The incidence, prevalence, treatment patterns, and disease management for atopic dermatitis in the UK

Academic contributors

Carsten Flohr[1], Simon de Lusignan[2]

[1] St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London

[2] Department of Clinical and Experimental Medicine, University of Surrey, Guildford, United Kingdom

The research is supported by Momentum Data Ltd

Email: info@momentumdata.co.uk

Visit: www.momentumdata.co.uk

Momentum Data Ltd is registered in England and Wales. Registration number 10909587. VAT number 277446075.

Abstract

Background

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic inflammatory skin condition however there are large variations in prevalence estimates. It is also associated with other atopic conditions, and mental health conditions although the strength of these associations has not been fully explored. It is also not clear how much healthcare resource utilisation there is by people with AD in the UK.

Objective

We aim to calculate current and accurate prevalence and incidence estimates for AD by age group and sociodemographic factors. We also aim to describe the burden of comorbidity in AD with a focus on atopic and mental health conditions. We also aim to describe the health care resource utilisation of this cohort in terms of prescription use, primary care appointments, and specialist referrals.

Method

We will define AD cases using a previously validated algorithm for case identification use clinical codes form primary care in the UK (Read codes). We will analyse the population prevalence and incidence of AD using this definition over a 10-year period (2008-2018). Within this population we will report the prevalence of autoimmune conditions (rheumatoid arthritis, inflammatory bowel disease, coeliac disease, type 1 diabetes, and multiple sclerosis) compared with a cohort of individuals without a diagnosis of AD, matched by age and sex at GP practice level. In the same cohort we will also report the annual use of topical and oral medications used for the treatment of AD, primary care appointments, and specialist referrals, overall and stratified by sociodemographic factors.

Lay Summary

Atopic dermatitis, commonly called eczema, is one of the most frequently occurring skin conditions. It is estimated to affect around one fifth of children in developed countries and is also becoming increasingly common in less developed countries. Exact estimates of how common eczema actually is, vary considerably and there has not been an in-depth analysis of the number of people with eczema in the UK. It is also unclear which groups of people are most affected and which treatment options are being used.

Most people with eczema are managed by their GP with only a few people requiring specialist care. GP records therefore provide an excellent opportunity to explore how common eczema is and which treatments are being used currently. Through these studies we aim to provide accurate estimates of the number of people with current eczema (prevalence), number developing new onset eczema (incidence), and the pattern of common comorbidities in people with eczema. We also aim describe current treatment patterns by age groups and other factors. We will look back over the last decade to identify how the number of people with eczema and treatments changing over time. We will also explore patterns in the people most commonly affected and in the treatments used.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin condition which affects around 200 million people worldwide.[1] It most commonly develops in the first year of life although the onset can occur at any age.[2,3] AD usually often follows a relapsing-remitting course and remission may require the use of maintenance therapies.[4] Whilst the majority of affected children will have resolution or improvement by late childhood,[2] a substantial proportion of people will have ongoing AD into adulthood and flares can occur even after long periods of remission.[3,5] AD can be extremely disabling and can have a significant psychological impact in both children and adults[6-8] and it has been estimated that around 30% of AD is moderate or severe.[9] The current treatment approach involves avoidance of individual trigger factors, the application of emollients, and a multistep approach to the use of anti-inflammatories depending on disease severity.[4]

In the UK prevalence estimates vary widely, especially in adults. Recent questionnaire-based studies suggest wide ranging prevalence rates of 2.5-15%.[10,11] Given that 97% of AD patients are seen and treated in principally in primary care in the UK, databases of electronic health records from GP practices provide a rich data source from which epidemiological analyses can be derived.[12] Using the UK Clinical Practice Research Datalink (CPRD), approximately 500,000 people were identified as having AD between 1998-2015 which scales to an approximate UK prevalence of 10%.[13] However, the limitation of this study is that it was originally designed to assess cardiovascular outcomes in AD not prevalence per se and only assessed the adult population. Incidence rates of eczema have been recently described in the UK to 2015, but only in children.[14,15]

AD is associated with a wide range of comorbidities. Children with AD are at increased risk of asthma and allergic rhinitis,[2] and depression is more common in both children and adults.[8] Severe and active AD was also demonstrated to be a risk factor for incident cardiovascular disease in a recent UK primary study,[13] and an association with an increased risk of new-onset rheumatoid arthritis and inflammatory bowel disease, but a decreased risk of type 1 diabetes,

Momentum Data Ltd is registered in England and Wales. Registration number 10909587. VAT number 277446075.

has been observed in population data.[16] However, high quality data on the overall pattern of comorbidity in individuals with AD are lacking.[17]

The burden of management falls largely on primary care in the UK with 97% of people with AD seen and treated primarily by their GP.[12] Attendance rates are also high with 96% children with AD reported to have had a primary care attendance within the preceding year.[18] It has been estimated that 16-30% of AD is moderate or severe,[9,18] and whilst those with more severe disease are more likely to be referred for specialist care, the majority of these cases are still managed without secondary care referral.[18] The most significant monetary costs for AD are also due to primary care attendances and prescribing.[19] Despite this high disease burden of AD a contemporary overview of healthcare and treatment utilisation in children and adults with AD in the UK is currently lacking.

Aims

In these retrospective cohort studies, we aim to describe:

1. The incidence and prevalence of AD in primary care in children and adults, including variation by sociodemographic factors and calendar year.
2. Patterns of possible AD-associated comorbidity post-diagnosis.
3. Prescribing patterns for individuals with AD, and how prescribing varies by sociodemographic factors and calendar time.
4. Patterns of treatment escalation in individuals with AD.

Methods

Study design and population

We aim to perform a retrospective cohort study using the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database. All adults and children of any age contributing data to the RCGP RCS database between January 1, 2008 and January 1, 2018 for at least one year, will be eligible for inclusion in the study.

Treatments for AD are also used to treat other conditions and the indication from treatment is not readily available from large datasets in the UK. We will therefore exclude people with potential confounding comorbidities from our AD cohort when assessing treatment utilisation. We will exclude people with skin conditions also excluded by Abuabara et al.[20] (psoriasis, contact dermatitis, photodermatitis, and ichthyosis), those with inflammatory bowel disease (IBD), or rheumatoid arthritis, and those with a history of organ transplantation. IBD and rheumatoid arthritis will be identified using approaches validated in UK primary care databases and previously described.[21-23] In the absence of a validated method to identify the presence of organ transplantation from routine UK primary care data, this will be identified using a Read code list generated in accordance with published guidance.[24,25]

Atopic dermatitis definition

Individuals with AD will be identified using a validated algorithm developed for use with the UK electronic health record,[20] and used in recent UK studies in AD.[13,14] The positive predictive value of this algorithm is 90% (95% Confidence interval (CI) 80-91%) in children and 82% (95% CI 73- 89%) in adults.[20] In brief, AD is identified by the presence of one diagnostic code and with at least two eczema-related treatment codes on separate days within three months before or one year after the diagnostic code.

AD severity will be defined using the approach used by Silverwood et al. in their study of cardiovascular outcomes in AD:[13] AD will be considered moderate at the prescription of a second potent topical corticosteroid treatment within one year or a first topical calcineurin inhibitor (TCI). AD will be considered severe at the first of a systemic immunosuppressant treatment, phototherapy, or a dermatology referral.

Active AD has been defined from electronic health records in a recent study as: The onset of active AD was defined as the later of two AD records appearing within any one year period.[13] Active AD was then assumed to last for one year, unless another AD record appeared in which case its duration was be prolonged for a further one year period.[13] We will utilise this approach

but use the first of two codes (rather than the latter) within one year to signify the onset of active AD, as this has been shown to have good agreement to physician confirmed onset.[20]

Primary care visits and specialist referrals definitions

A primary care visit for AD will be defined as any primary care attendance associated with either a diagnostic code for AD or a prescription for one or more AD treatments. Specialist referrals will be identified by the presence of a Read code for referral to; a dermatologist, a GP with a specialty interest in dermatology, or dermatology specialist nurse.

Definition of baseline variables

Age will be initially grouped in accordance with trial data reporting, as follows: 0-1, 2-6, 7-11, 12-17, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, >80 years. To examine how disease incidence varies across other sociodemographic factors stratified by age at diagnosis we will also define broader age groups. Ethnicity will be categorised as follows using a previously described informatics ontology for ethnicity and using the major UK census categories:[26,27] White, Asian, Black African/Caribbean, Mixed, Other, or not reported.

Deprivation will be defined based using the official national deprivation measure; index of multiple deprivation (IMD).[28] IMD is calculated based on patient postcode at the point of data extraction. Scores will be divided into quintiles based on the national distribution of IMD scores.

Other factors included for analysis comprise; smoking status, alcohol use, concomitant atopic diseases, depression, family history of atopy, biomarkers and laboratory test, and other comorbidities.

Definition of atopic dermatitis-associated conditions

AD-associated conditions considered will comprise: asthma, allergic rhinitis, depression, anxiety, other psychological disorders, rheumatoid arthritis, inflammatory bowel disease, coeliac disease, type 1 diabetes, multiple sclerosis, and alopecia.

Atopic dermatitis treatments

We will analyse prescription records for the following therapy classes commonly used to manage AD in the UK; emollients and soap substitutes, oral anti-histamines, topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), oral systemic treatments (ciclosporin, azathioprine, oral steroids, mycophenolate mofetil [MMF] and methotrexate), topical antimicrobial treatments, and phototherapy.

Treatment escalation

We will analyse three elements of treatment escalation in AD: Firstly, the proportion of people prescribed a potent or very potent topical steroid who have escalated from a prescription for a mild or moderate potency steroid in the preceding weeks. Secondly, the proportion of people prescribed a TCI who have escalated from potent topical steroid or less potent steroid in the preceding weeks. Thirdly, the proportion of people initiated on treatment with systemic therapies who have undergone previous treatment with phototherapy.

Statistical Analyses

Prevalence

We will estimate time trends of the prevalence of AD by calendar year over the study period, overall and by age group. Prevalent individuals will be defined those fulfilling the diagnostic criteria for AD at the mid-point (July 1) of the calendar year in question. Prevalence will be calculated by dividing the number of prevalent individuals by the total number of eligible individuals in the study population at the same time point. In the 2017 cohort of prevalent individuals we will then estimate the age group stratified prevalence of AD by sociodemographic factors (sex, ethnicity, IMD), and geographical region. All prevalence (and incidence) estimates will be standardised to UK population estimates. Prevalence of moderate and severe AD within the AD population (denominator) will be calculated using the same approach.

Incidence

Incident cases will be defined as individuals with a first ever diagnostic Read code for AD during the study period. Patients with a diagnosis of AD prior to the study period will be excluded. At

least one year follow-up prior to the diagnosis date will be required to confirm the diagnosis was incident. Individuals with a diagnosis within one year of registering with a practice will be excluded from the incident analysis, unless under one year old. Age-standardised incidence rates (per 100 person-years), stratified by age, other sociodemographic factors and calendar year, will be calculated by dividing the number of incident patients by the sum of person-years of follow-up for the total eligible population over the study period. Adjusted incidence rate ratios by sociodemographic factors will be estimated using Poisson regression.

In the incident cohort with AD we will examine disease trajectories by describing the proportion of individuals who developed moderate and severe AD post-diagnosis. We will evaluate the impact of sociodemographic predictors on time to first occurrence of moderate and severe AD using Cox proportional hazards models. Time to return to active AD will also be evaluated in the subset of individuals whose disease was defined as active at diagnosis using the same approach.

AD-associated conditions

In the prevalent cohort we will describe the prevalence of AD-associated comorbidities in all individuals at the start of follow-up. Start of follow-up for an individual with AD will be defined as the latest of: 1 Jan 2008, the date of diagnosis of AD, or 365 days after practice registration. Prevalence estimates will be compared to those of a matched unexposed cohort without AD. The matched unexposed cohort will be defined by matching individuals in the exposed cohort with individuals without a diagnosis of AD, by age and sex at GP practice level. The start of follow-up for each matched individual will be the start of follow-up of their matched counterpart. Unexposed individuals will be required at have at least one year of follow-up in RCGP RCS when matched to minimise the risk they have a non-recorded existing diagnosis of AD.

We will then examine the risk of new onset autoimmune conditions (RA, IBD, coeliac disease, type 1 diabetes, and MS) in individuals with AD without a pre-existing autoimmune condition at the start of follow-up compared to the matched unexposed cohort. Follow-up for all individuals will end at the earliest of the study end-date (January 1, 2018), the date of patient transfer from an included practice, date of death, or the date an individual developed an outcome of interest. We will include all individuals contributing at least 1 day of follow-up time in the analysis. We

will estimate the risk of each autoimmune condition separately using time to failure analysis. Initially, unadjusted Cox proportional hazards models, stratified by matched set (AD versus non-AD), will be used to provide overall hazard ratios as summary estimates for the association of the presence of AD with the time to each autoimmune condition. Models were subsequently adjusted for duration of disease, baseline sociodemographic factors, clinical measures, and comorbidities in multivariable analysis.

Prescribing patterns

Within the prevalent population we will describe prescribing patterns for AD and active AD overall, stratified by sociodemographic factors, and as yearly time trends. Prescribing rates will be calculated as the number of individuals with AD receiving at least one prescription for a particular medication class during a year divided by the number of eligible individuals with AD at the mid-point of that calendar year.

Treatment escalation

For the three treatment escalation steps we will describe overall rates of stepwise escalation (contrasted with immediate use of more potent treatment) and rates stratified by demographic factors.

Secondary analyses

Secondary analyses in the form of subgroup comparisons and sensitivity analyses using alternative statistical approaches to evaluation will be used where appropriate to corroborate or further explore any unexpected findings.

Ethical approval

Study approval will be requested from the Research Committee of the RCGP RSC. The study does not meet the requirements for formal ethics board review as defined using the NHS Health Research Authority research decision tool (http://www.hra-decisiontools.org.uk/research/).

Dissemination of results

We aim to produce high-quality publications for submission to a high impact journals.

Contributors

Research support for this project in several areas including data analysis, literature searching, and medication writing will be provided by Momentum Data. John Dennis and Andrew McGovern of Momentum Data have contributed to the writing of this protocol and to the study design. Funding for these studies has been provided by Pfizer UK.

Scientific rigor and study registration

The team ethos at Momentum Data is to support the highest quality research, for patient benefit, with rigorous scientific standards. Publication bias remains an issue in observational studies. Therefore, and in accordance with RCGP RSC requirements, if approval is granted the protocol will be registered as an observational study with ClinicalTrials.gov and made publicly available prior to the commencement of data analysis. Any protocol amendments will be published alongside this public record of the study and will be noted in any final publication with the rationale for the modification. Any changes will be assessed for the need for ethics approval and further RCGP RSC study approval; these will be sought if required.

References

1. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)* 2017; **390**(10100): 1211-59.
2. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *The Journal of allergy and clinical immunology* 2004; **113**(5): 925-31.
3. Garmhausen D, Hagemann T, Bieber T, et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy* 2013; **68**(4): 498-506.
4. Weidinger S, Novak N. Atopic dermatitis. *Lancet (London, England)* 2016; **387**(10023): 1109-22.
5. Peters AS, Kellberger J, Vogelberg C, et al. Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: a prospective cohort study. *The Journal of allergy and clinical immunology* 2010; **126**(3): 590-5.e1-3.
6. Howlett S. Emotional dysfunction, child-family relationships and childhood atopic dermatitis. *The British journal of dermatology* 1999; **140**(3): 381-4.
7. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *The Journal of allergy and clinical immunology* 2013; **131**(2): 428-33.
8. Dalgard FJ, Gieler U, Tomas-Aragones L, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015; **135**(4): 984-91.
9. Silverberg JI, Vakharia PP, Chopra R, et al. Phenotypical Differences of Childhood- and Adult-Onset Atopic Dermatitis. *The journal of allergy and clinical immunology In practice* 2018; **6**(4): 1306-12.
10. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy* 2018; **73**(6): 1284-93.
11. Kantar: Research daic. Atopic Dermatitis Prevalence – UK. *n/a* 2017
12. Abuabara K, Magyari AM, Hoffstad O, et al. Development and Validation of an Algorithm to Accurately Identify Atopic Eczema Patients in Primary Care Electronic Health Records from the UK. *The Journal of investigative dermatology* 2017; **137**(8): 1655-62.
13. Silverwood RJ, Forbes HJ, Abuabara K, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ (Clinical research ed)* 2018; **361**: k1786.
14. Ban L, Langan SM, Abuabara K, et al. Incidence and sociodemographic characteristics of eczema diagnosis in children: A cohort study. *The Journal of allergy and clinical immunology* 2018; **141**(5): 1927-9.e8.
15. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis : contact, atopic, occupational, drug* 2014; **25**(3): 107-14.
16. Schmitt J, Schwarz K, Baurecht H, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *Journal of Allergy and Clinical Immunology* 2016; **137**(1): 130-6.
17. Weidinger S, Novak N. Atopic dermatitis. *The Lancet* 2016; **387**(10023): 1109-22.
18. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in

the community and its relationship to secondary referral. *The British journal of dermatology* 1998; **139**(1): 73-6.
19. Verboom P, Hakkaart-Van L, Sturkenboom M, De Zeeuw R, Menke H, Rutten F. The cost of atopic dermatitis in the Netherlands: an international comparison. *The British journal of dermatology* 2002; **147**(4): 716-24.
20. Abuabara K, Magyari AM, Hoffstad O, et al. Development and Validation of an Algorithm to Accurately Identify Atopic Eczema Patients in Primary Care Electronic Health Records from the UK. *Journal of Investigative Dermatology* 2017; **137**(8): 1655-62.
21. Stapley SA, Rubin GP, Alsina D, Shephard EA, Rutter MD, Hamilton WT. Clinical features of bowel disease in patients aged <50 years in primary care: a large case-control study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2017; **67**(658): e336-e44.
22. Abrahami D, Douros A, Yin H, et al. Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ (Clinical research ed)* 2018; **360**.
23. Muller S, Hider SL, Raza K, Stack RJ, Hayward RA, Mallen CD. An algorithm to identify rheumatoid arthritis in primary care: a Clinical Practice Research Datalink study. *BMJ open* 2015; **5**(12): e009309.
24. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and drug safety* 2009; **18**(8): 704-7.
25. de Lusignan S, Liaw S-T, Michalakidis G, Jones S. Defining datasets and creating data dictionaries for quality improvement and research in chronic disease using routinely collected data: an ontology-driven approach. *Journal of innovation in health informatics* 2011; **19**(3): 127-34.
26. Tippu Z, Correa A, Liyanage H, et al. Ethnicity Recording in Primary Care Computerised Medical Record Systems: An Ontological Approach. *Journal of innovation in health informatics* 2017; **23**(4): 920.
27. Office for National Statistics. Ethnicity and National Identity in England and Wales: 20112012. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11 (accessed.
28. Department for Communities and Local Government. The English Indices of Deprivation. 2015.2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed.