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

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2020-215250).

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Received 9 May 2020
Revised 19 July 2020
Accepted 20 July 2020
Published Online First 11 September 2020

ABSTRACT

The ZZ genotype of alpha-1 antitrypsin deficiency (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-AATD or ZZ-AATD. We found no significant differences between MZ and SZ individuals regardless of never-smoking/ever-smoking ($p>0.05$ for all). ZZ-AATD was associated with lower $FEV1_{pp}$ than SZ, regardless of never-smoking/ever-smoking, as well as an increased OR of lung-index status and visually defined emphysema on CT ($p\leq0.002$ for all). In our registry cohort SZ-AATD is associated with a risk of lung disease comparable to MZ, not ZZ-AATD.

BACKGROUND

Alpha-1 antitrypsin deficiency (AATD) is a monogenic risk for COPD caused by mutations in the *SERPINA1* gene. Wild-type homozygous individuals (genotype MM) have a normal serum level of AAT (1–2 g/L),[1] 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.[2]

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

SZ-AATD results in AAT levels between MZ and ZZ-AATD, and a range which straddles the 'putative protective threshold' (PPT) of 0.57 g/L[1,7] historically considered a threshold for increased risk of COPD. Consequently, whether SZ-AATD represents a moderate or severe risk is debated[8] 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 (MM and MS individuals), but that smoking is associated with lower FEV_{1pp} than in control-smokers,[9] 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 MZ, SZ and ZZ-AATD on pulmonary function tests (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 supplementary file.

Inclusion was restricted to 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 ($_{pp}$) 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 on the basis of AAT levels above the PPT or below the PPT.

Clinical data

PFTs recorded in the registry were performed at the Department of Pulmonary Physiology, Beaumont Hospital, Dublin, as per American Thoracic Society/European Respiratory Society guidelines.[10 11] CT reports were reviewed for documented visually defined emphysema.

Statistical analysis

All analyses were performed in RStudio V.1.1.463 (www.cran.r-project.com). Full statistical methods are described in the online supplementary file. 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 and corrected for multiplicity using Bonferroni's method in pairwise analyses comparing baseline characteristics (table 1, online supplemental table 3). Linear mixed model analyses were used to perform multivariable analyses, with SZ genotype coded as the reference factor. Adjusted ORs 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 0.25 g/L for MZ:SZ:ZZ respectively, $p<0.001$ between all genotypes).

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To cite: Franciosi AN, Carroll TP, McElvaney NG. *Thorax* 2021;**76**:298–301.

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

	MZ	SZ	ZZ	P value		
n	**156**	**117**	**213**	**SZ vs MZ**	**MZ vs ZZ**	**SZ vs ZZ**
Age (Y)	51 (41.75 to 63.0)	51 (36.0 to 59.0)	49 (41.0 to 57.0)	0.134	0.027	0.563
Diagnosis age (Y)	49.5 (39.0 to 60.3)	50 (37.0 to 59.0)	48 (38.0 to 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	**0.001**
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 to 0.93)	0.59 (0.51 to 0.71)	0.25 (0.20 to 0.30)	**<0.001**	**<0.001**	**<0.001**
Height (cm)	166.8 (9.8)	169.3 (10.7)	170.7 (8.9)	0.049	**<0.001**	0.212
Weight (kg)	75.3 (63.0 to 88.1)	78 (65.0 to 91.5)	76 (65.7 to 86.1)	0.42	0.822	0.4
BMI (kg/m^2)	26 (23.0 to 30.4)	27 (23.0 to 30.5)	25.9 (22.6 to 29.0)	0.998	0.12	0.119
$FEV1_{pp}$	91.3 (70.0 to 109.0)	95 (83.0 to 107.0)	68 (41.0 to 99.0)	0.278	**<0.001**	**<0.001**
FVC_{pp}	106 (92.0 to 117.3)	104 (95.0 to 117.0)	101 (82.8 to 113.3)	0.976	0.018	0.022
FEV_1/FVC	0.72 (0.61 to 0.81)	0.76 (0.68 to 0.80)	0.56 (0.41 to 0.77)	0.085	**<0.001**	**<0.001**
$DLCO_{pp}$*(n=293)	84 (72.5 to 92.0)	86 (71.0 to 96.0)	68.5 (51.0 to 88.8)	0.417	**0.001**	**<0.001**
Never-smokers	**64**	**56**	**79**			
$FEV1_{pp}$	103 (81.8 to 110.3)	101.5 (91.0 to 111.0)	93 (68.5 to 103.5)	0.251	0.046	**0.002**
FVC_{pp}	107.5 (92.8 to 116.3)	108 (97.8 to 117.0)	106 (90.0 to 115.0)	0.662	0.291	0.148
FEV_1/FVC	0.77 (0.67 to 0.83)	0.77 (0.72 to 0.84)	0.73 (0.57 to 0.82)	0.274	0.28	0.023
$DLCO_{pp}$*(n=135)	84 (78.0 to 95.0)	89 (77.5 to 100.0)	84 (67.0 to 100.5)	0.23	0.884	0.246
Ever-smokers	**92**	**61**	**134**			
Pack-years	18 (8.2 to 46.3)	16 (7.5 to 37.5)	18 (6.5 to 30.9)	0.783	0.258	0.423
$FEV1_{pp}$	86.5 (62 to 105.0)	86 (71.0 to 98.0)	52.5 (37.0 to 86.0)	0.985	**<0.001**	**<0.001**
FVC_{pp}	105.5 (88.3 to 118.0)	101.0 (92.0 to 115.0)	98.0 (80.0 to 113.0)	0.652	0.05	0.132
FEV_1/FVC	0.69 (0.56 to 0.77)	0.72 (0.59 to 0.78)	0.47 (0.38 to 0.67)	0.512	**<0.001**	**<0.001**
$DLCO_{pp}$*(n=158)	82 (68.5 to 90.0)	83.0 (64.3 to 93.5)	57 (45.0 to 77.0)	0.926	**<0.001**	**<0.001**

Data are presented as mean (±SD) for parametric, median + (IQR) for non-parametric and number (%) for categorical. Bold values signify Bonferroni-adjusted significance threshold p<0.004.
AAT, alpha-1 antitrypsin; BMI, body mass index; DLCO, diffusion capacity for Carbon Monoxide; FEV_1/FVC, ratio of FEV_1 to FVC; pp, percentage predicted.

Preliminary analyses: age, smoking and lung-index status

The effect of age (figure 1), smoking (online supplementary figure 1) and lung-index status on FEV_{1pp} was examined in preliminary analyses. Full results are included in the online supplementary file. 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 ±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 ±0.19 vs SZ, p=0.039) (online supplementary figure 1). The OR of lung-index status was 2.11 for ZZs compared with 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) (online 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 with above-PPT (95% CI: 0.29 to 1.48, p=0.31) and no significant difference in FEV_{1pp} (+4.98% ±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 genotypes on lung function and emphysema relative to SZ

MZ versus SZ

No significant difference was found between MZ and SZ individuals FEV_{1pp}, 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_1/FVC ratio or $DLCO_{pp}$ was seen regardless of smoking or age stratification (p>0.05 for all, see online supplementary results and table 2).

ZZ versus SZ

A difference in FEV_{1pp} of −13.17% (95% CI: −21.28 to −5.06, p=0.002) was observed for never-smoking ZZs versus 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_{1pp} was −21.89% for ZZ versus SZ (95% CI: −30.50 to −14.47, p<0.0001). Significant differences were also seen in for SZ and ZZ in FEV_1/FVC ratio and $DLCO_{pp}$ (see online supplementary results and table 2).

CT data

448 CT reports were available (136 MZ, 102 SZ, 210 ZZ, online supplementary table 3). The OR of having emphysema reported on CT (adjusted for lung-index status, age and pack-years) was

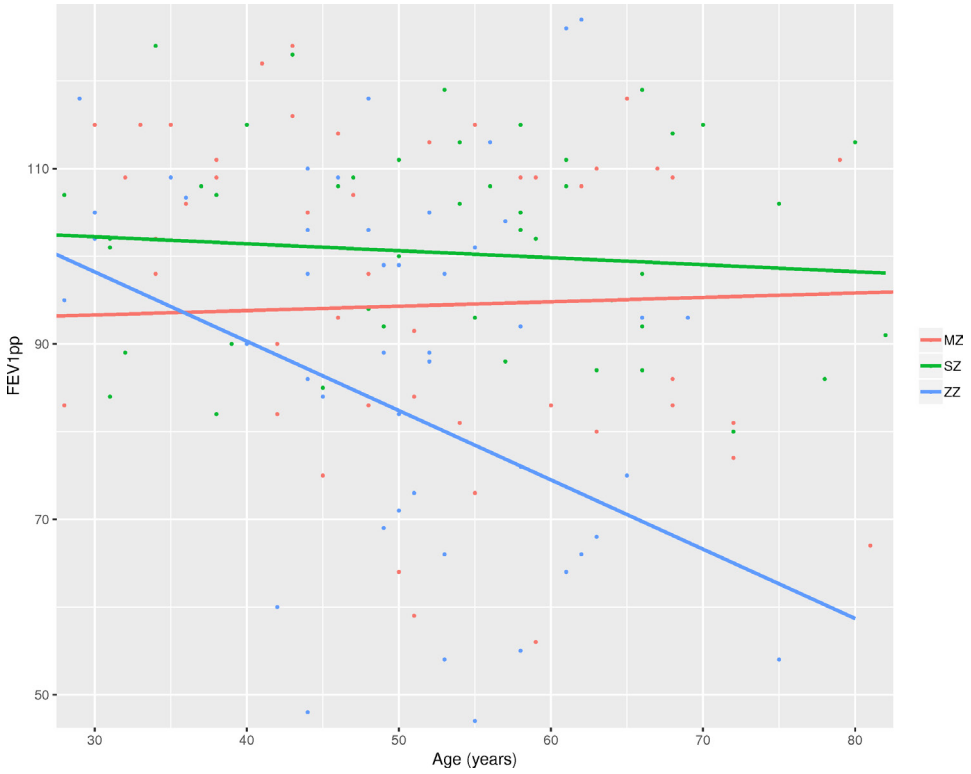

Figure 1 Never-smokers age (year): FEV_{1pp} correlation. No significant correlation with age is observed in the MZ (rho 0.01, p=0.9) or SZ (R −0.09, 95% CI: −0.35 to 0.17, p=0.49) cohorts. No significant difference in the effect of age on FEV_{1pp} between SZ and MZ cohorts is seen (MZ +0.13%/year ±0.24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

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_{1pp} 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 significantly worse FEV_{1pp} than SZ-AATD regardless of age or pack-years, as well as a higher OR of lung-index status and visually defined emphysema compared with SZ. Advancing age correlated with lower FEV1pp in never-smoker ZZ-AATD, as has been previously reported,[3] but not in SZs or MZs. Moreover, we found no visually defined emphysema among SZ or MZ never-smokers, compared with 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[9 12] 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_{1pp}, a

Table 2 Estimated effect of the MZ and ZZ genotypes on FEV_{1}pp relative to SZ

Never-smokers			
All never-smokers (n=199)	**FEV_{1pp} 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	**0.002**
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	**0.001**
Ever-smokers			
Ever-smokers (n=287)	**FEV_{1pp} 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	**<0.0001**
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	**0.0001**

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

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.

Acknowledgements The authors would like to sincerely thank all registry participants and Geraldine Kelly, Kitty O'Connor, Laura Fee, Margaret Molloy, Siobhán Lee, and Geraldine O'Brien current and former staff of Alpha-1 Foundation Ireland for invaluable help with registry recruitment and data collection.

Contributors ANF designed the study, performed statistical analyses and is the main author. TC consulted on study design, performed data curation and population building in the National Irish AATD Registry, coauthored the manuscript and is the study cosupervisor. NGM consulted on the study design, edited the manuscript and is the study cosupervisor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All participants of the National Irish AATD Registry provided written informed consent, which was approved by the Beaumont Hospital Research Ethics Committee (Ref. 05/03).

Provenance and peer review Not commissioned; externally peer reviewed.

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