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REVIEW

Physical Activity, Exercise Capacity and Sedentary Behavior in People with Alpha-1 Antitrypsin Deficiency: A Scoping Review

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Abstract: Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder and a genetic risk factor for chronic obstructive pulmonary disease (COPD). Physical activity (PA) is important for the prevention and treatment of chronic disease. Little is known about PA in people with AATD. Therefore, we aimed to map the research undertaken to improve and/or measure PA, sedentary behaviour (SB) or exercise in people with AATD. Searches were conducted in CINAHL, Medline, EMBASE and clinical trial databases for studies published in 2021. Databases were searched for keywords (physical activity, AATD, exercise, sedentary behavior) as well as synonyms of these terms, which were connected using Boolean operators. The search yielded 360 records; 37 records were included for review. All included studies (n = 37) assessed exercise capacity; 22 studies reported the use of the six-minute walk test, the incremental shuttle walk test and cardiopulmonary exercise testing were reported in three studies each. Other objective measures of exercise capacity included a submaximal treadmill test, the Naughton protocol treadmill test, cycle ergometer maximal test, endurance shuttle walk test, constant cycle work rate test, a peak work rate test and the number of flights of stairs a participant was able to walk without stopping. A number of participant self-reported measures of exercise capacity were noted. Only one study aimed to analyze the effects of an intensive fitness intervention on daily PA. One further study reported on an exercise intervention and objectively measured PA at baseline. No studies measured SB. The assessment of PA and use of PA as an intervention in AATD is limited, and research into SB absent. Future research should measure PA and SB levels in people with AATD and explore interventions to enhance PA in this susceptible population.

Keywords: lung disease, AATD, COPD, physical activity measurement, sedentary behavior, exercise capacity

Introduction

Alpha-1 antitrypsin deficiency (AATD) is one of the most common hereditary disorders in adults of European descent[1] and remains the most common, readily identifiable genetic risk factor for chronic obstructive pulmonary disease (COPD).[2] The pulmonary manifestations of AATD include a spectrum of disorders associated with COPD[3] including emphysema, chronic bronchitis, and bronchiectasis. The pathophysiology of AATD reflects the absence of alpha-1 antitrypsin (AAT) which normally protects the lung tissues from proteolytic destruction,[4] and an excess of abnormally folded AAT within the liver.[5] Extra-pulmonary associations with liver cirrhosis, hepatocellular cancer, vasculitis and panniculitis are well recognised in AATD.[6,7]

Physical activity (PA), defined as "any bodily movement produced by skeletal muscles that requires energy expenditure",[8] is fundamental for supporting physical and mental health and wellbeing across the life course[9] for all age groups and for those living with long-term conditions.[10] PA includes all activities done as part of daily living such as

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social and domestic activities, commuting, recreational and leisure activities and may or may not include exercise.[11] Exercise is a subcategory of PA that is planned, structured, repetitive, with a specific purpose ie to increase fitness or improve strength.[8] Exercise and PA are recognised as a key care feature and should be encouraged for all patients with chronic respiratory disease.[12] It is well established that people with chronic respiratory disease demonstrate lower PA levels compared to their healthy counterparts.[13–15] In addition, many patients with AATD develop a sedentary lifestyle,[16] increasing the risk of comorbidities. Sedentary behavior (SB) is defined as any behavior undertaken during waking hours, in sitting or reclining posture, that requires energy expenditure ≤1.5 metabolic equivalent tasks.[17] High levels of SB are associated with poorer cardiometabolic health, while high levels and intensity of PA are associated with improved cardiometabolic health.[10] Moreover, given people with severe AATD-related COPD tend to be younger than usual COPD,[18] it is imperative to support this high-risk population to engage in health enhancing PA and to reduce their SB.

It has been noted that updated guidance on lifestyle modifications in AATD is warranted.[19] In particular, further guidance is required to facilitate the appropriate implementation of non-pharmacologic treatment measures such as PA and exercise.[19] Certain medications including bronchodilator therapy have been demonstrated to increase exercise capacity in people with COPD.[20] The only specific pharmacological treatment for severe AATD-related lung disease is intravenous infusion of plasma-purified alpha-1 antitrypsin, known as augmentation therapy.[21] Given the recognised importance of PA in reducing hospitalisations, enhancing quality of life and improving life expectancy in people with COPD,[13,22] interventions to enhance PA and exercise and reduce SB in those medically optimised may be important for improving health outcomes in AATD. Preliminary searches of the literature suggest that this area is largely unexplored, and research is limited. To our knowledge, to date, there are no reviews published that explore either PA levels, exercise capacity or SB in people with AATD or reviews of interventions targeting PA, exercise or SB in people with AATD.

Therefore, this scoping review aims to map the research undertaken in the area of PA, exercise and SB in people with AATD. This will allow us to bring together, identify and describe interventions that support people with AATD to improve their PA levels, exercise capacity, and to reduce SB.

This scoping review aims to answer the following question: What is the "extent (size), range (variety) and nature (characteristics) of the evidence around PA, exercise and SB for people with AATD?"

Materials and Methods

This review was conducted in accordance with guidance from the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR).[23]

Eligibility Criteria

The inclusion and exclusion criteria were discussed and agreed by all authors. The inclusion criteria were: (a) research papers published from database inception to July 2021; (b) published in English; (c) quantitative, qualitative or mixed-method reports including abstracts, protocols, reviews and conference proceedings; (d) diagnosis with any form of AATD; (e) no age restriction; (f) Studies including any measure of exercise capacity, PA or SB (participant report or device measured). Restrictions on language were due to limited resources.

Search Strategy

The search strategy (Supplemental File 1) was developed alongside an academic librarian and members of the research team. The search strategy was made up of keywords (physical activity, AATD, exercise, pulmonary rehabilitation, sedentary behaviour) as well as synonyms of these terms, which were connected using Boolean operators.

Comprehensive searches were undertaken in Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE and Embase for all relevant studies from database inception to July 2021. Study/trial registries Australian New Zealand Clinical Trials Registry (ANZCTR), clinicaltrials.gov, The European Union Clinical Trials Register (EU CTR) and PROSPERO were searched to ensure that ongoing and recently completed studies were not missed. Reference lists of included studies were hand searched to identify additional studies that may have been missed in the original search.

The search results were imported into EndNote reference management software (version X9), where duplicates were removed.

Selection of Sources of Evidence

Five percent of the same titles and abstracts were assessed by two independent reviewers to confirm the eligibility criteria, consensus was agreed across these results and no changes were made to the eligibility criteria. The team determined the eligibility of articles using a two-stage screening process. First, the reviewers screened the titles and abstracts of all identified literature against the research question and inclusion criteria and categorised them as include, exclude or uncertain. Screening of titles/abstracts were divided amongst the review team. Doubts about the relevance of a study based on its abstract, resulted in retrieval of the full-text version. Uncertainties and disagreements were resolved through discussion and group consensus. Throughout the process, reviewers met regularly via an internet-based video conferencing platform and e-mail to further discuss the screening process. Full-text screening followed, using the same procedure.

Data Charting Process

Study details and data were extracted using a customized form, based on the objectives of the review. The charting form was available on an online portal allowing the team to see each other's contribution and discuss any concerns. The following data were independently extracted from each article: authors, year, title, aim, study design, participant demographics, outcome measure used to assess PA/exercise capacity/SB and intervention/treatment received.

Collating and Summarizing Results

The results grouped together according to study design and tabulated for ease of reporting.

Results

The PRISMA-ScR flow diagram of the literature search can be found in Figure 1. After the removal of duplicates, 137 titles and abstracts records were screened. Sixty-one full-text articles were retrieved. Thirteen records could not be retrieved, and attempts were made to contact the authors via the email. Thirty-three records fulfilled the inclusion criteria. A further four records were identified from screening the reference lists of records meeting the inclusion criteria. A total of 37 records were included in this review.

Study and Participant Characteristics

Study and participant characteristics are summarized in Table 1. A number of different study designs were identified: six cross-sectional studies,[24–29] six prospective studies,[30–35] three retrospective,[36–38] three randomized controlled trials (RCT),[16,39,40] and one non-randomized and non-concurrent trial.[41] Ten included reports were conference abstracts of which there were three retrospective studies,[42–44] two RCTs,[45,46] two case studies,[47,48] two cross-sectional[49,50] and one prospective study.[51] A further eight protocols[52–59] were identified: one cross-sectional study,[52] two prospective studies,[53,54] four RCTs[55–58] and one non-randomized parallel group study.[59] All reports were published between 1998 and 2021.

A total of 10,645 (range 1–3526) participants with AATD were included, and a further 3722 (25–3000) were planned to be recruited for protocol studies. Trials which reported on gender included 5617 males and 4960 females. The youngest average (standard deviation) age reported in a study was 46.1 (8.8) years,[21] and the oldest average age cohort was 70.1 (9.2) years.[40] The ZZ genotype was the most common AATD genotype included in the studies, other genotypes reported included ZZ, MZ, MS, MP, Null and other/unknown genotypes.

Interventions

The interventions are summarized in Table 2. For studies reporting an intervention or treatment, there were nine studies reporting on a surgical intervention or treatment: six on lung volume reduction surgery,[29–32,36,51] two endobronchial valve[42,44] and one lung transplant study,[33] all of which assessed exercise capacity. There were 11 studies reporting on an exercise intervention.[28,34,35,37,39,41,43,48,53,56] Only one of these results reported an aim related to improving daily PA.

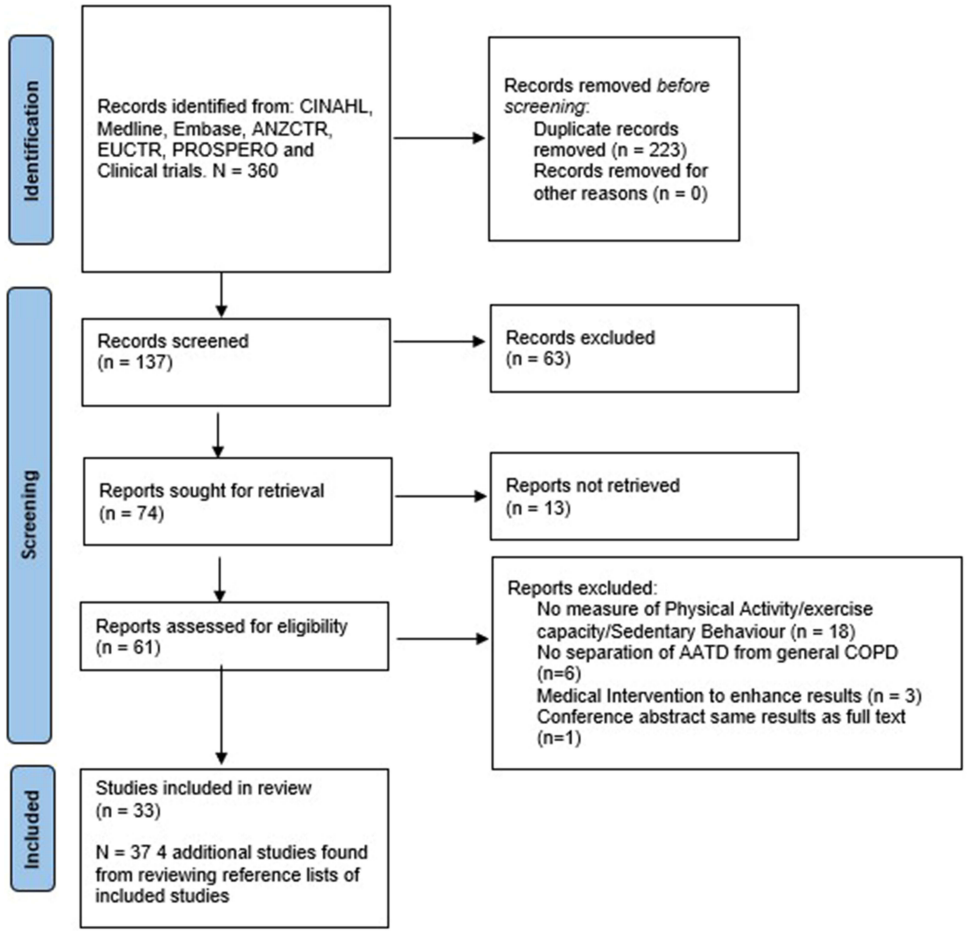

Figure 1 PRISMA flow diagram.
Note: Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

Choate et al 2017[43] (a conference abstract) reported aiming to identify whether a more intensive fitness intervention would improve physical activity and weight outcomes. A further three studies reported a treatment relating to a medicinal product, specifically oxygen therapy[36] and an alpha-1 proteinase inhibitor (known as augmentation therapy).[45,52] One study described an education self-management programme.[38] No studies reported specifically on a PA intervention or an intervention to reduce SB.

Outcome Measures to Assess Exercise Capacity, Physical Activity and Sedentary Behavior

The outcome measures reported are in Table 2. Regardless of the intervention focus (which was broad), exercise capacity was the most commonly reported outcome, 22 studies reported the use of the six-minute walk test to measure exercise capacity,[30–40,44,45,47,49–55,58] the incremental shuttle walk test and cardiopulmonary exercise testing were reported in three studies each.[26,29,43,53,56,57] Other objective measures of exercise capacity included a submaximal treadmill test,[24] the Naughton protocol treadmill test,[29] cycle ergometer maximal test,[39] endurance shuttle walk test, constant cycle work rate test,[59] a peak work rate test[42,51] and the number of flights of stairs a participant was able to walk without stopping.[27] A number of participant self-reported measures of exercise capacity were noted. For example, participants reporting on the regularity and location of the exercise,[25] individuals asked whether they exercised regularly, irregularly, or not at all,[28] participants reporting the number of exercise minutes per week.[16,46] Another study asked participants to categorise themselves as "does not exercise regularly, exercises regularly or has started to exercise"[41] and finally a case study

Table 1 Participant Demographics of Included Studies

Authors and Year	Number of Participants	Participant Gender	Mean Age (SD) (Unless Stated Otherwise)	Genotype	Lung Function (AATD Participants Only) (Mean (SD) Unless Otherwise Stated)
Wencker M and Konietzko N 2000[24]	N= 369	240M 129F	46.1 (8.8)	ZZ, SZ, Other/ Unknown	VC 3.6(1.2)L, 84(21)%; FEV1 1.34(0.63)L, 39(16)%; FEV1/ VC 37(11) 84 (21)%; RV 5.1L (1.7) 253(7)%; TLC 8.4 (2.3) L 130(30)%; RV/TLC 62(16) 189(51)%
Perkins JT et al 2016[25]	N= 3526	1832M 1653F	56.62 (11.76)	NR	Not reported
Olfert M et al 2014[26]	N=16	PiZZ (+aug therapy) 3M 3F PiZZ (- aug therapy) 2M 4F PiZZ (normal PF)T 1M 4F	PiZZ (+aug therapy) 56 (4) PiZZ (- aug therapy) 63 (5) PiZZ (normal PFT) 55(5)	ZZ, SZ	PiZZ (+aug therapy): FVC 3.85(0.42)L, 88(6)%; FEV1 1.23(0.25)L, 35(5)%; FEV1/FVC 31(3), 40 (4)% PiZZ (- aug therapy) FVC 2.88(0.16)L, 79(5)%; FEV1 1.35(0.22)L, 47(7)%; FEV1/FVC 47(7), 61(10)% PiZZ (normal PFT): FVC 4.27(0.64)L, 109(6)%; FEV1 3.22(0.47)L, 107(4)%; FEV1/FVC 76(7), FEV1/FVC 97(2)
Kohnlein T et al 2010[27]	N=267	132M 135F	53.8 (11.2)	ZZ, MZ, SS, SZ, MS, Null, SM and unknown	Not reported
Holm et al 2018[28]	N=3506	1865 M 164 F	52 or younger:n=1132, 53–64 n= 1440, 65 or older 934	MZ, SZ, ZZ	Not reported
Dowson LJ et al 2001[29]	N=29	19M 10F	Age (Median (IQR)) 52 (46–60)	ZZ	FEV1 1.03(0.84–1.41)L 35%; FEV1/VC: 0.31(0.25–0.43)L 37%; MEF 0.38 (0.31–0.49)L/s 10%; TLC 7.18 (6.08–8.35)L 122%; RV 2.88 (2.36–3.48)L 138%; RV/TLC: 0.42 (0.36–0.48) 125%; DLCO,: 4.99 (3.65–6.37) mmol/min/kPa 53%; DLCO/VA, 0.89 (0.69–1.21) mmol/min/kPa/L 6% Median (IQR)
Thabut G et al 2014[30]	N=191	119 M 72 F	50.8 (10.9)	ZZ, SZ and Null/Z	FEV1 42.5(19.9)% (n=140 participants)
Jarosch I et al 2016[31]	N=9	6 M 3 F	56 (7)	ZZ and MM	FEV1 32.9(8.9)%, 1.1 (0.4)L; DLCO, 32.9 (8.9) mmol/min/ kPa
Cassina PC et al 1998[32]	N=12	7M 5 F	49 (10)	ZZ	FEV1 0.8(0.3)L, 24(7)%; RV 342(68)%; TLC 139 (20)%; FRC 210(37)%

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Table 1 (Continued).

Authors and Year	Number of Participants	Participant Gender	Mean Age (SD) (Unless Stated Otherwise)	Genotype	Lung Function (AATD Participants Only) (Mean (SD) Unless Otherwise Stated)
Tutic et al 2004[33]	N=21	11 M 10 F	56 (2)	ZZ, ZO, SZ	FEV1 0.78 (0.04)L, 27(1.9)%; RV/TLC 0.67 (0.02)
Tanash et al 2011[34]	N= 153 (Transplantees n=83, Non-transplant n=70)	Transplantees 48M 35F Non-transplant 42M 28F	Transplantees 52 (32–66) Non-transplant 54 (35–70)	ZZ	Transplant: FEV1 22(9)%; FVC 62 (20)%; FEV1/FVC 30(9)%; DLCO 23(8)% Non transplant: FEV1 23(6)%; FVC 57(19)%; FEV1/FVC 35(9)%; DLCO 27(7)%
Dauriat G et al 2006[35]	N=17	NR	56 (9)	ZZ	FEV1 22.2(5.7)%; FEV1 6.13(1.63)L; FEV1 post-BD 24 (6.7)%; FVC 48(11)%; RV 278(48)%; FRC 201(35)%; TLC 138(18); IC 62(19)
Tanash et al 2014[36]	N=128	71M 57F	Age (Mean (range)) 53 (32–67)	ZZ	FEV1 22(8)%; FCV 63 (19)%; DLCO 25(11)%
Jarosch et al 2017[37]	N=140	59M 81F	56 (9)	ZZ	FEV1 1.0(0.3)L, 31(8)%; RV 6.0(1.4)L, 281(66)L
Kenn et al 2015[38]	N=127	58M 69F	M:51 (6.3) F: 52(8.2)	NR	FEV1 M 25.6 (9.2) F 27.3 (8.9)%; FVC M 58.6 (23.4) F 57.7 (19.8)%
Stoller et al 2007[39]	N=16	14M 2 F	Age (Median (range)) 66.3 (50.1, 77.0)	SZ, ZZ, NullNull and Other/ Unknown	Post-BD TLC 129.5 (121.0, 134.5%); RV 216.0 (183.5, 243.0)%; DLCO 29.0 (23.0, 38.0)% (Median IQR)
Stoller et al 2015[40]	N=55	Severe: 7m 4F Mild/moderate: 33M 11F	Severe AATD 61.2 (10.8) Mild/ moderate 70.1(9.2)	MZ, MS, SS, MP	Severe: Pre-BD FEV1 40.8(15.5%); FVC 82.4 (25.8)%; FEV1/FVC 0.37(0.08); Post-BD FEV1 43.6(16.4)%; FVC 86.0(27.3)%; FEV1/FVC 0.38(0.6); Mild/moderate Pre-BD FEV1 39.7(14.8)%; FVC 71.2(22.1)%; FEV1/FVC 0.41 (0.10); Post-BD FEV1 43.3 (16.4)%; FVC 76.7(23.2)%; FEV1/FVC 0.42(0.11)
Choate et al 2021[16]	N=429	234 F 195 M	57.8 (9.2)	N=348 ZZ	Not reported
Campos et al 2009[41]	N=878	464M 414F	54.4 (9.6)	N=860 ZZ	FEV1 1.2(0.7)L; FEV1 36.8(16.9)%; FEV1/FVC 42.8(14.0)
Heinzelmann et al 2015[42]	N=6	NR	57 (7)	ZZ	FEV1% 38 (6)
Chlumsky and Kusalova 2020[43]	N=113	77M 36 F	47.2 (14.1)	NR	FEV1 46.0(19.0)%

Balbi et al 2013[44]	N=30	19 M 11 F	Age (Median (range)) 54 (44–64)	ZZ, SZ, rare and undetermined	Not reported (50% were graded as severe according to the GOLD classification)
Delage et al 2019[45]	N=20	NR	NR	NR	FEV1 0.87(0.21)L; TLC 1.83(0.45)L
Choate et al 2017[46]	N=417	Control: 94M 111F Intervention: 104M 108F	Control 57.9(9.6), intervention 58.0(9.3)	NR	Not reported
Tseng Do et al 2019[47]	N=1	Male	53	NR	FVC 2.50L, 52%; FEV1 0.90 L, 26%; FEV1/FVC 38%; TLC 8.28L, 122%; RV 6.70L 298%
Menon et al 2017[48]	N=1	M	49	The F allelle was responsible for dysfunctional AA1T protein	FEV1/FVC 39%; RV 190%; TLC 107% DLCO 67%
Murray et al 2014[49]	N=128	NR	NR	ZZ	FEV1% predicted was 60.5 ± 32.1 and the mean % predicted DLCO was 54.9 ± 24.2.
Durkan et al 2019[50]	N=30	21M 9F	60(8)	ZZ	FEV1 50.72(21.12)%
Heinzelmann et al 2015[51]	N=10	NR	56 (7)	ZZ	FEV1 33(9)%
Strange et al 2015[52]	N=200	NA	N/A	MZ, ZZ	Not reported
Greulich et al 2020[53]	N=3000 in first 3 years	N/A	N/A	ZZ, SZ and other rare deficient variants.	Not reported
Endoscopic Lung Volume Reduction in Patients with Advanced Emphysema Due to alpha1 Antritrypsin Deficiency 2019[54]	N=25	N/A	N/A	ZS, ZZ, 0/0	FEV1, RV, TLC
Evaluate Efficacy and Safety of "Kamada-AAT for Inhalation" in Patients with AATD (InnovAATE 2019)[55]	N=220	NA	N/A	ZZ, Z/, or Null/ Null	FEV1, FVC

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Table 1 (Continued).

Authors and Year	Number of Participants	Participant Gender	Mean Age (SD) (Unless Stated Otherwise)	Genotype	Lung Function (AATD Participants Only) (Mean (SD) Unless Otherwise Stated)
Effects of Different Exercise Training Modalities in Alpha-1 Antitrypsin Deficiency Patients 2019[56]	N=30	N/A	N/A	ZZ	Not reported
Zemaira in Subjects With Emphysema Dua to Alpah1-Proteinase Inhibitor Deficiency 2005[57] *results available	N=180	98M 82F	53.13 (7.374)	ZZ, SZ, Z/null Other	FEV1 47.3(11.6)%; DLCO 14.3(5.5)mL/min/mmHg
Environment Effect on Six-Minute Walk Test Performance (6MWTAATD)[58] 2015	N=27	N/A	N/A	NR	FEV1 FVC
Effects of Pulmonary Rehabilitation on Skeletal Muscle in COPD Patients[59] 2016	N=40	N/A	N/A	NR	Not reported

Abbreviations: N/A, not applicable; NR, not reported; VC, vital capacity; FEV1, forced expiratory volume in the first second of a forced expiratory manoeuvre; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing lung capacity for carbon monoxide; IQR, interquartile range; V_A, alveolar volume; MEF, mid expiratory flow; BD, bronchodilator.

Table 2 The Study Design, Exercise or Physical Activity Outcome Measure, Intervention/Treatment Received and Control/Comparator and Aim of Included Studies

Authors and Year and Study Design	Exercise or Physical Activity Outcome Measure	Intervention/Treatment Received and Control/ Comparator (as Available)	Aim
Wencker and Konietzko 2000[24] Cross sectional	Symptom-limited submaximal treadmill exercise	N/A	To investigate whether blood gas concentrations at rest and during exercise in patients with severea1-Pi deficiency are correlated with severity of disease, as determined by FEV1 measurements.
Perkins et al 2017[25] Cross sectional	Exercise habits were originally categorized based on regularity and location of the exercise. These answers were combined so that any indication of exercise was considered a positive response for exercise	N/A	To describe characteristics of AATD patients enrolled in a disease management and prevention program
Olfert et al 2014[26] Cross sectional	CPET (VO2 peak)	N/A	To explore (i) if under resting conditions, α1-antitrypsin replacement therapy in AATD patients would result in lower expression of circulating and skeletal muscle inflammatory cytokines, compared to the other AATD individuals and/or the traditional (non-AATD) COPD patients and (ii)if circulating cytokine response to exercise would be lower in AATD patients receiving α1-antitrypsin replacement therapy compared to COPD or the other AATD subjects.
Kohnlein et al 2010[27] Cross sectional	Exercise capacity was assessed by counting the number of flights of stairs that a patient was able to climb without stopping.	N/A	To (i) describe the methods of identification of AATD patients, the latencies until establishment of the diagnosis, and the number of physicians involved until the final diagnosis was made, (ii) analyse the impact of environmental factors such as smoking, childhood smoke exposure, childhood chest infections, vaccinations, and augmentation therapy on age at symptom onset, exercise capacity, frequencies of exacerbations, hospitalizations, and emergency room visits.
Holm et al 2018[28] Cross sectional	Individuals were asked whether they exercised regularly, irregularly, or not at all. Individuals who indicated that they did not exercise at all were categorized as "does not exercise". Those who exercised irregularly or regularly were grouped together into a single category that captured engaging in some degree of exercise	N/A	To examine the association of genotype with smoking and other key health behaviors among individuals with AATD associated lung disease.

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Table 2 (Continued).

Authors and Year and Study Design	Exercise or Physical Activity Outcome Measure	Intervention/Treatment Received and Control/ Comparator (as Available)	Aim
Dowson et al 2001[29] Cross sectional	A symptom-limited exercise test on a treadmill according to the modified Naughton protocol. The workload was increased incrementally every 2 min by a combination of changes in speed and gradient ISWT	N/A	To investigate the relationship between exercise capacity, emphysema as quantified by high resolution computer tomography, physiological impairment, and health status in a homogeneous group of patients with AATD and predominantly lower zone emphysema
Thabut et al 2014[30] Prospective	6MWT	N/A	To validate the BODE index in a population of patients with AATD-related COPD, with survival as the outcome.
Jarosch et al 2016[31] Prospective	6MWT Sensewear armband	Treatment: The 3-week exercise training program inpatient. Control/comparator: Normal COPD	To compare PR effects on skeletal muscle adaptation in COPD patients with and with-out A1ATD.
Cassina et al 1998[32] Prospective	6MWT	Treatment: Bilateral LVRS Control/comparator: smokers emphysema	To compare the functional outcome over 2 years. of follow-up of patients with advanced α1PI-deficiency emphysema and heterogeneous smoker's emphysema who underwent bilateral LVRS
Tutic et al 2004[33] Prospective	6MWT	Treatment: LVRS Control/comparator: N/A	To study the course of dyspnoea, pulmonary function, and exercise tolerance in 21 patients with A1-ATD emphysema for as long as 5 years after surgery.
Tanash et al 2011[34] Prospective	6MWT	Treatment: LVRS Control/comparator: smokers emphysema	To determine whether there is a survival benefit of LTx in PiZZ individuals with severe emphysema.
Dauriat G et al 2006[35] Prospective	6MWT	Treatment: unilateral LVRS Control/comparator: Non AATD emphysema	To analyse the results of unilateral LVRS in our centre according to the α1 -AT status
Tanash et al 2014[36] Retrospective	6MWT	Treatment: Lung transplant Control/comparator: Normal COPD	To evaluate whether survival after LTx differs between severe AATD as compared with usual COPD.

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Jarosch I et al 2017[37] Retrospective	6MWT	Treatment: 4 week inpatient exercise programme Control/comparator: Normal COPD	To investigate PR effects on 6MWD in larger cohorts of AATD versus COPD patients
Kenn et al 2015[38] Retrospective	6MWT	Treatment: Pulmonary rehab 5–6 weeks, 5–6 sessions per week (25–30 sessions) Control/comparator: MMCOPD, CF, ILD, other (such as pulmonary hypertension, histiocytosis X, lymphangioleiomyomathosis, and other orphan diseases)	To evaluate the effects of a hospital-based PR on 6-min walking distance (6MWD) and HRQL in LTx candidates with different underlying diseases. In particular, we wanted to look if known predictors for PR outcome 16 are also relevant before LTx
Stoller et al 2011[39] RCT	6MWT Maximal, incremental, symptom-limited exercise on a cycle ergometer	Intervention: LVRS Control/comparator: Medical treatment	To explore (i) the frequency of severe AATD among NETT participants, (ii) the outcomes among participants with severe AATD randomized to LVRS versus medical therapy, (iii) the outcomes in AATD versus AAT replete participants among subjects undergoing LVRS in NETT
Stoller et al 2015[40] RCT	6MWT	Intervention: LTOT Control/comparator: LTOT	To compare use of supplemental oxygen vs not in subjects with COPD and moderate hypoxemia or normal oxygen saturation at rest and significant exercise desaturation
Choate et al 2021[16] RCT	Self-reported minutes of exercise activity per week	Intervention: Remote exercise intervention: 7 activities tailored according to the baseline BMI of the participants to improve their weight status. 5 year intervention period. Control/comparator: Both groups participated in a standard disease management program.	To examine the effectiveness of an intensive distance intervention in increasing exercise activity and improving BMI over time.

(*Continued*)

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Table 2 (Continued).

Authors and Year and Study Design	Exercise or Physical Activity Outcome Measure	Intervention/Treatment Received and Control/ Comparator (as Available)	Aim
Campos et al 2009[41] A non-randomized and non-concurrent trial	Self-report exercise (does not exercise regularly, exercises regularly, has started to exercise)	Intervention: An integrated system of directed patient self-education, including a comprehensive reference guide with detailed scientific and lay explanations about COPD and AATD, specifically directed towards a well-educated, informed patient. It was not intended to be a substitute for physician diagnosis and treatment Control/comparator: N/A	To evaluate the impact of the Alpha-1 Disease Management and Prevention Program in subjects with AATD.
Heinzelmann et al 2015[42] Conference abstract-retrospective	Peak work rate test	Treatment: 3 week exercise training Control/comparator: Normal COPD	In a retrospective analysis, we found that COPD patients (PiMM) showed higher improvements of exercise capacity following training intervention than AATD patients (PiZZ).
Chlumsky and Kusalova 2020[43] Conference abstract – retrospective	CPET	Treatment: N/A Control/Comparator: N/A	To report Czech data of subjects with severe AAT deficiency from the years 2006–2019
Balbi et al 2013[44] Conference abstract – retrospective	6MWT	Treatment: Pulmonary rehabilitation Control/Comparator: N/A	To determine effects of pulmonary rehabilitation in patients with COPD due to AATD
Delage et al 2019[45] Conference abstract – RCT	6MWT	Intervention: Endobronchial valve Control/comparator: Not reported	To report on the 6 and 12-month results of the AATD arm of the EMPROVE study

Choate et al 2017[46] Conference abstract – RCT	Self-reported number of exercise minutes per week.	Intervention: Remote exercise intervention: 7 activities tailored according to the baseline BMI of the participants to improve their weight status: to increase body weight in those in the low BMI category, maintain weight in the normal category, and reduce body weight in the high and very high BMI categories. 5 year intervention period. Control/comparator: Both groups participated in AlphaNet's standard disease management program.	To identify whether more intensive fitness intervention would improve physical activity and weight outcomes.
Tseng Do et al 2019[47] Conference abstract-Case study	6MWT	Treatment: The patient had four EBV placed in the left lower lobe for LVR Control: N/A	To highlight a case in which exercise ventilation perfusion scintigraphy and single photon emission computed tomography were used to isolate the target lobe for EBV treatment.
Menon et al 2017[48] Conference abstract – Case study	Distance walked in: can now walk from half a block to a block	Treatment: alpha 1 proteinase inhibitor Control/comparator: N/A	Not reported
Murray et al 2014[49] Conference abstract – cross sectional	6MWT	Treatment/intervention: N/A Control/comparator: N/A	To explore the impact of ZZ AATD on the diffusing capacity of the lung for carbon monoxide, and its relationship with functional exercise impairment among the Irish population of ZZ AATD individuals.
Durkan et al 2019[50] Conference abstract – cross sectional	6MWT	Treatment: N/A Control/comparator: Normal COPD	To explore whether exercise capacity is a better surrogate for health status in AATD COPD (ZZ) patients compared to alpha 1 antitrypsin replete MM COPD patients
Heinzelmann et al 2015[51] Conference abstract – prospective	6MWT Peak work rate test	Treatment: 3 week exercise training Control/comparator: Normal COPD	To explore if skeletal muscle adaptation is impaired in A1AD compared with COPD

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Table 2 (Continued).

Authors and Year and Study Design	Exercise or Physical Activity Outcome Measure	Intervention/Treatment Received and Control/ Comparator (as Available)	Aim
Strange et al 2015[52] Protocol- Cross-sectional study	6MWT	Intervention/treatment: N/A Control/comparator: comparing those on augmentation to those not receiving augmentation	To compare the lower respiratory tract microbiome and virome population diversity and content in age and stage matched individuals with PiZZ (based on Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines) not receiving augmentation therapy, individuals with PiZZ receiving augmentation therapy, PiMZ individuals not receiving augmentation therapy, and (normal nondeficient genotype) individuals with PiMM who have COPD 2. To determine correlations between BAL and peripheral blood gene expression patterns and patterns in lung microbial and viral populations across all cohorts 3. To correlate the presence or absence of CT-confirmed bronchiectasis and bronchiolectasis with patterns in the microbiome population diversity and content 4. To identify and define novel molecular phenotypes of AATD based on computational integration of clinical, transcriptomic, and microbiomic data
Greulich et al 2020[53] Protocol – Prospective	6MWT CPET	Intervention/treatment: N/A Control/comparator: N/A	To develop a pan-European, multicentre AATD registry incorporating baseline data from □3000 individuals during the first 3 years of the registry; To harmonise the data collection process between existing national registries and to ascertain high quality of the data by monitoring entered data closely; To generate longitudinal long-term, high-quality clinical data covering a pan-European population of AATD individuals of all age groups and all stages of disease severity; To understand the natural history and prognosis of AATD better with the goal to create and validate prognostic tools to support medical decision-making; To investigate the effect of AAT augmentation and other therapies on the progression of emphysema and to examine their potential impact on clinical and functional outcomes, such as FEV1, quality of life and mortality in a "real-life" population; To learn more about the course of the disease in patients suffering from severe AATD with genotypes other than PIZZ.

Endoscopic Lung Volume Reduction in Patients with Advanced Emphysema Due to alpha 1 Antitrypsin Deficiency 2019[54] Protocol – Prospective	6MWT	Intervention/treatment: LVRS Control/comparator: N/A	To explore the impact of endoscopic implantation of intrabronchial valves in patients with advanced heterogeneous emphysema due to alpha 1 antitrypsin deficiency
Evaluate Efficacy and Safety of "Kamada-AAT for Inhalation" in Patients with AATD (InnovAATE 2019)[55] Protocol – RCT	6MWT	Intervention: Kamada-AAT for Inhalation Control/comparator: Placebo	To evaluate Efficacy and Safety of "Kamada-AAT for Inhalation" in Patients With AATD
Effects of Different Exercise Training Modalities in Alpha-1 Antitrypsin Deficiency Patients 2019[56] Protocol – RCT	The ESWT is performed at 85% of the Peak gate Speed, measured during the Initial ISWT.	Intervention: High vs moderate Training intensity Control/comparator: N/A two intervention	To explore the impact of different training modalities in people with AATD
Zemaira in Subjects With Emphysema Due to Alpha 1-Proteinase Inhibitor Deficiency 2005[57] Protocol – RCT *results available	ISWT	Intervention: Zemaira Control/comparator: Placebo	To compare the efficacy and safety of Zemaira® with placebo in subjects with emphysema due to alpha 1-proteinase inhibitor deficiency.
Environment Effect on Six-Minute Walk Test Performance (6MWTAATD)2015[58] Protocol – RCT	6MWT	Intervention: 6MWT indoors 6MWT outdoors Control/comparator: participants served as their own controls	To explore the effect of the environment (indoors versus outdoors) on exercise capacity in people with AATD

(*Continued*)

https://doi.org/10.2147/COPD.S389001

Table 2 (Continued).

Authors and Year and Study Design	Exercise or Physical Activity Outcome Measure	Intervention/Treatment Received and Control/ Comparator (as Available)	Aim
Effects of Pulmonary Rehabilitation on Skeletal Muscle in COPD Patients 2016[59] Protocol- non randomized parallel group	Endurance time will be measured during a constant work rate cycling test	Intervention: 3-weeks of inpatient pulmonary Rehabilitation including exercise Training (daily endurance and strength Training) Control/comparator: Normal COPD	To compare the effects of pulmonary rehabilitation including exercise training on a) specific enzymes of energy metabolism reflecting the oxidative capacity of the skeletal muscle and b) the analogue gene expression of these oxidative enzymes in a cohort of PiMM and PiZZ COPD patients.

Abbreviations: AATD, Alpha-1 Antitrypsin Deficiency; BMI, Body mass index; COPD, Chronic Obstructive Pulmonary Disease; CPET, Cardiopulmonary exercise test; EBV, Endobronchial valve; Endurance Shuttle walk test; FEV1, forced expiratory volume in the first second of a forced expiratory manoeuvre; ISWT, Incremental shuttle walk test; LTOT, long term oxygen therapy; LTx, Lung transplant; LVRS, lung volume reduction surgery; N/A, not applicable; NETT, National Emphysema Treatment Trial; NR, not reported; PR, pulmonary rehabilitation; 6MWT/D, 6 minute walk test/distance; RCT, randomized controlled trial.

reported on the number of blocks the patient could walk pre- and post-treatment in an urban setting.[48] There was one device-based measure of PA recorded in an exercise intervention.[31] Nine AATD participants were included in this study of COPD patients with and without AATD. There were no measures of SB reported in the included studies.

Discussion

The aim of this study was achieved. There is a dearth in the assessment and reporting of PA in people with AATD. Only one study in this review objectively assessed PA in a small number of participants with AATD. Exercise capacity was the most commonly assessed outcome of interest.

Physical inactivity contributes to about five million deaths in the world each year from noncommunicable diseases.[60] Specifically, regular PA has been associated with a reduction in the risk for premature mortality and is an established means of reducing the risks for more than 25 chronic medical conditions including COPD.[61] PA has been established as the strongest predictor of mortality in people with COPD.[62] The current gap in the literature for the measurement of PA and PA interventions in people with AATD is therefore surprising. Eleven of the included studies reported on an exercise intervention. One could argue that the limitation of exercise interventions is that only a moderate to weak relationship has been established between PA and exercise capacity in people with COPD and other conditions.[63] Additionally, current evidence in the COPD population has demonstrated that improvements in exercise capacity do not automatically translate to enhanced PA levels, even when the improvements are gained through exercise training. Enhanced functional capacity and adaptive behavior change are necessary to achieve significant and lasting increases in daily PA in patients with COPD.[64] An added benefit of PA interventions in AATD is that the risk of liver disease related to AATD may also be reduced.[65] Future research should consider the impact of PA, exercise and SB on the entire clinical sequelae in people with AATD.

There has been increasing awareness around SB in recent years and the risks associated with premature mortality and morbidity for the general population.[66,67] A recent systematic review and meta-analysis demonstrated that high levels of SB are associated with a higher risk of metabolic syndrome which enhances the risk of both cardiovascular diseases and type 2 diabetes[68] which are common comorbidities observed in those with COPD.[69] Furthermore, a cohort study demonstrated the negative health impacts of prolonged SB in people with COPD including mortality risk and the development of type 2 diabetes.[70] There does not appear to be any published literature specifically exploring the impacts of SB in people with AATD. It is likely that intervention aimed at reducing SB by increasing participation in light-intensity PA is a realistic goal for people with AATD, which may be most applicable for those with marked functional impairment.[71] Future research is required to explore behavior change interventions that could enhance PA and reduce SB in people with AATD.

There are a wide range of validated and reliable tools for assessing PA and SB, including self-reported tools such questionnaires and device-based measures such as accelerometry which are routinely used in COPD research.[72–74] Given the availability of these tools, it is therefore unclear why researchers chose to use measurement methods which have not been validated or tested for reliability.

The use of these standardized tools is not only important to enhance the quality of the research in the AATD population but also to allow researchers to compare research studies and inform future research and practice. The use of validated and reliable outcome measures is recommended for future studies in this area. The inclusion of validated and reliable subjective measures of PA and SB as well as device-based measures could benefit future randomized controlled trials in AATD.

Strengths and Limitations

This scoping review covered a wide body of literature relating to PA in AATD. It has highlighted some important shortcomings in the AATD literature that if addressed, could improve the treatment of people with AATD. However, some relevant studies could have been excluded from this review as the authors did not distinguish the AATD population from other participants or they could have included people with underlying AATD that has not been diagnosed. Furthermore, some studies included in our review did not clarify if their AATD cohort was comprised of people with severe AATD, moderate AATD, or both. We have included three studies which are most likely duplicates due to reporting

in different platforms eg conference and full-text publications with some differences in terms of number of participants and participant characteristics. Given the broad scoping nature of this review, they were included.

Conclusion

Exercise capacity is the most commonly tested intervention and outcome measure in people with AATD. The assessment and use of interventions to enhance PA and reduce SB in AATD is limited. There is not only a need to test these interventions, but future research should use validated and reliable measures of PA and SB in this population.

Disclosure

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