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Article

Exploring Causal Effects of Sarcopenia on Chronic Obstructive Pulmonary Disease and Hospitalization Risk: A Bi-Directional Mendelian Randomization Study

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Abstract

Aims/Background: As the global population ages, age-related chronic obstructive pulmonary disease (COPD) and sarcopenia present significant clinical and economic concerns. Emerging evidence suggests that these conditions are interrelated; however, potential confounding factors may impact observational investigations. Therefore, this study employed a bi-directional Mendelian randomization analysis to systematically investigate the causal relationship—rather than merely conducting a correlation analysis, between sarcopenia-related traits and COPD and hospitalization risk. **Methods**: Univariate, two-sample, and bi-directional Mendelian randomization (MR) analyses were performed using data from genome-wide association studies. The data on Sarcopenia features, including appendicular lean mass (ALM), hand grip strength (HGS), usual walking pace (UWP), and moderate-to-vigorous physical activity (MVPA) were acquired from the UK Biobank. However, data on COPD and hospitalization risk were sourced from the FinnGen consortium. Inverse-variance weighted (IVW) MR and sensitivity analyses were performed to evaluate causal relationships. Additionally, the observed findings were validated using an independent COPD dataset sourced from the UK Biobank. **Results**: The forward MR analysis using IVW revealed a significant negative causality between ALM, HGS, UWP, MVPA, and COPD (all $p < 0.05$, all $p_{FDR} < 0.05$) (False Discovery Rate, FDR), as well as with COPD-related hospitalization (all $p < 0.05$, all $p_{FDR} < 0.05$). These findings were corroborated by validation analyses. Furthermore, reverse MR assessment demonstrated that COPD alleviates UWP ($p = 0.001$, $p_{FDR} = 0.015$); however, validation analysis did not confirm this result. Moreover, additional MR analyses yielded similar trends in causal relationships as evidenced by robust sensitivity tests. **Conclusion**: Our study supported a unidirectional, negative causality between sarcopenia-related traits and COPD and hospitalization risk. This provides possible evidence that sarcopenia increases the risk of COPD and hospitalization at the genetic level. Our findings suggest that improving sarcopenia may serve as a promising strategy for minimizing the incidence of COPD and hospitalization risk, thereby reducing the health burden on these patients.

Keywords: Mendelian randomization; sarcopenia; COPD; hospitalization

1. Introduction

Chronic obstructive pulmonary disease (COPD) and sarcopenia, present significant clinical and socioeconomic challenges within geriatric populations [1–3]. COPD is the third leading cause of death worldwide, with the estimated global financial impact of International Dollars (INT$) 4.3 trillion between 2020 and 2050 [3]. At the population level, a study on the economic burden of sarcopenia assessed its direct healthcare costs in the United States at $18.5 billion for the year 2000 [1].

COPD is a complex and heterogeneous condition characterized by persistent inflammation and various extrapulmonary manifestations [4–8]. Patients with COPD often exhibit comorbidities, including cardiovascular disease, metabolic dysfunctions, osteoporosis, muscular disorders, cachexia, and mental health conditions, all of which detrimentally affect patient outcomes [5,7,8]. Sarcopenia, characterized by age-related reductions in skeletal muscle mass, strength, and function, frequently coexists with COPD [9,10]. The extrapulmonary manifestations of COPD can severely influence performance by reducing physical activity and diminishing muscle mass and strength, thereby significantly compromising the quality of life [11–13]. These physical factors are strongly associated with the onset and progression of sarcopenia [14,15]. A recent systematic meta-analysis reported a higher prevalence of sarcopenia (27.5%) among COPD patients [16]. Furthermore, sarcopenia is related to a range of adverse outcomes, including extended hospitalization, increased risk of fractures, acute exacerbations, falls, disability, and mortality—serving as a strong prognostic indicator for worse disease progression [11,15]. While observational studies consistently suggest a close association between COPD and sarcopenia, the presence of confounding variables limits the capability to as-

certain a direct causal relationship. Therefore, more effective approaches are required to determine their causal relationship, informing targeted management and intervention strategies for these interrelated conditions.

Given the current research-based evidence, we hypothesized that sarcopenia has a causal relationship with both COPD and hospitalization risk, and we tested this assumption using a Mendelian randomization (MR) approach. MR analysis includes genetic variants as instrumental variables (IVs) to evaluate causal links between exposures and outcomes, effectively minimizing the risk of confounding factors and reversing causation [17]. Despite the clinical significance causal links between COPD and sarcopenia, limited studies have explored this association using MR approaches. To date, no randomized controlled trials (RCTs) have been performed to evaluate the bidirectional interactions between these two interrelated conditions. Therefore, we conducted a bi-directional two-sample MR analysis to assess causal associations between sarcopenia, COPD, and hospitalization risk, employing appendicular lean mass (ALM), hand grip strength (HGS), usual walking pace (UWP), and moderate-to-vigorous physical activity (MVPA).

2. Methods

2.1 Study Design

As shown in Fig. 1, a two-sample bidirectional MR analysis was conducted to examine the likelihood of sarcopenia-related traits causally impacting COPD and hospitalization risk, and vice versa. Subsequently, replication analyses were performed to validate the results from the initial MR analysis. The MR analysis is based on 3 key assumptions: (1) Independence, where the IVs must not be linked to any known confounders; (2) Relevance, where IVs must be associated with the exposures; (3) Exclusivity, where IVs must influence the outcomes exclusively through the exposures [18]. Reporting procedures adhered strictly to Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines [19]. Since this study reanalyzed previously published data, no additional ethical approval was required.

2.2 Data Sources

Since published genome-wide association studies (GWAS) data (https://www.ebi.ac.uk/gwas/) targeting sarcopenia are lacking, we explored causal relationships using sarcopenia-related traits. Based on the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus, sarcopenia diagnosis involves three key domains: muscle quantity/quality, physical performance, and muscle strength [20]. Therefore, in this MR analysis, we selected sarcopenia-related traits that reflect these three domains: ALM representing low muscle quantity, HGS indicating low muscle strength, and UWP and MVPA denoting low physical performance. These criteria were used as proxies for sarcopenia in this study. This approach enhances the accuracy and comprehensiveness of MR analyses assessing sarcopenia [21].

For this analysis, IVs were identified using publicly available GWAS summary statistics: ALM (n = 244,730) and MVPA (n = 377,234) were obtained from European Bioinformatics Institute, while right HGS (n = 461,089), left HGS (n = 461,026) and UWP (n = 459,915) were from UK Biobank, a prospective cohort comprising >500,000 cases of European ethnicity [22]. Detailed protocols for measuring these parameters are available in the UK Biobank Assessment Centre manual, with most observations adjusted for age, gender, and other associated covariates. GWAS data for COPD (n = 193,638) and COPD-related hospitalizations (n = 218,792), utilized in primary MR analysis, were acquired from the FinnGen consortium (https://www.finngen.fi/en) [23]. COPD was defined based on the International Classification of Diseases (ICD) codes obtained from Finland's national registries. For mixed-model logistic regression analyses, the Scalable and Accurate Implementation of the Generalized mixed model (SAIGE) approach was used in FinnGen data, with adjustments for sex, age, genotype batch, and 10 principal components [23].

Additionally, another GWAS dataset for COPD (n = 361,194) sourced from the UK Biobank was utilized for MR validation analysis. As the exposure and outcome datasets in the primary MR analysis were sourced from different sample repositories (with no sample geographic or temporal overlap between UK Biobank and FinnGen, and FinnGen officially confirming that its samples are independent of other international cohorts), there was no sample overlap, ensuring the independence of our analyses. All GWAS data were based on populations of European descent. The sources of the specific phenotypic data are summarized in Table 1.

2.3 Instrumental Variables (IVs) Selection

The IVs were selected following the three core assumptions of MR analysis [18]: the IV must be substantially related to exposure, must be independent of confounding factors, and should exclusively affect the outcome through exposure, thereby minimizing horizontal pleiotropy. The criteria used for IV selection were as follows:

(1) Single nucleotide polymorphisms (SNPs) exhibiting genome-wide significant association ($p < 5 \times 10^{-8}$) with the exposure were selected, a threshold widely accepted in the GWAS to minimize false positives. In cases with limited SNP availability, a less stringent criterion of $p < 1 \times 10^{-5}$ was applied.

(2) A linkage disequilibrium correlation coefficient of $r^2 < 0.001$ with a clumping window >10,000 kb was applied to ensure the independence of selected SNPs [24].

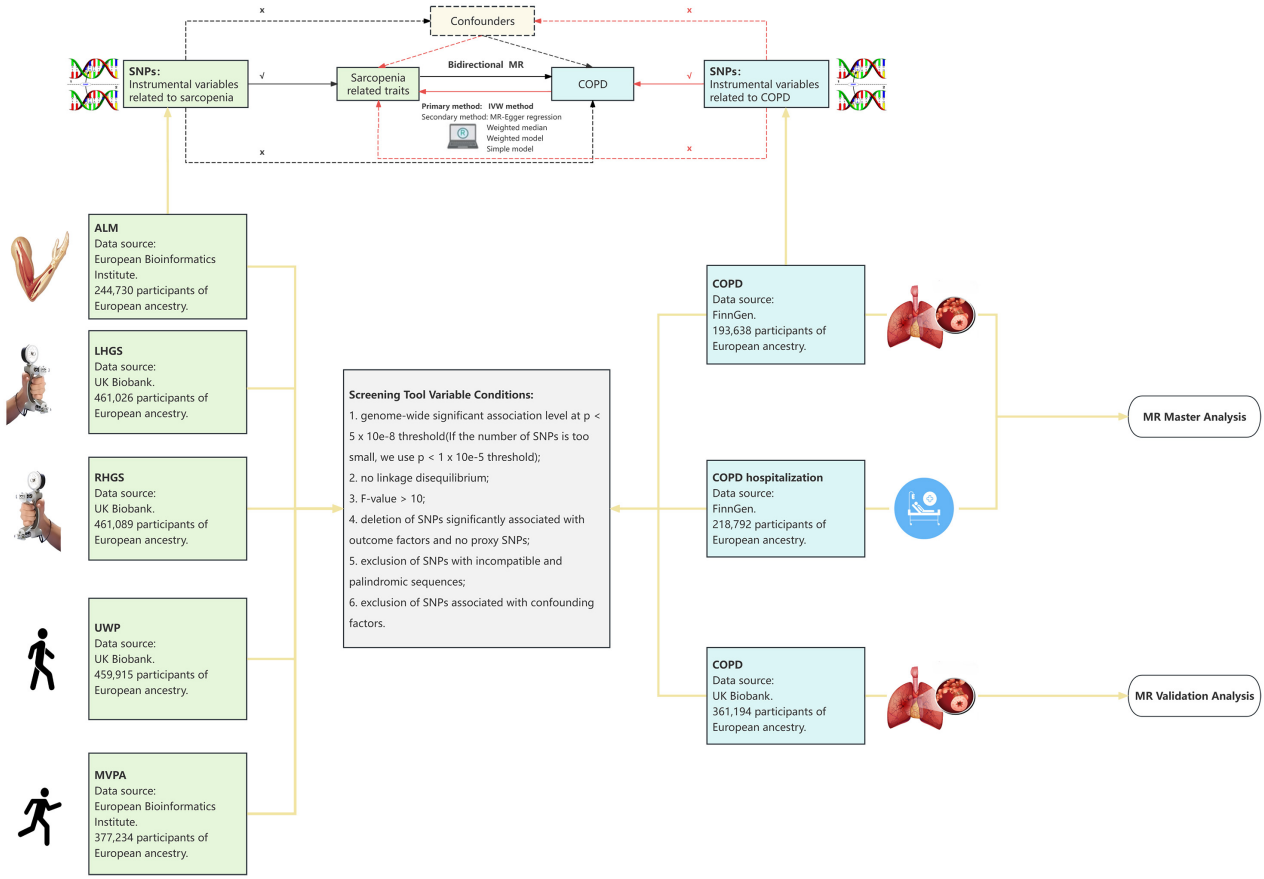

Fig. 1. A flow chart of study design. The lines and arrows indicate that instrumental variables (IVs) are linked to exposure and can influence the outcome only through this exposure. The dashed lines represent that the IVs are not influenced by any confounding variables. COPD, chronic obstructive pulmonary disease; MR, Mendelian randomization; IVW, inverse-variance weighted; ALM, appendicular lean mass; LHGS, left-hand grip strength; RHGS, right-hand grip strength; SNPs, single nucleotide polymorphisms; UWP, usual walking pace; MVPA, moderate-to-vigorous physical activity.

(3) The strength of each IV was evaluated using an F statistic >10, computed as $F = \beta^2(\text{exposure})/SE^2(\text{exposure})$ [25].

(4) SNPs linked to outcome factors were excluded, and proxy SNPs were absent.

(5) Harmonization of SNPs between outcome and exposure datasets was conducted, removing palindromic SNPs and incompatible alleles.

(6) IVs associated with known confounding factors, including smoking, air pollution, blood lipid levels, alcohol consumption, body mass index, were excluded using PhenoScanner v2. Comprehensive data on selected IVs are given in **Supplementary Table 1**. All of our analyses in PhenoScanner v2 were completed by March 8, 2024, after which date the site was discontinued, but its data source (GWAS Catalog) is still separately accessible even when PhenoScanner is not available. In this case, we directly used the GWAS Catalog (https://www.ebi.ac.uk/gwas/home) as an alternative.

2.4 Univariable, Two-Sample, and Bi-Directional MR Analyses

A random effects inverse-variance weighted (IVW) analysis was used to examine causal links between the exposures and outcomes, as this approach assumes that the selected SNPs represent valid IVs and offer greater precision under these conditions [26]. Supplementary analysis includes the weighted mode, simple mode, weighted median, and MR-Egger approaches [27]. Using multiple MR approaches improves the robustness of the causal estimates across various analytical scenarios.

2.5 Sensitivity Analysis

Three approaches were used for sensitivity analysis to ensure the robustness of our results: evaluation of heterogeneity, assessment of horizontal pleiotropy, and "leave-one-out (LOO)" analysis. Heterogeneity was evaluated by applying Cochran's Q test; significant heterogeneity ($p < 0.05$) was observed, a random-effects IVW was used for subsequent MR analysis, whereas a fixed-effects IVW was used in cases of no significant heterogeneity [28]. Horizon-

Table 1. A summary of relevant data in the selected GWASs.

Exposure/Ending	GWAS ID	Year	Sample size	Number of SNPs	PMID
ALM	ebi-a-GCST90000027	2020	244,730	18,164,071	33097823
HGS (left)	ukb-b-7478	2018	461,026	9,851,867	NA
HGS (right)	ukb-b-10215	2018	461,089	9,851,867	NA
UWP	ukb-b-4711	2018	459,915	9,851,867	NA
MVPA	ebi-a-GCST006097	2018	377,234	11,808,007	29899525
COPD	finn-b-J10_COPD	2021	193,638	16,380,382	NA
COPD hospitalization	finn-b-COPD_HOSPITAL	2021	218,792	16,380,466	NA
COPD	ukb-d-COPD_EARLYANDLATER	2018	361,194	10,360,720	NA

Note: GWAS, genome-wide association studies; NA, not available; ALM, appendicular lean mass; HGS, hand grip strength; UWP, usual walking pace; MVPA, moderate-to-vigorous physical activity; COPD, chronic obstructive pulmonary disease.

tal pleiotropy was examined based on the MR-Egger intercept test. The Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test determined potential pleiotropy [29,30]. Potential outliers SNPs were identified employing the MR-PRESSO outlier test. If an outlier was detected ($p < 0.05$), causal effects were re-estimated after eliminating the outlier SNPs. A p-value $<$ 0.05 indicated significant pleiotropic bias. To further evaluate the influences of each SNP on the overall causal estimates, a LOO analysis was conducted sequentially, excluding one SNP at a time [31].

2.6 Statistical Analysis

Two-sample MR analysis was performed through R (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria), using the 'TwoSampleMR' [32] and 'MR-PRESSO' [30] packages. These packages are accessible through the Comprehensive R Archive Network (CRAN). For dichotomous variable outcome, results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) to elucidate the causal links between sarcopenia-related traits and both COPD and hospitalization risk. A significance threshold was set at a p-value < 0.05. To enhance statistical power, a False Discovery Rate (FDR) was adjusted for multiple comparisons, and the risk of Type I error was minimized [33]. An FDR-adjusted p-value of <0.05 based on IVW results indicated a significant causal relationship. FDR analysis was conducted using the BioLadder platform (https://www.bioladder.cn).

3. Results

3.1 Screening of Instrumental Variables Based on Genome-Wide Significance

The screening process yielded 27–356 IVs that achieved genome-wide significance. All selected SNPs exhibited F statistics exceeding 10, ranging from 19.5 to 772.9, indicating the strength of genetic instruments. Through PhenoScanner, 108 SNPs were identified as potentially related to confounding factors. Specific details on these IVs are provided in **Supplementary Table 1**.

3.2 The Primary MR Analysis

In the forward MR analysis, sarcopenia-associated traits were used as exposure variables, while COPD and hospitalization risk were outcome variables. The IVW results indicated a causal influence of sarcopenia-associated traits on COPD and hospitalization risk (all $p < 0.05$, all $p_{FDR} < 0.05$; Table 2, Fig. 2). Specifically, high ALM, HGS, UWP, and MVPA were linked to reduced risks of COPD. A significant negative causal relationship was also observed with COPD-related hospitalization risk, suggesting that sarcopenia-related traits may influence hospitalization rates. Additional MR analyses overwhelmingly supported these causal effect trends (Fig. 2).

In the reverse MR analysis, genetically predicted COPD and hospitalization were examined as exposure variables, with sarcopenia-associated traits as outcomes to elucidate potential reverse causal effects. The IVW analysis suggested a significant negative correlation, indicating that COPD was associated with diminished UWP (OR_{UWP} = 0.993, 95% CI: 0.989–0.997, p = 0.001, p_{FDR} = 0.015) (Table 3, Fig. 3). However, no causal effects of COPD or hospitalization on ALM, HGS, and MVPA were observed ($p_{FDR} > 0.05$, Table 3). Furthermore, no evidence supported the causal effect of COPD-related hospitalization on UWP. Complete MR findings, including analysis using the weighted median, simple mode, weighted modes, and MR-Egger approaches, are illustrated in Fig. 3.

Following several sensitivity analyses, heterogeneity was assessed using Cochran's Q-test based on the MR-Egger and IVW frameworks, while MR-PRESSO and MR-Egger assessments evaluated horizontal pleiotropy. Heterogeneity was observed in the MR analysis assessing the effects of COPD and hospitalization on ALM and MVPA, as well as the impact of COPD on left HGS, requiring the utilization of random-effects IVW for these associations (Table 4). No significant heterogeneity was detected in the other two-sample MR analyses ($p > 0.05$).

Additionally, no evidence of horizontal pleiotropy was found across the two-sample MR analyses ($p > 0.05$). This suggests that the IVs likely impacted outcomes exclusively

Table 2. IVW results in the forward MR master analysis.

Exposures	Outcomes	OR	95% CI	*p*-value	p_{FDR}
ALM	COPD	0.904	0.824–0.992	0.033	0.034
LHGS	COPD	0.542	0.375–0.784	0.001	0.003
RHGS	COPD	0.613	0.440–0.855	0.004	0.006
UWP	COPD	0.255	0.127–0.515	1×10^{-4}	0.001
MVPA	COPD	0.650	0.459–0.920	0.015	0.020
ALM	Hospitalization	0.898	0.816–0.988	0.027	0.028
LHGS	Hospitalization	0.539	0.373–0.779	0.001	0.003
RHGS	Hospitalization	0.635	0.457–0.884	0.007	0.012
UWP	Hospitalization	0.290	0.142–0.592	0.001	0.003
MVPA	Hospitalization	0.659	0.455–0.956	0.028	0.028

Note: IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; FDR, False Discovery Rate.

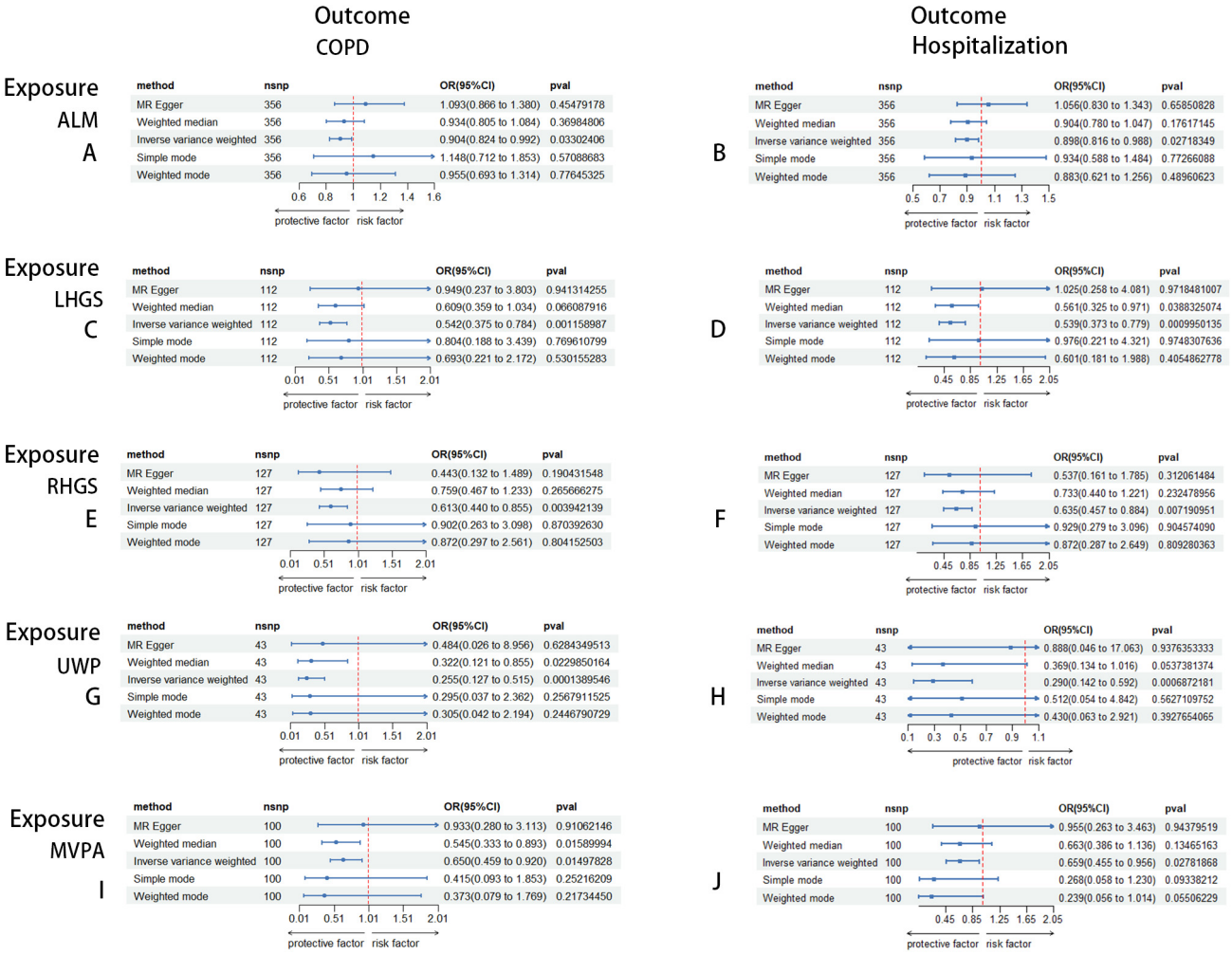

Fig. 2. Forest plots of the causal relationship between sarcopenia-related traits on COPD and hospitalization risk in the forward MR analysis. (A) The causal relationship between ALM and COPD. (B) The causal relationship between ALM and hospitalization. (C) The causal relationship between LHGS and COPD. (D) The causal relationship between LHGS and hospitalization. (E) The causal relationship between RHGS and COPD. (F) The causal relationship between RHGS and hospitalization. (G) The causal relationship between UWP and COPD. (H) The causal relationship between UWP and hospitalization. (I) The causal relationship between MVPA and COPD. (J) The causal relationship between MVPA and hospitalization.

Table 3. IVW results in the reverse MR master analysis.

Exposures	Outcomes	OR	95% CI	*p*-value	p_{FDR}
COPD	ALM	0.988	0.977–0.999	0.039	0.097
COPD	LHGS	0.994	0.988–1.000	0.048	0.097
COPD	RHGS	0.995	0.990–1.000	0.048	0.097
COPD	UWP	0.993	0.989–0.997	0.001	0.015
COPD	MVPA	0.994	0.985–1.004	0.233	0.290
Hospitalization	ALM	0.992	0.979–1.004	0.176	0.252
Hospitalization	LHGS	0.997	0.990–1.004	0.377	0.377
Hospitalization	RHGS	0.997	0.991–1.003	0.261	0.290
Hospitalization	UWP	0.994	0.990–0.999	0.011	0.053
Hospitalization	MVPA	0.991	0.982–1.001	0.065	0.109

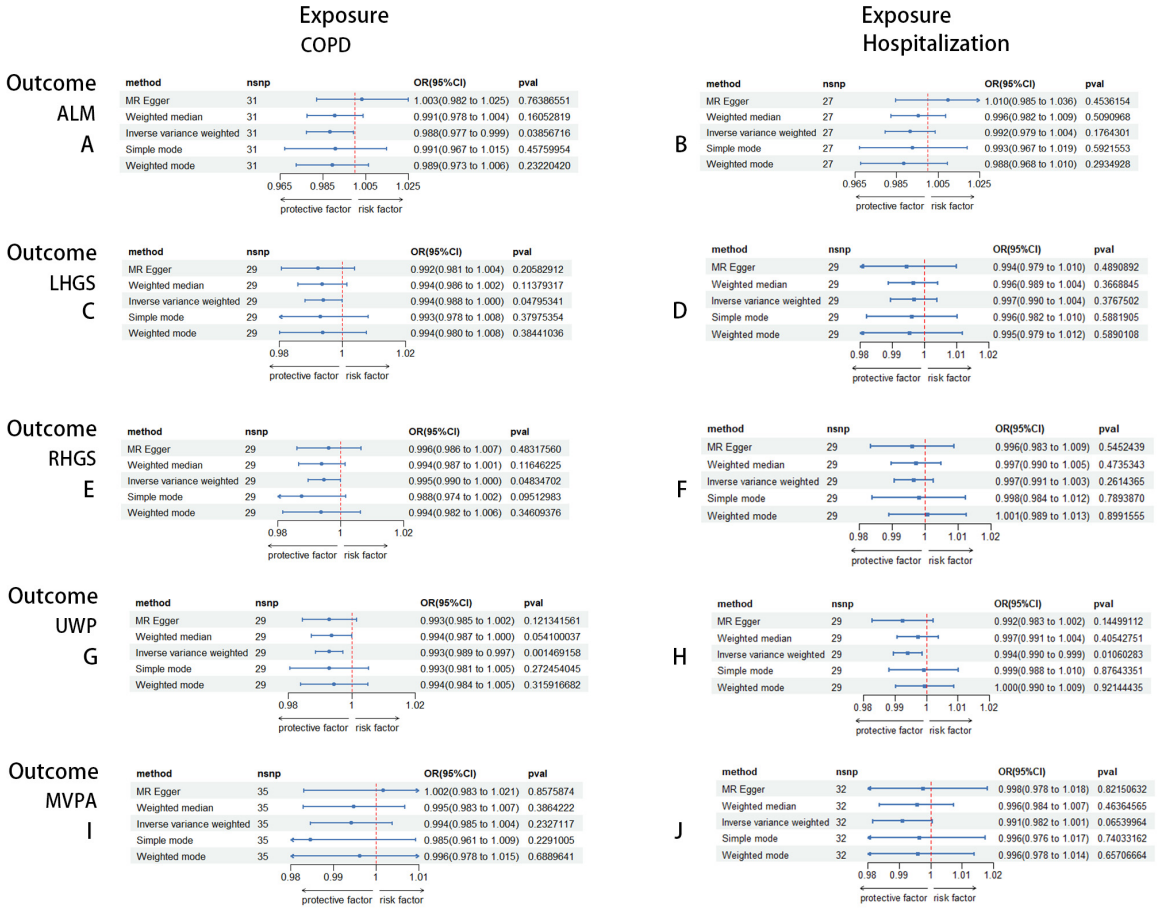

Fig. 3. Forest plots of the causal relationship between COPD and hospitalization risk on sarcopenia-related traits in the reverse MR analysis. (A) The causal relationship between COPD and ALM. (B) The causal relationship between hospitalization and ALM. (C) The causal relationship between COPD and LHGS. (D) The causal relationship between hospitalization and LHGS. (E) The causal relationship between COPD and RHGS. (F) The causal relationship between hospitalization and RHGS. (G) The causal relationship between COPD and UWP. (H) The causal relationship between hospitalization and UWP. (I) The causal relationship between COPD and MVPA. (J) The causal relationship between hospitalization and MVPA.

through the designated exposures, with no effect through alternate pathways. The LOO sensitivity analyses further confirmed that no single SNP influences the MR results (**Supplementary Fig. 1**), reinforcing the robustness of our findings.

3.3 The MR Validation Analysis

In the MR validation analysis, the causal influence of ALM, HGS, UWP, and MVPA on COPD was successfully replicated, with effect directions consistent with those observed in the primary MR analysis (**Supplementary Tables 2,3**). No causal impacts of COPD on sarcopenia-associated

Table 4. Sensitivity analysis results.

Exposures	Outcomes	Horizontal pleiotropy test	Horizontal pleiotropy test	Heterogeneity-test	Heterogeneity-test
		MR-Egger	MR-PRESSO	IVW	MR-Egger
		Intercept (*p*)	*p*	Cochran's Q (*p*)	Cochran's Q (*p*)
ALM	COPD	–0.005 (0.086)	0.086	391.1 (0.084)	387.8 (0.097)
ALM	Hospitalization	–0.004 (0.151)	0.089	399.2 (0.052)	396.9 (0.057)
LHGS	COPD	–0.007 (0.413)	0.199	123.55 (0.195)	122.79 (0.191)
LHGS	Hospitalization	–0.008 (0.346)	0.312	116.80 (0.335)	115.86 (0.332)
RHGS	COPD	0.004 (0.585)	0.315	133.67 (0.303)	133.35 (0.288)
RHGS	Hospitalization	0.002 (0.775)	0.729	117.02 (0.705)	116.93 (0.684)
UWP	COPD	–0.006 (0.661)	0.471	43.02 (0.427)	42.81 (0.393)
UWP	Hospitalization	–0.011 (0.448)	0.474	41.87 (0.433)	42.47 (0.451)
MVPA	COPD	–0.005 (0.540)	0.263	109.43 (0.223)	109.0 (0.210)
MVPA	Hospitalization	–0.005 (0.558)	0.088	119.11 (0.082)	118.69 (0.076)
COPD	ALM	–0.003 (0.119)	0.675	51.7 (0.008)	47.5 (0.016)
Hospitalization	ALM	–0.003 (0.121)	0.504	50.66 (0.003)	45.92 (0.007)
COPD	LHGS	3×10^{-4} (0.733)	0.058	38.9 (0.082)	38.7 (0.066)
Hospitalization	LHGS	4×10^{-4} (0.743)	0.407	58.56 (0.001)	58.32 (4.4×10^{-4})
COPD	RHGS	-3×10^{-4} (0.739)	0.346	29.5 (0.387)	29.3 (0.342)
Hospitalization	RHGS	1×10^{-4} (0.917)	0.085	38.77 (0.085)	38.76 (0.067)
COPD	UWP	-6×10^{-6} (0.993)	0.438	28.4 (0.441)	28.4 (0.387)
Hospitalization	UWP	2.7×10^{-4} (0.723)	0.287	31.75 (0.285)	31.60 (0.247)
COPD	MVPA	–0.002 (0.362)	0.246	64.07 (0.001)	62.46 (0.001)
Hospitalization	MVPA	–0.001 (0.474)	0.509	52.64 (0.009)	51.74 (0.008)

MR-PRESSO, The Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

traits were observed, and the observed association between COPD and UWP was not replicated in the MR validation analysis (**Supplementary Tables 2,3**). However, sensitivity analyses validated the robustness of these outcomes (**Supplementary Tables 2,3** and **Supplementary Fig. 2**). According to these findings, it was concluded that sarcopenia negatively impacts COPD causally.

4. Discussion

This study utilized an univariable two-sample bi-directional MR to systematically elucidate the causal links between sarcopenia-associated traits, including ALM, HGS, UWP, and MVPA and the risk of COPD and hospitalization. The findings revealed a significant negative causal relationship, demonstrating that genetically determined reduction in ALM, HGS, UWP, and MVPA increases the risk of COPD and hospitalization. Furthermore, these associations were successfully validated through replication analyses. Although the primary MR analysis suggested a negative correlation between COPD and diminished UWP, this finding was not replicated in the MR validation analysis. To our knowledge, this is the first bi-directional MR study to comprehensively evaluate the causal link between sarcopenia-associated traits and COPD and hospitalization risk, while accounting for potential confounders.

Previous observational studies have indicated that sarcopenia elevates the risk of COPD. A prospective, population-based cohort investigation undertaken in Rotterdam, The Netherlands, revealed a higher incidence of COPD among sarcopenic (26.9%) and pre-sarcopenic (29.1%) patients relative to the nonsarcopenic (13.4%) individuals [34]. Similarly, another study involving 469,830 participants from the UK Biobank indicated that gait-muscle group individuals had a 4.16-fold higher risk of COPD than those with the normal physical ability (HR: 4.16, 95% CI: 2.59–6.70), followed by those with severe sarcopenia (HR: 3.85, 95% CI: 2.24–6.62). Sarcopenia in this study was described based on the combination of 3 indicators of physical function: muscle mass, grip strength, and gait speed [35]. The Invecchiare in Chianti (InCHIANTI, Aging in the Chianti Region) study, which longitudinally analyzed 538 participants, revealed that sarcopenia was correlated with a higher hospitalization rate (60% vs. 48%, $p = 0.087$). Even after adjusting for potential confounders, sarcopenia remained notably associated with hospital admission (HR: 1.57; 95% CI: 1.03–2.41) [36]. Furthermore, a retrospective analysis of 174,808 COPD patients in the United States in 2011 reported associations between muscle loss and increased morbidity and mortality, with sarcopenic patients experiencing longer hospital stays and higher associated costs compared to non-sarcopenic patients. These observations are consistent with our results, indicating a causal association between sarcopenia and increased risks of COPD and hospitalization. According to EWGSOP definitions, the diagnosis of sarcopenia requires meeting both low grip strength and low muscle mass, with severe sar-

copenia characterized by reduced gait speed. Our findings demonstrate the substantial negative causal association between ALM, MVPA, UWP, and HGS with COPD and hospitalization, supporting the conclusion that sarcopenia increases the risk of COPD and related hospitalizations.

Several systematic reviews and meta-analyses of prior observational studies have suggested an association between COPD and an elevated risk of sarcopenia [11,16,37]. While epidemiological surveys across varied populations have shown different prevalence rates of sarcopenia among COPD patients, meta-analyses consistently underscore its frequent co-occurrence. However, in our study, no genetic evidence supports the causal impact of COPD and hospitalization on sarcopenia-related traits. While the primary MR analysis suggested a negative correlation between COPD and diminished UWP, this finding was not replicated in the MR validation analysis. Given our study's rigor in applying FDR correction for multiple comparisons and considering the complex interrelations between COPD and sarcopenia, these results warrant cautious interpretation. Further investigation is needed to assess these associations more thoroughly in future studies. Sarcopenia-related traits, like ALM and HGS, serve as key predictors of muscle mass, and low muscle mass has been linked to poor pulmonary function [38,39]. A cross-sectional study analyzing 452 COPD patients reported a significant association between reduced lean mass and elevated risk of emphysema, a crucial phenotype of COPD [40]. Meanwhile, UWP and MVPA are used as a measure of physical activity performance levels. Evidence suggests that prolonged sedentary behavior may lead to an inadequate physical exercise, adversely affecting both muscle and lung functions, thereby increasing the risk of COPD [41–43]. Conversely, higher physical activity has been associated with a lower risk of COPD, likely through preserving lean mass and reducing oxidative stress and minimizing chronic airway inflammation [44–48]. Moreover, MVPA has been reported to have positive effects on lung function at the population level [49]. Taken together, these interrelated clinical factors provided a considerable basis for the observed association between sarcopenia and the higher incidence of COPD and hospitalization risk.

The occurrence of comorbidities in sarcopenia and COPD involves a multidimensional biological interaction, with systemic inflammation playing a crucial role. Increased levels of serum pro-inflammatory factors, such as C-reactive protein (CRP), Interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) have been consistently found in COPD patients, where they accelerate myofibrillar protein degradation by upregulating the expression of muscle-specific ubiquitin ligases (MuRF1 and MAFbx) through activation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [50,51]. Oxidative stress may be another key mechanism, manifested by the excessive accumulation of reactive oxygen species (ROS) in COPD patients. ROS not only impairs mitochondrial function and muscle energy metabolism but also synergizes with inflammatory factors to activate inflammatory signaling pathways such as p38 Mitogen-Activated Protein Kinase (p38 MAPK), forming a vicious circle that aggravates muscle atrophy and dysfunction [52,53]. Additionally, an imbalance in actin regulation further elucidates the link between sarcopenia and COPD. For example, irisin promotes muscle growth and is usually elevated during physical activity but is reduced in patients with COPD, whereas levels of myostatin, an inhibitor of muscle regeneration, are elevated [54]. This imbalance skews muscle metabolism towards catabolic processes, accelerating the onset of sarcopenia. However, despite these promising insights, the specific pathophysiological mechanisms linking sarcopenia and COPD remain poorly understood.

The growing understanding of the biological mechanisms linking sarcopenia and COPD carries significant therapeutic implications. Evidence suggested that managing sarcopenia in COPD patients is both feasible and effective through well-structured exercise programs supported by a balanced nutritional intake. Various other events, such as resistance training, aerobic exercise, and pulmonary rehabilitation have been found to improve muscle strength and endurance, while adequate protein intake, vitamin D, omega-3s, and calories help preserve muscle mass [54–57]. Given the possible negative causal association observed in our study, combining these interventions may maximize therapeutic outcomes and reduce the risk of sarcopenia-related COPD exacerbation and hospitalization. These evidence-based strategies, based on the latest research findings, provide clinicians with a crucial framework for public health decision-making aimed at managing sarcopenia to reduce its impact on COPD patients.

The current study has several significant strengths. Firstly, it comprehensively evaluated critical features related to muscle quality, muscle strength, and physical performance, while also including hospitalization phenotypes alongside COPD, thereby enhancing the rigor and representativeness of the study. Secondly, MR studies, often considered natural randomized controlled trials, offer more robust findings than traditional observational studies. Furthermore, we executed extensive validation and sensitivity analyses to confirm the result's robustness, especially when heterogeneity was observed: a random-effects IVW was used to minimize its effect. Finally, we effectively excluded confounding factors such as air pollution, smoking, alcohol consumption, body mass index (BMI), and blood lipid levels, mitigating potential biases.

Nonetheless, we acknowledge certain limitations in our study. Specifically, our study population was limited to participants of European ancestry. Due to significant genetic differentiation between East Asian and European populations, with about 12% of SNPs exhibiting significant Fixation Index (FST) differences (indicative of considerable allele frequency differences), which may limit the

generalizability of the results across different ethnic groups [58]. Additionally, stratification based on common factors such as age and sex were unattainable due to constraints in the available summarized GWAS data. Moreover, the causal links between COPD-related hospitalization and sarcopenia-associated traits could not be validated due to a lack of relevant data. Lastly, there are inherent limitations in the MR approach. However, the use of MR-PRESSO helped to reduce the risk of horizontal pleiotropy by identifying and excluding outlier SNPs, its validity relies on the assumption of linearity and cannot entirely exclude the possibility of residual pleiotropy arising from nonlinear causation or epigenetic modulation [30].

It should also be noted that, in the partial MR analysis, we employed a relatively lenient threshold ($p < 1 \times 10^{-5}$) for IV selection due to the limited number of variants meeting the more stringent threshold ($p < 5 \times 10^{-8}$). Although all selected SNPs had F-values >10, thus meeting the threshold to reduce weak instrumental bias, and pleiotropic SNPs were excluded, the potential for weak instrument bias remains. Additionally, individual leave-one-out plots demonstrated that there are potentially influential SNPs driving the causal link between exposures and outcomes, suggesting the possibility of unrecognized pleiotropy in some SNPs that could influence the stability of our findings. In future studies, using a Polygenic Risk Score, colocalization analyses to prioritize causal SNPs, or the integration of proteomic MR to enhance biological specificity could further validate findings in this area.

5. Conclusion

In conclusion, this study indicates a causal association between sarcopenia and elevated risks of COPD and hospitalization, providing reliable genetic evidence for the adverse impacts of sarcopenia on both outcomes within the European population. These findings underscore the clinical and public health importance of targeting sarcopenia improvement as a promising strategy to reduce the incidence of COPD and minimize hospitalization risk.

Key Points

- This study employed a bi-directional two-sample MR approach to systematically investigate causal relationships between sarcopenia-related traits (ALM, HGS, UWP, MVPA) and both COPD and hospitalization risk, overcoming limitations of observational studies.
- Genetically predicted lower ALM, reduced HGS, slower UWP, and decreased MVPA significantly increased the risk of COPD and COPD-related hospitalization, supporting a unidirectional causal effect of sarcopenia on COPD exacerbation.
- The findings highlight that intervention targeting muscle preservation (e.g., resistance training, nutritional support) may reduce COPD incidence and hospitalization burden, offering practical strategies for mitigating age-related cardiopulmonary morbidity.
- Robust sensitivity analyses (MR-PRESSO, leave-one-out), FDR correction, and replication using independent UK Biobank dataset strengthened causal inferences, with minimal pleiotropy or heterogeneity observed (Cochran's Q $p > 0.05$ for most traits).
- While emphasizing sarcopenia's causal role, this study underscores the need for multi-ethnic cohorts, mechanistic exploration of muscle-lung interactions (e.g., oxidative stress pathways), and trials testing targeted sarcopenia therapies in COPD populations.

Availability of Data and Materials

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Author Contributions

ZK designed the study. SN acquired the data. ZK and SN interpreted the data. SN and XL drafted the manuscript. XL was involved in the analysis and interpretation of data in the clinical part of medicine. XL focused on participating in the writing of the medical clinical section. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM50164.

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