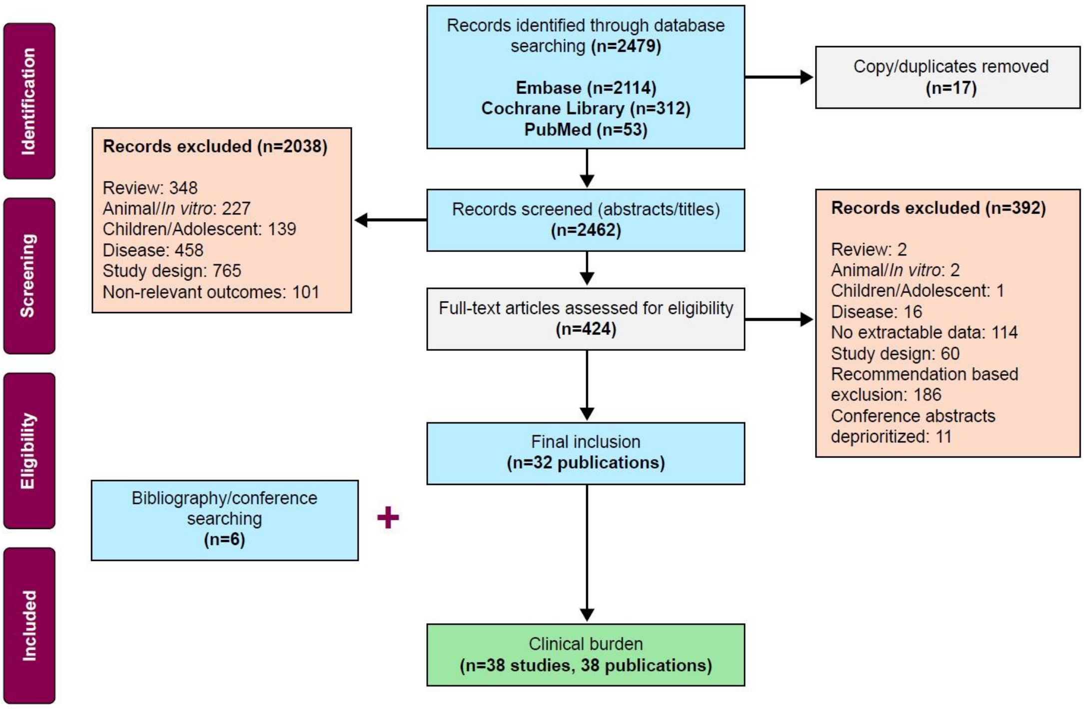
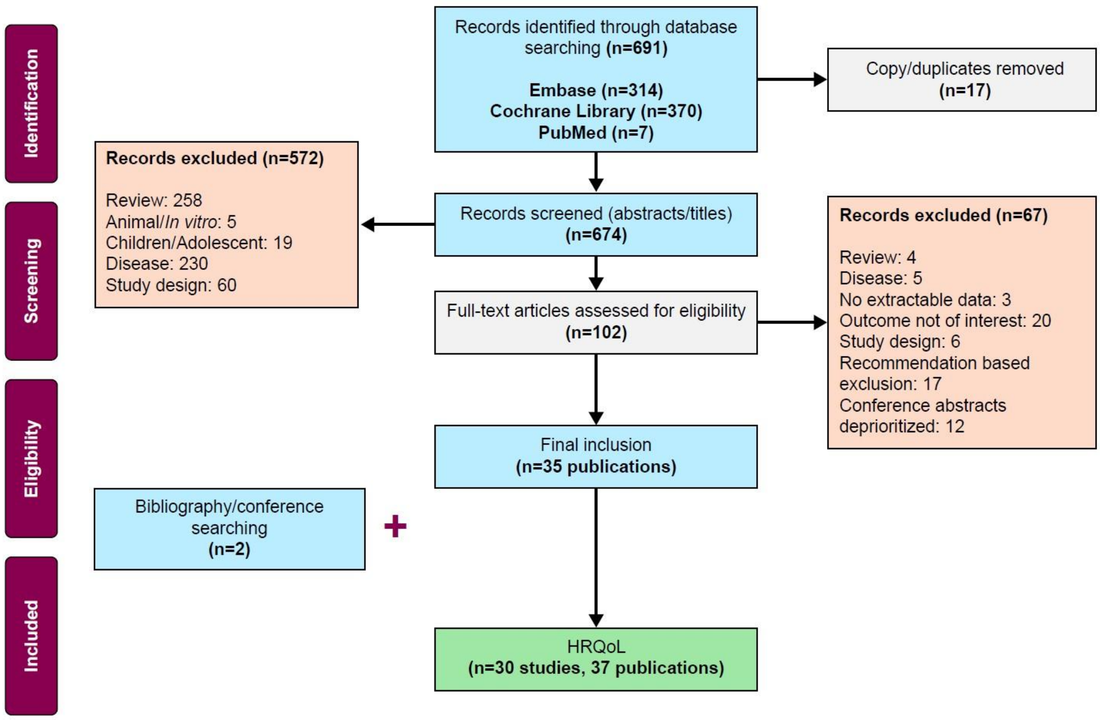
Supplementary material

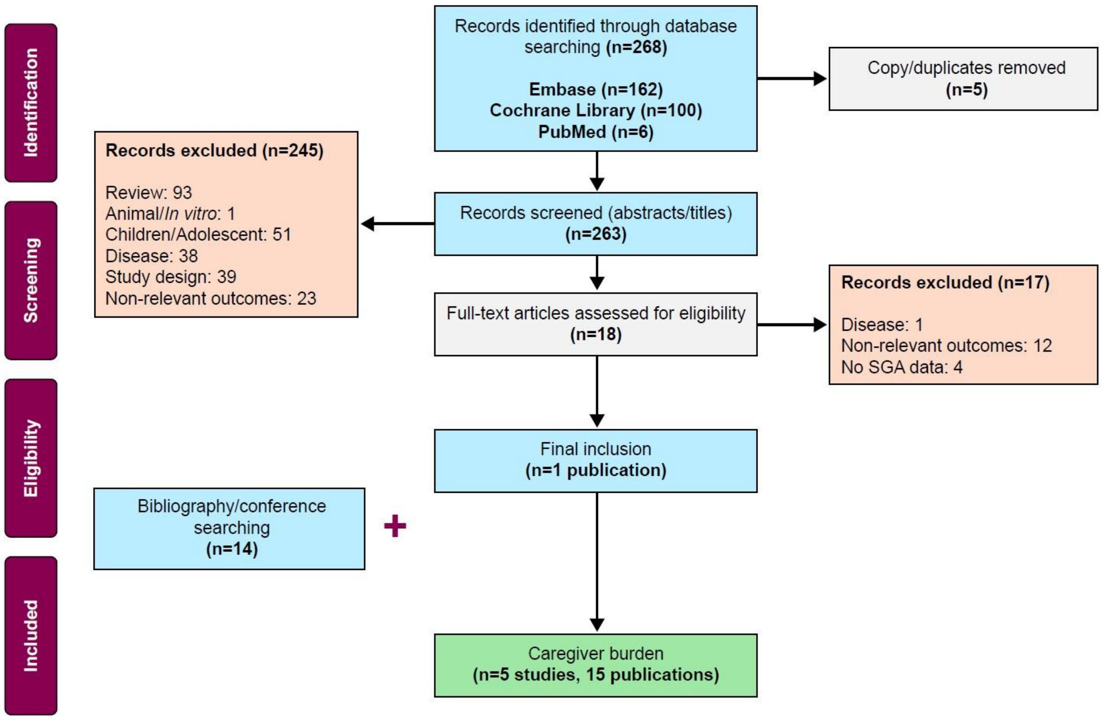
Supplementary FIGURE 1 Clinical burden review: PRISMA diagram



Supplementary FIGURE 2 QoL review: PRISMA diagram

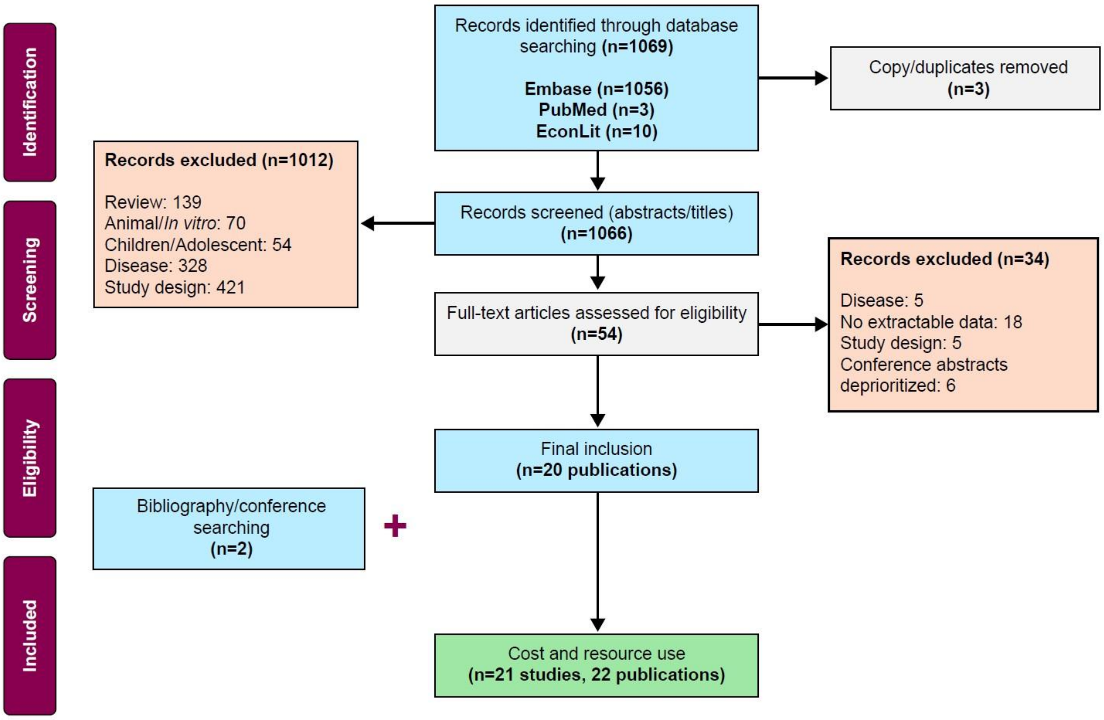


Supplementary FIGURE 3 Caregiver burden review: PRISMA diagram



SGA: subgroup analysis

Supplementary FIGURE 4 Economic burden review: PRISMA diagram



Search strategies

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature and the details were specified in the original study protocol. The reviews were based on a comprehensive search of Excerpta Medica Database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), MEDLINE In-Process, Cochrane Central Register of controlled trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) to identify studies related to cost and resource use burden, caregiver burden, epidemiology burden, clinical burden, quality of life burden and clinical review. For cost and resource use review, in addition to different biomedical databases, an extensive literature search was performed using the EconLit website since its inception to 2020. For clinical evidence, the HTA reports available from NICE, IQWIG, HAS, AETS, AGENAS, ICER, TGA and CADTH were also searched for relevant studies. In addition to the biomedical databases searched, abstracts from various conference proceedings were hand searched. All databases were searched since inception until April 2020, while conferences were searched for the past 3 years (2017–2020). Relevant systematic reviews identified through database searches were utilised for bibliography searching. Besides using Google search and scholar platforms the grey literature searching was done for the identification of relevant studies. Furthermore, Tufts registry, REDAAT and EUROCAT registries were searched for appropriate studies. Relevant publications provided by CSL Behring were also screened for identification of additional relevant studies.

Supplementary TABLE 1 Clinical burden review: Patient characteristics from included studies

Study name	Patient group	N	Mean age (years)	Gender	Smoking status (%)			Genotype (%)	
				Male (%)	Current	Former	Never	*PiZZ*	Others
Journal articles (n=21)									
Tanash 2019 [1]	Severe AATD	1595	47	49	54	–	46	100	–
Hiller 2019 [2]	Severe AATD	1132	45	48	9	48	43	–	–
Stone 2014 [3]	Severe AATD	651	–	–	10	60	30	100	–
Torres-Duran 2015 [4]	AATD	212	70[#]	18.9	–	–	100	–	100
Clark 2018 [5]	AATD	94	57	33	–	53.2	46.8	100	–
Hamesch 2019 [6]	Severe AATD	554	54.1	54.6	–	–	–	100	–
Choate 2019 [7]	AATD	3535	56.3	51.2	–	–	–	85.7	–
Basil 2020 [8]	Severe AATD	1577	47	49	8	46	46	100	–
	Controls	5969	45	50	26	21	53	0	–
Franciosi 2021 [9]	AATD MZ	91	58.0	39.6	–	53.8[¶]	–	0	100
	AATD SZ	72	57	51.4	–	56.9[¶]	–	0	100
	AATD ZZ/Rare	130	58	53.8	–	61.5[¶]	–	100	
Tanash 2020 [10]	AATD *PiZZ*	1545	47	50	8	46	46	100	–
	Controls	5883	45	50	26	21	53	0	–
Franciosi 2020 [11]	AATD *PiSZ*	70	52.9	44.3	–	47.1[¶]	–	–	100
	AATD *PiMM*/MS (control)	46	53.4	45.7	–	52.2[¶]	–	–	100
Fromme 2021 [12]	AATD *PiMZ* – cohort 1	17,006	56.9	45	–	–	–	–	100
	AATD *PiSS* – cohort 1	1014	56.4	46	–	–	–	–	100
	AATD *PiSZ* – cohort 1	864	56.6	45	–	–	–	–	100

Study name	Patient group	N	Mean age (years)	Gender	Smoking status (%)			Genotype (%)	
				Male (%)	Current	Former	Never	*PiZZ*	Others
	AATD *PiZZ* – cohort 1	138	56.1	53	–	–	–	100	
	Controls (non-carriers) – cohort 1	422,506	56.5	46	–	–	–	–	–
	AATD *PiZZ* – cohort 2	586	54.2	53.8	–	–	–	100	–
	AATD *PiSZ* – cohort 2	239	50.4	43.5	–	–	–	–	100
	Controls (non-carriers) – cohort 2	279	52.4	50.9	–	–	–	–	–
SCHNEIDER 2020 [13]	AATD *PiMZ* – cohort 1	419	45	44	–	–	–	–	100
	AATD *PiZZ* – cohort 1	309	50	51	–	–	–	100	-
	Control (non-carriers) – cohort 1	284	51	48	–	–	–	0	0
	AATD *PiMZ* – cohort 3	84	55	56	–	–	–	–	100
	AATD *PiZZ* – cohort 3	35	53	83	–	–	–	100	–
HAKIM 2021 [14]	No cirrhosis	311,178	56.9	46	–	–	–	–	–
	Cirrhosis	1493	59.0	68	–	–	–	–	–
ABU RMILAH 2021 [15]	AATD PIMM	1094	53.3	64.5	–	–	–	–	100
	AATD PIMZ	130	55.4	68.5	–	–	–	–	100
SAPEY 2020 [16]	AATD	68	55.3	57.4	3	–	–	–	–
	COPD	88	68.6	70.5	61	–	–	–	–
ESQUINAS 2018 [17]	AATD PiZZ	122	61.6	58	6.2	77.7	16.2	100	–
PARR 2007 [18]	AATD PiZ	74	50.6	71	5.4	73.0	–	–	100
GUPTA 2020 [19]	No deficiency	1149	66.8	56.3	16.3	48.8	34.9	–	–
	Mild deficiency	147	64.9	57.8	15	47.6	37.4	–	100
	Intermediate deficiency	59	68.8	61.0	15.3	59.3	25.4	–	100

Study name	Patient group	N	Mean age (years)	Gender	Smoking status (%)			Genotype (%)	
				Male (%)	Current	Former	Never	*PiZZ*	Others
	Severe deficiency	4	68.3	25	0	50	50	100	
Piras 2013 [20]	AATD PiZZ	547	49.7	56.9	9	56.9	32.7	100	–
	AATD PiSZ	124	51.1	54	10.5	46	42.7	–	100
	AATD Spain	416	50.5	60.8	7.2	60.8	30.5	78.6	18.3
	AATD Italy	329	49.1	52.6	11.9	48.9	38.3	66.9	14.6
Herrera 2021 [21]	Severe AATD	711	57.9	50.1	–	–	–	–	–
	Non-severe AATD	1963	52.8	46.0	–	–	–	–	–
Conference abstracts (n=17)									
Teckman 2019 [22]	AATD	93	54	47	–	–	–	–	–
Strnad 2017 [23]	AATD	115	49[#]	36	–	–	–	0	100
	Matched controls	100	–	–	–	–	–	0	–
Mandorfer 2017 [24]	Severe AATD	31	–	–	–	–	–	–	–
Costa 2017 [25]	Intermediate AATD	104	40.1	56.7	26.9		73.1	–	100
Arslanow 2017 [26]	AATD	19	–	–	–	–	–	36.8	–
Chakraborty 2016 [27]	AATD	212	58.2	48.6	6.2	56.4	37.4	49.7	–
Cortese 2016 [28]	AATD	475	–	–	–	–	–	–	–
Araujo 2015 [29]	AATD	110	–	–	–	–	–	–	–
Kumbhare 2014 [30]	AATD	2875	–	–	–	–	–	–	100
Kawkgi 2013 [31]	AATD	54	54	–	–	–	–	–	100
Ferrarotti 2012 [32]	Severe AATD	312	–	–	–	76	–	66	–
	Index	253	49.6	–	–	–	–	–	–

Study name	Patient group	N	Mean age (years)	Gender	Smoking status (%)			Genotype (%)	
				Male (%)	Current	Former	Never	*PiZZ*	Others
	Non-index	59	44.4	–	–	–	–	–	–
Guttmann 2011 [33]	Severe AATD	713	39.9	60.3	72	–	27	79.7	–
Mandich 2011 [34]	AATD	33	–	–	–	–	–	–	–
Subramanian 2010 [35]	AATD	497	–	–			–	100	–
Black 2020 [36]	Heterozygous AATD	23	60.9% <60	69.6	–	–	–	–	–
	Control	120	59.2% >60	50.0	–	–	–	–	–
Hiller 2020 [37]	AATD *PiZZ*	1585	–	–	–	–	–	100	–
	Controls	5999	–	–	–	–	–	0	–
Catterall 2020 [38]	AATD	195	–	–	–	–	–	–	

[#]Value is expressed as median. [¶]Ever-smoker.

AATD: alpha-1 antitrypsin deficiency; N: number of patients; *PiZZ*: *Pi* (or *SERPINA1* gene) *ZZ* allele.

Supplementary TABLE 2 QoL review: baseline characteristics and QoL instruments from included studies

Study	Patient group	N	Mean age (years)	Males (%)	Smoking status (%)			Genotype (%)		Comorbidities (%)			QoL instruments	Other PRO instruments
					Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma		
CHAPMAN 2015 [39]	AATD: AAT therapy	93	53.8	52	0	–	–	100[¶]	–	–	100	–	SGRQ	
	AATD: Placebo	87	52.4	57	0	–	–	100[¶]	–	–	100	–		
STOLK 2003 [40]	AATD	22	40.7	45.5	22.7	63.6	13.6	100	–	–	NR	–	SGRQ	
HOGARTH 2019 [41]	AATD	20	–	–	–	–	–	–	–	–	100	–	SGRQ, CAT	mMRC
DURKAN 2019 [42]	AATD + COPD	30	60	70	–	–	–	–	–	–	–	–	SF-36, SGRQ	
STOCKLEY 2018 [43]	AATD + COPD	84	42.4[#]	39	0	81	70	100	–	100	–	–	SGRQ	
	AATD without COPD	370	52.5[#]	64	0		19	100	–	0	–	–		
BERNHARD 2017 [44]	AATD-*PiZZ*	868	52.6	56.5	2.8	71.1	25.6	100	–	–	82.1	16.9	SGRQ	
	AATD-*PiSZ*	114	50.3	53.5	14	57	28.9	–	*PiSZ* (100)	–	52.6	19.3		
JAROSCH 2017 [45]	AATD-COPD	140	56	30	–	–	–	100	–	100	–	–	SF-36	

Study	Patient group	N	Mean age (years)	Males (%)	Smoking status (%)			Genotype (%)		Comorbidities (%)			QoL instruments	Other PRO instruments
					Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma		
KARL 2017 [46]	AATD	131	60.3	56.5	0.7	75.6	23.7	–	–	100	–	–	SGRQ, CAT, EQ-5D-3L utility and VAS	
PIITULAINEN 2017 [47]	AATD-*PiZZ*	120	39#	56	4	18	78	100	–	–	–	–	SGRQ,	mMRC
	AATD-*PiSZ*	46	39#	52	4	11	85	–	*PiSZ* (100%)	–	–	–		
STONE 2016 [48]	AATD-LT	32	53.6	72	–	–	–	100	–	–	–	–	SGRQ	
	AATD-Non-LT	48	53.0	71	–	–	–	100	–	–	–	–		
KENN 2015 [49]	AATD	127	51	58	–	–	–	–	–	–	–	–	SF-36	
LUISETTI 2015 [50]	AATD	422	48.2	52.5	11.4	45.3	41.2	61.1	*PISZ*: 17.5 Other: 21.3	9.2	62.9	7.7	SGRQ	
PONCE 2014 [51]	AATD-COPD	573	54.3	51	–	–	–	–	–	100	–	–	SGRQ, SF-36	
MANCA 2014 [52]	AATD	35	56.5	57.1	11.4	85.7	2.9	100	–	–	100	–	CAT, LCOPD, EQ-5D utility	

Study	**Patient group**	**N**	**Mean age (years)**	**Males (%)**	**Smoking status (%)**			**Genotype (%)**		**Comorbidities (%)**			**QoL instruments**	**Other PRO instruments**
					Current	**Former**	**Never**	***PiZZ***	**Others**	**COPD**	**Emphysema**	**Asthma**		
													and VAS	
Holm 2013 [53]	AATD-COPD	578	–	49.8	–	–	31.7	–	–	100	–	–	SGRQ	HADS, mMRC
Lascano 2010 [54]	AATD-COPD	646	–	–	–	–	–	–	–	–	–	–	SF-36, SGRQ	
Campos 2009 [55]	AATD-COPD	922	54.5	52.6	–	–	–	–	–	100	–	–	SGRQ, SF-36	
Dowson 2002 [56]	AATD-No CSE	67	51[#]	66	–	–	–	100	–	–	–	–	SGRQ, SF-36	
	AATD-CSE	50	51[#]	66	–	–	–	100	–	–	–	–		
Gunzerath 2001 [57]	AATD	76	51.7	61	–	–	–	–	–	–	–	–	Personality traits, Coping strategies	
Knebel 1999 [58]	AATD	45	49	67	–	–	–	–	–	–	–	–	CRQ	
Knebel 1998 [59]	AATD	33	47	64	–	85	–	–	–	–	–	–	CRQ (Dyspnoea inducing activities)	
Bradi 2015 [60]	AATD	290	52	50.3	3.7	58.2	38	–	–	–	63.4	16	SGRQ	
Dawkins	AATD-	33	51.2	26	–	–	–	100	–	–	–	–	SRGQ, SF-36	

Study	Patient group	N	Mean age (years)	Males (%)	Smoking status (%)			Genotype (%)		Comorbidities (%)			QoL instruments	Other PRO instruments
					Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma		
2009 [61]	fast tertile													
	AATD-middle tertile	34	52.7	22	–	–	–	100	–	–	–	–		
	AATD-slow tertile	33	49.1	19	–	–	–	100	–	–	–	–		
STOLLER 1994 [62]	Severe AATD	304	48.8	50	1.3	–	–	–	–	–	–	–	Symptoms and self-reported impact of disease	
	AATD-*PiSZ*	9	53	33	0	–	–	–	–	–	–	–		
	AATD-*PiMZ*	12	50.2	83	0	–	–	–	–	–	–	–		
GAUVAIN 2015 [63]	AATD	273	51.8	63	8.4	–	12.1	84.6	*PiSZ*: 5.5 *Null/Z*: 1.1	-	100	–	SGRQ	
MOLLOY 2017 [64]	AATD	159	–	–	–	–	–	–	–	–	–	–	Symptoms	
ANNUNZIATA (2021) [65]	AATD	16	61[#]	56.3	0	43.8	56.3	–	–	–	81.3	–	SGRQ, shortened[+]	
SCHRAMM	AATD	84	42	–	–	–	–	–	–	–	–	–	SGRQ	

Study	Patient group	N	Mean age (years)	Males (%)	Smoking status (%)			Genotype (%)		Comorbidities (%)			QoL instruments	Other PRO instruments
					Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma		
2020 [66]	(PIZZ)													
	Never-smoking control	72	42	–	–	–	–	–	–	–	–	–		
Sandhaus 2020 [67]	AATD (PiZZ or worse)	655	–	–	–	–	–	–	–	–	–	–	SGRQ	
	AATD without AAT therapy	655	–	–	–	–	–	–	–	–	–	–		
Crossley 2020 [68]	AATD	187	60.1	46	–	–	–	–	–	–	–	–	SGRC CAT	

[#]Value is expressed as median. [¶]All patients have severe disease, hence *PiZZ* assumed as 100%. [+]A modified QoL score, consisting of six questions to analyse the general state of health, subjective symptoms of the patient and impact of therapy on the patient's and family life was used instead of the full-length SGRQ.

AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; CAT: COPD assessment test; COPD: chronic obstructive lung disease; CRQ: chronic respiratory disease questionnaire; CSE: chronic sputum expectoration; HADS: hospital and anxiety depression scale; LCOPD: living with COPD; LT: lung transplant; mMRC: modified Medical Research Council dyspnoea scale; N: number of patients; *PiMZ/SZ/ZZ*: *Pi* (or *SERPINA1* gene) *MZ, SZ* and *ZZ* alleles; SF-36: 36-item short-form survey; SGRQ: St George's respiratory questionnaire.

Supplementary TABLE 3 Total and partial STROBE scores for the included studies

Study	Title and abstract (%)	Introduction (%)	Methods (%)	Results (%)	Discussion (%)	Funding (%)	Overall scores
DURKAN 2019 [42]	100	100	42.8	27	25	0	49.14
STOCKLEY 2018 [43]	100	100	50.0	27	50	100	71.17
BERNHARD 2017 [44]	100	100	42.8	27	75	100	74.14
JAROSCH 2017 [45]	100	100	42.8	36	25	100	67.31
KARL 2017 [46]	100	100	57.1	36	50	100	73.85
PIITULAINEN 2017 [69]	100	100	57.1	27	75	100	76.52
STONE 2016 [48]	100	100	35.7	27	75	100	72.95
KENN 2015 [49]	100	100	35.7	27	75	0	56.28
LUISETTI 2015 [50]	100	100	50.0	18	25	0	48.8
PONCE 2014 [51]	100	100	35.7	18	25	0	46.4

Study	Title and abstract (%)	Introduction (%)	Methods (%)	Results (%)	Discussion (%)	Funding (%)	Overall scores
MOLLOY 2017 [64]	100	100	35.7	18	0	0	42.2
MANCA 2014 [52]	100	100	42.8	18	25	100	64.3
HOLM 2013 [53]	100	100	35.7	27	50	100	68.7
LASCANO 2010 [54]	100	100	35.7	18	0	0	42.2
CAMPOS 2009 [55]	100	100	35.7	9	25	100	61.6
DOWSON 2002 [56]	100	100	42.8	27	25	100	65.8
GUNZERATH 2001 [57]	100	100	35.7	18	25	100	63.1
KNEBEL 1998 [59]	100	100	42.8	18	25	100	64.3
KNEBEL 1999 [58]	100	100	35.7	18	25	0	46.4
BRADI 2015 [60]	100	100	35.7	18	50	100	67.2
DAWKINS 2009	100	100	35.7	27	50	100	68.7

Study	Title and abstract (%)	Introduction (%)	Methods (%)	Results (%)	Discussion (%)	Funding (%)	Overall scores
[61]							
STOLLER 1994 [62]	100	100	35.7	27	25	0	47.9
GAUVAIN 2015 [63]	100	100	28.5	18	25	100	61.9
STOLK 2003 [40]	100	100	42.8	27	25	0	49.1
Average score	**100**	**100**	**38.8**	**22.3**	**36.9**	**60**	**59.6**

Supplementary TABLE 4 Quality of life review: CAT scores in patients with AATD

Study	Population/treatment	N	CAT score, mean (SD)		Main CAT score outcomes
Manca 2014 [52]	AATD + COPD	35	13.8	p=0.32	There were similar scores between AATD patients diagnosed with COPD and the non-AATD COPD cohort. Regression analysis to assess the relationship between CAT scores and FEV_1 showed that the relationship approached statistical significance in the AATD COPD group (r^2=0.108; p=0.054)
	Non-AATD COPD	61	12.1		
Karl 2017 [46]	AATD + COPD	131	18.6 (6.7)	–	There were no significant differences in CAT scores between patients with COPD who were receiving AAT therapy *versus* those who were not
	AATD + COPD + AAT therapy	106	18.9 (6.6)	–	
	AATD + COPD + without AAT therapy	25	17.2 (7.3)	–	
Crossely 2020 [68]	AATD	187	18.9 (12.0–25)	–	CAT test scores were related to disease severity as defined by the GOLD stage (p<0.0001). There were significant correlations between QoL measures and spirometry, as measured by FEV_1 (percent predicted), FVC (predicted), FEV_1/FVC (%) and with gas transfer coefficient, KCO (percent 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)

AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IQR: interquartile range; KCO: monoxide transfer coefficient; N: number of patients; py: pack-years (cumulative nicotine consumption); RV/TLC: residual volume/total lung capacity; SGRQ: St George's Respiratory Questionnaire.

Supplementary TABLE 5 QoL review: SF-36 scores reported in AATD-associated COPD patients

Study	Group	N	Timepoint	Domain	SF-36, mean (SD)
DURKAN 2019 [42]	AATD + COPD	30	NR	Vitality scores	58.5 (21.4)
JAROSCH 2017 [45]	AATD + COPD	140	Baseline	Mental score	44.9 (15.4)
				Physical score	26.3 (8.2)
	AATD + COPD + AAT therapy	80	Baseline	Mental score	45.2 (16.2)
				Physical score	28.1 (8.3)
	AATD + COPD without AAT therapy	60	Baseline	Mental score	48.4 (13.5)
				Physical score	23.7 (7.5)
PONCE 2014 [51]	AATD + COPD	573	Baseline	Physical score	36.7 (9.8)
	AATD + COPD	573	5-year	Physical score	33.3 (9.5)
CAMPOS 2009 [55]	AATD + COPD + AAT therapy	922	Baseline	Physical score	35.3 (9.7)
	AATD + COPD + AAT therapy	922	Baseline	Mental score	52.1 (11.7)

Study	Group	N	Timepoint	Domain	SF-36, mean (SD)
DAWKINS 2009 [61]	AATD + COPD with fast FEV_1 decline	33	–	Physical score	40.3 (9.41)
	AATD + COPD with middle FEV_1 decline	34	–	Physical score	33.9 (10.5)
	AATD + COPD with slow FEV_1 decline	34	–	Physical score	36.1 (12.0)
	AATD + COPD with fast FEV_1 decline	33	–	Mental score	48.4 (13.0)
	AATD + COPD with middle FEV_1 decline	34	–	Mental score	48.7 (10.4)
	AATD + COPD with slow FEV_1 decline	34	–	Mental score	49.5 (11.0)
LASCANO 2010 [54]	AATD + COPD + AAT therapy: Overweight	241	–	Physical score	OR: 1.6
	AATD + COPD + AAT therapy: obese	104	–	Physical score	OR: 2.3
	AATD + COPD + AAT therapy: Morbidly obese	61	–	Physical score	OR: 4.2

AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; COPD: chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 s; N: number of patients; NR: not reported; OR: odds ratio, QoL: quality of life; SD: standard deviation.

Supplementary TABLE 6 Economic burden review: patient characteristics from included studies

Study name	Patient group	N	Mean age, years	Gender	Race (%)			Smoking status (%)			Genotype (%)		Comorbidities (%)		
				Male, %	White	Asian	Black	Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma
Herrera 2021[21]	AATD severe course	711	57.9	50.1	–	–	–	–	–	–	–	–	34.8	14.5	27.8
	AATD non-severe course	1963	52.8	46.0											
Sieluk 2019 [70]	AATD	9117	–	48.0	61.0	6	5	–	–	–	–	–	54.0	–	–
Karl 2017 [46]	AATD + COPD	131	60.3	56.5	–	–	–	0.7	75.6	23.7	–	–	100	–	–
Greulich 2017 [71]	AATD	673	55.5		–	–	–	–	–	–	–	–	–	–	–
Zacherle 2015 [72]	AATD	279	64.6	–	–	–	–	–	–	–	–	–	–	–	–
Barros-Tizon 2012 [73]	AATD	127	51.7	63.3	–	–	–	3.2	79.4	17.4	93.6	6.4	–	–	–
Mullins 2003 [74] Mullins 2001 [75]	AATD	688	49.7	52.3	96.2	–	–	–	–	–	84.5	15.5	–	32.6	17.3

Study name	**Patient group**	**N**	**Mean age, years**	**Gender**	**Race (%)**			**Smoking status (%)**			**Genotype (%)**		**Comorbidities (%)**		
				Male, %	**White**	**Asian**	**Black**	**Current**	**Former**	**Never**	***PiZZ***	**Others**	**COPD**	**Emphysema**	**Asthma**
PIITULAINEN 2003 [76]	AATD	5	58.4	40.0	–	–	–	–	100	–	100	–	–	–	–
STOLLER 2000 [77]	AATD	712	49.3	52.3	96.2	–	–	2.1	73.3	24.1	70.7	13.0	–	54.2	38.6
AGGARWAL 2018 [78]	AATD	1493	56.4	–	–	–	–	–	–	–	–	–	–	–	–
CHOATE 2019 [7]	AATD	3535	56.3	51.2	98.2	–	0.4	73.1		–	–	14.3	–	–	–
STONE 2020 [79]	AATD	1258	49	45.7	–	–	–	–	–	–	–	–	51.1	–	–
SIELUK 2020 [80]	AATD + COPD	953	56.2	48	92	–	4	–	–	–	–	–	100	–	–
	COPD control	7928	55.2	48	95	–	3	–	–	–	–	–	100	–	–
RUEDA 2020 [81]	AATD	6832	–	–	–	–	–	–	–	–	–	–	–	–	–
BORGET 2020 [82]	AATD	365	56.6	61	–	–	–	–	–	–	–	–	–	–	–
SIELOFF 2021 [83]	AATD	1540[¶]	–	–	76.9	–	–	–	–	–	–	–	–	–	–
LEE 2020 [84]	AATD-related cirrhosis	1872	56		92.6	0.16	1.3								

Study name	Patient group	N	Mean age, years	Gender	Race (%)			Smoking status (%)			Genotype (%)		Comorbidities (%)		
				Male, %	White	Asian	Black	Current	Former	Never	*PiZZ*	Others	COPD	Emphysema	Asthma
	Non-AATD-related cirrhosis	7488													
Rozario 2019 [85]	AATD,	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	CF	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	EA	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	PIDD	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	HIV	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dye 2011 [86]	AATD	558	–	–	–	–	–	–	–	–	–	–	–	–	–
Attaway 2019 [87]	AATD	8039	–	–	–	–	–	–	–	–	–	–	24.3[§]	–	4.5

[#]2014 hospital discharges; [¶]Median age at hospital admission; [§]COPD and bronchiectasis.

AATD: alpha-1 antitrypsin deficiency; CF, cystic fibrosis, COPD: chronic obstructive pulmonary disease; EA, eosinophilic asthma; N: number of patients; NACLD: non-alcoholic chronic liver disease; PIDD, primary humoral immunodeficiency; *PiZZ*: *Pi* (or *SERPINA1* gene) *ZZ* allele.

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