Causal effects of physical activity and frailty on pneumothorax risk: a Mendelian randomization study

Yingwei Ding, Xiaojun Wang, Xiuhua Li, Laifa Kong*

Department of Emergency Medicine, Jinhua Municipal Central Hospital, Zhejiang, China

Submitted: 24 May 2025; **Accepted:** 3 August 2025
Online publication: 16 October 2025

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/208920

***Corresponding author:**
Laifa Kong
Department of Emergency Medicine
Jinhua Municipal Central Hospital
No. 365 Renmin East Road
Wucheng District, Jinhua City
Zhejiang Province, 321000, China
Tel: (86) 13857902828
E-mail: konglaifa@yeah.net

Abstract

Introduction: Pneumothorax is the presence of air in the pleural cavity, often resulting in respiratory distress and impaired lung function. Although clinical observations have shown that high intensity physical activity and frail state affect respiratory health, their causal role in pneumothorax development is unclear. This study is the first to use a two-sample Mendelian randomization method (TSMR) to investigate the causal relationship between physical activity and frailty and the risk of pneumothorax, with a view to providing new insights into the pathogenesis of pneumothorax and preventive strategies.

Material and methods: Using Mendelian randomization (MR) analyses, we examined the potential causal relationship between physical activity, frailty, and the risk of pneumothorax. Genetic instrumental variables (IVs) for relevant exposure factors were selected from genome wide association studies (GWAS). The study was analyzed using five different methods, mainly using inverse variance weighted (IVW) to draw causal inferences. Sensitivity analyses were performed to ensure the validity of the MR results. Sensitivity analyses included the detection of horizontal pleiotropy, i.e., genetic variants affecting the outcome through pathways other than the target exposure, which may lead to biased causal inference. Heterogeneity between genetic instrumental variables was also assessed and used to detect variability in effect estimates, which may reflect violations of MR assumptions or differences between populations.

Results: Our analyses found that light DIY reduced the risk of pneumothorax, but did not identify a causal association between other levels of physical activity and pneumothorax. In addition, frailty index (FI) showed a positive association with the risk of developing spontaneous pneumothorax, and this causal relationship persisted after adjustment for body mass index (BMI) and light DIY. Sensitivity analyses further validate the robustness of our findings.

Conclusions: Our findings support the ability of light DIY to reduce the risk of pneumothorax development. It also emphasizes the need for frail individuals to be more aware of the need to protect against pneumothorax in their daily lives. We encourage appropriate exercise to improve fitness and reduce the risk of pneumothorax.

Key words: pneumothorax, respiratory distress, abnormal pleural content, Mendelian randomization, physical activity, frailty, sensitivity analysis.

Introduction

Pneumothorax is a common clinical emergency characterized by the abnormal accumulation of air in the pleural cavity between the lungs and chest wall, which prevents lung expansion and can lead to lung atrophy through mechanisms such as alveolar collapse and impaired ventilation [1]. Pneumothorax is mainly classified into spontaneous and traumatic types [2]. Spontaneous pneumothorax includes primary and secondary types. Primary pneumothorax occurs when the thin walls of the alveoli, the tiny air sacs in the lungs responsible for gas exchange, rupture and allow air to enter the pleural cavity, causing lung collapse. Secondary pneumothorax occurs in patients with existing lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, or tuberculosis [3–5]. Traumatic pneumothorax results from blunt, penetrating, or explosive chest injuries. Clinically, pneumothorax often presents with sudden chest pain and dyspnea, and severe cases may progress to hypoxia, hypotension, or even death [6–11]. Epidemiological data reveal significant gender and age differences in pneumothorax incidence. Men are more susceptible than women, and this gender difference can be attributed to several factors, including higher rates of smoking in men, differences in body size (e.g., larger and taller body frames increase alveolar wall tension), and more [3]. Incidence peaks vary across age groups, reflecting complex underlying factors. Known risk factors include smoking, body mass index (BMI), height, exposure to toxic metals, and environmental influences [11–16].

Physical activity, defined as any bodily movement produced by skeletal muscles requiring energy expenditure, ranges from low-intensity walking to vigorous exercise [17, 18]. According to the World Health Organization (WHO), nearly one third of adults globally lack sufficient physical activity, which is linked to increased risks of cardiovascular disease, diabetes, certain cancers, and mental health disorders [19–23]. Emerging evidence suggests that both insufficient and excessive physical activity may influence lung health and potentially increase pneumothorax risk, especially in individuals with underlying pulmonary conditions [24–26]. Additionally, factors such as smoking and body habitus associated with pneumothorax risk may correlate with physical activity patterns [27–30].

Frailty is a geriatric syndrome characterized by weight loss, fatigue, muscle weakness, and reduced mobility, leading to diminished quality of life and increased risks of falls, hospitalization, and mortality [31, 32]. In epidemiological studies, risk factors for frailty include age, gender, chronic disease, poor nutrition and insufficient physical activity [33, 34]. Although the relationship between frailty and pneumothorax is not well studied, preliminary data indicate that frail individuals, particularly the elderly, may have compromised lung function, often demonstrating weakened respiratory muscles and reduced lung ventilation, which results in fragile alveoli that are more susceptible to spontaneous pneumothorax in the event of stress or external injury [35, 36]. Frailty is also linked to respiratory diseases such as COPD, which are established pneumothorax risk factors [37, 38]. This combination of diminished lung function and chronic comorbidities likely amplifies the vulnerability of frail patients to pneumothorax. In adolescents and young adults, frailty has also been identified as a potential risk factor for primary spontaneous pneumothorax [14, 16, 39].

Although studies suggest physical activity and frailty are linked to pneumothorax, these associations are often influenced by factors such as smoking, age, and sex. We hypothesized that more physical activity would be potentially protective against pneumothorax and that frailty would increase the risk of pneumothorax. Traditional studies struggle to prove this because of confounding and reverse causation. To address this, we used Mendelian randomization (MR), a genetic method that helps identify causal effects by using genetic variants as tools, reducing bias [40, 41]. We applied two-sample MR (TSMR) and multivariable MR (MVMR) to examine how physical activity and frailty independently affect pneumothorax risk. Our goal is to provide strong evidence on these causal links to support better prevention and treatment strategies.

Material and methods

Study design

The overall design of the MR analysis in this study is illustrated in Figure 1. We conducted a TSMR analysis to investigate the causal effects of physical activity or frailty on pneumothorax and spontaneous pneumothorax using genome-wide association study (GWAS) data. We applied two-sample MR leverages genetic variants as instrumental variables (IVs) derived from two independent GWAS datasets, one for the exposure and one for the outcome, to estimate causal relationships. This approach helps to minimize bias from confounding factors and reverse causation, as genetic variants are randomly assorted at conception and fixed throughout life [42]. The core assumptions for valid IVs are: (1) strong association with the exposure; (2) no association with confounders; (3) influence on the outcome only through the exposure. All GWAS datasets included in this study derive from large-scale European cohorts, primarily the UK Biobank and Integrative Epidemiology Unit (IEU) studies. Detailed information on sample

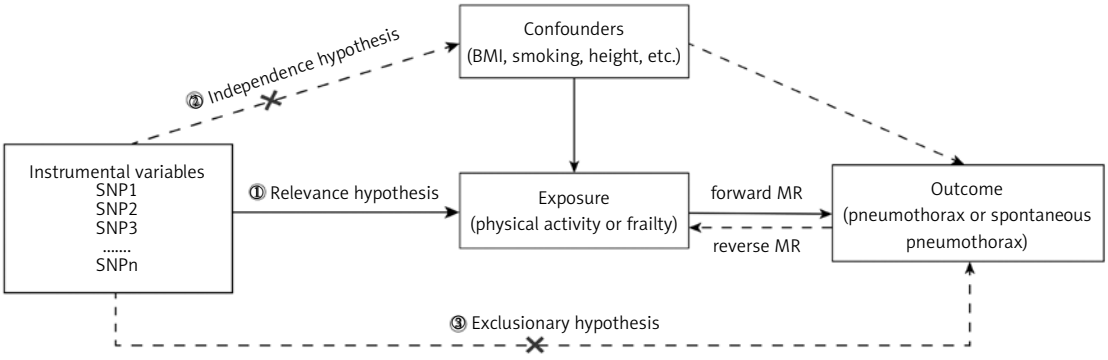


Figure 1. Flowchart of the Mendelian randomization (MR) study design

sizes, case-control numbers, and population characteristics are summarized in Table I. The study populations represent diverse localities across Europe, ensuring broad applicability within this ancestry group.

Data sources for exposure and outcome

Exposure data include physical activity (four categories) [43], frailty (Frailty Index (FI) [44, 45] and Frailty Phenotype (FP) [32, 46]), and body mass index (BMI) [47] as a confounder. Outcome data comprise pneumothorax [47] and spontaneous pneumothorax [48] GWAS summary statistics. Detailed dataset information and GWAS catalog IDs are listed in Table I. All datasets are publicly accessible via the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). Due to their availability in public databases, no additional ethical approval is required, allowing researchers unrestricted access. Further details regarding the data are provided in Supplementary Table SI.

Selection of instrumental variables

Single nucleotide polymorphisms (SNPs) were selected as IVs based on genome-wide significance (p < 5e-08), with relaxed thresholds (p < 5e-06) for exposures with fewer loci [49]. Linkage disequilibrium was controlled by clumping (r^2 = 0.001, distance > 10,000 kb). Single nucleotide polymorphisms with weak instrument bias (F-statistic < 10) or pleiotropic effects related to confounders (BMI, smoking, alcohol use, height, lung function, respiratory diseases) were excluded. By querying the LDtrait module in the LDlink database (https://ldlink.nih.gov/) [50], the system retrieved published GWAS results for each SNP associated with potential confounders. SNPs that reached the genomic significance level (p < 5e-08, r^2 = 0.001) in the associated confounding GWAS were excluded to reduce the effect of confounding bias. SNPs with palindromic structures were removed. Outlier SNPs identified by MR-PRESSO were removed [51, 52].

Analysis of Mendelian randomization

Five MR methods were applied: MR-Egger regression [53], inverse variance weighted (IVW) method [54], weighted median [55], weighted mode, and simple mode [56], with the IVW method being the primary approach [57]. Univariable MR (UVMR) assessed causal effects of physical activity and frailty on pneumothorax outcomes. In addition, to explore the possibility of reverse

Table I. Detailed information of the GWAS in our analysis

Exposure/Outcome	Year	ID	Population	Sample size	Control	Case
FI	2021	GCST90020053	European	175,226	–	–
FP	2023	–	European	–	–	–
Light do-it-yourself physical activity (DIY)	2018	ukb-b-11495	European	460,376	224,132	236,244
Heavy DIY	2018	ukb-b-13184	European	460,376	263,370	197,006
Strenuous sports	2018	ukb-b-7663	European	460,376	412,908	47,468
Other exercises	2018	ukb-b-8764	European	460,376	237,906	222,470
Body mass index	2021	ebi-a-GCST90018947	European	359,983	/	/
Pneumothorax	2021	ebi-a-GCST90018902	European	477,734	475,987	1,747
Spontaneous pneumothorax	2018	ukb-b-3693	European	462,933	461,836	1,097

causality, we also performed a bidirectional MR analysis [58] with pneumothorax (including spontaneous pneumothorax) as the exposure variable and light DIY or FI as the outcome. This reverse MR used the same workflow as the forward MR analysis and was designed to test for potential reverse causality. High BMI is associated with chronic diseases such as cardiovascular disease, diabetes, and certain cancers, and studies have shown that people with lower BMI may be at increased risk for spontaneous pneumothorax due to less chest wall fat and increased mechanical stress on lung tissue [59]. Moreover, BMI is a shared risk factor for pneumothorax, physical activity, and frailty. Here, BMI was used as a confounder or mediator variable in MVMR analyses to distinguish the independent effects of physical activity and debility on pneumothorax. The MVMR analysis adhered to the same IV selection criteria, with *F*-statistics of 10.3, 26.5, and 30.3 for BMI, light DIY, and FI respectively.

Sensitivity analysis

To ensure the reliability and robustness of our results, we performed sensitivity analyses including heterogeneity tests using Cochran's Q, horizontal pleiotropy assessment with MR-Egger regression, and leave-one-out analysis [49, 51, 60]. Random-effects IVW models were used when heterogeneity was significant ($p < 0.05$); otherwise, fixed-effects models were applied. A significant MR-Egger intercept ($p < 0.05$) indicated directional pleiotropy [52]. MR-PRESSO was used to detect and correct for outlying SNPs. Leave-one-out analysis was used to check whether any individual SNPs had a disproportionate effect on the results.

Statistical analysis

Analyses were conducted using R software (version 4.3.1) with the "TwoSampleMR" (version 0.6.8) and "MR-PRESSO" (version 1.0) packages. Statistical significance was set at $p < 0.05$.

Results

Causal association between physical activity and pneumothorax

We selected SNPs closely associated with four different intensities of physical activity through conditional filtering and conducted MR analyses to investigate the potential causal relationship between physical activity and pneumothorax. The MR analyses primarily relied on the IVW method. Results from supplementary analyses are presented in Supplementary Table SII. As shown in Figure 2 A, the results indicated a significant causal relationship between light DIY and pneumothorax (IVW: odds ratio (OR) = 0.2527, 95% CI: 0.0655–0.9745, $p = 0.0458$). No causal associations were observed between any physical activity and spontaneous pneumothorax (Figure 2 B). Our findings suggest that higher light DIY was associated with a lower risk of pneumothorax, serving as a protective factor.

Causal association between frailty and pneumothorax

To explore whether frailty has a potential impact on the development of pneumothorax, we selected the FI and FP as exposures for MR analysis. The primary results of the MR analysis were derived from the IVW method, with additional results presented in Supplementary Table SII. Our findings indicated that although no causal relationship was observed between frailty and pneumothorax (Figure 3 A), there was a significant causal relationship between the FI and spontaneous pneumothorax, suggesting that the FI may be a risk factor for spontaneous pneumothorax (IVW: OR = 1.0035, 95% CI: 1.0005–1.0066, $p = 0.0233$, Figure 3 B).

Results of inverse Mendelian randomization analysis

To investigate whether there are reverse causal effects between physical activity, frailty, and pneumothorax, we conducted reverse MR analyses on the positive findings obtained earlier. In these analyses, pneumothorax and spontaneous pneumothorax were used as exposures, while light DIY and the FI were used as outcomes. The results showed that a weak inverse association between light DIY and pneumothorax, with an effect size very close to no effect (IVW: OR = 0.9951, 95% CI: 0.9912–0.9989, $p = 0.0124$, Figure 4), but no reverse causal relationship was observed between the FI and spontaneous pneumothorax.

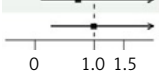
This suggests that a higher genetic liability to pneumothorax was associated with lower light DIY.

Results of multivariate Mendelian randomization analyses

To further investigate whether physical activity and frailty influence the development of pneumothorax after adjusting for BMI, physical activity or frailty, we conducted a MVMR analysis. The IVW results showed that light DIY, which originally had a causal effect on pneumothorax, no longer had a causal effect after adjusting for BMI and the FI (Figure 5 A). This suggests that BMI may play a mediating or confounding role in the association between light DIY and pneumothorax. However, after adjusting for BMI and light DIY activity, the FI still had a causal effect on spontaneous pneumo-

A

Exposure	Method	nSNP	*P*-value	OR (95% CI)	Outcome
Light DIY	MR Egger	75	0.0603	0.0054 (0.0000–1.1525)	pneumothorax
Light DIY	Weighted median	75	0.1704	0.2641 (0.0394–1.7722)	pneumothorax
Light DIY	IVW	75	0.0458	0.2527 (0.0655–0.9745)	pneumothorax
Heavy DIY	MR Egger	76	0.4139	0.1283 (0.0010–17.1952)	pneumothorax
Heavy DIY	Weighted median	76	0.6466	0.6382 (0.0936–4.3529)	pneumothorax
Heavy DIY	IVW	76	0.3774	0.5544 (0.1496–2.0544)	pneumothorax
Strenuous sports	MR Egger	39	0.1367	0.0002 (0.0000–10.9487)	pneumothorax
Strenuous sports	Weighted median	39	0.4970	0.2157 (0.0026–18.0288)	pneumothorax
Strenuous sports	IVW	39	0.3390	0.2189 (0.0097–4.9276)	pneumothorax
Other exercises	MR Egger	82	0.1381	101.4807 (0.2403–42857.0235)	pneumothorax
Other exercises	Weighted median	82	0.7455	0.7271 (0.1061–4.9813)	pneumothorax
Other exercises	IVW	82	0.9907	0.9924 (0.2747–3.5857)	pneumothorax



B

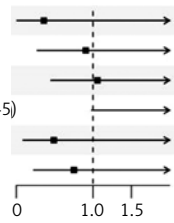
Exposure	Method	nSNP	*P*-value	OR (95% CI)	Outcome
Light DIY	MR Egger	30	0.4257	0.9628 (0.8783–1.0555)	spontaneous pneumothorax
Light DIY	Weighted median	30	0.2657	0.9944 (0.9846–1.0043)	spontaneous pneumothorax
Light DIY	IVW	30	0.1817	0.9953 (0.9884–1.0022)	spontaneous pneumothorax
Heavy DIY	MR Egger	25	0.1015	0.9298 (0.8553–1.0109)	spontaneous pneumothorax
Heavy DIY	Weighted median	25	0.3911	1.0047 (0.9940–1.0156)	spontaneous pneumothorax
Heavy DIY	IVW	25	0.4294	1.0031 (0.9954–1.0109)	spontaneous pneumothorax
Strenuous sports	MR Egger	16	0.2061	0.9137 (0.7997–1.0441)	spontaneous pneumothorax
Strenuous sports	Weighted median	16	0.6333	0.9946 (0.9728–1.0169)	spontaneous pneumothorax
Strenuous sports	IVW	16	0.9254	0.9993 (0.9839–1.0149)	spontaneous pneumothorax
Other exercises	MR Egger	31	0.9802	0.9989 (0.9185–1.0864)	spontaneous pneumothorax
Other exercises	Weighted median	31	0.7569	0.9984 (0.9885–1.0085)	spontaneous pneumothorax
Other exercises	IVW	31	0.9907	0.9984 (0.9917–1.0052)	spontaneous pneumothorax

Figure 2. Causal relationships between physical activity and the risk of pneumothorax and spontaneous pneumothorax. **A** – MR analysis of physical activity and pneumothorax. **B** – MR analysis of physical activity and spontaneous pneumothorax. Four different intensities of physical activity were used as exposure factors, with pneumothorax/spontaneous pneumothorax as the outcome. The inverse variance weighted (IVW) results were used as the primary reference, with $p < 0.05$ indicating statistically significant causal relationships

OR – odds ratio, per genetically predicted 1 standard deviation increase in exposure.

A

Exposure	Method	nSNP	*P*-value	OR (95%C1)	Outcome
FI	MR Egger	11	0.5934	0.3604 (0.0097–13.3754)	pneumothorax
FI	Weighted median	11	0.8733	0.9070 (0.2733–3.0107)	pneumothorax
FI	IVW	11	0.8966	1.0579 (0.4526–2.4727)	pneumothorax
FP	MR Egger	21	0.0655	633.9136 (0.9831–408736.7245)	pneumothorax
FP	Weighted median	21	0.4112	0.4910 (0.0900–2.6784)	pneumothorax
FP	IVW	21	0.6412	0.7520 (0.2267–2.4937)	pneumothorax



B

Exposure	Method	nSNP	*P*-value	OR (95% CI)	Outcome
FI	MR Egger	9	0.4818	0.9950 (0.9821–1.0082)	spontaneous pneumothorax
FI	Weighted median	9	0.3778	1.0019 (0.9977–1.0060)	spontaneous pneumothorax
FI	IVW	9	0.0233	1.0035 (1.0005–1.0066)	spontaneous pneumothorax
FP	MR Egger	10	0.8202	0.9935 (0.9413–1.0487)	spontaneous pneumothorax
FP	Weighted median	10	0.9019	0.9996 (0.9928–1.0064)	spontaneous pneumothorax
FP	IVW	10	0.7879	1.0008 (0.9951–1.0065)	spontaneous pneumothorax

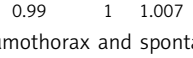


Figure 3. Causal relationships between frailty and the risk of pneumothorax and spontaneous pneumothorax. **A** – MR analysis of frailty and pneumothorax. **B** – MR analysis of frailty and spontaneous pneumothorax. Two frailty assessment metrics, FI and FP, were used as exposure factors, with pneumothorax/spontaneous pneumothorax as the outcome. The IVW results were used as the primary reference, with $p < 0.05$ indicating statistically significant causal relationships

FI – Frailty Index, FP – frailty phenotype, OR – odds ratio, per genetically predicted 1 standard deviation increase in exposure.

Exposure	Method	nSNP	*P*-value	OR (95%CI)	Outcome
pneumothorax	IVW	13	0.0124	0.9951 (0.9912–0.9989)	Light DIY
spontaneous pneumothorax	IVW	2	0.8575	0.4121 (0.0000–6590.4282)	FI

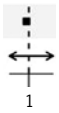
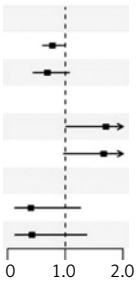


Figure 4. Results of reverse MR analyses for physical activity and frailty with pneumothorax. Pneumothorax and spontaneous pneumothorax were used as exposure factors, while light DIY and FI were used as outcomes. The IVW results were used as the primary reference, with $p < 0.05$ indicating statistically significant causal relationships

FI – Frailty Index, OR – odds ratio, per genetically predicted 1 standard deviation increase in exposure.

A

Exposure	Method	nSNP	*P*-value	OR (95% CI)	Outcome
Adjusted light DIY and FI					
Body mass index	IVW	318	0.0461	0.7793 (0.6099–0.9957)	pneumothorax
	MR Egger	318	0.0940	0.6894 (0.4461–1.0652)	Pneumothorax
Adjusted BMI and light DIY					
Frailty index	IVW	11	0.0442	1.7055 (1.0139–2.8689)	pneumothorax
	MR Egger	11	0.0610	1.6636 (0.9762–2.8352)	pneumothorax
Adjusted BMI and FI					
Light DIY	IVW	8	0.1181	0.4015 (0.1278–1.2611)	pneumothorax
	MR Egger	8	0.1510	0.4240 (0.1313–1.3690)	pneumothorax



B

Exposure	Method	nSNP	*P*-value	OR (95% CI)	Outcome
Adjusted light DIY and FI					
Body mass index	IVW	161	0.0006	0.9980 (0.9969–0.9992)	spontaneous pneumothorax
	MR Egger	161	0.4260	0.9990 (0.9970–1.0010)	spontaneous pneumothorax
Adjusted BMI and light DIY					
FI	IVW	9	0.0011	1.0044 (1.0022–1.0066)	spontaneous pneumothorax
	MR Egger	9	0.0000	1.0050 (1.0030–1.0070)	spontaneous pneumothorax
Adjusted BMI and FI					
Light DIY	IVW	4	0.0028	0.9987 (0.9931–1.0042)	spontaneous pneumothorax
	MR Egger	4	0.4950	0.9980 (0.9922–1.0039)	spontaneous pneumothorax

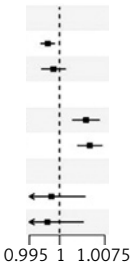


Figure 5. Results of MVMR analyses for physical activity and frailty with pneumothorax. **A** – MVMR analysis of physical activity and frailty with pneumothorax. **B** – MVMR analysis of physical activity and frailty with spontaneous pneumothorax. BMI, FI, and light DIY were used as exposure factors, with pneumothorax/spontaneous pneumothorax as the outcome. The IVW results were used as the primary reference, with $p < 0.05$ indicating statistically significant causal relationships

BMI – body mass index, FI – Frailty Index, OR – odds ratio, per genetically predicted 1 standard deviation increase in exposure.

thorax (IVW: OR = 1.0044, 95% CI: 1.0022–1.0066, $p = 0.0011$, Figure 5 B).

Sensitivity analysis results

To enhance the robustness and reliability of our findings, we employed multiple sensitivity analyses, including Cochran's Q tests, MR-Egger intercept tests, and MR-PRESSO global tests. For most exposures, the Cochran's Q test for heterogeneity yielded *p*-values greater than 0.05, indicating no significant heterogeneity observed. Although heterogeneity was detected in some results, it did not invalidate the MR estimates in this study, as the random-effects IVW model could balance the aggregated heterogeneity. Horizontal pleiotropy occurs when genetic variants related to the exposures of interest directly affect the outcomes through multiple pathways beyond the hypothesized exposure. Therefore, we further used MR-Egger intercept tests and MR-PRESSO global tests to detect pleiotropy and assess the robustness of our results. The results showed *p*-values greater than 0.05, indicating no significant pleiotropy observed. Detailed results are presented in Tables II, III, and Supplementary Table SIII. Additionally, the results of reverse MR analyses and MVMR analyses are provided in Supplementary Table SIII. Leave-one-out analyses, forest plot, scatter plots, and funnel plots further validated the stability of our findings (Supplementary Figures S1–S3). Overall, the sensitivity analyses ensured the robustness and reliability of our results.

Discussion

Pneumothorax remains a significant global health challenge, with treatment strategies ranging from conservative management to surgical interventions depending on disease severity and

Table II. Sensitivity analysis of the causal relationship between physical activity and pneumothorax or spontaneous pneumothorax

Exposure	Outcome	Heterogeneity				Pleiotropy		
		MR Egger		Inverse variance weighted		MR Egger intercept	*P*-value	MR-PRESSO Global
		Statistics Q	*P*-value	Statistics Q	*P*-value			*P*-value
Light DIY	pneumothorax	73.105	0.475	75.216	0.439	0.024	0.151	0.443
Heavy DIY	pneumothorax	78.65	0.334	79.05	0.352	0.009	0.544	0.377
Strenuous sports	pneumothorax	32.397	0.685	34.084	0.651	0.027	0.202	0.693
Other exercises	pneumothorax	89.660	0.216	92.317	0.183	-0.029	0.128	0.173
Light DIY	spontaneous pneumothorax	21.998	0.781	22.503	0.799	0.0002	0.484	0.773
Heavy DIY	spontaneous pneumothorax	12.117	0.969	15.311	0.911	0.0004	0.087	0.928
Strenuous sports	spontaneous pneumothorax	11.121	0.676	12.874	0.612	0.0003	0.207	0.617
Other exercises	spontaneous pneumothorax	43.498	0.041	43.498	0.053	-2.9e-6	0.990	0.056

Table III. Sensitivity analysis of the causal relationship between frailty and pneumothorax or spontaneous pneumothorax

Exposure	Outcome	Heterogeneity				Pleiotropy		
		MR Egger		Inverse variance weighted		MR Egger intercept	*P*-value	MR-PRESSO Global
		Statistics Q	*P*-value	Statistics Q	*P*-value			*P*-value
Frailty index	pneumothorax	9.924	0.357	10.324	0.413	0.025	0.562	0.435
Frailty phenotype	pneumothorax	16.699	0.610	21.014	0.396	–0.083	0.052	0.353
Frailty index	spontaneous pneumothorax	8.885	0.261	11.092	0.196	0.0002	0.229	0.056
Frailty phenotype	spontaneous pneumothorax	1.624	0.990	1.694	0.995	8.4e-5	0.798	0.994

clinical presentation [61–63]. Despite advances in minimally invasive surgical techniques, the complex etiology and high recurrence rate of pneumothorax highlight the need to better understand modifiable risk factors to improve prevention [64, 65]. There have been no large-scale observational or MR studies directly linking physical activity and frailty to pneumothorax in previous studies. However, observational studies have shown that physical activity is strongly associated with lung function[66]. The positive effects of physical activity on lung function have been demonstrated in a variety of respiratory diseases[67–69]. In addition, a part of the literature has highlighted the negative association between frailty and lung diseases and their complications[70, 71]. Our study found a causal association between light DIY and frailty with pneumothorax, suggesting that frailty may be an important risk factor for the development of pneumothorax. In particular, light DIY had an inverse causal association with pneumothorax, but this inverse association was very weak, suggesting that the inverse association may be influenced by shared pleiotropy or confounding factors (e.g., BMI). Further MVMR analyses showed that the independent effect of light DIY on pneumothorax disappeared after adjusting for BMI, suggesting that BMI may play a mediating or confounding role in the association between physical activity and pneumothorax. In contrast, the effect of FI on pneumothorax remained significant after adjustment, supporting its independent causal role. These findings contribute to a more accurate understanding of the mechanisms of physical activity and frailty in the development of pneumothorax.

Our study found that light DIY activities, such as pruning and watering lawns, may be potential-

ly protective against pneumothorax. Light DIY is defined as a type of low-intensity physical activity over the past four weeks. The impact of physical activity on pneumothorax may be related to changes in lung pressure during exercise [72, 73]. Regular physical activity can improve lung ventilation and gas exchange efficiency, and enhance alveolar stability, reducing the fragility of alveoli, thereby reducing the likelihood of pneumothorax [74, 75]. In addition, regular physical activity helps to improve systemic blood circulation, enhance oxygen supply, maintain lung tissue health, and reduce lung injury triggered by hypoxia [75]. Some studies suggest that insufficient physical activity may lead to decreased lung function, thereby increasing the risk of pneumothorax [76]. Of note, our analyses showed that not all types of physical activity had a significant effect on pneumothorax risk. With the exception of light DIY activities, other intensities of physical activity did not show significant causal associations. This result may partly stem from the nature of light DIY activities, which are typically low-impact, moderate exercises that improve lung ventilation and respiratory muscle function without exerting excessive mechanical stress on lung tissue. In contrast, high-intensity activities may cause rapid changes in intrathoracic pressure and increase the risk of alveolar rupture, which may explain the lack of protective effects seen with activities of other intensity levels. In addition, sample size differences in physical activity intensity and variable definitions may affect the efficacy of statistical tests. Some studies have also pointed out that the higher incidence of pneumothorax after strenuous or high-intensity physical activity may be due to increased mechanical stress on the lungs [77–82]. In conclusion, moderate physical activity has a potential protective effect against pneumothorax.

In addition, our study identified that frailty is an independent risk factor for the development of pneumothorax. This causal relationship remained significant even after adjusting for BMI and light DIY activity, suggesting the importance of frailty in pneumothorax risk assessment. The frailty syndrome is characterized by muscle weakness, weight loss, and reduced mobility, which not only reflects the deterioration of the patient's overall health, but also increases his or her susceptibility to lung disease [83]. From the point of view of physiological mechanisms, the impact of frailty on the risk of pneumothorax may be realized mainly through pulmonary dysfunction [84, 85]. Frail patients are often associated with fragility of alveolar structures and reduced respiratory muscle function, which makes lung tissue more susceptible to injury and rupture in response to mechanical stress or inflammatory states, which in turn induces pneumothorax [86]. In addition, frailty often coexists with chronic respiratory diseases such as COPD, further weakening the integrity of lung tissue and respiratory function through airway inflammation, airway remodeling and alveolar destruction, which superimposed on each other significantly increases the vulnerability of the lungs and the likelihood of pneumothorax occurrence [87–94]. In summary, frailty not only exists as an independent risk factor, but it contributes to the occurrence of pneumothorax by affecting lung tissue structure and respiratory muscle function, as well as interacting with chronic lung diseases. In future clinical management, emphasis should be placed on the identification and intervention of frailty status to reduce the incidence of pneumothorax.

Our findings reinforce the importance of tailored interventions promoting appropriate physical activity to strengthen pulmonary health, especially among frail and elderly populations. However, several limitations warrant consideration. Firstly, our study focused on individuals of European origin and there were some limitations in the sample size, which limits the generalisability of the study; future studies should include larger sample sizes and more diverse populations. Second, some potential residual confounders, such as smoking and other incompletely controlled confounders, may affect the accuracy of causal inferences. In addition, the *p*-values reported in this study were not corrected for multiple testing. For example, the association between light DIY physical activity and pneumothorax ($p = 0.0458$) was borderline significant and no longer statistically significant after Bonferroni multiple correction, suggesting a risk of false positives for this result, which needs to be further validated in larger samples and independent cohorts. Finally, while we provide evidence for causal links between physical activity, frailty, and pneumothorax, mechanistic pathways remain to be elucidated. In conclusion, this study highlights the dual roles of physical activity and frailty in pneumothorax risk, providing a foundation for developing preventive and therapeutic strategies aimed at improving patient outcomes.

Our results highlight the crucial roles of physical activity and frailty in pneumothorax risk. These findings highlight the importance of targeted prevention strategies for at-risk populations and provide a basis for future pneumothorax management. Future research should validate these results in diverse populations and explore the protective effects of physical activity through intervention studies.

Funding

This work was partially supported by Jinhua Science and Technology Plan Public Welfare Project

(No. 2022-4-10) and Provincial Medical and Health Science and Technology Plan Project Achievement Promotion Project (No. 2022ZH063).

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Imran JB, Eastman AL. Pneumothorax. JAMA 2017; 318: 974.
2. Tran J, Haussner W, Shah K. Traumatic pneumothorax: a review of current diagnostic practices and evolving management. J Emerg Med 2012; 61: 517-28.
3. Bobbio A, Dechartres A, Bouam S, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. Thorax 2015; 70: 653-8.
4. Roberts ME, Rahman NM, Maskell NA, et al. British Thoracic Society Guideline for pleural disease. Thorax 2023; 78: 1143-56.
5. Gottlieb M, Long B. Managing spontaneous pneumothorax. Ann Emerg Med 2023; 81: 568-576.
6. Slade M. Management of pneumothorax and prolonged air leak. Semin Respir Crit Care Med 2014; 35: 706-14.
7. Wolf SJ, Bebarta VS, Bonnett CJ, Pons PT, Cantrill SV. Blast injuries. Lancet 2009; 374: 405-415.
8. Reuter M. Trauma of the chest. Eur Radiol 1996; 6: 707-16.
9. Lewis FR Jr., Blaisdell FW, Schlobohm RM. Incidence and outcome of posttraumatic respiratory failure. Arch Surg 1977; 112: 436-43.
10. Bintcliffe O, Maskell N. Spontaneous pneumothorax. BMJ 2014; 348: g2928.
11. Mitani A, Hakamata Y, Hosoi M, et al. The incidence and risk factors of asymptomatic primary spontaneous pneumothorax detected during health check-ups. BMC Pulm Med 2017; 17: 177.
12. Hiyama N, Sasabuchi Y, Jo T, et al. The three peaks in age distribution of females with pneumothorax: a nationwide database study in Japan. Eur J Cardiothorac Surg 2018; 54: 572-8.
13. Huang YH, Chang PY, Wong KS, Chang CJ, Lai JY, Chen JC. An age-stratified longitudinal study of primary spontaneous pneumothorax. J Adolesc Health 2017; 61: 527-32.
14. Ayed AK, Bazerbashi S, Ben-Nakhi M, et al. Risk factors of spontaneous pneumothorax in Kuwait. Med Princ Pract 2006; 15: 338-42.
15. Han S, Sakinci U, Kose SK, Yazkan R. The relationship between aluminum and spontaneous pneumothorax; treatment, prognosis, follow-up? Interact Cardiovasc Thorac Surg 2004; 3: 79-82.
16. Akkas Y, Peri NG, Kocer B, Kaplan T, Alhan A. A novel structural risk index for primary spontaneous pneumothorax: Ankara Numune Risk Index. Asian J Surg 2017; 40: 249-53.
17. WHO Guidelines Approved by the Guidelines Review Committee. Pacific Physical Activity Guidelines for Adults: Framework for Accelerating the Communication of Physical Activity Guidelines. World Health Organization. Copyright © 2008, World Health Organization, Geneva 2008.
18. Ishikawa-Takata K, Tabata I. Exercise and physical activity reference for health promotion 2006 (EPAR2006). J Epidemiol 2007; 17: 177.
19. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health 2018; 6: e1077-86.
20. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012; 380: 219-29.
21. Vasankari V, Husu P, Vähä-Ypyä H, et al. Association of objectively measured sedentary behaviour and physical activity with cardiovascular disease risk. Eur J Prev Cardiol 2017; 24: 1311-8.
22. Smith AD, Crippa A, Woodcock J, Brage S. Physical activity and incident type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of prospective cohort studies. Diabetologia 2016; 59: 2527-45.
23. Rezende LFM, Sá TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. Br J Sports Med 2018; 52: 826-33.
24. Celis-Morales CA, Lyall DM, Anderson J, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. Eur Heart J 2017; 38: 116-22.
25. Criner GJ, Sue R, Wright S, et al. A Multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med 2018; 198: 1151-64.
26. Finn R, Sheil C, Morris J, Molloy MS. Spontaneous prevertebral emphysema following weight training in a 21-year-old female. Emerg Radiol 2022; 29: 1059-61.
27. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Ann Epidemiol 2015; 25: 406-413.e6.
28. Mesquita R, Gonçalves CG, Hayashi D, et al. Smoking status and its relationship with exercise capacity, physical activity in daily life and quality of life in physically independent, elderly individuals. Physiotherapy 2015; 101: 55-61.
29. Tart CD, Leyro TM, Richter A, Zvolensky MJ, Rosenfield D, Smits JA. Negative affect as a mediator of the relationship between vigorous-intensity exercise and smoking. Addict Behav 2010; 35: 580-5.
30. Furlanetto KC, Mantoani LC, Bisca G, et al. Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. Respirology 2014; 19: 369-75.
31. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 81: 752-62.
32. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-56.
33. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc 2010; 58: 681-7.
34. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012; 60: 1487-92.
35. Vaz Fragoso CA, Enright PL, McAvay G, Van Ness PH, Gillm TM. Frailty and respiratory impairment in older persons. Am J Med 2012; 125: 79-86.

36. Aceto P, Perilli V, Luca E, et al. Predictive power of modified frailty index score for pulmonary complications after major abdominal surgery in the elderly: a single centre prospective cohort study. Eur Rev Med Pharmacol Sci 2021; 25: 3798-802.
37. Osadnik CR, Brighton LJ, Burtin C, et al. European Respiratory Society statement on frailty in adults with chronic lung disease. Eur Respir J 2023; 62: 2300442.
38. Guo D, Huang K, Guan X, et al. Association between chronic respiratory diseases and frailty in Chinese elderly: a population-based longitudinal study. BMJ Open Respir Res 2025; 12: e002171.
39. Chang PY, Wong KS, Lai JY, et al. Rapid increase in the height and width of the upper chest in adolescents with primary spontaneous pneumothorax. Pediatr Neonatol 2015; 56: 53-7.
40. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018; 362: k601.
41. Birney E. Mendelian randomization. Cold Spring Harb Perspect Med 2022; 12: a041302.
42. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol 2013; 178: 1177-84.
43. Collins R. What makes UK Biobank special? Lancet 2021; 379: 1173-4.
44. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001; 1: 323-36.
45. Atkins JL, Jylhävä J, Pedersen NL, et al. A genome-wide association study of the frailty index highlights brain pathways in ageing. Aging Cell 2021; 20: e13459.
46. Ye Y, Noche RB, Szejko N, et al. A genome-wide association study of frailty identifies significant genetic correlation with neuropsychiatric, cardiovascular, and inflammation pathways, Geroscience 2023; 45: 2511-23.
47. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 2021; 53: 1415-24.
48. Rusk N. The UK Biobank. Nat Methods 2018; 15: 1001.
49. Jiang YJ, Xiong YQ, Huang T, Xiao YX. Toenail and blood selenium mediated regulation of thyroid dysfunction through immune cells: a mediation Mendelian randomization analysis. Front Nutr 2024; 11: 1378969.
50. Lin SH, Brown DW, Machiela MJ. LDtrait: an online tool for identifying published phenotype associations in linkage disequilibrium. Cancer Res 2020; 80: 3443-6.
51. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018; 7: e34408.
52. [52] B.L. Pierce, H. Ahsan, T.J. Vanderweele, Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants, Int J Epidemiol 40(3) (2011) 740-52.
53. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2025; 44: 512-25.
54. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013; 37: 658-65.
55. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016; 40: 304-14.
56. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 2017; 46: 1985-98.
57. Borges MC, Haycock PC, Zheng J, et al. Role of circulating polyunsaturated fatty acids on cardiovascular diseases risk: analysis using Mendelian randomization and fatty acid genetic association data from over 114,000 UK Biobank participants. BMC Med 2022; 20: 210.
58. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet 2014; 23 (R1): R89-98.
59. Tan J, Yang Y, Zhong J, et al. Association between BMI and recurrence of primary spontaneous pneumothorax. World J Surg 2017; 41: 1274-80.
60. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018; 50: 693-8.
61. Huan NC, Sidhu C, Thomas R. Pneumothorax: classification and etiology. Clin Chest Med 2021; 42: 711-27.
62. Tschopp JM, Bintcliffe O, Astoul P, et al. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. Eur Respir J 2015; 46: 321-35.
63. Brims FJ, Maskell NA. Ambulatory treatment in the management of pneumothorax: a systematic review of the literature. Thorax 2013; 68: 664-9.
64. Baumann MH, Noppen M. Pneumothorax. Respirology 2004; 9: 157-64.
65. Chen Y, Chen H, Xu F, Sun B, You J. [Port-only 4-Arms Robotic Segmentectomy Under Artificial Pneumothorax]. Zhongguo Fei Ai Za Zhi 2022; 25: 797-802.
66. Roda C, Mahmoud O, Peralta GP, et al. Physical-activity trajectories during childhood and lung function at 15 years: findings from the ALSPAC cohort. Int J Epidemiol 2020; 49: 131-41.
67. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006; 61: 772-8.
68. Eichenberger PA, Diener SN, Kofmehl R, Spengler CM. Effects of exercise training on airway hyperreactivity in asthma: a systematic review and meta-analysis. Sports Med 2013; 43: 1157-70.
69. Xiong T, Bai X, Wei X, et al. Exercise rehabilitation and chronic respiratory diseases: effects, mechanisms, and therapeutic benefits. Int J Chron Obstruct Pulmon Dis 2023; 18: 1251-66.
70. Landré B, Nadif R, Goldberg M, et al. Asthma is associated with frailty among community-dwelling adults: the GAZEL cohort. BMJ Open Respir Res 2020; 7: e000526.
71. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health 2018; 3: e323-32.
72. Gonzalez A, Mares AV, Espinoza DR. Common pulmonary conditions in sport. Clin Sports Med 2019; 38: 563-75.
73. Huang H, Peng X, Zhang H, Li W, Wang C. A retrospective case-control study on the chest wall and lung characteristics in patients with primary spontaneous pneumothorax. Med Sci Monit 2019; 25: 8482-91.
74. Collaud S, Touilloux B, von Garnier C, Marques-Vidal P, Kraege V. Physical activity and lung function association in a healthy community-dwelling European population. BMC Pulm Med 2024; 24: 169.

75. Roman MA, Rossiter HB, Casaburi R. Exercise, ageing and the lung. Eur Respir J 2016; 48: 1471-86.
76. Li LK, Cassim R, Perret JL, et al. The longitudinal association between physical activity, strength and fitness, and lung function: a UK Biobank cohort study. Respir Med 2023; 220: 107476.
77. Loung RP, Cooney M, Fallon EM, Langer JC, Katzman DK. Pneumothorax in a young man with anorexia nervosa. Int J Eat Disord 2016; 49: 895-8.
78. Franklin BA, Eijsvogels TMH, Pandey A, Quindry J, Toth PP. Physical activity, cardiorespiratory fitness, and cardiovascular health: A clinical practice statement of the ASPC Part I: Bioenergetics, contemporary physical activity recommendations, benefits, risks, extreme exercise regimens, potential maladaptations. Am J Prev Cardiol 2022; 12: 100424.
79. Michaels C. The importance of exercise in lung cancer treatment. Transl Lung Cancer Res 2016; 5: 235-8.
80. Chekroud SR, Gueorguieva R, Zheutlin AB, et al. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. Lancet Psychiatry 2018; 5: 739-46.
81. Schnohr P, Kristensen TS, Prescott E, Scharling H. Stress and life dissatisfaction are inversely associated with jogging and other types of physical activity in leisure time –The Copenhagen City Heart Study. Scand J Med Sci Sports 2005; 15: 107-12.
82. Filipowski M, Bozek A, Kozlowska R, Czyżewski D, Jarzab J. The influence of hospitalizations due to exacerbations or spontaneous pneumothoraxes on the quality of life, mental function and symptoms of depression and anxiety in patients with COPD or asthma. J Asthma 2014; 51: 294-8.
83. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019; 394: 1365-75.
84. Eckel SP, Louis TA, Chaves PH, Fried LP, Margolis AH. Modification of the association between ambient air pollution and lung function by frailty status among older adults in the Cardiovascular Health Study. Am J Epidemiol 2012; 176: 214-23.
85. Yang X, Cheng C, Ma W, Jia C. Longitudinal association of lung function with frailty among older adults: the English Longitudinal Study of Ageing. Eur Geriatr Med 2023; 14: 173-80.
86. Vidal MB, Pegorari MS, Santos EC, Matos AP, Pinto A, Ohara DG. Respiratory muscle strength for discriminating frailty in community-dwelling elderly: a cross-sectional study. Arch Gerontol Geriatr 2020; 89: 104082.
87. Norman K, Haß U, Pirlich M. Malnutrition in older adults-recent advances and remaining challenges. Nutrients 2021; 13: 2764.
88. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. Aging Clin Exp Res 2017; 29: 43-8.
89. Ligthart-Melis GC, Luiking YC, Kakourou A, Cederholm T, Maier AB, de van der Schueren MAE. Frailty, sarcopenia, and malnutrition frequently (co-)occur in hospitalized older adults: a systematic review and meta-analysis. J Am Med Dir Assoc 2020; 21: 1216-28.
90. Verduri A, Carter B, Rice C, et al. Frailty prevalence and association with clinical outcomes in interstitial lung disease, asthma, and pleural disease. Geriatrics (Basel) 2023; 8: 82.
91. Wijnant SRA, Benz E, Luik AI, et al. Frailty transitions in older persons with lung function impairment: a population-based study. J Gerontol A Biol Sci Med Sci 2023; 78: 349-56.
92. Weng SC, Hsu CY, Wu MF, Lee WH, Lin SY. The impact of frailty status on pulmonary function and mortality in older patients with chronic obstructive pulmonary disease. J Nutr Health Aging 2023; 27: 987-95.
93. Marzetti E, Calvani R, Tosato M, et al. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging Clin Exp Res 2017; 29: 35-42.
94. Gu X, Shen X, Chu JH, Fang TT, Jiang L. Frailty, illness perception and lung functional exercise adherence in lung cancer patients after thoracoscopic surgery. Patient Prefer Adherence 2023; 17: 2773-87.