Study information

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alopecia Areata
BMI	Body Mass Index
CPRD	Clinical Practice Research Datalink
DSP	Data Security and Protection
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
ESA113	Employment Support Allowance
GEP	Good Epidemiological Practice
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
IB113	Incapacity benefit
ICD10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IEA	International Epidemiological Association
IMD	Index of Multiple Deprivation
ISPE	International Society for Pharmacoepidemiology
ISPOR	Pharmacoeconomics and Outcomes Research
NHS	National Health Service
OPCRD	Optimum Patient Care Research Database
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre

SAP	Statistical Analysis Plan
SD	Standard Deviation
SES	Socioeconomic Status
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Report title:
Healthcare disparities in alopecia areata: UK population-based cohort study

Version:
1.0

Protocol date: 02 November 2022

Main author: Mr. John Nesnas, Pfizer Ltd.

Rationale and background:

Alopecia areata (AA) is a common, immune-mediated non-scarring form of alopecia. Our previous work has provided the most comprehensive analysis of the epidemiology of AA to date. We found that AA is more common in people of lower socioeconomic status and in people from Black, Asian, and mixed ethnic groups compared to those of White ethnicity. However, these data formed a small component of the initial study and there is substantial scope to expand on these initial data to provide a greater understanding of the total disease burden across these groups including reporting lifetime risk estimates.

Research question and objectives:

The overall purpose of the study is to provide an estimate of the cumulative lifetime incidence of AA in the population overall and by (important) sociodemographic groups. Moreover, to do a subgroup analysis in the AA population to identify health-related disparities across people in different socioeconomic strata, geographical distribution, sex and ethnic groups.

Study Design:

The study will use retrospectively collected anonymised data from all eligible patients in the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) dataset at the date of data extraction. A cross-sectional design (incidence) will be used to assess the total disease burden of AA, stratified by sociodemographic groups. A matched-cohort design will be used for incidence of AA related: Mental health conditions; work impact; healthcare utilisation.

Population:

The cohort for this study will consist of all adults and children (aged 12+) contributing to RCGP RCS database during the study period (between January 1, 2009 and December 31, 2018 inclusive). People diagnosed with AA will be identified using diagnosis codes specific to the condition.

Variables:

Exposure: People diagnosed with AA as defined by clinical diagnosis codes.

Outcomes: For the impacts of AA on different sociodemographic groups assessment outcomes will comprise: incidence of AA, depressive episodes, recurrent major depression, anxiety disorders, dermatology referrals, primary care visits, referrals for psychological therapy, psychiatric reviews, time off work for illness and unemployment.

Covariates: Three different adjustment sets will be used for each endpoint analysis. These include: an unadjusted model, a sex and age adjusted model, and a multivariable model with an adjustment set of: body mass index (BMI), smoking status, alcohol use, and common comorbidities: type 2 diabetes, hypertension, atrial fibrillation, angina, acute myocardial infarction, stroke, heart failure, chronic liver disease, dementia, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, chronic kidney disease, malignancy and inflammatory bowel disease.

Data sources:

The RCGP RSC is the longest running primary care network in the UK, collecting weekly data since 1964. The RCGP RSC database contains complete data on all events and clinical entities coded in UK primary care.

Study size:

The RCGP RSC cohort is drawn from a large GP practices network across England, currently covering a registered population of 2.6 million people, representing a broadly representative sample of the UK.

Data Analysis:

Cumulative lifetime incidence of AA will be estimated using cases of incident AA occurring during the observational study period (January 1, 2009 and December 31, 2018). For all analyses, the overall results including both adults (aged 18+) and children (aged 12-17) will be published, with stratification by sex, ethnicity, deprivation quintile, geographic region and urban/rural classification. The assessment of any associations with baseline characteristics and the outcomes of interest will be assessed using Cox proportional hazards models (time to event outcomes) and Poisson regression (repeated event outcomes) models. Three different adjustment sets will be used for each endpoint analysis.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	25-October-2022
End of data collection	24-January-2023
Study progress report	29-November-2022
Final study report	21-February-2023

7. RATIONALE AND BACKGROUND

Alopecia areata (AA) is a common, immune-mediated non-scarring form of alopecia. Our previous work has provided the most comprehensive analysis of the epidemiology of AA to date[1]. This study demonstrated that the incidence of AA is 0.26 per 1,000 person-years in the UK (United Kingdom), with a peak incidence at age 25-29; however incident AA occurs across the lifespan. We found that AA is more common in people of lower socioeconomic status and in people from Black, Asian, and mixed ethnic groups compared to those of White ethnicity[2]. However, these data formed a small component of the initial study and there is substantial scope to expand on these initial data to provide a greater understanding of the total disease burden across these groups including reporting lifetime risk estimates. Current lifetime risk estimates are taken from a single population-based study with just 530 AA cases in a single region of the United States (US)[3] and most reported age, sex and ethnicity prevalence estimates that have been produced from studies performed in secondary care[4-8]. These studies are likely to be missing a large proportion of cases and therefore substantially underestimate the total disease burden in these groups.

Our previous work strongly suggested there are significant socioeconomic and ethnic disparities in healthcare and outcomes in people with AA. A comprehensive assessment of these potential disparities in AA is needed, this would strongly complement the existing work and support the use of newer therapies in AA.

Our previous work has also demonstrated that AA is associated with significant psychological consequences including an increased incidence of depression and anxiety[9]. These data suggest a socioeconomic gradient in the mental health impacts of AA (with AA associated with a greater mental health burden in those with lower socioeconomic status). However, the study was not designed to assess this as a primary outcome, and further analysis is required to fully understand these potential relationships.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Study Objectives

The overall purpose of the study is to provide an estimate of the cumulative lifetime incidence of AA in the population overall and by sociodemographic groups (sex, ethnicity, deprivation, geographic location and urban-rural status). Moreover, to perform a subgroup analysis in the AA population to identify health-related disparities across people in different socioeconomic strata, geographical distribution, sex and ethnic groups. The disparities that will be considered are AA associated: Mental health conditions; healthcare utilisation; and work impact (time off work and unemployment).

8.2. Primary Objectives

8.2.1. Objective 1

Describe the total burden of AA (cumulative lifetime incidence) across sociodemographic groups (including geographical distribution).

8.2.2. Objective 2

Describe any disparities in AA related mental health conditions across sociodemographic groups.

8.2.3. Objective 3

Describe any disparities in AA healthcare utilisation across sociodemographic groups.

8.3. Secondary Objectives

8.3.1. Objective 4

Describe any disparities in AA related work impact (time off work and unemployment) across sociodemographic groups.

9. RESEARCH METHODS

9.1. Study design

The study will use retrospectively collected anonymised data from all eligible patients in the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) dataset at the date of data extraction. The cohort to be used for this study has already been specified for previous work as follows:

All adults and adolescents (aged 12+) registered with practices contributing data to RCGP RCS between January 1, 2009 and December 31, 2018, will be eligible for inclusion in the study. People who have opted out of record sharing will not be included (approximately 1.8% of the adult population) and have not been uploaded to the RCGP RCS database. Cumulative lifetime incidence of AA will be estimated using cases of incident AA occurring during the observational study period (January 1, 2009 and December 31, 2018). For all analyses, the overall results including both adults

(aged 18+) and children (aged 12-17) will be published, with stratification by sex, ethnicity, deprivation quintile, geographic region and urban/rural classification.

The assessment of any associations with baseline characteristics and the outcomes of interest (objectives 2-4) will be assessed using Cox proportional hazards models (time to event outcomes) and Poisson regression (repeated event outcomes) models. Three different adjustment sets will be used for each endpoint analysis. These include: an unadjusted model, a sex and age adjusted model, and a multivariable model with an adjustment set of: body mass index (BMI), smoking status, alcohol use, and common comorbidities: type 2 diabetes, hypertension, atrial fibrillation, angina, acute myocardial infarction, stroke, heart failure, chronic liver disease, dementia, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, chronic kidney disease, malignancy and inflammatory bowel disease.

9.1.1. Total disease burden; cumulative lifetime incidence

A cross-sectional design (incidence) will be used to assess the total disease burden of AA, stratified by sociodemographic groups.

9.1.2. Disparities in the impact of AA on mental health, work impact and healthcare utilisation

A matched-cohort design will be used for incidence of AA related: Mental health conditions; work impact; healthcare utilisation.

9.2. Setting

The RCGP RSC cohort is drawn from a large GP practices network across England, currently covering a registered population of 2.6 million people, representing a broadly representative sample of the UK.[10]

9.2.1. AA Definition

People diagnosed with AA will be identified using diagnosis codes specific to the condition.[11] People will be considered to have an AA diagnosis if they had an AA specific diagnosis code and, in the subsequent 365 days, no code for an alternative diagnosis (scarring alopecia[12], traction alopecia, congenital alopecia, androgenetic alopecia, telogen effluvium, tinea capitis, trichotillomania, or secondary syphilis of the scalp).

Incident cases will be defined as people with a first ever diagnosis code of AA during the study period. People with a diagnosis of AA prior to the study period will be excluded. To increase certainty that an AA diagnosis was incident, those diagnosed within six months of registering with a practice will be excluded.

9.2.2. Sociodemographic subgroups

Age, sex, socioeconomic status, ethnicity, major regions of England and urban/rural classification will comprise the sociodemographic factors used for stratification of the outcome measures.

Ethnicity will be grouped using the standardised definitions of major UK ethnic groups: Black, Asian, White mixed, and others.[13]

Socioeconomic status (SES) will be defined using the national deprivation measure; index of multiple deprivation (IMD) and stratified into quintiles of deprivation according to the national distribution.[14] IMD is calculated at the point of data extraction, using patient postcode.

Age will be stratified into four age categories: children aged 12-17, 18-29, 30-49 and 50+ based on our previous research into incidence of AA.[2]

Geographical distribution will consist of two subgroups including; geographic region and urban/rural classification. Geographic region within England comprises; Greater London, South East, South West, West Midlands, North West, North East, Yorkshire and the Humber, East Midlands, and East of England.

9.2.3. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. The cohort for this study will consist of all adults and children (aged 12+) contributing to RCGP RCS database during the study period (between January 1, 2009 and December 31, 2018 inclusive).

2. The AA population consists of patients newly diagnosed with AA at any point during the study period.

9.2.4. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. People with the alternative non-AA diagnoses (section 9.2.1).
2. People with AA diagnosis within 6 months of registration.
3. People with less than 1 year of follow up within the dataset.
4. People over the age of 95.

9.3. Variables

The variables to be utilised are listed below:

Variable	Role	Operational definition
Age	Baseline characteristic, subgroup variable, and potential confounder	Age will be defined as of the index date.
Sex	Baseline characteristic, subgroup variable, and potential confounder	Identified from primary care records using clinical codes.
Socioeconomic deprivation	Baseline characteristic, subgroup variable and potential confounder	Defined using the Index of Multiple Deprivation which is divided into national quintiles.
Ethnicity	Baseline characteristic, subgroup variable, and potential confounder	Identified from primary care records using clinical codes.
UK geographic region	Baseline characteristic, subgroup variable, and potential confounder	The United Kingdom will be divided into nine regions: Greater London, South East, South West, West Midlands, North West, North East, Yorkshire and the Humber, East Midlands, and East of England. Geographic region will be captured from enrollment data.
Urban/Rural classification	Baseline characteristic, subgroup variable, and potential confounder	Defined as urban or rural area which will be captured from enrollment data.
Alopecia Areata	Case definition	Identified from primary care records using clinical codes.
Depressive episodes	Outcome	Defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) classification, and identified using algorithms validated or use in UK primary care data.
Recurrent major depression	Outcome	Defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) classification, and identified using algorithms validated or use in UK primary care data.
Anxiety disorders	Outcome	Defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) classification, and identified using algorithms validated or use in UK primary care data.
Dermatology referrals	Outcome	Identified from primary care records using clinical codes.
Primary care visits	Outcome	Identified from primary care records using clinical codes.
Referrals for psychological therapy	Outcome	Identified from primary care records using clinical codes.
Psychiatric reviews	Outcome	Identified from primary care records using clinical codes.
Time off work for illness	Outcome	Defined using primary care codes for ‘sick leave’ or the issuing of a Med 3 certificate indicating time off work for illness
Unemployment	Outcome	Defined using primary care codes indicating unemployment or incapacity from work (IB113 [incapacity benefit] form or ESA113 form [Employment Support Allowance, which replaced IB113 from January 2011])
Body mass index	Potential confounder	Identified from primary care records using clinical codes.

Smoking status	Potential confounder	Identified from primary care records using clinical codes.
Alcohol use	Potential confounder	Identified from primary care records using clinical codes.
Type 2 diabetes	Potential confounder	Identified from primary care records using clinical codes.
Hypertension	Potential confounder	Identified from primary care records using clinical codes.
Atrial fibrillation	Potential confounder	Identified from primary care records using clinical codes.
Angina	Potential confounder	Identified from primary care records using clinical codes.
Acute myocardial infarction	Potential confounder	Identified from primary care records using clinical codes.
Stroke	Potential confounder	Identified from primary care records using clinical codes.
Heart failure	Potential confounder	Identified from primary care records using clinical codes.
Chronic liver disease	Potential confounder	Identified from primary care records using clinical codes.
Dementia	Potential confounder	Identified from primary care records using clinical codes.
Rheumatoid arthritis	Potential confounder	Identified from primary care records using clinical codes.
Asthma	Potential confounder	Identified from primary care records using clinical codes.
Chronic obstructive pulmonary disease	Potential confounder	Identified from primary care records using clinical codes.
Chronic kidney disease	Potential confounder	Identified from primary care records using clinical codes.
Malignancy	Potential confounder	Identified from primary care records using clinical codes.
Inflammatory bowel disease	Potential confounder	Identified from primary care records using clinical codes.

9.4. Primary Endpoints

Objective 1: An incident diagnosis of AA is the date of the first diagnosis code in the record and no alternative diagnosis that merits exclusion (any form of scarring alopecia[12], traction alopecia, congenital alopecia, androgenetic alopecia, telogen effluvium, tinea capitis, trichotillomania, or secondary syphilis of the scalp) diagnosed in the subsequent 365 days from date of AA diagnosis.

Objective 2: Mental health condition outcomes will be assessed up to two years post-AA diagnosis and will comprise new onset depressive episodes, recurrent major depression, and anxiety disorders, defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) classification, and identified using algorithms validated for use in UK primary care data.

Objective 3: Healthcare utilisation outcomes will comprise primary care visits, dermatology referrals, referrals for psychological therapy (including those via IAPT; Improving Access to Psychological Therapies) and psychiatric reviews in the two years post AA diagnosis.

9.5. Secondary Endpoints

Unemployment in the two years post-AA diagnosis will be identified using Read codes relating to unemployment recorded in the primary care record or the issuing of IB113 or ESA113 forms.

Time off work in the two years post-AA diagnosis will be indicated by the issuing of Med 3 certification from primary care (Statement of Fitness for Work certification).

9.6. Data sources

The RCGP RSC is the longest running primary care network in the UK, collecting weekly data since 1964. The RCGP RSC database contains complete data on all events and clinical entities coded in UK primary care. These include demographic information, clinical diagnoses, laboratory test results, primary care issued prescriptions, process of care codes (e.g. specialist dermatology reviews), and anthropometric measurements (e.g. BMI), and are coded using the Read Coding system.[15]

9.7. Study size

9.7.1. Sample size calculations

A sample size calculation is only applicable to the incidence of mental health conditions of anxiety and depression in people diagnosed with AA.

Assuming 80% power, a 5% level of statistical significance and a background population prevalence of 15% for anxiety and 10% for depression,[16] our anticipated sample size for AA (n = 6007) would be sufficient to detect a risk difference of 1.2% in depression between those with and without AA, and 1.5% difference in anxiety between those with and without AA. Sample size calculations were performed in OpenEpi,[17] results are presented using methods of Kelsey.[18]

9.8. Data management

This study will utilise the previously extracted data from our previously published study.[9] Individual patient data was anonymized at the point of data extraction. All data will remain in anonymized form and will be held on a secure server at the University of Oxford. The data will not be used for any purposes other than for the research which is described in the respective protocols and which has been approved by the RCGP RSC Research Committee. The sponsor, Pfizer Ltd, will not have access to the individual anonymised patient data.

All statistical analyses will be performed using R version 4.2.1.

9.9. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.10. Quality control

The sponsor delegates the conduct of this study to Momentum Data. The Momentum Data team will have full access to all the anonymized data in the study and all employees have completed information governance, information security, and data protection training provided by the University of Oxford and NHS (National Health Service) Digital. Data will be controlled in accordance with data protection legislation, protocols and policies of Momentum Data and NHS policies and processes, as defined in the NHS Data Security and Protection [DSP] toolkit for research and information governance. The research team at Momentum Data have extensive experience in working with routine healthcare data and have all completed relevant advanced degrees and have extensive experience using various large healthcare data sources from the UK including CPRD (Clinical Practice Research Datalink), The Health Improvement Network (THIN), RCGP RSC database, Optimum Patient Care Research Database (OPCRD), and others.

All codes lists utilised for data extraction will undergo the rigorous quality control process utilised by Momentum Data for multiple real world evidence studies. This process consists of manual code list generation by a coding expert with a clinical background. The list is then independently reviewed by a second coding expert. The lists then go through an automated quality control process to identify any potential formatting errors or coding inconsistencies. During the data extraction process, high frequency codes are independently reviewed by a third reviewer to ensure that the most commonly used codes correctly match the clinical entity they are being used to identify. A fourth quality control step may also be used to look for overlap between code or case definitions where multiple definitions are possible e.g., biochemical disease markers and clinical diagnosis codes for a condition. Finally once variables have been generated, the frequency and pattern of variable prevalence is compared with known data from previous analysis in other independent datasets and published literature. Any inconsistencies are reviewed and investigated as appropriate.

Statistical programming output is quality controlled by an independent statistical programmer. All final study outputs including tables and figures are subject to quality control review by two independent reviewers.

9.11. Limitations of the research methods

Disparities between sociodemographic subgroups will be interpreted based on the assumption of the primary/secondary outcomes being related to the AA. We have no definite way to identify that every occurrence of an outcome is related to AA in the context of healthcare utilisation and work impact outcomes.

This is an ecological study limited to the UK population and may not be generalisable to other populations.

We expect a substantial amount of missing data for the ethnicity variable which is a limitation of the dataset itself and could result in bias. Necessary sensitivity analyses will be undertaken to circumvent this and limit any impact this could have in our analysis.

We will perform additional exploratory analysis into the time between dermatology referral and dermatology review with the goal of potentially identifying NHS and private referrals and exploring regional differences. If this data is sufficient, based on provisional analysis, we will include additional study endpoints using this lag time between referral and dermatology review.

9.12. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymised structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymised structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10.
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in healthcare decision making

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)

- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

- Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

- Study reporting will be conducted in accordance with the relevant EQUATOR (Enhancing the QUAlity and Transparency Of health Research) guidelines.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse event *(AE)* /adverse reaction reporting is not required for this study design. It will not be possible to identify AEs from the data captured for this study.

This study involves data that exist as structured data by the time of study start. It is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (*i.e.,* identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study manuscript will be developed for submission to a scientific peer reviewed journal. Additional study outputs may be presented at conferences and/or scientific symposia.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

No study tables are included

15. LIST OF FIGURES

No figures are included

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.