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ORIGINAL RESEARCH

Unveiling the Role of Cathepsins on Lung Function in Chronic Obstructive Pulmonary Disease: A Mendelian Randomization Analysis

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Background: Cathepsins are a group of proteases that can degrade the extracellular matrix of the lungs, leading to lung tissue destruction and remodeling in chronic obstructive pulmonary disease (COPD). However, the causal relationship between cathepsins and COPD remains unclear.

Methods: We performed a two-sample Mendelian randomization (MR) analysis using genetic instruments for nine cathepsins (B, E, F, G, H, L2, O, S, and Z) and lung function measures (FVC, FEV1, FEV1/FVC, and PEF) in COPD. The MR analysis was conducted and reported as conducted and reported in accordance with the STROBE-MR Statement. We employed various MR methods and conducted sensitivity analyses to validate the results.

Results: We found a significant association of cathepsin B with PEF (IVW beta = 0.016, 95% CI = 0.007 to 0.024, P = 2.83E-4), the FEV1/FVC ratio (IVW beta = 0.014, 95% CI = 0.004 to 0.023, P = 0.004), and FEV1 (IVW beta = 0.010, 95% CI = 0.002 to 0.018, P = 0.012) in COPD. These associations were consistent across different MR methods and robust to pleiotropy and heterogeneity. Multivariate MR analysis confirmed the independent effect of cathepsin B on lung function after adjusting for other cathepsins. Reverse MR analysis and colocalization analysis showed no evidence of reverse causality or shared genetic pathways with smoking.

Conclusion: Our study suggested that elevated cathepsin B levels may reduce the risk of lung function decline in COPD. Targeting cathepsin B and its inhibitors could be a potential therapeutic strategy for COPD. Reduced serum levels of cathepsin B may serve as a biomarker of progressive decline in lung function in patients with COPD. However, further studies are needed to elucidate the underlying mechanisms and clinical implications of these findings.

Keywords: cathepsins, chronic obstructive pulmonary disease, lung function, Mendelian randomization, causal relationship

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory illness characterized by impeded airflow, predominantly due to prolonged exposure to smoking or other noxious airborne substances.[1] The primary pathological changes in COPD include inflammation of the airways, altered airway structure, and emphysema.[2] COPD poses a significant challenge to global public health by profoundly impacting patients' life expectancy and quality of life, and imposing a substantial burden on families and society.[3–6]

The prevailing hypothesis regarding the mechanism of emphysema formation centers on the imbalance between proteases and antiproteases.[7] It is rooted in the substantial correlation observed between alpha-1 antitrypsin deficiency and the onset of emphysema.[8,9] While the role of serine proteases such as neutrophil elastase has been extensively studied,[10] cysteine cathepsins have emerged as potential contributors to this imbalance.[11,12]

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Cathepsins, a group of lysosomal proteases, regulate extracellular matrix turnover, immune responses, and cellular signaling.[13–15] Dysregulation of cathepsin activity, particularly increased expression and enzymatic activity, has been implicated in the degradation of the extracellular matrix and lung matrix destruction in emphysema. Recent evidence underscores the involvement of cathepsin L in promoting eosinophil-mediated lung matrix destruction, thereby contributing to emphysema development, thereby contributing to emphysema development.[12]

Given the multifaceted roles of cathepsins, it is essential to explore the specific contributions of individual cathepsins in COPD pathogenesis. While multiple studies[12,16–18] have demonstrated a correlation between cathepsins and COPD, many of the reported associations could be confounded by unmeasured environmental and genetic factors or biased by reverse causation.

By leveraging genetic variants as instrumental variables for cathepsin levels, MR minimizes confounding and circumvents reverse causation, as genetic alleles are fixed at conception and unaffected by disease progression.[19] We employ MR to investigate the causal effects of cathepsins on lung function in COPD. Our analysis aims to provide novel insights into the potential therapeutic relevance of targeting cathepsins in COPD.

Methods

Study Design and Methodology

This study was conducted and reported in accordance with the STROBE-MR Statement.[20] The selection of instrumental variables was based on three core assumptions: instrumental variables are related to exposure, are not related to confounders, and have an effect on outcomes only through exposure. The STROBE-MR checklist was provided in Supplementary Material, Table S1. The study flowchart is presented in Figure 1.

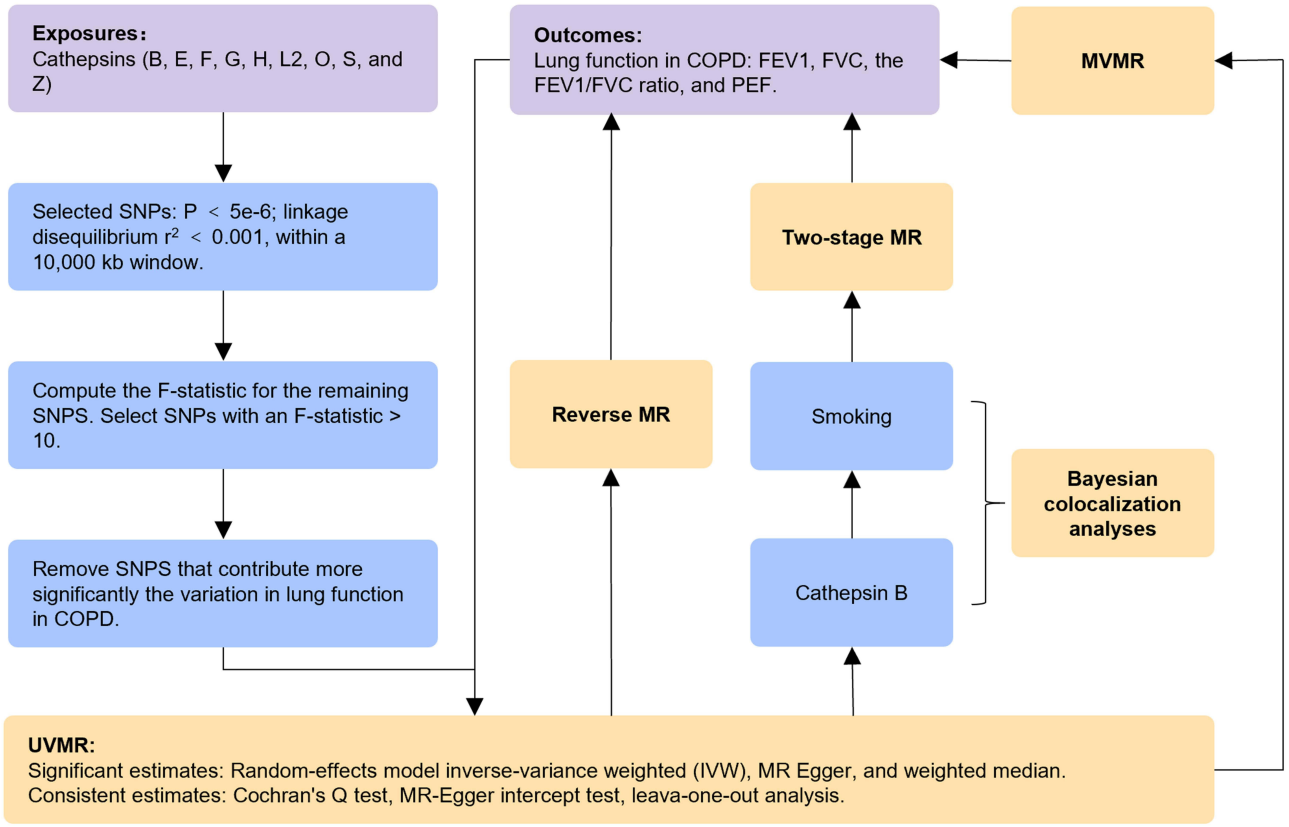

Figure 1 Flowchart of Mendelian randomization analyses.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; SNPs, single nucleotide polymorphisms; MR, Mendelian randomization; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization.

Instrumental Variables Selection

The genetic instruments for quantifying cathepsin levels (μg/L) were derived from the INTERVAL study,[21] which included 3301 individuals of European descent. Approval for the INTERVAL study was obtained from the National Research Ethics Service, and all participants provided informed consent. The summary data can be accessed at https://gwas.mrcieu.ac.uk. The cathepsin-related instrumental variables employed in the MR analyses were selected in accordance with specific criteria. These included an r^2 measure of linkage disequilibrium (LD) among the instruments of less than 0.001 within a 10,000 kb window, and P-values below 5E-06 (The value was established in the limitation of the sample size). The included single nucleotide polymorphisms (SNPs) included in the exposure data are presented in Table S2. A meta-analysis of genome-wide association studies (GWAS) on smoking was conducted involving 1,232,091 individuals of European descent.[22] The cutoff criteria for independently associated SNPs were set at $P < 5E-08$ and $r^2 < 0.001$.

Genetic Association of SNPs with Lung Function in COPD

A meta-analysis summarized GWAS data pertinent to lung function in COPD, encompassing forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, and peak expiratory flow (PEF). The data were acquired from GWAS Catalog at https://www.ebi.ac.uk/gwas. The summary data originated from a comprehensive genome-wide association study on lung function, involving a cohort of 400,102 individuals.[23] The study successfully identified 139 novel genetic associations for lung function, offering predictive insights for COPD. Notably, all participants in the genome-wide analyses were of European descent.

Mendelian Randomization Analysis

The calculations and graphical representations were conducted utilising the R software version 4.3.2. The MR analysis was performed with the TwoSampleMR package (version 0.5.8),[24] implementing three methodologies: random-effect inverse-variance weighted (IVW), MR Egger, and weighted median. The IVW method was employed as the primary approach for estimating the overall effect size in the trial.[25] To enhance the robustness of the IVW estimates, the MR Egger and weighted median methods were employed. The MR Egger method allows for the consideration of pleiotropic effects in all genetic variants, assuming that these effects are independent of the variant-exposure association.[26] The weighted median method determines the median by assigning weights to individual MR estimates based on their precision.[27]

To validate the underlying assumptions, a series of sensitivity analyses and statistical tests were conducted. The Cochran's Q test was employed to assess the heterogeneity of the SNPs, with a *P*-value above 0.05 indicating no significant heterogeneity. In the event of significant heterogeneity among the SNPs, a random-effects model was used; otherwise, a fixed-effects model was used.[28] The MR-PRESSO global test and the MR Egger intercept were employed to identify outliers and horizontal pleiotropic effects.[29] The MR Egger intercept indicates the average pleiotropic effect ($P < 0.05$), while the slope provides a robust pleiotropy MR estimate. The MR-PRESSO outlier test was employed to correct for horizontal pleiotropy, whereby outliers were removed or down-weighted when horizontal pleiotropy was significant ($P < 0.05$).

Furthermore, multivariable MR was employed to consider multiple cathepsins when analysing their causal effects on COPD and estimating the direct causal effects of each exposure in a single analysis, using the TwoSampleMR package.

For mediation analysis, a two-step MR,[30] involving two sequential MR analyses linked by a common variable, was used to determine whether one trait serves as a mediator. A colocalization analysis was conducted using the Coloc package[31] to determine whether specific genomic regions harbored shared common genetic variants within a specific genomic region between two traits.

In univariate MR analysis, significance was determined at $P < 0.05/36$, while $P < 0.05$ was considered nominally significant. For multivariate MR analysis, significance was determined at $P < 0.05$.

Reverse Mendelian Randomization

For reverse MR analyses, the same GWAS datasets previously described were utilised. Instrumental variables for lung function in COPD were selected from the same GWAS summary data, with cathepsin levels serving as outcomes.

Results

Univariate Mendelian Randomization Analysis

Two-sample MR analysis was conducted to assess the impact of various cathepsins on lung function in COPD, focusing on nine cathepsins (B, E, F, G, H, L2, O, S, and Z). The results of the univariate MR analyses indicated a significant association of cathepsin B and PEF (IVW beta = 0.016, 95% CI = 0.007 to 0.024, P = 2.83E-4), while FEV1/FVC (IVW beta = 0.014, 95% CI = 0.004 to 0.023, P = 0.004) and the FEV1 (IVW beta = 0.010, 95% CI = 0.002 to 0.018, P = 0.012) shown a nominally significant (Figure 2 and Table 1). These associations were corroborated using the weighted median and MR-Egger methods. The weighted median and MR-Egger methods confirmed similar significant correlations or nonsignificant associations but with analogous trends. The p-values for the Cochran Q-test exceeded 0.05, suggesting an absence of heterogeneity. Furthermore, the MR-Egger intercept p-values were also above 0.05, and analyses using MR-PRESSO and leave-one-out plots detected no outliers. The details were shown in Tables S3 – S9 and Figures S1 – S6.

Multivariate Mendelian Randomization Analysis

Multivariate MR analysis was conducted to investigate the association between various cathepsins and lung function in COPD. The findings demonstrate that, with adjustments for other cathepsins, cathepsin B remained significantly associated with PEF (beta = 0.018, 95% CI = 0.004 to 0.032, P = 0.013) and the FEV1/FVC ratio (beta = 0.014, 95% CI = 0.003 to 0.025, P = 0.014). Additionally, the multivariate MR analyses identified a significant correlation between cathepsin F and FEV1 (beta = −0.015, 95% CI = −0.030 to 0.000, P = 0.048), as well as between cathepsin Z and FEV1/FVC ratio (beta = −0.017, 95% CI = −0.029 to −0.004, P = 0.011), in the COPD cohort (Figures 3 and 4). The details were shown in Tables S10 – S13.

Reverse Mendelian Randomization Analysis

To investigate the potential for reverse causality, a reverse MR analysis was undertaken. The results demonstrated the absence of reverse causality between cathepsin B and lung function in COPD. Similarly, no reverse causality was found between other cathepsins and lung function. Consequently, there is no evidence suggesting a causal relationship from lung function to the various cathepsins in COPD.

Excluding Potential Mediating Effects of Smoking

Smoking is a major risk factor for COPD,[1] and our study examined the potential mediating effect of smoking on the association between cathepsin B and lung function in COPD. Two-stage MR was employed to assess the mediating role of smoking. The results revealed no significant causal link between cathepsin B and daily cigarette consumption (IVW beta = 0.007, 95% CI = −0.017 to 0.031, P = 0.580), and similarly, no significant relationship was observed in the reverse direction (IVW beta = −0.048, 95% CI = −0.160 to 0.256, P = 0.650). Additional Bayesian colocalization analyses were conducted to determine whether cathepsin B influences lung function in COPD through shared pathway effects with smoking. The results indicated that all of the hypothesized posterior probabilities (Ps) between cathepsin B and smoking fell below 0.05 (H4: P = 1.33E-02) within a 1000 kb window surrounding the target SNP. Consequently, there is no substantial evidence to suggest a shared causal variant between these two traits. Therefore, smoking does not appear to mediate the relationship between cathepsin B and lung function in COPD. Table S14 and Figure S7 provided a detailed overview of the Bayesian colocalization analyses.

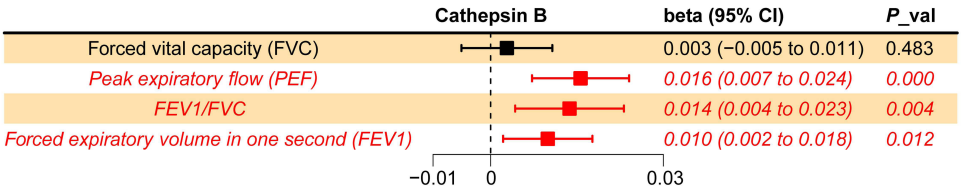

Figure 2 Forest plot of UVMR for cathepsin B and lung function in COPD.
Notes: The analysis was performed using the inverse-variance weighted method. Statistically significant results are highlighted in red.
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence intervals; UVMR, univariable Mendelian randomization.

Table 1 Causal Association of Cathepsins on Lung Function in COPD Estimated by UVMR

Cathepsin	SNPs	Inverse Variance Weighted		MR Egger		Weighted Median	
		Beta(95% CI)	*P*_value	Beta(95% CI)	*P*_value	Beta(95% CI)	*P*_value
Cathepsin B							
FVC	17	0.003(−0.005–0.011)	0.483	0.005(−0.013–0.024)	0.578	−0.002(−0.013–0.009)	0.662
PEF	17	0.016(0.007–0.024)	2.83e-04	0.10(−0.009–0.030)	0.326	0.012(0.000–0.024)	0.046
FEV1/FVC	17	0.014(0.004–0.023)	0.004	0.010(−0.013–0.032)	0.412	0.017(0.005–0.029)	0.004
FEV1	17	0.010(0.002–0.018)	0.012	0.011(−0.007–0.029)	0.232	0.007(−0.003–0.018)	0.189
Cathepsin E							
FVC	11	−0.008(−0.020–0.003)	0.167	−0.008(−0.034–0.018)	0.566	−0.006(−0.022–0.009)	0.406
PEF	11	−0.006(−0.019–0.007	0.385	−0.017(−0.046–0.012)	0.271	−0.002(−0.020–0.016	0.806
FEV1/FVC	11	−0.008(−0.020–0.004)	0.194	0.001(−0.025–0.028)	0.914	−0.006(−0.022–0.010)	0.431
FEV1	11	−0.010(−0.021–0.002)	0.092	−0.008(−0.033–0.018)	0.548	−0.010(−0.025–0.005)	0.206
Cathepsin F							
FVC	11	−0.005(−0.022–0.013)	0.611	−0.003(−0.050–0.044)	0.901	−0.004(−0.018–0.011)	0.633
PEF	11	−0.013(−0.029–0.004)	0.140	0.004(−0.039–0.047)	0.857	−0.001(−0.016–0.014)	0.926
FEV1/FVC	11	−0.008(−0.025,0.009)	0.346	−0.010(−0.056–0.035)	0.670	0.004(−0.017–0.010)	0.59
FEV1	10	−0.009(−0.030–0.012)	0.383	−0.006(−0.068–0.056)	0.852	−0.007(−0.021–0.008)	0.373
Cathepsin G							
FVC	10	0.008(−0.005–0.020)	0.237	−0.002(−0.031–0.025)	0.850	0.011(−0.005–0.027)	0.171
PEF	11	−0.004(−0.026–0.017)	0.684	0.003(−0.047–0.053)	0.910	−0.008(−0.026–0.011)	0.402
FEV1/FVC	11	−0.006(−0.021–0.009)	0.433	−0.002(−0.037–0.033)	0.929	−0.006(−0.024–0.011)	0.473
FEV1	11	0.006(−0.007–0.017)	0.401	0.0003(−0.027–0.028)	0.979	0.007(−0.010–0.024)	0.407
Cathepsin H							
FVC	11	0.001(−0.009–0.010)	0.860	−0.007(−0.019–0.005)	0.289	−0.002(−0.009–0.004)	0.517
PEF	11	−0.001(−0.007–0.005)	0.788	−0.004(−0.013–0.004)	0.328	−0.003(−0.010–0.003)	0.315
FEV1/FVC	11	0.003(−0.002–0.009)	0.259	0.001(−0.007–0.009)	0.825	0.002(−0.004–0.008)	0.825
FEV1	11	0.002(−0.007–0.011)	0.670	0.006(−0.016–0.004)	0.289	−0.001(−0.008–0.005)	0.663
Cathepsin L2							
FVC	9	0.008(−0.007–0.023)	0.311	0.010(−0.024–0.044)	0.593	0.001(−0.018–0.020)	0.923
PEF	9	−0.009(−0.038–0.020)	0.555	−0.013(−0.079–0.053)	0.711	−0.005(−0.027–0.016)	0.627
FEV1/FVC	9	−0.003(−0.017,0.011)	0.677	−0.007(−0.040–0.025)	0.675	−0.002(−0.020–0.015)	0.781
FEV1	9	0.004(−0.013–0.021)	0.617	0.005(−0.033–0.044)	0.792	−0.005(−0.025–0.014)	0.613
Cathepsin O							
FVC	23	0.009(−0.001–0.020)	0.084	0.018(0.000–0.035)	0.063	0.021(0.012–0.030)	1.06e-05
PEF	23	−0.004(−0.010–0.003)	0.305	−0.001(−0.012–0.010)	0.871	−0.005(−0.014–0.004)	0.191
FEV1/FVC	23	0.001(−0.008–0.009)	0.891	0.001(−0.013–0.016)	0.877	0.0003(−0.008–0.009)	0.932
FEV1	23	0.006(−0.003–0.015)	0.191	0.021(0.008–0.034)	0.004	0.015(0.006–0.025)	0.002
Cathepsin S							
FVC	11	−0.002(−0.014–0.009)	0.722	−0.007(−0.033–0.020)	0.627	−0.003(−0.019–0.012)	0.676
PEF	11	−0.006(−0.021–0.009)	0.422	−0.001(−0.038–0.035)	0.943	0.002(−0.015–0.019)	0.796
FEV1/FVC	11	−0.001(−0.013–0.011)	0.871	0.009(−0.018–0.035)	0.549	−0.006(−0.021–0.010)	0.453
FEV1	11	−0.002(−0.013–0.010)	0.787	−0.002(−0.028–0.024)	0.887	0.002(−0.018–0.015)	0.846
Cathepsin Z							
FVC	12	0.006(−0.003–0.015)	0.193	0.004(−0.010–0.019)	0.560	0.006(−0.004–0.018)	0.233
PEF	12	0.002(−0.008–0.013)	0.647	−0.006(−0.021–0.009)	0.439	−0.001(−0.012–0.010)	0.843
FEV1/FVC	12	−0.009(−0.020–0.002)	0.103	−0.020(−0.035 - −0.006)	0.022	−0.011(−0.022 - −0.001)	0.035
FEV1	12	0.001(−0.006–0.009)	0.715	−0.005(−0.017–0.007)	0.437	0.001(−0.009–0.012)	0.788

Abbreviations: FVC, forced vital capacity; PEF, peak expiratory flow; FEV1, forced expiratory volume in one second; IVW, inverse-variance weighted; UVMR, univariable Mendelian randomization.

Discussion

In this study, we used genetic methodologies to conduct a systematic analysis of the causal relationships between nine distinct cathepsins and lung function in COPD using genetic methodologies. This is the first extensive, consortium-based

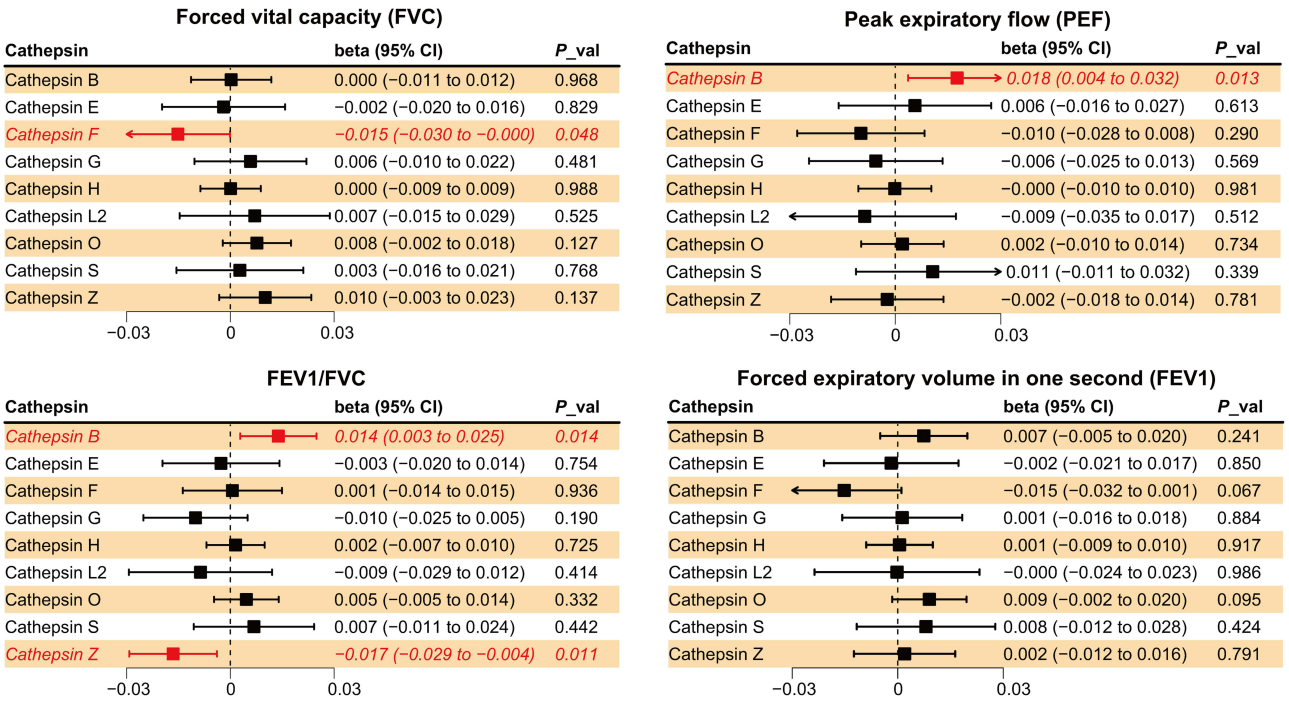

Figure 3 Forest plots of MVMR for various cathepsins and lung function in COPD.
Notes: The analysis was performed using the inverse-variance weighted method. Statistically significant results are highlighted in red.
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence intervals; MVMR, multivariable Mendelian randomization.

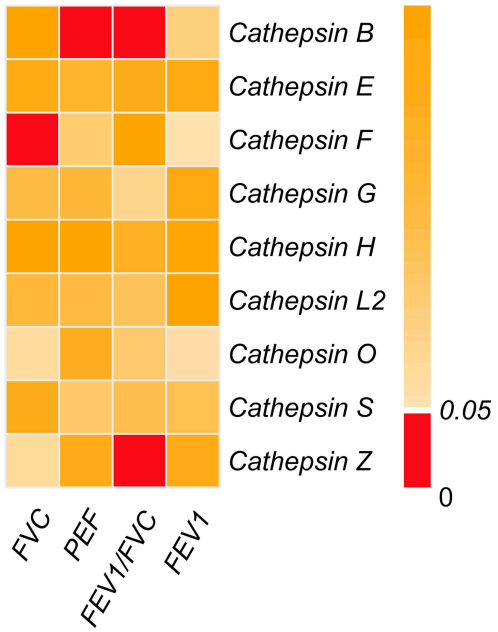

Figure 4 Heatmap of MVMR for various cathepsins and lung function in COPD.
Notes: Each block's color signified the IVW-derived *P*-values for each Mendelian Randomization analysis. *P*-values below 0.05 were displayed in red, while those above 0.05 were depicted in yellow or orange.
Abbreviations: COPD, chronic obstructive pulmonary disease; MVMR, multivariable Mendelian randomization; IVW, inverse-variance weighted.

MR analysis exploring the causal links between cathepsins and lung function in COPD. By integrating findings from univariate, multivariate, and reverse causation analyses, we have determined a strong association between cathepsin B and lung function in COPD.

This study indicated that elevated cathepsin B levels significantly correlate with improved PEF, FEV1/FVC ratio and FEV1. The results from the IVW approach are either consistent or directionally aligned with those from other complementary methods, showing no evidence of pleiotropy or reverse causation. Consequently, it may serve as a potential biomarker or therapeutic target for COPD. It suggests that reduced serum cathepsin B levels may emerge as a prognostic biomarker for progressive lung function decline in COPD. Conversely, therapeutic strategies aimed at elevating serum cathepsin B levels may be hypothesized to ameliorate pulmonary dysfunction in COPD.

Cathepsin B, a cysteine protease, is primarily localized within subcellular endosomal and lysosomal compartments. Cathepsin B is widely recognized in COPD pathophysiology for exacerbating disease progression through protease activity and inflammatory cascades.[32] Despite protease inhibitors demonstrating efficacy in vivo models of COPD, their translational outcomes in clinical settings remain suboptimal.[33–36]

Emerging evidence suggests its physiological role may confer protective regulatory effects. Specifically, Cathepsin B not only degrades extracellular matrix (ECM) components but also indirectly regulates ECM synthesis and repair by cleaving precursor proteins such as pro-matrix metalloproteinases (pro-MMPs).[11,14] In chronic inflammatory states, moderate ECM remodeling mediated by Cathepsin B may improve pulmonary function by facilitating the clearance of damaged tissues and promoting reparative fibrosis rather than destructive emphysema.[37] Furthermore, Cathepsin B enhances host defense mechanisms through bacterial component degradation in macrophages and epithelial cells,[38] while its mucolytic activity modulates mucus viscoelasticity.[39] In COPD patients, elevated Cathepsin B levels may paradoxically mitigate acute exacerbations by counteracting two key pathogenic drivers: recurrent infections and mucus retention. The functional diversity of cathepsins and their delicate regulatory interplay with antiproteases enable these enzymes to act as both guardians and destroyers in the pathogenesis of COPD. Further research is warranted to clarify the precise contributions of cathepsin B to COPD progression.

In addition, the results of multivariate MR analysis also showed a negative correlation between cathepsin F and FEV1, cathepsin Z and FEV1/FVC ratio. These findings provided new evidence for the classical proteases and antiproteases imbalance theory. However, the clinical significance of small effect sizes still needs to be verified in conjunction with experiments. Cathepsin F was shown to be required for TLR9 responses,[40] which may affect indirectly lung function by modulating the immune response. Cathepsin Z is predominantly localised in immune cells and has been shown to play a critical role in inflammatory signalling pathways. Recent studies[41,42] have indicated that cathepsin Z has been demonstrated to augment NLRP3 inflammasome-derived IL-1β expression, thereby potentiating the development of inflammation.

This study utilized MR analysis, leveraging genetic variation, to investigate the causal influence of various cathepsins on alterations in lung function in COPD patients. By integrating multifactorial and inverse MR analyses, the study reduced confounding factors and reverse causation bias. However, it is pertinent to mention that the participant cohort comprised solely individuals of European descent, potentially constraining the applicability of the findings to other ethnicities. Second, while MR suggests causality, experimental validation is essential. Moreover, due to limitations in the available data, we were unable to adjust for covariates for age and sex for lung function indicators to address age-related lung function decline or sex-related lung function differences. Further longitudinal assessment of the association between serum levels of multiple cathepsins and COPD in multiethnic cohorts is necessary to elucidate the complex network roles of cathepsins.

Conclusion

In conclusion, the primary genetic findings of this study indicate that elevated cathepsin B levels are associated with a reduced risk of lung function decline in COPD patients. Consequently, targeting cathepsin B and its inhibitors could offer a viable strategy for mitigating lung function deterioration in this patient group. Reduced serum levels of cathepsin B may serve as a biomarker of progressive decline in lung function in patients with COPD. However, the complexity of the disease and the interplay of various factors necessitate further research to fully elucidate the mechanisms involved and to translate these findings into clinical practice.

Abbreviations

COPD, chronic obstructive pulmonary disease; MR, Mendelian randomization; LD, linkage disequilibrium; GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; FEV1, forced expiratory volume in one second;

FVC, forced vital capacity; PEF, peak expiratory flow; IVW, inverse-variance weighted; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization.

Data Sharing Statement

All the data are publicly available. The datasets presented in this study can be found in online repositories.

Ethics Approval and Consent to Participate

In accordance with Article 32 of the Ethical Review Measures for Human Life Sciences and Medical Research (National Health Commission [2023], China), this study qualifies for exemption from ethics review. The legal rationale for waiving ethical approval is outlined below:

1. Data Characteristics: This research exclusively utilized publicly accessible secondary data resources, primarily summary-level statistics derived from genome-wide association studies (GWAS). The study involved no collection of sensitive personal information, posed no risk of participant privacy breaches, and presented no potential harm to human safety.

2. Regulatory Compliance: Legally sourced data: All datasets were obtained through lawful channels, with original data publicly available in compliance with open-access policies. Privacy safeguards: Data underwent rigorous anonymization and de-identification procedures, meeting the standards specified in China's Personal Information Protection Law (PIPL). Non-interventional design: The study constitutes secondary analysis of pre-existing data and did not involve human biological sample collection, clinical interventions, reproductive cloning, genetic modification, germline cell manipulation, or any other activities requiring specialized ethical oversight.

We hereby confirm that this study was designed and conducted in strict compliance with: The research team affirms its commitment to upholding data security protocols and ensuring adherence to national legal frameworks and academic integrity standards throughout the research process.

Code Availability

All packages utilised for data analysis in this study were open source in R software.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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