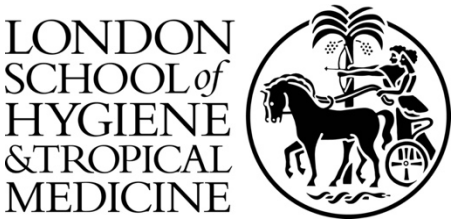

Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases

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Declaration

I, Julian Sean Matthewman, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, this has been indicated in the thesis. I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook.

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Abstract

Introduction: Inflammatory diseases (e.g. eczema, psoriasis, asthma, rheumatoid arthritis) and their treatments (e.g. glucocorticoids, targeted immune-modifying therapies) are associated with adverse health outcomes. Population-based studies in electronic health records data are suitable to study associations with many of these adverse health outcomes, and when well conducted can provide actionable evidence for decision makers, e.g. for which outcomes screening or preventive measures should be put in place.

Objectives: Using UK routinely collected health data, I aimed to 1. generate evidence on multiple outcomes to inform clinical care for people with eczema and other inflammatory diseases, 2. assess the validity of disease definitions by using linkage between data sources, and 3. efficiently conduct studies on multiple adverse outcomes.

Methods: 1. I investigated associations between inflammatory diseases or their treatments and various outcomes, making use of cohort study and cross-sectional designs and implementing different exposure definitions in the OpenSAFELY, CPRD GOLD and Aurum, and UK Biobank databases. 2. I assessed agreement concerning disease definitions between population cohorts (ALSPAC, UK Biobank) and linked electronic health records data and attempted to predict eczema subtypes in ALSPAC using linked EHR data. 3. I developed an approach to conduct studies on multiple outcomes and applied this to investigate adverse health outcomes for people with eczema.

Results: 1. I found evidence for associations between immune-mediated inflammatory diseases (IMIDs), but not most targeted immune modifying drugs, and severe COVID-19 outcomes. 2. I found that in older adults who receive large cumulative doses of oral glucocorticoids, those who receive them in low-intensity patterns (intermittently, over a longer period

of time or a larger number of prescriptions or with more gaps between prescriptions) were less likely to be prescribed recommended fracture preventive care (e.g., bisphosphonates) 3. I found evidence for an association between eczema/psoriasis and anxiety/depression across multiple study designs and data sources. 4. I found that there was considerable disagreement between eczema diagnoses derived from EHRs and questionnaires, and that agreement was better for other conditions including psoriasis and asthma. The poor agreement precluded using EHRs to predict eczema subtypes derived from questionnaires. 5. I showed that having eczema was associated with the subsequent development of several different adverse health outcomes, including a strongly increased risk of atopic and allergic conditions, skin infections and some immune-mediated skin conditions, a moderately increased risk of some liver and gastrointestinal conditions, a weakly increased risk of some cardiovascular, neurological and other outcomes and no increased risk of cancers, except lymphomas.

Conclusions: I approached electronic health records research on adverse health outcomes of inflammatory conditions from multiple angles. I generated evidence to inform clinical care, highlighted a need for further research into eczema definitions in observational studies, and demonstrated and put to use an efficient approach to investigate multiple outcomes.

Abbreviations

AAD	American Academy of Dermatology
AD	Atopic dermatitis
ALSPAC	Avon Longitudinal Study of Parents and Children
AUC	Area under the curve
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
DAG	Directed acyclic graph
dm+d	Dictionary of Medicines and Devices
EHR	Electronic health records
EMIS	Egton Medical Information Systems (software provider)
GAD-7	Generalised Anxiety Disorder Assessment
GP	General practice/General practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICES	(previously) Institute for Clinical Evaluative Sciences
IL	Interleukin
IMD	Index of Mulitple Deprivation

IMID	Immune-mediated inflammatory disease
JAK	Janus kinase
LSHTM	London School of Hygiene & Tropical Medicine
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
PCR	Polymerase chain reaction
PHQ-9	Patient Health Questionnaire
ROC	Receiver operating characteristic
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SES	Socioeconomic status
SNOMED-CT	Systematized Nomenclature of Medicine - Clinical Terms
TNF	Tumour necrosis factor
TPP	The Phoenix Partnership (software provider)
UK	United Kingdom
US	United States

Terminology

The terms eczema, atopic eczema and atopic dermatitis (AD) are used interchangeably within this thesis due to different naming preferences across working groups.
The terms oral corticosteroids and oral glucocorticoids are also used interchangeably. Strictly, while glucocorticoids are a subset of corticosteroids, I use both terms to refer to oral glucocorticoids.

1 Introduction

1.1 Thesis structure

This thesis brings together a related body of research from my work as an epidemiological researcher within the Electronic Health Records research group at the London School of Hygiene & Tropical Medicine. The thesis contains a collection of studies conducted using electronic health records (EHRs) to study inflammatory conditions, mainly eczema, but also psoriasis, asthma, COPD, and inflammatory bowel and joint disease.

- **Chapter 1**: The introduction chapter lays out the background and current state of the literature on the health-related topics of interest, including inflammatory diseases (with a focus on eczema), treatments, related adverse health outcomes, and how these can be studied using electronic health records data.
- **Chapter 2**: A materials & methods chapter includes a description of data sources, linkage between data sources, codelists (including a submitted manuscript that provides a checklist and guidance for codelist creation and sharing), and statistical methods.

5 paper-style chapters, based on published or submitted manuscripts, form the core of the thesis. They describe:

- **Chapter 3**: A nationwide cohort study on the risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies,
- **Chapter 4**: Population-based cohort studies in older adults in the UK and Canada to identify gaps in fracture preventive care for people prescribed oral corticosteroids,

- **Chapter 5**: A study using linkage of the UK Biobank and linked primary care data to compare associations between skin disease and mental illness,
- **Chapter 6**: A study using linkage to assess and predict eczema subtypes derived from a prospective cohort (ALSPAC) in linked primary care data,
- **Chapter 7**: A cohort study on multiple adverse health outcomes associated with eczema.

- **Chapter 8**: Finally, the discussion chapter puts findings from all studies into context and formulates recommendations for clinical care, public health and future research.

1.2 Immune-mediated inflammatory diseases (IMIDs)

1.2.1 Classification

Immune-mediated inflammatory diseases (IMIDs) are diseases that share a common mechanism in inflammation resulting from or triggered by, a dysregulation in the normal activity of the immune system. IMIDs are a diverse group of diseases and there exist multiple ways inflammatory diseases can be classified, including by mechanism, site of manifestation, and treatment. Commonly, IMIDs are thought to include inflammatory joint diseases (rheumatoid arthritis, spondyloarthritis), inflammatory skin diseases (psoriasis, eczema), inflammatory bowel disease (IBD), connective tissue disorders, asthma, and autoimmune neurological diseases such as multiple sclerosis.[1]

The inflammatory diseases studied in this thesis include those treated with similar targeted immune-modifying agents (inflammatory joint, bowel and skin disease including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis and hidradenitis suppurativa) in Chapter 3, those where flares are treated with oral glucocorticoids (asthma, eczema and chronic obstructive pulmonary disease) in Chapter 4, eczema and psoriasis in Chapter 5, and eczema only in Chapter 6 and Chapter 7.

It has been suggested that chronic systemic inflammation plays a role in many of the long-term adverse health outcomes faced by those with IMIDs such as cardiovascular disease,[2]

osteoporosis,[3,4] cancer,[5] and others such as diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease, and autoimmune and neurodegenerative disorders.[6] The fact that similar adverse health outcomes are reported for different inflammatory diseases (e.g., for eczema[7], inflammatory bowel disease[8], rheumatoid arthritis[9,10] psoriasis[11]) is further suggestive of chronic systemic inflammation being a mechanism for adverse outcomes.[1]

1.2.2 Eczema & Psoriasis

Eczema (also known as atopic eczema or atopic dermatitis) and psoriasis are the two most common chronic inflammatory immune-related skin diseases. Eczema is the leading cause of the global burden from skin disease.[12] Onset is typically in early childhood, however, eczema is also common in adults, both as persistent and new onset forms. Prevalence estimates for eczema vary considerably, with findings from different populations suggesting it affects about 10–30% of children and 2–10% of adults.[13] Psoriasis is more common in adults than in children,[14] with prevalence estimates ranging from 0% to 2.1% in children and 0.91% to 8.5% in adults.[15]

Eczema is characterised by itching and recurrent rashes. The causes of eczema are complex and likely multifactorial, with a strong genetic component.[16] Inflammation in eczema is mostly T-cell driven and displays a type 2 inflammatory signature, which is also found in asthma, chronic rhinitis and rhinosinusitis, allergic conjunctivitis, and eosinophilic oesophagitis. These conditions, which together with eczema are commonly referred to as atopic conditions, are also the most common disease associations in eczema.[17]

Psoriasis is characterised by patches of dry, scaly skin. The causes, as with eczema, are likely multifactorial, with both genetic susceptibility and environmental triggers (such as streptococcal infection, stress, smoking, obesity and alcohol consumption) playing a role. Psoriasis is strongly associated with the co-occurrence of psoriatic arthritis, observed in 10-40% of people with psoriasis, which typically lags behind the skin disease by about 10 years and shares immunological features with psoriasis.[18]

While the strongest disease associations differ between eczema, where atopic conditions are most common, and psoriasis, where psoriatic arthritis is most common, there are likely disease associations and mechanisms shared by both eczema and psoriasis. One such mechanism is chronic systemic inflammation, albeit the view that eczema is a systemic disease is more controversial.[16] Another mechanism may relate to the adverse effect of having a chronic illness or stigma due to visible skin disease on mental health. Associations with anxiety and depression have been described for both eczema and psoriasis.[19–21]

A current clinical knowledge summary from the UK National Institute of Health and Care Excellence (NICE) on adverse outcomes for eczema focuses on skin infections, psychosocial problems and atopic conditions.[22] For psoriasis, the NICE clinical knowledge summary acknowledges a larger range of associated conditions.[23] The clinical knowledge summary for eczema is, however, based largely on NICE clinical guidelines on "Atopic eczema in under 12s". Therefore, adverse health outcomes in adults may not have fully been considered.[24]

1.2.2.1 Eczema burden

The burden of AD is multidimensional and the effect on quality of life can be considerable, however this is largely dependent on severity. In the 2017 Global Burden of Disease Study, eczema had the highest burden among skin disease measured by disability-adjusted life-years and ranked 15th among all non-fatal diseases.[25] Of the signs and symptoms of eczema, itch is most commonly reported to impact patients' quality of life, before e.g., soreness, redness or dryness of skin. Eczema can impact different aspects of patients' lives, with psychological effects and sleep disturbance being frequently reported.[26]

The economic burden and burden on healthcare systems can also be considerable, owing to a high prevalence. Besides direct costs including healthcare utilisation and treatment costs, the indirect costs due to productivity loss (e.g., being absent from work due to eczema) may be more than double those of direct costs.[26] A 2023 report commissioned by the pharmaceutical industry estimated indirect costs of work impairment for adult patients with moderate to severe eczema between £6,741 and £14,166 per patient per year.[27]

1.2.2.2 Care pathways for eczema

Most people with eczema are managed in primary care.[28] The choice of treatment is based on severity, which is usually judged clinically based on reported symptoms and skin examination. There also exist tools such as visual analogue scales to judge patients assessment of severity, itch and sleeplessness, or the patient oriented eczema measure (POEM) where the frequency and severity of symptoms in the past week is assessed.[29]

Emollients are the recommended first-line treatment for all severities of eczema, even when skin is clear, to reduce frequency of flares. If eczema is mild, i.e., rashes are infrequent and there are only few inflamed areas, mild topical corticosteroids are recommended for areas of inflamed skin for treatment of flares. In case of non-response or in moderately severe eczema, i.e., more frequent or widespread inflammation, moderate potency topical corticosteroids are recommended. If flares are frequent, maintenance therapies may be considered, meaning treatments are given even when skin is clear. A maintenance regimen of topical corticosteroids or topical calcineurin inhibitors (non-steroid immunomodulatory agents) twice weekly has been demonstrated in trials to be beneficial. For severe eczema, with widespread areas of itchy red skin and incessant itching, potent or very potent topical corticosteroids can be prescribed, including as maintenance therapies. If response to these therapies is unsatisfactory, patients may be referred to specialist services and be prescribed phototherapy, systemic immunosuppressants, or targeted immune modifying drugs, such as dupilumab.[30]

In addition to the stepped approach, antihistamines can be given when itch is severe, including sedating antihistamines when itch affects sleep. When skin infection occurs, most commonly through Staphylococcus aureus, antibiotics should be prescribed. Oral corticosteroids should only be used for the treatment of severe flares, and in general should be avoided.[30]

1.2.2.3 Eczema subtypes

Subtypes are used to classify diseases with complex presentation and pathogenesis, the aim being to enable more personalised care. Eczema is considered to occur in such subtypes due to a variety in clinical presentation (e.g. flexural vs. non-flexural eczema), severity (e.g., itchiness, rash and area affected), trajectory (e.g., remitting vs. chronic), genetic and immunological features (e.g. presence of filaggrin [FLG] mutations or serum immunoglobulin E [IgE]), and probable multi-factorial aetiology (e.g. genetic predisposition, and exposure to environmental factors).[31] There has been emerging literature suggesting that different subtypes of eczema may be associated with different prognoses and adverse outcomes and respond to different treatments.[31,32]

1.2.2.4 Other inflammatory skin conditions

Other conditions may also be considered part of the group of immune-related skin diseases, including pemphigus or pemphigoid, however, these are characterised by bullous lesions, unlike eczema and psoriasis which are both non-bullous diseases and are much rarer.[33] These bullous skin conditions will not be discussed in this thesis. Another (more common) condition, acne vulgaris, also involves inflammation and may be chronic but it has less in common with eczema and psoriasis in terms of pathomechanisms and immunology and is unlikely to involve systemic inflammation. Acne will also not be discussed in this thesis. Hidradenitis suppurativa, another inflammatory skin disease, for which the only licensed therapy in the UK is Adalimumab, a tumour necrosis factor (TNF) inhibitor, is studied in Chapter 3 together with psoriasis and non-skin IMIDs that are treated with targeted immune-modifying therapies.[34]

1.2.3 Inflammatory conditions treated with targeted immune-modifying therapies

Given that many IMIDs share common underlying pathogenetic features, similar treatments are used to control inflammation, alter disease course, and achieve remission. In the 20th

century, broad-spectrum anti-inflammatory drugs such as oral glucocorticoids were a mainstay of therapy, however, these showed reduced benefit over time while having substantial adverse effects (e.g., on bone, cardiovascular, and metabolic systems). The start of the 21st century, corresponding roughly to the approval of the first Tumor Necrosis Factor (TNF) inhibitors in 1998, marked a shift towards more targeted therapies that have since achieved significant advances in disease control and remission.[1] Importantly, while therapeutic targets are still shared across some IMIDs, different IMIDs are now treated with different targeted medicines. Different cytokines are targeted based on an understanding of the different immune pathways for individual IMIDs. For example, many IMIDs are responsive to TNF alpha inhibition but differ in their responsiveness to inhibition of other cytokines (such as interleukins [IL] 1,6,17 and 23), and different drugs are associated with different adverse effects (e.g., increased risks of mycobacterium infection reactivation with TNF inhibitors; fungal infections with IL-17A inhibitors; shingles infection with Janus kinase [JAK] inhibitors).[1,35]

The immune-modifying drug dupilumab which targets IL-4 and IL-13 signaling, was approved in the UK for treating eczema in 2018.[36–38] This places eczema in the category of conditions treated with targeted immune modifying therapies, together with psoriasis and other IMIDs. However, eczema is generally not treated with other classes of targeted immune-modifying drugs (such as TNF inhibitors), is often seen as pathomechanistically different to other IMIDs, and is generally not considered an autoimmune condition.[39] Therefore, studies on IMIDs may not include eczema, as is the case in Chapter 3.

1.2.4 Inflammatory conditions treated with oral glucocorticoids

One disease area, or rather disease state, where oral glucocorticoids remain relatively commonly used is to treat flare-ups of relapsing-remitting conditions, in particular when flare-ups do not respond to inhaled glucocorticoids, e.g., for asthma and COPD, or to topical glucocorticoids, e.g., for eczema. Given the availability of treatments with better long-term safety profiles as described above, oral glucocorticoids are generally not recommended for longer-term use, but studies have shown that they remain commonly prescribed (including

for eczema).[40]

Asthma and chronic obstructive pulmonary disease (COPD) both affect the respiratory system and involve inflammation. Asthma is characterised by reversible airway obstruction often triggered by allergens or irritants, resulting in episodic wheezing, coughing, and shortness of breath.[41] COPD typically involves irreversible and progressive airflow limitation leading to chronic bronchitis and emphysema.[42] While inflammatory, COPD is not considered an IMID since it is predominantly caused by long-term cigarette smoking, as opposed to IMIDs where causes are often unclear and multifactorial and may include a genetic predisposition.

1.3 Studying IMIDs in EHRs

1.3.1 Electronic health records

Electronic health records (EHRs) are a type of routinely collected health data, i.e., data collected during routine interactions with the health care system, rather than for study-specific purposes. EHRs, such as those from general practice (primary care) or hospitals (secondary care), often contain a very broad range of information on an individual's health, compared to other routinely collected data sources which may only contain information on certain aspects of health (e.g. disease-specific registries).[43] EHRs have created opportunities to address questions that cannot be addressed using randomised trials or classical epidemiological studies. However, it is recognised that the use of EHRs comes with certain challenges, such as being confidently able to identify individuals with a certain disease, and the necessity to consider the context in which the data were collected.[44]

EHRs contain both unstructured and structured data. Unstructured data, such as free text doctors' notes, are typically not available for research purposes. Structured data use a controlled vocabulary such as ICD-10 codes to limit how a piece of medical information can be recorded.[45] The process of deciding which information is used to define a study variable (such as a disease, a drug, a referral, or a procedure) is sometimes called phenotyping. Commonly, this involves defining subsets of the controlled vocabulary, so-called codelists,

e.g., all the ICD-10 codes that would indicate a person has eczema. Sometimes, study variables are defined using algorithms that may involve multiple codelists, e.g., a person is only considered to have eczema if they have a diagnosis code for eczema and recorded prescriptions for the treatment of eczema. Methods of phenotyping in this thesis will be described in Section 2.2.

1.3.2 Studying adverse outcomes in EHRs

Studying adverse outcomes in people with IMIDs such as associations with other diseases is useful to inform clinical care, including determining priorities for screening and prevention. It is often not only of interest if people with the disease (exposure) of interest more commonly have an adverse health outcome, but also if the increased risk of an adverse health outcome is caused by having the exposure (i.e., rather than the association being confounded by other factors relating to both exposure and outcome). Hypotheses about causal questions need to be tested, which involves minimising the effect of confounding. These types of studies are sometimes referred to as "hypothesis-testing" studies; sometimes they may also be seen as "causal inference" studies. The intent of these studies is to elucidate the best ("most causal") effect estimate in the absence of randomised trials, however, there is justifiable caution in causal interpretation of results and use of causal language for observational studies as results may be due to confounding, sometimes through unmeasurable variables, selection or information bias. Nevertheless, acknowledging limitations and minimising the influence of bias and confounding, results from observational studies are regularly used to make decisions that relate to causal questions.[46]

EHRs can be well suited to address questions on adverse outcomes due to advantages such as information being available on a large number of health-related characteristics and events which can allow for the control of confounding, the ability to assess temporality, and large sample sizes from populations representative of the general population. In addition, the number of studies that can be conducted is not limited by new data collection.

Observational hypothesis-testing studies in EHRs often adhere to a typical structure. Measures of effect are estimated, often through the use of regression models adjusted for con-

founding, comparing those with the exposure to those without. Longitudinal (cohort) studies, i.e. where the exposure occurs temporally prior to the outcome, are generally considered to be the preferred study design.[47]

EHRs are also suitable to study adverse health outcomes related to treatments for IMIDs as they often contain detailed information on prescriptions, which may play an important part in risk associated with IMIDs. However, not all prescriptions are captured equally; while in the UK, most prescriptions will be captured in primary care, including those initially prescribed in hospital care, some may be subject to special approval processes, typically high-cost specialist medicines for the management of long-term conditions such as IMIDs.[48]

1.4 Research questions

Electronic health records became widespread in UK primary care by the 1990s,[49] with data sources like the Clinical Practice Research Datalink containing data collected from 1987 onwards.[50] Research using electronic health records has thus been ongoing for decades, giving researchers time to address a multitude of questions relating to IMIDs. What are priority unanswered research questions that should now be addressed using EHRs?

Firstly, while a multitude of studies have been conducted on disease associations with IMIDs, hundreds for eczema alone,[7] there remain unexplored disease associations for either newly emerged outcomes, such as COVID-19, or previously unexplored outcomes for which previous hypothesis-generating research may have suggested associations. Furthermore, the role of treatments in associations between IMIDs and adverse health outcomes often remains unclear. One reason for this may be that information on certain treatments has not been accessible in the past but is now becoming available.[48] Another reason may be that answering research questions on certain treatments may require more complex exposure definitions than have previously been used. For example, the effects of oral glucocorticoids may vary considerably by cumulative, peak, and average dose, and recency of use.[51,52]

Secondly, it is important to consider the components that are used in EHR research. Do people labelled as having eczema in EHRs represent the "true" population of people with

eczema; do other data sources provide better, or worse, information on eczema, and can EHR data be enriched with data from other sources? Opportunities to compare across data sources have recently opened up thanks to data linkage between EHRs and population cohorts.[53,54] Given EHRs and population cohorts have different strengths and weaknesses, exploring research questions in both sources may increase confidence in findings.

Thirdly, conducting multiple studies on adverse outcomes gives the opportunity to think about the organisation of such research.[47] Given the multitude of research questions to explore, gains in research efficiency may create actionable evidence for clinical care and public health decisions faster, with patients benefiting sooner. Results that are more comparable between outcomes may also help better judge the potential public health impacts of each outcome.

1.5 Aims & Objectives

Overall aim: Inform care priorities for people with eczema and other inflammatory diseases and people taking anti-inflammatory drugs

- Aim I: Use EHRs to investigate adverse health outcomes for people with inflammatory diseases and people taking anti-inflammatory drugs
  - Chapter 3: Investigate the association between immune-mediated inflammatory diseases, and treatments thereof, with severe COVID-19 outcomes
  - Chapter 4: Investigate gaps in fracture preventive care in people prescribed oral corticosteroids
  - Chapter 5: Investigate associations of eczema and psoriasis with anxiety and depression
  - Chapter 7: Investigate associations between eczema and 71 different adverse health outcomes
- Aim II: Assess the validity of disease definitions using linkage between EHRs and questionnaire responses from population cohorts

  - Chapter 5: In people with skin disease, compare associations with mental illness diagnoses defined using interview and survey responses to diagnoses defined using primary care EHRs
  - Chapter 6: Use primary care EHRs to replicate and validate eczema subtypes previously identified from parental questionnaire responses

- Aim III: Develop an approach to efficiently conduct multiple population-based cohort studies in EHRs
  - Chapter 7: Develop an approach to efficiently conduct multiple cohort studies in EHRs and apply said approach to investigate multiple adverse health outcomes related to eczema

1.6 Overview of studies

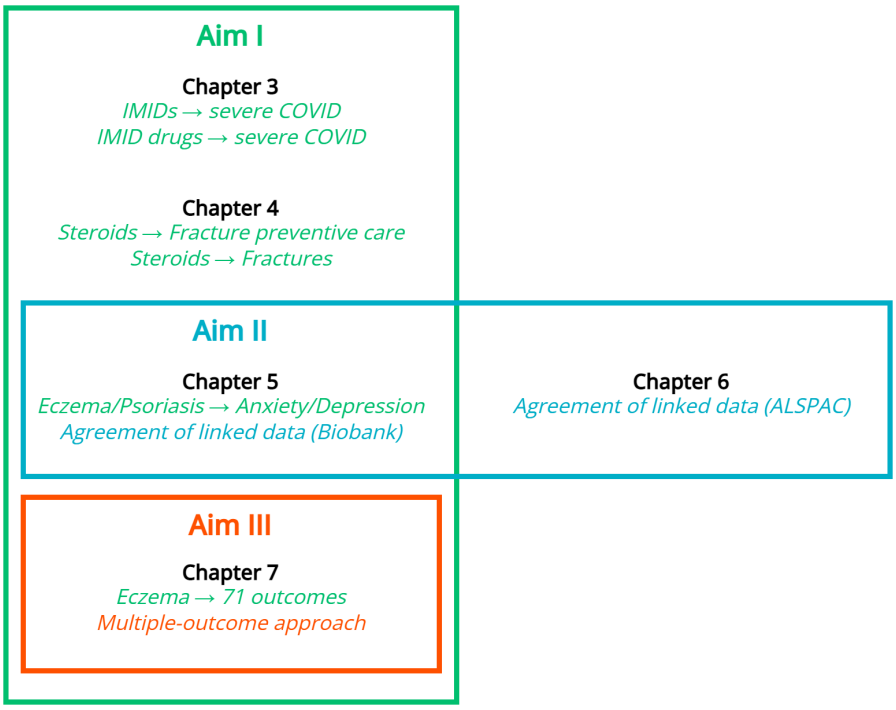

Figure 1.1: Overview of chapters and their research questions by thesis aim

1.6.1 Aim I: Studies on outcomes associated with inflammatory diseases and their treatments

In Chapter 3, Chapter 4, and Chapter 7, I present longitudinal cohort studies, investigating associations with inflammatory diseases and/or their treatments, in all studies making use of EHR data. Chapter 3 investigates the risk of severe COVID-19 outcomes associated with IMIDs and targeted immune-modifying treatments thereof. Chapter 4 investigates differences in fracture preventive care in people with inflammatory diseases receiving oral corticosteroids. Chapter 7 investigates adverse health outcomes associated with eczema.

All 3 studies adhere to the basic hypothesis-testing template to address causal questions with longitudinal data.[47] Main results are hazard ratios estimated from confounder-adjusted Cox regression, where the outcome occurs subsequent to the exposure. Within this basic template, there is however room to conduct considerably different types of studies. Chapter 3, for example, assesses the effect of having a disease (IMIDs) or being a user of a treatment (targeted treatments for IMIDs) on the occurrence of an acute adverse outcome (COVID-19-related death or hospitalisation). Chapter 7 focuses on a single exposure (eczema), and multiple adverse outcomes. Chapter 4 on the other hand assesses if people being prescribed oral glucocorticoids in certain patterns are more likely to miss out on appropriate preventive care.

In Chapter 5, I conduct cross-sectional studies investigating the risk of anxiety or depression in people with eczema or psoriasis. These studies provide weaker evidence of causality than cohort studies, primarily given the outcome and exposure are measured at the same time, which makes it impossible to establish temporality. Given the main aim was comparing between data sources, this is less of an issue.

1.6.2 Aim II: Studies validating disease definitions using linked data

In Chapter 5 and Chapter 6, I make use of linkage between prospective cohort data (the UK Biobank in Chapter 5 and the Avon Longitudinal Study of Parents and Children [ALSPAC] in Chapter 6) and linked primary care EHR data to assess the validity of disease definitions,

i.e., assess whether a disease recorded for an individual in one data source is also recorded in the other data source. Discrepancies between data sources can reveal the extent to which defining a disease variable for study purposes depends on the real-world context in which information on the disease is recorded.

While in Chapter 5 I use linkage to assess yes/no disease definitions, in Chapter 6 I consider subtypes of eczema previously identified through latent class analysis methods in ALSPAC data.[32] After assessing agreement concerning eczema between linked data sources, I also attempt to replicate eczema subtypes in EHRs. In Chapter 5, after assessing disease definition agreement between data sources, I also assess if associations between eczema/psoriasis and depression/anxiety can be replicated across both EHR and prospectively collected data. This approach can be considered part of efforts in triangulating a research question, given using EHRs is likely to come with different biases as compared to using interview and survey data.[55]

1.6.3 Aim III: A study organising inference on multiple outcomes

In Chapter 7, I demonstrate a new approach to the organisation of EHR research on adverse outcomes. The rationale for this approach is laid out in more detail in Section 7.4; in short, goals were to improve efficiency, comparability, reproducibility, and reduce the potential for researcher biases. Eczema serves as a suitable exposure to demonstrate this approach, given eczema may be associated with a host of atopic and non-atopic diseases. Recent American Academy of Dermatology (AAD) guidelines (2022) identify 32 different adverse health outcomes that have previously been studied.[7] However, the current evidence is largely of low or moderate certainty, associations remain poorly understood, and there is no internationally accepted approach to screening and prevention.[7,16]

1.7 Chapter summary

- Immune-mediated inflammatory conditions are a diverse group with both common and distinct pathomechanisms and treatments

- Studies in this thesis consider one of three types of inflammatory conditions: 1. the inflammatory skin conditions eczema and psoriasis; 2. relapsing-remitting conditions where flares are treated with oral glucocorticoids; 3. IMIDs that are treated with similar targeted immune-modifying therapies
- Eczema and other IMIDs are associated with adverse health outcomes such as the subsequent development of other diseases, possibly through mechanisms such as chronic inflammation, although the role of eczema as a systemic condition is less clear than for other IMIDs
- EHRs have been used to study adverse outcomes related to eczema and other IMIDs and have advantages in terms of large sample sizes and a generally comprehensive overview of multiple aspects of a person's health
- Studies in this thesis make use of new research opportunities that were created through linkage of EHR databases with population cohorts, through linkage with high-cost drug prescription data, and through harnessing the comprehensive information on diseases and prescriptions available in EHRs in new ways

2 Materials & Methods

2.1 Data sources

Table 2.1: Overview of data sources used in this thesis

Data source	Type	Size	Source population	Participant age	Linkages[1]
OpenSAFELY-TPP	EHR	24 million	English primary care population	all ages	high-cost drugs; hospital deaths and admisisons; SARS-CoV-2 testing
CPRD GOLD	EHR	20 million	UK primary care population	all ages	ONS death; IMD deprivation
CPRD Aurum	EHR	47 million	UK primary care population	all ages	none
ICES	EHR	17 million	Ontario general population	all ages	multiple
UK Biobank	Cohort	0.5 million	UK general population	40 to 69 at recruitment	primary care
ALSPAC	Cohort	14,541	Population in and around Bristol (south-west UK)	children followed up from birth	primary care

[1] *Linkages that were made use of in this thesis.*

2.1.1 OpenSAFELY-TPP

For Chapter 3, OpenSAFELY-TPP was used; a secure analytics platform for electronic health records that was created for NHS England and TPP (a GP [general practitioner] software provider). It provides a secure software interface that allows analysis of pseudonymised primary care records of ~24 million people currently registered at about 40% of GP practices in England. The platform was originally conceived to help inform responses to the

COVID-19 pandemic. Data within OpenSAFELY-TPP has been found to be generally representative of the English population as a whole in terms of key demographic characteristics.[56] Pseudonymised datasets from other data providers can be linked to the primary care data, which for Chapter 3 included UK Office for National Statistics (ONS) death data and SARS-CoV-2 testing data.[57] In addition, to define IMID treatments, information on high-cost specialist drug prescribing in hospitals was made available. The collation of a single national high-cost drug dataset had been arranged, containing submissions from April 2018 to March 2021 (the study period for Chapter 3 ended in September 2020). For OpenSAFELY, three variables were made available including the financial year and month of the drug being dispensed, the drug name and a description of the drug.[48]

2.1.2 CPRD

The Clinical Practice Research Datalink (CPRD) is a database of de-identified medical records from general practitioners in the UK. CPRD GOLD contains data contributed by practices using Vision® software. For Chapter 4 the January 2020 release of CPRD GOLD is used (there is no published data specification document for this release). The earliest currently available data specification document is from January 2021, where data contains a total of 19,483,855 research-acceptable patients, 3,020,680 currently registered research-acceptable patients, and 9,209,834 patients eligible for linkage.[58] The population within CPRD GOLD is broadly representative of the UK general population in terms of age, sex and ethnicity.[50] However, CPRD GOLD may have become less representative over time, with fewer practices using the Vision® software.

Linkage with small area level data based on patient postcode included the Index of Multiple Deprivation (IMD) which was used as a proxy for individual-level socioeconomic status.[59] The small areas have an average of 1,600 residents.[60] The IMD is derived from indicators on income, employment, education and skills, health, housing, crime, access to services, and living environment. The indices measure relative rather than absolute deprivation, which is why quintiles of the IMD are used.

Linkage with death registration data from the Office for National Statistics (ONS) was used

in Chapter 4 to better ascertain date of death.[61] There may be delays in date of death recordings in CPRD data, however, by 2013, 99% of deaths were in agreement within ±30 days between CPRD and ONS, which likely makes the CPRD death dates used in Chapter 7 sufficient for censoring follow-up.[62]

In Chapter 7, I made use of CPRD Aurum, which contains data contributed by practices using EMIS® software.[63] I used the March 2023 release, which covers 46,795,888 acceptable patients.[64] Given there has been a reduction in practices that use the Vision software in recent years, CPRD Aurum now represents the larger database with more information more recently recorded as compared to CPRD GOLD.[65]

The March 2023 release had 2,127,536 current acceptable patients (i.e. registered at currently contributing practices, excluding transferred out and deceased patients) from 228 currently contributing practices (i.e., contributing data to CPRD within 60 days of the database build being created), which marked a drop compared to earlier releases. This is explained by the circumstance that 1,491 practices had the same data as in the May 2022 release and were therefore classed as not currently contributing.[64] The May 2022 release had 13,300,067 current acceptable patients from 1,720 currently contributing practices.[66] Any impact on findings from Chapter 7 is unlikely, except for the end of follow-up occurring in May 2022 for many individuals.

2.1.3 UK Biobank

In Chapter 5, I used the UK Biobank, which is a cohort study with over 500,000 participants aged 40–69 years recruited in 2006–2010. The study collects phenotypic and genotypic detail, including data from questionnaires, physical measures, sample assays, accelerometry, multimodal imaging, genome-wide genotyping, and longitudinal follow-up for health-related outcomes.[67]

I made use of linkage to primary care data which was available for ~230,000 participants who had consented to this linkage and contained coded clinical events, prescribed medications, and administrative codes (e.g. referrals). Linkage was obtained from GP practices in Eng-

land using TPP (n=18,000) or Vision (n=165,000) software (but not EMIS), and from GP practices in Scotland (n=27,000) and Wales (21,000) using EMIS or Vision software.[53]

2.1.4 ALSPAC

In Chapter 6, I used the Avon Longitudinal Study of Parents and Children (ALSPAC); a transgenerational prospective observational study containing information on genetic, epigenetic, biological, psychological, social and environmental exposures and a range of health, social and developmental outcomes.[68] Data dictionaries and variable search tools can be found on the study website.[69] The children from 14,541 pregnancies were recruited in 1990–92. Follow-up included 59 questionnaires (4 weeks–18 years of age) and 9 clinical assessment visits (7–17 years of age). I made use of data on eczema subtypes derived from questionnaires about eczema severity and presence.[32]

I also made use of linked primary care data. Consent for linkages was obtained via a postal campaign, where ALSPAC formally sought to re-enrol study participants upon reaching adulthood, simultaneously seeking opt-out permission for linkage with EHRs. Linkage to de-identified local GP data (EHRs) was carried out for nearly 12,000 participants. The process for linkage was previously described (in the "Linkage to GP records" section in the supplement from an article by Cornish et al.).[70] In short, as part of the Secure Anonymised Information Linkage (SAIL) project linkages between ALSPAC and data from multiple sources, including local primary care data, were established.[54] After securing assent from GP practices via opt-in invitations, data was extracted based on mechanisms provided by EMIS, which supplied the software to most of the local practices. The extracted records were pseudonymised at source and transferred to a SAIL secure setting.

2.1.5 ICES

In addition to analyses with UK data, Chapter 4 analyses were run on data provided by ICES (previously Institute for Clinical Evaluative Sciences) by Deva Thiruchelvam, a collaborating analyst (I did not have access to ICES data). ICES includes deidentified data from over 17 million people in Ontario, Canada. These data consist of linkage between the Ontario

Drug Benefit Plan (ODB) database, the Ontario Health Insurance Plan (OHIP) database, Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD), Ontario Cancer Registry (OCR), and the Ontario Registered Persons Database (RPDB). Details on the individual data sources are described in eMethods 1 in the published supplementary materials in Section 4.3.

2.2 Variable definitions

2.2.1 EHR based

2.2.1.1 Codelists

EHRs contain information that is structured using clinical codes. For all studies, variables from EHRs were defined using codelists (also referred to as clinical code lists or code sets); lists of codes that represent a single clinical concept such as a diagnosis, a procedure, or a medication.[71] Table 2.2 shows which terminologies are used in each of the data sources used in this thesis.

Table 2.2: Terminologies used to define clinical events and prescriptions by data source

Data source	Clinical events	Prescriptions
OpenSAFELY	SNOMED-CT	dm+d, "Drug Name"[1]
CPRD GOLD	medcode from Read v2	prodcode (GOLD)
CPRD Aurum	MedCodeId from SNOMED, Read v2, local EMIS® codes	ProdCodeId (Aurum)
ALSPAC linked data	Read v2	SNOMED-CT
Biobank linked data	Read v2 and Read CTV3	dm+d

Abbreviations: BNF = British National Formulary; dm&d = dictionary of medicines and devices [1] The high-cost drugs dataset was not coded using an established terminology, rather records were extracted on the "DrugName" variable, i.e., codelists of drug names were created by carrying out keyword searches on the list of unique "DrugName" values.[48]

Different codelists had to be used for each data source, including for CPRD GOLD and Aurum. The CPRD GOLD medical dictionary contains unique "medcodes" based on Read v2 codes. In contrast, the CPRD Aurum medical dictionary contains unique "MedCodeIds"

based on a combination of SNOMED, Read v2 and local EMIS® codes, i.e., not every MedCodeId necessarily has a corresponding Read v2 code in CPRD Aurum.[72] To illustrate, Table 2.3 shows codelists for eczema from CPRD GOLD and Aurum (excluding codes that had less than 1000 observations in the CPRD Aurum code browser).

Table 2.3: Codelists for eczema from CPRD GOLD and Aurum

code	readcode	term
GOLD (medcode)		
13223	M11	Atopic dermatitis and related conditions
1741	M111	Atopic dermatitis/eczema
610	M112	Infantile eczema
1240	M113	Flexural eczema
5869	M114	Allergic (intrinsic) eczema
38673	M115	Besnier's prurigo
6180	M11z	Atopic dermatitis NOS
230	M12z1	Eczema NOS
22764	Myu22	[X]Exacerbation of eczema
Aurum (MedCodeId)		
308485016	M11	Atopic dermatitis
308497015	M11z	Atopic dermatitis NOS
889191000006114	M11z-99	Atopic eczema/dermatitis NOS
399917015	M12z1	Eczema
1779345010	M12z2	Infected eczema
497341000006116	M111	Atopic dermatitis/eczema
889161000006118	M111-98	Atopic eczema/dermatitis
150503015	M112	Infantile eczema
94953018	M113	Flexural eczema
477121000006119	M114	Allergic (intrinsic) eczema
309315018	Myu2	[X]Dermatitis and eczema
980491000006115	Myu22	Exacerbation of eczema
6661161000006111		Flexural atopic dermatitis
1137101000000119	8HTu	Referral to eczema clinic
2884301000006116		Atopic eczema
4510851000006113		Dry eczema

Excludes codes that had less than 1000 observations in the CPRD Aurum codebrowser. Rows where the readcode column is empty do not have a corresponding readcode.

2.2.1.2 Mapping codelists from GOLD to Aurum

While a large catalogue of 308 codelists was available in the CPRD GOLD medcode, Read v2, and ICD10 terminologies,[73] I required codelists in the MedCodeId terminology for CPRD Aurum. Roughly based on procedures described by researchers from the University of Cambridge primary care unit,[74] I mapped the existing CPRD GOLD medcodes to Readcodes and then to SNOMED Concept IDs (where one Readcode could correspond to multiple SNOMED Concept IDs). I then used the terms of the resulting list as searchterms to search the CPRD Aurum codebrowser, and added or removed searchterms (in particular stems of words, e.g. psoria*), and exclusionterms (only terms that definitely should not be included, e.g. family history), while iteratively checking the resulting codelist. Once the added or removed searchterms and exclusionterms had been finalised, I reviewed the final codelist and added additional exclusionterms if necessary.

2.2.1.3 Guidance on codelists

Despite the high importance of valid codelists for EHR research, there was a lack of guidance for researchers on how to ensure best practice on codelist development and sharing. I led a collaboration with members of the electronic health records group at LSHTM to create a manuscript (Section 2.4) including a checklist with accompanying step-by-step guidance (in the style of a reporting guideline) to facilitate best practice for future research. This manuscript integrates advice from the existing literature on codelists for electronic health records research with practical experience in creating codelists from researchers, refined in a workshop. The guidance was created during the course of this PhD and was finalised after all studies had been completed. Therefore, I did not necessarily follow the guidance exactly when creating codelists for the studies in this thesis. However, some codelists created may serve as examples for the guidance being partially employed. Note 1 shows the description of how the codelist for atopic eczema/atopic dermatitis was created in Chapter 7 for use with CPRD Aurum.

Note 1: Example description of eczema codelist creation

Metadata: Author: Julian Matthewman; Created on 12 July 2023; Created by searching the 2023_03 CPRD Aurum Medical code browser; Terminologies: CPRD Aurum MedCodeId, SNOMED-CT, Read v2

Short description: Codes for atopic dermatitis/atopic eczema, also including codes for unspecified forms of eczema that may be atopic

Subcategories: Symptom and diagnosis codes only (i.e., no codes for referrals, drugs, history of, etc..), definite atopic eczema

Reviewed by: Julian Matthewman, Sinéad Langan

Search strategy: Iteratively modified terms used to search and exclude codes, while checking for codes with the same SnomedCTConceptId and codes with a descendant Read code

Excludes: From the websites of the US [75] and UK [76] eczema societies, identified forms of eczema that are not considered atopic: Contact Dermatitis; Dyshidrotic Eczema; Neurodermatitis; Nummular (discoid) Eczema; Seborrheic Dermatitis; Stasis Dermatitis; Asteatotic eczema (craquele); Ear eczema; Eczema around the eyes; Facial eczema (Eczema of face); Female genital eczema; Hand eczema (likely also referred to as Hyperkeratotic fissured eczema of palms or soles)[77]; Male genital eczema; Pompholyx (dyshidrotic) eczema (also likely referred to as Pustular eczema and Vesicular eczema); Scalp eczema; Seborrhoeic dermatitis & cradle cap in infants Seborrhoeic dermatitis in adults; Varicose eczema (also known as gravitational eczema, and likely also referred to as Venous eczema)[78]

Also identified other terms labelled with "eczema" that are not atopic eczema: erythrodermic eczema (which is not necessarily atopic); Infectious eczematoid dermatitis (which is likely non-atopic)[79], but infected eczema is included; psoriasis; immunodeficiency syndromes; Friction eczema; Lip licking eczema; Desiccation eczema; Papular eczema; drug eruptions

Includes: The codelist includes (alongside the codes mentioned in the short description): eczema herpeticum, as this develops in patients with atopic dermatitis;[80] also includes history of eczema, referrals to eczema clinics, measures, adverse reactions to

eczema drugs

Checks: Number of observations by subcategory: full codelist: 17.4 million; diagnosis and symptom codes: 16.8 million; definite atopic eczema: 6.4 million

2.2.2 Questionnaire-based

Chapter 5 and Chapter 6, in addition to linked EHR data, data from ALSPAC/UK Biobank were used. Both ALSPAC and the UK Biobank are examples of population cohorts (of which several others exist in the UK)[81] where information on a large number of variables was prospectively collected (using questionnaires, measurements, biological samples, etc.) specifically for research purposes. I made use of questionnaire and interview responses, the questionnaires either being answered by the participants themselves (UK Biobank), or by a parent or carer (ALSPAC).

In both studies, eczema diagnoses were captured. In both studies, diagnoses were ascertained in questionnaires that collected information on several different diseases at once. In the UK Biobank, participants were asked to self-report previous diagnoses of serious illnesses or disabilities (psoriasis diagnoses were also captured using this approach). In ALSPAC, parents were asked if their child had experienced one of 22 different illnesses in the past year (or describe if any other), which was followed up by a question on whether a doctor had ever diagnosed asthma or eczema by 166 months. Presence of eczema symptoms was also ascertained, using questionnaire responses on flexural rash, e.g., "child had rash in joints & creases in the past year").

In the UK Biobank, mental illness diagnoses, in addition to being captured using self-reported diagnoses, were also captured using mental health specific scores. I used responses from the UK Biobank 2016 mental health follow-up survey to derive PHQ-9 (Patient Health Questionnaire)[82] and GAD-7 (Generalised Anxiety Disorder Assessment)[83] scores for depression and anxiety in the two weeks before the survey, with scores of 10 or more considered as being indicative of present anxiety/depression.

2.3 Statistical methods

Table 2.4: Overview of statistical methods

	Aim	Regression model	Estimates/metrics of interest
Chapter 3	Inference	Cox regression	Hazard ratios
Chapter 4	Inference	Cox regression	Hazard ratios
Chapter 5	Inference	Binomial logistic regression	Odds ratios
Chapter 6	Prediction	Regularised multinomial logistic regression	ROC AUC, sensitivity, specificity
Chapter 7	Inference	Cox regression	Hazard ratios

2.3.1 Survival analysis in EHR data

The electronic health records data used in this thesis (as well as most types of EHR data in general) are structured in a way that time-to-event analysis or survival analysis can be performed, which is often the preferred type of analysis as different lengths of follow-up time can be incorporated.[84]

In time-to-event analysis the following need to be defined:[85]

- the outcome, which in this thesis is a record of a certain diagnosis or treatment
- the time (date) at which the outcome occurs
- the time-origin (referred to as index date in this thesis), which differs by study:
  - in Chapter 3 it is a fixed date (the 1st March 2020 as the approximate start of the COVID-19 pandemic in the UK)
  - in Chapter 4 it is the date when individuals have received prescriptions for a large cumulative dose of oral glucocorticoids) for both comparison groups
  - in Chapter 7 it is the date when an individual is considered to have eczema, with people without eczema being matched to those with eczema and having the same time-origin
- a time scale, which in this thesis was time in days, since this is the level of granularity in which information is available in EHRs

Not all individuals will have the outcome or be observed until they have the outcome; this is called "censoring". Reasons for censoring in this thesis include people dying before they can get the outcome of interest, people leaving their GP practice or data not being collected on the individual anymore for any other reason.

Another important feature is that information on individuals is available before their index date, i.e. individuals are not followed up from their first observation. This makes it important to consider if individuals had the event of interest before their index date. In Chapter 4 and Chapter 7 people with the event of interest before indexdate are excluded; in Chapter 3 this was not necessary as it would generally not be possible for people to have COVID-19 before the start of the COVID-19 pandemic.

2.3.2 Cox regression

Through modelling of survival times it is possible to estimate how the risk of having an outcome depends on the values of one or more explanatory variables that are measured at index date. In this thesis, the effect of one variable (the exposure) while accounting for the effects of other variables (potential confounders) was of interest. The Cox model, since it was first described in 1972,[86] has been one of the most popular methods for time-to-event data. It is also called the "proportional hazards model" because it assumes that the effects of different variables on survival are constant over time.[87,88] The model doesn't assume a distribution for the baseline hazard, which can be useful for the complex survival patterns encountered in EHRs. Hazard ratios, i.e. the ratio of hazard rates can be estimated, the hazard being the instantaneous probability of having the event at a given time, conditional on survival up to that time. In this thesis, I made use of the survival R package to implement Cox regression.[89]

While the proportional hazards assumption may not hold exactly for all analyses in this thesis, the estimated hazard ratios should still provide a useful summary measure over the entire follow-up period, which is discussed further in Section 8.5.6.

2.3.3 Logistic regression

While the primary care EHRs linked to UK Biobank data in Chapter 5 also contained longitudinal data suitable for survival analysis methods, the data that was used from the UK Biobank recruitment interview was captured at a single time point. Since one aim of this chapter was to compare between data sources, a cross-sectional design was employed. To estimate the association between the exposure and the outcome, logistic regression was used and odds ratios were estimated. The outcome was binary, e.g., having or not having a disease at the time of measurement. Besides the exposure variable, other variables that could confound the association between the exposure and outcome are also included in the model, to adjust for their influence.[90]

2.3.4 Prediction using multinomial logistic regression

In all chapters relating to Aim I (studying the effect of exposures on outcomes), the regression analysis methods described above were used for inference. In inference, it is of interest how an exposure relates to the outcome. In contrast, in Chapter 6, one of the original objectives was to construct a model using existing data that, when given new data, could classify (or predict) an outcome variable. The process is described in the Statistical Analysis section in Section 6.2. In short, it involved splitting the available data into training and testing sets, fitting a multinomial (i.e., allowing for an outcome variable with more than two values) logistic regression model to the training set, and evaluating the model's predictive performance on the testing set. Regularisation (also referred to as penalisation) was applied to the multinomial logistic regression models. In short, regularisation makes the model "simpler", which can lead to better predictions by avoiding overfitting. Overfitting is when the model fits too closely to the training data, resulting in worse predictions with new data.[91]

Ultimately, as only became clear during the conduct of the study in Chapter 6, the prediction models developed had limited usefulness for clinical practice or future research due to the poor agreement between ALSPAC data and linked EHRs. Therefore, there is a greater

emphasis on assessing agreement between data sources in this thesis and less emphasis on results from the prediction models.

2.4 Submitted manuscript

Contribution

I am first author of a manuscript accepted for publication in NIHR Open Research in March 2024. This was a collaboration where I led on conceptualization, supervision, and writing, and contributed equally with other joint first authors and the senior author on organising a workshop with members of the electronic health records research group at LSHTM and evaluating feedback from this workshop. The submitted version of the manuscript is included here.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	lsh1901215	**Title**	Dr
First Name(s)	Julian		
Surname/Family Name	Matthewman		
Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	NIHR Open
Please list the paper's authors in the intended authorship order:	Julian Matthewman, Kirsty Andresen, Anne Suffel, Liang-Yu Lin, Anna Schultze, John Tazare, Krishnan Bhaskaran, Elizabeth Williamson, Ruth Costello, Jennifer Quint, Helen Strongman

Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This was a collaboration where I led on conceptualization, supervision, and writing, and contributed equally with other joint first authors and the senior author on organising a workshop with members of the electronic health records research group at LSHTM and evaluating feedback from this workshop.

SECTION E

Student Signature	
Date	20 March 2024

Supervisor Signature	
Date	20 March 2024

Checklist and guidance on creating codelists for electronic health records research

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Keywords: codelists, clinical codes, codesets, valuesets, electronic health records, checklist, reporting guidance, reproducibility

Author contributions

Hackathon group: Julian, Helen, Kirsty, Anne, Liang-yu
Writing group: Julian, Helen, Kirsty, Anne
EHR group: all that came to Hackathon meeting and commented
Advisory group: all that commented but didn't attend hackathon meeting

Conceptualization: hackathon group
Data Curation: Hackathon group
Formal Analysis: Hackthon group

Funding Acquisition: NA

Investigation: Hackathon group

Methodology: Hackathon group

Project Administration: Julian, Helen

Resources: NA or Hackathon + ehr group

Software: NA

Supervision: Julian, Helen

Validation: EHR group

Visualization: NA or Hackathon group

Writing – Original Draft Preparation: Writing group

Writing – Review & Editing: Writing group + Advisory group + EHR group

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Competing Interests

No competing interests were disclosed.

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Abstract

BACKGROUND Codelists are required to extract meaningful information on characteristics and events from electronic health records (EHRs). EHR research relies on codelists to define study populations and variables, thus, trustworthy codelists are important. Here, we provide a checklist, in the style of commonly used reporting guidelines, to help researchers adhere to best practice in codelist development and sharing.
METHODS Based on a literature review and a workshop with experienced EHR researchers we created a set of recommendations that are 1. broadly applicable to different datasets, research questions, and methods of codelist creation; 2. easy to follow, implement and document by an individual researcher, and 3. fit within a step-by-step process. We then formatted these recommendations into a checklist.
RESULTS We have created a 9-step checklist, comprising 26 items, with accompanying guidance on each step. The checklist advises on which metadata to provide, how to define a clinical concept, how to identify and evaluate existing codelist, how to create new codelists, and how to review, finalise and publish a created codelist.
CONCLUSIONS Use of the checklist can reassure researchers that best practice was followed during the development of their codelists, increasing trust in research that relies on these codelists and facilitating wider re-use and adaptation by other researchers.

Plain English Summary

Background

Electronic health records (EHRs), containing data routinely collected for patient care, are commonly used for epidemiological research, bringing opportunities to address questions not easily answered with clinical trials or research-specific data collection.1) EHRs contain data structured and coded based on dictionary ontologies or clinical vocabularies. These vary widely in scope and specificity of coding; for example International Classification of Diseases (2) has traditionally been used for administrative purposes such as recording of

deaths and hospital activity, whereas Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT) (3) was developed for use in clinical practice and includes a more extensive range of codes.

To extract meaningful information on health-related characteristics and events (e.g., diagnoses, prescriptions, referrals, test results, lifestyle factors, etc.) from EHRs, researchers create codelists (also referred to as clinical code lists, code sets, or value sets).(4) This is done by identifying relevant codes from the dictionary vocabulary (e.g. all the diagnosis, treatment, referral, etc. codes in SNOMED-CT indicating that a person has diabetes). In studies using EHRs, codelists define the study population, and other variables which researchers will use to answer the research question. Therefore, good practice in codelist development is an essential step in ensuring that codelists accurately capture the health-related characteristics or events of interest.

Checklists are increasingly being used in health research to promote adherence to recommended good practice,(5) including EHR research where the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement requires “a complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers”.(6) While a number of articles already provide guidance on creating, sharing and managing codelists, these focus on specific scenarios (e.g. specific coding systems, or using specific codelist creation tools or methods), or pertain to higher level recommendations (e.g. for organisations, funders, or journals, rather than individual researchers).(4,7–11) Thus, we created an easy to use checklist and step-by-step guidance that can be used by EHR researchers to ensure good practice.

Methods

We completed an initial literature search in PubMed to identify published papers describing methods and guidance for codelists. The most comprehensive review of the methodological literature on code lists was by Williams in 2017; this provides a set of best practice recommendations for future studies and software tools but did not aim to provide guidance for individual researchers on how to implement these recommendations. (4). We updated

this review, using the published search strategy, to find new literature released since 2017 (for a description of this literature search process see Box 1: Updated literature review). We also reviewed recommendations in other pertinent publications identified during this process (8–11) and features of different codelist sharing websites and general purpose research repositories. (12–15)

Box 1: Updated literature review

We performed a literature search based on, and using the same search strategy as, the existing review by *Williams R, et al., 2017* (4) to find new literature released since 2017 on the topic. Our systematic review was not intended to reevaluate recommendations proposed by Williams et al., rather to identify important new literature on codelists that could be used to inform the creation of our checklist and guidance. We title-and-abstract-screened 427 papers published between June 2017 and December 2022 and indexed in PubMed, of which we full-text-screened 24. From these we excluded papers specifically discussing the transition in the US from ICD9 to ICD10, papers with a higher-level focus on terminologies such as mappings between them but no focus on codelists, and applied papers, including papers that use codelists but do not discuss construction, reuse, validation, or sharing of codelists (as was done in Williams R, et al., 2017). There remained 9 papers from which we considered recommendations on codelist management. From these papers, we found 2 areas where additional recommendations we considered for inclusion in our checklist and guidance. The two identified topics are as follows:

1. When SNOMED CT is the available terminology, it may be preferrable to avoid "flat" codelists (i.e., a list of all codes to define a concept), in favour of using SNOMED CT concept hierarchies (i.e., a primary concept and its descendants optionally with additional relationships). These concept hierarchies may define more complex concepts (e.g. (Cerebrovascular accident OR History of Cerebrovascular accident) AND NOT Ruptured aneurysm) (16–18). For drugs, it may be possible to use other terminologies such as MeSH, ATC, etc. to create similar concept hierarchies rather than creating "flat" codelists (19). While a recommendation to make use of concept hierarchies was already included in the Williams et al. 2017 review which was adapted for our checklist and guidance, we decided not to include guidance

specific to the SNOMED-CT terminology, as this did not adhere to our criteria of being broadly applicable to different datasets, research questions, and methods of codelist creation.

2. If available, measures to check the quality of code sets should be made use of. The use of inter-terminology maps is recommended to check for codelists completeness when codelists exist in multiple terminologies (e.g. when creating a codelist in SNOMED CT, map an existing ICD-10 codelist to SNOMED and check for overlap and differences).(20) Some authors propose data centric natural-language processing methods to semi-automatically check codelists, however this will be dependent on the availability of such systems (21) Within excluded papers, we found multiple recommendations for use of common data models which may address problems with codelists on a higher level, which we did not focus in this work. We mention the use of inter-terminology maps in the guidance section on searching for existing codelists.

Based on these publications and our expertise in using EHRs, we drafted an initial checklist, encompassing a set of recommendations on codelist development and sharing that needed to fit the following criteria: 1. broadly applicable to different datasets, research questions, and methods of codelist creation; 2. easy to follow, implement and document by an individual researcher; 3. fit within a step-by-step process where some items should be completed before others. This draft checklist was presented to, and pilot tested on example codelists in a workshop with researchers of the Electronic Health records research group at the London School of Hygiene and Tropical Medicine (EHR research group). From this we gathered feedback which was used to further refine recommendations (for a description of this process, see Box 2: Feedback from workshop). Finally, we circulated the checklist to be reviewed and approved by the EHR research group at LSHTM and other stakeholders.

Box 2: Feedback from workshop

The EHR research group convened in a small group workshop to understand current codelist reporting practices and improve the process of creation, management, storage and sharing of codelists. Each group was provided with an example codelist (that had been employed in previous research), a draft version of the codelist

guidance document based on a review of existing literature, and a questionnaire. Each group used the questionnaire to assess the codelist against the provided draft guidelines. Attendees were then asked to provide input to the draft guidelines in a plenary session. The plenary session was structured in two main discussion topics: existing codelists and new codelists. The discussion centred on key themes contained within these discussion topics. Key themes for existing codelists included identifying published codelists and updating existing codelists. Key themes for creating new codelists included defining the clinical concept, creating the codelist, finalising the codelist and sharing the codelist. Several key takeaways emerged from these discussions:

1. Existing codelists: Participants stressed the need to create precise instructions for using previous codelists and updating them effectively. This would involve documenting instances of “absence of” evidence, for example, where no relevant codelists were found.
2. New codelists: Defining the clinical concept: Need for clear processes around defining the clinical concept. Participants advocated for clearly documenting and versioning iterative searches for synonyms and consulting experts early when defining the clinical concept. The participants stressed that these components should be part of the core documentation provided with the codelist and metadata.
3. Creating codelists: A suggestion was made to provide a cover sheet template to facilitate the implementation of information from the guidance.
4. Sharing codelists: Recognition of authorship: Participants emphasized the need to establish guidelines for recognizing and crediting individuals involved in codelist creation.
5. Improve knowledge about codelists and coding systems: The group advocated for an overview of codelists and coding systems to provide context and clarity in their usage.

In summary, the small group workshop discussions yielded valuable insights for enhancing codelist creation, and documentation practices, ultimately aiming to

improve the clarity and effectiveness of these processes for better healthcare data management and research.

Results

Below we provide a 9-step checklist (Table 1), comprising 26 items, with accompanying guidance on each step. We provide a filled-in example of the checklist in Table 2.

Table 1: Checklist

	Step No	Item	Information to be provided
Metadata			
Metadata	0	a. Name	*What is the name of the codelist?*
		b. Author(s)	*Who created the codelist?*
		c. Date finalised	*When was the codelist finalised?*
		d. Target data source	*What data is the codelist designed to be used with?*
		e. Terminology	*What is the terminology? (e.g., SNOMED, ICD)*
Define a clinical concept			
Define	1	a. Concept	*What is the clinical concept (e.g., the disease, drug, test result, etc…) of interest?*
		b. Timeframe	*Should the codelist capture new, current, and/or previous events?*
		c. Accuracy	*Should the codelist capture probable or definite codes?*
		d. Setting	*What is the (health care) setting (e.g., primary care, hospital care)?*
Identify and evaluate existing codelists			
Search	2	a. Sources searched	*Which sources were searched (e.g., internet search, codelist repositories)?*
		b. Existing codelists found	*Which suitable codelists did you find?*
Verify	3	a. Verified by others	*Which information is available to verify the quality of suitable codelists?*

		a. Verified by yourself	*Which checks did you conduct to verify the quality of suitable codelists?*
Reference	4	a. Existing codelists used	*Are you making use of any existing codelists? If yes, reference these, and specify how they are being used.*
Create a new codelist			
Prepare	5	a. Synonyms	*What are synonyms and related words for the clinical concept (e.g., different names for a disease/drug) and how did you identify these (e.g., source of clinical knowledge)?*
		b. Exceptions	*What should not be included in the codelist?*
Create	6	a. Method used	*Which method (e.g., a script, a tool) did you use to create the draft codelist?*
		b. Search terms	*Which search terms, and if applicable, exclusion terms did you use?*
		c. Hierarchy used to extend search	*Did you use a dictionary hierarchy (e.g., ICD-10 chapters, SNOMED-CT concepts) to modify your search? If yes, specify.*
		d. Decisions made while iterating	*Which decisions did you make while iteratively refining the draft codelist?*
		e. (Optional) Categories	*Did you specify subcategories within the codelist? If yes, specify.*
Review, finalise and publish			
Review	7	a. Reviewers	*Who reviewed the codelist and what expertise did reviewers have?*
		b. Scope of review	*What was reviewed (Just the draft codelist or also the method, terms, etc..)?*
		c. Evidence of review	*Where is the review process documented?*
	8	a. Codelist published	*Where is the codelist published?*

Publish		b. Resources published	*Where are the resources used to create the codelist (e.g., scripts, list of terms)?*

2Guidance

Step 1: Define

To find or create a suitable codelist, it is necessary to clearly state the following: Firstly, (**1a - Concept**) state what the code list intends to capture (e.g., a disease, drug, test results, etc..). Secondly, (**1b - Timeframe**) state if current (prevalent), new (incident) or previous events are of interest (e.g., a codelist for incident asthma may only aim at capturing codes indicating a first occurrence of asthma not including asthma-related administrative or treatment codes which are likely to indicate ongoing asthma). Thirdly, (**1c - Accuracy**) state if the codelist should prioritise sensitivity (i.e., includes codes "probably" indicating the clinical phenotype, e.g., "suspected asthma", "referred to asthma clinic") or specificity (e.g, includes codes that "definitely" match the concept)? Finally, (**1d - Setting**) state where the codes occur (e.g. the health care setting such as primary care or hospital care and what types of codes are included e.g. diagnostic codes, referrals, administrative codes, disease history codes). Together, this information makes up a clinical concept (e.g., "codes definitely describing current or previous asthma in primary care, including diagnostic, treatment, administrative and disease history codes").

Step 2: Search

(2a – Sources searched) Existing codelists that match your requirements can be identified (via an internet search (e.g, use a search-engine to search for "asthma codelist CPRD"), a search of publication databases, codelist repositories (e.g., the HDR UK phenotype library) or through existing collaboration and networks. Document which sources were searched.

(2b - Existing codelists found) This search does not need to be systematic, but rather should identify codelists that may be directly reused or codelists that can help in creating a new codelist. To choose potentially suitable codelists, check the codelist metadata, including which clinical concept the codelist aims to capture, when the codelist was created, which database it was used in, which terminology, and which version of the terminology was used (as different versions of the same data source and terminology can contain different codes), and if there are any copyright restrictions. Codelists in other terminologies may also be

useful, especially if these can be reliably mapped to the terminology of interest; however this is not always possible. Document which suitable codelists you found.

Step 3: Verify

In addition to matching your requirements (in terms of concept, terminology, etc.) the quality of existing codelists needs to be verified. **(3a - Verified by others)** Identify which information is available, besides the metadata, to allow you to judge if the codelist was created using good practice. Projects or published studies dedicated to, or including code list validation, may be of particular interest.(22) (**3b - Verified by yourself**) If available information isn't sufficient to judge the quality of an existing codelist, various checks can be conducted depending on the specific use-case. The codelist may be cross-checked with other existing codelists to verify if different authors consistently include the same codes. A review of the existing codelist may be performed, similar as would be done for a newly created codelist (see Step 7). If you have access to your study data or the number of observations for each code, you may also check the number of records the codelist retrieves, which may be compared to expectations based on clinical knowledge or previous studies.

Step 4: Reference

(**4a - Existing codelists used**) Any existing codelists that are used should be referenced, giving credit to the author(s), and making it easy for others to evaluate your study, or find and adapt the codelist for their own purposes. You should reference whether you have identified a codelist that suits your purposes without modification, whether it required changes to be suitable for your study, or whether it was used to check or inform the creation of a new codelist, the existing codelist . You should also state what the existing codelist was originally used for. We suggest wording such as "codelist(s) for [clinical concept] are from/were adapted from/were cross checked with …". References to existing codelist should include the author(s), year, and permanent identifier (such as a DOI, URL or manuscript reference). You may include these references directly as part of this checklist, in your study or codelist repository (see Step 8), or the section of your manuscript or manuscript appendix that describes study variables.

Step 5: Prepare

(5a - Synonyms) Identify synonyms and related words to the clinical concept (e.g, “asthma” for an asthma codelist; “stomach/gastric”, “cancer/neoplasm/malignant tumor”, etc., for a stomach cancer codelist; “beta-blocker”, “beta-adrenoceptor-antagonist”, and substance and trade names for a beta-blocker codelist). Consulting and referencing sources of clinical information can be useful. For example Medical Subject headings on Pubmed,(23) clinical knowledge summaries and guidelines (such as those provided by the National Institute for Health and Care Excellence (NICE) in the UK(24)), and websites of patient organisations may all contain useful information. **(5b - Exceptions)** At this stage, identifying exceptions to the concept that shouldn’t be included in the codelist is also important (e.g., if only “allergic” forms of asthma should be included, identify the words “non-allergic”, “exercise-induced”, etc.).

Step 6: Create

In this step, you create and iteratively refine a draft codelist. (**6a - Method used**) This can be done in a variety of ways. Guidance on the use of specific methods for creating codelists is available elsewhere, including on using Stata scripts,(8) online tools,(7) and for specific use-cases, such as drug codelists.(10) **(6b - Search terms)** Most approaches will involve searching a dictionary (also referred to as browser) firstly using search terms that correspond to the clinical concept or synonyms thereof, and secondly using exclusion terms to exclude codes that should not be in the codelist. For example, you create a script that searches for a list of predefined search terms (e.g., “asthma”, “inhaler”, etc..) and then exclude terms based on predefined exclusion terms (e.g., “referral”, “review”, etc..). Once finalised, report this list of search terms, and if applicable, exclusion terms. (**6c - Hierarchy used to extend search**) Make use of dictionary hierarchies, e.g., through checking codes that are in the same or a descendant chapter as already included codes, to identify further codes that are related but may have different names or labels (e.g., check which other names for a disease or brand names for drugs may be included in the same Read code or ICD chapter or SNOMED-CT concept). **(6d - Decisions made while iterating)** When developing the draft codelist, the search should be iteratively refined by repeatedly checking the retrieved and excluded codes, and adding terms to the list of search terms and exclusion terms. It may be better to also include codes where you are unsure if they should be in the codelist, as it is easier to exclude codes in the review stage than it is to add codes. Record important decisions made

while refining the search, e.g., document the reasons for in- or exclusions. If necessary, revisit the definition of the clinical concept, and record additional decisions in descriptions or comments. (**6e**) You may want to specify categories within the code list, e.g., incident and prevalent codes, more sensitive or specific, only diagnosis codes or diagnosis and administrative codes, (e.g., allowing for the conduct of secondary or sensitivity analyses).

Step 7: Review

Your codelist, and how it was created, needs to be reviewed to check for omissions and mistakenly included codes. **(7a - Reviewers)** A suitable reviewer with relevant knowledge about your clinical concept of interest and experience of the health care setting of your study should be identified. Reviewers may be within your research group or you may need to reach out to other researchers in the field (e.g., an asthma codelist may be reviewed by a general practitioner, asthma researcher or internal medicine physician). The actual review process can be handled in real time or asynchronously (e.g., via email or a GitHub issue thread). Having multiple reviewers that need to agree on the final codelist can further increase trust in the review process. **(7b - Scope of review)** The reviewer(s) should first read the description of the clinical concept, then, for each of the codes in the draft codelist, decide if the code is appropriate to include. Reviewing only the codelist, without reviewing the process of how it was generated risks missing codes that should be included; therefore, the method of how the codelist was created should also be reviewed. It is particularly important to give the full list of search terms and exclusion terms (e.g., are all terms included that could possibly refer to asthma?). Make sure to implement all the required changes and re-review if necessary. Whether or not to re-review is up to your judgment, but in general it will be more important when new search terms need to be added as compared to when only a few codes need to be dropped. **(7c - Evidence of review)** During the review process, interactions between the reviewer(s) and codelist creator(s) should be documented, e.g., via a GitHub Issue thread, or a spreadsheet where reviewers mark each code with yes/no or possible/probable/unlikely (e.g., “referral to asthma clinic”, may be marked as codes to be excluded, or codes to be included in a category of “possible asthma”).

Step 8: Publish

Finally, you should publish your codelist and metadata required by reporting guidelines such as RECORD. You should also publish resources used to create the codelist and related documentation to help readers to review, evaluate or reproduce your study, and reuse or adapt your codelist for future work. **(8a - Codelist published)** Codelists can be uploaded to general purpose repositories, ideally adhering to FAIR (Findable, Accessible, Interoperable, Reusable) principles. (25) Examples of such repositories include zenodo.org or the Open Science Framework. You may also be able to adhere to FAIR principles when using your organisation's research output repository, a Github or Gitlab repository, or uploading your codelist(s) as supplemental materials to your study. Codelists should be shared in a suitable format that is both human- and machine-readable (.txt, or .csv). **(8b - Resources published)** Share all resources used to create the codelist, such as search terms, scripts, and references, alongside the codelist. Depending on where the codelist is hosted, there may be predefined fields for metadata, or metadata can be included as part of the checklist.

Discussion

We have developed a checklist to support the creation, adaptation, and re-use of high-quality code lists for research using EHR data, accompanied by step-by-step guidance. These were developed by researchers with relevant expertise and experience including members of the EHR research group at LSHTM, which has employed codelist based data extraction for hundreds of studies for a large range of health-related topics. In Table 2 we include an example of a filled in checklist (Example of filled in checklist).

In comparison to previously published recommendations, the checklist and guidance here aim to be as universally applicable as possible, assuming as little as possible about the way of working, type of codelists to be created, type of terminology used, or tools used to create the codelist. As a consequence, it is not possible to cover every specific case in detail, therefore more narrow guidance may be useful. Examples of more specific guidance include guidance on creating drug codelists (10), SNOMED-CT codelists using concept hierarchies (16–18), codelists using Stata scripts (8), codelists using the "termset" method (7).

The guidance was developed with more challenging coding systems in mind, such as SNOMED-CT and Read codes, which have a complex or overlapping hierarchical structures. The checklist is designed to cope with this complexity, however some steps of the codelist creation process in other settings (e.g. using only ICD coding) may be simplified.

This guidance underwent different validation steps, (26) including a literature search, pilot testing and survey of peers. We have published the guidance in NIHR Open Research to support collaboration with the wider EHR community and to enable others to build upon the ideas presented here. Subsequent iterations, subject to funding, should involve pilot testing and input from larger groups of stakeholders, to ensure recommendations are useful for EHR researchers working in a range of different settings and on different topics.

Conclusion

Codelists form the foundation of EHR research, however they may often be of suboptimal standard, not capturing what they are supposed to capture, and the way in which they are created and shared often precludes reuse and reproducibility. With this work, we provide a checklist, and step-by-step guidance, to help researchers adhere to best practice.

Table 2: Example of filled in checklist

Table 2: Checklist

	Step No	Item	Information to be provided
Metadata			
Metadata	0	a. Name	*Atopic eczema*
		b. Author(s)	*Julian Matthewman*
		c. Date finalised	*1st January 2023*
		d. Target data source	*CPRD Aurum January 2023 release*
		e. Terminology	*SNOMED CT (mapped to CPRD Medcodeid)*
Define a clinical concept			
Define	1	a. Concept	*Atopic dermatitis/atopic eczema*
		b. Timeframe	*Current and previous*
		c. Accuracy	*Also including codes for unspecified forms of eczema that may be atopic*
		d. Setting	*Clinical records from UK primary care*
Identify and evaluate existing codelists			
Search	2	a. Sources searched	*Internet search, HDR UK phenotype library, LSHTM datacompass, opencodelists*
		b. Existing codelists found	*Identified a number of codelists but none for CPRD Aurum; one study describing validation of eczema codelists was found: Abuabara et al. 2017 (10.1016/j.jid.2017.03.029)*
Verify	3	a. Verified by others	*See validation study above*
		a. Verified by yourself	*No further checks conducted as codelists could not be used directly*
Reference	4	a. Existing codelists used	*Medcodes from Abuabara et al. 2017 (10.1016/j.jid.2017.03.029) used to crosscheck new codelist*

Create a new codelist			
Prepare	5	a. Synonyms	*Identified from existing codelist, including Eczema, atopic dermatitis, Besnier's prurigo*
		b. Exceptions	Non-atopic forms of eczema as specified on the websites of the US (https://nationaleczema.org/eczema/types-of-eczema/) and UK (https://eczema.org/information-and-advice/types-of-eczema/) eczema societies
Create	6	a. Method used	*Used search terms and exclusion terms in a script while iteratively refining terms*
		b. Search terms	*Search terms: eczema, atopic dermatitis, besnier's prurigo, allergic dermatitis Exclusion terms: fh, family history, contact, dyshidrotic, neurodermatitis, nummular, seborrheic, stasis, asteatotic, discoid, ear, otitis, auditory canal, eyes, eyelid, facial, female genital, vulval, hand, male genital, pompholyx, dyshidrotic, scalp, seborrhoeic, cradle cap, varicose, gravitational, pustular, erythrodermic, infectious, psoriasis, psoriasiform, immunodeficiency, vesicular, friction, hyperkeratotic, venous eczema, lip licking, desiccation, papular, drug eruption, infective, craquele*
		c. Hierarchy used to extend search	*Checked for codes with the same SnomedCTConceptId and codes with a descendant Read code*
		d. Decisions made while iterating	*In addition to non-atopic eczema from the eczema society website, also identified other non-atopic forms and other irrelevant codes, including erythrodermic eczema (erythroderma),*

			infectious eczematoid dermatitis (which is likely non-atopic), psoriasis, immunodeficiency syndromes, friction eczema, lip licking eczema, desiccation eczema, papular eczema, drug eruptions
		e. (Optional) Categories	*Symptom and diagnosis codes only (i.e., no codes for referrals, drugs, history of, etc..), definite atopic eczema (i.e., no codes for eczema that is possibly atopic)*
Review, finalise and publish			
Review	7	a. Reviewers	*Julian Matthewman (clinician; conducted multiple studies on atopic eczema using UK primary care data), Sinéad Langan (dermatologist and expert on atopic eczema research using electronic health records)*
		b. Scope of review	*Both the draft codelist and search and exclusion terms were reviewed*
		c. Evidence of review	*The review process is documented in a GitHub issue thread at (…)*
Publish	8	a. Codelist published	*The codelist is published on LSHTM datacompass and the study GitHub repository*
		b. Resources published	*All resources are available at the study GitHub repository, including scripts and terms*

References

1. Farmer R, Mathur R, Bhaskaran K, Eastwood SV, Chaturvedi N, Smeeth L. Promises and pitfalls of electronic health record analysis. Diabetologia. 2018 Jun;61(6):1241–8.

2. International Classification of Diseases (ICD) [Internet]. [cited 2023 Dec 6]. Available from: https://www.who.int/standards/classifications/classification-of-diseases

3. Vuokko R, Vakkuri A, Palojoki S. Systematized Nomenclature of Medicine–Clinical Terminology (SNOMED CT) Clinical Use Cases in the Context of Electronic Health Record Systems: Systematic Literature Review. JMIR Med Inform. 2023 Feb 6;11:e43750.

4. Williams R, Kontopantelis E, Buchan I, Peek N. Clinical code set engineering for reusing EHR data for research: A review. Journal of Biomedical Informatics. 2017 Jun;70:1–13.

5. Altman DG, Simera I. Using Reporting Guidelines Effectively to Ensure Good Reporting of Health Research. In: Moher D, Altman DG, Schulz KF, Simera I, Wager E, editors. Guidelines for Reporting Health Research: A User's Manual [Internet]. 1st ed. Wiley; 2014 [cited 2023 Sep 11]. p. 32–40. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9781118715598.ch4

6. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Medicine. 2015 Oct 6;12(10):e1001885.

7. Williams R, Brown B, Kontopantelis E, van Staa T, Peek N. Term sets: A transparent and reproducible representation of clinical code sets. Olier I, editor. PLoS ONE. 2019 Feb 14;14(2):e0212291.

8. Watson J, Nicholson BD, Hamilton W, Price S. Identifying clinical features in primary care electronic health record studies: methods for codelist development. BMJ Open. 2017 Nov;7(11):e019637.

9. 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.

10. Graul EL, Stone PW, Massen GM, Hatam S, Adamson A, Denaxas S, et al. Determining prescriptions in electronic healthcare record data: methods for development of standardized, reproducible drug codelists. JAMIA Open. 2023 Oct 1;6(3):ooad078.

11. What Are Codelists and How Are They Constructed? | Bennett Institute for Applied Data Science [Internet]. 2023 [cited 2023 Oct 18]. Available from: https://www.bennett.ox.ac.uk/blog/2023/09/what-are-codelists-and-how-are-they-constructed/

12. Phenotype Library [Internet]. [cited 2023 Dec 6]. Available from: http://phenotypes.healthdatagateway.org/

13. OpenCodelists [Internet]. [cited 2023 Dec 6]. Available from: https://www.opencodelists.org/

14. LSHTM Data Compass [Internet]. [cited 2023 Dec 6]. Available from: https://datacompass.lshtm.ac.uk/

15. Primary Care Unit [Internet]. [cited 2023 Dec 6]. CPRD @ Cambridge - Codes Lists (GOLD). Available from: https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/

16. Willett DL, Kannan V, Chu L, Buchanan JR, Velasco FT, Clark JD, et al. SNOMED CT Concept Hierarchies for Sharing Definitions of Clinical Conditions Using Electronic Health Record Data. Appl Clin Inform. 2018 Jul;9(3):667–82.

17. Chu L, Kannan V, Basit MA, Schaeflein DJ, Ortuzar AR, Glorioso JF, et al. SNOMED CT Concept Hierarchies for Computable Clinical Phenotypes From Electronic Health Record Data: Comparison of Intensional Versus Extensional Value Sets. JMIR Med Inform. 2019 Jan 16;7(1):e11487.

18. Elkheder M, Gonzalez-Izquierdo A, Qummer Ul Arfeen M, Kuan V, Lumbers RT, Denaxas S, et al. Translating and evaluating historic phenotyping algorithms using SNOMED CT. Journal of the American Medical Informatics Association. 2022 Sep 9;ocac158.

19. Bahr NJ, Nelson SD, Winnenburg R, Bodenreider O. Eliciting the Intension of Drug Value Sets – Principles and Quality Assurance Applications. 2017;5.

20. Fung KW, Xu J, Gold S. The Use of Inter-terminology Maps for the Creation and Maintenance of Value Sets. AMIA Annu Symp Proc. 2020 Mar 4;2019:438–47.

21. Li L, Grando A, Sarker A. A Data-Driven Iterative Approach for Semi-automatically Assessing the Correctness of Medication Value Sets: A Proof of Concept Based on Opioids. Methods Inf Med. 2021 Dec;60(S 02):e111–9.

22. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010 Jan;69(1):4–14.

23. Home - MeSH - NCBI [Internet]. [cited 2023 Dec 6]. Available from: https://www.ncbi.nlm.nih.gov/mesh/

24. CKS | NICE [Internet]. [cited 2023 Dec 6]. Available from: https://cks.nice.org.uk/

25. Wilkinson MD, Dumontier M, Aalbersberg IjJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016 Mar 15;3(1):160018.

26. Arundel C, James S, Northgraves M, Booth A. Study reporting guidelines: How valid are they? Contemporary Clinical Trials Communications. 2019 Jun 1;14:100343.

2.5 Chapter summary

- I made use of EHR data sources, including CPRD GOLD and Aurum (UK primary care data) and OpenSAFELY-TPP (UK primary care data linked to hospital data and high-cost drug prescribing information)
- I also made use of population cohorts, where data was collected specifically for research purposes, including the UK Biobank and ALSPAC, which were both linked to primary care data
- Variables were derived from EHRs using codelists and/or validated algorithms; variables in population cohorts were derived from questionnaires
- I co-developed guidance and a checklist to improve codelist creation for EHR research
- Given the structure of EHRs, I used survival analysis methods, in particular Cox regression, to estimate hazard ratios comparing an exposed group to an unexposed group

3 Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform

3.1 Introduction

The COVID-19 pandemic, which reached the UK in March 2020, demanded urgently addressing questions relevant to people with immune-mediated inflammatory diseases (IMIDs). For example, should people with IMIDs be considered as vulnerable, would they benefit from "shielding" (i.e., behavioural measures to decrease the risk of COVID-19 infection, such as avoiding contact with other people),[92] and would they be safely able to continue taking their treatments for IMIDs, without increasing their risk of severe COVID-19.

The OpenSAFELY platform was created to address these urgent COVID-19-related questions, allowing the conduct of studies with EHR data in near real-time.[93] Another benefit was the size of the data, containing information on around 24 million individuals which, together with combining approaches across different types of IMIDs, allowed investigation of even rare exposures. High-cost targeted immune modifying drugs were studied; data on which was made available for the first time.[48]

While the focus of my work related to this thesis was originally more on inflammatory skin conditions, it made sense to expand given pandemic-related need. In addition, in both this chapter and Chapter 4, it made sense to not just include individuals with a specific inflammatory disease but to include individuals with several different inflammatory conditions that share treatment pathways. A cross-disease focus allowed addressing research questions that are relevant for a larger number of people and increased the power of studies to investigate treatment-related outcomes.

3.2 Published manuscript

Contribution

I am joint first author on a manuscript published in June 2022 in *The Lancet Rheumatology*.[57] This was a large collaboration which I joined while analyses were ongoing and the study had been conceptualised. I contributed substantially to the statistical analysis, interpretation of findings, and writing and editing of the manuscript, warranting joint first author position on the published manuscript.

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SECTION A – Student Details

Student ID Number	lsh1901215	**Title**	Dr
First Name(s)	Julian		
Surname/Family Name	Matthewman		
Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Rheumatology		
When was the work published?	June 2022		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This was a large collaboration which I joined while analyses were ongoing and the study had been conceptualised. I contributed substantially to the statistical analysis, interpretation of findings, and writing and editing of the manuscript, warranting joint first author position on the published manuscript.

SECTION E

Student Signature	[redacted]
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Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform

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Summary

Background The risk of severe COVID-19 outcomes in people with immune-mediated inflammatory diseases and on immune-modifying drugs might not be fully mediated by comorbidities and might vary by factors such as ethnicity. We aimed to assess the risk of severe COVID-19 in adults with immune-mediated inflammatory diseases and in those on immune-modifying therapies.

Methods We did a cohort study, using OpenSAFELY (an analytics platform for electronic health records) and TPP (a software provider for general practitioners), analysing routinely collected primary care data linked to hospital admission, death, and previously unavailable hospital prescription data. We included people aged 18 years or older on March 1, 2020, who were registered with TPP practices with at least 12 months of primary care records before March, 2020. We used Cox regression (adjusting for confounders and mediators) to estimate hazard ratios (HRs) comparing the risk of COVID-19-related death, critical care admission or death, and hospital admission (from March 1 to Sept 30, 2020) in people with immune-mediated inflammatory diseases compared with the general population, and in people with immune-mediated inflammatory diseases on targeted immune-modifying drugs (eg, biologics) compared with those on standard systemic treatment (eg, methotrexate).

Findings We identified 17 672 065 adults; 1 163 438 adults (640 164 [55·0%] women and 523 274 [45·0%] men, and 827 457 [71·1%] of White ethnicity) had immune-mediated inflammatory diseases, and 16 508 627 people (8 215 020 [49·8%] women and 8 293 607 [50·2%] men, and 10 614 096 [64·3%] of White ethnicity) were included as the general population. Of 1 163 438 adults with immune-mediated inflammatory diseases, 19 119 (1·6%) received targeted immune-modifying therapy and 181 694 (15·6%) received standard systemic therapy. Compared with the general population, adults with immune-mediated inflammatory diseases had an increased risk of COVID-19-related death after adjusting for confounders (age, sex, deprivation, and smoking status; HR 1·23, 95% CI 1·20–1·27) and further adjusting for mediators (body-mass index [BMI], cardiovascular disease, diabetes, and current glucocorticoid use; 1·15, 1·11–1·18). Adults with immune-mediated inflammatory diseases also had an increased risk of COVID-19-related critical care admission or death (confounder-adjusted HR 1·24, 95% CI 1·21–1·28; mediator-adjusted 1·16, 1·12–1·19) and hospital admission (confounder-adjusted 1·32, 1·29–1·35; mediator-adjusted 1·20, 1·17–1·23). In post-hoc analyses, the risk of severe COVID-19 outcomes in people with immune-mediated inflammatory diseases was higher in non-White ethnic groups than in White ethnic groups (as it was in the general population). We saw no evidence of increased COVID-19-related death in adults on targeted, compared with those on standard systemic, therapy after adjusting for confounders (age, sex, deprivation, BMI, immune-mediated inflammatory diseases [bowel, joint, and skin], cardiovascular disease, cancer [excluding non-melanoma skin cancer], stroke, and diabetes (HR 1·03, 95% CI 0·80–1·33), and after additionally adjusting for current glucocorticoid use (1·01, 0·78–1·30). There was no evidence of increased COVID-19-related death in adults prescribed tumour necrosis factor inhibitors, interleukin (IL)-12/IL-23 inhibitors, IL-17 inhibitors, IL-6 inhibitors, or Janus kinase inhibitors compared with those on standard systemic therapy. Rituximab was associated with increased COVID-19-related death (HR 1·68, 95% CI 1·11–2·56), with some attenuation after excluding people with haematological malignancies or organ transplants (1·54, 0·95–2·49).

Interpretation COVID-19 deaths and hospital admissions were higher in people with immune-mediated inflammatory diseases. We saw no increased risk of adverse COVID-19 outcomes in those on most targeted immune-modifying drugs for immune-mediated inflammatory diseases compared with those on standard systemic therapy.

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Introduction

Although most people with COVID-19 have mild symptoms, estimates in unvaccinated individuals indicate that 15% develop pneumonia requiring hospital treatment and 5% progress to severe disease (ie, respiratory failure, septic shock, or multiple organ dysfunction).[1] Previous research has shown that immune-mediated inflammatory diseases, including those affecting joints (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), the bowel (Crohn's disease and ulcerative colitis), and skin (psoriasis and hidradenitis suppurativa), are associated with an increased risk of severe COVID-19. However, most studies, except for one on rheumatoid arthritis,[2] have found that this risk disappears after adjusting for comorbidities.[3,4] Most studies also show that use of targeted therapies does not confer risk of severe COVID-19, with the exception of rituximab or Janus kinase (JAK) inhibitors, with which some studies have reported worse outcomes.[3,5–9] The majority of these studies were from selected sources, such as disease-specific registries, rather than general population-based sources, and are hence subject to selection bias, small sample sizes, and absence of denominators.

We aimed to investigate risks of severe COVID-19 outcomes in people with immune-mediated inflammatory diseases and those on targeted immune-modifying therapies using English population-based electronic health record data linked to a new, unique national hospital prescribing dataset containing

Research in context

Evidence before this study

We searched PubMed on Nov 2, 2021, using the terms "COVID-19", "SARS-CoV-2" AND "rheumatoid arthritis", "psoriatic arthritis", "ankylosing spondylitis", "Crohn's disease", "ulcerative colitis", "hidradenitis suppurativa" AND "psoriasis", to identify primary research articles and systematic reviews, published in English, examining severe COVID-19 outcome risk in individuals with immune-mediated inflammatory diseases and those on immune-modifying therapy. Previous studies reported an increased risk of severe COVID-19 in people with immune-mediated inflammatory diseases that was largely mediated through comorbidities. Most published studies suggested that people on targeted therapies to treat immune-mediated inflammatory diseases were not at an increased risk of severe COVID-19 outcomes, with the exception of some studies reporting worse outcomes in those on rituximab or Janus kinase (JAK) inhibitors. Some therapies, such as tumour necrosis factor inhibitors, were found to be associated with a decreased risk of severe COVID-19 outcomes. The majority of studies focused on adverse outcomes in patients on systemic therapy for immune-mediated inflammatory diseases and used data from disease-specific registries, which can be subject to selection bias and lack denominator populations.

Added value of the study

In our large population-based study of more than 17 million individuals, including more than 1 million people with immune-mediated inflammatory diseases and about 200 000 receiving immune-modifying medications, people with immune-mediated inflammatory diseases had an increased risk of COVID-19-related death compared with the general population after adjusting for potential confounders and mediators. We also saw some evidence that patients with immune-mediated inflammatory diseases were more likely than the general population to have COVID-19-related critical care admission or death, and hospital admission. Non-White ethnic groups had a higher risk of severe COVID-19 than White ethnic groups. However, the increase in risk of severe COVID-19 associated with having an immune-mediated inflammatory disease was generally similar between ethnic groups. We saw no evidence of differences in severe COVID-19-related outcomes with most targeted immune-modifying therapies when compared with standard systemic therapy. However, rituximab was associated with an increased risk of COVID-19-related death, and critical care admission or death. There was also an increase in COVID-19-related hospital admissions in people prescribed rituximab or JAK inhibitors, compared with those on standard systemic therapy, although adjustment for confounding by unmeasured severity might explain at least part of this finding. This is the first study, to our knowledge, to use high-cost drug data on medicines supplied by hospitals at a national scale in England (to identify targeted therapies). The availability of these data fills an important gap in the medication record of patients with more specialist conditions treated by hospitals, creating an important opportunity to generate insights into these conditions and these medications

Implications of all the available evidence

Our study offers insights into future risk mitigation strategies and COVID-19 vaccination priorities for individuals with immune-mediated inflammatory diseases, as it highlights that patients with immune-mediated inflammatory diseases and those taking rituximab might be at risk of severe COVID-19 outcomes. Crucially, our study does not show a link between most targeted immune-modifying medications, compared with standard systemic therapy, and severe COVID-19 outcomes. However, the increased risk of adverse COVID-19 outcomes in people with immune-mediated inflammatory diseases and those treated with rituximab merits further study.

information on high-cost targeted immune-modifying therapies. The size of our study population and granularity of our data allowed us to perform post-hoc analyses stratified by ethnicity, which is an important risk factor for severe COVID-19.[10,11]

Methods

Study design and participants

For **OpenSAFELY** see https://www.opensafely.org/

We did a cohort study using OpenSAFELY, a new secure analytics platform for electronic health records that was created by our team for NHS England, and TPP, a general practitioner software provider. We used primary care records managed by TPP that are linked to the UK Office for National Statistics (ONS) death data, SARS-CoV-2 testing data, and a unique national hospital medication dataset (including high-cost drugs supplied by hospitals; appendix p 3).[12] We accessed all data through OpenSAFELY. OpenSAFELY provides a secure software interface that allows analysis of pseudonymised primary care records in near real time within the electronic health record vendor's highly secure data centre, avoiding the need for data transfer off-site (minimising the re-identification risk). Pseudonymised datasets from other data providers are securely provided by the electronic health record vendor and linked to primary care data. The dataset analysed within OpenSAFELY was based on 24 million people currently registered at about 40% of general practitioner practices in England.

See **Online** for appendix

We included adults aged 18 years or older on March 1, 2020, who were registered with TPP practices with at least 12 months of primary care records before March, 2020 (figure 1A). We followed up individuals from March 1, 2020 (UK SARS-CoV-2 outbreak start), to Sept 30, 2020 (study end), or until the specific outcome under analysis (ie, COVID-19-related death, critical care admission or death, or hospital admission).

We compiled diagnostic and therapeutic code lists (in machine-readable languages such as SNOMED-CT or UK National Health Service dictionary of medicines and devices) for all study variables (exposures, outcomes, and covariates). Detailed information on compilation and sources of code lists are freely available for inspection and re-use online. The study was approved by the Health Research Authority (Research Ethics Committee reference 20/LO/0651) and the London School of Hygiene and Tropical Medicine (London, UK) Ethics Board (reference 21863). All code used for data management and analyses, including all iterations of the prespecified study protocol archived with version control, is available online.

For more on the **code lists** see https://codelists.opensafely.org/

For **all code** see https://github.com/opensafely/immunosuppressant-meds-research

Exposures

Exposures were immune-mediated inflammatory diseases: inflammatory joint disease (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), inflammatory bowel disease (Crohn's disease, ulcerative colitis, or unclassified), and inflammatory skin disease (psoriasis or hidradenitis suppurativa); and prescription of systemic immune-modifying medication by general practitioners or supplied by hospitals through high-cost drug prescription procedures. We focused on these immune-mediated inflammatory diseases because they are similar in terms of disease mechanisms and therapies (eg, tumour necrosis factor [TNF] inhibitors).

We identified people with immune-mediated inflammatory diseases using diagnostic morbidity codes in primary care during the 3 years before March 1, 2020; people with multiple categories contributed to comparisons with the general population for all immune-mediated inflammatory disease categories for which they had records (eg, individuals with psoriatic arthritis and psoriasis, contributed to both joint and skin disease).

Immune-modifying medications were categorised as standard systemic therapy and targeted therapy. Standard systemic therapies included leflunomide, methotrexate, mycophenolate mofetil or mycophenolic acid, ciclosporin, sulphasalazine, mercaptopurine, thioguanine, and azathioprine. Targeted therapies comprised TNF inhibitors (etanercept, adalimumab, golimumab, certolizumab, and infliximab), interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, and brodalumab), IL-12/IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab), IL-6 inhibitors (tocilizumab and sarilumab), B-cell depletion therapy (rituximab), and JAK inhibitors (baricitinib and tofacitinib).[13–18] Individuals treated with both systemic therapy and targeted therapies were considered to be exposed to targeted therapies.

We identified standard systemic therapies using primary care prescribing data, and targeted immune-modifying medications using high-cost drugs invoices (appendix p 3). Drug exposure was defined by at least one prescription or delivery of medication to an individual before March 1, 2020 (date chosen because some medications were either specifically used or stopped owing to the pandemic). For each individual, we defined drug exposure on the basis of the closest drug recorded before the study start (March 1, 2020), allowing for a maximum of 6 months before the start of the study for all agents apart from rituximab, for which we permitted a 12-month exposure window (given the frequency of treatment and long duration of response).[19,20]

Outcomes

Outcomes were COVID-19-related death, critical care admission or death, and hospital admission. We identified COVID-19-related deaths based on records of COVID-19-related International Classification of Diseases, revision 10, codes (U071, U072) anywhere on death certificates. We used COVID-19-related critical care admission (using data from the UK Intensive Care National Audit and Research Centre[21]) or death as a

combined endpoint to reflect individuals with severe COVID-19 who died without being admitted to a critical care unit. We identified COVID-19-related hospital admission as a positive PCR test less than 28 days before admission and up to 5 days after admission to exclude nosocomial infection.

Statistical analysis

We selected potential confounders and mediators a priori based on clinical knowledge and previous evidence.[10] In the relationship between immune-mediated inflammatory diseases and severe COVID-19 outcomes, we considered age (categorical variable), sex, deprivation (using quintiles of the Index of Multiple Deprivation),[22,23] and smoking status to be potential confounders; we considered body-mass index (BMI), cardiovascular disease, diabetes, and current glucocorticoid use to be potential mediators. In the relationship between immune-modifying therapy and severe COVID-19 outcomes, we considered age, sex, deprivation, smoking status, BMI, specific immune-mediated inflammatory disease (inflammatory joint, bowel, and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end-stage renal failure, chronic liver disease, chronic respiratory disease, and diabetes as potential confounders; we considered current glucocorticoid use as a potential mediator. Ethnicity (in five categories of White, South Asian, Black, mixed or other, and unknown) was used as a stratifying variable for subgroup analyses. A post-hoc analysis explored the effect of ethnicity on COVID-19 outcomes in each of the immune-mediated inflammatory disease subpopulations. Covariates were assessed within 12 months of study start as baseline conditions (definitions and figures representing assumed relationships between covariates, primary exposures, and outcomes are in the appendix pp 4, 27–28).

We described characteristics of the general population, people with immune-mediated inflammatory diseases, and those with immune-mediated inflammatory diseases prescribed immune-modifying therapy. We used Cox regression to estimate hazard ratios (HRs) with 95% CI comparing adults with immune-mediated inflammatory diseases with the general population, and people with immune-mediated inflammatory diseases on standard systemic drugs with those on targeted therapies. We adjusted models for confounding based on assumptions inherent in our conceptual frameworks (appendix pp 27–28). We tested Cox model assumptions using Schoenfeld residuals.

We repeated our main analyses in sensitivity analyses assessing robustness of our findings (appendix pp 5–7). We considered immune-mediated inflammatory disease severity and degree of shielding (ie, stay-at-home advice for vulnerable populations[24]) to be potential unmeasured confounders of associations between specific immune-modifying therapy and COVID-19 outcomes. We did a quantitative bias analysis using E values to assess how strongly associated unmeasured confounders would need to be with exposure and outcome to potentially fully explain observed non-null associations (ie, association adjusted for both measured covariates and the unmeasured confounder would be null).[25]

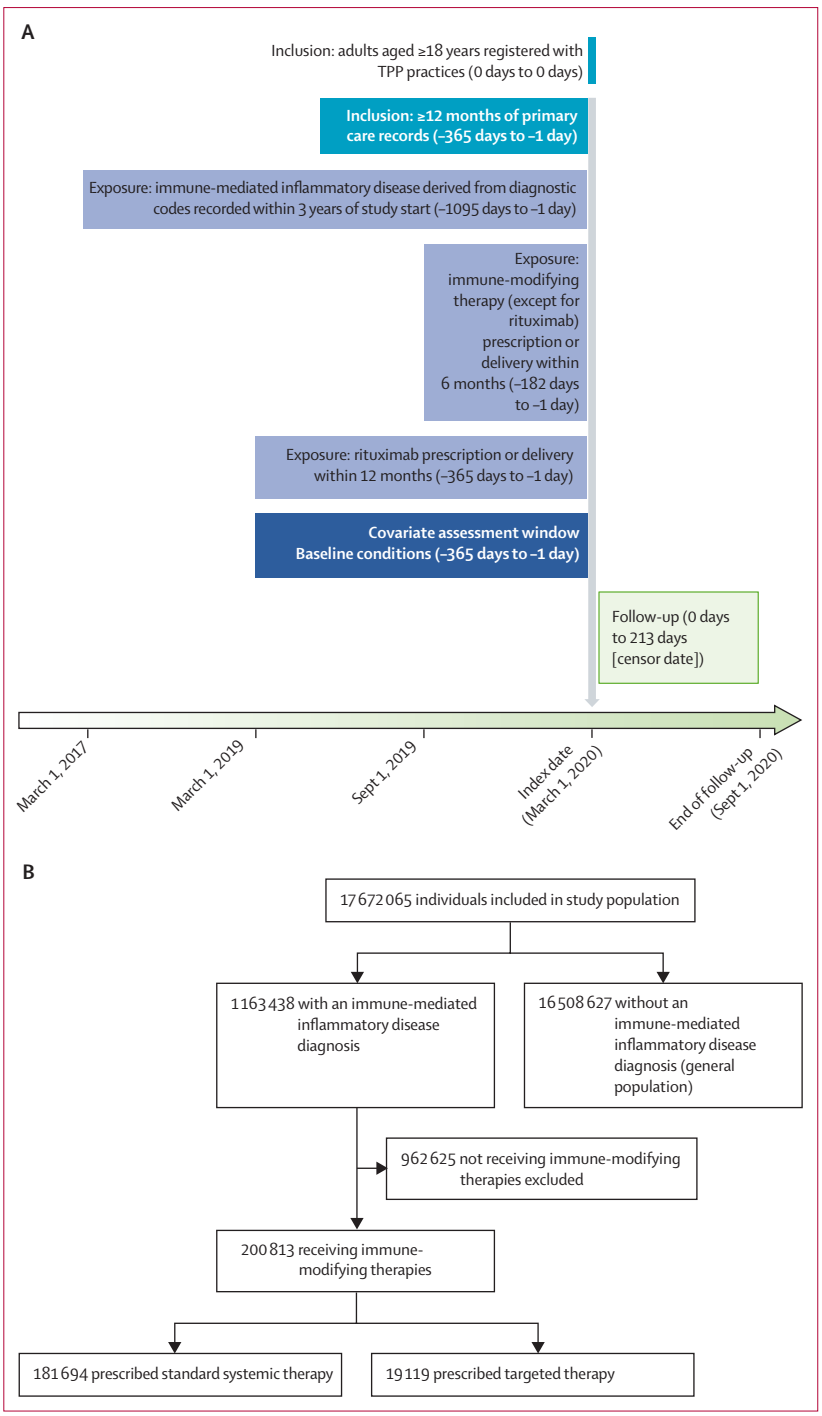


Figure 1: **Study design and flow**

We used Python for data management, and Stata (version 16) or Python for analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 17 672 065 people in the overall study population (figure 1B), 1 163 438 (6·6%) had an immune-mediated inflammatory disease diagnosis (table 1). Of these adults, 272 452 (23·4%) had inflammatory joint disease (183 485 [15·8%] with rheumatoid arthritis, 54 593 [4·7%] with psoriatic arthritis, and 35 138 [3·0%] with ankylosing spondylitis), 199 037 (17·1%) had an inflammatory bowel disease (69 788 [6·0%] with Crohn's disease, 100 617 [8·6%] with ulcerative colitis, and 32 093 [2·8%] with unclassified inflammatory bowel disease), and 769 816 (66·2%) had inflammatory skin disease (693 178 [59·6%] with psoriasis and 76 746 [6·6%] with hidradenitis suppurativa).

Compared with the general population, people with immune-mediated inflammatory diseases were older (≥70 years; 17·3% *vs* 24·5%), more likely to be female (49·8% *vs* 55·0%), White (64·3% *vs* 71·1%), and obese (BMI ≥30 kg/m²; 22·0% *vs* 29·8%), and with more

	General population (n=16 508 627)	Overall immune-mediated inflammatory diseases (n=1 163 438)	Inflammatory joint disease (n=272 452)	Inflammatory skin disease (n=769 816)	Inflammatory bowel disease (n=199 037)
Age, years					
18–39	5 808 217 (35·2%)	252 718 (21·7%)	25 238 (9·3%)	191 634 (24·9%)	46 099 (23·2%)
40–49	2 727 833 (16·5%)	183 130 (15·7%)	32 366 (11·9%)	130 758 (17·0%)	32 057 (16·1%)
50–59	2 882 387 (17·5%)	232 525 (20·0%)	56 192 (20·6%)	155 223 (20·2%)	39 513 (19·9%)
60–69	2 235 982 (13·5%)	209 384 (18·0%)	62 359 (22·9%)	129 432 (16·8%)	34 853 (17·5%)
70–79	1 797 487 (10·9%)	186 613 (16·0%)	62 200 (22·8%)	107 331 (13·9%)	31 215 (15·7%)
≥80	1 056 721 (6·4%)	99 068 (8·5%)	34 097 (12·5%)	55 438 (7·2%)	15 300 (7·7%)
Sex					
Male	8 293 607 (50·2%)	523 274 (45·0%)	107 104 (39·3%)	356 220 (46·3%)	96 054 (48·3%)
Female	8 215 020 (49·8%)	640 164 (55·0%)	165 348 (60·7%)	413 596 (53·7%)	102 983 (51·7%)
Ethnicity*					
White	10 614 096 (64·3%)	827 457 (71·1%)	195 851 (71·9%)	547 080 (71·1%)	141 986 (71·3%)
South Asian	999 881 (6·1%)	50 382 (4·3%)	12 771 (4·7%)	31 964 (4·2%)	8685 (4·4%)
Black	340 723 (2·1%)	9960 (0·9%)	2723 (1·0%)	6071 (0·8%)	1502 (0·8%)
Mixed or other	494 119 (3·0%)	16 797 (1·4%)	3655 (1·3%)	11 175 (1·5%)	2736 (1·4%)
Missing	4 059 808 (24·6%)	258 842 (22·2%)	57 452 (21·1%)	173 526 (22·5%)	44 128 (22·2%)
Body-mass index, kg/m²					
Underweight (<18·5)	314 887 (1·9%)	21 231 (1·8%)	5995 (2·2%)	11 280 (1·5%)	5158 (2·6%)
Normal (18·5–24·9)	4 576 346 (27·7%)	306 029 (26·3%)	74 283 (27·3%)	186 383 (24·2%)	63 902 (32·1%)
Overweight (25·0–29·9)	4 462 587 (27·0%)	351 450 (30·2%)	87 569 (32·1%)	226 580 (29·4%)	62 068 (31·2%)
Obese I (30·0–34·9)	2 255 908 (13·7%)	202 825 (17·4%)	50 614 (18·6%)	137 770 (17·9%)	30 048 (15·1%)
Obese II (35·0–39·9)	871 125 (5·3%)	88 344 (7·6%)	21 818 (8·0%)	62 536 (8·1%)	11 135 (5·6%)
Obese III (≥40·0)	502 285 (3·0%)	55 834 (4·8%)	12 896 (4·7%)	41 747 (5·4%)	5744 (2·9%)
Missing	3 525 489 (21·4%)	137 725 (11·8%)	19 277) (7·1%)	103 520 (13·4%)	20 982 (10·5%)
Index of Multiple Deprivation					
1 (least deprived)	3 337 475 (20·2%)	242 175 (20·8%)	57 464 (21·1%)	156 444 (20·3%)	44 874 (22·5%)
2	3 280 436 (19·9%)	235 706 (20·3%)	56 059 (20·6%)	152 956 (19·9%)	42 621 (21·4%)
3	3 294 811 (20·0%)	233 866 (20·1%)	56 398 (20·7%)	152 627 (19·8%)	40 775 (20·5%)
4	3 330 769 (20·2%)	228 552 (19·6%)	53 089 (19·5%)	152 678 (19·8%)	37 674 (18·9%)
5 (most deprived)	3 129 886 (19·0%)	213 903 (18·4%)	47 616 (17·5%)	148 866 (19·3%)	31 274 (15·7%)
Missing	135 250 (0·8%)	9236 (0·8%)	1826 (0·7%)	6245 (0·8%)	1819 (0·9%)
Smoking					
Never	7 687 903 (46·6%)	420 806 (36·2%)	102 798 (37·7%)	265 169 (34·4%)	79 651 (40·0%)
Former	5 310 393 (32·2%)	509 886 (43·8%)	128 484 (47·2%)	327 811 (42·6%)	91 893 (46·2%)
Current	2 774 203 (16·8%)	220 916 (19·0%)	40 007 (14·7%)	168 056 (22·8%)	25 350 (12·7%)
Missing	736 128 (4·5%)	11 830 (1·0%)	1163 (0·4%)	8780 (1·1%)	2143 (1·1%)

(Table 1 continues on next page)

	General population (n=16 508 627)	Overall immune-mediated inflammatory diseases (n=1 163 438)	Inflammatory joint disease (n=272 452)	Inflammatory skin disease (n=769 816)	Inflammatory bowel disease (n=199 037)
(Continued from previous page)					
Comorbidities					
Diabetes					
HbA_{1c} <58 mmol/mol (<7·5%)	1 033 685 (6·3%)	112 193 (9·6%)	32 631 (12·0%)	71 520 (9·3%)	17 366 (8·7%)
HbA_{1c} ≥58 mmol/mol (≥7·5%)	456 388 (2·8%)	48 951 (4·2%)	13 058 (4·8%)	32 388 (4·2%)	7766 (3·9%)
Unknown HbA_{1c}	240 398 (1·5%)	21 567 (1·9%)	5741 (2·1%)	14 071 (1·8%)	3482 (1·7%)
Cardiovascular disease	1 146 032 (6·9%)	129 065 (11·1%)	42 078 (15·4%)	76 916 (10·0%)	20 536 (10·3%)
Stroke	372 332 (2·3%)	40 523 (3·5%)	12 872 (4·7%)	24 075 (3·1%)	6587 (3·3%)
Cancer	962 622 (5·8%)	94 832 (8·2%)	27 779 (10·2%)	56 751 (7·4%)	17 150 (8·6%)
End-stage renal failure	22 408 (0·1%)	2190 (0·2%)	580 (0·2%)	1217 (0·2%)	550 (0·3%)
Chronic respiratory disease	666 384 (4·0%)	94 350 (8·1%)	33 690 (12·4%)	53 614 (7·0%)	14 725 (7·4%)
Chronic liver disease	98 012 (0·6%)	15 333 (1·3%)	3877 (1·4%)	9340 (1·2%)	3758 (1·9%)
Glucocorticoid use					
One or more prescriptions in past 3 months†	317 938 (1·9%)	64 151 (5·5%)	30 928 (11·4%)	27 673 (3·6%)	11 913 (6·0%)

Data are n (%). People with diagnoses across subcategories contributed to multiple categories (eg, a person with psoriasis and psoriatic arthritis contributed to both skin and joint categories of immune-mediated inflammatory diseases). HbA_{1c}=glycated haemoglobin. *Ethnicity was not adjusted for in the main analysis due to the high proportion of missing data, although we did adjust for ethnicity in a sensitivity analysis (appendix p 9). †Glucocorticoid use refers to individuals with one or more prescriptions for any dose of oral glucocorticoid in the 3 months before study start.

Table 1: **Descriptive characteristics of general population and people with immune-mediated inflammatory diseases**

comorbidities (table 1). There were differences between individuals with inflammatory joint, skin, and bowel diseases: for example, individuals with inflammatory joint disease were older than those with an inflammatory bowel disease or inflammatory skin disease (table 1).

After adjusting for age and sex, people with immune-mediated inflammatory diseases had a greater risk of COVID-19-related death compared with the general population (HR 1·27, 95% CI 1·23–1·31). Evidence of association between immune-mediated inflammatory diseases and COVID-19-related death remained after additionally adjusting for the confounders deprivation, and smoking status (HR 1·23, 95% CI 1·20–1·27) and after further adjusting for the potential mediators BMI, cardiovascular disease, diabetes, and current glucocorticoid use (HR 1·15, 95% CI 1·11–1·18; figure 2; appendix p 8).

After adjusting for age and sex, we saw increased COVID-19-related death in people with inflammatory joint (HR 1·51, 95% CI 1·44–1·58), bowel (1·15, 1·07–1·24), and skin (1·16, 1·11–1·20) diseases compared with the general population. After further adjusting for potential confounders, evidence for association between specific immune-mediated inflammatory disease types and COVID-19-related death persisted for all types of immune-mediated inflammatory diseases and was greatest for inflammatory joint disease (HR 1·47, 95% CI 1·40–1·54), with smaller effect estimates for inflammatory skin (1·12, 1·08–1·17) and bowel (1·12, 1·04–1·21) disease, and further attenuation after adjusting for potential mediators (figure 2; appendix p 8).

People with immune-mediated inflammatory diseases had greater risk of COVID-19-related critical care admission or death than the general population (HR 1·28, 95% CI 1·24–1·31), which persisted after adjusting for confounders (1·24, 1·21–1·28) and further adjusting for mediators (1·16, 1·12–1·19). Compared with the general population, there was evidence of increased COVID-19-related critical care admission or death in people with inflammatory joint, skin, and bowel diseases (figure 2; appendix p 8).

Compared with the general population, people with immune-mediated inflammatory diseases had greater risk of COVID-19-related hospital admission (HR 1·34, 95% CI 1·31–1·37), which remained after adjusting for potential confounders (1·32, 1·29–1·35) and mediators (1·20, 1·17–1·23). Risk of COVID-19-related hospital admission was increased in all immune-mediated inflammatory disease categories compared with the general population (figure 2; appendix p 8). Results from sensitivity analyses were broadly similar to the main analysis (appendix pp 9–10).

For age and sex distribution stratified by ethnicity see the appendix (p 29). 293 582 (35·5%) of 827 547 people in the White immune-mediated inflammatory disease population were younger than 50 years, versus 42 939 (55·7%) of 77 139 people in the non-White immune-mediated inflammatory disease population (p<0·0001). In analyses stratified by ethnicity and controlling for these age differences (appendix pp 30–33), we saw some attenuation of the estimates in people of South Asian ethnicity; for the other ethnic groups the numbers of events were small, leading to wide CIs. In the group with unknown ethnicity, we saw similar estimates to those for the White population. We also

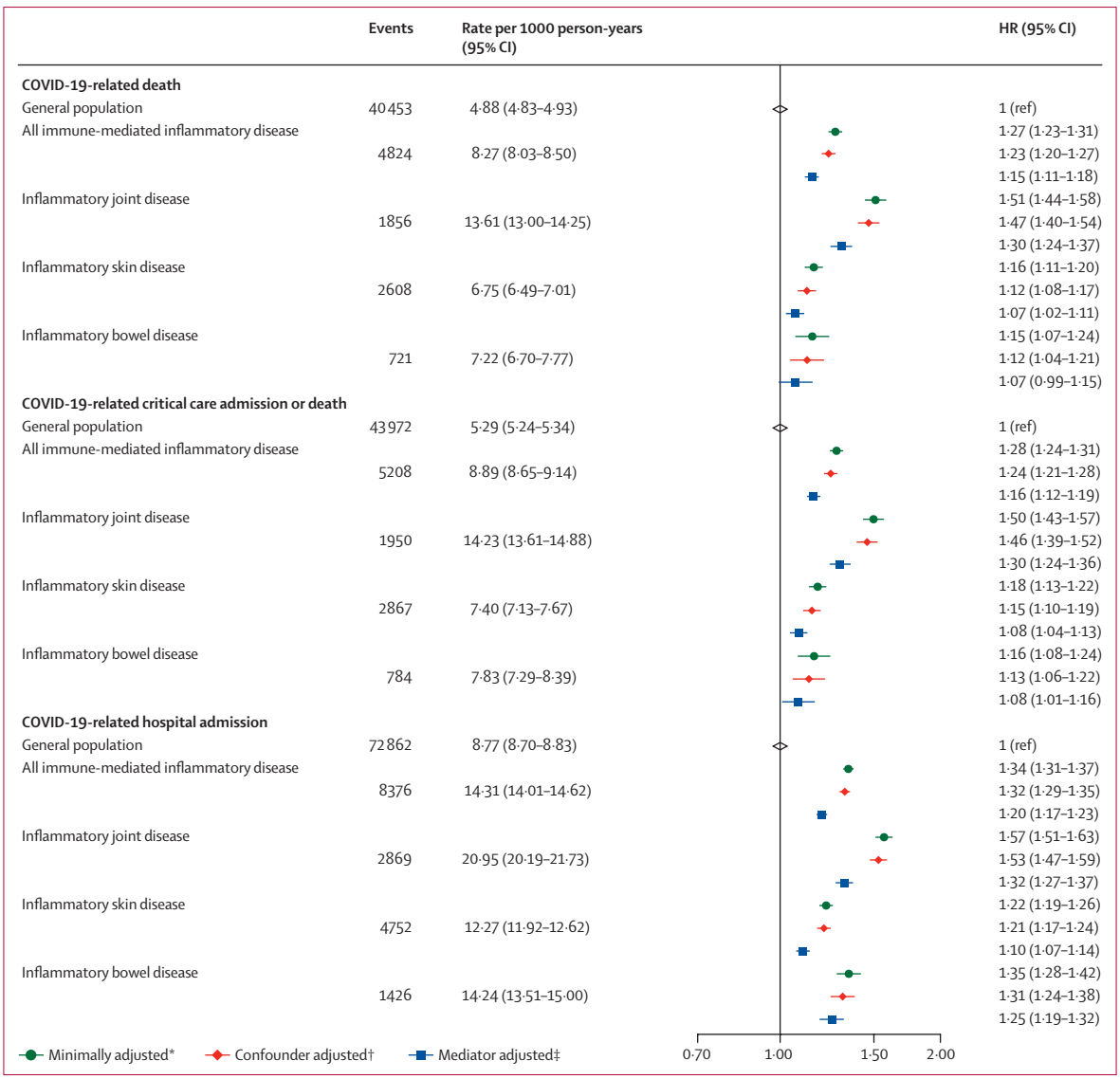


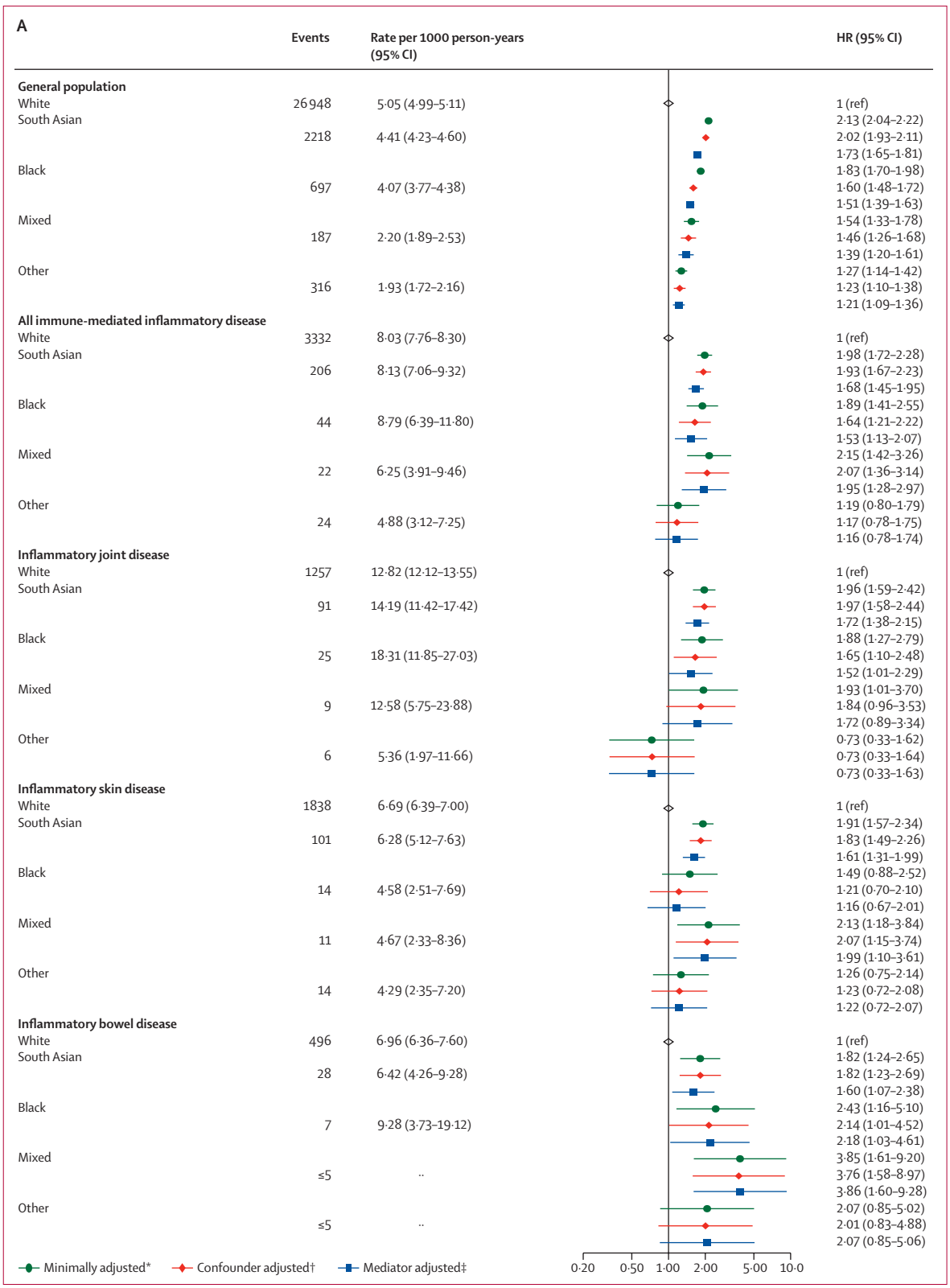
Figure 2: **COVID-19-related death, critical care admission or death, and hospital admission in people with immune-mediated inflammatory diseases versus the general population**

The general population event counts shown are for the analyses comparing people with immune-mediated inflammatory diseases with the general population. HR=hazard ratio. *Adjusted for age and sex. †Adjusted (immune-mediated inflammatory disease population) for age, sex, deprivation, and smoking status. ‡Adjusted (immune-mediated inflammatory disease population): age, sex, deprivation, smoking status, body-mass index, cardiovascular disease, diabetes, and current glucocorticoid use.

explored the effect of ethnicity itself on COVID-19 outcomes in each of the immune-mediated inflammatory disease subpopulations (figure 3). In each case, the effect of being in one of the non-White ethnic groups compared with the White population was similar to that observed in the general population.

200 813 (17·3%) of 1 163 438 adults with immune-mediated inflammatory diseases were prescribed either standard systemic therapy (181 694 [90·5%] of 200 813) or targeted immune-modifying therapy (19 119 [9·5%]; table 2; appendix p 11). Compared with people on standard systemic therapy, individuals receiving targeted therapy were younger and less likely to have comorbidities (eg, cardiovascular disease). The most commonly prescribed targeted therapies were TNF inhibitors, followed by rituximab, IL-12/IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors, and IL-6 inhibitors (table 2).

There was no difference in COVID-19-related death in people on targeted therapy compared with those on standard systemic therapy after adjusting for potential confounders (HR 1·03, 95% CI 0·80–1·33; adjusted for age, sex, deprivation, smoking status, BMI, immune-mediated inflammatory diseases [bowel, joint, skin], cardiovascular disease, cancer, stroke, end-stage renal



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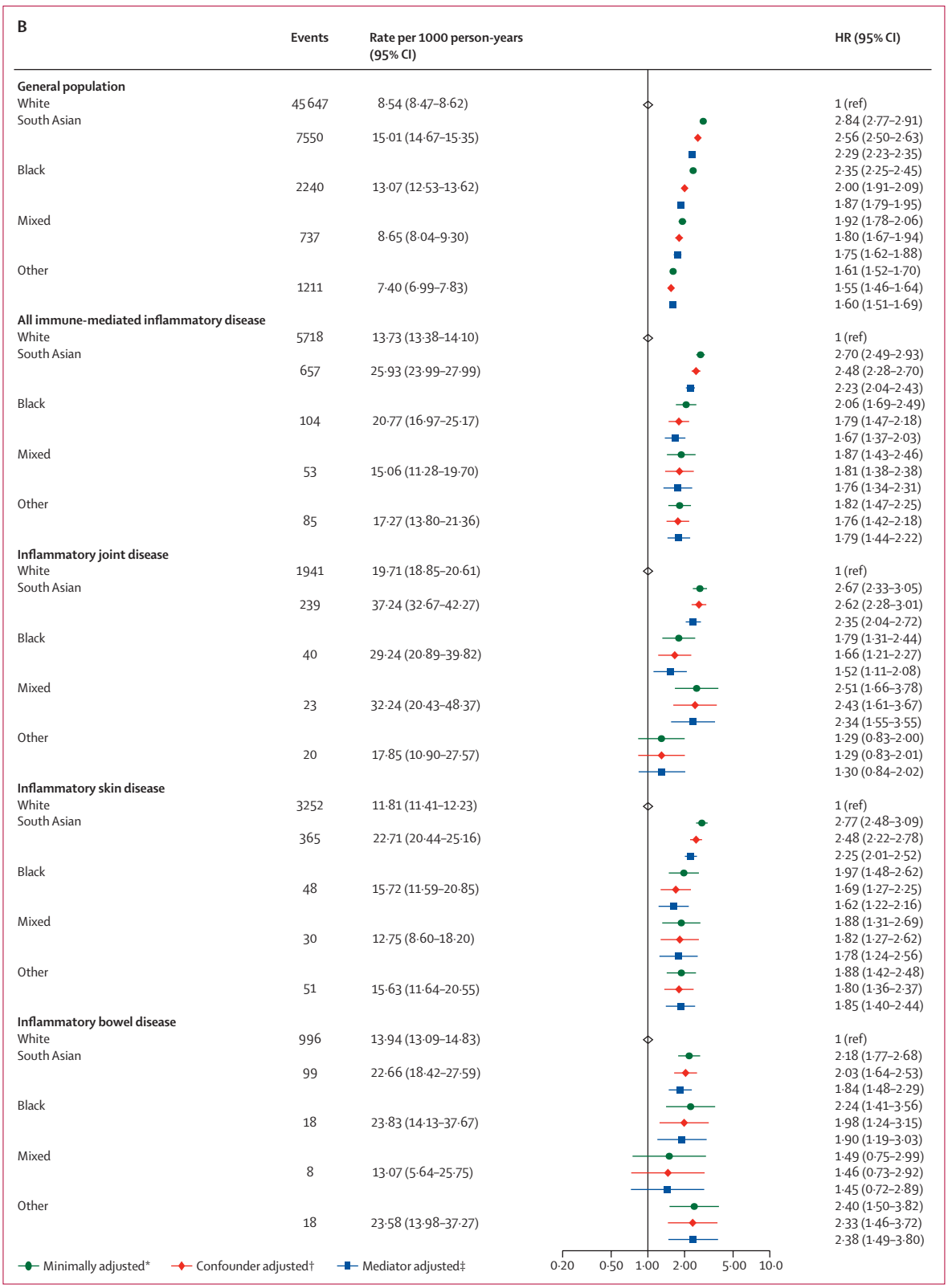

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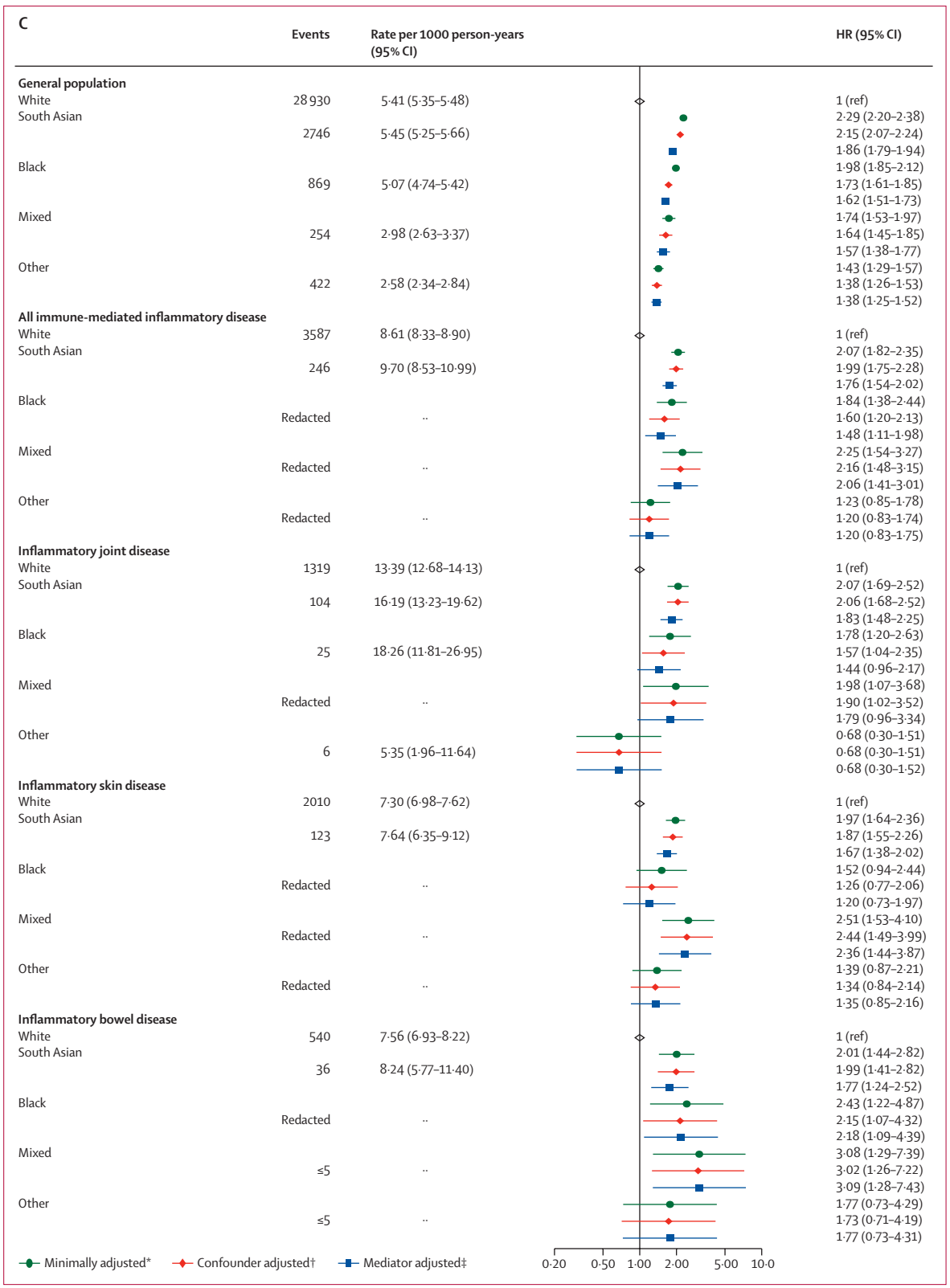

Figure 3: **COVID-19-related death (A), critical care admission or death (B), and hospital admissions (C) in the general population and immune-mediated inflammatory disease subgroups comparing non-White with White ethnicities**
Cells with counts less than or equal to five and cells that would potentially lead to a secondary risk of statistical disclosure have been redacted to protect anonymity. HR=hazard ratio. *Adjusted for age and sex. †Adjusted (immune-mediated inflammatory disease population) for age, sex, deprivation, and smoking status. ‡Adjusted (immune-mediated inflammatory disease population) for age, sex, deprivation, smoking status, body-mass index, cardiovascular disease, diabetes, and current glucocorticoid use.

failure, chronic liver disease, chronic respiratory disease, and diabetes) and mediators (1·01, 0·78–1·30; additionally adjusted for current glucocorticoid use; figure 4; appendix pp 12–13).

Compared with adults on standard systemic therapy, there was no observed increased risk of COVID-19 related death, COVID-19-related critical care admission or death, or COVID-19-related hospital admission, in individuals on TNF inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors, or IL-6 inhibitors, although CIs were wide in some groups (figure 4). Compared with people on standard systemic therapy, people receiving rituximab had an increased risk of COVID-19-related death (confounder-adjusted HR 1·68, 95% CI 1·11–2·56; based on 24 deaths in the rituximab group), and critical care admission or death (HR 1·92, 95% CI 1·31–2·81). We also observed an increased risk of COVID-19-related hospital admission in those

	Standard systemic therapy* (n=181 694)	Any targeted immune-modifying therapy (n=19 119)	TNF inhibitor (n=13 524)	IL-12/IL-23 inhibitor (n=1379)	IL-17 inhibitor (n=1036)	JAK inhibitor (n=871)	Rituximab (n=1998)	IL-6 inhibitor (n=758)
Immune-mediated inflammatory disease								
Joint disease	98 830 (54·4%)	12 929 (67·6%)	8778 (64·9%)	293 (21·2%)	670 (64·7%)	742 (85·2%)	1998 (100·0%)	758 (100·0%)
Skin disease	31 695 (17·4%)	5272 (27·6%)	3392 (25·1%)	893 (64·8%)	838 (80·9%)	96 (11·0%)	..	..
Bowel disease	79 239 (43·6%)	5094 (26·6%)	4443 (32·9%)	554 (40·2%)	11 (1·1%)	141 (16·2%)	..	..
Age, years								
18–39	24 898 (13·7%)	4276 (22·4%)	3467 (25·6%)	427 (31·0%)	252 (24·3%)	85 (9·8%)	68 (3·4%)	76 (10·0%)
40–49	23 140 (12·7%)	3301 (17·3%)	2456 (18·2%)	314 (22·8%)	246 (23·7%)	109 (12·5%)	175 (8·8%)	89 (11·7%)
50–59	36 588 (20·1%)	4405 (23·0%)	3068 (22·7%)	324 (23·5%)	274 (26·4%)	225 (25·8%)	432 (21·6%)	188 (24·8%)
60–69	40 134 (22·1%)	3826 (20·0%)	2523 (18·7%)	201 (14·6%)	177 (17·1%)	246 (28·2%)	565 (28·3%)	207 (27·3%)
70–79	38 842 (21·4%)	2616 (13·7%)	1603 (11·9%)	91 (6·6%)	75 (7·2%)	165 (18·9%)	579 (29·0%)	154 (20·3%)
≥80	18 092 (10·0%)	695 (3·6%)	407 (3·0%)	22 (1·6%)	12 (1·2%)	41 (4·7%)	179 (9·0%)	44 (5·8%)
Sex								
Male	76 134 (41·9%)	8341 (43·6%)	6259 (46·3%)	690 (50·0%)	595 (57·4%)	244 (28·0%)	557 (27·9%)	171 (22·6%)
Female	105 560 (58·1%)	10 778 (56·4%)	7265 (53·7%)	689 (50·0%)	441 (42·6%)	627 (72·0%)	1 441 (72·1%)	587 (77·4%)
Ethnicity†								
White	130 217 (71·7%)	13 353 (69·8%)	9481 (70·1%)	926 (67·2%)	711 (68·6%)	599 (68·8%)	1406 (70·4%)	535 (70·6%)
South Asian	8451 (4·7%)	1023 (5·4%)	671 (5·0%)	96 (7·0%)	73 (7·0%)	68 (7·8%)	119 (6·0%)	34 (4·5%)
Black	1 361 (0·7%)	179 (0·9%)	123 (0·9%)	Redacted‡	8 (0·8%)	Redacted‡	25 (1·3%)	Redacted‡
Mixed or other	2183 (1·2%)	277 (1·4 %)	201 (1·5%)	Redacted§	22 (2·1%)	Redacted§	20 (1·0%)	Redacted§
Missing	39 482 (21·7%)	4287 (22·4%)	3048 (22·5%)	335 (24·3%)	222 (21·4%)	176 (20·2%)	428 (21·4%)	169 (22·3%)
Body-mass index, kg/m²								
Underweight (<18·5)	3752 (2·1%)	482 (2·5%)	342 (2·5%)	37 (2·7%)	8 (0·8%)	22 (2·5%)	58 (2·9%)	21 (2·8%)
Normal (18·5–24·9)	52 050 (28·6%)	5161 (27·0%)	3761 (27·8%)	318 (23·1%)	168 (16·2%)	252 (28·9%)	560 (28·0%)	210 (27·7%)
Overweight (25·0–29·9)	59 223 (32·5%)	5627 (29·4%)	3989 (29·5%)	340 (24·7%)	299 (28·9%)	254 (29·2%)	646 (32·3%)	216 (28·5%)
Obese I (30·0–34·9)	32 671 (18·0%)	3424 (17·9%)	2334 (17·3%)	265 (19·2%)	227 (21·9%)	163 (18·7%)	388 (19·4%)	136 (17·9%)
Obese II (35·0–39·9)	13 370 (7·4%)	1636 (8·6%)	1071 (7·9%)	150 (10·9%)	132 (12·7%)	82 (9·4%)	172 (8·6%)	70 (9·2%)
Obese III (≥40·0)	7836 (4·3%)	1011 (5·3%)	650 (4·8%)	115 (8·3%)	88 (8·5%)	44 (5·1%)	89 (4·5%)	55 (7·3%)
Missing	12 792 (7·0%)	1778 (9·3%)	1377 (10·2)	154 (11·2)	114 (11·0%)	54 (6·2%)	85 (4·3%)	50 (6·6%)
Index of Multiple Deprivation								
1 (least deprived)	39 830 (21·9%)	4284 (22·4%)	3104 (23·0%)	254 (18·4%)	240 (23·2%)	187 (21·5%)	401 (20·1%)	189 (24·9%)
2	38 618 (21·3%)	4070 (21·3%)	2904 (21·5%)	281 (20·4%)	193 (18·6%)	218 (25·0%)	427 (21·4%)	150 (19·8%)
3	37 626 (20·7%)	3875 (20·3%)	2724 (20·1%)	288 (20·9%)	210 (20·3%)	156 (17·9%)	443 (22·2%)	149 (19·7%)
4	34 698 (19·1%)	3503 (18·3%)	2473 (18·3%)	272 (19·7%)	187 (18·1%)	146 (16·8%)	370 (18·5%)	Redacted‡
5 (most deprived)	29 508 (16·2%)	3236 (16·9%)	2209 (16·3%)	274 (19·9%)	195 (18·8%)	155 (17·8%)	345 (17·3%)	144 (19·0%)
Missing	1 414 (0·8%)	151 (0·8%)	110 (0·8%)	10 (0·7%)	11 (1·1%)	9 (1%))	12 (0·6%)	Redacted§
Smoking								
Never	68 915 (37·9%)	7156 (37·4%)	5214 (38·6%)	480 (34·8%)	Redacted§	311 (35·7%)	Redacted‡	276 (36·4%)
Former	89 418 (49·2%)	8437 (44·1%)	5769 (42·7%)	555 (40·2%)	Redacted§	439 (50·4%)	Redacted‡	355 (46·8%)
Current	22 338 (12·3%)	3300 (17·3%)	2352 (17·4%)	324 (23·5%)	Redacted§	117 (13·4%)	Redacted‡	120 (15·8%)
Missing	1023 (0·6%)	(226) (1·2%)	189 (1·4%)	20 (1·5%)	Redacted§	131 (15·0%)	Redacted‡	7 (0·9%)

(Table 2 continues on next page)

	Standard systemic therapy* (n=181 694)	Any targeted immune-modifying therapy (n=19 119)	TNF inhibitor (n=13 524)	IL-12/IL-23 inhibitor (n=1379)	IL-17 inhibitor (n=1036)	JAK inhibitor (n=871)	Rituximab (n=1998)	IL-6 inhibitor (n=758)
(Continued from previous page)								
Comorbidities								
Diabetes								
HbA_{1c} <58 mmol/mol (<7·5%)	19 572 (10·8%)	1654 (8·7%)	1007 (7·4%)	129 (9·4%)	105 (10·1%)	93 (10·7%)	292 (14·6%)	76 (10·0%)
HbA_{1c} ≥58 mmol/mol (≥7·5%)	7863 (4·3%)	831 (4·3%)	516 (3·8%)	72 (5·2%)	81 (7·8%)	49 (5·6%)	99 (5·0%)	34 (4·5%)
Unknown HbA_{1c}	3343 (1·8%)	390 (2·0%)	245 (1·8%)	37 (2·7%)	24 (2·3%)	22 (2·5%)	53 (2·7%)	15 (2·0%)
Cardiovascular disease	24 056 (13·2%)	1801 (9·4%)	1074 (7·9%)	109 (7·9%)	96 (9·3%)	111 (12·7%)	345 (17·3%)	94 (12·4%)
Stroke	7204 (4·0%)	480 (2·5%)	273 (2·0%)	36 (2·6%)	21 (2·0%)	35 (4·0%)	92 (4·6%)	36 (4·7%)
Cancer	16 721 (9·2%)	1143 (6·0%)	487 (3·6%)	48 (3·5%)	66 (6·4%)	59 (6·8%)	458 (22·9%)	50 (6·6%)
End-stage renal failure	477 (0·3%)	27 (0·1%)	14 (0·1%)	Redacted‡	Redacted‡	Redacted‡	7 (0·4%)	Redacted‡
Chronic respiratory disease	19 549 (10·8%)	1767 (9·2%)	976 (7·2%)	83 (6·0%)	67 (6·5%)	124 (14·2%)	452 (22·6%)	103 (13·6%)
Chronic liver disease	3175 (1·7%)	326 (1·7%)	202 (1·5%)	42 (3·0%)	37 (3·6%)	10 (1·1%)	38 (1·9%)	12 (1·6%)
Glucocorticoid use								
One or more prescription in past 3 months¶	20 254 (11·1%)	2318 (12·1%)	1292 (9·6%)	92 (6·7%)	69 (6·7%)	223 (25·6%)	537 (26·9%)	197 (26·0%)

Data are n (%). People with diagnoses across subcategories contributed to multiple categories (eg, someone with psoriasis and psoriatic arthritis, contributed to both skin and joint categories of immune-mediated inflammatory disease), therefore individuals may be included in more than one targeted immune-modifying treatment category. Individuals treated with both systemic therapy and targeted therapy were included in the targeted therapy cohort. HbA_{1c}=glycated haemoglobin. IL=interleukin. JAK=Janus kinase. TNF=tumour necrosis factor. *Standard systemic therapies included leflunomide, methotrexate, mycophenolate mofetil or mycophenolic acid, ciclosporin, sulphasalazine, mercaptopurine, thioguanine, and azathioprine. †Ethnicity was not adjusted for in the main analysis due to the high proportion of missing data, although we did adjust for ethnicity in a sensitivity analysis (appendix p 9). ‡Cells that introduce a potential secondary statistical disclosure have been redacted to protect anonymity. §Cells with counts of less than or equal to five are redacted to protect anonymity. ¶Glucocorticoid use refers to individuals with one or more prescription for any dose of oral glucocorticoid in the 3 months before study start.

Table 2: **Descriptive characteristics of immune-mediated inflammatory disease population on targeted and standard systemic immune-modifying therapy**

receiving rituximab (HR 1·59, 95% CI 1·16–2·18; 40 events) and JAK inhibitors (1·81, 1·09–3·01; 15 events), compared with people on standard systemic therapy.

Excluding people with haematological cancers and organ transplants attenuated the effect estimate for rituximab (HR 1·54, 95% CI 0·95–2·49; 18 events). Otherwise, results from sensitivity analyses were similar to the main analysis (appendix pp 14–16, 19). In a quantitative bias analysis of individuals with immune-mediated inflammatory diseases taking rituximab or JAK inhibitors compared with those taking standard systemic therapy, we noted that an unmeasured confounder moderately associated with both exposure and outcome could potentially explain associations of rituximab and JAK inhibitors with adverse COVID-19 outcomes (appendix pp 22–25, 34–35).

Discussion

In this large population-based study using data from OpenSAFELY, we found that people with immune-mediated inflammatory diseases have a higher risk of COVID-19-related death, critical care admission or death, and hospital admissions than people without immune-mediated inflammatory diseases of the same age, sex, deprivation level, and smoking status. Adults with inflammatory joint disease had a greater increase in risk of all outcomes than those with inflammatory skin or bowel disease. We saw some very minor attenuation of estimates in people of South Asian ethnicity, but numbers of events were small in other ethnicities, precluding definitive conclusions.

We showed that compared with standard systemic immune-modifying therapies for immune-mediated inflammatory diseases, there was no increased risk of COVID-19-related death in people prescribed TNF, IL-12/IL-23, IL-17, IL-6, or JAK inhibitors. Rituximab was associated with an increased risk of death and critical care admission. However, this finding could be explained by residual confounding from factors such as frailty, a mechanistic link might be more plausible in the context of the wider evidence base.[26–28]

Our findings suggest that people with immune-mediated inflammatory diseases were at an increased risk of COVID-19-related death compared with people without immune-mediated inflammatory diseases of the same age, sex, deprivation, and smoking status. The mediator-adjusted effect estimates of our study also suggest that not all of the increased risk can be explained by mediation through comorbidities, as was found to be the case in most previous studies.[3] Our finding that adults with immune-mediated inflammatory diseases were more likely to be admitted to hospital with COVID-19 than the general population is consistent with Canadian and Danish cohort studies[29,30] and reports of adverse COVID-19 outcomes for people with specific immune-mediated inflammatory diseases.[31] However, factors leading to adverse COVID-19 outcomes are probably multifactorial,

encompassing those associated with the likelihood of hospital admission, such as better access to care or a lower physician threshold for admission in patients on immune-modifying drugs, and factors associated with more severe symptoms. Explanations such as the presence of unmeasured confounders are also possible.

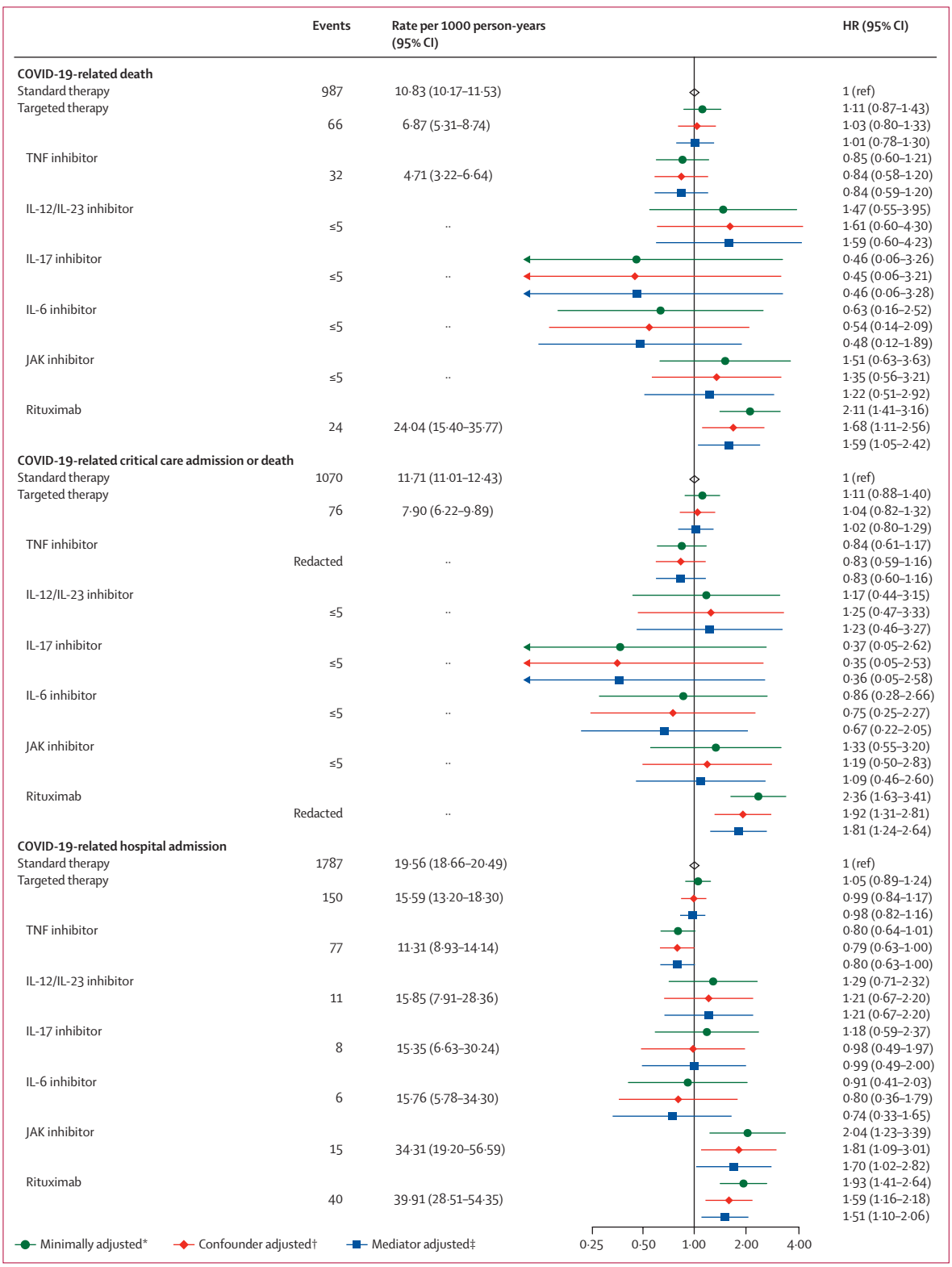

Figure 4: **COVID-19-related death, critical care admission or death, and hospital admission for targeted versus standard systemic immunosuppression**

The general population event counts shown are for the analyses comparing patients with immune-mediated inflammatory diseases with the general population. Cells with counts less than or equal to five and cells that would potentially lead to a secondary risk of statistical disclosure have been redacted to protect anonymity. HR=hazard ratio. IL=interleukin. JAK=Janus kinase. TNF=tumour necrosis factor. *Adjusted for age and sex. †Adjusted for age, sex, deprivation, smoking status, body-mass index, specific immune-mediated inflammatory disease (joint, bowel, and skin), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end-stage renal failure, chronic liver disease, chronic respiratory disease, and diabetes. ‡Adjusted for age, sex, deprivation, smoking status, body-mass index, specific immune-mediated inflammatory disease (joint, bowel, and skin), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end-stage renal failure, chronic liver disease, chronic respiratory disease, diabetes, and current glucocorticoid use.

Our observation that adults on targeted therapies (except rituximab) do not have an increased risk of COVID-19 related death is consistent with data from international registries.[3,5–7] A recent meta-analysis using data from registries included 2766 individuals with autoimmune diseases and COVID-19 diagnoses reported higher rates of hospital admission and death in people prescribed combination standard systemic therapy and biologics or JAK inhibitors, but lower rates in those prescribed TNF inhibitor monotherapy.[32] The Global Rheumatology Alliance reported no increase in COVID-19-related death with biological therapies compared with methotrexate monotherapy, but an increase in COVID-19-related death with JAK inhibitors and rituximab.[6,8,26] The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) reported no association in COVID-19-related death, critical care, or hospital admission in people on TNF inhibitors compared with those not prescribed TNF inhibitor therapy.[5] A further pooled analysis from three international COVID-19 registries (including multiple immune-mediated inflammatory diseases) reported a reduction in severe COVID-19 outcomes among TNF inhibitor monotherapy users compared with those on other treatment regimens.[9]

Our rituximab findings are consistent with previous reports of increased mortality in people treated with B cell-depleting agents (eg, including for oncology indications).[33] We were underpowered to assess effects of regular use of tocilizumab on COVID-19 outcomes, although trial data have shown benefit in patients admitted to hospital and critically ill patients.[34,35]

Analyses of outcomes stratified by ethnicity within each immune-mediated inflammatory disease sub-population showed that non-White groups were at a higher risk of death and hospital admission, consistent with a US-based study.[36] An increase in risk was also seen in the non-immune-mediated inflammatory disease population in our analyses, with similar estimates to previously published studies; however, we did not see that the effect of immune-mediated inflammatory diseases was different in different ethnic groups.[10,11] Although non-White groups had similar or lower crude rates of severe COVID-19 compared with White groups in our analyses, this finding can be explained by the younger age distribution seen in these populations.

The key strengths of this study are the scale and completeness of underlying electronic health record data: all raw, single-event-level clinical events for all individuals at 40% of all general practitioner practices in England, including all tests, treatments, diagnoses, and clinical and demographic information linked to various sources of hospital data, including, for the first time, a comprehensive dataset of medications supplied by hospitals. We recognise some limitations. Information on high-cost drug prescriptions was not available after March, 2020. Therefore, we were not able to evaluate whether individuals stayed on their therapies throughout the study period. An ideal analysis would have evaluated medication just before COVID-19 diagnosis, and without this information, we must acknowledge potential for some misclassification bias, which could explain some of the null associations in our findings. Although English primary care records are longitudinal and comprehensive, certain confounders were not captured. Shielding, as recommended for groups of clinically vulnerable people by the Chief Medical Officer,[24] might have reduced the risk of infection, thus likely biasing results towards the null. In mediator-adjusted models, we adjusted for concomitant use of oral glucocorticoids; however, this adjustment is likely to be imperfect, leading to residual confounding. We also considered cardiovascular disease and diabetes to be mediators in the relationship between immune-mediated inflammatory diseases and severe COVID-19 outcomes, but the timing of mediator assessment at index means that they could have predated the immune-mediated inflammatory disease diagnosis, and hence not be true mediators. Assessment of glucocorticoid exposure (and potentially immune-modifying drugs) is imperfect due to absent precise dose information, reducing dose regimens, low-cost medication administered in hospital alongside high-cost drugs, pandemic stockpiling, and patient-led discontinuation due to COVID-19-related concerns.

Finally, there is a possibility of misclassification of exposure status; this is highly unlikely for high-cost drug exposure because high-cost drug information is crucial for billing, but possible for standard systemic drugs resulting in underestimation of risks in the standard systemic group due to differential exclusion of patients whose first prescription was in hospital. We expect the effects of this misclassification to be minimal due to the short time window.

We have used one of the largest population-based datasets globally with linked data on immune-modifying drugs to describe COVID-19 risks for people with immune-mediated inflammatory diseases. We found that COVID-19 death and hospital admission were higher in people with immune-mediated inflammatory diseases; we saw no increased risk of adverse COVID-19 outcomes in adults on most targeted immune-modifying drugs for immune-mediated inflammatory diseases compared with standard systemics. The roll-out of a comprehensive vaccine programme alongside the development of other treatments for COVID-19 might mitigate some of the risks we describe. However, vaccine effectiveness in the immune-mediated inflammatory disease population on immunosuppressants has not been established[37–39] and emergent evidence on the negative effect of immunosuppression on vaccine immunogenicity—notably, rituximab—suggests that some individuals will remain at greater risk of severe COVID-19 outcomes.

Our findings provide an evidence-base to inform policy on booster vaccination prioritisation and risk-mitigating

behaviour advice, but must be interpreted in the context of UK public health policy on shielding. Findings will support health-care professionals engaging in shared decision making and communication of risk.

Contributors

BG conceived the OpenSAFELY platform and the approach. LS and BG led the project overall and are guarantors. SML, CHS, NAK, CL, JG, KEM, BM, and SJWE conceptualised the study. SB led on software development. AM led on information governance. CJB, CEM, DH, RC, GH, TW, SCJB, PI, JC, DE, JP, and SH curated data. SML, CHS, NAK, CL, JG, KEM, BM, KBh, CTR, CJB, CEM, IJD, AJW, HIM, JC, HF, HJC, JT, RME, LAT, RME, AYSW and JP conceptualised disease categories and code lists. MY, JG, NAK, KBe, JB, and JM wrote the statistical analysis code. KEM, KBe, NAK, JG, SN, MY, and JB did data visualisation. EW, HJC, LS, and BG obtained ethical approvals. CJB, CEM, SCJB, SD, AG, LF, PI, AJW, JC, DE, WH, and FH contributed to software development. AS, SML, BMK, KEM, DH, CHS, KBe, JG, SN, MY, NAK, JM, LAT, RME, AYSW, RM, and SJWE reviewed and edited the manuscript. All authors were involved in design and conceptual development, and reviewed and approved the final manuscript. NAK, AR, and LF had full access to and validated the data in the study. All authors had final responsibility for the decision to submit for publication.

For **all code** see github.com/OpenSAFELY

Declaration of interests

BG has received research funding from the Laura and John Arnold Foundation, the UK National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK (HDRUK), the Health Foundation, WHO, UK Research and Innovation (UKRI), Asthma UK, the British Lung Foundation, and the Longitudinal Health and Wellbeing strand of the National Core Studies programme; he also receives personal income from speaking and writing for lay audiences on the misuse of science and is a non-executive director of NHS Digital. CHS received departmental research funding from AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Leo, Pfizer, Novartis, Regeneron, SwedishOrphan Biovitrum, and Roche, and is an investigator within consortia that have industry partners. JG has received honoraria from AbbVie, Amgen, Celgene, Chugai, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Sobi, and UCB, and has research funding from Amgen, AstraZeneca, Gilead, Janssen, Medicago, Novovax, and Pfizer. MY has received honoraria from AbbVie and UCB. CWL has received honoraria from AbbVie, Bristol Myers Squibb, Celltrion, Ferring, Galapagos, Gilead, GlaxoSmithKline, Iterative Scopes, Janssen, Fresnius Kabi, Dr Falk, Vifor Pharma, Pfizer, Takeda, and Trellus Health. CHS and SML have received grants from the Horizon 2020 European Commission-funded consortium, which has industry partners involved in manufacture of treatments for immune-mediated inflammatory diseases (see the Biomap website for complete listing). EW has received payment from AstraZeneca for providing a training session, unrelated to the current manuscript. KEM has received consulting fees from Amgen. RM has received consulting fees from Amgen. LAT has received consulting fees from Bayer (payed to the institution), support for attending Medicines and Healthcare products Regulatory Agency meetings and is a member of two non-industry-funded trial advisory committees (unpaid). SN has received grants from Pfizer and honoraria for delivering educational presentations from Pfizer and Janssen. JB is funded by a studentship from GlaxoSmithKline. HIM was an occasional invited expert to the COVID-19 Vaccines Safety Surveillance Methodologies Expert Working Group, which has now come to a close. NAK has received departmental research funding from AbbVie, Biogen, Celgene, Celtrion, Galapagos, Merck Sharp & Dohme, Napp, Pfizer, Pharmacosmos, Roche, and Takeda; consulting fees from Amgen, Bristol Myers Squibb, Dr Falk, Janssen, Mylan, Pharmacosmos, Galapagos, Takeda, and Tillotts; honoraria from Allergan, Celltrion, Dr Falk, Ferring, Janssen, Pharmacosmos, Takeda, Tilllotts, and Galapagos; and support for meetings or travel from AbbVie, Dr Falk, and Janssen. All other authors declare no competing interests.

For the **consortia** see http://www.biomap-imi.eu

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Data sharing

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY are drawn from general practice data across England where TPP is the data processor. TPP developers (CB, JC, JP, FH, and SH) initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These tables are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. DataLab developers and principal investigators (BG, LS, CEM, SB, AJW, KW, WH, HJC, DE, PI, SD, GH, BBC, RMS, ID, KBh, EW, and CTR) holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY Data Access Agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data and to review the outputs of this code. All code for the full data management pipeline—from raw data to completed results for this analysis—and for the OpenSAFELY platform as a whole is available for review online.

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References

1 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323:** 1239–42.

2 England BR, Roul P, Yang Y, et al. Risk of COVID-19 in rheumatoid arthritis: a national Veterans Affairs matched cohort study in at-risk individuals. *Arthritis Rheumatol* 2021; **73:** 2179–88.

3 Fagni F, Simon D, Tascilar K, et al. COVID-19 and immune-mediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses. *Lancet Rheumatol* 2021; **3:** e724–36.

4 D'Silva KM, Jorge A, Cohen A, et al. COVID-19 outcomes in patients with systemic autoimmune rheumatic diseases compared to the general population: a US multicenter, comparative cohort study. *Arthritis Rheumatol* 2021; **73:** 914–20.

5 Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020; **159:** 481–491.e3.

6 Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79:** 859–66.

7 Mahil SK, Dand N, Mason KJ, et al. Factors associated with adverse COVID-19 outcomes in patients with psoriasis—insights from a global registry-based study. *J Allergy Clin Immunol* 2021; **147:** 60–71.

8 Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVID-19 Global Rheumatology Alliance physician registry. *Ann Rheum Dis* 2021; **80:** 1137–46.

9 Izadi Z, Brenner EJ, Mahil SK, et al. Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19. *JAMA Netw Open* 2021; **4:** e2129639.

10 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.

11 Mathur R, Rentsch CT, Morton CE, et al. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. *Lancet* 2021; **397:** 1711–24.

12 Rowan A, Bates C, Hulme W, et al. A comprehensive high cost drugs dataset from the NHS in England—an OpenSAFELY-TPP short data report. *Wellcome Open Res* 2021; **6:** 360.

13 National Institute for Health and Care Excellence. Psoriasis: assessment and management. Clinical guideline [CG153]. Oct 24, 2012. https://www.nice.org.uk/guidance/cg153/chapter/1-Recommendations (accessed Aug 26, 2021).

14 National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. NICE guideline [NG100]. July 11, 2018. https://www.nice.org.uk/guidance/ng100/chapter/Recommendations (accessed Aug 26, 2021).

15 National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management. NICE guideline [NG65]. Feb 28, 2017. https://www.nice.org.uk/guidance/NG65/chapter/Recommendations (accessed Aug 26, 2021).

16 National Institute for Health and Care Excellence. Crohn's disease: management. NICE guideline [NG129]. May 3, 2019. https://www.nice.org.uk/guidance/ng129/chapter/Recommendations (accessed Aug 26, 2021).

17 National Institute for Health and Care Excellence. Ulcerative colitis: management. NICE guideline [NG130]. May 3, 2019. https://www.nice.org.uk/guidance/ng130/chapter/Recommendations (accessed Aug 26, 2021).

18 National Institute for Health and Care Excellence. Adalimumab for treating moderate to severe hidradenitis suppurativa. Technology appraisal guidance [TA392]. June 22, 2016. https://www.nice.org.uk/guidance/TA392/chapter/1-Recommendations (accessed Aug 26, 2021).

19 Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; **70:** 909–20.

20 van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* 2010; **62:** 75–81.

21 Richards-Belle A, Orzechowska I, Gould DW, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. *Intensive Care Med* 2020; **46:** 2035–47.

22 Ministry of Housing. Communities and Local Government. English indices of deprivation 2015. Sept 30, 2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed Aug 26, 2021).

23 Noble M, Wright G, Smith G, Dibben C. Measuring multiple deprivation at the small-area level. *Environ Plann A* 2006; **38:** 169–85.

24 UK Government. Guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19 (accessed May 18, 2021).

25 Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology* 2016; **27:** 368–77.

26 Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021; **80:** 930–42.

27 Avouac J, Drumez E, Hachulla E, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. *Lancet Rheumatol* 2021; **3:** e419–26.

28 Sormani MP, De Rossi N, Schiavetti I, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol* 2021; **89:** 780–89.

29 Attauabi M, Seidelin JB, Felding OK, et al. Coronavirus disease 2019, immune-mediated inflammatory diseases and immunosuppressive therapies—a Danish population-based cohort study. *J Autoimmun* 2021; **118:** 102613.

30 Eder L, Croxford R, Drucker A, et al. OP0285 COVID-19 hospitalizations, ICU admission, and death among patients with immune mediated inflammatory diseases (IMID)—a population-based study. *Ann Rheum Dis* 2021; **80** (suppl 1): 173.

31 Ludvigsson JF, Axelrad J, Halfvarson J, et al. Inflammatory bowel disease and risk of severe COVID-19: a nationwide population-based cohort study in Sweden. *United European Gastroenterol J* 2021; **9:** 177–92.

32 Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021; **80:** 384–91.

33 Lamure S, Dulery R, Delord M, et al. Abstract S09-02: high incidence of persistent COVID-19 among patients with lymphoma treated with B-cell depleting immunotherapy. *Clin Cancer Res* 2021; **27:** S09–02 (abstr).

34 Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; **384:** 1491–502.

35 Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.

36 Gianfrancesco MA, Leykina LA, Izadi Z, et al. Association of race and ethnicity with COVID-19 outcomes in rheumatic disease: data from the COVID-19 Global Rheumatology Alliance Physician Registry. *Arthritis Rheumatol* 2021; **73:** 374–80.

37 Lin S, Kennedy NA, Saifuddin A, et al. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. *Nat Commun* 2022; **13:** 1379.

38 Mahil SK, Bechman K, Raharja A, et al. Humoral and cellular immunogenicity to a second dose of COVID-19 vaccine BNT162b2 in people receiving methotrexate or targeted immunosuppression: a longitudinal cohort study. *Lancet Rheumatol* 2022; **4:** e42–52.

39 Deepak P, Kim W, Paley MA, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. *Ann Intern Med* 2021; **174:** 1572–85.

3.3 Relevance for thesis

The study presented in this chapter on adverse COVID-19 outcomes for people with inflammatory diseases and people taking anti-inflammatory drugs (*Aim I*) provides evidence that can be used to inform priorities for their care (*Overall Thesis Aim*). The study demonstrates that new insights can be won from EHRs by leveraging data (on high-cost drugs) that was previously not accessible for research purposes. Learning from this large, comprehensive and in-depth study as a reference informed the conduct of the studies in subsequent chapters.

3.4 Chapter summary

- At the start of the COVID-19 pandemic, it was unclear whether people with IMIDs, and those taking targeted immune-modifying drugs, were at increased risk of severe COVID-19 outcomes
- The OpenSAFELY platform enabled research using linked primary care, hospital and high-cost drug-prescribing data
- I was part of a large collaborative that conducted a study investigating severe COVID-19 risk for people with different IMIDs (including of joint, bowel and skin), to inform risk-mitigation strategies
- We found an increased risk of COVID-19 deaths and hospital admissions in people with IMIDs (the largest increase of risk in those with inflammatory joint disease)
- We saw no increased risk of adverse COVID-19 outcomes in those on most targeted immune-modifying drugs (except rituximab) compared with those on standard systemic therapy

4 Identifying gaps in fracture preventive care for people prescribed oral corticosteroids: Population-based cohort studies in older adults in the UK and Canada

4.1 Introduction

Oral glucocorticoids have been in use for the treatment of inflammatory conditions for a long time. However, they have known adverse effects, which is why other drugs that may offer better safety profiles, such as the targeted immune modifying drugs discussed in Chapter 3, are becoming more widely used. One of the important adverse effects of oral glucocorticoids is increasing the risk of fractures, particularly major osteoporotic fractures in older people. While fracture preventive care, including bisphosphonates, is available and recommended for those who get prescribed high cumulative doses of oral glucocorticoids, it is known that these are underutilised. In this chapter, I explored a potential reason for missed opportunities for fracture preventive care. The hypothesis was that people prescribed high cumulative doses of oral glucocorticoids over the course of multiple prescriptions, over longer periods of time, or in multiple smaller doses with gaps between prescriptions, may be less likely to be recognised to be at risk of glucocorticoid-induced fractures. These prescribing patterns can be seen in people with relapsing-remitting conditions, such as eczema, asthma and COPD.[94–96]

As in Chapter 3, anti-inflammatory treatments are of interest here, however, the exposure

is defined as a prescribing pattern, rather than through a single prescription. This required processing EHR prescription data to calculate several variables that can be used to approximate prescribing patterns; e.g., I calculated how many days or how many prescriptions it took for people to reach high cumulative doses of oral glucocorticoids (see eFigure 1 in the published supplementary materials included in Section 4.3). The main outcome was the receipt of fracture preventive care, i.e., here, not experiencing the outcome was the potentially adverse situation. This "advantageous" outcome stands in contrast to the adverse outcomes in other chapters, and to the secondary outcome (major osteoporotic fracture) of this chapter.

I also include the published supplementary materials in Section 4.3. It contains more detailed descriptions of some of the methods, including details on data sources (eMethods 1), details on oral glucocorticoid prescription data cleaning (eMethods 2), and details on model diagnostics (eMethods 3). Results are also presented stratified by inflammatory disease status (eTable 3), and results using a continuous exposure definition (the log-10 Transformed Number of Days to Reach Risk Threshold) (eTable 4). In addition, a visualisation and explanation of the multi-state models, for which results are reported in the main manuscript, can be found in eFigure 1, and further study information is contained, including study flow diagrams (eFigure 3).

4.2 Published manuscript

Contribution

I am first author of a manuscript published in August 2023 in *JAMA Dermatology*.[97] I led the project, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing. This was a collaboration with researchers from Ontario, Canada, who conducted analyses in parallel on data from Ontario.

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Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

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Where was the work published?	JAMA Dermatology		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the project, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing. This was a collaboration with researchers from Ontario, Canada, who conducted analyses in parallel on data from Ontario.

SECTION E

Student Signature	[redacted]
Date	20 Marc 2024

Supervisor Signature	[redacted]
Date	20 March 2024

JAMA Dermatology | Original Investigation

Association of Different Prescribing Patterns for Oral Corticosteroids With Fracture Preventive Care Among Older Adults in the UK and Ontario

Julian Matthewman, MD, MSc; Mina Tadrous, PhD; Kathryn E. Mansfield, PhD; Deva Thiruchelvam, MSc; Donald A. Redelmeier, PhD; Angela M. Cheung, PhD; Iliana C. Lega, PhD; Daniel Prieto-Alhambra, PhD; Lawrence A. Cunliffe; Amy Mulick, MSc; Alasdair Henderson, PhD; Sinéad M. Langan, PhD; Aaron M. Drucker, MD, ScM

IMPORTANCE Identifying and mitigating modifiable gaps in fracture preventive care for people with relapsing-remitting conditions such as eczema, asthma, and chronic obstructive pulmonary disease who are prescribed high cumulative oral corticosteroid doses may decrease fracture-associated morbidity and mortality.

OBJECTIVE To estimate the association between different oral corticosteroid prescribing patterns and appropriate fracture preventive care, including treatment with fracture preventive care medications, among older adults with high cumulative oral corticosteroid exposure.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 65 195 participants with UK electronic medical record data from the Clinical Practice Research Datalink (January 2, 1998, to January 31, 2020) and 28 674 participants with Ontario, Canada, health administrative data from ICES (April 1, 2002, to September 30, 2020). Participants were adults 66 years or older with eczema, asthma, or chronic obstructive pulmonary disease receiving prescriptions for oral corticosteroids with cumulative prednisolone equivalent doses of 450 mg or higher within 6 months. Data were analyzed October 22, 2020, to September 6, 2022.

EXPOSURES Participants with prescriptions crossing the 450-mg cumulative oral corticosteroid threshold in less than 90 days were classified as having high-intensity prescriptions, and participants crossing the threshold in 90 days or more as having low-intensity prescriptions. Multiple alternative exposure definitions were used in sensitivity analyses.

MAIN OUTCOMES AND MEASURES The primary outcome was prescribed fracture preventive care. A secondary outcome was major osteoporotic fracture. Individuals were followed up from the date they crossed the cumulative oral corticosteroid threshold until their outcome or the end of follow-up (up to 1 year after index date). Rates were calculated for fracture preventive care and fractures, and hazard ratios (HRs) were estimated from Cox proportional hazards regression models comparing high- vs low-intensity oral corticosteroid prescriptions.

RESULTS In both the UK cohort of 65 195 participants (mean [IQR] age, 75 [71-81] years; 32 981 [50.6%] male) and the Ontario cohort of 28 674 participants (mean [IQR] age, 73 [69-79] years; 17 071 [59.5%] male), individuals with high-intensity oral corticosteroid prescriptions had substantially higher rates of fracture preventive care than individuals with low-intensity prescriptions (UK: 134 vs 57 per 1000 person-years; crude HR, 2.34; 95% CI, 2.19-2.51, and Ontario: 73 vs 48 per 1000 person-years; crude HR, 1.49; 95% CI, 1.29-1.72). People with high- and low-intensity oral corticosteroid prescriptions had similar rates of major osteoporotic fractures (UK: crude rates, 14 vs 13 per 1000 person-years; crude HR, 1.07; 95% CI, 0.98-1.15 and Ontario: crude rates, 20 vs 23 per 1000 person-years; crude HR, 0.87; 95% CI, 0.79-0.96). Results from sensitivity analyses suggested that reaching a high cumulative oral corticosteroid dose within a shorter time, with fewer prescriptions, or with fewer or shorter gaps between prescriptions, increased fracture preventive care prescribing.

CONCLUSIONS The results of this cohort study suggest that older adults prescribed high cumulative oral corticosteroids across multiple prescriptions, or with many or long gaps between prescriptions, may be missing opportunities for fracture preventive care.

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Supplemental content

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Oral corticosteroids are a major cause of secondary osteoporosis and subsequent fractures.[1-3] Older people are particularly vulnerable.[4] People using oral corticosteroids for 3 or more months at a prednisolone equivalent dose of 5 mg daily or higher (corresponding to a cumulative prednisolone equivalent dose threshold of 450 mg) should be considered at increased risk of fracture, and depending on other risk factors, such as age, should be referred for bone mineral density measurements and/or treated with fracture preventive care medications, such as bisphosphonates.[5] This guidance is reflected in the commonly used FRAX fracture risk assessment tool,[6,7] which is recommended in UK,[8] Canadian,[9] and US[10] guidelines.

Rather than providing a single prescription, or a small number of prescriptions sequentially without gaps (as might be the case for the long-term treatment of rheumatoid arthritis),[11] oral corticosteroids are often prescribed in short discontinuous bursts to treat disease flares of relapsing-remitting conditions, such as eczema,[12] asthma,[13] and chronic obstructive pulmonary disease (COPD).[14] We hypothesized that treating physicians' awareness of patients crossing a cumulative oral corticosteroid dose threshold is lower in the latter type of prescriptions to treat COPD, eczema, asthma, which would constitute a modifiable gap in fracture preventive care. Since these relapsing-remitting conditions are often managed by different specialist and generalist physicians, including dermatologists, respirologists, internists, family physicians, and emergency physicians, that gap in care would be relevant to many clinical settings. Identifying and mitigating that gap could reduce the high morbidity and mortality associated with fractures.[15]

The objective of this study was to determine whether oral corticosteroid prescribing patterns were differentially associated with receiving guideline-recommended fracture preventive care among older adults with eczema, asthma, or COPD.

Key Points

Question Are prescribing patterns for older people receiving high cumulative doses of oral corticosteroids associated with adequate fracture preventive care?

Findings This cohort study of 65 195 older adults in the UK and 28 674 older adults in Ontario, Canada, found that individuals who were prescribed high cumulative oral corticosteroid doses gradually or intermittently across multiple prescriptions were about half as likely as individuals prescribed a similar dose in 1 prescription or within a short period of time to receive guideline-indicated fracture preventive care.

Meaning Increasing attention to individuals receiving prescriptions for high cumulative oral corticosteroid doses discontinuously may help close an identified gap in fracture preventive care.

Methods

Study Design and Setting

We conducted parallel cohort studies using routinely collected UK general practice data (January 2, 1998, to January 31, 2020) and Ontario, Canada, population-based administrative health data (April 1, 2002, to September 30, 2020) (**Figure**). The UK study was approved by the Independent Scientific Advisory Committee, the London School of Hygiene & Tropical Medicine Research Ethics Committee, and the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee. For the Ontario study, ICES (previously Institute for Clinical Evaluative Sciences) is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. The use of data held at ICES is authorized under section 45 of Ontario's Personal Health Information Protection Act and does not require review by a research ethics board. This project was conducted under section 45 and approved by the ICES Privacy and Legal Office. The need to obtain informed consent was waived because all data were deidentified (UK) or were population-based administrative data (Ontario). This study followed the Reporting of Studies Conducted Using Observational Routinely-Collected Data for pharmacoepidemiology (RECORD-PE) reporting guideline (eAppendix in Supplement 1).

Data Sources

The UK study used deidentified primary care data from CPRD GOLD, which includes more than 11 million people from 674 practices in the UK[16] linked to deprivation data (Carstairs index)[17] and Office for National Statistics death data (linkages provided directly through CPRD). The Ontario study used population-based primary and secondary care administrative data from ICES, with linkages between multiple databases (eMethods 1 in Supplement 1).

Study Population

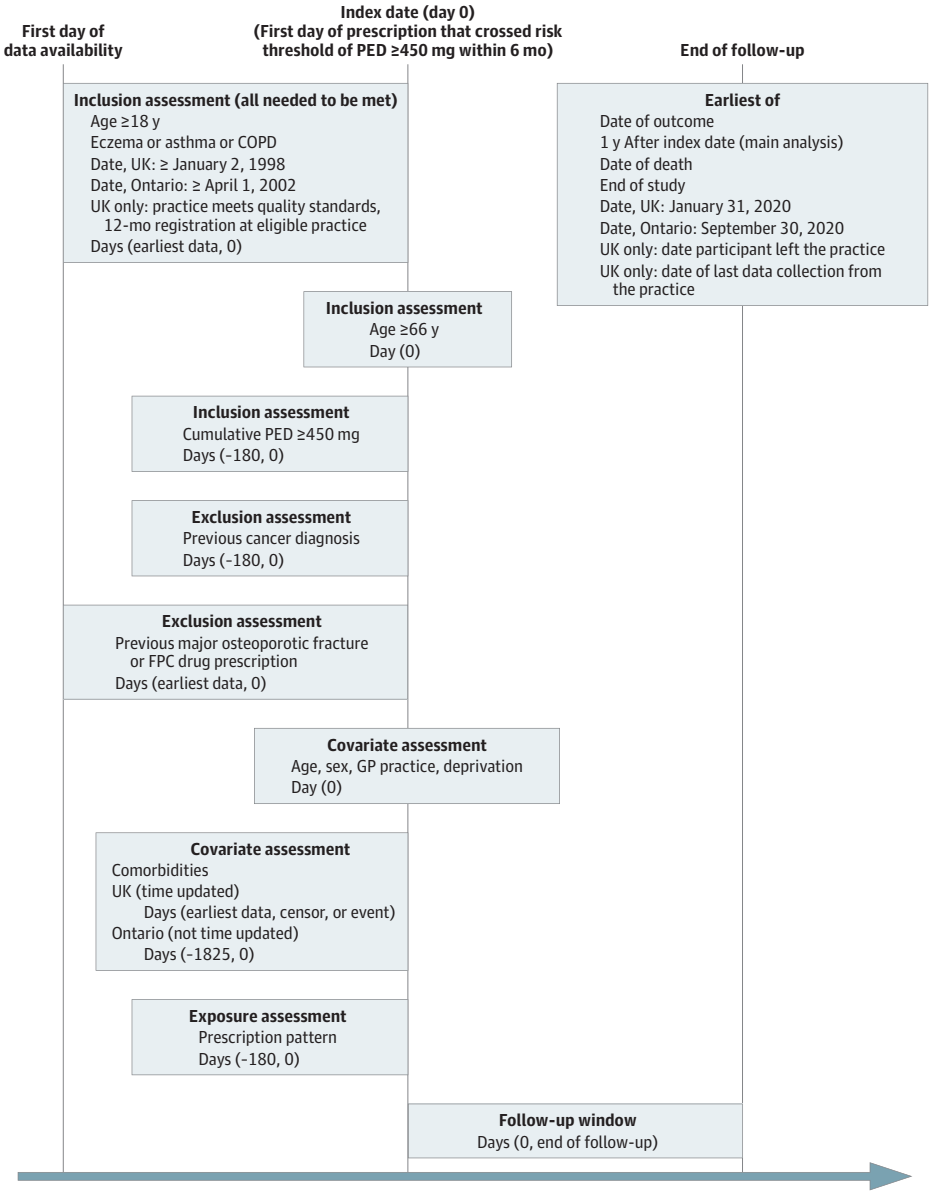
We identified cohorts of people with eczema, asthma, or COPD. In the UK, we included all individuals with at least 1 diagnostic code for eczema, asthma, or COPD, and in Ontario, we included people with at least 1 physician visit for eczema, presence of at least 1 hospitalization or 2 or more physician visits in a 2-year period for asthma,[18] and at least 1 hospitalization or at least 1 physician visit for COPD.[19] From these identified people, we selected a subset of adults 66 years of age or older crossing the cumulative oral corticosteroid dose high-risk threshold of 450 mg of the prednisolone equivalent dose in the last 6 months (eTable 6 in Supplement 1). According to FRAX recommendations, all of these people should be considered for fracture preventive care.[6] The index date was the start date of the first prescription that would surpass the risk threshold for that individual. We excluded people who previously received a fracture preventive care drug, experienced a major osteoporotic fracture, or showed evidence of receiving a cancer diagnosis in the previous 6 months (to identify actively treated cancers). Individuals could be included only once.

Exposures, Outcomes, and Covariates

Corticosteroid Prescribing Patterns

We used information on dose and duration of oral corticosteroid prescriptions from cleaned prescription data (eMethods 2 in Supplement 1). We ascertained the time taken to reach the risk

Figure. Study Design



Source population for the UK study was all people attending general practitioners (GPs) in the UK, and for the Ontario study, all people attending GPs in Ontario, Canada. Database population for the UK was individuals included in the Clinical Practice Research Datalink, and for the Ontario study, individuals included in the ICES database. Study population was people with eczema, asthma, or chronic obstructive pulmonary disease (COPD) who should be considered for fracture preventive care (FPC) (ie, individuals with prescriptions that crossed the risk threshold of a 450-mg prednisolone equivalent dose [PED]).

threshold (ie, cumulative prednisolone equivalent dose of 450 mg in 6 months), the number of gaps between prescriptions within that period, and the total length of these gaps.

For the primary exposure, we classified individuals as having low-intensity (≥90 days to cross the risk threshold) vs high-intensity (<90 days to cross the risk threshold) oral corticosteroid prescriptions (eFigure 1 in Supplement 1). In sensitivity analyses, we (1) defined exposure based on the number and total length of gaps between prescriptions, (2) used different cut points to classify exposure, and (3) used a log-transformed continuous exposure definition (**Table 1**).

Fracture Preventive Care

Our primary outcome was prescriptions for fracture preventive care medications, which are recommended in guidelines for this patient population (including bisphosphonates, bazedoxifene, burosumab, raloxifene, and teriparatide).[10] For a secondary outcome, we expanded the definition to include either prescriptions for fracture preventive medications or bone mineral density measurements (dual-energy x-ray absorptiometry; DEXA). In another secondary analysis for the UK cohort only, we used any calcium or vitamin D prescription as a secondary outcome definition.

Major Osteoporotic Fractures

Major osteoporotic fractures were a secondary outcome. For the UK cohort, we identified fractures of spine, hip (proximal femur), wrist, or pelvis, excluding surgical or cancer-related fractures, in primary care morbidity coding. For the Ontario cohort, we identified hip, vertebral, and humerus

Table 1. Exposure Definition, Study Cohort, and Model Covariate Changes in Sensitivity Analyses

Sensitivity analysis[a]	Justification
Exposure definition change[b]	
Use time to risk threshold (0 vs 1-180 d)	Prescribing a dose crossing the 450-mg prednisolone equivalent dose risk threshold in a single prescription may influence the decision to prescribe fracture preventive care.
Use total length of gaps (0-89 vs 90-180 d)	Lengths of gaps between prescriptions may influence awareness of previously prescribed cumulative doses.
Use total length of gaps (0 vs 1-180 d)	Prescribing a dose crossing the 450-mg prednisolone equivalent dose risk threshold in a single prescription may influence the decision to prescribe fracture preventive care.
Use No. of gaps (0-1 vs ≥2 gaps)	Number of gaps between prescriptions may influence awareness of previously prescribed cumulative doses.
Use No. of gaps (0 vs ≥1 gaps)	Prescribing a dose crossing the 450-mg prednisolone equivalent dose risk threshold in a single prescription may strongly influence the decision to prescribe fracture preventive care.
Use log-transformed continuous variable of $\log_{10}$ (days to risk threshold + 1)	Likelihood of receiving fracture preventive care may decrease rapidly at first and then slow with the No. of days to reach risk threshold. Estimate hazard ratios with the exposure as a continuous variable by $\log_{10}$-transformed No. of days to reach risk threshold (+ 1 to avoid a zero value at 0 d)
Cohort composition change[c]	
Follow-up not limited	Effect of (missed opportunities for) fracture preventive care is likely to occur over a longer period of time; therefore, considered analyses with follow-up time not limited to 1 y as the main analyses for the fracture outcome. For fracture preventive care outcome, performed these analyses as sensitivity analyses.
UK only: age not limited to ≥66 y, ie, all adults ≥18 y are eligible	Fracture preventive care drugs are rarely prescribed to younger individuals; however, it may be appropriate to include individuals of all ages to not miss special cases in which fracture preventive care is prescribed to younger individuals.
UK only: use different method to clean oral corticosteroid prescription information with more values imputed (for prescription quantity information, in addition to values that were recorded as missing, values that were recorded as 0 were imputed).	Data cleaning of oral corticosteroid prescription data alters the cohort composition. Oral corticosteroid prescriptions with 0 recorded as the quantity may be prescribed "as needed" or may constitute cases in which true quantity is not entered.
Model covariate change[d]	
Adjust for age group, sex, and deprivation	Although cohort was selected by age (≥66 y), there may still be differences in age, sex, and deprivation between groups with high- vs low-intensity prescriptions.
Adjust for age group, sex, deprivation, eczema, asthma, COPD, and rheumatoid arthritis	Groups differed in disease status, which may be associated with the rate of fracture preventive care prescribing or fractures.
Ontario only: covariates of the main analysis, rurality, dementia, drugs decreasing fracture risk, drugs increasing fracture risk, inhaled or nasal corticosteroids, injectable corticosteroids, topical corticosteroids, other corticosteroids, oral corticosteroid in the year prior to cohort entry, health care use in the year prior to cohort entry (physician visits [0-12, ≥13], hospitalization [yes, no], No. of physicians prescribing oral corticosteroid [1, ≥2]), specialty of physician prescribing oral corticosteroid (family practice, dermatology, emergency medicine, and other)	Other variables may confound the association between oral corticosteroid prescribing pattern and fracture preventive care or fractures.

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] For both Ontario and UK analyses unless otherwise stated.

[b] Exposure definition for main analysis in both UK and Ontario cohorts defined using time to risk threshold as high (0-89 days) vs low (90-180 days) intensity.

[c] Cohort composition for main analysis in both UK and Ontario cohorts fracture preventive care outcome had follow-up time limited to 1 year, with follow-up time not limited for fracture outcome. People were included only if they were aged 66 years or older. For UK only, due to missing information in electronic health records, values for quantity and daily dose of prescriptions that were recorded as missing were imputed.

[d] Models not adjusted for any covariates in main analysis in both UK and Ontario cohorts.

and forearm fractures using standardized administrative algorithms.[20]

Negative Control Outcomes

Negative control outcomes are outcomes that are known not to be associated with exposure but share the same potential sources of bias with the primary outcome.[21] For negative control outcomes, we included prescriptions for epilepsy and migraine medications (UK) as drugs that should not be associated with oral corticosteroid prescribing, and drugs used for anxiety (UK and Ontario) as medications potentially associated with oral corticosteroid prescribing but that should not be associated with the pattern of oral corticosteroid prescribing.

UK Covariates

We identified age and sex at the index date. All individuals had at least 1 of eczema, asthma, or COPD to be eligible for inclusion. Eczema, asthma, and COPD were also defined as time-updated variables with status changing on first record. That is, people were considered as not having the disease until the first record of an appropriate primary care diagnostic code. We also identified comorbid rheumatoid arthritis. As a measure of socioeconomic status, we used quintiles of the Carstairs in-

dex of material deprivation (at the individual level if available, otherwise at the practice level) from 2011.

Ontario Covariates

We obtained individuals' age, sex, and home location at the index date. We identified eczema, asthma, COPD, rheumatoid arthritis, and dementia during a 5-year look back, which required at least 2 physician visits with the diagnosis. We identified medications that may increase or decrease fracture risk, including other types of corticosteroids (inhaled or nasal, injectable, topical, and other) used in the year prior to the index date. We identified health care use during the year prior to the index date, including the number of physician visits and hospital visits. We established the specialty of the physician, or physicians prescribing any oral corticosteroid that contributed to crossing the risk threshold. As a measure of socioeconomic status, we used quintiles based on neighborhood income.

Statistical Analysis

We calculated descriptive statistics, including participant counts and distribution of characteristics by oral corticosteroid prescribing pattern exposure status.

Individuals were followed up until they either experienced an outcome (fracture preventative care or fracture) or were censored (earliest of 1 year after index date [main analysis], death, left practice [UK only], last data collection from the practice [UK only], or end of the study [UK, January 31, 2020; Ontario, September 30, 2020]). We limited follow-up to 1 year after index date for the fracture preventive care outcome so that any prescriptions for fracture preventive care would be associated with crossing the risk threshold of 450-mg cumulative prednisolone equivalent dose. Since both a detrimental association of oral corticosteroid use with bone health and a beneficial association of oral corticosteroid use with fracture preventive care may take longer than 1 year to occur, we did not limit the follow-up time in analyses for the fracture outcome.

We calculated crude rates and estimated hazard ratios (HRs), with follow-up time as the underlying timescale, for the association between oral corticosteroid prescribing pattern and the outcome using Cox proportional hazards regression analysis. We fitted crude models, and models adjusted for age, sex, deprivation, eczema, asthma, COPD, and rheumatoid arthritis (which is included as a risk factor in FRAX and is treated with oral corticosteroids). In Ontario, we additionally fit models adjusting for all other covariates (including other medications and health care use) (eTable 1 in Supplement 1). We performed model diagnostics (eMethods 3 and eFigures 4 and 5 in Supplement 1). To test whether our results changed under a range of different assumptions, we performed 3 categories of sensitivity analyses: changing the exposure definition, changing the study cohort, and changing the model covariates (Table 1).

As a secondary analysis for the UK cohort, we estimated HRs from a 3-state Cox proportional hazards regression model (1, entry state; 2, received fracture preventive care; and 3, experienced fracture) for switching from one state to another (eFigure 2 in Supplement 1).

In the UK, prescriptions were sometimes missing information on the number of pills to be consumed. We therefore imputed missing values using other information contained in the same prescription, other prescriptions for the same individual, and other prescriptions from the same demographic groups (eMethods 2 in Supplement 1).

We reported any amendments to the original study protocol (eMethods 4 in Supplement 1). Data management and statistical analyses were conducted October 22, 2020, to September 6, 2022, using R, version 4.20 (R Project for Statistical Computing), and SAS Enterprise Guide, version 7.1 (SAS Institute Inc). Statistical significance was defined as a 95% CI excluding 1.

Results

Descriptive Statistics

The UK study identified 65 195 people 66 years of age or older (mean [IQR] age, 75 [71-81] years; 65 195 [50.6%] male) with a diagnostic code for eczema, asthma, or COPD who were prescribed 450 mg or more of a prednisolone equivalent dose in 6 months (eFigure 3 in Supplement 1). Of these, 69% had high-intensity oral corticosteroid prescriptions, and 31% had low-intensity prescriptions. For analysis with fracture preventive care medications as the outcome, individuals were followed up for a mean of 0.8 years (total 52 948 person-years), and for analysis with fracture as the outcome for a mean of 3.8 years (total 208 354 person-years) (eTable 2 in Supplement 1). Baseline characteristics were similar between groups of oral corticosteroid prescribing patterns, except for the distribution of inflammatory diseases (high- vs low-intensity prescriptions: eczema 23.5% vs 17.0%; asthma 56.2% vs 61.2%; COPD 55.6% vs 66.2%, respectively) (**Table 2**).

The study in Ontario identified 28 674 people 66 years of age or older (mean [IQR] age, 73 [69-79] years; 17 071 [59.5%] male), with eczema, asthma, or COPD who were prescribed 450 mg or more of a prednisolone equivalent dose in 6 months. Of these, 82.7% had high-intensity oral corticosteroid prescriptions, whereas 17.3% had low-intensity prescriptions. For analysis with fracture preventive care medications as the outcome, individuals were followed up for a mean of 0.9 years (total 25 600 person-years), and for analysis with fracture as the outcome, for a mean of 5.0 years (total 142 607 person-years) (eTable 2 in Supplement 1). Baseline characteristics were similar between oral corticosteroid prescribing-pattern groups, except for the distribution of inflammatory diseases within 5 years of the index date (high- vs low-intensity prescriptions: eczema, 27.2% vs 19.1%; asthma, 18.3% vs 27.9%; COPD, 41.0% vs. 63.2%, respectively) (Table 2).

Oral Corticosteroid Prescription Patterns and Fracture Preventive Care

In the UK 1 year after the index date, 8.9% of people who had reached the risk threshold of a 450-mg prednisolone equivalent dose had received fracture preventive care medication: 10.7% with high-intensity oral corticosteroid prescriptions vs 4.8% with low-intensity prescriptions (crude rates, 134 vs 57

Table 2. Characteristics of the Study Populations at Index Date

Characteristic	UK participants, No. (%)		Ontario participants, No. (%)	
	Oral corticosteroid prescription intensity[a]		Oral corticosteroid prescription intensity[a]	
	High	Low	High	Low
Total No.	44 989	20 206	23 727	4947
Age, mean (IQR), y	75 (71-81)	75 (70-80)	73 (69-79)	73 (69-79)
Male	23 044 (51.2)	9937 (49.2)	14 178 (59.8)	2893 (58.5)
Female	21 945 (48.8)	10 269 (50.8)	9549 (40.2)	2054 (41.5)
Deprivation quintile[b]				
5 (Most deprived)	8606 (19.1)	4428 (21.9)	4970 (20.9)	1169 (23.6)
4	11 584 (25.7)	5437 (26.9)	5185 (21.9)	1087 (22.0)
3	9444 (21.0)	4012 (19.9)	4786 (20.2)	1006 (20.3)
2	7246 (16.1)	2907 (14.4)	4455 (18.8)	917 (18.5)
1 (Least deprived)	5051 (11.2)	1890 (9.4)	4262 (18.0)	754 (15.2)
Missing	3058 (6.8)	1532 (7.6)	69 (0.3)	14 (0.3)
Eczema[c]	10 579 (23.5)	3436 (17.0)	6451 (27.2)	946 (19.1)
Asthma[c]	25 306 (56.2)	12 361 (61.2)	4336 (18.3)	1378 (27.9)
COPD[c]	25 030 (55.6)	13 371 (66.2)	9730 (41.0)	3125 (63.2)
Rheumatoid arthritis	1203 (2.7)	424 (2.1)	790 (3.3)	145 (2.9)

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Low-intensity prescription defined as 90 or more days to cross the risk threshold of the cumulative prednisolone equivalent dose of 450 mg; high-intensity prescription, less than 90 days to cross the risk threshold.

[b] Quintiles of the Carstairs index in the UK cohort and income quintiles in the Ontario cohort; 1 indicates, least deprived and highest income; 5, most deprived and lowest income.

[c] Presence of a disease code before the index date; an individual can have multiple diseases.

Table 3. Hazard Ratios for Different Fracture Preventive Care Outcomes, With Follow-Up Maximum of 1 Year, and for Major Osteoporotic Fracture, With Follow-Up Time Not Limited

Cohort	Oral corticosteroid prescription intensity[a]	HR (95% CI)[b]	Person-years	Event	Rate[c]
Fracture preventive care drugs[d]					
UK	Low	1.00 (1.00-1.00)	17 150	971	57
UK	High	2.34 (2.19-2.51)	35 798	4810	134
Ontario	Low	1.00 (1.00-1.00)	4522	219	48
Ontario	High	1.49 (1.29-1.72)	21 078	1534	73
Fracture preventive care drugs or referral for DEXA scan					
UK	Low	1.00 (1.00-1.00)	17 105	1061	62
UK	High	2.24 (2.10-2.39)	35 675	5019	141
Ontario	Low	1.00 (1.00-1.00)	4373	501	115
Ontario	High	1.27 (1.15-1.39)	20 302	2959	146
Calcium and vitamin D					
UK	Low	1.00 (1.00-1.00)	15 899	2761	174
UK	High	1.46 (1.40-1.53)	33 133	8592	259
Anxiety drugs[e]					
UK	Low	1.00 (1.00-1.00)	15 838	2743	173
UK	High	1.02 (0.98-1.07)	34 737	6208	179
Ontario	Low	1.00 (1.00-1.00)	3817	1181	309
Ontario	High	0.97 (0.91-1.04)	18 207	5494	302
Epilepsy drugs[e]					
UK	Low	1.00 (1.00-1.00)	16 378	1913	117
UK	High	0.97 (0.92-1.02)	36 110	4108	114
Major osteoporotic fracture (follow-up time not limited)					
UK	Low	1.00 (1.00-1.00)	74 833	945	13
UK	High	1.07 (0.98-1.15)	169 708	2295	14
Ontario	Low	1.00 (1.00-1.00)	21 775	501	23
Ontario	High	0.87 (0.79-0.96)	120 832	2445	20

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HR, hazard ratio.

[a] Low intensity: reached risk threshold in 90 to 180 days; high intensity: reached risk threshold within 89 days.

[b] Hazard ratios (95% CIs) estimated from Cox proportional hazards regression models (with CIs from robust SEs accounting for clustering by general practitioner practice in UK analyses).

[c] Rate per 1000 person-years.

[d] Fracture preventive care drugs, including bisphosphonates and other drugs affecting bone metabolism (etidronate, clodronate, bazedoxifene, burosumab, raloxifene, and teriparatide).

[e] Negative control outcomes.

per 1000 person-years; crude HR, 2.34; 95% CI, 2.19-2.51; adjusted HR, 2.13; 95% CI, 1.99-2.29) (**Table 3**). Estimates were similar for the fracture preventive care medication or DEXA scan outcome and lower for the calcium and vitamin D outcome. We saw no evidence for an association between oral corticosteroid prescribing pattern and our negative control outcomes.

Analyses by disease subgroup comparing high- vs low-intensity oral corticosteroid prescriptions showed highest HRs for being prescribed fracture preventive care among people with eczema (HR, 3.00; 95% CI, 2.60-3.47) followed by people with asthma (HR, 2.15; 95% CI, 1.96-2.35) and people with COPD (HR, 1.72; 95% CI, 1.57-1.88) (eTable 3 in Supplement 1). Effect estimates were similar in sensitivity analyses with changes to

the exposure definition, study cohort composition, and model covariates (**Table 4**). Using a continuous log-transformed exposure variable (number of days to reach the risk threshold) found an approximate 50% decrease in the hazard of being prescribed fracture preventive care every 10 additional days starting from 0 days (eTable 4 in Supplement 1).

In the Ontario study, 1 year after the index date, 6.1% of people who had reached the risk threshold of a 450-mg prednisolone equivalent dose had received fracture preventive care: 6.4% with high-intensity oral corticosteroid prescriptions, and 4.4% with low-intensity prescriptions (crude rates, 73 vs 48 per 1000 person-years, respectively; crude HR, 1.49; 95% CI, 1.29-1.72; adjusted HR, 1.47; 95% CI, 1.27-1.70) (Table 3). Estimates were lower for fracture preventive care medication or DEXA scan outcome. Analyses by disease subgroups comparing people with high- vs low-intensity oral corticosteroid prescriptions found the highest HRs for being prescribed fracture preventive care in people with COPD (HR, 1.58; 95% CI, 1.30-1.91) followed by people with asthma (HR, 1.42; 95% CI, 1.07-1.88) but no substantially increased risk for people with eczema (HR, 1.15; 95% CI, 0.89-1.50) (eTable 3 in Supplement 1). Effect estimates were similar in sensitivity analyses with changes to the exposure definition, study cohort composition, and model covariates.

Oral Corticosteroid Use Patterns and Fracture

By the end of the UK study period, 5.1% of people who had reached the risk threshold with high-intensity oral corticosteroid prescriptions had experienced a (major osteoporotic) fracture, vs 4.7% with low-intensity prescriptions (crude rates, 14 vs 13 per 1000 person-years; crude HR, 1.07; 95% CI, 0.98-1.15; adjusted HR, 1.12; 95% CI, 1.03-1.21) (Table 3). Effect estimates were similar in sensitivity analyses (eTable 5 in Supplement 1).

By the end of the Ontario study period, 10.3% of people who had reached the risk threshold with high-intensity oral corticosteroid prescriptions had experienced a (major osteoporotic) fracture, vs 10.1% with low-intensity prescriptions (crude rates, 20 vs 23 per 1000 person-years; crude HR, 0.87; 95% CI, 0.79-0.96; adjusted HR, 0.91; 95% CI, 0.73-1.12) (Table 3). Effect estimates were similar in sensitivity analyses (eTable 5 in Supplement 1).

Results From the 3-State Model

In the UK study, people with high- vs low-intensity oral corticosteroid prescriptions had a higher hazard of moving from the entry state to the fracture preventive care state (HR, 1.53; 95% CI, 1.47-1.60), a somewhat higher hazard for moving from the entry state directly to the fracture state (HR, 1.07; 95% CI, 0.99-1.17), and a slightly lower hazard for moving from the fracture preventive care state to the fracture state (HR, 0.89; 95% CI, 0.75-1.05) albeit with CIs overlapping the null.

Table 4. Hazard Ratios for Being Prescribed Fracture Preventive Care Drugs, From Sensitivity Analyses Comparing High- vs Low-Intensity Oral Corticosteroid Prescriptions

Sensitivity analysis	Hazard ratio (95% CI)[a]	
	UK	Ontario
Main		
Main analysis (maximum follow-up, 1 y)	2.34 (2.19-2.51)	1.49 (1.29-1.72)
Exposure definition change		
Use total length of gaps (0 vs 1-180 d)	3.19 (3.00-3.38)	1.67 (1.52-1.83)
Use total length of gaps (0-89 vs 90-180 d)	2.61 (2.42-2.82)	1.63 (1.39-1.91)
Use No. of gaps (0 vs ≥1)	3.18 (3.00-3.38)	1.67 (1.52-1.83)
Use No. of gaps (0-1 vs ≥2)	2.34 (2.17-2.52)	1.15 (0.97-1.36)
Use time to risk threshold (0 vs 1-180 d)	2.56 (2.38-2.76)	1.49 (1.36-1.65)
Cohort definition change		
Impute more missing values of oral corticosteroid prescriptions	2.50 (2.34-2.67)	
Include all follow-up time	1.49 (1.43-1.55)	
Include people of all ages	2.21 (2.09-2.35)	
Model covariate changes		
Include age, sex, deprivation, comorbidities[b]	2.13 (1.99-2.29)	1.47 (1.27-1.70)
Include age, sex, deprivation	2.36 (2.20-2.53)	
Include age, sex, deprivation, comorbidities, and other[c]		1.37 (1.18-1.59)

[a] Hazard ratio and 95% CIs estimated from Cox proportional hazards regression models (with CIs from robust SEs accounting for clustering by general practitioner practice in UK analyses).

[b] Comorbidities: eczema, asthma, rheumatoid arthritis, and chronic obstructive pulmonary disease.

[c] Other medication: inhaled corticosteroids, injected corticosteroids, topical corticosteroids, other corticosteroids, ever received oral corticosteroids more than 1 year before index date, other drugs affecting fracture risk; health care use: urban or rural home address, number of physician visits in past year (1-12, 13-21, or ≥22), number of hospital admissions (0 or ≥1), number of physicians prescribing oral corticosteroid (1 or ≥2).

Discussion

In this cohort study conducted in 2 separate populations in the UK and Ontario, Canada, among older people with eczema, asthma, or COPD who received oral corticosteroid prescriptions with a 450-mg prednisolone equivalent dose or higher in 6 months, individuals with a high-intensity prescription pattern were more likely than individuals with a low-intensity pattern to receive fracture preventive care. Except in subgroups of people with eczema, these findings were consistent in parallel cohorts from the UK and Ontario and in analyses that included DEXA scans in the definition of fracture preventive care. People with eczema in the UK study showed the largest increase in rate of fracture preventive care prescribing, but there was no increase in rate in this subgroup in the Ontario study. The UK study found no increase in the rate of fractures among people with low-intensity oral corticosteroid prescriptions, and the Ontario study found a small increase.

While previous studies have explored the association of oral corticosteroid prescribing patterns with the risk of fracture[22] and fracture preventive care,[23] we found no studies exploring the association of oral corticosteroid prescribing patterns independent of cumulative dose. Our study conducted that investigation by including only people crossing a risk threshold of a

450-mg prednisolone equivalent dose. The low overall percentage of people in the UK study 1 year after the index date who received fracture preventive care (8.9%) is consistent with previous studies showing low adherence to fracture prevention guidelines for glucocorticoid-induced osteoporosis more generally.[13,14] In the present study, we identified a population with particularly low rates of fracture preventive care.

Some electronic medical software may provide warnings when high-dose individual oral corticosteroid prescriptions are issued; however, these systems are unlikely to incorporate information on cumulative dose from multiple prescriptions over time.[24] We found no publicly available information to confirm this assumption. Implementing clinical decision support systems that account for cumulative dose could improve care for people prescribed high-dose oral corticosteroid intermittently; such strategies warrant evaluation. Although fracture risk was similar for people prescribed oral corticosteroids in high- and low-intensity patterns in this study despite differences in fracture preventive care, our study was not designed to assess the efficacy of fracture prevention. There is substantial literature supporting the efficacy of fracture prevention in this population.[8-10]

In addition to being important for clinicians practicing family medicine, internal medicine, and respirology, our findings may be particularly important for dermatologists and others treating people with eczema. Oral corticosteroids are not generally recommended for eczema,[25] but they are still commonly prescribed; in a recent trial for a new biologic to treat eczema, roughly a third of participants reported having used oral corticosteroids.[26] Therefore, dermatologists and other clinicians caring for people with eczema should minimize oral corticosteroid prescribing and be aware that patients with eczema commonly reach high cumulative oral corticosteroid doses, know the patient's fracture risk, and consider prescribing fracture prevention or raise the issue with the patient's primary care team.

In the UK, most people with eczema, asthma, or COPD are managed in primary care. Our UK findings may not apply to people with severe eczema, asthma, or COPD treated in secondary care. Our Ontario cohort includes ambulatory prescriptions from all physicians, including secondary and tertiary care. Different results observed in the present study between the UK and Ontario for subgroups of people with eczema may be due to differences in fracture preventive care prescribing between primary and secondary or tertiary care. For example, there may be greater attention to a patient's longitudinal eczema treatment, including cumulative oral corticosteroid prescribing, for people with more severe eczema treated in secondary or tertiary care than in primary care, potentially explaining the larger effect estimate found in the UK. Further research could investigate fracture preventive care prescribing for people with skin disease in different countries and health care settings.

Strengths and Limitations

This study has strengths. Prescribing patterns are analytically challenging due to the need for complex exposure definitions. We conducted multiple sensitivity analyses using varied exposure definitions, and effect estimates were generally similar. We used large, representative population-based databases from 2 countries that offer free access to health care. Similar main analysis results from UK and Canadian data, and broadly consistent results across multiple sensitivity analyses, lend credence to the results.

This study has several limitations. We did not have data on whether medications were taken as prescribed. In the UK, we had only data on whether the prescription was written, and in Ontario, on whether it was filled. There may be other unmeasured confounders, such as frailty, that may explain the association between oral corticosteroid prescribing patterns and receipt of fracture preventive care or fractures. Results from adjusted analyses showed somewhat attenuated HRs. A possible explanation is that some inflammatory diseases of interest may be associated with increased fracture risk independent of oral corticosteroids.[27] Eczema, asthma, and COPD are treated with topical and inhaled corticosteroids, respectively, but it is controversial whether they are associated with clinically meaningful fracture risk.[28,29] Null effects observed for all negative control outcomes suggest that there were no major sources of bias.

Conclusions

In this cohort study conducted in the UK and Ontario, Canada, older adults prescribed high cumulative oral corticosteroid doses gradually or intermittently across multiple prescriptions were approximately half as likely to receive guideline-indicated fracture preventive care compared with older adults receiving similar oral corticosteroid doses in 1 prescription or within a short period of time. These findings suggest missed opportunities to initiate fracture prevention for older people prescribed oral corticosteroids. Clinicians, including dermatologists, respirologists, general practitioners, and internists, should be aware of recent cumulative oral corticosteroid dose, regardless of the prescribing pattern, and initiate fracture preventive care if indicated.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Matthewman, Tadrous, Thiruchelvam, Cheung, Lega, Mulick, Henderson, Langan, Drucker.
Drafting of the manuscript: Matthewman, Lega, Cunliffe, Drucker.
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Supervision: Prieto-Alhambra, Mulick, Langan, Drucker.

Conflict of Interest Disclosures: Drs Mansfield and Cheung reported receiving personal fees from Amgen outside the submitted work.
Dr Prieto-Alhambra reported receiving grants from Amgen, Chiesi, Eli Lilly and Company, Janssen, Novartis, and UCB Biopharma and consultancy fees from AstraZeneca and UCB Biopharma outside the submitted work and funding or support for training programs organized by his department from Amgen, Astellas Pharma, Janssen, Synapse Research Management Partners, and UCB Biopharma.
Ms Mulick reported receiving personal fees from Veramed Ltd outside the submitted work. Dr Langan reported receiving grants from the Horizon 2020 European Commission–funded consortium outside the submitted work. Dr Drucker reported receiving grants from the Canadian Dermatology Foundation during the conduct of the study; grants to his institution from the National Eczema Association, Eczema Society of Canada, Canadian Dermatology Foundation, Canadian Institutes for Health Research, US National Institutes of Health, and Physicians Services Incorporated Foundation; and compensation from the *British Journal of Dermatology*, American Academy of Dermatology, National Eczema Association, and Canadian Agency for Drugs and Technologies in Health. No other disclosures were reported.

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Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: For the UK study, the findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders. For the Ontario study, the analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Data Sharing Statement: See Supplement 2.

Additional Contributions: IQVIA Solutions Canada Inc provided the use of its Drug Information File. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health. IQVIA Solutions Canada Inc had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Additional Information: The UK study was based on data from the Clinical Practice Research Datalink obtained under license from the U.K. Medicines and Healthcare products Regulatory Agency. The UK study data were provided by patients and collected by the National Health Service as part of its care and support. This study used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information and the Ontario Ministry of Health.

REFERENCES

1. van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)*. 2000;39(12):1383-1389. doi:10.1093/rheumatology/39.12.1383
2. Lim LS, Hoeksema LJ, Sherin K; ACPM Prevention Practice Committee. Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. *Am J Prev Med*. 2009;36(4):366-375. doi:10.1016/j.amepre.2009.01.013
3. Boling EP. Secondary osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clin Ther*. 2004;26(1):1-14. doi:10.1016/S0149-2918(04)90001-X
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465-475. doi:10.1359/jbmr.061113
5. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine*. 2018;61(1):7-16. doi:10.1007/s12020-018-1588-2
6. Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clinical practice. *Bone*. 2009;44(5):734-743. doi:10.1016/j.bone.2009.01.373
7. FRAX. Fracture risk assessment tool. Accessed June 24, 2023. https://frax.shef.ac.uk/FRAX/
8. National Institute for Health and Care Excellence. Clinical guideline [CG146]: osteoporosis: assessing the risk of fragility fracture. Published August 8, 2012; updated February 7, 2017. Accessed June 25, 2023. https://www.nice.org.uk/guidance/cg146
9. Papaioannou A, Morin S, Cheung AM, et al; Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ*. 2010;182(17):1864-1873. doi:10.1503/cmaj.100771
10. American College of Rheumatology. American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis guideline. 2022. Accessed May 17, 2023. https://rheumatology.org/glucocorticoid-induced-osteoporosis-guideline
11. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. Last updated October 12, 2020. Accessed June 25, 2023. https://www.nice.org.uk/guidance/ng100/chapter/Recommendations
12. Alexander T, Maxim E, Cardwell LA, Chawla A, Feldman SR. Prescriptions for atopic dermatitis: oral corticosteroids remain commonplace. *J Dermatolog Treat*. 2018;29(3):238-240. doi:10.1080/09546634.2017.1365112
13. Bénard-Laribière A, Pariente A, Pambrun E, Bégaud B, Fardet L, Noize P. Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France. *BMJ Open*. 2017;7(7):e015905. doi:10.1136/bmjopen-2017-015905
14. Liao K-M, Chiu K-L, Chen C-Y. Prescription patterns in patients with chronic obstructive pulmonary disease and osteoporosis. *Int J Chron Obstruct Pulmon Dis*. 2021;16:761-769. doi:10.2147/COPD.S289799
15. Nazrun AS, Tzar MN, Mokhtar SA, Mohamed IN. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. *Ther Clin Risk Manag*. 2014;10:937-948.
16. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098
17. Wheeler B. Carstairs Index 2011 for lower-layer super output areas. Published 2019. Accessed June 25, 2023. https://reshare.ukdataservice.ac.uk/851497/
18. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J*. 2009;16(6):183-188. doi:10.1155/2009/963098
19. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD*. 2009;6(5):388-394. doi:10.1080/15412550903140865
20. O'Donnell S; Canadian Chronic Disease Surveillance System (CCDSS) Osteoporosis Working Group. Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: results from a feasibility study. *Arch Osteoporos*. 2013;8:143. doi:10.1007/s11657-013-0143-2
21. Arnold BF, Ercumen A. Negative control outcomes: a tool to detect bias in randomized trials. *JAMA*. 2016;316(24):2597-2598. doi:10.1001/jama.2016.17700
22. De Vries F, Bracke M, Leufkens HGM, Lammers JW, Cooper C, Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum*. 2007;56(1):208-214. doi:10.1002/art.22294
23. Liu RH, Albrecht J, Werth VP. Cross-sectional study of bisphosphonate use in dermatology patients receiving long-term oral corticosteroid therapy. *Arch Dermatol*. 2006;142(1):37-41. doi:10.1001/archderm.142.1.37
24. Ardens Health Informatics. NPSA Steroid Alerts. 2022. Accessed June 25, 2023. https://support-ew.ardens.org.uk/support/solutions/articles/31000158989-npsa-steroid-alerts
25. Drucker AM, Eyerich K, de Bruin-Weller MS, et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br J Dermatol*. 2018;178(3):768-775. doi:10.1111/bjd.15928
26. Simpson EL, Gooderham M, Wollenberg A, et al; ADhere Investigators. Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: a randomized clinical trial (ADhere). *JAMA Dermatol*. 2023;159(2):182-191. doi:10.1001/jamadermatol.2022.5534
27. Matthewman J, Mansfield KE, Prieto-Alhambra D, et al. Atopic eczema–associated fracture risk and oral corticosteroids: a population-based cohort study. *J Allergy Clin Immunol Pract*. 2022;10(1):257-266.
28. Loke YK, Gilbert D, Thavarajah M, Blanco P, Wilson AM. Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis. *BMJ Open*. 2015;5(11):e008554. doi:10.1136/bmjopen-2015-008554
29. Egeberg A, Schwarz P, Harsløf T, et al. Association of potent and very potent topical corticosteroids and the risk of osteoporosis and major osteoporotic fractures. *JAMA Dermatol*. 2021;157(3):275-282. doi:10.1001/jamadermatol.2020.4968

4.3 Published appendices

Supplementary Online Content

Matthewman J, Tadrous M, Mansfield KE, et al. Association of different prescribing patterns for oral corticosteroids with fracture preventive care among older adults in the UK and Ontario. Published online August 9, 2023. *JAMA Dermatol*. doi:10.1001/jamadermatol.2023.2495

This supplementary material has been provided by the authors to give readers additional information about their work.

A.1 eMethods

eMethods 1: Details on Data Sources

UK:

- Linked data from the Office for national statistics (ONS): Death registration.
- Small area level data: Patient postcode and practice postcode linked Carstairs Index using 2011 census data. The Carstairs index is an index of material deprivation at the small area level, based on four measures from the UK census.[29]
- Clinical practice research datalink (CPRD): All other variables.

Ontario:

- Registered Persons Database (RPDB): Date of birth and death, sex, postal code (updated annually); use Canadian census data to allow neighbourhood-level income estimates.[30, 31]
- Canadian Institutes of Health Information Discharge Abstract Database (CIHI-DAD): Demographic and clinical information about all hospital admissions and discharges, including transfers and deaths using standard diagnosis (ICD-9/ICD-10-CA) and procedure/intervention codes (CCP/CCI). In a hospital medical record re-abstraction study (14,500 hospital discharges, 18 Ontario hospitals), median agreement between the original and re-abstracted records for the 50 most common diagnoses was 81%.[32]
- National Ambulatory Care Reporting System (NACRS): All hospital- and community-based ambulatory care including emergency department (ED) visits; ED discharge diagnoses are mapped to ICD-10 codes.
- Ontario Health Insurance Plan (OHIP): Physicians submit claims for each service provided, with diagnostic codes based on ICD criteria. Outpatient visits are complete and reliable.[33]
- Ontario Drug Benefit Database (ODB): Prescription medication data is collected for Ontarians ≥65 years old with an error rate of <1%.[34, 35]
- ICES Physician Database (IPDB): Contains data on physician specialty.
- Ontario Cancer Registry (OCR): Computerized database on all people in Ontario diagnosed with cancer since 1965, maintained by Cancer Care Ontario. 95% of all cancers captured.[36]

We obtained individuals' age, sex, and home location at the time of the index date from RPDB. We identified eczema, asthma, COPD, rheumatoid arthritis, and dementia during a 5-year look back requiring at least two physician visits with the diagnosis in the OHIP database. We identified medications that may increase or decrease fracture risk, including other types of corticosteroids (inhaled/nasal, injectable, topical and other) used in the year prior to index date from ODB. We identified healthcare utilisation during the year prior to the index date in OHIP and DAD databases, including the number of physician visits and hospital visits. We established the specialty of the physician, or physicians, prescribing any OCS that contributed to crossing the risk threshold from ODB and ICES physician database. As a measure of socio-economic status, we used quintiles based on neighbourhood income using the Statistics Canada algorithm.

eMethods 2. OCS Prescription Data Cleaning

UK: We identified prescriptions for oral corticosteroids from primary care therapy data including information on the substance, start date, quantity and daily dose. We identified substance classes, and calculated the prednisolone equivalent dose for each prescription using conversion factors from eTable 6.[37] We then identified the total prednisolone equivalent dose and duration for each prescription. We used a "Hot Deck" approach to imputation.[38] We imputed missing values for quantity by taking the median of the patient's prescription quantity and if this was not available, the median of all prescription quantities. We imputed missing values (and 0 values as a sensitivity analysis) for daily dose by taking the median value from (in order of most preferred to least proffered) 1. the same patient, same dose and quantity, 2. the same patient, same dose and quantity group (quantity above and below 42), 3. the same patient with same dose 4. people from the same age group, sex, dose and quantity 5. people from the same age group, sex, dose and quantity group.

Ontario: Prescription claims and drug identification numbers from the Ontario Drug Benefit Plan (ODB) database were used to calculate prednisolone equivalent dose for each prescription (without imputation of missing values).

eMethods 3. Model Diagnostics

We checked the proportional hazards assumption for Cox models by plotting survival curves and Schoenfeld residual plots for the fracture and fracture preventive care outcomes for the exposure (high-intensity vs low-intensity OCS use). The Schoenfeld Individual Test p values was significant for the fracture preventive care outcome, with the curve gradually approaching 0, suggesting that the prescription pattern (high intensity vs low intensity) is most strongly associated with the outcome at the beginning of follow-up, dropping to almost no associated by the end of the year. Given we limited the follow-up time to one year, we concluded it is reasonable to use Cox proportional hazards models, although there may be some violation of the proportional hazards assumption. eFigure 4 eFigure 5

eMethods 4. Amendments to Study Protocol

We changed two aspects of the study design after the original protocol was submitted, as was approved by the CPRD's Independent Scientific Advisory Committee (ISAC Protocol Number 22_002190).

Firstly, we changed the study population from people with eczema, as was originally proposed, to people with eczema, asthma or COPD. This was done to better represent the population of people receiving oral corticosteroids in gradual or intermittent patterns, and to make findings useful for researchers and guideline authors focusing on specific inflammatory diseases.

Secondly, we changed our exposure definition. Our originally proposed exposure definition was based on measuring the proportion of time a participant was prescribed OCSs in consecutive 90-day windows after the index date. Through visualisation of a sample of participants prescription timelines, and implementation of negative control outcomes, we recognised that this exposure definition was likely prone to time-dependent bias, and we therefore changed the exposure definition to using only information occurring before the index date.

A.2 eTables

eTable 1. Characteristics of the Ontario Study Population at Index Date

Characteristic	Level	high intensity, N=23,727	low intensity, N=4,947
Age	Age	73 (69-79)	73 (69-79)
Sex	Male	14,178 (59.8%)	2,893 (58.5%)
Income	Lowest	4,970 (20.9%)	1,169 (23.6%)
	Next to lowest	5,185 (21.9%)	1,087 (22.0%)
	Middle	4,786 (20.2%)	1,006 (20.3%)
	Next to highest	4,455 (18.8%)	917 (18.5%)
	Highest	4,262 (18.0%)	754 (15.2%)
	Missing	69 (0.3%)	14 (0.3%)
Eczema	Eczema	6,451 (27.2%)	946 (19.1%)
Asthma	Asthma	4,336 (18.3%)	1,378 (27.9%)
COPD	COPD	9,730 (41.0%)	3,125 (63.2%)
Rheumatoid arthritis	Rheumatoid arthritis	790 (3.3%)	145 (2.9%)
Rurality	Urban	19,167 (80.8%)	4,028 (81.4%)
	Rural	*4533 - 4537	*914 - 918
	Missing	*23 - 27	*1 - 5
Physician visits in the year prior to index date	0-12 physician visits	8,774 (37.0%)	1,539 (31.1%)
	13-21 physician visits	7,392 (31.2%)	1,617 (32.7%)
	22+ physician visits	7,561 (31.9%)	1,791 (36.2%)
Hospitalisations in the year prior to index date	hospital admission=0	17,296 (72.9%)	3,287 (66.4%)
	hospital admission>=1	6,431 (27.1%)	1,660 (33.6%)
Number of physicians prescribing OCS	Missing	1,089 (4.6%)	97 (2.0%)
	1 physician	14,619 (61.6%)	1,854 (37.5%)
	2+ physician	8,019 (33.8%)	2,996 (60.6%)
Index diagnosis: Eczema	Yes	10,682 (45.0%)	1,088 (22.0%)
Index diagnosis: Asthma	Yes	2,826 (11.9%)	760 (15.4%)
Index diagnosis: COPD	Yes	10,307 (43.4%)	3,116 (63.0%)
Dementia within 5 years prior to index date	Yes	1,446 (6.1%)	263 (5.3%)
Rheumatoid arthritis within 5 years prior to index date	Yes	790 (3.3%)	145 (2.9%)
Inhaled steroid within 1 year prior to index date	Yes	5,985 (25.2%)	1,645 (33.3%)
Injectable steroid within 1 year prior to index date	Yes	962 (4.1%)	215 (4.3%)
Topical steroid within 1 year prior to index date	Yes	9,157 (38.6%)	1,484 (30.0%)
Other medications affecting fracture risk within 1 year prior to index date	Yes	1,513 (6.4%)	370 (7.5%)
Oral corticosteroids within 1 year prior to index date	Yes	6,019 (25.4%)	1,481 (29.9%)
Year of index date	2002-2005	4,119 (17.4%)	501 (10.1%)
	2006-2012	8,094 (34.1%)	1,441 (29.1%)
	2013-2019	11,514 (48.5%)	3,005 (60.7%)

*Values given as ranges to avoid small cells for re-identification purposes

eTable 2: Total and average follow-up time (years)

Cohort	overall[1]	high intensity (0-89 days)[1]	low intensity (90-180 days)[1]	analysis
FPC drugs				
UK	52,948 (0.8)	35,798 (0.8)	17,150 (0.8)	Max. 1 year follow-up
UK	208,354 (3.2)	141,294 (3.1)	67,060 (3.3)	Include all follow up time
Ontario	25,600 (0.9)	21,078 (0.9)	4,522 (0.9)	Max. 1 year follow-up
Major osteoporotic fracture				
UK	56,106 (0.9)	38,550 (0.9)	17,555 (0.9)	Max. 1 year follow-up
UK	244,541 (3.8)	169,708 (3.8)	74,833 (3.7)	Include all follow up time
Ontario	142,607 (5.0)	120,832 (5.1)	21,775 (4.4)	Include all follow up time
[1] Years: total (average)				

eTable 3: Hazard Ratios For Fracture Preventive Care Drugs by Disease Subgroup (Follow-Up Time: Max. 1 Year)

Cohort	Pattern[1]	HR (95%CI)[2,3]		person-years	event	rate[4]
People with COPD[5]						
UK	low intensity		1.00 (1.00-1.00)	11,266	615	55
UK	high intensity		1.72 (1.57-1.88)	20,112	1,896	94
Ontario	low intensity		1.00 (1.00-1.00)	2,752	260	94
Ontario	high intensity		1.58 (1.30-1.91)	8,643	1,116	129
People with eczema[5]						
UK	low intensity		1.00 (1.00-1.00)	2,848	212	74
UK	high intensity		3.00 (2.60-3.47)	7,910	1,816	230
Ontario	low intensity		1.00 (1.00-1.00)	940	161	171
Ontario	high intensity		1.15 (0.89-1.50)	9,242	1,505	163
People with asthma[5]						
UK	low intensity		1.00 (1.00-1.00)	10,697	576	54
UK	high intensity		2.15 (1.96-2.35)	20,788	2,425	117
Ontario	low intensity		1.00 (1.00-1.00)	694	83	120
Ontario	high intensity		1.42 (1.07-1.88)	2,493	351	141

[1] Oral corticosteroid prescription pattern, either low intensity (reached risk threshold within 90 to 180 days) or high intensity (reached risk threshold within 89 days.

[2] Hazard ratios (95% confidence intervals) estimated from Cox models (with confidence intervals from robust standard errors accounting for clustering by GP practice in UK analyses). The dotted line represents the null (HR=1), the square and error bar the estimated hazard ratio and confidence interval respectively.

[3] Fracture preventive care (FPC) drugs, including bisphosphonates and other drugs affecting bone metabolism (etidronate, clodronate, bazedoxifene, burosumab, raloxifene, teriparatide).

[4] Rate per 1,000 person-years

[5] Individuals with a diagnostic code for the respective inflammatory disease any time before index date (UK)/ within 5 years prior to index date (Ontario). Individuals can have more than one inflammatory disease.

eTable 4. Hazard Ratios for Fracture Preventive Care Comparing High Intensity to Low Intensity OCS Use With Log-10 Transformed Number of Days to Reach Risk Threshold as the Exposure Variable (Max. 1 Year Follow-Up)

	UK		Ontario	
Outcome	**HR (95%CI)[1]**	**Adjusted HR (95%CI)[2]**	**HR (95%CI)[1]**	**Adjusted HR (95%CI)[2]**
Fracture preventive care	0.56 (0.54-0.58)	0.60 (0.58-0.63)	0.84 (0.81-0.88)	
Bisphosphonates	0.55 (0.53-0.57)	0.59 (0.57-0.61)	0.78 (0.74-0.83)	0.77 (0.72-0.81)
Calcium & Vitamin D	0.75 (0.72-0.77)	0.78 (0.76-0.81)		
DXA Scans	0.84 (0.74-0.94)	0.87 (0.77-0.99)		
Major osteoporotic fracture	0.96 (0.87-1.06)	0.93 (0.84-1.03)	1.04 (0.94-1.15)	
Anxiety drugs[3]	1.01 (0.98-1.05)	0.99 (0.96-1.02)		
Epilepsy drugs[3]	1.07 (1.03-1.11)	1.06 (1.02-1.10)		
Migraine drugs[3]	0.91 (0.77-1.08)	0.97 (0.81-1.16)		

[1] Crude Hazard ratios (95% confidence intervals) from Cox models estimating the hazard for a 10 day increase in the number of days taken to reach the risk threshold

[2] adjusted for age, sex, deprivation, eczema, asthma, COPD, and rheumatoid arthritis

[3] negative control outcomes

eTable 5. Hazard Ratios From Sensitivity Analyses Comparing High Intensity to Low Intensity OCS Use for the Major Osteoporotic Fracture Outcome. Outcome: Major Osteoporotic Fracture

	HR (95%CI)[1]			
Sensitivity analysis	UK		Ontario	
Main				
Main analysis (follow- up not limited)		1.07 (0.98-1.15)		0.87 (0.79-0.96)
Changed exposure definition				
Define exposure using total length of gaps (0 vs 1-180)		0.98 (0.91-1.07)		0.95 (0.88-1.02)
Define exposure using total length of gaps (0-89 vs 90-180)		1.07 (0.98-1.17)		0.89 (0.81-0.99)
Define exposure using number of gaps (0 vs 1+)		0.98 (0.91-1.07)		0.95 (0.88-1.02)
Define exposure using number of gaps (0-1 vs 2+)		0.96 (0.89-1.03)		0.85 (0.75-0.97)
Define exposure using time to risk threshold (0 vs 1-180)		0.93 (0.84-1.02)		0.92 (0.85-0.99)
Changed model covariates				
+ age, sex, deprivation, comorbidities[2]		1.12 (1.03-1.21)		0.93 (0.85-1.03)
+ age, sex, deprivation		1.09 (1.00-1.19)		
+ age, sex, deprivation, comorbidities, other[3]				0.93 (0.84-1.03)

[1] Hazard ratios (95% confidence intervals) estimated from Cox models (with confidence intervals from robust standard errors accounting for clustering by GP practice in UK analyses). The dotted line represents the null (HR=1), the square and error bar the estimated hazard ratio and confidence interval respectively.

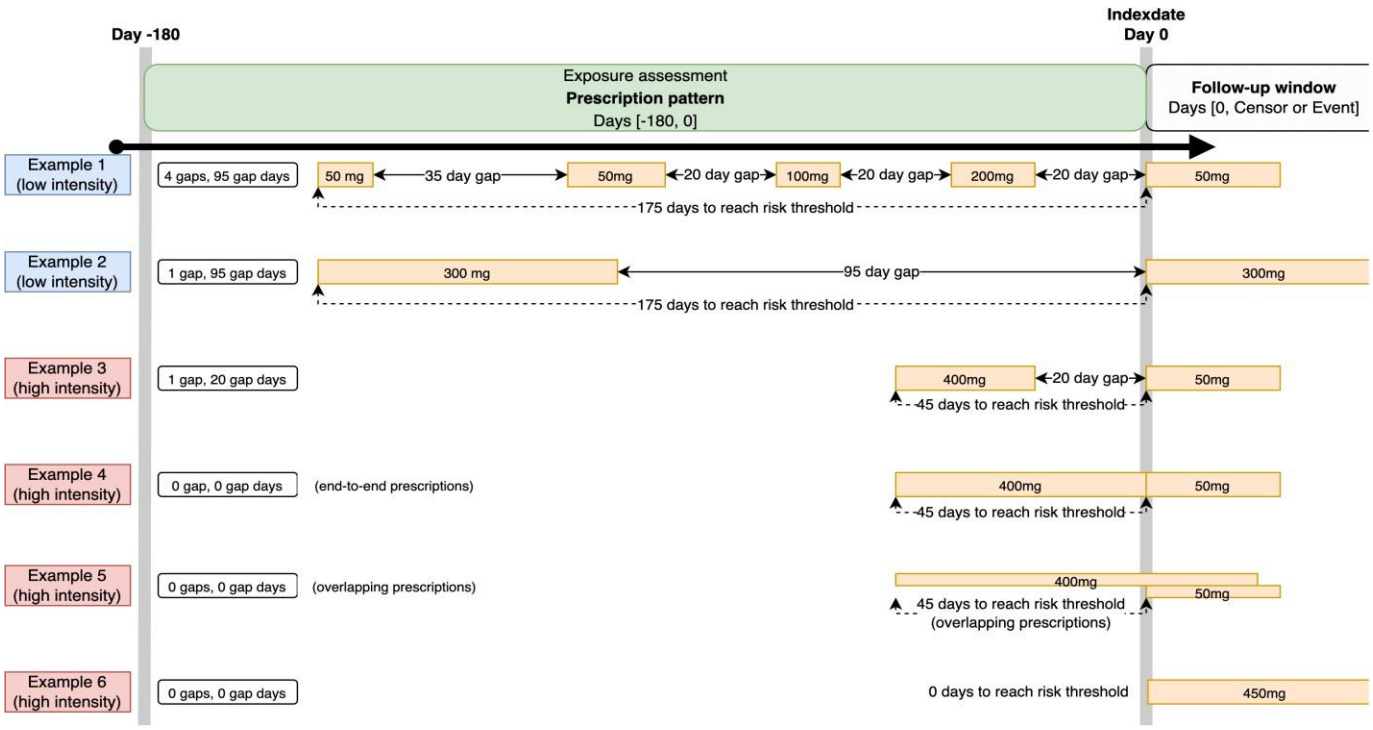
[2] Comorbidities: asthma, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD).

[3] Other medication: inhaled corticosteroids, injected corticosteroids, topical corticosteroids, other corticosteroids, ever received oral corticosteroids more than 1 year before index date, other drugs affecting fracture risk; Healthcare utilisation: urban/rural home address, number of physician visits in past year (1-12/13-21/22+), number of hospital admissions (0/1+), number of physicians prescribing OCS (1/2+).

eTable 6. Equivalent Doses of Oral Corticosteroids

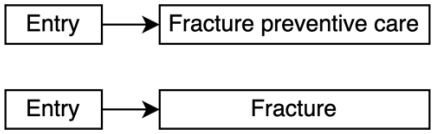
Drug	Dose equivalent to 1mg prednisolone
Betamethasone	0.15
Betamethasone sodium phosphate	0.15
Deflazacort	1.20
Dexamethasone	0.15
Dexamethasone Sodium Phosphate	0.15
Dexamethasone sodium phosphate	0.15
Hydrocortisone	4.00
Hydrocortisone Acetate	4.00
Hydrocortisone Sodium Phosphate	4.00
Hydrocortisone Sodium Succinate	4.00
Hydrocortisone acetate	4.00
Hydrocortisone sodium phosphate	4.00
Hydrocortisone sodium succinate	4.00
Methylprednisolone	0.80
Methylprednisolone Acetate	0.80
Methylprednisolone acetate	0.80
Methylprednisolone sodium succinate	0.80
Prednisolone	1.00
Prednisolone Sodium Phosphate	1.00
Prednisolone Steaglate	1.00
Prednisolone acetate	1.00
Prednisolone sodium phosphate	1.00
Prednisone	1.00
Triamcinolone Acetonide	0.80
Triamcinolone Hexacetonide	0.80
Triamcinolone acetonide	0.80
Triamcinolone hexacetonide	0.80

A.3 eFigures

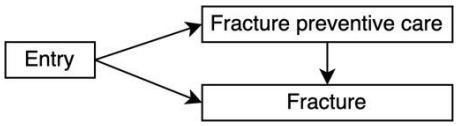


eFigure 1. Example Demonstrating Exposure Definition (Not Real Data)

6 different examples, each showing an individual's oral corticosteroid (OCS) prescriptions with prednisolone equivalent dose (PED) (in orange) in the 180 days (approximately 6 months) leading up to the time of crossing the risk threshold of 450mg PED (index date). We categorised OCS use according to the number of days taken to reach the risk threshold of 450mg PED within 180 days (main analysis), and according to the number, and total length of gaps within that time (sensitivity analyses).



(a) Main analyses (two separate two-state analyses)



(b) Multistate analysis (one three-state analysis)

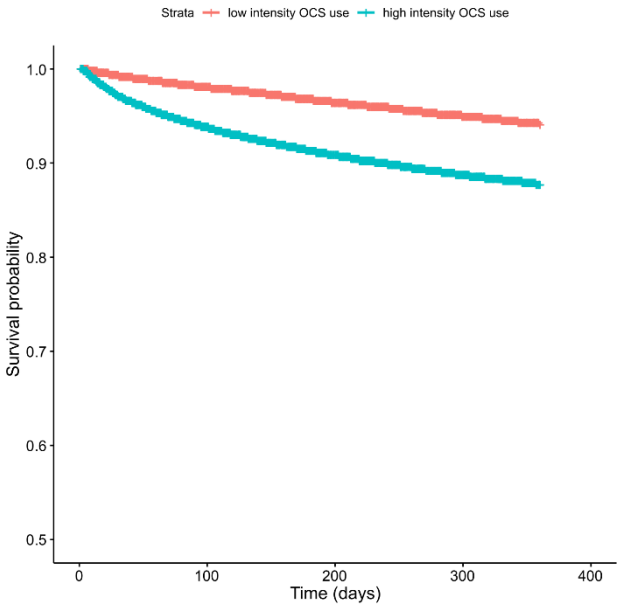
eFigure 2. Diagram of States and Possible Directions of Movement Between States

Diagrams showing the different analytic approach used for the main analyses (two-state analyses for both the fracture preventive care and fracture outcomes), and the multi-state analysis (three-state analysis combining both outcomes). In the multi-state analysis, people are censored only when they experience a fracture (absorbing state, i.e. cannot switch to another state thereafter), but not when they receive fracture preventive care.

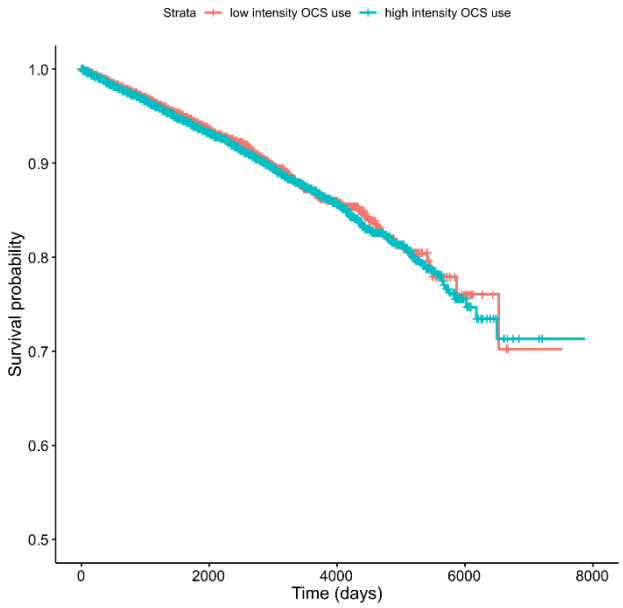
UK Ontario

eFigure 3. Study Flow Diagrams

Number of participants and person-years at each step of the data management process.
UK database population: People ever registered in a CPRD eligible UK general practice from January 2nd 1998 to January 31st 2020 from CPRD.
Ontario database population: administrative health data from April 1st 2002 to September 30th 2020 from ICES data sources.
* Previous event: previous prescription for a fracture preventive care drug or major osteoporotic fracture.
* Other eligibility criteria: at least 18 years old, study start date has passed (UK ≥ January 2, 1998; *Ontario:* ≥ 1st April 2002), practice meets quality standards (UK only), 12 months registration at eligible practice (UK only).



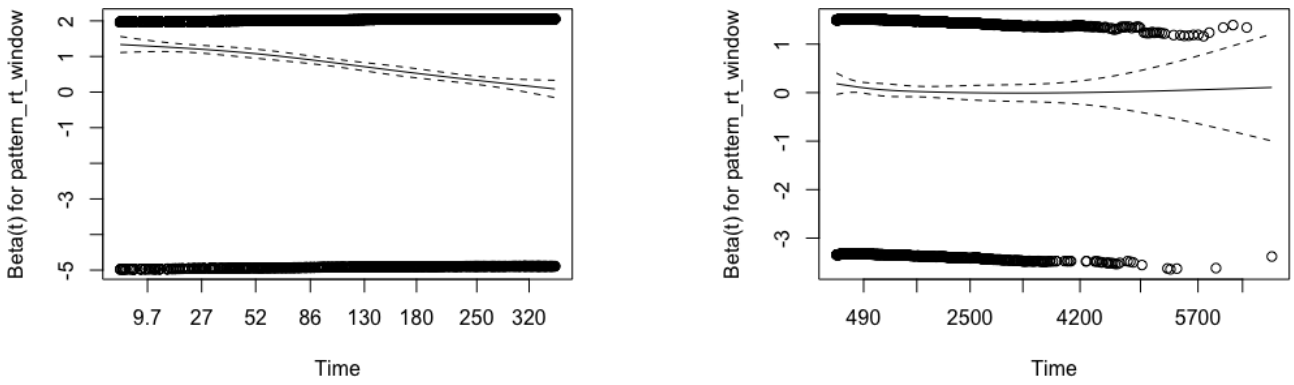
for the fracture preventive care outcome



for the fracture outcome

eFigure 4. Survival Curves by Exposure

Survival curves showing the probability of survival (i.e. staying outcome-free) over time for the fracture preventive care (follow-up time limited to one year) and fracture (follow-up time not limited) outcomes.



(a) for the fracture preventive care outcome *(b) for the fracture outcome*

eFigure 5. Plots of Scaled Schoenfeld Residuals

Plots of scaled Schoenfeld residuals, along with smoothed curves, to estimate the time dependence of the exposure for the outcome. For the fracture preventive care outcome, the curve gradually approaching 0 suggests that the prescription pattern (high intensity vs low intensity) is most strongly associated with the outcome at the beginning of follow-up, dropping to almost no associated by the end of the year. For the fracture outcome, where follow-up time was not limited, the curve being approximately horizontal and close to 0 suggests proportional hazards.

A.4 eAppendix. RECORD-PE checklist

The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data.[39]

Title and abstract

1. Title and abstract

- (STROBE) Indicate the study's design with a commonly used term in the title or the abstract. Abstract
- (STROBE) Provide in the abstract an informative and balanced summary of what was done and what was found. Abstract
- (RECORD) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. Abstract
- (RECORD) If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. Abstract
- (RECORD) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. Abstract

Introduction

2. Background rationale

- (STROBE) Explain the scientific background and rationale for the investigation being reported. Background

3. Objectives

- (STROBE) State specific objectives, including any prespecified hypotheses. Background

Methods

4. Study design

- (STROBE) Present key elements of study design early in the paper. Study design and setting
- (RECORD-PE) Include details of the specific study design (and its features) and report the use of multiple designs if used. Study design and setting
- (RECORD-PE) The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant. Figure 1

5. Setting

- (STROBE) Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. Data sources, Study population

6. Participants

- (STROBE) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. ~~Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants.~~ Exposures, outcomes, and covariates Statistical analyses

- ~~(STROBE) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.~~
- (RECORD) The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. Exposures, outcomes, and covariates
- (RECORD) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. Exposures, outcomes, and covariates
- (RECORD) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. eFigure 3
- (RECORD-PE) Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs. Study population, Statistical analyses, Figure 1

7. Variables

- (STROBE) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Exposures, outcomes, and covariates
- (RECORD) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. Exposures, outcomes, and covariates
- (RECORD) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. Access
- (RECORD-PE) Describe how the drug exposure definition was developed. Exposures, outcomes, and covariates
- (RECORD-PE) Specify the data sources from which drug exposure information for individuals was obtained. Data sources
- (RECORD-PE) Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. Exposures, outcomes, and covariates
- (RECORD-PE) Justify how events are attributed to current, prior, ever, or cumulative drug exposure. Statistical analyses
- (RECORD-PE) When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. Exposures, outcomes, and covariates
- (RECORD-PE) Use of any comparator groups should be outlined and justified. Exposures, outcomes, and covariates
- (RECORD-PE) Outline the approach used to handle individuals with more than one relevant drug exposure during the study period. Exposures, outcomes, and covariates

8. Data sources/measurement

- (STROBE) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Exposures, outcomes, and covariates
- (RECORD-PE) Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed. Data sources

9. Bias

- (STROBE) Describe any efforts to address potential sources of bias. Statistical analyses

10. Study size

- (STROBE) Explain how the study size was arrived at. Study population

11. Quantitative variables

- (STROBE) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. Exposures, outcomes, and covariates

12. Statistical methods/Data access and cleaning methods/Linkage

- (STROBE) Describe all statistical methods, including those used to control for confounding. Statistical analyses
- (STROBE) Describe any methods used to examine subgroups and interactions. Statistical analyses
- (STROBE) Explain how missing data were addressed. Exposures, outcomes, and covariates
- (STROBE) Cohort study—if applicable, explain how loss to follow-up was addressed. ~~Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy.~~ Section 2.2.5
- (STROBE) Describe any sensitivity analyses. Statistical analyses, Table 1
- (RECORD-PE) Describe the methods used to evaluate whether the assumptions have been met. Statistical analyses, Table 1
- (RECORD-PE) Describe and justify the use of multiple designs, design features, or analytical approaches. Statistical analyses, Table 1
- (RECORD) Authors should describe the extent to which the investigators had access to the database population used to create the study population. Appendix
- (RECORD) Authors should provide information on the data cleaning methods used in the study. Appendix
- (RECORD) State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. Appendix

Results

13. Participants

- (STROBE) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). eFigure 3
- (STROBE) Give reasons for non-participation at each stage. eFigure 3
- (STROBE) Consider use of a flow diagram. eFigure 3
- (RECORD) Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage.

The selection of included individuals can be described in the text or by means of the study flow diagram. eFigure 3

14. Descriptive data

- (STROBE) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. Table 2
- (STROBE) Indicate the number of participants with missing data for each variable of interest. Table 2
- (STROBE) Cohort study—summarise follow-up time (eg, average and total amount). eTable 2

15. Outcome data

- (STROBE) Cohort study—report numbers of outcome events or summary measures over time. ~~Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross-sectional study—report numbers of outcome events or summary measures.~~ Table 3

16. Main results

- (STROBE) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. Table 3
- (STROBE) Report category boundaries when continuous variables are categorised. Table 3
- (STROBE) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.

17. Other analyses

- (STROBE) Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses. Appendix

Discussion

18. Key results

- (STROBE) Summarise key results with reference to study objective. Discussion

19. Limitations

- (STROBE) Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. Discussion
- (RECORD) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. Discussion
- (RECORD-PE) Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest. Discussion

20. Interpretation

- (STROBE) Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Discussion
- (RECORD-PE) Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant. Discussion

21. Generalisability

- (STROBE) Discuss the generalisability (external validity) of the study results. Discussion

Other information

22a. Funding/Accessibility of protocol, raw data, and programming code

- (STROBE) Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Funding
- (RECORD) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. Access

A.5 eReferences.

29 Clinical Practice Research Datalink. Small area level data based on patient postcode. 2022.

30 Wilkins R. Use of postal codes and addresses in the analysis of health data. *Health Rep* 1993;**5**:157–77.https://www.ncbi.nlm.nih.gov/pubmed/8292756

31 Glazier RH, Creatore MI, Agha MM, *et al.* Socioeconomic misclassification in ontario's health care registry. *Can J Public Health* 2003;**94**:140–3.https://www.ncbi.nlm.nih.gov/pubmed/12675172

32 Juurlink D, Preyra C, Croxford R, *et al.* Canadian institute for health information discharge abstract database: A validation study. 2006.

33 Williams J, Young W. A summary of studies on the quality of health care administrative databases in canada. *Patterns of health care in Ontario: the ICES practice atlas 2nd ed Ottawa: Canadian Medical Association* 1996;**339**:45.

34 Levy AR, O'Brien BJ, Sellors C, *et al.* Coding accuracy of administrative drug claims in the ontario drug benefit database. *Can J Clin Pharmacol* 2003;**10**:67–71.https://www.ncbi.nlm.nih.gov/pubmed/12879144

35 Ontario Ministry of Finance. Ontario Demographic Quarterly: Highlights of first quarter. 2021.http://www.ontario.ca/page/ontario-demographic-quarterly-highlights-first-quarter

36 Robles SC, Marrett LD, Clarke EA, *et al.* An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988;**41**:495–501. doi:10.1016/0895-4356(88)90052-2

37 British National Formulary. Glucocorticoid therapy. https://bnf.nice.org.uk/treatment-summaries/glucocorticoid-therapy/

38 Andridge RR, Little RJA. A Review of Hot Deck Imputation for Survey Non-response. Int Stat Rev. 2010 Apr;78(1):40–64.

39 Langan SM, Schmidt SA, Wing K, *et al.* The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ* 2018;k3532. doi:10.1136/bmj.k3532

4.4 Relevance for thesis

The study presented in this chapter on missed opportunities for fracture preventive care for people taking anti-inflammatory drugs (*Aim I*) provides evidence that can be used to inform priorities for their care (*Overall Thesis Aim*). The study demonstrates that new insights can be won from EHRs by leveraging granular information contained in prescriptions and implementing complex drug exposure definitions. Learnings, in particular on how to implement several different exposure definitions and sensitivity analyses within the same analysis pipeline, were important for the other chapters in this thesis.

4.5 Chapter summary

- There may be modifiable gaps in fracture preventive care for people with relapsing-remitting inflammatory conditions who are prescribed high cumulative oral glucocorticoid doses
- I made use of the granular prescription information on oral glucocorticoids that is contained in EHRs
- Analyses were conducted with data from the UK and Ontario (Canada) in parallel, study populations consisting of individuals with eczema, asthma, or chronic obstructive pulmonary disease who were 66 or older
- Follow-up started when eligible individuals received a prescription for oral glucocorticoids that crossed a risk threshold of 450 mg prednisolone equivalent within 6 months
- The risk threshold could be reached either through a high-intensity or low-intensity pattern of oral glucocorticoid prescribing, the latter being defined as taking a longer time or more prescriptions, or there being more gaps or longer gaps between prescriptions as compared to the former
- People with low-intensity prescribing patterns were less likely to receive fracture preventive care than those with high-intensity patterns (more than half as likely in the UK cohort), but no increase in fractures was seen

5 Anxiety and Depression in People with Eczema or Psoriasis: A Comparison of Associations in UK Biobank and Linked Primary Care Data

5.1 Introduction

An association between eczema and psoriasis, and anxiety and depression had been previously described in various data sources, including EHRs and population cohorts that assessed diagnoses via questionnaires.[19,20,98] The UK Biobank establishing linkage to primary care data presented an opportunity to study this association not just with information from two different data sources, but with information on the same people from two different data sources. Thus, the aim of this chapter was twofold. Firstly, strengthen the evidence on the association between eczema and psoriasis and anxiety and depression. Using two different data sources, from which different biases may arise, helps triangulate research questions. Secondly, assess agreement concerning the conditions under study between data sources, which is especially important for conditions like eczema, anxiety and depression, where diagnoses may sometimes be uncertain, there are no confirmatory laboratory tests, and the study setting may influence whether or not a diagnosis is captured.

The association between eczema, and depression and anxiety, will be studied again in Chapter 7, and the different emphasis of the two chapters will be discussed further in Section 8.2.2. Similar approaches to comparing between linked data sources will be applied in Chapter 6.

5.2 Published manuscript

Contribution

I am first author of a manuscript published in August 2023 in *Clinical Epidemiology.*[99] I led the project together with the senior author of the paper, Alasdair Henderson, contributing equally to data management and statistical analysis, and leading on interpretation of findings, and manuscript writing.

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First Name(s)	Julian		
Surname/Family Name	Matthewman		
Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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When was the work published?	August 2023		
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SECTION E

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Date	20 March 2024

Supervisor Signature	[redacted]
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ORIGINAL RESEARCH

Anxiety and Depression in People with Eczema or Psoriasis: A Comparison of Associations in UK Biobank and Linked Primary Care Data

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Introduction: Previous research has shown associations between eczema and psoriasis and anxiety and depression. We investigated whether associations are consistent across different settings of ascertainment for depression and anxiety, including interview and survey responses from UK Biobank (a large longitudinal cohort recruiting individuals aged 40–69 years between 2006–2010), and linked primary care data, with the aim of drawing more reliable conclusions through triangulation.

Methods: In cross-sectional studies, we estimated associations between eczema or psoriasis and anxiety or depression, defining anxiety or depression as 1) self-reported previous diagnosis at UK Biobank recruitment interview; 2) PHQ-9/GAD-7 score indicating depression or anxiety from a UK Biobank mental health follow-up survey in 2016; and 3) diagnosis in linked primary care electronic health record data.

Results: We analysed 230,047 people with linked Biobank and primary care data. We found poor agreement between the data sources for eczema, psoriasis, anxiety, and depression. Eg, 9474 had a previous eczema diagnosis in primary care data, 4069 self-reported previous eczema diagnosis at the UK biobank interview, and 1536 had eczema in both data sources (for depression 40,455; 13,320; and 9588 respectively). Having eczema or psoriasis (recorded in primary care or baseline interview) was associated with higher odds of anxiety and depression. Eg, the adjusted odds ratio for depression comparing those with eczema to those without was greater than 1 when defining the outcome from 1) the recruitment interview (1.36, 95% confidence interval 1.27–1.45); 2) the follow-up survey (1.24, 1.09–1.39), and 3) primary care records (1.56, 1.50–1.62).

Discussion: Our findings support increased prevalence of mental illness in people with psoriasis and eczema across multiple data sources, which should be considered in planning of mental health services. However, we found poor agreement in disease ascertainment between settings, with implications for data interpretation in electronic health records.

Keywords: eczema, psoriasis, anxiety, depression, ascertainment, cross-sectional study, data linkage, UK Biobank, electronic health records

Introduction

Atopic eczema (referred to as eczema throughout) is common, affecting up to 10% of adults, while psoriasis affects 1–2% of adults in the UK.[1,2] Previous evidence, including from cohort studies using UK primary care electronic health records, has found that existing eczema and psoriasis are associated with newly reported anxiety and depression.[3–6]

To increase trust in associations found between eczema/psoriasis and anxiety/depression it is important to triangulate findings using different approaches.[7] Firstly, the effects should be demonstrated across multiple types of data sources, eg, both routinely collected health records and survey data. Secondly, for diseases that are heterogenous in their severity, progression, and real-world diagnosis context, it is important to demonstrate similar effects using multiple disease definitions (eg, clinician diagnosis, self-report). Differences in the extent to which conditions are captured in different data sources may be explained by social desirability, recall bias, consultation behaviour, or differences in clinicians' coding behaviour (eg, due to changes in how general practitioners record mental illness).[8]

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Defining mental health outcomes, in UK Biobank and elsewhere, is complex, making it important that multiple measures for ascertaining mental illness status are used.[9] Considering different mental illness outcome definitions is also especially important in the context of studying associations with skin disease exposures. For example, while it is likely that anxiety and depression are underreported and underdiagnosed in primary care in the general population,[10] it is possible that any underreporting of anxiety/depression is worse in people with eczema/psoriasis; consultations may focus on skin conditions, as there is evidence that those presenting with physical symptoms (eg, symptoms of skin conditions) are less likely to have their mental illness detected or prioritised.[11–14]

UK Biobank is a large UK longitudinal cohort study established in 2006 that is regularly used for observational research of skin diseases,[15] and mental illnesses.[16,17] UK Biobank recently linked a proportion of their cohort to primary care data, affording the opportunity to look at associations (eg, between a chronic conditions like eczema/psoriasis, and adverse health outcomes like anxiety/depression) in and beyond primary care, within the same population.[18] We used Biobank baseline data, follow-up mental health questionnaire data from 2016, and linked primary care electronic health record data, all from the same study population, with the aim of estimating the associations between eczema/psoriasis and anxiety/depression across multiple settings of disease ascertainment to increase confidence in the previously observed association.

Methods

Study Population

We used data from UK Biobank, a database including approximately half a million participants aged 40–69 years at recruitment between 2006 and 2010. Of these, we included only participants with linked primary care data (n=230,047).

Exposure and Outcome Measurement

We defined eczema and psoriasis exposure using both UK Biobank recruitment interview responses (self-reported previous diagnosis of serious illnesses or disabilities; as was also done in previous UK Biobank studies),[19,20] and primary care records based on a previously validated algorithm (one eczema diagnostic code and two records for eczema therapy recorded on separate days; one diagnostic code for psoriasis).[21]

We defined anxiety and depression outcomes in three ways: 1) UK Biobank recruitment interview responses (self-reported previous diagnosis of serious illnesses or disabilities) coded as depression or anxiety/panic attacks (Appendix Section "Exposure & Outcomes in UK Biobank", Supplementary Table 1); 2) Biobank 2016 mental health follow-up survey response derived PHQ-9 (Patient Health Questionnaire)[22] and GAD-7 (Generalised Anxiety Disorder Assessment)[23] scores for depression and anxiety in the two weeks before the 2016 mental health follow-up survey, with scores of 10 or more considered as being indicative of present anxiety/depression (Appendix Section "PHQ-9/GAD-7 scores"); 3) primary care morbidity coding defined based on a single morbidity code for anxiety or depression, including diagnoses and symptoms of anxiety/depression, recorded prior to the Biobank interview/2016 mental health follow-up survey (primary care data available from approximately 1990 onwards).

To calculate PHQ-9/GAD-7 scores, the respondent is asked to judge "Over the last 2 weeks, how often have you been bothered by any of the following problems?" with nine/seven responses taken for PHQ-9/GAD-7 (eg, "Little interest or pleasure in doing things" for PHQ-9; "Becoming easily annoyed or irritable" for GAD-7). The overall scores are calculated by assigning scores of 0 ("not at all"), 1 ("several days"), 2 ("more than half the days"), and 3 ("nearly every day"), and adding together the scores for the nine/seven questions.

We used lists of primary care morbidity codes for diagnoses, symptoms, and prescriptions to identify eczema/psoriasis and anxiety/depression in primary care data. We used morbidity code lists used in previous electronic health record research developed with input from UK-practicing clinicians (for more detail see Appendix Section "Codelists", Supplementary Table 2).[4,21,24–26] All data management and statistical analysis code is available on GitHub (repository to be published together with manuscript).

Statistical Analysis

We described the baseline characteristics of our study population (Ie, the subset of the Biobank cohort with linked primary care data), and of the entire Biobank cohort by linkage status. We described the number of people with and without eczema/psoriasis who had anxiety/depression separately for all exposure and outcome pairs (ie, different exposure/outcome definitions). We additionally described how many people self-reported anxiety/depression symptoms that occurred any time before the Biobank mental health follow-up survey. We assessed agreement between recruitment interview and primary care data for all exposures (eczema/psoriasis) and outcomes (anxiety/depression).

We conducted cross-sectional studies, using logistic regression to estimate the association (odds ratios [OR] and 95% confidence intervals [95% CI]) between eczema/psoriasis and anxiety/depression. We adjusted models for key potential confounders (age, sex, deprivation, ethnicity) (Appendix Section "Covariates"). We estimated odds ratios comparing the odds of each anxiety/depression outcome definition (self-reported diagnosis at initial interview; PHQ-9/GAD-7 ≥10 in mental health follow-up survey; coded in primary care data) in people with eczema/psoriasis (captured in either electronic health records or on baseline Biobank survey) compared to people without eczema/psoriasis (Figure 1). All code is available online.[27]

Results

We included 230,047 people from Biobank with linked primary care data (Figure 2). The study population was aged 40–69 years at recruitment, included more women than men (55% female), and was mostly of people who reported their ethnicity to be "British" (89%). Our study population (people with primary care data linkage) had similar distribution of baseline characteristics to those without linkage; those within our study population that responded to the mental health survey where from more affluent areas and were less likely to be retired than those who did not respond to the survey (Supplementary Figure 1, Supplementary Table 3).

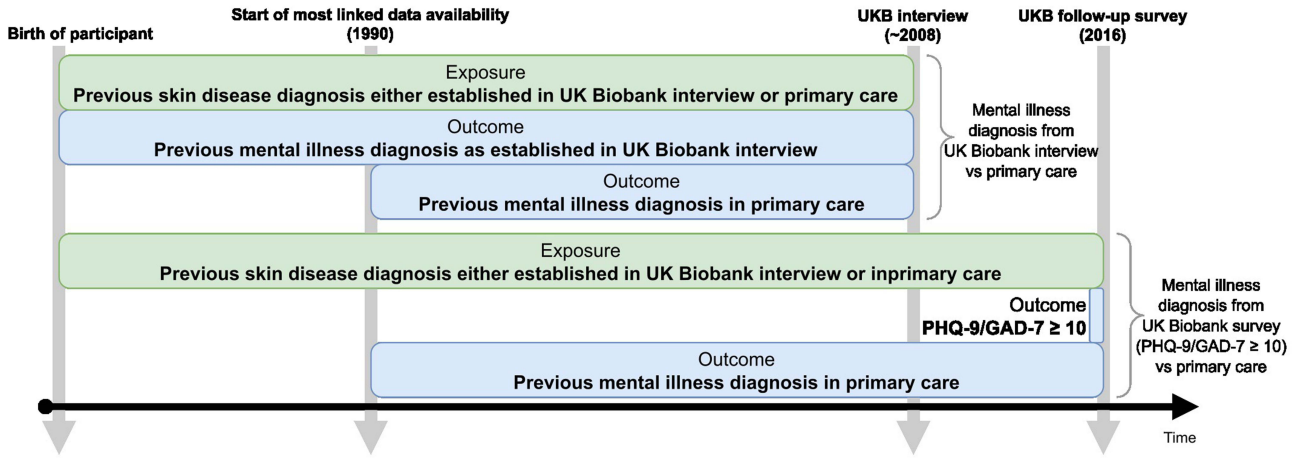

Figure 1 Timeline showing when exposure and outcome for both cross-sectional comparisons were defined and the timeframes from when the actual diagnoses/self-reports would be from. Most participants with primary care data only had data available from 1990 onwards, whereas self-reported previous diagnoses could potentially have occurred before that time. In green: The exposure (eczema/psoriasis) was defined as a previous doctor's diagnosis either reported at the UK Biobank interview around 2008 or at least 1 code for eczema diagnosis and 2 codes for eczema treatments on different days in primary care data. Only data from before the UK Biobank interview or the UK Biobank follow-up survey was used. In blue: The outcome (anxiety/depression) was defined as a previous doctor's diagnosis reported at the UK Biobank interview around 2008, at least 1 diagnosis code in primary care data, or a PHQ-9/GAD-7 score of more than 10 at the UK Biobank mental health follow-up survey.

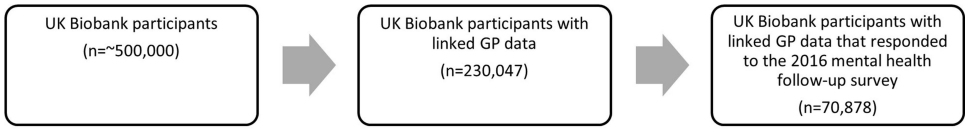

Figure 2 Participant flow.

Table 1 UK Biobank Recruitment Interview Compared to Primary Care Morbidity Coding at or Before Recruitment

	Anxiety as Defined in		Depression as Defined in	
	Interview[a]	Primary Care[b]	Interview[a]	Primary Care[b]
No Eczema n=214,968 (100%)	2971 (1.4%)	23,439 (11%)	12,189 (5.7%)	36,783 (17%)
Eczema n=15,079 (100%)	271 (1.8%)	2390 (16%)	1137 (7.5%)	3672 (24%)
No Psoriasis n=222,139 (100%)	3101 (1.4%)	24,677 (11%)	12,825 (5.77%)	38,691 (17%)
Psoriasis n=7886 (100%)	141 (1.8%)	1152 (15%)	500 (6.34%)	1758 (22%)

Notes: Number of people with and without eczema/psoriasis (based on recruitment interview and/or primary care data up to recruitment) who have anxiety/depression (and percentage of people with anxiety/depression of total people with/without eczema/psoriasis) as defined in [a]Reponses from UKB interview (around 2008; people were asked if they had ever been diagnosed by a doctor with any serious illnesses), [b]Primary care data up to date of UKB interview. Percentages are row percentages.

Agreement Between Data Sources

More individuals were identified as having previous eczema, psoriasis, depression, and anxiety in their primary care records than was reported on recruitment interview (eg, 11,010 had an eczema record in their electronic health records, compared to 5605 reporting previous eczema on recruitment interview; 7187 vs 2557 for psoriasis; 40,455 vs 13,326 for depression; 49,268 vs 3242 for anxiety) (Table 1). A minority of participants met the disease definition in both data sources: eczema 8%, psoriasis 25%, depression 22%, anxiety 7% (Figure 3).

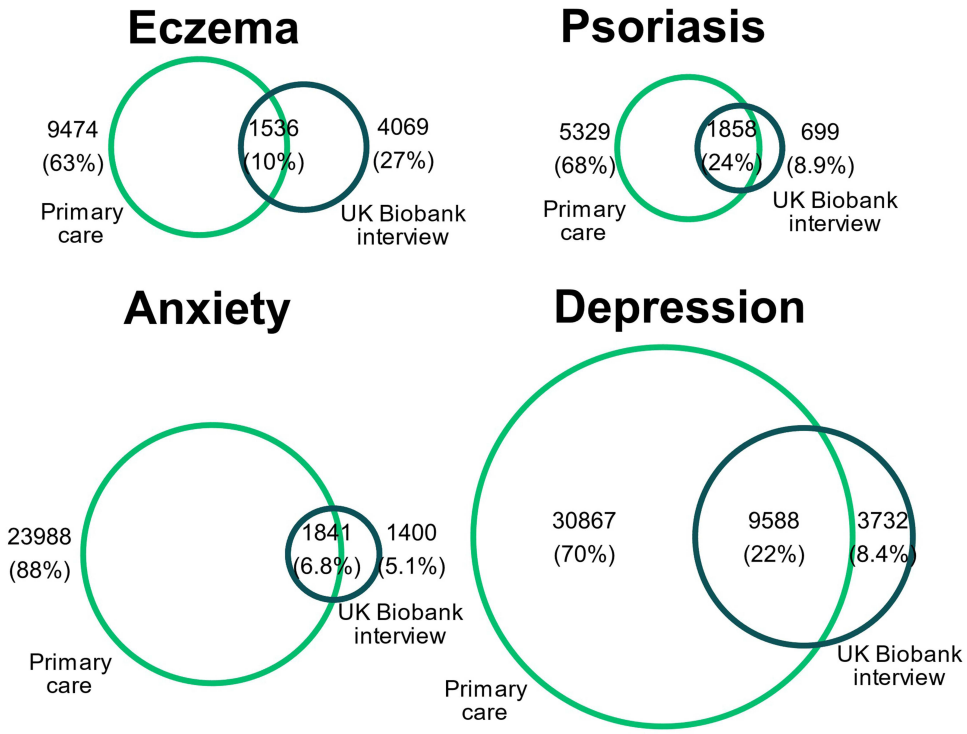

Figure 3 Exposure and outcome definition agreement between UK Biobank interview at recruitment, and primary care records. For each exposure/outcome the Venn diagram show the number of people that identified the condition in their baseline interview and the number of people who have a corresponding record in primary care.

Table 2 UK Biobank Mental Health Follow-Up Survey (in 2016) Compared to Primary Care Morbidity Coding at or Before Survey

	Anxiety as Defined in		Depression as Defined in	
	Survey (GAD-7 ≥ 10)[a]	Primary Care[b]	Survey (PHQ-9 ≥ 10)[a]	Primary Care[b]
No Eczema n=66,253 (100%)	2937 (4.5%)	6371 (9.6%)	3800 (5.8%)	10,005 (15%)
Eczema n=4628 (100%)	240 (5.3%)	637 (14%)	313 (6.9%)	994 (21%)
No Psoriasis n=68,584 (100%)	3060 (4.5%)	6715 (9.8%)	3962 (5.9%)	10,553 (15%)
Psoriasis n=2294 (100%)	117 (5.2%)	293 (13%)	151 (6.7%)	446 (19%)

Notes: Number of people with and without eczema/psoriasis (based on recruitment interview and/or primary care data up to survey) who have anxiety/depression (and percentage of people with anxiety/depression of total people with/without eczema/psoriasis) as defined in [a]UKB follow-up survey, as a score of ≥10 in the PHQ-9 score for depression/the GAD-7 score for anxiety, which take into account symptoms in the 2 weeks leading up to the 2016 UKB follow-up survey, [b]Linked GP data up to date of UKB survey, including only people who answered the survey. Percentages are row percentages.

A total of 70,878 of those with primary care records responded to the 2016 mental health follow-up survey, of whom 4113 (5.8%) had a PHQ-9 score indicating current depression, and 3177 (4.4%) had a GAD-7 score indicating current anxiety; 10,999 (15.5%) ever had a primary care record indicating depression, and 7008 (9.9%) a recording indicating anxiety up to the date of the mental health follow-up survey (Table 2).

Eczema/Psoriasis and Anxiety/Depression

Having eczema or psoriasis was associated with higher odds of having both anxiety and depression, regardless of the method used to define the mental illness (Biobank interview, mental health survey, or primary care data). The adjusted (age, sex, deprivation, ethnicity) odds ratios for the association between eczema or psoriasis and anxiety or depression were larger when defining anxiety or depression using primary care records compared to UK Biobank interview/survey data. This was true both for the comparison at recruitment (eg exposure: eczema, outcome: depression defined in Biobank interview, OR 1.36, 95% CI 1.27–1.45; outcome defined in prior primary care data, OR 1.56, 95% CI 1.50–1.62) and the comparison at the mental health survey (eg, exposure: eczema, outcome: depression defined from Biobank mental health survey: OR 1.24, 95% CI 1.09–1.39; outcome defined in pre-survey primary care records: OR 1.50, 95% CI 1.39–1.63) (Table 3).

Table 3 Odds Ratios from Logistic Regression by Data Source of Outcome Definition

	Outcome Definition[b]	Exposure: Eczema[a]		Exposure: Psoriasis[a]	
		OR (95% CI)[c]	n[d]	OR (95% CI)[c]	n[d]
UK Biobank					
Depression	Interview-reported diagnosis	1.36 (1.27–1.45)	229,393	1.11 (1.01–1.21)	229,371
Anxiety	Interview-reported diagnosis	1.30 (1.14–1.47)	229,393	1.29 (1.08–1.52)	229,371
Depression	PHQ-9 ≥ 10 (survey)	1.24 (1.09–1.39)	69,420	1.19 (1.00–1.41)	69,417
Anxiety	GAD-7 ≥ 10 (survey)	1.20 (1.05–1.37)	69,737	1.19 (0.98–1.44)	69,734

(*Continued*)

Table 3 (Continued).

	Outcome Definition[b]	Exposure: Eczema[a]		Exposure: Psoriasis[a]	
		OR (95% CI)[c]	n[d]	OR (95% CI)[c]	n[d]
Linked GP data					
Depression	≥ 1 diagnosis pre-interview	1.56 (1.50–1.62)	229,378	1.38 (1.31–1.46)	229,356
Anxiety	≥ 1 diagnosis pre-interview	1.53 (1.46–1.60)	229,390	1.38 (1.29–1.47)	229,368
Depression	≥ 1 diagnosis pre-survey	1.50 (1.39–1.63)	64,499	1.37 (1.22–1.54)	64,496
Anxiety	≥ 1 diagnosis pre-survey	1.43 (1.30–1.58)	64,502	1.39 (1.21–1.59)	64,499

Notes: [a]Exposures defined using self-reported previous diagnosis at the UK Biobank recruitment interview, or through records in linked GP data prior to the timepoint (at least 1 diagnosis + 2 prescription codes on separate days for eczema; 1 diagnosis for psoriasis). [b]At the Initial interview timepoint (in grey), outcomes are defined either as a self-reported previous doctor's diagnosis, or at least 1 diagnosis code in linked GP data prior to the interview. At the 2016 mental health follow-up survey (70,878 responded), outcomes are defined either as a score of ≥10 in the PHQ-9 score for depression/the GAD-7 score for anxiety, which take into account symptoms in the 2 weeks prior to the survey, or at least 1 diagnosis code in linked GP data prior to the follow-up survey. [c]Odds ratios (95% confidence intervals) estimated from logistic regression for having a mental illness (adjusted for age, sex, deprivation and ethnicity) comparing people with the respective skin disease to people without the respective skin disease. [d]Number of observations that went into the model. Observations with missing values were dropped. "Prefer not to answer" and "Do not know" were treated as missing values. For the follow-up survey timepoint, only used GP data where all of the questions of the mental health follow-up survey were answered.

Discussion

We found poor agreement between populations of people with eczema, psoriasis, anxiety or depression as captured in UK Biobank versus linked primary care data. This lack of agreement in diagnoses between primary care and survey data demonstrates that, depending on the specific disease, it is likely that there will be differential capture of conditions depending on data sources and setting of ascertainment. Despite low agreement, we found consistent evidence from primary care and UK Biobank data that people with two common inflammatory skin conditions – eczema and psoriasis – are more likely to experience anxiety and depression regardless of whether we captured anxiety/depression in primary care records or through UK Biobank interview/survey data (albeit with weaker strengths of associations with interview/survey data). This is consistent with previous findings from other studies, including those in UK primary care data.[3,4]

We found a lower prevalence of all exposures (eczema/psoriasis) and outcomes (anxiety/depression) in UK Biobank survey/interview data compared to linked primary care records. The interview question at baseline in UK Biobank was "[…] you have been told by a doctor that you have other serious illnesses or disabilities, could you now tell me what they are?". Many people with a record in primary care of one of eczema, psoriasis, anxiety or depression, did not report this at the interview (eg of 9474 people with a primary care record for eczema, 1536 also reported this at the interview), which may suggest that only the most severe cases of eczema/psoriasis and anxiety/depression were reported in UK Biobank. Additionally, individuals may not report their mental illness in an interview due to social desirability bias.[28] For mental health outcome measures, poor agreement between UK Biobank and linked data sources has been previously described,[9] and for psoriasis, previous research has recommended using UK Biobank in conjunction with another data source to improve accuracy.[29]

Strengths and Weaknesses

The major strength of this study is that we have applied consistent study design and analyses to the same population with information from three different sources (UK Biobank interview, UK Biobank survey and primary care) and have found consistent associations between eczema or psoriasis and anxiety or depression.

Given the cross-sectional design of our study, we were not able to consider whether eczema or psoriasis preceded anxiety or depression, therefore we were unable to assess temporality. In addition, while we adjusted for key confounders of associations between skin conditions and mental illness (age, sex, deprivation, ethnicity), it is likely unmeasured confounding remains, especially with regard to comorbidities. However, we selected a more parsimonious model for two reasons: 1) we were primarily interested in the comparability of estimates between data sources and not causal inference, so a simpler model specification was preferred; and 2) we wanted to reduce the influence of covariate misclassification

between data sources. We found that the agreement between all four exposure/outcome definitions was low, so it is likely that this problem would exist for covariates as well. We therefore did not include other covariates in our analysis to limit possible explanations for differences in our findings between the data sources.

Another limitation of our findings, especially in comparison to research from UK wide primary care records,[4] is that the UK Biobank population is subject to strong selection pressures.[30] In general, the UK Biobank cohort are from a certain age range (40–69 at recruitment in 2006–2010), and predominantly of white ethnicity. The select Biobank population limits the generalisability of our findings to the wider UK population. However, selection bias will not limit internal validity, as we were comparing results from Biobank interviews and surveys to the linked primary care records for the same individuals. Despite the highly selected population, research using UK Biobank data has been previously found to produce generalisable estimates of risk factor associations.[31]

Selection bias is a particular limitation of the analysis of the 2016 mental health questionnaire (31% of the study population). We believe, however, that the selection would likely be non-differential by eczema/psoriasis status, supported by the similar distribution of eczema (2.7% vs 2.3%) and psoriasis (1.1% vs 1.1%) we saw at recruitment in those who did and did not respond to the survey. However, the results from the mental health questionnaire data may be inconsistent with findings from the whole UK Biobank or UK population. Despite the select population, even in this restricted sample measuring recent anxiety or depression we found worse scores in people with eczema and psoriasis.

While our findings were consistent across different mental illness definitions, including using the PHQ-9/GAD-7 scores, we acknowledge that PHQ-9/GAD-7 instruments will only capture recent anxiety and depression symptoms and may not be directly comparable to having a previous anxiety/depression diagnosis, which the other definitions were capturing. While self-reported symptoms that were used to derive PHQ-9 and GAD-7 scores will not be subject to the same kind of differences in ascertainment that can occur in routinely collected health data, they do only capture current disease.

We found stronger associations (greater magnitude odds ratios) in our results from primary care data only, compared to those from UK Biobank interview/survey data. However, both primary care-based and interview/survey-based estimates may be subject to different biases that may explain the higher magnitude ORs in primary care data in ways that are unrelated to the association between eczema or psoriasis and anxiety or depression. Results from primary care data may be subject to differential ascertainment of anxiety or depression between people with and without skin conditions. People with eczema or psoriasis may consult their GP more frequently, giving more opportunity to have other conditions diagnosed. Alternatively, results from Biobank recruitment interview and follow up mental health survey may be influenced by differential capture of anxiety or depression outcomes between those with and without eczema or psoriasis. It is possible that there will be differences in how people with and without eczema or psoriasis answered interview questions and self-defined their symptoms. It is not possible to differentiate these mechanisms in this study; however, our work does demonstrate that the choice of data source and method of outcome assessment will influence observed associations.

Implications and Future Research

Our research question was "Are eczema and psoriasis associated with depression or anxiety?". We found an association in the same population across multiple settings of disease ascertainment, which increases confidence in the existence of this association as the question was addressed using a number of different approaches.[7] Taken together with findings from the existing body of literature on this topic,[3] this motivates improved planning of mental health services for people with eczema and psoriasis.

Our findings suggest that the method of ascertainment of study conditions influences what is captured in observational epidemiological studies regardless of whether these use electronic health records or survey/interview data. These key differences in study definitions may impact interpretability when comparing findings from UK Biobank interview/survey data alone to those where diseases are defined in primary care records. In particular, from UK Biobank data it may only be possible to capture serious or currently active eczema/psoriasis and anxiety/depression. We therefore recommend future research to better understand the phenotypic differences between groups with the same health condition identified from different health care record data sources.

We found that associations between eczema or psoriasis and anxiety or depression were of a slightly lower magnitude when using interview/survey responses to define anxiety or depression compared to using morbidity coded primary care

records. Further research into who does and does not consult their GP with these symptoms is necessary to target interventions and help effectively.

Conclusion

We found that capturing the same health conditions (eczema/psoriasis/anxiety/depression) in primary care records and interview/survey data in the same group of individuals had poor agreement. Despite these differences in who was identified as having eczema/psoriasis and anxiety/depression in our study, we consistently found evidence of an association between eczema/psoriasis and anxiety/depression, regardless of how anxiety/depression were defined, including as self-reported previous doctors' diagnosis, current adverse mental health as captured by PHQ-9/GAD-7 questionnaires, or previous records in primary care data.

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Disclosure

Sinéad M. Langan is a co-investigator in a consortium with industry and multiple academic partners (BIOMAP-IMI.eu), an investigator on a Horizon 2020 IMI grant with industry partners but is not in receipt of industry funding. Joseph F. Hayes has received consultancy fees from the Wellcome, grants from UKRI, personal fees from Juli Health, during the conduct of the study; grants from UKRI, personal fees from Juli Health, outside the submitted work; In addition, Dr Joseph F Hayes has a patent juli health pending to United States Patent and Trademark Office; and juli Health. Kathryn E. Mansfield reports personal consultancy fees from AMGEN. Catherine H Smith is an investigator in consortia with industry and academic partners (see BIOMAP-IMI.eu and HIPPOCRATES-IMI.eu); MRC CASE PhD studentships (Boehringer Ingelheim, Astra Zeneca). The authors report no other conflicts of interest in this work.

References

1. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284–1293. doi:10.1111/all.13401
2. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Investig Dermatol*. 2013;133(2):377–385.
3. Bao Q, Chen L, Lu Z, et al. Association between eczema and risk of depression: a systematic review and meta-analysis of 188,495 participants. *J Affect Disord*. 2018;238:458–464.

4. Schonmann Y, Mansfield KE, Hayes JF, et al. Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study. *J Allergy Clin Immunol*. 2020;8(1):248–257.e16.
5. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol*. 2010;146(8):891–895.
6. Ferreira BR, Pio-Abreu JL, Reis JP, Figueiredo A. Analysis of the prevalence of mental disorders in psoriasis: the relevance of psychiatric assessment in dermatology. *Psychiatr Danub*. 2017;29(4):401–406.
7. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol*. 2016;45(6):1866–1886.
8. Mitchell C, Dwyer R, Hagan T, Mathers N. Impact of the QOF and the NICE guideline in the diagnosis and management of depression: a qualitative study. *Br J Gen Pract*. 2011;61(586):e279–89.
9. Davis KAS, Cullen B, Adams M, et al. Indicators of mental disorders in UK Biobank—a comparison of approaches. *Int J Methods Psychiatr Res*. 2019;28(3):e1796.
10. Bell RA, Franks P, Duberstein PR, et al. Suffering in silence: reasons for not disclosing depression in primary care. *Ann Fam Med*. 2011;9(5):439–446. doi:10.1370/afm.1277
11. Menchetti M, Belvederi Murri M, Bertakis K, Bortolotti B, Berardi D. Recognition and treatment of depression in primary care: effect of patients' presentation and frequency of consultation. *J Psychosom Res*. 2009;66(4):335–341.
12. Pfaff JJ, Almeida OP. A cross-sectional analysis of factors that influence the detection of depression in older primary care patients. *Aust N Z J Psychiatry*. 2005;39(4):262–265.
13. Nuyen J, Volkers AC, Verhaak PFM, Schellevis FG, Groenewegen PP, den Bos GAM V. Accuracy of diagnosing depression in primary care: the impact of chronic somatic and psychiatric co-morbidity. *Psychol Med*. 2005;35(8):1185–1195.
14. Aragonès E, Piñol JL, Labad A, Folch S, Mèlich N. Detection and management of depressive disorders in primary care in Spain. *Int J Psychiatry Med*. 2004;34(4):331–343.
15. Budu-Aggrey A, Brumpton B, Tyrrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. *PLoS Med*. 2019;16(1):e1002739.
16. Kandola AA, Del Pozo Cruz B, Osborn DPJ, Stubbs B, Choi KW, Hayes JF. Impact of replacing sedentary behaviour with other movement behaviours on depression and anxiety symptoms: a prospective cohort study in the UK Biobank. *BMC Med*. 2021;19(1):133.
17. Mutz J, Hoppen TH, Fabbri C, Lewis CM. Anxiety disorders and age-related changes in physiology. *Br J Psychiatr*. 2022;221(3):528–537.
18. Wilkinson T, Schnier C, Bush K, et al.; On behalf of Dementias Platform UK and UK Biobank. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019;34(6):557–565.
19. Johansson Å, Rask-Andersen M, Karlsson T, Ek WE. Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Hum Mol Genet*. 2019;28(23):4022–4041.
20. Ek WE, Karlsson T, Hernándes CA, Rask-Andersen M, Johansson Å. Breast-feeding and risk of asthma, hay fever, and eczema. *J Allergy Clin Immunol*. 2018;141(3):1157–1159.e9.
21. 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. *J Investig Dermatol*. 2017;137(8):1655–1662.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
23. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097.
24. 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*. 2018;2018:k1786.
25. Lowe KE, Mansfield KE, Delmestri A, et al. Atopic eczema and fracture risk in adults: a population-based cohort study. *J Allergy Clin Immunol*. 2020;145(2):563–571.e8.
26. Matthewman J, Mansfield KE, Prieto-Alhambra D, et al. Atopic eczema–associated fracture risk and oral corticosteroids: a population-based cohort study. *J Allergy Clin Immunol*. 2021;2021:154.
27. Henderson A, Matthewman J. hendersonad/2022_biobank: first release for paper submission. Zenodo; 2023. Available from: https://zenodo.org/record/7767171. Accessed July 25, 2027.
28. Latkin CA, Edwards C, Davey-Rothwell MA, Tobin KE. The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. *Addict Behav*. 2017;73:133–136.
29. Saklatvala JR, Hanscombe KB, Mahil SK, et al. Genetic validation of psoriasis phenotyping in UK Biobank supports the utility of self-reported data and composite definitions for large genetic and epidemiological studies. *J Invest Dermatol*. 2023;20:254.
30. Swanson JM. The UK Biobank and selection bias. *Lancet*. 2012;380(9837):110.
31. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ*. 2020;368:m131.

5.3 Relevance for thesis

The study presented in this chapter on adverse mental health outcomes for people with inflammatory skin diseases (*Aim I*) strengthens the existing evidence base needed to inform priorities for their care (*Overall Thesis Aim*). The study also demonstrates the value of linking data from different sources. It reveals a striking mismatch concerning disease definitions between those derived from UK Biobank questionnaire responses and those derived from linked EHRs (*Aim II*), with implications for the interpretation of research findings. Together, this chapter and Chapter 6 provide a basis for discussion of eczema definitions in observational studies.

5.4 Chapter summary

- An association between eczema and psoriasis, and anxiety and depression, had previously been described in various settings
- I conducted a study where information on the same people was available in two settings
- The UK Biobank contains self-reported diagnoses from a recruitment interview and PHQ-9/GAD-7 scores for depression/anxiety from a mental health follow-up survey
- For about 230,000 people in UK Biobank, linkage with primary care EHR data was established, i.e. for these people records for diagnoses and prescriptions by GPs are also available
- I found that agreement between data sources was poor, i.e., people who had a condition recorded in primary care did not necessarily report that condition in the UK Biobank interview, and vice-versa
- I conducted cross-sectional studies adjusting for demographic variables
- Despite poor agreement, I found an association between eczema and psoriasis (exposures), and anxiety and depression (outcomes), both when outcomes were defined through questionnaires, PHQ-9/GAD-7 scores, or records from primary care

6 Disagreement concerning atopic dermatitis subtypes between an English prospective cohort (ALSPAC) and linked electronic health records

6.1 Introduction

The severity, trajectory, presentation and genotype of eczema vary considerably, as introduced in Section 1.2.2.3. Efforts are ongoing to establish subtypes of eczema to help better targeting of treatments and interventions. A set of subtypes had been developed using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), that classified eczema based on its severity trajectory throughout childhood. The subtypes were derived using latent class analysis using parents' responses from an approximately yearly questionnaire on whether their child had a flexural rash and how severe it was.[32]

The initial aim of this chapter was to reconstruct these subtypes in EHRs, which would unlock eczema subtype research on a much larger scale. For this purpose, as in Chapter 5 with the UK Biobank, linkage of the population cohort with primary care electronic health records data was available, this time with ALSPAC. The plan was to develop a prediction model that could be used to predict people's subtypes (as previously established in ALSPAC data) using information from EHRs.

However, as already suggested by the findings from Chapter 5, the information on eczema from study questionnaires may not correspond to what is seen in primary care EHRs. This

turned out to also be the case in this chapter, which ultimately precluded developing a useful model to predict the ALSPAC phenotype from EHR data. On the other hand, findings from this chapter further highlight the need for research on validating eczema diagnoses.

Poor agreement concerning eczema subtypes necessitated taking a step back and looking at whether data sources agreed upon whether or not an individual had eczema in the first place. I conducted several comparisons some of which are included in the submitted manuscript appendix in Section 6.3, which also contains additional visualisations and tables that are referenced in the manuscript.

6.2 Submitted manuscript

> **Contribution**
>
> I am the first author of a manuscript first submitted in November 2023. I led the project, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	lsh1901215	**Title**	Dr
First Name(s)	Julian		
Surname/Family Name	Matthewman		
Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Clinical and Experimental Dermatology
Please list the paper's authors in the intended authorship order:	Julian Matthewman, Amy Mulick, Nick Dand, Daniel Major-Smith, Alasdair Henderson, Neil Pearce, Spiros Denaxas, Rita Iskandar, Amanda Roberts, Rosie P Cornish, Sara J Brown, Lavinia Paternoster, Sinéad M Langan
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author of a submitted manuscript. I led the project, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing.

SECTION E

Student Signature	[redacted]
Date	arc

Supervisor Signature	[redacted]
Date	arc

Disagreement concerning atopic dermatitis subtypes between an English prospective cohort (ALSPAC) and linked electronic health records

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Conflicts of interest

Julian Matthewman, Amy Mulick, Nick Dand, Daniel Major-Smith, Rita Iskandar, Rosie Cornish, Neil Pearce, Spiros Denaxas, Amanda Roberts, Alasdair Henderson have no conflicts of interest to report.

Sara Brown is a co-investigator in a consortium with industry and multiple academic partners (BIOMAP-IMI.eu) and she has received support from multiple pharma partners via BIOMAP; her research is funded by the Wellcome Trust, British Skin Foundation, Charles Wolfson Charitable Trust, Rosetrees Trust and anonymous philantrophic donations.

Sinéad M. Langan is a co-investigator in a consortium with industry and multiple academic partners (BIOMAP-IMI.eu) but is not in receipt of industry funding.

Lavinia Paternoster is a co-investigator in a consortium with industry and multiple academic partners (BIOMAP-IMI.eu).

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Data availability

All analysis code and codelists used for this study are available at … under the DOI … .

Access to ALSPAC data is through a system of managed open access. Information about access to this data is given on the study website (http://www.bristol.ac.uk/alspac/researchers/access/) and in the data management plan (http://www.bristol.ac.uk/alspac/researchers/data-access/documents/alspac-data-managementplan.pdf). Data used for this submission will be made available on request to the Executive (alspacexec@bristol.ac.uk). The datasets presented in this article are linked to ALSPAC project number B2510, please quote this project number during your application. For additional details on accessing the ALSPAC linkage data, see: http://www.bristol.ac.uk/alspac/researchers/our-data/linkage/.

Ethics

The UK study was approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (ID 14602).

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. At age 18, study children were sent 'fair processing' materials describing ALSPAC's intended use of their health and administrative records and were given clear means to consent or object via a written form. Data were not extracted for participants who objected, or who were not sent fair processing materials. Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and local research ethics committees (NHS Haydock REC: 10/H1010/70).

Plain language summary

Atopic dermatitis (AD), also known as eczema, is an itchy skin condition that is common in childhood. Children can have a different experience of eczema during childhood in terms of how often they have symptoms and how severe these are. Some may have severe rashes often, in some the frequency of rashes declines over time, and some only have occasional mild rashes. These different presentations of the same condition are sometimes called subtypes. Recently, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) were used to classify the participating children into either not having AD or into

having one of four subtypes of AD: Severe–Frequent, Moderate–Frequent, Moderate–Declining or Mild–Intermittent.

In this study, we wanted to find out whether these subtypes could be found in the same children's medical records from their family doctor (general practitioner, GP), since there may be differences in what parents report and what doctors diagnose and record. Identifying children's subtypes from their medical records alone, without the need for a dedicated study involving e.g., questionnaires, would be useful in further studying AD in large databases.

First, we looked at whether information on AD in children's medical records matched what was seen in ALSPAC. While this was generally the case with children with more severe AD subtypes having more AD-related records, we found some key differences. Not all children with more severe AD subtypes had records indicating AD in their medical records and some people who were classified as not having AD in ALSPAC had GP records indicating AD.

Next, we used a wider range of information available in the medical records to classify children's AD subtype. We found that the subtype classified with EHRs did not always match the subtype children had originally been assigned in ALSPAC, with those with milder subtypes being most difficult to correctly classify. Reasons why classifying subtypes between data sources was less accurate may include differences in what data were collected, how, and when between the different sources, but it might also be because the subtypes themselves might have features that overlap between them.

Therefore, at the end of the study we found that what is recorded in children's medical records doesn't necessarily match what parents reported in ALSPAC. We recommend that researchers are aware of these differences, and consider using a combination of data sources when possible.

Key points

What is already known about this topic?

- Childhood atopic dermatitis (AD) subtypes based on timing and severity of symptom reports were identified in prospective cohort data (ALSPAC). It is not understood whether these data agree with what is seen in electronic health records (EHRs) in AD.

What does this study add?

- Our findings indicate some correlation between ALSPAC symptom and severity reports, and the presence and number of AD-related EHRs. Between individuals with different ALSPAC subtypes, including the Unaffected subtype, there was however considerable overlap concerning their AD-related EHRs, not only making it difficult to classify individuals ALSPAC subtypes using EHRs, but also suggesting that the two data sources often do not agree on whether an individual has AD or not.

Abstract

BACKGROUND Subtypes of atopic dermatitis (AD) have been derived from the Avon Longitudinal Study of Parents and Children (ALSPAC) based on presence and severity of symptoms reported in questionnaires (Severe–Frequent, Moderate–Frequent, Moderate–Declining, Mild–Intermittent, Unaffected/Rare). Good agreement between ALSPAC and linked electronic health records (EHRs) would increase trust in the clinical validity of these subtypes and allow inferring subtypes from EHRs alone, which would enable their study in large primary care databases.

OBJECTIVES 1. Explore if presence and number of AD records in EHRs agrees with AD symptom and severity reports from ALSPAC; 2. Explore if EHRs agree with ALSPAC-derived AD subtypes; 3. Construct models to classify ALSPAC-derived AD subtype using EHRs.

METHODS We used data from the ALSPAC prospective cohort study from 11 timepoints until age 14 years (1991 – 2008), linked to local general practice EHRs. We assessed how far ALSPAC questionnaire responses and derived subtypes agreed with AD as established in EHRs using different AD definitions (e.g., diagnosis and/or prescription) and other AD-related records. We classified AD subtypes using EHRs, fitting multinomial logistic regression models tuning hyperparameters and evaluating performance in the testing set (ROC AUC, accuracy, sensitivity, and specificity).

RESULTS 8,828 individuals out of a total 13,898 had both been assigned an AD subtype and had linked EHRs. The number of AD-related codes in EHRs generally increased with severity of AD subtype, however not all with the Severe-Frequent subtypes had AD in EHRs, and many with the Unaffected/Rare subtype did have AD in EHRs. When predicting ALSPAC AD subtype using EHRs, the best tuned model had ROC AUC of 0.65, sensitivity of 0.29 and specificity of 0.83 (both macro averaged); when different sets of predictors were used, individuals with missing EHR coverage excluded, and subtypes combined, sensitivity was not considerably improved.

CONCLUSIONS ALSPAC and EHRs disagreed not just on AD subtypes, but also on whether children had AD or not. For AD studies, there is potential benefit in combining different data sources for triangulation, however, researchers should be aware that individuals considered as having AD in one source may not be considered as having AD in another.

Body

Introduction

Atopic dermatitis (AD) is a common itchy skin disease with a high global burden in morbidity and health-care costs.(1) Four well defined and recognisable subtypes (or phenotypes) of AD severity trajectories have been derived in the Avon Longitudinal Study of Parents and Children (ALSPAC) with latent class analysis using information on AD

symptom presence and severity from questionnaires at 11 ages between 6 and 166 months (13.8 years): Severe–Frequent (n = 230; 3.9% [of the development cohort]), Moderate–Frequent (n = 408; 6.9%), Moderate–Declining (n = 676; 11%), Mild–Intermittent (n = 684; 12%), and Unaffected/Rare (n = 3929; 66%).(2)

Observing, in the same people, AD-related electronic health records (EHRs) that indicate similar timing and severity of AD compared to what was seen in ALSPAC could increase trust in the clinical validity of measures from both data sources. E.g., if a parent had reported a severe rash in ALSPAC and there are AD-related records from the general practitioner (GP) diagnosing AD and prescribing an AD treatment in the same year, we can more easily trust that the child truly had severe symptoms of AD that year. Previous studies have however shown that longitudinal cohorts (like ALSPAC) don't always agree with EHRs. (3,4)

Besides assessing agreement, linkage between prospective cohorts such as ALSPAC and EHRs can potentially be used to enhance one data source using information from the other. If, using linkage, we could establish ways to determine children's AD severity trajectories using EHRs alone, we could capitalise on the advantages of EHRs such as larger sample sizes compared to prospectively collected cohorts like ALSPAC. Current studies on AD in EHRs usually define AD as a single yes/no variable,(5) where individuals with different subtypes, are grouped together, which may result in inadequately broad recommendations or risk assessments. For example, development of a food allergy is a common comorbidity of AD, but the risk of this may vary depending on the AD subtype.

Here, we first explored agreement concerning AD between EHRs and ALSPAC cohort symptom and severity reports, then ALSPAC subtypes, and then developed and internally validated prediction models, with ALSPAC-derived AD subtypes as the outcome, to classify AD subtype using linked EHRs.

Methods

Participants & Data sources

ALSPAC originally enrolled 14,541 pregnant women living in Avon, UK with expected dates of delivery between 1 April 1991 and 31 December 1992 of which there were 14,062 live births and 13,988 children who were alive at 1 year of age, 96% of white ethnicity (see study website for details, data dictionary and variable search tool (6–8)). We had access to data of 13,898 children in the core phase of ALSPAC, of which we included individuals with both information on AD subtype and linked EHR data.

Via postal campaign, ALSPAC formally sought to re-enrol study participants upon reaching adulthood, simultaneously seeking opt-out permission for linkage with EHRs; after which linkage to anonymised local GP data (EHRs) was carried out for nearly 12,000 participants. For some participants linkage could only be established for parts of the study period, e.g., if participants moved out of the area or to another practice without the EMIS patient record system. (for details see "Linkage to GP records" in the supplement from Cornish et al.(9)). For our study we extracted records from EHRs, using Read (version 2) codes and

dictionary of medicines and devices (dm+d) product codes, that were present in any of the prespecified codelists (eTables 1-3).(10)

Variables from ALSPAC

ALSPAC questionnaire responses

Variables from ALSPAC questionnaire responses at ages 6, 18, 30, 42, 57, 69, 81, 103, 128, 140, and 166 months included presence of AD symptoms (questions on flexural rash, e.g., "child had rash in joints & creases in the past year"), and severity of these AD symptoms (e.g., "Severity of child's itchy dry, skin rash" with answers "no problem", "mild", "quite bad", or "very bad") (eTable 4).

In secondary analyses, we defined parent-reported doctor's AD/asthma diagnosis using the response to the question in ALSPAC if a doctor had ever diagnosed asthma or eczema by 166 months ("Has a doctor ever actually said that he/she has asthma or eczema?").

ALSPAC subtypes

We used the subtypes derived from ALSPAC, from children in both the development and validation cohorts. In sensitivity analyses we combined categories of the original subtypes.

Variables from EHRs

Timepoint-specific variables indicating AD

For each of the 11 timepoints in ALSPAC, using data from the 12 months prior to the respective timepoint, we assessed if an individual had an AD diagnosis, either an AD diagnosis or treatment (emollients, oral corticosteroids, systemic immunosuppressants, topical calcineurin inhibitors, or topical corticosteroids), or both an AD diagnosis and a treatment in EHRs.

Variables derived from the entire follow-up period

From EHRs, we extracted information on allergic rhinitis, asthma related records, asthma diagnosis, AD, more definite AD (only codes M11z., M11.., M111., M114.), AD-related infections, eosinophilic oesophagitis, folliculitis, food allergy, poor sleep, phototherapy, urticaria, and a range of medications used for allergic conditions (adrenaline pens, antibiotics, antihistamines, asthma inhalers, emollients, insomnia drugs, oral corticosteroids, systemic immunosuppressants, topical antibiotics, topical calcineurin inhibitors, mild/moderate/potent/very portent topical corticosteroids) (for most common codes from each codelist see eTable 5). From these data, we created different sets predictor sets. For the main analysis we used binary variables for each year describing if an AD diagnosis, diagnosis or treatment, or diagnosis and treatment were present (for other predictor sets see Table 1).

Statistical analysis

We calculated summary statistics for characteristics of the cohort, including AD subtype, sex, social class, and parental AD and asthma, by EHR linkage availability, and calculated mean and median coverage of the study period in EHRs.

At each timepoint, and across all timepoints, we calculated sensitivity and specificity of AD symptom presence comparing EHRs to ALSPAC questionnaire response as the reference standard. We assessed the presence and frequency of AD-related EHRs by ALSPAC AD subtype and assessed intersections (with UpSet plots) of children who had an ALSPAC subtype consistent with having AD (any except Unaffected/Rare) and children who had an AD diagnosis in EHRs. In secondary analyses, we assessed intersections of children with parent-reported doctor's AD diagnosis and children who had AD in EHRs; and as a comparison, parent-reported doctor's asthma diagnosis and asthma in EHRs.

Using EHR data up to age 14 years of age, we classified the AD subtype using multinomial logistic regression methods.(11–13) We split data into 3/4 training and 1/4 testing data. We normalised numeric data to have a standard deviation of one and a mean of zero. We created dummy variables from categorical variables (i.e., converted nominal data into numeric binary model terms). We fitted multinomial logistic regression, and tuned the "penalty" and "mixture" hyperparameters (a mixture of 1 specifies a pure lasso model, a mixture of 0 specifies a ridge regression model, and a mixture between 0 and 1 specifies an elastic net model, interpolating lasso and ridge).(14) We fitted the final model (with the best ROC AUC) to the training set and evaluated the test set. We estimated out-of-sample accuracy and ROC AUC for each level. We calculated macro averaged sensitivity and specificity. We plotted a mosaic plot of the confusion matrix to compare the ALSPAC-derived AD subtype ("truth") to the AD subtype classified using EHRs ("prediction"). We plotted variable importance to visualise which variables were relatively influential in predicting the outcome. We used different sets of variables individually and in combination as predictors in models (Table 1). We used the TRIPOD reporting guideline (Appendix: TRIPOD checklist).

Results

Descriptive statistics and linkage

Of **13,898** individuals in the source data, **11,745** (from both the development and validation cohorts) had been assigned an AD subtype using parent-reported data (including those with unaffected/rare subtype) and had not withdrawn consent for participation. Of those, **8,830** also had linked GP data; these individuals formed the main study cohort, of which 50% were female and 50% male. The median EHR coverage of the study period (0-14 years) was 99% (interquartile range 70-99%). **90%** of the main study cohort had at least one record from any of the prespecified codelists.

Before splitting data into training and testing sets, there were **356** with Severe–Frequent, **716** with Moderate–Frequent, **1125** with Moderate–Declining, **872** with Mild–Intermittent, **5,759** with Unaffected/Rare.

Those with and without linked primary care data were similar in terms of sex, social class and parental asthma and AD status (Table 2).(2)

Agreement between ALSPAC AD parental reports and EHRs

By age 14, the number of children who reported AD at least once/twice was **5,138** (**58%** of the cohort)/ **3,383** (**38%** of the cohort), of which **36**%/**44%** also ever had AD, **59**%/**69%** ever had AD or an AD treatment, and **28**%/**35%** ever had AD and an AD treatment in EHRs, respectively (eTable 6).

At timepoints where AD symptoms in ALSPAC were reported, the percentage who also had a record for AD in EHRs up to one year before the timepoint ranged from **10%** (minimum) at 6 months to **21%** (maximum) at 166 months; the percentage who had AD or an AD treatment ranged from **16%** at 6 months, to **41%** at 128 months (eFigure1a). When a "very bad" rash was reported, the percentage ranged from **23%** at 6 months to **49%** at 140 months for AD, and **35%** at 6 months to **86%** at 128 months for AD or an AD treatment (eFigure1b).

From secondary analyses, **4,222** responded to the question about previous doctor's AD or asthma diagnoses. Of **2,044** with AD in either ALSPAC or EHRs, **676 (33%)** had AD in both ALSPAC and EHRs. When a more definite codelist for AD was used in EHRs, of **1,678** with AD in either ALSPAC or EHRs, **676 (25%)** had AD in both ALSPAC and EHRs. Of **1,517** with asthma in either ALSPAC or EHRs, **953 (63%)** had asthma in both ALSPAC and EHRs (eFigures 2,3,4).

Agreement between ALSPAC AD subtypes and EHRs

Of the study cohort (n=8830), **3069 (35%)** had a subtype other than Unaffected/Rare, **2816 (32%)** ever had AD in EHRs, and **1532 (17% of the study cohort; 35% of the 4,353 that had AD in either source)** had both (Figure 1) (for sensitivity analysis with more definite AD codelist in EHRs see eFigure 5).

The mean number of AD-related records in EHRs, and the proportion who had a given record, generally increased with more severe and frequent AD subtypes, e.g. individuals with the Unaffected-Rare, Mild-Intermittent, Moderate-Declining, Moderate-Frequent, and Severe-Frequent had on average (mean) **0.6, 1.5, 1.5, 3.5 and 7.6** records for AD; **22%, 42%, 41%, 60% and 76%** ever had a record for AD, respectively (for all variables, see Figure 2; for proportions with AD/AD and AD treatment/AD or AD treatment see eTable 7).

From visual inspection of density plots, there was considerably more overlap between patterns in EHRs by subtype (how often and when records for AD and topical corticosteroids occur) as compared to symptom and severity reports from ALSPAC by subtype (how often, how severe and when did AD symptoms occur) (eFigure 6).

Classifying ALSPAC AD subtypes using EHRs

There were **6,622** observations used in the final model with predictor set 1 (AD diagnosis and/or treatment codes for each year). The tuned model hyperparameters were 0 for mixture (i.e. Ridge regression), and $1x\ 10^{-10}$ for penalty. Fitting the tuned model to the

training data and evaluating the testing data showed ROC AUC of **0.65** and model accuracy of **0.68**. Sensitivity was **0.29** and specificity was **0.83** (both macro averaged). Individual ROC was best for the Severe-Frequent subtype, and worst for the moderate-declining and mild-intermittent subtypes (eFigure 7). The model classified more people as having the Unaffected/Rare subtype than actually had the Unaffected/Rare subtype (Figure 3; eTable 8).

Predictive performance was similar with different predictor sets, and in sensitivity analyses excluding observations from individuals 1. that did not have GP data available before age 2 and up to at least age 13, 2. where responses were not recorded for all ALSPAC questionnaires, 3. with the Unaffected/Rare subtype. Performance when outcome variables with fewer subtype categories were used was somewhat improved (e.g. ROC AUC of 0.72 when moderate/frequent, moderate/declining and mild/intermittent were combined) (eTable 9).

When using ever/never or count variables to classify AD subtypes, both resulting in more parsimonious Lasso regression models with the best ROC, ever having records for emollients, moderate topical corticosteroids and eczema, and for count variables the number of potent topical corticosteroids, were most important in predicting the outcome (eFigure 8).

Discussion

Our main findings were firstly, that individuals were more likely to have AD recorded in EHRs if their parents had reported more frequent or more severe AD symptoms in ALSPAC. Secondly, while those with more severe subtypes had greater prevalence and more records for AD-related variables in EHRs, there was considerable overlap between patterns in EHRs by subtype and there was disagreement between having a subtype consistent with having AD and having AD in EHRs. This disagreement and overlap explain why, thirdly, using data from EHRs to classify ALSPAC derived subtypes resulted in poor sensitivity predictions.

Both ALSPAC and EHRs may have wrongly classified AD and AD severity trajectories. Parental reports in ALSPAC may have been subject to measurement error and subject to differential parental perception of disease severity, which may have resulted in individuals' assigned ALSPAC subtype not corresponding to their actual severity trajectory. EHRs may not have adequately captured AD, e.g., EHRs could both miss AD diagnoses (e.g. less severe cases of AD not consulting the GP, GPs not re-recording diagnoses that had already been recorded previously or diagnoses from specialist care not being recorded in primary care), but also misclassify individuals that do not have AD as having AD (e.g. if GPs use diagnosis codes for AD to record other non-AD rashes; however there was still considerable disagreement when AD in EHRs was defined using a more definite codelist).

With prevalence estimates ranging from 10-30% in other studies,(15–18) having one of the subtypes consistent with having AD (35%), and ever having a record for AD in EHRs (32%) may capture slightly more individuals than actually have AD. However, we can also not conclude that the 17% that had AD in both sources, represent a cohort who truly have AD,

since this cohort would exclude some individuals where EHRs clearly indicate AD or whose parents frequently reported very bad AD symptoms in ALSPAC.

Other results were more consistent with clinical expectations. For example, since not every child with AD symptoms should be considered as having AD, only about one third of individuals that report AD symptoms once in ALSPAC had an AD diagnosis code in EHRs; the proportion increased for those where rashes were reported at least twice. At timepoints where a "very bad" rash was reported, up to 86% at 128 months had records for an AD diagnosis or treatment in EHRs, suggesting that most did receive care. There was, however, variation by age, with the smallest proportion of EHR diagnoses and treatments in those who reported rashes at the earliest time-points, even though this may be the period of highest actual prevalence,(15,16,18) possibly due to different approaches to prescribing or different diagnostic codes used for infants than for older children.

From secondary analyses, agreement (diagnosis in both sources) between parent-reported doctor's diagnoses from ALSPAC and records in EHRs, was much better, albeit not perfect, for asthma (63%) as compared to AD (33%), suggesting that the disagreement found in this study may be a problem particular to AD. Reasons for disagreement, that may also explain the remaining disagreement for asthma, may include parents not recalling that their child had been diagnosed, or the questionnaire may have led parents to only report more recent diagnoses, since the question if "a doctor has ever actually said [the child] has eczema" followed up a form recording illnesses in the past 12 months.

Context to previous studies

We did not find any other studies where classifying disease subtypes in ALSPAC was attempted using EHRs. Primary care EHRs linked to ALSPAC have previously been used to assess and predict ALSPAC derived common mental health disorder diagnoses, where EHRs generally underestimated the prevalence of mental health conditions compared to ALSPAC.(19) Another study in ALSPAC and linked primary care data, investigating the performance of parent-reported responses in identifying physician-confirmed asthma in EHRs showed high agreement (88.5% sensitivity, 95.7% specificity).(20)

Previous studies have used latent class analysis to identify childhood AD subtypes in birth cohort studies,(21,22) including ALSPAC,(23) without incorporating reports of symptom severity. Future research may evaluate if subtypes based on trajectory of symptom presence but not severity, may be better replicated in EHR data.

Limitations

Not all individuals had EHR coverage for the whole study period, i.e., some AD-related codes may have been missed in EHRs, however, predictive performance was not improved when individuals with less complete EHR coverage were excluded. Access to EHRs was also restricted to events with a code in one of the pre-specified codelists and we may have missed codes that could have helped predictive performance.

While multinomial logistic regression has been used for multi-class classification in previous studies with similar aims,(19) utilising other machine learning methods may have

yielded better predictive performance. While Lasso regression allows shrinking of coefficients to 0, i.e., dropping non-predictive variables from the model, Ridge or elastic net have advantages if covariates are highly correlated,(24) which was likely the case in our setting, which is why we tuned the mixture parameter.

Conclusions

While AD subtypes correlated with several AD-related variables in EHRs, there was considerable overlap in EHRs on an individual level, and even disagreement between data sources on whether children had AD or not, precluding sensitive classification using EHRs. While using multiple data sources to triangulate may help more accurately determine who has AD, we cannot conclude from this study alone that the intersection of AD in ALSPAC and EHRs represents true AD cases. Further research validating AD-related study information is needed, and when interpreting research on AD in either ALSPAC or UK primary care EHRs, it needs to be kept in mind that people considered as having AD in one source may not be considered as having AD in another.

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. The Lancet. 2020 Aug;396(10247):345–60.

2. Mulick A r., Mansfield K e., Silverwood R j., Budu-Aggrey A, Roberts A, Custovic A, et al. Four childhood atopic dermatitis subtypes identified from trajectory and severity of disease and internally validated in a large UK birth cohort. Br J Dermatol. 2021;185(3):526–36.

3. Matthewman J, Mansfield KE, Hayes JF, Adesanya EI, Smith CH, Roberts A, et al. Anxiety and Depression in People with Eczema or Psoriasis: A Comparison of Associations in UK Biobank and Linked Primary Care Data. Clin Epidemiol. 2023 Dec 31;15:891–9.

4. Knuppel A, Boyd A, Macleod J, Chaturvedi N, Williams DM. The long COVID evidence gap: comparing self-reporting and clinical coding of long COVID using longitudinal study data linked to healthcare records [Internet]. medRxiv; 2023 [cited 2023 Aug 25]. p. 2023.02.10.23285717. Available from: https://www.medrxiv.org/content/10.1101/2023.02.10.23285717v1

5. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al. AAD Guidelines: awareness of comorbidities associated with atopic dermatitis in adults. J Am Acad Dermatol. 2022 Jan;S0190962222000809.

6. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2013 Feb;42(1):111–27.

7. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013 Feb;42(1):97–110.

8. University of Bristol. Avon Longitudinal Study of Parents and Children. University of Bristol; [cited 2022 Nov 20]. Explore data and samples. Available from: https://www.bristol.ac.uk/alspac/researchers/our-data/

9. Cornish RP, Macleod J, Boyd A, Tilling K. Factors associated with participation over time in the Avon Longitudinal Study of Parents and Children: a study using linked education and primary care data. Int J Epidemiol. 2021 Feb 1;50(1):293–302.

10. Williams R, Brown B, Kontopantelis E, van Staa T, Peek N. Term sets: A transparent and reproducible representation of clinical code sets. Olier I, editor. PLOS ONE. 2019 Feb 14;14(2):e0212291.

11. Kuhn M, Vaughan D, Posit Software, PBC. parsnip Reference. [cited 2023 Sep 1]. Multinomial regression via glmnet — details_multinom_reg_glmnet. Available from: https://parsnip.tidymodels.org/reference/details_multinom_reg_glmnet.html

12. Kuhn M, Johnson K. Applied predictive modeling. Corrected at 5th printing. New York: Springer; 2016. 600 p.

13. Hastie T, Tibshirani R, Wainwright M. Statistical Learning with Sparsity: The Lasso and Generalizations [Internet]. 0 ed. Chapman and Hall/CRC; 2015 [cited 2023 Sep 1]. Available from: https://www.taylorfrancis.com/books/9781498712170

14. Multinomial regression — multinom_reg [Internet]. [cited 2023 Jun 6]. Available from: https://parsnip.tidymodels.org/reference/multinom_reg.html

15. National Institute for Health and Care Excellence. Clinical Knowledge Summaries. 2023 [cited 2023 Aug 29]. Prevalence | Background information | Eczema - atopic | CKS | NICE. Available from: https://cks.nice.org.uk/topics/eczema-atopic/background-information/prevalence/

16. Nutten S. Atopic Dermatitis: Global Epidemiology and Risk Factors. Ann Nutr Metab. 2015 Apr 24;66(Suppl. 1):8–16.

17. Bylund S, Kobyletzki L, Svalstedt M, Svensson A. Prevalence and Incidence of Atopic Dermatitis: A Systematic Review. Acta Derm Venereol. 2020;100(12):adv00160.

18. Abuabara K, Magyari A, McCulloch CE, Linos E, Margolis DJ, Langan SM. Prevalence of Atopic Eczema Among Patients Seen in Primary Care: Data From The Health Improvement Network. Ann Intern Med. 2019 Mar 5;170(5):354–6.

19. Smith D, Willan K, Prady SL, Dickerson J, Santorelli G, Tilling K, et al. Assessing and predicting adolescent and early adulthood common mental disorders using electronic primary care data: analysis of a prospective cohort study (ALSPAC) in Southwest England. BMJ Open. 2021 Oct 18;11(10):e053624.

20. Cornish RP, Henderson J, Boyd AW, Granell R, Van Staa T, Macleod J. Validating childhood asthma in an epidemiological study using linked electronic patient records. BMJ Open. 2014 Apr 23;4(4):e005345.

21. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrländer C, et al. Phenotypes of Atopic Dermatitis Depending on the Timing of Onset and Progression in Childhood. JAMA Pediatr. 2017 Jul 1;171(7):655–62.

22. Hu C, Duijts L, Erler NS, Elbert NJ, Piketty C, Bourdès V, et al. Most associations of early-life environmental exposures and genetic risk factors poorly differentiate between eczema phenotypes: the Generation R Study. Br J Dermatol. 2019 Dec 1;181(6):1190–7.

23. Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. J Allergy Clin Immunol. 2018 Mar 1;141(3):964–71.

24. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Stat Soc Ser B Stat Methodol. 2005;67(2):301–20.

Figures

Figure 1: Intersection of individuals with a subtype indicating AD in ALSPAC and with AD in EHRs

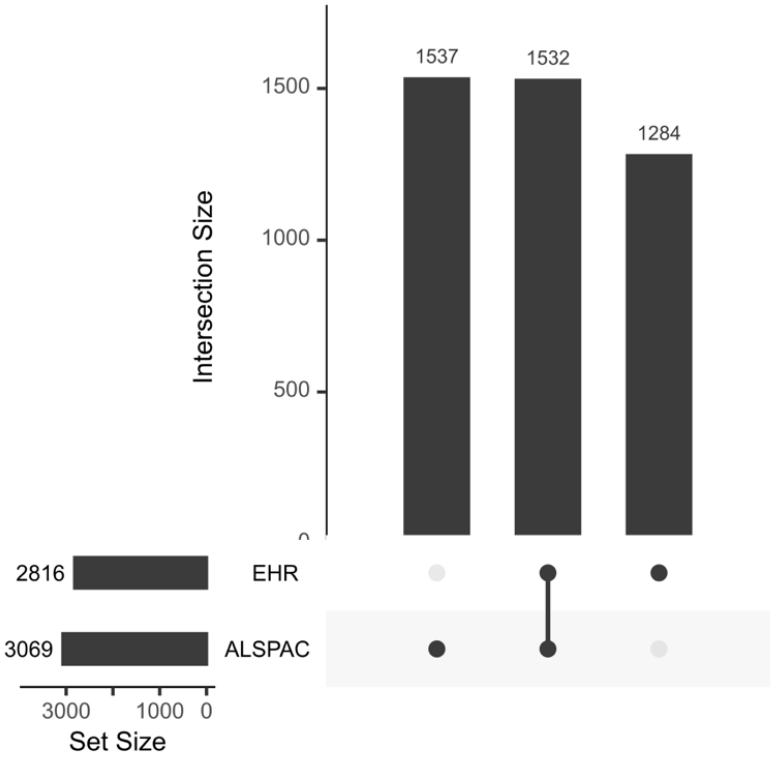


Figure Legend: EHR=Individuals that have at least one diagnosis code for AD at any time before 166 months (14 years); ALSPAC=Individuals, who were assigned any of the AD subtypes, except Unaffected/Rare. Explanation of UpSet plot: Of the entire study population (n=8,830), 2,816 (32%) have AD in EHR, 3,069 (35%) have a non-Unaffected subtype in ALSPAC; 1284 have AD in EHR only, 1532 have both a non-Unaffected subtype in ALSPAC and AD in EHR, and 1537 have a non-Unaffected subtype in ALSPAC only.

Figure 2: Records in EHRs by AD subtype

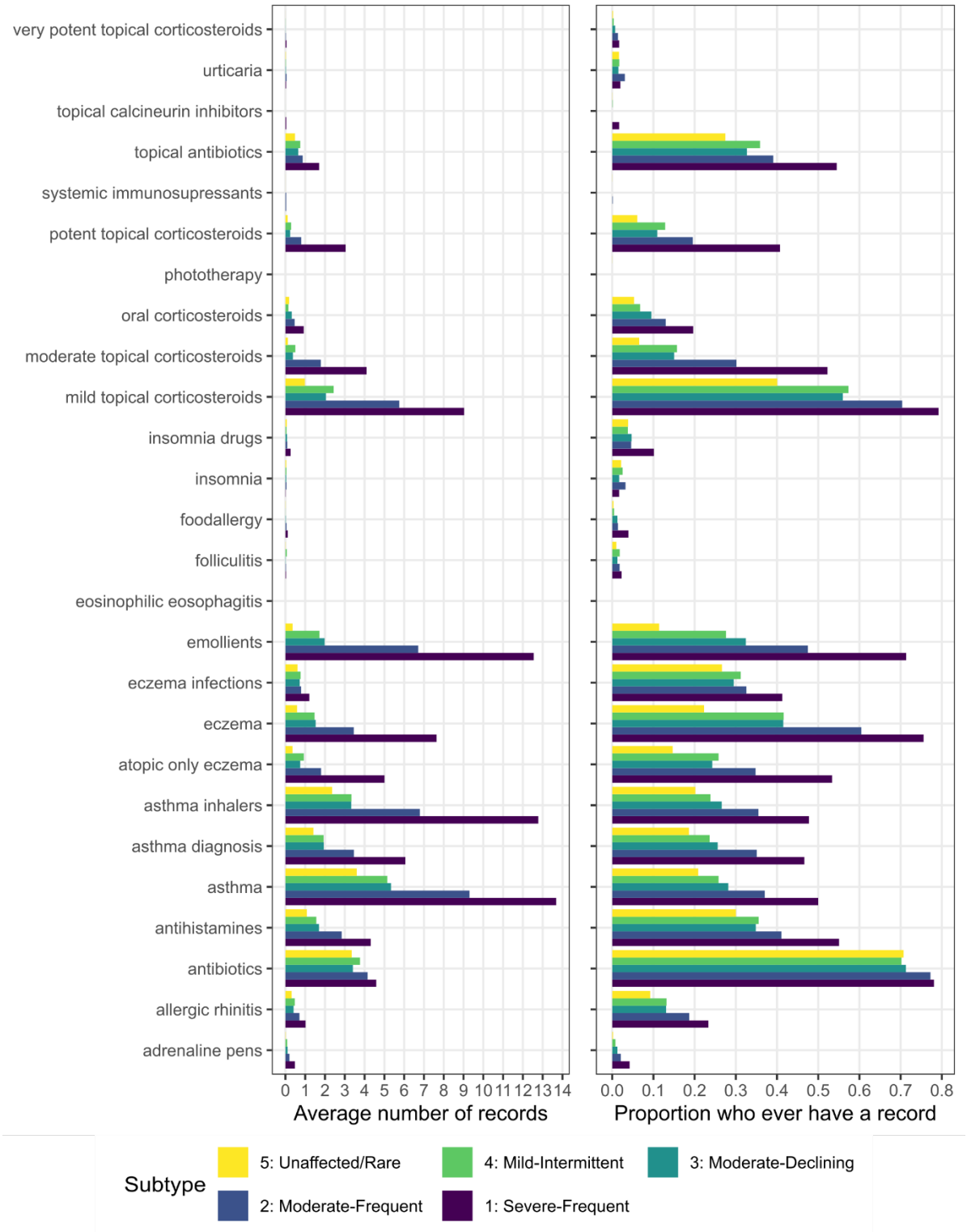


Figure Legend: left: Percent that ever have a record; right: Average (mean) number of codes per person in EHRs by ALSPAC AD subtype
1=Severe-Frequent; 2=Moderate-Frequent; 3=Moderate-Declining; 4=Mild-Intermittent; 5=Unaffected/Rare

Figure 3: Mosaic plot of the confusion matrix

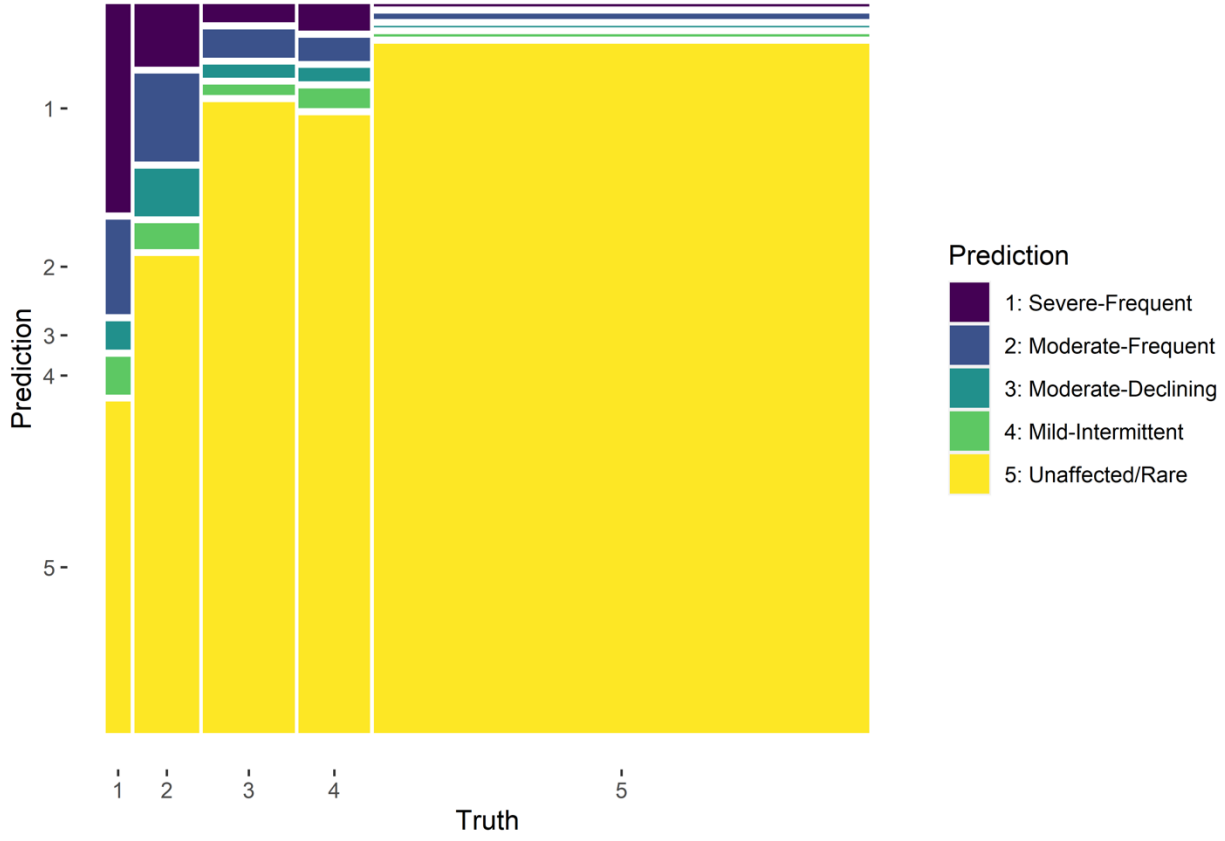


Figure Legend: Mosaic plot showing the predicted (classified) subtypes in rows and coloured, versus the actual subtypes (Truth) in columns. Explanation of plot: Almost 2 thirds had subtype 5 (Unaffected/Rare). Almost all of individuals where the true subtype is 5 (Unaffected/Rare) were correctly classified as subtype 5 (Unaffected/Rare). Only a small proportion of individuals with subtypes 3 (Moderate-Declining) and 4 (Mild-Intermittent) were correctly classified, with most being classified as subtype 5 (Unaffected/Rare). Almost one third of individuals with subtype 1 (Severe-Frequent) were correctly classified, however almost half were classified as having subtype 5 (Unaffected/Rare).

Tables

Table 1: Predictor sets

#	Description	Examples
1	Presence of AD prescription[a] and diagnosis codes in 1-year windows	Did not have AD diagnosis code between age 0 and 1; had AD diagnosis code between age 2 and 3; had AD diagnosis or treatment code between age 5 and 6; had AD treatment code between age 10 and 11
2	Ever/never had code for a given disease/treatment[b]	Had asthma code; never had food allergy code; had potent topical corticosteroid code
3	How often had codes for a given disease/treatment[b]	Had 2 asthma codes; had 0 food allergy codes; had 15 potent topical corticosteroid codes
4	Age of first instance of code for a given disease/treatment[b]	Had first asthma code at age 5; never had a food allergy code; had first potent topical corticosteroid code at age 6
5	Presence of code for a given disease/treatment[b] in 1-year windows	Did not have asthma code between age 0 and 1; had asthma code at age 5; did not have asthma code at age 6; had asthma code at age 7

[a]Prescriptions for AD include phototherapy, emollients, topical calcineurin inhibitors and mild/moderate/potent/very portent topical corticosteroids.

[b]All disease/treatment codes include allergic rhinitis, asthma related codes, asthma diagnosis, AD diagnosis, more definite AD diagnosis, AD related infections, eosinophilic oesophagitis, folliculitis, food allergy, insomnia, phototherapy, urticaria, adrenaline pens, antibiotics, antihistamines, asthma inhalers, emollients, insomnia drugs, oral corticosteroids, systemic immunosuppressants, topical antibiotics, topical calcineurin inhibitors and mild/moderate/potent/very portent topical corticosteroids.

Table 2: Characteristics of individuals with and without linked primary care data

Characteristic	EHRs available (N= 10,859)	EHRs not available (N= 3,945)
Atopic dermatitis subtype		
Severe-Frequent	356 (4.0%)	117 (4.0%)
Moderate-Frequent	716 (8.1%)	200 (6.8%)
Moderate-Declining	1,125 (13%)	327 (11%)
Mild-Intermittent	872 (9.9%)	277 (9.5%)
Unaffected/Rare	5,761 (65%)	1,994 (68.0%)
Missing	2,029	1,035
Sex		
Male	5,437 (50%)	2,126 (54%)
Female	5,422 (50%)	1,819 (46%)
Missing	12	14
Social Class[a]		
I	1,030 (12%)	475 (16%)
II	3,459 (41%)	1,302 (44%)
III(n)	2,272 (27%)	644 (22%)
III(m)	1,171 (14%)	376 (13%)
IV	448 (5.3%)	131 (4.5%)
V	87 (1.0%)	14 (0.5%)
Missing	2,404	1,017
Parental asthma	1,779 (20%)	579 (18%)
Parental AD	2,705 (30%)	885 (28%)
Start age of EHR data	Mean (SD) 2.2 (4.6); Median (IQR) 0.1 (0.1-2.1)	
End age of EHR data	Mean (SD) 22 (8); Median (IQR) 23 (19-30)	
EHR coverage (years)[b]	Mean (SD) 10.9 (5.0); Median (IQR) 13.8 (9.8-13.9)	
EHR coverage (proportion)[b]	Mean (SD) 0.78 (0.36); Median (IQR) 0.99 (0.70-0.99)	

[a]higher social class of either parent, I, professional occupations; II, managerial and technical occupations; III(n), skilled occupations–nonmanual; III(m), skilled occupations–manual; IV, partly skilled occupations; V, unskilled occupations.

[b]Coverage within the study period from 0 to 14 years of age, for those where EHRs were available.

Table 3: Metrics by predictor set used

Predictor Set	ROC AUC[a]	Accuracy	Sensitivity[b]	Specificity[b]
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.65	0.68	0.29	0.83
2: Ever/never had code for a given disease/treatment	0.63	0.66	0.28	0.82
3: How often had code for a given disease/treatment	0.63	0.66	0.25	0.82
4: Age of first occurrence for a given disease/treatment	0.64	0.66	0.27	0.83
5: Presence of code for a given disease/treatment in 1-year windows	0.63	0.65	0.27	0.83
1 + 3	0.68	0.67	0.31	0.83
1+ 3 + 5	0.64	0.67	0.30	0.83

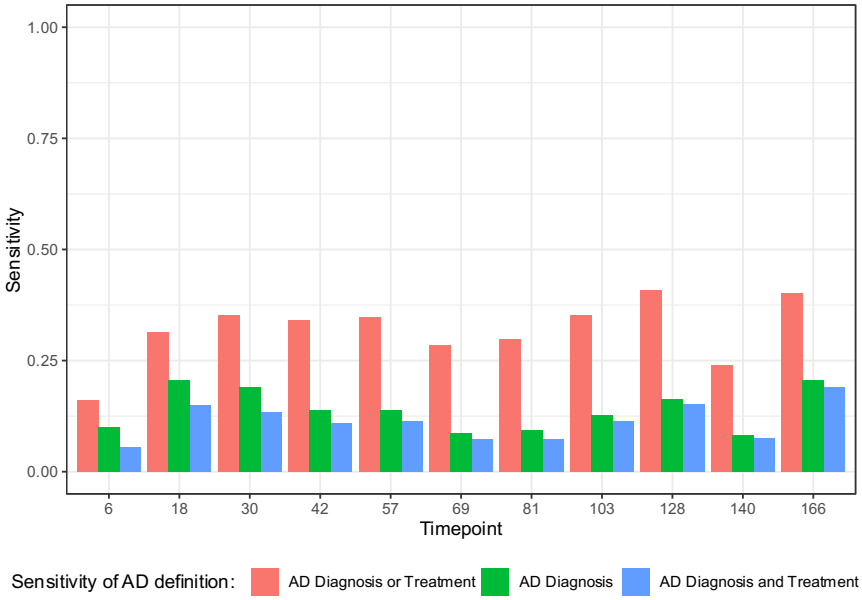
[a]ROC AUC is averaged using the method by Hand, Till (2001).

[b]Sensitivity and specificity are macro averaged.

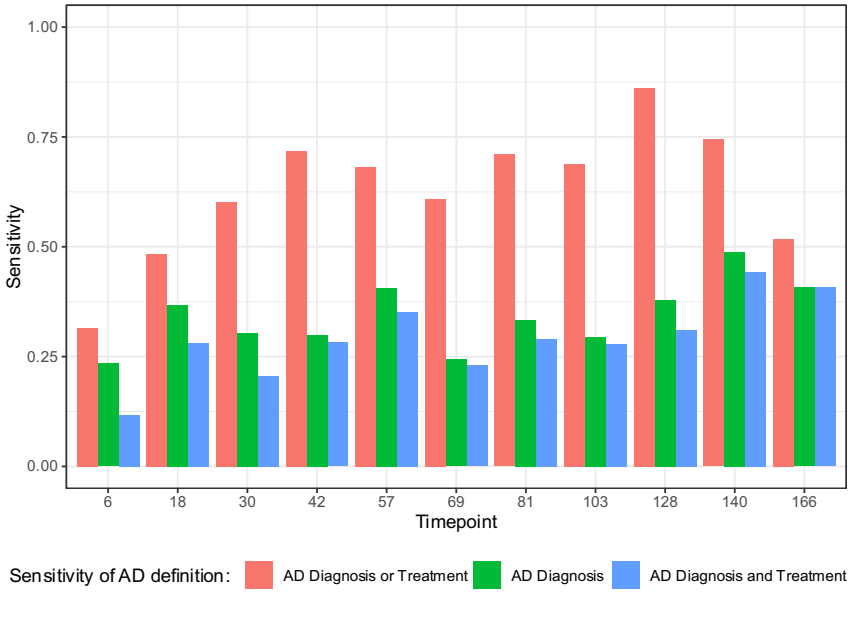
6.3 Submitted appendices

Supplementary for Disagreement concerning atopic dermatitis subtypes between an English prospective cohort (ALSPAC) and linked electronic health records

eFigure 1: Sensitivity at each timepoint



(a)



(b)

Figure Legend: Sensitivity at each timepoint, comparing (a) a positive ALSPAC symptom report, (b) a positive ALSPAC symptom report where a "very bad" rash was reported, as the reference standard to information from EHRs from the past 12 months. E.g. (a) at 30 months, of those who reported flexural dermatitis in ALSPAC, x% had an AD diagnosis, x% had an AD diagnosis or treatment, and x% had an AD diagnosis and treatment in the past year. Specificity, i.e., the proportion of those who didn't report AD symptoms in ALSPAC and also didn't have an AD diagnosis in EHRs was >85% across all timepoints and definitions of AD in EHRs.
Dx_and_rx: AD diagnosis and prescription, Dx_or_rx: AD diagnosis or prescription, dx: AD diagnosis

eFigure 2: UpSet plot showing the intersection of parent-reported doctor's AD diagnosis in ALSPAC and AD in EHRs

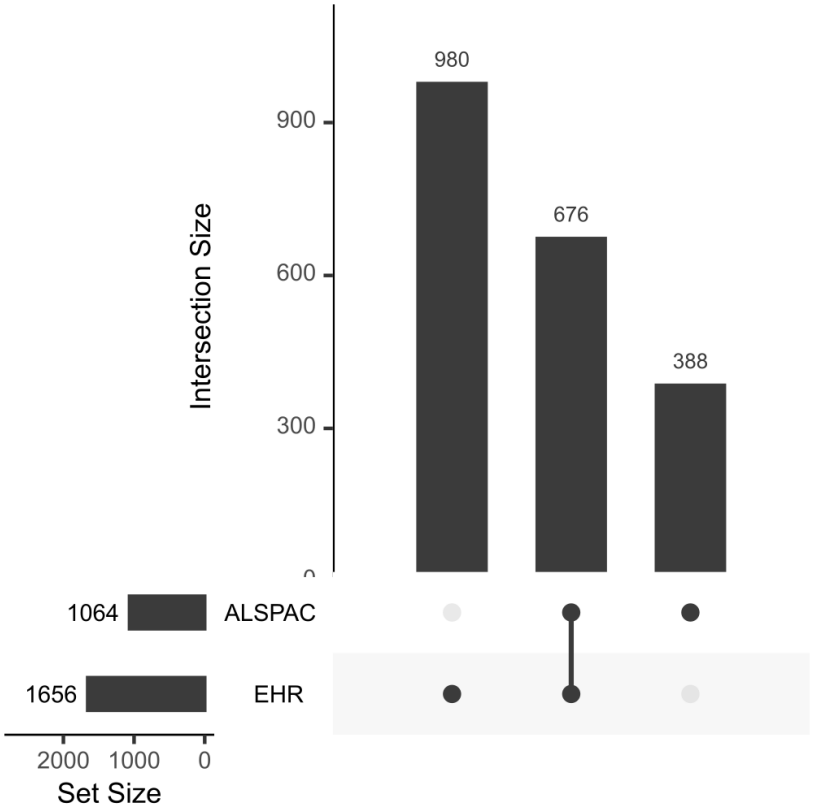


Figure Legend: ALSPAC=Individuals, whose parents or carer responded "Yes, eczema" or "Yes, asthma and eczema" to the question if the child had ever been diagnosed by a doctor with asthma or eczema at 166 months (exact wording of question: "Has a doctor ever actually said that he/she has asthma or eczema?); EHR=Individuals that have at least one record for AD at any time before 166 months (14 years). Both ALSPAC and EHR from are from a total of 4,222 that responded to the question in ALSPAC.

eFigure 3: UpSet plot showing the intersection of parent-reported doctor's AD diagnosis and AD, using a more definite AD codelist, in EHRs

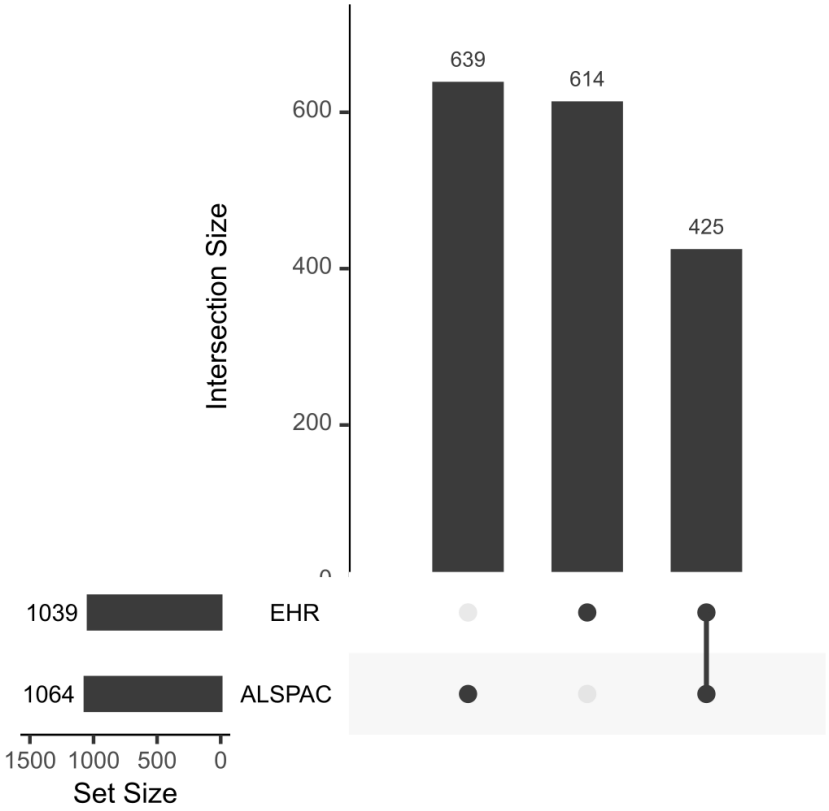


Figure Legend: ALSPAC=Individuals, whose parents or carer responded "Yes, eczema" or "Yes, asthma and eczema" to the question if the child had ever been diagnosed by a doctor with asthma or eczema at 166 months (exact wording of question: "Has a doctor ever actually said that he/she has asthma or eczema?); EHR=Individuals that have at least one record for "M11z. atopic dermatitis/eczema", "M11.. atopic dermatitis and related", "M111. atopic dermatitis nos" or "M114. Allergic (intrinsic) eczema" at any time before 166 months (14 years). Both ALSPAC and EHR from are from a total of 4,222 that responded to the question in ALSPAC.

eFigure 4: UpSet plot showing the intersection of parent-reported doctor's asthma diagnosis in ALSPAC and asthma in EHRs

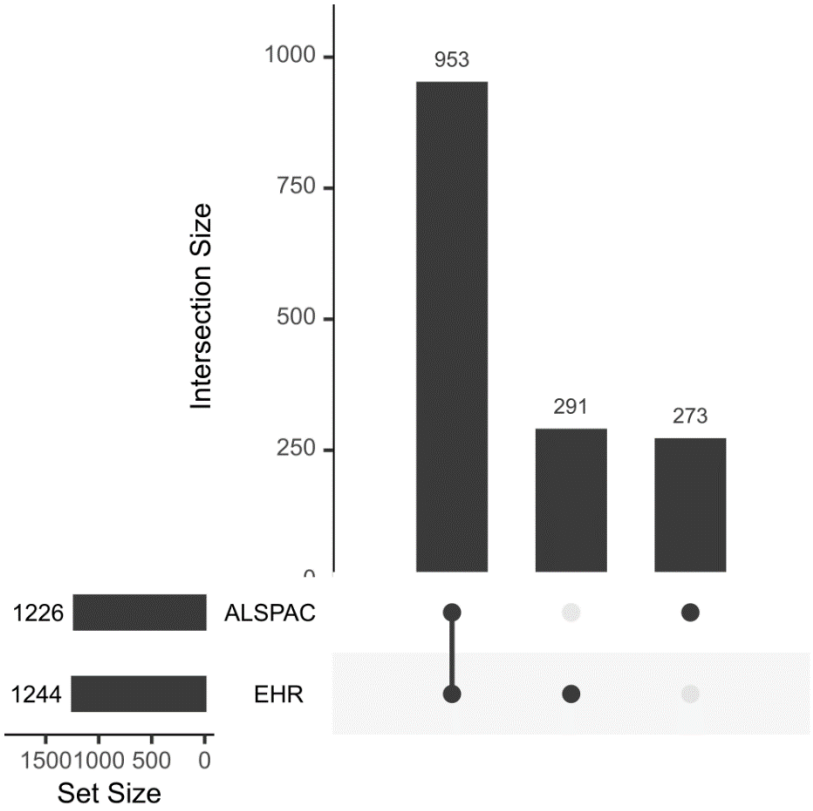


Figure Legend: ALSPAC=Individuals, whose parents or carer responded "Yes, asthma" or "Yes, asthma and eczema" to the question if the child had ever been diagnosed by a doctor with asthma or eczema at 166 months (exact wording of question: "Has a doctor ever actually said that he/she has asthma or eczema?); EHR=Individuals that have at least one record for asthma at any time before 166 months (14 years). Both ALSPAC and EHR from are from a total of 4,222 that responded to the question in ALSPAC.

eFigure 5: UpSet plot showing the intersection having a subtype indicating AD in ALSPAC and having AD in EHRs, using a more definite AD codelist

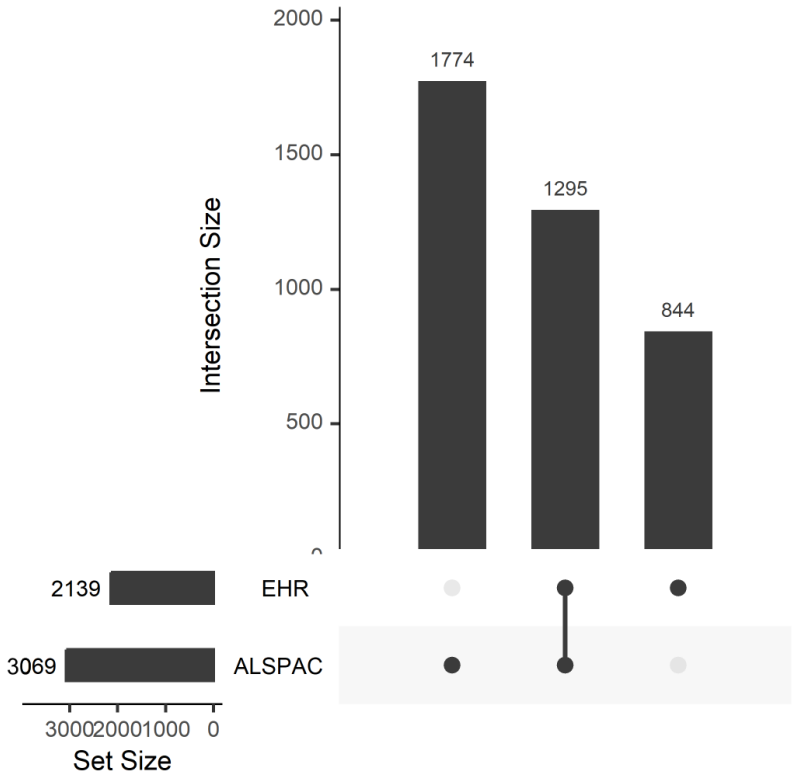
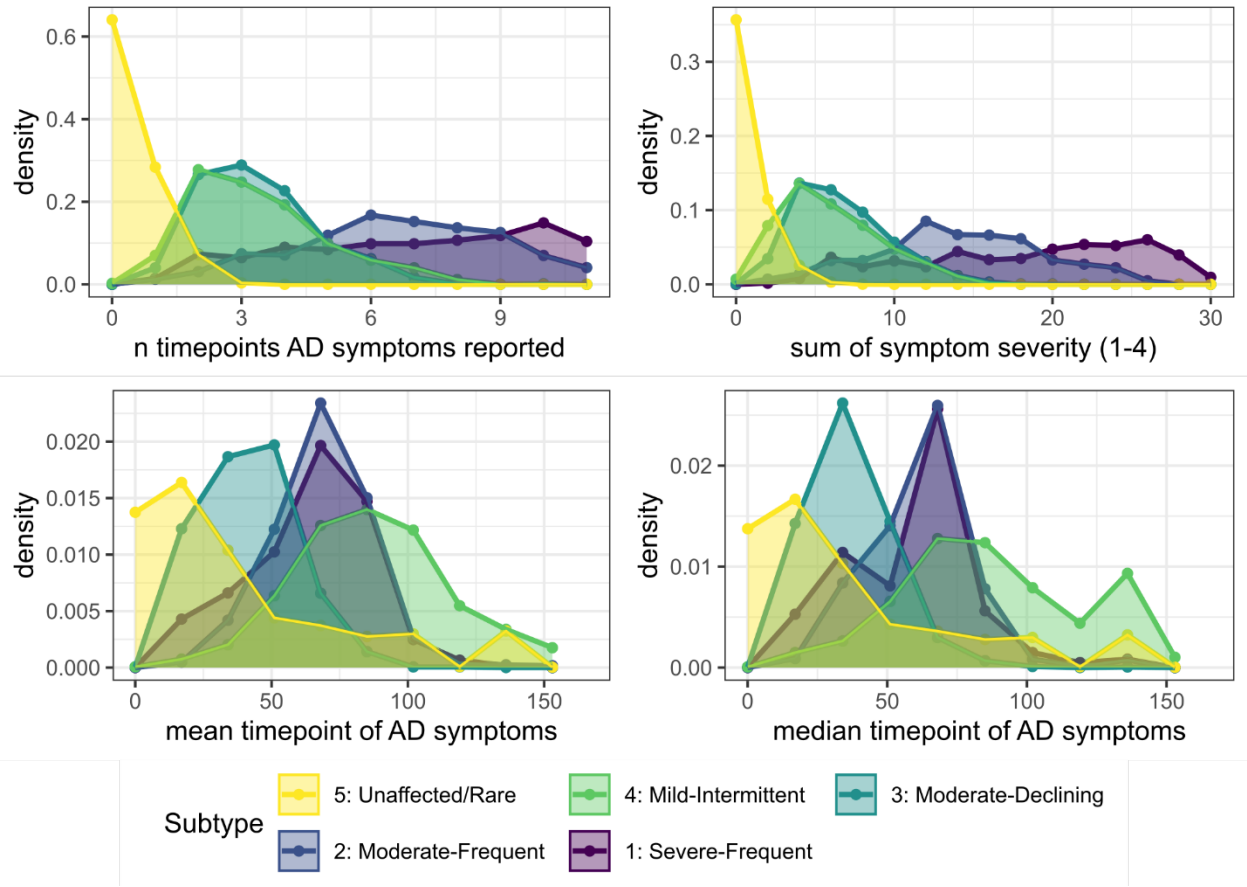
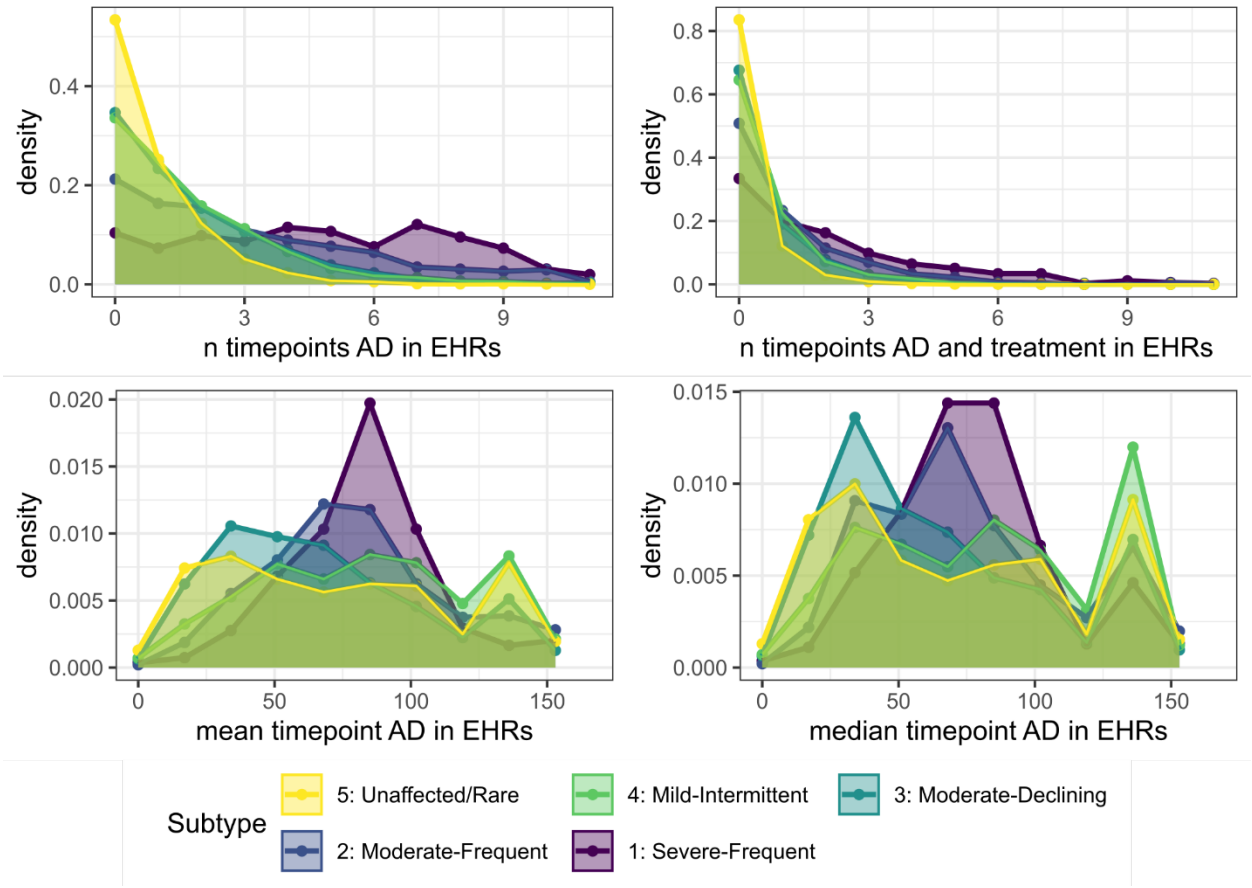


Figure Legend: EHR=Individuals that have at least one record for "M11z. atopic dermatitis/eczema", "M11.. atopic dermatitis and related", "M111. atopic dermatitis nos" or "M114. Allergic (intrinsic) eczema" at any time before 166 months (14 years); ALSPAC=Individuals, whose parents or carer responded "Yes, eczema" or "Yes, asthma and eczema" to the question if the child had ever been diagnosed by a doctor with asthma or eczema at 166 months (exact wording of question: "Has a doctor ever actually said that he/she has asthma or eczema?).

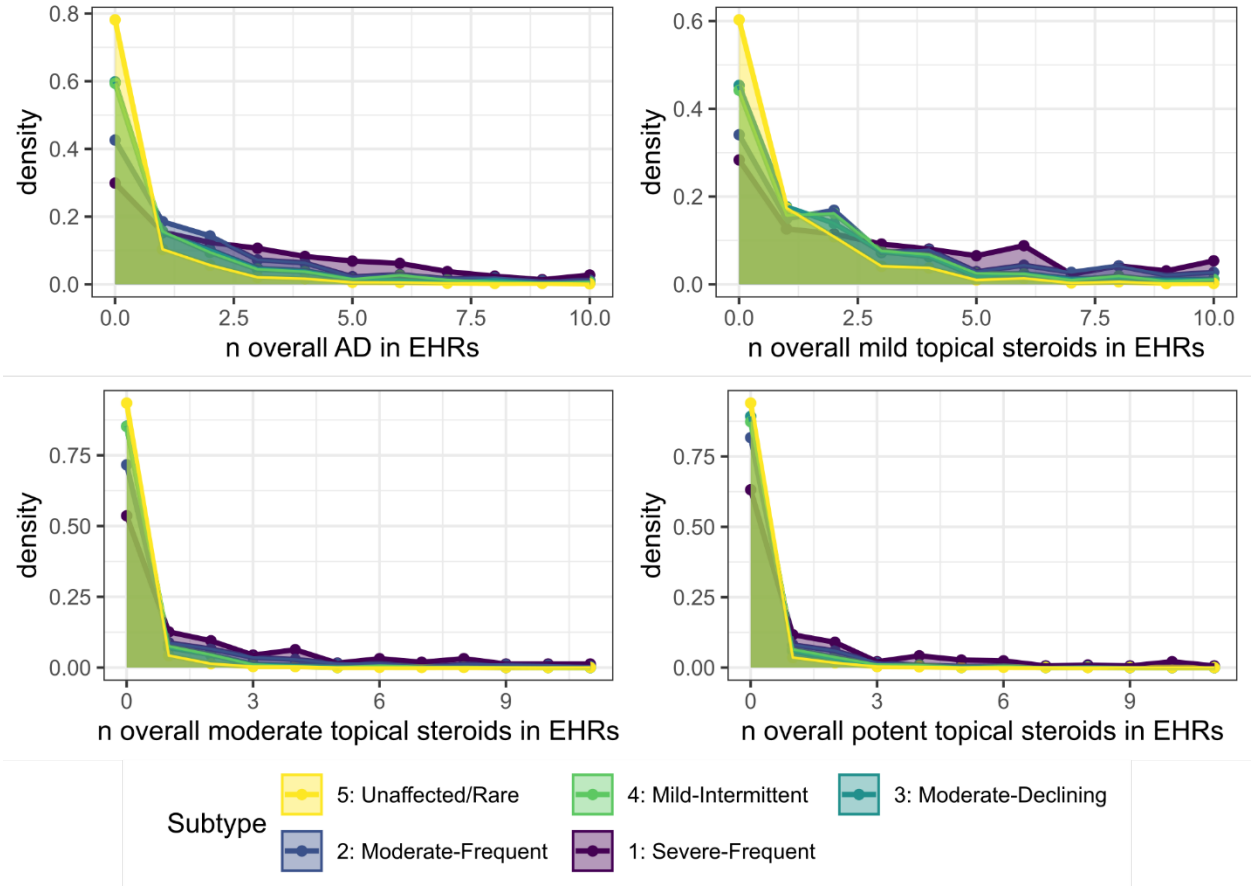
eFigure 6: Density plots



(a) from ALSPAC symptom and severity reports



(b) from time-point specific EHR variables



(c) from overall EHR variables

Figure Legend: Density plots showing how many individuals had a certain number/sum/mean/median for variables from: (a) the original ALSPAC AD symptom and severity reports; (b) timepoint-specific variables in EHRs; (c) overall count variables in EHRs (for (c), x-axis limit set at 10, however individuals could have more than 10 records).

eFigure 7: Receiver operating characteristic (ROC) curves

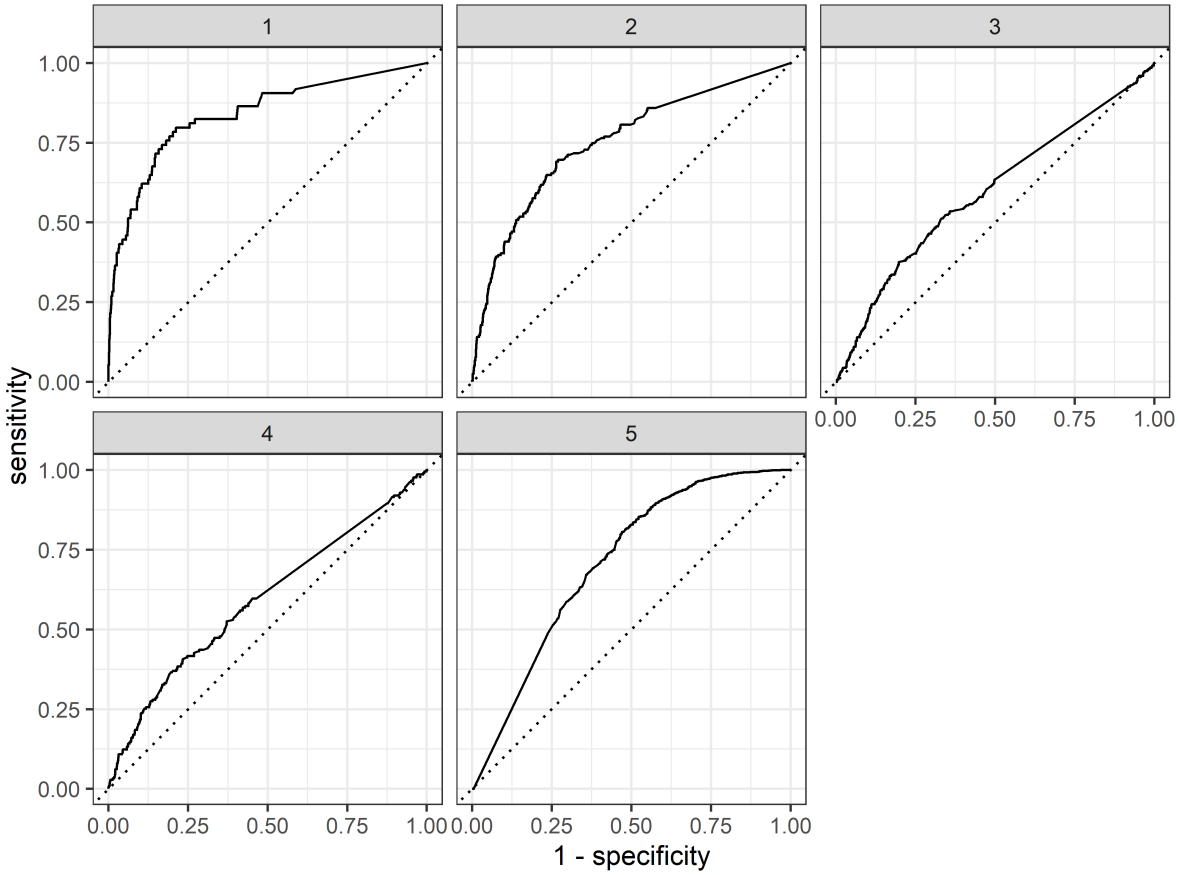
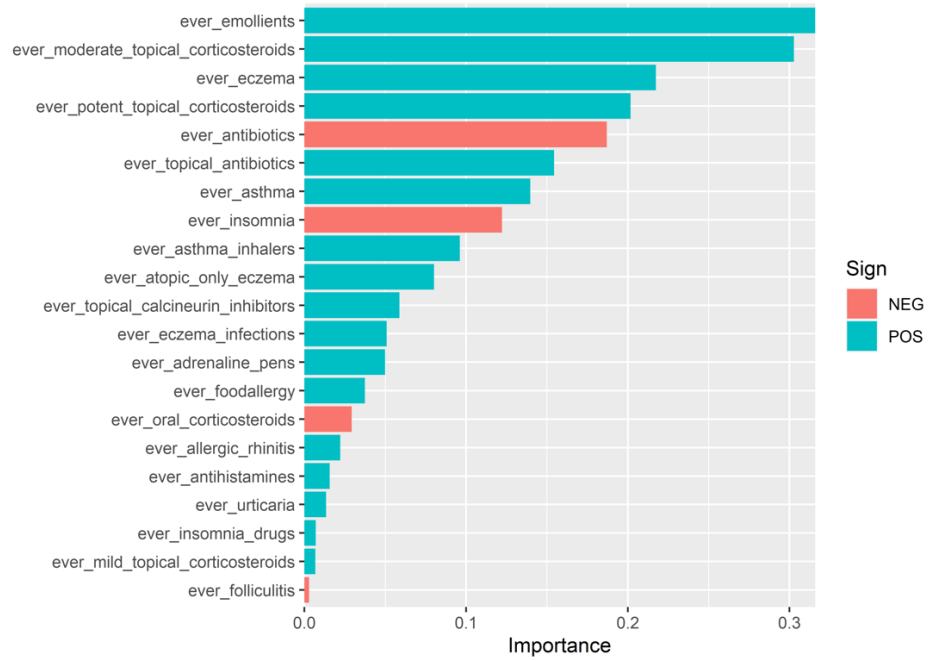
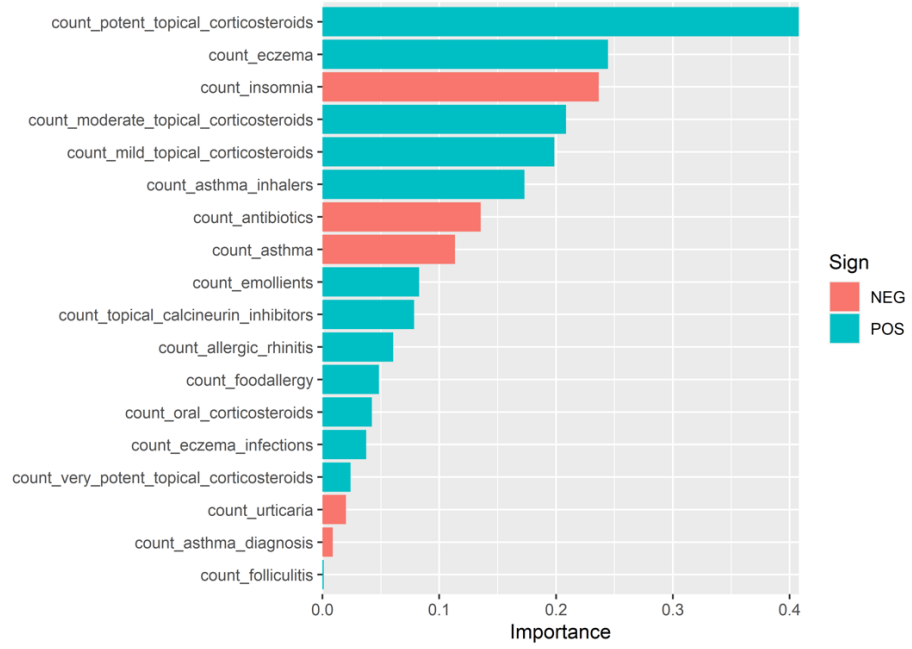


Figure Legend: Receiver operating characteristic (ROC) curves, illustrating the diagnostic ability of a binary classifier system as its discrimination threshold is varied.

eFigure 8: Variable Importance Plot



(a: when using count variables to classify AD subtype)



(b: when using ever/never variables to classify AD subtype)

Figure Legend: Variable Importance plots showing the relative importance of a variable in predicting the outcome.

eTable 1: Codelists

Variable	Description
allergic rhinitis	allergic rhinitis and related allergies, including hay fever, dust (mite), pollen and animal allergies
asthma	codes that only people with current asthma would have recorded (including things like severity assessments, clinic visits, management plans, etc..), excluding codes where it is equally likely that the person does not have asthma (e.g. asthma screening)
asthma diagnosis	asthma diagnosis codes, excluding asthma related codes like clinic visits, assessments, etc...
atopic dermatitis	atopic dermatitis/atopic eczema, excluding codes for unspecific forms of eczema
atopic dermatitis related infections	skin infections related to atopic dermatitis, excluding secondary complications of these infections (e.g. ocular, systemic infections, etc...)
eosinophilic eosophagitis	Eosinophilic eosophagitis
folliculitis	codes for infectious folliculitis, not inflammatory diseases (e.g. folliculitis deplians, decalvans, etc...)
food allergy	Food allergies, not including intolerances (e.g. lactose intolerance)
insomnia	Insomnia related codes
phototherapy	Phototherapy, including photochemotherapy, excluding photodynamic therapy (usually a therapy for skin cancers)
urticaria	atopy related urticaria, excluding drug induced urticaria or mast cell disorders (like urticaria pigmentosa, neonatorum, etc...)
adrenaline pens	Adrenaline auto-injectors ("EpiPens")
antibiotics	oral antibiotics used to treat skin infections, excluding topical
antihistamines	non-specific list of antihistamines, including those prescribed for sleep or coughs and colds (e.g. those with paracetamol, ibuprofen), excluding drugs for nausea, vomiting and vertigo which can be part of the same substance class
asthma inhalers	Asthma inhalers
emollients	Emollients and moisturisers, including all from https://bnf.nice.org.uk/drugs/emollient-creams-and-ointments-paraffin-containing/medicinal-forms/
insomnia drugs	Medicines for insomnia including hypnotics, benzodiazepines, anxiolytics, herbal remedies, and sedating antihistamines
mild topical corticosteroids	Mild topical corticosteroids as per https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/
moderate topical corticosteroids	Moderate topical corticosteroids as per https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/
oral corticosteroids	Oral corticosteroids and glucocorticoids, excluding oestrogen steroid hormones (e.g. oestradiol, estrone, exemestane) and steroids with predominantly mineralocorticoid activity (e.g. fludrocortisone)
potent topical corticosteroids	Potent topical corticosteroids as per https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/
systemic immunosuppressants	Systemic immunosuppressants, including cyclosporine, azathioprine, methotrexate, mycophenolate, tacrolimus
topical antibiotics	Topical antibiotics for impetigo and other skin infections, including Fusidin and Mupirocin according to NICE Guidance

	(https://www.nice.org.uk/guidance/ng153/chapter/recommendations#choice-of-antimicrobial)
topical calcineurin inhibitors	Topical calcineurin inhibitors
very potent topical corticosteroids	Very potent topical corticosteroids as per https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/

eTable 2: Termsets

Searchterms	Exclusionterms
allergic rhinitis	
"allergic rhinitis", "allergic rhinosinusitis", "pollinosis", "perennial rhinitis", "hay fever", "cat allergy", "dander allergy", "house dust allergy", "dog allergy", "feather allergy", "animal allergy"	"fh:", "h/o:", "family history", "eye drops", "past history", "preps"
asthma diagnosis	
"\"asthma\"", "asthma", "status asthmaticus"	"monitoring", "number of", "limits walking", "treatment compliance", "daytime symptoms", "night symptoms", "attendance", "currently", "restricts", "admission", "medication", "severity", "management", "limiting", "limits", "disturbing", "disturbs", "causing", "overlap", "administration", "monitored", "monitor", "review", "trigger", "control", "prophylaxis", "nedocromil", "sodium", "causes", "education", "drug", "reporting", "indicators", "clinic", "family history", "adverse reaction", "specialist", "leaflet", "screening", "resolved", "study", "detergent", "assessment", "action plan", "fh:", "h/o:", "suspected", "society", "absent", "follow-up", "symptoms", "at risk of", "questionnaire"
atopic dermatitis related infections	
"molluscum contagiosum", "herpes simplex", "hsv", "eczema herpe*", "impetig*", "varicelliform eruption", "molusc*", "cold sore", "mollusc*", "cellulitis", "staph* skin", "whitlow", "scrum pox", "herpesviral vesicular dermatitis", "herpetic gingivostomatitis", "herpetic stomatitis", "herpes labialis"	"neonatorum", "ophthalmic", "meningitis", "keratitis", "iridocyclitis", "pneumonia", "otitis", "septicaemia", "genital", "detection", "therapy", "pharynx", "vocal cords", "larynx", "seminal vesicle", "eosinophilic cellulitis", "periurethral", "gonococcal", "serologic test", "cream", "encephalitis", "polymerase chain reaction", "level", "virus isolation", "parametritis", "pelvic cellulitis", "oral cellulitis", "impetigo herpetiformis", "floor of mouth", "soft tissue cellulitis", "visceral herpes", "antigen"
eosinophilic eosophagitis	
eosinophilic oesophagitis	NONE
folliculitis	
folliculitis	"sycosis", "depilans", "abscedens et suffodiens", "ulerythematosa", "decalvans"
foodallergy	
"food allergy", "egg allergy", "fruit allergy", "tomato allergy", "banana allergy", "soya allergy", "strawberries allergy", "strawberry allergy", "mushroom allergy", "shellfish allergy", "seafood allergy", "fish allergy", "wheat allergy", "nut allergy", "peanut allergy"	none
insomnia	

"insomnia", "poor sleep", "delayed sleep", "restless sleep", "sleep disorder*", "sleep disturb*", "sleep dysfunction*", "sleep problem*"	"nonorganic", "sleep apnoea", "non-organic", "arousal", "emotional", "asthma", "eating", "chronic obstructive pulmonary disease"
phototherapy	
"puva", "light therapy", "phototherapy", "ultraviolet b therapy", "ultraviolet a therapy"	"device", "complication"
urticaria	
"urticaria", "hives", "nettle rash"	"test", "amyloid nephropathy with deafness and urticaria", "factitial", "drug induced", "menstrual", "familial febrile", "pigmentosa", "solar", "neonatorum", "due to serum"
antibiotics	
"flucloxacillin", "clarithromycin", "erythromycin", "amoxicillin"	"cutaneous", "ointment", "solution", "overdose", "adverse reaction", "test", "resistant", "immunoglobulin", "sensitivity", "allergy", "measurement", "poisoning", "parenteral", "lotion", "ophthalmic"
antihistamines	
"antihistamine", "antazoline", "carbinoxamine", "diphenhydramine", "pyrrobutamine", "tripelennamine", "brompheniramine", "mepyramine", "methapyrilene", "triprolidine", "dexchlorpheniramine", "hydroxyzine", "clemastine", "chlorphenamine", "fexofenadine", "levocabastine", "ketotifen", "chlorpheniramine", "phenyltoloxamine", "meclozine", "pheniramine", "loratadine", "dexbrompheniramine", "dimetindene", "bromazine", "diphenylpyraline", "piprinhydrinate", "homochlorcyclizine", "clocinizine", "bromodiphenhydramine"	"adverse reaction", "allergy", "measurement", "trimethobenzamide", "cinnarizine", "flunarizine", "poisoning", "prophylaxis", "overdose"
emollient	
"emollient", "animal fat substance", "petrolatum substance", "wool fat", "water in oil agent substance", "spermaceti", "titanium dioxide substance", "waxes substance", "yellow wax", "white wax substance", "cocoa butter substance", "cold cream substance", "white lotion substance", "colophony substance", "primin substance", "styrax substance", "tar substance", "alene substance", "methylated naphthalene substance", "wood preservative substance", "balsam substance", "cetylpyridinium substance", "prophyllin"	"adverse", "procedure", "cathartic", "disorder", "blood group", "margarine", "control"
insomnia drugs	
"zolpidem", "stilnoct", "zopiclone", "zimovane", "chloral hydrate", "cloral betaine", "loprazolam", "lormetazepam", "flurazepam", "dalmane", "nitrazepam", "mogadon", "temazepam", "diazepam", "diazemuls", "stesolid", "lorazepam", "ativan", "oxazepam", "promethazine hydrochloride", "phenergan", "sominex", "melatonin", "syncrodin",	"overdose", "poisoning", "adverse reaction", "level", "dependence", "allergy", "screening", "measurement", "concentration", "urine", "rectal", "parenteral", "injection", "suppository", "gel"

"slenyto", "circadin", "hydroxyzine", "ramelteon", "tasimelteon"	
mild topical corticosteroids	
"hydrocortisone cream", "hydrocortisone lotion", "hydrocortisone cutaneous", "hydrocortisone topical", "hydrocortisone ointment", "hydrocortisone acetate", "fluocinolone acetonide 25 microgram/1 gram"	"adverse reaction", "hydrocortisone butyrate", "eye ointment", "eye drops", "rectal", "suppository", "ear drops", "injection", "lidocaine", "pramoxine"
moderate topical corticosteroids	
"betamethasone cream", "betamethasone cutaneuous", "betamethasone lotion", "betamethasone ointment", "clobetasone topical", "clobetasone cutaneous", "fludroxycortide cutaneous", "alclometasone topical", "alclometasone cutaneous", "fluocinolone acetonide 62.5 microgram/g cutaneous"	"betamethasone dipropionate", "betamethasone 0.1%", "eye ointment", "calcipotriene"
potent topical corticosteroids	
"beclomethasone dipropionate cutaneous", "betamethasone valerate 0.1%", "betamethasone valerate 2.25mg", "betamethasone 0.1% foam", "fluticasone topical", "fluticasone cutaneous", "mometasone topical", "mometasone cutaneous", "hydrocortisone butyrate topical", "hydrocortisone butyrate cutaneous", "triamcinolone cutaneous", "triamcinolone topical", "triamcinolone cream", "triamcinolone ointment", "betamethasone dipropionate salicylic", "fluocinolone acetonide 250 microgram/g cutaneous", "\"diflucortolone valerate 1 mg/g cutaneous\""	none
systemic immunosupressants	
"azathioprine", "mycophenolate", "cyclosporin", "ciclosporin", "cyclosporine", "azathioprin"	"poisoning", "disorder", "observable entity", "situation", "procedure", "embryopathy", "overdose", "adverse reaction", "induced by", "long-term current use", "caused by", "allergy", "nephrotoxicity", "level", "ophthalmic", "index", "measurement"
topical antibiotics	
"fusidic", "fusidate", "mupirocin"	"oral", "ophthalmic", "eye drops", "overdose", "poisoning", "adverse reaction", "allergy", "parenteral", "injection", "nasal", "infection"
topical calcineurin inhibitors	
"tacrolimus topical", "tacrolimus cutaneous", "pimecrolimus"	none
very potent topical corticosteroids	
"clobetasol", "\"diflucortolone valerate 3 milligram/1 gram\""	disorder

eTable 3: Topical corticosteroid potency

Name	Potency[1]	Compound	Generic[2]
Hydrocortisone 2.5%	mild		not found
Dioderm	mild		Hydrocortisone 0.1% cream
Mildison	mild		Hydrocortisone 1% cream
Synalar 1 in 10 dilution	mild		Fluocinolone acetonide 0.0025% cream
Canesten HC	mild	with antimicrobials	Hydrocortisone 1% / Clotrimazole 1% cream
Daktacort	mild	with antimicrobials	Hydrocortisone 1% / Miconazole 2% ointment
Econacort	mild	with antimicrobials	Econazole 1% / Hydrocortisone 1% cream
Fucidin H	mild	with antimicrobials	Hydrocortisone acetate 1% / Fusidic acid 2% cream
Hydrocortisone with chlorhexidine hydrochloride and nystatin	mild	with antimicrobials	not found
Terra-Cortril	mild	with antimicrobials	Oxytetracycline 3% / Hydrocortisone 1% ointment; Generic Terra-Cortril Nystatin cream
Timodine	mild	with antimicrobials	Generic Timodine cream
Betnovate-RD	moderate		Betamethasone valerate 0.025% cream
Eumovate	moderate		Clobetasone 0.05% cream
Haelan	moderate		Fludroxycortide 0.0125% cream; Fludroxycortide 4micrograms/square cm tape 7.5cm
Modrasone	moderate		Alclometasone 0.05% cream
Synalar 1 in 4 Dilution	moderate		Fluocinolone acetonide 0.00625% cream
Ultralanum Plain	moderate		Fluocortolone 0.25% / Fluocortolone hexanoate 0.25% ointment
Trimovate	moderate	with antimicrobials	Clobetasone 0.05% / Oxytetracycline 3% / Nystatin 100,000units/g cream
Alphaderm	moderate	with urea	Hydrocortisone 1% / Urea 10% cream
Beclometasone dipropionate 0.025%	potent		not found
Betamethasone valerate 0.1%	potent		Betamethasone valerate 0.1% cream
Betacap	potent		Betamethasone valerate 0.1% scalp application
Betesil	potent		Betamethasone valerate 2.25mg medicated plasters
Bettamousse	potent		Betamethasone 0.1% foam
Betnovate	potent		Betamethasone valerate 0.1% cream

Cutivate	potent		Fluticasone 0.05% cream; Fluticasone 0.005% ointment
Diprosone	potent		Betamethasone dipropionate 0.05% cream
Elocon	potent		Mometasone 0.1% cream
Hydrocortisone butyrate	potent		Hydrocortisone butyrate 0.1% cream
Locoid	potent		Hydrocortisone butyrate 0.1% cream
Locoid Crelo	potent		Hydrocortisone 0.1% topical emulsion
Metosyn	potent		Fluocinonide 0.05% cream
Mometasone furoate 0.1%	potent		Mometasone furoate 0.1%
Nerisone	potent		Diflucortolone 0.1% cream
Synalar	potent		Fluocinolone acetonide 0.025% ointment
Aureocort	potent	with antimicrobials	Triamcinolone acetonide 0.1% / Chlortetracycline 3.09% ointment
Betamethasone and clioquinol	potent	with antimicrobials	not found
Betamethasone and neomycin	potent	with antimicrobials	not found
Fucibet	potent	with antimicrobials	Betamethasone valerate 0.1% / Fusidic acid 2% cream
Lotriderm	potent	with antimicrobials	Betamethasone dipropionate 0.064% / Clotrimazole 1% cream
Synalar C	potent	with antimicrobials	Fluocinolone acetonide 0.025% / Clioquinol 3% ointment
Synalar N	potent	with antimicrobials	Fluocinolone acetonide 0.025% / Neomycin 0.5% cream
Diprosalic	potent	with salicylic acid	Betamethasone dipropionate 0.05% / Salicylic acid 3% ointment
Clarelux	very potent		Clobetasol 500micrograms/g foam
Dermovate	very potent		Clobetasol 0.05% cream
Etrivex	very potent		Clobetasol 500micrograms/g shampoo
Nerisone Forte	very potent		Diflucortolone 0.3% ointment
Clobetasol with neomycin and nystatin	very potent	with antimicrobials	not found
[1]Potency as per https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/			
[2]Virtual Medicinal Product (VMP) as per https://services.nhsbsa.nhs.uk/dmd-browser/			

eTable 4: ALSPAC variables for flexural dermatitis presence and severity

	Presence		Severity	
timepoint (months)	name	label	name	Label[a]
6	kb086	CH had rash in joints & creases	kb087	Severity of rash
18	kd085	CH Had Rash in Joints Since Aged 6 MTHS	kd086	Severity of Rash in Joints
30	kf110	Child had rash in joints > 18 months	kf111	Severity of child's rash
42	kj100	CH Had Dry Itchy Rash In Joints	kj101	Severity of CHs Skin PROB
57	kl100	A8a: Child had itchy, dry skin rash in joints since age 3	kl101	A8b: Severity of child's dry, itchy rash
69	kn1120	A7a: Child had dry skin rash on joints and body creases in past 15 months	kn1121	A7b: Severity of child's skin rash on joints and creases in past 15 months
81	kq090	A7a: CH Had Itchy/Dry Skin Rash In Past Year	kq091	A7b: How Bad Was CH Itchy/Dry Rash
103	ks1280	A11a: Child had itchy, dry skin rash in the joints/creases of body	ks1281	A11b: Extent of itchy dry skin rash
128	kv1111	A8b: Child had itchy/dry rash in joints in past year	kv1112	A8c: What is the severity of these problems
140	kw1280	A16a: Child had any itchy, dry skin rash in the joints and creases of body in the past year	kw1281	A16b: Severity of the rash
166	tb1111	A8b: Child had itchy dry, skin rash in the last year	tb1112	A8c: Severity of child's itchy dry, skin rash

[a]parents could answer with very bad, quite bad, mild, no problem

eTable 5: Most common codes

eczema	**n**
atopic dermatitis/eczema	6461
eczema nos	3269
infantile eczema	2075
atopic dermatitis and related	1528
flexural eczema	536
atopic_only_eczema	
atopic dermatitis/eczema	6461
atopic dermatitis and related	1528
atopic dermatitis nos	411
allergic_rhinitis	
hay fever - unspec allergen	2243
hay fever - pollens	1325
allergic rhinitis	470
allergic rhinitis nos	168
asthma	
asthma	16247
asthma monitoring	14228
asthma monitored	4848
asthma annual review	1864
exercise induced asthma	1831
asthma_diagnosis	
asthma	16247
exercise induced asthma	1831
intrinsic asthma	1686
allergic asthma	822
acute exacerbation of asthma	401
eczema_infections	
impetigo	4079
molluscum contagiosum	1252
cellulitis/abscess - finger	509
cellulitis/abscess of toe	348
herpes simplex	212
folliculitis	
seborrhoea capitis	234
foodallergy	
peanut allergy	87
nut allergy	68
food allergy	61
insomnia	
[d]sleep disturbances	145
sleep disorders	115
c/o - insomnia	95
[d]insomnia nos	68
urticaria	
allergic urticaria	172
hives	96
adrenaline_pens	

epipen jr. 150micrograms/0.3ml (1 in 2,000) solution for injection auto-injectors (meda pharmaceuticals ltd)	461
epipen 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors (meda pharmaceuticals ltd)	271
antibiotics	
amoxicillin 125mg/5ml oral suspension	18745
amoxicillin 250mg/5ml oral suspension	2879
amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)	1861
amoxicillin 250mg capsules	1827
amoxicillin 250mg/5ml oral suspension sugar free	1753
antihistamines	
cetirizine 10mg tablets	2837
loratadine 5mg/5ml oral solution	2832
cetirizine 1mg/ml oral solution sugar free	1857
chlorphenamine 2mg/5ml oral solution	1665
loratadine 10mg tablets	1460
asthma_inhalers	
salbutamol 100micrograms/dose inhaler cfc free	12059
beclometasone 100micrograms/dose inhaler	8563
becotide 50 inhaler (glaxosmithkline uk ltd)	1725
salbutamol 100micrograms/dose breath actuated inhaler cfc free	1593
salmeterol 25micrograms/dose inhaler	1339
insomnia_drugs	
phenergan 5mg/5ml elixir (sanofi)	764
hydroxyzine 10mg tablets	53
emollients	
oilatum emollient (glaxosmithkline consumer healthcare)	8669
e45 cream (forum health products ltd)	4124
diprobase cream (bayer plc)	1479
unguentum m cream (almirall ltd)	771
emulsiderm emollient (dermal laboratories ltd)	382
mild_topical_corticosteroids	
hydrocortisone 1% cream	7234
hydrocortisone 1% ointment	2992
hydrocortisone 0.5% cream	1998
timodine cream (alliance pharmaceuticals ltd)	1667
fucidin h cream (leo pharma)	1460
moderate_topical_corticosteroids	
eumovate 0.05% cream (glaxosmithkline uk ltd)	1674

eumovate 0.05% ointment (glaxosmithkline uk ltd)	1335
clobetasone 0.05% cream	829
clobetasone 0.05% ointment	679
alphaderm 1%/10% cream (alliance pharmaceuticals ltd)	166
potent_topical_corticosteroids	
fucibet cream (leo pharma)	598
betnovate rd 0.025% ointment (glaxosmithkline uk ltd)	536
betamethasone valerate 0.1% / fusidic acid 2% cream	267
betnovate rd 0.025% cream (glaxosmithkline uk ltd)	248
betnovate 0.1% cream (glaxosmithkline uk ltd)	231
oral_corticosteroids	
prednisolone 5mg soluble tablets	1464
prednisolone 5mg gastro-resistant tablets	481
prednisolone 5mg tablets	407
hydrocortisone 10mg tablets	116
betamethasone 500microgram soluble tablets sugar free	55
topical_antibiotics	
fucidin 20mg/g cream (leo pharma)	1895
fucidin h cream (leo pharma)	1460
fusidic acid 2% cream	1064
fucidin h ointment (leo pharma)	407
mupirocin 2% ointment	298

eTable 6: Comparing AD in EHRs to AD symptom reports in ALSPAC as the reference standard

Definition of AD in EHRs	True positives[a]	True negatives[a]	False positives[a]	False negatives[a]	Sensitivity[a]	Specificity[a]
>1 reports of AD symptoms in ALSPAC as the reference standard						
AD diagnosis and prescription	1425	3336	354	3713	0.28	0.90
AD diagnosis or prescription	3017	2538	1152	2121	0.59	0.69
AD diagnosis	1832	3171	519	3306	0.36	0.86
>2 reports of AD symptoms in ALSPAC as the reference standard						
AD diagnosis and prescription	1162	4828	617	2221	0.34	0.89
AD diagnosis or prescription	2275	3551	1894	1108	0.67	0.65
AD diagnosis	1466	4560	885	1917	0.43	0.84

[a]True positives, true negatives, false positives, false negatives, sensitivity, and specificity when comparing AD in EHRs (using different definitions), to having >1 or >2 reports of AD symptoms in ALSPAC as the reference standard.

eTable 7: Proportions of people with AD in primary care, by subtype

	AD in primary care?		
AD definition in EHRs	yes	no	Proportion
Severe-frequent			
AD diagnosis and treatment	237	119	67%
AD diagnosis or treatment	327	29	92%
AD diagnosis	269	87	76%
Moderate-frequent			
AD diagnosis and treatment	352	364	49%
AD diagnosis or treatment	600	116	84%
AD diagnosis	433	283	60%
Moderate-declining			
AD diagnosis and treatment	364	761	32%
AD diagnosis or treatment	786	339	70%
AD diagnosis	467	658	42%
Mild-intermittent			
AD diagnosis and treatment	309	563	35%
AD diagnosis or treatment	606	266	69%
AD diagnosis	363	509	42%
Unaffected/Rare			
AD diagnosis and treatment	948	4813	16%
AD diagnosis or treatment	2881	2880	50%
AD diagnosis	1284	4477	22%

Explanatory examples: Of those with Severe-Frequent AD subtype in ALSPAC, 76% ever had AD, 92% ever had AD or an AD treatment, and 67% ever had AD and an AD treatment in EHRs. Of those with unaffected/rare AD subtype in ALSPAC, 22% ever had AD, 50% ever had AD or an AD treatment, and 16% ever had AD and an AD treatment in EHRs.

eTable 8: Confusion Matrix

	Truth				
Prediction	1	2	3	4	5
1	22	17	<10	<10	<10
2	10	24	11	<10	11
3	<10	13	<10	<10	<10
4	<10	<10	<10	<10	<10
5	35	130	244	186	1437

1=Severe-Frequent; 2=Moderate-Frequent; 3=Moderate-Declining; 4=Mild-Intermittent; 5=Unaffected/Rare

eTable 9: Metrics by definition of outcome variable and by predictor set used

Predictor Set	ROC AUC	Accuracy	Sensitivity	Specificity
Original Subtypes (n=6,622)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.65	0.68	0.29	0.83
2: Ever/never had code for a given disease/treatment	0.63	0.66	0.28	0.82
3: How often had code for a given disease/treatment	0.63	0.66	0.25	0.82
4: Age of first occurrence for a given disease/treatment	0.64	0.66	0.27	0.83
5: Presence of code for a given disease/treatment in 1-year windows	0.63	0.65	0.27	0.83
1 + 3	0.68	0.67	0.31	0.83
1+ 3 + 5	0.64	0.67	0.3	0.83
Binary Subtypes (n=6,622)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.7	0.72	0.26	0.96
2: Ever/never had code for a given disease/treatment	0.69	0.7	0.37	0.89
3: How often had code for a given disease/treatment	0.71	0.71	0.27	0.94
4: Age of first occurrence for a given disease/treatment	0.73	0.74	0.42	0.91
5: Presence of code for a given disease/treatment in 1-year windows	0.7	0.72	0.29	0.96
1 + 3	0.72	0.73	0.26	0.97
1+ 3 + 5	0.71	0.74	0.33	0.95
Three category Subtypes (n=6,622)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.69	0.7	0.42	0.74
2: Ever/never had code for a given disease/treatment	0.7	0.7	0.45	0.75
3: How often had code for a given disease/treatment	0.7	0.7	0.41	0.73
4: Age of first occurrence for a given disease/treatment	0.71	0.69	0.44	0.75
5: Presence of code for a given disease/treatment in 1-year windows	0.7	0.67	0.4	0.72
1 + 3	0.71	0.69	0.45	0.74
1+ 3 + 5	0.71	0.68	0.41	0.72
Four category Subtypes (n=6,622)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.66	0.66	0.33	0.78
2: Ever/never had code for a given disease/treatment	0.66	0.66	0.32	0.79
3: How often had code for a given disease/treatment	0.67	0.67	0.32	0.79
4: Age of first occurrence for a given disease/treatment	0.66	0.66	0.33	0.79
5: Presence of code for a given disease/treatment in 1-year windows	0.66	0.69	0.35	0.8
1 + 3	0.68	0.68	0.37	0.79

1+ 3 + 5	0.67	0.68	0.36	0.79
Orignial (with more complete EHRs) (n=4,232)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.66	0.66	0.29	0.83
2: Ever/never had code for a given disease/treatment	0.63	0.65	0.28	0.82
3: How often had code for a given disease/treatment	0.62	0.65	0.28	0.83
4: Age of first occurrenc**e** for a given disease/treatment	0.64	0.63	0.27	0.83
5: Presence of code for a given disease/treatment in 1-year windows	0.65	0.66	0.28	0.83
1 + 3	0.67	0.67	0.3	0.83
1+ 3 + 5	0.65	0.67	0.28	0.82
Original (with complete ALSPAC follow-up) (n=657)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.72	0.31	0.24	0.81
2: Ever/never had code for a given disease/treatment	0.61	0.31	0.22	0.81
3: How often had code for a given disease/treatment	0.67	0.36	0.29	0.83
4: Age of first occurrenc**e** for a given disease/treatment	0.63	0.3	0.23	0.81
5: Presence of code for a given disease/treatment in 1-year windows	0.66	0.34	0.27	0.81
1 + 3	0.67	0.41	0.31	0.83
1+ 3 + 5	0.69	0.37	0.29	0.83
Original (excluding Unaffected/Rare) (n=2,302)				
1: Presence of AD prescription and diagnosis codes in 1-year windows	0.66	0.43	0.33	0.78
2: Ever/never had code for a given disease/treatment	0.64	0.39	0.27	0.76
3: How often had code for a given disease/treatment	0.67	0.41	0.32	0.77
4: Age of first occurrenc**e** for a given disease/treatment	0.65	0.39	0.29	0.77
5: Presence of code for a given disease/treatment in 1-year windows	0.68	0.43	0.34	0.78
1 + 3	0.68	0.42	0.35	0.78
1+ 3 + 5	0.67	0.42	0.35	0.78

[a]Outcomes:
2 categories (1: Unaffected/Rare; 2: Mild-Intermittent + Moderate-Declining + Moderate-Frequent + Severe-Frequent).
3 categories (1: Unaffected/Rare; 2: Mild-Intermittent + Moderate-Declining + Moderate-Frequent; 3: Severe-Frequent)
4 categories (1: Unaffected/Rare; 2 Mild-Intermittent + Moderate-Declining; 3: Moderate-Frequent; 4: Severe-Frequent)
Except for the 2 category outcome variable, ROC AUC is averaged using the method by Hand, Till (2001), and sensitivity and specificity are macro averaged.

TRIPOD check-list for Prediction Model Development

Title and Abstract

1. Title: Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. Title
2. Abstract: Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. Abstract

Introduction

3. Background and objectives
    a. Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. Introduction
    b. Specify the objectives, including whether the study describes the development or validation of the model or both. Objectives

Methods

4. Source of data

    a. Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. Data sources
    b. Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. Data sources
5. Participants

    a. Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. Data sources
    b. Describe eligibility criteria for participants. Participants
    c. (Give details of treatments received, if relevant.)
6. Outcome

    a. Clearly define the outcome that is predicted by the prediction model, including how and when assessed. Outcomes
    b. Report any actions to blind assessment of the outcome to be predicted. Statistical analysis
7. Predictors

    a. Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. Predictors
    b. Report any actions to blind assessment of predictors for the outcome and other predictors. Statistical analysis

8. Sample size: Explain how the study size was arrived at. Participants

9. Missing data: Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. Participants, Statistical analysis

10. Statistical analysis methods

    a. Describe how predictors were handled in the analyses. Statistical analysis
    b. Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. Statistical analysis
    c. Specify all measures used to assess model performance and, if relevant, to compare multiple models. Statistical analysis

11. (Risk groups: Provide details on how risk groups were created, if done.)

Results

13. Participants

    d. Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. Descriptive statistics and linkage
    e. Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. Descriptive statistics and linkage

14. Model development

    a. Specify the number of participants and outcome events in each analysis. Descriptive statistics and linkage; eTable: Metrics by Definition of outcome variable
    b. (If done, report the unadjusted association between each candidate predictor and outcome.)

15. Model specification

    a. Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). eTable: Full model specification
    b. Explain how to the use the prediction model. Discussion

16. Model performance: Report performance measures (with CIs) for the prediction model. Predicting ALSPAC subtypes from primary care records

Discussion

18. Limitations: Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). Limitations

19. Interpretation: Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence. Conclusions

20. Implications: Discuss the potential clinical use of the model and implications for future research. Conclusions

Other information

21. Supplementary information: Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. Appendix

22. Funding: Give the source of funding and the role of the funders for the present study. Acknowledgements

6.4 Relevance for thesis

The study presented in this chapter on eczema subtypes reveals a striking mismatch concerning eczema-related information reported by parents in questionnaires and recorded in EHRs (*Aim II*). The study demonstrates the value of linking data from different sources. While EHRs could not be enhanced with information on children's eczema subtypes, the comparison of linked data has important implications for eczema research. Together with findings in Chapter 5, a basis for discussion of eczema definitions in observational studies is provided.

6.5 Chapter summary

- Questionnaire responses from ALSPAC had previously been used to derive subtypes of eczema severity trajectories in children
- ALSPAC had been linked to local primary care EHRs
- I assessed differences in EHRs by ALSPAC subtype and found that the number of eczema-related codes in EHRs generally increased with the severity of eczema subtype, however not all with the Severe-Frequent subtypes had eczema in EHRs, and many with the Unaffected/Rare subtype did have eczema in EHRs.
- I assessed who would be considered to have eczema (of any subtype) in both data sources, and found that there was poor agreement
- I developed prediction models to classify the ALSPAC subtype using EHRs and achieved unsatisfactory predictive performance; the best-tuned model had ROC AUC of 0.65
- In the published appendix, I provide further comparisons of eczema definitions across data sources, visualise how patterns in EHRs were too similar to be able to discern different ALSPAC phenotypes, list which variables in EHRs were most predictive, and further information
- Findings from this chapter suggest that further research validating eczema-related study information is needed

7 Cohort studies on 71 different adverse health outcomes among people with atopic eczema in UK primary care data

7.1 Introduction

Eczema has been suggested to be associated with multiple adverse outcomes. In previous chapters, I already considered outcomes that may be mediated through treatments such as oral corticosteroids, as studied in Chapter 4, and outcomes due to adverse effects on mental health which may be shared with other visible skin conditions like psoriasis, as studied in Chapter 5. Hundreds of observational studies have been conducted in the past, investigating many other outcomes. A review by the American Academy of Dermatology (AAD) on awareness of comorbidities associated with atopic dermatitis in adults, published in January 2022, gives an up-to-date overview of the literature on this topic.[7] Of note is that for many of the outcomes on which statements were produced, the evidence was of low or moderate certainty. Additionally, other literature had suggested associations with outcomes not included in the review.[100]

The situation of having insufficient evidence on multiple different outcomes, but a resource that could be used to improve the evidence on many of these outcomes (i.e., large EHRs), first prompted the idea for this chapter. This came hand in hand with realising that many of the best quality EHR studies on individual outcomes shared many similarities and that differences between studies could further be reduced while maintaining the original interpretation. Thus I set out to address the need for better evidence at scale.

In this chapter, in Section 7.2 I first present a literature review of EHR cohort studies on eczema adverse health outcomes, to provide an overview of similarities between these previous studies. The review informed the study design used in the published manuscript in Section 7.3. Then in Section 7.4, I provide further rationale for multiple outcome approaches, that are not specific to eczema research.

7.2 Literature review

To inform the choice of generic study design to be applied to investigate multiple adverse health outcomes for eczema, I conducted a literature review to identify cohort studies in electronic health records data that studied adverse outcomes related to eczema and extracted details on the individual study design elements and overlap between them. I searched studies included in the 2022 American Academy of Dermatology (AAD) guidelines, from the list of all studies that were not marked as having "follow up: Cross-sectional" (from the appendix of AAD guidelines).[7] Additionally, I also considered 24 studies retrieved with a Pubmed search for "(eczema OR atopic eczema OR atopic dermatitis) AND (CPRD OR clinical practice research datalink OR"english primary care")" in December 2022, to include any studies in CPRD that were missing in the AAD guidelines.

I identified 12 [101–112] studies from the AAD guidelines and 3 additional studies from the search for CPRD studies [20,52,113], that 1. employed a cohort study design, 2. used routinely collected data as the data source, 3. studied adverse outcomes (not death) related to eczema (not factors related with the subsequent development of eczema; not people with eczema and another disease compared to people with only the other disease, e.g. [114]).

The most commonly used designs were matched (most commonly on age and sex) cohort studies, including incident and prevalent cases of eczema, excluding people with the outcome before the index date, and estimating rate or hazard ratios (most commonly with Cox regression). Regression analyses were adjusted for covariates which varied between studies, however, there was significant overlap. The minimum age at index date differed between studies, with some where individuals could be included from birth, some from childhood and adolescence, and others from early and later adulthood. Some studies included additional

phenotypes for eczema, most commonly a measure of eczema severity based on treatments. Studies extracted variables using codes in various disease and drug classification systems such as ICD (revisions 8, 9, or 10), Read and ATC (Table 7.1).

Table 7.1: Study designs of previous studies on eczema adverse outcomes

Characteristic	**N = 15**[1]
Data Source	
AOK PLUS cohort	1 (6.7%)
CPRD & HES	4 (27%)
CPRD & HES & Danish National Registry of Patients	1 (6.7%)
Danish National Registry of Patients	3 (20%)
Hospital Episode Statistics (HES)	1 (6.7%)
Taiwan National Health Insurance Research Database	4 (27%)
The Health Improvement Network	1 (6.7%)
Main statistical analysis	
Cox regression	11 (73%)
multilevel mixed-effects logistic regression	1 (6.7%)
Poisson regression	2 (13%)
Rate ratios from standardised rates	1 (6.7%)
Matched on	
age, sex	4 (27%)
age, sex, calendar period	4 (27%)
age, sex, comorbidities (partially)	1 (6.7%)
age, sex, general practice	1 (6.7%)
age, sex, SES, region	1 (6.7%)
none	2 (13%)
sex, general practice, calendar time at cohort entry	2 (13%)
Includes Incident/Prevalent atopic dermatitis	
incident	2 (13%)
incident & prevalent	11 (73%)
prevalent	2 (13%)
Minimum age at inclusion	
0	3 (20%)
10	1 (6.7%)
12	1 (6.7%)
15	1 (6.7%)
18	6 (40%)
20	2 (13%)
40	1 (6.7%)
Other atopic dermatitis defintions	
none	7 (47%)
severity	7 (47%)

severity, activity	1 (6.7%)
Exclusion criteria	
none	1 (6.7%)
outcome before index date	11 (73%)
outcome or related diagnoses before index date	3 (20%)

[1] n (%)

Data sources from countries: Taiwan National Health Insurance Research Database - Taiwan; Hospital Episode Statistics (HES) - UK; AOK PLUS cohort - Germany; CPRD & HES - UK; Danish National Registry of Patients - Denmark; The Health Improvement Network - UK; CPRD & HES & Danish National Registry of Patients - UK & Denmark

From the studies, I also identified the outcomes and covariates of each study.

- Cheng et al. 2015 Outcomes: depression, anxiety; Covariates: age, sex, SES, asthma, rhinitis, allergic conjunctivitis
- Singhal et al. 2014 Outcomes: self-harm; Covariates: none
- Standl et al 2017 Outcomes: myocardial infarction, angina pectoris, stroke, hypertension, peripheral arterial disease; Covariates: age, sex, SES
- Silverwood et al. 2018 Outcomes: myocardial infarction, unstable angina, heart failure, atrial fibrillation, stroke; Covariates: age, sex, GP, calendar period, SES, BMI, smoking, harmful alcohol use, asthma, depression, anxiety, diabetes, hypertension, hyperlipidaemia
- Su et al. 2014 Outcomes: ischemic stroke, myocardial infarction, heart failure; Covariates: age, sex, diabetes, atrial fibrillation, hypertension, coronary artery disease, valvular heart disease, peripheral arterial disease, chronic kidney disease, dyslipidaemia, lung cancer, COPD, rhinitis, asthma, psoriasis, cholesterol-lowering drugs, antihypertensives, antiplatelet drugs
- Riis et al. 2016 Outcomes: myocardial infarction; Covariates: age, sex, calendar period, SES, diabetes, hypertension, hyperlipidaemia, stroke, asthma, rhinitis
- Andersen et al. 2016 Outcomes: myocardial infarction, stroke; Covariates: age, sex, SES, smoking, harmful alcohol use, hypertension, inflammatory bowel disease, cardiac dysrhythmias, topical corticosteroids, systemic corticosteroids, systemic anti-

inflammatory (nonsteroids), topical calcineurin inhibitors, cholesterol-lowering drugs, antidepressants, antiplatelet drugs, loop diuretics

- Sung et al. 2017 Outcomes: stroke; Covariates: age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, hyperlipidaemia
- Andersen et al. 2017 Outcomes: type 2 diabetes; Covariates: age, sex, SES, smoking, harmful alcohol use, hypertension, inflammatory bowel disease, rheumatoid arthritis, topical corticosteroids, systemic corticosteroids, systemic anti-inflammatory (nonsteroids), topical calcineurin inhibitors, cholesterol-lowering drugs
- Wu et al. 2017 Outcomes: osteoporosis; Covariates: age, sex, hypertension, hyperlipidaemia, diabetes, depression, systemic corticosteroids, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, Charlson comorbidity index
- Lowe et al. 2020 Outcomes: major osteoporotic fracture; Covariates: age, sex, GP, cohort entry, calendar period, IMD, asthma, BMI, smoking, harmful alcohol use, SES, ethnicity, high dose oral corticosteroid use
- Langan et al. 2017 Outcomes: cutaneous infections, systemic infections; Covariates: age, sex, GP
- Schonmann et al. 2020 Outcomes: depression, anxiety; Covariates: age, calendar period, sex, SES, ethnicity, BMI, smoking status, harmful alcohol use, high dose oral corticosteroid use
- Matthewman et al. 2021 Outcomes: major osteoporotic fracture; Covariates: age, sex, GP, cohort entry, calendar period, IMD, asthma, BMI, smoking, harmful alcohol use, SES, ethnicity, oral corticosteroids (high dose use, recency, cumulative dose, current dose, peak dose)
- Mansfield et al. 2020 Outcomes: cancer; Covariates: age, sex, cohort entry, GP, calendar period, SES, BMI, smoking, harmful alcohol use
- All variables used across all studies (63): age, sex, SES, asthma, rhinitis, allergic conjunctivitis, GP, calendar period, BMI, smoking, harmful alcohol use, depression, anxiety, diabetes, hypertension, hyperlipidaemia, atrial fibrillation, coronary artery

disease, valvular heart disease, peripheral arterial disease, chronic kidney disease, dyslipidaemia, lung cancer, COPD, psoriasis, cholesterol-lowering drugs, antihypertensives, antiplatelet drugs, stroke, inflammatory bowel disease, cardiac dysrhythmias, topical corticosteroids, systemic corticosteroids, systemic anti-inflammatory (nonsteroids), topical calcineurin inhibitors, antidepressants, loop diuretics, rheumatoid arthritis, chronic liver disease, chronic obstructive pulmonary disease, Charlson comorbidity index, cohort entry, IMD, ethnicity, high dose oral corticosteroid use, smoking status, oral corticosteroids (recency, cumulative dose, current dose, peak dose), self-harm, myocardial infarction, angina pectoris, unstable angina, heart failure, ischemic stroke, type 2 diabetes, osteoporosis, major osteoporotic fracture, cutaneous infections, systemic infections, cancer

- Secondary/more granular outcomes of the studies (26): major depression, ischaemic stroke, haemorrhagic stroke, spine fracture, hip fracture, wrist fracture, pelvis fracture, cutaneous warts, dermatophyte infection, herpes simplex virus, impetigo, molluscum contagiosum, otitis media, pneumonia, streptococcal throat infection, lung cancer, breast cancer, prostate cancer, pancreas cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukaemia, multiple myeloma, central nervous system cancer, melanoma, nonmelanoma skin cancer Variables here summarised as socioeconomic status (SES) included measures such as income-related insured amount (Taiwan), index of multiple deprivation (UK), inferred through area postcode (Germany).

I concluded that a matched (on age, sex and general practice) cohort design, including incident and prevalent cases of eczema and more detailed phenotypes thereof (e.g. eczema severity), excluding individuals with the outcome before the start of follow-up, estimating hazard ratios from Cox regression should be suitable to investigate several adverse outcomes associated with eczema. Outcome-specific inclusion/exclusion criteria, e.g. in terms of the minimum age at inclusion, and considering eczema drugs as potential confounders were two areas to allow for heterogeneity between outcomes.

7.3 Published manuscript

Contribution

I am the first author of a manuscript submitted for peer review and published as a preprint in February 2024.[115] I led all aspects of the study, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing.

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SECTION A – Student Details

Student ID Number	lsh1901215	**Title**	Dr
First Name(s)	Julian		
Surname/Family Name	Matthewman		
Thesis Title	Efficient organisation and valid phenotypes in electronic health records research: applied examples relating to atopic eczema and other inflammatory diseases		
Primary Supervisor	Sinéad Langan		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	SSRN		
When was the work published?	February 2024		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led all aspects of the study, including study conceptualisation, design, data management, analysis, interpretation of findings, and manuscript writing.

SECTION E

Student Signature	[redacted]
Date	20 Marc 2024

Supervisor Signature	[redacted]
Date	20 March 2024

Cohort studies on 71 different adverse health outcomes among people with atopic eczema in UK primary care data

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Keywords: eczema; atopic eczema; atopic dermatitis; adverse health outcomes; comorbidities; outcome-wide; pipeline

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Conflicts of Interest

Julian Matthewman, Spiros Denaxas, Krishnan Bhaskaran, and Helen Strongman have no conflicts of interest to report.
Anna Schultze is employed on a fellowship sponsored by GSK, unrelated to the current research.
Sinéad M. Langan is a co-investigator in a consortium with industry and multiple academic partners (BIOMAP-IMI.eu) but is not in receipt of industry funding.
Kathryn E Mansfield has received consultancy fees from AMGEN outside of the current work.

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Data availability

All analysis code and codelists used for this study are available at https://zenodo.org/doi/10.5281/zenodo.10649715.

No additional unpublished data are available as this study used existing data from the UK CPRD electronic health record database, which is only accessible to researchers with protocols approved by the CPRD's independent scientific advisory committee and data access may incur a cost.

Ethics
The study was approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (Reference number: 29781).
This study is based on data from the CPRD obtained under license from the U.K. Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The study was approved by the Independent Scientific Advisory Committee (Protocol reference number: 23_002665). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders.
Julian Matthewman and Anna Schultze have directly accessed and verified the underlying data.

Author contributions
JM contributed to Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, and Writing – review & editing.
SML contributed to Methodology, Supervision, Validation, and Writing – review & editing.
AS contributed to Methodology, Validation, and Writing – review & editing.
All other authors contributed to Methodology and Writing – review & editing.

Research in Context

Evidence before this study

The 2022 American Academy of Dermatology guidelines on comorbidities associated with eczema – systematic reviews, meta-analyses, and grading of evidence – suggest that for many of the 32 comorbidities considered, there is only low or moderate certainty evidence. A hypothesis-generating study published in the same year suggests associations with gastrointestinal and neurological conditions that were not included in the guidelines, and additional hypothesis-testing studies have explored other outcomes.

Added value of this study

On links between eczema and subsequent diagnosis of different adverse health outcomes, we provide a comprehensive evidence resource, containing comparable and confounding-adjusted estimates derived from large UK primary care data, that can be used to inform clinical practice, guidelines, and future research.
Our findings suggest that, of the common outcomes currently not considered in guidelines, eczema is associated with some gastrointestinal conditions (including irritable bowel syndrome, oesophagitis, gastritis, duodenitis, gastro oesophageal reflux disease), thromboembolic disease, obesity, and peripheral neuropathies. Eczema was also strongly associated with some less common conditions including lymphomas (but not other cancers), inflammatory bowel diseases, coeliac disease, and some liver diseases.
Implications of all the available evidence
The increased risk found for being diagnosed with conditions subsequent to eczema emphasises the importance of a multi-disciplinary approach to care for these individuals. More research is needed on how/whether good eczema control/treatment helps minimise these excess risks. Our findings highlight a number of outcomes that may warrant increased attention from both clinicians and researchers regarding prevention, monitoring and mitigation.

Abstract

INTRODUCTION Atopic eczema may be related to multiple subsequent adverse health outcomes, however, high quality evidence is limited. The existing evidence base, encompassing hundreds of studies employing heterogenous approaches to study design, analysis and data management, hinders comparison, and has been slow and expensive to build.
METHODS We conducted 71 cohort studies using primary care electronic health records data from Clinical Practice Research Datalink Aurum (1997 - 2023), with cohort sizes of up to 3.6 million with eczema matched (on age, sex and general practice) to 16.8 million without eczema. Applying an outcome-wide study design and confounding-adjustment strategy, we fitted Cox models, estimating hazard ratios (HRs) for each outcome comparing people with eczema to people without. We also assessed the effect of eczema severity, estimated absolute effects, and conducted a range of sensitivity analyses.
RESULTS Eczema was associated with outcomes with adjusted HRs (99% confidence intervals) of up to 4.02 (3.95-4.10) for food allergy. We found strong evidence of associations, dose-response relationships (with eczema severity), and large rate differences for several outcomes that are not acknowledged in current guidelines, namely: irritable bowel syndrome (1.31 [1.29-1.33]), oesophagitis (1.26 [1.24-1.27]), gastro oesophageal reflux disease (1.25 [1.24-1.26]), thromboembolic disease (1.25 [1.23-1.27]), obesity (1.22 [1.21-1.23]), gastritis and duodenitis (1.22 [1.20-1.23]) and peripheral neuropathies (1.21 [1.20-1.22]). Associations with larger HRs but lower rate differences included: Hodgkin's lymphoma (1.83 [1.64-2.04]), Crohn's disease (1.62 [1.54-1.69]), coeliac disease (1.43 [1.38-1.48]), autoimmune liver disease (1.35 [1.54-1.69]), and ulcerative colitis (1.41 [1.35-1.47]).
INTERPRETATION We identified several novel strong associations between eczema and adverse health outcomes, including some where individuals with eczema, clinicians, and guideline authors may benefit from increased awareness of these risks. Results closely matched those from previous studies specifically designed to investigate cancer, fracture,

cardiovascular and mental illness outcomes, suggesting our approach to studying multiple outcomes produces valid estimates.

Lay Summary

Eczema, an itchy skin disease that is common in children and adults, may increase the risk of developing other health problems. The research on this topic has shown potential links with diseases, such as asthma, heart disease, broken bones, and others. However, for many diseases it is unclear whether links with eczema exist, or whether potential links could be explained by other factors or problems with how these links were studied. Routinely collected health records from general practice in the UK are suitable for studies on this topic, as they contain information about many different diseases. So far researchers have mostly studied one disease at a time, e.g. does eczema increase the risk of breaking a bone, having an issue with the heart, or getting a skin infection. Each of these investigations are costly in time and money, and results may not be directly comparable to another. With this project we systematically and consistently studied multiple diseases that may be linked to eczema. This approach has many advantages for cost, efficiency, and comparability of results.

We compared 4 million people with eczema to 16 million without eczema which allowed us to study links with even quite rare conditions. We found several new links (e.g., eczema was linked with inflammatory bowel diseases such as Crohn's disease and diseases of the oesophagus). This awareness of risks is essential for doctors and public health decision makers to improve care for people with eczema. We still need a better understanding of how eczema may be linked to these diseases, and if better treatment of eczema may decrease the risks.

Background

Eczema, also referred to as atopic eczema or atopic dermatitis, is one of the most common chronic conditions worldwide,[1] and is associated with a substantial morbidity burden and cost for health care systems.[2] Eczema, besides being associated with atopic diseases such as allergies and asthma, may also be associated with non-atopic diseases, possibly due to mechanisms such as chronic inflammation (which could explain observed cardiovascular outcomes),[3] psychological stress, low self-esteem, and sleep deprivation (which could explain observed anxiety and depression outcomes).[1,4] Recent guidelines published by the American Academy of Dermatology (AAD) included statements on 32 different adverse health outcomes, for each judging whether an association is likely to exist and the quality of the evidence.[5] While there was clear evidence for associations between eczema and other atopic conditions (e.g., asthma and food allergies) the prior evidence for most adverse health outcomes included in the review (including mental illness, cardiovascular disease, metabolic disease, osteoporosis and fractures, and skin infections) was less clear. A hypothesis-generating study published in the same year suggests associations with gastrointestinal and neurological conditions which weren't included in the guidelines, [6] and other important outcomes may exist but may have not been discovered. There is no internationally accepted approach to screening and prevention of adverse outcomes, [1] despite potentially substantial impact at reducing morbidity and costs for health care systems, given eczema is common.

Studies on a range of health outcomes linked to eczema have typically focused on single, or small sets of, outcomes. Here, using the Clinical Research Practice Datalink (CPRD) Aurum, we employed best-practice epidemiological study design, an outcome-wide confounding-adjustment strategy, and suitable approaches to sensitivity and secondary analyses across 71 outcomes to efficiently and systematically generate high-quality evidence on associations.

Methods

Study design and setting

We used a matched cohort study design with deidentified routinely collected UK primary care electronic health records (EHR) data (April 1st 1997, to March 31st 2023) from CPRD Aurum, which includes over 46 million people, and has been found to be representative of the general population of England in terms of age, sex, geographical spread and deprivation.[7]

Study population

We created different cohorts based on minimum age at inclusion (Figure 1). For all cohorts, we used an algorithm to identify individuals with eczema based on one that has been previously validated in UK primary care data (at least one record of an eczema diagnostic code and at least two records for eczema therapies [emollients, topical glucocorticoids, topical calcineurin inhibitors, oral glucocorticoids or systemic immunosuppressants] on two separate days).[8] We then included individuals in the eczema exposed group on the latest of: (1) Date they met the eczema definition ; (2) One year since practice registration (to allow us to reliably capture baseline health status); (3) Study start (April 1, 1997); and (4) 18th (18+ cohort) or 40th birthday (40+ cohort), or no age limitation (any age cohort). For the 18+ and 40+ cohorts, meeting the eczema definition could occur before individuals became eligible (i.e., individuals with both new and existing eczema were included, a recommended approach for relapsing conditions like eczema to better assess longer-term effects of an exposure).[9]

Eczema exposed individuals were matched (without replacement) to up to 5 unexposed individuals with at least 1-year prior registration, on age (2-year calliper), sex, and general practice in calendar date order. The index date for comparators was set to the index date of the exposed individual they were matched to. Comparators were censored on the day they met the eczema definition themselves, and could then be re-matched, this time as exposed individuals. Individuals were followed up until the date of outcome, or until they were censored (death, left practice, or for comparators, when they met the eczema definition). For each outcome-specific analysis, individuals who had the outcome before their index date were excluded (Figure 1).

For sensitivity analyses, we created an additional cohort, where individuals were only considered exposed when they had an additional record indicating more severe eczema after having met the eczema definition (i.e., the comparators matched to these exposed individuals also included individuals with eczema considered to be less severe). Records indicating more severe eczema included records for phototherapy, or prescriptions for

potent topical corticosteroids, topical calcineurin inhibitors or systemic immunosuppressants (azathioprine, methotrexate, ciclosporin, mycophenolate).[3,4,10–12]

For secondary analyses, eczema severity was defined as mild or moderate-to-severe as a time-updated variable. People with eczema were assumed to have mild disease in the absence of any evidence for moderate-to-severe disease, and the status was updated on the first date that individuals met the definition for moderate-to-severe eczema, namely when they were first prescribed potent topical steroids, calcineurin inhibitors or systemic drugs (azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil), or had a record for phototherapy. Individuals' assigned severity could progress from mild to moderate-to-severe, but not revert to mild disease; hence this variable denoted whether a person had *ever* experienced moderate-to-severe eczema. The approach is similar to previous studies, however we did not incorporate information from hospital records .[3,4,10–12]

Outcomes

We included all adverse health outcomes (except those defined by death) on which statements were released in the AAD guidelines on comorbidities for adults with eczema, covering a wide range of atopic and allergic, immune-mediated, mental health and substance use, cardiovascular, metabolic, bone health and skin infection outcomes. We also included outcomes that had been previously studied in relation to eczema (i.e., cancers, dementia) [11,13] or which had been identified as an area of particular interest by previous hypothesis-generating work (i.e., digestive system, neurological conditions).[6] We used code lists and algorithms from previous studies [3,4,10–12,14,15] and mapped these to CPRD Aurum medical and product codes (code lists available in the study repository: link). The most commonly occurring codes for each outcome are in eTable 1.

Statistical analysis

We presented descriptive statistics of the cohorts at baseline by eczema-exposure status. We used Cox proportional hazards regression, stratifying on matched set, to estimate hazard ratios (HRs) for the effect of eczema on each outcome. For each analysis, we estimated minimally-adjusted (implicitly adjusted through matching on age, sex and general practice, and calendar time, as comparators entered the cohort on the same day as exposed individuals) and comorbidity-adjusted HRs (additionally adjusted for history of each other outcome at baseline). As sensitivity analysis, we also estimated drug-adjusted (additionally adjusting the comorbidity-adjusted model for oral corticosteroids and systemic immunosuppressants, defined as history of at least one prescription at the index date) HRs, to account for drugs that are sometimes used in eczema treatment but are more commonly used in the treatment of other conditions. We also calculated crude rate differences and estimated adjusted rate differences based on the hazard ratio (as the rate in those without eczema times the inverse of the hazard ratio subtracted from the rate in those with eczema).

The validity of our confounding adjustment strategy for multiple outcomes has been previously described. In summary, covariates that are causes of either the exposure or of any outcome are adjusted for, which in our study includes baseline values of all outcomes and other pre-exposure covariates (i.e., age, sex, general practice).[16]

To account for multiple testing, we reported wider 99% instead of usual 95% confidence intervals. While in our interpretations we do not rely on significance cut-offs, we have additionally reported whether effect estimates were significant for each outcome under Bonferroni correction when counting all outcomes (with 71 outcomes considered, estimates would be considered significant under Bonferroni correction with a p-value less than 0.05/71= 0.0007).

To benchmark results from our study against results from studies specifically designed to assess the risk of certain outcomes, we report whether our results were similar to those from four previous CPRD GOLD studies.[3,4,11,12]

Pipeline

For all 71 outcomes, we ran analyses for all four cohorts (any age, 18+, 40+, more-severe), for all three models (minimally-adjusted, comorbidity-adjusted, drug-adjusted). We considered our primary results to be those from comorbidity-adjusted models, and from the age cohort that was most relevant to the typical age of onset for each given outcome (e.g. the any-age cohort for asthma, the 18+ cohort for hypertension, the 40+ cohort for dementias - a full specification for each outcome is listed in eTable 1). We considered the following as sensitivity analyses for given outcomes: 1) results from both minimally- and drug-adjusted models; 2) from the cohorts with the other minimum ages at inclusion; and 3) the more-severe cohort.
We used R version 4.3.1 and organised the research pipeline using the targets R package. Each analysis and data management step was represented by a single function that was mapped across all combinations of outcomes, cohorts and models, ensuring reproducibility of the computationally expensive pipeline. [17]

Role of the funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, or report writing.

Results

Descriptive Statistics

From the Aurum population (N=46,795,888), we identified 3,823,770 individuals meeting the eczema definition who were eligible for matching, and were matched with unexposed individuals, resulting in a cohort of 20,399,42 (with and without eczema) for the any-age-cohort (Figure 1). Individuals were followed up for a median (IQR) of 4.7 (1.8, 9.9) years per person in the any-age cohort, 4.3 (1.7, 9.1) for the 18+ cohort, 5.7 (2.4, 10.7) for the 40+ cohort. After matching, cohorts were balanced in terms of age and sex, but there were differences in comorbidities (e.g., previous asthma 8.6% in unexposed versus 17% in exposed) (Table 1).

Associations between eczema and adverse health outcomes

For all outcomes, comorbidity-adjusted hazard ratios with 99% confidence intervals, and estimated rate differences (RD) per 1,000 person-years from their respective main cohorts

are shown in Figure 2, eTable 1, and described by category in eSection 1. Associations were strongest for food allergy (adjusted HR [aHR] 4.02, 99% confidence-interval [3.95-4.10]), allergic conjunctivitis (2.02 [1.99-2.05]), and for allergic rhinitis (1.93 [1.91-1.94]). Outcomes with hazard ratios closest to the null included prostate cancer (aHR 1.01 [0.99-1.04]), breast cancer (aHR 1.03 [1.01-1.06]) and Parkinson's disease (aHR 1.02 [0.98-1.06]). Estimated rate differences based on the adjusted hazard ratio were highest for allergic rhinitis (5.4 per 1,000 person-years), asthma (5.4) and dermatophyte infections (3.8). Comorbidity-adjusted hazard ratios were generally attenuated as compared to minimally-adjusted hazard ratios (Figure 2, eTable 1).

Outcomes that were not included in the AAD guidelines where we found all three of 1. strong confounder-adjusted associations (aHR > 1.2), 2. dose-response relationships (with eczema severity), and 3. considerable absolute rate differences (RD ≥ 0.49) were: irritable bowel syndrome (aHR 1.31 [1.29-1.33]; RD 0.67), oesophagitis (aHR 1.26 [1.24-1.27]; RD 0.49), gastro oesophageal reflux disease (aHR 1.25 [1.24-1.26]; RD 1.12), thromboembolic disease (aHR 1.25 [1.23-1.27]; RD 0.51), obesity (aHR 1.22 [1.21-1.23]; RD 0.78), gastritis and duodenitis (aHR 1.22 [1.20-1.23]; RD 0.61) and peripheral neuropathies (aHR 1.21 [1.20-1.22]; RD 2.15). Associations with larger hazard ratios (aHR > 1.3), dose-response relationships, with lower rate differences (RD ≤ 0.10) included: Hodgkin's lymphoma (aHR 1.83 [1.64-2.04]; RD 0.02), Crohn's disease (aHR 1.62 [1.54-1.69]; RD 0.09), coeliac disease (aHR 1.43 [1.38-1.48]; RD 0.10), autoimmune liver disease (aHR 1.35 [1.24-1.47]; RD 0.02), and Ulcerative colitis (aHR 1.41 [1.35-1.47]; RD 0.08).

Results from sensitivity analyses that used the other cohorts and models additionally adjusted for drugs (oral glucocorticoids and systemic immunosuppressants) are shown in Figure 3, and described by category in eSection 1. Models additionally adjusted for drugs did not considerably change results for any outcomes. Results from the other cohorts were similar to results from the main cohort for most outcomes, however for some outcomes there were considerable changes, e.g., food allergy (any-age cohort 4.02[3.95-4.10]; 18+ cohort: 2.03 [1.96-2.10]; 40+ cohort: 1.66 [1.58-1.74]).

Associations between mild and moderate-to-severe eczema and adverse health outcomes

Results from the secondary analysis of time-updated eczema severity are shown in Figure 3, and described by category in eSection 1. Outcomes which were found to be strongly associated with eczema (e.g., food allergy) were generally found to be more strongly associated with moderate-to-severe eczema (aHR 7.35 [6.85-7.89]) than mild eczema (aHR 3.87 [3.81-3.94]). For some less strongly associated outcomes, results did not suggest a dose-response relationship with more severe eczema (e.g., migraine: mild aHR 1.18 [1.17-1.19]; moderate-to-severe aHR 1.20 [1.16-1.24]), while for others they did (e.g., peripheral artery disease: mild aHR 1.19 [1.17-1.21]; moderate-to-severe aHR 1.31 [1.21-1.42]). For some outcomes, including some that were strongly associated, confidence intervals for moderate-to-severe eczema were wide (Hodgkin lymphoma: mild aHR 1.82 [1.65-2.00]; moderate-to-severe aHR 2.09 [1.43-3.05]).

Benchmarking against previous studies

Adjusted hazard ratios from our study were very similar to those from previous studies that used the similar CPRD GOLD database with similar study designs, but bespoke covariate selection. The CIs from our study were almost all within the CIs from the CPRD GOLD studies (eFigure 1). We compared with studies on (1) anxiety (our aHR 1.16 [1.16-1.17], their aHR 1.17[1.14-1.19]) and Depression (our aHR 1.16 [1.15-1.17], their aHR 1.14[1.12-1.16]).[4]; (2) cardiovascular outcomes, including myocardial infarction (our aHR 1.09 [1.07-1.11], their aHR 1.06[0.98-1.15]), heart failure (our aHR 1.17 [1.15-1.19], their aHR 1.19[1.10-1.30]) and stroke (our aHR 1.09 [1.08-1.11], their aHR 1.10[1.02-1.19]). [3]; (3) fracture outcomes (e.g., Hip fracture: our aHR 1.10 [1.08-1.13], their aHR 1.09[1.06-1.12]); (4) and cancer outcomes, where there was also no association with solid organ cancers (e.g., lung cancer: our aHR 1.05 [1.02-1.08], their aHR 1.08[1.01-1.16]; breast cancer: our aHR 1.03 [1.01-1.06], their aHR 0.99[0.94-1.04]; prostate cancer: our aHR 1.01 [0.99-1.04]; their aHR 1.06[1.00-1.13]), but associations with non-melanoma skin cancer (our aHR 1.14 [1.12-1.15], their aHR 1.11[1.06-1.15]) and Non-Hodgkin lymphoma (our aHR 1.26 [1.21-1.32], their aHR 1.20[1.07-1.34]) and a strong association with Hodgkin lymphoma (our aHR 1.83 [1.64-2.04], their aHR 1.48[1.07-2.04]), however with wider confidence intervals than in our study.[11]

Discussion

Summary of the most relevant findings

We have identified novel and potentially important associations between eczema and common outcomes including irritable bowel syndrome, oesophagitis, gastro oesophageal reflux disease, thromboembolic disease, obesity, gastritis and duodenitis and peripheral neuropathies; and less common but more strongly associated outcomes including Hodgkin's lymphoma, Crohn's disease, coeliac disease, autoimmune liver disease, and ulcerative colitis.

Associations considered in the AAD guidelines

The largest associations were found with atopic and allergic conditions, urticaria and alopecia areata, which is already well known from clinical practice, and recognised in the AAD guidelines on awareness of eczema comorbidities.[5] We also found evidence of a link with skin infection, which is also well known clinically, staphylococcus infection being a diagnostic criterion for eczema.[18]

For some less well-characterised associations, our findings are (approximately) in line with statements in the AAD guidelines. For example, our results would support small relative, but potentially considerable absolute, increased risks for depression and anxiety, and weaker evidence for alcohol abuse and cigarette smoking.

Our findings may also support statements on uncertain evidence and/or weak associations with autism, and to a lesser extent attention deficit hyperactivity disorder (ADHD). However our findings for autism should be interpreted with caution as results from analyses where the 40+ cohort were used showed a large increase in the hazard ratio, which unexpected, given autism is a usually diagnosed in childhood, and it is unlikely people with eczema would have higher rates of autism in adulthood.

We found a somewhat increased risk of thromboembolic (e.g., deep vein thrombosis, phlebitis) and peripheral artery disease, with weaker evidence for heart failure, coronary artery disease and hypertension, and only very weak, or for a very small increased risk, for

stroke and myocardial infarction. While we saw no dose response in our study, a previous study has suggested associations primarily with severe eczema as defined by hospital records which were not available for our study. [3]
Our findings would support stating that eczema may not be associated with diabetes, and that there is very low certainty evidence for metabolic syndrome (few events occurring in our study). We also found somewhat stronger evidence for obesity and dyslipidaemia.

Our findings are less in line with statements on osteoporosis, which was one of the few outcomes in the AAD guidelines where an association with eczema was graded as being of high certainty,[5] based on three studies,[19,20] one population-based matched cohort study from Taiwan[21] showing HRs of more than 4 (as compared to our HR of 1.19 [1.16-1.20]). In our study there was evidence of only small increases of risk, that could potentially be explained by confounding for osteoporosis and to a lesser extent for fractures. No evidence of dose response with increased eczema severity was seen in our study as compared to previous studies on fracture outcomes, which, as was the case for cardiovascular outcomes, used hospital records to define severe disease and fracture outcomes.[10]

Associations not considered in the AAD guidelines

We found evidence for associations with autoimmune liver disease and liver fibrosis/sclerosis/cirrhosis, albeit with small rate differences, and fatty liver, with a larger, but still relatively small, rate difference. We found no previous studies examining these associations, so it is likely there was little awareness of these potential links, however given the relatively small rate differences these outcomes may be less important to consider in screening and prevention contexts.
We found an association with COPD, however of a smaller effect size than from a new (published after the 2022 AAD guidelines) cross-sectional study.[22]
We found relatively strong evidence for associations with inflammatory bowel diseases, coeliac disease, irritable bowel disease and diseases of oesophagus. None of these outcomes were included in the AAD guidelines. However, a new study from a UK population-based data source showed similar results for inflammatory bowel dieases.[23] Gastro oesophageal reflux may be partially explained by an increased risk of developing eosinophilic oesophagitis, for which awareness is increasing but may still be misdiagnosed.[24]
We found relatively strong evidence, with relatively large rate differences for peripheral neuropathies, about half of the records that made up this outcome being for sciatica. This association has not been previously described. There was also some evidence for an association with migraine, a new study showing similar effect sizes (HR from fully adjusted model 1.2 [1.2 – 1.26]) to ours (aHR 1.18 [1.17-1.19]) [25]. There was no strong evidence for any of the other neurological outcomes.
Our findings are consistent with those from a previous study that showed no evidence for association with solid organ cancers but associations with lymphomas.[11] The larger sample size of our study allowed more precisely estimation of the association with Hodgkin's lymphoma, which has one of the largest effect estimates of any outcomes, but a low absolute difference.

Strengths

Our study has several strengths, including the use of the large and representative CPRD Aurum database, meaning our results are likely to be generalizable to the general population of England. [3,4,7,10–12]

The novel approach we took to conducting epidemiological studies has advantages compared to traditional approaches, the most obvious benefit being vastly increased efficiency and speed of evidence generation. The results for each outcome are also directly comparable to each other, providing the opportunity to put results in context with outcomes that are well known to be linked to eczema (e.g., food allergy), and outcomes that are unlikely to be linked to eczema (e.g., cancer), acting as positive and negative controls respectively. This may be particularly useful when interpreting and comparing absolute rate differences across outcomes, which may help in judging public health impact of interventions.

We used a strategy for confounding-adjustment, the suitability of which to produce correct confounder-adjusted effect estimates across multiple outcomes has been previously described theoretically and demonstrated practically.[16] Requirements, including large sample sizes and information on a large number of variables (and their timing) that may confound the association between the exposure and any of the outcomes, is met by our data source and large study population. Our results were almost identical to those from four previous CPRD GOLD studies, for which dedicated strategies to adjust for confounding were developed, suggesting our approach is broadly suitable for producing confounder-adjusted estimates across multiple outcomes. Our results were more conservative than from studies done across a range of other data sources and designs,[5] suggesting effects may have often been over-estimated in the past, possibly due to inadequate adjustment for confounding.[5]

Consistently running analyses for all cohorts across all outcomes, provides the opportunity for closer inspection when results are considerably different, for example, while for many outcomes the use of other cohorts did not change results, for atopic and allergic conditions, using cohorts of adults or older adults instead of cohorts of any age, considerably reduced effect estimates; a finding that makes sense clinically, as eczema in childhood may be more strongly linked to allergies than in adulthood. An additional advantage of consistently having results available from the any-age cohort for all outcomes, is that the any-age cohort included only newly-diagnosed eczema, while the 18+ and 40+ cohorts included both newly-diagnosed and previously-diagnosed eczema, and therefore acted as a further sensitivity analysis.

The approach has additional strengths that may help avoid researcher biases. Firstly, in epidemiological research, hundreds of tests across multiple studies are often performed using the same data source. However, multiple testing is rarely considered since these tests are done across many different studies. In our study it was straightforward to include adjustments for multiple testing (although this was less important to consider in our study given the large sample size supplied high power to test multiple outcomes). Secondly, our approach limits the possibility that study design choices and covariate selection were made to explicitly increase or decrease the results for a particular outcome by necessitating that

one study design, including all variations on cohort composition and covariate sets, was applied to, and reported for all outcomes.

Limitations

Our study has limitations. We were not able to account for missing data, given that there are no explicitly missing values. We used data from primary care only, which may miss diagnoses only captured in other care settings, or for diagnosis for which an individual does not consult. Ascertainment in primary care is better for some conditions than for others. While this is not a concern for eczema, as almost all eczema is managed in primary care,[26] some outcomes (e.g., especially those that are acute and serious such as myocardial infarction) are mostly managed in secondary care, and despite feedback from secondary to primary care, some of these diagnoses might be missed. While linking to secondary care data may have helped address some of these issues, this would have come at the cost of reducing sample size, length of follow-up and generalisability of CPRD data.[27]

Despite adjusting each analysis for a large range of confounders, as in all observational studies, residual and unmeasured confounding cannot be excluded. We did not explicitly adjust for deprivation (e.g., using the index of multiple deprivation which can be linked to CPRD Aurum data) however given it is based on small area units with an average of 1,600 residents from the 2011 census,[28] it may not provide better adjustment for deprivation than is already achieved by matching on GP practice. We did not adjust for ethnicity, as the proportion of missing ethnicity data may have introduced selection bias. Most previous studies that did adjust for ethnicity found little difference to main results when additionally adjusting for ethnicity.[3,4,10,11] Future research may consider more detailed investigations of the role of ethnicity, not just as a confounding factor. By excluding individuals with the outcome of interest before index date we aimed to minimise reverse causation, however, reverse causation may still partially explain findings as timing of diagnoses in EHRs may not accurately represent the actual start of conditions.

There may also be limitations relating to defining eczema. Our eczema definition was based on a validated algorithm, and we ran sensitivity analyses with a cohort of individuals with more severe, and therefore likely more definite eczema. However, eczema may still be difficult to establish in primary care records (as individuals, particularly those with milder disease, may not consult for their symptoms), or even in clinical practice itself, and our exposed group may include different subtypes of eczema (which may be associated with different sets of outcomes). Our eczema severity definition is based on prescriptions, which makes it impossible to separate effects of therapy and severity,[3] and we did not include hospital records which may have allowed for a more granular assessment of eczema severity.

Our approach of exploring multiple outcomes may also have limitations compared to studies focused on a narrower set of outcomes. Such studies may reveal more about the mechanisms behind associations, for example, by considering which individual variables confound, mediate, or modify the association and may benefit from more detailed application of expert knowledge, including reviews of the existing literature, to each exposure-outcome relationship.

Interpretation

Our study results can be used to judge the plausibility and strength of links between eczema and the subsequent development of a given adverse health outcome. Absolute measures of effect allow judging the potential public health relevance. Whether these represent causal associations, that would imply effective diagnosis and treatment for eczema could prevent the development of these comorbidities, is not possible to determine from this study alone. However, irrespective of causality, the increased risk found for being diagnosed with conditions subsequent to eczema emphasises the importance of a multi-disciplinary approach to care for these individuals. Future research may aim to investigate mechanisms through which eczema may be associated with outcomes, such as sleep deprivation, antihistamine use, low self-esteem[1], common causes of eczema and outcomes such as atopy, and the role of eczema as a systemic disorder associated with systemic inflammation.[29]

Conclusion

In this study we identified several novel associations between eczema and adverse health outcomes, including those where large confounder-adjusted relative and absolute effect estimates and dose-response relationships indicate relevance for eczema care: irritable bowel syndrome, oesophagitis, gastro oesophageal reflux disease, thromboembolic disease, obesity, gastritis and duodenitis and peripheral neuropathies; and those with larger relative but smaller absolute effect estimates for Hodgkin's lymphoma, Crohn's disease, coeliac disease, autoimmune liver disease, and ulcerative colitis. Clinicians treating individuals with eczema may benefit from increased awareness of these associations. Our results further support existing evidence for many outcomes with the largest population-based cohort studies on the topic to date and demonstrate an efficient approach to using electronic health records to study adverse health outcomes.

References

1 Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *The Lancet* 2020; **396**: 345–60.

2 Drucker AM, Wang AR, Li W-Q, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *Journal of Investigative Dermatology* 2017; **137**: 26–30.

3 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* 2018; : k1786.

4 Schonmann Y, Mansfield KE, Hayes JF, *et al.* Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. *The Journal of Allergy and Clinical Immunology: In Practice* 2020; **8**: 248-257.e16.

5 Davis DMR, Drucker AM, Alikhan A, *et al.* AAD Guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *Journal of the American Academy of Dermatology* 2022; : S0190962222000809.

6 Mulick AR, Henderson AD, Prieto-Merino D, *et al.* Novel multimorbidity clusters in people with eczema and asthma: a population-based cluster analysis. *Sci Rep* 2022; **12**: 21866.

7 Wolf A, Dedman D, Campbell J, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International Journal of Epidemiology* 2019; **48**: 1740–1740g.

8 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**: 1655–62.

9 Vandenbroucke J, Pearce N. Point: Incident Exposures, Prevalent Exposures, and Causal Inference: Does Limiting Studies to Persons Who Are Followed From First Exposure Onward Damage Epidemiology? *American Journal of Epidemiology* 2015; **182**: 826–33.

10 Lowe KE, Mansfield KE, Delmestri A, *et al.* Atopic eczema and fracture risk in adults: A population-based cohort study. *Journal of Allergy and Clinical Immunology* 2020; **145**: 563-571.e8.

11 Mansfield KE, Schmidt SAJ, Darvalics B, *et al.* Association Between Atopic Eczema and Cancer in England and Denmark. *JAMA Dermatol* 2020; **156**: 1086.

12 Matthewman J, Mansfield KE, Prieto-Alhambra D, *et al.* Atopic Eczema–Associated Fracture Risk and Oral Corticosteroids: A Population-Based Cohort Study. *The Journal of Allergy and Clinical Immunology: In Practice* 2021; **0**. DOI:10.1016/j.jaip.2021.09.026.

13 Magyari A, Ye M, Margolis DJ, *et al.* Adult atopic eczema and the risk of dementia: A population-based cohort study. *Journal of the American Academy of Dermatology* 2022; **87**: 314–22.

14 Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis DJ. Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis—A Cohort Study. *Journal of Investigative Dermatology* 2017; **137**: 1375–7.

15 Kuan V, Denaxas S, Gonzalez-Izquierdo A, *et al.* A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. *The Lancet Digital Health* 2019; **1**: e63–77.

16 VanderWeele TJ, Mathur MB, Chen Y. Outcome-Wide Longitudinal Designs for Causal Inference: A New Template for Empirical Studies. *Statist Sci* 2020; **35**. DOI:10.1214/19-STS728.

17 Landau W. The targets R package: a dynamic Make-like function-oriented pipeline toolkit for reproducibility and high-performance computing. *JOSS* 2021; **6**: 2959.

18 Hanifin JM, Rajka G. Diagnostic Features of Atopic Dermatitis. *Acta Dermato-Venereologica* 1980; **60**: 44–7.

19 Arima K, Gupta S, Gadkari A, *et al.* Burden of atopic dermatitis in Japanese adults: Analysis of data from the 2013 National Health and Wellness Survey. *The Journal of Dermatology* 2018; **45**: 390–6.

20 Shaheen MS, Silverberg JI. Atopic dermatitis is associated with osteoporosis and osteopenia in older adults. *Journal of the American Academy of Dermatology* 2019; **80**: 550–1.

21 Wu C-Y, Lu Y-Y, Lu C-C, Su Y-F, Tsai T-H, Wu C-H. Osteoporosis in adult patients with atopic dermatitis: A nationwide population-based study. *PLOS ONE* 2017; **12**: e0171667.

22 Smith B. Association Between Atopic Dermatitis and Chronic Obstructive Pulmonary Disease Among US Adults in the 1999-2006 NHANES Survey. *Cutis* 2023; **112**. DOI:10.12788/cutis.0906.

23 Chiesa Fuxench ZC, Wan J, Wang S, *et al.* Risk of Inflammatory Bowel Disease in Patients With Atopic Dermatitis. *JAMA Dermatology* 2023; **159**: 1085–92.

24 Muir A, Falk GW. Eosinophilic Esophagitis: A Review. *JAMA* 2021; **326**: 1310–8.

25 Lee JH, Kim SH, Lee G, Han K, Lee JH. Association of atopic dermatitis with new-onset migraine: A nationwide population-based cohort study. *Journal of the European Academy of Dermatology and Venereology* 2023; **37**: e236–8.

26 de Lusignan S, Alexander H, Broderick C, *et al.* Patterns and trends in eczema management in UK primary care (2009–2018): A population-based cohort study. *Clin Exp Allergy* 2021; **51**: 483–94.

27 McDonald L, Schultze A, Carroll R, Ramagopalan SV. Performing studies using the UK Clinical Practice Research Datalink: to link or not to link? *European Journal of Epidemiology* 2018; **33**: 601–5.

28 Clinical Practice Research Datalink. Small area level data based on patient postcode. 2022.

29 Brunner PM, Silverberg JI, Guttman-Yassky E, *et al.* Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *Journal of Investigative Dermatology* 2017; **137**: 18–25.

Tables

Table 1: Baseline characteristics

Characteristic	Without eczema	With eczema
N (any-age cohort)	16,756,039 (100%)	3,642,426 (100%)
Female	9,363,784 (56%)	2,012,577 (55%)
Age at index date (median [IQR])	27 (7, 51)	24 (5, 49)
Indexdate (median [IQR])	2011-12-05 (2006-02-10, 2017-03-17)	2012-03-19 (2006-05-30, 2017-05-03)
Follow-up time (median [IQR])	4.5 (1.7, 9.7)	5.5 (2.2, 11.1)
Presence of condition before index date		
Asthma	1,434,793 (8.6%)	613,488 (17%)
Food allergy	108,080 (0.6%)	78,277 (2.1%)
Allergic rhinitis	926,571 (5.5%)	423,076 (12%)
Allergic conjunctivitis	121,964 (0.7%)	68,831 (1.9%)
Eosinophilic oesophagitis	620 (<0.1%)	269 (<0.1%)
Alopecia Areata	27,529 (0.2%)	12,467 (0.3%)
Urticaria	354,016 (2.1%)	164,799 (4.5%)
Anxiety	1,267,923 (7.6%)	366,579 (10%)
Depression	1,842,411 (11%)	512,190 (14%)
Alcohol abuse	124,790 (0.7%)	34,595 (0.9%)
Cigarette smoking	4,246,880 (25%)	1,019,705 (28%)
ADHD	54,875 (0.3%)	14,505 (0.4%)
Autism	52,980 (0.3%)	18,166 (0.5%)
Hypertension	1,544,686 (9.2%)	374,220 (10%)
Coronary artery disease	763,143 (4.6%)	198,497 (5.4%)
Peripheral artery disease	91,642 (0.5%)	27,192 (0.7%)
Myocardial infarction	150,065 (0.9%)	37,463 (1.0%)
Stroke	126,393 (0.8%)	32,708 (0.9%)
Heart failure	129,302 (0.8%)	34,968 (1.0%)
Thromboembolic diseases	128,716 (0.8%)	39,042 (1.1%)
Obesity	460,252 (2.7%)	137,112 (3.8%)
Dyslipidaemia	613,553 (3.7%)	158,540 (4.4%)
Diabetes mellitus	554,901 (3.3%)	139,175 (3.8%)
Metabolic syndrome	3,166 (<0.1%)	944 (<0.1%)
Hip fracture	52,126 (0.3%)	13,121 (0.4%)
Pelvis fracture	22,189 (0.1%)	5,747 (0.2%)
Spine fracture	33,488 (0.2%)	8,942 (0.2%)
Wrist fracture	348,405 (2.1%)	90,199 (2.5%)
Osteoporosis	187,577 (1.1%)	49,973 (1.4%)
Molluscum contagiosum	174,204 (1.0%)	105,985 (2.9%)
Impetigo	470,936 (2.8%)	239,223 (6.6%)
Herpes simplex	226,185 (1.3%)	92,269 (2.5%)
Dermatophyte infection	741,569 (4.4%)	339,743 (9.3%)
Cutaneous warts	944,353 (5.6%)	352,344 (9.7%)
Lung cancer	10,710 (<0.1%)	2,910 (<0.1%)
Breast cancer	88,834 (0.5%)	21,584 (0.6%)
Prostate cancer	61,227 (0.4%)	14,639 (0.4%)
Pancreatic cancer	1,559 (<0.1%)	428 (<0.1%)

Characteristic	Without eczema	With eczema
Non-Hodgkin lymphoma	14,735 (<0.1%)	3,956 (0.1%)
Hodgkin lymphoma	3,805 (<0.1%)	1,137 (<0.1%)
Myeloma	4,058 (<0.1%)	883 (<0.1%)
CNS cancers	12,934 (<0.1%)	3,368 (<0.1%)
Melanoma	49,366 (0.3%)	13,079 (0.4%)
Nonmelanoma skin cancer	185,477 (1.1%)	48,775 (1.3%)
Alzheimer's dementia	48,524 (0.3%)	11,127 (0.3%)
Vascular dementia	24,979 (0.1%)	5,902 (0.2%)
Abdominal hernia	417,122 (2.5%)	112,287 (3.1%)
Appendicitis	157,027 (0.9%)	39,257 (1.1%)
Autoimmune liver disease	4,936 (<0.1%)	1,414 (<0.1%)
Barett's oesophagus	29,850 (0.2%)	8,091 (0.2%)
Cholecystitis	45,705 (0.3%)	12,194 (0.3%)
Coeliac disease	29,195 (0.2%)	9,659 (0.3%)
Crohn's disease	24,704 (0.1%)	9,439 (0.3%)
Diverticular disease	224,058 (1.3%)	62,124 (1.7%)
Fatty liver	60,286 (0.4%)	18,908 (0.5%)
Gastritis and duodenitis	295,604 (1.8%)	92,566 (2.5%)
Gastro oesophageal reflux	667,875 (4.0%)	211,045 (5.8%)
Irritable bowel syndrome	407,450 (2.4%)	132,633 (3.6%)
Fibrosis/sclerosis/cirrhosis	16,850 (0.1%)	5,140 (0.1%)
Oesophageal varices	4,060 (<0.1%)	1,161 (<0.1%)
Oesophagitis	304,717 (1.8%)	95,568 (2.6%)
Pancreatitis	29,695 (0.2%)	7,849 (0.2%)
Peptic ulcer disease	82,063 (0.5%)	22,069 (0.6%)
Peritonitis	11,158 (<0.1%)	2,802 (<0.1%)
Ulcerative colitis	36,285 (0.2%)	12,205 (0.3%)
Epilepsy	129,534 (0.8%)	37,350 (1.0%)
Migraine	531,150 (3.2%)	159,344 (4.4%)
Multiple sclerosis	18,866 (0.1%)	5,022 (0.1%)
Parkinson's disease	29,740 (0.2%)	6,362 (0.2%)
Peripheral neuropathies	783,668 (4.7%)	227,291 (6.2%)
COPD	229,128 (1.4%)	68,677 (1.9%)
oral glucocorticoids	1,074,222 (6.4%)	481,038 (13%)
Systemic immunosuppressants	84,129 (0.5%)	26,627 (0.7%)
N (18+ cohort)	12,588,513 (100%)	2,566,905 (100%)
Age at index date (median [IQR])	37 (23, 58)	37 (23, 59)
Follow-up time (median [IQR])	4.2 (1.7, 8.9)	4.8 (1.9, 9.9)
N (40+ cohort)	7,002,522 (100%)	1,428,787 (100%)
Age at index date (median [IQR])	56 (43, 69)	56 (43, 70)

Characteristic	Without eczema	With eczema
Follow-up time (median [IQR])	5.6 (2.4, 10.5)	6.2 (2.7, 11.3)
N (more severe cohort)	9,169,637 (100%)	1,840,577 (100%)
Age at index date (median [IQR])	35 (19, 59)	35 (19, 59)
Follow-up time (median [IQR])	4.8 (1.9, 9.6)	5.3 (2.1, 10.5)

ADHD: Attention deficit hyperactivity disorder; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease
Numbers are N (%) unless otherwise indicated

Figures

Figure 1: Study design and flow diagram

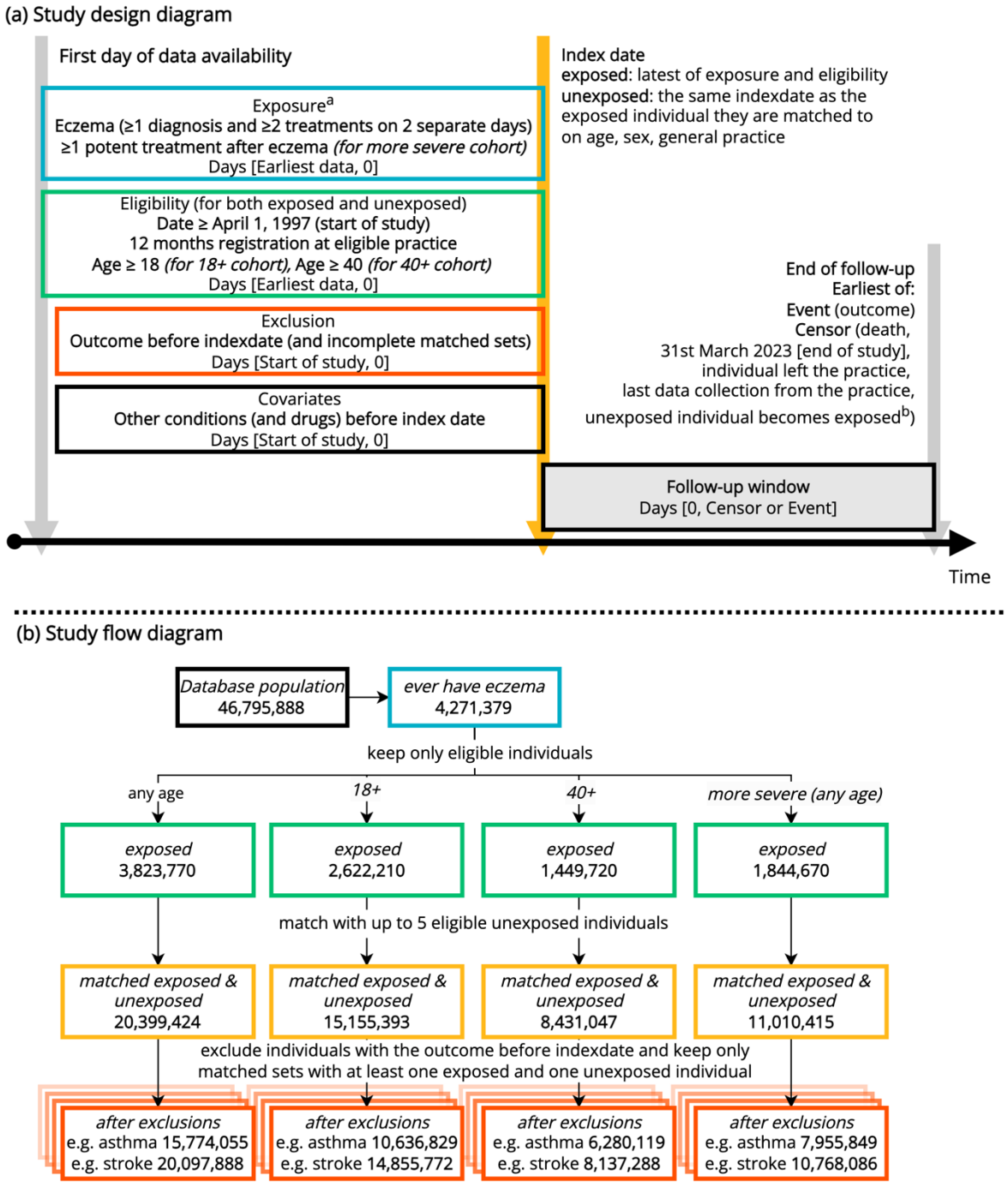


Figure 1: (a) Study design diagram and (b) Study flow diagram, colour-coded by step.
[a] Treatments include emollients, topical glucocorticoids, topical calcineurin inhibitors, systemic immunosuppressants (azathioprine, methotrexate, ciclosporin, mycophenolate), and oral glucocorticoids. Potent treatments include phototherapy, potent topical glucocorticoids, topical calcineurin inhibitors or systemic immunosuppressant.
[b] Unexposed individuals are censored on the day they meet the eczema diagnostic algorithm themselves, and can then be re-matched, this time as exposed individuals.

Figure 2: Main results- Eczema compared to no eczema

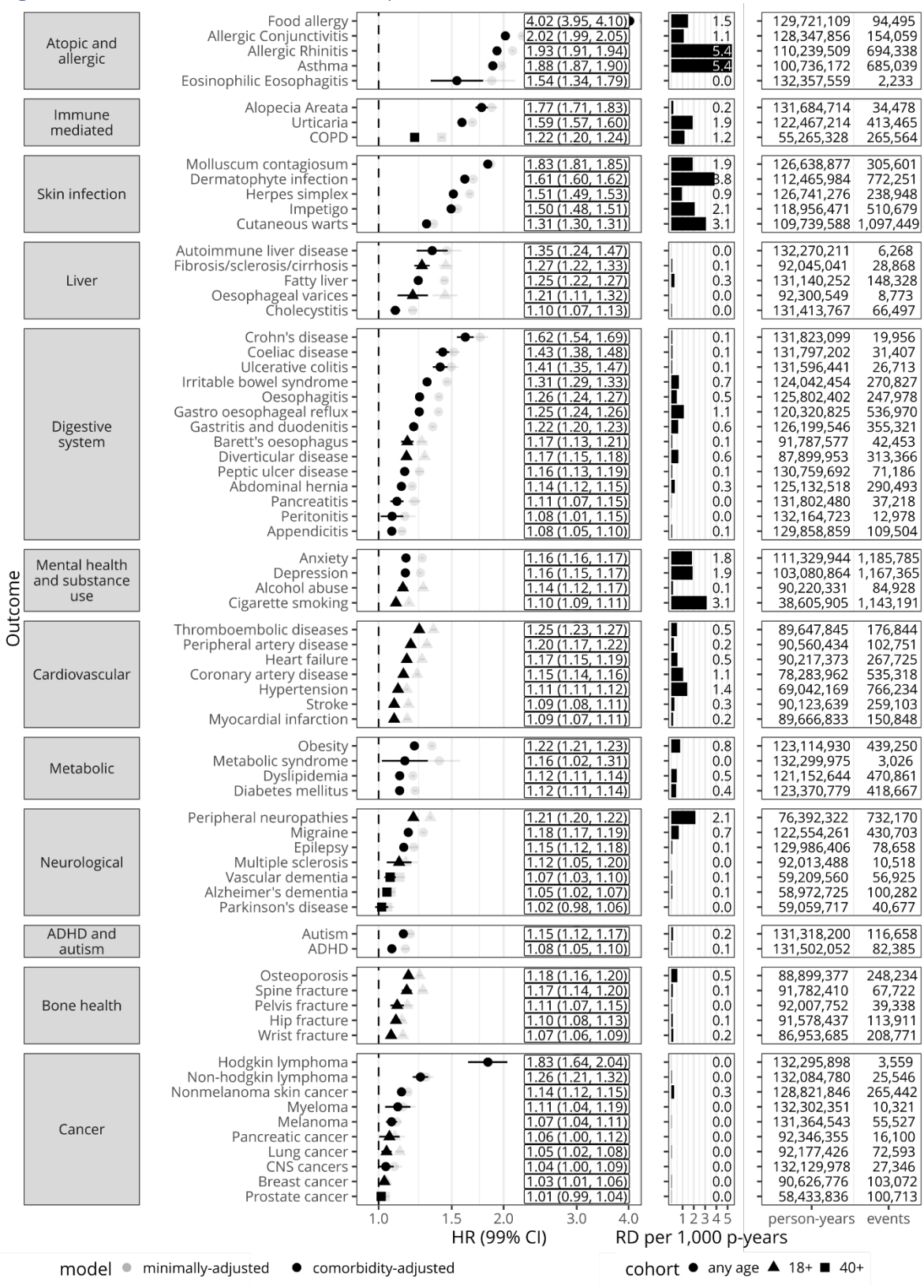


*Figure 2: Hazard ratios (HR) with 99% confidence intervals (99%CI) from Cox regression, estimated absolute rate difference per 1,000 person-years (RD per 1,000 p-years) (rate in those with eczema – estimated rate in those without eczema; the rate in those without eczema is estimated as the rate in the exposed * [1/hazard ratio]), person-years and number of events. Hazard ratios in labels are from adjusted models. Estimates and counts are from the respective main cohort after excluding*

individuals with the respective outcome before index date (which explains differences in follow-up time between outcomes)
ADHD: Attention deficit hyperactivity disorder; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease

Figure 3: Results from sensitivity and secondary (severity) analyses

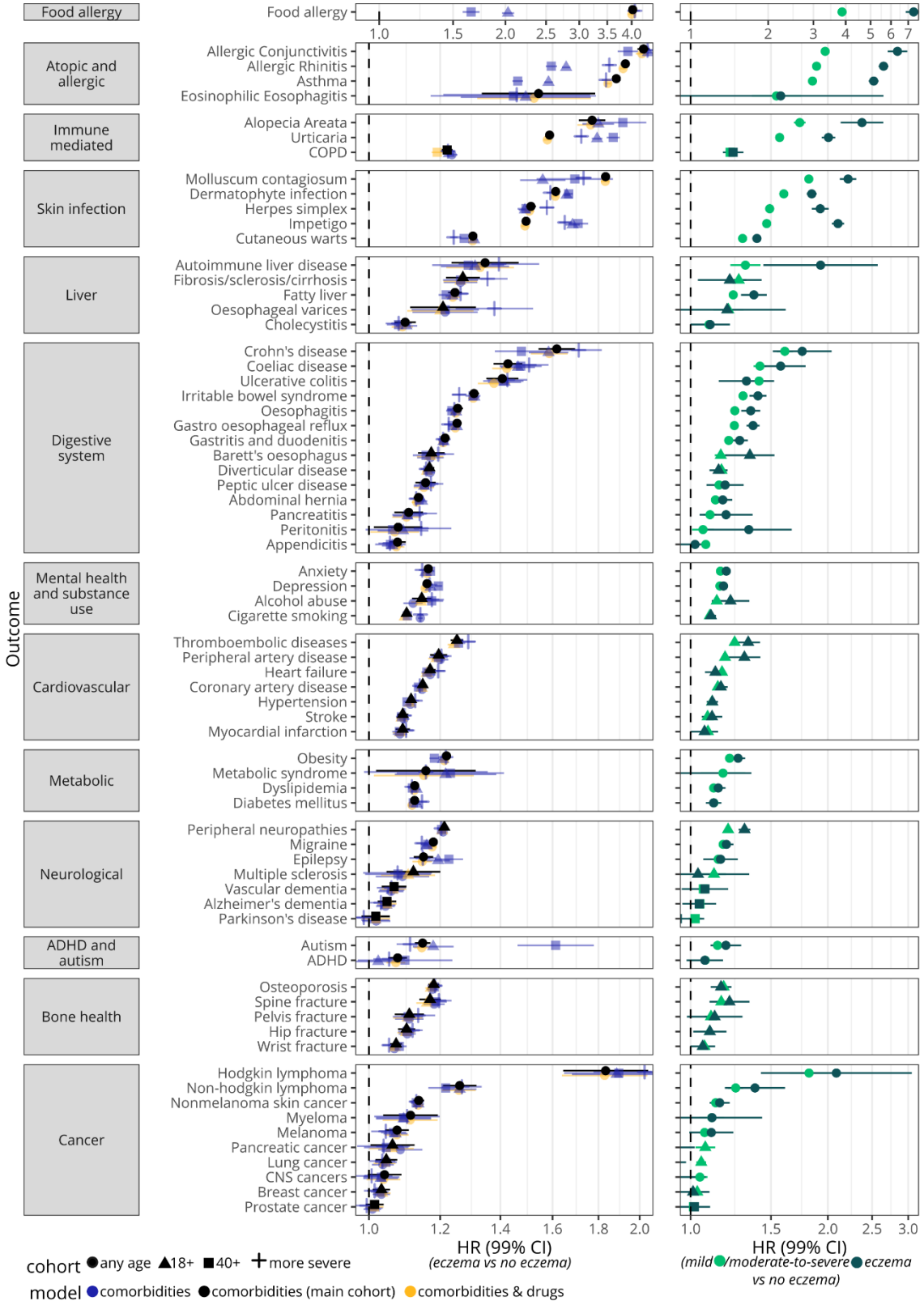


Figure 3: Left: Main hazard ratios (in black), comorbidity-adjusted results from analyses where the other cohorts were used (in blue), and results from additionally drug adjusted models (in yellow). In the "more severe" cohort, individuals are considered exposed when they had an additional record indicating more severe eczema (phototherapy, or prescriptions for potent topical corticosteroids, topical calcineurin inhibitors or systemic immunosuppressants) after having met the eczema diagnosis algorithm (i.e., the comparators matched to these exposed individuals also included individuals with eczema considered to be less severe).

Right: Comorbidity-adjusted Hazard ratios from Cox regression comparing those with mild eczema (in light green) and moderate-to-severe eczema (in dark green) to those without eczema.
Both left and right: Results for food allergy are displayed with their own x-axis since HRs were considerably higher than for any other outcome.

Appendix

eSection 1: Results by category

Atopic and allergic diseases

Of all outcomes, eczema was most strongly associated (i.e., the largest adjusted hazard ratios) with **food allergy** (adjusted HR [aHR] 4.02 [3.95-4.10]; rate difference per 1,000 person-years [RD] 1.48). There were strong associations with **allergic conjunctivitis** (aHR 2.02 [1.99-2.05]; RD 1.10), **asthma** (aHR 1.88 [1.87-1.90]; RD 5.36), and **allergic rhinitis** (aHR 1.93 [1.91-1.94]; RD 5.37), with asthma and allergic rhinitis having the largest rate differences of all outcomes. The was also a strong association with **eosinophilic esophagitis**, however with wider confidence intervals and a small rate difference (aHR 1.54 [1.34-1.79]; RD 0.01).

There were considerable attenuations in effect size when restricting the analyses to adults for food allergy (18+ cohort: 2.03 [1.96-2.10]; 40+ cohort: 1.66 [1.58-1.74]), asthma (18+ cohort: 1.58 [1.57-1.60]; 40+ cohort: 1.46 [1.44-1.48]), and allergic rhinitis (18+ cohort: 1.66 [1.64-1.67]; 40+ cohort: 1.60 [1.57-1.62]).

For all outcomes in this category moderate-to-severe eczema was associated with a considerably larger risk (e.g., asthma aHR mild 1.85 [1.84-1.86]; aHR mod.sev. 2.52 [2.46-2.58]), except eosinophilic esophagitis where confidence intervals were wide (aHR mild 1.54 [1.36-1.75]; aHR mod.sev. 1.58 [0.94-2.65]).

Immune mediated diseases

Eczema was strongly associated with **alopecia areata** (aHR 1.77 [1.71-1.83]; RD 0.19) and **urticaria** (aHR 1.59 [1.57-1.60]; RD 1.88). There was also an association with chronic obstructive pulmonary disease (**COPD)** (aHR 1.22 [1.20-1.24]; RD 1.18).

Effect estimates were larger when the 18+ or 40+ cohorts were used instead of the any-age cohort for alopecia areata (18+ aHR 1.80 [1.73-1.87] 40+ aHR 1.92 [1.80-2.03]) and urticaria (18+ aHR 1.79 [1.77-1.82]; 40+ aHR 1.87 [1.84-1.90]). Effect estimates were also larger when using the more severe cohort instead of the any-age cohort for alopecia areata (2.16 [2.07-2.26]) and urticaria (1.72 [1.70-1.75]).

Effect estimates were larger for moderate-to-severe eczema than for mild eczema for alopecia areata (aHR mild 1.73 [1.68-1.79]; aHR mod.sev. 2.38 [2.13-2.65]) and urticaria (aHR mild 1.57 [1.55-1.58]; aHR mod.sev. 2.01 [1.94-2.08]) but not for COPD.

Skin infection

Eczema was strongly associated with **molluscum contagiosum** (aHR 1.83 [1.81-1.85]; RD 1.89), **impetigo** (aHR 1.50 [1.48-1.51]; RD 2.09), **herpes simplex** (aHR 1.51 [1.49-1.53]; RD 0.94), **dermatophyte infection** (aHR 1.61 [1.60-1.62]; RD 3.84), and **cutaneous warts** (aHR 1.31 [1.30-1.31]; RD 3.07), with rate differences larger than in any other category except atopic and allergic conditions.

While effect estimates were attenuated when using the other cohorts instead of the any age cohort for molluscum contagiosum (18+ aHR 1.56 [1.47-1.65]; 40+ aHR 1.69 [1.54-1.87]), they were increased for impetigo (18+ aHR 1.68 [1.65-1.72]; 40+ aHR 1.71 [1.67-1.75]), and were not considerably changed for dermatophyte infection, herpes simplex and cutaneous warts.

Effect estimates were larger for moderate-to-severe than for mild eczema for all outcomes in this category (e.g., Impetigo aHR mild 1.47 [1.46-1.48]; aHR mod.sev. 2.10 [2.04-2.17]).

Liver diseases

Eczema was associated with **autoimmune liver disease** (aHR 1.35 [1.24-1.47]; RD 0.02), **fibrosis/sclerosis/cirrhosis** (aHR 1.27 [1.22-1.33]; RD 0.09), **fatty liver** (aHR 1.25 [1.22-1.27]; RD 0.28), **oesophageal varices** (aHR 1.21 [1.11-1.32]; RD 0.02), and to a lesser extent with **cholecystitis** (aHR 1.10 [1.07-1.13]; RD 0.05), with relatively low rate differences for all outcomes in this category. Effect estimates were somewhat increased when using the more severe cohort for fibrosis/sclerosis/cirrhosis (aHR 1.35 [1.29-1.43]) and oesophageal varices (aHR 1.38 [1.25-1.52]).

Effect estimates were considerably larger for moderate-to-severe eczema than mild eczema for autoimmune liver disease (aHR mild 1.32 [1.22-1.42]; aHR mod.sev. 1.93 [1.44-2.57]) and fatty liver (aHR mild 1.24 [1.22-1.26]; aHR mod.sev. 1.38 [1.29-1.47]), but not for the other outcomes in this category.

Digestive system – inflammatory bowel diseases

Eczema was strongly associated with **Crohn's disease** (aHR 1.62 [1.54-1.69]; RD 0.09), and **ulcerative colitis** (aHR 1.41 [1.35-1.47]; RD 0.08).

For Crohn's disease, but not for ulcerative colitis, using the other cohorts changed estimates, however confidence intervals from different cohorts overlapped (18+ aHR 1.58 [1.51-1.67]; 40+ aHR 1.48 [1.38-1.58]; more severe aHR 1.71 [1.61-1.81]).

Effect estimates were larger for moderate-to-severe eczema than for mild eczema, however with confidence intervals overlapping, for Crohn's disease (aHR mild 1.61 [1.54-1.68]; aHR mod.sev. 1.76 [1.51-2.04]), but not for ulcerative colitis.

Digestive system – diseases of the oesophagus

Eczema was associated with **oesophagitis** (aHR 1.26 [1.24-1.27]; RD 0.49), **gastro oesophageal reflux** (aHR 1.25 [1.24-1.26]; RD 1.12), and to a lesser extent with **Barrett's oesophagus** (aHR 1.17 [1.13-1.21]; RD 0.08). Using the other cohorts caused little change in effect estimates. Effect estimates were larger for moderate-to-severe eczema than for mild eczema for gastro oesophageal reflux (aHR mild 1.25 [1.24-1.26]; aHR mod.sev. 1.37 [1.33-1.42]), oesophagitis (aHR mild 1.25 [1.23-1.26]; aHR mod.sev. 1.35 [1.29-1.42]), and Barrett's oesophagus (aHR mild 1.16 [1.13-1.20]; aHR mod.sev. 1.35 [1.19-1.53]).

Digestive system – other

Eczema was strongly associated with **coeliac disease** (aHR 1.43 [1.38-1.48]; RD 0.10) and **irritable bowel syndrome** (aHR 1.31 [1.29-1.33]; RD 0.67). Eczema was also associated with **gastritis and duodenitis** (aHR 1.22 [1.20-1.23]; RD 0.61), and to a lesser extent with **diverticular disease** (aHR 1.17 [1.15-1.18]; RD 0.63), **peptic ulcer disease** (aHR 1.16 [1.13-1.19]; RD 0.08), and **abdominal hernia** (aHR 1.14 [1.12-1.15]; RD 0.31). Eczema was only weakly associated with **pancreatitis** (aHR 1.11 [1.07-1.15]; RD 0.03), **peritonitis** (aHR 1.08 [1.01-1.15]; RD 0.01) and **appendicitis** (aHR 1.08 [1.05-1.10]; RD 0.07). Using the other cohorts caused little change in effect estimates.

Effect estimates were larger for moderate-to-severe eczema than for mild eczema for irritable bowel syndrome (aHR mild 1.30 [1.29-1.32]; aHR mod.sev. 1.40 [1.35-1.47]), and gastritis and duodenitis (aHR mild 1.21 [1.20-1.22]; aHR mod.sev. 1.28 [1.23-1.33]), and larger, however with confidence intervals overlapping, for coeliac disease (aHR mild 1.42 [1.37-1.47]; aHR mod.sev. 1.58 [1.39-1.79]).

Mental health disorders and substance use

Eczema was associated with **anxiety** (aHR 1.16 [1.16-1.17]; RD 1.84) and **depression** (aHR 1.16 [1.15-1.17]; RD 1.88) with rate differences on par with skin infections and larger than those from any other category other than atopic and allergic conditions. Eczema was also associated, however with a much lower rate difference, with **alcohol abuse** (aHR 1.14 [1.12-1.17]; RD 0.15). Eczema was also associated to a lesser extent with **cigarette smoking** (aHR 1.10 [1.09-1.11]; RD 3.14), with a large rate difference.

Effect estimates were not considerably changed when using the any-age, 40+ or more severe cohorts instead of the 18+ cohort for any of the outcomes in this category.

Effect estimates were larger, by a small amount, for moderate-to-severe eczema than for mild eczema for anxiety (aHR mild 1.16 [1.16-1.17]; aHR mod.sev. 1.20 [1.17-1.22]) and depression (aHR mild 1.16 [1.15-1.17]; aHR mod.sev. 1.18 [1.16-1.21]).

Cardiovascular diseases

Eczema was associated with **thromboembolic diseases** (aHR 1.25 [1.23-1.27]; RD 0.51) and **peripheral artery disease** (aHR 1.20 [1.17-1.22]; RD 0.23), and to a lesser extent with **heart failure** (aHR 1.17 [1.15-1.19]; RD 0.53), **coronary artery disease** (aHR 1.15 [1.14-1.16]; RD 1.06), **hypertension** (aHR 1.11 [1.11-1.12]; RD 1.41), **myocardial infarction** (aHR 1.09 [1.07-1.11]; RD 0.16) and **stroke** (aHR 1.09 [1.08-1.11]; RD 0.28).

Using the other cohorts instead of the 18+ cohort did not change effect estimates considerably.

While effect estimates were larger for moderate-to-severe eczema than for mild eczema for peripheral artery disease (aHR mild 1.19 [1.17-1.21]; aHR mod.sev. 1.31 [1.21-1.42]) and thromboembolic diseases (aHR mild 1.25 [1.23-1.27]; aHR mod.sev. 1.34 [1.26-1.42]), this was not the case for hypertension, coronary artery disease, myocardial infarction, stroke, and heart failure (e.g. for heart failure aHR mild 1.17 [1.16-1.19]; aHR mod.sev. 1.13 [1.08-1.19]).

Results from this study were very similar to those from a previous study on cardiovascular outcomes, including myocardial infarction (aHR 1.06 [0.98-1.15]), heart failure (aHR 1.19[1.10-1.30]) and stroke (aHR 1.10 [1.02-1.19]). [3]

Metabolic diseases

Eczema was associated with **obesity** (aHR 1.22 [1.21-1.23]; RD 0.78), and to a lesser extent with **dyslipidaemia** (aHR 1.12 [1.11-1.14]; RD 0.48), **diabetes mellitus** (aHR 1.12 [1.11-1.14]; RD 0.43) and **metabolic syndrome** (aHR 1.16 [1.02-1.31]; RD 0.00).

Using the other cohorts instead of the any-age cohorts caused little change in effect estimates, with only a small increase in hazard ratio for metabolic syndrome when using the 18+ (1.22 [1.07-1.39]) or 40+ (1.23 [1.07-1.41]) cohorts.

Effect estimates were larger for moderate-to-severe eczema than for mild eczema for obesity (aHR mild 1.22 [1.21-1.23]; aHR mod.sev. 1.27 [1.23-1.32]), and to a lesser extent for dyslipidaemia (aHR mild 1.12 [1.11-1.13]; aHR mod.sev. 1.15 [1.11-1.19]), but not for diabetes mellitus or metabolic syndrome.

Neurological diseases

Eczema was associated with **peripheral neuropathies** (aHR 1.21 [1.20-1.22]; RD 2.15) with a considerable rate difference similar to that of allergic rhinitis. Eczema was also associated to

migraine (aHR 1.18 [1.17-1.19]; RD 0.66), and to a lesser extent to **epilepsy** (aHR 1.15 [1.12-1.18]; RD 0.09) and **multiple sclerosis** (aHR 1.12 [1.05-1.20]; RD 0.01). Eczema was not, or only very weakly, associated with **Alzheimer's dementia** (aHR 1.05 [1.02-1.07]; RD 0.09), **vascular dementia** (aHR 1.07 [1.03-1.10]; RD 0.07) and **Parkinson's disease** (aHR 1.02 [0.98-1.06]; RD 0.01).
Using the other cohorts caused little change in effect estimates, except small increases when using the 18+ or 40+ cohorts for epilepsy (18+ aHR 1.19 [1.16-1.23]; 40+ aHR 1.23 [1.18-1.27]).
Effect estimates were larger for moderate-to-severe eczema than for mild eczema for Peripheral neuropathies (aHR mild 1.21 [1.20-1.22]; aHR mod.sev. 1.31 [1.27-1.35]), but not considerably different for the other outcomes in this category.

ADHD and autism

Eczema was weakly associated with **ADHD** (aHR 1.08 [1.05-1.10]; RD 0.06) and **autism** (aHR 1.15 [1.12-1.17]; RD 0.15).
While using any of the other cohorts instead of the any-age cohort for ADHD caused little change in the effect estimates and widened confidence intervals to include the null, for autism, using the 40+ cohort instead of the any-age cohort considerably increased the effect estimate (aHR 1.61 [1.46-1.78]).
Effect estimates were similar for moderate-to-severe and mild eczema.

Bone health

Eczema was associated with **osteoporosis** (aHR 1.18 [1.16-1.20]; RD 0.53), and to a lesser extent (in order of decreasing aHR) with **spine fracture** (aHR 1.17 [1.14-1.20]; RD 0.13), **pelvis fracture** (aHR 1.11 [1.07-1.15]; RD 0.05), **hip fracture** (aHR 1.10 [1.08-1.13]; RD 0.13), and **wrist fracture** (aHR 1.07 [1.06-1.09]; RD 0.18).
Using the other cohorts, instead of the 18+ cohort caused little change in effect estimates.
Effect estimates for moderate-to-severe eczema were only somewhat larger than for mild eczema (with confidence intervals overlapping) for Spine fractures (aHR mild 1.17 [1.14-1.20]; aHR mod.sev. 1.22 [1.10-1.35]) and were not larger for the other outcomes in this category (e.g., Osteoporosis aHR mild 1.18 [1.17-1.20]; aHR mod.sev. 1.17 [1.11-1.23]).

Cancer

Eczema was not, or only very weakly, associated with solid organ cancers including **lung cancer** (aHR 1.05 [1.02-1.08]; RD 0.04), **breast cancer** (aHR 1.03 [1.01-1.06]; RD 0.04), **prostate cancer** (aHR 1.01 [0.99-1.04]; RD 0.03), **pancreatic cancer** (aHR 1.06 [1.00-1.12]; RD 0.01), **central nervous system cancers** (aHR 1.04 [1.00-1.09]; RD 0.01), and **melanoma** (aHR 1.07 [1.04-1.11]; RD 0.03). Eczema was weakly associated with **myeloma** (aHR 1.11 [1.04-1.19]; RD 0.01), and **non-melanoma skin cancer** (aHR 1.14 [1.12-1.15]; RD 0.27), Nonmelanoma skin cancer having the largest rate difference of any cancer, however still lower than many other outcomes. Eczema was associated with **non-Hodgkin's lymphoma** (aHR 1.26 [1.21-1.32]; RD 0.05) and strongly associated with **Hodgkin lymphoma** (aHR 1.83 [1.64-2.04]; RD 0.02), however with very small rate differences for both outcomes. Using the other cohorts caused little change in effect estimates.
Effect estimates were not considerably different for moderate-to-severe eczema and mild eczema in solid organ cancers (e.g., prostate cancer aHR mild 1.01 [1.00-1.03]; aHR mod.sev. 1.02 [0.94-1.10]), and while they were larger for moderate-to-severe eczema than for mild

eczema for lymphomas (e.g. Hodgkin lymphoma aHR mild 1.82 [1.65-2.00]; aHR mod.sev. 2.09 [1.43-3.05]), confidence intervals overlapped.

eTable 1: Eczema compared to no eczema

Outcome	Main cohort	Events	Person-years	Crude rate (per 1,000 person-years)		Crude rate difference	Estimated rate difference[2]	Hazard ratio (99% confidence interval)[1]		
				Exposed	Unexposed			Minimally-adjusted	Comorbidity-adjusted	Drug-adjusted
Atopic and allergic										
Food allergy	any age	94,495	129,721,109	2.0	0.4	1.54	1.48	4.35 [4.27-4.44]*	4.02 [3.95-4.10]*	4.00 [3.93-4.08]*
Allergic Conjunctivitis	any age	154,059	128,347,856	2.2	1.0	1.23	1.10	2.22 [2.19-2.25]*	2.02 [1.99-2.05]*	2.01 [1.98-2.04]*
Allergic Rhinitis	any age	694,338	110,239,509	11.2	5.1	6.07	5.37	2.10 [2.09-2.12]*	1.93 [1.91-1.94]*	1.92 [1.90-1.93]*
Asthma	any age	685,039	100,736,172	11.4	5.6	5.82	5.36	1.98 [1.96-1.99]*	1.88 [1.87-1.90]*	1.84 [1.83-1.86]*
Eosinophilic Oesophagitis	any age	2,233	132,357,559	0.0	0.0	0.01	0.01	1.87 [1.64-2.13]*	1.54 [1.34-1.79]*	1.53 [1.32-1.77]*
Cancer										
Hodgkin lymphoma	any age	3,559	132,295,898	0.0	0.0	0.02	0.02	1.84 [1.66-2.04]*	1.83 [1.64-2.04]*	1.83 [1.64-2.04]*
Non-Hodgkin lymphoma	any age	25,546	132,084,780	0.2	0.2	0.04	0.05	1.30 [1.25-1.36]*	1.26 [1.21-1.32]*	1.26 [1.21-1.31]*
Nonmelanoma skin cancer	any age	265,442	128,821,846	2.2	2.0	0.19	0.27	1.18 [1.16-1.19]*	1.14 [1.12-1.15]*	1.13 [1.12-1.15]*
Myeloma	any age	10,321	132,302,351	0.1	0.1	0.00	0.01	1.15 [1.07-1.23]*	1.11 [1.04-1.19]*	1.11 [1.04-1.19]*
Melanoma	any age	55,527	131,364,543	0.4	0.4	0.00	0.03	1.11 [1.07-1.14]*	1.07 [1.04-1.11]*	1.07 [1.04-1.11]*
Pancreatic cancer	18+	16,100	92,346,355	0.2	0.2	0.02	0.01	1.10 [1.04-1.16]*	1.06 [1.00-1.12]	1.06 [1.00-1.12]
Lung cancer	18+	72,593	92,177,426	0.9	0.8	0.09	0.04	1.13 [1.10-1.15]*	1.05 [1.02-1.08]*	1.04 [1.01-1.07]*
CNS cancers	any age	27,346	132,129,978	0.2	0.2	0.00	0.01	1.09 [1.05-1.14]*	1.04 [1.00-1.09]	1.04 [0.99-1.08]
Breast cancer	18+	103,072	90,626,776	1.2	1.1	0.08	0.04	1.04 [1.02-1.07]*	1.03 [1.01-1.06]*	1.03 [1.01-1.06]*
Prostate cancer	40+	100,713	58,433,836	1.8	1.7	0.14	0.03	1.04 [1.02-1.06]*	1.01 [0.99-1.04]	1.01 [0.99-1.04]
Skin infection										
Molluscum contagiosum	any age	305,601	126,638,877	4.2	2.0	2.16	1.89	1.86 [1.84-1.88]*	1.83 [1.81-1.85]*	1.83 [1.81-1.85]*
Dermatophyte infection	any age	772,251	112,465,984	10.1	6.1	4.03	3.84	1.69 [1.68-1.70]*	1.61 [1.60-1.62]*	1.61 [1.60-1.62]*
Herpes simplex	any age	238,948	126,741,276	2.8	1.7	1.11	0.94	1.66 [1.64-1.68]*	1.51 [1.49-1.53]*	1.51 [1.49-1.53]*
Impetigo	any age	510,679	118,956,471	6.3	3.8	2.50	2.09	1.55 [1.54-1.56]*	1.50 [1.48-1.51]*	1.49 [1.48-1.50]*
Cutaneous warts	any age	1,097,449	109,739,588	13.2	9.2	3.94	3.07	1.36 [1.35-1.37]*	1.31 [1.30-1.31]*	1.30 [1.30-1.31]*
Immune mediated										
Alopecia Areata	any age	34,478	131,684,714	0.4	0.2	0.20	0.19	1.87 [1.81-1.93]*	1.77 [1.71-1.83]*	1.76 [1.71-1.83]*

Outcome	Main cohort	Events	Person-years	Crude rate (per 1,000 person-years)		Crude rate difference	Estimated rate difference[2]	Hazard ratio (99% confidence interval)[1]		
				Exposed	Unexposed			Minimally-adjusted	Comorbidity-adjusted	Drug-adjusted
Urticaria	any age	413,465	122,467,214	5.1	3.0	2.13	1.88	1.68 [1.67-1.70]*	1.59 [1.57-1.60]*	1.58 [1.56-1.59]*
COPD	40+	265,564	55,265,328	6.5	4.4	2.04	1.18	1.42 [1.40-1.44]*	1.22 [1.20-1.24]*	1.19 [1.17-1.21]*
Digestive system										
Crohn's disease	any age	19,956	131,823,099	0.2	0.1	0.10	0.09	1.76 [1.68-1.84]*	1.62 [1.54-1.69]*	1.59 [1.51-1.66]*
Coeliac disease	any age	31,407	131,797,202	0.3	0.2	0.12	0.10	1.52 [1.46-1.57]*	1.43 [1.38-1.48]*	1.42 [1.37-1.48]*
Ulcerative colitis	any age	26,713	131,596,441	0.3	0.2	0.08	0.08	1.50 [1.44-1.56]*	1.41 [1.35-1.47]*	1.38 [1.32-1.44]*
Irritable bowel syndrome	any age	270,827	124,042,454	2.9	2.0	0.84	0.67	1.46 [1.44-1.48]*	1.31 [1.29-1.33]*	1.31 [1.29-1.32]*
Oesophagitis	any age	247,978	125,802,402	2.4	1.9	0.54	0.49	1.40 [1.38-1.42]*	1.26 [1.24-1.27]*	1.25 [1.23-1.27]*
Gastro oesophageal reflux	any age	536,970	120,320,825	5.5	4.2	1.35	1.12	1.39 [1.38-1.41]*	1.25 [1.24-1.26]*	1.25 [1.24-1.26]*
Gastritis and duodenitis	any age	355,321	126,199,546	3.4	2.7	0.76	0.61	1.35 [1.34-1.36]*	1.22 [1.20-1.23]*	1.21 [1.20-1.22]*
Barett's oesophagus	18+	42,453	91,787,577	0.6	0.4	0.12	0.08	1.27 [1.23-1.31]*	1.17 [1.13-1.21]*	1.17 [1.13-1.21]*
Diverticular disease	18+	313,366	87,899,953	4.4	3.4	1.04	0.63	1.29 [1.28-1.31]*	1.17 [1.15-1.18]*	1.16 [1.15-1.17]*
Peptic ulcer disease	any age	71,186	130,759,692	0.6	0.5	0.08	0.08	1.26 [1.22-1.29]*	1.16 [1.13-1.19]*	1.15 [1.12-1.18]*
Abdominal hernia	any age	290,493	125,132,518	2.6	2.3	0.31	0.31	1.20 [1.19-1.22]*	1.14 [1.12-1.15]*	1.13 [1.12-1.14]*
Pancreatitis	any age	37,218	131,802,480	0.3	0.3	0.04	0.03	1.22 [1.18-1.26]*	1.11 [1.07-1.15]*	1.10 [1.06-1.14]*
Peritonitis	any age	12,978	132,164,723	0.1	0.1	0.01	0.01	1.16 [1.09-1.23]*	1.08 [1.01-1.15]	1.07 [1.00-1.14]
Appendicitis	any age	109,504	129,858,859	1.0	0.8	0.15	0.07	1.14 [1.12-1.16]*	1.08 [1.05-1.10]*	1.07 [1.05-1.10]*
Liver										
Autoimmune liver disease	any age	6,268	132,270,211	0.1	0.0	0.02	0.02	1.46 [1.35-1.58]*	1.35 [1.24-1.47]*	1.33 [1.22-1.45]*
Fibrosis/sclerosis/cirrhosis	18+	28,868	92,045,041	0.4	0.3	0.13	0.09	1.45 [1.40-1.51]*	1.27 [1.22-1.33]*	1.26 [1.21-1.32]*
Fatty liver	any age	148,328	131,140,252	1.4	1.1	0.37	0.28	1.44 [1.42-1.47]*	1.25 [1.22-1.27]*	1.24 [1.22-1.26]*
Oesophageal varices	18+	8,773	92,300,549	0.1	0.1	0.04	0.02	1.45 [1.35-1.55]*	1.21 [1.11-1.32]*	1.20 [1.10-1.31]*
Cholecystitis	any age	66,497	131,413,767	0.6	0.5	0.06	0.05	1.21 [1.18-1.24]*	1.10 [1.07-1.13]*	1.09 [1.06-1.12]*
Cardiovascular										
Thromboembolic diseases	18+	176,844	89,647,845	2.5	1.8	0.67	0.51	1.36 [1.34-1.38]*	1.25 [1.23-1.27]*	1.24 [1.22-1.26]*
Peripheral artery disease	18+	102,751	90,560,434	1.4	1.1	0.33	0.23	1.31 [1.28-1.33]*	1.20 [1.17-1.22]*	1.19 [1.16-1.22]*
Heart failure	18+	267,725	90,217,373	3.7	2.8	0.88	0.53	1.27 [1.26-1.29]*	1.17 [1.15-1.19]*	1.16 [1.14-1.18]*
Coronary artery disease	18+	535,318	78,283,962	8.2	6.5	1.70	1.06	1.24 [1.23-1.25]*	1.15 [1.14-1.16]*	1.14 [1.13-1.16]*

Outcome	Main cohort	Events	Person-years	Crude rate (per 1,000 person-years)		Crude rate difference	Estimated rate difference[2]	Hazard ratio (99% confidence interval)[1]		
				Exposed	Unexposed			Minimally-adjusted	Comorbidity-adjusted	Drug-adjusted
Hypertension	18+	766,234	69,042,169	13.8	10.4	3.32	1.41	1.17 [1.16-1.18]*	1.11 [1.11-1.12]*	1.11 [1.10-1.12]*
Stroke	18+	259,103	90,123,639	3.3	2.8	0.58	0.28	1.18 [1.16-1.20]*	1.09 [1.08-1.11]*	1.09 [1.07-1.10]*
Myocardial infarction	18+	150,848	89,666,833	1.9	1.6	0.30	0.16	1.17 [1.15-1.19]*	1.09 [1.07-1.11]*	1.08 [1.06-1.10]*
Metabolic										
Obesity	any age	439,250	123,114,930	4.3	3.4	0.92	0.78	1.34 [1.33-1.36]*	1.22 [1.21-1.23]*	1.21 [1.20-1.23]*
Metabolic syndrome	any age	3,026	132,299,975	0.0	0.0	0.01	0.00	1.40 [1.25-1.57]*	1.16 [1.02-1.31]	1.15 [1.01-1.31]
Dyslipidaemia	any age	470,861	121,152,644	4.3	3.8	0.58	0.48	1.21 [1.20-1.22]*	1.12 [1.11-1.14]*	1.12 [1.11-1.13]*
Diabetes mellitus	any age	418,667	123,370,779	3.9	3.3	0.62	0.43	1.22 [1.21-1.24]*	1.12 [1.11-1.14]*	1.12 [1.10-1.13]*
Neurological										
Peripheral neuropathies	18+	732,170	76,392,322	12.2	9.0	3.26	2.15	1.33 [1.32-1.34]*	1.21 [1.20-1.22]*	1.21 [1.20-1.22]*
Migraine	any age	430,703	122,554,261	4.4	3.3	1.07	0.66	1.28 [1.27-1.29]*	1.18 [1.17-1.19]*	1.18 [1.16-1.19]*
Epilepsy	any age	78,658	129,986,406	0.7	0.6	0.13	0.09	1.22 [1.19-1.25]*	1.15 [1.12-1.18]*	1.15 [1.12-1.17]*
Multiple sclerosis	18+	10,518	92,013,488	0.1	0.1	0.02	0.01	1.16 [1.09-1.24]*	1.12 [1.05-1.20]*	1.11 [1.03-1.18]*
Vascular dementia	40+	56,925	59,209,560	1.1	0.9	0.18	0.07	1.13 [1.09-1.16]*	1.07 [1.03-1.10]*	1.07 [1.03-1.10]*
Alzheimer's dementia	40+	100,282	58,972,725	1.9	1.7	0.26	0.09	1.07 [1.05-1.10]*	1.05 [1.02-1.07]*	1.05 [1.02-1.07]*
Parkinson's disease	40+	40,677	59,059,717	0.7	0.7	0.07	0.01	1.05 [1.02-1.09]*	1.02 [0.98-1.06]	1.02 [0.98-1.06]
Bone health										
Osteoporosis	18+	248,234	88,899,377	3.5	2.6	0.82	0.53	1.26 [1.24-1.27]*	1.18 [1.16-1.20]*	1.17 [1.16-1.19]*
Spine fracture	18+	67,722	91,782,410	0.9	0.7	0.22	0.13	1.28 [1.25-1.31]*	1.17 [1.14-1.20]*	1.16 [1.13-1.19]*
Pelvis fracture	18+	39,338	92,007,752	0.5	0.4	0.08	0.05	1.17 [1.13-1.22]*	1.11 [1.07-1.15]*	1.10 [1.06-1.15]*
Hip fracture	18+	113,911	91,578,437	1.4	1.2	0.22	0.13	1.14 [1.11-1.16]*	1.10 [1.08-1.13]*	1.10 [1.08-1.12]*
Wrist fracture	18+	208,771	86,953,685	2.7	2.3	0.36	0.18	1.14 [1.13-1.16]*	1.07 [1.06-1.09]*	1.07 [1.05-1.09]*
Mental health and substance use										
Anxiety	any age	1,185,785	111,329,944	13.1	10.0	3.03	1.84	1.27 [1.27-1.28]*	1.16 [1.16-1.17]*	1.16 [1.15-1.17]*
Depression	any age	1,167,365	103,080,864	13.6	10.7	2.86	1.88	1.26 [1.25-1.27]*	1.16 [1.15-1.17]*	1.15 [1.15-1.16]*
Alcohol abuse	18+	84,928	90,220,331	1.2	0.9	0.26	0.15	1.28 [1.25-1.31]*	1.14 [1.12-1.17]*	1.14 [1.11-1.17]*
Cigarette smoking	18+	1,143,191	38,605,905	34.1	28.3	5.80	3.14	1.18 [1.18-1.19]*	1.10 [1.09-1.11]*	1.10 [1.09-1.10]*

Outcome	Main cohort	Events	Person-years	Crude rate (per 1,000 person-years)		Crude rate difference	Estimated rate difference[2]	Hazard ratio (99% confidence interval)[1]		
				Exposed	Unexposed			Minimally-adjusted	Comorbidity-adjusted	Drug-adjusted
ADHD and autism										
Autism	any age	116,658	131,318,200	1.2	0.8	0.37	0.15	1.19 [1.17-1.22]*	1.15 [1.12-1.17]*	1.14 [1.12-1.17]*
ADHD	any age	82,385	131,502,052	0.8	0.6	0.24	0.06	1.16 [1.13-1.19]*	1.08 [1.05-1.10]*	1.07 [1.05-1.10]*

[1] Hazard ratios (99% confidence intervals) estimated from Cox models comparing people with eczema to those without eczema. * Indicates that the result is significant under Bonferroni-correction.

[2] Rate difference calculated using the estimated rate in the unexposed (rate in the exposed * (1/hazard ratio))

eTable 2: Mild and moderate to severe eczema compared to no eczema

	Events			Person-years			Rate (per 1,000 person-years)			Hazard ratio (99% confidence interval)[1]	
Outcome	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Mild	Mod.-sev.
Atopic and allergic											
Asthma	448,093	220,121	16,825	79,984,549	19,721,618	1,030,005	5.6	11.2	16.33	1.85 [1.84-1.86]*	2.52 [2.46-2.58]*
Allergic Rhinitis	449,870	226,325	18,143	88,344,923	20,808,629	1,085,957	5.1	10.9	16.71	1.89 [1.88-1.90]*	2.65 [2.59-2.72]*
Allergic Conjunctivitis	98,754	50,965	4,340	103,077,037	23,962,460	1,308,359	1.0	2.1	3.32	1.97 [1.95-2.00]*	2.84 [2.70-2.99]*
Eosinophilic Oesophagitis	1,509	680	44	106,218,635	24,765,644	1,373,279	0.0	0.0	0.03	1.54 [1.36-1.75]*	1.58 [0.94-2.65]
Food allergy	44,325	45,776	4,394	104,207,029	24,188,357	1,325,723	0.4	1.9	3.31	3.87 [3.81-3.94]*	7.35 [6.85-7.89]*
Immune mediated											
Alopecia Areata	23,417	10,211	850	105,675,817	24,644,421	1,364,476	0.2	0.4	0.62	1.73 [1.68-1.79]*	2.38 [2.13-2.65]*
Urticaria	290,433	115,246	7,786	98,271,261	22,945,526	1,250,427	3.0	5.0	6.23	1.57 [1.55-1.58]*	2.01 [1.94-2.08]*
COPD	200,116	61,864	3,584	45,155,940	9,686,434	422,954	4.4	6.4	8.47	1.22 [1.21-1.24]*	1.24 [1.18-1.30]*
Mental health and substance use											
Anxiety	886,864	281,138	17,783	88,444,081	21,686,772	1,199,091	10.0	13.0	14.83	1.16 [1.16-1.17]*	1.20 [1.17-1.22]*
Depression	872,138	276,963	18,264	81,343,782	20,598,502	1,138,579	10.7	13.4	16.04	1.16 [1.15-1.17]*	1.18 [1.16-1.21]*
Alcohol abuse	65,766	18,153	1,009	73,579,315	15,901,093	739,923	0.9	1.1	1.36	1.14 [1.12-1.17]*	1.22 [1.11-1.34]*
Cigarette smoking	846,620	282,342	14,229	29,910,251	8,315,422	380,232	28.3	34.0	37.42	1.10 [1.10-1.11]*	1.11 [1.08-1.14]*
ADHD and autism											
ADHD	61,091	20,311	983	105,512,659	24,623,432	1,365,962	0.6	0.8	0.72	1.08 [1.05-1.10]*	1.07 [0.98-1.18]
Autism	86,004	29,216	1,438	105,380,429	24,575,500	1,362,272	0.8	1.2	1.06	1.15 [1.13-1.17]*	1.19 [1.11-1.29]*
Cardiovascular											
Hypertension	580,592	175,456	10,186	55,560,790	12,905,722	575,657	10.4	13.6	17.69	1.11 [1.11-1.12]*	1.12 [1.08-1.15]*
Coronary artery disease	414,123	114,232	6,963	63,534,534	14,111,284	638,144	6.5	8.1	10.91	1.15 [1.14-1.16]*	1.17 [1.13-1.21]*
Peripheral artery disease	79,356	22,126	1,269	73,905,785	15,914,677	739,972	1.1	1.4	1.71	1.19 [1.17-1.21]*	1.31 [1.21-1.42]*
Myocardial infarction	118,971	30,250	1,627	73,113,613	15,818,525	734,695	1.6	1.9	2.21	1.09 [1.07-1.11]*	1.07 [1.00-1.15]
Stroke	203,636	52,539	2,928	73,554,610	15,833,219	735,809	2.8	3.3	3.98	1.09 [1.08-1.10]*	1.11 [1.06-1.17]*
Heart failure	206,541	58,048	3,136	73,612,815	15,866,376	738,182	2.8	3.7	4.25	1.17 [1.16-1.19]*	1.13 [1.08-1.19]*
Thromboembolic diseases	135,319	39,343	2,182	73,159,072	15,756,766	732,007	1.8	2.5	2.98	1.25 [1.23-1.27]*	1.34 [1.26-1.42]*
Metabolic											
Obesity	333,121	99,854	6,275	98,453,496	23,367,818	1,293,617	3.4	4.3	4.85	1.22 [1.21-1.23]*	1.27 [1.23-1.32]*
Dyslipidaemia	364,337	100,543	5,981	96,663,359	23,202,471	1,286,814	3.8	4.3	4.65	1.12 [1.11-1.13]*	1.15 [1.11-1.19]*

	Events			Person-years			Rate (per 1,000 person-years)			Hazard ratio (99% confidence interval)[1]	
Outcome	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Mild	Mod.-sev.
Diabetes mellitus	321,635	91,673	5,359	98,428,919	23,630,197	1,311,663	3.3	3.9	4.09	1.12 [1.11-1.14]*	1.12 [1.08-1.17]*
Metabolic syndrome	2,293	704	29	106,168,863	24,758,175	1,372,938	0.0	0.0	0.02	1.18 [1.05-1.32]*	0.78 [0.45-1.36]
Bone health											
Hip fracture	90,000	22,720	1,191	74,782,108	16,048,493	747,836	1.2	1.4	1.59	1.10 [1.08-1.12]*	1.10 [1.01-1.20]
Pelvis fracture	30,992	7,922	424	75,148,104	16,108,909	750,739	0.4	0.5	0.56	1.11 [1.07-1.14]*	1.13 [0.98-1.30]
Spine fracture	52,347	14,570	805	74,960,642	16,072,895	748,873	0.7	0.9	1.07	1.17 [1.14-1.20]*	1.22 [1.10-1.35]*
Wrist fracture	165,097	41,743	1,931	70,745,784	15,481,755	726,146	2.3	2.7	2.66	1.07 [1.06-1.09]*	1.06 [1.00-1.13]
Osteoporosis	191,596	53,654	2,984	72,517,164	15,655,275	726,938	2.6	3.4	4.10	1.18 [1.17-1.20]*	1.17 [1.11-1.23]*
Skin infection											
Molluscum contagiosum	202,922	97,332	5,347	101,913,645	23,440,633	1,284,599	2.0	4.2	4.16	1.82 [1.80-1.83]*	2.21 [2.12-2.31]*
Impetigo	363,305	138,188	9,186	95,566,086	22,210,513	1,179,872	3.8	6.2	7.79	1.47 [1.46-1.48]*	2.10 [2.04-2.17]*
Herpes simplex	169,370	64,548	5,030	101,640,692	23,797,566	1,303,018	1.7	2.7	3.86	1.49 [1.47-1.51]*	1.92 [1.84-2.01]*
Dermatophyte infection	546,348	211,881	14,022	90,080,029	21,247,043	1,138,912	6.1	10.0	12.31	1.60 [1.59-1.61]*	1.84 [1.80-1.89]*
Cutaneous warts	808,959	271,433	17,057	87,809,567	20,810,461	1,119,560	9.2	13.0	15.24	1.30 [1.29-1.31]*	1.40 [1.37-1.43]*
Cancer											
Lung cancer	57,993	13,926	674	75,289,491	16,135,868	752,067	0.8	0.9	0.90	1.05 [1.03-1.08]*	0.88 [0.78-0.98]
Breast cancer	82,998	19,022	1,052	73,945,632	15,939,517	741,627	1.1	1.2	1.42	1.03 [1.01-1.05]*	1.01 [0.93-1.10]
Prostate cancer	81,279	18,390	1,044	47,863,342	10,123,952	446,542	1.7	1.8	2.34	1.01 [1.00-1.03]	1.02 [0.94-1.10]
Pancreatic cancer	12,907	3,059	134	75,436,623	16,156,625	753,107	0.2	0.2	0.18	1.08 [1.02-1.13]*	0.81 [0.64-1.02]
Non-Hodgkin lymphoma	19,722	5,492	332	105,984,442	24,728,832	1,371,506	0.2	0.2	0.24	1.26 [1.21-1.30]*	1.38 [1.19-1.61]*
Hodgkin lymphoma	2,511	978	70	106,165,669	24,757,486	1,372,743	0.0	0.0	0.05	1.82 [1.65-2.00]*	2.09 [1.43-3.05]*
Myeloma	8,217	1,992	112	106,169,332	24,760,048	1,372,971	0.1	0.1	0.08	1.11 [1.05-1.18]*	1.11 [0.86-1.43]
CNS cancers	21,889	5,210	247	106,020,801	24,737,363	1,371,813	0.2	0.2	0.18	1.05 [1.01-1.09]	0.91 [0.76-1.08]
Melanoma	44,478	10,434	615	105,364,056	24,634,411	1,366,076	0.4	0.4	0.45	1.07 [1.04-1.10]*	1.11 [0.99-1.24]
Nonmelanoma skin cancer	208,738	53,605	3,099	103,213,797	24,261,513	1,346,536	2.0	2.2	2.30	1.13 [1.12-1.15]*	1.16 [1.10-1.22]*
Neurological											
Alzheimer's dementia	79,942	19,231	1,109	48,327,017	10,194,736	450,972	1.7	1.9	2.46	1.05 [1.03-1.07]*	1.04 [0.96-1.14]
Vascular dementia	45,043	11,260	622	48,531,645	10,225,496	452,419	0.9	1.1	1.37	1.07 [1.04-1.10]*	1.07 [0.96-1.21]
Epilepsy	60,326	17,279	1,053	104,166,918	24,463,933	1,355,555	0.6	0.7	0.78	1.15 [1.12-1.17]*	1.16 [1.07-1.27]*
Migraine	323,142	101,076	6,485	97,924,162	23,341,032	1,289,068	3.3	4.3	5.03	1.18 [1.17-1.19]*	1.20 [1.16-1.24]*
Multiple sclerosis	8,308	2,104	106	75,144,189	16,117,967	751,331	0.1	0.1	0.14	1.13 [1.06-1.20]*	1.04 [0.80-1.34]

	Events			Person-years			Rate (per 1,000 person-years)			Hazard ratio (99% confidence interval)[1]	
Outcome	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Unexposed	Mild	Mod.-sev.	Mild	Mod.-sev.
Parkinson's disease	32,750	7,537	390	48,393,218	10,214,642	451,857	0.7	0.7	0.86	1.02 [0.99-1.06]	0.93 [0.82-1.07]
Peripheral neuropathies	555,749	167,024	9,397	61,964,387	13,805,085	622,850	9.0	12.1	15.09	1.21 [1.20-1.22]*	1.31 [1.27-1.35]*
Digestive system											
Abdominal hernia	226,021	61,040	3,432	100,050,966	23,763,351	1,318,201	2.3	2.6	2.60	1.13 [1.12-1.15]*	1.18 [1.12-1.23]*
Appendicitis	84,733	23,376	1,395	104,069,506	24,434,709	1,354,645	0.8	1.0	1.03	1.08 [1.06-1.10]*	1.02 [0.95-1.10]
Barett's oesophagus	33,057	8,864	532	74,961,460	16,077,323	748,795	0.4	0.6	0.71	1.16 [1.13-1.20]*	1.35 [1.19-1.53]*
Coeliac disease	22,718	8,149	540	105,750,524	24,679,045	1,367,633	0.2	0.3	0.39	1.42 [1.37-1.47]*	1.58 [1.39-1.79]*
Crohn's disease	13,916	5,636	404	105,767,872	24,686,272	1,368,954	0.1	0.2	0.30	1.61 [1.54-1.68]*	1.76 [1.51-2.04]*
Diverticular disease	241,745	67,850	3,771	71,680,723	15,502,039	717,191	3.4	4.4	5.26	1.17 [1.16-1.18]*	1.15 [1.10-1.21]*
Gastritis and duodenitis	269,160	81,307	4,854	101,050,637	23,829,939	1,318,970	2.7	3.4	3.68	1.21 [1.20-1.22]*	1.28 [1.23-1.33]*
Gastro oesophageal reflux	402,927	126,194	7,849	96,126,893	22,919,343	1,274,590	4.2	5.5	6.16	1.25 [1.24-1.26]*	1.37 [1.33-1.42]*
Irritable bowel syndrome	199,859	66,410	4,558	99,184,928	23,556,082	1,301,444	2.0	2.8	3.50	1.30 [1.29-1.32]*	1.40 [1.35-1.47]*
Oesophagitis	187,625	56,814	3,539	100,666,999	23,816,834	1,318,568	1.9	2.4	2.68	1.25 [1.23-1.26]*	1.35 [1.29-1.42]*
Pancreatitis	29,037	7,739	442	105,741,117	24,692,109	1,369,255	0.3	0.3	0.32	1.10 [1.07-1.14]*	1.20 [1.05-1.37]*
Peptic ulcer disease	55,484	14,824	878	104,838,387	24,560,144	1,361,162	0.5	0.6	0.65	1.15 [1.13-1.18]*	1.19 [1.08-1.31]*
Peritonitis	10,257	2,556	165	106,051,238	24,741,639	1,371,846	0.1	0.1	0.12	1.06 [1.01-1.12]	1.34 [1.08-1.67]*
Ulcerative colitis	19,754	6,545	414	105,567,675	24,660,760	1,368,006	0.2	0.3	0.30	1.41 [1.36-1.46]*	1.33 [1.15-1.52]*
Liver											
Autoimmune liver disease	4,690	1,478	100	106,143,209	24,754,417	1,372,586	0.0	0.1	0.07	1.32 [1.22-1.42]*	1.93 [1.44-2.57]*
Cholecystitis	52,102	13,620	775	105,414,674	24,633,158	1,365,936	0.5	0.6	0.57	1.10 [1.07-1.12]*	1.10 [1.00-1.22]
Fatty liver	111,402	34,870	2,056	105,220,919	24,557,252	1,362,082	1.1	1.4	1.51	1.24 [1.22-1.26]*	1.38 [1.29-1.47]*
Fibrosis/sclerosis/cirrhosis	21,795	6,709	364	75,176,529	16,117,532	750,980	0.3	0.4	0.48	1.28 [1.23-1.33]*	1.22 [1.04-1.43]
Oesophageal varices	6,662	1,996	115	75,397,752	16,150,027	752,770	0.1	0.1	0.15	1.21 [1.12-1.30]*	1.20 [0.89-1.62]

[1] Hazard ratios (99% confidence intervals) estimated from Cox models comparing people with severe eczema to those without eczema. * Indicates that the result is significant under Bonferroni-correction.

eTable 3: Eczema compared to no eczema (different cohort age cut-offs)

	Hazard ratio (99% confidence interval)[1]			
Outcome	Any age	18+	40+	More severe (any age)
Atopic and allergic				
Allergic Conjunctivitis	**2.02 [1.99-2.05]***	2.04 [2.00-2.09]*	1.94 [1.89-1.99]*	2.04 [2.00-2.08]*
Food allergy	**4.02 [3.95-4.10]***	2.03 [1.96-2.10]*	1.66 [1.58-1.74]*	4.07 [3.96-4.18]*
Allergic Rhinitis	**1.93 [1.91-1.94]***	1.66 [1.64-1.67]*	1.60 [1.57-1.62]*	1.85 [1.83-1.87]*
Asthma	**1.88 [1.87-1.90]***	1.58 [1.57-1.60]*	1.46 [1.44-1.48]*	1.84 [1.81-1.86]*
Eosinophilic Oesophagitis	**1.54 [1.34-1.79]***	1.49 [1.26-1.76]*	1.45 [1.17-1.79]*	1.46 [1.21-1.76]*
Cancer				
Hodgkin lymphoma	**1.83 [1.64-2.04]***	1.89 [1.68-2.11]*	1.90 [1.65-2.18]*	2.03 [1.78-2.31]*
Non-Hodgkin lymphoma	**1.26 [1.21-1.32]***	1.26 [1.21-1.32]*	1.22 [1.16-1.27]*	1.27 [1.21-1.33]*
Nonmelanoma skin cancer	**1.14 [1.12-1.15]***	1.14 [1.12-1.15]*	1.13 [1.11-1.14]*	1.13 [1.11-1.15]*
Myeloma	**1.11 [1.04-1.19]***	1.09 [1.02-1.17]	1.09 [1.02-1.17]	1.10 [1.01-1.20]
Melanoma	**1.07 [1.04-1.11]***	1.07 [1.04-1.10]*	1.07 [1.03-1.10]*	1.04 [1.01-1.08]
Pancreatic cancer	1.08 [1.02-1.15]*	**1.06 [1.00-1.12]**	1.05 [0.99-1.11]	1.04 [0.97-1.11]
Lung cancer	1.04 [1.01-1.07]	**1.05 [1.02-1.08]***	1.04 [1.02-1.07]*	1.03 [1.00-1.07]
Breast cancer	1.03 [1.01-1.06]*	**1.03 [1.01-1.06]***	1.03 [1.01-1.05]	1.01 [0.99-1.04]
CNS cancers	**1.04 [1.00-1.09]**	1.03 [0.99-1.08]	1.03 [0.99-1.08]	1.01 [0.95-1.06]
Prostate cancer	1.01 [0.99-1.03]	1.01 [0.99-1.04]	**1.01 [0.99-1.04]**	0.99 [0.97-1.02]
Immune mediated				
Alopecia Areata	**1.77 [1.71-1.83]***	1.80 [1.73-1.87]*	1.92 [1.80-2.03]*	2.16 [2.07-2.26]*
Urticaria	**1.59 [1.57-1.60]***	1.79 [1.77-1.82]*	1.87 [1.84-1.90]*	1.72 [1.70-1.75]*
COPD	1.24 [1.22-1.25]*	1.23 [1.21-1.24]*	**1.22 [1.20-1.24]***	1.22 [1.20-1.25]*
Skin infection				
Impetigo	**1.50 [1.48-1.51]***	1.68 [1.65-1.72]*	1.71 [1.67-1.75]*	1.65 [1.63-1.68]*
Dermatophyte infection	**1.61 [1.60-1.62]***	1.66 [1.64-1.67]*	1.67 [1.65-1.68]*	1.59 [1.58-1.61]*
Molluscum contagiosum	**1.83 [1.81-1.85]***	1.56 [1.47-1.65]*	1.69 [1.54-1.87]*	1.73 [1.70-1.77]*
Herpes simplex	**1.51 [1.49-1.53]***	1.49 [1.47-1.51]*	1.50 [1.46-1.53]*	1.58 [1.55-1.61]*
Cutaneous warts	**1.31 [1.30-1.31]***	1.31 [1.30-1.32]*	1.28 [1.26-1.29]*	1.24 [1.23-1.25]*
Digestive system				
Crohn's disease	**1.62 [1.54-1.69]***	1.58 [1.51-1.67]*	1.48 [1.38-1.58]*	1.71 [1.61-1.81]*
Coeliac disease	**1.43 [1.38-1.48]***	1.46 [1.40-1.53]*	1.48 [1.40-1.56]*	1.51 [1.43-1.58]*
Ulcerative colitis	**1.41 [1.35-1.47]***	1.42 [1.36-1.48]*	1.41 [1.34-1.49]*	1.43 [1.35-1.50]*
Irritable bowel syndrome	**1.31 [1.29-1.33]***	1.31 [1.29-1.33]*	1.31 [1.28-1.33]*	1.26 [1.24-1.28]*
Gastro oesophageal reflux	**1.25 [1.24-1.26]***	1.25 [1.24-1.26]*	1.24 [1.22-1.25]*	1.23 [1.21-1.24]*
Oesophagitis	**1.26 [1.24-1.27]***	1.25 [1.23-1.27]*	1.24 [1.22-1.26]*	1.24 [1.22-1.27]*
Gastritis and duodenitis	**1.22 [1.20-1.23]***	1.21 [1.20-1.23]*	1.21 [1.19-1.23]*	1.21 [1.19-1.23]*
Barett's oesophagus	1.17 [1.13-1.21]*	**1.17 [1.13-1.21]***	1.16 [1.12-1.20]*	1.19 [1.15-1.24]*
Diverticular disease	1.17 [1.16-1.18]*	**1.17 [1.15-1.18]***	1.16 [1.15-1.18]*	1.16 [1.14-1.18]*
Peptic ulcer disease	**1.16 [1.13-1.19]***	1.15 [1.12-1.18]*	1.15 [1.12-1.19]*	1.17 [1.14-1.21]*
Abdominal hernia	**1.14 [1.12-1.15]***	1.15 [1.13-1.16]*	1.14 [1.12-1.15]*	1.13 [1.11-1.15]*
Pancreatitis	**1.11 [1.07-1.15]***	1.10 [1.06-1.15]*	1.11 [1.06-1.15]*	1.14 [1.09-1.19]*
Peritonitis	**1.08 [1.01-1.15]**	1.09 [1.02-1.16]*	1.06 [0.99-1.14]	1.14 [1.06-1.23]*
Appendicitis	**1.08 [1.05-1.10]***	1.06 [1.03-1.09]*	1.06 [1.02-1.10]*	1.06 [1.02-1.09]*

Outcome	Hazard ratio (99% confidence interval)[1]			
	Any age	18+	40+	More severe (any age)
Liver				
Autoimmune liver disease	**1.35 [1.24-1.47]***	1.31 [1.20-1.43]*	1.29 [1.18-1.41]*	1.39 [1.26-1.55]*
Fibrosis/sclerosis/cirrhosis	1.26 [1.21-1.32]*	**1.27 [1.22-1.33]***	1.26 [1.21-1.32]*	1.35 [1.29-1.43]*
Fatty liver	**1.25 [1.22-1.27]***	1.24 [1.22-1.26]*	1.22 [1.20-1.24]*	1.26 [1.24-1.29]*
Oesophageal varices	1.22 [1.12-1.32]*	**1.21 [1.11-1.32]***	1.22 [1.12-1.33]*	1.38 [1.25-1.52]*
Cholecystitis	**1.10 [1.07-1.13]***	1.10 [1.07-1.13]*	1.08 [1.05-1.11]*	1.08 [1.04-1.12]*
Metabolic				
Metabolic syndrome	**1.16 [1.02-1.31]**	1.22 [1.07-1.39]*	1.23 [1.07-1.41]*	1.16 [0.99-1.36]
Obesity	**1.22 [1.21-1.23]***	1.21 [1.20-1.22]*	1.18 [1.17-1.20]*	1.22 [1.20-1.23]*
Diabetes mellitus	**1.12 [1.11-1.14]***	1.13 [1.12-1.14]*	1.12 [1.11-1.13]*	1.15 [1.13-1.16]*
Dyslipidaemia	**1.12 [1.11-1.14]***	1.13 [1.12-1.14]*	1.12 [1.11-1.13]*	1.12 [1.10-1.13]*
Neurological				
Peripheral neuropathies	1.21 [1.20-1.22]*	**1.21 [1.20-1.22]***	1.20 [1.19-1.22]*	1.20 [1.19-1.22]*
Epilepsy	**1.15 [1.12-1.18]***	1.19 [1.16-1.23]*	1.23 [1.18-1.27]*	1.15 [1.11-1.19]*
Migraine	**1.18 [1.17-1.19]***	1.16 [1.15-1.17]*	1.16 [1.14-1.18]*	1.15 [1.13-1.16]*
Multiple sclerosis	1.09 [1.02-1.17]	**1.12 [1.05-1.20]***	1.08 [0.99-1.17]	1.08 [0.99-1.18]
Vascular dementia	1.06 [1.03-1.09]*	1.06 [1.03-1.09]*	**1.07 [1.03-1.10]***	1.06 [1.02-1.10]*
Alzheimer's dementia	1.04 [1.02-1.07]*	1.05 [1.02-1.07]*	**1.05 [1.02-1.07]***	1.03 [1.00-1.06]
Parkinson's disease	1.02 [0.98-1.06]	1.02 [0.98-1.05]	**1.02 [0.98-1.06]**	0.99 [0.95-1.03]
Cardiovascular				
Peripheral artery disease	1.20 [1.18-1.23]*	**1.20 [1.17-1.22]***	1.20 [1.17-1.22]*	1.20 [1.17-1.24]*
Heart failure	1.17 [1.15-1.19]*	**1.17 [1.15-1.19]***	1.16 [1.14-1.18]*	1.19 [1.17-1.21]*
Coronary artery disease	1.15 [1.14-1.16]*	**1.15 [1.14-1.16]***	1.14 [1.12-1.15]*	1.14 [1.13-1.15]*
Hypertension	1.11 [1.10-1.12]*	**1.11 [1.11-1.12]***	1.10 [1.09-1.11]*	1.13 [1.11-1.14]*
Stroke	1.09 [1.08-1.11]*	**1.09 [1.08-1.11]***	1.09 [1.07-1.10]*	1.10 [1.08-1.11]*
Myocardial infarction	1.08 [1.06-1.10]*	**1.09 [1.07-1.11]***	1.08 [1.06-1.10]*	1.10 [1.08-1.12]*
Bone health				
Osteoporosis	1.18 [1.16-1.19]*	**1.18 [1.16-1.20]***	1.18 [1.17-1.20]*	1.18 [1.16-1.20]*
Spine fracture	1.18 [1.15-1.21]*	**1.17 [1.14-1.20]***	1.19 [1.15-1.22]*	1.20 [1.16-1.24]*
Pelvis fracture	1.11 [1.07-1.15]*	**1.11 [1.07-1.15]***	1.11 [1.06-1.15]*	1.13 [1.09-1.18]*
Hip fracture	1.10 [1.08-1.13]*	**1.10 [1.08-1.13]***	1.10 [1.08-1.13]*	1.12 [1.09-1.15]*
Wrist fracture	1.07 [1.06-1.08]*	**1.07 [1.06-1.09]***	1.08 [1.06-1.10]*	1.05 [1.04-1.07]*
ADHD and autism				
Autism	**1.15 [1.12-1.17]***	1.18 [1.12-1.24]*	1.61 [1.46-1.78]*	1.11 [1.07-1.15]*
ADHD	**1.08 [1.05-1.10]***	1.02 [0.97-1.08]	1.10 [0.97-1.24]	1.05 [1.01-1.10]
Mental health and substance use				
Depression	**1.16 [1.15-1.17]***	1.17 [1.16-1.18]*	1.19 [1.18-1.21]*	1.17 [1.16-1.18]*
Anxiety	**1.16 [1.16-1.17]***	1.16 [1.15-1.16]*	1.17 [1.16-1.18]*	1.15 [1.14-1.16]*
Alcohol abuse	1.12 [1.09-1.15]*	**1.14 [1.12-1.17]***	1.17 [1.14-1.21]*	1.17 [1.14-1.21]*
Cigarette smoking	1.14 [1.13-1.15]*	**1.10 [1.09-1.11]***	1.10 [1.09-1.11]*	1.14 [1.13-1.15]*

[1] Hazard ratios (99% confidence intervals) estimated from Cox models comparing people with eczema to those without eczema. * Indicates that the result is significant under Bonferroni-correction. Results from the main cohort are in bold.

eTable 4: Most commonly occurring codes

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
ADHD	1. Attention deficit hyperactivity disorder 639,300 (72.5%); 2. Attention deficit with hyperactivity 65,400 (79.9%); 3. Child attention deficit disorder 55,200 (86.1%); 4. Hyperactive behaviour 35,900 (90.2%); 5. Attention deficit disorder 33,000 (94.0%)
Abdominal hernia	1. Inguinal hernia 782,300 (22.1%); 2. Primary repair of inguinal hernia 557,200 (37.8%); 3. Umbilical hernia 484,300 (51.4%); 4. Right inguinal hernia 322,200 (60.5%); 5. Left inguinal hernia 246,000 (67.4%); 6. Repair of umbilical hernia 177,700 (72.4%); 7. Paraumbilical hernia 141,900 (76.4%); 8. Primary mesh repair of inguinal hernia 61,300 (78.2%); 9. Inguinal hernia NOS 46,700 (79.5%); 10. Ventral hernia 44,500 (80.7%); 11. Bilateral inguinal hernia repair 39,400 (81.8%); 12. Primary laparoscopic repair of inguinal hernia 36,200 (82.9%); 13. Femoral hernia 35,300 (83.9%); 14. Hernia of abdominal cavity 30,100 (84.7%); 15. Repair of recurrent inguinal hernia 28,400 (85.5%); 16. Primary repair of inguinal hernia NOS 26,700 (86.3%); 17. Simple umbilical hernia 26,300 (87.0%); 18. H/O: abdominal hernia 25,000 (87.7%); 19. Inguinal herniotomy 24,100 (88.4%); 20. Primary repair of femoral hernia 23,600 (89.0%); 21. Uncomplicated inguinal hernia 21,900 (89.7%)
Alcohol abuse	1. Alcohol dependence syndrome 1,142,800 (34.5%); 2. Alcohol problem drinking 847,100 (60.1%); 3. Alcoholic cirrhosis of liver 329,200 (70.0%); 4. Alcohol detoxification 167,200 (75.1%); 5. Alcoholism 155,400 (79.8%); 6. Alcohol dependence syndrome NOS 109,200 (83.1%); 7. Alcohol withdrawal syndrome 88,300 (85.7%); 8. Alcohol dependence 70,000 (87.8%); 9. Chronic alcoholism 62,800 (89.7%)
Allergic Conjunctivitis	1. Atopic conjunctivitis 586,100 (82.3%); 2. Chronic allergic conjunctivitis 76,200 (93.1%); 3. Acute allergic conjunctivitis 30,100 (97.3%); 4. Acute atopic conjunctivitis 12,800 (99.1%); 5. Seasonal allergic conjunctivitis 4,000 (99.6%)
Allergic Rhinitis	1. Hay fever - pollens 2,515,300 (30.7%); 2. Allergic rhinitis 1,339,900 (47.0%); 3. Hay fever 1,126,700 (60.8%); 4. Allergic rhinitis due to allergen 676,900 (69.0%); 5. Allergic rhinitis due to pollens 588,800 (76.2%); 6. H/O: hay fever 583,200 (83.3%); 7. Allergic rhinitis due to pollen 253,100 (86.4%); 8. Perennial allergic rhinitis 247,600 (89.5%)
Alopecia Areata	1. Alopecia areata 206,300 (95.9%); 2. [X]Other alopecia areata 8,700 (100.0%); 3. Ophiasis 0 (100.0%); 4. Ophiasis 0 (100.0%)
Alzheimer's dementia	1. Alzheimer's disease 803,600 (54.6%); 2. [X]Dementia in Alzheimer's disease 324,400 (76.6%); 3. [X]Dementia in Alzheimer's dis, atypical or mixed type 118,600 (84.6%); 4. Dementia in Alzheimer's disease with late onset 56,300 (88.5%); 5. [X]Alzheimer's dementia unspec 54,500 (92.2%)
Anxiety	1. Mixed anxiety and depressive disorder 18,609,100 (55.2%); 2. Anxiety disorder 6,194,400 (73.6%); 3. Anxiety state 1,161,500 (77.0%); 4. Panic attack 922,700 (79.7%); 5. [X]Mixed anxiety and depressive disorder 706,800 (81.8%); 6. Anxiousness 684,900 (83.9%); 7. Generalised anxiety disorder 7 item score 631,700 (85.7%); 8. Anxiousness - symptom 603,400 (87.5%); 9. [X]Anxiety NOS 550,600 (89.2%)
Appendicitis	1. Appendicectomy 415,900 (43.3%); 2. Emergency appendicectomy 164,800 (60.4%); 3. Acute appendicitis 105,200 (71.4%); 4. Emergency appendicectomy NEC 38,000 (75.3%); 5. Appendicitis 30,700 (78.5%); 6. Excision of appendix 29,500 (81.6%); 7. Emergency excision of appendix 24,200 (84.1%); 8. Laparoscopic appendicectomy 22,500 (86.4%); 9. Other excision of appendix NOS 20,700 (88.6%)
Asthma	1. Asthma 20,390,400 (15.8%); 2. Asthma annual review 12,636,600 (25.6%); 3. Asthma not disturbing sleep 8,515,200 (32.2%); 4. Asthma not limiting activities 8,182,100 (38.6%); 5. Asthma management 5,969,400 (43.2%); 6. Asthma medication review 5,688,400 (47.6%); 7. Asthma never causes daytime symptoms 4,757,100 (51.3%); 8. Asthma monitoring check done 4,690,400 (55.0%); 9. Asthma monitoring call first letter 4,570,900 (58.5%); 10. Asthma monitoring by nurse 2,183,300 (60.2%); 11. Asthma causes daytime symptoms 1 to 2 times per month 2,129,400 (61.8%); 12. Asthma causes daytime symptoms most days 2,058,600 (63.4%); 13. Asthma causes daytime symptoms 1 to 2 times per week 1,984,300 (65.0%); 14. Asthma self-management plan agreed 1,984,000 (66.5%); 15. Asthma control test score 1,942,500 (68.0%); 16. Asthma monitoring call second letter 1,910,900 (69.5%); 17. Number of asthma exacerbations in past year 1,792,700 (70.9%); 18. Acute exacerbation of asthma 1,725,400 (72.2%); 19. Asthma never disturbs sleep 1,719,300 (73.6%); 20. Asthma monitoring 1,534,400 (74.8%); 21. Asthma limiting activities 1,496,200 (75.9%); 22. Asthma daytime symptoms 1,465,700 (77.1%); 23. Asthma never restricts exercise 1,365,300 (78.1%); 24. Asthma follow-up 1,362,900 (79.2%); 25. Asthma sometimes restricts exercise 1,332,800 (80.2%); 26. Asthma disturbing sleep 1,295,800 (81.2%); 27. Emergency asthma patient visit since last encounter 1,247,600 (82.2%); 28. Asthma monitoring call third letter 1,052,600 (83.0%); 29. Asthma control step 2 1,039,200 (83.8%); 30. H/O: asthma 1,009,900 (84.6%); 31. Asthma monitoring invitation SMS (short message service) text message 973,200 (85.3%); 32. Asthma monitoring by doctor 893,600 (86.0%); 33. Excepted from asthma quality indicators - informed dissent 892,100 (86.7%); 34. Asthma treatment compliance satisfactory 824,700 (87.4%); 35. Health education - asthma 728,000 (87.9%); 36. Asthma control step 3 688,000 (88.5%); 37. Asthma self-management plan review 567,000 (88.9%); 38. Asthma NOS 521,100 (89.3%); 39. Patient has a written asthma personal action plan 490,700 (89.7%)
Autism	1. Autistic spectrum disorder 178,300 (24.9%); 2. Asperger's syndrome 163,300 (47.7%); 3. Autism 107,500 (62.6%); 4. Autism spectrum disorder 93,600 (75.7%); 5. Autistic disorder 78,300 (86.6%)

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
Autoimmune liver disease	1. Primary biliary cirrhosis 167,000 (53.3%); 2. Autoimmune hepatitis 98,700 (84.7%); 3. Primary sclerosing cholangitis 32,600 (95.1%); 4. Autoimmune chronic active hepatitis 15,000 (99.9%); 5. Primary biliary cholangitis 300 (100.0%)
Barett's oesophagus	1. Barrett's oesophagus 691,000 (71.3%); 2. Barrett's oesophagus 255,400 (97.6%); 3. Barrett's ulcer of oesophagus 22,000 (99.9%); 4. Barrett esophagus 400 (99.9%); 5. Barretts esophagus 300 (100.0%)
Breast cancer	1. Malignant neoplasm of female breast 3,077,800 (70.7%); 2. Ca female breast 542,100 (83.2%); 3. Malignant neoplasm of female breast NOS 204,100 (87.9%); 4. [RFC] Breast cancer 76,600 (89.6%); 5. Malignant tumour of breast 69,400 (91.2%)
CNS cancers	1. Malignant neoplasm of brain 115,600 (16.8%); 2. Cerebral meningioma 62,900 (26.0%); 3. Glioblastoma 61,300 (34.9%); 4. Glioblastoma multiforme 54,700 (42.8%); 5. Schwannoma 49,200 (50.0%); 6. [M]Astrocytoma NOS 34,400 (55.0%); 7. Secondary malignant neoplasm of brain 32,200 (59.7%); 8. Meningioma 30,200 (64.1%); 9. [M]Glioma NOS 20,200 (67.0%); 10. Malignant glioma 19,800 (69.9%); 11. Oligodendroglioma - category 15,400 (72.1%); 12. Malignant neoplasm of brain NOS 13,700 (74.1%); 13. Anaplastic astrocytoma 12,700 (76.0%); 14. [M]Gliomas 12,600 (77.8%); 15. [M]Glioma NOS 12,200 (79.6%); 16. Ependymoma - category 11,400 (81.2%); 17. Pilocytic astrocytoma 10,100 (82.7%); 18. Medulloblastoma 8,000 (83.9%); 19. Malignant neoplasm of frontal lobe 6,700 (84.9%); 20. [M]Meningioma NOS 6,600 (85.8%); 21. Cerebral tumour - malignant 5,700 (86.6%); 22. Astrocytoma 5,400 (87.4%); 23. Anaplastic oligodendroglioma 5,100 (88.2%); 24. Secondary malignant neoplasm of brain and spinal cord 4,700 (88.8%); 25. Paraganglioma 4,400 (89.5%)
COPD	1. Chronic obstructive pulmonary disease 5,454,200 (23.1%); 2. Chronic obstructive pulmonary disease annual review 4,009,500 (40.1%); 3. Number of chronic obstructive pulmonary disease exacerbations in past year 1,809,600 (47.8%); 4. Chronic obstructive pulmonary disease monitoring 1,290,000 (53.3%); 5. Chronic obstructive pulmonary disease monitoring first letter 1,167,000 (58.2%); 6. Acute exacerbation of chronic obstructive airways disease 1,082,100 (62.8%); 7. Chronic obstructive pulmonary disease assessment test score 959,000 (66.9%); 8. Moderate chronic obstructive pulmonary disease 954,600 (70.9%); 9. COPD self-management plan given 850,700 (74.5%); 10. Mild chronic obstructive pulmonary disease 756,300 (77.7%); 11. Severe chronic obstructive pulmonary disease 536,100 (80.0%); 12. Chronic obstructive airway disease 416,100 (81.8%); 13. Chronic obstructive pulmonary disease monitoring second letter 367,900 (83.3%); 14. Chronic obstructive lung disease 294,600 (84.6%); 15. Issue of chronic obstructive pulmonary disease rescue pack 257,200 (85.7%); 16. COPD medication review 228,300 (86.6%); 17. Chronic obstructive pulmonary disease self-management plan agreed 183,400 (87.4%); 18. Chronic obstructive pulmonary disease follow-up 180,800 (88.2%); 19. COAD - Chronic obstructive airways disease 171,100 (88.9%); 20. Chronic obstructive pulmonary disease clinical management plan 165,700 (89.6%)
Cholecystitis	1. Acute cholecystitis 202,600 (58.8%); 2. Cholecystitis 82,600 (82.8%); 3. Chronic cholecystitis 30,700 (91.7%); 4. Gallbladder calculus with acute cholecystitis 7,900 (94.0%); 5. Empyema of gallbladder 4,100 (95.1%)
Cigarette smoking	1. Smoking cessation advice 43,453,800 (35.8%); 2. Cigarette smoker 21,309,600 (53.4%); 3. Smoking cessation education 14,267,400 (65.2%); 4. Current smoker 13,615,700 (76.4%); 5. Moderate cigarette smoker (10-19 cigs/day) 2,686,300 (78.6%); 6. Trying to give up smoking 2,300,000 (80.5%); 7. Light cigarette smoker (1-9 cigs/day) 2,235,200 (82.3%); 8. Tobacco smoking consumption 1,505,600 (83.6%); 9. Rolls own cigarettes 1,283,200 (84.6%); 10. Seen by smoking cessation advisor 1,214,600 (85.6%); 11. Heavy cigarette smoker (20-39 cigs/day) 1,136,600 (86.6%); 12. Referral to smoking cessation advisor 1,086,400 (87.5%); 13. Not interested in stopping smoking 1,034,300 (88.3%); 14. Smoking cessation advice declined 999,600 (89.2%); 15. Nicotine replacement therapy 909,800 (89.9%)
Coeliac disease	1. Coeliac disease 544,700 (91.2%); 2. Gluten intolerance 21,800 (94.8%); 3. Coeliac disease NOS 9,400 (96.4%); 4. Coeliac disease annual review 6,500 (97.5%); 5. Coeliac disease monitoring 3,900 (98.1%)
Coronary artery disease	1. Ischaemic heart disease 4,902,100 (32.2%); 2. Framingham coronary heart disease 10 year risk score 2,542,400 (49.0%); 3. Coronary heart disease annual review 2,185,000 (63.3%); 4. Coronary heart disease monitoring 1st letter 1,645,700 (74.1%); 5. IHD - Ischaemic heart disease 1,238,400 (82.3%); 6. Primary prevention of ischaemic heart disease 395,100 (84.9%); 7. Coronary heart disease monitoring 2nd letter 381,200 (87.4%); 8. Coronary heart disease risk 236,300 (88.9%)
Crohn's disease	1. Crohn's disease 739,600 (70.6%); 2. Crohn's regional enteritis 207,900 (90.5%); 3. CC - Crohn's colitis 40,900 (94.4%); 4. Crohn's disease of terminal ileum 16,200 (95.9%); 5. Regional enteritis - Crohn 11,700 (97.0%)
Cutaneous warts	1. Verruca plantaris 1,659,100 (24.6%); 2. Viral wart 1,216,000 (42.6%); 3. Plantar wart 767,500 (54.0%); 4. Hand wart 577,800 (62.5%); 5. Seborrhoeic wart 370,300 (68.0%); 6. Plain wart 346,900 (73.1%); 7. Seborrhoeic wart 295,800 (77.5%); 8. Seborrhoeic wart 274,400 (81.6%); 9. Genital warts 260,700 (85.4%); 10. Verruca vulgaris 206,000 (88.5%)
Depression	1. Mixed anxiety and depressive disorder 18,609,100 (33.1%); 2. Depression 5,639,500 (43.1%); 3. Low mood 5,469,100 (52.9%); 4. Depressive disorder 4,668,000 (61.2%); 5. Depression interim review 3,236,600 (66.9%); 6. Depressed 2,810,500 (71.9%); 7. Depressed mood 1,558,600 (74.7%); 8. Depression medication review 1,268,400 (77.0%); 9. H/O: depression 1,255,900 (79.2%); 10. Depressive episode 966,600 (80.9%); 11. [X]Moderate depressive episode 781,100 (82.3%); 12. [X]Mixed anxiety and depressive disorder 706,800 (83.6%); 13. Reactive depression (situational) 678,400 (84.8%); 14. [X]Depressive episode, unspecified

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
	642,200 (85.9%); 15. Postpartum depression 573,500 (86.9%); 16. Symptoms of depression 502,700 (87.8%); 17. C/O - feeling depressed 485,900 (88.7%); 18. Depressive episode 425,700 (89.5%)
Dermatophyte infection	1. Fungal nail infection 1,473,100 (27.0%); 2. Athlete's foot 608,000 (38.1%); 3. Dermatophytosis 458,300 (46.5%); 4. Ringworm 448,000 (54.7%); 5. Dermatophytosis of nail 338,800 (60.9%); 6. Tinea pedis 337,000 (67.0%); 7. Tinea cruris 326,500 (73.0%); 8. Onychomycosis 289,600 (78.3%); 9. Tinea corporis 248,000 (82.9%); 10. Dermatophytosis of foot 230,100 (87.1%); 11. Dermatophytosis of the body 113,700 (89.1%)
Diabetes mellitus	1. Type 2 diabetes mellitus 22,645,700 (27.4%); 2. Diabetic annual review 8,575,500 (37.8%); 3. O/E - Right diabetic foot at low risk 7,472,900 (46.9%); 4. O/E - Left diabetic foot at low risk 7,433,600 (55.9%); 5. Diabetes mellitus 4,912,200 (61.9%); 6. Diabetic on oral treatment 4,810,900 (67.7%); 7. Type 1 diabetes mellitus 2,238,400 (70.4%); 8. Diabetic on diet only 1,698,500 (72.5%); 9. Type II diabetic dietary review 1,523,000 (74.3%); 10. Diabetic on insulin 1,379,800 (76.0%); 11. O/E - Right diabetic foot at moderate risk 1,323,500 (77.6%); 12. O/E - Left diabetic foot at moderate risk 1,316,700 (79.2%); 13. Agreeing on diabetes care plan 1,265,300 (80.7%); 14. Diabetes self-management plan agreed 1,142,400 (82.1%); 15. Background diabetic retinopathy 820,000 (83.1%); 16. Diabetes management plan given 763,600 (84.0%); 17. Diabetic foot examination 703,100 (84.9%); 18. Diabetes medication review 703,000 (85.7%); 19. Patient on maximal tolerated therapy for diabetes 655,900 (86.5%); 20. Non-insulin dependent diabetes mellitus 650,000 (87.3%); 21. Type II diabetes mellitus 620,400 (88.0%); 22. Insulin treated Type 2 diabetes mellitus 556,900 (88.7%); 23. O/E - right eye background diabetic retinopathy 537,600 (89.4%)
Diverticular disease	1. Diverticular disease 809,600 (31.4%); 2. Diverticulosis 745,800 (60.3%); 3. Diverticulitis 573,900 (82.5%); 4. Diverticula of intestine 152,100 (88.4%); 5. Diverticular disease of colon 132,500 (93.5%)
Dyslipidaemia	1. Pure hypercholesterolaemia 2,694,100 (33.9%); 2. Hyperlipidaemia 2,020,100 (59.4%); 3. Mixed hyperlipidaemia 560,800 (66.5%); 4. Lipid-lowering therapy 448,300 (72.1%); 5. Patient on maximal tolerated lipid lowering therapy 390,000 (77.0%); 6. Hyperlipidaemia screen 269,300 (80.4%); 7. Disorder of lipid metabolism 257,000 (83.6%); 8. Hypercholesterolaemia 244,400 (86.7%); 9. Serum lipids high 142,100 (88.5%)
Eosinophilic Oesophagitis	1. Eosinophilic oesophagitis 22,900 (99.9%); 2. Eosinophilic esophagitis 0 (100.0%)
Epilepsy	1. Epilepsy 2,319,900 (38.1%); 2. Epilepsy medication review 1,277,000 (59.1%); 3. Epilepsy monitoring 596,400 (68.9%); 4. Generalised epilepsy 201,800 (72.2%); 5. No epilepsy drug side effects 134,400 (74.4%); 6. Epilepsy NOS 118,100 (76.4%); 7. Temporal lobe epilepsy 110,400 (78.2%); 8. Contraceptive advice for patients with epilepsy 97,500 (79.8%); 9. Follow-up epilepsy assessment 89,000 (81.2%); 10. H/O: epilepsy 78,700 (82.5%); 11. Pre-conception advice for patients with epilepsy 67,700 (83.6%); 12. Pregnancy advice for patients with epilepsy 67,600 (84.8%); 13. Seen in epilepsy clinic 64,600 (85.8%); 14. Epilepsy monitoring call first letter 45,500 (86.6%); 15. Petit mal (minor) epilepsy 41,400 (87.3%); 16. Complex partial epileptic seizure 39,900 (87.9%); 17. Pregnancy advice for patients with epilepsy not indicated 35,600 (88.5%); 18. Epilepsy management plan given 34,700 (89.1%); 19. Contraceptive advice for patients with epilepsy not indicated 34,500 (89.6%)
Fatty liver	1. Non-alcoholic fatty liver 323,400 (47.0%); 2. Fatty liver 168,200 (71.5%); 3. Steatosis of liver 75,700 (82.5%); 4. Fatty change of liver 49,100 (89.6%); 5. Alcoholic fatty liver 44,600 (96.1%)
Fibrosis/sclerosis/cirrhosis	1. Alcoholic cirrhosis of liver 329,200 (29.9%); 2. Alcoholic liver damage 181,000 (46.4%); 3. Cirrhosis of liver 174,600 (62.2%); 4. Primary biliary cirrhosis 167,000 (77.4%); 5. Cirrhosis and chronic liver disease 105,300 (87.0%)
Food allergy	1. Nut allergy 224,800 (25.9%); 2. Food allergy 199,200 (48.9%); 3. Allergy to peanuts 140,000 (65.1%); 4. Allergy to eggs 122,100 (79.1%); 5. H/O: food allergy 71,600 (87.4%)
Gastritis and duodenitis	1. Gastritis 961,500 (39.5%); 2. Gastritis and duodenitis 387,800 (55.4%); 3. Acute gastritis 320,700 (68.5%); 4. Duodenitis 241,800 (78.5%); 5. [X]Other gastritis 117,900 (83.3%); 6. Helicobacter-associated gastritis 78,500 (86.5%); 7. Chronic gastritis 66,700 (89.3%)
Gastro oesophageal reflux	1. Reflux oesophagitis 2,436,800 (35.5%); 2. Gastro-oesophageal reflux 1,984,900 (64.4%); 3. Acid reflux 768,000 (75.6%); 4. Gastric reflux 349,200 (80.7%); 5. Oesophageal reflux 268,800 (84.6%); 6. Gastrooesophageal reflux disease 242,700 (88.2%)
Heart failure	1. Heart failure 920,900 (19.2%); 2. Congestive heart failure 679,200 (33.3%); 3. Left ventricular failure 668,000 (47.2%); 4. Congestive cardiac failure 488,500 (57.4%); 5. Left ventricular systolic dysfunction 279,100 (63.2%); 6. Echocardiogram shows left ventricular systolic dysfunction 184,100 (67.1%); 7. Heart failure annual review 181,200 (70.8%); 8. Seen in heart failure clinic 156,700 (74.1%); 9. Impaired left ventricular function 115,400 (76.5%); 10. Seen by community heart failure nurse 94,000 (78.5%); 11. Heart failure monitoring first letter 81,800 (80.2%); 12. Referral to heart failure clinic 62,700 (81.5%); 13. Heart failure 6 month review 60,400 (82.7%); 14. Pulmonary oedema 55,700 (83.9%); 15. Impaired left ventricular function 54,700 (85.0%); 16. Heart failure review completed 50,200 (86.1%); 17. Cardiac failure 37,500 (86.9%); 18. Left ventricular diastolic dysfunction 35,900 (87.6%); 19. Heart failure follow-up 35,100 (88.3%); 20. Echocardiogram shows left ventricular diastolic dysfunction 34,200 (89.0%); 21. Heart failure NOS 34,200 (89.8%)
Herpes simplex	1. Herpes simplex 418,000 (26.1%); 2. Cold sore (herpetic) 406,000 (51.4%); 3. Genital herpes simplex 277,200 (68.7%); 4. Herpes labialis 64,300 (72.8%); 5. O/E-herpes labialis-cold sore 61,800 (76.6%); 6. O/E - cold sore 53,900 (80.0%); 7. Herpetic gingivostomatitis 50,600 (83.1%); 8. Genital herpes unspecified 48,800

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
	(86.2%); 9. Eczema herpeticum - Kaposi's varicelliform eruption 30,100 (88.1%); 10. Herpes simplex viral infection 28,200 (89.8%)
Hip fracture	1. Fracture of neck of femur 1,040,000 (66.9%); 2. Hip fracture 207,800 (80.3%); 3. Closed fracture of neck of femur 76,400 (85.2%); 4. Primary open reduction and internal fixation of proximal femoral fracture with screw/nail and plate device 43,400 (88.0%); 5. Primary open reduction of fracture of neck of femur and open fixation using dynamic hip screw 33,200 (90.1%)
Hodgkin lymphoma	1. Hodgkin's disease 110,900 (63.7%); 2. Hodgkin lymphoma 13,100 (71.2%); 3. Hodgkin's disease, nodular sclerosis 9,500 (76.7%); 4. Hodgkin's disease (clinical) 9,100 (81.9%); 5. Hodgkin lymphoma 5,000 (84.8%); 6. [M]Hodgkin's disease 4,200 (87.2%); 7. Hodgkin's disease NOS 2,300 (88.6%); 8. Hodgkin lymphoma, nodular sclerosis 2,300 (89.8%)
Hypertension	1. Essential hypertension 35,271,200 (61.1%); 2. Hypertensive disease 10,600,000 (79.4%); 3. Hypertension annual review 4,693,700 (87.5%); 4. Hypertension six month review 1,240,200 (89.7%); 5. Hypertension 969,300 (91.4%)
Impetigo	1. Impetigo 2,513,600 (93.8%); 2. Impetigo NOS 129,700 (98.6%); 3. Impetigo contagiosa unspecified 10,400 (99.0%); 4. Bullous impetigo 8,400 (99.3%); 5. Impetigo follicularis 5,500 (99.5%)
Irritable bowel syndrome	1. Irritable bowel syndrome 2,523,300 (72.6%); 2. Irritable colon - Irritable bowel syndrome 709,000 (93.0%); 3. Irritable colon 97,200 (95.8%); 4. Irritable bowel syndrome with diarrhoea 64,400 (97.7%); 5. Irritable bowel - IBS 57,500 (99.3%)
Lung cancer	1. Lung cancer 612,400 (33.4%); 2. Malignant tumour of lung 505,400 (61.0%); 3. Malignant neoplasm of lower respiratory tract 221,200 (73.1%); 4. Secondary malignant neoplasm of lung 67,400 (76.8%); 5. Primary malignant neoplasm of lung 65,600 (80.4%); 6. Malignant neoplasm of upper lobe of lung 53,700 (83.3%); 7. Malignant neoplasm of upper lobe, bronchus or lung 47,900 (85.9%); 8. Malignant neoplasm of main bronchus 40,700 (88.2%)
Melanoma	1. Malignant melanoma of skin 471,100 (36.5%); 2. Malignant neoplasm of skin 201,700 (52.1%); 3. Malignant melanoma 69,500 (57.5%); 4. Excision of melanoma 59,300 (62.0%); 5. Lentigo maligna 52,200 (66.1%); 6. Malignant melanoma of lower leg 26,000 (68.1%); 7. Malignant neoplasm of skin NOS 24,300 (70.0%); 8. Malignant melanoma of back 22,100 (71.7%); 9. History of primary malignant neoplasm of skin 18,700 (73.1%); 10. Superficial spreading melanoma 16,400 (74.4%); 11. Malignant neoplasm of skin of lower limb and hip 14,500 (75.5%); 12. H/O Malignant melanoma 14,100 (76.6%); 13. Melanoma in situ 12,500 (77.6%); 14. Melanoma in situ of skin 11,300 (78.5%); 15. Malignant melanoma of thigh 10,200 (79.2%); 16. Malignant melanoma of lower limb and hip 9,900 (80.0%); 17. Malignant melanoma of skin NOS 9,800 (80.8%); 18. Malignant neoplasm of skin of trunk 9,500 (81.5%); 19. [M]Lentigo maligna melanoma 9,500 (82.2%); 20. Malignant neoplasm of skin of nose (external) 8,200 (82.9%); 21. Malignant melanoma of skin of trunk 8,100 (83.5%); 22. Malignant melanoma of upper arm 7,700 (84.1%); 23. Malignant melanoma of eye 7,400 (84.7%); 24. Malignant neoplasm of skin of upper limb and shoulder 6,700 (85.2%); 25. Malignant neoplasm of skin of cheek, external 6,000 (85.7%); 26. Nodular melanoma 5,900 (86.1%); 27. Malignant neoplasm of scalp 5,800 (86.6%); 28. Malignant melanoma of upper limb 5,700 (87.0%); 29. Malignant neoplasm of skin of forehead 5,700 (87.4%); 30. Malignant melanoma of forearm 5,000 (87.8%); 31. Malignant neoplasm of skin of lower leg 4,800 (88.2%); 32. Malignant melanoma of choroid 4,700 (88.6%); 33. Malignant melanoma of breast 4,700 (88.9%); 34. Malignant melanoma of scalp and neck 4,000 (89.2%); 35. Malignant melanoma of neck 3,800 (89.5%); 36. Malignant neoplasm of skin of temple 3,800 (89.8%)
Metabolic syndrome	1. Cardiac syndrome X 18,800 (56.5%); 2. Metabolic syndrome 10,900 (89.2%); 3. Metabolic syndrome X 3,300 (98.9%); 4. Reaven's syndrome 300 (99.9%); 5. Reaven's syndrome 100 (100.0%)
Migraine	1. Migraine 4,230,600 (76.7%); 2. H/O: migraine 352,900 (83.1%); 3. Migraine with typical aura 299,900 (88.6%); 4. Migraine NOS 190,400 (92.0%); 5. Migraine with aura 67,900 (93.3%)
Molluscum contagiosum	1. Molluscum contagiosum infection 1,070,300 (99.0%); 2. Molluscum contagiosum infection of eyelid 5,800 (99.5%); 3. [SHHAPT] Molluscum contagiosum 4,900 (100.0%); 4. Genital Molluscum contagiosum 0 (100.0%); 5. Molluscum Contagiosum 0 (100.0%)
Multiple sclerosis	1. Multiple sclerosis 768,900 (87.6%); 2. [RFC] Multiple sclerosis 24,400 (90.4%); 3. Relapsing remitting multiple sclerosis 15,800 (92.2%); 4. Multiple sclerosis NOS 15,600 (93.9%); 5. Multiple sclerosis - relapsing remitting 12,000 (95.3%)
Myeloma	1. Multiple myeloma 367,400 (70.1%); 2. [M]Myeloma NOS 89,100 (87.1%); 3. Plasmacytoma 15,100 (90.0%); 4. [M]Plasma cell myeloma 10,900 (92.0%); 5. Lambda light chain myeloma 10,400 (94.0%)
Myocardial infarction	1. Acute myocardial infarction 1,389,800 (49.9%); 2. Acute non-ST segment elevation myocardial infarction 487,700 (67.5%); 3. MI - acute myocardial infarction 281,900 (77.6%); 4. Acute ST segment elevation myocardial infarction 203,700 (84.9%); 5. Acute myocardial infarction of inferior wall 86,900 (88.0%); 6. Old myocardial infarction 50,800 (89.8%)
Non-Hodgkin lymphoma	1. Non-Hodgkin's lymphoma 208,300 (23.9%); 2. [M]Lymphoma NOS 104,500 (35.9%); 3. Diffuse large B-cell lymphoma 50,800 (41.7%); 4. [M]Non-Hodgkin's lymphoma 46,300 (47.0%); 5. Follicular lymphoma NOS 45,200 (52.2%); 6. B-cell non-Hodgkin's lymphoma 39,900 (56.8%); 7. Follicular non-Hodgkin's lymphoma 33,500 (60.6%); 8. Malignant lymphoma 32,700 (64.3%); 9. Malignant neoplasm lymphatic or

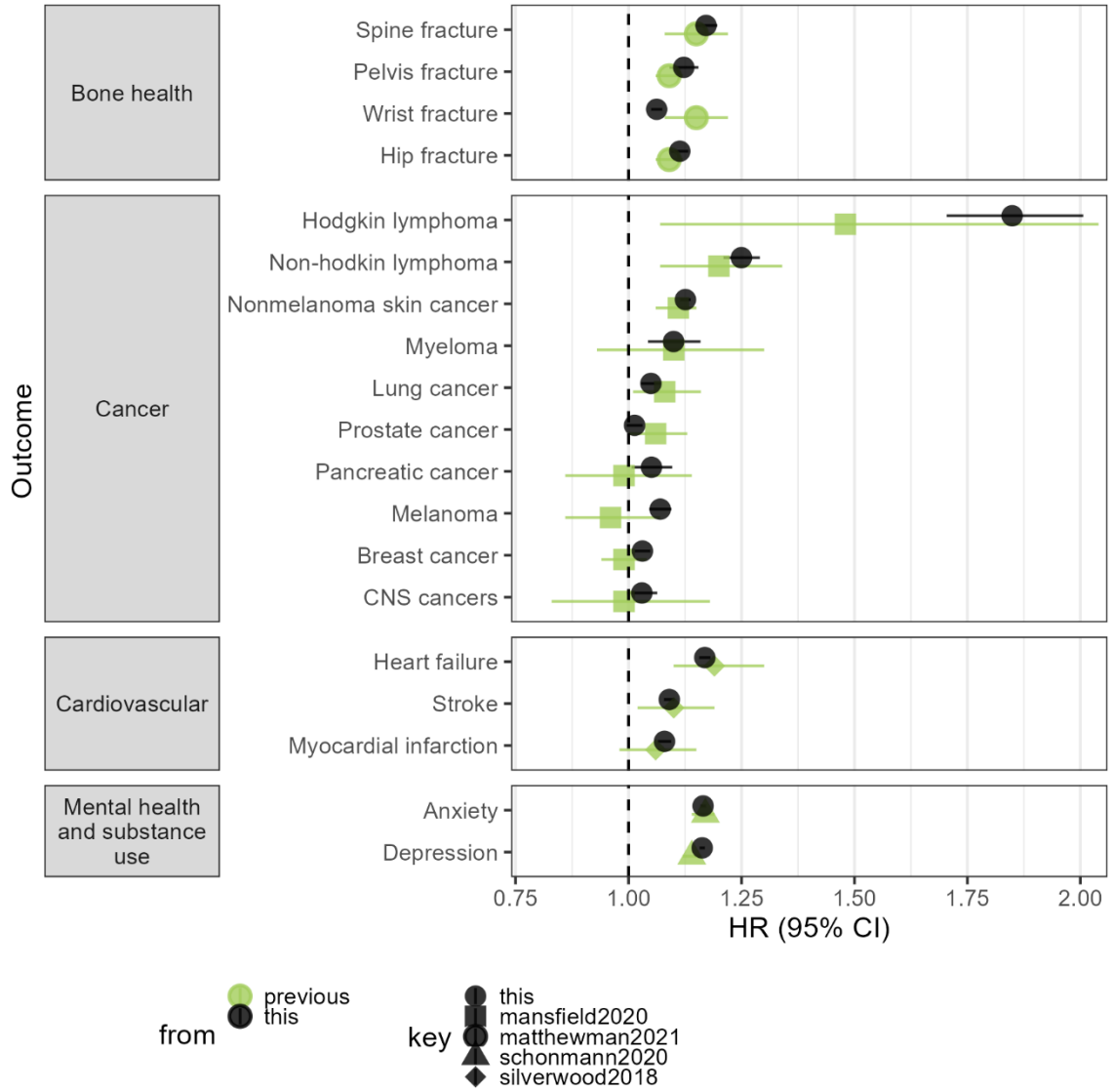
Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
	haematopoietic tissue NOS 28,300 (67.6%); 10. Non hodgkin lymphoma 25,800 (70.5%); 11. Non-Hodgkin's lymphoma (clinical) 21,300 (73.0%); 12. Malignant lymphoma (clinical) 17,200 (74.9%); 13. Mantle cell lymphoma 17,000 (76.9%); 14. Malignant lymphoma 16,300 (78.8%); 15. Non-Hodgkin lymphoma (category) 13,200 (80.3%); 16. [M]Malignant lymphoma, non-Hodgkin's type 12,500 (81.7%); 17. [M] Cutaneous lymphoma 7,700 (82.6%); 18. Follicular lymphoma 7,700 (83.5%); 19. Suspected lymphoma 7,200 (84.3%); 20. Burkitt's lymphoma 7,100 (85.1%); 21. [X]Non-Hodgkin's lymphoma NOS 5,800 (85.8%); 22. Low grade B-cell lymphoma 5,300 (86.4%); 23. [M]Lymphocytic lymphoma NOS 5,200 (87.0%); 24. Malignant lymphoma NOS 5,200 (87.6%); 25. Monocytoid B-cell lymphoma 4,800 (88.1%); 26. [M]Malignant lymphoma, lymphoplasmacytoid type 4,400 (88.6%); 27. [M]Lymphomas, NOS or diffuse 4,200 (89.1%); 28. Peripheral T-cell lymphoma 4,000 (89.6%); 29. Cutaneous T-cell lymphoma 3,500 (90.0%)
Nonmelanoma skin cancer	1. Basal cell carcinoma of skin 2,654,800 (56.1%); 2. Squamous cell carcinoma - category 585,100 (68.5%); 3. Bowen's disease of skin 404,700 (77.0%); 4. Squamous cell carcinoma of skin 314,100 (83.7%); 5. Basal cell carcinoma 235,000 (88.7%)
Obesity	1. Obesity 1,901,800 (35.1%); 2. Body mass index 30+ - obesity 1,802,300 (68.5%); 3. Obesity monitoring 502,000 (77.7%); 4. Intervention for risk to health associated with overweight and obesity, general advice on healthy weight and lifestyle 260,400 (82.5%); 5. Morbid obesity 153,100 (85.4%); 6. Follow-up obesity assessment 149,200 (88.1%)
Oesophagitis	1. Reflux oesophagitis 2,436,800 (45.0%); 2. Oesophagitis 1,320,100 (69.4%); 3. Barrett's oesophagus 691,000 (82.1%); 4. Barrett's oesophagus 255,400 (86.9%); 5. Gastro-oesophageal reflux disease without oesophagitis 229,400 (91.1%)
Oesophageal varices	1. Oesophageal varices 88,400 (54.2%); 2. Oesophageal varices with bleeding 26,400 (70.4%); 3. Oesophageal varices NOS 15,300 (79.7%); 4. Fibreoptic endoscopic banding of oesophageal varices 11,700 (86.9%); 5. Oesophageal varices in alcoholic cirrhosis of the liver 7,400 (91.5%)
Osteoporosis	1. Osteoporosis 2,565,700 (77.7%); 2. Pathological fracture due to osteoporosis 99,400 (80.7%); 3. Health education - osteoporosis 88,900 (83.4%); 4. Osteoporotic vertebral collapse 58,500 (85.1%); 5. Lumbar DXA scan result osteoporotic 46,300 (86.5%); 6. Seen in osteoporosis clinic 43,900 (87.9%); 7. Referral to osteoporosis clinic 30,100 (88.8%); 8. Osteoporosis NOS 28,300 (89.6%)
Pancreatic cancer	1. Malignant tumour of pancreas 289,700 (67.5%); 2. Malignant tumour of head of pancreas 51,700 (79.5%); 3. [M]Pancreatic adenomas and carcinomas 25,000 (85.4%); 4. Malignant neoplasm of pancreas NOS 23,200 (90.8%); 5. [M]Pancreatic adenoma or carcinoma NOS 12,300 (93.6%)
Pancreatitis	1. Acute pancreatitis 187,400 (41.0%); 2. Chronic pancreatitis 123,800 (68.1%); 3. Pancreatitis 71,700 (83.8%); 4. Gallstone acute pancreatitis 25,300 (89.3%); 5. Alcohol-induced chronic pancreatitis 24,100 (94.6%)
Parkinson's disease	1. Parkinson's disease 1,141,900 (82.7%); 2. Dementia in Parkinsons disease 80,300 (88.5%); 3. Parkinson's disease NOS 69,900 (93.6%); 4. Seen by Parkinson's disease service 23,200 (95.3%); 5. Secondary parkinsonism 11,900 (96.1%)
Pelvis fracture	1. Closed fracture pelvis, single pubic ramus 119,700 (25.4%); 2. Fracture or disruption of pelvis 48,400 (35.7%); 3. Closed fracture of pelvis 48,100 (45.9%); 4. Fracture of acetabulum 33,700 (53.1%); 5. Closed fracture pubis 33,300 (60.2%); 6. Closed fracture pelvis, multiple pubic rami - stable 31,900 (66.9%); 7. Fracture of pubis 28,000 (72.9%); 8. Fracture of coccyx 22,000 (77.6%); 9. Fracture of pubic rami 20,300 (81.9%); 10. Fracture of sacrum 14,600 (85.0%); 11. Closed fracture acetabulum 10,200 (87.1%); 12. Closed fracture sacrum 9,400 (89.1%)
Peptic ulcer disease	1. Duodenal ulcer 308,100 (33.0%); 2. Gastric ulcer 202,000 (54.7%); 3. H/O: peptic ulcer 40,700 (59.0%); 4. Duodenal ulcer NOS 39,600 (63.3%); 5. Peptic ulcer 38,500 (67.4%); 6. Gastric erosions 37,200 (71.4%); 7. Gastric ulcer NOS 34,700 (75.1%); 8. Peptic ulcer NOS 29,400 (78.3%); 9. Peptic ulcer symptoms 16,200 (80.0%); 10. Chronic duodenal ulcer NOS 12,600 (81.3%); 11. Acute duodenal ulcer with haemorrhage 12,400 (82.7%); 12. Acute duodenal ulcer with perforation 11,100 (83.9%); 13. H/O: duodenal ulcer 10,900 (85.0%); 14. Duodenal erosion 9,000 (86.0%); 15. Closure of perforated duodenal ulcer 8,500 (86.9%); 16. Chronic duodenal ulcer 7,800 (87.7%); 17. Duodenal ulcer disease 7,600 (88.5%); 18. H/O: gastric ulcer 7,500 (89.3%)
Peripheral artery disease	1. Intermittent claudication 437,900 (38.0%); 2. Raynaud's phenomenon 166,200 (52.4%); 3. Peripheral vascular disease NOS 98,700 (60.9%); 4. Claudication 60,000 (66.1%); 5. Raynaud's disease 46,800 (70.2%); 6. Mixed diabetic ulcer - foot 45,000 (74.1%); 7. Percutaneous transluminal angioplasty of femoral artery 35,700 (77.2%); 8. Ischaemic ulcer diabetic foot 29,700 (79.8%); 9. Ischaemic leg 28,200 (82.2%); 10. Percutaneous transluminal angioplasty of iliac artery 18,400 (83.8%); 11. Gangrene of toe 17,000 (85.3%); 12. Femoral endarterectomy 13,800 (86.5%); 13. Peripheral ischaemic vascular disease 12,900 (87.6%); 14. Percutaneous angioplasty of popliteal artery 8,600 (88.3%); 15. Peripheral ischaemia 8,600 (89.1%); 16. Diabetic peripheral angiopathy 6,000 (89.6%)
Peripheral neuropathies	1. Sciatica 3,168,700 (39.2%); 2. Carpal tunnel syndrome 1,502,900 (57.8%); 3. Lumbago with sciatica 699,600 (66.5%); 4. Peripheral neuropathy 353,700 (70.8%); 5. Bell's palsy 309,500 (74.7%); 6. Trigeminal neuralgia NOS 277,500 (78.1%); 7. CTS - Carpal tunnel syndrome 179,200 (80.3%); 8. Meralgia paraesthetica 107,900 (81.6%); 9. Trigeminal neuralgia 99,500 (82.9%); 10. Morton's metatarsalgia 91,900 (84.0%); 11. Acute vestibular neuronitis 79,500 (85.0%); 12. Brachial (cervical) neuritis 70,700 (85.9%); 13. Lumbar disc

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
	prolapse with radiculopathy 68,500 (86.7%); 14. Peripheral nerve disease 54,500 (87.4%); 15. Ulnar nerve entrapment 53,000 (88.0%); 16. Radiculopathy 51,300 (88.7%); 17. Ulnar neuropathy 38,800 (89.2%); 18. Cauda equina syndrome 36,400 (89.6%)
Peritonitis	1. Peritonitis 18,900 (14.7%); 2. Perforated diverticulum 17,700 (28.4%); 3. Acute duodenal ulcer with perforation 11,100 (37.1%); 4. Acute appendicitis with peritonitis 9,000 (44.1%); 5. Closure of perforated duodenal ulcer 8,500 (50.7%); 6. Perforated diverticulum of colon 8,500 (57.3%); 7. Acute gangrenous appendicitis 7,500 (63.1%); 8. Perforated chronic duodenal ulcer 5,600 (67.5%); 9. Acute gastric ulcer with perforation 2,800 (69.6%); 10. Duodenal ulcer with perforation 2,500 (71.6%); 11. Chronic duodenal ulcer with perforation 2,200 (73.3%); 12. Closure of perforated gastric ulcer 2,000 (74.9%); 13. Perforated diverticulum of intestine 1,800 (76.2%); 14. Subphrenic abscess 1,700 (77.6%); 15. Acute appendicitis without peritonitis 1,700 (78.9%); 16. Faecal peritonitis 1,600 (80.1%); 17. Acute peptic ulcer with perforation 1,600 (81.4%); 18. Retroperitoneal abscess 1,500 (82.5%); 19. Drainage of intraperitoneal abscess 1,200 (83.5%); 20. Acute peritonitis 1,200 (84.4%); 21. Spontaneous bacterial peritonitis 1,200 (85.4%); 22. Perforated diverticulum of large intestine 1,200 (86.3%); 23. Perforated chronic gastric ulcer 1,100 (87.1%); 24. Peritonitis - bacterial 1,100 (88.0%); 25. Peritonitis NOS 700 (88.6%); 26. Diverticular disease of both small and large intestine with perforation and abscess 700 (89.1%); 27. Peritoneal dialysis-associated peritonitis 700 (89.6%)
Prostate cancer	1. Malignant tumour of prostate 4,324,100 (93.4%); 2. QCancer prostate cancer risk 80,200 (95.2%); 3. [RFC] Cancer of the prostate 51,200 (96.3%); 4. Gleason prostate grade 5-7 (medium) 36,800 (97.1%); 5. Gleason grade finding for prostatic cancer 29,000 (97.7%)
Spine fracture	1. Fracture of lumbar vertebra 114,800 (13.4%); 2. Fracture of thoracic vertebra 98,200 (24.8%); 3. Closed fracture thoracic vertebra, wedge 86,500 (34.9%); 4. Closed fracture lumbar vertebra, wedge 67,300 (42.7%); 5. Closed fracture lumbar vertebra 63,000 (50.1%); 6. H/O: vertebral fracture 58,800 (56.9%); 7. Closed fracture of cervical spine 41,400 (61.8%); 8. Closed fracture thoracic vertebra 38,000 (66.2%); 9. Fracture of spine without mention of spinal cord injury 24,800 (69.1%); 10. Osteoporosis with pathological fracture of thoracic vertebrae 20,400 (71.5%); 11. Osteoporosis with pathological fracture of lumbar vertebrae 18,800 (73.7%); 12. Closed fracture of vertebral column 18,200 (75.8%); 13. Fracture of vertebra without spinal cord lesion 15,200 (77.6%); 14. Fracture of lumbar spine 14,500 (79.3%); 15. Fracture of cervical spine 11,600 (80.6%); 16. Fracture of thoracic spine 11,500 (81.9%); 17. Multiple fractures of thoracic spine 10,800 (83.2%); 18. Closed fracture axis, odontoid process 8,800 (84.2%); 19. Closed fracture lumbar vertebra, transverse process 5,600 (84.9%); 20. Fracture of second cervical vertebra 4,600 (85.4%); 21. Balloon kyphoplasty of fracture of spine 4,600 (85.9%); 22. Multiple fractures of cervical spine 4,300 (86.4%); 23. Fracture of spine with spinal cord lesion 4,200 (86.9%); 24. Closed multiple fractures of thoracic spine 4,200 (87.4%); 25. Fatigue fracture of vertebra 4,100 (87.9%); 26. Fracture of vertebral column 4,000 (88.4%); 27. Vertebroplasty of fracture of spine 3,600 (88.8%); 28. Closed fracture lumbar vertebra, burst 3,600 (89.2%); 29. Fracture of spine without mention of spinal cord lesion NOS 3,500 (89.6%); 30. Fixation of spinal fracture 3,300 (90.0%)
Stroke	1. Stroke monitoring 506,000 (19.8%); 2. Stroke/transient ischaemic attack monitoring first letter 404,900 (35.6%); 3. Seen in stroke clinic 232,700 (44.7%); 4. Cerebral infarction 184,100 (51.9%); 5. Stroke / transient ischaemic attack referral 160,500 (58.2%); 6. CVA - cerebrovascular accident due to cerebral artery occlusion 137,100 (63.6%); 7. Stroke/transient ischaemic attack monitoring second letter 116,400 (68.1%); 8. Cerebral arterial occlusion 112,700 (72.5%); 9. Stroke unspecified 92,200 (76.1%); 10. Referral to stroke clinic 90,600 (79.7%); 11. Stroke/transient ischaemic attack monitoring third letter 43,600 (81.4%); 12. Stroke 36,100 (82.8%); 13. Cerebellar infarction 35,600 (84.2%); 14. H/O: stroke 32,600 (85.5%); 15. Left sided cerebral infarction 32,400 (86.7%); 16. Stroke due to cerebral arterial occlusion 29,300 (87.9%); 17. [RFC] Stroke 28,400 (89.0%)
Thromboembolic diseases	1. Deep venous thrombosis 738,400 (43.9%); 2. Deep vein thrombosis 187,000 (55.1%); 3. Phlebitis and thrombophlebitis 156,400 (64.4%); 4. Deep vein phlebitis and thrombophlebitis of the leg 149,200 (73.3%); 5. Thrombophlebitis 71,500 (77.5%); 6. H/O: Deep Vein Thrombosis 56,600 (80.9%); 7. Suspected deep vein thrombosis 48,600 (83.8%); 8. Deep vein thrombosis of lower limb 43,800 (86.4%); 9. Referral to deep vein thrombosis clinic 38,700 (88.7%); 10. Portal vein thrombosis 13,100 (89.5%)
Ulcerative colitis	1. Ulcerative colitis 920,000 (79.7%); 2. Ulcerative colitis and/or proctitis 116,200 (89.8%); 3. Ulcerative proctitis 35,200 (92.8%); 4. Ulcerative proctocolitis 34,000 (95.8%); 5. H/O: ulcerative colitis 17,500 (97.3%)
Urticaria	1. Urticaria 1,496,100 (63.5%); 2. Allergic urticaria 304,700 (76.4%); 3. Urticaria NOS 116,000 (81.3%); 4. Angioneurotic oedema 115,700 (86.2%); 5. Idiopathic urticaria 86,700 (89.9%)
Vascular dementia	1. Vascular dementia 600,600 (91.5%); 2. [X]Vascular dementia, unspecified 23,400 (95.0%); 3. Mixed cortical and subcortical vascular dementia 10,900 (96.7%); 4. VAD - Vascular dementia 7,000 (97.8%); 5. Subcortical vascular dementia 6,000 (98.7%)
Wrist fracture	1. Closed fracture of distal end of radius 811,500 (17.9%); 2. Fracture of metacarpal bone 806,600 (35.8%); 3. Closed fracture of wrist 608,200 (49.2%); 4. Fracture of scaphoid bone of wrist 392,000 (57.9%); 5. Closed Colles' fracture 344,800 (65.5%); 6. Closed fracture of the scaphoid 217,000 (70.3%); 7. Closed fracture of metacarpal bone(s) 115,700 (72.8%); 8. Hand fracture - metacarpal bone 115,200 (75.4%); 9. Closed fracture finger metacarpal 106,400 (77.7%); 10. Fracture at wrist and hand level 83,700 (79.6%); 11. Fracture of other metacarpal bone 76,600 (81.3%); 12. Greenstick fracture of distal radius 73,900 (82.9%);

Outcome	Numbered list of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences
	13. Closed fracture radial styloid 70,900 (84.5%); 14. Closed fracture radius and ulna, distal 66,700 (85.9%); 15. Closed reduction of fracture of wrist 46,900 (87.0%); 16. Closed fracture finger metacarpal neck 42,600 (87.9%); 17. Fracture of forearm 41,900 (88.9%); 18. Closed fracture navicular 37,900 (89.7%)

eTable 1: Numbered lists of the most commonly occurring codes with rounded number of occurrences and cumulative percentage of all occurrences (e.g., the code "Attention deficit hyperactivity disorder" makes up 72.5% of all codes for the ADHD outcome; the codes "Attention deficit hyperactivity disorder" and "Attention deficit with hyperactivity" together make up 79.9% of all codes for the ADHD outcome, etc…)

eFigure 1: Comparison with previous studies



eFigure 1: Hazard ratios from Cox regression compared to results from previous studies using CPRD GOLD.
mansfield2020: Mansfield KE, Schmidt SAJ, Darvalics B, et al. Association Between Atopic Eczema and Cancer in England and Denmark. JAMA Dermatol 2020; 156: 1086.
matthewman2021: Matthewman J, Tadrous M, Mansfield KE, et al. Association of Different Prescribing Patterns for Oral Corticosteroids With Fracture Preventive Care Among Older Adults in the UK and Ontario. JAMA Dermatology 2023; 159: 961–9.
schonmann2020: Schonmann Y, Mansfield KE, Hayes JF, et al. Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. The Journal of Allergy and Clinical Immunology: In Practice 2020; 8: 248-257.e16.
silverwood2018: Silverwood RJ, Mansfield KE, Mulick A, et al. Atopic eczema in adulthood and mortality: UK population-based cohort study, 1998-2016. J Allergy Clin Immunol 2021; 147: 1753–63.

RECORD checklist

The RECORD checklist of items, extended from the STROBE statements, which should be reported in non-interventional studies using routinely collected health data.

B.0.1 Title and abstract

1. Title and abstract

- (STROBE) Indicate the study's design with a commonly used term in the title or the abstract. **Title**
- (STROBE) Provide in the abstract an informative and balanced summary of what was done and what was found. **Abstract**
- (RECORD) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. **Abstract**
- (RECORD) If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. **Title and Abstract**
- (RECORD) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. **Not applicable**

B.0.2 Introduction

2. Background rationale

- (STROBE) Explain the scientific background and rationale for the investigation being reported. **Background**

3. Objectives

- (STROBE) State specific objectives, including any prespecified hypotheses. **Background**

B.0.3 Methods

4. Study design

- (STROBE) Present key elements of study design early in the paper. **Methods > Study design and setting**

5. Setting

- (STROBE) Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. **Methods > Study design and setting**

6. Participants

- (STROBE) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. ~~Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants.~~ **Methods > Study population**
- ~~(STROBE) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.~~
- (RECORD) The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. **Methods > Study population**

- (RECORD) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. **Methods > Study population**
- (RECORD) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. **Not applicable**

7. Variables

- (STROBE) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **Methods > Study population; Outcomes**
- (RECORD) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. **Data availability**

8. Data sources/measurement

- (STROBE) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. **Methods > Study design and setting**

9. Bias

- (STROBE) Describe any efforts to address potential sources of bias. **Methods > Statistical analysis**

10. Study size

- (STROBE) Explain how the study size was arrived at. **Methods > Statistical analysis**

11. Quantitative variables

- (STROBE) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. **Methods > Statistical analysis**

12. Statistical methods/Data access and cleaning methods/Linkage

- (STROBE) Describe all statistical methods, including those used to control for confounding. **Methods > Statistical analysis**
- (STROBE) Describe any methods used to examine subgroups and interactions. **Methods > Statistical analysis**
- (STROBE) Explain how missing data were addressed. **Methods > Statistical analysis; Discussion > Limitations**
- (STROBE) Cohort study—if applicable, explain how loss to follow-up was addressed. ~~Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy.~~ **Methods > Statistical analysis**
- (STROBE) Describe any sensitivity analyses. **Methods > Statistical analysis**
- (RECORD) Authors should describe the extent to which the investigators had access to the database population used to create the study population. **Methods > Ethics**

- (RECORD) Authors should provide information on the data cleaning methods used in the study. **Methods > Statistical analysis**

- (RECORD) State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. **Not applicable**

B.0.4 Results

13. Participants

- (STROBE) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). **Figure 1**
- (STROBE) Give reasons for non-participation at each stage. **Figure 1**
- (STROBE) Consider use of a flow diagram. **Figure 1**
- (RECORD) Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram. **Figure 1; Methods > Study population**

14. Descriptive data

- (STROBE) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. **Table 1**
- (STROBE) Indicate the number of participants with missing data for each variable of interest. **Table 1**
- (STROBE) Cohort study—summarise follow-up time (eg, average and total amount). **Table 1**

15. Outcome data

- (STROBE) Cohort study—report numbers of outcome events or summary measures over time. ~~Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.~~ **Figure 2; Figure 3; eTable 1; eTable 2**

16. Main results

- (STROBE) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. **Figure 2; Figure 3; eTable 1; eTable 2**
- (STROBE) Report category boundaries when continuous variables are categorised. **Table 1**

17. (STROBE) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. **Figure 2; eTable 1**

18. Other analyses

- (STROBE) Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses. **Figure 3; eTable 2; eTable 3**

B.0.5 Discussion

18. Key results

- (STROBE) Summarise key results with reference to study objective. **Discussion**

19. Limitations

- (STROBE) Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. **Discussion > Limitations**
- (RECORD) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. **Discussion > Limitations**

20. Interpretation

- (STROBE) Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **Discussion**

21. Generalisability

- (STROBE) Discuss the generalisability (external validity) of the study results. **Discussion**

B.0.6 Other information

22a. Funding/Accessibility of protocol, raw data, and programming code

- (STROBE) Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. **Funding**

- (RECORD) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. **Data availability**

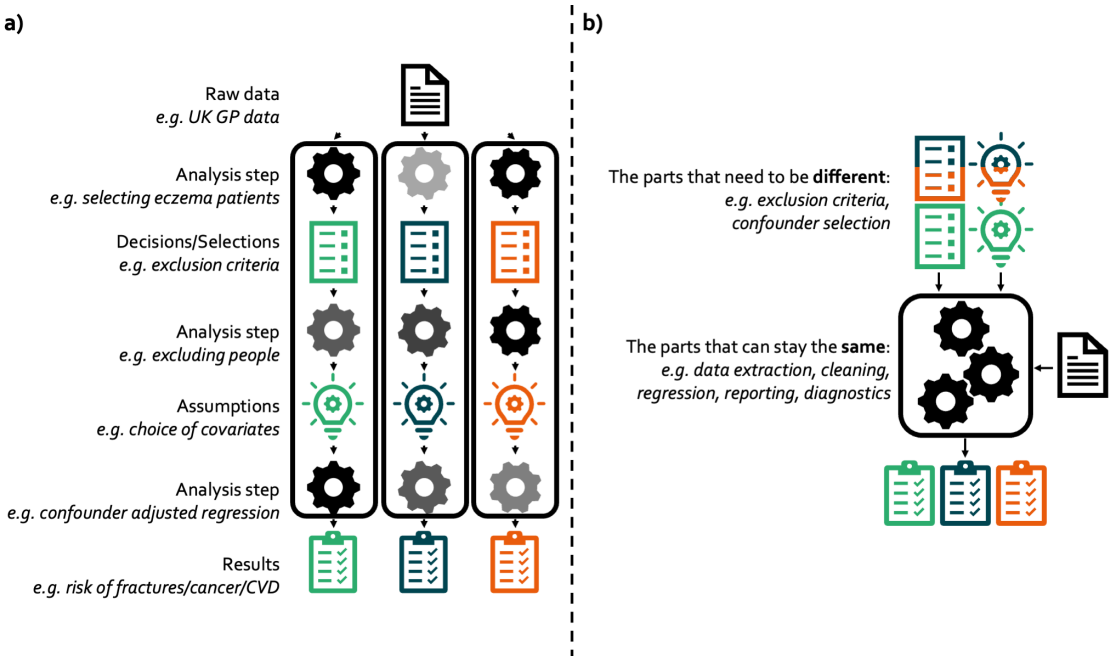
7.4 Rationale

Here I provide a more general rationale for conducting research on multiple outcomes, not related to the specific exposure of eczema. As discussed in Section 1.3, studies in EHRs are suitable, and widely used, to address questions of adverse outcomes related to exposures, such as drugs, environmental factors and other diseases. For any given exposure it is likely studies in EHR could be used to explore several causally plausible but unexplored, or not adequately explored, associations, investigate broadly explored associations with more granularity and update and replicate existing analyses.

While the number of potential research questions relating to a single exposure is large, studies are typically conducted one at a time, each focused only on one outcome, or a small set of related outcomes, and often built from the ground up, which has several disadvantages. The rationale for more efficient approaches to evidence generation stems from the recognition of these disadvantages, some of which are described here:

Slow & inefficient: Epidemiological studies in routinely collected data on the same exposure and different associated adverse health outcomes usually share much of their design but typically each has separate planning, approvals, data management, analysis, hypothesis development, coding, and publication phases. While some of this work is justifiably bespoke to the research question under investigation, much of the work that goes into these studies may be repeated. For example, data management and statistical analysis code may be shared between studies, and approvals and publications may contain much of the same information, and if there are differences it may often be unclear if these differences between studies are justifiable or wanted.[116] Considering how to conduct studies across multiple outcomes, while requiring an upfront investment in planning, may not just lead to a much faster output of research, but may help investigators decide upon and justify which design choices are appropriate for which outcomes. Parts of studies that are unnecessarily repeated can be identified and applied consistently within the larger project. These ideas are similar to the "Don't repeat yourself" approach in software development while allowing for heterogeneity between outcomes where it is wanted.

Not directly comparable: While different studies may employ different but equally valid



A simplified comparison between a) the status quo of conducting exposure-outcome studies in EHR data, and b) the approach applied in this thesis. Each black box can be seen as one study (which would typically be published as one manuscript). In a) separate studies are conducted for each outcome using the same data source and exposure. The analysis steps are shared between studies but are not verifiably equivalent to each other (unwanted heterogeneity) (represented through cogs in slightly different shades of grey). The study-specific decisions, selections and assumptions (represented through lists and light bulbs) are not easily separated from the shared parts of the analyses. In b) a shared set of analysis steps is used to produce results for all three studies, and some of the decisions, selections and assumptions can be shared between outcomes.

Figure 7.1: Visualisation of how studies on multiple outcomes can be organised

statistical methods and use different study-specific inputs, each with different assumptions, strengths and limitations (wanted heterogeneity), studies may also differ in a way that results are not directly comparable. For example, differences in results may be due to heterogeneous approaches taken to the processing of EHR data, rather than actual differences in effects (unwanted heterogeneity). Consistent re-use of methods for multiple outcomes and the transparent reporting of choice of variations thereof at each step in the pipeline makes results much easier to compare, which is essential for decision-makers faced with identifying which adverse outcomes are most relevant to people with a given exposure.

Subject to researcher biases: The need for researchers to publish as many studies in as high-ranking journals as possible to progress their careers can bias the literature at large.[117–119] As studies that find a larger effect are most likely to be published in a high-ranking journal, investigators may refrain from publishing studies that found no, or a small effect, or may be consciously or unconsciously biased to conduct studies to produce larger effects. By transparently reporting results for all outcomes from all variations of study design, "investigator degrees of freedom" are limited, i.e., it is not possible to pick the model or analysis which the investigator likes best, as this would also change results for other outcomes, safeguarding against this practice.[47]

Other issues, while certainly possible to overcome within studies that only focus on a single or small set of outcomes, may be greatly facilitated with more efficient approaches:

Difficult to reproduce: Reproducibility is a central tenet of science, however, the individual conduct of studies may disincentivise making research reproducible as it requires time investment, delaying publication of results. Even if study code is shared, systems guaranteeing reproducibility may not be in place, i.e. the code can only be run with knowledge of the original investigator(s). In addition, preparation steps are rarely reported adequately, although assumptions made during these can influence results.[120] Both inadequate code sharing and reporting of methods can lead to study results not being reproducible.[121] Studies on many outcomes with large data sources essentially necessitate the use of reproducible analysis pipelines, as they would be difficult to manage otherwise. In addition, the time investment required to ensure computational reproducibility is proportionally much smaller per outcome.

Finally, there are further disadvantages of the status quo, that, while not addressed in this thesis, could be addressed by extending the approach to conducting studies on multiple outcomes.

Abandoned after publication: Study findings and methods are usually communicated via a published manuscript and open questions that arise before or after publication of said manuscript, including questions that could have been answered using the same data source and study, are deferred to calls for future research. The current way of working is not equipped to efficiently update evidence after a given state of the research is declared final. This is suboptimal, as decision-makers, including funders, clinical guideline authors and others, depend on evidence from a given source being the best possible achievable using the given data source. Open, but answerable questions may in some cases render the results from a given study effectively unusable, leading to delays in decision-making and possibly, missed opportunities for care. One could imagine that updating studies after they have been first published and peer-reviewed could be useful and efficient, as the original study infrastructure (e.g., data management and analysis code, approvals, etc.) is still in place. For example, it may be straightforward to add additional outcomes to a multi-outcome study. A possible template for this type of updating of research may be the living systematic review.[122]

Overconfidence in a single approach: Individual studies often produce results using a single statistical method. However, different but equally legitimate results could be produced from the same data depending on the statistical method, and disease definitions used. Therefore, relying on a single result may not be appropriate and promote overconfidence in results.[123] It is therefore recommended to "triangulate" answers to research questions, through considering results produced using multiple approaches that differ in their sources of potential bias.[55] While triangulation is possible using results from multiple studies, it may be useful for a study on multiple outcomes to report results from multiple different statistical approaches and alternative disease definitions across all outcomes.

7.5 Relevance for thesis

The study presented in this chapter on adverse outcomes for people with eczema (*Aim I*) provides evidence that can be used to inform priorities for their care (*Overall Thesis Aim*). The study demonstrates that new insights can be won from EHRs more quickly and efficiently by expanding the scope to multiple outcomes (*Aim III*). The study incorporates learnings from all other chapters of this thesis and may demonstrate an innovative new approach to EHR research.

7.6 Chapter summary

- Many different adverse health outcomes for people with eczema had been previously investigated, but the evidence was often of low or moderate quality
- Large and comprehensive EHRs (such as CPRD Aurum) provide the opportunity to study many different outcomes, and studies on different outcomes often share similar study designs, as identified in a literature search
- By using a study design and confounding adjustment strategy that works across different outcomes, I investigated 71 different outcomes
- For some outcomes, results matched those from clinical expectations, such as for atopic and allergic conditions
- For some outcomes, results matched those from previous studies, for example for cardiovascular, fracture, mental illness, and cancer outcomes, which also helped benchmark the multiple-outcome approach
- For some outcomes, results provide evidence of associations for which there was previously little awareness, for example for several gastrointestinal conditions
- Besides increased efficiency, the approach has other benefits including better comparability between outcomes and potentially fewer researcher biases, and the approach may be applicable beyond eczema research

8 Discussion

8.1 Introduction

In this final chapter, I present a discussion of the studies and findings of this thesis. First, I consider each of the three thesis aims separately. For each aim, I include a summary of findings, a discussion of relevant study features, and implications for clinical practice and future research. Then, I discuss strengths, limitations and further considerations that are relevant across all thesis aims. Finally, I summarise this chapter and give my overall conclusions from this thesis.

8.2 Aim I

8.2.1 Summary of findings

8.2.1.1 Eczema, psoriasis, and other IMID exposures, and the risk of adverse health outcomes

In Chapter 3, I showed that, in the general population, those who have an immune-mediated inflammatory disease (IMID), including those affecting joints (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), the bowel (Crohn's disease and ulcerative colitis), and skin (psoriasis and hidradenitis suppurativa), had an increased risk of COVID-19 related death, critical care admission, and hospital admission. Adjusted hazard ratios were largest for inflammatory joint disease for all outcomes (e.g., for COVID-19 death: HR 1.47,

95% CI 1.40–1.54), with smaller effect estimates for inflammatory skin (1.12, 1.08–1.17), and bowel (1.12, 1.04–1.21) disease.

In Chapter 5, I showed that having eczema or psoriasis was associated with an increased risk of also having anxiety and depression, and this was found both when using questionnaire responses from the UK Biobank and when using primary care electronic health records to define anxiety and depression (with odds ratios ranging from 1.20 to 1.56). The cross-sectional design assessed if people with skin conditions were at increased risk of also having anxiety or depression. The cohort design of Chapter 7 assessed whether having eczema is associated with the *subsequent* (i.e., after being diagnosed with eczema) development of anxiety or depression. Here, I found a smaller effect estimate (an adjusted hazard ratio of 1.16 for both anxiety and depression), however, even a small increase in risk may be important to consider given how common eczema and psoriasis (eczema in particular) are.

In Chapter 7, I showed that having eczema was associated with the development of several different adverse health outcomes, including a strongly increased risk of atopic and allergic conditions, skin infections and some immune-mediated skin conditions, a moderately increased risk of some liver and gastrointestinal conditions, a weakly increased risk of some cardiovascular, neurological and other outcomes, and no increased risk of cancers, except lymphomas.

8.2.1.2 Anti-inflammatory treatments and the risk of adverse health outcomes

In Chapter 3, in a population of people with inflammatory joint, bowel, and skin diseases (not including eczema), I showed that there was no increased risk of severe COVID-19 in those on targeted immune-modifying therapies compared to those on standard immunosuppressants. For most investigations of individual targeted immune-modifying therapies, relatively few severe COVID-19 events occurred, i.e., there was low power to detect increased risk. However, there was an increased risk seen for people on rituximab, for all outcomes including death, hospitalisation, and critical care admission.

In Chapter 4, I used population-based data from the UK and Ontario to study people with eczema, asthma, and COPD who were treated with high cumulative doses of oral

glucocorticoids. I found an increased risk of missing recommended fracture preventive care in those who were prescribed oral glucocorticoids in high cumulative doses with low-intensity patterns (compared to high cumulative doses with high-intensity patterns). However, there was no increased risk of fractures.

8.2.2 Emphasis on Causality

Studies had different emphasis on addressing causal questions, i.e., aiming to asses whether the exposure causes the outcome, rather than just co-occurring with the outcome. Adjustment for confounding was implemented in different ways and to different extents. All studies employed confounding adjustment through inclusion of covariates in regression models and most studies used a number of different covariate sets. Table 8.1 gives an overview of the study design characteristics and covariates included in regression models to adjust for confounding.

Table 8.1: Overview of study designs and covariates

	Design	Confounding-adjustment through design features	Regression model covariates	Covariate sets
Chapter 3	Cohort	none	age, sex, deprivation, lifestyle, comorbidities, glucocorticoid use, specific immune-mediated inflammatory disease	two per exposure[1]
Chapter 4	Cohort	include only people 1. 66 or older, 2. with eczema or asthma or COPD, 3. who received a cumulative prednisolone equivalent dose of >= 450 mg	age, sex, deprivation, specific inflammatory condition, drugs associated with fracture risk, use of healthcare system	three[2]
Chapter 5	Cross-sectional	none	age, sex, deprivation, and ethnicity	two[3]
Chapter 7	Cohort	matched exposed to unexposed on age, sex, and general practice	comorbidities, oral glucocorticoid, systemic immunosuppressants	three[4]

[1]for IMIDs adjusted regression models for: 1. age, sex, deprivation, and smoking status; 2. + body-mass index, cardiovascular disease, diabetes, and current glucocorticoid use; for targeted immunosuppressants adjusted regression models for: 1. specific immune-mediated inflammatory disease (joint, bowel, and skin), cardiovascular disease, cancer (excluding nonmelanoma skin cancer), stroke, end-stage renal failure, chronic liver disease, chronic respiratory disease, and diabetes; 2. + current glucocorticoid use

[2]adjusted regression models for 1. nothing for main analysis, 2. age group, sex, deprivation, eczema, asthma, COPD, and rheumatoid arthritis, 3. + rurality, dementia, drugs decreasing fracture risk, drugs increasing fracture risk, inhaled or nasal corticosteroids, injectable corticosteroids, topical corticosteroids, other corticosteroids, oral corticosteroid in the year prior to cohort entry, health care use in the year prior to cohort entry (physician visits [0-12, 13], hospitalization [yes, no], Number of physicians prescribing oral corticosteroid [1, 2]), specialty of physician prescribing oral corticosteroid (family practice, dermatology, emergency medicine, and other)

[3]adjusted regression models for 1. nothing, 2. age, sex, deprivation, and ethnicity

[4]adjusted regression models for 1. nothing, 2. + comorbidities (history of any other outcomes before index date); 2. + history of oral glucocorticoid and systemic immunosuppressant use before index date

In Chapter 3 (COVID outcomes), adjustment for confounding was implemented by adjusting regression models for covariates. Directed acyclic graphs (DAGs) were drawn and expert knowledge was incorporated to select a bespoke set of covariates, which was different between the IMID and drug exposures. Since informing risk-mitigation strategies and COVID-19 vaccination priorities was the ultimate goal, generating estimates that were as close as possible to causal estimates, within the limitations of observational study design, was important. For example, to inform whether stopping treatments would mitigate or worsen increased COVID risks, accounting for confounding by indication was necessary. People with IMIDs and those taking targeted immune-modifying treatments may have had different comorbidity profiles than the general population, which were (at least partially) adjusted for, also through the use of an active comparator. However, there may still have been residual confounding given those on targeted immune-modifying therapies were likely to have more severe inflammatory disease than those on standard immunosuppressants, and disease severity was not measured.

In Chapter 4 (fracture preventive care outcomes), adjustment for confounding was primarily implemented through study inclusion criteria, i.e., the two comparison populations were made similar to each other by selectively including individuals from a certain age (66 or older), with certain conditions (conditions that may be treated with oral glucocorticoids, including eczema, asthma and COPD), and individuals who had received a large cumulative dose of oral glucocorticoids within the past 6 months. Main analyses were not adjusted for any covariates. Sensitivity analyses where Cox regression models were additionally adjusted for covariates were not considerably different from main results, which suggests

that inclusion criteria had already (at least partially) accounted for confounding. The research question for this study was rather complex: "Are older people who should be receiving fracture preventive care due to being prescribed large cumulative doses of oral glucocorticoids, less likely to receive fracture preventive care if oral glucocorticoids were prescribed over longer periods of time, a larger number of prescriptions, or with more or longer gaps between prescriptions?". A bespoke covariate selection in this context, e.g., by drawing a DAG, may have been difficult to implement and/or justify. Therefore, a different approach to covariate selection was taken in sensitivity analyses, which were broadly adjusted for demographics and, in the Ontario analyses, broadly adjusted for variables that may impact fracture preventive care. Another tool that was used in the absence of reliable knowledge of confounders of the association of interest was negative control outcomes (anxiety drugs and epilepsy drugs). Null effects observed for these suggest that strong sources of bias were unlikely.

In Chapter 5 (anxiety/depression outcomes), adjustment for confounding is implemented by adjusting regression models for covariates, however, the covariate selection was limited to demographic characteristics. Given that the main aim of Chapter 5 was to explore whether the association between eczema/psoriasis and anxiety/depression were consistent across data sources, optimising confounding adjustment was not a priority here. The cross-sectional design also precluded knowing whether eczema/psoriasis preceded anxiety/depression. Nevertheless, in the context of awareness of increased co-occurrence of anxiety or depression in people with eczema or psoriasis, knowing about associations rather than causation may already be useful.

In Chapter 7 (71 outcomes), adjustment for demographic factors, including age, sex, and general practice (which may further serve as a proxy for socioeconomic status, region, and health care access) is achieved through matching unexposed to exposed individuals on these factors. In addition, adjustment for comorbidities was achieved through an outcome-wide adjustment strategy (which is discussed in more detail in Section 8.4.2). Chapter 7 (eczema -> multiple outcomes) is similar to Chapter 3 (IMIDs -> COVID), in that causality, rather than co-occurrence, is of interest. Knowing to what extent the exposure causes outcomes would have a greater relevance to inform screening and prevention for people with eczema,

and if better eczema control may mitigate adverse outcomes. Again, given the limitations of observational studies, such as residual confounding, and of electronic health records studies, such as information bias, it is not possible to definitively conclude causality of associations. Nevertheless, studies provide a range of information that can be used to judge the plausibility of causal associations.

8.2.3 Strength of evidence for causality

The Bradford Hill criteria for causation may help judge evidence of causal relationships for the exposure-outcome associations explored in this thesis.[124] These criteria include strength of association (effect size), consistency (reproducibility) across different samples, specificity (i.e., there is another explanation for a disease), temporality (i.e., the effect has to occur after the cause), biological gradient (dose-response relationship), plausibility (i.e., a biologically plausible mechanism), coherence (with laboratory findings), experiment (i.e., experimental evidence), and analogy (with other associations). I will discuss biological gradient (sometimes known as dose-response) and reversibility, which are considered by some authors as separate criteria,[125] together. It is unlikely experimental evidence, e.g., in the form of a randomised clinical trial, can be found for studies where a disease (eczema, psoriasis, IMIDs) is the exposure, but it is possible when drugs are the exposure. Three examples of applying the Bradford Hill criteria to findings from this thesis are included below.

8.2.3.1 Example: Does eczema cause food allergy?

For this, it is useful to consider an example directly from Bradford Hills' paper, where he states that smokers have a nine to ten times higher rate of dying from lung cancer.[124] Obviously, most associations studied in epidemiology will be considerably less strong than this one. However, among associations studied in this thesis, there is one example of a **very strong association**, namely between eczema and subsequent food allergy with a hazard ratio of > 4 (and >7 for people with moderate-to-severe eczema) in Chapter 7. Useful in this context is also to be able to directly compare the size of this association with others,

including other associations that are well known from clinical practice such as asthma, allergic rhinitis and skin infections, which were all strong (with hazard ratios of around 2), but considerably less strong than for food allergy. Thus there is a **specificity** in magnitude for the association between eczema and food allergy. The study was also designed to capture the effect of eczema on the subsequent development, not the co-occurrence, of outcomes, i.e., **temporality** is established (given no major bias is introduced through imprecise capture of disease onset timing in electronic health records). There is **consistency** with previous evidence across multiple populations and data sources for this association[7], and **coherence** with laboratory findings, where epicutaneous allergic sensitization has been studied in mouse models that mimic eczema.[126] Sensitization to allergens through the skin may also be a **biologically plausible mechanism**, and has frequently been discussed in the literature; there may also be analogies to the development of other atopic conditions, such as asthma and allergic rhinitis, as often discussed together on the literature on the "atopic march".[127] In summary, a causal link between eczema and food allergy seems very plausible.

8.2.3.2 Example: Does eczema cause anxiety and depression?

From findings in Chapter 7, the **strength of association** with anxiety and depression was not strong (with HR of 1.16). While larger effect estimates were seen in Chapter 5, the cohort study design in Chapter 7 provides evidence of **temporality** which the cross-sectional design in Chapter 5 does not. The association was seen with both study designs and across both data sources used in Chapter 5, thus there is **consistency** with results from this thesis, as well as with other studies.[7] There is no good evidence for **specificity** (or specificity of magnitude), given a host of other associations of similar strength of effect can be found, and there are several other causes for anxiety and depression. Eczema (or psoriasis, or visible skin conditions in general) causing depression or anxiety is (biologically, or rather sociologically) **plausible**, for example, through mechanisms such as low self-esteem or stigmatization due to visible skin lesions. However, such mechanisms would be difficult to study or confirm. In Chapter 7, there was only evidence of a very small **dose-response** relationship, with individuals with moderate-to-severe eczema having slightly higher hazards of experiencing depression or anxiety. Finally, even a weak association is not consistent

with findings from a Mendelian randomisation study, often used to strengthen evidence of causality, where no association could be found.[128] In summary, while eczema (and psoriasis) may be associated with anxiety and depression, it may not be possible, from this thesis taken together with other evidence on the topic, to determine whether the link is causal. However, given how common eczema, anxiety and depression are, the association may have public health relevance.

8.2.3.3 Example: Does eczema cause Hodgkin's lymphoma?

As with food allergy, but on a lower level, there is a **strong association** with Hodgkin's lymphoma. There is a **specificity of magnitude** compared to other (solid-organ) cancers which were not found to be associated with eczema, and compared to non-Hodgkin's lymphoma, which was found to be associated, but with a much lower hazard ratio (1.26; 99%CI 1.21, 1.32) than Hodgkin's lymphoma (1.83; 99%CI 1.64, 2.04). Again, the study design allowed establishing **temporality**, however, it is important to consider timeframes here. From the study, it is not possible to tell whether the risk of Hodgkin's lymphoma increases with longer exposure to eczema. A **dose-response** relationship could not be established, given the only 70 cases of Hodgkin's lymphoma in people with moderate-to-severe eczema, making confidence intervals too wide to exclude the possibility of a chance finding. There is **consistency** with previous findings, including from a systematic review and meta-analysis.[129] Finally, it has to be mentioned that Hodgkin's lymphoma is very rare, in the study in Chapter 7 only occurring 3,559 times in a population of more than 20 million people. Increased awareness of Hodgkin's lymphoma risk for people with eczema, or implementing screening or prevention would therefore most likely not be appropriate. Nevertheless, the finding adds to the evidence that immune system malfunction after allergic disease is central to the development of Hodgkin's lymphoma.[130]

8.2.4 Future Research and implications for clinical practice

Recommendations for clinical practice and future research are included in the discussion sections of the corresponding chapters. In short, findings from Chapter 3 suggest potential

importance for booster vaccine prioritisation and risk mitigation policy for people with IMIDs. Research on these topics was indeed conducted since the study was published, including, for example, on the role of vaccines in people with IMIDs.[131] Clinical practice may have also been informed, for example, by taking into account findings into expert consensus statements.[132]

Chapter 4, where a gap in fracture preventive care was identified across two different population-based data sources, strengthens the recommendation that clinicians should be aware of recent cumulative oral glucocorticoid doses and initiate fracture preventive care when indicated. Future research may evaluate if implementing cumulative dose tracking for oral glucocorticoids in clinical software may mitigate risk.

Both Chapter 5 and Chapter 7 suggest individuals with eczema or psoriasis may benefit from better access to mental health services and/or increased awareness amongst health care providers, especially given how common both the skin and mental health conditions were. Research on drivers of the association between skin disease and poor mental health has been ongoing, a recent study suggested that mediators such as poor sleep quality may be important.[21]

The list of other potential implications on clinical practice from Chapter 7 is extensive. In short, the study provides evidence of associations for which there was previously little awareness and allows updating the evidence on several outcomes. Future research should consider different and potentially larger sets of outcomes to explore and make use of linkage between primary care and hospital data to confirm if findings hold when outcomes can be defined using multiple sources. Furthermore, replicating this type of study in a different setting, potentially electronic health records from different countries, would further strengthen the evidence.

8.3 Aim II

8.3.1 Summary of findings

Both Chapter 5 and Chapter 6 showed that there was considerable disagreement between eczema diagnoses derived from EHRs and questionnaires. While agreement was also suboptimal for other conditions, including psoriasis, asthma, anxiety and depression, I focus the discussion on eczema, as eczema was studied in both UK Biobank and ALSPAC. Figure 8.1 shows the proportion of individuals that had eczema and other conditions according to EHRs, questionnaires, or both. When measuring agreement as the percentage of individuals who are considered to have the condition in both data sources out of those who have the condition in at least one data source, there is only 10% agreement for eczema between UK Biobank questionnaires and linked EHRs. In ALSPAC, there is about 33% agreement between EHRs and questionnaires, both with parent-reported diagnoses and with phenotypes derived from symptom reports. In both studies, agreement was better for other conditions as compared to eczema. In UK Biobank, agreement was 24% for psoriasis and 22% for depression, and in ALSPAC, agreement was 63% for asthma.

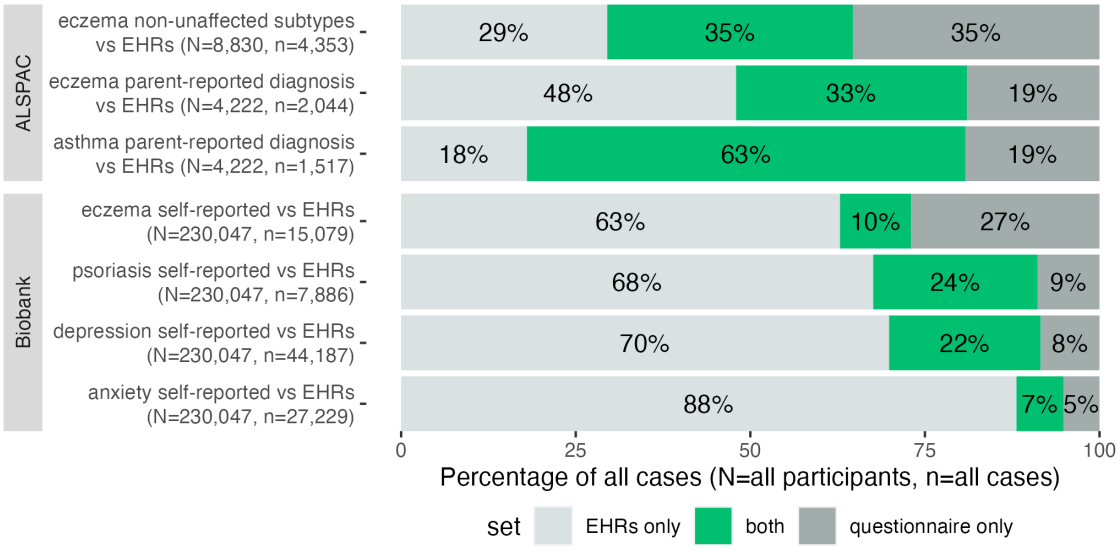


Figure 8.1: Agreement concerning diagnoses in UK Biobank and ALSPAC

In Chapter 6, the objective of accurately classifying eczema subtypes using linked EHRs

proved not feasible given poor agreement. With a best ROC AUC of 0.68, the developed prediction models cannot be used to learn about individuals' eczema subtypes (as defined in ALSPAC) from EHRs alone. However, it is not possible to conclude from Chapter 6 that EHRs do not contain sufficient information to identify subtypes of eczema. It is possible that subtypes previously developed using symptom reports from ALSPAC do not accurately represent actual subtypes of severity trajectories. It may also be possible that subtypes are less distinct from one another, and severity trajectories occur on a more continuous scale.

It is also not possible to conclude from Chapter 5 and Chapter 6 that EHRs are less accurate in classifying eczema status as compared to ALSPAC or UK Biobank, since there is no gold standard. The prevalence of eczema was lower in UK Biobank (2.4%) than in EHRs (4.8%). While both prevalences fall within the 2-10% range of prevalence estimates for adults from previous studies[13], some studies have suggested that the UK has a high prevalence of eczema of at least 5-10% in adults.[133] If this is the case, the prevalence of 2.4% found in UK Biobank is likely to be an underestimate, and therefore, EHRs may better capture eczema status.

For the children in the ALSPAC study, given other studies have found prevalences in children ranging from 10-30%,[13] both prevalences from EHRs (32%) and from ALSPAC (as defined as a non-unaffected subtype) (35%) are likely to be overestimated. Since a similar number, but different children are considered to have eczema between the two data sources, it is unclear which data source better captures eczema status.

8.3.2 Reasons for poor agreement between data sources

In general, there are different influential factors which may contribute to differences between routinely collected EHRs and questionnaire responses collected for study purposes. In routinely collected data the health care setting (e.g., primary care, secondary care) and access to it (e.g., free/paid, long/short waiting times), and use of it (e.g., consultation frequency, switching of practices) may all play a role in whether, how, and when, information for a given disease is recorded. In Chapter 5 and Chapter 6 I did not have access to linked hospital data or primary care free text data, which may have been used to supplement structured

primary care data.

If data are collected for study purposes, ideally, many of these considerations are built in at the design stage (e.g., the study questionnaire is standardised and administered to all participants in the same way, validated high sensitivity and specificity definitions are used, questionnaires are administered at regular intervals, etc…), but these approaches may also be subject to different problems such as reporting or recall bias, and selection bias. It is also important to consider that population cohorts such as ALSPAC and the UK Biobank are not designed to investigate only a single research question. Questionnaires are supposed to capture information on many aspects of a person's health. Therefore, while the information is captured for research purposes, it is not captured to answer one specific study question, as might be the case with a clinical trial or a study specifically established to focus on eczema.

It is also important to consider that population cohorts such as ALSPAC and the UK Biobank are not designed to investigate only a single research question. Questionnaires are supposed to capture information on many aspects of a person's health. Therefore, while the information is captured for research purposes, it is not captured to answer one specific study question, as might be the case with a clinical trial.

The codelists that were used to define a given disease in EHRs, especially in the primary care data linked to UK Biobank, may also partially explain poor agreement. Here, for eczema, psoriasis, depression, and anxiety, the number of people who self-reported conditions was much lower than the number of people with corresponding primary care records. For example, the most common codes in the codelist for anxiety, which had the worst agreement, were for "*Anxiety state nos*", "*Mixed anxiety and depressive disorder*", "*Anxiousness*", "*Anxiety states*" (as listed in Supplementary Table 3 in the online supplementary materials).[99] People may have been considered to have anxiety, who actually had transient anxiety states or depression. On the other hand, for psoriasis, the most common codes seem specific for psoriasis, suggesting an unspecific codelist was not the main reason for poor agreement.

8.3.3 Reasons for poor agreement concerning eczema

Questionnaires can be subject to several biases and may have been unsuitable to determine eczema status.[134] For example, both questionnaires in ALSPAC and UK Biobank may have been subject to recall bias. Parental reports in ALSPAC may have been subject to differential parental perception of disease status (e.g., some parents may have already reported mild rashes whereas other parents may have only reported more severe rashes). Understanding of disease status may also differ between patients/parents and doctors.

More closely inspecting the wording of questionnaires may also reveal potential opportunities for misclassification. For example, in ALSPAC the parent-reported doctor's eczema/asthma diagnosis was determined using the response to the question if a doctor had ever diagnosed asthma or eczema by 166 months (questions A5: "Has a doctor ever actually said that he/she has asthma or eczema?"). In the question before the parent was asked for a list of 23 different health issues (including eczema and asthma) to specify if "he/she had any of the following in the past 12 months?" (question A4). From just the questionnaire it may be unclear if parents should have reported eczema or asthma in question A5 if they did not report eczema or asthma in the past 12 months in question A4. Therefore, only more recent cases of eczema or asthma may have been captured in question A5. Similarly, in UK Biobank, eczema and psoriasis were defined using recruitment interview responses where participants were asked if they had any "previous diagnosis of serious illnesses or disability". It is possible that participants did not consider eczema or psoriasis as serious illnesses, and may not have reported these.[135]

On the other hand, linked EHRs may also not have adequately captured eczema. For example, EHRs could miss diagnoses (e.g., less severe cases of eczema that do not consult the GP, or diagnoses from specialist care not being transferred in primary care), but could also wrongly label individuals as having a condition when they do not (e.g., if GPs use diagnosis codes for atopic eczema to record other forms of eczema or other rashes).

A comparison with other conditions is useful, as is available in this thesis. Psoriasis and asthma both had better agreement than eczema (Figure 8.1). For asthma, a previous study

using linkage between ALSPAC and primary care records was able to achieve better specificity for asthma by using detailed wheezing questionnaires and concluded that there was good agreement between ALSPAC and EHRs.[136] Poorer agreement for eczema than for other diseases suggests that the problem may be specific to eczema. Reasons why eczema may be particularly prone to disagreement include it being a relapsing-remitting condition which may not be detectable in periods of remission. It is also a non-life-threatening condition for which regular follow-up may not be required, and no formal diagnostic test is available.

Table 8.2: Overview of reasons for poor agreement between data sources

EHRs	Questionnaires
Codelist quality	Questionnaire quality
Healthcare system use	Reporting and recall bias
Missing data (unrecorded)	Missing data (recorded as missing)
Wrong diagnosis	Wrong diagnosis (self-reported)

8.3.4 Implications of Aim II findings on Aim I findings

Findings from Chapter 5 suggest that those who have an eczema diagnosis in EHRs do not necessarily correspond to those who self-reported having had eczema in the past. Similarly, findings from Chapter 6 suggest that those who have an eczema diagnosis in EHRs do not necessarily correspond to those whose parents reported symptoms of eczema. Does this disagreement have implications for studies investigating adverse health outcomes for those with eczema?

As stated above, given the lack of a gold standard, it is not possible to definitively conclude how well EHRs can classify eczema. The eczema definitions used in our EHR studies were based on a previously validated algorithm, which was found to have a positive predictive value of 86% for a physician-confirmed diagnosis of eczema.[137] However, the validation also had limitations. The algorithm may only be directly applicable to the data source it was validated in (The Health Improvement Network)[138] albeit this data source has substantial overlap with CPRD, making the algorithm suitable for studies in this thesis. The algorithm was validated using physician recall and review of medical records, which introduces the

possibility of physicians relying on what had been coded in medical records if they did not recall a given patient's eczema status. A validation where patients themselves confirm their eczema diagnosis may be preferable, although this may still be susceptible to recall bias and selection bias.

The eczema definition based on the validated algorithm required individuals to have at least two prescriptions for eczema treatments on two separate days, which is likely to have increased specificity. In Chapter 6, I also saw improved specificity when a diagnosis and a prescription in EHRs were required (as compared to having at least one/two symptom reports in ALSPAC; see eTable 6 in Section 6.3).

While it may not be possible to judge the amount of misclassification of eczema in EHRs, it is useful to consider the effect such misclassification would have. Given the scenario that eczema in EHRs is indeed misclassified, but the amount of misclassification is similar between those that do and those that do not develop outcomes (i.e., non-differential misclassification of exposure), effect estimates would be biased towards the null, as the two groups would be more similar to each other. It is, however, also possible that misclassification of exposure may have occurred more, or less, commonly in people who go on to develop outcomes (i.e., differential misclassification of exposure), which would make the direction of bias more difficult to predict. While it is not possible to say if these scenarios are likely, misclassification may explain some of the effects seen or may have led to underestimating effects.

If ALSPAC were a suitable gold standard (which it is not), it would suggest that in EHRs both the exposed group would include people who do not actually have eczema, and the unexposed group would include people who have eczema (e.g., 22% of people with the unaffected phenotype had a record for eczema in EHRs, and 24% with the severe-frequent phenotype did not have a record for eczema in EHRs; see Results section in Section 6.2). Similarly, in UK Biobank some people self-reported eczema that did not have a record in EHRs and some people who did not self-report eczema had a record in EHRs. In Chapter 7, in addition to defining a cohort of people with eczema based on one diagnosis and two prescriptions, for a sensitivity analysis, I also defined people with likely more severe eczema based on one additional prescription indicating more severe eczema after they were

considered as having eczema. This cohort was compared to a cohort of people who were not considered to have more severe eczema. Findings from this sensitivity analysis were similar to those from main analyses, which gives reassurance that findings hold under two different exposure definitions.

8.3.5 Implications of Aim II findings for eczema studies in UK Biobank

Given the potential for misclassification of eczema status and the especially poor agreement concerning eczema diagnoses between UK Biobank interviews at recruitment and primary care records, there might be implications for studies that use these types of self-reports to define eczema. While this includes studies done using the UK Biobank, this is likely also of concern for other population cohorts that employ similar questionnaire or interview-based methods to ascertain eczema. I conducted a literature search (Note 2) on studies using the UK Biobank to define eczema to ascertain which information is used.

> **Note 2: Literature search for studies using UK Biobank to define eczema**
>
> I searched Pubmed, using the query **((eczema) OR (atopic eczema) OR (atopic dermatitis)) AND (UK Biobank)** to identify studies on eczema in UK Biobank in January 2024. Of 31 results, nine were irrelevant (because UK Biobank was not used to define eczema), and for five no description of how eczema was defined using UK Biobank was found. In ten of the 17 remaining studies,[128,139–147] eczema was defined using self-reported diagnosis from a UK Biobank questionnaire and/or from the baseline interview. Six studies,[99,148–152] including the study presented in Chapter 5,[99] used both self-reported eczema diagnoses and records from either primary care or hospital EHRs. One study relied on EHRs only.[153] One study, in addition to using UK Biobank data, also used data from ALSPAC, which was defined using parent-reported eczema by age 14, as was done in Chapter 6.[139]

I found that most studies (10/17) used self-reported diagnoses from UK Biobank, while some studies additionally used EHRs (6/17) to define eczema. As was shown in Chapter 5, these two populations differ considerably, and a population that uses linked EHRs to define

eczema will be considerably larger, with implications for comparability between studies.

Many of the studies found were genetic studies, including genome-wide association studies that use eczema as the phenotype and Mendelian randomisation studies that use eczema as the exposure or outcome. In Mendelian randomisation studies, non-differential misclassification of eczema status could lead to bias both when used as an exposure or outcome. When used as an exposure, it can lead to weak instrument bias, i.e., when there is no strong relation between the genetic instrumental variable and the exposure. When used as an outcome, it can lead to imprecision of estimates.[154] Phenotypic misclassification can also bias the effect size estimates from genome-wide association studies.[155] In summary, genetic studies that use potentially misclassified eczema status to define phenotypes may be subject to bias.

8.3.6 Future research

Chapter 5 and Chapter 6 make it clear that future research should invest in validating eczema diagnoses in EHRs and population cohorts that use questionnaires to define eczema status. Chart-review-based validation, as was done by Abuabara et al.,[137] may be useful, however, comparison with other sources for eczema definitions may be necessary, possibly patient-reported or physician-confirmed, without chart review. Agreement (between data sources) for eczema should be further compared to agreement found for other conditions (which was done in this thesis for asthma and psoriasis, for both of which agreement was considerably better than for eczema). Larger scale assessments of agreement, possibly across multiple diseases, may prove useful, and it may turn out that eczema is one of only a few conditions with such poor agreement.

In clinical trials on eczema, where diagnoses may be firmly established throughout the recruitment process, the Harmonising Outcome Measures for Eczema (HOME) initiative has also defined a core set of outcomes, including clinical signs, symptoms, quality of life, and long-term control of flares.[156] In studies using electronic health records however, there is no such harmonisation, a recent systematic review found several eczema definitions in use

that were associated with up to a threefold difference in prevalence estimates,[157] and another study came to a similar conclusion for childhood eczema.[158]

Finally, research on eczema subtypes lacks uniform and consistent definitions across studies, as suggested by a recent systematic review.[31] Based on the findings from Chapter 6 it is difficult to judge if the severity-trajectory subtypes derived from ALSPAC [32] could be derived from other data sources. A different ALSPAC-derived eczema subtype classification, based on trajectory but not severity, showed consistency with a birth cohort from the Netherlands,[159] but consistency with EHRs is unknown. Thus, there may be a need for further research into eczema subtypes.

8.4 Aim III

8.4.1 Summary of findings

An approach to efficiently conduct cohort studies on multiple outcomes in EHRs was developed and applied to investigate adverse health outcomes for people with eczema (as described for Aim I). In summary, the process was to:

1. select a set of outcomes, including outcomes that have previously been investigated and outcomes that previously haven't been investigated
2. apply a cohort study analysis to each of these outcomes, adjusting for all other outcomes and additional variables at baseline
3. define a set of variations in study design which are consistently run across all outcomes, then select a main analysis from these variations in study design for each outcome, with all other variations being considered as sensitivity analyses, results of which should be inspected closer if they are considerably different from those of the respective main analysis

Several findings from Chapter 7 strengthen the case that this approach to conducting hypothesis testing research in EHRs is suitable. Firstly, results closely match those from

previous studies in CPRD GOLD that were designed specifically to investigate the association with one particular outcome or set of outcomes.[20,52,113,160] Secondly, results are in many cases more conservative than studies designed specifically to investigate one particular outcome or set of outcomes, while still showing expected strong effect estimates for known outcomes.[7] Thirdly, the consistent application of sensitivity analyses across all outcomes has produced a manageable list of additional results that need to be considered in more detail, with most results from sensitivity analyses being very close to those from main analyses, thus not requiring further discussion. Most outcomes where there were considerable differences between main and sensitivity analyses have likely explanations that can be derived from previous knowledge, e.g., that the risk of food allergy and asthma will be increased more in a cohort including younger people as compared to a cohort that excludes younger people. I only found one outcome where differences between main and sensitivity analyses were not easily explained, which was a larger hazard ratio for autism when using a cohort of older individuals instead of a cohort without age-based exclusion, which may highlight issues with the underlying data for that particular outcome, and suggest caution in the interpretation may be required.

8.4.2 Outcome-wide designs

While the approach used in Chapter 7 originally stems from a recognition of similarities between studies investigating different adverse health outcomes for eczema, it shares much with "Outcome-Wide Longitudinal Designs for Causal Inference", a template for empirical studies proposed by VanDerWeele (et al.).[47] The most important lesson I incorporated from outcome-wide designs was the strategy for confounding-adjustment. While different sets of covariates could have been adjusted for different outcomes, the case laid out by VanDerWeele that only a single set of covariates is sufficient to correctly adjust for confounding is compelling. Importantly, findings from Chapter 7 suggest that the approach works, given associations from studies with bespoke confounding-adjustment strategies could be precisely replicated, and estimates for outcomes acting as positive and negative control outcomes are as expected.

It is, however, possible that an outcome-wide covariate set may have worked better for some outcomes than others. VanDerWeele states that causes of the exposure or causes of any of the outcomes should be adjusted for, including baseline values of all outcomes whenever appropriate. Only variables that are thought to be a cause of neither the treatment nor any outcome need to be discarded from the adjustment set. It is difficult to check for every outcome-specific analysis whether any variables that are neither causes of the outcome nor the exposure were included. Therefore, the confounding adjustment strategy could also be seen as being similar to the "pre-exposure" approach, where all pre-exposure variables are adjusted for, which is also a commonly used approach in epidemiology.[47]

In theory, "M-Bias" could be introduced when a baseline value of a variable is adjusted for, which acts as a collider between an unobserved cause of the exposure and an unobserved cause of the outcome. However, it has been demonstrated that the magnitude of M-bias tends to be small compared to confounding bias, suggesting that choosing to adjust for a given covariate is generally the superior choice.[161]

In summary, it may have been possible to remove from the set of covariates the baseline values of those outcomes that are neither the cause of eczema nor the cause of *any* outcome. However, it would have been difficult to verify if a given variable was indeed the cause of none of the outcomes, and the bias arising from adjusting for such a variable would likely have been minimal.

It may have also been possible to select a different set of covariates for each outcome. However, VanDerWeele advises against this, as this approach could enable investigator bias by allowing investigators to select the models "they like best" after seeing the results. With a single set of covariates used for all outcomes it is not possible for investigators to select a model for one outcome without changing the results for all other outcomes, thus alleviating concerns of investigator bias.[47]

There are several differences between the approach used in Chapter 7 and the template provided for outcome-wide designs.[47] Rather than using Poisson or logistic regression, I used Cox regression which is suitable for the structure of electronic health records data, where variables can be measured at any timepoint (whenever a GP enters information),

rather than at the same fixed timepoints for every individual. Competing risk survival analysis, while also commonly used with electronic health records, was not considered as it may require outcome-specific selection of competing events.

I also allowed for variations in study design, e.g., using different cohorts based on age cut-offs. Of these variations, I chose a main analysis for each outcome, and other variations were considered sensitivity analyses. Importantly, analyses with all variations in study design were run consistently for all outcomes, to prevent investigator bias as was discussed above for the issue of covariate selection.

I also did not report e-values, which are defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain the exposure-outcome association.[162] However, this could have easily been implemented, as they are based on effect estimates and do not require additional information, which may also be seen as a limitation of e-values in that they do not offer additional information compared to effect estimates.[163]

Finally, adjustment for multiple testing, while implemented by using 99% instead of the conventional 95% confidence intervals, and reporting Bonferroni-corrected p-values, was given less prominence than recommended by VanDerWeele. This decision was made to avoid reliance on significance cut-offs.[164] In general, which may seem counter-intuitive, investigating multiple outcomes in one study has advantages concerning multiple testing as opposed to conducting multiple individual studies on the same exposure and different outcomes. When multiple testing happens on a research-community-wide level, there is little oversight of how many studies have already been conducted using the same data source on the same exposure, and corrections for multiple testing are rarely applied.[165] When multiple testing happens in the same study, the number of tests conducted is known, and corrections can easily be applied. However, there are also different recommendations on whether corrections for multiple testing should be applied in general, with some authors stating that they should not be used, raising concerns such as increased type II error rates and stating that careful interpretation of results is preferable.[166,167]

8.4.3 Hypothesis-testing vs hypothesis-free

Chapter 7 may be considered to describe both a hypothesis-testing as well as a hypothesis-free approach. While there is no single hypothesis that was specifically developed before conducting the study, in fact, hypotheses that eczema may be associated with all of the included outcomes did exist, either from other studies on particular outcomes or at least from hypothesis-generating work on broader outcome categories.[100] The study could also be seen as conducting "exploratory hypothesis tests", which, some have argued, may have advantages as compared to "confirmatory hypothesis tests", for example by avoiding researcher biases, reducing the probability of data fraud, facilitating inference to the best explanation, and allowing peer reviewers to make additional contributions.[168]

8.4.4 Deciding on outcomes to investigate

Outcomes selected for Chapter 7 included:

- Those for which statements had been produced in the recent American Academy of Dermatology guidelines on comorbidities.[7]
- Cancers and Dementias, which weren't described in the guidelines, but on which studies had been conducted in the CPRD GOLD database.[113,169]
- Neurological and digestive system outcomes, using those from a previously created phenotype catalogue, excluding those where an association with eczema would be implausible, for example, conditions that are most often congenital, such as cerebral palsy.[73]

This approach of selecting outcomes made sure that the most important outcomes related to eczema were included, which is also relevant for the confounding-adjustment strategy, together with outcomes of priority research interest, as identified by previous studies.[100] However, another approach could have been to select all outcomes included in a large phenotype catalogue, e.g., 308 conditions included in a study by Kuan (et al.).[73] While this may have surfaced associations that were not studied in Chapter 7, it may have missed outcomes such as food allergy, which was not included in this phenotype catalogue. Computational

limitations also become important here, with analyses on 71 outcomes already taking more than one week to run on optimised code (see next section), i.e., adding further outcomes would have required more investment into optimising code and/or using high-performance computing resources.

8.4.5 Technical requirements

Implementing a multi-outcome pipeline with a large dataset like CPRD Aurum required considerations on how to reproducibly organise analyses in the context of expensive computations, i.e., analyses that can take days to complete. Developments in the field of data science and corresponding releases of open-source tools have made efficient and reproducible research possible for epidemiologists without the need for extensive software development skills or resources, or reliance on analytics platforms. While many of these techniques, such as pipelines, have become widely used in several fields that deal with large numbers of inputs, such as omics research, they are still noticeably infrequently used in some areas of epidemiology, such as in the conduct of longitudinal population-based cohort studies.

Build automation tools, with which research pipelines can be constructed, such as GNU make,[170] while language agnostic, are seldomly used in conjunction with software packages that are commonly used for biostatistics. Programming languages such as Python, for which several language-specific pipeline tools are available, are rarely used for statistical analyses in biostatistics and epidemiology,[171] meaning that most researchers in this field would require additional programming skills or resources to implement pipelines. Until recently, there were no full-featured pipeline tools available for the R programming language, which is popular in biostatistics. However, the recent release of the "targets" package, and the availability of high-efficiency file formats, such as "parquet", means that tools to handle large datasets are now easy to combine with the rich statistical ecosystems that epidemiologists rely on. I used the targets R package, to keep track of each step of the workflow, provide tangible evidence that the results stem from the underlying code and data, and track dependencies so that only steps of the analysis need to be run that are out of date. Within the pipeline, I used branching techniques which allow the flexible addition of new inputs without having

to re-run branches that have already been run.[172] Finally, the publishing of analysis code on a public repository, sometimes necessitated by journals,[173] seems especially important for such large-scale analyses. Therefore, all analysis code was published together with the pre-print of the manuscript.

8.4.6 Future research

There are several ways this type of multi-outcome research could be expanded. Firstly, federated data analyses, i.e., incorporating multiple data sources, would greatly strengthen the evidence for any particular association. A common data model could be used to facilitate running the same analysis code for different data sources.[174]

Another direction for future research could be to systematically make use of an outcome set based on a disease classification hierarchy, such as ICD-chapters. For example, each study performed could investigate the association of eczema with one of the 21 ICD-10 chapters (e.g., 1. Certain infectious and parasitic diseases, 2. Neoplasms). Then, one could investigate with more granularity if associations are found. For example, if a strong association is found between atopic eczema and the ICD-10 chapter "Diseases of the digestive system", then all descendent ICD-10 subchapters ("Diseases or disorders of orofacial complex", "Diseases of the oesophagus", "Diseases of the stomach or the duodenum'', etc…). could be explored.

Further possible extensions were already mentioned in Section 7.4, including creating a "living" updateable analysis pipeline, and implementing a greater number of statistical approaches (e.g., confounding adjustment through propensity scores, alternative survival analysis methods; see also Section 8.5.6).

In summary, approaches to studying multiple outcomes, made possible by large EHR databases, may both become more comprehensive and more in-depth in the future. Gains in research efficiency can hopefully have a large impact on improving the care of patients.

8.5 Overall strengths, limitations, and further considerations

8.5.1 Sample size

Large sample sizes are one of the major strengths of EHR databases, in many situations providing high power for statistical tests, minimising the possibility of chance findings. However, when questions for specific populations need to be answered, even data sources with information on millions of people may not provide sufficient power. This was seen in Chapter 3, where the study was underpowered to assess the effects of some targeted immune-modifying drugs. Creating groups that encompassed multiple targeted immune-modifying drugs (in Chapter 3), and multiple inflammatory conditions (in Chapter 3 and Chapter 4) increased study power, at the cost of inference being less specific to a given disease or drug.

Chapter 7 demonstrates the value of the very large sample sizes EHRs can provide even for a common exposure such as eczema. It was possible to estimate hazard ratios with relatively narrow confidence intervals even for very rare outcomes (such as Hodgkin's lymphoma) and use 99% confidence intervals instead of the usual 95% confidence intervals to account for multiple testing. Limited sample size only became an issue in secondary analyses of eczema severity, where in populations of people with severe eczema sometimes only hundreds of events were recorded, as compared to often hundreds of thousands of events in the main analysis.

The UK Biobank also has a large sample size of almost half a million, including 230,047 with linked primary care data that were used in Chapter 5, providing sufficient power to address the study questions. In Chapter 6, the smaller sample size of the ALSPAC cohort was less of an issue, as no statistical hypothesis testing was performed.

8.5.2 Generalisability

The EHR data sources used in this thesis are generally representative of their underlying populations (as described in Section 2.1).[50,56,63] Depending on the research question, they may also be generalisable to other populations, in particular populations of other high-income countries that may have similar population structures. However, the generalisability

beyond a UK setting may need to be evaluated for each study separately. For example, the context of UK COVID-19 testing and shielding policy, together with the UK model of care for people with IMIDs may need to be considered when interpreting findings from Chapter 3. Similarly, prescribing of fracture preventive care may differ by country,[175] and different results were in fact seen for the UK and Ontario cohorts in Chapter 4.

For findings from Chapter 7, population-specific incidences of outcomes may be important to consider. For example, despite relatively small hazard ratios for depression and anxiety outcomes, the absolute rate differences were among the highest found in the study, suggesting public health relevance in a UK setting, which may not be the case in other settings.

The two population cohorts used in this thesis contained information on smaller segments of the general population; the UK Biobank recruited people aged 40-69, and ALSPAC recruited pregnant mothers living around Bristol and followed up their children from birth. In general, considerations on generalisability are different when a study requires active participation, as compared to allowing one's routinely collected EHR data to be shared (i.e., not opting out). For example, the UK Biobank had a very low response rate, however, a recent study found that estimates for disease associations in UK Biobank were similar to studies with much higher response rates.[176] Therefore, generalisability may be given in a UK context.

8.5.3 Disease and drug definitions

To avoid misclassification and associated bias, exposure, outcome, and covariate definitions in EHR studies need to be as sensitive and specific as possible, i.e., capture as many people as possible who have the disease/drug/characteristic, but not people who do not. Sometimes it is straightforward to differentiate between those who do, and those who do not have a characteristic. For example, while some diseases can be established clearly from a medical examination, history or tests, such as a broken bone, diabetes mellitus, or a heart attack, for other diseases, it is less straightforward to establish a consistent definition, e.g., which frequency, severity, and patterns of symptoms constitute a case of eczema.

8.5.3.1 Disease definitions

For Chapter 3, it was generally possible to use relatively simple definitions of inflammatory diseases, in that individuals were considered to have the disease of interest from the first occurrence of a diagnostic code. IMID diagnostic codes are likely to be relatively specific, at least compared to some of the other conditions studied in this thesis, such as eczema, anxiety and depression. For example, someone who has a single record for eczema may not necessarily have atopic eczema, but rather a transient rash or other skin condition. Therefore, in Chapter 5 and Chapter 7, people were only considered to have eczema if they had two records of eczema treatment on separate days in addition to an eczema diagnosis code, based on a previously validated algorithm.[137] In Chapter 6, the sensitivity and specificity of the eczema definition in EHRs was varied (most sensitive: diagnosis or treatment code; most specific: diagnosis and treatment code). I did not make use of a definition requiring one diagnosis and two treatment codes, as sensitivity (when comparing to ALSPAC data) was already poor with the most sensitive definition.

In Chapter 4, the eczema definition was not based on the validated algorithm, but rather on any code for eczema, to make cohort definitions more similar across the UK and Ontario data sources, as no validated eczema algorithm existed for Ontario data. Defining eczema with only a single code may be less specific, i.e., someone with a diagnosis code may be suffering from another form of rash, rather than (atopic) eczema. However, given that the study objective was foremost to capture people receiving high doses of oral corticosteroids, specificity of diagnostic codes was less important for this study.

For Chapter 3, COVID-19 infections are likely to have been captured relatively reliably in hospitals from about March 2020, the beginning of the COVID-19 pandemic in the UK. ICD-10 emergency codes on death certificates and records for positive PCR tests prior to hospital admission were used. These emergency codes were introduced by the WHO,[177] and have been shown to be recorded with high validity in some settings.[178] However, it may have been difficult for the coding clinicians to distinguish between COVID-19-related adverse outcomes and unrelated adverse outcomes in the presence of COVID-19, which introduces some potential for misclassification.

The 71 different outcomes assessed in Chapter 7 (and major osteoporotic fractures that were a secondary outcome in Chapter 4) were outcomes that were either chronic conditions (e.g., asthma, cancer), serious acute events (e.g., fractures, stroke, myocardial infarction), or less-serious acute events that are likely to present in primary care (e.g., skin infections). However, for some outcomes, there may have been delays in the transfer from hospital data to primary care data. For some outcomes, such as myocardial infarction, using primary care data only may have missed some cases.[179] While the effect estimate for the myocardial infarction outcome in Chapter 7 was very close to that from a previous study that additionally used hospital data to identify cases of myocardial infarction, the absolute rate difference may need to be interpreted with caution since this is dependent on the observed incidence.

For Chapter 7 it also needs to be mentioned that ascertainment of some outcomes may have been improved through, ideally validated, algorithms rather than simply using occurrence of any of the records contained in the respective codelist. Such algorithms may also require the availability of linked hospital data.

8.5.3.2 Drug exposure definitions

In Chapter 3, being exposed to anti-inflammatory drugs was defined simply through any record for a prescription ("never vs ever"), however, it is interesting to consider the exposure assessment timeframes. The exposure to immune-modifying therapies, both standard and targeted, was assessed in the 6 months before the 1st of March 2020, except for Rituximab, which has a low frequency of treatment and a long treatment response. In Chapter 4, the presence of any prescriptions was detected similarly for the outcome (of receiving fracture preventive care medication). Here, the timeframe of capture is determined through the follow-up window which was limited to one year, so that any fracture preventive care prescriptions captured may relate to the preceding period of exposure to oral corticosteroids.

These "never vs ever" (within a specified timeframe) definitions of drug exposure are suitable for drugs that are likely prescribed in consistent patterns and predictable dosages, such as high-cost immunosuppressants or fracture preventive care medications. However, oral corticosteroids, especially when used to treat (flares of) relapsing-remitting conditions, are

often prescribed in considerably varying patterns and dosages, which may be important to consider when assessing associated adverse effects.[51] Defining more detailed drug exposure definitions requires access to full prescription information; in CPRD GOLD these include information on timings, quantity, strength, and daily dose of the drug. In Chapter 4 I make use of all of this information to derive a measure of prescribing patterns. These are challenging to define or categorise, but a relevant concept in real-world clinical practice. To increase trust in findings produced using such complex exposure definitions, it was essential to conduct multiple sensitivity analyses, varying cut-offs and using both continuous and categorical definitions.

8.5.4 Missing data

Missing data in EHRs poses a unique challenge. For most variables used in this thesis, there were no explicitly missing values, i.e., if a person did not have a record for a given disease, characteristic or prescription two scenarios are possible. Either, the person truly did not have the disease or characteristic, or didn't receive the prescription. Alternatively, the disease, characteristic or prescription was not recorded. In practice, it is difficult or not possible to differentiate between these two scenarios.

Increased healthcare utilisation, e.g., by people with poorer overall health (e.g., multiple comorbidities), may reduce the possibility of missing data, as there are more opportunities for documentation.[180] Such differences in ascertainment by (disease) exposure status may impact the estimated associations between the exposure and outcome. For example, people with eczema may consult more frequently at their GP due to their eczema and may therefore have other conditions recorded more quickly and more consistently. Future research may incorporate information on healthcare utilisation to reduce bias caused by missing data.

There are also instances of explicitly missing values in this thesis, in particular for questionnaires as these are to be answered at pre-specified time points, but also for EHRs. For example, there were missing values for ethnicity, BMI and smoking status that were ascertained around the start of follow-up from primary care in Chapter 3. In Chapter 4, there were also prescriptions with partially missing values, for example, recorded prescriptions

where only the quantity or daily dose values were missing. Here, I applied a "hot deck" approach to impoutation (described in eMethods 2 in Section 4.3).[181]

8.5.5 Benefits and limitations of linkage

One way to decrease the potential for missing records and improve disease ascertainment is through data linkage. Both in Chapter 5 and Chapter 6 the number of people considered to have the disease of interest would be much larger when both data sources are used as compared to only using one of the data sources. However, the poor overall agreement between data sources makes it difficult to conclude which combination of observations in EHRs and questionnaire responses comprises the true population with the disease.

Linking primary and secondary care EHRs is a common practice, with studies suggesting that for some conditions ascertainment can be considerably improved.[179] Use of linkage between primary and secondary care data in this thesis was limited. In Chapter 3, IMID exposures were defined in primary care only, while high-cost drug exposures and COVID-19 outcomes were defined in hospital care only. In Chapter 4 and Chapter 7 no linkage with hospital data was utilised.

Primary care data can be linked to other sources, for example death registration data from the Office for National Statistics.[182] For some conditions, especially for acute life-threatening events such as myocardial infarction, this approach may have further improved ascertainment. An example of a dataset that may have improved ascertainment for anxiety and depression in Chapter 5 and Chapter 7 would be the Mental Health Services Data Set, which provides information on individuals in contact with mental health services.[183]

While disease or prescribing ascertainment in this thesis may have been improved with linkage, it may have come at the cost of reducing sample size, length of follow-up and generalisability of CPRD data.[184] In addition, linkage error (missed or false links) can lead to information or selection bias.[185] Ultimately, performing analyses with both linked and unlinked data may be the preferable approach.

8.5.6 Assessing the proportional hazards assumption

Regression modelling serves as a core statistical tool in this thesis (as described in Section 2.3). Different models come with different assumptions about the underlying data, and if these are not met results may be less trustworthy. One of the core assumptions of the Cox model is the proportional hazards assumption, i.e., the hazard ratio remains constant from the start to the end of follow-up.

Findings from a recent study suggest that many studies do not check, or do not report checks of, the proportional hazard assumption (the study was done in arthroplasty research, but findings are likely generalisable to many other fields that make use of Cox regression modelling).[186] Indeed, in Chapter 3 and Chapter 7, the proportional hazards assumption was not explicitly checked, and in Chapter 4, where it was checked (see eFigure 5 in Section 4.3), there is some indication that for the main analysis, it may not hold. Is this likely to have impacted the interpretability of the estimated hazard ratios?

There is ongoing discussion around the value of checking for proportional hazards in medical research. Stensrud and Hernan suggest that in medical research, non-proportional hazards are the norm and that statistical tests for proportional hazards are unnecessary. They state that hazard ratios should be interpreted as a weighted average of the true hazard ratios over the entire follow-up time.[187] Thus, hazard ratios may still provide a useful summary of the data, even if hazards are not proportional. However, in response, Sjölander and Dickman suggest that even though the proportional hazards assumption may rarely hold *exactly*, there is value in checking if it holds *approximately*.[188]

Stensrud and Hernan also suggest reporting survival differences or restricted mean survival differences at prespecified times.[187] Implementing these for the studies in this thesis may have provided further useful insights, and may be an area for future research. Another area for future research may be investigating the potential implications of unchecked proportional hazard assumptions across multiple outcomes.

8.5.7 Learning from data exploration

In this thesis, there are examples of unexpected properties of the data that were only found during the conduct of the studies. For example, one of the pre-specified objectives in Chapter 6 was to establish eczema subtypes in EHRs using ALSPAC subtypes as a Gold standard. Here, earlier recognition of poor agreement may have led me to conclude that any prediction models generated in this data would have limited relevance for future research or clinical practice. This may demonstrate a case when an initial data analysis may have been useful.

Initial data analysis involves data screening and initial data reporting before refining and updating the research analysis plan. This should ensure the conditions are met to conduct appropriate statistical analyses to answer predefined research questions (as compared to exploratory data analysis, which is a hypothesis-generating activity).[189] In Chapter 6 for example, one may have concluded that the conditions to attempt the classification of ALSPAC subtypes using EHRs are not met.

There were also some amendments to the approved protocol in Chapter 4 (described in eMethods 4 in Section 4.3) where through visualisation of a sample of participants' prescription timelines, and implementation of negative control outcomes, I recognised that the exposure definition in the original protocol was likely prone to time-dependent bias. This may also be seen as a form of initial data analysis. A more formal process that expects refining the protocol, rather than considering amendments as unexpected deviations, may better serve the realities of medical research.

8.6 Chapter summary

- For Aim I, to investigate outcomes associated with inflammatory diseases and their treatments, I conducted studies that assessed the effect of diseases (e.g., eczema or psoriasis), drugs (e.g., targeted immune modifying treatments), and drug prescribing patterns (low-intensity oral glucocorticoid prescribing patterns)

- I describe the emphasis on causality these studies had and give examples of how the strength of evidence for causality can be judged for different associations
- For Aim II, to validate disease definitions using linked data, I assessed whether people were considered to have eczema (or psoriasis) in both or only one of two data sources. I found a considerable mismatch, in particular for eczema
- I discuss what this could mean for the other findings from this thesis, and studies using eczema definitions from population cohorts, and suggest areas for future research including validation of eczema definitions in observational studies
- For Aim III, where I demonstrate an approach to more efficiently organise inference on multiple outcomes, I generate confounding-adjusted estimates for 71 outcomes for eczema
- I discuss how this approach is similar to and differs from "outcome-wide designs" that have recently been described in the literature, how the set of outcomes was selected and how the pipeline was implemented
- For the thesis overall, I discuss strengths and limitations concerning sample size, generalisability, disease and drug definitions, missing data, and discuss further considerations including model assumptions and the value of initial data analysis

8.7 Conclusions

People with IMIDs face an increased risk of adverse health outcomes, in part due to IMID treatments. While for some of these adverse health outcomes, there is already awareness (from clinical practice or evidence created through clinical trials or observational studies), other potentially important outcomes remain unexplored, or research has been insufficient for strong evidence-based recommendations.

In this thesis, I demonstrated different ways of leveraging large electronic health records databases to generate evidence that can be used to inform clinical practice, and health policy (e.g., on screening, prevention and risk mitigation). Some of the evidence created, in particular on COVID-19 outcomes may have already found its way into clinical guidelines, while other evidence suggests a need for further research, including implementation

research (e.g., on implementing ways of ensuring all people at risk of osteoporosis due to oral glucocorticoid use are offered the appropriate fracture preventive care).

I also found a mismatch between which people are considered to have eczema (and to a lesser extent psoriasis) between electronic health records and UK population cohorts. While I judge the possibility that misclassification of eczema could greatly alter the conclusions of this thesis as unlikely, it may be important for studies interested in finding the prevalence and incidence of eczema. Future research validating eczema diagnoses could be useful. One study objective, classifying eczema subtypes using EHRs by training a prediction model on eczema subtypes from ALSPAC, was rendered impossible through the mismatch between data sources.

Finally, I demonstrate a way to more efficiently make use of electronic health records data, by estimating associations between eczema and the subsequent development of 71 different outcomes. Several findings from this study, including the fact that results were almost identical to those from 4 high-quality outcome-bespoke studies and that the estimates for positive and negative control outcomes are as expected, suggest the approach delivers results that aren't subject to major bias. Furthermore, the approach delivers additional benefits such as improved comparability between results. The large number of results may be used in several ways, including the updating of guidelines on awareness of adverse health outcomes for people with eczema, and to inform priorities for future research.

In conclusion, this thesis provides evidence for several adverse health outcomes faced by people with eczema and other IMIDs, highlights eczema definitions in observational studies as an important area for future research, and demonstrates an approach to more efficiently make use of the vast untapped potential of large electronic health records databases.

References

1 McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol*. 2021;21:680–6. doi: 10.1038/s41577-021-00603-1

2 Libby P. Inflammation and cardiovascular disease mechanisms. *The American Journal of Clinical Nutrition*. 2006;83:456S–460S. doi: 10.1093/ajcn/83.2.456S

3 Ginaldi L, Di Benedetto M, De Martinis M. Osteoporosis, inflammation and ageing. *Immun Ageing*. 2005;2:14. doi: 10.1186/1742-4933-2-14

4 Mundy GR. Osteoporosis and Inflammation. *Nutrition Reviews*. 2008;65:S147–51. doi: 10.1111/j.1753-4887.2007.tb00353.x

5 Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860–7. doi: 10.1038/nature01322

6 Furman D, Campisi J, Verdin E, *et al.* Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25:1822–32. doi: 10.1038/s41591-019-0675-0

7 Davis DMR, Drucker AM, Alikhan A, *et al.* AAD Guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *Journal of the American Academy of Dermatology*. 2022;S0190962222000809. doi: 10.1016/j.jaad.2022.01.009

8 Wu H, Hu T, Hao H, *et al.* Inflammatory bowel disease and cardiovascular diseases: a concise review. *European Heart Journal Open*. 2022;2:oeab029. doi: 10.1093/ehjopen/oeab029

9 Hansildaar R, Vedder D, Baniaamam M, *et al.* Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *The Lancet Rheumatology*. 2021;3:e58–70. doi: 10.1016/S2665-9913(20)30221-6

10 Sparks JA, Chang S-C, Liao KP, *et al.* Rheumatoid Arthritis and Mortality Among Women During 36 Years of Prospective Follow-Up: Results From the Nurses' Health Study. *Arthritis Care & Research*. 2016;68:753–62. doi: 10.1002/acr.22752

11 Liu L, Cui S, Liu M, *et al.* Psoriasis Increased the Risk of Adverse Cardiovascular Outcomes: A New Systematic Review and Meta-Analysis of Cohort Study. *Frontiers in Cardiovascular Medicine*. 2022;9.

12 Hay RJ, Johns NE, Williams HC, *et al.* The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol*. 2014;134:1527–34. doi: 10.1038/jid.2013.446

13 National Institute for Health and Care Excellence. Associated conditions | Background information | Psoriasis | CKS | NICE. Clinical Knowledge Summaries. 2023. https://cks.nice.org.uk/topics/psoriasis/background-information/associated-conditions/ (accessed 14 March 2024)

14 National Institute for Health and Care Excellence. Prevalence | Background information | Psoriasis | CKS | NICE. 2023. https://cks.nice.org.uk/topics/psoriasis/background-information/prevalence/ (accessed 18 March 2024)

15 Parisi R, Symmons DPM, Griffiths CEM, *et al.* Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *Journal of Investigative Dermatology*. 2013;133:377–85. doi: 10.1038/jid.2012.339

16 Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *The Lancet*. 2020;396:345–60. doi: 10.1016/S0140-6736(20)31286-1

17 Kolkhir P, Akdis CA, Akdis M, *et al.* Type 2 chronic inflammatory diseases: targets, therapies and unmet needs. *Nat Rev Drug Discov*. 2023;22:743–67. doi: 10.1038/s41573-023-00750-1

18 Griffiths CEM, Armstrong AW, Gudjonsson JE, *et al.* Psoriasis. *The Lancet*. 2021;397:1301–15. doi: 10.1016/S0140-6736(20)32549-6

19 Bao Q, Chen L, Lu Z, *et al.* Association between eczema and risk of depression: A systematic review and meta-analysis of 188,495 participants. *J Affect Disord*. 2018;238:458–64. doi: 10.1016/j.jad.2018.05.007

20 Schonmann Y, Mansfield KE, Hayes JF, *et al.* Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8:248–257.e16. doi: 10.1016/j.jaip.2019.08.030

21 Henderson AD, Adesanya E, Mulick A, *et al.* Common mental health disorders in adults with inflammatory skin conditions: nationwide population-based matched cohort studies in the UK. *BMC Med*. 2023;21:285. doi: 10.1186/s12916-023-02948-x

22 National Institute for Health and Care Excellence. Complications | Background information | Eczema - atopic. Clinical Knowledge Summaries. 2023. https://cks.nice.org.uk/topics/eczema-atopic/background-information/complications/ (accessed 14 March 2024)

23 National Institute for Health and Care Excellence. Prevalence | Background information | Eczema - atopic | CKS | NICE. Clinical Knowledge Summaries. 2023. https://cks.nice.org.uk/topics/eczema-atopic/background-information/prevalence/ (accessed 29 August 2023)

24 National Institute for Health and Care Excellence. Overview | Atopic eczema in under 12s: diagnosis and management | Guidance. 2007. https://www.nice.org.uk/guidance/cg57 (accessed 22 March 2024)

25 Laughter Mr, Maymone Mbc, Mashayekhi S, *et al.* The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017*. *British Journal of Dermatology.* 2021;184:304–9. doi: 10.1111/bjd.19580

26 Fasseeh AN, Elezbawy B, Korra N, *et al.* Burden of Atopic Dermatitis in Adults and Adolescents: a Systematic Literature Review. *Dermatol Ther (Heidelb).* 2022;12:2653–68. doi: 10.1007/s13555-022-00819-6

27 Dawson A. The Cost of Atopic Dermatitis. 2023.

28 de Lusignan S, Alexander H, Broderick C, *et al.* Patterns and trends in eczema management in UK primary care (2009–2018): A population-based cohort study. *Clin Exp Allergy.* 2021;51:483–94. doi: 10.1111/cea.13783

29 Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. *Archives of Dermatology.* 2004;140:1513–9. doi: 10.1001/archderm.140.12.1513

30 NICE. Eczema - atopic | CKS. 2024. https://cks.nice.org.uk/topics/eczema-atopic/ (accessed 3 July 2024)

31 Bosma Al, Ascott A, Iskandar R, *et al.* Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics. *Journal of the European Academy of Dermatology and Venereology.* 2022;36:807–19. doi: 10.1111/jdv.18008

32 Mulick Ar, Mansfield Ke, Silverwood Rj, *et al.* Four childhood atopic dermatitis subtypes identified from trajectory and severity of disease and internally validated in a large UK birth cohort. *British Journal of Dermatology.* 2021;185:526–36. doi: 10.1111/bjd.19885

33 Pezzolo E, Naldi L. Epidemiology of major chronic inflammatory immune-related skin diseases in 2019. *Expert Review of Clinical Immunology*. 2020;16:155–66. doi: 10.1080/1744666X.2020.1719833

34 Hasan SB, Harris C, Collier F. Hidradenitis suppurativa. *BMJ*. 2022;379:e068383. doi: 10.1136/bmj-2021-068383

35 Schett G, Elewaut D, McInnes IB, *et al.* How Cytokine Networks Fuel Inflammation: Toward a cytokine-based disease taxonomy. *Nat Med*. 2013;19:822–4. doi: 10.1038/nm.3260

36 National Eczema Society. Dupilumab. National Eczema Society. 2020. http://eczema.org/information-and-advice/treatments-for-eczema/dupilumab/ (accessed 24 February 2024)

37 Gooderham MJ, Hong HC, Eshtiaghi P, *et al.* Dupilumab: A review of its use in the treatment of atopic dermatitis. *Journal of the American Academy of Dermatology*. 2018;78:S28–36. doi: 10.1016/j.jaad.2017.12.022

38 Gade A, Ghani H, Rubenstein R. Dupilumab. *StatPearls*. Treasure Island (FL): StatPearls Publishing 2024.

39 Nelson S. Is Eczema an Autoimmune Disease? Spoiler Alert: Nope. National Eczema Association. 2022. https://nationaleczema.org/blog/is-eczema-autoimmune-disease/ (accessed 24 February 2024)

40 Drucker AM, Eyerich K, de Bruin-Weller MS, *et al.* Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *British Journal of Dermatology*. 2018;178:768–75. doi: 10.1111/bjd.15928

41 Hashmi MF, Tariq M, Cataletto ME. Asthma. *StatPearls*. Treasure Island (FL): StatPearls Publishing 2024.

42 Agarwal AK, Raja A, Brown BD. Chronic Obstructive Pulmonary Disease. *StatPearls*. Treasure Island (FL): StatPearls Publishing 2024.

43 Benchimol EI, Smeeth L, Guttmann A, *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Medicine*. 2015;12:e1001885. doi: 10.1371/journal.pmed.1001885

44 Farmer R, Mathur R, Bhaskaran K, *et al.* Promises and pitfalls of electronic health record analysis. *Diabetologia*. 2018;61:1241–8. doi: 10.1007/s00125-017-4518-6

45 Pendergrass SA, Crawford DC. Using Electronic Health Records to Generate Phenotypes for Research. *Curr Protoc Hum Genet*. 2019;100:e80. doi: 10.1002/cphg.80

46 Hernán MA, Hsu J, Healy B. A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. *CHANCE*. 2019;32:42–9. doi: 10.1080/09332480.2019.1579578

47 VanderWeele TJ, Mathur MB, Chen Y. Outcome-Wide Longitudinal Designs for Causal Inference: A New Template for Empirical Studies. *Statist Sci*. 2020;35. doi: 10.1214/19-STS728

48 Rowan A, Bates C, Hulme W, *et al.* A comprehensive high cost drugs dataset from the NHS in England - An OpenSAFELY-TPP Short Data Report. *Wellcome Open Res*. 2021;6:360. doi: 10.12688/wellcomeopenres.17360.1

49 McMillan B, Eastham R, Brown B, *et al.* Primary Care Patient Records in the United Kingdom: Past, Present, and Future Research Priorities. *J Med Internet Res*. 2018;20:e11293. doi: 10.2196/11293

50 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology*. 2015;44:827–36. doi: 10.1093/ije/dyv098

51 Robinson DE, van Staa TP, Dennison EM, *et al.* The limitations of using simple definitions of glucocorticoid exposure to predict fracture risk: A cohort study. *Bone*. 2018;117:83–90. doi: 10.1016/j.bone.2018.09.004

52 Matthewman J, Mansfield KE, Prieto-Alhambra D, *et al.* Atopic Eczema–Associated Fracture Risk and Oral Corticosteroids: A Population-Based Cohort Study. *The Journal of Allergy and Clinical Immunology: In Practice*. 2021;0. doi: 10.1016/j.jaip.2021.09.026

53 UK Biobank. Resource 591: Primary Care Linked Data. 2019. https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=591 (accessed 22 December 2023)

54 Jones K, Ford D, Thompson S, *et al.* A Profile of the SAIL Databank on the UK Secure Research Platform. *Int J Popul Data Sci*. 2019;4:1134. doi: 10.23889/ijpds.v4i2.1134

55 Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *International Journal of Epidemiology*. 2016;45:1866–86. doi: 10.1093/ije/dyw314

56 Andrews C, Schultze A, Curtis H, *et al.* OpenSAFELY: Representativeness of electronic health record platform OpenSAFELY-TPP data compared to the population of England. 2022.

57 MacKenna B, Kennedy NA, Mehrkar A, *et al.* Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. *The Lancet Rheumatology.* 2022;4:e490–506. doi: 10.1016/S2665-9913(22)00098-4

58 Clinical Practice Research Datalink. CPRD GOLD January 2021. 2021.

59 Noble M, Wright G, Smith G, *et al.* Measuring Multiple Deprivation at the Small-Area Level. *Environ Plan A.* 2006;38:169–85. doi: 10.1068/a37168

60 Clinical Practice Research Datalink. Small area level data based on patient postcode. 2022.

61 Clinical Practice Research Datalink. ONS death registration data and CPRD primary care data. 2022.

62 Gallagher AM, Dedman D, Padmanabhan S, *et al.* The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. *Pharmacoepidemiology and Drug.* 2019;28:563–9. doi: 10.1002/pds.4747

63 Wolf A, Dedman D, Campbell J, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International Journal of Epidemiology.* 2019;48:1740–1740g. doi: 10.1093/ije/dyz034

64 Clinical Practice Research Datalink. CPRD Aurum March 2023. 2023.

65 Jick S, Vasilakis-Scaramozza C, Persson R, *et al.* Use of the CPRD Aurum Database: Insights Gained from New Data Quality Assessments. *CLEP.* 2023;15:1219–22. doi: 10.2147/CLEP.S434832

66 Clinical Practice Research Datalink. CPRD Aurum May 2022. 2022.

67 Sudlow C, Gallacher J, Allen N, *et al.* UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Medicine.* 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779

68 Boyd A, Golding J, Macleod J, *et al.* Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol.* 2013;42:111–27. doi: 10.1093/ije/dys064

69 University of Bristol. Explore data and samples. Avon Longitudinal Study of Parents and Children. https://www.bristol.ac.uk/alspac/researchers/our-data/ (accessed 20 November 2022)

70 Cornish RP, Macleod J, Boyd A, *et al.* Factors associated with participation over time in the Avon Longitudinal Study of Parents and Children: a study using linked education and primary care data. *International Journal of Epidemiology.* 2021;50:293–302. doi: 10.1093/ije/dyaa192

71 Williams R, Kontopantelis E, Buchan I, *et al.* Clinical code set engineering for reusing EHR data for research: A review. *Journal of Biomedical Informatics.* 2017;70:1–13. doi: 10.1016/j.jbi.2017.04.010

72 Clinical Practice Research Datalink. Defining your study population. 2023. https://www.cprd.com/defining-your-study-population (accessed 28 December 2023)

73 Kuan V, Denaxas S, Gonzalez-Izquierdo A, *et al.* A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. *The Lancet Digital Health.* 2019;1:e63–77. doi: 10.1016/S2589-7500(19)30012-3

74 Saunders K. Developing Multimorbidity Codelists for CPRD Aurum.

75 National Eczema Association. 7 Types of Eczema. National Eczema Association. https://nationaleczema.org/eczema/types-of-eczema/ (accessed 9 January 2024)

76 National Eczema Society. Types of eczema. National Eczema Society. 2019. https://eczema.org/information-and-advice/types-of-eczema/ (accessed 9 January 2024)

77 Politiek K, Loman L, Pas HH, *et al.* Hyperkeratotic hand eczema: Eczema or not? *Contact Dermatitis.* 2020;83:196–205. doi: 10.1111/cod.13572

78 NHS. Varicose eczema. Health A-Z. 2023. https://www.nhs.uk/conditions/varicose-eczema/ (accessed 9 January 2024)

79 Yamany T, Schwartz Ra. Infectious eczematoid dermatitis: a comprehensive review. *Journal of the European Academy of Dermatology and Venereology.* 2015;29:203–8. doi: 10.1111/jdv.12715

80 Xiao A, Tsuchiya A. Eczema Herpeticum. *StatPearls.* Treasure Island (FL): StatPearls Publishing 2023.

81 UKRI. Cohort directory. 2023. https://www.ukri.org/councils/mrc/facilities-and-resources/find-an-mrc-facility-or-resource/cohort-directory/ (accessed 9 January 2024)

82 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x

83 Spitzer RL, Kroenke K, Williams JBW, *et al.* A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Archives of Internal Medicine.* 2006;166:1092–7. doi: 10.1001/archinte.166.10.1092

84 Keret N, Gorfine M. Analyzing Big EHR Data—Optimal Cox Regression Subsampling Procedure with Rare Events. *Journal of the American Statistical Association.* 2023;118:2262–75. doi: 10.1080/01621459.2023.2209349

85 Collett D. *Modelling Survival Data in Medical Research.* 3rd ed. New York: Chapman and Hall/CRC 2015.

86 Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society: Series B (Methodological).* 1972;34:187–202. doi: 10.1111/j.2517-6161.1972.tb00899.x

87 Collett D. The Cox regression model. *Modelling Survival Data in Medical Research.* New York: Chapman and Hall/CRC 2015.

88 Abd ElHafeez S, D'Arrigo G, Leonardis D, *et al.* Methods to Analyze Time-to-Event Data: The Cox Regression Analysis. *Oxid Med Cell Longev.* 2021;2021:1302811. doi: 10.1155/2021/1302811

89 Therneau T. A package for survival analysis in R. Published Online First: 13 February 2024.

90 Sperandei S. Understanding logistic regression analysis. *Biochem Med (Zagreb).* 2014;24:12–8. doi: 10.11613/BM.2014.003

91 Kuhn M, Silge J. *Tidy Modeling with R.* 2023.

92 UK Health Security Agency, UK Department of Health and Social Care. COVID-19: guidance for people whose immune system means they are at higher risk. GOV.UK. 2023. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/ (accessed 19 December 2023)

93 Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584:430–6. doi: 10.1038/s41586-020-2521-4

94 Alexander T, Maxim E, Cardwell LA, *et al.* Prescriptions for atopic dermatitis: oral corticosteroids remain commonplace. *Journal of Dermatological Treatment.* 2018;29:238–40. doi: 10.1080/09546634.2017.1365112

95 Bénard-Laribière A, Pariente A, Pambrun E, *et al.* Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France. *BMJ Open.* 2017;7:e015905. doi: 10.1136/bmjopen-2017-015905

96 Liao K-M, Chiu K-L, Chen C-Y. Prescription Patterns in Patients with Chronic Obstructive Pulmonary Disease and Osteoporosis. *Int J Chron Obstruct Pulmon Dis.* 2021;16:761–9. doi: 10.2147/COPD.S289799

97 Matthewman J, Tadrous M, Mansfield KE, *et al.* Association of Different Prescribing Patterns for Oral Corticosteroids With Fracture Preventive Care Among Older Adults in the UK and Ontario. *JAMA Dermatology.* 2023;159:961–9. doi: 10.1001/jamadermatol.2023.2495

98 Kurd SK, Troxel AB, Crits-Christoph P, *et al.* The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. *Arch Dermatol.* 2010;146:891–5. doi: 10.1001/archdermatol.2010.186

99 Matthewman J, Mansfield KE, Hayes JF, *et al.* Anxiety and Depression in People with Eczema or Psoriasis: A Comparison of Associations in UK Biobank and Linked Primary Care Data. *Clinical Epidemiology.* 2023;15:891–9. doi: 10.2147/CLEP.S417176

100 Mulick AR, Henderson AD, Prieto-Merino D, *et al.* Novel multimorbidity clusters in people with eczema and asthma: a population-based cluster analysis. *Sci Rep.* 2022;12:21866. doi: 10.1038/s41598-022-26357-x

101 Su VY-F, Chen T-J, Yeh C-M, *et al.* Atopic dermatitis and risk of ischemic stroke: a nationwide population-based study. *Ann Med.* 2014;46:84–9. doi: 10.3109/07853890.2013.870018

102 Andersen YMF, Egeberg A, Gislason GH, *et al.* Adult atopic dermatitis and the risk of type 2 diabetes. *Journal of Allergy and Clinical Immunology.* 2017;139:1057–9. doi: 10.1016/j.jaci.2016.08.049

103 Andersen YMF, Egeberg A, Gislason GH, *et al.* Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology.* 2016;138:310–312.e3. doi: 10.1016/j.jaci.2016.01.015

104 Wu C-Y, Lu Y-Y, Lu C-C, *et al.* Osteoporosis in adult patients with atopic dermatitis: A nationwide population-based study. *PLOS ONE.* 2017;12:e0171667. doi: 10.1371/journal.pone.0171667

105 Sung Y-F, Lin C-C, Yin J-H, *et al.* Increased risk of stroke in patients with atopic dermatitis: A population-based, longitudinal study in Taiwan. *Journal of Medical Sciences*. 2017;37:12. doi: 10.4103/1011-4564.200737

106 Riis JL, Vestergaard C, Hjuler KF, *et al.* Hospital-diagnosed atopic dermatitis and long-term risk of myocardial infarction: a population-based follow-up study. *BMJ Open*. 2016;6:e011870. doi: 10.1136/bmjopen-2016-011870

107 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*. 2018;k1786. doi: 10.1136/bmj.k1786

108 Standl M, Tesch F, Baurecht H, *et al.* Association of Atopic Dermatitis with Cardiovascular Risk Factors and Diseases. *Journal of Investigative Dermatology*. 2017;137:1074–81. doi: 10.1016/j.jid.2016.11.031

109 Singhal A, Ross J, Seminog O, *et al.* Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. *J R Soc Med*. 2014;107:194–204. doi: 10.1177/0141076814522033

110 Cheng C-M, Hsu J-W, Huang K-L, *et al.* Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: A nationwide longitudinal study. *Journal of Affective Disorders*. 2015;178:60–5. doi: 10.1016/j.jad.2015.02.025

111 Langan SM, Abuabara K, Henrickson SE, *et al.* Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis—A Cohort Study. *Journal of Investigative Dermatology*. 2017;137:1375–7. doi: 10.1016/j.jid.2017.01.030

112 Lowe KE, Mansfield KE, Delmestri A, *et al.* Code lists for 'Atopic eczema and fracture risk in adults: a population-based cohort study'. Published Online First: 2019. doi: 10.17037/DATA.00001156

113 Mansfield KE, Schmidt SAJ, Darvalics B, *et al.* Association Between Atopic Eczema and Cancer in England and Denmark. *JAMA Dermatol*. 2020;156:1086. doi: 10.1001/jamadermatol.2020.1948

114 Schonmann Y, Mansfield KE, Mulick A, *et al.* Inflammatory skin diseases and the risk of chronic kidney disease: population-based case-control and cohort analyses. *Br J Dermatol*. 2021;185:772–80. doi: 10.1111/bjd.20067

115 Matthewman J, Schultze A, Strongman H, *et al.* Cohort Studies on 71 Different Adverse Health Outcomes Among People with Atopic Eczema in UK Primary Care Data. 2024.

116 Goldacre B, Morley J. Better, broader, safer: using health data for research and analysis. 2022.

117 Ioannidis JPA. Why Most Published Research Findings Are False. *PLOS Medicine*. 2005;2:e124. doi: 10.1371/journal.pmed.0020124

118 Lash TL, Collin LJ, Van Dyke ME. The replication crisis in epidemiology: snowball, snow job, or winter solstice? *Curr Epidemiol Rep*. 2018;5:175–83. doi: 10.1007/s40471-018-0148-x

119 Fanelli D. Do Pressures to Publish Increase Scientists' Bias? An Empirical Support from US States Data. *PLOS ONE*. 2010;5:e10271. doi: 10.1371/journal.pone.0010271

120 Pye SR, Sheppard T, Joseph RM, *et al.* Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. *Pharmacoepidemiology and Drug Safety*. 2018;27:781–8. doi: 10.1002/pds.4440

121 Wang SV, Sreedhara SK, Schneeweiss S. Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. *Nat Commun*. 2022;13:5126. doi: 10.1038/s41467-022-32310-3

122 Simmonds M, Elliott JH, Synnot A, *et al.* Living Systematic Reviews. *Methods Mol Biol*. 2022;2345:121–34. doi: 10.1007/978-1-0716-1566-9_7

123 Wagenmakers E-J, Sarafoglou A, Aczel B. One statistical analysis must not rule them all. *Nature*. 2022;605:423–5. doi: 10.1038/d41586-022-01332-8

124 Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295–300. doi: 10.1177/003591576505800503

125 Howick J, Kelly P, Kelly M. Establishing a causal link between social relationships and health using the Bradford Hill Guidelines. *SSM Popul Health*. 2019;8:100402. doi: 10.1016/j.ssmph.2019.100402

126 Smeekens JM, Kulis MD. Mouse Models of Food Allergy in the Pursuit of Novel Treatment Modalities. *Front Allergy*. 2021;2:810067. doi: 10.3389/falgy.2021.810067

127 Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. *J Clin Cell Immunol*. 2014;5:202. doi: 10.4172/2155-9899.1000202

128 Budu-Aggrey A, Joyce S, Davies NM, *et al.* Investigating the causal relationship between allergic disease and mental health. *Clinical & Experimental Allergy.* 2021;51:1449–58. doi: 10.1111/cea.14010

129 Legendre L, Barnetche T, Mazereeuw-Hautier J, *et al.* Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology.* 2015;72:992–1002. doi: 10.1016/j.jaad.2015.02.1116

130 Rafiq M, Hayward A, Warren-Gash C, *et al.* Allergic disease, corticosteroid use, and risk of Hodgkin lymphoma: A United Kingdom nationwide case-control study. *Journal of Allergy and Clinical Immunology.* 2020;145:868–76. doi: 10.1016/j.jaci.2019.10.033

131 Cheung MW, Dayam RM, Shapiro JR, *et al.* Third and Fourth Vaccine Doses Broaden and Prolong Immunity to SARS-CoV-2 in Adult Patients with Immune-Mediated Inflammatory Diseases. *The Journal of Immunology.* 2023;211:351–64. doi: 10.4049/jimmunol.2300190

132 Candel FJ, Barreiro P, Salavert M, *et al.* Expert Consensus: Main Risk Factors for Poor Prognosis in COVID-19 and the Implications for Targeted Measures against SARS-CoV-2. *Viruses.* 2023;15:1449. doi: 10.3390/v15071449

133 Cork MJ, Danby SG, Ogg GS. Atopic dermatitis epidemiology and unmet need in the United Kingdom. *Journal of Dermatological Treatment.* 2020;31:801–9. doi: 10.1080/09546634.2019.1655137

134 Choi BCK, Pak AWP. A Catalog of Biases in Questionnaires. *Prev Chronic Dis.* 2004;2:A13.

135 UK Biobank. Verbal Interview stage. 2012.

136 Cornish RP, Henderson J, Boyd AW, *et al.* Validating childhood asthma in an epidemiological study using linked electronic patient records. *BMJ Open.* 2014;4:e005345. doi: 10.1136/bmjopen-2014-005345

137 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;137:1655–62. doi: 10.1016/j.jid.2017.03.029

138 Blak BT, Thompson M, Dattani H, *et al.* Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care.* 2011;19:251–5. doi: 10.14236/jhi.v19i4.820

139 Budu-Aggrey A, Kilanowski A, Sobczyk MK, *et al.* European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. *Nat Commun.* 2023;14:6172. doi: 10.1038/s41467-023-41180-2

140 Lopez DJ, Singh A, Waidyatillake NT, *et al.* The association between domestic hard water and eczema in adults from the UK Biobank cohort study*. *British Journal of Dermatology.* 2022;187:704–12. doi: 10.1111/bjd.21771

141 Sliz E, Huilaja L, Pasanen A, *et al.* Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis. *Journal of Allergy and Clinical Immunology.* 2022;149:1105–1112.e9. doi: 10.1016/j.jaci.2021.07.043

142 Johansson Å, Rask-Andersen M, Karlsson T, *et al.* Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Human Molecular Genetics.* 2019;28:4022–41. doi: 10.1093/hmg/ddz175

143 Manousaki D, Paternoster L, Standl M, *et al.* Vitamin D levels and susceptibility to asthma, elevated immunoglobulin E levels, and atopic dermatitis: A Mendelian randomization study. *PLoS Med.* 2017;14:e1002294. doi: 10.1371/journal.pmed.1002294

144 Marley J, Nicholl BI, Macdonald S, *et al.* Associations between long-term conditions and upper gastrointestinal cancer incidence: A prospective population-based cohort of UK Biobank participants. *J Comorb.* 2021;11:26335565211056136. doi: 10.1177/26335565211056136

145 Zhu Z, Lee PH, Chaffin MD, *et al.* A genome-wide cross-trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases. *Nat Genet.* 2018;50:857–64. doi: 10.1038/s41588-018-0121-0

146 Ferreira MAR, Vonk JM, Baurecht H, *et al.* Age-of-onset information helps identify 76 genetic variants associated with allergic disease. *PLOS Genetics.* 2020;16:e1008725. doi: 10.1371/journal.pgen.1008725

147 Ferreira MAR, Vonk JM, Baurecht H, *et al.* Eleven loci with new reproducible genetic associations with allergic disease risk. *Journal of Allergy and Clinical Immunology.* 2019;143:691–9. doi: 10.1016/j.jaci.2018.03.012

148 Gu X, Jing D, Xiao Y, *et al.* Association of air pollution and genetic risks with incidence of elderly-onset atopic dermatitis: A prospective cohort study. *Ecotoxicology and Environmental Safety.* 2023;253:114683. doi: 10.1016/j.ecoenv.2023.114683

149 Shirai Y, Nakanishi Y, Suzuki A, *et al.* Multi-trait and cross-population genome-wide association studies across autoimmune and allergic diseases identify shared and distinct genetic component. *Annals of the Rheumatic Diseases.* 2022;81:1301–12. doi: 10.1136/annrheumdis-2022-222460

150 Hussain S, Ronaldson A, Arias de la Torre J, *et al.* Depressive and anxiety symptomatology among people with asthma or atopic dermatitis: A population-based investigation using the UK Biobank data. *Brain, Behavior, and Immunity.* 2020;90:138–44. doi: 10.1016/j.bbi.2020.08.003

151 Tang Z, Shen M, Xiao Y, *et al.* Association Between Atopic Dermatitis, Asthma, and Serum Lipids: A UK Biobank Based Observational Study and Mendelian Randomization Analysis. *Frontiers in Medicine.* 2022;9.

152 Harrison S, Davies AR, Dickson M, *et al.* The causal effects of health conditions and risk factors on social and socioeconomic outcomes: Mendelian randomization in UK Biobank. *International Journal of Epidemiology.* 2020;49:1661. doi: 10.1093/ije/dyaa114

153 Wjst M. Exome variants associated with asthma and allergy. *Sci Rep.* 2022;12:21028. doi: 10.1038/s41598-022-24960-6

154 Clayton GL, Gonçalves A, Soares, *et al.* A framework for assessing selection and misclassification bias in mendelian randomisation studies: an illustrative example between body mass index and covid-19. *BMJ.* 2023;381:e072148. doi: 10.1136/bmj-2022-072148

155 Burstein D, Hoffman G, Mathur D, *et al.* Detecting and Adjusting for Hidden Biases due to Phenotype Misclassification in Genome-Wide Association Studies. *medRxiv.* 2023;2023.01.17.23284670. doi: 10.1101/2023.01.17.23284670

156 Schmitt J, Spuls PI, Thomas KS, *et al.* The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *Journal of Allergy and Clinical Immunology.* 2014;134:800–7. doi: 10.1016/j.jaci.2014.07.043

157 Dizon MP, Yu AM, Singh RK, *et al.* Systematic review of atopic dermatitis disease definition in studies using routinely collected health data. *Br J Dermatol.* 2018;178:1280–7. doi: 10.1111/bjd.16340

158 Nakamura T, Haider S, Colicino S, *et al.* Different definitions of atopic dermatitis: impact on prevalence estimates and associated risk factors. *Br J Dermatol.* 2019;181:1272–9. doi: 10.1111/bjd.17853

159 Paternoster L, Savenije OEM, Heron J, *et al.* Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *Journal of Allergy and Clinical Immunology.* 2018;141:964–71. doi: 10.1016/j.jaci.2017.09.044

160 Silverwood RJ, Mansfield KE, Mulick A, *et al.* Atopic eczema in adulthood and mortality: UK population-based cohort study, 1998-2016. *J Allergy Clin Immunol.* 2021;147:1753–63. doi: 10.1016/j.jaci.2020.12.001

161 Ding P, Miratrix LW. To Adjust or Not to Adjust? Sensitivity Analysis of M-Bias and Butterfly-Bias. *Journal of Causal Inference.* 2015;3:41–57. doi: 10.1515/jci-2013-0021

162 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167:268–74. doi: 10.7326/M16-2607

163 Ioannidis JPA, Tan YJ, Blum MR. Limitations and Misinterpretations of E-Values for Sensitivity Analyses of Observational Studies. *Ann Intern Med.* 2019;170:108. doi: 10.7326/M18-2159

164 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature.* 2019;567:305–7. doi: 10.1038/d41586-019-00857-9

165 Panagiotou OA, Heller R. Inferential Challenges for Real-world Evidence in the Era of Routinely Collected Health Data: Many Researchers, Many More Hypotheses, a Single Database. *JAMA Oncology.* 2021;7:1605–7. doi: 10.1001/jamaoncol.2021.3537

166 Michels KB, Rosner BA. Data trawling: to fish or not to fish. *The Lancet.* 1996;348:1152–3. doi: 10.1016/S0140-6736(96)05418-9

167 Rothman KJ. No Adjustments Are Needed for Multiple Comparisons. *Epidemiology.* 1990;1:43–6.

168 Rubin M, Donkin C. Exploratory hypothesis tests can be more compelling than confirmatory hypothesis tests. *Philosophical Psychology.* 2022;0:1–29. doi: 10.1080/09515089.2022.2113771

169 Magyari A, Ye M, Margolis DJ, *et al.* Adult atopic eczema and the risk of dementia: A population-based cohort study. *Journal of the American Academy of Dermatology.* 2022;87:314–22. doi: 10.1016/j.jaad.2022.03.049

170 Free Software Foundation. Make - GNU Project. https://www.gnu.org/software/make/ (accessed 24 November 2021)

171 Masuadi E, Mohamud M, Almutairi M, *et al.* Trends in the Usage of Statistical Software and Their Associated Study Designs in Health Sciences Research: A Bibliometric Analysis. *Cureus.* 2021;13:e12639. doi: 10.7759/cureus.12639

172 Landau W. The targets R package: a dynamic Make-like function-oriented pipeline toolkit for reproducibility and high-performance computing. *JOSS.* 2021;6:2959. doi: 10.21105/joss.02959

173 Stodden V, Guo P, Ma Z. Toward Reproducible Computational Research: An Empirical Analysis of Data and Code Policy Adoption by Journals. *PLoS One.* 2013;8:e67111. doi: 10.1371/journal.pone.0067111

174 Biedermann P, Ong R, Davydov A, *et al.* Standardizing registry data to the OMOP Common Data Model: experience from three pulmonary hypertension databases. *BMC Medical Research Methodology.* 2021;21:238. doi: 10.1186/s12874-021-01434-3

175 Skjødt MK, Khalid S, Ernst M, *et al.* Secular trends in the initiation of therapy in secondary fracture prevention in Europe: a multi-national cohort study including data from Denmark, Catalonia, and the United Kingdom. *Osteoporos Int.* 2020;31:1535–44. doi: 10.1007/s00198-020-05358-4

176 Batty GD, Gale CR, Kivimäki M, *et al.* Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ.* 2020;368:m131. doi: 10.1136/bmj.m131

177 WHO. Emergency use ICD codes for COVID-19 disease outbreak. 2020. https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak (accessed 14 March 2023)

178 Wu G, D'Souza AG, Quan H, *et al.* Validity of ICD-10 codes for COVID-19 patients with hospital admissions or ED visits in Canada: a retrospective cohort study. *BMJ Open.* 2022;12:e057838. doi: 10.1136/bmjopen-2021-057838

179 Herrett E, Shah AD, Boggon R, *et al.* Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ.* 2013;346:f2350. doi: 10.1136/bmj.f2350

180 Wells BJ, Chagin KM, Nowacki AS, *et al.* Strategies for Handling Missing Data in Electronic Health Record Derived Data. *EGEMS (Wash DC).* 2013;1:1035. doi: 10.13063/2327-9214.1035

181 Andridge RR, Little RJA. A Review of Hot Deck Imputation for Survey Non-response. *Int Stat Rev.* 2010;78:40–64. doi: 10.1111/j.1751-5823.2010.00103.x

182 Clinical Practice Research Datalink. CPRD linked data. 2024. http://www.cprd.com/cprd-linked-data (accessed 7 July 2024)

183 NHS Digital. Mental Health Services Data Set (MHSDS). NHS England Digital. 2024. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-sets/mental-health-services-data-set (accessed 7 July 2024)

184 McDonald L, Schultze A, Carroll R, *et al.* Performing studies using the UK Clinical Practice Research Datalink: to link or not to link? *European Journal of Epidemiology.* 2018;33:601–5.

185 Doidge JC, Harron KL. Reflections on modern methods: linkage error bias. *International Journal of Epidemiology.* 2019;48:2050–60. doi: 10.1093/ije/dyz203

186 Kuitunen I, Ponkilainen VT, Uimonen MM, *et al.* Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. *BMC Musculoskeletal Disorders.* 2021;22:489. doi: 10.1186/s12891-021-04379-2

187 Stensrud MJ, Hernán MA. Why Test for Proportional Hazards? *JAMA.* 2020;323:1401–2. doi: 10.1001/jama.2020.1267

188 Sjölander A, Dickman P. Why test for proportional hazards – or any other model assumptions? *American Journal of Epidemiology.* 2024;kwae002. doi: 10.1093/aje/kwae002

189 Baillie M, le Cessie S, Schmidt CO, *et al.* Ten simple rules for initial data analysis. *PLoS Comput Biol.* 2022;18:e1009819. doi: 10.1371/journal.pcbi.1009819

Appendix

Appendix

A.1 Ethical approvals for Chapter 3

A.1.1 Public Website: Ethical approval from Health Research Authority

Open Corona Research Platform - Phase I [COVID-19]

Research type
Research Study

Full title
Open Coronavirus Research Platform - Phase I: Retrospective analyses of healthcare records for patients hospitalised with COVID-19.

IRAS ID
282148

Contact name
Ben Goldacre

Contact email
ben.goldacre@phc.ox.ac.uk

Sponsor organisation
NHS England

Duration of Study in the UK
2 years, 0 months, 1 days

Research summary
We are conducting urgent observational research on Covid-19 using very large existing primary care electronic health record datasets (for >20 million patients in England) linked to intensive care records, Covid-19 lab data and mortality. We are rapidly building a secure, collaborative analytics platform for approved users. Initially this will contain key datasets: GP data on NHS patients managed by the EHR provider TPP (who cover 40% of practices in the country); and outcomes data matched on from the new NHS England and NHSX data store (CPNS deaths data; ICNARC ITU admissions data; ECDS A&E patient-level data; ONS deaths data; all pseudonymised). This big data approach is necessary to get sufficient statistical power to detect associations with specific medications and medical conditions as early as possible during the pandemic and thereby save lives by modifying patient, clinician, and population behaviour. We are working in collaboration with NHS England, who are acting as Data Controller for the purposes of this urgent project. Our DPIA approving data flows and access to these datasets has already been signed by the DPO at NHS England. \n\n[Study relying on COPI notice]

REC name

London - City & East Research Ethics Committee

REC reference
20/LO/0651

Date of REC Opinion
6 Apr 2020

REC opinion
Favourable Opinion

A.2 Ethical approvals for Chapter 4

A.2.1 Letter: Ethical approval from LSHTM

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Julian Matthewman
LSHTM

23 November 2021

Dear Julian

Study Title: Fractures Associated with Corticosteroids for Eczema Treatment (FACET)

LSHTM Ethics Ref: 26627

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	FACET protocol	27/10/2021	1.0
Investigator CV	CV Julian Matthewman 2021	05/11/2021	1
Investigator CV	Langan_CV_Oct2021	05/11/2021	1
Investigator CV	Kathryn Mansfield 20210913v2_CV[1]	05/11/2021	1
Other	Julian Matthewman Research_Ethics_online_training_certificate	05/11/2021	1
Other	Sinead Langan Research_Ethics_online_training_certificate	05/11/2021	1
Other	Kate Mansfield RETC_Certificate	05/11/2021	1
Local Approval	CPRD study review confirmation email	19/11/2021	1
Covering Letter	Cover Letter 26627	19/11/2021	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

A.3 Ethical approvals for Chapter 5

A.3.1 Letter: Original ethical approval from LSHTM

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Kathryn Mansfield
LSHTM

8 November 2019

Dear Dr Mansfield

Study Title: Mental illness in atopic eczema and psoriasis: how big is the problem and why does it happen?

LSHTM Ethics Ref: 17815

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	CIx1_20180822_SineadLangan	22/08/2018	v1
Investigator CV	CIx2_20180822_CatherineSmith	22/08/2018	v1
Investigator CV	CIx3_20180822_JoesephHayes	22/08/2018	v1
Investigator CV	CIx4_20180822_LiamSmeeth	22/08/2018	v1
Investigator CV	CIx5_20180822_RohiniMathur	22/08/2018	v1
Investigator CV	PI_20180822_KathrynMansfield	22/08/2018	v1
Other	RETC_Certificate	07/11/2019	1
Protocol / Proposal	20191107_ISAC-AEpsoriasisMentalIllness_LEO	07/11/2019	1
Protocol / Proposal	20191108_BiobankApplication	08/11/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

A.3.2 Public Website: UK Biobank approved research

Approved Research

Mental illness in atopic eczema and psoriasis: how big is the problem and why does it happen

Principal Investigator: **Dr Alasdair Henderson**
Approved Research ID: 74311
Approval date: **July 15th 2022**

London School of Hygiene and Tropical Medicine

Lay summary

AIM

To explore why adults with eczema and psoriasis are more likely to develop mental illness and identify who is at greatest risk of mental health problems.

SCIENTIFIC RATIONALE

Mental illness is more common in people with skin conditions like eczema and psoriasis, but we do not know why. Possible causes include socioeconomic deprivation, poor sleep quality, poor lifestyle choices or inflammation. Identifying the types of people most at risk of mental illness would help target screening to identify psychological distress at those who need it most. Earlier recognition and management of mental illness would help improve people's lives.

METHODS

We will look at people with and without skin conditions to see how much more likely those with skin conditions are to develop mental illness. Then we will look in detail to identify the risk factors and people with skin conditions most affected. We will use information from a large study of adults across the UK (UK Biobank). Biobank includes over half a million adults who are being followed over time from an initial comprehensive questionnaires and health assessments. Biobank has collected information on important measures (including sleep quality) that might explain why people with skin conditions are more likely to have mental illness.

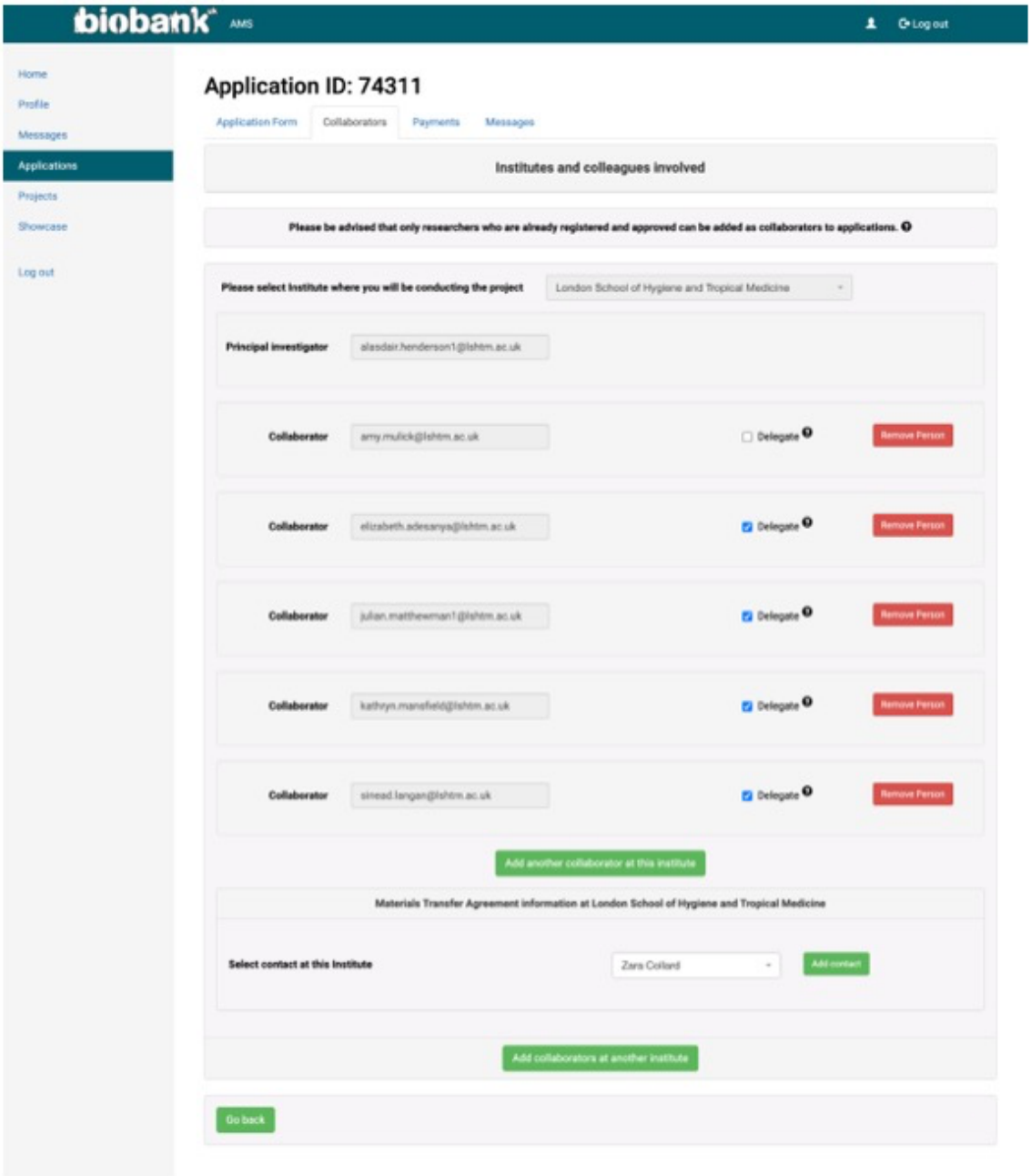
PROJECT DURATION

24 months

PUBLIC HEALTH IMPACT

We expect that the knowledge generated by our project will serve as a 'call to arms' for doctors, researchers and policy makers, highlighting the importance of identifying mental illness in those with visible and potentially stigmatising skin conditions. It will also offer opportunities to identify risk factors contributing to mental illness (such as sleep problems) that we might be able to change, and people who would particularly benefit from targeted mental illness screening. This knowledge will help us identify mental illness in people with skin conditions earlier and manage it better, limiting their impact and cost, promoting a holistic approach to managing skin conditions.

A.3.3 Researcher Portal Website: Confirmation of Collaborators



A.4 Ethical approvals for Chapter 6

A.4.1 Letter: Original ethical approval from LSHTM

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Sinead Langan
Associate Professor and Wellcome Senior Clinical Fellow
Department of Non-communicable Disease Epidemiology (NCDE)
LSHTM

17 November 2017

Dear Dr Langan

Study Title: UNDERSTANDING ECZEMA STUDY

LSHTM Ethics Ref: 14602

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	CVSep2017	01/09/2017	1
Protocol / Proposal	Protocol v2_18.10.2017	18/10/2017	2
Protocol / Proposal	Information sheet v2_18.10.2017	18/10/2017	2
Protocol / Proposal	Wound care leaflet v2_18.10.2017	18/10/2017	2
Protocol / Proposal	Staff pilot information sheet v2_18.10.2017	18/10/2017	2
Protocol / Proposal	Reminder letter v2_18.10.2017	18/10/2017	2
Information Sheet	Information sheet v2_18.10.2017	18/10/2017	2
Information Sheet	Consent form v1	18/10/2017	1
Information Sheet	Participants Consent Form	18/10/2017	1
Local Approval	227443 17 SW 0203 Ltr- Further Info Fav Opinion- 23.10.17	23/10/2017	1
Local Approval	SL-AR2_Non-CTIMP_Standard_Conditions	23/10/2017	1
Investigator CV	Liam Smeeth 2 page CV	01/11/2017	1
Investigator CV	cv neil pearce one-page	07/11/2017	1
Investigator CV	Henderson_biosketch_network web service	07/11/2017	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

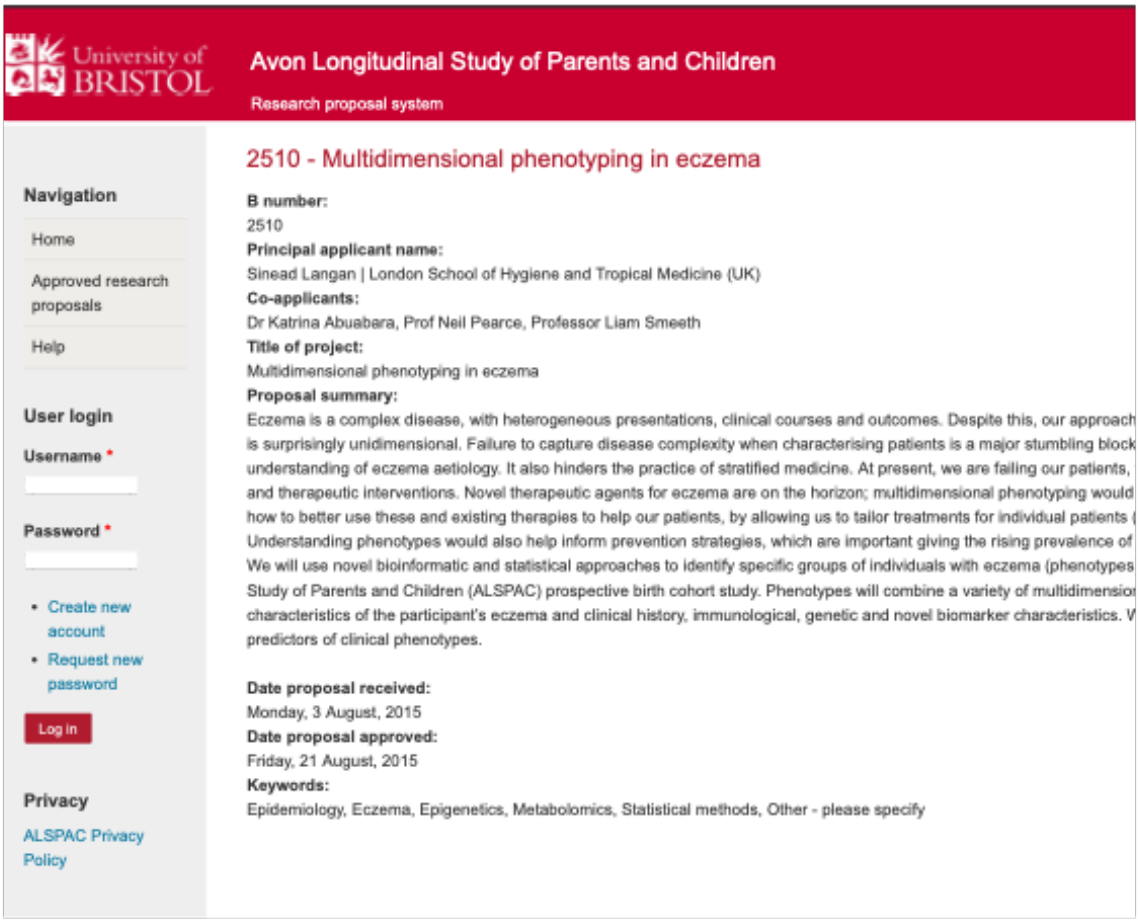
Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

A.4.2 Public Website: Ethical approval from University of Bristol



University of BRISTOL

Avon Longitudinal Study of Parents and Children

Research proposal system

Navigation

Home

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Help

User login

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- Create new account
- Request new password

Log in

Privacy

ALSPAC Privacy Policy

2510 - Multidimensional phenotyping in eczema

B number:
2510
Principal applicant name:
Sinead Langan | London School of Hygiene and Tropical Medicine (UK)
Co-applicants:
Dr Katrina Abuabara, Prof Neil Pearce, Professor Liam Smeeth
Title of project:
Multidimensional phenotyping in eczema
Proposal summary:
Eczema is a complex disease, with heterogeneous presentations, clinical courses and outcomes. Despite this, our approach is surprisingly unidimensional. Failure to capture disease complexity when characterising patients is a major stumbling block understanding of eczema aetiology. It also hinders the practice of stratified medicine. At present, we are failing our patients, and therapeutic interventions. Novel therapeutic agents for eczema are on the horizon; multidimensional phenotyping would how to better use these and existing therapies to help our patients, by allowing us to tailor treatments for individual patients (Understanding phenotypes would also help inform prevention strategies, which are important giving the rising prevalence of We will use novel bioinformatic and statistical approaches to identify specific groups of individuals with eczema (phenotypes Study of Parents and Children (ALSPAC) prospective birth cohort study. Phenotypes will combine a variety of multidimensio characteristics of the participant's eczema and clinical history, immunological, genetic and novel biomarker characteristics. V predictors of clinical phenotypes.

Date proposal received:
Monday, 3 August, 2015
Date proposal approved:
Friday, 21 August, 2015
Keywords:
Epidemiology, Eczema, Epigenetics, Metabolomics, Statistical methods, Other - please specify

A.4.3 Correspondence: Approval of manuscript submission by ALSPAC Executive Committee

Saturday, March 9, 2024 at 13:42:53 Greenwich Mean Time

Subject:	ALSPAC Exec Approved – C3190 – Assessing agreement concerning atopic dermatitis phenotypes between an English prospective cohort (ALSPAC) and linked electronic health records
Date:	Monday, 2 October 2023 at 09:56:23 British Summer Time
From:	Alspac Exec Mailbox
To:	Julian Matthewman
CC:	Alspac Exec Mailbox, Alspac Media Mailbox[redacted]
Attachments:	ALSPAC-AD-phenotypes-agreement manuscript draft for exec.docx

Dear Julian,

The ALSPAC Executive Committee has approved your paper for submission.

It has been logged under the above C number. Please include this in all future correspondence.

It is your responsibility to make any paper open access where necessary. Please refer to section 6.7.1.1 of the ALSPAC Access Policy for further information: (http://www.bristol.ac.uk/alspac/researchers/data-access/)

You don't need to send minor revisions back to ALSPAC Executive for approval in the submission process. But if there are any changes that substantially alter the message of the paper or data the Executive Committee would need to see them. **Please inform us if the title of the paper or the first author changes** - we need to be able to identify papers that have been published in order to accurately report back to our funders and such changes mean we may miss your paper.

If your paper included an author from the University of Bristol, please can we remind you to include ALSPAC as a 'structured keyword' when you add this paper to PURE.

Please can we also remind you to contact the data buddy team (alspac-data@bristol.ac.uk) to arrange the return of any derived variables from your project **B2510** (if you haven't already done so). By 'derived variables', we are not referring to simple recodes; rather, if you have used a combination of existing variables to derive something new. If you have created derived variables using linked data, please return these to the linkage team directly (alspac-linkage@bristol.ac.uk). If you have generated such variables, please complete this form, and provide as much detail as possible on how these derived variables were created. Please return the completed form to your data buddy within one month, along with the do file/syntax/script used to create the data. Before sharing any data back with your data buddy, please reach out to them as they will provide you with a link to securely upload the data.

Data must never be shared via email.

Finally, please inform the ALSPAC Executive as well as our media team when your manuscript has been accepted for publication (alspac-exec@bristol.ac.uk alspac-media@bristol.ac.uk) and send both of us a copy of, or link to, the final version.

With many thanks,

[redacted]

On Behalf of the ALSPAC Executive

ALSPAC (Children of the 90s)

1 of 2

Oakfield House
Oakfield Grove
Bristol
BS8 2BN
alspac-executive@bristol.ac.uk

-----Original Message-----
From: Julian Matthewman <Julian.Matthewman1@lshtm.ac.uk>
Sent: Friday, September 22, 2023 6:02 PM
To: Alspac Exec Mailbox <alspac-exec@bristol.ac.uk>
Cc: Sinead Langan <Sinead.Langan@LSHTM.ac.uk>
Subject: Manuscript draft

Dear ALSPAC exec team,

please find attached the publication checklist and draft manuscript for our study on Atopic dermatitis phenotypes, which we plan to submit shortly.

Many thanks in advance!
Best wishes
Julian Matthewman
(Research fellow, LSHTM)

A.5 Ethical approvals for Chapter 7

A.5.1 Letter: Ethical approval from LSHTM

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Julian Matthewman
LSHTM

31 August 2023

Dear Dr Julian Matthewman

Study Title: Adverse health outcomes among people with atopic eczema: a consistent application of cohort study design to multiple outcomes

LSHTM Ethics Ref: 29781

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	Julian Matthewman Research_Ethics_online_training_certificate	05/11/2021	1
Protocol / Proposal	Adverse-health-outcomes-among-people-with-atopic-eczema-a-consistent-application-of-cohort-study-design-to-multiple-outcomes-23-002665 (1)	15/08/2023	1
Investigator CV	CV Julian Matthewman 2021 (1)	15/08/2023	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

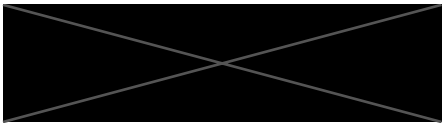
An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. The date the first annual report is due is 31/08/2024

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,



Professor David Leon and Professor Clare Gilbert

Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/