Trends of testing for and diagnosis of α_1-antitrypsin deficiency in the UK: more testing is needed

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

Affiliations: [1]Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid and SEPAR, Madrid, Spain. [2]Respiratory Effectiveness Group, Cromer, UK. [3]Plymouth University Peninsula School of Medicine and Dentistry, Plymouth, UK. [4]Pneumology Dept, Hospital Universitari Vall d'Hebron and CIBERES, Barcelona, Spain. [5]Optimum Patient Care Ltd, Cambridge, UK. [6]Peterhead Medical Practice, Peterhead, UK. [7]Observational and Pragmatic Research Institute (OPRI) Pte Ltd, Singapore, Singapore. [8]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK. [9]Dept of Respiratory Medicine, Cambridge NIHR BRC, Addenbrookes Hospital, Cambridge, UK.

Correspondence: Joan B. Soriano, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Diego de León 62, Madrid 28030, Spain. E-mail: jbsoriano2@gmail.com

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AATD remains markedly underdiagnosed in COPD patients and case-finding strategies for both conditions should be implemented http://ow.ly/wXK830k3RNf

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ABSTRACT α_1-antitrypsin deficiency (AATD) significantly increases the risk of developing chronic obstructive pulmonary disease (COPD), and testing of all COPD patients for AATD is recommended by the World Health Organization, European Respiratory Society and Global Initiative for Chronic Obstructive Lung Disease (GOLD). We aimed to determine trends for testing and diagnosing AATD from 1990 to 2014.

This study analysed all patients diagnosed with COPD from about 550 UK Optimum Patient Care Research Database 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 forced expiratory volume in 1 s % pred 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.

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Introduction

α_1-antitrypsin (AAT) deficiency (AATD) is a genetic condition characterised by low serum levels of AAT (also known as α_1-proteinase inhibitor), the main protease inhibitor in human serum. The clinical expression manifests as pulmonary emphysema, liver cirrhosis, skin panniculitis or 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 [1]. AATD clinical manifestations are most commonly due to homozygous PiZZ [2–4].

AATD is considered a rare disease, which is defined as any disease that affects <1 in 2000 individuals [5]. It is estimated within Europe that 1 in 2000–5000 newborns has homozygous PiZZ AATD [6]. Although the World Health Organization (WHO) recommends that all patients with chronic obstructive pulmonary disease (COPD) must be tested for AAT [7], 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) [8]. Diagnosis is made by the demonstration of reduced blood levels of AAT. A reduced or absent α_1-globulin peak on serum protein electrophoresis can be an indication to determine the levels of blood AAT, as AAT makes up most of the α_1-globulins. Genotyping of the different deficient alleles (Z, S or rare alleles) is needed to better categorise patients and their clinical characteristics [9].

Previous estimates of the prevalence of AATD individuals in the UK come from old registries and extrapolations of small case series, likely outdated [10]. However, a UK AATD registry was initiated in 1997 and by 2014 included 1196 patients with the deficiency [11].

More evidence on the population distribution and determinants of AATD is needed, as there are newly available recommendations for screening [12], while the UK National Institute for Health and Care Excellence (NICE) is currently reconsidering and reviewing AATD treatment and management recommendations [13] in light of new evidence of treatment efficacy [14]. 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

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

Database source

Data were obtained from the Optimum Patient Care Research Database (OPCRD; opcrd.co.uk), 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 dataset was generated it contained data from 747 628 asthma and 107 024 COPD patients [15]. A preliminary search by Read code C3762 identified approximately 600 AATD patients. The 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 committee (ADEPT1617). The study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS21791). We have followed and endorsed the STROBE guidance for reporting observational evidence (strobe-statement.org).

Patients were diagnosed with COPD codes available in the UK Quality Outcomes Framework (QOF) [16]. The QOF established incentives for improved data recording at general practitioner (GP) practices from April 1, 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 (supplementary table S1). A diagnosis of AATD was defined as serum AAT <1 $g{\cdot}L^{-1}$ (this level would include most MZ and all ZZ and SZ genotypes) and/or one or more compatible Read codes for AATD (C3762, C3761, X101o and 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

The incidence and prevalence rates of AATD, along with the frequency of any and new AATD testing, by calendar year, was calculated by sex and age at testing. Summary statistics (sample size, percentage and mean with standard deviation) were produced for AATD patient demographics and clinical characteristics, including sex, age, smoking status, body mass index (BMI), major comorbidities and spirometric severity as assessed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) post-bronchodilator spirometric thresholds; GOLD 2017 staging was also explored. AATD patient demographics and clinical characteristics were compared with COPD patients who tested negative for AATD, using Mann–Whitney, Chi-squared or Fisher's exact tests, as appropriate. Following Chi-squared 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

AATD testing in patients with COPD under 60 years of age

From a total of 107 024 individuals with COPD in the source population OPCRD database, we identified 29 596 (27.6%) individuals diagnosed with COPD before 60 years of age, of whom 667 out of 29 596 (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, 157 out of 663 (23.7%, 95% CI 20.5–27.1%) were diagnosed with AATD.

Trends in the incidence of testing and diagnosis of AATD by sex and age group

Between 1994 and 2013 the incidence rates of AATD diagnosis generally increased, reflecting an increased frequency of new testing (figure 2a and b). Trends appeared very similar by sex, although since 2006 the average annual incidence of AATD diagnosis has fallen in females (p=0.001) (figure 2e). The frequency of new testing increased in all ages, but was highest in those aged 45–65 years (figure 2b). The low incidence of AATD diagnosis in those tested after the age of 65 years (figure 2c and d) likely reflects the low frequency of new testing in this population (figure 2b). 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

Trends in the prevalence of testing and diagnosis of AATD by sex and age group

The prevalence of any testing for AATD was similar between males and females (figure 3a), but the prevalence of AATD was higher in males (figure 3e). Interpretation of the prevalence of AATD in males and females grouped by age at testing (figure 3c and d) is complicated by the differences in the prevalence of testing across the age groups (figure 3b); testing for AATD was most prevalent in those aged 45–65 years and least prevalent in those aged >65 years (figure 3b).

When prevalence was calculated as a percentage of those tested, AATD was more prevalent in males (28.0%, 95% CI 23.4–33.0%) compared with females (18.8%, 95% CI 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); 27.8% (95% CI 21.9–34.4%) of those tested between the ages of 20 and 44 years had AATD, compared with 22.0% (95% CI

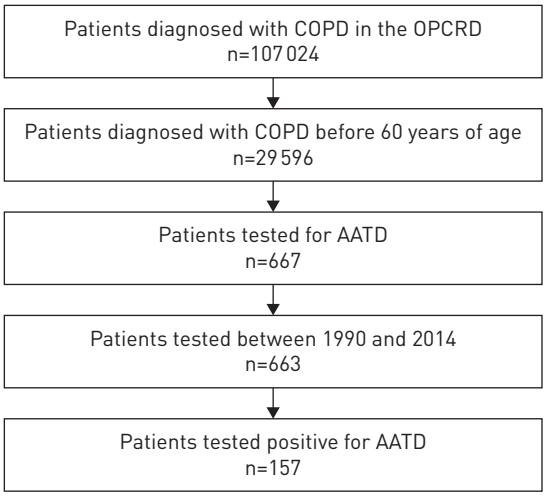

FIGURE 1 STROBE flowchart of study participants. COPD: chronic obstructive pulmonary disease; OPCRD: Optimum Patient Care Research Database; AATD: α_1-antitrypsin deficiency.

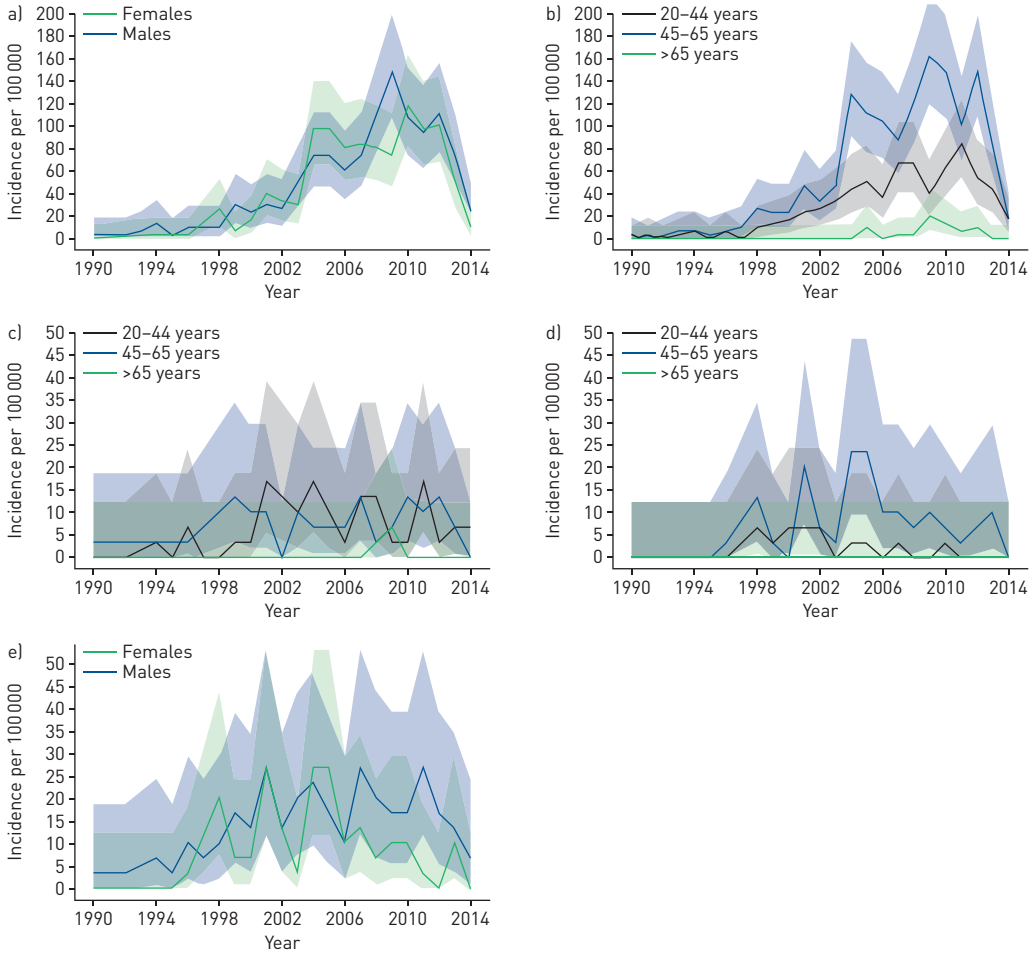

FIGURE 2 Trends of several α_1-antitrypsin deficiency (AATD) incidence indicators from 1990 to 2014, with their 95% exact binomial confidence intervals (shaded areas): a) frequency of new AATD testing by sex, b) frequency of new AATD testing by age, c) incidence of AATD in males by age, d) incidence of AATD in females by age and e) incidence of AATD by sex.

18.2–26.3%) of those tested between the ages of 45 and 65 years and 15.0% (95% CI 3.2–37.9%) of those tested after 65 years of age (table 1).

Characteristics of patients under 60 years of age with AATD-associated COPD

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 a current smoker. Those with AATD had more severe disease with a lower forced expiratory volume in 1 s (FEV_1) % pred. Furthermore, 58.4% of those with AATD had airflow limitation classed as severe or very severe compared with 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 grades C and D at diagnosis compared with 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 AATD 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 of age), 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

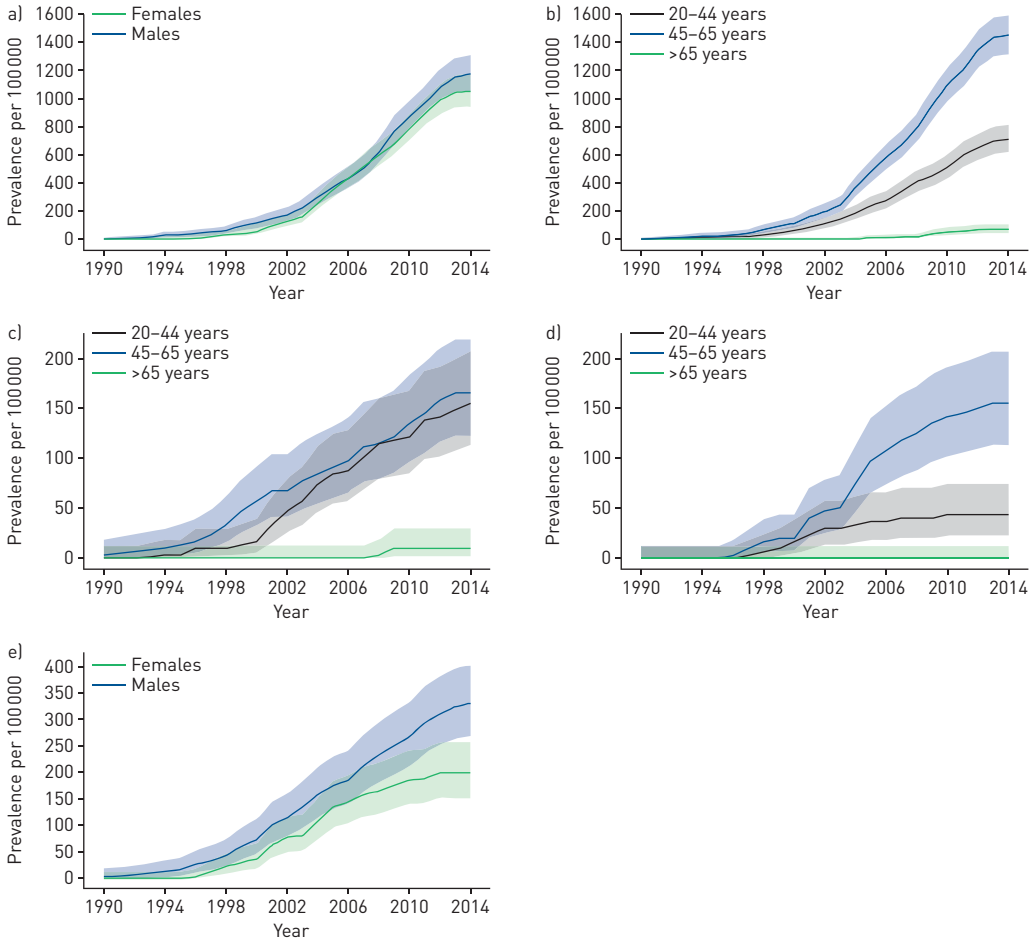

FIGURE 3 Trends of several α_1-antitrypsin deficiency (AATD) prevalence indicators from 1990 to 2014, with their 95% exact binomial confidence intervals (shaded areas): a) frequency of any AATD testing by sex, b) frequency of any AATD testing by age, c) prevalence of AATD in males by age, d) prevalence of AATD in females by age and e) prevalence of AATD by sex.

TABLE 1 Prevalence of α_1-antitrypsin deficiency (AATD) as a percentage of those chronic obstructive pulmonary disease (COPD) individuals tested by sex and age

	AATD n/COPD n	Percentage (95% CI)
Both sexes		
20–44 years	59/212	27.8 (21.9–34.4)
45–65 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)
Female		
20–44 years	13/86	15.1 (8.3–24.5)
45–65 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)
Male		
20–44 years	46/126	36.5 (28.1–45.6)
45–65 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 α_1-antitrypsin deficiency (AATD) and found to have or not have AATD

	AATD patients	Non-AATD patients	p-value
Subjects	157	506	
Age at COPD diagnosis years	46.4±7.8	47.7±7.7	0.061
Age at AATD testing years	48.3±9.0	49.9±9.2	0.016#
Sex			
Female	59 (37.6)	254 (50.2)	0.007#
Male	98 (62.4)	252 (49.8)	
BMI kg·m^{-2}			
<18.5 (underweight)	11 (7.3)	35 (7.2)	0.066
18.5–24.9 (normal)	74 (49.3)	200 (40.9)	
25.0–29.9 (overweight)	42 (28.0)	129 (26.4)	
⩾30 (obese)	23 (15.3)	125 (25.6)	
Missing	7 (4.5)	17 (3.4)	
Smoking status			
Current smoker	56 (36.8)	260 (51.7)	0.004#
Ex-smoker	75 (49.3)	179 (35.6)	
Nonsmoker	21 (13.8)	64 (12.7)	
Missing	5 (3.2)	3 (0.6)	
GOLD spirometric severity			
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)	
FEV_1 % pred			
<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)	
GOLD 2017 grade			
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)	
Annual exacerbation rate (in the year prior to AATD testing)			
0	80 (51.0)	201 (39.7)	0.110
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)	

Data are presented as n, mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s. p-values from the Chi-squared test or the Mann–Whitney test, as appropriate. Following Chi-squared tests the residuals were used to determine the nature of the dependence where necessary. #: p<0.05.

TABLE 3 Frequency of comorbidities in individuals with α_1-antitrypsin deficiency (AATD) and in the reference group of chronic obstructive pulmonary disease without AATD

	AATD patients	Non-AATD patients	p-value
Subjects	157	506	
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
Gastro-oesophageal reflux disease	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

Data are presented as n or n (%), unless otherwise stated. p-values from Fisher's exact test or the Chi-squared test, as appropriate.

groups (20–44 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, the forerunner of the current Clinical Practice Research Datalink (CPRD), to conduct research on COPD [17]. Since then a number of groups have further explored collaterally the epidemiology and pharmacoepidemiology of COPD [18–20]. However, to the best of our knowledge, no research on AATD has been conducted yet in the CPRD or the more recently established OPCRD.

Literature review

Despite the substantial individual and societal burden of respiratory diseases, 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 epidemiological surveys, de Serres *et al.* [21], 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 appears to have been quite accurate, by applying the proportion that AATD accounts for 1–2% of all expected 174 million COPD cases worldwide, from the Global Burden of Disease 2015 study [22]. Extensive descriptions of the geographical and epidemiological burden of AATD in several populations can be found elsewhere [6, 23]. Recently, Barrecheguren *et al.* [24] identified an increase of AATD testing in two periods (2007–2008 and 2010–2011) by exploring a primary care database in Catalonia, Spain.

Clinical significance of these findings

We identified that a diagnosis of AATD was associated with a number of demographic (male and being an ex-smoker) and clinical (lower FEV_1 % pred and GOLD 2017 grade C or D) characteristics. The clinical significance of these for case-finding results might be explored elsewhere. Paradoxically, the annual COPD exacerbation rate was not significantly different in those with AATD ($p<0.05$), 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 hypothesise that given both a universal underdiagnosis of COPD [25, 26] and of AATD [27–29], those within the subset of individuals identified by the system may lead to a "diagnostic fallacy", *i.e.* an inaccurate view of the nature and causes of AATD, as indeed only a few instances of disease are seen by clinicians [30, 31].

For instance, by studying 1066 individuals from the German AATD registry, Fähndrich *et al.* [32] recently reported that female AATD patients had lower numbers of pack-years and lower BMI, and a longer diagnostic delay (of 2 years later) than their male counterparts.

Finally, on comorbidities, Greulich *et al.* [33] 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 [34].

Limitations of study design/analysis

There are a numbers of intrinsic limitations that can be envisaged. As noted earlier, 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 <100 mg·dL^{-1} will be mildly reduced levels associated with the carrier state, *i.e.* individuals for whom augmentation therapy is not recommended. The reliability of Read codes in primary care needs to be further explored. Clinical records show a diagnosis of AATD in individuals with a serum level just below the threshold of normal values (*i.e.* 100 mg·dL^{-1}), 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 us to quantify how frequently such serum testing was followed by appropriate genotyping. The decision to focus on COPD diagnosed before 60 years of age is arbitrary but clinically informed, as current recommendations apply to COPD patients of all ages [7]. 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 [35].

Our main focus on the severity of AATD was related to lung function impairment. However, as nonindex cases, patients with liver disease or others might not develop significant lung disease. Other potentially limiting factors for the use of primary care databases, in respiratory disease in general and in AATD in particular, are the lack of valid (incomplete) information on respiratory function, weight, and alcohol and tobacco consumption (except for alcohol, all have been required by QOF since 2004). 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 can also have variable effects on GP recording practices for AATD. However, during the last decade, recent advances in the scope and content of primary care databases, such as those already effective in the OPCRD, can overcome these limitations and become a 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

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 and other pollutants) and for family screening to detect relatives affected early in the course of the disease. While global guidance from the WHO [7], and also by the European Respiratory Society (ERS) [12] and the GOLD strategy [36], advises 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 the UK may stem from the NICE guidelines [13], 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 AATD. The British Lung Foundation states "At the moment, NICE does not recommend any specific treatment in the UK for [AATD]. If you have a condition caused by AATD, such as COPD or liver disease, the focus is on usual treatment for those conditions" [37]. 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 [29, 38]. NICE is currently re-appraising augmentation therapy [13].

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

Conclusions

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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