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SHORT COMMUNICATION

Causal relationship between cathepsin H and type 1 diabetes: A Mendelian randomization study

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Abstract

Introduction: Epidemiological studies investigating the relationship between cathepsins and diabetes mellitus (DM) have reported inconsistent results.
Objective: The objective of the study is to evaluate the potential causal relationship between cathepsins and DM 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 DM. Both univariable and multivariable MR analyses were employed to assess the individual and combined effects of cathepsins.
Results: Univariable MR analysis revealed a significant association between cathepsin H and an increased risk of type 1 DM using the inverse-variance weighted method (odds ratio = 1.104; 95% confidence interval = 1.065 – 1.145; p<0.001). Reverse MR analysis and sensitivity analysis supported the robustness of this finding. In the multivariable MR analysis, elevated cathepsin H levels were found to be significantly associated with an increased risk of type 1 DM (odds ratio = 1.090; 95% confidence interval = 1.048 – 1.133; p<0.001), even after adjusting for other cathepsin types. No significant associations were observed between cathepsins and the risk of type 2 DM or gestational DM.
Conclusion: The study highlights a significant causal relationship between cathepsin H and the risk of type 1 DM.

Keywords: Causal effect; Cathepsins; Diabetes mellitus; Mendelian randomization; Risk

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1. Introduction

Diabetes mellitus (DM) has emerged as a major global health concern, with its increasing prevalence posing significant challenges to public health systems worldwide.[1-3] The continuous increase in DM incidence highlights its widespread impact on societies globally.[4,5] Several factors contribute to this continuous rise in diabetes rates – including population aging, sedentary lifestyles, unhealthy dietary habits, and the global obesity epidemic.[6-8] In addition, urbanization and socioeconomic transitions have further exacerbated these trends by encouraging physical inactivity and the increased consumption of processed, calorie-dense foods.[9,10] These lifestyle changes, combined

with genetic susceptibility, have contributed to the growing burden of all major forms of diabetes.[11]

This multifaceted disease arises from a complex interplay between genetic susceptibility and environmental factors.[12] Type 1 DM (T1DM) is an autoimmune disease characterized by the immune-mediated destruction of pancreatic islet β-cells, leading to absolute insulin deficiency.[13,14] In contrast, type 2 DM (T2DM) is a chronic metabolic disorder caused by impaired function of pancreatic β-cells, resulting in relative insulin deficiency accompanied by insulin resistance.[15,16] Gestational DM (GDM) is characterized by increased glucose demands from both the mother and fetus during pregnancy, coupled with reduced insulin sensitivity in pregnant women.[17] The interplay between hereditary and lifestyle factors contributes to the complex etiology of diabetes.[18] As the global burden of DM continues to grow, a deeper understanding of its multifactorial nature is essential for developing effective strategies to reduce its rising prevalence and address its significant impact on public health.[19]

Cathepsins are a class of lysosomal proteases that play a pivotal role in maintaining cellular homeostasis and mediating protein degradation within lysosomes.[20,21] These enzymes perform a wide range of biological functions, including antigen processing, tissue remodeling, and apoptosis.[22,23] Their regulatory involvement in multiple cellular processes highlights their importance in preserving physiological balance.[24,25]

Previous studies demonstrated that cathepsins influence insulin sensitivity, β-cells function, and inflammation, suggesting their involvement in DM pathogenesis.[26-28] In an *in vitro* study, Li *et al.*[29] observed that overexpression of cathepsin B inhibits the degradation of insulin receptor substrate 1 and glucose transporter type 4, thereby reducing palmitate-induced insulin resistance in human skeletal muscle cells. He *et al.*[30] reported that vitamin D alleviates oxidative stress in T1DM patients by downregulating cathepsin G expression, which inhibits $CD4^+$ T cell activation and protects β-cells from immune-mediated damage. In addition, Liu *et al.*[31] found that cathepsin B aggravates diabetic cardiomyopathy by regulating nucleotide oligomerization domain-like receptor protein 3-mediated cardiomyocyte inflammation and proptosis in mice.

Existing literature on the association between cathepsins and DM faces notable limitations.[32-34] Although previous studies have provided valuable insights into potential associations, they do not establish a definitive causal link due to inherent biases and confounding factors.[35] This lack of causal evidence hinders progress toward developing effective therapeutic strategies targeting cathepsins in DM.

To address this issue, the present study employs Mendelian randomization (MR), which uses genetic variants as indicators of risk factors to examine the causal relationships between cathepsins and DM. The strength of MR lies in its ability to mimic randomized controlled trials, thereby overcoming the limitations inherent to observational studies.[36] By utilizing genetic data, MR analysis offers more robust evidence on the direct impact of cathepsins on DM development. This approach offers valuable insights into the etiological role of cathepsins and has the potential to 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 causal relationship between cathepsins and DM, using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs).[37] To ensure robust and reliable results, three fundamental assumptions were rigorously tested and confirmed throughout the analysis.[38] First, genetic variants (SNPs) significantly associated with cathepsin levels were identified from independent cohorts and used as indicators to estimate the effect of cathepsins on diabetes outcomes. Second, it was verified that these SNPs are independent of confounding factors – such as environmental influences or other genetic traits – which could affect both cathepsins (exposure) and DM (outcome). Third, the analysis confirmed that the SNPs affect DM solely through their effect on cathepsins, with no direct pathways affecting diabetes outcomes (e.g., T1DM, T2DM, or GDM) independent of cathepsin levels (Figure 1).

The univariable MR analysis was conducted to investigate the association between each individual cathepsin and DM. In this approach, the causal relationship between each cathepsin (e.g., cathepsin B) and DM was assessed using SNPs specifically associated with that cathepsin. Conversely, multivariable MR analysis was employed to disentangle the independent effects of closely related cathepsins on diabetes risk by considering their combined effect simultaneously. This method allows for examining how interactions among multiple cathepsins may contribute to the development of diabetes.

This study used genome-wide association study (GWAS) summary statistics obtained from previously published studies.[39] Genetic instruments for cathepsins were extracted from the INTERVAL study, which included 3,301 European participants (Table S1).[39] DM outcomes – including T1DM, T2DM, and GDM – were obtained from the FinnGen database (Round 9, https://r9.risteys.finngen.fi/) (Table S2). Samples sizes were

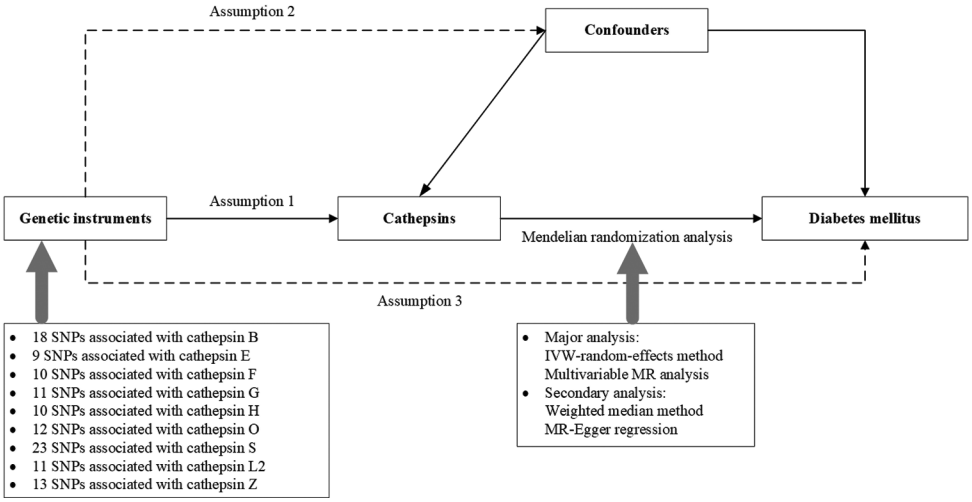

Figure 1. Overview of the Mendelian randomization design, illustrating the process from instrumental variable selection to causal effect estimation using the inverse-variance weighted method. Single nucleotide polymorphisms were employed as instrumental variables to evaluate the causal relationship between genetic factors and disease outcomes.
Abbreviations: IVW: Inverse-variance weighted; MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms.

4,196 cases and 308,252 controls for T1DM; 57,698 cases and 308,252 controls for T2DM; and 13,039 cases and 197,831 controls for GDM. Ethical approval and informed consent for these datasets were obtained in the original studies. As this analysis used only secondary data, no additional ethical approval or informed consent was required for the current study.

2.2. Statistical analyses

The fixed-effect inverse-variance weighted (IVW) method was employed as the primary approach for MR analysis. In cases where heterogeneity among instrumental SNPs was detected, a random-effects model was applied to account for potential variability across instruments.[40] To provide a comprehensive assessment of the potential causal relationship, four additional methods were employed: simple mode, weighted mode, MR-Egger, and weighted median. Although these methods offer a comprehensive evaluation, they generally have lower statistical power compared to the IVW test. Cochran's *Q* statistic was utilized to assess heterogeneity, while the MR-Egger intercept test was applied to evaluate horizontal pleiotropy.

2.3. Genetic instrument selection

In the univariable MR analysis, independent SNPs associated with cathepsins were identified using linkage disequilibrium clumping, with an r^2 threshold of 0.001 and a window size of 10 MB. To minimize redundancy, only SNPs reaching genome-wide significance ($p<5 \times 10^{-6}$) for each trait were selected. A multivariable MR analysis was conducted based on the IVW method to estimate the direct impacts of cathepsins on T1DM, T2DM, and GDM.

2.4. Sensitivity analyses

To evaluate the robustness of the causal relationships identified between cathepsins and DM, a series of sensitivity analyses was performed. Cochran's *Q* statistic was employed to assess heterogeneity among the IVs, while the MR-Egger intercept test was used to evaluate the presence of horizontal pleiotropy[41,42] To examine the influence of individual SNPs on the overall causal estimates, a leave-one-out analysis was performed by sequentially removing each SNP. In addition, reverse MR analyses were conducted to investigate the potential reverse causal relationship between cathepsins and DM, complementing the forward MR findings. All analyses were conducted using R software (version 4.2.0, The R Foundation for Statistical Computing, Austria) and RStudio (version 2022.02.2, RStudio, PBC, USA).

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 was identified for cathepsin O and cathepsin S in relation to T2DM, as well as cathepsin S in relation to GDM, based on Cochran's *Q* test ($p<0.05$; Table S3). The presence of heterogeneity suggests that the instrumental SNPs may exert variable effects on the exposure. To account for this variation across the

instruments, a random-effects model was applied in the MR analysis.

Based on the IVW method, there was a significant association between cathepsin H and T1DM risk (odds ratio [OR] = 1.104; 95% confidence interval [CI] = 1.065 – 1.145; p<0.001) (Figure 2 and Table S4). Reverse MR analysis was performed to examine the potential causal impact of DM on cathepsin levels. The findings show no evidence of a reverse causal relationship between DM and any of the cathepsins (Table S5). A leave-one-out analysis showed that the exclusion of any single SNP does not significantly alter the causal effect estimates for T1DM (Figure S1), T2DM (Figure S2), or GDM (Figure S3), thereby supporting the robustness of the findings.

3.2. Multivariable MR analysis

This study used multivariable MR analysis to explore the effect of each cathepsin on the risk of DM (Table S6). The analysis evaluated the association of each cathepsin with T1DM, T2DM, and GDM outcomes while adjusting for the influence of other cathepsins. This method allows for a more precise estimation of the independent effects of each cathepsin on the risk of diabetes, accounting for potential interactions between them. The findings demonstrate that even after adjusting for other cathepsin types, elevated cathepsin H levels remained significantly associated with an increased risk of T1DM (OR = 1.090; 95% = 1.048 – 1.133; p<0.001) (Figure 3). In addition, the MR-Egger intercept analysis indicates no presence of horizontal pleiotropy (Table S7).

4. Discussion

In univariable MR analysis using the IVW method, there was a significant association between cathepsin H and T1DM, indicating that elevated cathepsin H levels are causally linked to increased T1DM risk.

The univariable MR analysis was used to evaluate the causal relationship between cathepsin H and T1DM, while the multivariable MR analysis adjusted for other cathepsin

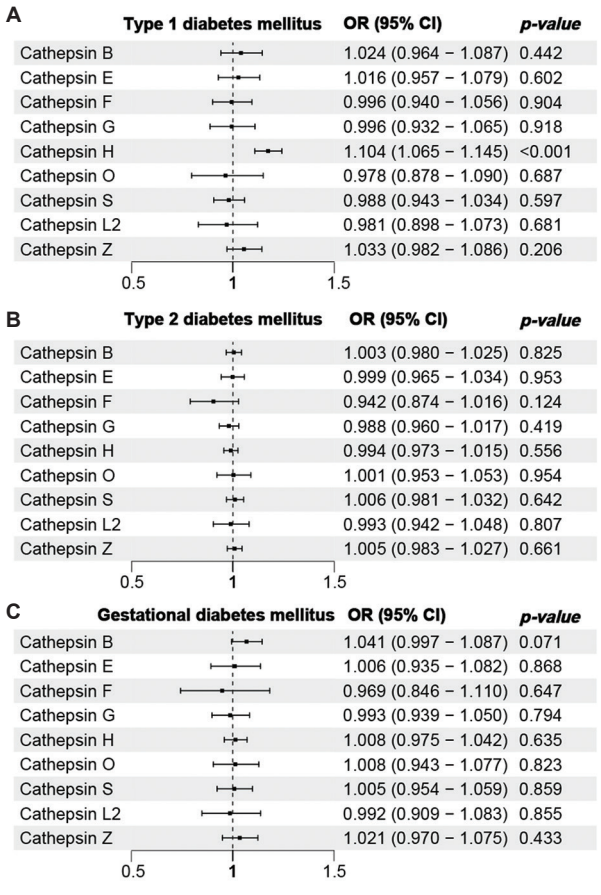

Figure 2. Univariable Mendelian randomization results using the inverse-variance weighted method for: (a) type 1 diabetes mellitus; (b) type 2 diabetes mellitus; and (c) gestational diabetes mellitus
Abbreviations: CI: Confidence interval; OR: Odds ratio.

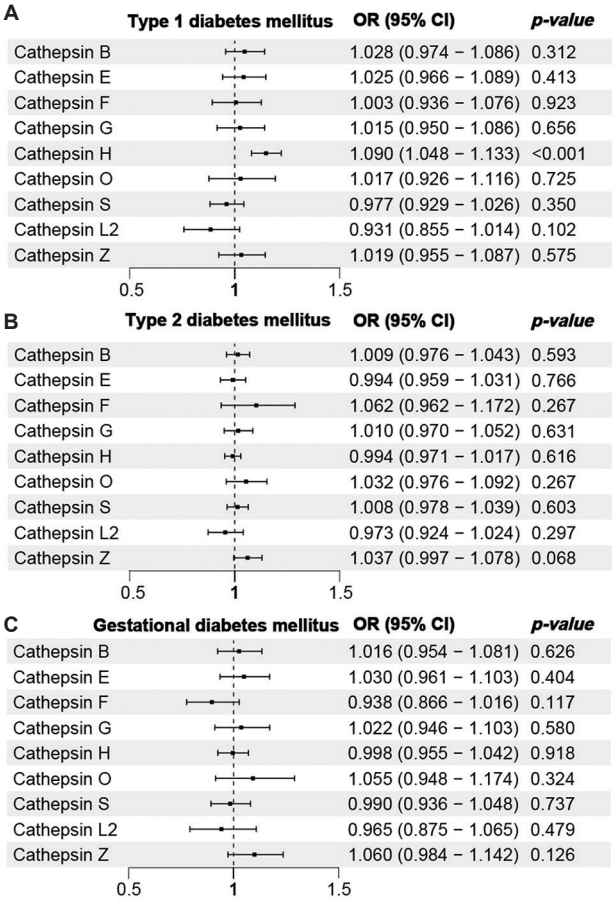

Figure 3. Multivariable Mendelian randomization results using the inverse-variance weighted method for: (a) type 1 diabetes mellitus; (b) type 2 diabetes mellitus; and (c) gestational diabetes mellitus.
Abbreviations: CI: Confidence interval; OR: Odds ratio.

types. The findings demonstrate that higher cathepsin H levels are significantly associated with an increased risk of T1DM, even after accounting for potential confounding by other cathepsins. This supports a robust and independent causal relationship between cathepsin H and T1DM.

To elucidate the underlying mechanisms of this association, it is essential to consider the potential biological role of cathepsin H in the development of diabetes. Cathepsin H is a lysosomal cysteine protease involved in various physiological processes, including protein degradation and immune response modulation. Its involvement in diabetes appears to be multifaceted, potentially influencing both inflammatory pathways and metabolic regulation.

One potential mechanism involves the role of cathepsin H in modulating inflammation and immune responses. T1DM is an autoimmune disease characterized by extensive destruction of pancreatic islet β-cells, resulting in absolute insulin deficiency and ultimately, insulin dependence. Cathepsin H has been shown to promote the activation of immune cells – particularly macrophages – and enhance the production of pro-inflammatory cytokines.[43,44] Elevated cathepsin H levels may contribute to immune dysregulation, fostering an inflammatory environment that accelerates β-cell destruction and diabetes development.[45] Furthermore, cathepsin H may directly induce β-cell apoptosis through its proteolytic activity, further exacerbating cell loss in T1DM.[46] Collectively, these findings suggest that cathepsin H plays a crucial role in both the immune-mediated destruction of β-cells and the persistence of the inflammatory processes in T1DM.

This study's findings align with previous research while also providing new insights. The significant association between cathepsin H and T1DM observed in both univariable and multivariable MR analyses corroborates the findings of Fløyel *et al.*[47] who identified cathepsin H as a key regulatory factor in T1DM progression, affecting the survival and function of pancreatic β-cells targeted by autoimmune attacks. In addition, Ye *et al.*[48] identified cathepsin H as a risk gene for T1DM, emphasizing the association between its elevated expression and early-onset T1DM.

However, both univariable and multivariable MR analyses revealed no significant association between cathepsins and T2DM. These findings contradict those of Jing *et al.*[49] who reported elevated cathepsin S levels in T2DM patients, linked to an increased risk of cardiovascular disease. Furthermore, Karimkhanloo *et al.*[50] highlighted the role of cathepsin S in regulating glucose output in mice liver cells, suggesting a potential association between cathepsin S and blood glucose control. These discrepancies may be due to variations in study design, population characteristics, or the specific cathepsin isoforms investigated. The MR analysis, which uses genetic variants as IVs, provides a robust and unbiased assessment of causality while also minimizing confounding factors. Regardless, it is important to recognize that the complex functions of cathepsins and their interactions across various tissues may also contribute to the observed disparities.

While previous studies focused on specific cathepsin isoforms and their roles in T2DM and glucose regulation, this study conducted a comprehensive analysis of various cathepsins but did not find a significant association with T2DM risk. Further research is needed to clarify these findings and investigate the potential tissue-specific functions of cathepsins in T2DM. Gaining a deeper understanding of these differences could provide more comprehensive insights into the role of cathepsins in DM, thereby guiding targeted therapeutic interventions.

Several limitations remain in this study. First, the MR analyses rely on key assumptions – particularly the absence of pleiotropy and horizontal pleiotropy – which are crucial for ensuring the validity of the causal inferences. Given that multiple cathepsins may share genetic loci or biological pathways, there is a risk of overlap in the genetic instruments used, potentially introducing horizontal pleiotropy. Although robust genetic instruments and sensitivity analyses – such as the MR-Egger intercept test – were employed to address these issues, completely eliminating residual confounding remains challenging. Further research is needed to explore and address these potential pleiotropic effects, as they may influence the interpretation of the causal relationships between cathepsins and diabetes. In addition, this study focused solely on the genetic effects of cathepsins on DM risk. While multivariate MR analysis adjusted for multiple cathepsins, other influential factors – such as environmental and lifestyle variables – were not considered. Future studies should aim to integrate these factors into their analyses to provide a more comprehensive understanding of the causal mechanisms underlying the association between cathepsins and DM.

In this study, the significant association between cathepsin H and T1DM – observed in both univariable and multivariable MR analyses – provides compelling evidence for the potential role of cathepsin H in diabetes susceptibility. This finding aligns with previous studies highlighting the involvement of cathepsin H in immune modulation and inflammatory processes – both of which are central to the development of T1DM. Elevated cathepsin H levels may contribute to immune system

dysregulation, promoting β-cell destruction in T1DM. In contrast, the absence of a significant association between cathepsins and T2DM in this study raises the possibility of tissue-specific roles of cathepsins. Cathepsins may exert different functional effects in T2DM compared to T1DM. Future studies should explore how cathepsins interact within specific tissues – such as the pancreas, liver, and adipose tissue – in contributing to the pathophysiology of T2DM. Although MR analysis reduces confounding, studies incorporating environmental and lifestyle factors are needed to gain a more comprehensive understanding of the mechanisms involved. Overall, these findings suggest that cathepsins, particularly cathepsin H, may serve as potential biomarkers or therapeutic targets for T1DM, highlighting the need for further investigation into their roles in immune-mediated diseases.

5. Conclusion

This study identified a significant association between cathepsin H and T1DM, highlighting the potential role of cathepsins in the etiology of diabetes. These findings contribute to a deeper understanding of the complex interaction between cathepsins and diabetes and may pave the way for the development of targeted treatment strategies.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Rui Jin Ran, Ao Wang
Investigation: Rui Jin Ran, Ao Wang
Methodology: Rui Jin Ran, Ke Yi
Formal analysis: Ao Wang, Ke Yi
Writing – original draft: Rui Jin Ran, Ao Wang
Writing – review & editing: Rui Jin Ran, Ke Yi

Ethics approval and consent to participate

This study involves human participants; however, it utilized GWAS summary statistics obtained from previously published studies. Ethical approval for the GWAS data was granted in the original studies where all participants gave informed consent before joining the study and the National Research Ethics Service approved this study (11/EE/0538). As this research utilized secondary data, no additional informed consent was required.

Consent for publication

This study is a MR analysis based on previously published data. All data used were obtained from studies in which participants had provided informed consent before their enrollment.

Availability of data

Data are available from the corresponding author upon reasonable request.

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