International Journal of Chronic Obstructive Pulmonary Disease

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Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Pulmonary Function Decline in Alpha-1 Antitrypsin Deficiency: A Systematic Review and Meta-Analysis

Alice M Turner[1], Priscilla Wittkopf[2], Caroline von Wilamowitz-Moellendorff[2], Kyle Fahrbach[3], Mariana Farraia[4], May Hagiwara[5], Ed G Marins[5], Anne E Wyman[5], Lisi Wang[5], Suna Park[5]

[1]School of Health Sciences, University of Birmingham, Birmingham, UK; [2]Evidence Synthesis, Health Economics and Market Access, Evidera, London, UK; [3]Evidence Synthesis, Health Economics and Market Access, Evidera, Waltham, MA, USA; [4]Evidence Synthesis, Health Economics and Market Access, Evidera, Ede, Netherlands; [5]Takeda Development Center Americas, Inc., Cambridge, MA, USA

Correspondence: Alice M Turner, School of Health Sciences, University of Birmingham, Birmingham, UK, Tel +44 (0)121 371 3885, Email a.m.turner@bham.ac.uk

Background: Limited data exist on pulmonary function decline in patients with alpha-1 antitrypsin deficiency (AATD)-associated lung and/or liver disease. This study aimed to conduct a systematic literature review (SLR) and meta-analysis of pulmonary function decline and associated risk factors, clinical outcomes, and health-related quality of life (HRQoL) in patients with AATD-associated lung and/or liver disease.

Methods: Following PRISMA guidelines, studies were identified from MEDLINE/Embase (2003–2023) using Population, Intervention, Comparison, Outcomes, and Study criteria; key congresses were hand-searched (2021–2023). For each publication, two independent reviewers determined eligibility for inclusion and quality was assessed using relevant JBI tools. Meta-analyses were conducted on select outcomes that were deemed appropriate.

Results: Overall, 77 publications were included in the SLR and 32 reported pulmonary function decline in patients with AATD-associated lung and/or liver disease. Eight publications that evaluated forced expiratory volume in 1 second (FEV1) in mL, five that evaluated FEV1% predicted and four that evaluated HRQoL (as measured by St. George's Respiratory Questionnaire [SGRQ]) were deemed eligible for meta-analysis. In patients with AATD-associated lung disease, based on the random effects model, annualized change (95% confidence interval) in FEV1 was –39.1 (–45.2, –32.9) mL/year and –1.1 (–1.2, –0.9) %/year, and there was a slight worsening in SGRQ score (1.3 [0.6, 1.9] points/year). Data in patients with AATD-associated liver disease with or without comorbid lung disease were too limited to calculate an annualized rate of decline in pulmonary function or SGRQ.

Conclusion: This comprehensive SLR and meta-analysis provides an estimate for annual pulmonary function decline in patients with AATD-associated lung disease and highlights an evidence gap in patients with AATD-associated liver disease with or without comorbid lung disease. Further insights into risk factors or potential biomarkers of pulmonary function decline may support clinical strategies for optimizing treatment.

Keywords: alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, emphysema, meta-analysis, respiratory function test, quality of life

Introduction

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant genetic disorder primarily affecting the lungs and/or liver.[1] AATD is characterized by low levels of serum alpha-1 antitrypsin (AAT; a protease inhibitor [Pi] produced in the liver to maintain the protease–antiprotease balance within the lungs), leading to lung disease, and the accumulation of misfolded AAT (Z-AAT) in hepatocytes, which can result in liver disease.[2] The most severe AAT deficiency, and clinical features, are associated with the Pi*ZZ genotype, caused by a single homozygous substitution (Glu342Lys) in *SERPINA1* leading to the accumulation of Z-AAT in hepatocytes and an increased risk of developing liver disease. The Pi*SZ genotype is generally associated with less-severe lung and liver manifestations.[2]

https://doi.org/10.2147/COPD.S552227
Received: 17 July 2025
Accepted: 13 December 2025
Published: 9 January 2026

Patients with AATD-associated lung disease experience a decline in pulmonary function, with estimates of annualized rates of decline in forced expiratory volume in 1 second (FEV1) in those with a Pi*ZZ genotype ranging from 28 to 109 mL/year.[3,4] In patients with AATD-associated lung disease, emphysema and chronic obstructive pulmonary disease (COPD) are the most frequently observed lung manifestations. Treatment options include weekly intravenous infusions of plasma-derived AAT and largely focus on reducing the burden of pulmonary symptoms and exacerbations.[5–7]

Patients with AATD-associated liver disease have a variable clinical presentation, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma, and may be asymptomatic at early stages of liver disease.[8] Currently, there are no approved pharmacological therapies for patients with AATD-associated liver disease; the only treatment option for patients with end-stage liver disease is liver transplantation.[7,9]

Patients with AATD may also present with comorbid lung and liver disease with estimates ranging from 17.0% to 37.7% of patients with AATD and a Pi*ZZ genotype displaying both liver and lung disease.[10–12] Understanding the heterogeneity in disease manifestation, exacerbation, and lung function trajectories in patients with AATD-associated lung and/or liver disease may help guide treatment decisions and health policy.

AATD-associated lung and/or liver disease impose a significant clinical and health-related quality of life (HRQoL) burden on affected individuals and the factors contributing to pulmonary function decline over time in these patients are not fully understood.[13] To the best of our knowledge, no systematic literature review (SLR) has been published to date that examines change in HRQoL in patients with AATD-associated lung disease. In addition, prior SLRs of lung disease progression were restricted in scope (eg only analyzed patients receiving augmentation therapy or those assessed by computed tomography [CT]) or had potential methodological issues (eg combined studies in a single meta-analysis without consideration of clinical and methodological heterogeneity).[14–16] Therefore, we aimed to conduct a methodologically robust SLR and meta-analysis in patients with AATD-associated lung and/or liver disease to investigate pulmonary function decline and associated risk factors, clinical outcomes of pulmonary function change, and HRQoL outcomes.

Materials and Methods

Systematic Literature Review

The SLR was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions guidelines.[17,18]

Data Sources

Searches were conducted on July 20, 2023 using MEDLINE and Embase for publications of observational studies and randomized controlled trials (RCTs) from 2003 to 2023 (the search strategy is detailed in Table S1). Data were assessed over a 20-year time period to ensure that the most recent peer-reviewed evidence was identified and highlighted. Congress publications (European Association for the Study of the Liver, American Thoracic Society, and European Respiratory Society) were hand-searched from 2021 to 2023.

Eligibility Criteria

Population, Intervention, Comparison, Outcomes, and Study (PICOS) eligibility criteria are presented in Table 1. Publications reporting lung function tests, risk factors for pulmonary function decline, and HRQoL outcomes in patients with AATD-associated lung and/or liver disease were included.

Screening and Data Extraction

The titles and abstracts from publications identified in the searches were screened against the predefined PICOS eligibility criteria. The full texts of abstracts deemed eligible for inclusion were further reviewed to assess their eligibility for data extraction. For title and abstract screening and full-text review, two independent reviewers determined the eligibility of each publication for inclusion, with any disagreements resolved by a third reviewer, as necessary. Data from included studies were extracted into a data extraction table designed in Microsoft Excel by one reviewer; a second

Table 1 PICOS Inclusion/Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	• Adult and pediatric patients with: ○ AATD-associated lung disease ○ AATD-associated liver disease ○ AATD-associated lung and liver disease • Subgroups of interest including: ○ patients with AATD and a Pi*MZ, Pi*SZ, or Pi*ZZ genotype ○ adults with AATD ○ children with AATD	• Publications with mixed populations (ie those in which not all patients have AATD or lung/liver disease) will be included only if: ○ data are reported stratified for the population of interest ○ at least 80% of the mixed population is eligible for inclusion
Interventions/ comparators	• Any or none	• Not applicable
Outcomes	• Lung function tests including: ○ spirometry (FEV1, FVC, FEV1/FVC) ○ CT lung densitometry ○ DLCO • Lung and/or liver transplantation • Risk factors for lung function decline including: ○ age ○ sex ○ phenotype ○ smoking status (including passive smokers) ○ comorbidities ○ lung disease or surgery ○ prior exacerbations and infections ○ respiratory therapy (ie AAT augmentation therapy and long-term oxygen therapy) ○ predictors of acute exacerbation of COPD (eg chronic bronchitis) • HRQoL (assessed using validated generic instruments: EQ-5D, SF-36/SF-12; and disease-specific instruments: SGRQ, CRQ-SR, Liver Disease QoL questionnaire, Chronic Liver Disease questionnaire)	• Relevant outcomes are not reported, or data are not extractable (ie only available from figures needing to be digitized) • Studies evaluating a mixed population but results are not reported for AATD-associated lung disease, AATD-associated lung and liver disease, or AATD-associated liver disease separately • Lung function tests reported only at baseline with no change over time • Studies comparing outcomes of patients with AATD-associated lung and/or liver disease compared with those with lung or liver disease and no AATD
Study design	• Observational studies (cohort, cross-sectional, case-control), including prospective, retrospective cohort studies (eg database analyses) and registries • Correlation studies (including multivariate and/or univariate analyses) • RCTs	• Conference abstracts published prior to 2021 • Editorial, erratum, trial protocol, guideline, case report, narrative review, etc. • In vitro, ex vivo, animal, or pharmacokinetic studies, etc. • SLRs/NMAs from the past 3 years on lung function decline in patients with AATD-associated lung and/or liver disease to be used for citation chasing[†] but will not be included in the SLR
Limits	• Geographical limits: none • Time limits: 2003 onwards • Language: English language	

Note: [†]Citation chasing is the screening of titles of studies included in a published SLR to determine if any were eligible for inclusion in this review.

Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; CRQ-SR, Chronic Respiratory Questionnaire – Self Reported; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; EQ-5D, EuroQol 5-Dimension questionnaire; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRQoL, health-related quality of life; NMA, network meta-analysis; Pi, protease inhibitor; PICOS, Population, Intervention, Comparison, Outcomes, and Study; QoL, quality of life; RCT, randomized controlled trial; SF-12, 12-item Short-Form Health Survey; SF-36, 36-item Short-Form Health Survey; SGRQ, St. George's Respiratory Questionnaire; SLR, systematic literature review.

reviewer assessed the entries to ensure consistency and accuracy against the source article. Extracted data included publication details, study characteristics (eg sample size, geographical location, follow-up duration, eligibility criteria), patient characteristics (eg age, AATD genotype, comorbidities, treatment characteristics), and reported outcomes (as defined in Table 1).

Quality Assessment

Study quality was assessed by evaluating comparability of intervention group, exposure and outcome measurements, handling of confounding factors, potential for bias, and statistical analysis, using the relevant study design-specific critical appraisal tool from the JBI.[19] Quality assessments were performed by one reviewer and validated by a second reviewer. Quality was determined by evaluating responses to specific criteria: studies that had any question classified as "no" were considered to have "some concern", those with at least one "unclear" response were noted as "unclear", and all domains with responses of "yes" or "not applicable" were considered to have "adequate" quality. The quality assessment is detailed in Table S2.

Meta-Analysis

A feasibility assessment was conducted to identify publications with sufficient clinical and methodological similarity to be amenable to quantitative synthesis. Fixed- and random-effects frequentist meta-analyses were conducted for outcomes deemed eligible for meta-analysis to calculate an annualized rate of decline. Annualized rate of decline was calculated as the total number of events divided by total follow-up in years for each study arm, assuming a linear relationship. Analyses used all available data and were stratified by AAT augmentation therapy status. For each outcome, the mean and 95% confidence interval (CI) were reported and heterogeneity across studies was investigated and quantified using the I^2 measure. All meta-analyses were conducted using a restricted maximum-likelihood approach with the package *metafor* (version 4.6–0) in R software (version 4.1.3).

Results

Systematic Literature Review

In total, 77 publications (50 unique data sources) met the PICOS eligibility criteria for the SLR (Figure 1). Of these, 49 publications (34 unique data sources; 4,971 patients) reported longitudinal change over time in pulmonary function and CT lung densitometry, clinical outcomes associated with pulmonary function and/or CT lung densitometry, and risk factors for disease progression based on pulmonary function and/or CT lung densitometry (Table 2).[3,13,14,20–65] The remaining 28 articles reported cross-sectional data and were, therefore, not relevant for the SLR; these articles are not discussed herein.

Study Characteristics

Eleven publications that reported on seven RCTs and one open-label extension were included (Table S2),[14,20–29] all of which included patients with AATD-associated lung disease. Across RCTs, population size by trial arm ranged from 6 to 133 patients and mean study duration ranged from 35 weeks to 2.5 years. Studies recruited patients based in Europe (6 RCTs; 10 publications),[14,20–22,24–29] North America (4 RCTs; 7 publications),[22,23,25–29] and Asia-Pacific (2 RCTs; 5 publications).[25–29] All RCTs investigated treatments and their efficacy, including augmentation therapies containing plasma-derived alpha-1 proteinase inhibitor such as prolastin, lung volume reduction surgery, long-acting bronchodilators, and inhaled corticosteroids.[14,20–29]

In total, 38 observational study publications in patients with AATD-associated lung disease (30 publications),[3,30–58] AATD-associated lung and liver disease (7 publications),[13,59–63,65] and AATD-associated liver disease (1 publication)[64] were included in the SLR (Table S3). Population size ranged from 11 to 14,644 patients and follow-up time from 6 months to 17 years; publications reported patients based in Europe (30 publications)[3,13,30–40,44–56,58,62,63,65] and/or North America (9 publications).[39,41–43,57,59–61,64]

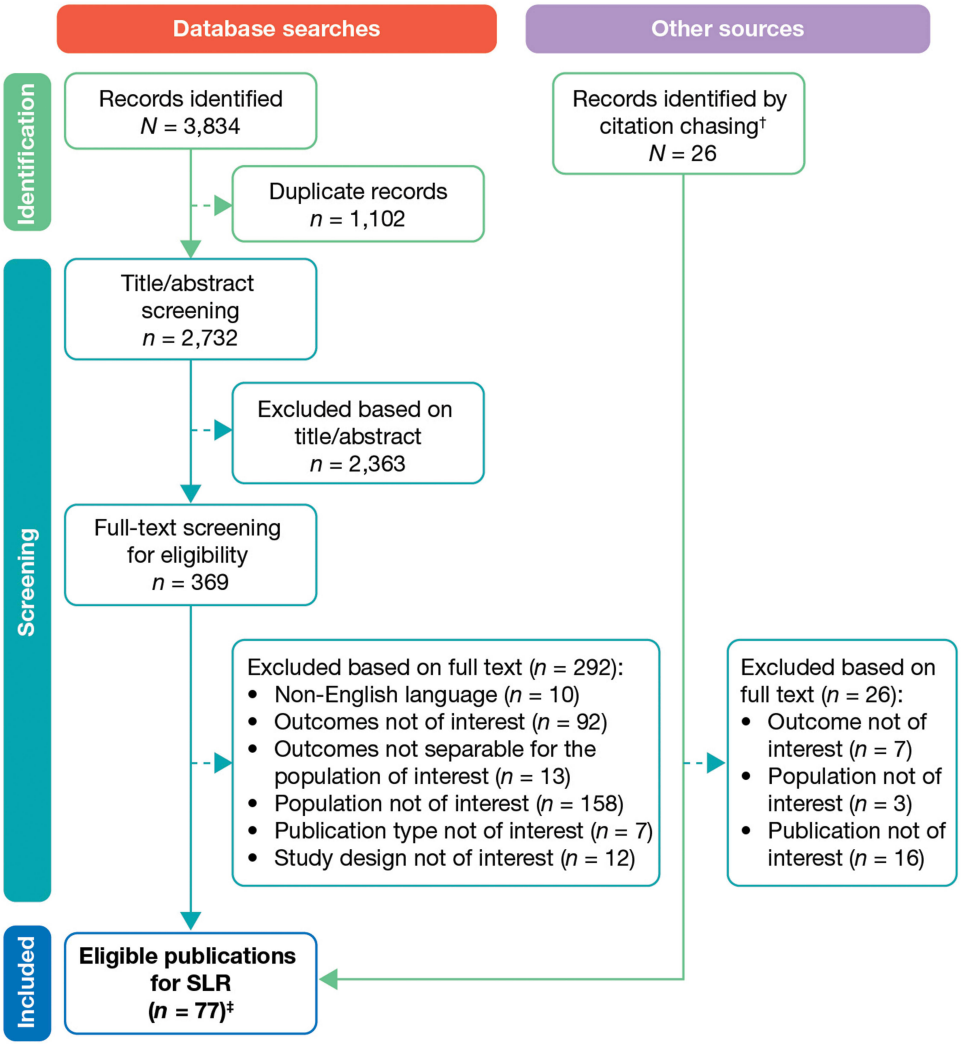

Figure 1 PRISMA Flow Diagram. †Citation chasing is the screening of titles of studies included in a published SLR to determine if any were eligible for inclusion in this review. ‡50 unique data sources.
Abbreviations: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR, systematic literature review.

Patient Baseline Characteristics

Of seven RCTs (8 publications) that evaluated patients with AATD-associated lung disease,[14,20,22–25,27,28] four and three RCTs reported patients with emphysema and COPD, respectively. All publications included adults with AATD. All seven RCTs included patients with a Pi*ZZ genotype; patients with other rare genotypes were reported in four of these RCTs (Table S4). In six of seven RCTs,[14,20,22,24,25,28] the reported mean (standard deviation [SD]) baseline FEV1% predicted values ranged from 40% (12%) in 8 patients who received long-acting bronchodilators and placebo or inhaled corticosteroids to 51.2% (14.5%) in 27 patients who received placebo.[14,24] In the remaining study, median (interquartile range) FEV1% predicted at baseline in patients with emphysema who received lung volume reduction surgery (n = 10) or other medical treatment (n = 6) was 27.0% (26.0%, 32.0%) and 25.0% (21.0%, 33.0%), respectively.[23]

Of observational studies that reported patients with AATD-associated lung disease,[3,30,31,34,35,37–58] all included adults with AATD and most described patients with a Pi*ZZ genotype, although other genotypes (such as Pi*MZ, Pi*MS, Pi*SS, Pi*SZ, and Pi*ZNull) were also reported (Table S5). For patients with AATD-associated lung disease, pulmonary function at baseline varied across publications; for 14 publications that reported mean (SD) FEV1% predicted, values ranged from 22.2% (5.7%) in 17 patients who underwent unilateral lung volume reduction surgery[47] to 65.0% (23.7%) in 113 patients with AATD and COPD.[34]

https://doi.org/10.2147/COPD.S552227

Table 2 Publications Included in the SLR by Research Question

Research Question	Number of Publications (Unique Data Sources)[†]							
	Total		AATD-Associated Lung Disease		AATD-Associated Lung and Liver Disease		AATD-Associated Liver Disease	
How does pulmonary function and CT lung densitometry change/decline over time?	RCT: 10 (8) Observational: 22 (16)	32 (n = 2,813)	RCT: 10 (8) Observational: 19 (13)	29 (n = 1,952)	RCT: 0 Observational: 2 (2)	2 (n = 738)	RCT: 0 Observational: 1 (1)	1 (n = 123)
What are the clinical outcomes associated with change in pulmonary function and/or CT lung densitometry?	RCT: 4 (4) Observational: 18 (15)	22 (n = 3,983)	RCT: 4 (4) Observational: 11 (9)	15 (n = 2,525)	RCT: 0 Observational: 6 (5)	6 (n = 1,335)	RCT: 0 Observational: 1 (1)	1 (n = 123)
What are the risk factors that impact pulmonary function and/or CT lung densitometry change/decline?	RCT: 1 (1) Observational: 8 (6)	9 (n = 1,602)	RCT: 1 (1) Observational: 6 (4)	7 (n = 883)	RCT: 0 Observational: 2 (2)	2 (n = 719)	RCT: 0 Observational: 0	0 (n = 0)
Total number of included studies[†]	RCT: 11 (8) Observational: 38 (26)	49 (n = 4,971)	RCT: 11 (8) Observational: 30 (19)	41 (n = 3,513)	RCT: 0 Observational: 7 (6)	7 (n = 1,335)	RCT: 0 Observational: 1 (1)	1 (n = 123)

Note: [†]Sample sizes were calculated assuming no overlap in patient populations between studies and denoted with n = . To minimize double counting of patients and potential heterogeneity between observational cohorts, for the meta-analysis, a single publication was selected from each observational data source according to its relevance, the availability of patient characteristics, and the population size. [‡]Total number of included studies may sum to less than the sum of the above three rows because some studies addressed more than one research question.

Abbreviations: AATD, alpha-1 antitrypsin deficiency; CT, computed tomography; RCT, randomized controlled trial; SLR, systematic literature review.

https://doi.org/10.2147/COPD.S552227

Of observational studies that reported patients with AATD-associated lung and liver disease (7 publications),[13,59–63,65] emphysema and COPD were the most common lung manifestations reported, and non-specified liver disease and cirrhosis were the most common liver disease manifestations (Table S5). All publications reported patients with a Pi*ZZ genotype; Pi*SZ and other rare variants were described in three publications. Of publications that reported mean (SD) baseline FEV1% predicted values (4 publications),[13,62,63,65] values ranged from 32% (19%) in 284 patients with COPD and long-term oxygen therapy to 68% (31%) in 155 patients with severe AATD (Pi*ZZ, Pi*ZNull, or Pi*NullNull genotype).[63,65] One observational study reported patients with AATD-associated liver disease only; 50/123 patients (40.7%) had a Pi*ZZ genotype and mean (SD) baseline FEV1% predicted was 82.8% (22.6%).[64]

Pulmonary Function Decline

Overall, 32 publications (24 unique data sources) reported changes in pulmonary function over time, largely noting a decline (negative change). Of these, 29 publications reported patients with AATD-associated lung disease,[3,14,20–25,27–29,31–36,38,40,44,45,47–49,52,53,55,56,58] two publications reported patients with AATD-associated lung and liver disease,[59,62] and one publication reported patients with AATD-associated liver disease.[64] A narrative synthesis of the results of these studies is provided in the Supplementary Text and Tables S6–S20.

A comprehensive meta-analysis feasibility assessment was conducted to evaluate the comparability of baseline characteristics and outcomes relating to pulmonary function decline across all publications included in the SLR. The feasibility assessment concluded that a meta-analysis was possible for eight publications that evaluated FEV1 in mL and five publications that evaluated FEV1% predicted to calculate an annualized rate of FEV1 decline (in mL or % predicted).[20,25,28,31,35,40,44,48,49,59] Outcomes relating to forced vital capacity (FVC % predicted; Table S9 and Table S13), FEV1/FVC (Table S8 and Table S15), diffusing capacity of the lung for carbon monoxide (DLCO % predicted; Table S17 and Table S18), lung and/or liver transplantation (Table S21), and risk factors for pulmonary function decline (Table S22) were not deemed eligible for meta-analysis owing to the limited number of publications reporting data, as well as methodological and clinical heterogeneity (Table S23 and Table S24).

Eight publications reported decline in FEV1 (mL) (Table 3).[20,22,28,31,40,48,49,59] Patient populations ranged from 42 to 584 patients and five publications had a follow-up time of at least 2 years;[20,31,40,48,49] where reported, baseline FEV1

Table 3 Studies Contributing to a Meta-Analysis of Change in FEV1 (mL) Over Time in Patients with AATD-Associated Lung Disease

Trial Name, Author, Year	Study Design	Follow-Up Time	Study Arm	Study Size, n	Baseline FEV1 (mL), Mean (SD)	AATD Genotype, %
EXACTLE, Dirksen, 2009[20]	RCT	Median: 2.0–2.5 years	Augmentation	38	1,440 (600)	Pi*ZZ: 100
			No augmentation	39	1,350 (620)	
NCT01217671, Stolk, 2019[22]	RCT	Median: 50 weeks	Augmentation	79	1,320 (490)	Pi*ZZ or other rare genotypes: 100
			No augmentation	81	1,330 (530)	
REPAIR, Stolk, 2012[28]	RCT	Median: 12 months	Augmentation	110	1,560 (600)	NR
			No augmentation	117	1,510 (600)	
NR, Bradi, 2015[59]	Retrospective cohort	NR	Overall population	42	NR	Pi*ZZ: 90; Pi*SZ: 5.5; other rare variants: 4.5
NR, Hiller, 2019[49]	Retrospective cohort	At least 4 years	Overall population	584	NR	NR
NR, O'Brien, 2015[48]	Retrospective cohort	Median: 5 years	Overall population	72	NR	Pi*ZZ: 100

(*Continued*)

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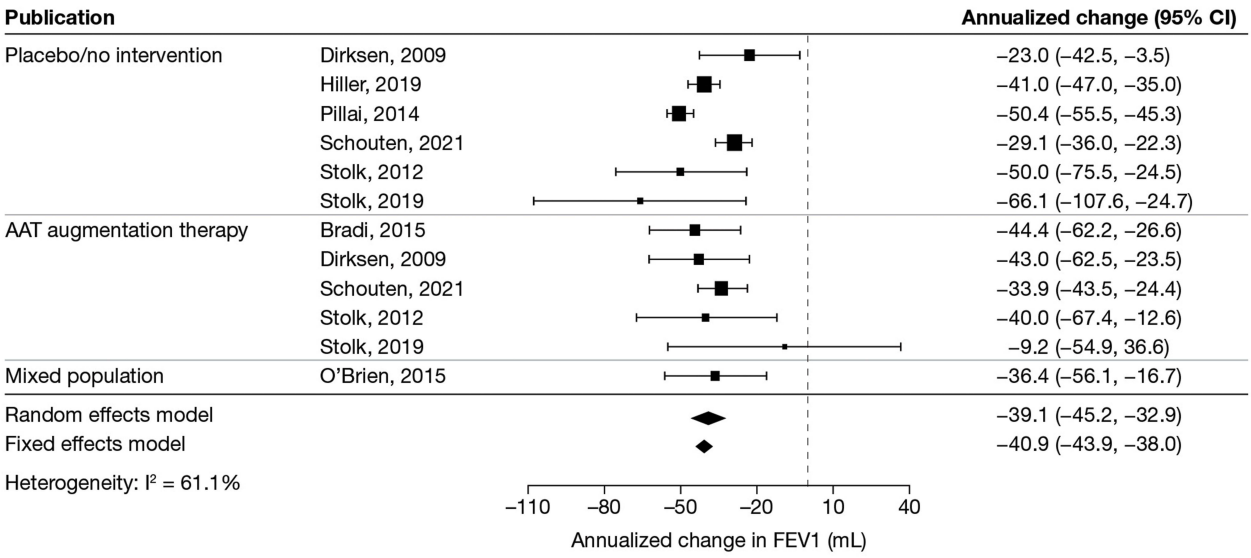
Table 3 (Continued).

Trial Name, Author, Year	Study Design	Follow-Up Time	Study Arm	Study Size, n	Baseline FEV1 (mL), Mean (SD)	AATD Genotype, %
NR, Pillai, 2014[31]	Retrospective cohort	Median (range): 9 (3–15) years	Overall population	502	NR	Pi*ZZ: 100
NR, Schouten, 2021[40]	Retrospective cohort	Mean (SD): 8.60 (3.34) years	Augmentation	128	NR	Pi*ZZ: 100
		Mean (SD): 8.59 (2.62) years	No augmentation[†]	246	NR	

Note: [†]Patients either were known to not receive augmentation therapy (Spain, Germany, and Italy; those who did not have known augmentation therapy status were excluded) or came from countries where augmentation therapy was not available and reimbursed (Netherlands and the UK).
Abbreviations: AATD, alpha-1 antitrypsin deficiency; FEV1, forced expiratory volume in 1 second; NR, not reported; Pi, protease inhibitor; RCT, randomized controlled trial; SD, standard deviation.

ranged from 1,320 mL to 1,560 mL. Most publications reported FEV1 (mL) decline in patients with AATD-associated lung disease; only one publication evaluated patients with AATD-associated lung and liver disease,[59] and no studies evaluated patients with AATD-associated liver disease only. Annualized decline (95% CI) in FEV1 (mL) in patients with AATD-associated lung disease was –39.1 (–45.2, –32.9) mL/year in the random effects model with moderate heterogeneity (I^2 = 61.1%; Figure 2). Patients who received placebo or no intervention had a numerically greater annualized decline in FEV1 in mL (–40.2 [–50.2, –30.2] mL/year) than patients who received AAT augmentation therapy (–36.8 [–44.1, –29.4] mL/year; Figure 2).

Five publications reported decline in FEV1% predicted in patients with AATD-associated lung disease (Table 4).[22,25,35,40,44] Sample size ranged from 11 to 482 patients and three publications had a follow-up time of at



	Overall	Placebo/no intervention	AAT augmentation therapy
Random effects model	–39.1 (–45.2, –32.9)	–40.2 (–50.2, –30.2)	–36.8 (–44.1, –29.4)
Fixed effects model	–40.9 (–43.9, –38.0)	–41.9 (–45.2, –38.6)	–36.8 (–44.1, –29.4)
Heterogeneity (I^2)	61.1%	82.6%	0%

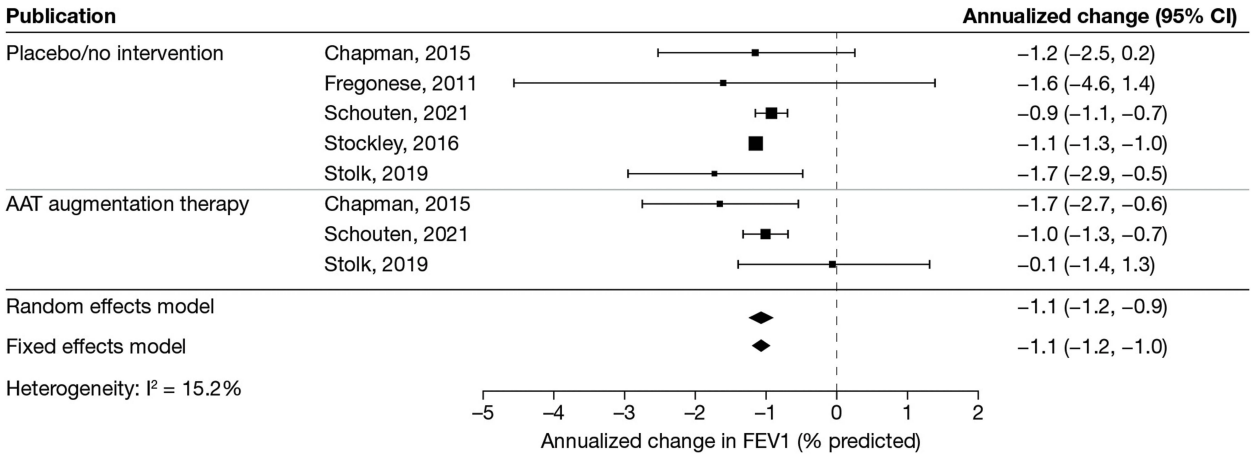
Figure 2 Annualized Decline in FEV1 (mL) in Patients with AATD-associated Lung Disease.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; FEV1, forced expiratory volume in 1 second.

Table 4 Studies Contributing to a Meta-Analysis of Change in FEV1 (% Predicted) Over Time in Patients with AATD-Associated Lung Disease

Trial Name, Author, Year	Study Design	Follow-Up Time	Study Arm	Study Size, n	Baseline FEV1 (% Predicted), Mean (SD)	AATD Genotype, %
NR, Stolk, 2019[22]	RCT	Median: 50 weeks	Augmentation	79	42.8 (14.8)	Pi*ZZ or other rare genotypes: 100
			No augmentation	81	41.8 (14.7)	
RAPID, Chapman, 2015[25]	RCT	2 years	Augmentation	93	47.4 (12.1)	Pi*ZZ: 93
			No augmentation	87	47.2 (11.1)	
NR, Fregonese, 2011[44]	Retrospective cohort	14 months	Overall population	11	44.2 (SE: 5)	Pi*ZZ: 100
NR, Schouten, 2021[40]	Retrospective cohort	Mean (SD): 8.62 (3.34)	Augmentation	128	NR	Pi*ZZ: 100
		Mean (SD): 8.59 (2.62)	No augmentation†	246	NR	
NR, Stockley, 2016[35]	Retrospective cohort	3 years	Overall population	482	53.1 (21.9)	Pi*ZZ: 100

Note: †Patients either were known to not receive augmentation therapy (Spain, Germany, and Italy; those who did not have known augmentation therapy status were excluded) or came from countries where augmentation therapy was not available and reimbursed (Netherlands and the UK).
Abbreviations: AATD, alpha-1 antitrypsin deficiency; FEV1, forced expiratory volume in 1 second; NR, not reported; Pi, protease inhibitor; RCT, randomized controlled trial; SD, standard deviation; SE, standard error.

least 2 years. Where reported, average baseline FEV1% predicted ranged between 41.8% and 53.1%. Annualized decline (95% CI) in FEV1% predicted in patients with AATD-associated lung disease was –1.1 (–1.2, –0.9) %/year in the random effects model with little heterogeneity (I^2 = 15.2%; Figure 3). Patients who received placebo or no intervention



	Overall	Placebo/no intervention	AAT augmentation therapy
Random effects model	–1.1 (–1.2, –0.9)	–1.1 (–1.3, –0.9)	–1.0 (–1.3, –0.7)
Fixed effects model	–1.1 (–1.2, –1.0)	–1.1 (–1.2, –1.0)	–1.0 (–1.3, –0.7)
Heterogeneity (I^2)	15.2%	28.6%	0%

Figure 3 Annualized Decline in FEV1 (% Predicted) in Patients with AATD-associated Lung Disease.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; FEV1, forced expiratory volume in 1 second.

https://doi.org/10.2147/COPD.S552227

Table 5 Studies Contributing to a Meta-Analysis of Change in SGRQ Score Over Time in Patients with AATD-Associated Lung Disease

Trial Name, Author, Year	Study Design	Follow-Up Time	Study Arm	Study Size, n	Baseline SGRQ Score, Mean (SD)	AATD Genotype, %
RAPID, Chapman, 2015[25]	RCT	2 years	Augmentation	93	44.3 (17.1)	Pi*ZZ: 93
			No augmentation	87	42.4 (18.0)	
EXACTLE, Dirksen, 2009[20]	RCT	Median: 2.0–2.5 years	Augmentation	38	41.9 (17.9)	Pi*ZZ: 100
			No augmentation	39	46.1 (17.2)	
NR, Stockley, 2016[35]	Retrospective cohort	3 years	Overall population	482	48.2 (33.9, 62.4)[†]	Pi*ZZ: 100
NR, Ellis, 2023[39]	Retrospective cohort	Mean (SD): 4.72 (1.96) years	Augmentation	426	43.9 (19.1)	Pi*ZZ: 95.3; Z Null: 2.8; Other: 1.9
		Mean (SD): 3.77 (1.57) years	No augmentation	115	44.9 (18.6)	Pi*ZZ: 93.9; Z Null: 2.6; Other: 3.5

Note: [†]Median (IQR).
Abbreviations: AATD, alpha-1 antitrypsin deficiency; IQR, interquartile range; NR, not reported; Pi, protease inhibitor; RCT, randomized controlled trial; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

and patients who received AAT augmentation therapy demonstrated similar rates of annualized decline in FEV1% predicted (–1.1 [–1.3, –0.9] %/year vs –1.0 [–1.3, –0.7] %/year; Figure 3).

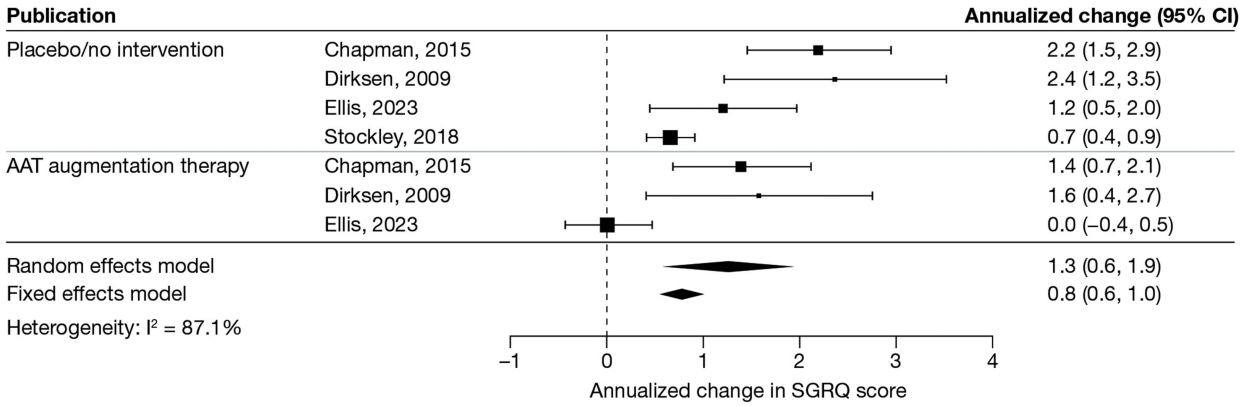
Patient-Reported Outcomes

All reported HRQoL outcomes were related to the St. George's Respiratory Questionnaire (SGRQ; scored from 0 to 100 with higher scores indicating worse HRQoL). Narrative synthesis results are provided in the Supplementary Text, Table S25 and Table S26.

Following the meta-analysis feasibility assessment described above, four publications that reported change in SGRQ score were deemed eligible for meta-analysis (Table 5).[20,25,35,39] Of these, all reported change in SGRQ score in patients with AATD-associated lung disease; the population size ranged from 38 to 482 patients and all studies had a follow-up duration of at least 2 years. Across study arms, mean baseline SGRQ score ranged from 41.9 to 46.1[20] and one study reported a median baseline SGRQ score of 48.2.[35] Annualized change (95% CI) in SGRQ score in patients with AATD-associated lung disease was 1.3 (0.6, 1.9) points/year in the random effects model but statistical heterogeneity was high (I^2 = 87.1%; Figure 4) and could not be explained by the stratification of patients by receipt of placebo or no intervention versus AAT augmentation therapy (1.5 [0.7, 2.3] points/year vs 0.9 [−0.1, 1.9] points/year; Figure 4).

Risk Factors for Pulmonary Function Decline

Although it is an important consideration when assessing patient baseline characteristics in a meta-analysis, risk factors for pulmonary function decline were not assessed for meta-analysis feasibility but were included in the SLR. Three publications reported on risk factors for pulmonary function decline in patients with AATD-associated lung disease (2 publications)[3,31] and AATD-associated lung and liver disease (1 publication)[60] (Table S22). In one study of 502 patients with AATD-associated lung disease with a median follow-up of 9 years, age and mild COPD were independently predictive of FEV1 (mL) decline per year, while sex and smoking status were not associated with FEV1 (mL) decline.[31] Severe COPD was an independent predictor of decline in carbon monoxide transfer coefficient, while age, sex, and smoking status were not.[31] In 41 patients with AATD-associated lung and liver disease and a median follow-up of 4 months, smoking status was associated with a decline in FEV1% predicted, while no association was found between pulmonary function decline and age, sex, and type of liver disease.[60]



	Overall	Placebo/no intervention	AAT augmentation therapy
Random effects model	1.3 (0.6, 1.9)	1.5 (0.7, 2.3)	0.9 (–0.1, 1.9)
Fixed effects model	0.8 (0.6, 1.0)	0.9 (0.7, 1.1)	0.5 (0.2, 0.9)
Heterogeneity (I^2)	87.1%	84.5%	83.2%

Figure 4 Annualized Decline in HRQoL Measured by SGRQ Score in Patients with AATD-associated Lung Disease.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire.

Discussion

This SLR and meta-analysis synthesized data from both clinical trials and observational studies to provide annualized rates of pulmonary function decline across studies in patients with AATD-associated lung disease, thus enabling comparisons between studies regardless of their duration. Our findings highlight the gradual deterioration in lung function and HRQoL of these patients, albeit with high heterogeneity, and emphasized the lack of evidence on pulmonary function change in patients with AATD-associated liver disease with or without lung disease. These observations may have implications for clinical trial design and clinical care.

In patients with AATD-associated lung disease, there was an overall decline in annualized rate of pulmonary function, as measured by FEV1 in mL and % predicted, and a slight worsening in HRQoL, as measured by SGRQ score. As it was anticipated that augmentation therapy may alter the natural course of disease progression,[39] meta-analyses were conducted stratified by augmentation therapy status. Another consideration is the duration of time that patients received augmentation therapy because the literature suggests that pulmonary function decline is not necessarily linear.[66,67] Therefore, our estimates of annualized rates of pulmonary function decline, which assume linear progression, may not be fully representative of the AATD disease trajectory.

In the meta-analysis, patients who received AAT augmentation therapy reported a slightly lower annualized rate of decline in FEV1 in mL than patients who received placebo or no intervention (–36.8 mL/year vs –40.2 mL/year). However, the placebo or no intervention group showed high heterogeneity (I^2 = 82.6%), indicating that the true annual decline likely varies across different study designs (ie RCTs and observational studies) and patient characteristics (eg disease severity and baseline pulmonary function values). For annualized change in FEV1% predicted, rates of decline were similar between patients who received augmentation therapy and those who received placebo or no intervention, with little statistical heterogeneity observed in each analysis. For annualized change in SGRQ, patients who received augmentation therapy reported a numerically smaller increase in score (0.9 points/year) than those who received placebo or no intervention (1.5 points/year), indicating poorer HRQoL in patients who received placebo or no intervention, which is consistent with prior literature.[39] While these observations indicate a difference between these groups, it should be noted that the minimum clinically important differences for FEV1 in mL and SGRQ score are 100 mL[68] and 4 points,[69] respectively, suggesting that longer follow-up (~5.0 years) may be needed to detect clinically significant change, whether on or off augmentation therapy. These data are consistent with a recent Delphi consensus survey in patients with AATD-

https://doi.org/10.2147/COPD.S552227

associated lung disease which recommended annual lung function testing in patients with and without respiratory disease and implied long-term follow-up.[70]

Age, COPD severity, smoking status, history of pneumonia, and baseline lung function were identified as potential predictors of pulmonary function decline from individual studies identified in the SLR. These variables may be of interest when designing studies of therapies that aim to modify lung disease trajectories. Additionally, these data highlight the need to consider individual patient characteristics when assessing risk for accelerated decline. Despite these observations, patients with a history of pneumonia and frequent exacerbations or infections are often excluded from clinical trials owing to the risk of adverse events. These patients may be important to include in future analyses because they are more likely to show pulmonary function decline, and thus inclusion might improve estimates of pulmonary function decline by focusing on those at high risk, even with small population sizes.

Whilst changes were observed in lung function and HRQoL, it was notable that changes were relatively small, perhaps challenging the established paradigm that patients with AATD-associated lung disease deteriorate faster than patients with non-AATD-associated COPD. A meta-analysis of studies of patients with COPD showed that the annual rate of FEV1 (in mL) decline ranged from –46 mL/year to –81 mL/year in patients who received placebo.[71] It is possible that the availability of AAT augmentation therapy in patients with AATD has modified pulmonary function decline and resulted in a greater focus on disease progression as an outcome at an individual level; the true value of pulmonary function decline in patients with non-AATD-associated COPD may be refined over time. Irrespective of the reason for these differences, high heterogeneity implies that other methods of analysis or assessment of surrogate markers of deterioration may be required to optimize detection of worsening pulmonary function in clinical practice, and to enable reasonable sample sizes in studies in which amelioration of pulmonary function decline is the aim. Despite being the outcome measure of choice in studies of augmentation therapy to date, densitometric analysis of CT scans is currently only recommended in research settings owing to the lack of standardization and validation of CT methodology and analysis protocols.[70] Biomarkers associated with protease balance have been suggested as markers of disease activity, although further validation is required.[27,72,73]

Owing to the rarity of AATD and the limited size and duration of clinical trials, this analysis included all publications that reported observational data from registries and hospital records, regardless of patient severity, to capture larger cohorts over longer time periods. While this approach enhances generalizability, it is acknowledged that biases may exist that are inherent to the respective study designs (including population selection bias, confounding and incomplete data). Additionally, although this study may have excluded some articles published in languages other than English, it is anticipated that restriction to English language would capture relevant and high-quality studies and minimize likelihood of bias. Furthermore, it was expected that some overlap of patient populations may exist across publications presented in the SLR, and it is not possible to determine the extent of the overlap. Nevertheless, for the meta-analysis, a single "primary" publication for each data source was selected based on relevance, population size, and patient characteristics, to minimize double counting. In addition, owing to heterogeneity of the data between publications, including variability in units of the reported outcomes, varying definitions of AATD, and severity of the comorbid conditions across publications, it was not possible to conduct a meta-analysis on all outcomes.

Conclusions

This comprehensive SLR showed an overall slow decline in FEV1 in mL and FEV1% predicted, and worsening SGRQ scores in patients with AATD-associated lung disease. Although rates of deterioration in pulmonary function and HRQoL were slightly improved in patients who received augmentation therapy, impact of therapy was limited over short-term follow-up. Continued monitoring of larger cohorts of patients with and without therapy over longer study durations (> 5 years) is warranted to better understand the natural course of pulmonary function decline and impact on HRQoL. Additionally, this SLR has highlighted the paucity of such data in patients with AATD-associated liver disease with or without comorbid lung disease, underscoring gaps in our understanding of the natural progression of AATD.

Abbreviations

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1,

forced expiratory volume in 1 second; FVC, forced vital capacity; HRQoL, health-related quality of life; Pi, protease inhibitor; PICOS, Population, Intervention, Comparison, Outcomes, and Study; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized controlled trial; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; SLR, systematic literature review.

Acknowledgments

At the direction of the authors, medical writing assistance was provided by Rebecca Tooze, PhD, of Oxford PharmaGenesis, Oxford, UK, funded by Takeda Development Center Americas, Inc.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Takeda Development Center Americas, Inc.

Disclosure

AMT has received grant support via her institution or honoraria from AstraZeneca, Chiesi, CSL Behring, GlaxoSmithKline, Grifols, Takeda Pharmaceuticals, and Vertex Pharmaceuticals. She is also funded by the National Institute for Health and Care Research Midlands Patient Safety Research Collaboration, as well as the National Institute for Health and Care Research Efficacy and Mechanism Evaluation and Health Technology Assessment. The views expressed are those of the author and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care. PW, CvW-M, KF, and MF are employees of Evidera, which received funding for this study from Takeda Development Center Americas, Inc. MH, EGM, AEW, LW, and SP are employees and stockholders of Takeda Development Center Americas, Inc.

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