Cathepsin in Alzheimer's Disease, Parkinson's Disease and Dementia with Lewy Bodies: Mendelian Randomization Study

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Abstract

Background

Observational studies indicate a strong association between most neurodegenerative disorders and cathepsin, although the causative link remains unclear.

Methods

This research utilized Mendelian Randomization (MR) with genetic markers linked to cathepsins as instrumental variables, and analyzed public Genome-Wide Association Studies (GWASs) summary data of individuals with European ancestry for Alzheimer's disease (AD), Parkinson's disease (PD), and dementia with Lewy bodies (DLB) as the outcomes. The study applied the inverse variance-weighted (IVW) method to assess the causal effects of cathepsins on AD, PD, and DLB. Several sensitivity analyses and a heterogeneity test were conducted to evaluate the effectiveness of the results. Confounding variables were accounted for using multivariable MR (MVMR). Additionally, reverse MR research was done to improve forward MR analysis. Lastly, we utilize Bayesian Weighted MR (BWMR) to further validate the robustness of the results.

Results

The MR investigation found an association between cathepsin H and AD and DLB risk. However, there was a negative correlation between PD risk and cathepsin B levels. Effect estimates in MVMR and BWMR analyses with cathepsins as variables remained constant. According to reverse MR analysis, PD decreased cathepsin B levels, and DLB negatively correlated with cathepsin Z levels. However, no reverse causal relationship was found between AD and cathepsins.

Conclusion

While higher cathepsin H levels were associated with AD and DLB risk, the bidirectional association between PD and cathepsin B. By studying how cathepsin influences the development and advancement of AD, PD, and DLB, novel methods for diagnosis and treatment might be investigated.

INTRODUCTION

Typical neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and dementia with Lewy bodies (DLB) are characterized by the gradual loss of neurons and continuous deterioration of brain tissue [1–3]. The global health crisis is being significantly impacted by the increasing number of elderly individuals, higher rates of neurological diseases, and inadequate treatment results [4]. Predictions indicate that by 2050 [5], the global prevalence of dementia will surpass
100 million; this will undoubtedly contribute to the growing population of individuals with NDs. Clinical diagnosis of NDs is primarily based on the individual's symptoms and characteristics. Neuronal degeneration occurs before the manifestation of symptoms. Therefore, seeking effective early diagnostic biomarkers and identifying therapeutic and preventive risk factors are crucial in clinical practice.

Neurodegeneration and aging have been associated with impaired endo/lysosomal systems and disturbed cellular homeostasis [6]. The family of lysosomal proteases known as cathepsins has a remarkable variety of functions. The human body possesses fifteen forms of cathepsins, all essential for preserving neural homeostasis, taking part in lysosomal breakdown, and promoting autophagy [7]. Several studies have examined the involvement of cathepsins in developing neurodegenerative disorders [8]. According to recent research, neuroinflammation generated by astrocytes and microglia is closely linked to cysteine cathepsins, which may impact the development of NDs [9]. The activation of microglial cells is induced by the aggregation of Amyloid-β (Aβ), α-Synuclein (α-Syn), and mutant huntingtin proteins, leading to the release of cysteine cathepsins (B, H, C, X), as well as proinflammatory cytokines. This cascade enhances neurotoxicity, ultimately culminating in neurodegeneration [10]. Identifying significant cause-and-effect explanations from observational studies is challenging because of the subtle impact of environmental risk factors on neurodegenerative diseases, particularly in the presence of potential confounding factors, both known and unknown [11].

A rapidly developing technique for determining causal effects is Mendelian randomization (MR) [12]. Therefore, MR analysis was employed in this work to ascertain the causal link between cathepsins and NDs. The results could be beneficial in predicting the course of disease and developing novel strategies for treatment. Due to their significant association, genetic variations or single nucleotide polymorphisms (SNPs) are used as instrumental variables (IVs) to investigate the causal link between exposure and outcome [13]. This method offers more dependable causal conclusions compared to observational studies by minimizing the influence of confounding variables and addressing reverse causation [14]. A two-sample MR is more feasible than randomized controlled trials (RCTs) because it utilizes summary-level statistics from two databases [15]. In the present study, Univariable MR, multivariable MR (MVMR), and Bayesian Weighted MR (BWMR) analysis were used to assess the causal relationship between genetically determined levels of cathepsins and the risk of AD, PD, and DLB.

**Materials and Methods**

**Study Design**

For a successful MR analysis, the instrumental variables must meet three requirements: IVs and exposure are related. IVs have no association with any confounding factor in the exposure-outcome connection. IVs only affect the result because of their relationship to the exposure. Figure 1 shows a summary of the MR research design.

**Data Sources and Instrument Selection**
The genetic information to assess the different cathepsin levels (µg/L) came from 3,622 plasma proteins obtained from 3,301 European study participants [16]. The National Research Ethics Service (11/EE/0538) approved the INTERVAL project. The pertinent data may be found at MRCIEU and have been made publicly available.

The following three neurodegenerative diseases (NDs) were selected in relative terms: AD, PD, and DLB. The genetic data used in this study was sourced from the latest available research, had large sample sizes, and were from the European population to minimize bias due to demographic stratification. The report published in 2022 included summary data on AD. The study included 401,577 controls, 46,828 proxy AD cases (individuals with a parent(s) who had dementia), and 39,106 clinically diagnosed cases of European descent [17]. Information on 449,056 controls with European ancestry and 33,674 cases of PD was supplied by the International Parkinson Disease Genomics Consortium (IPDGC) Study [18]. A recently published GWAS provided the DLB summary statistics [19], with 4,027 neurologically healthy adults and 2,591 patients with DLB from 44 different institutions or consortia. Please refer to the original publication for comprehensive information on sample collection, analytical techniques, and findings. Table S1 is a summary of the information. The study's ethical approval and participant informed consent are provided in the associated research, and the study's data is publicly available.

The genome-wide significant genetic tools were utilized, screening the exposure variables with a $5 \times 10^{-6}$ threshold to validate and choose SNPs for cathepsin levels. Independent and significant SNPs were used to perform linkage disequilibrium (LD) clustering based on the European 1,000 Genomes Project reference panel ($R^2 < 0.001$, window size = 10,000 kb). The formula $F = R^2 (n-k-1) / k (1-R^2)$ was used to assess the suitability of an SNP for MR analysis. An F-statistic of at least 10 was considered sufficient for MR analysis [20].

**Statistical Analysis**

The primary method employed in this Mendelian randomization study to evaluate the causal links between cathepsins and different neurodegenerative diseases was the technique known as inverse variance-weighted (IVW) [21]. The IVW method may introduce bias when confounding genetic variants (pleiotropy) are present. MR-Egger and the weighted median (WM) approach were utilized to improve and validate the study results. In MR-Egger analysis, the intercept's p-value was utilized to detect and adjust for potential pleiotropy[22]. The WM technique requires over 50% of SNPs to serve as reliable instrumental variables and accounts for potential horizontal pleiotropy among these variables [23]. The MR-PRESSO method provides corrected estimates following the exclusion of outliers [24]. The study also assessed data heterogeneity and identified variances in the results using Cochran's Q test, which is crucial for ensuring result accuracy [25]. The fixed-effects IVW model was used unless significant data heterogeneity was present ($p < 0.05$), in which case the random-effects IVW model was employed [26]. A sensitivity analysis, known as "leave-one-out," was conducted to determine if a specific SNP was driving the association between the exposure and outcome variables by systematically removing one SNP at a time [27]. The MR analysis results were illustrated using funnel and forest plots.
Multivariate MR (MVMR) was utilized to account for potential confounding effects on cathepsin levels [28]. This investigation assessed the causal effects of nine cathepsins on various types of NDs by examining the direct causative impacts of each exposure in a single research study. BWMR, a statistical method for causal inference using GWAS summary data, was utilized to enhance the credibility of the results [29]. Not only does BWMR allow the interpretation of estimated weak effects and uncertainty related to low-level pleiotropy, but it also adaptively detects outliers that arise from a minority of large-level pleiotropic effects [30].

The R and RStudio software versions 4.3.1 were used for all analyses, with the TwoSampleMR [31] package version 0.5.8, "MRPRESSO" [24], Bayesian weighted MR using BWMR R package, and "MendelianRandomization" packages [32]. Statistical significance was set at p < 0.05 for detecting differences.

## Results

### Instrumental variable selection

Tables S2-5 contain the specific traits of SNPs linked to cathepsin, AD, PD, and DLB.

### The causal effect of Cathepsins on AD, PD, and DLB

The Two-Sample MR study was conducted to assess the correlation between cathepsin levels (B, E, F, G, H, L2, O, S, and Z) and the risk of several NDs (AD, PD, and DLB) (Table 1). Genetically determined elevated levels of cathepsin H were associated with a higher risk of developing AD in the IVW MR study (odds ratio (OR) = 1.042 [95% confidence interval (CI): 1.014–1.070], p<sup>IVW</sup> = 0.003; Fig. 2). The MR-Egger and weighted median methods validated these consistently significant associations. Furthermore, a higher level of cathepsin B was linked to a lower risk of developing PD (OR = 0.890 [95% CI: 0.831–0.954], p<sup>IVW</sup> = 0.001; Fig. 2), and the weighted median and MR-Egger analyses supported this association. The probability of DLB was positively correlated with the levels of cathepsin H (OR = 1.126 [95% CI: 1.028–1.233], p<sup>IVW</sup> = 0.011; Fig. 2), and the weighted median analysis supported this relationship.

### The causal effect of AD, PD, and DLB on Cathepsins

A reverse MR analysis was conducted to investigate reverse causal linkages (Table S6). The results obtained using only the IVW method showed that PD decreased cathepsin B levels (OR = 0.925 [95% CI: 0.872–0.982], p<sup>IVW</sup> = 0.011; Fig. 2). The cathepsin Z levels were negatively correlated with DLB (OR = 0.942 [95% CI: 0.898–0.988], p<sup>IVW</sup> = 0.014), and the Weighted Median approach confirmed this relationship (Fig. 2). No evidence indicated a reverse causal relationship between AD and cathepsin.

### Sensitive analysis

The MR analysis of tissue protease H and AD showed heterogeneity, as indicated by Cochrane’s Q test (Q = 19.091, Q <pval> = 0.039; Table S7). No pleiotropy or heterogeneity was seen in any other MR analysis.
group, and leave-one-out analysis suggested that no potentially significant SNP impacted the causal relationship. The MR-Egger intercept and MR-PRESSO tests did not provide directional pleiotropic evidence for these causal relationships (Table S7).

**Multivariable Mendelian Randomization**

A multivariable MR analysis was performed to assess the causal relationships between genetic susceptibility to different cathepsins and various NDs. The results demonstrated that even after adjusting for other cathepsins, higher levels of cathepsin H maintained its capacity to increase the risk of AD (OR = 1.037 [95% CI: 1.010–1.065], $p_{IVW} = 0.007$; Fig. 3 and Table S8). There was a positive correlation between the risk of developing DLB and the levels of cathepsin H (OR = 1.126 [95% CI: 1.014–1.250], $p_{IVW} = 0.026$; Fig. 3 and Table S8). However, there was a negative correlation observed between cathepsin B levels and the risk of PD (OR = 0.888 [95% CI: 0.823–0.957], $p_{IVW} = 0.002$; Fig. 3 and Table S8).

**Bayesian Weighted Mendelian Randomization**

The BWMR approach was used to confirm the accuracy and reliability of the results. The results indicate a causal relationship between cathepsin H and AD (OR = 1.042 [95%CI: 1.015–1.071], $p_{BWMR} = 0.003$; Table S9). Furthermore, a causal relationship between PD and cathepsin B was observed (OR = 0.888 [95%CI: 0.827–0.953], $p_{BWMR} = 0.001$), as well as between cathepsin H and DLB (OR = 1.126 [95%CI: 1.027–1.235], $p_{BWMR} = 0.011$; Table S9).

**Discussion**

In recent years, the pathogenic pathways of neurodegenerative disorders have been examined, and the relevance of cathepsins is now increasingly investigated. The development of cell-toxic protein aggregates and inclusions, mostly generated by cathepsins, the principal lysosome mediators of protein breakdown, has been linked to several NDs [33]. NDs and neuronal death are often associated with aberrant cathepsin activity and degradation of protein [34, 35]. Using univariate, bidirectional, and multivariate MR analysis, this work assessed genetically determined cathepsin involvement in common NDs and their causal association. The study indicated that having a genetic predisposition to cathepsin B protects against PD. Conversely, having cathepsin H is associated with a higher risk of developing AD and DLB. These cathepsins might prove to be valuable indicators in assessing and predicting the development of NDs. This work is the first to introduce the concept of the initial application of MR methods to explore the causative relationships between cathepsins and the risk of developing NDs.

Extracellular aggregates of amyloid-β (Aβ) proteins result in amyloid plaques, while tau proteins are hyperphosphorylated, which causes glial cell activation and neuronal-peripheral inflammatory responses [36]. This is considered a crucial step in the development of AD and one of its clinical features. Research indicates that cathepsins are essential for activating microglial cells in AD chronic neuroinflammation [37, 38]. It has been observed that increased amyloid plaques, neuroinflammation, and other NDs in AD are associated with elevated levels or activity of cathepsin B [39, 40]. Proinflammatory mediators with
high molecular weight accumulating in the AD brain can impact phagocytosis and the activities of cathepsin S and L, potentially influencing the function of microglial cells [41]. The present research showed that a higher expression of cathepsin H was associated with an increased risk of AD. This result aligns with a recent study demonstrating the genetic regulatory mechanism of cathepsin H in the pathogenesis of AD, and cathepsin H was implicated in the genetic predisposition to AD [42]. Although Cochrane's Q test indicates heterogeneity, it does not impact the IVW analysis results. Moreover, observational research suggests that cathepsin B in extracellular vesicles could be involved in the pathophysiology of Aβ proteins in AD [43]. The cognitive function of AD is associated with elevated levels of cathepsin B, which can occur throughout both the moderate and severe stages of the disease [44]. However, the current MR analysis does not support this correlation, and further research is necessary.

The most prevalent degenerative neurocognitive condition is AD, with DLB coming in second. DLB is characterized by rapid advancement, and early onset dementia, with a significant decline in quality of life [45]. Currently, clinical symptoms are the primary means of diagnosing DLB, and reliable biomarkers for early disease detection are lacking. This study showed that elevated H levels are linked to an increased risk of DLB. Microglial cells and reactive astrocytes both contain cathepsin H of the cysteine protease family [46]. Through its connection to cellular protein degradation pathways, cathepsin H overexpression may be associated with the reaction to misfolded proteins resulting from ubiquitin-proteasome system malfunction, ultimately contributing to the degeneration of motor neurons [47]. Therefore, the mechanism associated with cathepsin H in AD and DLB is highly complex, necessitating further research to elucidate the role of cathepsin H in AD and DLB development and progression. Moreover, DLB has lower cathepsin Z expression, according to reverse MR analysis. The terms cathepsin Z and cathepsin X relate to the same enzyme that was separately reported under different designations by two other research groups [48, 49]. A recent study indicated that cathepsin X may play a role in neurodegenerative diseases caused by neuroinflammation and could be a potential target for treating neuroinflammatory conditions [50]. From a genetic standpoint, this work offers crucial new information regarding how DLB affects cathepsin Z expression.

Aggregation of α-synuclein (α-syn) and loss of neurons that produce dopamine are symptoms of PD [51]. Therefore, enhancing α-syn degradation may be an effective approach for PD treatment. Studies suggest that lysosomes are the primary site for the breakdown of accumulated α-syn. According to reports, there is an association between the structure of α-synuclein and the function of cathepsins, particularly cathepsin B and cathepsin L, which are essential for breaking down α-synuclein in lysosomes [17, 52]. According to new research, decreased cathepsin B function hinders lysosomal pathways linked to PD development, whereas increased cathepsin B activation may enhance the removal of pathogenic α-syn [53]. In cellular models of PD, the protein or activity levels of cathepsin B are decreased [54, 55]. The study's findings indicate a bidirectional causal relationship between PD and genetically estimated levels of cathepsin B, indicating that elevating cathepsin B levels might be a feasible therapeutic strategy. Additionally, cathepsin B has potential as a biomarker for early PD diagnosis, providing significant support for the early detection of the disease.
There are various advantages to this study. First, the information is based on large-scale GWAS summary data accessible to the public. The study thoroughly evaluated the causative association between cathepsins and NDs using the MR method. This method provides novel perspectives for clinical diagnosis, treatment, and prevention in the future, along with valuable resources for further scientific investigation. Second, this research minimizes the possible influence of unidentified confounding factors on the study's findings. It is based on instrumental variables rather than observational studies, offering a genetic perspective for the causal association between cathepsins and the development of AD, PD, and DLB. Finally, the study utilizes BWMR, MVMR, bidirectional MR, and thorough sensitivity analyses to generate reliable and robust research results. The research study has introduced a Bayesian approach for two-sample MR that deals with the uncertainty of weak effects expected in GWAS and the issue of horizontal pleiotropy within a single statistical framework [56].

There are several limitations to this study. One limitation is the restricted applicability of the analysis due to its use of GWAS data exclusively from individuals of European descent. To determine if these results are relevant to other populations with different genetic backgrounds, such as Asian populations, further research and validation are necessary. Secondly, while this study can demonstrate a causative link between blood cathepsin and AD, PD, and DLB, it does not assess the association with cathepsin levels in cerebrospinal fluid or specific brain regions.

CONCLUSION

To summarize, the results of this MR study support the idea that there is a link between higher cathepsin H levels and a higher risk of AD and DLB. There is a bidirectional causal correlation between cathepsin B levels and PD. The findings of the current investigation provide newer perspectives on developing innovative biomarkers and prospective treatment targets for various prevalent NDs.

Declarations

DATA AVAILABILITY STATEMENT

The study’s dataset can be found in an online repository; the article and supplementary materials contain information about the repository, including its name and accession number. Questions about further information should be sent to the relevant author.

Funding

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ETHICS STATEMENT
We conduct a secondary review of previously published research as well as publically accessible GWAS summary data for our study. The original papers of this study contain information about the consent statements and ethical approvals for each of the GWAS.

Consent for publication

Not applicable.

Author Contributions

The study's conception and design were aided by WS and JZ. The literature review and data extraction were carried out by GR, LZ, and HL, while the data analysis was done by AZ, BL and DW. JZ and WS both helped with the manuscript's drafting, while WS was in charge of data synthesis and interpretation. Funding support for this work was given by XW. JZ worked hard to revise the manuscript. Each author contributed significantly to the work and gave their approval for the finished draft.

Acknowledgments

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Conflict of Interest

All authors declare no conflict of interest.

References


Tables

Table 1 is available in the Supplementary Files section.

Figures

Fig. 1 The diagram of Mendelian randomization (MR): three assumptions should be met: ① IVs and exposure are related. ② IVs have no association with any confounding factor in the exposure-outcome connection. ③ IVs only affect the result because of their relationship to the exposure. IVs, instrumental variables; SNPs, single nucleotide polymorphisms; AD, Alzheimer’s disease; PD, Parkinson’s disease; DLB, Dementia with Lewy bodies; NDs, neurodegenerative diseases.
Figure 1

See image above for figure legend.

Figure 2

See image above for figure legend.
### Table 1

<table>
<thead>
<tr>
<th>Exposure</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Cathepsin B</td>
<td>1.0065 (0.9650 - 1.0374)</td>
<td>0.9767</td>
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<tr>
<td>Cathepsin E</td>
<td>0.9918 (0.9411 - 1.0453)</td>
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<td>Cathepsin F</td>
<td>1.0438 (0.9981 - 1.0915)</td>
<td>0.0804</td>
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<td>Cathepsin G</td>
<td>0.9795 (0.9349 - 1.0262)</td>
<td>0.3833</td>
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<td>Cathepsin H</td>
<td>1.0373 (1.0102 - 1.0651)</td>
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<td>Cathepsin O</td>
<td>0.9757 (0.9186 - 1.0363)</td>
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<td>Cathepsin S</td>
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<tr>
<td>Cathepsin L2</td>
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<td>Cathepsin Z</td>
<td>0.9717 (0.9316 - 1.0132)</td>
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### Table 2

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<td>Cathepsin F</td>
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<td>Cathepsin G</td>
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<td>Cathepsin O</td>
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<td>Cathepsin S</td>
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<td>Cathepsin L2</td>
<td>0.9506 (0.8401 - 1.0757)</td>
<td>0.4221</td>
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<td>Cathepsin Z</td>
<td>0.9905 (0.9035 - 1.0858)</td>
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### Table 3

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<td>Cathepsin O</td>
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<td>Cathepsin S</td>
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<td>Cathepsin L2</td>
<td>0.9308 (0.7564 - 1.1453)</td>
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<tr>
<td>Cathepsin Z</td>
<td>1.1911 (0.9702 - 1.4623)</td>
<td>0.0947</td>
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</tbody>
</table>

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**Figure 3**

See image above for figure legend.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.
• Table1.xlsx
• Table.xlsx