

Review

Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease Patients With Underlying Alpha-1 Antitrypsin Deficiency: A Systematic Review and Practical Recommendations

Fawaz A. Alwadani, MSc^{1,2} Kyrie Wheeler, BMBS, MSc³ Harriet Pittaway, MBBS⁴ Alice M. Turner, MBChB, PhD¹

Abstract

Background: Alpha-1 antitrypsin deficiency (AATD) is an often-overlooked genetic condition that makes individuals susceptible to early onset of chronic obstructive pulmonary disease (COPD). The established benefits of exercise-based pulmonary rehabilitation (PR) for usual COPD patients are unclear for those with underlying AATD, especially given potentially differing muscle adaptations to exercise. This review seeks to compare PR outcomes between AATD and usual COPD patients and to consolidate current knowledge on exercise intervention outcomes for the AATD population.

Methods: A thorough search of 4 databases (Ovid, Medline, CINAHL, CENTRAL) was conducted based on 3 search concepts: (1) alpha-1 antitrypsin deficiency, (2) pulmonary rehabilitation OR exercise, and (3) muscle morphology. A dual review process and quality assessment were independently implemented throughout all stages of the review.

Results: Four studies highlighted modest exercise capacity and quality of life in AATD patients undergoing PR. However, one study reported unique muscle and mitochondrial responses compared to usual COPD patients. Additionally, a moderate exercise session did not alter pro-inflammatory cytokine levels in AATD patients, despite higher levels of tumor necrosis factor- α levels in muscle biopsies compared to usual COPD patients.

Conclusions: The current literature base insufficiently addresses the efficacy of PR on AATD, with indications that exercise adaptation may deviate from that of usual COPD patients. Further research is needed to optimize PR, particularly in identifying the most suitable exercise intensity, and delivery setting, and addressing specific educational needs for individuals with AATD.

1. Institute for Applied Health Research, University of Birmingham, Birmingham, United Kingdom
2. Department of Physical Therapy, Jazan University, Jazan, Saudi Arabia
3. Heartlands Hospital, Birmingham, United Kingdom
4. Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom

Abbreviations:

%pred=percentage predicted; **6MWT**=6-minute walk test; **AATD**=alpha-1 antitrypsin deficiency; **AAT**=alpha-1 antitrypsin; **BMI**=body mass index; **CFR**=capillary to fibers ratio; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **CRP**=C-reactive protein; **CT**=computed tomography; **FEV₁**=forced expiratory volume in 1 second; **FVC**=forced vital capacity; **HRQoL**=health-related quality of life; **IL**=interleukin; **MCID**=minimal clinically important difference; **PaO₂**=partial pressure of arterial oxygen; **PaCO₂**=partial pressure of arterial carbon dioxide; **PCO₂**=partial pressure of carbon dioxide in arterial or venous blood; **PGC-1 α** =peroxisome proliferator-activated receptor gamma coactivator 1-alpha; **PFT**=pulmonary function test; **PR**=pulmonary rehabilitation; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **PWR**=peak work rate; **SF36**=short form health survey; **TFAM**=mitochondrial transcription factor; **TNF α** =tumor necrosis factor alpha

Funding Support:

N/A

Citation:

Alwadani FA, Wheeler K, Pittaway H, Turner AM. Pulmonary rehabilitation for chronic obstructive pulmonary disease patients with underlying alpha-1 antitrypsin deficiency: a systematic review and practical recommendations. *Chronic Obstr Pulm Dis*. 2024;11(1):121-132. doi: <https://doi.org/10.15326/jcopdf.2023.0434>

Publication Dates:

Date of Acceptance: October 3, 2023

Published Online Date: October 9, 2023

Address correspondence to:

Alice M. Turner, MBChB, PhD
Institute for Applied Health Research
University of Birmingham
Birmingham, United Kingdom B15 2TT
Phone: +44 (0)7825683519
Email: a.m.turner@bham.ac.uk

Keywords:

alpha-1 antitrypsin deficiency; AATD; chronic obstructive pulmonary disease; pulmonary rehabilitation; exercise therapy

This article has an online supplement**Introduction**

Alpha-1 antitrypsin deficiency (AATD) is an underdiagnosed genetic disorder characterized by low circulating alpha-1-antitrypsin (AAT) levels and specific disease-associated genotypes.^{1,2} AAT, a vital enzyme, shields lung elastic tissue from harmful neutrophil elastase, particularly during lung infections or inflammation. Insufficient AAT has been linked to the early onset of obstructive lung diseases like emphysema and chronic obstructive pulmonary disease (COPD).^{3,4} Studies reveal that COPD patients with AATD are, on average, 10 years younger and have a significantly shorter history of smoking compared to usual COPD patients.^{5,6}

Despite its rarity (about 1 in 2000 individuals of European descent), AATD is found in 2%–5% of usual COPD patients.^{3,4,7} These patients experience COPD symptoms, but often with greater dyspnea, rapid exercise-induced oxygen desaturation, and poorer lung function outcomes.^{5,8,9} These severe symptoms are linked to accelerated emphysematous changes in lung tissue as AATD progresses.¹⁰ Additionally, a high prevalence of liver disease is seen among AATD patients and is indicative of the hepatocytes' inability to release AAT into the serum.^{9,11,12}

Management strategies for these patients often involve regular COPD recommendations, including the use of inhalers, steroids, and antibiotics based on the severity of exacerbation and its underlying cause.¹³ In addition, select AATD patients receive intravenous infusion of AAT enzyme, commonly referred to as augmentation therapy, with some evidence that suggests a slower rate of emphysema progression on a computed tomography (CT) scan for those augmented with the deficient enzyme.^{13,14} However, evidence of its clinical efficacy in terms of reducing the number of exacerbations and improving quality of life has been limited.¹⁵

AATD patients with chronic lung conditions are also eligible candidates to participate in a pulmonary rehabilitation (PR) program, a multifaceted health care service that includes exercise therapy and educational sessions with each component serving a different purpose.^{16,17} The clinical effectiveness of PR, particularly its exercise component, in enhancing the functional capacity and quality of life of patients with lung diseases cannot be overlooked.¹⁸ However,

the integration and potential varying needs of AATD patients in PR programs, considering factors like age, disease stage, educational content, and exercise intensity, are less understood. Notably, one study underlined a difference in exercise response between usual COPD and those with underlying AATD, indicating that the latter group experienced less improvement in slow oxidative muscle fibers after a 3-week exercise intervention.¹⁹

This review has 2 principal objectives: (1) extensively assess PR effectiveness in managing COPD patients with AATD, focusing on exercise-related impacts on functionality and quality of life, and (2) compile existing evidence regarding exercise interventions for AATD patients.

Methods**Search Strategy**

We searched 4 databases - Ovid via Embase, Medline via Embase, CINAHL plus via EBSCO, Cochrane Central Register of Controlled Trials via Wiley - and clinicaltrials.gov for relevant studies from September 2022 to October 2022. The search combined MeSH terms related to "alpha-1 antitrypsin deficiency" AND "pulmonary rehabilitation" OR "exercise" and separately "alpha-1 antitrypsin deficiency" AND "muscle morphology". This was done in accordance with our registered protocol at PROSPERO, an international prospective register of systematic reviews (CRD42022367250). Supplementary materials (in the online supplement) provide more details on the search terms and syntaxes used.

Inclusion and Exclusion Criteria

The inclusion criteria for the studies included in the review covered prospective and retrospective trials of PR or other exercise-focused interventions for AATD COPD patients, and case series of over 10 AATD patients, due to the disease's rarity. The search focused on studies of exclusively AATD patients, defined by severe deficiency variant genotypes (SZ and ZZ) or AAT levels below the protective threshold of 0.57g/L. Comparators were AATD patients on usual care, or usual COPD patients on PR or exercise intervention. Primary outcomes were exercise capacity measures, such as the 6-minute walk test (6MWT), shuttle walking, and quality-of-life assessments. There were no limitations on study outcomes or publication language.

Data Extraction and Analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was implemented for the screening process. Studies identified were screened for their titles and abstracts using the Rayyan tool²⁰ by 2 independent

reviewers. Persistent disagreements were resolved through full-text reviews and consultation with a third reviewer. Study quality was assessed independently by the same reviewers using ROBINS-1 for quasi-experimental and retrospective cohort studies, and RoB2 for randomized clinical trials.²¹ For the quality assessment, a third reviewer was consulted for finalization. Data extraction was initially performed by the primary author and then reviewed and finalized by a second reviewer. Three studies that reported the primary outcome of interest (mean improvement in 6MWT) were pooled in a meta-analysis using a random-effects model.²² The effect size was determined by mean differences with 95% confidence intervals (CIs), considering a *P*-value <0.05 as statistically significant.

Results

Study Selection

Figure 1 shows the result of the screening process following the PRISMA model. Initially, we retrieved 1016 records from the 4 identified databases in addition to 2 other records for ongoing clinical trials from www.clinicaltrials.gov. Of these, 221 were duplicates and were, thus, removed at the beginning of the screening process. After screening the titles and abstracts, 768 records were excluded, while 29 records qualified for full text review. Full text articles were not available for 3 conference abstracts, and 2 ongoing clinical trials, and they were excluded after contacting the authors and confirming their unavailability for full text review. We were also unable to retrieve the full text of 3 other abstracts because they were relatively old, and they were not available on any accessible database. Of the 21 publications which were reviewed in full, only 5 articles were found to be eligible for inclusion, 4 pertaining to PR and one to a single exercise session intervention.

Pulmonary Rehabilitation as the Main Intervention for Alpha-1 Antitrypsin Deficiency Patients

Four studies were identified that explored the impact of PR on AATD patients. The first, a small quasi-experimental study based in Germany,¹⁹ involved 2 groups of 9 AATD patients and 10 usual COPD patients, matched by age and with comparable baseline characteristics, except for significantly higher partial pressure of arterial carbon dioxide (PaCO₂) levels of 43.8mmHg among the latter. Over 3 weeks of inpatient PR, both groups showed an upward trend in exercise capacity, as determined by the 6MWT and peak work rate (PWR). However, improvements in PWR were more pronounced in usual COPD patients (*p*<0.05). Interestingly, muscle morphology differed between groups. The usual COPD group exhibited a minor increase in type I muscle fiber with no observable change in the AATD group. Also, while type II muscle fibers decreased in the usual COPD

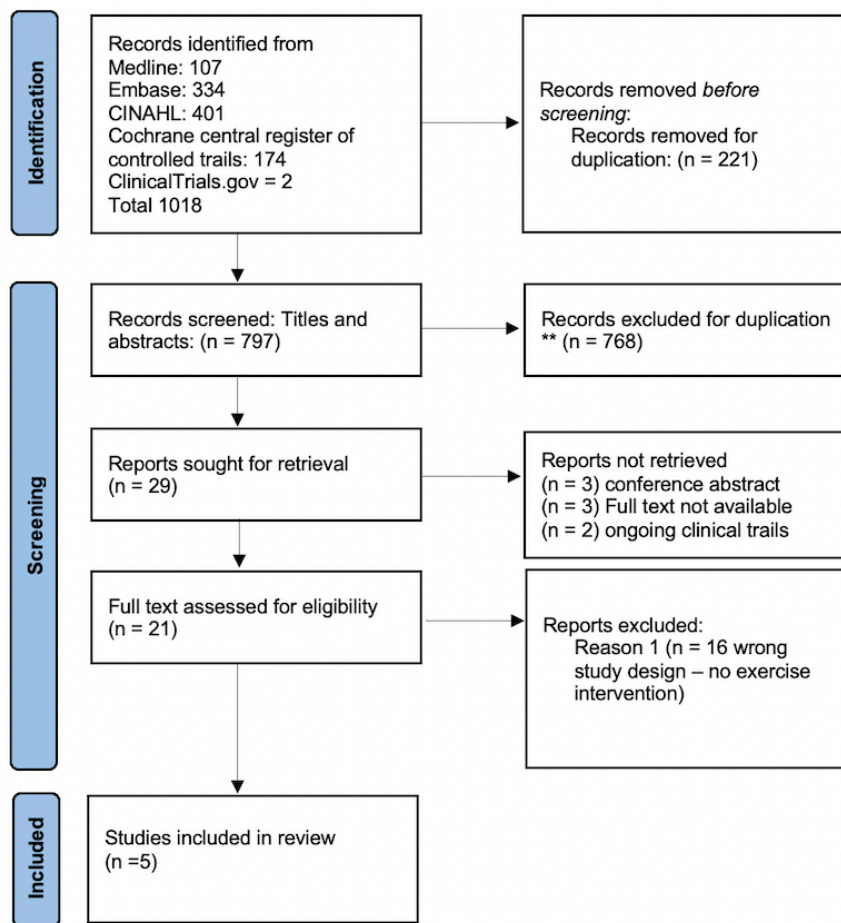
group, an opposite trend was observed in the AATD group. As for mitochondrial signaling, key markers peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) significantly increased in the usual COPD group but not in the AATD group. Capillary to fibers ratio (CFR), however, increased in the AATD group with no marked changes in the usual COPD group (see Table 1).

Two other retrospective cohort studies from Germany,^{23,24} involving significantly larger sample sizes (267 AATD and 640 usual COPD patients), reported similar findings in exercise capacity measured by the 6MWT. Both groups showed improvement after undergoing 4 and 5 weeks of inpatient PR, respectively. However, the AATD group in the 2017 study by Jarosch et al²⁴ had a higher baseline 6MWT, leading to the exclusion of 682 participants via propensity score matching. Additionally, the 2015 study by Kenn et al²³ reported incomplete data for quality of life, as assessed by the short form health survey (SF36), for more than half of the participants from both groups. Despite this, both groups demonstrated significant improvement in mental health measurements, but the improvement in the physical domain was significant for the AATD group only.

Finally, a 5-year longitudinal study in the United States by Choate et al²⁵ divided AATD patients into a control group, receiving only educational materials, and an intervention group receiving additional exercise equipment and virtual PR. Participants' baseline characteristics were similar across both groups, with most participants being White (98.3%). However, baseline characteristics for lung function or exercise capacity were not reported. The findings demonstrated that the intervention group engaged in significantly more exercise during the study (18.8 additional minutes of weekly exercise) and experienced a greater reduction in body mass index (BMI): 2.56% reduction as compared to 0.84% in the control group.

Proinflammatory Cytokines in Alpha-1 Antitrypsin Deficiency Patients During Exercise Intervention

In the 2014 study by Olfert et al,²⁶ differences in proinflammatory cytokines during a single moderate-intensity exercise session were explored among various groups: AATD patients receiving augmentation therapy, AATD patients not on therapy, usual COPD patients, a healthy control group, and an AATD group with normal lung function. The groups were age and BMI-matched, with COPD patients with underlying AATD presenting significantly poorer lung function, as illustrated by lower forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio. Researchers evaluated circulating inflammatory cytokines (C-reactive protein [CRP], interleukin [IL]-6, IL-1 beta, and tumor necrosis factor alpha [TNFα]) in arterial and venous blood during and post-exercise, which

Figure 1. PRISMA Flow Diagram for the Screening Process

involved a 1-hour, moderate-intensity single knee extension. Additionally, pre and postexercise muscle biopsies from the vastus lateralis were examined to determine skeletal muscle cytokine expression (Table 2).

The study's findings revealed that usual COPD patients had the highest circulating cytokine levels. While COPD patients with underlying AATD had elevated CRP levels compared to the healthy group, these were less than those found in usual COPD patients. Interestingly, the exercise session did not significantly alter serum cytokine levels in any of the groups postexercise. However, muscle biopsies showed a higher expression of TNF α in AATD COPD patients not receiving augmentation therapy compared to all other groups.

Changes in the 6-Minute Walk Test After Pulmonary Rehabilitation

In 3 individual studies,^{19,23,24} both the AATD and the usual COPD groups showed significant improvement in the 6MWT following PR. However, the usual COPD patients demonstrated slightly better mean improvement compared to the AATD group, and these differences were not significant in any of the studies (see Table 1). Interestingly, the quantitative meta-analysis revealed a

significant difference in the 6MWT distance gain between the AATD and usual COPD groups. AATD patients exhibited a lower gain with a Z-score of 2.06, p -value of 0.04, and I² of 0, with a CI of -7.83m to -0.39m (see Figure 2). It is worth noting that while the numerical difference is lower, it falls within a range that is less than the minimal clinically important difference (MCID) for the 6MWT, making its clinical significance debatable.²¹

Quality Appraisals of the Included Studies

In the assessment using the ROBINS-I tool, Jarosch et al (2017 and 2016)^{19,23} demonstrated serious risk of bias, with areas of missing information further complicating their evaluation. Kenn et al²³ and Olfert et al²⁶ both exhibited a moderate risk, though the latter had fewer areas of missing data. The study by Choate et al,²⁵ assessed using the RoB tool for randomized trials, showed a predominantly low risk across categories, but there were some concerns regarding the selection of reported results. Overall, while some studies presented robust methodologies, several had gaps that introduced uncertainty and potential biases. Further details are available in the supplementary materials (see Table 2 and Table 3 in the online supplement, respectively).

Table 1. Data Extraction: Pulmonary Rehabilitation is the Main Intervention for Alpha-1 Antitrypsin Deficiency Patients

Authors	Country	Study Design	Participants	Intervention	Study Outcomes	Main Findings
Jarosch et al 2016	Germany	Quasi-Experimental	<p>Total Participants: 19</p> <p>COPD AATD: 9 Gender: male (6), female (3) Age years: 56±7 BMI: 24. 2±2.7 Pack Yrs: NR Baseline 6MWT (m): NR FEV₁, l: 1.1±0.4 FEV₁ %pred: 32.9±8.9. PaO₂, mm Hg: 58.3±4.8 PaCO₂, mm Hg: 36.7±2.4 Physical Activity Level: 1.71±0.30</p> <p>COPD non-AATD: 10 Gender: male (6), female (4) Age: 62±7 BMI: 23.3±4.1 Pack Years: NR Baseline 6MWT (m): NR FEV₁, l: 0.8±0.2 FEV₁ %pred: 28.3±3.8 PaO₂, mm Hg: 57.2±7 PaCO₂, mm Hg: 43.8±5 Physical Activity Level: 1.63±0.25</p>	3-week inpatient PR. The exercise sessions consisted of endurance training using a cycle ergometer at 60% peak work rate, and resistance exercises for major muscle groups (3 sets and 20 reps).	<p>6MWT</p> <p>Skeletal muscle biopsy analysis for muscle fiber distribution of type I, IIA, IIX, and hybrid fibers I/IIA and IIA/IIX.</p> <p>PWR</p> <p>CFR</p> <p>Mitochondrial signalling PGC-1α (a controller of mitochondrial biogenesis) and TFAM (a key activator of mitochondrial transcription)</p>	<p>Baseline participants' characteristics were comparable between the 2 groups except that non-AATD COPD group had significantly greater baseline of PCO₂ mm Hg.</p> <p>Following the PR, exercise capacity measured by the 6MWT improved in both groups as such walking distance increased in the COPD AATD group by 29±28 m, and by 31±44 m in the non-AATD COPD.</p> <p>Muscle fiber type I remained the same in the COPD AATD group but increased slightly in the non-AATD COPD group. The AATD group saw an uptick in glycolytic myofiber type IIA and a minor drop in hybrid fiber types IIA/IIX. In contrast, the non-AATD group experienced reductions in both. When assessing all glycolytic type II fibers combined, the AATD group remained unchanged post-PR, while the non-AATD group showed a trend toward a decrease.</p> <p>PWR improved in both groups, COPD AATD patients increased by 9±11 W, and increased by 18±19 W in the non-AATD COPD group, between group difference <i>P</i> < 0.05.</p> <p>CFR increased in the COPD AATD group, but it did not change in the non-AATD COPD group.</p> <p>Mitochondrial signaling PGC-1α and TFAM increased in the non-AATD group, and they did not change in the COPD AATD group.</p>
Kenn et al 2015	Germany	Retrospective Cohort Analysis	<p>Total Participants: 487</p> <p>COPD AATD: 127 Gender: male (58), female (69) Age: 51.5±7.4 BMI: 23.7±4.5 Pack Years: NR Baseline 6MWT (m): 269±119 FEV₁, l: NR FEV₁, %pred: 26.6±9. PaO₂, mm Hg: 57±8 PaCO₂, mm Hg: 40.3±7.3 Listed for Lung Transplant, n (%): 61 (48)</p> <p>COPD non-AATD: 360 Gender: male (143), female (217) Age: 54±7.4 BMI: 22.4±4.8 Pack Years: NR Baseline 6MWT (m): 246.3±118.5 FEV₁, l: NR FEV₁, %pred: 25.3±9.3. PaO₂, mm Hg: 57±8.9 PaCO₂, mm Hg: 43.9±7.5 Listed for Lung Transplant, n (%): 168 (47)</p>	5-week inpatient PR	<p>6MWT</p> <p>Health-related quality of life SF36 for the physical and mental components</p>	<p>Both groups improved in exercise capacity measured by the 6MWT, the AATD group improved by 47±54.5 (m) and the non-AATD COPD group improved by 60.6±65.2 (m).</p> <p>209 non-AATD COPD patients were included in the post PR analysis for the SF36 HRQoL assessment, while only 64 COPD AATD patients were included. The improvement was significant in the physical and mental components for both groups, except that there was no significant effect on the SF36 physical component for the non-AATD COPD group.</p>
Jarosch et al 2017	Germany	Retrospective Cohort Analysis	<p>Total Participants: 420</p> <p>COPD AATD: 140 Gender: male (58) female (82)</p>	4-week inpatient PR	6MWT	668 COPD patients, and 14 AATD patients were removed from the final analysis to adjust for the differences in the baseline 6MWT measurement

(continued on next page)

For personal use only. Permission required for all other uses.

			Age: 56±9 BMI: 24.5±4 Pack Years: 21±15 Baseline 6MWT (m): 331±106 FEV ₁ , %pred: 31±8 PaO ₂ , mm Hg: 58±6.9 PaCO ₂ , mm Hg: 37±4.5 Creatine Level, mg/dL: 0.9±0.2 COPD non-AATD: 280 Gender: male (112), female (168) Age: 56±9 BMI: 24.2±4.7 Pack Years: 38±27 Baseline 6MWT (m): 326±101 FEV ₁ , %pred: 31±8 PaO ₂ , mm Hg: 60.8±8.4 PaCO ₂ , mm Hg: 40.6±6.2 Creatine Level, mg/dL: 0.8±0.2			using the propensity score matching. The analysis revealed clinically significant improvement in the 6MWT measurement following the inpatients PR for both groups. The mean improvement in AATD patients was 49±49 (m), and the mean improvement in non-AATD COPD patients was 53±52 (m).
Choate et al 2021	United States	RCT	Total Participants: 429 COPD AATD (Intervention Group): 218 Gender: male (106), female (112) Age: 57.9±9.1 History of Smoking n (%): 162 (76) Use of Oxygen n (%): 121 (55.5) BMI, n (%): Low ≤ 19: 10 (4.6) Normal 20–25: 82 (38) High ≥ 25–30: 79 (36.5) Very High ≥ 30: 45 (20.8) COPD AATD (Control Group): 211 Gender: male (99) female (112) Age: 57.6±9 History of Smoking n (%): 153 (74.2) Use of Oxygen n (%): 105 (48) BMI, n (%): Low ≤ 19: 9 (4.4) Normal 20 – 25: 102 (49.5) High ≥ 25 – 30: 61 (29.6) Very High ≥ 30: 34 (16.5)	A 5-year double-blinded control trial; both the intervention and standard care groups received educational resources and dietary guidance. The intervention group received additional exercise equipment and a custom virtual PR program, tailored to their baseline BMI aims weight reduction, maintenance, or increase.	Self-reported exercise activities as the sum of the total weekly warm up, strength, and endurance exercises per minutes. BMI	On average, participants in the intervention group engaged in an additional 18.83 minutes of weekly exercise (95% CI: -11.16–48.81) compared to those receiving standard care alone. In the intervention group, the BMI saw a reduction of 2.56%, whereas in the standard care group, it decreased by 0.84%. The difference in reduction between the 2 groups was statistically significant. After the intervention, there was a notable improvement in BMI for participants categorized as normal, high, and very high within the intervention group. In contrast, only participants with a high BMI in the control group exhibited a significant improvement.

COPD=chronic obstructive pulmonary disease; AATD=alpha-1 antitrypsin deficiency; BMI=body mass index; 6MWT=6-minute walk test; NR=non relevant; FEV₁=forced expiratory volume in 1 second; %pred=percentage predicted; PaO₂=partial pressure of arterial oxygen; PCO₂=partial pressure of carbon dioxide; PR=pulmonary rehabilitation; PWR=peak work rate; CFR=capillary to fiber ratio; PGC-1α=peroxisome proliferator-activated receptor gamma coactivator1-alpha; TFAM=mitochondrial transcription factor; SF36=short form health survey; HRQoL=health-related quality of life; CI=confidence interval

Discussion

This review has confirmed there is a paucity of good quality evidence regarding PR in AATD. The key findings of the 4 studies where PR is the main intervention^{19,23,24,25} showed AATD patients improved in exercise capacity, quality of life, and weekly exercise routine. Although the evidence presented suggests that undergoing PR is effective for AATD patients, just as in any other group of patients with chronic lung conditions there were suggestions in the studies that further optimization or personalization of PR for AATD patients may be valuable.

COPD Alpha-1 Antitrypsin Deficiency Patients' Characteristics

Cohort studies from Germany included AATD and usual COPD patients who were of similar age and exhibited similar lung function before undergoing a PR program.^{23,24} However, conflicting results emerged from other studies, indicating that COPD patients with AATD displayed poorer lung function when compared to their counterparts with usual COPD.²⁶ This aligns with previous research indicating that AATD patients are generally younger by a decade and suffer from more severe lung dysfunction.^{11,26-29}

Notably, despite their poorer lung function, AATD patients demonstrated superior baseline exercise capacity,

Table 2. Data Extraction: Exercise is the Main Intervention for Alpha-1 Antitrypsin Deficiency Patients

Authors	Olfert et al 2014					
Study Design	Quasi- Experimental					
Country	United States					
Total Participants:	Characteristics	AATD+AUG	AATD-AUG	AATD PFTnorm	COPD non-AATD	Healthy
28	Gender (male,female)	6 (3,3)	6 (2,4)	4 (1,3)	7 (4,3)	5 (3,2)
	Age	56±4	63±5	55±5	64±2	56±1
	BMI	25±2	28±3	26±3	29±2	29±2
	FEV₁ (liters)	1.23±0.25	1.35±0.22	3.22±0.47	1.49±0.11	3.07±0.35
	FEV₁ (%pred)	35±5	47±7	107±4	54±7	93±4
	FEV₁/FVC	31±3	47±7	76±7	56±4	79±2
	FEV₁/FVC (% pred)	40±4	61±10	97±2	71±6	99±3
	Cycle Ergometer Exercise , watts	62±6	46±11	176±47	70±11	126±17
	VO₂Peak (ml/kg/min) Bike Exercise	12.6±0.5	9.5±1.1	26.9±5.6	14.9±1.7	20.3±3.3
	Serum AAT level (mg/dl)	96±22	<20±0	<20±0	113±11	109±12
Intervention	Single session of knee extension exercise (1 hour exercise at 50% capacity)					
Study Outcomes	Femoral venous and arterial level of cytokines (TNFα, IL-1β, 1 L-6 andCRP)					
	Femoral venous minusarterial difference					
	Skeletal muscle expression for cytokines					
Main Findings	Non-AATD COPD group had the highest femoral venous and arterial circulating cytokines among all other groups.					
	CRP concentrations were elevated in both COPD AATD groups on, and off augmentation therapy compared to healthy controls and AATD patients with normal lung functions. However, CRP was lower in COPD AATD groups compared to non-AATD COPD group.					
	No differences in all cytokines between COPD AATD on and off augmentation therapy, except that COPD receiving augmentation therapy had higher venous TNFα.					
	Response to exercise: Exercise did not affect the level of cytokines in the serum for all groups following the exercise session.					
	Femoral venous minusarterial difference: TNFα showed significant difference across the groups in venous minus arterial difference analysis, it was greater in COPD AATD receiving augmentation compared those not receiving augmentation, and COPD non-AATD group.					
	Skeletal muscle expression for cytokines: TNFα showed significant difference across the groups, it was greater in COPD AATD not receiving augmentation compared to all other groups.					

AATD=alpha-1 antitrypsin deficiency; AUG=augmentation; PFTnorm=pulmonary function tests; COPD=chronic obstructive pulmonary disease; BMI=body mass index; FEV₁=forced expiratory volume in 1 second; %pred=percentage predicted; FVC=forced vital capacity; VO₂=maximal oxygen uptake; TNFα=tumor necrosis factor alpha; IL-1β=interleukin 1beta; IL-6=interleukin 6; CRP=C-reactive protein

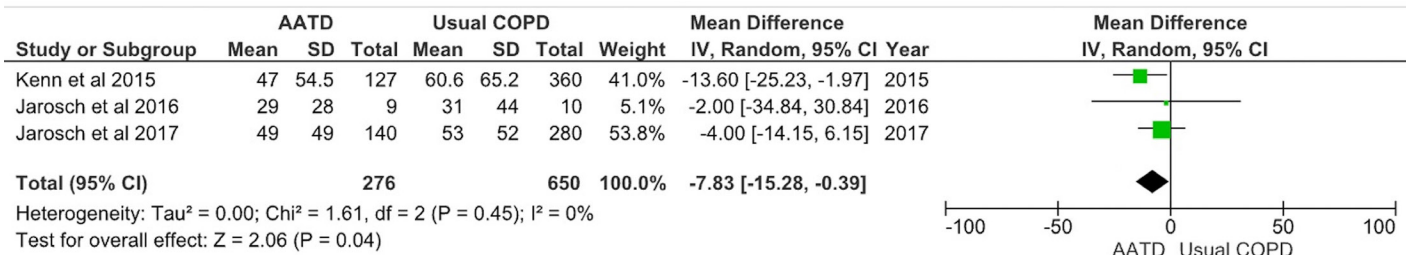
as evidenced by better performance in the 6MWT.²⁴ This echoes a recent finding where AATD patients could walk longer distances than usual COPD patients, albeit with more frequent exercise desaturations.²⁸ However, AATD patients endure twice as many yearly exacerbations, which also last longer, than usual COPD patients. These frequent exacerbations, linked to higher hospitalization rates and reduced quality of life,³⁰⁻³³ combined with more pronounced dyspnea, may impact AATD patients' engagement in PR programs.^{34,35}

Pulmonary Rehabilitation: The Exercise Component

Exercise training as part of PR is beneficial for patients with lung diseases, including those with AATD. These patients demonstrate improvement in both exercise capacity and quality of life, albeit less than those with usual COPD (Table 1). However, the implementation of PR in the included studies varied, and the program duration, exercise intensity, and supervision level often differed from what is recommended

by some health systems.¹⁶ Three studies from Germany implemented inpatient PR programs for AATD patients that were shorter in duration (3–5 weeks) but higher in frequency (daily exercise).^{19,24,36} These studies justified this approach as cost-effective and equally beneficial as conventional outpatient PR.³⁷ Yet, this format may limit patients' day-to-day activities and make it challenging for them to maintain an exercise routine postdischarge. Moreover, it might not be as cost-effective or even possible in countries with fewer hospital beds per capita. Home-based virtual PR presents a viable alternative. The Choate et al study reported the effectiveness of virtual PR among AATD patients, demonstrating an increase in exercise activity and a reduction in BMI over a 5-year follow-up period.²⁵ However, this study did not examine other potential benefits of such an intervention, like the impact on patients' quality of life and exercise capacity, reported elsewhere for usual COPD patients.³⁸⁻⁴⁰

Exercise is beneficial for muscles, particularly in reversing the muscle dysfunction characteristics linked to

Figure 2. Forest Plot of the 6-Minute Walk Test

AATD=alpha-1 antitrypsin deficiency; COPD=chronic obstructive pulmonary disease; SD=standard deviation; CI=confidence interval

aging and the progression of COPD. Advanced COPD patients often exhibit reduced muscle size, an increased proportion of type II glycolytic muscle fibers, a decreased proportion of oxidative type I muscle fibers, diminished mitochondrial signaling, and a reduced capillary-to-fiber ratio.^{41,42}

One study in this review found distinct differences in muscle adaptation between AATD patients and usual COPD patients following 3 weeks of PR.¹⁹ In AATD patients, there was no improvement in oxidative muscle fiber type I, a notable increase in glycolytic type II muscle fibers, no enhancement in mitochondrial signaling, and an increased fiber to capillary ratio. Although these findings suggest AATD patients may have a different muscle response to exercise, the study was limited by a small participant pool and the specific design of the exercise intervention.

Interestingly, there was a difference in muscle composition between the groups at baseline, which made it harder to draw conclusions from the changes between groups after intervention.¹⁹ Furthermore, their intervention method was suboptimal for promoting changes in muscle fiber distribution, as evidenced by other studies.^{42,43} The authors reported using moderate intensity exercise,¹⁹ but a recent review concluded that combining resistance exercise with high intensity interval training optimally shifted muscle fiber distribution towards an increase in type I fibers, which consequently improved exercise capacity in usual COPD patients.⁴¹ These findings raise questions about the most beneficial exercise modality for AATD patients to optimally improve muscle morphology and functionality. Different types of muscle fibers are specialized for specific functions during exercise or daily activities. Type I oxidative fibers are resistant to fatigue and are recruited during endurance exercise, while type II glycolytic fibers generate power and are used during resistance exercise.⁴⁴ This underscores the importance of understanding muscle composition when considering exercise interventions for individuals with AATD, noting awaited results from 2 clinical trials investigating the effect of moderate versus high intensity exercise for AATD patients [NCT03802357] [NCT02915614].

Pulmonary Rehabilitation: The Education Component

Education serves as a crucial element of PR programs, especially for patients coping with chronic lung diseases such as COPD.^{17,45} This aspect aims to provide a deep understanding to patients of their medical condition and offers valuable insights on how to manage their day-to-day activities effectively. Traditional educational components typically cover a wide range of topics including the anatomy and physiology of the respiratory system, the functioning of lungs, correct use of inhalers, oxygen therapy, energy conservation, welfare benefits, and the importance of maintaining regular exercise routines postprogram.^{46,47}

However, in the PR programs scrutinized in this review, the educational component was either overlooked or merely briefly touched upon.²³ Instead, these were described as standard education sessions intended for COPD patients. This highlights an area of potential improvement since patients with AATD, despite having lung disease, have distinct educational requirements due to the unique genetic underpinning of their condition.⁴⁸ For instance, one area of particular interest among AATD patients is augmentation therapy. Although this treatment option may not be available in every country,⁴⁹ it often piques the interest of these patients. Therefore, tailored education sessions exploring such topics could be highly beneficial for these patients, enabling them to better understand their treatment options and potential outcomes.

Furthermore, it's worth noting that AATD is a known predisposing factor for liver disease. This occurs because of the accumulation of AAT polymers in the liver, leading to endoplasmic reticulum stress and ultimately causing liver fibrosis and cirrhosis.^{50,51} Despite the severity of this potential complication, education about liver disease and its implications is largely absent from current PR programs. Nonetheless, some self-management interventions, such as AlphaNet, a patient support system in the United States, have ventured into this area. They have developed a self-administered alpha-1 disease management program that includes comprehensive education about the underlying risk of liver disease for AATD patients. Patients who engaged

with this program reported an increased understanding of their health condition and a heightened motivation to adopt preventative measures, thus, improving their overall wellbeing.⁴⁹

Lastly, there is a noticeable gap in evidence regarding the logistics of PR for AATD patients. The question of how these patients can be integrated into usual COPD groups is a complex one. Usual COPD patients are often older and may grapple with different challenges associated with work, family life, and aging. Given these factors, more thought should be put into how PR programs are tailored and implemented to accommodate the unique needs of AATD patients.

Systemic Inflammatory Cytokines in Usual COPD Patients Versus Alpha-1 Antitrypsin Deficiency Patients

In typical COPD patients, elevated proinflammatory cytokines correlate with frequent exacerbations and reduced lung function.^{52,54} Yet, a study by Olfert et al²⁶ revealed that AATD patients, irrespective of their augmentation therapy status, had lower serum levels of these cytokines. This might be surprising, given that systemic inflammation indicators, such as elevated CRP, would be anticipated to be greater in AATD patients due to their inferior lung function. This deviation is speculated to be due to potential hepatocyte malproduction of CRP, a phenomenon possibly linked to AATD digenesis.²⁶ Another notable observation was the elevated TNF α post exercise in muscle biopsies of AATD patients. This irregularity could make them more susceptible to cachexia, emphasizing the need for more research into the disease progression pathophysiology and related exercise outcomes in the AATD population.⁵⁵

Moreover, the study's exercise regimen didn't alter baseline proinflammatory cytokines for any group, contrasting with the typical response in healthy individuals where exercise boosts proinflammatory cytokine levels, balanced by postexercise anti-inflammatory responses.⁵⁶ While the results align with some prior research,^{57,58} the literature remains ambiguous, with conflicting studies reporting an increase in inflammatory cytokines following exercise in usual COPD patients.^{59,60} Once seen as additional inflammatory stress, regular exercise is now viewed as beneficial for its long-term anti-inflammatory effects and possible contribution to improved longevity.^{61,62}

Conclusion

The available evidence on the effectiveness of PR for AATD patients remains limited, necessitating further research in this area. Key areas of interest for investigation include identifying the most beneficial type of exercise, determining the optimal approach to education, and finding the best method for delivering PR services to individuals with AATD.

Acknowledgements

Author contributions: FA drafted the initial manuscript and contributed to the screening process and data extraction. AT provided valuable supervision, guidance, and edited the manuscript. KW and HP were involved in article screening, data extraction, and conducting quality assessments. All authors critically reviewed and provided input for the final draft of the manuscript, ensuring its accuracy and coherence. All authors approved the manuscript.

Declaration of Interest

All authors declare no conflict of interest.

References

1. Stockley RA. Alpha-1 antitrypsin review. *Clin Chest Med*. 2014;35(1):39-50. <https://doi.org/10.1016/j.ccm.2013.10.001>
2. Fahy B, Lareau S, Meek P, Strange C. What is alpha-1 antitrypsin deficiency? *Am J Respir Crit Care Med*. 2018;198(12):23-24. <https://doi.org/10.1164/rccm.19812P23>
3. Strange C. Alpha-1 antitrypsin deficiency associated COPD. *Clin Chest Med*. 2020;41(3):339-345. <https://doi.org/10.1016/j.ccm.2020.05.003>
4. Ioachimescu OC, Stoller JK. A review of alpha-1 antitrypsin deficiency. *COPD*. 2005;2(2):263-275. <https://doi.org/10.1081/COPD-57602>
5. Stoller JK, Aboussouan LS, Kanner RE, Wilson LA, Diaz P, Wise R. Characteristics of alpha-1 antitrypsin-deficient individuals in the long-term oxygen treatment trial and comparison with other subjects with chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2015;12(12):1796-1804. <https://doi.org/10.1513/AnnalsATS.201506-389OC>
6. McElvaney NG, Stoller JK, Buist AS, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha-1 antitrypsin deficiency. Alpha-1 Antitrypsin Deficiency Registry Study Group. *Chest*. 1997;111(2):394-403. <https://doi.org/10.1378/chest.111.2.394>
7. Blanco I, Bueno P, Diego I, et al. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. *Int J Chron Obstruct Pulmon Dis*. 2017;12:561-569. <https://doi.org/10.2147/COPD.S125389>
8. Carone M, Bruletti G, Bertella E, et al. Quality of life evaluation in patients with alpha-1 antitrypsin deficiency: a 3-year prospective study. *Eur Respir J*. 2011;38:3632 (Suppl. 55) <https://www.ers-education.org/lr/show-details/?idP=110210>
9. Choate R, Mannino DM, Holm KE, Sandhaus RA. Comparing patients with ZZ versus SZ alpha-1 antitrypsin deficiency: findings from AlphaNet's disease management program. *Chronic Obstr Pulm Dis*. 2019;6(1):29-39. <https://doi.org/10.15326/jcopdf.6.1.2018.0134>
10. Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. *Can Med Assoc J*. 2012;184(12):1365-1371. <https://doi.org/10.1503/cmaj.111749>
11. Greulich T, Nell C, Hohmann D, et al. The prevalence of diagnosed alpha-1 antitrypsin deficiency and its comorbidities: results from a large population-based database. *Eur Respir J*. 2017;49:1600154 <https://doi.org/10.1183/13993003.00154-2016>
12. Tanash HA, Piitulainen E. Liver disease in adults with severe alpha-1 antitrypsin deficiency. *J Gastroenterol*. 2019;54(6):541-548. <https://doi.org/10.1007/s00535-019-01548-y>
13. Barjaktarevic I, Campos M. Management of lung disease in alpha-1 antitrypsin deficiency: what we do and what we do not know. *Thor Adv Chronic Dis*. 2021;12. Suppl:20406223211010172. <https://doi.org/10.1177/20406223211010172>
14. Chapman KR, Chorostowska-Wynimko J, Koczulla AR, Ferrarotti I, McElvaney NG. Alpha-1 antitrypsin to treat lung disease in alpha 1 antitrypsin deficiency: recent developments and clinical implications. *Int J Chronic Obstruct Pulmon Dis*. 2018;13:419-432. <https://doi.org/10.2147/COPD.S149429>
15. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Database Syst Rev*. 2016;9(9):CD007851. <https://doi.org/10.1002/14651858.CD007851.pub3>
16. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64 [https://doi.org/10.1016/S0302-2838\(13\)00460-0](https://doi.org/10.1016/S0302-2838(13)00460-0)
17. Blackstock FC, Evans RA. Rehabilitation in lung diseases: 'education' component of pulmonary rehabilitation. *Respirology*. 2019;24(9):863-870. <https://doi.org/10.1111/resp.13582>
18. Gloeckl R, Schneeberger T, Jarosch I, Kenn K. Pulmonary rehabilitation and exercise training in chronic obstructive pulmonary disease. *Dtsch Arztebl Int*. 2018;115(8):117-123. <https://doi.org/10.3238/arztebl.2018.0117>
19. Jarosch I, Gehlert S, Jacko D, et al. Different training-induced skeletal muscle adaptations in COPD patients with and without alpha-1 antitrypsin deficiency. *Respiration*. 2016;92(5):339-347. <https://doi.org/10.1159/000449509>
20. Ouzzani M, Hammady H, Fedroowicz Z, Elagarmid A, Rayyan—aweb and mobile app for systematic reviews. *Syst Rev*. 2016;5:210. <https://doi.org/10.1186/s13643-016-0384-4>
21. Sterne JAC, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ*. 2016; 355: i4919. <https://doi.org/10.1136/bmj.i4919>
22. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. *BMC Med Res Methodol*. 2015;15:35. <https://doi.org/10.1186/s12874-015-0024-z>
23. Kenn K, Gloeckl R, Soennichsen A, et al. Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. *Transplantation*. 2015;99(5):1072-1077. <https://doi.org/10.1097/TP.0000000000000472>
24. Jarosch I, Hitzl W, Koczulla AR, et al. Comparison of exercise training responses in COPD patients with and without alpha-1 antitrypsin deficiency. *Respir Med*. 2017;130:98-101. <https://doi.org/10.1016/j.rmed.2017.07.009>

25. Choate R, Mannino DM, Holm KE, Beiko T, Boyd B, Sandhaus RA. Home-based multicomponent intervention increases exercise activity and improves body mass index: results of a 5-year randomized trial among individuals with alpha-1 antitrypsin deficiency-associated lung disease. *Chronic Obstr Pulm Dis*. 2021;8(1):7-18. <https://doi.org/10.15326/jcopdf.8.1.2020.0183>
26. Olfert IM, Malek MH, Eagan TM, Wagner H, Wagner PD. Inflammatory cytokine response to exercise in alpha-1-antitrypsin deficient COPD patients 'on' or 'off' augmentation therapy. *BMC Pulm Med*. 2014;14:106. <https://doi.org/10.1186/1471-2466-14-106>
27. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. *COPD*. 2005;2(1):125-129. <https://doi.org/10.1081/COPD-200050527>
28. Stoller JK, Aboussouan LS, Kanner RE, Wilson LA, Diaz P, Wise R. Characteristics of alpha-1 antitrypsin-deficient individuals in the long-term oxygen treatment trial and comparison with other subjects with chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2015;12(12):1796-1804. <https://doi.org/10.1513/AnnalsATS.201506-389OC>
29. Greulich T, Altraja A, Barrecheguren M, et al. Protocol for the EARCO Registry: a pan-European observational study in patients with alpha-1 antitrypsin deficiency. *ERJ Open Res*. 2020;6:00181-2019. <https://doi.org/10.1183/23120541.00181-2019>
30. Vijayasaritha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *Chest*. 2008;133(1):34-41. <https://doi.org/10.1378/chest.07-1692>
31. Stockley RA, Edgar R, Hughes S, Turner A. Decline in health status in alpha-1 antitrypsin deficiency. *Eur Respir J*. 2017;50:402. <https://doi.org/10.1183/1393003.congress-2017.PA402>
32. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608-1613. <https://doi.org/10.1164/ajrccm.161.5.9908022>
33. Smith DJ, Ellis PR, Turner AM. Exacerbations of lung disease in alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis*. 2020;8(1):162-176. <https://doi.org/10.15326/jcopdf.2020.0173>
34. Holm KE, Borson S, Sandhaus RA, et al. Differences in adjustment between individuals with alpha-1 antitrypsin deficiency (AATD)-associated COPD and non-AATD COPD. *COPD*. 2013;10(2):226-234. <https://doi.org/10.3109/15412555.2012.719049>
35. Stone PW, Hickman K, Steiner MC, Roberts CM, Quint JK, Singh SJ. Predictors of pulmonary rehabilitation completion in the UK. *ERJ Open Res*. 2021;7(1):00509-2020. <https://doi.org/10.1183/23120541.00509-2020>
36. Gloeckl R, Kenn K, Soennichsen A, et al. Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. *Eur Respir J*. 2014;44:1712. https://erj.ersjournals.com/content/44/Suppl_58/1712
37. Clini E, Foglio K, Bianchi L, Porta R, Vitacca M, Ambrosino N. In-hospital short-term training program for patients with chronic airway obstruction. *Chest*. 2001;120(5):1500-1505. <https://doi.org/10.1378/chest.120.5.1500>
38. Jung T, Moorhouse N, Shi X, Amin MF. A virtual reality-supported intervention for pulmonary rehabilitation of patients with chronic obstructive pulmonary disease: mixed methods study. *J Med Internet Res*. 2020;22(7):e14178. <https://doi.org/10.2196/14178>
39. Rutkowski S, Rutkowska A, Kiper P, et al. Virtual reality rehabilitation in patients with chronic obstructive pulmonary disease: a randomized controlled trial. *Int J Chron Obstruct Pulmon Dis*. 2020;15:117-124. <https://doi.org/10.2147/COPD.S223592>
40. Jangalee JV, Ghasvareh P, Guenette JA, Road J. Incorporating remote patient monitoring in virtual pulmonary rehabilitation programs. *Can J Respir Ther*. 2021;57:83-89. <https://doi.org/10.29390/cjrt-2021-015>
41. De Brandt J, Spruijt MA, Derave W, Hansen D, Vanfleteren LEGW, Burtin C. Changes in structural and metabolic muscle characteristics following exercise-based interventions in patients with COPD: a systematic review. *Expert Rev Respir Med*. 2016;10(5):521-545. <https://doi.org/10.1586/17476348.2016.1157472>
42. Jaitovich A, Barreiro E. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. what we know and can do for our patients. *Am J Respir Crit Care Med*. 2018;198(2):175-186. <https://doi.org/10.1164/rccm.201710-2140CI>
43. Nilwik R, Snijders T, Leenders M, et al. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. *Exp Gerontol*. 2013;48(5):492-498. <https://doi.org/10.1016/j.exger.2013.02.012>
44. Qaisar R, Bhaskaran S, Van Remmen H. Muscle fiber type diversification during exercise and regeneration. *Free Radic Biol Med*. 2016;98:56-67. <https://doi.org/10.1016/j.freeradbiomed.2016.03.025>
45. Roberts NJ, Kidd L, Kirkwood K, Cross J, Partridge MR. A systematic review of the content and delivery of education in pulmonary rehabilitation programmes. *Respir Med*. 2018;145:161-181. <https://doi.org/10.1016/j.rmed.2018.11.002>
46. Blackstock FC, Lareau SC, Nici L, et al. Chronic obstructive pulmonary disease education in pulmonary rehabilitation. An official American Thoracic Society/Thoracic Society of Australia and New Zealand/Canadian Thoracic Society/British Thoracic Society workshop report. *Ann Am Thorac Soc*. 2018;15(7):769-784. <https://doi.org/10.1513/AnnalsATS.201804-253WS>
47. Wilson JS, O'Neill B, Reilly J, MacMahon J, Bradley JM. Education in pulmonary rehabilitation: the patient's perspective. *Arch Phys Med Rehabil*. 2007;88(12):1704-1709. <https://doi.org/10.1016/j.apmr.2007.07.040>
48. Rangaraju M, Turner AM. Why is disease penetration so variable in alpha-1 antitrypsin deficiency? The contribution of environmental factors. *Chronic Obstr Pulm Dis*. 2020;7(3):280-289. <https://doi.org/10.15326/jcopdf.7.3.2019.0177>

49. Rahaghi FF. Alpha-1 antitrypsin deficiency research and emerging treatment strategies: what's down the road? *Ther Adv Chronic Dis*. 2021;12_suppl. doi:10.1177/20406223211014025
https://doi.org/10.1177/20406223211014025
50. Hamesch K, Mandorfer M, Pereira VM, et al. Liver fibrosis and metabolic alterations in adults with alpha-1 antitrypsin deficiency caused by the Pi*ZZ mutation. *Gastroenterology*. 2019;157(3):705-709. https://doi.org/10.1053/j.gastro.2019.05.013
51. Miravittles M, Herepath M, Priyendu A, et al. Disease burden associated with alpha-1 antitrypsin deficiency: systematic and structured literature reviews. *Eur Respir Rev*. 2022;31:210262. https://doi.org/10.1183/16000617.0262-2021
52. Aldonyte R, Jansson L, Piitulainen E, Janciauskiene S. Circulating monocytes from healthy individuals and COPD patients. *Respir Res*. 2003;4:11. https://doi.org/10.1186/1465-9921-4-11
53. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax*. 1996;51(8):819-824. https://doi.org/10.1136/thx.51.8.819
54. Eagan TM, Ueland T, Wagner PD, et al. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. *Eur Respir J*. 2010;35:540-548. https://doi.org/10.1183/09031936.00088209
55. Webster JM, Kempen LJAP, Hardy RS, Langen RCJ. Inflammation and skeletal muscle wasting during cachexia. *Front Physiol*. 2020;11:597675. https://doi.org/10.3389/fphys.2020.597675
56. Cerqueira É, Marinho DA, Neiva HP, Lourenço O. Inflammatory effects of high and moderate intensity exercise: a systematic review. *Front Physiol*. 2019;10:1550. https://doi.org/10.3389/fphys.2019.01550
57. Spruit MA, Troosters T, Gosselink R, Kasran A, Decramer M. Acute inflammatory and anabolic systemic responses to peak and constant-work-rate exercise bout in hospitalized patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2007;2(4):575-583. https://doi.org/10.2147/copd.s12159992
58. Davidson WJ, Verity WS, Traves SL, Leigh R, Ford GT, Eves ND. Effect of incremental exercise on airway and systemic inflammation in patients with COPD. *J Appl Physiol*. 2012;112(12):2049-2056. https://doi.org/10.1152/jappphysiol.01615.2011
59. Rabinovich RA, Figueras M, Ardite E, et al. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J*. 2003;21:789-794. https://doi.org/10.1183/09031936.03.00042702
60. van Helvoort HA, Heijdra YF, de Boer RC, Swinkels A, Thijs HM, Dekhuijzen PN. Six-minute walking-induced systemic inflammation and oxidative stress in muscle-wasted COPD patients. *Chest*. 2007;131(2):439-445. https://doi.org/10.1378/chest.06-1655
61. Dowson LJ, Newall C, Guest PJ, Hill SL, Stockley RA. Exercise capacity predicts health status in alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2001;163(4):936-941. https://doi.org/10.1164/ajrccm.163.4.2007048
62. van der Vlist J, Janssen TW. The potential anti-inflammatory effect of exercise in chronic obstructive pulmonary disease. *Respiration*. 2009;79(2):160-174. https://doi.org/10.1159/000233264