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ORIGINAL RESEARCH

Exploring the Causal Relationship Between Frailty and Chronic Obstructive Pulmonary Disease: Insights From Bidirectional Mendelian Randomization and Mediation Analysis

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Background: Observational studies have underscored a robust association between frailty and chronic obstructive pulmonary disease (COPD), yet the causality remains equivocal.

Methods: This study employed bidirectional two-sample Mendelian randomization (MR) analysis. Univariable MR investigated the causal relationship between frailty and COPD. Genetic correlation was assessed using linkage disequilibrium score (LDSC) regression. Multivariable MR and mediation analysis explored the influence of various confounders and their mediating effects. The primary analytic approach was inverse variance weighted (IVW).

Results: LDSC analysis revealed moderate genetic correlations between frailty and Global Biobank Meta-Analysis Initiative (GBMI) COPD ($r_g = 0.643$, $P = 6.66\times10^{-62}$) as well as FinnGen COPD ($r_g = 0.457$, $P = 8.20\times10^{-28}$). IVW analysis demonstrated that frailty was associated with increased risk of COPD in both the GBMI cohort (95% CI, 1.475 to 2.158; $P = 2.40\times10^{-9}$) and the FinnGen database (1.411 to 2.434; 9.02×10^{-6}). Concurrently, COPD was identified as a susceptibility factor for frailty ($P < 0.05$). These consistent findings persisted after adjustment for potential confounders in MVMR. Additionally, mediation analysis revealed that walking pace mediated 19.11% and 15.40% of the impact of frailty on COPD risk, and 17.58% and 23.26% of the effect of COPD on frailty risk in the GBMI and FinnGen cohorts, respectively.

Conclusion: This study has strengthened the current evidence affirming a reciprocal causal relationship between frailty and COPD, highlighting walking pace as a pivotal mediator.

Keywords: frailty, COPD, Mendelian randomization, mediation analysis, causality

Introduction

Chronic obstructive pulmonary disease (COPD) persists as the third leading cause of mortality worldwide and ranks seventh in contributing to global health impairment, placing a substantial economic strain on healthcare systems.[1] Recent estimates indicated that COPD affects roughly 174 million individuals globally[2] and up to 300 million people.[3] Moreover, the incidence and prevalence of COPD have shown a consistent upward trend in recent decades, primarily attributed to demographic aging and prolonged exposure to risk factors.[4]

Frailty, an emerging geriatric syndrome characterized by multi-system decline in physiological functioning, is cumulatively prevalent in aging populations.[5] The Frailty Index (FI) is a widely utilized metric for assessing frailty status.[6,7] A higher FI is associated with a range of adverse health outcomes, including disability, impaired mobility, multiple chronic conditions, increased hospitalizations, and elevated mortality rates.[7–10] While frailty involves impairments across multiple systems, its connections with obstructive lung diseases are notably pronounced. Previous

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observational studies have indicated an association between COPD and frailty risk.[11–13] The presence of frailty often signifies a poorer prognosis and is linked to decreased survival, particularly among COPD patients.[14,15] As such, frailty represents a modifiable risk factor that, if effectively managed, could potentially improve COPD management and patient outcomes.[5,16] Nonetheless, uncertainties persist regarding the precise causal relationship between frailty and COPD, including the potential bidirectional nature of their association influenced by unmeasured confounders and reverse causation inherent in observational studies.

Mendelian randomization (MR) represents a valuable analytical approach for assessing causal relationships between exposures and outcomes.[17] By leveraging genetic variants associated with exposures, it enables estimation of the causal impact of exposures on outcomes while mitigating confounding effects and avoiding reverse causation biases.[18] In this study, we employed a bidirectional, two-sample MR methodology to investigate the causal relationship between frailty, quantified by the frailty index (FI),[19] and COPD.

Materials and Methods

Study Design

This MR study was conducted in two phases and an overview was illustrated in Figure 1. In Phase 1, we initially examined genetic relationships between frailty and COPD, followed by an investigation into the causal effects of frailty on COPD and vice versa (Figure 1A). Phase 2 involved assessing the mediating effects of several potential confounders on the causal associations between frailty and COPD (Figure 1B). Our MR analyses adhered to three core assumptions: (1) the relevance assumption, ensuring that single nucleotide polymorphisms (SNPs) are associated with the exposure of interest; (2) the independence assumption, asserting that SNPs share no common causes with the outcome; and (3) the exclusion restriction assumption, indicating that SNPs do not influence the outcome except through the exposure.[20] The fixed nature of genotypes, established at conception in accordance with Mendel's Laws of Inheritance, minimizes susceptibility to reverse causation and confounding impacts in MR results.[20] We followed the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) for this study.[21] Genome-wide association study (GWAS) summary-level data were sourced from predominantly European cohorts or consortia with established reliability. Details regarding the GWAS datasets utilized are provided in Table 1, while ethical approvals for the GWASs are referenced in their respective publications cited below.

Data Sources

Data Source for Frailty

The datasets utilized in this study were publicly accessible, and ethical approvals were obtained from the original publications. Frailty-related SNPs were derived from a comprehensive GWAS meta-analysis involving European participants from UK Biobank (n = 164,610, aged 60 to 70 years, 51.3% females) and TwinGene (n = 10,616, aged 41 to 87 years, 52.5% females), as detailed by Atkins et al.[19] Frailty was assessed by the frailty index, which aggregates 49 health deficits over the life course,[19] a well-established validated measure in clinical practice.[5,22]

Data Source for Chronic Obstructive Pulmonary Disease

The COPD outcome phenotype data were obtained from the Global Biobank Meta-Analysis Initiative (GBMI).[23] As of November 2023, the GBMI has established a collaborative network involving 24 biobanks across 15 countries spanning four continents, encompassing over 2.2 million consented individuals and around 70 million genetic variants. GBMI offers the most extensive multi-ancestry GWAS data on COPD to date, including GWAS summary data for individuals of European ancestry (58,559 cases and 937,358 controls). These datasets were derived from meta-analyses that integrated cohorts from 12 and 4 biobanks, respectively. To address potential biases associated with reliance on a single dataset, additional validation was performed using supplementary replication datasets from the latest R10 release of the FinnGen consortium (20,066 cases and 338,303 controls).[24]

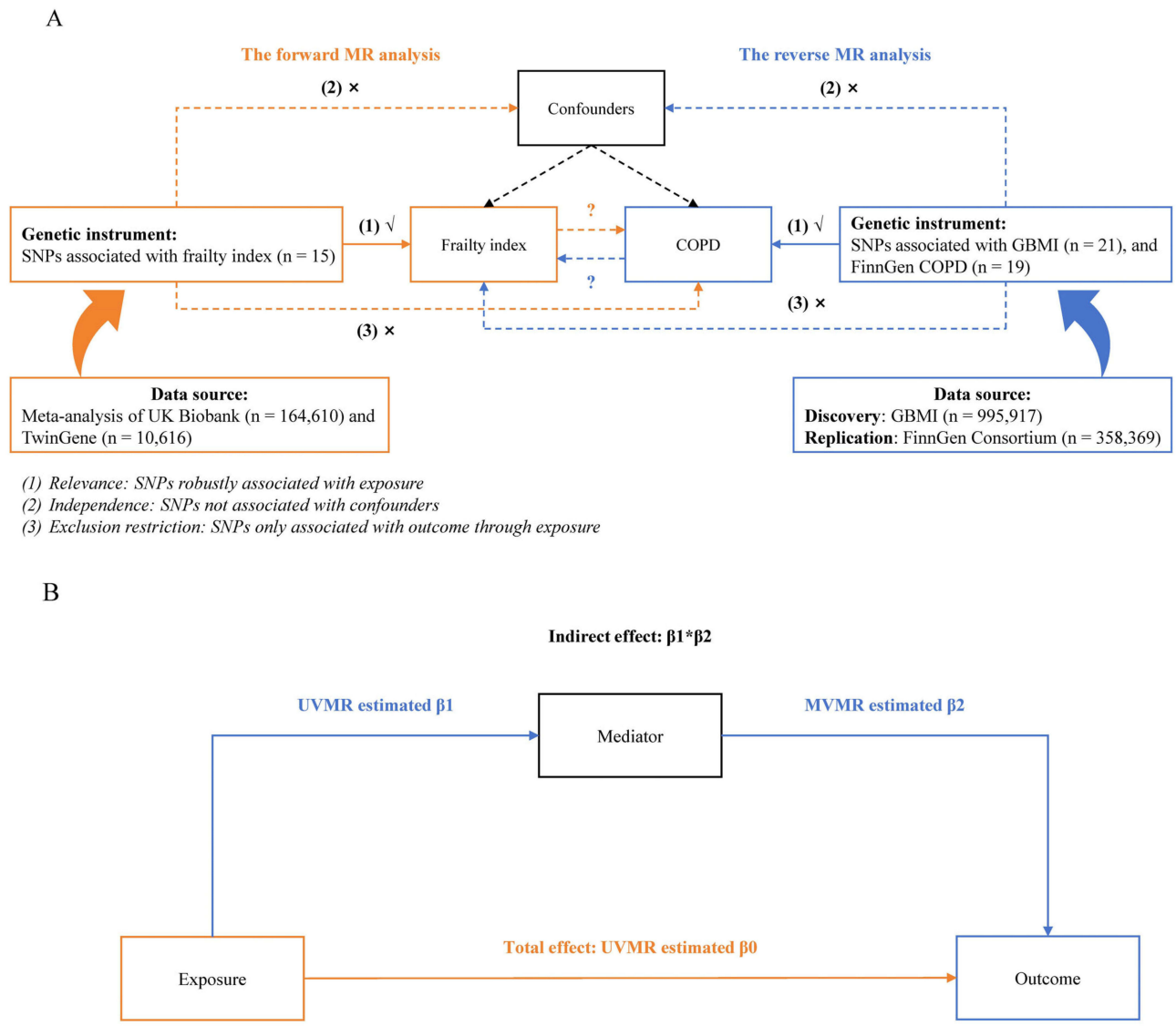

Figure 1 (**A**) Overview of this bidirectional MR study design. (**B**) Two-step MR analysis framework. The first step was to estimate the causal effect of the exposure on the potential mediators by UVMR, with each estimate denoted as β1. The second step was to estimate the causal effect of the mediators on outcome using MVMR with adjustment for exposure and to denote the MVMR estimate as β2. The mediation proportion of mediator in the association between exposure and outcome was calculated as the product of β1 and β2 divided by the total causal effect of exposure on the outcome (β0), and the 95% CI of the mediation proportion was obtained using the delta method.

Data Sources for Possible Mediators

The study explored potential mediators influencing frailty and COPD, including variables such as body mass index (BMI), smoking status (age of smoking initiation, cigarettes per day and smoking initiation) and sarcopenia-related traits (grip strength, appendicular lean mass, whole-body lean mass and walking pace). Genetic associations for BMI were derived from the Genetic Investigation of Anthropometric Traits (GIANT) consortium,[25] while age of smoking initiation (ASI), cigarettes per day (CPD), and smoking initiation (SI) were sourced from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN).[26] Grip strength (GS), appendicular lean mass (ALM), whole-body lean mass (WBLM) and walking pace data were obtained from the UK Biobank.[27,28]

Instrumental Variables Selection

SNPs robustly associated with exposures were initially screened at genome-wide significance ($P < 5\times10^{-08}$). Subsequently, SNPs showing high linkage disequilibrium ($r^2 > 0.001$ or within clump windows < 10,000 kb) were

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Table 1 Information of GWAS Datasets Used in the MR Study

Phenotype	Sample Size (case/control)	Population	Consortium or Cohort Study	Year of Publication	PMID
Frailty index	1,75,226	European	Atkins JL	2021	34431594
COPD	58,559/937,358	European	GBMI	2022	36777996
COPD	20,066/338,303	European	FinnGen	2023	36653562
Body mass index	6,81,275	European	GIANT	2018	30124842
Age of smoking initiation	3,41,427	European	GSCAN	2019	30643251
Cigarettes per day	3,37,334	European	GSCAN	2019	30643251
Smoking initiation	311,629/321,173	European	GSCAN	2019	30643251
Grip strength	4,61,026	European	UK Biobank	2018	29846171
Appendicular lean mass	4,50,243	European	UK Biobank	2020	33097823
Whole-body lean mass	4,54,850	European	UK Biobank	2018	29846171
Walking pace	4,59,915	European	UK Biobank	2018	29846171

Abbreviations: COPD, chronic obstructive pulmonary disease; GBMI, Global Biobank Meta-Analysis Initiative; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use.

excluded using the 1000 Genomes European reference panel.[29] The LDTrait tool (https://ldlink.nih.gov/?tab=home) was employed to confirm traits independence.[30] To assess potential weak instrument bias, the F statistic was calculated as in previous studies, with SNPs having an F statistic less than 10 deemed weak and removed.[31] Following exposure and outcome dataset harmonization with palindromic SNPs, the remaining SNPs were utilized for MR analysis. Proxy SNPs ($r^2 > 0.8$) were omitted to ensure result accuracy. Any identified confounders were adjusted for in subsequent analyses.

Statistical Analysis

Linkage Disequilibrium Score (LDSC) regression, facilitating assessment of SNP-based genetic heritability correlation between two traits,[32] was initially employed to assess the genetic correlation (r_g) between frailty and COPD, with European ancestry samples from the 1000 Genomes Project being the reference panel.[29]

MR estimates were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for binary outcomes and β coefficients with standard errors (SEs) for continuous outcomes. The causal associations of frailty with COPD were evaluated using univariable MR (UVMR), where estimates were denoted as β0. Additionally, considering that BMI, smoking status (age of smoking initiation, cigarettes per day and smoking initiation) and sarcopenia-related traits (grip strength, appendicular lean mass, whole-body lean mass and walking pace) were potential risk factors for both COPD and frailty, we adjusted for these confounders in multivariate MR analyses. This allowed exploration of the direct effect of frailty on COPD and COPD on frailty.

Two-step MR was conducted to investigate whether potential confounding factors mediate the causal association between frailty and COPD. In the first step, UVMR was utilized to estimate the causal effect of frailty on each possible confounder, denoted as β1. In the second step, the causal effect of each confounder on outcome was estimated using UVMR and MVMR, adjusting for frailty, with the MVMR estimate denoted as β2. The proportion of mediation of each mediator in the causal association between frailty and the outcome was calculated as the product of β1 and β2 divided by β0,[33] with the 95% CI obtained using the delta method.[34] To ensure robustness of the findings, two-step MR analyses were conducted in both the GBMI and FinnGen databases, and results were compared for consistency.

The primary analytical method employed in this MR study was the inverse variance weighted (IVW) method. The F statistic was utilized to assess the presence of weak instrument bias in MR analysis. Cochran's Q statistic was computed to evaluate the heterogeneity among instrumental variables (IVs), and subsequent analyses were conducted using either random-effects or fixed-effects models based on the presence or absence of heterogeneity. Several sensitivity analyses were performed to assess the robustness of the IVW results. Additionally, for UVMR, three sensitivity analyses were conducted, including the weighted median, MR Egger, and RadialMR methods. The weighted median method yields consistent estimates provided that at least 50% of the contributing information is derived from valid IVs.[35] The

MR Egger method detects and adjusts for bias due to directional pleiotropy under the InSIDE (Instrument Strength Independent of Direct Effect) assumption.[35] RadialMR analysis identifies potential outliers, evaluates horizontal pleiotropy, and generates radial plots to visually depict outliers for thorough assessment and potential removal.[36] Furthermore, for MVMR, the multivariable MR Egger (MVMR Egger) method was employed as a sensitivity analysis.

All MR analyses were conducted using R software (version 4.2.3; R Development Core Team, Vienna, Austria) with the ldscr (version 0.1.0), TwoSampleMR (version 0.6.4), MendelianRandomization (version 0.10.0), and RadialMR (version 1.1) packages. A significance level of 0.05 was applied. Causal associations were inferred based on significant results in both the IVW analysis and at least one sensitivity analysis in UVMR, or significant results in both multivariable IVW (MV-IVW) and MVMR Egger analysis in MVMR.

Results

Genetic Correlation

The results of linkage disequilibrium score regression (LDSC) revealed that frailty exhibited moderate genetic correlations with Global Biobank Meta-Analysis Initiative (GBMI) COPD (GC), and FinnGen COPD (FC). Specifically, the genetic correlation (r_g) values were 0.643 (SE = 0.03, $P = 6.66\times10^{-62}$) for GBMI COPD and 0.457 (SE = 0.042, $P = 8.20\times10^{-28}$) for FinnGen COPD (Supplementary Table S1).

Characteristics of Selected Genetic Variants

Based on predefined criteria, a total of 15, 21, and 19 single-nucleotide polymorphisms (SNPs) associated with frailty, GC, and FC, respectively, were selected and detailed in Supplementary Tables S2-S4. The SNPs collectively explained approximately 0.345%, 1.102%, and 0.279% of the variance (R^2) in frailty, GC, and FC, respectively. Importantly, all F statistics exceeded 10, suggesting a minimal risk of weak instrument bias in MR analyses.

Univariable MR Analysis

Causal Effect of Frailty on COPD

The findings of the univariable MR analysis investigating the causal impact of frailty on COPD are depicted in Figure 2. MR-Egger regression intercept terms indicated no significant directional pleiotropy among the SNPs across both datasets, with P values exceeding 0.05. Furthermore, no notable heterogeneity was observed among genetic variants associated with frailty and Global Biobank Meta-Analysis Initiative COPD (GC) (Cochran's Q = 15.19, $P = 0.231$) or FinnGen COPD (FC) (Cochran's Q = 10.04, $P = 0.691$). Therefore, the inverse variance weighted (IVW) method under a fixed-effects model was employed to assess the causal relationships between frailty and GC as well as FC. The IVW method revealed that a genetically predicted higher frailty index was significantly associated with an elevated risk of GC [odds ratio (OR), 1.784; 95% confidence interval (CI), 1.475 to 2.158; $P = 2.40\times10^{-9}$]. The association was replicated in the FinnGen dataset with a similar effect size (OR, 1.854; 95% CI, 1.411 to 2.434; $P = 9.02\times10^{-6}$). Comparison with supplementary methods, such as weighted median, supported the consistent risk effect of frailty on GC and FC, affirming the robustness of results obtained through the IVW method. When odds ratios of 1.784 and 1.854 were observed, sufficient statistical power was attained to detect the association between them, thereby enhancing the robustness of the causal evidence. (Supplementary Table S5).

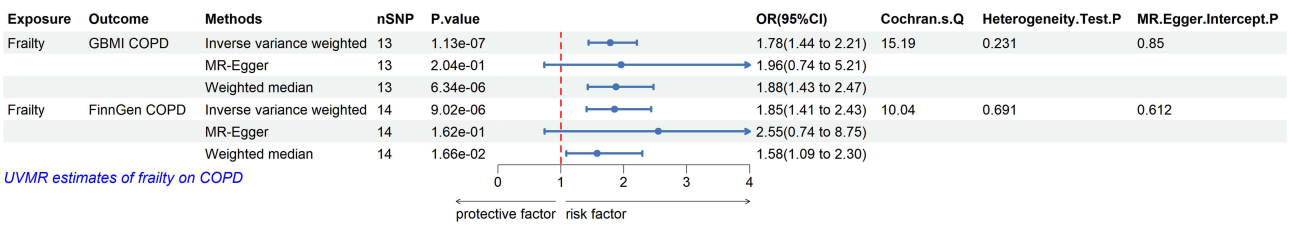

Figure 2 Univariate MR estimates of frailty on COPD. *P* value for heterogeneity based on Cochran's Q statistic. *P* value for pleiotropy based on MR-Egger regression intercept.

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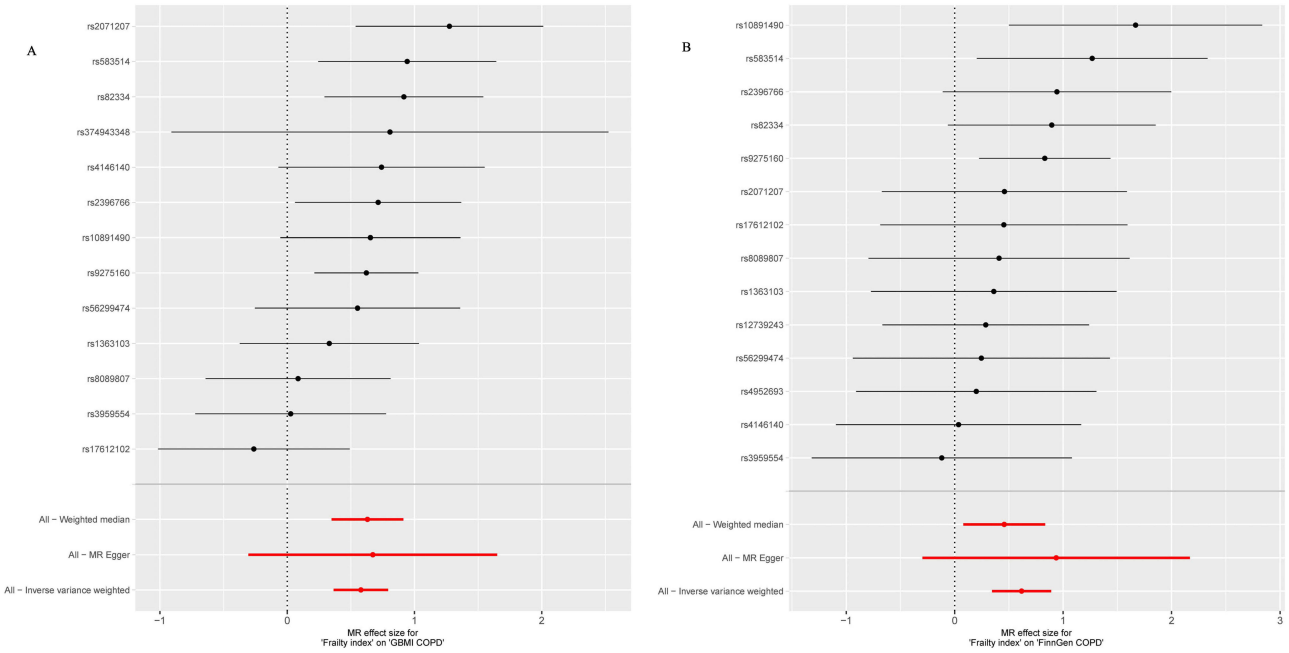

Figure 3 Forest plot of the individual and combined effect of frailty on GBMI COPD (**A**) and FinnGen COPD (**B**). Data were presented as OR and 95% CI.

The scatter plots depicting SNP potential effects on frailty versus COPD were visualized in Supplementary Figure S1, where the slope of each plot signifies the effect size assessed by the respective method. The individual and combined effects of frailty on COPD were further elucidated in Figure 3. Among the 15 SNPs analyzed, five SNPs (rs201207, rs583514, rs82334, rs2396766 and rs9275160) were associated with increased risk of PD (Figure 3A), whereas three SNPs (rs10891490, rs583514, and rs9275160) showed similar associations with FD risk (Figure 3B). The remaining SNPs did not demonstrate significant associations. Results from the leave-one-out analysis were displayed in Supplementary Figure S2, revealing that no single SNP exerted disproportionate influence on the overall findings.

Causal Effect of COPD on Frailty

Figure 4 presents the results of reverse MR analyses using genetic liability for GC and FC as exposures. The random-effects IVW methods provided compelling evidence of a causal effect of GC on a higher frailty index (β, 0.104; 95% CI, 0.058 to 0.151; $P = 1.25\times10^{-5}$). This causal association was further supported by the weighted median method (β, 0.101; 95% CI, 0.041 to 0.161; $P = 0.001$). Consistently, findings from the FinnGen data replicated these results, with IVW (β, 0.050; 95% CI, 0.020 to 0.079; $P = 9.22\times10^{-4}$) and weighted median (β, 0.064; 95% CI, 0.023 to 0.105; $P = 0.002$) confirming the association. When the betas are 0.104 and 0.050, we achieved adequate statistical power to detect their association, thereby bolstering the robustness of the causal evidence. (Supplementary Table S5).

Supplementary Figure S3 presented the scatter plots illustrating SNP potential effects on COPD versus frailty. The forest plots depicting the individual and combined effects of GC and FC on frailty were shown in Figure 5,

Exposure	Outcome	Methods	nSNP	P.value	Beta(95%CI)	Cochran.s.Q	Heterogeneity.Test.P	MR.Egger.Intercept.P
GBMI COPD	Frailty	Inverse variance weighted	10	1.25e-05	0.10(0.06 to 0.15)	10.44	0.316	0.134
		MR-Egger	10	9.20e-01	-0.01(-0.15 to 0.13)			
		Weighted median	10	1.04e-03	0.10(0.04 to 0.16)			
FinnGen COPD	Frailty	Inverse variance weighted	13	9.22e-04	0.05(0.02 to 0.08)	9.34	0.674	0.146
		MR-Egger	13	9.33e-01	-0.00(-0.08 to 0.07)			
		Weighted median	13	2.04e-03	0.06(0.02 to 0.10)			

UVMR estimates of COPD on frailty

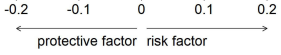

Figure 4 Univariate MR estimates of COPD on frailty. *P* value for heterogeneity based on Cochran's Q statistic. *P* value for pleiotropy based on MR-Egger regression intercept.

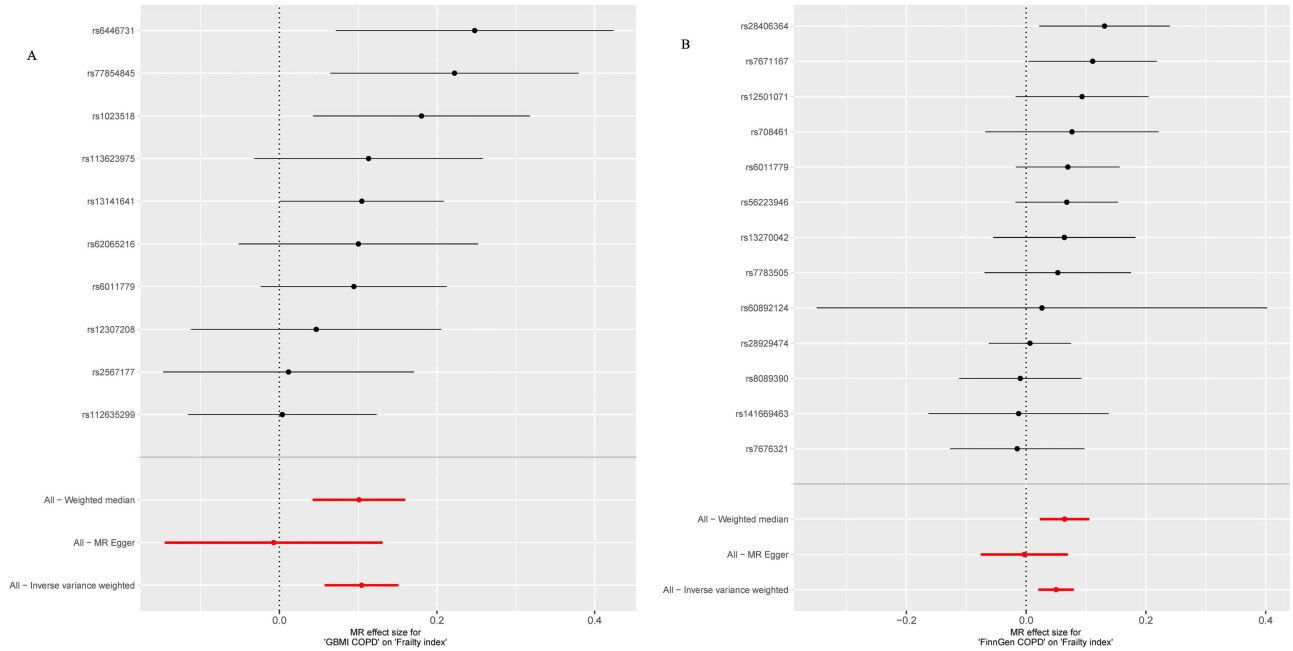

Figure 5 Forest plot of the individual and combined effect of GBMI COPD (**A**) and FinnGen COPD (**B**) on frailty. Data were presented as β and 95% CI.

respectively. Out of 10 SNPs associated with PD, 4 (rs6446731, rs77854845, rs1023518 and rs13141641) (Figure 5A) and out of 13 SNPs associated with FD, 2 (rs28406364 and rs7671167) (Figure 5B) were positively correlated with the frailty index, while the remaining SNPs did not exhibit significant correlations. Consistent with the leave-one-out analyses depicted in Supplementary Figure S4, these findings suggest the overall effects were not driven by a single genetic variant.

Multivariable MR Analysis

The results of multivariable MR (MVMR), adjusted for body mass index (BMI), smoking status (age of smoking initiation, cigarettes per day and smoking initiation) as well as sarcopenia-related traits (grip strength, appendicular lean mass, whole-body lean mass and walking pace), to investigate the bidirectional causal relationship between frailty and COPD, were presented in Figure 6. Following adjustment for potential confounders, including BMI (OR, 2.344; 95% CI, 1.929 to 2.847; $P = 9.90\times10^{-18}$), ASI (OR, 1.593; 95% CI, 1.260 to 2.015; $P = 1.01\times10^{-04}$), SI (OR, 1.705; 95% CI, 1.331 to 2.193; $P = 2.40\times10^{-05}$), GS (OR, 2.356; 95% CI, 1.827 to 3.038; $P = 3.85\times10^{-11}$), ALM (OR, 2.247; 95% CI, 1.858 to 2.717; $P = 6.69\times10^{-17}$), WBLM (OR, 2.216; 95% CI, 1.852 to 2.652; $P = 3.80\times10^{-18}$) and walking pace (OR, 1.705; 95% CI, 1.298 to 2.239; $P = 1.28\times10^{-4}$), MVMR analysis indicated that a higher frailty index remained associated with increased risks of GC. However, upon further adjustment for CPD (OR, 1.604; 95% CI, 0.972 to 2.646; $P = 0.064$), the IVW method suggested that the causal relationship between frailty and GC was no longer statistically significant (Figure 6A). Conversely, subsequent MVMR analysis revealed that COPD patients were also more likely to exhibit a higher frailty index after adjusting for the aforementioned confounding factors (Figure 6B).

Two-Step MR Analysis

Causal Effect of Frailty on Possible Mediators

In UVMR, each 1-SD genetically determined increase in the frailty index was associated with elevated levels of ALM, SI and walking pace (IVW-estimated β for frailty index: −0.108, 95% CI: −0.210 to −0.005 for ALM; 0.234, 0.007 to 0.461 for SI; −0.107, −0.145 to −0.070 for walking pace; Supplementary Table S6). However, no significant associations were observed with BMI, ASI, CPD, GS, or WBLM.

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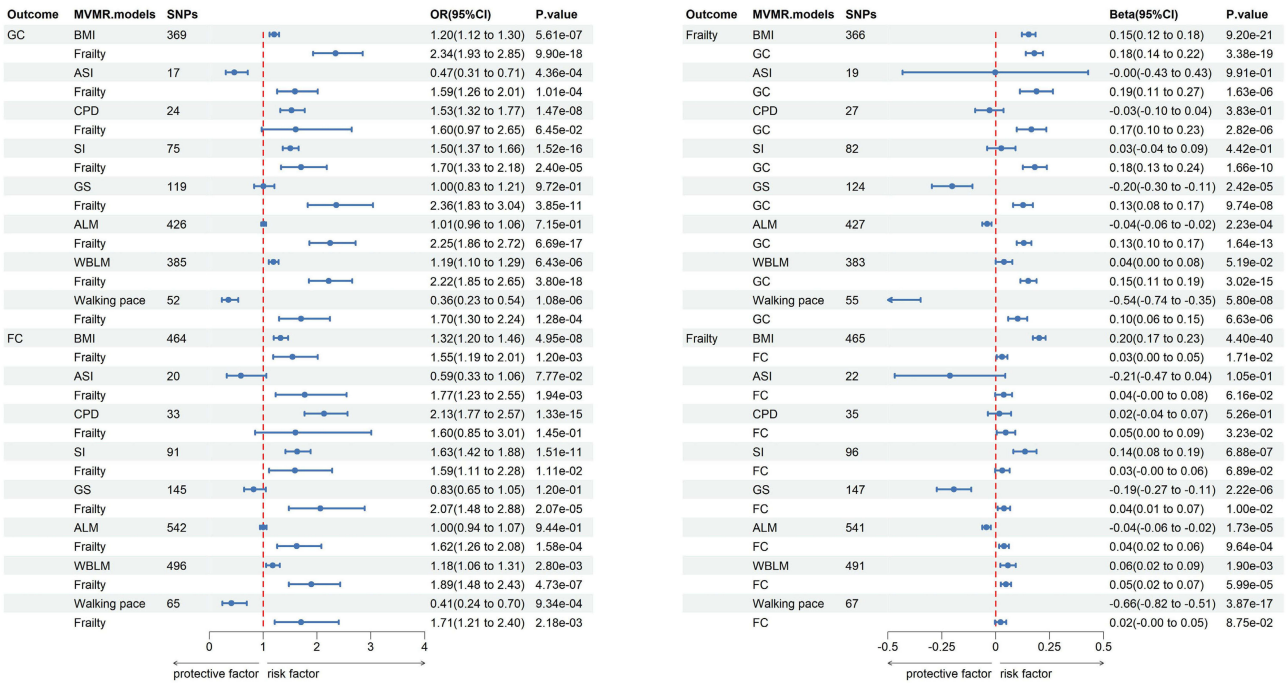

Figure 6 Adjustment for MVMR analysis in frailty on COPD (**A**) and COPD on frailty (**B**).

The MR Egger pleiotropy test indicated potential horizontal pleiotropy between frailty and ALM, SI or walking pace. Nevertheless, subsequent reanalysis excluding 4,6 and 0 potentially pleiotropic SNPs via RadialMR confirmed the robustness of the original findings. Heterogeneity among IVs may exist.

Causal Effects of Possible Mediators on COPD

In UVMR, genetically determined SI was associated with an elevated risk of COPD (OR, 1.581; 95% CI, 1.438 to 1.739; $P = 3.62\times10^{-21}$), while higher walking pace was associated with a decreased risk of COPD (OR, 0.243; 95% CI, 0.164 to 0.362; $P = 3.06\times10^{-12}$). These associations were consistently observed across both the discovery and replication datasets, confirming the robustness of these causal relationships ($P < 0.05$) (Supplementary Table S6).

In MVMR, adjusting for frailty index had minimal impact on the causal associations of BMI, ASI, CPD, SI, WBLM and walking pace with COPD. However, the relationships of GS and ALM with COPD were no longer statistically significant. In the replication dataset, after accounting for frailty index, the associations of BMI, GS, ALM and walking pace with COPD remained consistent. Conversely, the associations of ASI, CPD, SI, and WBLM with COPD did not reach statistical significance (Figure 6, Supplementary Table S7).

Mediation Effect of Walking Pace in the Association Between Frailty and COPD

After a systematic exploration of exposure-mediators-outcome causal pathways, we employed two-step MR to evaluate the roles of walking pace and smoking initiation in mediating the causal effects of frailty on COPD (Figure 1B). We found that walking pace explained 19.11% (95% CI, 7.17% to 31.05%; $P = 2.27\times10^{-4}$) of the total effect of frailty on COPD, whereas smoking initiation did not show a significant mediation effect ($P = 0.0501$), instead acting as a confounder. Additionally, our analysis revealed that walking pace partially mediated the causal impact of COPD on frailty, explaining 17.58% (95% CI, 2.63% to 32.53%; $P = 0.006$) of this relationship. Furthermore, findings from the replication dataset were consistent with those from the discovery dataset, supporting that walking pace significantly mediated the relationship between frailty and COPD, accounting for 15.40% of the influence of frailty on COPD and 23.26% of the impact of COPD on frailty (Table 2).

Table 2 Proportion Mediated by Walking Pace in the Causal Association Between Frailty and COPD

Exposure	β1 (SE)	Mediator	β2 (SE)	Outcome	β0 (SE)	Mediation Proportion (%) (95% CI)	*P* value
Frailty	−0.107 (0.019)	walking pace	−1.034 (0.212)	GBMI COPD	0.579 (0.097)	19.11 (7.17, 31.05)	2.27E-04
	−0.107 (0.019)	walking pace	−0.888 (0.268)	FinnGen COPD	0.617 (0.139)	15.40 (2.82, 27.98)	0.004
GBMI COPD	−0.034 (0.011)	walking pace	−0.544 (0.100)	Frailty	0.104 (0.024)	17.58 (2.63, 32.53)	0.006
FinnGen COPD	−0.018 (0.007)	walking pace	−0.663 (0.019)		0.050 (0.151)	23.26 (0.97, 45.55)	0.009

Abbreviations: COPD, chronic obstructive pulmonary disease; GBMI, Global Biobank Meta-Analysis Initiative; CI, confidence interval.

Discussion

This MR study investigated the independent causal effects of frailty on COPD, examining whether these effects operate through possible mediators. We found that genetically determined higher frailty index was causally associated with increased risks of COPD. Furthermore, our reverse direction analyses revealed compelling evidence indicating a significant correlation between genetic predisposition to COPD and an elevated frailty index. Specifically, we identified walking pace as a mediator in the causal relationships between frailty and COPD, with mediation proportions of 19% for the effect of frailty on COPD and 18% for the effect of COPD on frailty. Even after adjusting for walking pace, the direct effects of frailty on COPD and COPD on frailty remained stable, indicating that walking pace partially explains these associations. These findings underscore a bidirectional causal relationship between frailty and COPD, highlighting the substantial mediating role of walking pace in this complex interaction.

In recent decades, there has been a growing scholarly focus on investigating the association between frailty and chronic diseases. Studies have consistently shown that frailty is associated with an elevated risk of various chronic conditions,[37] including coronary artery disease, myocardial infarction, heart failure,[38] stroke, and type 2 diabetes.[39] Observational researches have further highlighted the prevalence of frailty among individuals diagnosed with COPD,[11,14,15,40,41] though the causality of this relationship remains uncertain. In this study, we contribute new evidence supporting a causal relationship between baseline frailty and the onset of COPD. This causal inference is substantiated by the identification of overlapping risk factors common to both frailty and COPD.

Our findings suggest that COPD may contribute to the development of frailty syndrome, aligning with prior observational studies. With advancing age within the population, the prevalence of both frailty and COPD increases. Recent research has underscored the increased susceptibility to frailty observed in individuals diagnosed with COPD.[11,15,40,41] A population-based study demonstrated a greater prevalence of frailty among individuals with COPD compared to those without,[40] with this prevalence correlating strongly with the degree of airflow limitation even following adjustment for confounding factors.[41] Meta-analytic evidence indicates that individuals with COPD have a twofold increased likelihood of physical frailty compared to non-COPD counterparts.[11] A prospective study has bolstered this association by revealing a notable incidence of physical frailty among individuals with COPD.[14] Furthermore, the co-occurrence of frailty and dyspnea is linked to a markedly increased risk of functional impairment and mortality.[41] However, it is crucial to note that our analysis indicates COPD may contribute to an elevation in the frailty index, yet it does not conclusively establish frailty as a direct consequence thereof. The summary-level GWAS data utilized for frailty evaluation involve the treatment of the frailty index as a continuous metric. Gaining insights into the shared biological mechanisms underlying frailty and COPD could inform strategies for prevention or management of these conditions in aging populations.

Our research has contributed to strengthening the evidence supporting the reciprocal relationship between frailty and COPD, where the presence of both conditions exacerbates each other. This bidirectional association is conjectured to be mediated via common pathophysiological mechanisms, including aging, tobacco use, neuroendocrine dysregulation, and inflammatory processes.[11,42] These reciprocal associations are not unique to COPD but extend to other comorbidities, encompassing cardiometabolic diseases, mental disorders, periodontal diseases and visual impairment.[37,39,43–45]

More importantly, our study has illuminated the mediating role of walking pace and quantified its contribution between frailty and COPD. While the precise mechanistic links between frailty and COPD remain elusive, current

experimental and epidemiological evidence strongly implicates walking pace in these pathways.[46,47] Consistent with epidemiological investigations, our findings underscore the significant impact of walking pace in mitigating both COPD and frailty risks. In addition, prior research and our MR analysis suggest that exercise-based interventions may improve physical function in frail older adults and potentially decrease COPD susceptibility.[48] Moreover, recent MR studies have bolstered evidence supporting bidirectional causal associations between typical walking pace and COPD risk.[49]

Our findings bear substantial implications for public health and clinical practice. Frailty represents a potential modifiable risk factor with greater prospects for intervention compared to more advanced health outcomes, suggesting that efforts aimed at modifying frailty could offer opportunities to delay or mitigate the onset of COPD. Exercise interventions continue to serve as a robust strategy for mitigating respiratory diseases and frailty among older adults. Additionally, targeted interventions have shown promise in improving frailty status in this demographic.[50] Conversely, the heightened prevalence of frailty among individuals with COPD contributes significantly to poorer health outcomes. Therefore, it is advisable to integrate frailty screenings and comprehensive geriatric assessments for the identification of related issues and facilitates the development of personalized interventions aimed at enhancing outcomes. Early therapeutic interventions for COPD may also potentially avert the development of frailty. Given the increasing acknowledgement of bidirectional associations between COPD and frailty, interventions targeting shared risk factors for both conditions hold promise for improving patient management. Our study identified a potentially modifiable factor, walking pace, which plays a causal role in both COPD and frailty. Therefore, promoting optical walking pace represents an effective intervention strategy to reduce the high prevalence of COPD-frailty co-occurrence. Taken together, these insights offer valuable guidance for reducing adverse outcomes, thereby enhancing the quality of life for older adults.

The primary strength of this investigation lies in the application of a two-sample bidirectional MR approach, which mitigates many of the causality errors inherent in conventional observational studies thanks to confounding variables and reverse causality. Rigorous adherence to MR assumptions and utilization of GWAS data from the largest available sample sizes enhance the robustness of our findings. Moreover, the inclusion of participants exclusively of European ancestry in the GWAS datasets ensures homogeneity and minimizes population heterogeneity biases. To our knowledge, this study stands as the most exhaustive MR investigation thus far concerning the interrelations between frailty and COPD, with a specific focus on elucidating a potential mediation pathway via walking pace. These insights deepen our mechanistic understandings and provide evidence supporting preventive strategies. However, certain limitations should be noted. Firstly, despite efforts to avoid sample overlap, the use of summary data from the UKB introduces potential biases. Detailed participant-level information to address this issue was not accessible in public datasets, which may impact the robustness of our MR results. Secondly, our findings are primarily applicable to individuals of European descent and their generalizability to other populations may be limited. Thirdly, the choice of frailty indices and COPD phenotypes may not fully capture the complexity of these conditions. Variability in how frailty and COPD are experienced or reported could influence our study outcomes. Additionally, although our study identified walking pace as a significant bidirectional mediator, we were unable to determine the specific value at which the bidirectional maximum benefit could be achieved. Lastly, despite adjusting for several potential confounders, there may be unmeasured or residual confounding factors that impact the observed associations. Given these complexities and limitations, further research involving more diverse populations and comprehensive datasets is essential to validate and expand upon our findings.

Conclusions

In summary, this study elucidates a bidirectional causal relationship between a higher frailty index and COPD, highlighting the mediating role of walking pace in this association pathway. Our findings underscore the potential of enhancing physical activity as a proactive measure against frailty and COPD. Particularly, improving walking pace emerges as a crucial target for preventing and intervening in the risks of frailty-associated COPD and COPD-related frailty. Future research should explore more direct measurements of walking pace and employ diverse research strategies to validate the findings of this study.

Data Sharing Statement

All the GWAS data used in this study were public. The GWAS summary statistics for frailty index are available through the GWAS catalog (https://www.ebi.ac.uk/gwas/) under accession no. GCST90020053. The GWAS summary statistics for COPD are available through the GWAS catalog (https://www.ebi.ac.uk/gwas/) under accession no. GCST90399694 and for download at https://console.cloud.google.com/storage/browser/finngen-public-datar10/summary_stats, respectively. The GWAS summary statistics for BMI are available through the GIANT website (https://portals.Broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files). The GWAS summary statistics for ASI, CPD, and SI are available through the GSCAN Consortium website (https://conservancy.umn.edu/). The GWAS summary statistics for grip strength, ALM, WBLM, and walking pace are available from the MRC-IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/).

Ethics Approval and Consent to Participate

In accordance with the People's Republic of China's Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research, this study qualifies for exemption from ethical review, as specified in the provisions discussed within the regulation. Specifically, ethical approval was deemed unnecessary based on the following criteria:

1. Exemption Premise: This study exclusively utilized publicly available data, primarily summary-level data from GWAS. The research did not involve sensitive personal information, pose any risk of harm to individuals, or compromise privacy.

2. Exemption Provision: The study aligns with the exemption conditions. All data used were lawfully obtained and publicly accessible. The datasets were fully anonymized, ensuring robust protection of individual privacy and confidentiality. Furthermore, the study involved secondary analyses of existing data and did not include interventions, human biological samples, or activities involving reproductive cloning, genetic modification, or germ cells.

Given the scope of this research and its adherence to the exemption criteria, explicit ethical approval was not required. We affirm that this study was conducted in strict compliance with applicable laws, regulations, and ethical standards.

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Disclosure

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