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REVIEW

The Relationship Between Gas Transfer Measurements, Lung Volumes, and Spirometric Indices in Alpha-1 Antitrypsin Deficiency and Non-AATD COPD: A Systematic Review

Mohammed Alshahrani[1,2], Abdulrahman Alshehri[1,3], Elizabeth Sapey[4,5], Robert Andrew Stockley[1]

[1]Department of Inflammation and Ageing, School of Infection, Inflammation and Immunity, University of Birmingham, Birmingham, UK; [2]Department of Respiratory Therapy, College of Applied Medical Sciences, University of Bisha, Bisha, Saudi Arabia; [3]Rehabilitation Health Sciences, Collage of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia; [4]Midlands NIHR Patient Safety Research Collaboration, University of Birmingham, Birmingham, UK; [5]Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence: Mohammed Alshahrani, Department of Inflammation and Ageing, School of Infection, Inflammation and Immunity, College of Medicine and Health, University of Birmingham, Birmingham, UK, Tel +966596668989, Email mxa1362@student.bham.ac.uk

Background: Alpha-1 Antitrypsin Deficiency (AATD) is associated with persistent airflow limitation with a predominant emphysema phenotype. While spirometry is the gold standard for diagnosis and staging of airflow obstruction, gas transfer is more specific for alveolar damage and may support early diagnosis. We performed a systematic review of the published evidence to support measurements of gas transfer in AATD, with comparison to non-AATD Chronic Obstructive Pulmonary Disease (COPD).

Methods: The systematic review was conducted using standardised methodology (protocol registration number: CRD42024516788). Electronic databases were searched and randomised controlled trials, observational studies, and case series of ≥10 participants with AATD which compared gas transfer tests with spirometry were included. Non-AATD COPD studies were included only where they contained a separate AATD comparative cohort. Risk of bias was assessed using Newcastle-Ottawa Scale. The primary outcome was the relationship between gas transfer and airflow obstruction. Additional outcomes included gas transfer measurements with other lung function measures, respiratory symptom scores, exacerbation frequency, mortality, and imaging markers of emphysema.

Results: Twenty-two studies were included. Gas transfer impairment was common in patients with AATD and generally associated with worse airflow obstruction. Gas transfer impairment related strongly with imaging markers of emphysema and was consistently associated with worse health-related quality of life (HRQL), greater exacerbation frequency, and increased mortality, most strongly in AATD, but also in non-AATD COPD patients. In several studies, impaired gas transfer was present with normal spirometry and studies of never smokers identified through screening suggested that impairments in gas transfer were an early marker of disease. However, all studies highlighted the heterogeneity of lung function decline and presentation in AATD, which could only be partially explained by antitrypsin genotype.

Conclusion: Gas transfer measurements provide valuable, early information in assessing physiological impairment and risk of poor outcomes in both AATD and non-AATD COPD.

Keywords: obstructive lung disease, physiology, emphysema, lung function, imaging

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition characterised by persistent airflow obstruction usually associated with cigarette smoking in most developed countries.[1] Alpha-1 Antitrypsin Deficiency (AATD) is a rare genetic disease that affects between 1 in 1500 to 3500 people in European populations, and predisposes to COPD with an emphysema predominant phenotype, even in the absence of smoking.[2] Both airflow obstruction and emphysema significantly impact quality of life, leading to substantial morbidity and mortality worldwide.[3]

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Several physiological parameters are used to assess lung function and monitor disease progression in obstructive airway diseases. These classically include spirometry for airflow obstruction, measured as forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC); static lung volumes including total lung capacity (TLC) and residual volume (RV); and gas transfer efficiency assessed by diffusing capacity of the lung for carbon monoxide (DLco), and its transfer coefficient (Kco).[4]

Traditionally, spirometry has been the gold standard for the diagnosis and severity staging of COPD, with and without AATD. The FEV_1/FVC ratio is used to detect airflow obstruction (the defining feature of COPD) and FEV_1% predicted (corrected for age, sex and height) is used to assess its severity.[5] However, there is increasing recognition that spirometry alone does not capture the heterogeneity of both AATD and non-AATD COPD.[6,7]

Gas transfer measurements, including DLco/TLco, and Kco are increasingly recognised as important tools in evaluating the progression of lung disease.[8] However, the relationship between gas transfer and spirometric indices, as well as other clinical parameters, is still not fully documented either in AATD or non-AATD COPD. Furthermore, national guidelines do not routinely recommend measurements of gas transfer during the assessment of non-AATD COPD[9] and only during the initial assessment of AATD in some guidelines,[10] despite some studies suggesting that gas transfer impairment could precede spirometric abnormalities in COPD,[11] supporting the detection of early disease. This may be particularly relevant in AATD, where early detection and intervention may be crucial in reducing disease development and progression.

This systematic review aimed to summarise the current evidence of the relationship between gas transfer measurements, lung volumes, and spirometric indices in assessing the severity of lung disease and outcome in AATD patients including comparing these findings to non-AATD COPD where both cohorts were included in individual studies.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the current review.[12] The protocol was registered on PROSPERO (registration number: CRD42024516788) prior to starting any searches. There were no date or language restrictions to inclusion, and all published articles were considered if published before December 2025.

Eligibility Criteria

Eligibility criteria for the included studies were based on the PICO model shown in Table 1.

The review excluded children under 18 years old, and studies with a primary focus on other lung diseases or where no patients had confirmed AATD. Studies were also excluded from the analysis if they reported inconsistent or incomplete data on lung gas transfer measurements, used indirect methods for assessing gas exchange such as estimations based on

Table 1 Eligibility Criteria for the Included Studies Were Based on the PICO Model

	Definition
Population	Adults aged 18 years or older. Diagnosed with AATD (smokers/never smokers/ex-smokers).
Intervention	Measures of gas transfer defined as DLco, TLco, or Kco.
Comparison	Spirometry to assess airflow obstruction by measuring FEV_1/FVC ratio and the severity of airflow obstruction by FEV_1% predicted.
Outcomes	Primary outcome: The relationship between gas transfer and airflow obstruction severity, based on spirometric FEV1 % predicted (for age sex and height) and an FEV1/FVC ratio of less than 0.7. Additional outcomes include comparison of gas transfer with other lung function measures when available (eg. MMEF, FEF75), respiratory symptom scores (eg, SGRQ, CAT), exacerbation frequency, mortality, and any imaging markers of emphysema as identified by chest X-rays, CT scans, and CT densitometry.

arterial blood gases, reported spirometry values without appropriate baseline adjustments for age, height, and sex, or used alternative methods like body plethysmography without clear comparisons to spirometry data. Where possible, these studies were still reported using a narrative synthesis.

Case studies or case series (with < 10 participants) and review articles were also excluded as were other systematic reviews, but individual studies included in systematic reviews were screened. All papers also had references hand screened for additional studies.

Searching Strategy, Data Management and Study Selection

A preliminary literature search was carried out to identify relevant keywords and MeSH terms for the review. The search was conducted in the following databases: Web of science, Scopus, EBSCOhost including (AMED & CINAHL), Ovid including (EMBASE & Medline), and ProQuest. Keywords and index terms are shown in supplementary material S1. The searches were performed without limitations on language or publication date. All results were uploaded to Rayyan.[13] Results were exported to Endnote (Clarivate, UK) once study selection was complete.

Two reviewers (MA, ES) independently carried out the study screening process, first assessing abstracts and selecting full text articles and data extraction based on eligibility criteria. Any discrepancies between reviewers were resolved through discussion or through a third reviewer (RAS). Reasons for excluding studies were documented, and the overall selection process was outlined using a PRISMA flow diagram (see Figure 1). Data from each selected study was extracted using customised excel spreadsheet piloted prior to use. One reviewer carried out the initial data extraction, with a second reviewer verifying the information for accuracy. Any disagreements were resolved by a third reviewer.

Risk of Bias and Quality Assessment

Risk of bias of included studies was assessed independently by two reviewers (MA, ES) with disagreement resolved by a third reviewer (RAS). The Newcastle-Ottawa Scale was used, which evaluates non-randomised studies across three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcomes. This tool provides a star-based scoring system, with a maximum of nine stars indicating the lowest risk of bias. Stars are assigned in the three domains: Selection of study groups (maximum 4 stars), Comparability of the groups (maximum 2 stars), and Outcome/Exposure (maximum 3 stars).[14]

Data Synthesis

A meta-analysis was initially planned but the reported outcomes did not support this and a narrative analysis was undertaken.

Results

From 1096 studies initially identified, 199 were removed as duplicates. After title and abstract screening, 824 were removed and the remaining 73 studies were screened for full text review. From these, 22 publications were eligible to be included in the systematic review[15–36] and 51 were excluded and the reasons documented (see Figure 1: PRISMA flow diagram).

Of the 22 studies included in the current review, 17 were rated as good quality, scoring between 7 and 9 stars, while 5 studies were rated as fair quality, scoring 6 stars. None of the studies were rated as poor quality, (see Table 2).

Most studies only included patients with AATD. However, four studies included both AATD and non-AATD COPD[32,34–36] and one study compared AATD with normal lung function to a healthy control group[33] All studies were observational in nature and all were conducted in Western Europe with four being multi-national registry studies, one in each of France, Italy, Sweden and Germany and the rest being conducted in the United Kingdom (Table 3). Studies were conducted between 2001 and 2025. In total, 9641 AATD patients, 867 non-AATD COPD patients and 107 healthy (or ex-smokers with normal lung function) controls were included. Sample sizes varied considerably (range from 23 participants[20] to 1565 patients.[31] Twelve studies came from ADAPT, the UK national registry for AATD[37] and 4 studies came from The European Alpha-1 Research Collaboration registry (EARCO)[38] (see Table 3). It was not possible to determine if the same patients had been included in multiple observational studies included in this review.

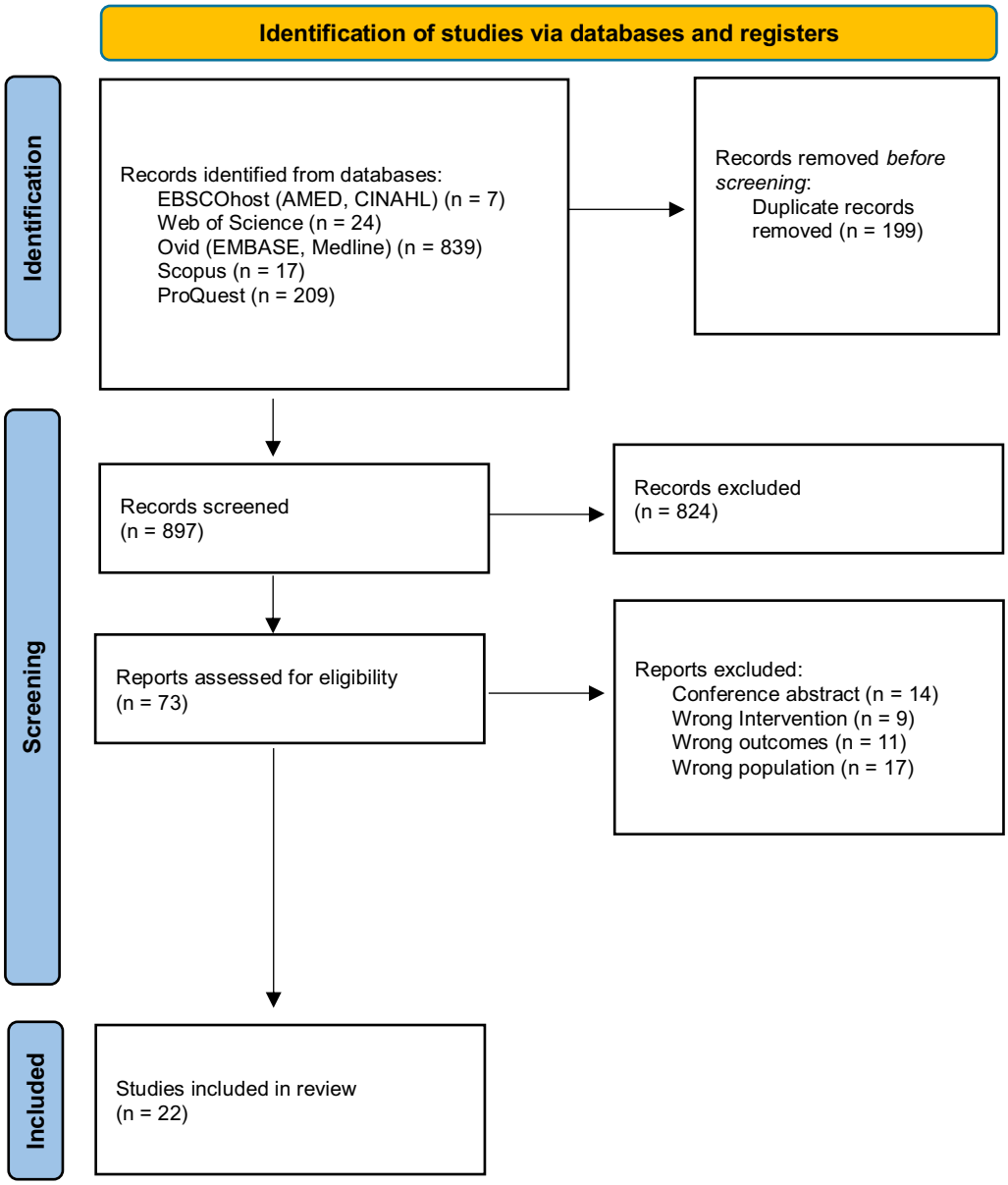

Figure 1 PRISMA flow diagram showing the study selection process.

Where stated, AATD diagnosis was confirmed using AAT serum levels[16,18,27,28,35] and non-AATD COPD diagnoses were confirmed using post-bronchodilator $FEV_1/FVC < 0.70$.[17,22,25,26,32,34] Where reported, disease severity was based on GOLD staging in 6 studies[24–27,34,35] and ERS criteria in one.[32] All studies included individuals with the severely deficient PiZZ genotype. However, several studies also included individuals with another genotypes, such as Pi*Mmalton, PiSZ, PiMZ, PiSS or PiMM (normal genotype).[27,28,30,33,35,36]

Eight studies included longitudinal data collection[17,18,20,22–25,36] but these were most frequently from retrospective patient visits as part of on-going registry studies and therefore, there was some variation in the frequency of lung function assessment although most data points were collected annually. For an overview of the studies, see Table 3.

Table 2 The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies

Study Name	Selection	Comparability	Outcome	Total Score	Risk of Bias Assessment
L. J. Dowson, 2001[15]	★★★★	★	★★★	8	Good quality
L. J. Dowson, 2002[16]	★★★	★	★★	6	Fair quality
P. A. Dawkins, 2003[17]	★★★	★	★★★	7	Good quality
M. Needham, 2005[18]	★★★★	★	★★★	9	Good quality
J Holme, 2007[19]	★★★★	★	★★★	8	Good quality
J Holme, 2013[21]	★★★★	★	★★★	8	Good quality
K. Vijayasaratha, 2012[20]	★★	★	★★★	6	Fair quality
H. Ward, 2014[22]	★★★★	★	★★★	8	Good quality
R.I Carter, 2015[23]	★★★★	★	★★★	8	Good quality
R.A. Stockley, 2016[24]	★★★★	★	★★	7	Good quality
R.A. Stockley, 2018[25]	★★★	★	★★★	7	Good quality
D. Crossley, 2020[26]	★★★	★	★★★	7	Good quality
C. Gauvain, 2015[27]	★★★	★	★★	6	Fair quality
M. Miravitlles, 2022[28]	★★★★	★	★★★	8	Good quality
C. Premuda, 2025[29]	★★★	★	★★	6	Fair quality
B. D. Ferraz, 2025[30]	★★★	★	★★★	7	Good quality
D. Karadoğan, 2025[31]	★★★★	★	★★★	8	Good quality
E.J.R. van Beek, 2009[32]	★★★	★	★★	6	Fair quality
E. Bernspång, 2010[33]	★★★★	★	★★★	8	Good quality
J. D. Crapo, 2023[34]	★★★★	★	★★★	8	Good quality
D. Piloni, 2024[35]	★★★★	★	★★★	8	Good quality
C.E. Green, 2015[36]	★★★★	★	★★★	8	Good quality

Notes: Each study has been assessed for bias using The Newcastle-Ottawa Scale, which evaluates non-randomised studies across three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcomes. This tool provides a star-based scoring system, with a maximum of nine stars indicating the lowest risk of bias. Stars are assigned in the three domains: Selection of study groups (maximum 4 stars), Comparability of the groups (maximum 2 stars), and Outcome/Exposure (maximum 3 stars).

Gas Transfer and Spirometry in AATD

Cross Sectional Studies

In general, the most reported finding across all studies was that airflow obstruction was associated with impairment in gas transfer and that gas transfer was most commonly abnormal in patients with severe airflow obstruction. However, there were patients with abnormal, obstructive spirometry and normal measures of gas transfer and conversely patients with normal spirometry and abnormal measures of gas transfer.

Some studies stratified AATD patients into those with and without spirometrically defined airflow obstruction. Those without airflow obstruction were more likely to be younger, less likely to be index patients (those identified as a result of symptoms rather than random or family screening), had a lesser smoking history and were more likely to be never smokers.[24,25] In these patients, Kco was often at the lower end of the normal range compared to spirometric measures, which tended to be at the higher end of the normal range.[24,25] Where airflow obstruction was present, patients were older, had a greater smoking history, were more likely to be index cases and measures of gas transfer were generally reduced.

Table 3 Overview of Studies Included in the Systematic Review

Study	Study Design	Country	Data Base	Sample Size	Age	Gender	AATD Genotype	Non-AATD COPD Included?	Severity	Primary Outcome
L. J. Dowson., 2001[15] High-resolution computed tomography scanning in alpha1-antitrypsin deficiency	Retrospective cohort study. Baseline data reported. Single centre	UK	ADAPT[a]	111	50	M: 74 F: 37	PiZZ	No	NR	Relationship between HRCT (pixel index) and lung function and health status in PiZZ AATD patients
L. J. Dowson., 2002[16] The relationship of chronic sputum expectoration to physiologic, radiologic, and health status characteristics in alpha(1)-antitrypsin deficiency (PiZ)	Prospective, cross-sectional study. Baseline data reported. Single centre	UK	ADAPT[a]	117	51	M: 77 F: 40	PiZZ	No	Severe (median)	The relationship between CSE and physiological, radiological, and health status characteristics in AATD patients
P. A. Dawkins., 2003[17] Predictors of mortality in alpha 1-antitrypsin deficiency	Prospective longitudinal cohort study Single centre. Baseline HRCT report and follow up for mortality over 5 years.	UK	ADAPT[a]	256	NR	NR	PiZZ	No	NR	Identification of physiological, radiological, and health status predictors of all-cause and respiratory mortality in PiZZ AATD patients

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M. Needham., 2005[18] Exacerbations in α1-antitrypsin deficiency	Prospective, longitudinal observational study. 178 followed for 12 months and 87 followed for 3 years. Single centre	UK	ADAPT[a]	265	49.9	M: 167 F: 98	PiZZ	No	NR	Frequency, nature, and impact of exacerbations on lung function and health status in AATD
J. Holme., 2007[19] Radiologic and clinical features of COPD patients with discordant pulmonary physiology: lessons from a-1-antitrypsin deficiency	Cross-sectional, retrospective, observational study Single centre. Baseline data reported. Patients grouped into those with normal spirometry and normal KCO (Group 1); Abnormal FEV_1 but normal Kc0 (Group 2); normal spirometry but abnormal Kco (Group 3); abnormal spirometry and Kco (group 4).	UK	ADAPT[a]	50	Group 1: 44.4 Group 2: 48.4 Group 3: 48.0 Group 4: 53.7	Group 1: M: 9, F: 6 Group 2: M: 2, F: 8 Group 3: M: 7, F: 8 Group 4: M: 2, F: 8	PiZZ	No	NR	How different physiological phenotypes (based on FEV_1 and Kco) in AATD relate to emphysema distribution on CT and health status.
K. Vijayasaratha., 2012[20] Relationship between frequency, length, and treatment outcome of exacerbations to baseline lung function and lung density in alpha-1 antitrypsin-deficient COPD	Longitudinal, prospective, observational study. Baseline lung function and CT. Diary card data collected for 2 years. Single centre	UK	ADAPT[a]	23	52.5	M: 17, F: 6	PiZZ	No	NR	Assessing how baseline Kco and CT lung density relate to exacerbation frequency

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Table 3 (Continued).

Study	Study Design	Country	Data Base	Sample Size	Age	Gender	AATD Genotype	Non-AATD COPD Included?	Severity	Primary Outcome
J. Holme., 2013[21] Age related development of respiratory abnormalities in non-index alpha-1 antitrypsin deficient studies	Retrospective cohort study. Baseline data reported. Single centre	UK	ADAPT[a]	591	Non-index never smoked: 44.8 Non-index ex/current smokers: 46.9 Index never smoked: 60.5 Index ex/current smokers: 49.7	Non-index never smoked M:18 Non-index ex/current smokers M:49 Index never smoked M:53 Index ex/current M:227	PiZZ	No	Normal to severe	The age at which spirometry, gas transfer, CT changes, and health status begin to deviate from normal
H. Ward., 2014[22] Spirometric and gas transfer discordance in Alpha-1-anti trypsin Deficiency: Patient characteristics and progression	Retrospective, cross-sectional and longitudinal study. 275 patients reported baseline data only and 255 followed for 3 years. Single centre Grouped into Normal FEV_1/FVC ratio and normal Kco (Group N); Normal FEV_1/FVC ratio and abnormal Kco (Group K); Abnormal FEV_1/FVC ratio and normal Kco (Group F) and abnormal FEV_1 /FVC ratio and Kco (group B).	UK	ADAPT[a]	530 Group N: 59 Group K: 8. Group F: 150 Group B: 313.	M: 51 F: 50.4	M: 316 F: 215	PiZZ	No	NR	Comparison of spirometry and gas transfer phenotypes and their impact on progression in PiZZ AATD

R. I. Carter., 2015[23] The relationship of the fibrinogen cleavage biomarker aα-val360 with disease severity and activity in α1-antitrypsin deficiency	Retrospective, cross-sectional and longitudinal – with at least 4 lung function data collection over at least 3 years. Single centre	UK	ADAPT[a]	378	51.34	M: 221 F: 157	PiZZ	No	NR	The relationship between A a -Val 360 and disease severity in AATD patients
R. A. Stockley., 2016[24] Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management?	Retrospective, longitudinal, observational study. Four data collection points over at least 3 years. Single centre Divided into those with and without COPD.	UK	ADAPT[a]	482	AATD COPD: 52.9 AATD without COPD: 44.8	AATD COPD: F: 153/242 AATD without COPD: F: 56/31	PiZZ	No	Normal to moderate	Evaluating individual rates of FEV_1 and Kco decline in PiZZ AATD patients and assess their implications for prognosis and personalized treatment
R. A. Stockley., 2018[25] Health status decline in α-1 antitrypsin deficiency: A feasible outcome for disease modifying therapies?	Retrospective observational, longitudinal study with at least 4 consecutive datapoints over up to 7 years. Divided cohort into those with and without COPD. Single centre	UK	ADAPT[a]	454	Obstruction: 52.5 No obstruction: 42.4	No obstruction: M: 33, F: 51 Obstruction: M: 235, F: 135	PiZZ	No	Normal to very severe	Annual decline in health status and its relationship to lung function decline in AATD patients

(*Continued*)

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Table 3 (Continued).

Study	Study Design	Country	Data Base	Sample Size	Age	Gender	AATD Genotype	Non-AATD COPD Included?	Severity	Primary Outcome
D. Crossley., 2020[26] Relationship of CT densitometry to lung physiological parameters and health status in alpha-1 antitrypsin deficiency: Initial report of a centralised database of the NIHR rare diseases translational research collaborative	Prospective observational cohort study. Baseline data reported. Multi-centre	UK	Birmingham, Nottingham, London Brompton, London University College London/Royal Free Hospital, Cambridge, Southampton and Leicester	187	60.1	M: 86 F: 101	PiZZ	No	Mild to very severe	Relationship between CT lung densitometry and spirometry, gas transfer, and health status measures in AATD
C. Gauvain.,2015[27] Health-Related Quality of Life in Patients with Alpha-1 Antitrypsin Deficiency: The French Experience	Prospective, multi-centre cohort study. Baseline data reported.	France	AATD French registry	273	51.8	M: 172 F: 101	PiZZ PiSZ Null/Z	No	GOLD 1,2,3	Evaluating baseline health-related quality of life (SGRQ scores) in AATD patients
M. Miravitlles., 2022[28] Clinical and functional characteristics of individuals with alpha-1 antitrypsin deficiency: EARCO international registry	Observational study. Baseline data reported. Multi-centre	Multi-national Europe	EARCO[b] registry	1044	55.6	M: 324 F: 398	PiZZ PiSZ PiSS	No	NR	Characterisation of clinical phenotypes, functional impairment patterns, and predictors of impaired lung function in AATD

C. Premuda., 2025[29] Lung disease in never-smokers with severe alpha 1 antitrypsin deficiency: the EARCO Registry	Retrospective, observational study Multi-centre. Baseline data reported. Divided patients into Index (diagnosed through symptoms) and non-index (diagnosed through screening).	Multi-national Europe	EARCO[b] registry	941	Ever smokers: 56.8 Never smokers Index 61.8 Never smokers non-index 55.3	Ever smokers F: 207 M: 265 Never smokers Index F: 189 M: 131 Never smokers non index F: 70 M:50	PiZZ	No	Mild to severe	Differences in characteristics and lung function in never smokers with PiZZ AATD compared to ever smokers with AATD.
B. D. Ferraz., 2025[30] Characterization of the Mmalton carrier's cohort within the EARCO (European Alpha- 1 Antitrypsin Research Collaboration) registry	Retrospective, observational study Baseline data reported. Multi-centre.	Multi-national Europe	EARCO[b] registry	827 PiZZ 26 moderate and 33 severe PI*Mmalton		PiZZ F: 394 M: 432 PI*Mmalton F: 21 M: 38	PI*Mmalton	No	Mild to severe	Characterisation of PI*Mmalton carriers within the EARCO registry compared to PI*ZZ individuals.
D. Karadoğan, 2025[31] Clinical characteristics of AATD-related COPD patients vary with age at diagnosis: data from the EARCO international registry	Retrospective, observational study. Baseline data reported. Multicentre	Multi-national Europe	EARCO[b] registry	1565	60	F: 644 M: 921	PiZZ	No	Mild to severe	Clinical characteristics of COPD patients with AATD according to their age at diagnosis.

(*Continued*)

Table 3 (Continued).

Study	Study Design	Country	Data Base	Sample Size	Age	Gender	AATD Genotype	Non-AATD COPD Included?	Severity	Primary Outcome
Studies which included non-AATD groups										
E.J.R. van Beek., 2009[32] Hyperpolarised 3He MRI versus HRCT in COPD and normal volunteers: PHIL trial	Prospective case-control study. Multi-centre. Baseline data reported.	Germany	NR	94 in total 52 with non-AATD COPD 13 with AATD and 29 healthy controls	62	M: 63 F: 31	NR	Yes and a healthy control group	Mild to severe	The effectiveness of hyperpolarised helium-3 MRI and HRCT in identifying lung abnormalities
E. Bernspång., 2011[33] CT lung densitometry in young adults with alpha-1-antitrypsin deficiency	Cross-sectional, prospective, observational study. Baseline data reported. Multi centre	Sweden	Newborn screening program	53 in total 25 PiZZ 11 PiSZ 17 PiMM	32 for all cohorts	PiZZ: M:15, F:10 PiSZ: M: 7, F: 4 PiMM: M: 11, F: 6	PiZZ PiSZ PiMM	PiMM but with normal lung function	NR	Assessing whether CT densitometry detects early emphysematous changes in young adults with AATD compared to age-matched controls

J. D. Crapo., 2023[34] Baseline characteristics from a 3-year longitudinal study to phenotype subjects with COPD: the FOOTPRINTS study	Cross-sectional observational study. Multi centre. Baseline data report from ongoing study.	UK	FOOTPRINT study	463 in total 19 with AATD, 61 ex smokers with normal lung function 382 with non-AATD COPD	60.7 53.9 years for ex smokers 62 years for COPD GOLD stage 1, 61.8 years for COPD GOLD stage 2, 62.9 years for COPD GOLD stage 3 52.8 years for AATD	M: 294 F: 169	PiZZ in AATD	Yes and an ex-smoking healthy control group	GOLD 1,2,3	Baseline characterization of lung function, CT imaging, and biomarkers in COPD and AATD
D. Piloni, 2024[35] Comparison among populations with severe and intermediate alpha1-antitrypsin deficiency and chronic obstructive pulmonary disease	Prospective, observational study. Baseline data. Multi-centre.	Italy	AATD Italian registry, the Centre for Diagnosis of Inherited AATD in Pavia, from the routine activities of the outpatient clinic at the Section of Pneumology, IRCCS San Matteo Polyclinic Foundation, Pavia	613 all with COPD 330 PiZZ 183 PiMZ 100 PiMM	PiZZ: 49.5 PiMZ: 54 PiMM: 71	PiZZ: M: 158/F: 172 PiMZ: M: 105/F: 78 PiMM: M: 77/ F:23	PiZZ PiMZ PiMM	Yes	All severity stages	Comparison of lung function, symptom, and health status across PiZZ, PiMZ, and PiMM populations
C. E. Green., 2015[36] PiSZ alpha-1 antitrypsin deficiency (AATD): pulmonary phenotype and prognosis relative to PiZZ AATD and PiMM COPD	Retrospective, longitudinal cohort study. Baseline CT data and lung function decline data based on 4 data points over at least 3 years follow up. Single centre	UK	ADAPT[a]	1141 in total. PiZZ 699, PiSZ 190, PiMM (non AATD COPD) 316	PiZZ: 50.8 PiSZ: 53.5 PiSZ index: 55.4 PiMM: 68.4	PiZZ: M: 404, F: 295 PiSZ: M: 71, F: 55 PiSZ index: M:38, F: 26 PiMM: M: 182, F: 134	PiZZ PiSZ PiMM	Yes	All severity stages	Comparison of pulmonary phenotype, lung function decline, and survival in PiSZ versus PiZZ and PiMM patients

Notes: Characteristics of the studies included in this systematic review. [a]ADAPT = Antitrypsin Deficiency Assessment and Programme for Treatment-based in UK, [b]EARCO = European Alpha-1 Research Collaboration based across European countries.

Abbreviations: F, Female; M, Male; UK, United Kingdom; NR, not reported.

For example, Stockley et al[25] found that AATD patients with airflow obstruction had reduced TLco (median 66.2% predicted, IQR 52–77 compared to median 92.5% IQR 81–109 in those without airflow obstruction p<0.001). Similarly, Kco was also lower in those with airflow obstruction (median 63.6%; IQR 52–74 compared to median 91.9%; IQR 79–100 respectively; p<0.001).

To assess this further, studies divided patients into those with and without abnormalities in FEV_1 FVC ratio and/or measures of gas transfer. For example. Ward et al[22] studied 530 AATD patients. Of these, 11% had a normal FEV_1 /FVC ratio and Kco (Group N), 59% had both an abnormal FEV_1/FVC ratio and Kco (Group B), 28% had an abnormal FEV_1/FVC ratio but normal Kco (Group F) and 2% had a reduced Kco in the absence of airflow obstruction (Group K). Those in Group N were younger, less likely to be an index patient and less likely to have smoked than those with airflow obstruction with and without abnormalities in Kco. Those with an isolated abnormality in Kco were proportionally a smaller group but had a higher burden of symptoms to those with normal lung function (group N) despite a similar smoking history and age. In this paper, Ward described a modal distribution of Kco but a bimodal distribution of FEV1/FVC ratio (assessed using standardised residuals) suggesting discordant processes driving the development of emphysema compared to airflow obstruction.[22] These results were replicated by Miravitlles et al,[28] who studied 1044 AATD patients from centres across Europe as part of the EARCO international registry This replication study reported baseline lung function, dividing patients into those treated or not treated with augmentation therapy and those with and without airflow obstruction. Of the 449 PiZZ patients with reported measurements of both FEV_1 and Kco, 55% had abnormalities of both measures, 21% had preserved FEV_1 and Kco measurements and 23.6% had discordant lung function measurements, with either an impaired FEV_1 and a normal Kco or vice versa.[28] Both Ward and Miravitlles noted that an isolated defect in Kco was more likely in never smokers compared to those with impaired FEV_1 and those with impairments in FEV_1 and Kco had significant emphysema in the lower and upper lung zones (determined by CT densitometry).[22] This finding was also replicated in a study by Parr et al which focused on emphysema distribution and symptoms.[39]

Longitudinal Comparisons

Several longitudinal studies have evaluated lung function decline in AATD, particularly focusing on changes in FEV_1 and gas transfer with time.[18,22,24,25] In those patients with airflow obstruction, a decline in both FEV_1 and gas transfer occurs with time but a vary between individuals and patient groups. Needham et al[18] studied 87 PiZZ AATD patients for 3 years The FEV_1 showed a significant median decline of −41 mL per year (IQR −96 to −15) – approximately −1% predicted per year, while TLco declined by −0.21 $mmol/min^{-1}/kPa^{-1}$ per year – approximately −1.8% predicted per year, both therefore exceeding the expected decline with age.

When studies have included AATD patients without clinically defined COPD, longitudinal assessment identifies some AATD patients who have no excessive decline in lung function (beyond that due to age alone), some with a predominant decline in DLco/Kco, some with a predominant decline in FEV_1% and some with concordant declines in both measures. Ward[22] (described above) also included a longitudinal component, studying 255 AATD patients with 4 lung function measurements over 3 years, using the same groups at baseline, namely N (normal FEV_1 and Kco), B (abnormal FEV_1 and Kco), F (abnormal FEV_1 but not Kco) and K (abnormal Kco and not FEV_1). There was no difference in the rate of decline in FEV_1 across the four groups and no association between the rate in decline in FEV_1 and the rate of decline in Kco. However, the group with an isolated Kco impairment(K) demonstrated the steepest annual FEV_1 decline (−124.3 mL/year SEM: 22.9) compared to AATD patients with either normal lung function, an isolated deficit in FEV_1 or with both impaired FEV_1 and Kco (declining at −53.2, −31.1, and −46.3 mL/year, respectively). Factors associated with developing an impaired Kco over the study period included more upper-zone emphysema and a greater proportion of patients who had smoked, which would be in keeping with these radiological findings.

Stockley et al[24] assessed lung function decline in 482 patients with AATD also using four sets of physiological readings taken over three years, separating patients into those with and without established COPD. Patients were divided into those whose lung function decline (either FEV_1 or Kco) was consistent with normal ageing (change <-0.1% predicted per year), slow deterioration (−0.1% to,-0.5%), moderate deterioration (−0.5% to,-1.0%), and rapid deterioration (>-1.0%). Firstly, the authors demonstrated that 30% and 34% of AATD patients with COPD and 36% and 63% of

AATD patients without COPD experienced no or only a slow decline in Kco or FEV_1 and these patients were distributed across all severities of lung disease in the COPD group (defined by FEV_1). A rapid decline in FEV_1 was most commonly present in those with established airflow obstruction and an FEV_1 in the mid severity -range (mean 58% predicted). A rapid decline in Kco was more evenly distributed across those with and without COPD and across all FEV_1 decline groups. In keeping with this, there was a weak relationship between the decline in gas transfer and FEV_1 in AATD patients without COPD (r=0.218; P,0.025) but no relationship in AATD patients with established COPD (r=0.008; P=not significant), suggesting independent progression in FEV_1 and Kco in AATD. In 2018, Stockley et al[25] extended this study to include 7 years of follow up, this time assessing changes in health status as the primary outcome of the study. Those without airflow obstruction had a slower rate of decline in FEV_1% predicted (−0.25% predicted slope/year) compared to those with airflow obstruction −1.02% predicted slope/year) but there was no difference in the rate of Kco decline between groups. There was also no relationship between the rate of deterioration (increase in symptom scores), measured using the SGRQ, and Kco although there was a wide range of FEV_1 and Kco decline, with defined rapid decliners seen in both groups.

The Relationship Between Gas Transfer and Imaging in AATD

Imaging studies, particularly high-resolution computed tomography (HRCT) and advanced magnetic resonance imaging (MRI), have linked structural changes in the lung to physiologic impairment in AATD.

Dowson et al[15] studied 111 patients with PiZZ AATD, assessing relationships between HRCT scans, lung function and health status. Ninety patients had macroscopic evidence of emphysema. Those without macroscopic emphysema were younger (median 39 versus 51 years), had smoked less (62% never smokers versus 17% respectively) and had better pulmonary function and health status. HRCT results and the presence of emphysema related strongly with symptoms. HRCT findings also related strongly with lung function, and most strongly with measures of gas transfer, with a Spearman correlation coefficient (rho) of −0.76 and −0.64 for Kco.

Holme et al[19] studied 50 patients with AATD using HRCT scans assessing lung density determined by voxel index. Here, impairment in FEV_1 alone was associated with a basal-predominant emphysema, and impairment in Kco alone was associated with relatively more upper zone emphysema and an increased prevalence of ex-smoking compared to never smoking, potentially identifying differences in distribution/pathological processes influencing physiological measurements. This data provided further support for the paper produced by Parr et al who had demonstrated that upper zone emphysema related better to gas transfer than a basal distribution which related more strongly to the FEV1[39].

van Beek et al[32] studied 13 patients with AATD, 50 patients with non-AATD COPD and 29 healthy controls (all non-smokers), to assess the ability of hyperpolarised (HP) 3He magnetic resonance imaging (MRI) to identify non deficient COPD and AATD compared to HRCT physiological measures of lung function. Visual and quantitative analysis of the 3He MRI and HRCT scans in AATD identified both ventilation defects (MRI) and pathology (HRCT) in all cases. When the COPD, AATD and healthy control data was pooled, DLco was closely related to apparent diffusion coefficient (ADC) values from hyperpolarized helium-3 MRI identifying micro-structural changes on a spatial scale smaller than the resolution of HRCT. However, relationships with airflow obstruction were less strong.

Bernspång et al[33] included 53 younger patients with AATD (aged 32) identified from the Swedish newborn screening programme. All lung function tests were within the normal range and CT densitometry did not detect emphysema. However, there was a strong relationship between PD15 (15th percentile density, a CT scan-derived measurement that represents the Hounsfield Unit value below which 15% of the lung's voxels are distributed and a sensitive tool for quantifying emphysema) and diffusing capacity ($r = -0.72$, $p < 0.001$).

Crossley et al[26] studied 187 AATD patients from 8 UK centres assessing cross sectional lung function and CT imaging, analysed for voxel index (% voxels less dense than −950 HU) and PD15 to quantify emphysema. Kco related positively to PD15 ($r = 0.479$, $p < 0.001$), and inversely to voxel index ($r = -0.54$, $p < 0.001$), reflecting lung densitometry being the most direct measure of pathological emphysema and gas transfer being a more direct measure of alveolar dysfunction compared to spirometry. An additional element of this study was to assess the recruitment of AATD patients with severe lung impairment in UK regional centres in comparison to studies using the Birmingham

ADAPT national AATD clinic. This comparison found no evidence of acquisition bias when assessing one recruitment site to multiple regional sites.

Development of Lung Function Impairment with Time

To determine when lung function begins to deviate from normal in AATD, Holme et al[21] studied 591 patients recruited to the UK National AATD database, determining the earliest age at which >50% of the never smoker cohort consistently had test results worse than the average for a healthy population by logistic regression modelling. On average, non-index patients identified through family screening, upper zone emphysema (defined by voxel index) and Kco were predicted to become persistently abnormal at an average age of 29 and 32, respectively. Whereas FEV_1/FVC and lower zone voxel index were predicted to deviate from normality at age ~50 and FEV_1 deviated at an average age 63. In ex/current smokers analysed the same way Kco deviated from normal before the age of 20.

In July 2025, the EARCO international registry of AATD assessed differences in the age of diagnosis of AATD in 1565 patients (Karadogan et al)[31] Patients were grouped into three groups (<45 years, 45–65 years and ≥65 years) according to their age at AATD diagnosis. Comparisons were made regarding their demographic and clinical characteristics.

This study found almost a fifth of patients with COPD associated with AATD were diagnosed at the age of 65 or older. Those diagnosed at an older age had milder pulmonary function impairments, a lower symptom burden and functional impairment (assessed by CAT score[40] and BODE index[41]), and better quality of life. Conversely, those diagnosed when aged <45 years old were more likely to have a severe deficiency (PiZZ genotype), more severely impaired FEV_1 and Kco, a greater smoking history and a higher burden of symptoms and clinical function.

Premuda et al[29] assessed lung function in AATD patients who had never smoked, comparing these to ever smokers. Never smokers had a lower Kco% predicted than FEV_1% predicted, while in ever-smokers, this relationship was reversed. Never smokers were further divided into index (presenting due to symptoms) and non-index cases (diagnosed though screening). Never smoker index patients were diagnosed in their sixties after moderate symptom development with mildly impaired FEV_1, a preserved FEV_1/FVC ratio and with the greatest impairment of Kco (Mean 73% predicted, SD ± 22.6). Non-index cases tended to be diagnosed earlier (mid fifties) before symptoms were prominent but had mild symptoms according to CAT score with normal spirometry, no airflow obstruction but mild impairment in Kco, suggesting the change in Kco is an early feature of AATD in the absence of smoking consistent with the study by Holme et al.[21]

The Relationship Between Gas Transfer and Other Health Outcomes in AATD

Health Status

Holme et al[19] demonstrated that patients with an isolated impairment in Kco had higher (indicating worse) Saint George Respiratory Questionnaire (SGRQ) scores than those with normal lung function demonstrating the impact of gas transfer impairment on health.[42] Ward et al[22] also provided a comparative assessment of health status across the four phenotypic subgroups of N, K, F and B (described above). The worst SGRQ scores were reported in patients with both gas transfer and FEV_1 impairment (median total SGRQ score 53.67, IQR 39–65), followed by those with isolated FEV_1 impairment (median score 45.24, IQR 30–59), then those with an isolated impairment in Kco (median score 31.09, IQR 28–47), which in turn was greater than those with both normal spirometry and Kco (19.59; IQR 6–37).

Crossley et al,[26] described that Kco % predicted (but not absolute Kco) was associated with symptoms using both the COPD Assessment Tool (CAT) and SGRQ scores (CAT $r = –0.26$, $p < 0.01$: total SGRQ score $r = –0.23$, $p < 0.01$) in 187 AATD patients. However, the FEV_1% predicted demonstrated stronger inverse associations with CAT ($r = –0.41$, $p < 0.01$) and SGRQ ($r = –0.55$, $p < 0.01$) scores suggesting airflow obstruction has a greater impact on symptoms.

Gauvain et al[27] assessed 312 AATD patients from the French AATD national registry (PiZZ, PiSZ and PiNull/Z), recruited from 56 centres including 130 patients receiving augmentation therapy. In this study, total SGRQ score was negatively associated with DLco % predicted, ($r = −0.52$, $p < 0.0001$), FEV_1% predicted, ($r = −0.53$, $p < 0.0001$) and the 6-min walking distance ($r = −0.53$, $p < 0.0001$) but the authors did not assess differences in relationships within different genotypes.

Stockley et al[25] (described above) demonstrated associations between SGRQ scores and FEV1% predicted ($r^2 = 0.34$, $p<0.0001$) and Kco ($r^2 = -0.105$; $p < 0.0001$) in a cohort of 454 patients, and a similar relationship between SGRQ and Kco in a sub-cohort of patients with airflow obstruction, but not in those without spirometric COPD. Longitudinal results showed there was no relationship between worsening SGRQ and gas transfer measurements but the decline in FEV_1 was weakly related to increases in SGRQ total score (equating to more symptoms) for the whole group ($r^2 = 0.04$ $p<0.0001$).

Chronic Sputum Expectoration and Exacerbation Frequency

Dowson et al[16] assessed 50 AATD patients with and 67 AATD patients without chronic sputum expectoration (CSE - defined as sputum expectoration on most days for at least 3 consecutive months of the year for ≥ 2 consecutive years). Patients with CSE had worse airflow obstruction and more emphysema on HRCT scans compared to those without CSE when matched for age and smoking history, but there was no difference in absolute Kco (reported as mL/min/mmHg/L) between groups.

Needham et al[18] (described above) demonstrated that exacerbation frequency was an independent predictor of TLco decline over time ($r = –0.19$; $p = 0.037$), accounting for 5% of the variability. In contrast, no such relationship was found between exacerbations and FEV_1 decline.

Vijayasaratha et al[20] observed a negative relationship between Kco% predicted and both the frequency of treated exacerbations ($r = –0.432$; $p = 0.022$) and the resolution rate post-treatment ($r = –0.647$; $p = 0.007$) in 23 patients with AATD. Lower FEV_1 also related to the likelihood of an exacerbation that resulted in therapeutic intervention ($r = –0.386$; $p = 0.038$), earlier initiation of treatment ($r = 0.272$; $p = 0.036$), and higher symptom scores at the onset of the defined exacerbation ($r = –0.234$; $p = 0.003$), but less strongly than Kco% predicted.

Mortality

Dawkins et al[17] analysed 5 years of data for 256 patients with AATD. During this time there were 22 deaths in the cohort. There was an association between Kco and death with each unit increase in Kco% predicted being associated with a 3.6% reduction in all-cause mortality risk (HR 0.964; 95% CI: 0.941–0.987; $p = 0.002$) and a 3.8% reduction in respiratory-related mortality (HR 0.962; 95% CI: 0.933–0.993; $p = 0.012$). In contrast, FEV_1 (% predicted) was not significantly associated with all-cause mortality (HR 0.986; $p = 0.158$), though it was predictive of respiratory deaths (HR 0.941; $p = 0.015$).

Inflammation

Carter et al[23] assessed 378 AATD patients over a 5.6 year period to determine the relationship between Aα-Val360—a plasma marker of lung neutrophil elastase activity — with changes in lung function. At baseline, there were weak associations between Aα-Val360 and Kco, FEV_1, emphysema assessed by voxel index (upper and lower zone) and SGRQ, with increased Aα-Val360 associated with worse disease severity and health status. Multivariate analysis demonstrated significant independent relationships between $A\alpha\text{-Val}^{360}$ and both the Kco and FEV_1. Aα-Val360 was significantly associated with accelerated % predicted Kco decline ($r = –0.193$, $p = 0.025$) but not with a decline in FEV_1 (% predicted).

The Impact of AATD Phenotype

Variability in clinical expression among individuals with AATD is partly attributable to differences in genotype/phenotype.

Bernspång et al[33] included 25 younger adult patients (aged 32) with PiZZ AATD, 11 patients with PiSZ AATD and 17 with PiMM (normal phenotype). At this age, there were no differences between the different Pi subgroups including lung function or multi-slice CT parameters in both smoking and ex-smoking AATD patients compared to those without AATD.

Green et al[36] studied 699 PiZZ, 126 PiSZ and 316 PiMM subjects without AATD but with established COPD (termed non-AATD COPD). Those with PiSZ AATD were older and had smoked more than those with PiZZ AATD, but had comparatively preserved lung function. The authors concluded that that PiSZ patients had a lower risk of lung disease

and were less susceptible to effects of cigarette smoke than AATD PiZZ individuals, perhaps exhibiting characteristics more in keeping with non-AATD COPD.

Piloni et al[35] studied 613 patients who met diagnostic criteria for COPD: 330 with the PiZZ genotype, 183 with the heterozygotic PiMZ genotype and 100 with the PiMM genotype (non-AATD COPD). Lung function and assessments of health status were performed at baseline and then after sixteen to thirty months. The study was limited by incomplete baseline and follow-up lung function measurements, which the authors mentioned but did not clarify. However, the study reported a modest decline in both FEV_1 and DLco in the PiMM COPD group, stable FEV_1 and DLco in the PiMZ group, but a clear decline in DLco in the PiZZ group, with authors concluding that PiMZ subjects do not have an increased risk of developing COPD compared to smoking PiMM subjects.

Ferraz et al[30] compared Pi*Mmalton carriers to PiZZ individuals, dividing the rarer mutation into moderate and severe deficiency depending on whether the allele was carried in combination with another deficient allele associated with severe or non-severe disease. The population of Pi*Mmalton variants were small (26 moderate and 33 severe). The severe group had similar baseline lung function to PiZZ patients, while the moderate group had more preserved lung function. The authors used this to highlight the benefits of understanding the exact genetic variant present as this might lead to more stratified approaches to therapy.

Comparing AATD and Non-AATD COPD

While most studies in this review focussed exclusively on individuals with AATD, four have included comparator groups with non-AATD COPD.

Crapo et al[34] included 382 ex-smokers with COPD (GOLD stages 1–3), 19 ex-smokers with AATD and airflow obstruction and a control group of 61 ex-smokers without airflow obstruction. The study found that measures of gas transfer (DLco and DLco/Kco measured in mmol/min/kPa and expressed as % predicted), were significantly lower in the AATD group than all non AATD -COPD groups, despite having a comparable FEV_1 (all with GOLD stage 2 disease). This was in keeping with a higher burden of advanced destructive emphysema in the AATD group and the association of gas transfer as a differentiating measure.

van Beek et al[32] studied 52 patients with non-AATD COPD, 13 patients with AATD and COPD and 29 healthy controls. As well as the relationships with gas transfer and imaging described above, the study highlighted differences in the regional pattern of ventilation impairment across groups with AATD patients demonstrating greater mid-zone ventilation defects, reflecting their more typical basal emphysema distribution, whereas non-AATD COPD showed more heterogeneous impairment.

In the study by Green et al[36], 699 PiZZ, 126 PiSZ and 316 PiMM (non-AATD COPD) were compared Usual COPD patients (PiMM) were (on average) 18 years older than those with PiZZ AATD, had smoked more, but had a similar lung function to the PiZZ patients, suggesting a faster decline in lung function (on average) in the PiZZ group compared to usual COPD.

Discussion

This systematic review examined the published role of gas transfer in assessing both severity and disease progression in individuals with AATD across 22 studies, with some comparisons to non-AATD COPD.

The relationship between spirometric indices of airflow obstruction and gas transfer measurements is shown to be complex, variable across disease stages and AATD phenotypes and only partially overlapping. While impairments in gas transfer commonly co-exists with reduced FEV_1 and FEV_1/FVC, particularly in advanced disease, numerous studies identify clinically relevant discordance, including preserved spirometry with impaired gas transfer and, less frequently, airflow obstruction with relatively preserved Kco.[22,24,28] These patterns are consistently observed across national and international registries and image-linked cohorts, suggesting that they reflect genuine biological heterogeneity rather than acquisition artefact.

Longitudinal data further support the partial independence of emphysema-related physiological decline from airflow obstruction in AATD. Rates of decline in Kco and FEV_1 are either weakly related or unrelated in several published cohorts, particularly once COPD is established, and rapid Kco decline occurs across a broad range of spirometric

severities.[18,22,24,25] Importantly, patients with isolated Kco impairment may demonstrate accelerated subsequent FEV_1 decline, raising the possibility that gas transfer abnormalities identify an early or active emphysema-predominant disease trajectory that precedes, rather than parallels, spirometric deterioration.[22] This observation challenges spirometry-centred models of disease monitoring and highlights the risk of underestimating or ignoring progression especially when the FEV_1 is stable.

Mechanistically, this dissociation is biologically plausible. Emphysema in AATD is driven primarily by protease–antiprotease imbalance, with unopposed neutrophil elastase activity[23,43] leading to progressive destruction of alveolar walls and loss of gas-exchange surface area which is captured physiologically by reductions in DLco and Kco. In contrast, airflow obstruction reflects a broader set of processes including small airway inflammation,[44] mucus hypersecretion,[45] airway remodelling, and dynamic airways collapse during forced expiration and these may evolve independently of parenchymal destruction. Biomarker studies linking circulating markers of neutrophil elastase activity to accelerated Kco decline but not FEV_1 decline further support the concept that gas transfer more directly reflects the core pathological process in emphysema-predominant AATD.[23] Imaging studies reinforce this physiological distinction. Quantitative CT densitometry and advanced MRI techniques consistently show stronger relationships between emphysema burden and gas transfer than with spirometric measures, and abnormalities in gas transfer may be detectable even when spirometry remains within the normal range.

Importantly, some screened cohorts, including the well-characterised Swedish birth cohort, have not routinely incorporated gas transfer measurements into longitudinal follow-up.[30,46,47] Although these studies could not be included in this systematic review as they did not include longitudinal gas transfer, it is noteworthy that respiratory symptoms occurred in this cohort in the presence of normal spirometry for most participants,[47] a finding replicated in other studies included in the systematic review and often associated with an impaired DLco or Kco. Not assessing gas transfer may represent a missed opportunity to detect and define the natural history of emphysema physiology across early and mid-adulthood in AATD and risks overlooking subclinical but biologically active disease.

These findings have direct clinical implications, particularly for risk stratification and augmentation therapy decision-making. Current treatment frameworks have traditionally prioritised spirometric thresholds,[10,48,49] yet this review suggests that patients with early and rapid Kco decline, especially those with severe deficiency genotypes, may represent a high-risk subgroup with active parenchymal destruction, even when FEV_1 is stable or decline is modest.[17,22,24] Of note, modelling has also suggested that patients with an established fast decline in Kco % predicted may also form a subgroup in which to conduct clinical trials of interventional therapy, due to the manageable patient numbers needed to be included to detect a 25% reduction in decline.[25] Gas transfer may therefore add incremental value in characterising patients and following disease progression whilst also identifying patients at risk of poor outcomes, including exacerbations, their nature and mortality. In addition, this background could help identify patient selection for closer monitoring with or without imaging, or therapeutic intervention. While further prospective evidence is still required, incorporating routine gas transfer assessment into clinical follow-up and research protocols may improve clinical phenotyping, better align treatment with underlying pathology, and support a more personalised approach to disease modification in AATD.

In studies that included both AATD and non-AATD COPD populations, patterns were generally similar but with some important distinctions. Both groups show associations between reduced gas transfer and worse airflow obstruction, quality of life, and emphysema severity. However, gas transfer abnormalities appear earlier and are more pronounced in AATD, particularly in PiZZ patients, even when spirometry can remain relatively preserved. For example, Piloni et al[35] and Crapo et al[34] reported that DLco decline was steeper and more predictive of disease progression in AATD than in non-AATD COPD. These differences likely reflect the distinct pathophysiological mechanisms underlying each condition and their anatomical localisation.

Strength and Limitations

This review benefits from a comprehensive search strategy, strict inclusion criteria, and thorough quality assessment using the Newcastle-Ottawa Scale, with most included studies rated as good quality. It integrates diverse outcome measures, physiological, radiological, and patient-reported, to provide a multidimensional evaluation of lung function in AATD.

However, limitations exist. High heterogeneity in study design, measurement techniques, and outcome reporting precluded meta-analysis. Few studies reported calibration methods or standardised reference equations for gas transfer, limiting cross-study comparability. The predominance of retrospective data and the underrepresentation of early-stage or asymptomatic patients also restrict generalisability. Furthermore, variation in AATD genotypes and smoking history introduces additional heterogeneity. Finally, most studies were conducted using retrospective data from local national and international registries. Although this raises the possibility of some participant overlap across studies, findings have also been replicated in separate cohorts demonstrating agreement.

Future research in more diverse populations is needed to validate these results further with similar extensive characterisation and strict standardised operating procedures for data collection and reporting. However, the increasingly widespread use of augmentation therapy and the increasing number of recent Phase 2 clinical trials of newer therapies provides a real challenge to the continued assessment of the natural history.

Conclusion

This systematic review highlights the value of gas transfer measurements alongside spirometry in the assessment of AATD lung disease. Gas transfer indices provide additional insights into disease severity, structural lung damage, and prognosis often identifying abnormalities before spirometric decline in AATD. The associations with imaging, health status, exacerbation risk, and mortality reinforce the clinical utility of gas transfer in both diagnosis and symptom assessment as well as longitudinal monitoring. Incorporating gas transfer into routine evaluation may enhance early detection and improve personalised risk assessment and health care strategies in AATD.

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