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Soriano, JB

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# Trends of testing for and diagnosis of alpha-1 antitrypsin deficiency in the UK: more testing is needed

Joan B. Soriano <sup>1,2</sup>, Sarah J. Lucas <sup>3</sup>, Rupert Jones <sup>4</sup>, Marc Miravittles <sup>5</sup>, Victoria Carter <sup>6</sup>, Iain Small <sup>7</sup>, David Price <sup>8</sup>, and Ravi Mahadeva <sup>9</sup>, and on behalf of the Respiratory Effectiveness Group'

<sup>1</sup> Instituto de Investigación Hospital Universitario de la Princesa (IISP) Universidad Autónoma de Madrid, Madrid, Spain

<sup>2</sup> Scientific and Methodological Consultant of SEPAR [www.separ.es](http://www.separ.es)

<sup>3</sup> Respiratory Effectiveness Group, UK

<sup>4</sup> Plymouth University Peninsula School of Medicine & Dentistry, UK

<sup>5</sup> Pneumology Department, Hospital Universitari Vall d'Hebron. CIBER de Enfermedades Respiratorias (CIBERES) Barcelona, Spain

<sup>6</sup> Optimum Patient Care Ltd, Cambridge, UK

<sup>7</sup> Peterhead Medical Practice, Peterhead, UK

<sup>8</sup> Observational and Pragmatic Research Institute (OPRI) Pte, Singapore, Singapore

<sup>9</sup> Department of Respiratory Medicine, Cambridge NIHR BRC, Addenbrookes Hospital, Cambridge, UK

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**FUNDING:** Optimum Patient Care Research Database and Respiratory Effectiveness Group.

**TWITTER FEED:** AATD remains markedly underdiagnosed in COPD patients, and case-finding strategies for both conditions should be implemented. **TOTAL: 111 characters**

## ABSTRACT

Alpha-1-antitrypsin deficiency (AATD) significantly increases the risk of developing COPD, and testing of all COPD patients for AATD is recommended by the WHO, ERS and GOLD. We aimed to determine trends for testing and diagnosing of AATD from 1990 to 2014.

This study analyzed all patients diagnosed with COPD from about 550 UK OPCRd general practices, including a subgroup of those diagnosed before the age of 60 years.

We identified 107,024 COPD individuals, of whom 29,596 (27.6%) were diagnosed before 60 years of age. Of them, only 2.2% (95% CI 2.09% - 2.43%;) had any record of being tested for AATD. Of those tested 23.7% (95% CI 20.5% - 27.1%) were diagnosed with AATD. Between 1994 and 2013 the incidence of AATD diagnosis generally increased. A diagnosis of AATD was associated with being male, being an ex-smoker, more severe COPD with a lower %pred FEV<sub>1</sub>, and higher GOLD 2017 stages (all p<0.05).

Despite an increase in the frequency of AATD testing since 1990, only 2.2% of patients diagnosed with COPD before the age of 60 years were tested. AATD prevalence was 23.7% in those tested. Thus, it appears that AATD remains markedly underdiagnosed in COPD patients.

**Keywords:** alpha1-antitrypsin deficiency; epidemiology; geographical variability; OPCRd; prevalence; UK; underdiagnosis

## INTRODUCTION

Alpha<sub>1</sub>-antitrypsin deficiency (AATD) is a genetic condition characterized by low serum levels of AAT (also known as alpha-1 proteinase inhibitor, Pi), the main protease inhibitor in human serum. The clinical expression manifests as pulmonary emphysema, liver cirrhosis, skin panniculitis, or as vasculitis. Indeed, although AAT is produced in and secreted by the liver, it has an important physiological role in the lungs, where it protects the alveoli from damage.<sup>1</sup> AATD clinical manifestations are most commonly due to homozygous PiZZ.<sup>2,3,4</sup>

AATD is considered a rare disease, which is defined as any disease that affects fewer than 1 in 2,000 individuals.<sup>5</sup> It is estimated that within Europe, one in every 2,000–5,000 newborns has homozygous PiZZ AATD.<sup>6</sup> Although the WHO recommends that all patients with COPD must be tested for AAT,<sup>7</sup> AATD is an underdiagnosed condition. Population-based screening and case-finding (also known as targeted detection) can help to identify a rare condition within a specific population of individuals with a higher probability of having the condition (i.e., COPD in the case of AATD).<sup>8</sup> Diagnosis is made by the demonstration of reduced blood levels of AAT. Reduced or absent alpha-1 globulin peak on serum protein electrophoresis can be an indication to determine the levels of blood AAT, as AATD comprises most of alpha-1 globulins. The genotyping of the different deficient alleles (Z, S or rare alleles) is needed to better categorize patients and their clinical characteristics.<sup>9</sup>

Previous estimates of the prevalence of AATD individuals in the UK come from old registries and extrapolations of small case series, likely outdated.<sup>10</sup> However, a UK AATD registry was initiated in 1997 and by 2014 included 1,196 patients with the deficiency.<sup>11</sup>

More evidence on the population distribution and determinants of AATD is needed, as there are newly available recommendations for screening,<sup>12</sup> while NICE is currently reconsidering and reviewing AATD treatment and management recommendations,<sup>13</sup> in light of new evidence of treatment efficacy.<sup>14</sup> Therefore, we aimed to determine recent trends in testing and diagnosing AATD, and the incidence and prevalence of AATD in the UK using available data sources.

## METHODS

### *Study Design*

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This was an epidemiological study in UK primary care with the objective to identify existing practices in AATD diagnosis. Particularly, we define trends in AATD testing and diagnosis between 1994 and 2013, globally and by sex and age group. Secondly, since most physicians think of AATD in COPD developing at a younger age, we analyze the rate of testing in patients diagnosed with COPD under the age of 60; and finally we describe and compare the clinical characteristics of patients diagnosed with COPD under 60 with AATD with those of non-AATD related COPD of the same age group.

### *The Database Source*

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Data were obtained from the Optimum Patient Care Research Database (OPCRD),<sup>15</sup> which is a primary care research database developed by Optimum Patient Care, a social enterprise providing respiratory review services. It contains anonymous, longitudinal electronic medical record data extracted from over 650 UK practices, and over 4.5 million patient records. At the time our database was generated it contained data from 747,628 asthma and 107,024 COPD patients.<sup>16</sup> A preliminary search by Read code C3762 identified approximately 600 AATD patients. OPCRD is approved by the NHS Health Research Authority for clinical research use and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research.

The study protocol was approved by the Anonymised Data & Protocol Transparency (ADEPT) committee (No. ADEPT1617). The study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, No. EUPAS21791). We have followed and endorsed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance for reporting observational evidence.<sup>17</sup>

Patients were diagnosed with COPD codes available in the UK Quality Outcomes Framework (QOF).<sup>18</sup> QOF established incentives for improved data recording at GP practices from 1 April 2004. It includes the annual reward and incentive programme detailing GP practice achievement results. The indicators for the QOF change annually, with new measures and indicators being retired regularly. From these a cohort population was identified with codes compatible with AATD testing/diagnosis ([Online Appendix eTable 1](#)). A diagnosis of AATD was defined as serum AAT <1g/l (this level would include most MZ, all ZZ and SZ genotypes), and/or one or more compatible Read codes for AATD (C3762, C3761, X101o, X772S). No exclusion criteria were applied. The index date for each AATD patient in the cohort was the time of recording of the first code compatible with testing positive for a diagnosis of AATD.

### *Data And Statistical Analysis*

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The incidence and prevalence rates of AATD, along with the frequency of any and new AATD testing, by calendar year, was calculated by gender and age at testing. Summary statistics (sample size, percentage, mean  $\pm$  standard deviation (SD)) were produced for AATD patient demographics and clinical characteristics, including: gender, age, smoking status, BMI, major comorbidities, and spirometric severity as assessed according to GOLD post-BD spirometric thresholds; the GOLD 2017 staging was also explored. AATD patient demographics and clinical characteristics were compared to COPD patients who tested negative for AATD, using Mann-Whitney, Chi<sup>2</sup> or Fisher's exact tests, as appropriate. Following Chi<sup>2</sup> tests, the nature of any differences was determined using residuals. Confidence intervals of rates are the 95% exact binomial confidence intervals. In all comparisons, a p value <0.05 was considered for statistical significance.

## RESULTS

### *1. Trends in the incidence of testing and diagnosis of AATD by sex and age group*

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Between 1994 and 2013 the incidence rates of AATD diagnosis generally increased, reflecting an increased frequency of new testing (**Figure 2 A & B**). Trends appeared very similar by gender (**Figure 2 B, C & E**), although since 2006 the average annual incidence of AATD diagnosis has fallen in females ( $p=0.001$ , **Figure 2 E**). The frequency of new testing increased in all ages, but was highest in those aged 45-65 years (**Figure 2 B**). The low incidence of AATD diagnosis in those tested after the age of 65 years (**Figure 2 C & D**), likely reflects the low frequency of new testing in this population (**Figure 2 B**). The incidence of testing appears to fall in 2014, but this likely reflects only data from the first half of 2014 being included in the dataset

### *2. Trends in the prevalence of testing and diagnosis of AATD by sex and age group*

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The prevalence of any testing for AATD is similar between males and females (**Figure 3 A**), but the prevalence of AATD is higher in males (**Figure 3 E**). Interpretation of the prevalence of AATD in males and females grouped by age at testing (**Figure 3 C & D**) is complicated by the differences in the prevalence of testing across the age groups (**Figure 3 B**); testing for AATD is most prevalent in those aged 45-65 years and least prevalent in those aged over 65 years (**Figure 3 B**).

When prevalence was calculated as a percentage of those tested, AATD was more prevalent in males 28.0 % (95% C.I. 23.4-33.0) compared to females 18.8% (95% C.I. 14.7-23.6;  $p=0.007$ ; **Table 1**). There was a trend to higher prevalence of AATD in those tested at younger ages ( $p=0.19$ ; **Table 1**); 27.8% (95% C.I. 21.9% -34.4%) of those tested between the ages of 20-44 years has AATD, compared to 22.0 % (95% C.I. 18.2%-26.3%) of those tested between 45-65 years, and 15.0% (95% C.I. 3.2%-37.9%) of those tested after 65 years of age.

### *3. AATD testing in patients with COPD under 60 years of age*

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From a total of 107,024 individuals with COPD in the source population OPCR database, we identified 29,596 (27.6%) individuals diagnosed with COPD before 60 years of age, of whom 667/29,596, that is only 2.2% (95% CI 2.09% - 2.43%) had any record of being tested for AATD (**Figure 1**). Of those tested between 1990 and 2014, 23.7% (95% CI 20.5% - 27.1%; 157/663) were diagnosed with AATD.

### *4. Characteristics of patients under 60 with AATD associated COPD*

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Within the COPD cohort tested for AATD (**Table 2**), a diagnosis of AATD was associated with being male, and being an ex-smoker rather than current smoker. Those with AATD had more severe disease with a lower % predicted FEV<sub>1</sub>. Furthermore, 58.4 % of those with AATD had airflow limitation classed as severe or very severe compared to 36.6 % of those without AATD. COPD exacerbation risk was higher in those patients diagnosed with AATD, as 69.0% of those diagnosed with AATD were in GOLD 2017 risk categories C and D at diagnosis, compared to 56.6 % of those without AATD; however, the annual COPD exacerbation rate in the year prior to testing for AATD was not significantly different in those diagnosed with AATD ( $p>0.05$ ).

Finally, there was no difference between those with and without AATD in the occurrence of any of the comorbidities investigated (all  $p > 0.05$  [Table 3](#)).

## DISCUSSION

Severe alpha<sub>1</sub> antitrypsin deficiency is associated with early onset debilitating emphysema. We report the epidemiological trends in testing and diagnosing AATD, and the incidence and prevalence of AATD for the last two decades in the UK. We report highly novel data in the general UK population. We identified a low frequency of AATD testing (only 2.2% of those with COPD diagnosed before 60 years), but a recent increasing prevalence of AATD diagnosis, observed both in males and females. The latter can be largely attributed to an increased frequency of new or any testing, particularly observed in COPD patients in the younger age groups (20-44 years and 45-65 years). We also identified for the first time some demographic and clinical determinants of AATD diagnosis, discussed later.

In 2000, we first explored the General Practitioner Research Database (GPRD), forerunner of the current Clinical Practice Research Datalink (CPRD), to conduct research on COPD.<sup>19</sup> Since then, a number of groups have further explored collaterally the epidemiology and pharmacoepidemiology of COPD.<sup>20,21,22</sup> However, to our knowledge, no research on AATD has been conducted yet in CPRD or the more recently established Optimum Patient Care Research Database (OPCRD).

### *Literature review*

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Despite the substantial individual and societal burden of respiratory disease, they continue to be largely underdiagnosed, and the number of cases of AATD and COPD in the world has been the subject of intense debate in respiratory medicine. Based on an analysis of published genetic epidemiologic surveys, de Serres F, et al.,<sup>23</sup> concluded 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.”* This figure can be quite accurate, by applying the proportion that AATD accounts for 1-2% of all expected 174 million COPD cases worldwide, from the GBD 2015 study.<sup>24</sup> Extensive descriptions of the geographical and epidemiological burden of AATD in several populations can be found elsewhere.<sup>25,26</sup> Recently, Barrecheguren M, et al.,<sup>27</sup> identified an increase of AATD testing in two periods (2007-2008 and 2010-2011) by exploring a Primary Care database in Catalunya, Spain.

### *Clinical significance of these findings*

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We identified that a diagnosis of AATD was associated with a number of demographic (male, being an ex-smoker) and clinical characteristics (lower % predicted FEV<sub>1</sub>, and GOLD 2017 stages C or D). The clinical significance of these for case-finding might be explored elsewhere. Paradoxically, the annual COPD exacerbation rate was not significantly different in those with AATD (all  $p < 0.05$ ), and there was no difference between those with and without AATD in occurrence of any of the comorbidities investigated (all  $p > 0.05$ ). We can hypothesize that given both a universal underdiagnosis of COPD,<sup>28,29</sup> and an underdiagnosis



of AATD,<sup>30,31,32</sup> those within the subset of individuals identified by the system, may lead to the “diagnostic fallacy”, that is an inaccurate view of the nature and causes of AATD, as indeed only a few instances of disease are seen by clinicians.<sup>33,34</sup>

For instance, by studying 1,066 individuals from the German AATD registry, Fähndrich S, et al.<sup>35</sup> recently reported that female AATD patients had lower numbers of pack-years and lower BMI, and a longer diagnostic delay (of two years later), than their male counterparts.

Finally on comorbidities, Greulich T, et al.,<sup>36</sup> reported a high frequency of most respiratory comorbidities in AATD compared with matched COPD individuals without AATD, which is at odds with our findings in **Table 3**. However, the frequency and nature of comorbidities in other AATD populations is highly variable, as reported elsewhere.<sup>37</sup>

#### *Limitations Of Study Design / Analysis*

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There are a numbers of intrinsic limitations that can be envisaged, including:

As above mentioned, our study only applies to diagnosed patients with COPD and AATD, but does not include the majority of individuals with AATD that may/may not develop COPD. Therefore, the results will be biased towards a more severe expression of lung disease and other conditions associated with AATD, because only those with clinical manifestations will likely be diagnosed by a GP or identified within the UK medical system, and included in the study, *ergo* the “diagnostic fallacy”. Indeed, given high rates of underdiagnosis of both COPD and AATD, and as most COPD patients are never tested for AAT levels, some/many COPD patients in the population may have undiagnosed AATD.

Our AATD definition would include carriers as well as the severely deficient. In the absence of genotyping, it may well be that the majority of serum levels below 100 mg/dL will be mildly reduced levels associated with the carrier state, that is individuals for whom augmentation therapy is not recommended. The reliability of Read codes in Primary Care needs to be further explored. It can be observed in clinical records a diagnosis of AATD in individuals with a serum level just below the threshold of normal values (i.e. 100 mg/dL), usually corresponding to a heterozygote or even a normal phenotype. Again, as the majority of reduced AAT serum levels likely are mildly reduced levels of carriers, genotyping is needed to distinguish the carrier state from severe deficiency. Regrettably, our database does not allow to quantify how frequently such serum testing was followed by appropriate genotyping.

The decision of focusing on COPD diagnosed before 60 years of age is arbitrary but clinically informed, as current recommendations apply to COPD patients of all ages.<sup>7</sup>

There is also the possibility that testing for AATD is undertaken in secondary care, and may not appear in the primary care records, especially when it is normal. However, this does not change the main thrust of our research, as only a small minority of UK primary care COPD patients attend secondary care.<sup>38</sup>

Our main focus in the severity of AATD was related to lung function impairment. However, as non-index cases, cases with liver disease, or other, might not develop significant lung disease.

Other potentially limiting factors for use of primary care databases, in respiratory disease in general, and AATD in particular, are the lack of valid (incomplete) information on respiratory function, weight, alcohol, and tobacco consumption (except for alcohol, all been required by QOF since 2004); also, screening by dry blood, genotyping, or the new Alpha test, by clinical suspicion or via a proband, and consistent management and recording at the primary to tertiary level, which can have variable effects on GP recording practices of AATD. However, during the last decade, recent advances in scope and contents of primary care databases, like those already effective in OPCR, can overcome these limitations and become a tremendous, powerful asset for rare disease monitoring, and other related Public Health uses. It is therefore necessary to explore the recording of testing and diagnosis in other large primary care populations and datasets.

### *Implications of our research*

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It is generally accepted that AATD diagnosis is important even if no augmentation therapy is available. It is very relevant for the patient in order to avoid exposure (tobacco, alcohol, other pollutants) and for family screening to detect relatives affected early in the course of the disease. While global guidance from the WHO,<sup>7</sup> and also by the ERS<sup>12</sup> and the GOLD strategy<sup>39</sup> advise that all patients with a diagnosis of COPD should be screened, less encouragement comes from UK national advice. Thus the lack of testing for AATD in UK may be stem from the NICE guidelines<sup>13</sup> which state that testing should occur in COPD if early onset, minimal smoking history or family history appear, but that replacement therapy is not recommended for patients with alpha-1 antitrypsin deficiency. The British Lung foundation states “At the moment, NICE does not recommend any specific treatment in the UK for alpha-1-antitrypsin deficiency (AATD). If you have a condition caused by AATD, such as COPD or liver disease, the focus is on usual treatment for those conditions.” This may lead to a general assumption that, apart from smoking cessation and testing in families, there is little to be gained for patients to find out if they are positive.<sup>32,40</sup> NICE is currently re-appraising augmentation therapy.<sup>41</sup>

Given that the NICE advice is different from WHO, ERS and GOLD, and while this may explain the low testing rates, NICE might consider being aligned to global advice because of substantial under-testing and lack of augmentation therapy, and considering to developing further government-commissioned specialised centres.

### *Concluding remarks*

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We conclude that despite an increase in the frequency of AATD testing since 1990, only 2.2% of patients diagnosed with COPD before the age of 60 years were tested. Given an AATD prevalence of 23.7% in those tested, it appears that AATD remains largely underdiagnosed in COPD patients in the UK.

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**Figure 1.** STROBE flowchart of participants in the study

**Figure 2.** Trends of several incidence AATD indicators from 1990 to 2014, with their 95% exact binomial confidence intervals (shaded areas), for: A) Frequency of new AATD testing by gender; B) Frequency of new AATD testing by age; C) Incidence of AATD in males by age; d) Incidence of AATD in females by age; and E) Incidence of AATD by gender

**Figure 3.** Trends of several prevalence AATD indicators from 1990 to 2014, with their 95% exact binomial confidence intervals (shaded areas), for: A) Frequency of any AATD testing by gender; B) Frequency of any AATD testing by age; C) Prevalence of AATD in males by age; D) Prevalence of AATD in females by age; and E) Prevalence of AATD by gender

Figure 1.

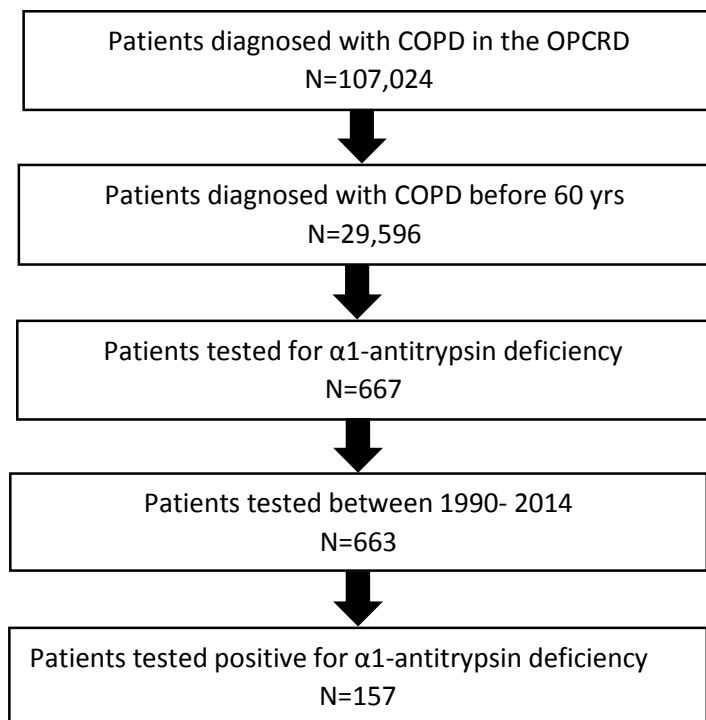
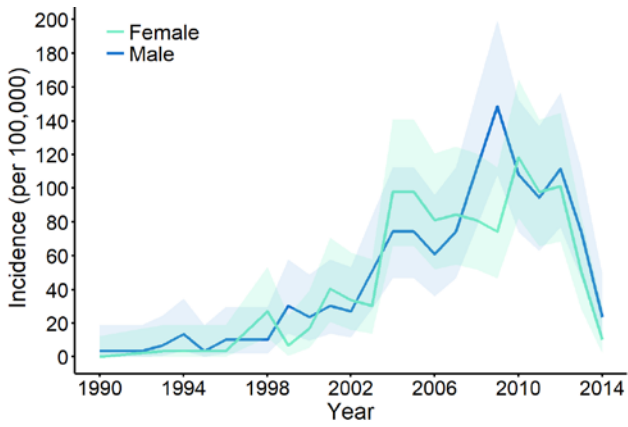
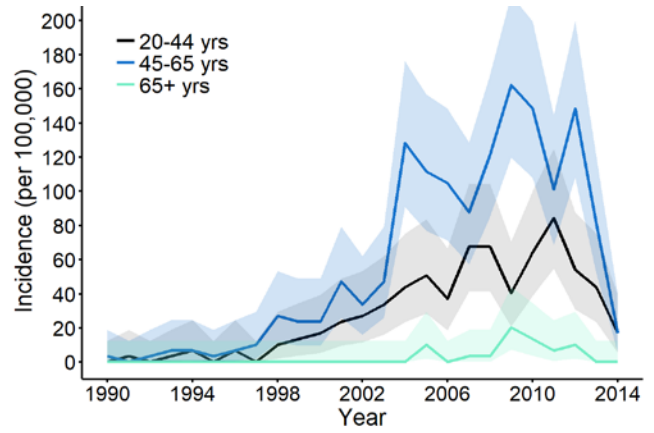


Figure 2.

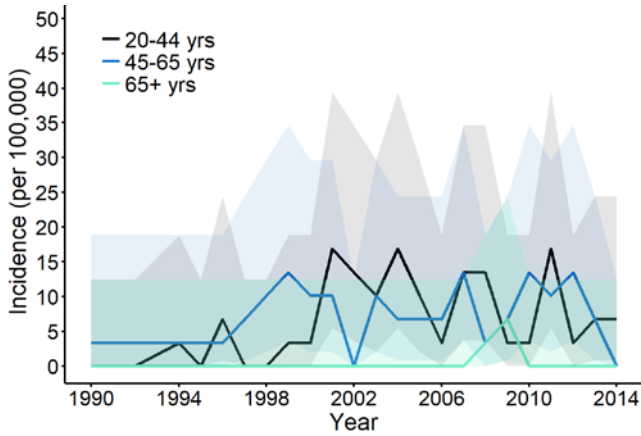
A) Frequency of new testing of AATD by gender



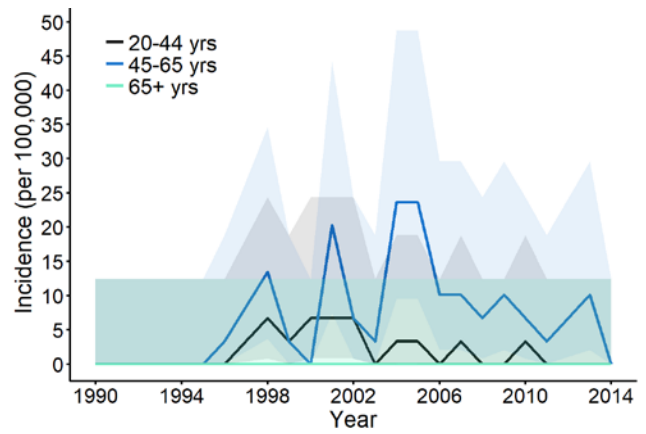
B) Frequency of new testing of AATD by age



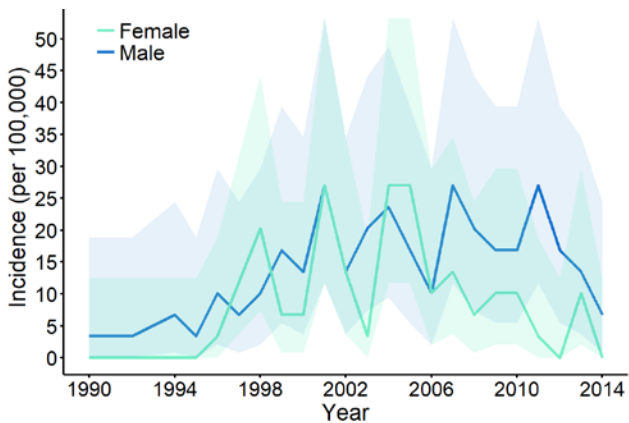
C) Incidence of AATD in males by age



D) Incidence of AATD in females by age

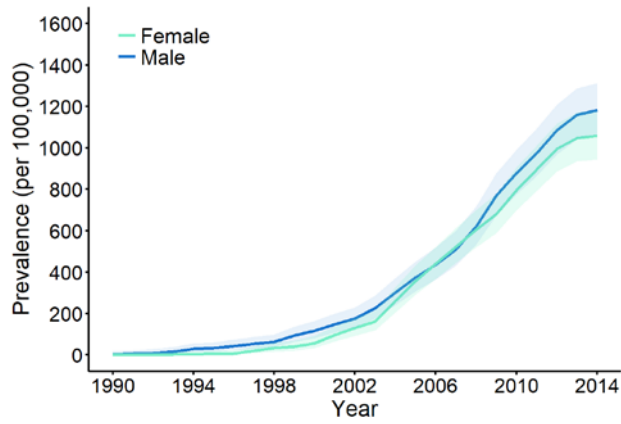


E) Incidence of AATD by sex

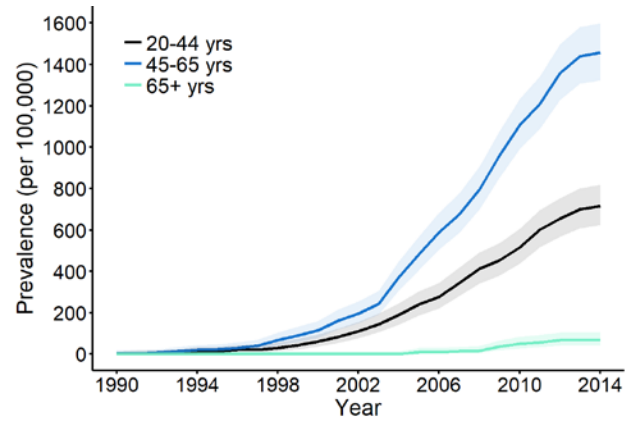


**Figure 3.**

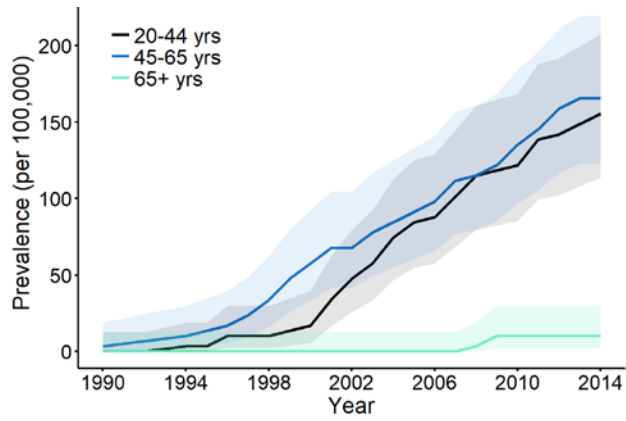
A) Frequency of any testing of AATD by gender



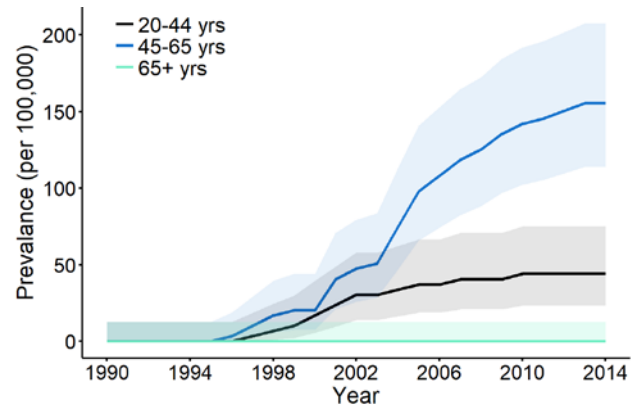
B) Frequency of any testing of AATD by age



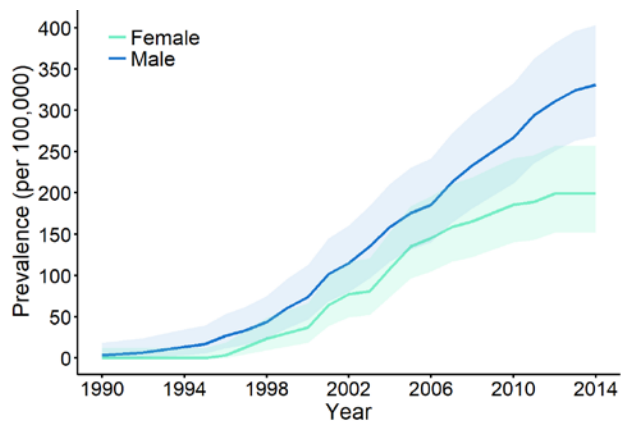
C) Prevalence of AATD in males by age



D) Prevalence of AATD in females by age



E) Prevalence of AATD testing by gender



**Table 1.** Prevalence of AATD as the percentage of those COPD individuals tested, by gender and age

	n AATD/ N COPD	Percentage & 95% C.I.
<b>Both genders</b>		
20-44 years	59/212	27.8 (21.9-34.4)
45-64 years	95/431	22.0 (18.2-26.3)
65+ years	3/20	15.0 (3.2-37.9)
All	157/663	23.7 (20.5-27.1)
<b>Female</b>		
20-44 years	13/86	15.1 (8.3-24.5)
45-64 years	46/218	21.1 (15.9-27.1)
65+ years	0/9	0.0 (0.0-33.6)
All	59/313	18.8 (14.7-23.6)
<b>Male</b>		
20-44 years	46/126	36.5 (28.1-45.6)
45-64 years	49/213	23.0 (17.5-29.2)
65+ years	3/11	27.3 (6.0-61.0)
All	98/350	28.0 (23.4-33.0)

**Table 2.** Demographic and clinical characteristics of individuals tested for AATD and found to have or not have AATD

	AATD patients (n=157)	Non-AATD patients (n=506)	P-value
<b>Age at COPD diagnosis</b> mean±SD	46.4±7.8	47.7±7.7	0.061
<b>Age at AATD testing</b> mean±SD	48.3±9.0	49.9±9.2	0.016*
<b>Gender</b> n(%)			
Female	59 (37.6%)	254 (50.2%)	0.007*
Male	98 (62.4%)	252 (49.8%)	
<b>BMI (kg/m<sup>2</sup>)</b> n(%)			
Underweight	11 (7.3%)	35 (7.2%)	0.066
Normal	74 (49.3%)	200 (40.9%)	
Overweight	42 (28.0%)	129 (26.4%)	
Obese	23 (15.3%)	125 (25.6%)	
Missing	7 (4.5%)	17 (3.4%)	
<b>Smoking status</b> n(%)			
Current Smoker	56 (36.8%)	260 (51.7%)	0.004*
Ex-Smoker	75 (49.3%)	179 (35.6%)	
Non-Smoker	21 (13.8%)	64 (12.7%)	
Missing	5 (3.2%)	3 (0.6%)	
<b>GOLD Spirometric Severity</b> n(%)			
Mild	20 (14.6%)	76 (16.0%)	<0.001*
Moderate	37 (27.0%)	225 (47.4%)	
Severe	44 (32.1%)	127 (26.7%)	
Very Severe	36 (26.3%)	47 (9.9%)	
Missing	20 (12.7%)	31 (6.1%)	
<b>FEV<sub>1</sub> percentage of predicted</b> n(%)			
<10%	0 (0.0%)	2 (0.4%)	<0.001*
≥10<20%	9 (6.6%)	14 (2.9%)	
≥20<30%	27 (19.7%)	31 (6.5%)	
≥30<40%	26 (19.0%)	65 (13.7%)	
≥40<-50%	18 (13.1%)	62 (13.1%)	
≥50<60%	7 (5.1%)	78 (16.4%)	
≥60<70%	14 (10.2%)	78 (16.4%)	
≥70<80%	14 (10.2%)	67 (14.1%)	
≥80<90%	9 (6.6%)	33 (6.9%)	
≥90%	13 (9.5%)	45 (9.5%)	
Missing	20 (12.7%)	31 (6.1%)	
<b>GOLD 2017 Risk</b> n(%)			
A	24 (24.0%)	128 (29.4%)	0.018*
B	7 (7.0%)	61 (14.0%)	
C	39 (39.0%)	108 (24.8%)	
D	30 (30.0%)	138 (31.7%)	
Missing	57 (36.3%)	71 (14.0%)	
<b>Annual exacerbation rate</b> (in the year prior to AATD testing)			
0	80 (51.0%)	201 (39.7%)	0.11



	<b>AATD patients</b> (n=157)	<b>Non-AATD patients</b> (n=506)	<b>P-value</b>
1	30 (19.1%)	126 (24.9%)	
2	21 (13.4%)	71 (14.0%)	
3	9 (5.7%)	47 (9.3%)	
4	11 (7.0%)	30 (5.9%)	
5	5 (3.2%)	15 (3.0%)	
6+	1 (0.6%)	16 (3.2%)	

P-values from Chi<sup>2</sup> or Mann-Whitney test, as appropriate. Following Chi<sup>2</sup> tests residuals were used to determine the nature of the dependence where necessary. \* p<0.05.

**Table 3.** Frequency of comorbidities in individuals with AATD and in the reference group of COPD without AATD

	<b>AATD patients</b> (n=157)	<b>Non-AATD patients</b> (n=506)	<b>P-value</b>
Asthma	59 (37.6%)	227 (44.9%)	0.13
Bronchiectasis	7 (4.5%)	18 (3.6%)	0.78
Rhinitis	2 (1.3%)	5 (1.0%)	0.67
GERD	2 (1.3%)	7 (1.4%)	1.00
Eczema	2 (1.3%)	14 (2.8%)	0.38
Osteoporosis	8 (5.1%)	28 (5.5%)	0.99
Chronic Kidney Disease	0 (0.0%)	7 (1.4%)	0.21
Diabetes	12 (7.6%)	66 (13.0%)	0.09
Hypertension	8 (5.1%)	43 (8.5%)	0.22
Cardiovascular Disease	15 (9.6%)	70 (13.8%)	0.21
Ischaemic Heart Disease	9 (5.7%)	27 (5.3%)	1.00
Heart Failure	2 (1.3%)	4 (0.8%)	0.63
Myocardial Infarction	2 (1.3%)	9 (1.8%)	1.00
Cerebrovascular Disease	1 (0.6%)	14 (2.8%)	0.21
Anxiety and/or Depression	11 (7.0%)	50 (9.9%)	0.35

P-values from Fisher's exact or Chi<sup>2</sup> test, as appropriate.

## ONLINE APPENDIX

**eTable 1:** Read codes used to determine AATD diagnosis/testing. Codes compatible with AATD diagnosis are highlighted in blue

Read Code	Read Term
44C6.	Serum A1 antitrypsin
C3762	Alpha 1 antitrypsin deficiency
4L00.	Alpha 1 antitrypsin phenotype
44N4.	Electrophoresis: alpha-1-glob.
4L15.	Alpha 1 antitrypsin genotyping
C3761	Alpha 1 antitrypsin hepatitis
X101o	Pulm emphysema, alpha 1 PI def
X772R	Alpha 1 antitry phenotype PiMM
X772S	Alpha 1 antitry phenotype PiZZ
X772T	Alpha 1 antitryp phenotyp PiSS
X772U	Alpha 1 antitryp phenotyp PiSZ
X772V	Alpha 1 antitryp phenotyp PiMZ
X772W	Alpha 1 antitryp phenotyp PiMS
X772X	Alpha 1 antitryp phenotyp null
X77WB	Alpha 1 antitryps phenotyping
X80Md	Alpha 1 antitrypsin

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