



α_1 -Antitrypsin deficiency: count me in please!

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Knowing the number of AATD patients is a first step to tackling the AATD problem
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Respiratory medicine is facing formidable challenges in the 21st century. Indeed, most respiratory medical research is becoming interconnected, translational and transnational, all embedded within so-called “planetary health” [1]. However, renewing estimates and trends from classical, descriptive epidemiology, including how many patients of a given condition are around, and how many are expected in the future, remain ongoing chores. Continuous updates from the World Health Organization’s Global Burden of Disease initiative reiterate that respiratory diseases rank high in morbidity and mortality, even with widespread underdiagnosis [2]. Perhaps there is no better example of a respiratory condition that requires further epidemiological and population refreshing than severe α_1 -antitrypsin deficiency (AATD). Severe AATD is considered a rare disease, which is defined as any disease that affects less than 1 in 2000 individuals [3]. The prevalence of AATD in the general population in Europe is approximately 1 in 2000–5000.

Despite the recognised potential for life-threatening disease at a young age, this condition continues to be largely underdiagnosed; on a worldwide scale it is estimated that only 0.35% of expected AATD cases are detected [3]. Moreover, the majority of individuals continue to experience a substantial delay of several years before diagnosis [4]. The number of cases of AATD and chronic obstructive pulmonary disease (COPD) worldwide has been the subject of intense debate in respiratory medicine. Based on an analysis of published genetic epidemiological surveys, DE SERRES *et al.* [5] concluded back in 2002 that “... it has been estimated that 3.4 million individuals in the world have an AATD genotype that leads to a deficiency of this protein”. From a distance, this estimate appears to be quite accurate, nowadays as high as 3.3 million, by applying the estimate that AATD accounts for 1% of all 332 million COPD cases worldwide from the Global Burden of Disease study [2].

More recently, genetic epidemiological studies on the prevalence of AATD in 97 countries [6] identified Latvia as having the highest prevalence of deficiency alleles: PI*S 31.3 per 1000 population and PI*Z 45.1 per 1000 population. Although considerable variation was apparent between geographic regions and between countries in the same continent, the overall result was the same: AATD can be identified in any region and in any country, if it is searched for actively. However, data on the current prevalence and estimated numbers of AATD patients are missing in many countries, and we need to identify these patients and make sure that they do not smoke, or help them with smoking cessation first, before considering other management decisions.

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In this issue of the *European Respiratory Journal*, GREULICH *et al.* [7] explore the prevalence of AATD in Germany and investigate associated comorbidities using a healthcare database. Despite knowledge of the disease for over 50 years, it is surprising that there is dearth of such information on AATD and hence the study is very welcome in this regard. GREULICH *et al.* [7] estimate there are 19162 AATD cases in Germany. As expected, AATD prevalence increased with age and was higher in men than women, and compared with age- and sex-matched cohorts of patients with COPD, emphysema or asthma, AATD patients had more comorbidities, and a higher individual and societal burden. Furthermore, compared with usual COPD, AATD individuals required significantly longer hospital admission for exacerbations, and had more frequent exacerbations and consultations. This may be explained by the excess pulmonary inflammation described in AATD [8]. The pulmonary disease in AATD is recognised to occur at a young age, but can be variable in terms of phenotype and progression. Despite these complexities, many AATD patients are managed in the same way as usual COPD. Furthermore, there is inequity of access across and within countries within Europe to specialists in AATD, including variable access to optimal management approaches such as augmentation therapy for those who may benefit. The study adds further weight to the case that AATD should be managed differently to usual COPD from the pulmonary perspective. It is already recognised that AATD assessment should also encompass hepatology, transplantation, occasionally dermatology, genetic and paediatric advice, but these findings also indicate that there are possibly other organ systems to consider. Moreover, like all good epidemiological studies, it stimulates us to consider a wide range of issues. Can we better understand the impact of augmentation therapy using additional tools? Does the *in vitro* anti-inflammatory and immunomodulatory role of antitrypsin have relevance to the association with other organ disease [9]? Are we serving AATD patients in the optimal way, both in terms of healthcare systems and personalising their consultation, in concept perhaps more akin to cystic fibrosis than COPD? More work is needed.

Reassuringly, the well-known association of liver disease with AATD was confirmed in this study by GREULICH *et al.* [7], giving support to the methodology utilised. The novelty of this “real-world” AATD analysis, recently also applied to obstructive sleep apnoea [10, 11], can provide us with hints of the population distribution and trends of respiratory conditions as seen in primary care and chest clinics. Despite the continuing controversy over population spirometry for COPD screening [12], recent case-finding strategies in COPD proved successful [13]. We have to keep emphasising the international consensus recommendation that all COPD patients should be tested for AATD [14, 15] and reinforce registries for rare diseases, such as the European AlphaOne registry and others to be created [16].

The data highlight the importance of viewing AATD differently from usual COPD, both in terms of severity and potential comorbidities, and hence support patient’s need for appropriately designed pathways of care. These findings should stimulate further case-finding efforts to unravel AATD in Germany, and be replicated and expanded in other countries in order to deepen our understanding of this complex, poorly understood and often neglected disease. Knowing the size and scope of the problem is a first step in the right direction to tackle the AATD “planetary” problem. Please, one at a time, keep counting (figure 1) in AATD!

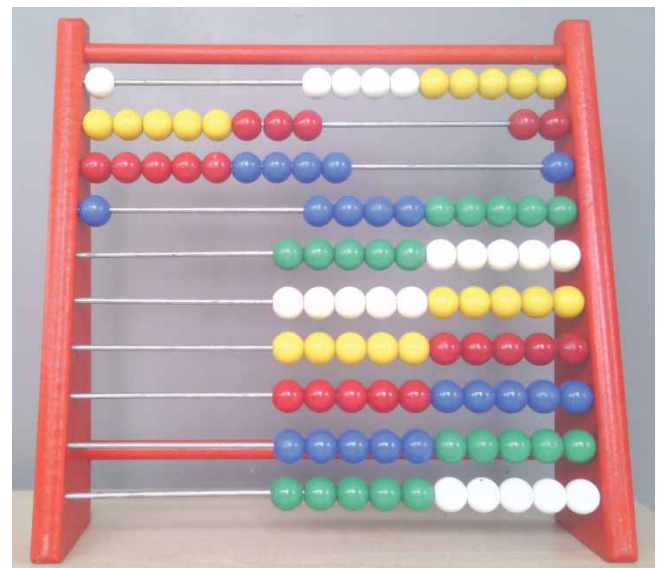


FIGURE 1 Abacus to count your α_1 -antitrypsin deficiency patients. Image by Mattias.Campe [Own work] [CC BY-SA 4.0 (<http://creativecommons.org/licenses/by-sa/4.0/>)], via Wikimedia Commons.

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