. Cathepsin B, for example, has been implicated in the regulation of inflammation through the activation of certain pro-inflammatory cytokines such as IL-1β and TNF-α, which are central to the pathophysiology of several autoimmune diseases [48]. In systemic lupus erythematosus, cathepsins are thought to modulate the immune response by influencing the processing of self-antigens, potentially contributing to the breakdown of immune tolerance and the development of autoimmune reactions [49,50].

Furthermore, cathepsins are involved in the regulation of cell death pathways, such as apoptosis and autophagy, both of which play a critical role in the maintenance of immune homeostasis [51,52]. Dysregulation of these pathways can result in the accumulation of damaged cells or the inappropriate activation of immune responses, both of which are hallmarks of autoimmune disease. For instance, cathepsins have been shown to modulate the activation of caspases, key enzymes involved in the apoptotic pathway, suggesting their role in regulating immune cell turnover and maintaining tolerance to self-antigens [53].

Comparing our findings with existing literature reveals both alignments and novel insights. Previous studies have suggested a role for cathepsins in autoimmune diseases, but our research provides more robust evidence of these associations using Mendelian randomization. For instance, our observation of cathepsin B's link to rheumatoid arthritis resonates with previous researches. Mishiro et al. found that the serum levels of cathepsin B and thrombin-like activity in rheumatoid arthritis group were significantly higher than those in osteoarthritis group [54]. Tong et al. found that cathepsin B causes joint destruction in rheumatoid arthritis by promoting the invasive phenotype of fibroblast-like synoviocytes in an ex-vivo invasion model [55].

The novel aspect of our research lies in the identification of specific cathepsins, such as cathepsin F, cathepsin G, and cathepsin Z, as potential key factors in the development and progression of myasthenia gravis. These findings expand upon the existing body of literature, as prior researches primarily focused on the association of cathepsin S with myasthenia gravis. Previous research by Kala et al. suggested a potential role for cathepsin S in autoimmune susceptibility, particularly in myasthenia gravis, due to its involvement in invariant chain processing and MHC class II peptide loading [56]. However, our Mendelian Randomization analysis did not support this hypothesis, as we found no substantial association between cathepsin S and myasthenia gravis risk.

Previous work, such as the study by Wu et al. [57], has explored similar associations between cysteine cathepsins and autoimmune diseases; our research extends their findings in several important ways. Wu et al. identified associations between elevated levels of specific cathepsins (such as cathepsins B, F, H, and Z) and autoimmune diseases, including psoriasis, ulcerative colitis, and type 1 diabetes. However, their analysis was primarily focused on individual cathepsins and did not account for the potential interrelations between different cathepsins in influencing disease risk. In contrast, our study utilized a multivariable MR approach, which allowed us to evaluate the combined and independent effects of multiple cathepsins on autoimmune disease susceptibility. This more comprehensive analysis revealed that

adjusting for other cathepsins provided new insights into disease risk, such as the finding that cathepsin F was associated with a reduced risk of myasthenia gravis, which was not apparent in the univariable analysis. Additionally, while Wu et al. focused primarily on a subset of autoimmune diseases, our study included a broader range of diseases, such as myasthenia gravis, systemic lupus erythematosus, and rheumatoid arthritis, which provided a more diverse perspective on the role of cathepsins across different autoimmune conditions.

Interestingly, our analysis reveals that other cathepsin types, namely cathepsin G, F, and Z, exhibit notable associations with myasthenia gravis. Elevated levels of cathepsin G are significantly associated with an increased risk of developing myasthenia gravis, even after adjusting for other cathepsin types. Conversely, cathepsin F levels correlate with a lower risk, and cathepsin Z with a higher risk, although these associations were not statistically significant in univariate Mendelian randomization analysis. The divergent effects of different cathepsins, as observed in our study, suggest that the relationship between cathepsins and autoimmune diseases may not be straightforward and could depend on multiple factors. This complexity is further exemplified by contrasting findings in different organ-specific autoimmune models, as seen in prior research, indicating that the therapeutic potential of cathepsin S inhibitors in autoimmune diseases must be empirically determined [58].

It is important to note that our study has several limitations. Firstly, MR analysis relies on stringent assumptions regarding the validity of instrumental variables. Although we have employed sensitivity analyses and reverse Mendelian randomization to mitigate pleiotropic bias as much as possible, residual confounding from unmeasured factors (e.g., pathogen exposure or epigenetic interactions) may persist, potentially introducing directional bias. The limited variance explained by genetic instruments could amplify such confounding, though our use of strong IVs and multivariable MR adjustments aimed to minimize this risk. Moreover, while we employed multiple analyses, including sensitivity tests, to ensure the reliability of our findings, we acknowledge that the MR analysis has inherent limitations in fully capturing the dynamic effects of environmental factors such as infections, pharmacological interventions, or other unmeasured variables. These factors may contribute to residual confounding, which could still influence the observed relationships between cathepsins and autoimmune diseases. To further strengthen causal inferences, longitudinal studies or randomized controlled trials are needed to provide supplementary evidence. Additionally, the genetic instrumental variables used in this study were derived from the INTERVAL study of European participants, without addressing the potential impact of ethnic specificity on the results. Ethnic differences may lead to variations in genetic background and environmental factors, potentially affecting the generalizability of the findings.

In conclusion, this Mendelian randomization study identifies distinct causal relationships between various cathepsins and autoimmune diseases. Specifically, cathepsin G is associated with an increased risk of myasthenia gravis, while cathepsin B appears to influence the risk of rheumatoid arthritis and systemic lupus erythematosus. These findings highlight the potential of cathepsins as biomarkers for autoimmune disease risk. Further validation of these associations and exploration of the underlying biological mechanisms are necessary. Such research could provide

valuable insights that inform more personalized approaches to the diagnosis, prevention, and treatment of autoimmune diseases, improving patient outcomes.

Supplementary materials: The supplementary materials include additional tables and figures that support the main findings of the study. Supplementary Tables provide detailed results from various Mendelian randomization analyses, including univariable and multivariable approaches, as well as additional information from GWAS and the FinnGen study. Supplementary Figures display leave-one-out analyses of the effects of cathepsins on several diseases, including Ankylosing spondylitis, Asthma, and Crohn's disease, among others.

Acknowledgments: We sincerely thank the contributors in the openGWAS project.

Data availability statement: 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.

Conflict of interest: The authors declare no conflict of interest.

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