

## SZ alpha-1 antitrypsin deficiency and pulmonary disease: more like MZ, not like ZZ

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**Title: SZ alpha-1 antitrypsin deficiency and pulmonary disease: more like MZ, not like ZZ.**

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**Abstract (word count 117)**

The ZZ-genotype of AATD is associated with COPD regardless of smoking. Heterozygous MZ-AATD is recognised as a moderate deficiency state, increasing the risk of COPD only among smokers. The risk attributable to SZ-AATD remains debated. We compared 486 AATD-registry participants, to determine whether SZ-AATD was associated with pulmonary outcomes more comparable to MZ- or ZZ-AATD. We found no significant differences between MZ and SZ individuals regardless of never-/ever-smoking ( $p > 0.05$  for all). ZZ-AATD was associated with lower FEV<sub>1pp</sub> than SZ, regardless of never-/ever-smoking, as well as an increased OR of lung-index status and visually-defined emphysema on CT ( $p \leq 0.002$  for all). In our registry cohort SZ-AATD is associated with a risk of lung disease comparable to MZ, not ZZ-AATD.

## MAIN TEXT – (Word count 1339)

### Background

Alpha-1 antitrypsin deficiency (AATD) is a monogenic risk for COPD caused by hereditary mutations in the *SERPINA1* gene. Wild-type homozygous individuals (genotype-MM) have a normal serum levels of AAT (1-2g/L)<sup>1</sup>, with the MS, MZ, SZ and ZZ genotypes resulting in progressively greater deficiency. The accepted wisdom has been the greater the degree of deficiency the greater the risk of lung disease<sup>2</sup>.

ZZ-AATD is associated with COPD, even in never-smokers<sup>3</sup>. MZ-AATD has been shown to increase risk of COPD, but only among smokers<sup>4 5</sup>. Consequently, MZ-AATD is considered a moderate risk genotype, and intravenous AAT augmentation is not recommended<sup>6</sup>.

SZ-AATD results in AAT levels between MZ and ZZ-AATD, and a range which straddles the “putative protective threshold” (PPT) of 0.57g/L<sup>1 7</sup>, historically considered a threshold for increased risk of COPD. Consequently, whether SZ-AATD represents a moderate or severe risk is debated<sup>8</sup> and intravenous AAT augmentation is frequently prescribed for SZ-AATD due to it being perceived by many as severe deficiency. We recently reported that never-smoking SZs have spirometry comparable to controls (genotype MM and MS individuals), but that smoking is associated with lower FEV<sub>1pp</sub> than in control-smokers<sup>9</sup>, suggesting it may be more comparable to MZ, and not ZZ-AATD. No study has compared the three genotypes to assess their clinical features.

We hypothesised that SZ-AATD poses a moderate, and not severe, risk of lung disease and that by controlling for confounders we could determine the magnitude of difference in clinical outcomes between SZ-AATD and the MZ and ZZ genotypes.

## Methods

### Study design

We performed a retrospective comparative study examining the effect of the MZ, SZ and ZZ-AATD on PFTs at first presentation, and the prevalence of visually-defined emphysema on CT among individuals enrolled in the National Irish AATD Registry (Beaumont Hospital Ethics REC No.05-03). Full methods are provided in the online supplement.

Inclusion was restricted to the MZ, SZ and ZZ genotypes and required availability of age, sex, ascertainment-mode, smoking history, height, weight and AAT level at time of diagnosis, as well as absolute and percentage predicted (<sub>pp</sub>) pulmonary function test (PFT) values. Individuals diagnosed due to pulmonary disease were designated “lung-index” with others designated “non-lung-index”. The effect of the PPT was examined in the SZ cohort, comparing individuals by AAT levels above- or below- the PPT.

### Clinical data

PFTs recorded in the registry were performed at the Department of Pulmonary Physiology, Beaumont Hospital, Dublin, as per ATS/ERS guidelines<sup>10 11</sup>. CT reports were reviewed for documented visually-defined emphysema.

### Statistical analysis

All analyses were performed in RStudio Version 1.1.463 ([www.cran.r-project.com](http://www.cran.r-project.com)). Full statistical methods are described in the online supplement. The results of the first demographic, anthropomorphic and clinical data recorded in the registry for each subject were compared. A p value of <0.05 was considered significant. Linear mixed model analyses were used to perform multivariable analyses, with SZ genotype coded as the reference factor. Adjusted odds ratios (OR) were calculated using binomial logistic regression in generalised mixed models.

## Results

486 individuals were included (156 MZ, 117 SZ, 213 ZZ, table 1), with spirometry available for all and diffusion capacity available for 293. Mean AAT levels differed significantly between genotypes (0.83 vs 0.59 vs 0.25g/L for MZ:SZ:ZZ respectively,  $p<0.001$  between all genotypes).

### Preliminary analyses: age, smoking and lung-index status

The effect of age (figure 1), smoking (supplementary figure 1), and lung-index status on  $FEV_{1pp}$  was examined in preliminary analyses. Full results are included in the online supplement. No significant correlation between age and  $FEV_{1pp}$  was seen for MZ or SZ never-smokers (rho 0.02,  $p=0.9$  and  $R -0.09$ , 95% CI; -0.35 to 0.17,  $p=0.49$  respectively), while the relationship between smoking and  $FEV_{1pp}$  did not differ between ever-smoking MZs and SZs (+0.08%/pack-year  $\pm 0.17$ ,  $p=0.63$ ). Finally, the OR of lung-index status was comparable between SZs and MZs (OR 1.28 for MZ vs SZ, 95% CI; 0.77 to 2.12,  $p=0.32$ ).

Conversely, increasing age correlated negatively with  $FEV_{1pp}$  in ZZ-AATD never smokers (rho -0.51 by Spearman Rank correlation,  $p<0.0001$ , figure 1), while the effect of the interaction of pack-years with ZZ-AATD on  $FEV_{1pp}$  was significantly greater than in SZ-AATD (-0.39%/pack-year  $\pm 0.19$  vs SZ,  $p=0.039$ )(supplementary figure 1). The OR of lung-index status was 2.11 for ZZs compared to SZs (95% CI; 1.31 to 3.39,  $p<0.001$ ). Across all genotypes the effect of lung-index status on  $FEV_{1pp}$ , examined in a mixed model adjusting for smoking (ever vs never) and genotype was found to be -15.06% (95% CI; -19.59 to -9.88 vs non-lung-index,  $p<0.0001$ )(supplementary table 1).

Among SZs, no effect on outcomes was attributable to AAT levels below-PPT, with an OR of 0.65 of lung-index status compared to above-PPT (95% CI; 0.29 to 1.48,  $p=0.31$ ) and no significant difference in  $FEV_{1pp}$  (+4.98%  $\pm 6.0$  vs above-PPT,  $p=0.411$ ) when adjusting for age, pack-years and lung-index status.

## Final Analyses: Effect of MZ and ZZ genotype effect on lung function and emphysema relative to SZ.

### MZ vs SZ

No significant difference was found between MZ and SZ individuals FEV<sub>1pp</sub>, both in never-smokers (-5.77% vs SZ, 95% CI; -14.07 to 2.52, p=0.177) and ever-smokers (+1.93%, 95% CI; -5.98 to 9.86, p=0.64). Furthermore, no difference in FEV<sub>1</sub>/FVC ratio or DLCO<sub>pp</sub> was seen regardless of smoking or age stratification (p >0.05 for all, see supplementary table 2).

### ZZ vs SZ

A difference in FEV<sub>1pp</sub> of -13.17% (95% CI; -21.28 to -5.06, p=0.002) was observed for never-smoking ZZs vs SZs, increasing to -22.21% (95% CI; -34.94 to -9.49, p=0.001) by stratifying for >50 year-old never-smokers. Among ever-smokers the estimated difference in FEV<sub>1pp</sub> was -21.89% for ZZ vs SZ (95%CI; -30.50 to -14.47, p<0.0001). Significant differences were also seen in for SZ and ZZ in FEV<sub>1</sub>/FVC ratio and DLCO<sub>pp</sub> (see supplementary results and table 2).

### CT Data

448 CT reports were available (136 MZ, 102 SZ, 210 ZZ, supplementary table 3). The OR of having emphysema reported on CT (adjusted for lung-index status, age and pack-years) was not significant for MZs (OR 1.18, 95% CI; 0.49 to 2.80, p=0.70) but was for ZZs (OR 13.51, 95% CI; 6.19 to 29.47, p<0.0001) relative to SZ individuals. No emphysema was reported in MZ or SZ never-smokers (0/64 and 0/56).

## Discussion

We sought to examine whether the clinical features of SZ-AATD, previously considered a severe deficiency genotype, more closely resemble those of moderate MZ or severe ZZ-AATD. To our knowledge, this is the first such analysis reported to date.

As with all registry based and retrospective studies, potential weaknesses arise from questions regarding generalisability of the characteristics of the registry participants and whether they indeed represent the wider population with the same genotypes. We have sought to address this by discriminating between individuals diagnosed with AATD in the course of investigating pulmonary complaints and those identified for other reasons. Certainly the fact that never-smoking MZ and SZ cohorts demonstrated mean FEV<sub>1pp</sub> greater than 100%, and that none had visually-reported emphysema on CT scan reports would suggest that in the main they are not significantly biased towards a sicker clinical phenotype than the general population.

We found no significant difference in PFT or CT findings between SZ and MZ cohorts, whereas ZZ-AATD was associated with worse FEV<sub>1pp</sub> than SZ-AATD regardless of age or pack-years, as well as a higher odds ratio of lung-index status and visually-defined emphysema compared to SZ. Age correlated with lower FEV<sub>1pp</sub> in never-smoker ZZ-AATD, as has been previously reported<sup>3</sup>, but not in SZs or MZs. Moreover, we found no visually-defined emphysema among SZ or MZ never-smokers, compared to 35% of ZZ never-smokers. The nature of our data did not permit us to analyse the severity or patterns of distribution of emphysema between genotypes. Nevertheless, previous studies<sup>9 12</sup> have reported that SZ individuals with emphysema demonstrate a largely upper-zone predominant distribution of disease, rather than the lower zone predominance seen in ZZ individuals, reinforcing our findings of a significant difference between the two genotypes. Finally, lung-index status was associated with significantly worse FEV<sub>1pp</sub>, a finding that should be considered in future comparative studies.

## Conclusion

The results of this national registry analysis suggest that SZ-AATD results in a risk for COPD which is comparable to the MZ, and not the ZZ genotype.



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None.

**Author contributions**

Dr Franciosi designed the study, performed statistical analyses and is the main author.

Dr Carroll consulted on study design, performed data curation and population building in the National Irish AATD Registry, co-authored the manuscript and is the study co-supervisor.

Prof McElvaney consulted on the study design, edited the manuscript and is the study co-supervisor and senior author.

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## Tables

	MZ	SZ	ZZ	P value		
n	156	117	213	SZ vs MZ	MZ vs ZZ	SZ vs ZZ
Age (Y)	51 [41.75, 63.0]	51 [36.0, 59.0]	49 [41.0, 57.0]	0.134	0.027	0.563
Diagnosis Age (Y)	49.5 [39.0, 60.3]	50 [37.0, 59.0]	48 [38.0, 55.0]	0.604	0.07	0.209
Sex = Male (%)	65 (41.7)	56 (47.9)	118 (55.4)	0.307	0.009	0.189
Lung Index (%)	81 (51.9)	51 (43.6)	131 (61.5)	0.173	0.065	<b>0.001</b>
Ever-smokers (%)	92 (59.0)	61 (52.1)	134 (62.9)	0.259	0.443	0.057
AAT Level (g/L)	0.83 [0.74, 0.93]	0.59 [0.51, 0.71]	0.25 [0.20, 0.30]	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Height (cm)	166.8 (9.8)	169.3 (10.7)	170.7 (8.9)	0.049	<b>&lt;0.001</b>	0.212
Weight (Kg)	75.3 [63.0, 88.1]	78 [65.0, 91.5]	76 [65.7, 86.1]	0.42	0.822	0.4
BMI (kg/m <sup>2</sup> )	26 [23.0, 30.4]	27 [23.0, 30.5]	25.9 [22.6, 29.0]	0.998	0.12	0.119
FEV <sub>1pp</sub>	91.3 [70.0, 109.0]	95 [83.0, 107.0]	68 [41.0, 99.0]	0.278	<b>&lt;0.001</b>	<b>&lt;0.001</b>
FVC <sub>pp</sub>	106 [92.0, 117.3]	104 [95.0, 117.0]	101 [82.8, 113.3]	0.976	0.018	0.022
FEV <sub>1</sub> /FVC	0.72 [0.61, 0.81]	0.76 [0.68, 0.80]	0.56 [0.41, 0.77]	0.085	<b>&lt;0.001</b>	<b>&lt;0.001</b>
DLCO <sub>pp</sub> * (n = 293)	84 [72.5, 92.0]	86 [71.0, 96.0]	68.5 [51.0, 88.8]	0.417	<b>0.001</b>	<b>&lt;0.001</b>
<b>Never Smokers</b>	<b>64</b>	<b>56</b>	<b>79</b>			
FEV <sub>1pp</sub>	103 [81.8, 110.3]	101.5 [91.0, 111.0]	93 [68.5, 103.5]	0.251	0.046	<b>0.002</b>
FVC <sub>pp</sub>	107.5 [92.8, 116.3]	108 [97.8, 117.0]	106 [90.0, 115.0]	0.662	0.291	0.148
FEV <sub>1</sub> /FVC	0.77 [0.67, 0.83]	0.77 [0.72, 0.84]	0.73 [0.57, 0.82]	0.274	0.28	0.023
DLCO <sub>pp</sub> * (n = 135)	84 [78.0, 95.0]	89 [77.5, 100.0]	84 [67.0, 100.5]	0.23	0.884	0.246
<b>Ever smokers</b>	<b>92</b>	<b>61</b>	<b>134</b>			
Pack-years	18 [8.2, 46.3]	16 [7.5, 37.5]	18 [6.5, 30.9]	0.783	0.258	0.423
FEV <sub>1pp</sub>	86.5 [62, 105.0]	86 [71.0, 98.0]	52.5 [37.0, 86.0]	0.985	<b>&lt;0.001</b>	<b>&lt;0.001</b>
FVC <sub>pp</sub>	105.5 [88.3, 118.0]	101.0 [92.0, 115.0]	98.0 [80.0, 113.0]	0.652	0.05	0.132
FEV <sub>1</sub> /FVC	0.69 [0.56, 0.77]	0.72 [0.59, 0.78]	0.47 [0.38, 0.67]	0.512	<b>&lt;0.001</b>	<b>&lt;0.001</b>
DLCO <sub>pp</sub> * (n = 158)	82 [68.5, 90.0]	83.0 [64.3, 93.5]	57 [45.0, 77.0]	0.926	<b>&lt;0.001</b>	<b>&lt;0.001</b>

**Table 1:** Baseline demographics of the study population, presented by genotype.

Data are presented as mean ( $\pm$  standard deviation) for parametric, median + [interquartile range] for non-parametric and number (%) for categorical. BMI = body mass index, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, FEV<sub>1</sub>/FVC = ratio of FEV<sub>1</sub> to FVC, DLCO = diffusion capacity for Carbon Monoxide, pp = percentage predicted.



Never-smokers			
All never-smokers (n=199)	FEV <sub>1pp</sub> effect	95% CI	P value
MZ vs SZ	-5.77%	-14.07 to 2.52	0.177
ZZ vs SZ	-13.17%	-21.28 to -5.06	<b>0.002</b>
Never-smokers > Age 50 (n=99)			
MZ vs SZ	-6.83%	-19.67 to 6.01	0.308
ZZ vs SZ	-22.21%	-34.94 to -9.49	<b>0.001</b>
Ever-smokers			
Ever-smokers (n=287)	FEV <sub>1pp</sub> effect	95% CI	P value
MZ vs SZ	+1.93%	-5.98 to 9.86	0.64
ZZ vs SZ	-21.89%	-30.50 to -14.47	<b>&lt;0.0001</b>
Ever-Smoker > Age 50 (n=149)			
MZ vs SZ	-6.78%	-17.22 to 3.62	0.21
ZZ vs SZ	-21.11%	-30.16 to -11.46	<b>0.0001</b>
Method: mixed model			
Adjusted for age, and lung-index status (and pack-years in smokers analyses)			
Never-smokers, n=64 MZ, 56 SZ, 79 ZZ			
Never-smokers > Age 50, n=31 MZ, 28 SZ, 40 ZZ			
Ever-smokers, n=92 MZ, 61 SZ, 134 ZZ			
Ever-Smoker > Age 50, n=54 MZ, 34 SZ, 63 ZZ			

**Table 2:** Estimated effect of the MZ and ZZ genotypes on FEV<sub>1pp</sub> relative to SZ.

Significant differences between SZs and ZZs are seen in all age and smoking stratifications. No significant difference is observed between MZ and SZ cohorts.

## Figure legends

**Figure 1:** Never-smokers age (year): FEV<sub>1pp</sub> correlation. No significant correlation with age is observed in the MZ (rho 0.01, p = 0.9) or SZ (R -0.09, 95% CI; -0.35 to 0.17, p = 0.49) cohorts. No significant difference in the effect of age on FEV<sub>1pp</sub> between SZ and MZ cohorts is seen (MZ +0.13%/year  $\pm$ 0.24 vs SZ, p = 0.59), while a significant difference between SZ and ZZ cohorts (-0.71%/year  $\pm$ 0.23, p = 0.002) is demonstrated.