

SUPPLEMENTARY MATERIAL

Supplementary table 1: Characteristics of key previous PiSZ cohorts

*Patients included in the pooled analysis of COPD risk, based on clinical or spirometric diagnosis of COPD. Other analyses of clinical characteristics were reported in the paper.

#Primary purpose of the study was to ascertain AATD gene frequencies (PiS & Z) in a COPD clinic, where COPD was clinically diagnosed, rather than to study PiSZ per se

Study	Study design	N	Age (yrs)	FEV1% predicted	Current or ex smokers	FEV1 decline (ml/year)	OR (95% CI) of COPD v PiMM
Dahl et al ³	Meta-analysis	42*	Means for pooled analysis not reported				3.26 (1.24-8.57)
Bartmann et al ⁴	Cohort#	18	Not reported				24.46 (3.25-185.94)
Holme et al ⁸	Cohort	63	50.6	84	73%	Not reported	
Hutchison et al ¹⁷	Cohort	25	51.3	75.6	88%	Not reported	
Turino et al ²²	Cohort	59	46.6	67	62%	Not reported	

Supplementary table 2: Characteristics stratified by index status in PiSZ patients

Those patients who did not know why they had been tested were excluded from analysis. Data is shown as n (%) or *mean (SE)*

Feature	Lung Index N=64	Non-lung index N=41	p value
Male	38 (59.4)	22 (53.7)	0.564
Age	55.4 (1.5)	43.5 (2.3)	<0.001
Smoking status			
Ex smoker	37 (57.8)	8 (19.5)	<0.001
Never smoked	15 (23.4)	25 (61.0)	
Current smoker	12 (18.8)	8 (19.5)	
Pack years smoked	26.2 (3.0)	9.0 (2.6)	<0.001
COPD	43 (67.2)	8 (19.5)	<0.001
Emphysema	35 (54.7)	3 (7.3)	<0.001
Chronic bronchitis	18 (28.1)	6 (14.6)	0.175
Bronchiectasis	11 (17.2)	7 (17.1)	0.778
AAT level	14.9 (3.7)	13.5 (5.3)	0.034
AAT <11µM	3 (4.7)	6 (14.6)	0.059
FEV1pp	76.5 (2.6)	106.4 (4.3)	<0.001
FEV1/FVC (%)	55.0 (2.7)	78.0 (1.7)	<0.001
TLCpp	109.2(1.9)	104.2 (1.7)	0.059
RVpp	107.9 (4.6)	88.7 (3.9)	0.003
DLCOpp	76.5 (3.1)	97.3 (2.8)	<0.001
KCOpp	78.1 (3.0)	95.8 (2.3)	<0.001
UZVI	30.2(4.6)	9.9 (1.7)	0.005
LZVI	31.6 (5.2)	11.0 (2.0)	0.001
UZ/LZVI	1.1 (0.1)	1.1 (0.2)	0.251
Follow up time (years)	7.8 (0.6)	9.3 (1.6)	0.894
Deceased	7 (10.9)	1 (2.4)	0.145

Supplementary table 3: Characteristics of smoke exposed & never smoking PiSZ and ZZ patients

Data is shown as n (%) or *median (IQR)*. In light of the known influence of smoke exposure on parameters shown here p values have not been computed between smokers and never smokers.

Feature	PiZZ smoke exposed N=536	PiSZ smoke exposed N=66	PiZZ never smoker N=160	PiSZ never smoker N=60
Male	329 (61.4)	51 (77.3)	75 (46.9)	20 (33.3)
Age	49.7 (12.0)	51.6 (14.0)	56.0 (23.0)	53.7 (15.0)
Packyears smoked	19 (6.4)	30 (34.3)	-	-
COPD	488 (91.0)	53 (80.3)	96 (60.0)	13 (21.7)
FEV1≥80%	32 (6.0)	11 (16.7)	23 (14.4)	7 (11.7)
50-80%	132 (24.6)	21 (31.8)	33 (20.6)	5 (8.3)
>30<50%	158 (29.5)	15 (25.0)	27 (16.9)	0
<30%	166 (31.0)	6 (9.1)	13 (8.1)	1 (1.7)
Emphysema	383 (71.5)	36 (54.5)	77 (48.1)	4 (6.7)
Chronic bronchitis	203 (37.9)	21 (31.8)	43 (26.9)	5 (8.3)
Bronchiectasis	129 (24.1)	8 (12.1)	52 (32.5)	11 (18.3)
FEV1pp	36.5 (33.0)	81.0 (61.0)	74.3 (66.7)	110.0 (11.8)
FEV1/FVC (%)	35.9 (22.4)	60.0 (44.5)	58.0 (43.5)	82.0 (12.3)
KCOpp	62.3 (26.5)	92 (40.5)	84.1 (37.8)	91.5 (18.5)
UZVI	32.3 (28.4)	20.7 (32.3)	19.9 (28.2)	12.7 (10.2)
LZVI	51.6 (28.3)	21.3 (31.4)	32.9 (39.5)	13.9 (15.9)
UZ/LZVI	0.7 (0.4)	0.8 (0.6)	0.7 (0.4)	1.0 (0.5)
Deceased	142 (26.5)	9 (13.6)	30 (18.8)	1 (1.7)

Matched analysis PiSZ v PiZZ

Patients in the matched analysis had the following characteristics (medians): age 52.6 years, 15pack year smoke exposure, FEV1 52% predicted. 5 PiSZ patients could not be adequately matched to PiZZ due to high smoke exposure and were excluded. Comparisons of matched patients showed that all differences in lung disease phenotype remained as in the primary analysis, such that PiSZ patients had lower prevalence of emphysema and better lung function. Data on physiological decline was available in 66 PiSZ and 120 PiZZ patients respectively. There was no difference in annual decline of FEV1 or gas transfer (DLCO and KCO, all p>0.2) and PiSZ patients were less likely to die (7.9% v 20.6%, p=0.004).

Supplementary table 4: FEV1 decline in other key PiZZ cohorts

Study	N	Method of calculating FEV1 decline	FEV1 decline (ml/year)
Seersholm et al ¹⁵	161	Difference between 2 spirometries ≥1 year apart	81 (all patients) 52 (ex-smokers)
AATD registry study group ²⁵	927	Regression of ≥2 spirometry measurements ≥1 year apart	54
Hutchison et al ¹⁷	71	Regression of 6-13 spirometry measurements	66.3
Wu et al ²⁷	80	Regression of ≥2 spirometry measurements ≥6 months apart	60 (never & ex smokers) 80 (current smokers)
Burdon et al ²⁸	50	Linear regression of ≥2 spirometry measurements over 2-6 years	88