REG STUDY PROTOCOL

TITLE (LONG):

Exploratory Protocol: Epidemiological trends of Alpha$_1$-antitrypsin deficiency (AATD) in the UK: prevalence and incidence from 1990 to 2015.

REG ref REG-RES1604; RiRL Project Number R02216

Title (short): Modern Epidemiology of Alpha$_1$-antitrypsin deficiency (AATD) in the UK

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ABBREVIATIONS

AATD: Alpha$_1$-antitrypsin deficiency

COPD: Chronic obstructive pulmonary disease

CPRD: Clinical Practice Research Datalink

GPRD: General Practitioner Research Database

NICE: National Institute for Health and Care Excellence

OPCRD: Optimum Patient Care Research Database

RiRL Research in Real-Life

LAY SUMMARY

This exploratory protocol aims to determine the epidemiological trends of Alpha1-antitrypsin deficiency (AATD) in the UK: size of the problem, prevalence and incidence from 1990 to 2015. It is a collaboration of external researchers with REG reference: REG-RES1604 and RiRL Project Number: R02216. It will be a case-series only study design.

AIM & OBJECTIVE

To determine the epidemiological pattern and characteristics of AATD in COPD patients in the UK population.

Specifically-

1) Prevalence and incidence of AATD, in all and by age and gender.
2) Determine the demographic and clinical characteristics associated with AATD.

BACKGROUND & RATIONALE

Background

Alpha$_1$-antitrypsin deficiency (AATD) is a genetic condition characterized by low serum levels of alpha-1 proteinase inhibitor, 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 by

proteolytic enzymes through inhibition of neutrophil elastase.[1] Mutations in the SERPINA1 gene lead to reduced levels of AAT in a co-dominant pattern, i.e. both alleles contribute to the protein level. AATD is associated with an increased risk of developing COPD, especially in smokers.[2]

Emphysema in AATD is thought to result from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin. This mechanism is called a "toxic loss of function". Specifically, cigarette smoking and infection increase elastase production in the lung, thus increasing lung degradation.[3]

AATD is considered a rare disease, which is defined as any disease that affects fewer than 1 in 2,000 individuals.[4] The prevalence of AATD in the general population in the UK and/or Europe is unknown, but it estimated that within Europe, one in every 2,000–5,000 newborns has AATD.

Despite the substantial individual and societal burden of AATD, this condition continues 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., 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."[5] This estimate can be quite accurate, nowadays as high as 3.3 million, by applying the estimate that AATD accounts for 1% of all 174 million COPD cases worldwide from the Global Burden of Disease study.[6]

More recently, genetic epidemiological studies on the prevalence of AATD in 97 countries were used to estimate the numbers of individuals in each of the AATD five main phenotypic classes, by combinations of M allele (normal or wild type) that produces normal levels with different types of mutant alleles (Z, S) that produce reduced levels, of which the Z allele is most common: Pi*MS, Pi*MZ, Pi*SS, Pi*SZ, and Pi*ZZ.[7] To facilitate a comparison of numbers between immediately adjacent countries, the countries were grouped into 10 major geographic regions: North Africa, Central and South Africa, Northern Europe, Eastern Europe, Western & Central Europe, North & Central Asia, Southeast Asia, North & Central America, Caribbean, and South America. Among the 97 countries, Latvia was shown to have the highest prevalence of deficiency alleles: PI*S: 31.3 per 1,000 population,

and PI*Z 45.1% per 1,000 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.

Previous estimates of the prevalence and counts of individuals in the UK come from old registries and extrapolations of small case series, mostly outdated;[8,9,10,11] therefore, the current prevalence of AATD in the UK is unknown. Of interest, NICE is currently reconsidering and reviewing his AATD treatment and management recommendations.[12]

On a worldwide scale, it is estimated that only 0.35% of expected AATD cases are detected.[4]

The two main methods for identifying AATD cases are population-based screening and case-finding (Inset).

Conditions in which to consider AATD

- Early onset emphysema (<45 years)
- Emphysema without a recognised risk factor (smoking, occupational dust exposure, *etc.*)
- Emphysema with prominent basilar hyperlucencies
- Otherwise unexplained liver disease
- Necrotising panniculitis
- Anti-proteinase 3-postive vasculitis (c-ANCA positive): antineutrophil cytoplasmic antibody-positive vasculitis
- Family history of any of the following: emphysema, bronchiectasis, liver disease or panniculitis
- Bronchiectasis without evident aetiology

Other more extensive recommendations previously issued by WHO proposed the determination of AAT levels in all asthma and COPD patients.

Modified from American Thoracic Society & European Respiratory Society Guidelines on AATD, Am J Respir Crit Care Med 2003; 168: 818–900.

Through population-based screening and case-finding (also known as targeted detection) can help to identify a rare conditions (e.g., AATD) within a specific population of individuals with a higher probability of having the condition (i.e., COPD in the case of AATD). Generally, to identify cases of AATD, it is more efficient to target a defined population such as individuals with airflow limitation or COPD.

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 as identified from its record in clinical and scientific expertise. The genotyping of the different deficient alleles (Z, S or rare alleles) is needed to better categorise patients and their clinical characteristics.

Rationale

In 2000, the General Practitioner Research Database (GPRD), forerunner of the current Clinical Practice Research Datalink (CPRD), was first explored to conduct research on COPD.[13] Since then, a number of groups have further explored collaterally the epidemiology and pharmacoepidemiology of COPD.[14,15,16] 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).

Potentially limiting factors for OPCRD use, which is the only data source in this exploratory protocol, in respiratory disease in general, and AATD in particular, are the lack of valid (incomplete) information on respiratory function, weight, alcohol, and tobacco consumption. 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, 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 OPCRD, can overcome these limitations and become a tremendous, powerful asset for AATD disease monitoring and other related Public Health uses. It is therefore necessary to explore the recording of testing and diagnosis in a large primary care dataset. This pilot study is expected to provide information to guide a larger epidemiological study that would also aim to investigate the natural history of AATD and benchmark AATD with other respiratory and non-respiratory diseases, by comparison with matched cohorts.

DATA SOURCE, STUDY DESIGN AND METHODOLOGY

Data Source

A dataset of patients from OPCRD will be used for analyses.

OPCRD is a respiratory-focused primary care research database developed by Optimum Patient Care, a social enterprise providing chronic respiratory review services. It contains anonymous, longitudinal data extracted from over 500 UK practices, and as of February 2016, current number of participants is 2,488,927. The database currently contains data from 747,628 asthma and 167,062 COPD patients.[17] A preliminary search by Read code C3762 -alpha-1-antitrypsin deficiency (includes hetero- and homozygotes) identified approximately 600 AATD registered patients. It is approved by Trent Multi Centre Research Ethics Committee for clinical research use and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research. The

OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The anonymised, longitudinal patient data offer a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad-range of respiratory areas.

Study Design

This is a pilot study to assess the frequency of AATD testing, and the incidence and prevalence of AATD.

This will be a descriptive, historical database study of OPCRD individuals who were diagnosed with COPD before the age of 60 years, and have been tested for AATD (i.e. Read code for AATD, see appendix) between 1990 and 2015. A diagnosis of AATD is defined as a serum AAT level of <1g/l or one of the following Read codes-

C3762	Alpha 1 antitrypsin deficiency
C3761	Alpha 1 antitrypsin hepatitis
X101o	Pulm emphysema, alpha 1 PI def
X772S	Alpha 1 antitry phenotype PiZZ

STUDY POPULATION

Inclusion criteria

To be eligible for inclusion in the study, patients must have:

- been diagnosed with COPD before the age of 60 years.
- a Read code associated with AATD diagnosis or testing, ever (See list of AATD Read codes in Appendix)

Exclusion criteria

No exclusion criteria will be applied.

OUTCOMES

1) Prevalence and incidence of AATD, by year, in total and by covariates.
2) Characterisation of AATD patients.

COVARIATES

- Gender
- Age
- Calendar year of AATD diagnosis/testing
- Smoking status
- BMI
- Comorbidities
    - Asthma
    - Bronchiectasis
    - Rhinitis
    - Ischemic Heart Disease
    - Cardiovascular Heart Disease
    - Heart failure
    - GERD
    - Eczema
    - Depression & Anxiety
    - Hypertension
    - Diabetes
    - Osteoporosis
    - Chronic Kidney Disease
    - Myocardial Infarction
    - Cerebrovascular Disease
- Spirometry
- GOLD severity/risk categories
- Number of COPD exacerbations in the yr prior to AATD testing

SAMPLE SIZE AND POWER CALCULATION

Being exploratory and descriptive, there is no formal sample size calculation in this study.

Initial searches suggest more than 600 patients with AATD are available for analyses.

DATA AND STATISTICAL ANALYSIS

Summary statistics will be produced for prevalence and incidence of AATD, by all covariates.

The number of patients/observations and percentage per category, mean plus standard deviation and median plus inter-quantile range will be given, as appropriate.

Statistical tests (e.g. F-tests, t-tests, chi-squared tests) and models (e.g. linear models) will be used, as appropriate.

Statistically significant results will be defined as $p<0.05$.

Proposed tables and figures:

Table 1. Characteristics of AATD patients- demographic and clinical.

Figure 1. STROBE flow-chart of the population
Figure 2. Prevalence (%) of AATD in the UK from 1990 to 2015 by sex.

Figure 3. Age- and sex specific prevalence of AATD (per thousand) in the UK from 1990 to 2015. Rates are plotted for men () and women () on a log scale for subjects aged 65+, 45–65, and 20–44 years.

Figure 4. Age- and sex specific incidence of AATD (per thousand) in the UK from 1990 to 2015. Rates are plotted for men () and women () on a log scale for subjects aged 65+, 45–65, and 20–44 years.

PATIENT INVOLVEMENT

There are no plans to involve patients at this stage.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

This is an exploratory protocol. There are a number of intrinsic limitations we can already envisage, that will be listed and incorporated in discussion of the manuscript, including:

- A limitation of the study is that it will be conducted in a dataset comprising UK practice data only, which may limit its generalisability to non-UK cough patient populations treated in different healthcare settings. Moreover, although the OPCRD comprises records of patients drawn from a wide and heterogeneous range of UK practices, the practices have not been specifically selected to be representative of the UK as a whole.
- This study will only apply to patients diagnosed with COPD before the age of 60 years, so will exclude those tested for AATD who do not have a diagnosis of COPD or those diagnosed with COPD after the age of 60 yrs.
- Given universal levels of high underdiagnosis of both COPD and AATD, and as most COPD patients are never tested for AAT, many COPD patients may have

undiagnosed AATD. This study will however give an indication into the frequency of testing.

- The reliability of Read codes in Primary Care for diagnosing AATD may be an issue. It is very frequent to observe in clinical records a diagnosis of AATD in individuals with a serum level just below the threshold of normal values (i.e. 1 g/L), usually corresponding to a heterozygote or even a normal phenotype.

DATA DISSEMINATION PLANS

Results of this study will be presented initially as a conference abstract, followed by a manuscript submitted to an appropriate peer-reviewed scientific journal within 12 months of completion of the study.

STUDY TEAM

Scientific Committee:

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All participated with REG and RiRL in the protocol development and, jointly with other REG investigators, will be leading the publication/s and dissemination of results.

REG:

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ETHICS

Approval by ADEPT will be requested. As per REG policy, and once is endorsed by all parties, this protocol will be registered with ENCePP.

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APPENDIX: DATASET TO BE USED FOR ANALYSIS

Read codes used

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

Positive results