COPD in individuals with the PiMZ alpha-1 antitrypsin genotype

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ABSTRACT Since the discovery of severe alpha-1 antitrypsin deficiency as a genetic risk factor for emphysema, there has been ongoing debate over whether individuals with intermediate deficiency with one protease inhibitor Z allele (PiMZ, or MZ) are at some risk for emphysema. This is important, because MZ individuals comprise 2–5% of the general population. In this review we summarise the evidence about the risks of the MZ population to develop emphysema or asthma. We discuss the different study designs that have tried to answer this question. The risk of emphysema is more pronounced in case–control than in population-based studies, perhaps due to inadequate power. Carefully designed family studies show an increased risk of emphysema in MZ smokers. This is supported by the rapid decline in lung function of MZ individuals when compared to the general population after massive environmental exposures. The risk of asthma in MZ subjects is less studied, and more literature is needed before firm conclusions can be made. Augmentation therapy in MZ individuals is not supported by any objective studies. MZ smokers are at increased risk for emphysema that is more pronounced when other environmental challenges are present.

Introduction

Alpha-1 antitrypsin (AAT) is a proteinase inhibitor produced by the SERPINA1 gene that protects the alveoli against the destructive effects of neutrophil elastase and other proteases [1]. In 1963, Laurell and Eriksson [2] described five cases with severe AAT deficiency diagnosed using agar gel electrophoresis, three of whom developed emphysema at a young age (ranging from 30 to 42 years). A unique nomenclature is used in AAT deficiency in which the proteins are named using the prefix "Pi" (protease inhibitor), and their variants are assigned letters based on the position of the serum protein bands on acid starch gel electrophoresis, with M being the normal variant and Z the most common pathogenic one [3]. Individuals in whom both alleles make Z type protein (PiZZ, often abbreviated to ZZ) have severe AAT deficiency, with sera levels reaching only 10–15% of those in whom both proteins are M (PiMM, or MM) [4]. After the SERPINA1 genes on chromosome 14 were discovered, the protein nomenclature was adopted for the individual alleles and, by inference, the population affected by these genes. ZZ individuals, and especially smokers, have a faster decline in forced expiratory volume in 1 s (FEV_1) and a shorter life expectancy than the normal population [5, 6]. The goal here is to review the evidence concerning the risk for chronic obstructive pulmonary disease (COPD) and asthma in individuals that carry one Z allele and one M allele (MZ), who have serum AAT levels intermediate between MM and ZZ individuals (figure 1).

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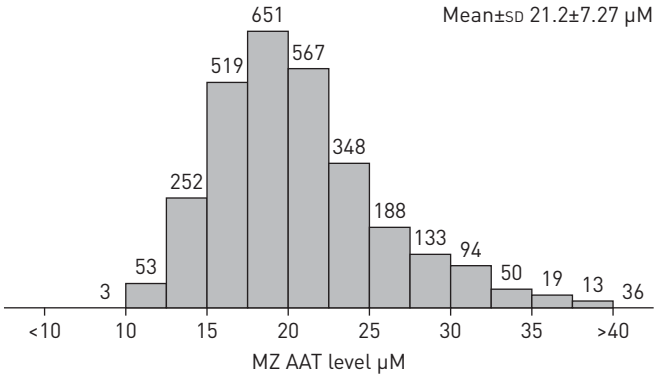

FIGURE 1 Distribution of alpha-1 antitrypsin (AAT) levels among an MZ cohort (n=2923). Bars and numbers represent subjects with the corresponding level of AAT depicted on the x-axis. Data obtained from the Alpha-1 Coded Testing Study at the Medical University of South Carolina (Charleston, SC, USA) [7].

Currently, AAT augmentation therapy is recommended for ZZ individuals based on evidence from some observational studies that show improved survival [8, 9] and randomised controlled trials that show slower progression of emphysema [10, 11].

As the debates about the efficacy of intravenous augmentation therapy for ZZ individuals come to a close, individuals with serum levels higher than the ZZ population but lower than MM subjects remain more controversial. Serum AAT levels in MZ individuals are about 60% of the levels in their MM counterparts [12]. Because MZ individuals constitute larger portions of the overall population than ZZ individuals, any testing programme that is focused on COPD cohorts will find many individuals with emphysema and MZ genotypes. The frequency of MZ individuals in the general population depends, in part, on population ethnicity, but ranges from 1.8% to 5% in most cohorts with significant European descent [13]. This is compared to an average PiZZ prevalence of 0.07–0.1% for Caucasian populations [13]. In a review of worldwide databases that have studied PIMZ prevalence, the MZ population was estimated to be at least 27 million [14]. In screening programmes, the percentage of MZ individuals varies significantly, even within the same country, from 3.6% to up to 22% (figure 2) [15, 16].

Prevalence of COPD in MZ individuals

Several studies have evaluated whether COPD is more prevalent in MZ individuals than in MM ones. Although this seems like a simple task, there are many biases that can interfere with study design. The main sources of bias include ascertainment bias and differential smoking prevalence or age as confounders. When coupled with a rare disease that does not have universal testing and the many ways that COPD has been diagnosed over the past 40 years, the data become more difficult to interpret.

Population-based cross-sectional studies

Many different study designs have been used to study the hypothesis that MZ individuals have an increased risk for COPD. The strongest data would emerge from population-based studies. Some

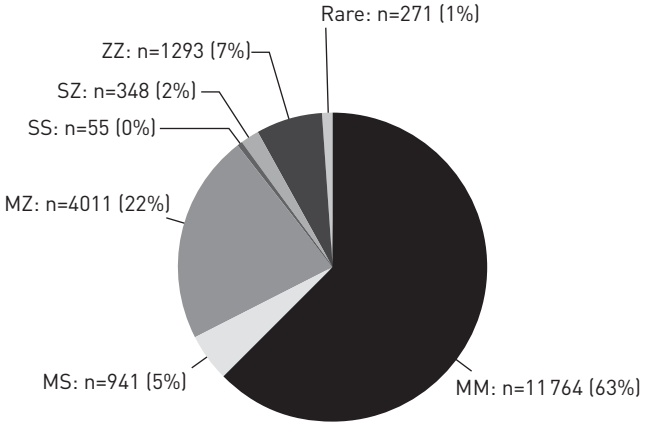

FIGURE 2 Frequency of the alpha-1 antitrypsin phenotypes in the targeted screening programme carried out by Greulich *et al.* [15] in Germany over the period 2003–2015. Reproduced and modified from [15] with permission.

population-based cross-sectional studies show significantly lower lung function and evidence of emphysema in MZ smokers than in MM smokers [17, 18]. Other similar studies do not show any difference in spirometry in MZ compared to MM populations [19, 20]. The extent to which these data are attributable to inadequate matching for COPD risk factors, such as age and smoking, remains under debate. One cross-sectional study from Tulsa, a mining centre in Bosnia, found statistically less smoking and working in mining among MZ individuals when compared to MM ones [21]. One explanation proposed was that self-awareness of respiratory symptoms leads MZ individuals in this cohort to avoid mining and smoking [21]. However, the majority of studies that have used population-based cohorts to match MZ to MM individuals failed to show any difference in spirometry [22–28]. Some of these studies included subjects aged <50 years in their statistical analyses [22, 25, 26, 28]. Because some ZZ individuals may not experience decline in lung function until the age of 50 years [29], it seems reasonable not to draw strong conclusions from spirometry-based studies that include young MZ individuals. Hersh *et al.* [30] conducted a meta-analysis of 16 studies to estimate the net risk of COPD in MZ as compared to MM individuals. Five studies were population-based in design and showed an odds ratio of 1.50 (95% CI 0.97–2.31) that MZ individuals had increased risk for COPD. In contrast, 11 case–control studies had a higher odds ratio of 2.97 (95% CI 2.08–4.26) that MZ individuals did have an excess risk for COPD [30].

Because FEV_1 and FEV_1/forced vital capacity (FVC) are not sensitive measurements for individuals destined to advance to defined airway obstruction, some investigators evaluated other lung function parameters. Lam *et al.* [31] examined a group of 22 MZ individuals aged ⩾30 years and found a statistically significant decrease in peak expiratory flows and an increase in pulmonary resistance in MZ subjects who smoked when compared to nonsmokers. Because smoking is a major confounder of COPD risk, some studies compared MZ nonsmokers to MM nonsmokers and found lower peak expiratory flows in the former [32, 33]. However, other studies did not show any decrease in mid-expiratory flow rates among MZ subjects [22, 34, 35]. This was also true when MZ were carefully matched to MM, and even when smokers from each group were compared [22, 35]. Other studies showed increased closing capacity and residual volume as well as small loss in elastic recoil in MZ individuals (including nonsmokers) compared to MM individuals [33, 36].

In some of these cross-sectional studies there was no difference in the reported respiratory symptoms suggestive of obstructive lung disease [18, 19, 22, 25]. This can be explained by the fact that it takes a significant drop in lung function before respiratory symptoms ensue. In addition, some studies on the prevalence of respiratory symptoms in MZ individuals included a significant number of subjects aged <40 years among their samples [19, 22, 25].

Case–control studies

Many case–control studies have shown a higher prevalence of MZ subjects among patients with COPD compared to normal controls without COPD [37–44]. A significant limitation in some of these studies is the lack of adjustment for important confounders such as age and smoking [37, 39, 41–44]. Some studies matched for age and smoking and still found an increased prevalence of MZ among COPD cases, identified by spirometry and/or chest radiography [38, 40, 45]. In a cohort of smokers, Sandford *et al.* [45] found more MZ individuals in the group with COPD, identified based on FEV_1/FVC <0.7, than the smoker control group that did not have COPD. The mean age of the two groups ranged from 59 to 64 years [45]. In the meta-analysis by Hersh *et al.* [30], the studies that adjusted for smoking had a less pronounced odds ratio of 1.61 (95% CI 0.92–2.81).

The higher odds ratio in case–control studies when compared to population cross-sectional studies is not uncommon in rare genetic diseases. One critical issue is to find a large enough population-based sample to include an adequate number of individuals with the genetic and environmental risks for clinical disease. If no effort is made to ascertain that cases and controls are from the same at-risk population, genetic differences may exist and there may be genes other than MZ responsible for the obstructive lung disease in the COPD arms in case–control studies.

Subsequent to the meta-analysis of Hersh *et al.* [30], a case–control study including 1669 subjects from Norway was published by Sørheim *et al.* [46]. Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric stage II COPD subjects (n=834; 790 MM and 44 MZ) and controls with normal spirometry (n=835; 801 MM and 34 MZ) were Caucasians aged ⩾40 years with current or ex-smoking of ⩾2.5 pack-years. Standardised high-resolution computed tomography (CT) scans of the chest were obtained in 50% of the subjects. Quantitative assessment of low attenuation areas showed more disease in MZ individuals, a mean 3.5% lower FEV_1/FVC, but no difference in the age, sex, height and pack-years of smoking adjusted COPD risk by genotype [46].

In summary, the data from case–control studies find more emphysema and lower lung function in MZ than in MM populations when appropriately adjusted for age and smoking covariates. The strength of

these studies is moderate, and better when emphysema is quantified independently of spirometric variables. Because CT emphysema is correlated to mortality in AAT deficiency while lung function is not [47], these studies are sufficient to demonstrate an increased risk for COPD in MZ subjects.

Family-based studies

Family-based studies attempt to compare siblings who have different genes at the SERPINA1 locus to determine if the COPD risk is different. The advantage to these studies is that childhood environmental exposures and some other genetic variations are shared in these populations. In a study conducted by Kueppers *et al.* [48], 114 siblings of COPD patients were compared to 114 siblings of healthy controls and found no difference in MZ prevalence. Of note, the percentage of MZ in controls was higher than is usually reported in such populations, which raises a concern about selection bias. In fact, the authors found a higher percentage of MZ subjects in siblings of index cases when compared to normal blood donors from the same institution (7.9% *versus* 2.4%; p<0.02) [48]. In some family studies, MZ subjects had abnormal ventilation–perfusion scans in the lower lobes, even among MZ children [49, 50]. Sørheim *et al.* [46] conducted a multicentre family-based study in Europe and North America and included 2707 subjects. COPD probands had a smoking history of ⩾5 pack-years and had at least one sibling who had smoked for ⩾5 pack-years. They were also required to have a FEV_1 of <60% predicted and a FEV_1/vital capacity (VC) ratio of <90% predicted. Most of the included relatives were siblings of their respective probands. Chest CT, spirometry and respiratory questionnaires were obtained in all subjects [46, 51]. The COPD proband group had 984 subjects (941 MM and 43 MZ) and the relatives group included 1723 subjects (1651 MM and 72 MZ). After adjusting for covariates, MZ individuals had more emphysema on CT scan and a 3.9% lower FEV_1/VC ratio than MM individuals [46]. In another family study Molloy *et al.* [52] demonstrated that MZ subjects are at increased risk for COPD only if they smoke. This study adjusted for sex, age and years of smoking. Most importantly, in this study, the MZ COPD probands were excluded from analysis. In family-based genetic studies, selection bias can influence results. Because this study included a homogeneously ethnic group, adjusted for important covariates, and avoided sampling bias, it provides strong and clear evidence that ever-smoker MZ individuals are at higher risk for COPD than MM counterparts [52].

Complications of our understanding by common biases in genetic studies

In addition to the usual biases encountered in general epidemiological studies, distinctive biases exist when studying genetic epidemiology. For instance, genotyping errors have been reported to range from 0.5% to 30% in some studies [53]. Genotyping errors have been reported during the diagnosis of AAT deficiency [54, 55].

Because SERPINA1 is known to be associated with COPD, this gene has been purposefully removed from some genetic association analyses by excluding known AAT-deficient patients [56]. However, when this was not done, the MZ genotype was seen to be associated with COPD and COPD progression in some open-ended genome-wide association studies when SERPINA1 was included as one of the loci studied [57]. In summary, case–control studies, family studies and genome-wide association studies all suggest that MZ individuals are more susceptible to COPD than those with MM genotypes, particularly if cigarette smoking is present during ageing.

Progression of obstructive lung disease in MZ individuals

Whether lung function and respiratory symptoms worsen more over time in MZ than in MM individuals has been studied in a few cohorts (table 1). Some of these longitudinal studies are limited by short interval follow-up (2–3 years), and this may explain their negative results [58, 59]. In a 6-year longitudinal study, Madison *et al.* [60] found 20–40 mL more yearly FEV_1 decline in MZ than in MM individuals, regardless of smoking status. In a prospective cohort that followed iron-ore miners for 5 years, MZ individuals had more decline in FEV_1/FVC than MM ones, but there was no difference in respiratory symptoms [61]. In another 10-year longitudinal study among a cohort of nonsmokers matched for age, height and body weight, pulmonary elasticity was measured and was found to decrease significantly over time in the MZ group when compared to the MM group [62]. In smokers there was a significant difference in FEV_1, with annual decline of 75 mL in MZ *versus* 53 mL in MM subjects [63]. In an 11-year prospective cohort, the annual decline in forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) among persistent smokers was 108.2 $mL \cdot s^{-1} \cdot year^{-1}$ *versus* 66.8 $mL \cdot s^{-1} \cdot year^{-1}$ in MZ and MM subjects, respectively [64].

Silva *et al.* [58] followed a randomly selected population from Arizona (USA) for an average of 15 years and found no difference in the annual decline of lung function in 58 MZ and 1802 MM individuals in this potentially underpowered study [65]. The longest longitudinal study was the population-based prospective cohort study conducted by Dahl *et al.* [66]. They randomly selected 9187 adults from the Danish general population and followed them over 21 years. One of the strengths of the study is that the frequency of

TABLE 1 Studies that compare the decline of lung function over time between MM and MZ individuals

First author [ref.]	Year	Average follow-up duration years	Population	Adjustment for confounders	Faster decline in lung function in MZ compared to MM individuals?
de Hamel [59]	1981	3	499 MM compared to 32 MZ individuals from New Zealand	Matched a subgroup of population to adjust for confounders	No
Madison [60]	1981	6	82 MM compared to 42 MZ individuals	Yes	Only in MZ men
Eriksson [63]	1985	6	31 MM compared to 32 MZ individuals	Yes	Only in MZ smokers
Pierre [61]	1988	5	757 MM compared to 21 MZ iron-ore miners	No difference in age, length of employment, or smoking	Yes
Tarján [62]	1994	10	28 nonsmoking matched MM and MZ pairs	Yes	Yes
Sandford [57]	2001	5	283 subjects with rapid decline compared to 308 subjects with no decline in lung function	Yes	More MZ individuals were found in the rapid decline group
Dahl [66]	2002	21	9187 adults randomly selected from the Danish general population: 7037 MM compared to 451 MZ	Yes	Yes
Silva [58]	2003	15	1802 MM compared to 58 MZ individuals selected randomly from an Arizona population	Yes	No
Thun [64]	2012	11	4207 MM compared to 112 MZ individuals	Yes	Only in $FEF_{25-75\%}$ among persistent smokers

$FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity.

alleles did not differ significantly from that predicted by Hardy–Weinberg equilibrium [66]. The MZ genotype was found in 451 participants. After adjusting for age, sex, tobacco consumption and FEV_1 at study entry, MZ individuals had 50% more incidence of COPD, as well as 50% more chance of hospitalisation and death from COPD, when compared to MM subjects. Although there was a statistical difference in the annual decline of FEV_1 in MZ compared to MM individuals, the mean difference was only 4 mL, with mean±SD annual decline of 25±1.9 mL in MZ *versus* 21±0.5 mL in the MM population. Interestingly, when grouped based on smoking status, the decline in FEV_1 was similar among MZ and MM smokers. When nonsmokers were compared, the difference in annual decline in FEV_1 was worse by 7 mL every year in MZ (20±2.9 mL) compared to MM individuals (13±0.7 mL) [66]. Sandford *et al.* [57] found a threefold increased frequency of MZ individuals among smokers with rapid decline in FEV_1 (-154 ± 3 mL·year^{-1}) *versus* smokers that did not have rapid decline ($+15\pm2$ mL·year^{-1}). The association of MZ with rapid decline in lung function among smokers was more pronounced, with an odds ratio of 9.7, among currently smoking MZ individuals who had a family history of COPD [57].

Effects of environmental and occupational exposures

Environmental and occupational exposures are linked to the development of COPD in the general population [67–70]. In homozygous ZZ individuals, exposure to dust, gas and fumes leads to a greater decline in lung function, even in nonsmoking ZZ subjects, particularly after the age of 50 years [71, 72]. In children exposed to passive smoking, MZ individuals had a greater decline in lung function than MM children [73, 74]. To account for environmental exposures, some population-based cross-sectional studies compared MZ to MM groups among industry workers [18, 61, 75]. Some of the studies that found an increased frequency of MZ genotypes in industry workers with COPD lacked matching for age and smoking [61, 76]. Horne *et al.* [18] compared MZ and MM grain workers and matched for age, years of employment and smoking. FEV_1 and FEV_1/FVC were worse in the MZ group, but there was no difference in respiratory symptoms [18]. In another group of saw mill and grain workers there was no difference in respiratory symptoms or spirometry between MM and MZ subjects. However, their mean age was <40 years and there was no adjustment for smoking [75]. A group of MZ and MM individuals who worked in the New York City Fire Department rescue workforce during the World Trade Center collapse on September 11, 2001, were followed for 4 years. The average age was 46 years and 40 years in MZ and MM individuals, respectively. After September 11, the MZ subjects exhibited a 110 mL annual decline in

FEV1, compared to 25–50 mL in their MM counterparts [77]. Mehta *et al.* [78] also found that exposure to dust, vapour, gas and fumes was associated with a greater decline in lung function among 97 MZ when compared to 3546 MM individuals with the same level of exposure. In the same study, MZ subjects exposed to small particulate matter (⩽10 μm) also trended towards more decline in lung function compared to their MM counterparts with the same level of exposure [78]. Cumulatively, the data suggest that MZ individuals may lose lung function faster than the MM population when exposed to air and industrial pollution.

MZ level heterogeneity and impact of the acute phase response

During the acute phase response, AAT serum concentrations increase above the normal range [79]. In states of infection or inflammation, neutrophils are recruited into the lungs and the plasma concentration of AAT increases [80, 81]. The imbalance between neutrophil elastase and AAT is implicated in the pathogenesis of emphysema as well as other pulmonary diseases [82]. Consequently, MZ individuals may be more vulnerable to lung damage during acute inflammatory states if they are not able to raise their AAT sera levels high enough to cope with the surge of neutrophil elastase (figure 3). In asymptomatic nonsmoker MZ individuals, sputum showed levels of neutrophils and interleukin-8 similar to patients with COPD and higher than healthy controls [83]. Thun *et al.* [64] found that MZ individuals had more COPD, defined as FEV1/FVC <0.7, than MM subjects with similar levels of C-reactive protein. AAT levels are very variable in MZ individuals, so serial AAT testing is not clinically recommended, because the impact of the acute phase response on AAT level is still an imprecise science. Hence, in this population, assessment of COPD risk is a complex process influenced by interactions between different factors (figure 4).

Risk of asthma in the MZ population

The risk of asthma in the MZ population has not been studied as extensively as the risk for COPD. Neutrophil elastase plays an important role in the development of airway inflammation and hyperresponsiveness, which are key factors in the pathophysiology of asthma [84]. Compared to healthy controls, patients with bronchial asthma have a higher activity of neutrophil elastase [85, 86]. In asthmatics, Vignola *et al.* [87] showed that neutrophil elastase activity is negatively correlated with FEV1. Therefore, clinical epidemiology is needed to support these biochemical observations.

In the National Heart, Lung and Blood Institute Registry of AAT Deficiency, a physician diagnosis of asthma was reported in 35% of ZZ individuals. Wheezing without associated upper respiratory tract infections was reported in 20% of ZZ individuals who had FEV1 ⩾80% and in 70% of those with FEV1

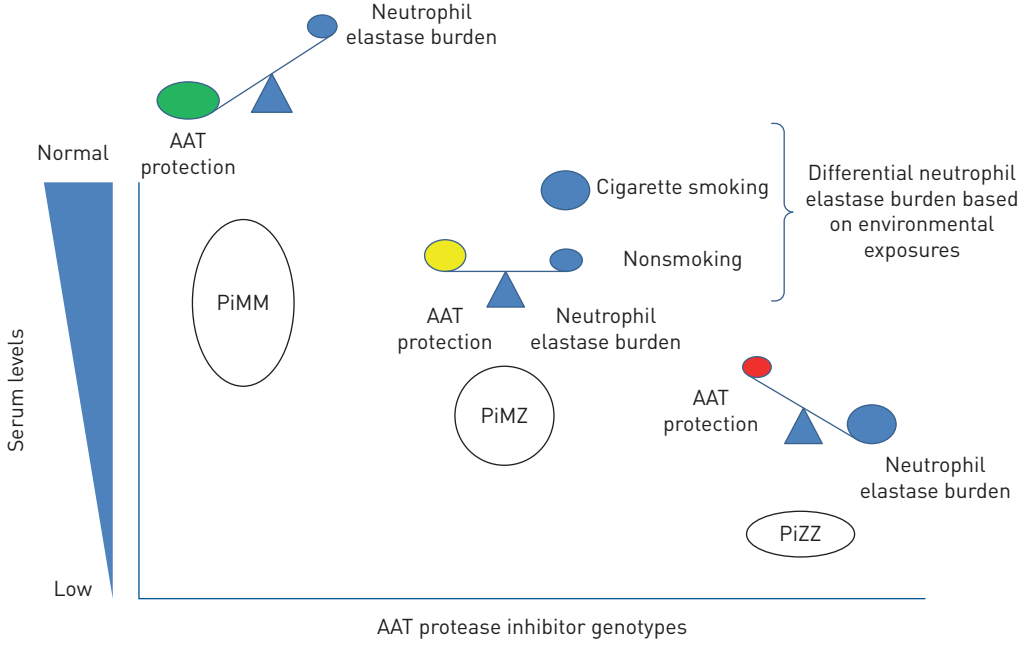

FIGURE 3 Conceptual model of the balance between alpha-1 antitrypsin (AAT) and neutrophil elastase, by genotype.

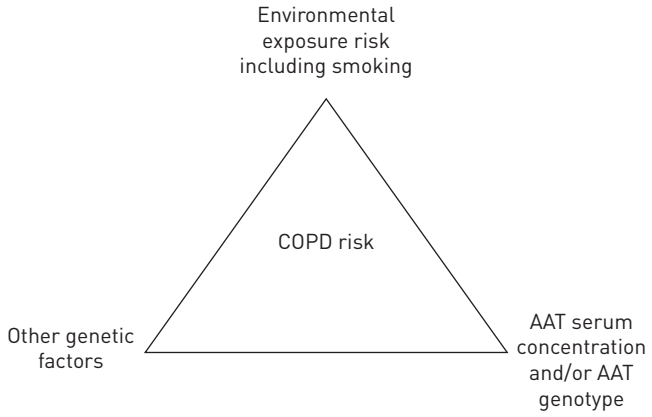

FIGURE 4 Conceptual framework of the interaction between environmental exposure including smoking, alpha-1 antitrypsin (AAT) level and/or AAT genotype, other genetic factors and chronic obstructive pulmonary disease (COPD) risk. Note that there are no studies that show that genotype is more important than blood concentration of AAT for COPD risk assessment.

<80% [88]. When compared to non-AAT-deficient COPD patients, ZZ individuals have more reversible airway obstruction, wheezing and atopy [89].

Although the AAT/neutrophil elastase imbalance is less in MZ than in ZZ individuals, MZ individuals have more asthma, nasal polyposis, family history of atopy, and peripheral eosinophilia than the general population [90]. In another study, a physician diagnosis of asthma was reported in up to one-third of MZ subjects [91]. By contrast, a study by Wencker *et al.* [16] found only 2.9% MZ individuals among asthmatics referred for treatment of respiratory diseases in seven physicians' offices. In a subsequent study, only one MZ individual was found in a cohort of 122 patients with severe asthma [92]. In our opinion, although some evidence suggests an increased asthma risk, more studies are needed, particularly in paediatric populations.

Should we ever, sometimes or never treat the MZ population?

Historically, AAT serum levels of 11 µM were considered protective against emphysema [4, 9]. This was based on a variety of assumptions that included suggestions that MZ individuals are not at increased risk of emphysema [4, 93]. Clinical data regarding whether an individual COPD patient has emphysema from environmental factors such as cigarette smoking or from the low AAT level associated with the MZ carrier state, or both, are impossible to assemble. Therefore, the majority of the pulmonary community has awaited trials showing improved outcome with augmentation in an MZ study before prescribing this expensive therapy. A minority opinion suggests that emphysema that is out of proportion to age and smoking is sufficient reason to begin augmentation.

Some studies are in progress that may have an impact on these recommendations. So far, studies of AAT augmentation therapy in ZZ individuals have used a weekly, intravenous (*i.v.*) 60 $mg \cdot kg^{-1}$ dose to maintain serum levels above an 11 µM threshold [8, 94–97]. Gadek *et al.* [93] studied the bronchoalveolar lavage (BAL) AAT levels in five ZZ individuals, which improved from 15% predicted pre-infusion to 60–70% predicted as compared to BAL AAT levels in MM individuals after 2–4 weeks of infusion therapy.

Because epithelial lining fluid anti-elastase capacity is not returned to normal with this dose, ongoing studies are evaluating the effect of 120 $mg \cdot kg^{-1}$ weekly doses to establish whether CT density decline over 3 years is less on the high dose compared to the usual dose (60 $mg \cdot kg^{-1}$) of AAT. The SPARTA (Study of ProlAstin-c Randomized Therapy with Alpha-1) augmentation trial is currently comparing the 120 $mg \cdot kg^{-1}$ *i.v.* dose that produces a mean trough serum level of 27.7 µM to 60 $mg \cdot kg^{-1}$ *i.v.* doses weekly that produce trough levels of 17.3 µM [98, 99]. Because the AAT level in serum and in BAL of MZ individuals averages at 20 µM, a positive trial will prompt a re-evaluation of the evidence by which most MZ subjects remain untreated. Designing such studies should take into consideration experience from the last 40 years of augmentation studies in ZZ subjects, particularly regarding study power [100]. Although it will be easier to recruit MZ individuals than ZZ participants because they are less rare, the rate of decline in lung function or CT densitometry may be slower. Therefore, longer follow-up periods or larger numbers of participants would be needed. Such studies should also be powered to detect differences in exacerbation rate and measure other important clinical outcomes that target the patient experience.

Conclusions

Data suggest that MZ subjects have an increased risk of emphysema that is clinically manifest most commonly in those who have smoked cigarettes. Although the risk of emphysema is higher, there are no data that support augmentation therapy in MZ individuals [101]. Much more research needs to be done to better understand the pulmonary disease burden within the MZ community, a group of individuals that make up 2–5% of world populations with significant European descent.

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