Disease burden associated with alpha-1 antitrypsin deficiency: systematic and structured literature reviews

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Shareable abstract (@ERSpublications)
AATD is a rare genetic disorder associated with a considerable burden of lung and liver disease and high healthcare resource utilisation. However, available data are scarce and further research is needed to better understand the burden of this disease. https://bit.ly/3IWtQQ1

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder characterised by reduced levels of circulating alpha-1 antitrypsin and an increased risk of lung and liver disease. Recent reviews of AATD have focused on diagnosis, epidemiology and clinical management; comprehensive reviews examining disease burden are lacking. Therefore, we conducted literature reviews to investigate the AATD disease burden for patients, caregivers and healthcare systems. Embase, PubMed and Cochrane libraries were searched for AATD publications from database inception to June 2021, in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Most published AATD studies were small and short in duration, with variations in populations, designs, measures and outcomes, complicating cross-study comparisons. AATD was associated with significant pulmonary and hepatic morbidity. COPD, emphysema and bronchiectasis were common lung morbidities, where smoking was a key risk factor. Fibrosis and steatosis were the most common liver complications reported in patients with a *PiZ* allele. Health status analyses suggested a poorer quality of life for AATD patients diagnosed with COPD *versus* those with non-AATD-associated COPD. The burden for caregivers included loss of personal time due to caring responsibilities, stress and anxiety. AATD was also associated with high direct medical costs and healthcare resource utilisation.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder characterised by reduced levels of the proteinase inhibitor alpha-1 antitrypsin (AAT) in the circulation [1]. Individuals with AATD typically have a mutation in the *SERPINA1* (or protease inhibitor (*Pi*)) gene, leading to a change in the structure of the AAT protein [1]. Normal alleles are known as *PiM*, while the most common deficiency alleles are *PiS* and *PiZ*, with *PiMS*, *PiMZ*, *PiSS*, *PiSZ* and *PiZZ* genotypes accounting for most variants [2]. >90% of patients with AATD express the *PiZZ* genotype; however, there are hundreds of rare and ultra-rare genotypes that result in circulating AAT concentrations of <11 µM, including the *null*/*null* genotype, which produces no AAT [2, 3]. Worldwide, it has been estimated that there are 3.4 million individuals with deficiency allele combinations (*PiZZ*, *PiSZ* or *PiSS* genotypes), and ⩾116 million carriers of deficiency alleles (*i.e.* heterozygous for the *PiZ* and *PiS* genotypes) [4].

AAT is produced mainly in the liver and circulates to the lungs, where it inhibits neutrophil elastase [5, 6]. If AAT is significantly reduced or absent, excess neutrophil elastase can degrade the lung extracellular

matrix, as well as alveolar structures and blood vessels [7]. Individuals with AATD are therefore at increased risk of developing pulmonary disease, especially emphysema, which is often found in the basal areas of the lung [6]. AATD affects males and females equally, and the approximate age of diagnosis is 40–45 years [8].

Some individuals with AATD are prone to developing liver disease, which is secondary to accumulation of mutant AAT in hepatocytes [1, 6]. Patients with the *Z* variant (both heterozygotes and homozygotes) can develop liver disease due to abnormal folding of the *Z* AAT protein, which enables individual *PiZ* AAT proteins to polymerise and aggregate within the endoplasmic reticulum with eventual apoptosis of hepatocytes leading to toxicity, liver injury and increased risk of liver disease [9]. Liver complications are not observed in patients who have the *null*/*null* phenotype, because of the lack of aggregation of mutant proteins in the endoplasmic reticulum [10].

Infusion of purified human plasma-derived AAT protein (AAT therapy) has been available to treat AATD since it was first authorised by the United States Food and Drug Administration in 1987. Approval of this therapy was based on biochemical efficacy outcomes, *i.e.* inhibiting neutrophil elastase activity *ex vivo*, and maintaining AAT concentrations above presumed therapeutic thresholds in both serum and bronchoalveolar lavage fluid samples in patients with AATD [11]. In 2015, the RAPID trial reported a significantly reduced rate of lung density decline as measured by computed tomography (CT) for AAT therapy *versus* placebo [12, 13].

Although CT densitometry is useful for evaluating patients' responses to AATD therapies [14], the assessment of disease severity and progression is conventionally based on pulmonary function tests, such as forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide (D_{LCO}), where declines over time are largely accepted as indicative of disease progression [2]. These measures can correlate with changes in quality of life (QoL), as measured by QoL instruments specifically designed for patients with obstructive airways disease, such as the St George's Respiratory Questionnaire (SGRQ) [14]. As for most pulmonary diseases, exacerbation severity and frequency can accelerate disease progression in AATD. Dyspnoea is a common complaint among patients with AATD and can be assessed using the modified Medical Research Council (mMRC) dyspnoea scale. These measures provide a means to assess disease burden in patients with AATD, comparing it with observations in patients with non-AATD-associated COPD.

Recent reviews of AATD have focused on the epidemiology and distribution of genetic variants, disease screening, diagnosis and care, as well as AAT therapy [2, 3, 15–19]. In contrast, comprehensive reviews that assess the burden of AATD on patients, caregivers and healthcare systems are lacking. An increased understanding of this burden may help improve awareness and diagnosis rates, as well as healthcare resource planning and allocation. Consequently, we conducted systematic and structured literature reviews to assess the clinical, economic and QoL-related disease burden associated with AATD worldwide.

Methods

Systematic reviews of the AATD literature were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The objective of this analysis was to assess 1) clinical burden and mortality associated with AATD; 2) QoL for patients; 3) caregiver burden; and 4) healthcare costs and resource utilisation.

Data sources

Embase, MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the Essential Reference Tool for Economics Literature were collectively searched from database inception to June 2021 to identify English-language studies on AATD using defined search strategies. Congress proceedings from 2017–2021 were also searched. In addition, registry websites (including the Tufts Cost-effectiveness Analysis Registry, the Alpha-1 Antitrypsin Deficiency Spanish Registry (REDAAT) and EUROCAT) and health technology assessment reports were searched for relevant studies. Finally, relevant systematic reviews identified through database searches were used for bibliography searching.

Population characteristics

The patient population of interest was adults (aged ⩾18 years) of any race or gender with AATD. There were no restrictions on inclusion of studies based on intervention and comparator, country or publication timeframe. Publications that included patients with other diseases and studies that enrolled a mixed population of children and adults were excluded if subgroup data for adult patients with AATD were not available.

Search strategy, procedures and information extraction

All titles were downloaded into a systematic review database. Citations obtained from the searches were initially screened by two independent reviewers and conflicts resolved by a third independent reviewer/consensus. Citations that did not match the eligibility criteria were excluded, as were any duplicates due to overlap in coverage of the databases. Full-text papers were then screened in a similar fashion, with any discrepancies between the two reviewers resolved by a third independent reviewer. One reviewer then extracted data into a pre-defined extraction grid, which was validated by another independent reviewer. Where more than one publication was identified as describing a single study, the data were compiled into a single entry to avoid double counting of patients and studies. The search strategies used are shown in the supplementary figures.

Critical appraisal

Critical appraisal of included randomised controlled trials was conducted using comprehensive assessment criteria based on recommendations by the National Institute for Health and Care Excellence [21]. Observational studies were critically appraised using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [22].

Results

Clinical burden review

A total of 38 studies were included in the clinical burden review (supplementary figure S1), 17 of which were conference abstracts. 23 studies were conducted in Europe; nine in North America; and the remainder did not report the study location. Study sample size ranged from 19 patients in a small case–control study [23] to 422 506 patients from a UK population-based cohort [24]. 31 of the included studies reported clinical characteristics of patients with AATD (supplementary table S1). Mean age ranged from 39.9 to 69.6 years across 29 studies, and the proportion of males was ⩾50% in 18 studies. Data on smoking status were reported in 17 studies; in 15 of these, most patients were current or former smokers (52–84%) [25–35]. The remaining two studies involved nonsmoking patients, who comprised all patients in one study [36] and 73% of patients in the other study [29]. *PiZZ* was the most commonly identified genotype, and was the only genotype identified in 10 studies [25, 27, 30, 31, 37–42].

Of the 38 included studies, all reported data regarding specific morbidities in patients with AATD including pulmonary, liver and skin disease; overall, 50 different morbidities were reported (table 1) [23–30, 32–59]. Pulmonary morbidity was commonly reported, and included COPD with a prevalence of 36.3–75.8% [25, 26, 33, 43, 49], emphysema (14.4–53.8%) [29, 43, 46, 47] and bronchiectasis (3.8–73.1%) (table 1) [29, 45–47].

One study reported lung nodules in 26.8% of patients [40]. Risk factors for developing lung morbidity in individuals with AATD were reported in 10 studies. Smoking was cited as a risk factor in six studies [26, 35, 47–50], and current smoking, age (40–59 years) and frequent severe exacerbations of COPD were associated with an accelerated decline of FEV_1 in individuals with severe AATD [26, 35]. The remaining studies did not examine the influence of smoking on risk.

There are mixed results reported for the influence of genotype on lung disease, with some studies reporting that *PiSZ* is a risk for exacerbation of lung disease [44, 47], others that *PiZZ* results in more severe disease [34, 46, 50] and one study reporting no increased risk of COPD due to *PiSZ* (table 1) [33]. One study reported on the effects of *PiSS* and *PiMM* and reported a significant four-fold increase in lung cancer risk in never-smokers with *PiSS* compared with *PiMM* genotypes (OR 4.64, 95% CI 1.08–19.92) [36].

Liver fibrosis was the most reported hepatic morbidity, with a wide variation in prevalence (1–88%) in those with AATD [23, 24, 27, 31, 38, 39, 52, 53, 55]. Advanced liver fibrosis was reported in 0.5–25.6% of patients [23, 31, 38, 53]. Cirrhosis was seen in 4–11% of patients [23–25, 37, 56]. A single study reported hepatocellular carcinoma in 2% of patients and hepatitis in 1% [25]. Genotype was an important risk factor for liver morbidity, with *PiZZ* associated with an increased risk of advanced liver fibrosis [38] and steatosis [53] (table 1). Among individuals with a *PiZZ* genotype, additional risk factors for liver disease included male sex [25, 38, 39] and the presence of metabolic dysfunction including diabetes [25, 27], metabolic syndrome and obesity [27]. Age >50 years, elevated liver enzyme levels, hepatitis viral infection and COPD were also associated with liver disease [25]. In addition, while *PiZZ* individuals had more liver stiffness and raised liver enzymes than individuals with an *PiMZ* or a wild-type *PiMM* genotype, *PiMZ* carriers appeared to have an intermediate risk of hepatic morbidity *versus* those without AATD-associated genotypes [55].

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TABLE 1 Clinical burden review: morbidity associated with alpha-1 antitrypsin deficiency (AATD)

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Pulmonary morbidity					
Herrera, 2021 [43]	Severe AATD (n=711) Nonsevere AATD (n=1963) Severe AATD (n=711) Nonsevere AATD (n=1963)	COPD COPD Emphysema Emphysema	75.8 56.9 33.8 23.8	Not evaluated	Patients with severe AATD-related PM requiring hospitalisation are substantially burdened by more frequent events and a more severe clinical course.
Tanash, 2019 [25]	Severe AATD (n=1595)	COPD	53		The proportion of subjects with COPD was higher among individuals with than those without liver disease.
Hiller, 2019 [26]	Severe AATD (n=1132)	COPD	52	Smoking# Middle age# Frequent exacerbation# Respiratory symptoms#	Active smoking, age, respiratory symptoms at baseline and repeated severe exacerbations of COPD were associated with accelerated decline of lung function in severe AATD.
Choate, 2019 [44]	AATD (*PiZZ* n=3031) AATD (*PiSZ* n=504)	Exacerbation over the past year (lung condition not specified)	75.6 78.3	Not evaluated	*PiSZ* patients reported more frequent exacerbations than *PiZZ* patients, even after adjusting for age, sex, current smoking status and CCI score.
Costa, 2017 [29]	AATD (*PiSS* and *PiMS* n=32; *PiMZ* n=64; *PiSZ* n=8) AATD (*PiSS* and *PiMS* n=32; *PiMZ* n=64; *PiSZ* n=8)	Bronchiectasis Emphysema	3.8 21.2	Not evaluated	Patients with intermediate AATD were often symptomatic and some had mild obstruction and emphysema. Exposure to risk factors seemed to be more important than AATD serum level in determining lung function.
Cortese, 2016 [45]	AATD (n=475)	Bronchiectasis	12	Patients with bronchiectasis had more comorbidities (p=0.008) and were more frequently affected by pneumonia (p=0.024) than those without bronchiectasis	The presence or absence of bronchiectasis should be ascertained in patients affected by severe AATD because of its clinical consequences.
Araújo, 2015 [46]	AATD (n=110) AATD with bronchiectasis (n=26)	Bronchiectasis Emphysema	24 53.8	*PiZZ*#	*PiZZ* individuals were significantly more likely to have severe bronchiectasis *versus* those with other alleles.
Kawkgi, 2013 [47]	AATD (*PiSZ*) with smoking history (n=29) AATD (*PiSZ*) with smoking history (n=29)	Emphysema Bronchiectasis	36 54	Smoking#	Individuals with the *SZ* phenotype were at risk of developing emphysema if they smoked; however, the rate of bronchiectasis in this population was high, regardless of smoking history.
Ferrarotti, 2012 [48]	Severe AATD (n=312)	Overall (not specified)	79	Smoking and possession of rare deficient allele other than *S* or *Z*#	This database enabled a detailed characterisation of the natural course of the disease and the status of patient care.
Guttmann, 2011 [49]	Severe AATD (n=713)	COPD	73	Smoking# Dust exposure#	AATD led to significant morbidity in affected subjects.

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TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Subramanian, 2010 [40]	AATD *PiMZ* (n=497)	Lung nodule	26.8	hs-CRP due to lung nodule (p<0.005)	An association between the presence of lung nodules (accompanied by a significant increase in hs-CRP) and the subsequent development of COPD was suggested.
Torres-Durán, 2015 [36]	AATD (n=212)	Lung cancer	*PiMM* 70 *PiMS* 21.1 *PiMZ* 3.8 *PiSZ* 1.4 *PiSS* 3.3		There was a significant four-fold increase in lung cancer risk in never-smokers with *PiSS* compared with *PiMM* genotypes (OR 4.64; 95% CI 1.08–19.92).
Gupta, 2020 [32]	No deficiency (n=1149) Mild deficiency (n=147) Intermediate deficiency (n=59) Severe deficiency (AATD) (n=4)	Emphysema			Patients with severe AATD (*ZZ*, *SZ* and $S_{Donosti}Z$) had lower diffusion capacity and greater CT-based emphysema *versus* patients without AATD.
Franciosi, 2021 [50]	AATD *PiMZ* (n=91) AATD *PiSZ* (n=72) AATD *PiZZ*/rare (n=130)	Lung disease, airflow obstruction[¶]	47.3 45.9 74.6	Smoking	Patients with AATD and a *PiZZ* genotype were more likely to have been diagnosed with AATD due to lung disease, demonstrated by worse airflow obstruction.
Franciosi, 2020 [33]	AATD *PiSZ* (n=70) AATD *PiMM/MS* (controls) (n=46)	COPD	Not stated	Not stated	*PiSZ* never-smokers demonstrated no increased risk of COPD, regardless of AAT concentration.
Esquinas, 2018 [35]	AATD *PiZZ* (n=122)	Emphysema Chronic bronchitis Bronchiectasis Asthma	83.1 44.6 42.3 20	Tobacco consumption (p=0.001) Previous pneumonia (p=0.026) Higher baseline FEV_1 % (p=0.010)	Tobacco consumption, previous pneumonia and better lung function at baseline were related to a faster decline in FEV_1.
Parr, 2007 [51]	AATD *PiMZ* (n=74)	Bronchiectasis	27 (clinically significant)		Emphysema was the predominant component of COPD in AATD, but the prevalence and impact of airway disease was expected to be greater than is currently recognised.
Piras, 2013 [34]	AATD *PiZZ* (n=547)	Chronic bronchitis Emphysema Asthma Bronchiectasis COPD	26 63.1 11 19 78.4		*PiZZ* patients had more severe respiratory disease than those with *PiSZ*, despite lower smoking levels.
	AATD *PiSZ* (n=124)	Chronic bronchitis Emphysema Asthma Bronchiectasis COPD	22.6 33.9 17.7 12.9 43.5		
	AATD Spain (n=416)	Chronic bronchitis Emphysema Asthma Bronchiectasis COPD	36.1 66.6 15.9 27.2 76.2		

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TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
	AATD Italy (n=329)	Chronic bronchitis Emphysema Asthma Bronchiectasis COPD	9.4 45.9 5.5 4 67.8		
Hepatic morbidity					
Teckman, 2019 [52]	AATD with liver disease (n=93) AATD with liver disease (n=93) AATD with liver disease (n=93) AATD with liver disease (n=93)	Liver fibrosis (Ishak score 0–1) Liver fibrosis (Ishak score 2) Liver fibrosis (Ishak score 3) Liver fibrosis (Ishak score 4–6)	88 2 2 8	Not evaluated	This study documented a highly variable range of findings with fibrosis.
Ferrarotti, 2012 [48]	Severe AATD (n=312)	Overall (not specified)	10	Not evaluated	This database enabled a detailed characterisation of the natural course of the disease and the status of patient care.
Chakraborty, 2016 [28]	AATD (n=212)	Overall (not specified)	29	AST (p=0.001) BMI (p=0.04) Platelet reduction (OR 0.97, 95% CI 0.96–0.98)	Liver disease in this AATD cohort was high, with obese individuals at greatest risk.
Mandorfer, 2017 [53]	Severe AATD with PM (n=31) Severe AATD with PM (n=31) Severe AATD with PM (n=31)	Advanced liver fibrosis Liver fibrosis Liver steatosis	3 23 <Stage 1 65 <Stage 2 52	Not evaluated	Patients with severe pulmonary manifestation AATD rarely developed advanced liver fibrosis during adulthood. Autopsy reports, which observed cirrhosis in about one-third of *PiZZ* patients, may have overestimated the risk of end-stage liver disease.
Strnad, 2017 [39]	AATD with *PiMZ* without known liver disease (n=115) Matched controls without AAT mutations (n=100)	Liver fibrosis	18 6	Not evaluated	*PiMZ* heterozygotes had higher serum ALT, AST and GGT levels than controls. Alcohol misusers carrying the *PiZ* variant were more prone to develop cirrhosis.
Arslanow, 2017 [23]	AATD (n=19) AATD (n=19) AATD (n=19)	Advanced liver fibrosis Liver steatosis Cirrhosis	21 37 11	Not evaluated	AATD presented with both impaired body composition and liver function tests. A third of the patients displayed abnormal TE measurements, indicating steatosis or advanced fibrosis.
Hamesch, 2019 [38]	AATD with homozygous *PiZZ* (n=403) AATD without *PiZ* mutation (n=234) AATD with homozygous *PiZZ* (n=403) AATD without *PiZ* mutation (n=234)	Liver fibrosis (LSM) Liver fibrosis (LSM) Advanced liver fibrosis (LSM) Advanced liver fibrosis (LSM)	23.6 6.4 13.6 1.3	Age >50 years Male sex Elevated ALT/AST/GGT Reduced platelet count Lung function *PiZ* carrier (OR 19.8, 95% CI 4.6–84.1)	Male sex, age >50 years, increased levels of ALT/AST/GGT and low numbers of platelets were associated with a higher liver fibrosis burden. No evidence for a relationship between lung function and liver fibrosis was found.

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TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
	AATD with homozygous *PiZZ* (n=403)	Liver fibrosis (APRI)	19.6		
	AATD without *PiZ* mutation (n=234)	Liver fibrosis (APRI)	5.4		
	AATD with homozygous *PiZZ* (n=403)	Advanced liver fibrosis (APRI)	4.5		
	AATD without *PiZ* mutation (n=234)	Advanced liver fibrosis (APRI)	0.5		
	AATD with homozygous *PiZZ* (n=403)	Liver fibrosis (HepaScore)	36.3		
	AATD without *PiZ* mutation (n=234)	Liver fibrosis (HepaScore)	13.5		
	AATD with homozygous *PiZZ* (n=403)	Advanced liver fibrosis (HepaScore)	25.6		
	AATD without *PiZ* mutation (n=234)	Advanced liver fibrosis (HepaScore)	4.1		
	AATD with homozygous *PiZZ* (n=403)	Liver steatosis (mild)	61.1		
	AATD without *PiZ* mutation (n=234)	Liver steatosis (mild)	48.2		
	AATD with homozygous *PiZZ* (n=403)	Liver steatosis (severe)	38.7		
	AATD without *PiZ* mutation (n=234)	Liver steatosis (severe)	28.4		
Tanash, 2019 [25]	*PiZZ* AATD (n=1595) *PiZZ* AATD (n=1595)	Cirrhosis Hepatocellular carcinoma	7 2	Male gender (risk ratio 1.45, 95% CI 1.15–2.14; p=0.03) Age >50 years (risk ratio 2.02, 95% CI 1.30–3.16; p=0.002) Ever-smokers (risk ratio 0.85, 95% CI 0.56–1.30; p=0.46) Repeated elevated LFTs (risk ratio 7.66, 95% CI 5.10–11.73) Hepatitis infection (risk ratio 3.12, 95% CI 1.21–8.08; p=0.02) COPD (risk ratio 2.20, 95% CI 1.32–3.70; p=0.003) Diabetes (risk ratio 3.87, 95% CI 2.18–6.87) Hypertension (risk ratio 0.91, 95% CI 0.50–1.66; p=0.76)	In this large study, the prevalence of liver disease in *PiZZ* individuals was 10%. Age >50 years, male gender, repeated elevated liver enzymes, hepatitis and the presence of diabetes mellitus and COPD were risk factors for developing liver disease.
Stone, 2014 [37]	AATD (n=651)	Cirrhosis	4	Not evaluated	

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TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Clark, 2018 [27]	AATD (n=94)	Liver fibrosis	35.1	Sex (p=0.04) Diabetes (p=0.002) Impaired fasting glucose (p=0.003) Obesity (p=0.01) Metabolic syndrome (p<0.001)	Individuals with large amounts of AAT on biopsy may be at risk of liver injury and fibrosis. Metabolic syndrome was associated with a greater degree of liver injury.
Black, 2020 [54]	Heterozygous AATD (chronic liver disease + AAT globules) (n=23) Controls (chronic liver disease, no AAT globules) (n=120)	Liver disease	Stage 1 13.0 Stage 2 8.7 Stage 3 26.1 Stage 4 52.2 Stage 1 30.8 Stage 2 23.3 Stage 3 24.2 Stage 4 21.7	Stage 4 (p=0.017)	Heterozygous AATD may potentiate the progression of concurrent liver diseases.
Fromme, 2022 [24]	AATD *PiMZ* (n=17 006): cohort 1	Liver fibrosis/cirrhosis	Liver fibrosis/cirrhosis was 20 times more common in *PiZZ versus* noncarriers (adjusted OR 21.7, 95% CI 8.8–53.7; p<0.0001), but also markedly enriched in *Pi*SZ* subjects (adjusted OR 3.1, 95% CI 1.1–8.2; p=0.027) and moderately in *Pi*MZ* participants (adjusted OR 1.7, 95% CI 1.2–2.2; p=0.001)		The higher fibrosis burden was confirmed in a multinational cohort. Male sex, age ⩾50 years, obesity and the presence of diabetes were associated with significant liver fibrosis.
	AATD *PiSS* (n=1014): cohort 1 AATD *PiSZ* (n=864): cohort 1 AATD *PiZZ* (n=138): cohort 1 Controls (noncarriers n=422 506): cohort 1	Liver primary cancer	*PiSZ* and *PiZZ* increased the risk of primary liver cancer (adjusted OR 6.6, 95% CI 1.6–26.9 and adjusted OR 44.5, 95% CI 10.8–183.6) *versus* noncarriers		
	AATD *PiZZ* (n= 586): cohort 2 AATD *PiSZ* (n=239): cohort 2 Controls (noncarriers n= 279): cohort 2	Liver fibrosis/cirrhosis	24 13 5		
	AATD *PiMZ* (n=419): cohort 1	Liver fibrosis	10		

Continued

TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Schneider, 2020 [55]	AATD *PiZZ* (n=309): cohort 1	LSM >7.1 kPa	25		Obesity and diabetes were the most important factors associated with LSM ⩾7.1 kPa in subjects with the *PiMZ* genotype.
	Control (noncarriers n=284): cohort 1		4		
	AATD *PiMZ* (n=84): cohort 2	Liver steatosis	Stage 1 40.5 Stage 2 28.5 Stage 3 15.5		
	AATD *PiZZ* (n=35): cohort 2		Stage 1 34.3 Stage 2 37.1 Stage 3 2.9		
	AATD *PiMZ* (n=84): cohort 2	Liver fibrosis	Stage 1 13.1 Stage 2 28.6 Stage 3 28.6 Stage 4 16.7		
	AATD *PiZZ* (n=35): cohort 2		Stage 1 5.7 Stage 2 20.0 Stage 3 42.9 Stage 4 28.6		
	AATD *PiMZ* (n=84): cohort 3	Perisinusoidal fibrosis	69.1		
	AATD *PiZZ* (n=35): cohort 3		97.1		
Hakim, 2021 [56]	SERPINA 1 *Z* allele (n=299 939)	Cirrhosis	0.5	The SERPINA1 *Z* allele was associated with cirrhosis in an allele dose-dependent manner (OR 1.69; $p=2.3\times10^{-07}$)	SERPINA1 *Z* allele heterozygosity was an important risk factor for liver disease.
	SERPINA 1 *PiMZ* (n=12 603)		0.7		
	SERPINA 1 *PiZZ* (n=129)		4.7	The SERPINA1 *Z* allele was associated with higher odds of cirrhosis in both heterozygotes *versus* noncarriers (OR 1.53; $p=1.1\times10^{-04}$) and homozygotes *versus* noncarriers (OR 11.8; $p=1.8\times10^{-09}$)	
Abu Rmilah, 2021 [57]	AATD *PiMM* with cirrhosis (n=1094)	Cryptogenic cirrhosis	76.9		Rates of pre-operative and post-operative pulmonary complications were found to be higher for *PiMZ* than *PiMM*. The *MZ* phenotype was significantly enriched in NASH, ALD and cryptogenic cirrhosis.
		NASH	67.3		
		ALD	70.6		
		Autoimmune	87.5		
		Viral hepatitis	87.5		
		PSC/PBC	88.8		
		Others	89.3		
	AATD *PiMZ* with cirrhosis (n=130)	Cryptogenic cirrhosis	23.0		
		NASH	22.0		
		ALD	20.0		
		Autoimmune	10.0		
		Viral hepatitis	5.6		
		PSC/PBC	3.2		
		Others	10.7		

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TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Other morbidity					
Tanash, 2019 [25]	Severe AATD (n=1595)	Panniculitis	<1	Four out of 1595 patients with a *PiZZ* genotype	No patients with panniculitis developed liver disease.
Stone, 2014 [37]	AATD (n=651)	Panniculitis	0.9		The prevalence of inflammatory bowel disease and hypothyroidism was higher than that predicted in the UK, supporting a potential link between AATD and these conditions.
		Granulomatosis with polyangiitis	0.8		
		Inflammatory bowel disease (UC and Crohn disease)	1.5		
		Hypothyroidism	4		
Choate, 2019 [44]	AATD *PiZZ* (n=3031)	High blood pressure	38.4		A statistically significant greater proportion of *PiSZ* in our cohort were diagnosed with the six most prevalent comorbidities.
		Reflux	33.9		
		Sinus disease	15.4		
		Heart rhythm problems	12.0		
		Tumour/cancer	11.2		
		Diabetes	7.3		
		Skin problems (including panniculitis)	8.6		
		Pulmonary hypertension	6.3		
		PVD	6.3		
		CTD	6.0		
	AATD (*PiSZ*=504)	High blood pressure	52.0		
		Reflux	40.4		
		Sinus disease	20.4		
		Heart rhythm problems	18.6		
		Tumour/cancer	16.2		
		Diabetes	17.0		
		Skin problems (including panniculitis)	7.0		
		Pulmonary hypertension	8.1		
		PVD	7.0		
		CTD	7.4		
Basil, 2021 [30]	Severe AATD	VTE	7	Unadjusted HR 6.5, 95% CI 4.9–8.6	Subjects with severe AATD had considerably increased risk of developing VTE *versus* the general population, even after accounting for risk factors.
	Controls		1	Adjusting for risk factors: male, age, COPD, cancer and liver disease HR 5.2, 95% CI 3.7–7.4	

Continued

TABLE 1 Continued

First author, year [ref.]	Patient population	Type of complication	Patients affected %	Risk factors for morbidity (value estimate)	Main outcomes
Tanash, 2020 [41]	AATD (*PiZZ*) (n=1545) Controls (n=5883)	Ischaemic heart disease	8 12	HR 1.8, 95% CI 1.4–2.3 Ever-smokers HR 2.1, 95% CI 1.5–2.9 Never-smokers HR 1.5, 95% CI 1.1–2.2	*PiZZ* individuals had a lower risk of developing incident ischaemic heart disease than controls with known smoking habits.
Hiller, 2020 [42]	AATD (*PiZZ*) (n=1585) Controls (n=5999)	Cancer	12 10	Adjusted HR 1.6, 95% CI 1.3–1.9 Ever-smokers HR 1.5, 95% CI 1.2–1.8 Never-smokers HR 1.7, 95% CI 1.3–2.2	*PiZZ* individuals had a lower risk of developing incident cancer than the general population adjusting for age and sex, both in ever- and never-smokers.
Sapey, 2020 [58]	AATD (n=68) COPD (n=88)	Periodontitis	88 95	Periodontitis severity associated with lung disease severity (AATD, periodontitis *versus* no periodontitis; FEV_1 56% *versus* 99% predicted; T_{LCO} 59% *versus* 81% predicted; p<0.0001 for both)	The results supported shared pathophysiology between periodontitis and COPD, especially when associated with AATD.
Mandich, 2011 [59]	AATD (n=33)	Bipolar disorder Schizophrenia Depression Anxiety	3.0 0 18.2 15.2		The incidence of psychiatric disorders was higher than the national incidence.

PM: pulmonary manifestation; *PiMM*/*MZ*/*SZ*/*ZZ*: *Pi* (or *SERPINA1* gene) *MM*, *MZ*, *SZ* and *ZZ* alleles; CCI: Charlson Comorbidity Index; hs-CRP: high-sensitivity C-reactive protein; CT: computed tomography; AAT: alpha-1 antitrypsin; FEV_1: forced expiratory volume in 1 s; AST: aspartate aminotransferase; BMI: body mass index; ALT: alanine aminotransferase; GGT: γ-glutamyl transferase; TE: transient elastography; LSM: liver stiffness measurement; APRI: AST-to-platelet ratio index; LFT: liver function test; NASH: nonalcoholic steatohepatitis; ALD: alcoholic liver disease; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis; UC: ulcerative colitis; PVD: peripheral vascular disease; CTD: connective tissue disease; VTE: venous thromboembolism; HR: hazard ratio; T_{LCO}: transfer factor of the lung for carbon monoxide. [#]: no estimated value was presented, although a qualitative statement establishing a relationship between variable and complication was reported (the majority were conference abstracts); [¶]: Global Initiative for Chronic Obstructive Lung Disease classification 1–4 representing airflow obstruction with an FEV_1 80–100% pred, 50–79% pred, 30–49% pred and <30% pred, respectively.

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Panniculitis, a neutrophilic inflammation of subcutaneous fat, was reported in <1–8.6% of patients with AATD across three studies [25, 37, 44] (table 1). Other complications associated with AATD included increased psychiatric disorders [59], inflammatory bowel disease [37], venous thromboembolism [30] and cancer [24, 25, 36, 42, 44], and decreased ischaemic heart disease [41].

Mortality

13 publications discussed mortality associated with AATD (table 2) [60–72], four of which were conference abstracts. Four Swedish studies included the same population, although different aspects were analysed [61, 62, 70, 71].

Sample sizes of the studies ranged from 143 to 8039; however, one study examined death certificate records from the United States National Center for Health Statistics, which comprised >26 000 000 cases [64]. In general, these studies showed that mortality in patients with AATD resulted primarily from respiratory diseases, followed by liver complications. The Attaway *et al.* [60] study, which examined inpatient hospitalisations among patients with AATD, reported an in-hospital mortality rate of 3.1%. One study from Sweden reported a standardised mortality ratio of 3.6 compared with the general population [61], whereas another reported a standardised mortality ratio of 6.3 among National Heart, Lung, and Blood Institute AATD registry patients [63]. Respiratory disease, hepatic disease, diverticulitis and pulmonary embolism were associated with a higher risk of mortality among patients with AATD in the Swedish study [61]. Another study confirmed that patients who were treated with AAT therapy had prolonged survival or time to lung transplantation compared with those who were AAT therapy-naïve [68]. Although patients with the *PiZZ* genotype had a higher rate of mortality compared with patients without AATD [61, 65, 71], one study observed no difference in mortality rates between never-smoking *PiZZ* individuals and never-smoking controls [61, 71].

Quality of life

The QoL review included 30 studies (supplementary figure S2), 23 of which were journal articles. The sample size ranged from 16 patients [73] to 922 patients [74]. Where reported, the mean age ranged from 40.7 years [14] to 60.3 years [75], and there were more males than females in 19 out of 30 studies, with the proportion of males ranging from 50.3% to 83% (supplementary table S2) [12, 76–78]. Most studies assessed QoL using the SGRQ (22 studies; table 3 [12, 14, 73–76, 78–93]). Other disease-specific patient-reported outcomes included the COPD Assessment Test (CAT), the Chronic Respiratory Disease Questionnaire (CRQ) and the Living with COPD (LCOPD) scale. The generic 36-item short-form survey (SF-36) was used in eight studies and the EQ-5D in two [75, 77] (see supplementary table S2 for the QoL instruments used in each study).

Two of the 30 included studies were randomised controlled trials. One of these studies evaluated AAT therapy which used the SGRQ [12] and another that assessed endobronchial valves in patients with AATD which used the SGRQ, mMRC and CAT [86]. The overall STROBE scores [22] among the remaining 24 studies are shown in supplementary table S3.

SGRQ scores (table 3) tended to be worse in patients with AATD who were diagnosed with COPD at baseline *versus* those with AATD, but without COPD at baseline [12, 88, 90] and in those with frequent exacerbations *versus* those without [74].

In addition, SGRQ scores were better in patients who never smoked compared with current or former smokers [79, 80, 83]. Several studies examined correlations between SGRQ score, lung function and other measures of physiological decline in AATD [14, 76, 82, 85, 88, 89, 91, 92], while others evaluated the impact of treatment on SGRQ score (table 3 and supplementary table S2) [12, 75, 81, 82].

Finally, a study reported worse QoL among patients with AATD diagnosed with chronic sputum expectoration *versus* those without chronic sputum expectoration [78].

Among studies reporting CAT scores, one reported similar scores between AATD patients diagnosed with COPD and a non-AATD COPD cohort, despite the AATD group being significantly younger, and having significantly fewer pack-years of smoking and significantly less comorbidity [77]. Regression analysis to assess the relationship between CAT scores and FEV_1 showed that the relationship approached statistical significance in the group of AATD patients diagnosed with COPD [77]. A second study reported no significant differences in CAT scores between patients with COPD who were receiving AAT therapy *versus* those who were not (supplementary table S4) [75].

TABLE 2 Mortality associated with alpha-1 antitrypsin deficiency (AATD)

First author, year [ref.]	Country	Years	Subjects n	Main mortality outcomes
Attaway, 2019 [60]	USA	2004–2014	8039[#]	In-hospital mortality rate (2004): 3.1% (unchanged over the study period) Higher rates of mortality associated with sepsis: 56/351 (16%) and respiratory failure: 42/741 (5.7%) Univariate analysis for higher mortality, mean+SD: congestive heart failure 2.07+0.70; pulmonary hypertension 2.29+0.83; cirrhosis 2.47+0.69; malnutrition 2.62+1.36; acute renal failure 6.59+1.87
Tanash, 2016 [61]	Sweden	1991–2014	1561[#,¶]	Total deaths n=524 SMR (95% CI) *PiZZ versus* Swedish population 3.6 (3.3–3.9) Main causes of death were COPD + complications (respiratory failure and infections) (n=281, 54%); liver diseases (n=74, 14%); CVD (n=76, 15%); and cancer (n=87, 17%) Cause-specific SMR (95% CI): IHD 0.5 (0.3–0.8); COPD 48.4 (43.0–54.5), n=28; liver failure/complications 47.8 (35.8–64.2), n=44 Cause-specific SMR (95% CI) in ever-smokers: COPD 71.3 (62.1–81.6), n=214; liver failure/complications 47.2 (30.5–69.6), n=25 Cause-specific SMR (95% CI) in never-smokers: COPD 24 (18.5–30.4), n=67; liver failure/complications 48.7 (29.3–76.1), n=19
Tanash, 2008 [62]	Sweden	1991–2007	568	Total deaths n=93 (16%) SMR (95% CI) for whole study population 2.32 (1.87–2.83); no difference between sexes. SMR (95% CI) for respiratory and nonrespiratory cases was 2.55 (1.91–2.83) and 2.07 (1.49–2.81), respectively. SMR (95% CI) for subgroups in nonrespiratory cases 0.70 (0.14–2.04) for individuals identified by family/population screening. Emphysema and liver cirrhosis were the most common causes of death (45% and 28%, respectively). Malignant transformation was found in 38% of cirrhosis cases
Stoller, 2005 [63]	USA	1989–1992	1129[#,+]	Total deaths n=204 (18.1%) Attributable mortality SMR 6.3 Male *versus* female SMR 5.8 *versus* 7.4 Emphysema and cirrhosis were the most common causes of death: 85/118 (72%) and 12/118 (10%), respectively, and SMR indicated that excess mortality was due to lung and liver disease.
Browne, 1996 [64]	USA	1979–1991	Overall records 26 866 600[#]	Number of individuals who died with AATD listed as cause of death n=1930 Rate per 100 000 deaths 7.18 Rate ratio of males to females 1.35 Proportion with COPD or hepatic disease 1206/1930 (62%) and 413/1930 (21%), respectively
Catterall, 2020 [65]	UK	1999–2020	195	22 (35.4%) *PiZZ* patients died within the audit period Mortality was higher for *PiZZ* patients compared with the overall COPD population
Dawkins, 2009 [66]	UK	1996–2005	488	Total deaths n=56 Cause of death: emphysema n=30; lung transplant n=4; liver disease n=6; malignancy n=5; cardiovascular n=3; cardiac n=3; PE n=2; other n=3 Mortality: 2% per year. Cumulative mortality of 18.1% over 9-year period. FEV_1 % predicted: severe impairment had increased mortality (p<0.001) *versus* mild, with a direct relationship between severity and mortality Severe impairment had increased mortality *versus* mild impairment when categorised for K_{CO} % predicted (p<0.001), RV/TLC ratio (p<0.001) or emphysema score on CT scan (p<0.001 upper zone)
Dawkins, 2003 [67]	UK	1996–2001	256	Total deaths n=22 Respiratory deaths n=10; lung transplant n=3; liver transplant n=1; nonrespiratory deaths n=8 Mortality rate ~4% per year Baseline FEV_1, K_{CO} and CT scores were significantly lower in nonsurvivors than survivors Upper-zone expiratory scan had best association with all-cause (p=0.001) and respiratory mortality (p=0.001) FEV_1 (p=0.158 all-cause, p=0.015 respiratory) and K_{CO} (p=0.002 all-cause, p=0.012 respiratory) had poorer associations with mortality Age provided further independent predictive information for all-cause or respiratory mortality when CT scan was entered into survival analyses

Continued

TABLE 2 Continued

First author, year [ref.]	Country	Years	Subjects n	Main mortality outcomes
Ellis, 2019 [68]	UK/USA		1535	Estimated mean (95% CI) survival was significantly longer in the treatment group: AAT therapy 20.3 (19.4–21.2) years, control 13.7 (13.1–14.3) years; p<0.001
Seersholm, 1994 [69]	Denmark	1978–1992	397	Total deaths n=112 Median survival 54.2 years Survival for index cases *versus* nonindex cases regardless of smoking history (49.4 years, 95% CI 42.4–53.6 years and 69.3 years, 95% CI 65.9–82.1 years, respectively) Survival of smokers was significantly less than for nonsmokers (p<0.0001) with a median survival time of 51.8 years (95% CI 47.2–56.1 years) for smokers and 66.8 years (95% CI 65.3–75.1 years) for never-smokers
Tanash, 2010 [70]	Sweden	1991–2008	1339	Total deaths n=315 (24%) SMR respiratory deaths 4.70 (95% CI 4.10–5.40) SMR nonrespiratory deaths 3.0 (95% CI 2.35–3.70) SMR smokers 4.80 (95% CI 4.20–5.50) SMR never-smokers 2.80 (95% CI 2.30–3.40) Rate ratio 1.70 (95% CI 1.35–2.20) Cause of death: respiratory 58%; hepatic 12%; other 30%
Tanash, 2017 [71]	Sweden	1991–2015	*PiZZ* 1585 Controls 5999	Total deaths *PiZZ* 473 (30%); controls 747 (12%) *PiZZ* patients had a significantly shorter survival time than controls (p<0.001) No increase in risk of death in never-smoking *PiZZ* patients identified by screening, compared with never-smoking controls, HR 1.2 (95% CI 0.6–2.2) After adjustment for gender, age, smoking habits and presence of respiratory symptoms, the risk of death for the *PiZZ* patients *versus* controls was HR 3.2 (95% CI 2.8–3.6; p<0.001) Causes of death: *PiZZ* respiratory disease 52%; CVD 16%; hepatic disease 15%; cancer 11%
Da Costa Dias de Souza, 2017 [72]	Portugal	2006–2016	143	Total deaths n=19 Mean age 60 years; males 63% Cause of death for all: liver disease 44%; respiratory disease 31%; other 25% Main cause of death for *PiZZ* and *PiMZ*: respiratory disease 83%; liver disease 57%, respectively Obstructive ventilatory disease was present in 42%; 78% with a FEV_1 <50% predicted. 42% were smokers/former smokers. The most frequent radiological finding was emphysema (57%)

PiZZ: *Pi* (or *SERPINA1* gene) *ZZ* allele; SMR: standardised mortality ratio; CVD: cardiovascular disease; IHD: ischaemic heart disease; PE: pulmonary embolism; FEV_1: forced expiratory volume in 1 s; K_{CO}: transfer coefficient of the lung for carbon monoxide; RV: residual volume; TLC: total lung capacity; CT: computed tomography; AAT: alpha-1 antitrypsin; HR: hazard ratio. [#]: no treatment reported; [¶]: during follow-up, 86 out of 1561 patients underwent lung transplantation; [+]: receipt of AATD therapy was considered a model parameter in the multivariate analyses.

Other disease-specific measures were reported in several studies. One study reported no differences in LCOPD scores between AATD patients diagnosed with COPD and patients with general COPD (7.2 *versus* 7.9, p=0.60) [77]. Linear regression analysis showed a significant correlation between FEV_1 (%) and LCOPD in both groups with a stronger relationship in AATD patients diagnosed with COPD (r^2=0.252, p=0.002 *versus* r^2=0.092, p=0.017 for general COPD) [77]. In another study, patients with AATD-related COPD were found to have a similar level of QoL impairment to patients with AATD and non-AATD-related COPD, but there was no correlation between CRQ scores and FEV_1 over time [94].

Six studies evaluated QoL in patients with AATD diagnosed with COPD using the nonspecific SF-36 instrument [74, 87, 89, 91, 92, 95], and two studies evaluated patients with AATD and emphysema with this tool [78, 96] (supplementary tables S2 and S5) [74, 87, 89, 91, 92, 95]. Higher SF-36 scores, indicating better health status, were reported in patients with AATD diagnosed with COPD and a *PiZZ* genotype (n=30) compared with patients diagnosed with general COPD (n=9) who had the same COPD severity, as measured by FEV_1 and D_{LCO} [87]. Exacerbation frequency was associated with significantly poorer SF-36 scores across all domains in patients with AATD diagnosed with COPD receiving AAT therapy [74]. Better QoL was reported for patients with AATD diagnosed with COPD receiving AAT therapy (pulmonary rehabilitation) compared with patients with non-AATD-related COPD [95]. Two studies in patients with AATD diagnosed with COPD suggested that obesity or increased body mass index

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TABLE 3 Quality of life review: St George's Respiratory Questionnaire (SGRQ) scores in patients with alpha-1 antitrypsin deficiency (AATD)

First author, year [ref.]	Population/ treatment	Subjects n	Time point	SGRQ scores				Main SGRQ outcomes
				Total	Symptoms	Activity	Impact	
Bernhard, 2017 [79]	AATD (*PiZZ*): never-smokers	223		36.9±21.8	44.5±23.8	45.3±26.8	28.7±21.5	In contrast to never- and intensive (ex-) smokers, moderate-smoking *PiSZ* individuals had a significantly better SGRQ total score (p=0.020) and fewer exacerbations (p=0.037) than individuals with a *PiZZ* genotype.
	AATD (*PiSZ*): never-smokers	33		22.5±21.6	35.0±23.9	25.2±29.6	16.7±19.3	
	AATD (*PiZZ*): moderate (ex-) smokers (0<pack-years<30)	491		46.9±19.8	55.7±22.7	58.3±22.6	37.3±21.0	
	AATD (*PiSZ*): moderate (ex-) smokers (0<pack-years<30)	44		38.9±25.6	43.3±28.2	48.8±30.4	29.0±24.3	
	AATD (*PiZZ*): intensive (ex-) smokers (⩾30 pack-years)	126		53.2±16.5	62.8±19.7	67.5±18.1	41.9±18.7	
	AATD (*PiSZ*): intensive (ex-) smokers (⩾30 pack-years)	33		59.8±19.0	62.1±20.7	71.6±20.1	49.2±22.3	
Piitulainen, 2017 [80]	AATD (*PiZZ*): never-smokers	152		3.7 (0–56.3)	2.5 (0–78.4)	6.0 (0–59.5)	0 (0–47.6)	*PiZZ* current smokers had a significantly higher median SGRQ activity score than the *PiZZ* never-smokers (p=0.032).[#] *PiMM* current smokers had significantly higher SGRQ activity (p<0.001), symptom (p<0.001) and total (p=0.001) scores than *PiMM* never-smokers.
	AATD (*PiZZ*): former smokers	40		5.0 (0–34.4)	7.5 (0–52.2)	8.8 (0–41.1)	0 (0–24.2)	
	AATD (*PiZZ*): current smokers	19		14.2 (2.9–20.1)	18.4 (5.9–36.3)	24.6 (6.0–47.7)[#]	2.8 (0–8.7)	
	AATD (*PiSZ*): never-smokers	152		6.2 (61.8)	11.8 (0–58.9)	12.2 (0–66.9)	0 (0–59.9)	
	AATD (*PiSZ*): former smokers	40		4.7 (2.0–7.3)	5.5 (0–18.4)	12.2 (6.0–18.5)	0 (0–0)	
	AATD (*PiSZ*): current smokers	19		13.9	37.8	18.5	14.2	
Luisetti, 2015 [81]	AATD	52	Baseline	29.8±26.3				Patients who received AAT therapy had poorer baseline QoL *versus* patients who did not receive AAT therapy (p=0.001).
	AATD index cases	35	Baseline	41.2±24.4				
	AATD non-index cases	17	Baseline	6.3±8.3				
	AATD + AAT therapy	18	Baseline	52.7±20.6				
	AATD without AAT therapy	19	Baseline	28.0±21.8				
Gauvain, 2015 [76]	AATD	273	Baseline	49.0±20.0	52.5±22.0	63.6±22.3	39.4±22.2	The number of exacerbations in the past year was significantly associated with SGRQ score (R=0.36; p<0.0001) and SGRQ scores had the strongest association with dyspnoea (R=0.65; p<0.0001). Multivariate analysis suggested that 57% of the variability seen in SGRQ scores resulted from dyspnoea (p<0.0001), D_{LCO} (% predicted) (p<0.001), chronic bronchitis (p=0.002), age (p=0.0088) and 6-min walk distance (p=0.037).
	AATD: females	101	Baseline	52.7±20.7				
	AATD: males	172	Baseline	46.8±18.2				

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TABLE 3 Continued

First author, year [ref.]	Population/ treatment	Subjects n	Time point	SGRQ scores				Main SGRQ outcomes
				Total	Symptoms	Activity	Impact	
Bradi, 2015 [82]	AATD + AAT therapy AATD without AAT therapy	24	1 year	50±14 34±22				AAT therapy status was significantly correlated with SGRQ scores when controlling for baseline FEV_1 (p=0.014).
Stolk, 2003 [14]	AATD AATD	22 22	Baseline 30 months	32.4±20.1 CFB: 6.5 (–2.9–17.5)				Changes in lung density as measured by CT scan (15th percentile point and relative area <–950 HU) were correlated with SGRQ total scores (R= –0.56, p=0.007 and R=0.6, p=0.003, respectively).
Annunziata, 2021 [73]	AATD AATD	16 16	Baseline 3 months	18.0±3.0 22.6±3.3				All the questionnaires completed at 3 months showed an increase in score compared with the questionnaire completed during the last hospital administration session (p<0.01).
Schramm, 2020 [83]	AATD (*PiZZ*) Never-smoking control	84 72		12.0 3.8	14.0 4.5	18.8 7.8	7.3 1.0	There was no significant difference in SGRQ score between *PiZZ* ever-smokers and never-smokers, but *PiZZ* ever-smokers had significantly higher scores in all categories compared with never-smoking controls (symptom p=0.04, activity p=0.01, impact p=0.03, total p<0.01).
Sandhaus, 2020 [84]	AATD (*PiZZ* or worse) + AAT therapy AATD without AAT therapy	655 655						Annual worsening of SGRQ total was on average 1.3 points per year worse in control group patients *versus* those receiving AAT therapy (95% CI 0.41–2.19, p=0.004).
Crossley, 2020 [85]	AATD	187		45.2 (3.3–62.1)				Median SGRQ score was 45.2 (33.3–62.1) and related to the GOLD stage (p<0.001). There were significant correlations between QoL measures and spirometry, as measured by FEV_1 (% predicted), FVC (% predicted), FEV_1/FVC (%) and with gas transfer coefficient (% predicted) and gas trapping as measured by RV/TLC (%) (p<0.01 all comparisons). Total SGRQ correlated significantly with CT density, although the relationship was weak (r^2<0.1).
AATD plus COPD or emphysema								
Hogarth, 2019 [86]	AATD + severe emphysema	20 20 20	Baseline 6 months 12 months	55.2±16.0 CFB: –14.3±12.9 CFB: –8.2±12.9				After 6 months, SGRQ had decreased substantially compared with baseline in patients fitted with an endobronchial valve.

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TABLE 3 Continued

First author, year [ref.]	Population/ treatment	Subjects n	Time point	SGRQ scores				Main SGRQ outcomes
				Total	Symptoms	Activity	Impact	
Durkan, 2019 [87]	AATD + COPD	30	NR	36.5±18.5	42.4±41.6		24.9±17.3	For the same level of COPD impairment, *PiZZ* patients presented with lower SGRQ scores than *PiMM* patients.
Stockley, 2018 [88]	AATD (without obstruction)	84	Baseline	14.0 (4.8–5.5)	30.9 (11.7–57.1)	12.2 (0–41.6)	5.8 (0–21.4)	Baseline SGRQ scores were correlated with baseline FEV_1 in patients with AATD with or without COPD (r^2=0.34, p<0.0001). Annual SGRQ decline was greater for patients with AATD diagnosed with COPD who had a rapid FEV_1 decline.
	AATD + COPD	370	Baseline	48.2 (33.9–62.4)	62.5 (46.2–78.6)	60.4 (47.4–79.7)	34.9 (21.3–49.9)	
	AATD with no FEV_1 decline	35	Baseline	16.2 (4.8–35.5)	35 (11.7–57.1)	23.3 (0–41.6)	11.2 (0–21.4)	
	AATD with FEV_1 decline	22	Baseline	11.5 (33.9–62.4)	30.5 (46.2–78.6)	11.7 (47.4–79.7)	5.3 (21.3–49.9)	
	AATD + COPD with no FEV_1 decline	72	Baseline	51.8 (35.0–63.3)	62.4 (51.5–78.1)	66.6 (47.7–80.9)	35.6 (22.3–49.5)	
	AATD + COPD with FEV_1 decline	189	Baseline	45.2 (30.5–61.5)	60.5 (42.9–74.6)	59.5 (41.4–79.9)	34.1 (17.0–47.2)	
	AATD (without obstruction)	84	Annual decline	0.2 (–0.8–1.1)	0.00 (–2.5–2.0)	0.00 (–0.8–1.4)	0.14 (–0.5–0.9)	
	AATD + COPD	370	Annual decline	0.7 (–0.8–2.4)	0.21 (–2.3–2.1)	1.2 (–0.5–3.6)	0.4 (–1.1–2.2)	
	AATD with no FEV_1 decline	35	Annual decline	0.04 (–0.7–0.8)	–0.2 (–3.0–1.6)	0.05 (–1.4–1.3)	0.03 (–0.6–0.7)	
	AATD with FEV_1 decline	22	Annual decline	0.5 (–1.0–1.9)	0.9 (–1.5–2.3)	0.9 (0.0–3.0)	0.3 (–1.0–1.3)	
	AATD + COPD with no FEV_1 decline	72	Annual decline	0.5 (–0.8–1.5)	–0.2 (–1.9–1.3)	0.7 (–0.4–2.3)	0.1 (–0.9–1.5)	
	AATD + COPD with FEV_1 decline	189	Annual decline	1.07 (–1.1–2.9)	0.5 (–2.6–2.7)	1.5 (–0.5–4.3)	0.7 (–1.0–3.0)	
Karl, 2017 [75]	AATD + COPD	131	NR	44.8±17.2				No significant differences in SGRQ scores were observed between patients with AATD diagnosed with COPD who were recipients and non-recipients of AAT therapy.
	AATD + COPD + AAT therapy	106	NR	46.6±16.4				
	AATD + COPD without AAT therapy	25	NR	37.5±20.2				

Continued

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TABLE 3 Continued

First author, year [ref.]	Population/ treatment	Subjects n	Time point	SGRQ scores				Main SGRQ outcomes
				Total	Symptoms	Activity	Impact	
Chapman, 2015 [12]	AATD + emphysema + A1P1 therapy	93	Baseline	44.3±17.1	46.5±22.7	62.1±18.6	33.6±18.4	Improvements were reported in only the SGRQ symptom domain after 24 months of treatment.
	AATD + emphysema + placebo	87	Baseline	42.4±18.0	44.1±24.8	60.1±21.4	31.4±17.6	
	AATD + emphysema + AAT therapy	93	24 months	CFB: 1.4±11.1	CFB: –1.4±16.7	CFB: 1.7±12.4	CFB: 2.1±14.8	
	AATD + emphysema + placebo	87	24 months	CFB: 2.2±11.7	CFB: 2.0±20.1	CFB: 2.6±13.5	CFB: 1.8±12.5	
Ponce, 2014 [89]	AATD + COPD	573	Baseline	46.0±17.8				Poorer SGRQ scores were observed in obese *versus* non-obese AATD patients diagnosed with COPD.
	AATD + COPD	573	5 years	51.0±17.7				
Holm, 2013 [90]	AATD + COPD	578		48.5±19.4				AATD patients diagnosed with COPD had an SGRQ total score almost 5 points higher than non-AATD patients diagnosed with COPD when adjusting for demographic and health characteristics.
Lascano, 2010 [91]	AATD + COPD + AAT therapy: overweight	241	1 year	47.2±16.0				SGRQ scores were higher in obese patients *versus* patients with a normal BMI; however, the obese patients had similar FEV_1 to the normal BMI group, but more comorbidity. Underweight patients had worse QoL and significantly lower FEV_1 *versus* normal BMI individuals.
	AATD + COPD + AAT therapy: obese	104	1 year	48.7±17.1				
	AATD + COPD + AAT therapy: morbidly obese	61	1 year	55.5±17.1				
	AATD + COPD + AAT therapy: normal BMI	204	1 year	43.4±16.6				
Campos, 2009 [74]	AATD + COPD + AAT therapy	922	Baseline	48.1±18.4				Subjects with frequent exacerbations had the worst baseline HRQoL scores, as well as more physician visits, emergency room visits and hospitalisations.
	AATD + COPD + AAT therapy; no exacerbations	83	Baseline	37.3±17.3	33.1±43.5	57.5±23.4	27.0±16.5	
	AATD + COPD + AAT therapy; 1–2 exacerbations per year	391	Baseline	44.5±16.6	43.0±22.1	64.1±21.2	33.6±16.5	
	AATD + COPD + AAT therapy; ⩾3 exacerbations per year	448	Baseline	52.4±16.5	54.0±21.4	71.0±20.5	41.2±17.6	
Dawkins, 2009 [92]	AATD + COPD with fast FEV_1 decline	33		49.6±20.1				SGRQ total scores in fast decliners as measured by FEV_1 were not significantly different from middle or slow decliners.
	AATD + COPD with middle FEV_1 decline	34		56.2±18.5				
	AATD + COPD with slow FEV_1 decline	34		51.6±24.7				

Continued

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TABLE 3 Continued

First author, year [ref.]	Population/ treatment	Subjects n	Time point	SGRQ scores				Main SGRQ outcomes
				Total	Symptoms	Activity	Impact	
AATD with other comorbidity								
Stone, 2016 [93]	AATD + lung transplant	32	Baseline	64.2±2.5	75.4±2.5	93 (73–95)	50.1±2.9	Pre-transplant, although matched for FEV_1, the transplant group had worse health status. Post-transplant, physiology and health status improved significantly (p<0.002).
	AATD + no transplant	48	Baseline	55.3±2.0	67.4±2.2	79 (59–91)	40.3±2.4	
	AATD + pre-transplant	14	Baseline	67.5 (51.0–77.8)	76.5 (64.5–88.5)	93.0 (4.8–98.3)	50.0 (31.3–65.5)	
	AATD + post-transplant	14	1 year	7.5 (5.0–13.8)	14.0 (9.0–30.3)	11.0 (1.3–20.3)	4.5 (1.0–9.5)	
Dowson, 2002 [78]	AATD with chronic sputum expectoration	50		64.4 (48.3–74.4)	75.6 (68.0–83.7)	82.9 (60.4–100)	49.9 (33.0–62.7)	Patients with chronic sputum expectoration had worse health status, as assessed by SGRQ (p<0.01 for all domains), than patients who did not.
	AATD without chronic sputum expectoration	67		42.0 (23.9–59.5)	47.6 (28.9–66.7)	59.5 (32.7–86.3)	28.9 (11.7–47.6)	

Data are presented as mean±SD or median (range), unless otherwise stated. *PiSZ/ZZ*: *Pi* (or *SERPINA1* gene) *SZ* and *ZZ* alleles; AAT: alpha-1 antitrypsin; QoL: quality of life; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; CFB: change from baseline; CT: computed tomography; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; NR: not reported; A1P1: α1 proteinase inhibitor; BMI: body mass index; HRQoL: health-related QoL. #: p=0.032 *versus PiZZ* never-smokers.

(BMI) were associated with poorer QoL compared with patients with normal BMI, where obesity was associated with greater comorbidity (table 3) [89, 91]. The association of poorer QoL in patients with a BMI >30 $kg \cdot m^{-2}$ *versus* normal BMI was shown to be independent of FEV_1 decline in one of these studies [91]. SF-36 scores improved following implementation of comprehensive pulmonary rehabilitation in patients with AATD diagnosed with emphysema awaiting lung transplant [96].

The majority of the papers identified in this review focused on physical aspects of QoL, although mental component scores were reported for the SF-36 questionnaire; most of these were baseline measurements (supplementary table S5) [74, 92, 95]. One study utilising a patient survey reported that patients with severe deficiency were found to have adverse effects on their relationships [97]. No studies within the scope of this review reported on emotional or psychological burden in patients with AATD.

There is no consensus on the difference in QoL burden in patients with AATD with COPD compared with patients with general COPD. No difference between these patient groups was reported in two studies [77, 94]. Better QoL was reported in patients with AATD with COPD *versus* general COPD in patients with the *PiZZ* AATD genotype in two studies [87, 95].

Caregiver burden

Five studies were included in the caregiver burden review (supplementary figure S3). The studies were performed in the USA [98–100], Sweden [101] and England (table 4) [102]. All studies were qualitative, with no specific instruments used to measure this burden.

A review of the key issues for caregivers and family members of patients with AATD reported loss of flexibility in their work and social lives as the partner or spouse was forced to change schedules to provide care [103]. Caregivers also reported anxiety, stress and despair as a result of having to see their diagnosed family members struggling with their condition (table 4) [98, 101, 102]. In addition, some felt guilty that their genetic makeup may have been responsible for the disease in the affected family member, with many reporting fears for future generations [99, 100]. A study examining outcomes 20 years after an AATD neonatal screening programme in Sweden reported more anxiety among mothers of children with AATD than those without [101].

Financial pressure for caregivers in England was reported to result from the need to work reduced hours or taking time off work to attend medical appointments or provide care [102]. There was also concern about the lack of public and healthcare provider knowledge on AATD, as well as a lack of access to information for both patients and caregivers in the USA [99].

Economic burden

The cost and resource use review included 21 studies (supplementary figure S4): 10 were from the USA, and nine out of 21 were presented as conference abstracts. The sample size of studies ranged from five [104] to 9117 [105] patients, and the mean age of AATD patients was 48.3–64.6 years across studies. Where smoking status was reported, patients were typically former smokers (72.9–100%) (supplementary table S6). 14 studies reported the years for which costs were estimated, which ranged from 1997 to 2017 (table 5).

Resource use overall was higher in patients with AATD diagnosed with COPD *versus* those with general COPD [75, 106–108] and those with more severe disease [43]. AlphaNet's Disease Management and Prevention Program in the USA reported greater resource use (primary care, lung specialist visits and hospitalisation) for patients with *PiSZ versus PiZZ* genotypes who had lung disease, but the authors noted that this may have been due to the latter having better adherence to management recommendations and maintaining a healthier lifestyle [44].

TABLE 4 Caregiver burden review: summary of included studies

First author, year [ref.]	Study design	Country	Affected domain
Bruscino, 2019 [98]	Survey	USA	Anxiety, despair
Wienke, 2014 [99]	Registry-based study	USA	Delayed diagnosis, genetic discrimination, travel time
Williams, 2013 [100]	Survey	USA	Genetic discrimination, decisional burden to test
Mahadeva, 2013 [102]	Survey	England	Finance, routine, delayed diagnosis
Sveger, 1999 [101]	Prospective study	Sweden	Mental anxiety

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TABLE 5 Economic burden review: cost and resource use associated with alpha-1 antitrypsin deficiency (AATD)

First author, year [ref.]	Country	Subjects n	Cost-year	Healthcare cost	Healthcare resource use	Main economic burden outcomes
Herrera, 2021 [43]	USA	5109	2017	Median (IQR) annual total healthcare costs USD 9753 (3070–45 266) Median (IQR) total medical costs USD 4927 (1569–16 340) Median (IQR) total pharmacy costs USD 2063 (214–10 000)	Mean±SD annual number of visits: ER visits: 0.5±2.4 Inpatient visits: 0.6±2.7 Outpatient visits: 6.4±12.1 Other visits: 2.0±7.3	Patients with severe AATD-related pulmonary manifestations requiring hospitalisation are substantially burdened by higher healthcare resource use.
Rozario, 2019 [113]	USA	NR	NR	Impact of a missed AAT therapy dose on total monthly healthcare costs (not including AAT therapy cost) With dose: USD 1862 Without dose: USD 2100 Difference: +USD 238	NR	The increased cost for patients with AATD who missed a dose of AATD therapy was possibly due to the higher downstream systemic healthcare costs that are associated with nonadherence to therapy.
Sieluk, 2018 [105]	USA	9117	2017	Annual direct costs for AAT therapy users: Total: USD 127 537 Physician visits: USD 15 064 AAT therapy: USD 82 002	NR	There were higher costs for AAT therapy users for all cost drivers (physician and emergency visits, inpatient stays, AAT therapy and other drugs). A consistent trend of increasing cost was observed between 1993 and 2015, although inpatient and physician visit costs remained steady over the last 10 years of the study.
Choate, 2019 [44]	USA	3535	NR	NR	Annual visits *SZ versus ZZ* genotypes of AATD[#] Primary physician visits: 3.7 *versus* 3.1 Lung specialist visits: 3.2 *versus* 2.9 Hospitalisations: 0.8 *versus* 0.6	Patients with a *PiSZ* genotype reported more primary physician visits ($p<0.001$), lung specialist visits ($p<0.001$) and hospitalisations ($p=0.012$) than patients with a *PiZZ* genotype.
Attaway, 2019 [60]	USA	8039	NR	NR	Hospitalisation average length of stay: 5.3 days	There was a stable low rate of in-hospital mortality throughout the study (2004–2014).
Aggarwal, 2018 [109]	USA	1493	2015	Hospitalisation Overall cost per stay: USD 50 612 0–18 years: USD 120 026 18–45 years: USD 39 192 45–59 years: USD 53 118 >60 years: USD 48 613	Hospitalisation Mean length of stay: 5.43 days 0–18 years: 8 days 18–45 years: 4.4 days 45–59 years: 5.6 days >60 years: 5.4 days	Higher inpatient costs in the USA were reported for adults aged ⩾45 years with AATD compared with adults aged <45 years based on national inpatient data.

Continued

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TABLE 5 Continued

First author, year [ref.]	Country	Subjects n	Cost-year	Healthcare cost	Healthcare resource use	Main economic burden outcomes
Karl, 2017 [75]	Germany	131	2012	Annual direct cost for AATD patients diagnosed with COPD (excluding AAT therapy cost[¶]) Patients receiving AAT therapy: EUR 7117 Patients not receiving AAT therapy: EUR 6099 Annual indirect costs (human capital approach) Patients receiving AAT therapy: EUR 18 813 Patients not receiving AAT therapy: EUR 16 171	AATD patients diagnosed with COPD *versus* those with COPD alone Outpatient visits: two-fold higher with AATD Hospitalisation: 24% *versus* 39% Inpatient length of stay: 2.3 *versus* 5.8 days Patients with AATD receiving AAT therapy *versus* those without Inpatient length of stay: 2.2 *versus* 2.7 days	For patients with AATD in Germany, annual direct medical costs in 2012 were higher for those receiving AAT therapy than for those not on AAT therapy. The study excluded the mean annual AAT therapy cost of EUR 72 255. Indirect costs were based on a human capital approach that considered full labour costs for all sick days and premature retirement at age <65 years.
Greulich, 2017 [106]	Germany	590	NR	NR	Consultations and hospitalisation rates higher in patients with AATD than in matched patients in reference groups (COPD, emphysema or asthma)	When compared with non-AATD patients diagnosed with COPD, AATD patients had significantly more consultations.
Zacherle, 2015 [107]	USA	279	NR	Total annual healthcare costs AATD *versus* COPD USD 27 674 greater for AATD	Annual visits AATD *versus* COPD Emergency: 58.4% *versus* 42.5% Inpatient: 58.0% *versus* 19.5%	Higher mean annual costs were reported for AATD patients diagnosed with COPD *versus* those with general COPD (p<0.001); 13% of the AATD cohort were receiving AAT therapy.
Blanchette, 2015 [110]	USA	684	2009	Mean hospitalisation cost Age 20–39 years: USD 13 820 Age >80 years: USD 16 079	Mean hospital stay Age 20–39 years: 5.0 days Age >80 years: 8.2 days	There was an increased cost for AATD inpatients *versus* general COPD patients (+USD 1487 per stay; p=0.0251).
Barros-Tizón, 2012 [111]	Spain	127	NR	Hospitalisation cost before AAT therapy use *versus* after Savings per patient: EUR 417 Savings in patients with exacerbations: EUR 907	Hospitalisation with *versus* without AAT therapy Length of stay with no exacerbations: 3.0 *versus* 3.9 days Length of stay with exacerbations: 4.6 *versus* 6.7 days	There were substantial hospitalisation-derived cost savings in patients who were treated with AAT therapy.
Dye, 2011 [112]	Australia	558	2007–2008	Direct cost Hospitalisation per patient: USD 36 764 Per admission: USD 7145	Hospital admissions 5.14 per patient over 6 years	AATD was reported to be one of the most expensive single-gene and chromosome disorders evaluated in this study.

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TABLE 5 Continued

First author, year [ref.]	Country	Subjects n	Cost-year	Healthcare cost	Healthcare resource use	Main economic burden outcomes
Mullins, 2003 [114]; Mullins, 2001 [115]	USA	688	1998	Direct costs associated with treatment[+], physician visits, emergency department visits and hospitalisation Annual: USD 36 471 *PiZZ*: USD 38 632 Non-*PiZZ*: USD 30 604	Physician visits: 8.5 per year	Self-reported medical costs were higher for patients with a *PiZZ* genotype *versus* non-*ZZ* individuals. AAT therapy was the major driver of self-reported cost.
			1997–1999	Total annual healthcare costs associated with all medical visits, medications, and all other expenditures (*e.g.* emergency department visits) *PiZZ*: USD 30 948 Non-*PiZZ*: USD 20 673	NR	Annual healthcare costs for patients with *ZZ* AATD were high *versus* non-*ZZ*, whether they were receiving augmentation therapy or not.
Piitulainen, 2003 [104]	Sweden	5	2002	Annual direct cost associated with AAT therapy Tailored dose: SEK 1 560 400 Standard dose: SEK 2 600 000	NR	Tailored pharmacokinetic dosing of human AAT reduces the total annual dose and cost of *i.v.* AAT therapy.
Stoller, 2000 [116]	USA	712	1997–1999	NR	Resource use (number of physician visits)	The mean±SD number of physician visits reported by patients with AATD was 7.8±9.4 per year.
Stone, 2020 [117]	USA	1258	2011–2017	After adjustment, compared with pre-diagnosis (USD 24 782±161 896), median±SD total healthcare costs were USD 9962 greater (USD 34 744±80 792; p<0.05) in year 1 post-diagnosis; USD 3703 less (USD 21 079±51 186; p>0.05) in year 2; and USD 12 567 less (USD 12 215±46 594; p>0.05) in year 3 Adjusted median±SD medical costs in the pre-diagnosis year were USD 10 825±89 936; USD 2304 greater (USD 13 129±52 953); p>0.05) in year 1; USD 791 less (USD 10 034±26 600; p<0.05) in year 2; and USD 5186 less (USD 5639±9838; p<0.05) in year 3	Adjusted median±SD number of inpatient events per patient in the pre-diagnosis year were 0.34±0.75; 26% less (0.27±0.58; p<0.05) in year 1; 240% less (0.10±0.42); p<0.05) in year 2; and 340% less (0.00±0.35; p<0.05) in year 3 post-diagnosis	Healthcare costs increased in the first year following diagnosis of AATD; however, they decreased in subsequent years, primarily due to the reduction of inpatient admissions and medical costs.

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TABLE 5 Continued

First author, year [ref.]	Country	Subjects n	Cost-year	Healthcare cost	Healthcare resource use	Main economic burden outcomes
Sieluk, 2020 [108]	USA	8881	2000–2017	Adjusted total all-healthcare cost ratios for AATD patients diagnosed with COPD *versus* controls were 2.04 (95% CI 1.60–2.59) and 1.98 (95% CI 1.55–2.52), while the incremental cost difference totalled USD 6861 (95% CI 3025–10 698) and USD 5772 (95% CI 1940–9604) per patient before and after the index date, respectively	AATD patients diagnosed with COPD had higher expenditures and use of office visits and other services, as well as office visits, outpatient, ER and prescription drugs before and after the index date, respectively	12 months before and after their initial COPD diagnosis, patients with AATD incurred higher healthcare utilisation costs that were double the cost of similar COPD patients without AATD. Increased costs of AATD-associated COPD were not solely attributable to AAT therapy use.
Rueda, 2020 [118]	USA	6832	2010–2015	The introduction of a DMP was estimated to decrease costs of the management of patients with AATD by USD 13.5 million over 5 years	The savings attributed to the programme were due to 2555 exacerbations, 5180 ER visits, 9342 specialist visits and 105 358 GP visits avoided	A comprehensive DMP for a rare condition might provide cost savings to a health plan. BIAs for rare disease may be more informative if they focus on DMPs rather than on individual drugs.
Borget, 2020 [119]	France	365	2014–2017	Mean annual cost per patient was EUR 13 680 (excluding AAT therapy) driven by ambulatory-related costs (45%) and hospital-related costs (35%). Paid sick time represents 20% of the total annual cost.		This was the first study to evaluate the number of patients treated and the economic burden of AATD in France.
Sieloff, 2021 [120]	USA		2002–2014		In 2014, hospitalisation costs adjusted to 2020 dollars for AATD was USD 108 million relative to all annual NIS discharges	AATD was associated with the greatest number of hospitalisations of all the genetic liver diseases over the 12-year study period for both NACLD and NALC.
Lee, 2020 [121]	USA	1872 AATD-related cirrhosis, 7488 non-AATD-related cirrhosis	2011–2017		Hospitalisation costs for AATD-related cirrhosis *versus* non-AATD-related cirrhosis (USD 72 406 *versus* USD 59 386; p=0.38)	There was no difference in hospitalisation costs for AATD-related cirrhosis *versus* non-AATD-related cirrhosis.

IQR: interquartile range; ER: emergency room; NR: not reported; AAT: alpha-1 antitrypsin; *PiSZ/ZZ*: *Pi* (or *SERPINA1* gene) *SZ* and *ZZ* alleles; *i.v.*: intravenous; DMP: disease management programme; GP: general practitioner; BIA: budget impact analysis; NIS: National Inpatient Sample; NACLD: nonalcoholic chronic liver disease; NALC: nonalcoholic liver cirrhosis. [#]: a greater proportion of *ZZ*s than *SZ*s received AAT therapy (93.5% *versus* 87.1%, p<0.001); [¶]: total direct costs do not include AAT therapy costs; [+]: values given as 1998 USD.

Across studies, the mean length of hospital stay ranged from 2.3 to 8.2 days [60, 75, 109–112] (table 5 [43, 44, 60, 75, 104–121]). The hospitalisation rate and length of stay increased with age [109, 110].

The annual direct medical cost for patients with AATD in the USA was estimated to be USD 127537 for users of AAT therapy *versus* USD 15874 for nonusers [105]. A second US study reported that the median annual total healthcare costs were USD 9753, and the median total medical costs were USD 4927 and total pharmacy costs were USD 2063, although the proportion of patients receiving AAT therapy was not reported [43] (table 5). In Germany, the mean annual direct medical costs per patient were EUR 6099 for users of AAT therapy *versus* EUR 7117 for nonusers, excluding costs for AAT therapy [75].

Discussion

This review summarises the available evidence on various facets of disease burden in patients with AATD. Based on the studies reviewed, the evidence suggests that AATD is a significant burden for patients, caregivers and healthcare systems. However, the included studies differed greatly in their sample sizes, populations, observational periods, designs, measures and outcomes, making meta-analysis or cross-study comparisons and generalisations difficult.

Many studies in this review included <100 patients, which is expected given the rarity of AATD, and study follow-up also tended to be relatively short, with many prospective studies assessing patients for ⩽1 year. Only the larger registries [25, 26, 122] or retrospective, population-based studies [43, 60, 64, 109] were able to include a robust sample size and consider a longer time frame. Moreover, many studies were published only as conference abstracts, particularly those discussing the clinical burden (20 out of 40 studies) and economic burden (nine out of 21), limiting the details available for analysis. Approximately half of all the papers included in this review were published in 2015 or later, particularly those that discussed clinical burden, of which only six studies of clinical burden were published before 2015. Other publications that discussed QoL and costs were ⩾10 years old, with some published in the 1990s. Therefore, the standards of care that are discussed are likely to be outdated. In addition, standards of care and medical costs vary regionally and between countries, making it particularly difficult to compare studies from the USA and Europe that report resource use and costs.

Patients with AATD typically develop pulmonary and hepatic morbidity, and our review suggests that this represents a considerable clinical burden. Among studies reporting lung morbidity in AATD, COPD and emphysema were common (occurring in up to 76% and 54% of patients, respectively). Unsurprisingly, smoking was identified as a key risk factor for the development of lung morbidity in patients with AATD. However, a single study suggested an increased risk of lung cancer in never-smokers with AATD [36]. Fibrosis was the most common liver complication in the studies reviewed here. Risk factors associated with liver fibrosis included male sex, diabetes and age >50 years. Panniculitis is a rare AATD comorbidity that was reported in <1% of patients in two studies reviewed here, whereas in a third study 8.6% of *PiZZ* patients had skin conditions including panniculitis [25, 37, 44]. The reason for the relatively high prevalence in the third study appears to be the reporting of panniculitis within a general comorbidity of “skin conditions” [44]. There was little consistency between the reporting of mortality rates between the studies [60, 61, 64] (table 2). Mortality data that are derived from index cases of AATD often indicate higher mortality rates compared with the general population; however, the data are difficult to interpret because severely affected individuals are systematically over-represented in registries. Survival was shown to be prolonged among patients with AATD and lung disease who received AAT therapy [68]; however, among never-smokers, there may not be any difference in survival for individuals with a *PiZZ* genotype *versus* the general population [69, 71].

Studies reporting QoL in individuals with AATD were heterogeneous, with a variety of disease-specific and generic instruments used across studies. While most studies used the SGRQ, a QoL questionnaire developed for respiratory diseases, many studies used generic QoL measures, including the SF-36, which do not account for parameters that may be unique to patients with AATD, such as having to receive weekly infusions of AAT therapy. Other disease-specific measures that assess dyspnoea and are predictive of survival in COPD, such as the CAT, CRQ and LCOPD scales, were reported in only a few studies. Among studies that used the SGRQ (table 3) and had baseline results, most reported a total mean score >40, indicating moderate impairment of QoL in patients with AATD. In general, worse QoL outcomes were reported for patients with AATD diagnosed with COPD than for patients diagnosed with general COPD, and for current smokers *versus* never-smokers or former smokers. No studies within the scope of this review reported on emotional or psychological burden in patients with AATD.

Tools used to measure the impact and progression of AATD, including pulmonary function tests (*e.g.* FEV_1) and QoL instruments (*e.g.* SGRQ) are not sensitive to the small changes that occur over

clinically feasible trial periods of 1–3 years in a disease that typically progresses over decades [2, 88]. Trials aimed at detecting a treatment effect over periods of >3 years are impractical to conduct due to the ethical concerns of prolonged placebo exposure and patient retention. Moreover, standards of care could change during study conduct, confounding data interpretation. Recruiting a large enough number of patients, *e.g.* >1000, to overcome the insensitivity of the measurements is also unfeasible in AATD, given its rarity [123]. The European Respiratory Society statement on AATD reported that a sample size of 550 per treatment group over 3 years would be needed to examine FEV_1 decline as an outcome [2]. In addition, data from the UK AATD registry indicated that in order to detect the minimal clinically important difference in SGRQ (a four-point increase), a sufficiently powered, placebo-controlled trial of up to 8 years' duration would be needed. In addition, this study determined that >8000 patients per treatment arm would be required to detect a 25% reduction in SGRQ score [88].

Patients with AATD and rapid FEV_1 decline had worse QoL than those with slower FEV_1 decline in one large study (n=772), but not in a second smaller study (n=101) [88, 92]. Clinical disease burden and QoL are likely to be influenced by the rate at which the disease progresses, the sensitivity of progression measurements and the time at which a diagnosis is finally given. Some patients with AATD have been reported to be "fast decliners", as measured by CT lung density [13] and FEV_1 [124]. However, the minimum clinically important difference for either of these outcomes in patients with AATD has not been established [13, 14, 88, 125–128].

Our review suggests that patients with AATD who have frequent exacerbations (⩾3 per year) or chronic sputum expectoration have a poorer QoL than patients without [74], and that SGRQ scores may be significantly correlated with both exacerbations and dyspnoea [76]. Exacerbations are often associated with long-term sequelae including significant, permanent loss of lung function [26, 129, 130]. However, exacerbations are random events that are driven by infections and outcomes can vary substantially. The clinical trials conducted so far with either intravenous or inhaled AAT therapy showed inconclusive results in terms of prevention of exacerbations, which may be due to lack of power (or similar) [126, 131]. However, it is important to note that in these studies the event rate and sample sizes were limited, and no plausible mechanism linking the effect to AAT therapy was confirmed.

Our literature search identified limited evidence describing the impact of AATD on the life of caregivers, with only five published studies [98–102]. All studies were qualitative, and no specific instruments were used to measure the burden. This review suggests that caregivers of family members with AATD experience disruption to previously established routines and experience stress and anxiety.

Estimates of the total direct healthcare cost of AATD reviewed here came mainly from the USA and suggested median annual costs of USD 9753 excluding AAT therapy [43]. In Europe, annual costs were approximately EUR 1000 higher for patients who received AAT therapy *versus* those who did not [75]. The major direct cost drivers were AAT therapy, physician visits and inpatient stays. Little information was available on costs from other countries, making comparisons difficult. Only one study from Germany [75] attempted to estimate indirect costs, highlighting the need for further studies. Resource-use data suggest more annual visits, consultations and longer stays for patients with AATD compared with patients with general COPD and for patients with more severe AATD.

Disease burden is typically measured by the frequency of specific outcomes in a patient population, whether it is change in lung function, QoL or prevalence of a specific morbidity. Only registries can accurately capture such "big data" for AATD. While registries have existed historically, they were mainly national entities that were not centrally coordinated and as a result were not well harmonised in terms of the measurements used and the data collected [132]. Our review found wide variation in the clinical burden and other outcomes for patients with AATD across studies, highlighting the need for more thorough analyses with more consistent measures.

Implications for future research

This review illustrates the difficulties with drawing consistent and meaningful conclusions based on small, variable population samples and study designs. This has serious clinical consequences, as characterising efficacy and safety profiles of treatments is complex in the absence of a clear understanding of the burden, natural history and prognosis of the disease. Hence, there is an urgent need to include all affected patients in a multinational registry based on a consistent and structured reporting framework, and patients, caregivers, healthcare professionals and researchers are urged to form multinational collaborations in order to achieve this. The European Alpha-1 Research Collaboration (EARCO) [133] is seeking to coordinate clinical sites internationally and harmonise methodologies by carrying out quality control of data

collection. This registry aims to provide an understanding of the natural history of the disease, to assess the value of AAT therapy in the real world, to evaluate QoL scores and to examine genotypes. This should enable more effective comparative research into the burden of AATD supporting future clinical development, which is an ongoing challenge for rare diseases. In addition, the authors would urge researchers in the field to publish their findings in peer-reviewed journals to increase the impact and reliability of the published literature.

Conclusion

This review found that AATD is associated with a significant clinical and QoL burden, and high direct medical costs and healthcare resource utilisation when compared with the general population. However, there were inconsistencies in the data, with many studies being small, of short duration and with a variety of different measures used for the same outcomes. As a result, considerable gaps in the true burden of this disease remain.

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