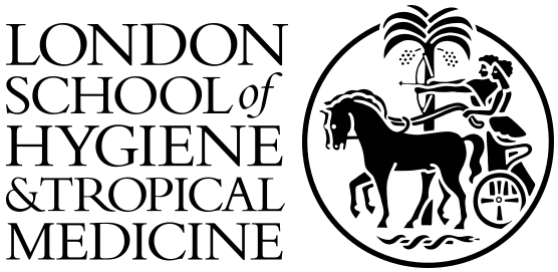

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Depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
of the
University of London

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Funded by British Skin Foundation

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Declaration

I, Elizabeth Ilerioluwa Adesanya, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Elizabeth Ilerioluwa Adesanya

December 2022

COVID-19 Impact Statement

Several aspects of this PhD project have been adversely affected by the COVID-19 pandemic.

Study delays

The second reviewer in my systematic review (a vital component of my study) is a GP who was exceptionally busy during the pandemic (e.g., patient care, delivering COVID-19 vaccinations). Consequently, double screening of articles for inclusion in the review was delayed from October 2020 to March 2021 when I was able to find another reviewer.

Access to essential electronic health record data required for the studies included in the thesis was delayed, postponing data management and analysis. Except for the systematic review, the research included in my thesis used confidential patient-level data from the Clinical Practice Research Datalink (CPRD). CPRD protocol approval and amendments took longer due to prioritisation of time-sensitive COVID-19 work (e.g., applying for a protocol amendment for one of my studies delayed access to essential data for over a month). Additionally, I was only able to access data from computers within physical London School of Hygiene and Tropical Medicine buildings, meaning I was unable to access data I needed for many months due to COVID-19 restrictions.

Working from home

During COVID-19 lockdowns in 2020 and 2021, I was required to work from home. In March 2020, during the UK's first national lockdown, I did not have a suitable work from home set-up (i.e., a desk or chair) so I struggled to find somewhere to work. I was unable to buy a desk, chair and monitor until April 2020. With both parents at home, meetings with my supervisors were challenging, this was compounded by insufficient internet bandwidth and technical problems with my computer audio.

I also did not have access to adequate computational power for my work. I was initially unable to access the high-powered computer need for my work due to COVID-19 restrictions. When I finally able to access a high-powered computer

remotely (after a month), I struggled for over 5 months with unreliable access. My remote computer frequently turned off causing data management steps and analyses to fail. Finding someone in the building to switch to reboot my computer was difficult due to limited occupancy as a result of the restrictions. Our research group did initiate a system to rapidly identify onsite staff who could reboot PCs, helping limit disruption, but when some data management can take hours to run, any interruption to the process can have considerable cumulative effect. Additionally, the secure drive, where confidential patient-level data are stored, had frequent technical problems and crashed, delaying progress.

Mental health

I lived at home with my parents during the PhD. During the pandemic, my dad was identified as clinically vulnerable and advised to shield. My mum also has underlying health conditions; however, she was a key worker in a hospital and continued to work through the pandemic. Apart from the practical issues I faced living in a flat with someone who was shielding, my mental health was negatively affected. I felt anxious and worried about both of my parents' health and safety making it difficult to focus on my work. My anxiousness only heightened when restrictions eased and a few weeks later in August 2020, both of my parents were ill with COVID-19. Luckily, their symptoms were mostly mild, and both recovered within a month, but as the only person who could look after them both within that time, my project was not the priority.

Acknowledgments

I would firstly like to express my deepest thanks to my supervisors Kate Mansfield, Sinéad Langan, and Alasdair Henderson without whom I would not have been able to complete this project. They have been patient, supportive and encouraging, and consistently provided constructive feedback, regardless of how many consecutive drafts were sent! I'm forever grateful for their guidance throughout this journey.

I would also like to thank Joseph Hayes, Rohini Mathur, Amy Mulick, Catherine Smith, Caroline Morton, Helena Carreira, Sujit Rathod and Alexandra Lewin for their feedback and suggestions on the manuscripts included in this thesis. I would also like to give special thanks to Yochai Schonmann and Julian Matthewman for their help duplicating the screening processes in the systematic review.

I would also like to thank all the members of the Skin Disease Epidemiology and Health Data Research Group and the Electronic Health Research Group at LSHTM for their support.

Thank you to my friends, both at LSHTM and beyond, and my family. Thank you for the conversations, and the advice. I am very grateful for your support. Thank you to my mum, my biggest cheerleader. You inspire and support me every day to achieve my goals. Thank you for listening to my frustrations and encouraging me to carry on, even when things were difficult. I couldn't have done this without you.

I would like to thank the members of the eczema patient and public involvement group – discussions of your lived experiences with atopic eczema helped to shape this project. Lastly, thank you to those that contributed data to the studies included in this thesis.

Abstract

Atopic eczema (AE) and psoriasis are common inflammatory skin diseases associated with substantial morbidity for affected individuals. Evidence suggests associations between AE or psoriasis, and depression, anxiety, and severe mental illness (SMI). However, there is limited evidence on: (1) factors associated with the mental health conditions among those with AE or psoriasis; (2) longitudinal associations between AE or psoriasis, and SMI; and (3) associations between AE and depression and anxiety in different ethnic groups.

This thesis aims to: (1) systematically review available evidence on factors associated with depression, anxiety, and SMI among adults with AE or psoriasis; (2) investigate longitudinal associations between AE or psoriasis and incident SMI among adults using electronic health records from the UK's Clinical Practice Research Datalink (CPRD); and (3) investigate whether associations between AE and incident depression or anxiety differs between adults from white and minority ethnic groups using CPRD data.

The systematic review included 21 studies and identified factors that were associated with depression (being female, psoriatic arthritis) and anxiety (being female, psoriatic arthritis, moderate-to-severe psoriasis) among adults with psoriasis. Evidence from included trials suggested AE or psoriasis treated with placebo was associated with higher depression and anxiety than targeted biologic treatment. AE and psoriasis were associated with increased SMI risk, and among those with AE, the increased risk was largely mediated by problems with sleep. Adults with AE were also at increased risk of depression and anxiety. Depression and anxiety risk was higher in individuals from minority ethnic groups compared to those of white ethnicity.

In conclusion, evidence from this thesis suggests a large burden of mental health conditions among those with AE or psoriasis. The introduction of mental health promotion and prevention strategies in the management of individuals with AE or psoriasis may improve health outcomes and reduce mental health burden.

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List of abbreviations

AE	Atopic Eczema
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CMD	Common Mental Disorder
DAG	Directed Acyclic Graph
EHR	Electronic Health Record
GP	General Practitioner
HES APC	Hospital Episode Statistics Admitted Patient Care
HR	Hazard Ratio
ICD-10	International Classification of Diseases, Version 10
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
MeSH	Medical Subject Headings
MHDS	Mental Health Data Set
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
OR	Odds Ratio
PI	Prediction Interval
PPI	Patient and Public Involvement
PPV	Positive Predictive Value
QOF	Quality and Outcomes Framework

RCT	Randomised Controlled Trial
SMI	Severe Mental Illness
UK	United Kingdom
US	United States

1 Introduction

Atopic eczema and psoriasis are chronic inflammatory skin diseases associated with considerable morbidity and impaired quality of life for those affected.[1,2] Atopic eczema is estimated to affect up to 10% of adults,[3] while the prevalence of psoriasis is estimated to be up to 2% in adults.[2] Mental health conditions as a whole are the second leading cause of years lived with disability worldwide.[4] This thesis focuses on depression, anxiety, and severe mental illness (SMI), which are responsible for a substantial proportion of the years lived with disability. Depression and anxiety are common mental disorders (CMDs) that can affect the physical and social functioning of affected individuals.[4–6] SMIs (including schizophrenia, bipolar disorder, and other non-organic psychotic conditions) are associated with substantial morbidity and mortality.[7]

There are several evidence gaps in the literature regarding relationships between atopic eczema or psoriasis and depression, anxiety, and SMI. Firstly, although there is evidence suggesting associations between atopic eczema or psoriasis and mental health conditions,[8,9,18–24,10–17] factors associated with depression, anxiety, and SMI among adults with atopic eczema and psoriasis are unclear and have not been systematically evaluated. Identifying factors associated with depression, anxiety, or SMI among individuals with atopic eczema or psoriasis offers an opportunity to identify high-risk groups who may benefit from mental health promotion and prevention strategies, and modifiable factors that could be targeted to reduce the risk of mental health conditions.

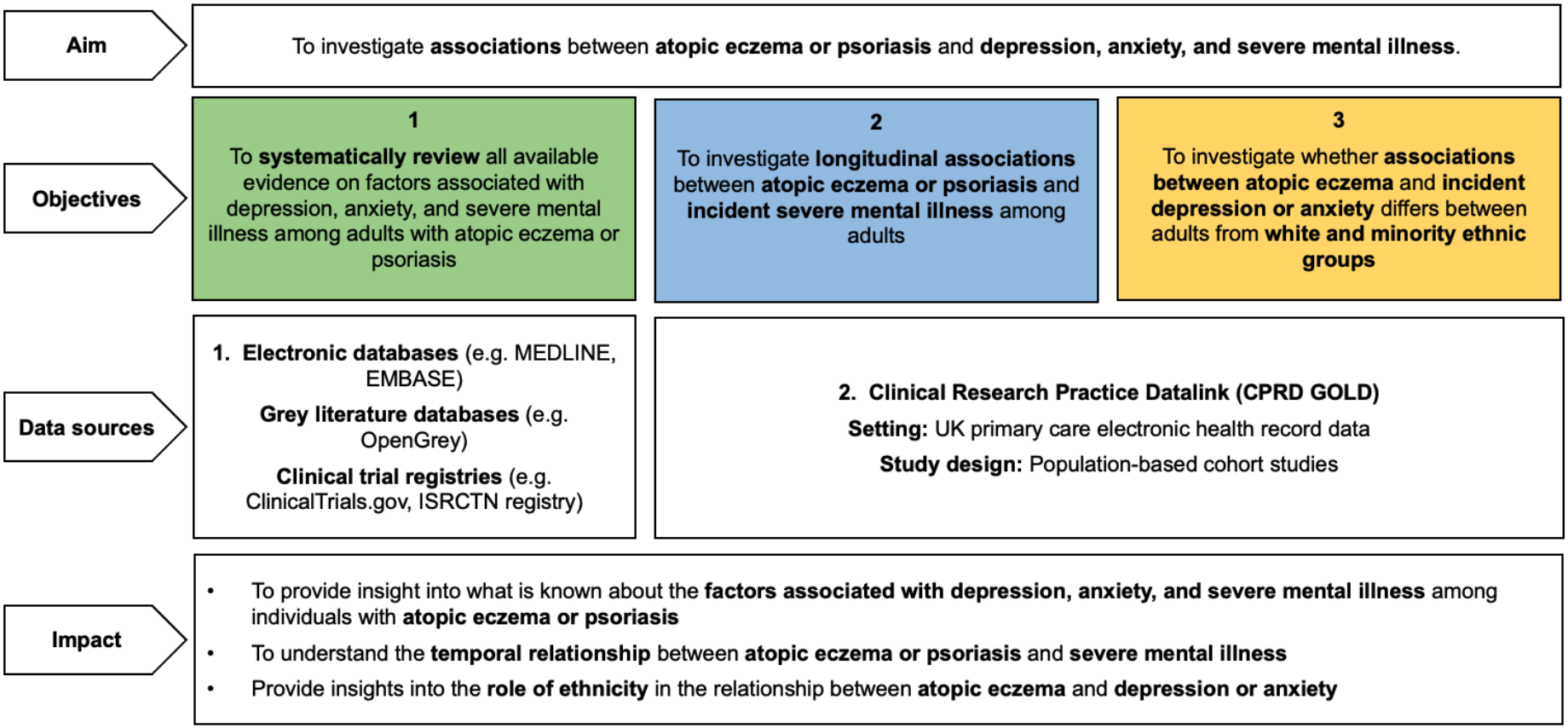
Secondly, longitudinal evidence of associations between atopic eczema or psoriasis and SMI is limited, with only a few studies – with important limitations – aiming to address temporal associations.[25–28] Temporal associations between atopic eczema or psoriasis and SMI are therefore unclear, and due to how common atopic eczema and psoriasis are, and the substantial morbidity and mortality associated with SMI, it is important to identify if temporal associations are present. Finally, the role of ethnicity in temporal associations between atopic eczema or psoriasis and depression or anxiety has not been considered in previous research. Given the

paucity of previous research, and the health inequalities experienced by individuals from minority ethnic groups (e.g., barriers to healthcare access, racism, deprivation), it is important to identify whether associations between atopic eczema and depression or anxiety differ between ethnic groups, and whether individuals with atopic eczema from minority ethnic groups may benefit from targeted mental health promotion and prevention strategies.

Therefore, this thesis investigated associations between atopic eczema or psoriasis and depression, anxiety, and SMI by: (1) systematically reviewing all available evidence on factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis; (2) investigating longitudinal associations between atopic eczema or psoriasis and incident SMI among adults using electronic health records from the UK's Clinical Practice Research Datalink (CPRD); and (3) investigating whether associations between atopic eczema and incident depression or anxiety differ between adults from white and minority ethnic groups using CPRD data.

This chapter provides an outline of the thesis, including a brief introduction to the background literature, the evidence gaps present, and a description of the aims and objectives of the thesis to fill the evidence gaps identified. **Figure 1.1** shows an overview of the research covered in this thesis, including the aim and objectives of the project, the data sources used, and the expected impact of the research. This chapter will also outline each of the chapters included in the thesis and describe how individuals with atopic eczema were involved in the research conducted.

Figure 1.1: Overview of PhD project including aims, objectives, data sources and expected impact.



1.1 Aim

The overall aim of this thesis is to investigate associations between atopic eczema or psoriasis and depression, anxiety, and severe mental illness (SMI).

1.2 Objectives

Specific research objectives are:

1. To systematically review all available evidence on factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis.
2. To investigate longitudinal associations between atopic eczema or psoriasis and incident SMI among adults.
3. To investigate whether associations between atopic eczema and incident depression or anxiety differ between adults from white and minority ethnic groups.

1.3 Importance of the research

The research conducted as part of this thesis may: (1) provide insight into whether individuals with atopic eczema or psoriasis are at increased risk of developing SMI compared to individuals without the skin conditions; (2) identify high-risk groups with atopic eczema or psoriasis that may benefit from mental health promotion and prevention strategies; and (3) lead to the identification of potentially modifiable factors in people with atopic eczema or psoriasis that could be targeted to reduce the risk of mental health conditions.

1.4 Thesis structure

This is a ‘research paper style’ thesis comprised of chapters including research papers, alongside more traditional ‘book style’ chapters.

Chapter 2: Background

Provides a summary of relevant background literature including: (1) background information on atopic eczema, psoriasis, depression, anxiety, and SMI; (2) a description of the existing literature on associations between atopic eczema or psoriasis and depression, anxiety, and SMI. The aim of this chapter is to justify the aims of the thesis, and present previous work that this thesis builds upon.

Chapter 3: Factors associated with depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis: a systematic review and meta-analysis

Describes the systematic review I conducted to address the first objective of this thesis – identifying factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis.

Chapter 4: Overview of data sources

Presents an overview of the electronic health record data sources used in the population-based cohort studies in this thesis.

Chapter 5: Overview of common variables used in included studies

Describes how the variables (skin disease and ethnicity exposures, mental health outcomes, and covariates) used in the population-based cohort studies were defined and captured using CPRD GOLD data and its linkages.

Chapter 6: Directed acyclic graphs to guide covariate selection for associations between atopic eczema or psoriasis and depression, anxiety, and severe mental illness

Presents and describes the directed acyclic graphs I developed to illustrate and understand the roles of key variables in associations between atopic eczema or psoriasis (exposures), and depression, anxiety, or SMI (mental health outcomes) that are investigated in the population-based cohort studies of this thesis (i.e., **Chapters 7,8**).

Chapter 7: Severe mental illness among adults with atopic eczema or psoriasis: population-based matched cohort studies within UK primary care

Presents the population-based cohort studies I conducted to investigate longitudinal associations between atopic eczema or psoriasis and incident SMI among adults.

Chapter 8: Ethnic differences in depression and anxiety among adults with atopic eczema: population-based matched cohort studies within UK primary care

Describes the population-based cohort studies that I conducted to investigate whether associations between atopic eczema and incident depression or anxiety differed between adults from white and minority ethnic groups.

Chapter 9: Discussion

Presents a summary of the findings of the thesis as a whole and comparisons to existing literature. The strengths and limitations of the thesis are also discussed, as well as the implications of the work for clinical practice, and avenues for future research.

1.5 Patient and public involvement

Patient and public involvement (PPI) was central to the work conducted in this thesis. Over the course of the PhD, I met with eight to twelve individuals with atopic eczema in five separate meetings. Members of the PPI group were involved in shaping the aims and objectives of studies, providing feedback on the interpretations of results, and ensuring that research outputs were suitable for lay audiences. Regular meetings with members of the PPI group motivated my research and strengthened my understanding of atopic eczema and psoriasis as I was able to listen to first-hand experiences of the impact the condition had on day-to-day life of affected individuals. I was also able to update the members on the progress of the research and gain their insights into possible avenues for future research.

2 Background

2.1 Introduction

In the previous chapter, I briefly introduced the thesis and described the overall aims and objectives. In this chapter, I will present an overview of the relevant background literature. I will firstly discuss the skin diseases (atopic eczema and psoriasis) and mental health conditions (depression, anxiety, and severe mental illness) under investigation, including detail on their definitions, epidemiology, pathogenesis, diagnosis, and treatment. I will then describe the existing literature regarding associations between atopic eczema or psoriasis and depression, anxiety, or severe mental illness. Finally, using the background information I presented, I will highlight the limitations and evidence gaps in existing research and describe why it is important they are addressed to justify the aims and objectives of this thesis.

2.2 Atopic eczema and psoriasis

2.2.1 Definition

2.2.1.1 Atopic eczema

Atopic eczema (also known as eczema or atopic dermatitis) is a chronic inflammatory skin disease characterised by eczematous lesions and intense itching.[1] Atopic eczema usually refers to eczema that occurs as a result of allergen sensitisation and elevated levels of immunoglobulin E (IgE), while eczema is used as an umbrella term for both IgE-mediated and non-IgE-mediated forms of the disease.[1,29] However, in the context of this thesis, and more generally in the literature, atopic eczema and eczema are used synonymously and often used to refer to both atopic and non-atopic forms of atopic eczema.

2.2.1.2 Psoriasis

Psoriasis is a chronic, immune mediated inflammatory skin disease characterised by red, scaly patches or plaques.[2] There are several types of psoriasis, each of which

varies in their signs and symptoms, however, most variants share three clinical features – erythema (redness), skin thickening, and scaly lesions.[30] Plaque psoriasis is the most common variant of psoriasis and accounts for 80-90% of psoriasis cases.[30,31] Plaque psoriasis can occur anywhere on the body, but most commonly affected areas include the elbows, knees, scalp, and lower back.[30,31] Less common forms of psoriasis that occur in only 2-3% of psoriasis cases include guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis.[30]

2.2.2 Aetiology and pathogenesis

2.2.2.1 Atopic eczema

Two major hypotheses have been proposed to explain the aetiology of atopic eczema: (1) the Inside-Out hypothesis, and (2) the Outside-In hypothesis. The Inside-Out hypothesis suggests that dysregulation of the immune system and inflammation triggers skin barrier dysfunction,[32] while the Outside-In hypothesis theorises that a compromised skin barrier (either due to external influences or mutations in genes that encode the skin barrier protein filaggrin) results in immune dysregulation and inflammation.[32,33]

Both hypotheses suggest that genetics play in the development of atopic eczema. However, environmental factors may also play a role in the aetiology of atopic eczema. Living in an urban area compared to a rural area,[34] higher socioeconomic status,[35] tobacco smoke, pollution, and obesity have been associated with increased atopic eczema prevalence.[36] The hygiene hypothesis – which states that a reduction in exposure to infections in early childhood leads to increased susceptibility of atopic eczema[36] – has also been described as a possible explanation for the influence of environmental factors in the development of atopic eczema.

2.2.2.2 Psoriasis

Genetic and immune mediated hypotheses have been proposed to explain the aetiology of psoriasis. Genome-wide association studies have identified multiple alleles and loci linked with psoriasis susceptibility.[37] The most prominent loci identified is PSORS1 of which up to 50% of the heritability of psoriasis has been attributed.[31] Other genetic variants found to be associated with psoriasis are involved

in the functioning of the immune system, specifically inflammation and antigen presentation.[31] This is relevant as excessive activation of parts of the immune system is hypothesised to be central to the pathogenesis of psoriasis.[30] Secretion of excess cytokines results in an inflammatory cascade that leads to psoriatic inflammation and disease.[30,31]

Evidence from family-based studies further highlights the genetic component in the aetiology of psoriasis. Individuals with first or second-degree relatives with psoriasis have an increased risk of developing psoriasis,[31] with the risk as high as 50% in those with two affected parents.[38] Although there is evidence of a genetic component to the development of psoriasis, not all individuals with susceptibility genes go on to develop the disease, suggesting that there may be other important risk factors for psoriasis. In genetically susceptible individuals, comorbidities (e.g., metabolic syndrome, obesity, diabetes, hypertension), skin injury, and environmental factors (air pollution, sun exposure, infection, smoking, alcohol consumption) may lead to the onset or exacerbation of psoriasis.[39]

2.2.3 Epidemiology

2.2.3.1 Atopic eczema

Atopic eczema is one of the most common inflammatory skin diseases. Although atopic eczema can occur at any age, the usual age of onset is in early childhood, with the highest incidence at age 3-6 months,[40] and 85% of cases occurring before 5 years of age.[41] Worldwide, approximately 230 million people have atopic eczema,[1] and the prevalence is estimated to be 1-3% in adults,[36] however, estimates vary by country. In the United States (US), atopic eczema prevalence is estimated to be up to 10% in adults, a figure which is greater than estimates in the UK (5%) and South Korea (3%).[3] Overall, studies suggest that atopic eczema prevalence estimates are plateauing over time in high-income countries, and increasing in low- middle-income countries with the largest increase occurring over the past 30 years.[1,41] Environmental factors (i.e., the hygiene hypothesis, socioeconomic status, urban versus rural living) have been suggested as a possible explanation for the increase in low- and middle-income countries.

2.2.3.2 Psoriasis

Psoriasis can occur at any age, however, the mean age of onset for the first presentation of psoriasis is between 15-20 years of age, with a second peak between 55-60 years.[42] Most affected individuals present with psoriasis before 35 years of age.[2] Psoriasis is common; worldwide, approximately 125 million people have psoriasis,[30] and the physician diagnosed prevalence is estimated to be up to 2%, a figure which is lower than the estimated prevalence of 2.8% in the UK.[2,43] Psoriasis prevalence estimates vary considerably by country, with the highest estimates seen in high-income countries such as Australia (2.38%) and Norway (2.36%), and the lowest estimates seen in Taiwan (0.07%).[2]

2.2.4 Diagnosis

2.2.4.1 Atopic eczema

The diagnostic approach for atopic eczema frequently is a clinical diagnosis, often made by general practitioners (GPs) or general practice nurses assessing individuals who present to primary care. Diagnostic criteria have been developed to help guide practitioners and for research purposes. The most widely used diagnostic criteria by researchers, and to a lesser extent, clinicians is the Hanifin and Rajka criteria which identifies essential (eczematous lesions, intense itching, chronic or relapsing disease), common (general skin dryness, disease onset in the first 2 years of life, personal/family history of atopic disease) and non-specific features of atopic eczema.[1,29,44] If atopic eczema is diagnosed, the next step is to assess the severity of symptoms. In the UK, the National Institute for Health and Care Excellence (NICE), an independent organisation that provides national guidance to improve public health and social care services,[45] recommends that at each GP consultation, atopic eczema severity should be assessed through physical examination of all affected skin and asking affected individuals about itching.[46] The use of validated tools to assess atopic eczema severity such as the Patient Oriented Eczema Measure should also be considered.[46]

2.2.4.2 Psoriasis

Psoriasis is often diagnosed by GPs within primary care. GPs ask individuals about the areas of the body involved and associated symptoms (I.e., irritation, pain, scaling) to classify the type of psoriasis.[47] Plaque psoriasis, the most common manifestation of psoriasis, has a chronic or relapsing course and presents as well demarcated red scaly plaques that are typically located on the scalp, trunk, extensor surfaces or extremities, but can also occur anywhere on the body.[30] Other less common forms of psoriasis have clinical signs that are specific to them, for example, pustular psoriasis tends to be localised to the palms or soles of the feet, or in rare situations, be generalised.[30] GPs can also assess the severity of psoriatic lesions during consultations. The six-point Static Physician's Global Assessment score is recommended by NICE as a clinical measure of psoriasis severity, with a warning that redness may be underestimated in individuals with darker skin.[47,48]

2.2.5 Treatment

2.2.5.1 Atopic eczema

The main aim of atopic eczema treatment is to improve symptoms and control disease by minimising the number of 'flares' (exacerbations of atopic eczema).[1,29] Treatment strategies for atopic eczema are varied and depend on the severity of the disease. Mild forms of atopic eczema can be managed by avoiding factors that may trigger exacerbations (e.g., non-cotton fabrics) and using emollients which increase skin hydration and reduce itching.[29,49]

Topical corticosteroids (e.g., hydrocortisone) are regarded as the first-line anti-inflammatory pharmacologic treatment for atopic eczema.[1,29] In the UK, topical corticosteroids are available in four potencies (mild, moderate, potent, very potent) based on their ability to cause vasoconstriction.[29,50] More potent topical corticosteroids are mainly used for those with more severe disease, or in people experiencing short-term severe flares.[1] Appropriate and intermittent use of topical corticosteroids is safe, however, inappropriate use (e.g., long-term use of very potent preparations) can cause local side-effects including stretch marks, skin-thinning, atrophy, and acne.[1,29] Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)

can be used to manage atopic eczema in individuals who have not responded adequately to topical corticosteroids.[51] Calcineurin inhibitors have the potency of mild to moderate corticosteroids, however, they can be used in delicate areas of the skin where prolonged treatment with corticosteroids may be inappropriate as they do not cause skin atrophy.[29,51] However, their high costs and the burning sensation often experienced within the first few applications restrict their use.[1,41]

In individuals whose atopic eczema cannot be controlled using topical treatments, 1-3 months of phototherapy using narrowband Ultraviolet B radiation can be considered.[1,29] However, clinicians are often cautious when prescribing phototherapy as extensive use can cause premature skin aging and increase the risk of skin cancer.[29] Oral systemic corticosteroids (specifically glucocorticoids, including prednisolone and hydrocortisone) are generally not recommended for treating atopic eczema, and are generally discouraged due to their side-effect profile (e.g., osteoporosis, adrenal suppression) and increased risk of disease relapse on stopping therapy.[52,53] Standard systemic therapies including methotrexate are used for more severe disease unresponsive to topical therapies. In recent years, biological therapies in the form of targeted monoclonal antibodies (i.e., dupilumab, tralokinumab) and small molecule medications including Janus Kinase inhibitors (such as abrocitinib and upadacitinib) have been approved by the NICE for use in England and Wales for treatment of moderate-to-severe atopic eczema in eligible adults.[54,55] Other biological and small molecule therapies are currently under investigation in phase 2 and 3 trials.[56,57]

2.2.5.2 Psoriasis

The aims of psoriasis treatment are to manage symptoms and prevent exacerbations. Treatment options for psoriasis vary depending on disease severity. In mild psoriasis, treatment options include topical treatments (i.e., corticosteroids, calcineurin inhibitors, vitamin D analogues, keratolytics) and targeted phototherapy to treat localised plaques.[30] Vitamin D analogues (e.g., calcipotriol, calcitriol) work by binding to vitamin D receptors on skin cells to block their proliferation.[30] Keratolytics (e.g., salicylic acid) help to soften the skin by breaking down the scaly plaque that is characteristic of psoriasis.[30] Topical corticosteroids and calcineurin inhibitors used to

treat mild psoriasis are the same as those used to treat mild forms of atopic eczema and have been described previously (**Section 2.2.5.1**).

Moderate-to-severe forms of psoriasis require either phototherapy, oral or injectable systemic treatments, biologics, or small molecule drugs. Narrowband Ultraviolet B and psoralen plus Ultraviolet A are the main types of phototherapies used to treat moderate-to-severe psoriasis that has not responded to other treatment.[30,31,58] Psoralens (e.g., methoxalen) are administered orally or topically prior to Ultraviolet A irradiation.[30] Psoralen plus Ultraviolet A is more effective than narrowband Ultraviolet B, however, long-term use is associated with an increased risk of developing skin cancer.[30,58]

Oral systemic treatments (including methotrexate, ciclosporin, acitretin, apremilast) are immunomodulators that prevent excess activation of the immune system.[31] The side effects associated with these treatments vary significantly and can range from lip dryness (a side-effect of acitretin) to kidney damage (a side-effect of ciclosporin), therefore careful consideration of which to prescribe is required.[58] Biological treatments (e.g., etanercept, infliximab, adalimumab, guselkumab, risankizumab, secukinumab, ixekizumab) can also be used to treat moderate-to-severe psoriasis.[30,31]

2.2.6 Associated comorbidities

2.2.6.1 Atopic eczema

There is clear evidence that children or adults with atopic eczema are at increased risk of other allergic diseases (e.g., asthma, allergic rhinitis, and food allergies) compared to those without atopic eczema.[59–62] Evidence also suggests that the prevalence and severity of atopic comorbidities is increased in individuals with more severe atopic eczema.[59] Some studies have suggested that atopic eczema may be the first step in what is known as the ‘atopic march’, described as the sequential manifestation of atopic disease where clinical signs of atopic eczema precede the development of asthma and allergic rhinitis, with eczema resolving with increasing age.[63] While there are multiple longitudinal studies that support the atopic march,[64–66] criticisms have been made of their methods of data collection and disease

identification.[67] Additionally, evidence from other longitudinal research and studies using machine learning methods further challenge the 'atopic march' by suggesting different patterns of atopic disease trajectory (e.g., children with asthma developing atopic eczema, or children developing asthma and allergic rhinitis without atopic eczema).[68,69] Evidence from a large longitudinal study has also shown that atopic eczema symptoms do not resolve with age, and instead persist into adulthood.[70]

Apart from other atopic diseases, evidence supports that more severe atopic eczema is associated with cardiovascular disease (e.g., hypertension, coronary heart disease, heart failure),[59,71–73] and this association may be due to the higher prevalence of cardiometabolic risk factors (e.g., sedentary lifestyle, increased alcohol consumption, cigarette smoking, diabetes) in individuals with atopic eczema compared to the general population.[74,75] However, evidence regarding the association between atopic eczema and some cardiovascular outcomes such as myocardial infarction and stroke is conflicting. Some observational studies have found no evidence of an association,[76,77] while others reported an increased risk.[72,78] Associations between atopic eczema and infections,[1,79] fractures,[80] and several psychological outcomes including attention-deficit hyperactivity disorder and suicidal ideation/self-harm have also been found.[1,79] There is evidence of associations between atopic eczema and depression, anxiety, and severe mental illness that will be discussed in further detail later in this chapter (**Sections 2.6, 2.7**).

2.2.6.2 Psoriasis

Psoriasis has been associated with several diseases including psoriatic arthritis, metabolic syndrome, and cardiovascular disease. Psoriatic arthritis is the most common comorbidity, with approximately 30% of psoriasis patients developing the condition within their lifetime.[81] Psoriatic arthritis is characterised by joint pain, stiffness or swelling,[30] and in about 5% of patients, it can progress to severe, debilitating arthritis and joint destruction.[30,81] In approximately 85% of people, psoriasis precedes the development of psoriatic arthritis by up to 10 years,[30,81] but in approximately 15% of people, psoriatic arthritis precedes or occurs concurrently with psoriasis.[81] Evidence from a meta-analysis reported that individuals with psoriasis have more than twice the risk of metabolic syndrome (type 2 diabetes mellitus,

hypertension, obesity, hyperlipaemia) compared to the general population.[82] Moderate-to-severe psoriasis, has also been demonstrated to be an independent risk factor for cardiovascular outcomes including myocardial infarction,[83] stroke,[84] and cardiovascular mortality.[85] Individuals with psoriasis are also at increased risk of other comorbidities such as depression, anxiety, and severe mental illness, which will be discussed in further detail later in this chapter (**Sections 2.6, 2.7**).

2.2.7 Quality of life

2.2.7.1 Atopic eczema

Among the skin diseases, atopic eczema has the highest disease burden as measured using disability-adjusted life-years.[86] The associated burden may be due in part to the profound effect that atopic eczema can have on the quality of life of affected individuals. Studies of quality of life in adults with atopic eczema reported that atopic eczema had a considerable effect on physical, emotional, and social aspects of their lives.[87] Chronic and intense itching is the major manifestation of atopic eczema associated with impaired quality of life in those affected. Itching continues throughout the day and gets worse at night, leading to sleep disturbance or deprivation.[41] In a large US population-based cross-sectional study, over 50% of adults reported that atopic eczema limited their lifestyle (e.g., choice of clothing, wearing makeup), while 40% of the adults reported that atopic eczema impacted activity, and led to avoidance of social interactions.[88] This same study, along with other research suggest an association between atopic eczema severity and quality of life, with individuals with more severe disease experiencing worse quality of life outcomes.[88–90] In addition to physical and social symptoms, atopic eczema can also lead to feelings of embarrassment, stigma, and low self-esteem in affected individuals.[91] Studies investigating the impact of atopic eczema on the families of affected individuals are scarce, however, a French cross-sectional study reported that the appearance of atopic eczema impaired the sex life of affected individuals and their partners.[92]

2.2.7.2 Psoriasis

Evidence suggests that psoriasis leads to a reduced quality of life comparable to conditions such as cancer, arthritis, hypertension, heart disease, and diabetes.[93] Studies using validated tools (such as the Dermatology Life Quality Index) or self-administered questionnaires to evaluate quality of life in individuals with psoriasis found that moderate-to severe psoriasis,[94] extensive body surface area involvement,[94], comorbid psoriatic arthritis,[94] female sex,[95] psoriasis lesions located on the hands, feet, genital area, or other exposed parts of the body were associated with reduced quality of life.[95] Individuals with psoriasis often experience both social stigmatisation (lack of acceptance from others) and self-stigmatisation (low self-esteem due to a lack of self-acceptance) potentially resulting in impaired social functioning (e.g., social activities, personal relationships).[96,97] Psoriasis can also adversely affect daily activities (e.g., walking, clothing choice, increased bathing frequency), and inhibit work and school tasks.[94]

2.2.8 Comparing atopic eczema and psoriasis

Atopic eczema and psoriasis are two of the most common inflammatory skin diseases, accounting for a substantial proportion of the burden of skin disease worldwide.[98] Both conditions share similarities, including common features in their pathogenesis (e.g., immune dysregulation, excessive expression of proinflammatory cytokines, altered skin barrier) and their associations with significant morbidity and impaired quality of life. However, both atopic eczema and psoriasis differ in terms of their aetiology, disease distribution, and clinical features. Due to the similarities and differences between atopic eczema and psoriasis, I will investigate the associations of both skin diseases with depression, anxiety, and severe mental illness as any similarities/differences in the associations between atopic eczema or psoriasis and mental health conditions may point to specific mechanisms as potential explanations for the associations.

2.3 Mental health conditions

Mental health conditions (also referred to as mental disorders or mental illness) include a range of conditions characterised by disturbances in the cognition, emotional regulation, and behaviour of affected individuals.[99] Over 970 million people worldwide are living with a mental health condition,[4] and in England, one in four people experience a mental health condition each year.[100] Mental health conditions as a whole are the second leading cause of years lived with disability and the seventh leading cause of disability-adjusted life-years worldwide.[4] There are many different types of mental health condition, however, the research in this thesis will focus on depression, anxiety, and severe mental illness. Depression and anxiety are two of the most common mental disorders (CMDs), and together with severe mental illness, they account for a significant proportion of the years lived with disability and disability-adjusted life-years associated with mental health conditions.

2.3.1 Depression

Depressive disorders (including major depressive disorder, dysthymic disorder, and persistent depressive disorder) are characterised by symptoms of low mood, persistent sadness, and loss of interest or pleasure in previously enjoyable activities.[101] Several other symptoms may also be present with varying degrees of severity including loss of concentration, feelings of guilt and hopelessness, low self-worth, feelings of worthlessness, and change in appetite or weight.[101]

2.3.1.1 Aetiology and pathogenesis

The aetiology of depression is complex, and several hypotheses have been proposed. Family studies have provided considerable evidence of the role of genetics in the development of major depressive disorder with first-degree relatives of affected individuals with depression at more than twice the risk of developing major depressive disorder compared to controls.[102]

Research previously suggested that abnormalities in levels of key neurotransmitters (i.e., serotonin, norepinephrine, dopamine) in the brain have been linked to changes in behavioural functions (e.g., appetite, concentration, sleep, response to pain) that

are seen in depression.[101] However, more recent systematic reviews of the literature do not support the hypothesis that depression is caused by reduced levels of serotonin.[103]

Depression may also occur as a response to stressful or major life events. Life events that precede the development of depression may include bereavement, divorce or separation, negative family relationships, redundancy, poverty, abuse, and major accidents.[101,102] In people that have already been diagnosed with depression, stressful life events may limit the effectiveness of treatment or lead to relapse.[101]

Several inflammatory cytokines have also been implicated in the development of depression.[101] Although the research is not conclusive, several mechanisms have been proposed to explain the associations between the inflammatory cytokines and depression, including: (1) a dose-response gradient between elevated levels of pro-inflammatory cytokines and depression; (2) specific cytokines inducing depression-like symptoms; and (3) chronic stress leading to immune dysfunction and subsequent stress induced depression.[101] Research has also shown that antidepressant use can reduce levels of circulating cytokines, evidence that further supports an inflammation mediated pathogenesis.[104]

2.3.1.2 Epidemiology

In 2019, an estimated 280 million people worldwide were living with depression.[4] A meta-analysis of the global prevalence of common mental disorders between 1980 and 2013 estimated the pooled 12 month period prevalence of depressive disorders at 5.4%, with a pooled lifetime prevalence of 9.6%.[105] Pooled period and lifetime prevalence estimates were estimated to be higher in women (period 7.3%, lifetime 14.0%) compared with men (period 4.0%, lifetime 7.3%).[105] In England, in any given week, 3 in 100 people are diagnosed with depression, and 8 in 100 people are diagnosed with mixed depression and anxiety.[100] Prevalence of depression peaks in older adulthood (individuals aged between 55-74 years), but can also occur, at a lower level than adults, in children and adolescents below the age of 15.[106]

2.3.1.3 Diagnosis

Individuals who experience symptoms of depression for most of the day, every day, for over two weeks are advised to consult their GP.[107] At this appointment, the GP will ask the individual questions about how they are feeling, how this is affecting their daily functioning, and general questions pertaining to their lifestyle (diet, physical activity, sleep, alcohol and or substance misuse).[108] NICE also recommends that self-administered validated questionnaires such as the Patient Health Questionnaire-9 and Hospital Anxiety and Depression Scale should be used to assess for depression and the severity of symptoms.[108]

The analysis of several primary care electronic health record (EHR) databases suggests that GPs identify and record depressive symptoms rather than record depression diagnosis, suggesting that using primary care records to identify depression requires use of both diagnostic and symptom codes. For example, a study examining The Health Improvement Network database found that between 1996 and 2006, the incidence of diagnosed depression fell from 22.5 to 14.0 per 1000 PYAR, but the incidence of depressive symptoms rose from 5.1 to 15.5 per 1000 PYAR.[109] Similarly, another study found that after the introduction of the Quality and Outcomes Framework (QOF), a system to remunerate GPs for providing quality care in 2006,[110] GPs used fewer diagnostic codes and more symptom codes to record new episodes of depression.[111]

2.3.1.4 Associated burdens

Studies have shown that depression is associated with reduced levels of physical and social functioning. For example, people with depression are less likely to perform daily activities (i.e., personal hygiene, preparing meals, doing housework),[5] fulfil their roles at work or during social activities, both of which can affect their relationships with partners and family members.[112]

Depression and anxiety also often co-occur, with approximately 85% of patients with depression experiencing significant anxiety.[113] Research on the association between depression and other chronic conditions suggest that depression increases the risk of developing other diseases, and in people with another medical condition, depression can worsen prognosis and increase mortality.[101] One of the ways that

depression can worsen prognosis of another medical condition is by reducing treatment adherence, or even lead to treatment noncompliance, subsequently reducing the effectiveness of treatment and therefore leading to adverse health outcomes.[114] Evidence from systematic reviews and other epidemiological research suggest that depression is an independent risk factor for the development of chronic conditions such as hypertension, diabetes, asthma, chronic respiratory disorders, and cardiovascular diseases.[101,115] This relationship may also be bidirectional as individuals with long-term physical conditions can experience distress and develop depression or other psychological conditions.

2.3.1.5 Treatment

Methods recommended for the treatment of depression vary depending on the severity and pattern of depressive episodes over time. Individuals with mild depression may be recommended exercise or self-help resources (e.g., self-help manuals or self-help groups) by their GPs to improve symptoms.[116] If these do not work, their GPs may refer them to talking therapies.[116,117] The overall aim of talking therapies is to get affected individuals to discuss their thoughts and feelings and teach coping skills.[117] Individuals with moderate to severe depression are prescribed antidepressant medication, either alone or in combination with talking therapies.[116–118]

2.3.2 Anxiety

Anxiety disorders include generalised anxiety disorder, panic disorder (with and without agoraphobia), social anxiety disorder, and others, and are characterised by feelings of unease, excessive fear, or worry.[119] Anxiety disorders can occur in isolation, but more commonly occur with other anxiety and depressive disorders.[120] Approximately up to 85% of people with an anxiety disorder also have a depressive disorder.[113]

2.3.2.1 Aetiology and pathogenesis

The aetiology of anxiety disorders is complex and multifactorial, with both genetic and environmental factors playing an important role. Family studies suggest that the risk of anxiety disorders is 4-6 times higher in first-degree relatives of people with

anxiety compared to relatives of people without anxiety.[102] Childhood adversity, including parental loss, sexual abuse and bullying, has been associated with an increased risk of anxiety disorders in adulthood.[121] In adults, a history of physical, sexual or emotional trauma and sociodemographic factors (e.g., low socioeconomic status, unemployment, low education levels) are associated with increased risk of anxiety disorders.[120] Reduced levels of various neurotransmitters (e.g., dopamine, serotonin) are also implicated in the aetiology of anxiety, however, current research is inconclusive.[122]

Inflammation may also be involved in the aetiology of anxiety disorders. Evidence from a systematic review of cytokine levels reported significantly raised levels of proinflammatory cytokines in individuals with generalised anxiety disorder compared to controls.[123] Another study reported immune dysregulation and elevated cytokine levels in people with late-onset anxiety disorders.[124] Mechanisms linking anxiety and inflammation are unclear, however, chronic stress has been suggested to cause changes in the immune system that could lead to anxiety.[124]

2.3.2.2 Epidemiology

In 2019, over 301 million people worldwide were estimated to be living with an anxiety disorder.[4] A meta-analysis of the global prevalence of common mental disorders between 1980 and 2013 estimated the pooled 12-month period prevalence of anxiety disorders at 6.7%, and the pooled lifetime prevalence at 12.9%.[105] Period and lifetime prevalence estimates are higher in women (period 8.7%, lifetime 18.2%) compared with men (period 1.3%, lifetime 10.1%).[105] In the UK, the prevalence of generalised anxiety is estimated at 6.6%.[100]

2.3.2.3 Diagnosis

Diagnosis of anxiety disorders usually occurs within primary care.[125] The use of a validated assessment tool such as the Generalised Anxiety Disorder-7 questionnaire is recommended by NICE to identify and determine the severity of anxiety disorders.[125] Similar to depressive disorders, GPs predominantly use symptom morbidity codes, rather than diagnostic codes, to record anxiety. An analysis of the Clinical Practice Research Datalink (CPRD), a primary care EHR database in the UK, reported that between 2003 and 2018, the incidence of anxiety symptoms rose

from 6.2 to 14.7 per 1000 PYAR, while the incidence of anxiety diagnoses fell from 13.2 to 10.1 per 1000 PYAR,[126] suggesting that using primary care records to identify anxiety requires use of both diagnostic and symptom codes.

2.3.2.4 Associated burdens

Evidence suggests that anxiety disorders are associated with an elevated risk of several chronic comorbidities including cardiovascular diseases and respiratory diseases.[115] The relationship may also be bidirectional, as people with chronic illness may go on to develop anxiety because of their condition.[120] The presence of anxiety in people with chronic physical illnesses such as cancer and cardiovascular disease has been shown to negatively affect disease prognosis and adherence to treatment.[120] Anxiety has also been associated with impaired work, family, and social functioning, all of which can impact the quality of life of affected individuals.[6]

2.3.2.5 Treatment

Treatments for anxiety are effective and reduce anxiety symptoms while improving quality of life. Psychological therapies are considered first-line treatments for anxiety, and include guided self-help courses, cognitive behavioural therapy, and applied relaxation (a method to relax muscles during stressful situations).[120,127] In individuals who do not respond to psychological therapies, or in those with more severe or complex disease, anxiolytic medication can be prescribed.[120]

2.3.3 Severe mental illness

Severe mental illnesses (SMIs, also referred to as serious mental illnesses) are defined as debilitating, long-lasting psychological conditions that result in serious functional impairment and limit participation in daily life.[7] SMIs include schizophrenia, bipolar disorder, and other non-organic psychotic conditions.[128] Symptoms of SMI are condition specific. Individuals with schizophrenia or other psychoses may experience persistent delusions, hallucinations, or disorganised behaviour.[129] People with bipolar disorder may experience depressed mood or a loss of pleasure in activities during a depressive episode, or feelings of euphoria or irritability during a manic episode.[130]

2.3.3.1 Aetiology and pathogenesis

The aetiology of SMI is poorly understood; however, it is believed that a complex combination of genetic and environmental factors leads to an individual developing the condition. In both schizophrenia and bipolar disorder, family studies have provided strong evidence that the conditions are highly heritable. First-degree relatives of individuals with schizophrenia have 2-9% greater risk of developing the condition compared to relatives of controls, [131] while first-degree relatives in individuals with bipolar disorder have 5-10% greater risk.[132] Genome wide association studies have also identified multiple genes associated with schizophrenia and bipolar disorder, including genes that have important roles in immunity, providing support for the link between the immune system dysfunction and SMI.[133,134]

However, the genes associated with genetic risk are thought to have small effects, suggesting that genetics alone are insufficient for the development of SMI and environmental factors may also play a role. Obstetric complications (low birthweight, premature labour, asphyxia during birth, preeclampsia) may lead to impaired development of the central nervous system, and subsequent development of schizophrenia.[135] Evidence suggests that cannabis use may be an independent risk factor for the development of schizophrenia, and may also precipitate schizophrenia in predisposed individuals or cause a drug-induced psychosis.[131] Stressful life events (e.g., bereavement, abuse) leading to high-expressed emotion can trigger SMI in susceptible individuals.[136]

2.3.3.2 Epidemiology

In 2019, schizophrenia was estimated to affect approximately 27 million people worldwide, while bipolar disorder affected roughly 40 million people.[4] In England, the prevalence of SMI is estimated to be approximately 1%, with a higher prevalence seen in males, people aged 35-74 and people living in the most deprived areas.[7] In terms of specific SMI diagnoses, diagnosis of schizophrenia and other psychoses is more common in men, while diagnosis of bipolar disorder is more common in women.[128] The incidence of bipolar disorder is estimated as 7 per 100,000 PYAR.[137] A meta-analysis of English studies reported a pooled incidence of 15.2 per 100,000 PYAR for schizophrenia, and 31.7 per 100,000 PYAR for all psychoses.[138]

2.3.3.3 Diagnosis

SMIs are not diagnosed in primary care. Instead, individuals who GPs suspect to be showing symptoms of psychosis, schizophrenia, or bipolar disorder are referred from primary care to a secondary care specialist mental health service where a consultant psychiatrist can assess their mental health.[139,140] Although diagnosis of SMIs do not take place in primary care, GPs and primary care have a central role in the holistic care of people with SMIs.[141] The QOF has offered financial incentives to GPs since its inception in 2004 for the care of people with SMIs. Currently, GPs receive renumeration for maintaining a register of individuals with an SMI diagnosis, developing, and maintaining comprehensive care plans, and conducting annual health checks (where BMI, blood pressure and smoking status are monitored) in those with an SMI diagnosis.[142] Additionally, one-third of people with SMI are seen only in primary care and do not interact with secondary care.[141] Because of the role of GPs, it is expected that SMI diagnoses are well recorded in primary care EHR databases. A study investigating the recording of SMI in UK primary care between 2000 and 2010 found that 'other non-organic psychoses' codes were the most common method of recording psychosis in primary care, a finding which may reflect the hesitance of psychiatrists to prematurely assign a stigmatising diagnosis.[128]

2.3.3.4 Associated burden

SMIs are associated with reduced social and physical functioning, including a reduced ability to complete daily activities, reduced self-esteem, and an inability to work.[143] Individuals with SMI experience substantial health inequalities including a shorter life expectancy of up to 20 years compared to the general population.[7] It is estimated that the major cause of premature death in people with SMI are from chronic physical illnesses that can be prevented. These chronic physical conditions include asthma, cardiovascular disease, respiratory disease, hypertension that people with SMI are at an elevated risk of.[7,144]

2.3.3.5 Treatment

Treatment of SMI consists of a combination of medication and talking therapies that aim to target and reduce symptoms, prevent relapse, and enhance social and occupational functioning.[145,146] Antipsychotics are the initial treatment prescribed for

acute schizophrenic episodes.[145] Antipsychotics can also be used to treat bipolar disorder, however, the main treatment prescribed is lithium, a mood stabiliser used to treat mania and regular periods of depression.[146]

2.4 Atopic eczema/psoriasis and CMDs

2.4.1 Evidence of associations

There is extensive evidence from cross-sectional[8–14] and case-control[15–20] studies suggesting that people with atopic eczema or psoriasis are at increased risk of depression and anxiety. Some studies have reported that individuals with atopic eczema have up to twice the risk of depression and anxiety compared to those without atopic eczema.[10,16] In individuals with psoriasis, one study found that the risk of depression was up to twice the risk in controls,[13] while another found the risk of anxiety was up to 44% higher compared to people without psoriasis.[19] Temporal evidence from longitudinal cohort studies suggests that atopic eczema and psoriasis usually precede diagnosis or identification of depression and anxiety.[9,25,147–151] Atopic eczema was associated with a 14% increase in the risk of newly diagnosed depression, and a 17% increase in the risk of newly-diagnosed anxiety.[148] Psoriasis was associated with a 39% increase in the risk of incident depression, and a 31% increase in the risk of incident anxiety.[150]

2.4.2 Potential explanations for associations

Although there is substantial evidence of associations between atopic eczema or psoriasis and depression or anxiety, the factors associated with depression and anxiety among people with atopic eczema or psoriasis are unclear. Potential explanations for the associations are therefore not well understood, however, they are likely to be multifactorial and include demographic factors (age, sex, deprivation), lifestyle factors (body mass index, smoking, alcohol use), skin disease related factors (itch and sleep disturbance in atopic eczema, stigma, inflammation), comorbidities, or genetics. Further details on the factors potentially involved in the

associations between atopic eczema or psoriasis and depression or anxiety are described in **Chapter 6**.

2.4.2.1 Demographic factors

Although both atopic eczema and psoriasis can occur at any age, both conditions have usual ages of onset. For atopic eczema, the usual age of onset is in early childhood. However, evidence suggests that atopic eczema prevalence increases with age among older adults, and decreases with age among children.[152] For psoriasis, there are two peaks for the age of onset – between 15-20 years of age, and between 55-60 years.[42] Depression and anxiety can also affect people of all ages; however, prevalence rates by age vary between the two conditions. Prevalence of depression peaks in older adulthood (individuals aged between 55-74 years), but it can also occur at a lower level than adults in children and adolescents below the age of 15.[106] On the other hand, prevalence rates of anxiety do not differ considerably between age groups, however, prevalence tends to decrease among older age groups.[106]

Female sex and higher socioeconomic status (and therefore lower socioeconomic deprivation) are associated with increased prevalence of atopic eczema.[35,152,153] There is inconclusive evidence as to whether psoriasis prevalence varies by sex, [2,154] however, individuals with psoriasis are more likely to have low socioeconomic status.[155] The prevalence of depression and anxiety also vary by sex and levels of deprivation. Depression and anxiety are more common among females than males.[105,106,109] There is also strong evidence that people of lower socioeconomic status (and high levels of deprivation) are more likely to develop and experience mental health problems such as depression and anxiety.[109,156]

2.4.2.2 Lifestyle factors

Evidence suggests that individuals with atopic eczema or psoriasis have a higher body mass index (BMI),[75,157,158] consume more alcohol and have a higher prevalence of alcohol use disorders,[74,159,160] and are more likely to smoke than populations without skin disease.[74,161] Higher levels of BMI,[162–164] alcohol use[165,166] and smoking[167] are also associated an increased risk of depression and anxiety in the general population. Specifically in individuals with atopic eczema, a relationship

has been demonstrated between smoking status and an increased risk of depression,[168] however, this study was limited by a small number of participants.

2.4.2.3 Skin-disease related factors

Individuals with atopic eczema may be more likely to experience symptoms of depression and anxiety through the effects of disturbed sleep due to chronic and severe itch.[41,169,170] The use of high-dose oral glucocorticoids in people with moderate or severe atopic eczema, to treat acute disease flares of eczema or associated asthma, has been linked to temporary symptoms of depression.[1,29,171] The presence of visible skin lesions in people with atopic eczema and psoriasis can lead to stigma, and subsequently increase the risk of depression.[91,172]

The increased risk of depression and anxiety among people with atopic eczema or psoriasis may also be attributed to elevated levels of circulating pro-inflammatory cytokines seen in people with inflammatory skin diseases.[29–31] These cytokines may be further amplified in individuals with more severe skin disease, with evidence suggesting a link between atopic eczema or psoriasis severity, and increasing levels of inflammatory markers such as IL-8.[173,174] Both depression and anxiety have been associated with increased inflammatory response of the immune system,[175] while clinical trials of biologics (e.g., dupilumab, infliximab) that target inflammatory cytokines in those with atopic eczema or psoriasis have found that these drugs may also be associated with a reduction in symptoms of depression and anxiety.[176,177]

2.4.2.4 Comorbidities

Comorbidities may also be involved in the associations between atopic eczema or psoriasis and depression or anxiety. Atopic eczema is associated with an increased risk of other allergic diseases (e.g., asthma, allergic rhinitis, and food allergies),[59–62] while approximately 30% of psoriasis patients develop psoriatic arthritis within their lifetime.[81] Both atopic eczema and psoriasis are also associated with several chronic conditions (e.g., diabetes, cardiovascular disease), that along with allergic comorbidities and psoriatic arthritis can lead to depression and anxiety in affected individuals.[115,178]

2.4.2.5 Genetics

There is also limited evidence of a shared familial and genetic link between atopic eczema and depression that may explain the increased risk.[179] However, evidence from a recent Mendelian randomisation study using data from UK Biobank – a large (n=500,000) population-based study that allows investigations into determinants of disease[180,181] – found no evidence of a direct causal effect of atopic eczema onset on the onset of depression or anxiety.[182] However, genetic, or causal effects of atopic eczema progression on the risk of mental health conditions have not been investigated, so they may be present.

2.4.3 The role of ethnicity

Ethnicity is a potentially important factor that has not been fully explored when investigating the associations between atopic eczema or psoriasis, and depression or anxiety. It is unknown whether the risk of depression or anxiety in people with atopic eczema or psoriasis varies by ethnicity. Previous longitudinal studies have either not investigated the role of ethnicity in the associations between atopic eczema or psoriasis and depression or anxiety,[9,25,147,149–151] or conducted sensitivity analyses.[148]

Evidence suggests that individuals from minority ethnic groups experience greater atopic eczema prevalence and incidence compared to individuals of white ethnicity.[183] On the other hand, psoriasis is more common in people of white ethnicity.[184] There is also evidence of ethnic variations in the prevalence of depression and anxiety. Data from the US suggests that African Americans, and people from a Hispanic background exhibit elevated rates of depression compared to those of white ethnicity,[185] while white Americans are more likely to be diagnosed with anxiety disorders than those from minority ethnic groups.[186] Within UK primary care, the prevalence of depression has been shown to be higher in minority ethnic groups as well as in migrant populations.[187]

There are several potential mechanisms by which ethnicity may affect the association between atopic eczema or psoriasis and depression or anxiety. Firstly, skin colour varies between ethnic groups, and there are important nuances in the

visual appearance of atopic eczema and psoriasis in skin of colour. Erythema may be missed in people with darker skin,[183,184] suggesting that skin disease scoring systems such as the Eczema Area and Severity Index and the Static Physician's Global Assessment may underestimate severity in darker skin types. This hypothesis is supported by existing research that reports higher atopic eczema and psoriasis severity in minority ethnic groups.[188,189] Underestimation of atopic eczema severity may lead to less aggressive treatment or diagnosis at a later stage when disease is more severe in people with darker skin. Undertreatment of atopic eczema or psoriasis may be associated with an increased risk of depression or anxiety. Additionally individuals with darker skin are at increased risk of developing post-inflammatory dyspigmentation following atopic eczema or psoriasis diagnosis.[183,184] Dyspigmentation is more noticeable in darker skin due to increased contrast, and this may be distressing for affected individuals, further exacerbating feelings of discomfort and stigma, contributing to the increased risk of depression and anxiety.

Secondly, skin diseases are associated with various beliefs and taboos in different cultures that can have a profound effect on the psychological needs of those affected. Although large, quantitative studies are scarce, one qualitative study on the lived experience of adults with atopic eczema in the UK found that individuals from minority ethnic groups perceived a lack of education and understanding about atopic eczema within their communities, with some participants reporting that individuals within their community viewed their condition as contagious.[190] One female participant of Pakistani British ethnicity described how as a result of her husband and his family not being accepting of her eczema, she had to resort to divorce.[190] A study on the lived experience of psoriasis patients in Iran reported that affected individuals experienced a lack of social support, inappropriate labelling of being contagious, rejection and isolation because of their psoriasis.[191] Differences in the perception of atopic eczema and psoriasis, feelings of stigmatisation, and lack of support within communities can cause distress and may contribute to an increased risk of depression and anxiety.

Finally, research has shown that individuals from Black, Asian and other minority ethnic groups are less likely to adhere to therapy,[192] seek help for various medical

conditions (sometimes due to lack of trust in the healthcare system),[193,194] and are more likely to experience barriers to accessing health services (due to language, cultural differences) compared to those of white ethnicity.[195] Additionally, in England, minority ethnic groups are disproportionately affected by socioeconomic deprivation, racism, and discrimination, all of which can reinforce health inequalities, and are also known to have a negative impact on mental health.[196] In individuals with atopic eczema or psoriasis from minority ethnic groups, all of these factors could contribute to an increased risk of depression or anxiety.

2.5 Atopic eczema/psoriasis and SMIs

2.5.1 Evidence of associations

Evidence regarding associations between atopic eczema or psoriasis and SMIs are limited,[16,21–24,197] however, they suggest that individuals with atopic eczema or psoriasis are more likely to have SMIs compared to those without atopic eczema or psoriasis.[16,21–24,197] Longitudinal evidence for associations between atopic eczema or psoriasis are particularly scarce, with only a few studies aiming to address temporal associations.[25–28] A cohort study conducted using data from the Taiwan National Health Insurance Program of over 5000 adolescents with atopic diseases and over 44,000 controls, reported that individuals with atopic diseases had over twice the risk of bipolar disorder compared to controls (HR=2.51, 95% CI=1.71,3.67).[25] A larger study (n=186,588) using the same data and in the same study population found that the risk of psychiatric disorders was 65% higher in those with atopic diseases than those without (HR=1.66, 95% CI=1.60,1.72).[26] A cohort study conducted using US health insurance data (n=44,424) reported that after controlling for patient characteristics (sex, region, comorbidity profile), there was no evidence of an association between psoriasis and bipolar disorder (HR=1.55, 95% CI=1.00,2.42).[27] Another historical cohort study in Denmark (n=39,076) of the association between autoimmune disease (including psoriasis) and schizophrenia reported that prior autoimmune disease increased the risk of schizophrenia by 29% (IRR=1.29; 95% CI=1.18,1.41).[28] In all of the cohort studies, the skin disease preceded the diagnosis of SMI.

However, these longitudinal studies have important limitations. Firstly, all the cohort studies were either restricted to children/adolescent populations[25–27] or included both adults and children in the cohorts.[28] This is a limitation as there are known differences in psychiatric diagnostic practices between adults and children, so any associations identified may not be directly applicable to adult populations. The Taiwanese cohort studies also investigated the association between atopic disorders overall and SMI,[25,26] so there are no estimates for the relationship between atopic eczema and SMI specifically. Similarly, the cohort study from Denmark investigated associations between autoimmune diseases in general and schizophrenia, so no estimates of the relationship between psoriasis and schizophrenia could be estimated.[28] The study population of the US study that used data from an administrative health insurance database may not be representative of people with psoriasis as people with health insurance in the US may be systematically different to people without.[27] Additional limitations of the longitudinal cohort studies include: (1) investigating specific SMIs such as schizophrenia, bipolar disorder, or psychoses, rather than SMI altogether which in some cases limited the statistical power, (2) smaller study populations, and (3) an inability to explore reasons for associations identified between atopic disorders or psoriasis and SMI.

The limitations of these longitudinal studies therefore suggest that the temporality of associations between atopic eczema or psoriasis and SMI in adults are unclear. Temporal associations between atopic eczema or psoriasis and SMI in adults could be a significant public health concern as both atopic eczema and psoriasis are common, and high morbidity and mortality are associated with SMI.

2.5.2 Potential explanations for associations

Although limited, the evidence from cross-sectional, case-control, and longitudinal studies suggest that there are associations between atopic eczema or psoriasis and SMIs. However, the factors associated with SMIs among people with atopic eczema or psoriasis are unclear. Potential explanations for the relationships between atopic eczema or psoriasis and SMIs are therefore not well understood, however, they are likely to be complex and include demographic factors (age, sex, deprivation,

ethnicity), lifestyle factors (body mass index, smoking, alcohol use, substance misuse), skin disease related factors (itch and sleep disturbance in atopic eczema, inflammation), or genetics. Further details on the variables potentially involved in the associations between atopic eczema or psoriasis and SMIs are described in **Chapter 6**.

2.5.2.1 Demographic factors

The prevalence of atopic eczema has been shown to vary by age, sex, ethnicity, and socioeconomic status with younger individuals,[41] women,[152,153] those from Black and minority ethnic groups,[183] and individuals of higher socioeconomic status more likely to have atopic eczema.[35] On the other hand, psoriasis is more common in people aged 35 and under, [2] people of white ethnicity, low socioeconomic status,[155] and evidence of psoriasis prevalence varying by sex is conflicting.[2,154] SMI prevalence also varies by age, sex, socioeconomic status, and ethnicity. In England, prevalence of SMI overall is highest in males,[7] individuals from Black and South Asian minority ethnic groups,[138] among people aged 35-74 compared to those aged 15-34, and among those living in the most deprived areas.[7]

2.5.2.2 Lifestyle factors

Lifestyle factors may also be involved in associations between atopic eczema or psoriasis and SMI. Research shows that individuals with atopic eczema or psoriasis are more likely to have a high BMI,[75,157,158] consume more alcohol,[74,159,160] and are more likely to smoke than people without atopic eczema or psoriasis.[74,161] A high BMI,[198] heavy drinking,[199] and daily smoking have also been identified as risk factors for SMI.[200] Alcohol withdrawal after dependence has also been reported to induce hallucinations,[201] a symptom that is characteristic of psychosis. Evidence from cross-sectional studies suggest that people with atopic eczema or psoriasis are more likely to misuse substances such as cannabis (due to its anti-itch effect) when compared to the general population.[202,203] Heavy and regular use of cannabis can trigger schizophrenia or psychosis in people who are at risk of SMI.[204]

2.5.2.3 Skin-disease related factors

In individuals with atopic eczema, chronic and intense itching is a major symptom of the disease that can lead to sleep disturbance or deprivation.[41] High levels of sleep deprivation have been linked to SMI like symptoms such as hallucinations.[205] The use of high-dose oral glucocorticoids in people with moderate or severe atopic eczema to treat acute disease flares of eczema has been linked psychiatric side effects including mania and psychosis,[1,29,171] however, their effect is temporary.[171] the associations between atopic eczema or psoriasis and SMIs may be explained in part by the inflammatory process itself. Both atopic eczema and psoriasis are characterised by elevated levels of circulating pro-inflammatory cytokines.[29–31] Inflammatory biomarkers seen in people with atopic eczema or psoriasis have also been identified in people with SMIs such as schizophrenia or bipolar disorder.[206]

2.5.2.4 Genetics

There is limited evidence of a shared genetic aetiology from genome wide association studies between psoriasis and schizophrenia that may involve immune signalling pathways.[207]

2.6 Motivation for thesis

There are gaps in the literature regarding associations between atopic eczema or psoriasis and depression, anxiety, or SMI. This thesis aims to fill the identified evidence gaps by investigating associations between atopic eczema or psoriasis and depression, anxiety, and SMI.

Evidence gap 1: Factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis

Firstly, although there is substantial evidence in the literature to suggest associations between atopic eczema or psoriasis and depression or anxiety, and limited evidence suggesting associations between atopic eczema or psoriasis and SMIs, factors associated with mental health conditions among adults with atopic eczema or psoriasis are unclear. Individual studies may have explored the factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis, but

to my knowledge, a systematic review of the literature has not been conducted. Therefore, the first objective of this thesis was to systematically review all available evidence on factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis. Identifying factors associated with depression, anxiety, and SMI among individuals with atopic eczema or psoriasis provides the opportunity to potentially identify high-risk groups that may benefit from mental health promotion and prevention strategies and identify modifiable factors that could be targeted to reduce the risk of mental health conditions. Identifying factors associated with depression, anxiety, and SMI among individuals with atopic eczema or psoriasis may also have methodological implications, as the factors identified can be adjusted for in regression analysis to estimate direct and indirect effects of atopic eczema and psoriasis exposure on mental health conditions.

Evidence gap 2: Longitudinal associations between atopic eczema or psoriasis and SMIs

There is limited longitudinal evidence of associations between atopic eczema or psoriasis and SMIs. The few existing longitudinal studies have important limitations, making the temporal associations between atopic eczema or psoriasis and SMI unclear. Therefore, the second objective of this thesis was to investigate longitudinal associations between atopic eczema or psoriasis and incident SMI among adults. Understanding the temporal relationship between atopic eczema or psoriasis and SMI has important clinical implications. Atopic eczema and psoriasis are common, and SMIs are associated with substantial morbidity and mortality. If individuals with atopic eczema are at increased risk of SMI, this could suggest an important population impact. Establishing temporal associations will also inform mental health promotion strategies and highlight whether individuals with atopic eczema or psoriasis may benefit from increased monitoring.

Evidence gap 3: Associations between atopic eczema and depression or anxiety in white and minority ethnic groups

Existing longitudinal research has also not explored the role of ethnicity in associations between atopic eczema or psoriasis, and depression or anxiety. Previous longitudinal studies have either not investigated the role of ethnicity or only

considered ethnicity in sensitivity analyses. It is therefore unknown whether the risk of depression or anxiety in people with atopic eczema or psoriasis varies by ethnic groups. Differences in the prevalence of mental health conditions in people of different ethnic groups, variations in the visual appearance of atopic eczema or psoriasis, cultural taboos about skin disease, and disproportionate effects of socioeconomic deprivation, discrimination, and health inequalities by ethnic group may contribute to a difference in risk. Therefore, the final objective of this thesis was to investigate whether associations between atopic eczema and incident depression or anxiety differs between adults from white and minority ethnic groups. It is important to identify whether associations between atopic eczema and depression or anxiety differ between ethnic groups as individuals from minority ethnic groups already experience health inequalities, and if those with atopic eczema or psoriasis are found to be at increased risk of depression or anxiety, then these groups may benefit from targeted mental health promotion and prevention strategies. Unfortunately, I was unable to investigate whether associations between psoriasis and depression or anxiety differed by ethnic groups due to limited statistical power.

2.7 Summary

- Atopic eczema and psoriasis are two of the most common inflammatory skin diseases that account for a substantial proportion of the skin disease burden worldwide. While they differ in aetiology, disease distribution and clinical features, they are both associated with substantial morbidity and impaired quality of life.
- Mental health conditions are the second leading cause of years lived with disability worldwide, and the mental health conditions under investigation in this thesis (depression, anxiety, and SMI) account for a considerable amount of this burden.
- This thesis will investigate associations between atopic eczema or psoriasis and depression, anxiety, and SMI.

- In the following chapter, I will describe the first study conducted as part of this thesis – a systematic review of all available evidence on factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis.

3 Factors associated with depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis: a systematic review and meta-analysis

3.1 Introduction

In the previous chapter, I presented a detailed discussion of the background literature to justify the aims and objectives of this thesis and present the previous work that this thesis builds upon. In this chapter, I will describe the systematic review I conducted to directly address the first objective of this thesis (to systematically review factors associated with depression, anxiety, and severe mental illness (SMI) among adults with atopic eczema or psoriasis). The results of this review informed the identification of key covariates for use in the population-based cohort studies included in this thesis. This chapter is comprised of two papers (the protocol for the review and the systematic review itself).

3.2 Systematic review protocol

I developed a detailed protocol, which was registered in the International Prospective Register of Systematic Reviews (PROSPERO), prior to carrying out the systematic review. The protocol was later published in an open access, peer reviewed scientific journal (BMJ Open) and is provided in the following pages. The supplementary material referred to in the article is provided in **Appendix 1** of this thesis.

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Surname/Family Name	Adesanya		
Thesis Title	Depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis		
Primary Supervisor	Dr Kathryn Mansfield		

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?	BMJ Open		
When was the work published?	December 28th 2020		
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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, along with my supervisors Kathryn Mansfield and Sinéad Langan had the original idea for the review. All authors were involved in the design of the study. I wrote the first draft of the protocol and all authors contributed to further drafts and approved the final protocol.

SECTION E

Student Signature	E.Adesanya
Date	8th December 2022

Supervisor Signature	K. Mansfield
Date	12th December 2022

Open access Protocol

BMJ Open

Risk factors for mental illness in adults with atopic eczema or psoriasis: protocol for a systematic review

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ABSTRACT

Introduction Evidence indicates that people with the common inflammatory skin diseases atopic eczema or psoriasis are at increased risk of mental illness. However, the reasons for the relationship between skin disease and common mental disorders (ie, depression and anxiety) or severe mental illnesses (ie, schizophrenia, bipolar disorder and other psychoses) are unclear. Therefore, we aim to synthesise the available evidence regarding the risk factors for mental illness in adults with atopic eczema or psoriasis.

Methods and analysis We will conduct a systematic review of randomised controlled trials, cohort, case–control and cross-sectional studies. We will search the following databases from inception to March 2020: Medline, Embase, Global Health, Scopus, the Cochrane Library, Web of Science, Base, PsycInfo, the Global Resource of Eczema Trials, and the grey literature databases Open Grey, PsycExtra and the New York Academy of Medicine Grey Literature Report. We will also search the bibliographies of eligible studies and relevant systematic reviews to identify additional relevant studies. Citation searching of large summary papers will be used to further identify relevant publications. Two reviewers will initially review study titles and abstracts for eligibility, followed by full text screening. We will extract data using a standardised data extraction form. We will assess the risk of bias of included studies using the Quality in Prognosis Studies tool. We will synthesise data narratively, and if studies are sufficiently homogenous, we will consider a meta-analysis. We will assess the quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation framework.

Ethics and dissemination Ethical approval is not required for a systematic review. Results of the review will be published in a peer-reviewed journal and disseminated through conferences.

PROSPERO registration number CRD42020163941.

Strengths and limitations of this study

- This protocol promotes transparent review methods, enables comparison of our final review to our initial plans, minimises risk of bias, and reduces the chance of unplanned duplication.
- Our systematic review will be the first to critically evaluate studies of the risk factors for mental illness in adults with atopic eczema or psoriasis.
- We will ensure our review is comprehensive by searching multiple scientific literature databases (including specific grey literature databases), including a range of study types and not limiting to English-language studies.
- However, the studies we include may use heterogenous methods and be of variable quality, which may limit our ability to calculate pooled estimates from meta-analysis and may limit our conclusions.

INTRODUCTION

Psoriasis and atopic eczema are inflammatory skin conditions associated with considerable morbidity and reduced quality of life for both sufferers and their families. Atopic eczema and psoriasis are common in the UK population—psoriasis affects between 1.3% and 2.6% of adults,[1] and the prevalence of atopic eczema in adults is approximately 2.5%.[2] Similarly, mental illness is common. According to the 2017 Global Burden of Disease Study, mental illness is one of the leading causes of years lived with disability worldwide.[3] In England, 17% of adults have common mental disorders (CMD- including depression or anxiety).[4] Severe mental illness (SMI—including schizophrenia, bipolar affective disorder and other psychoses) affects nearly 1% of the UK population.[4] Individuals with SMI experience substantial health inequalities; they are at increased risk of serious health problems (eg, diabetes mellitus and cardiovascular disease) and die up to 20 years earlier than the general population.[4 5]

Associations between atopic eczema or psoriasis and mental illness are well established. Evidence suggests that people with atopic eczema or psoriasis are at increased risk of mental illness.[6–14] The temporal sequence of the associations between skin disease and mental illness is also well recognised, with evidence suggesting that atopic eczema or

psoriasis precedes mental illness diagnosis.[10 12] However, the reasons for the relationship between inflammatory skin disease and mental illness are unclear. To the best of our knowledge, there are no existing systematic reviews addressing risk factors for the relationship between atopic eczema or psoriasis and mental illness in adults. Previous systematic reviews have aimed to establish summary measure of effects for the association between either atopic eczema or psoriasis and specific mental illnesses (eg, depression); the majority have focused on the relationship between atopic eczema or psoriasis and CMDs.[15–19] One systematic review has investigated the risk factors that mediate the association between atopic eczema and mental illness in children and adolescents only. The majority of studies in this review of children were conducted in European countries or territories. Meta-analysis of the 35 studies included in the review found that although demographic factors such as age, sex and socioeconomic status did not moderate the risk of developing mental illness in children with atopic eczema, children from predominantly minority ethnic backgrounds were more likely to be diagnosed with a mental illness in comparison with their Caucasian counterparts.[20]

The primary aim of this systematic review will be to explore, synthesise and critically evaluate the strength and quality of all available evidence on the risk factors associated with the development of mental illness (CMDs and SMIs) in adults with atopic eczema or psoriasis. If possible, we will also compare and contrast the risk factors associated with the development of mental illness in adults with atopic eczema to the risk factors in psoriasis. In the context of this systematic review, we will use the term 'risk factor' to refer to variables associated with an increased risk of mental illness in individuals with atopic eczema or psoriasis.

METHODS

This study protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[21]

Patient and public involvement

Patients and/or the public were not involved in this systematic review protocol.

Eligibility criteria

We will screen studies for potential inclusion in our review according to the eligibility criteria presented in table 1.

Information sources

We will search the following databases for relevant articles from inception to March 2020: Medline, Embase, Global Health, Scopus, the Cochrane Library (which includes Cochrane Reviews, Cochrane Protocols, Trials, Editorials, Special Collections, Clinical Answers and Other Reviews),

Table 1 Eligibility criteria

	Inclusion criteria	Exclusion criteria
Study design and characteristics	All RCTs, cohort, case–control and cross-sectional studies where an effect estimate (ie, ratio or difference measures) of the risk factors for mental illness in adults with atopic eczema or psoriasis is reported. Studies in any language and from any geographical setting will be considered.	Ecological studies, case series studies, case reports and systematic reviews (however, relevant summary reviews will be flagged and reference lists searched for eligible studies). Studies where correlates (without a measure of effect) have been calculated to estimate the association between a risk factor and mental illness in adults with atopic eczema or psoriasis. Conference proceedings, letters, editorials, opinion articles and reports (however, relevant conference proceedings/ letters will be flagged to try and identify full text).
Participants	Human participants aged 18 and over with atopic eczema or psoriasis. Studies including both adults and children where data for adults is reported separately.	Studies conducted in children or adolescents only. Animal or cell studies.
Exposure	Risk factors for mental illness (CMD or SMI).	
Comparators	Studies must compare adults with atopic eczema or psoriasis with the risk factors of interest with adults with atopic eczema or psoriasis without the risk factors of interest.	
Outcomes	Study outcomes must be a CMD or SMI, either clinically diagnosed or self-reported with or without validated tools.	

CMD, common mental disorder; RCT, randomised controlled trial; SMI, severe mental illness.

Table 2 Keywords included in the search strategy for all databases

Search term	Keywords
Risk factor terms	risk OR risk factor* OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR caus* OR path*
Atopic eczema or psoriasis terms	atopic dermatitis OR eczema OR atopy OR psoriasis OR psoria* OR (pustulo* AND palmopl* OR palmari* OR palmar)
Mental illness terms	mental health OR mental* ill* OR mental disorder* OR psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease* OR psychological* ill* OR psychological* disorder* OR psychological* disease* OR affective* OR anxi* OR depress* OR phobi* OR panic OR bipolar* OR schizophrenia OR schizo* OR delusion* OR psychotic* OR psychos#s OR psychological* distress

Web of Science (which includes the Science Citation Index Expanded, the Social Sciences Citation Index, the Arts & Humanities Citation Index, the Conference Proceedings Citation Index-Science, the Conference Proceedings Citation Index—Social Science & Humanities and the Emerging Sources Citation Index), Base, PsycInfo and the Global Resource of Eczema Trials. Both Medline and Embase capture a large amount of published literature—Medline indexes more than 5200 journals, and Embase indexes almost 8500 journals[22 23]—while the other databases are likely to contain appropriate papers for this review. To ensure that all relevant literature is included in the review, we will also search for grey literature in Open Grey, the New York Academy of Medicine Grey Literature Report and PsycExtra. Finally, we will search the five largest clinical trial registries—ClinicalTrials.gov, the EU Clinical Trials Register, the Japan Primary Registries Network, International standard Randomised Controlled Trial Number (ISRCTN) and the Australian New Zealand Clinical Trials Registry—to identify relevant trials.[24]

Search strategy

We will search medical subject headings and free text (in titles, abstracts and keywords) for synonyms relating to three key concepts: (1) 'risk factors', (2) 'atopic eczema or psoriasis' and (3) 'mental illness' (table 2). We will combine the three key concepts in the search strategy using the Boolean logic operator 'AND'. We have developed and piloted an initial search strategy in the Medline database that has been peer reviewed by a librarian (online supplemental table 1), and we will adapt it appropriately for other databases. We will also manually scrutinise the reference lists and bibliographies of relevant systematic reviews to identify additional papers for inclusion. Finally, we will use citation searching on large summary papers to identify any further relevant publications.

Study records

Data management

A single reviewer (EA) will import all results returned from the electronic database searches into the reference management tool EndNote V.X9 (Clarivate Analytics, V.9.2/2019). After identifying and removing duplicate records, we will import the search results into Rayyan (a web application for systematic reviews),[25] where the integrated deduplication function will be used to identify any previously missed duplicates.

Study selection

Two reviewers (EA and YS) will independently screen the titles and abstracts of the search results for potentially relevant studies. Both reviewers will then screen the full text of all potentially relevant studies for inclusion using the eligibility criteria. Any disagreements during this process will be discussed by EA and YS, with consultation from a third reviewer (KM) if necessary. We will record and report in a flowchart the reasons for study rejection following full text screening.

Data extraction

We will develop a standardised data extraction form (to extract information described below), which will be piloted by two reviewers (EA and YS) who will extract data from the larger of either 10% or five of the eligible studies. Any disagreements between the two reviewers will be discussed, with a third reviewer (KM) available to arbitrate if required, and changes made to the data extraction form if necessary. A single reviewer (EA) will complete the extraction of data for the remaining studies. We will use a modified version of the Population, Intervention, Comparator(s), Outcome(s) and Study Design (PICOS) framework to summarise data for extraction.[26] However, due to the inclusion of observational studies in our review, we will replace the term 'intervention' with 'exposure', and 'study design' will be replaced by 'study characteristics'. We will extract information for each component of the PICOS framework, in addition to study results for each study included in the review (table 3).

Exposures

Our exposures of interest will be risk factors for mental illness in people with atopic eczema or psoriasis. We will consider any variable that authors of included papers have conducted analyses to assess whether they are associated with mental illness in people with atopic eczema or psoriasis as potential risk factors. These may include sociodemographic factors (eg, sex, ethnicity and deprivation), lifestyle factors (eg, level of physical activity, diet and alcohol consumption) or environmental factors.

Outcomes

Our primary outcome of interest will be mental illness in individuals with atopic eczema or psoriasis. Mental

Table 3 Items that will be collected using the data extraction form

Parameter	Information for extraction
Population	Participant inclusion and exclusion criteria Demographic characteristics (age, sex and ethnicity distributions) Sample size
Exposure	Definition and identification of individuals with the risk factor(s) of interest Number of individuals with the risk factor(s) of interest
Comparator	Definition and identification of individuals without the risk factor(s) of interest Number of individuals without the risk factor(s) of interest
Outcome	Definition and identification of mental illness outcome(s) Number of individuals in exposed and comparison group with the outcome
Study characteristics	Bibliographic information (authors, journal, publication year, volume, page numbers and doi) Study design Study setting Study sampling frame Methods of participant recruitment Aims and objectives
Study results	Unadjusted and fully adjusted effect estimates for the association between risk factors and mental illness Confounders measured and adjusted for analysis

illness will be grouped into two broad categories (CMD or SMI); unless there are sufficient studies looking at specific mental illnesses (eg, depression), then we will also explore by specific mental illness subgroup. We will include studies regardless of how they capture mental illness outcomes (ie, we will include clinical diagnoses or self-reported mental illness established with or without validated tools).

Risk of bias assessment for individual studies

Two reviewers (EA and YS) will independently assess the risk of bias for the larger of 10%, or five, of the included studies. Any disagreements will be discussed so that a consensus can be reached. A third reviewer (KM) will be available to arbitrate if required. A single reviewer (EA) will then assess risk of bias for the remaining studies. We will use the Quality in Prognosis Studies (QUIPS) tool to assess the risk of bias of included studies.[27] QUIPS assesses and evaluates the risk of bias in six different domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding and (6) statistical analysis and reporting.[27] For each study included, we will assess and categorise the risk of bias for each domain into one of three qualitative categories (low, moderate or high risk of bias) using the prompting items provided within the tool. We will produce separate risk of bias tables for observational studies and randomised controlled trials (RCTs) along with justifications for the decisions made.

Data synthesis and meta-bias(es)

We will synthesise our results narratively. We will describe and tabulate the results of the studies included in the review according to the study design (RCT, cohort, case–control or cross-sectional studies), skin disease type (either atopic eczema or psoriasis), risk factor under investigation and outcome measure (either CMD or SMI). We will describe and tabulate the results of the RCTs separately from the results of other studies included in the review. If possible, we will also identify risk factors that are common and distinct between atopic eczema and psoriasis. If at least two studies are sufficiently homogeneous (in terms of study design, study population, risk factor assessed and outcome), we will consider a meta-analysis to pool the effect estimates. We will use the I^2 statistic to quantify levels of statistical heterogeneity (I^2 of 0%–40% may indicate negligible heterogeneity, 30%–60% may indicate moderate heterogeneity, 50%–90% may indicate substantial heterogeneity and 75%–100% may indicate considerable heterogeneity).[24] If possible, we will also consider meta-regression to investigate whether study characteristics (eg, study design, risk of bias, study outcome and skin disease) or the demographics of the study population (eg, age and sex) are associated with the magnitude of effects and can explain any observed statistical heterogeneity. We will assess the risk of publication bias for the studies included in the review using funnel plots. We will use STATA V.16.0 to perform all statistical analysis.

Confidence in cumulative evidence

We will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to evaluate and summarise the quality of cumulative evidence for each broad outcome (CMD or SMI) and risk factor pair.[28] If more than one study are identified for a specific subtype of a CMD or SMI (such as depression or schizophrenia) and a specific risk factor, we will use GRADE to summarise the quality of evidence for that subtype. We will categorise the strength of evidence into four qualitative categories: 'high', 'moderate', 'low' or 'very low'. The quality of evidence for included studies will be upgraded if there is a large magnitude of effect or a dose-response gradient.[28] The quality of evidence will be rated down if there is a high risk of bias, imprecision in the study estimate, a high probability of publication bias or inconsistent results.[28] We will present the judgements made during this process in a 'Summary of Findings' table.

Ethics and dissemination

As this study is a systematic review that does not involve human participation, we do not require ethical approval. We will disseminate the results of this review by publishing

in an open access, peer-reviewed journal and presenting at conferences. We will document any important amendments and protocol deviations, along with justifications, and publish them as an appendix in the final review.

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3.3 Systematic review article

I reported the results of the systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The manuscript has published in a peer reviewed scientific journal (British Journal of Dermatology) and is provided on the following pages. The supplementary material referred to in the systematic review article is provided in **Appendix 2** of this thesis.

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Student ID Number	1800708	**Title**	Ms
First Name(s)	Elizabeth Ilerioluwa		
Surname/Family Name	Adesanya		
Thesis Title	Depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis		
Primary Supervisor	Dr Kathryn Mansfield		

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

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Where is the work intended to be published?	British Journal of Dermatology
Please list the paper's authors in the intended authorship order:	Elizabeth I Adesanya, Julian Matthewman, Yochai Schonmann, Joseph F Hayes, Alasdair Henderson, Rohini Mathur, Amy R Mulick, Catherine H Smith, Sinéad M Langan, Kathryn E Mansfield
Stage of publication	**In press**

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, along with my supervisors Kathryn Mansfield and Sinéad Langan had the original idea for the review. All authors were involved in the design of the study. I wrote the first draft of the protocol and all authors contributed to further drafts and approved the final protocol. I searched the electronic databases. I and two other reviewers (Yochai Schonmann Julian Matthewman) screened the titles and abstracts. I extracted the data for all studies included in the review, and Julian Matthewman extracted the data for six studies. I wrote the first draft of the manuscript. All authors contributed to further drafts and approved the final manuscript.

SECTION E

Student Signature	E.Adesanya
Date	8th December 2022

Supervisor Signature	K. Mansfield
Date	12th December 2022

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Systematic Review

Factors associated with depression, anxiety and severe mental illness among adults with atopic eczema or psoriasis: a systematic review and meta-analysis

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Abstract

Background Evidence suggests an association between atopic eczema (AE) or psoriasis and mental illness; however, the factors associated with mental illness are unclear.

Objectives To synthesize and evaluate all available evidence on factors associated with depression, anxiety and severe mental illness (SMI) among adults with AE or psoriasis.

Methods We searched electronic databases, grey literature databases and clinical trial registries from inception to February 2022 for studies of adults with AE or psoriasis. Eligible studies included randomized controlled trials (RCTs), cohort, cross-sectional or case–control studies where effect estimates of factors associated with depression, anxiety or SMI were reported. We did not apply language or geographical restrictions. We assessed risk of bias using the Quality in Prognosis Studies tool. We synthesized results narratively, and if at least two studies were sufficiently homogeneous, we pooled effect estimates in a random effects meta-analysis.

Results We included 21 studies (11 observational, 10 RCTs). No observational studies in AE fulfilled our eligibility criteria. Observational studies in people with psoriasis mostly investigated factors associated with depression or anxiety – one cross-sectional study investigated factors associated with schizophrenia. Pooled effect estimates suggest that female sex and psoriatic arthritis were associated with depression [female sex: odds ratio (OR) 1.62, 95% confidence interval (CI) 1.09–2.40, 95% prediction intervals (PIs) 0.62–4.23, $I^2 = 24.90\%$, $\tau^2 = 0.05$; psoriatic arthritis: OR 2.26, 95% CI 1.56–3.25, 95% PI 0.21–24.23, $I^2 = 0.00\%$, $\tau^2 = 0.00$] and anxiety (female sex: OR 2.59, 95% CI 1.32–5.07, 95% PI 0.00–3956.27, $I^2 = 61.90\%$, $\tau^2 = 0.22$; psoriatic arthritis: OR 1.98, 95% CI 1.33–2.94, $I^2 = 0.00\%$, $\tau^2 = 0.00$). Moderate/severe psoriasis was associated with anxiety (OR 1.14, 95% CI 1.05–1.25, I^2 0.00%, $\tau^2 = 0.00$), but not depression. Evidence from RCTs suggested that adults with AE or psoriasis given placebo had higher depression and anxiety scores compared with comparators given targeted treatment (e.g. biologic agents).

Conclusions Our review highlights limited existing research on factors associated with depression, anxiety and SMI in adults with AE or psoriasis. Observational evidence on factors associated with depression or anxiety in people with psoriasis was conflicting or from single studies, but some identified factors were consistent with those in the general population. Evidence on factors associated with SMIs in people with AE or psoriasis was particularly limited. Evidence from RCTs suggested that AE and psoriasis treated with placebo was associated with higher depression and anxiety scores compared with skin disease treated with targeted therapy; however, follow-up was limited. Therefore, long-term effects on mental health are unclear.

What is already known about this topic?

- Previous studies have found evidence of an association between atopic eczema (AE) or psoriasis, and mental health conditions (i.e. depression, anxiety and severe mental illness).
- However, the factors associated with depression, anxiety or severe mental illness among individuals with AE or psoriasis are unclear.

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What does this study add?

- Pooled effect estimates from observational studies suggest that female sex and psoriatic arthritis are associated with increased depression and anxiety, while moderate/severe psoriasis is associated with increased anxiety.
- Trial evidence suggests that AE or psoriasis treated with placebo is associated with increased depression and anxiety compared with skin disease treated with targeted therapy.

Atopic eczema (AE) and psoriasis are inflammatory skin diseases with a lifetime prevalence of 1–3% and up to 10% respectively in adults.[1,2] Mental illness is a leading cause of years lived with disability worldwide.[3]

Evidence from cross-sectional studies and a systematic review suggest that AE and psoriasis are associated with depression, anxiety and severe mental illnesses (SMI), such as schizophrenia, bipolar disorder and other psychoses.[4–8] Longitudinal evidence indicates that AE and psoriasis precede mental illness diagnoses, and are associated with increased newly diagnosed anxiety, depression and bipolar disorder.[9–11]

While associations between AE, psoriasis and mental illness are acknowledged, factors associated with depression, anxiety and SMI in people with AE or psoriasis are unclear. There are plausible mechanisms to explain the association. For example, evidence suggests that individuals with AE or psoriasis engage in unhealthy lifestyle behaviours (e.g. poor diet, smoking or harmful alcohol intake),[12–17] which are associated with increased depression or anxiety risk.[18,19] Disrupted sleep – experienced by individuals with AE as a result of chronic itch – has been recognized as a risk factor for depression.[20] It is possible that inflammation in AE or psoriasis may influence mental illness through elevated proinflammatory cytokines or immune reactivity contributing to depressive symptoms or SMI.[21–24]

Coexisting AE or psoriasis and mental illness may negatively affect skin disease. For example, depression may reduce skin treatment adherence,[25] potentially reducing benefits leading to worsening skin condition, with subsequent potential for mental illness exacerbation. Consequently, it is important to identify factors associated with mental illness among those with AE or psoriasis. This may lead to recognition of groups who would benefit from targeted mental health prevention strategies, or modifiable factors that may modify risk.

This systematic review aims to synthesize and evaluate all available evidence on factors associated with depression, anxiety and SMI among adults with AE or psoriasis.

Materials and methods

We registered this review with PROSPERO (CRD42020163941) and the review was conducted and reported following PRISMA guidelines.[26] A detailed protocol has been published elsewhere.[27]

Eligibility criteria

We included observational studies (cohort, case–control, cross-sectional studies) or randomized controlled trials (RCTs) in adults (age $\geq$ 18 years) with AE or psoriasis where effect estimates of factors associated with depression, anxiety or SMI were reported (Table 1). Language or geographical restrictions were not applied. We included RCTs that investigated AE or psoriasis treatment with biologic therapies to study skin disease treated using placebo – compared with skin disease treated using targeted therapy (i.e. biologic agents) – as a factor potentially associated with depression, anxiety or SMI. Depression and anxiety scores identified using validated questionnaires in included RCTs were considered outcomes, although scores may not correspond to a clinical diagnosis of depression or anxiety,[28] and changes in scores may not be clinically important.[29] As we were not investigating the effectiveness of interventions, we considered RCTs as randomized cohort studies for analyses and when assessing risk of bias.

Search strategy

We searched eight electronic databases (MEDLINE, Embase, Global Health, Scopus, Cochrane Library, Web of Science, Base, PsycInfo), three grey literature databases (PsycExtra, Open Grey, New York Academy of Medicine Grey Literature Report), five large clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register, Japan Primary Registries Network, Australian New Zealand Clinical Trials Registry, International Standard Randomised Controlled Trial Number Registry), and a specialist eczema trial registry [Global Resource of Eczema Trials (GREAT)] from inception to February 2022. Updates to the New York Academy of Medicine Grey Literature Report ceased in January 2017, while updates to GREAT ceased in September 2017. Our search strategy included terms relating to the following three key concepts: (i) 'association' terms; (ii) 'AE or psoriasis'; and (iii) 'mental illness'. We identified additional papers through citation searching large summary papers identified by our search, and manually searching references of included papers (Appendix S1; see Supporting Information).

Data extraction

Two reviewers (E.I.A. and Y.S. or E.I.A. and J.M.) independently screened titles and abstracts of all articles returned by the search. Full-text screening was conducted by two reviewers (E.I.A., J.M.) in accordance with eligibility criteria. Disagreements were discussed by reviewers (E.I.A. and Y.S. or E.I.A. and J.M.), with consultation from a third (K.E.M.) and fourth (S.M.L.) reviewer, if necessary. We developed two data extraction and risk of bias assessment forms (one for observational studies, another for RCTs) to extract information from each article included (Appendix S2; see Supporting Information). Two reviewers (E.I.A. and J.M.) piloted both forms by independently extracting data from a random selection of the larger of 10% or five eligible studies.

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Table 1 Systematic review eligibility criteria

Eligibility criteria	Rationale
Studies with adult participants (aged ≥ 18 years) with atopic eczema or psoriasis were eligible for inclusion. Studies including both adults and children where data for adults are reported separately were also eligible	Studies with participants aged < 18 years were excluded as there may be differences in the factors associated with mental illness in children compared with adults
Randomized controlled trials (RCTs), case–control, cohort, or cross-sectional studies	RCTs where the intervention was atopic eczema or psoriasis treatment were considered as randomized cohort studies and were included to investigate skin disease treated using placebo, as these included factors potentially associated with mental illness, compared with skin disease treated with targeted (i.e. biologic) therapy. We investigated this by comparing the change in mental illness from baseline measurements with postintervention measurements (between groups receiving the intervention with groups receiving no intervention) to examine the effect that treating skin disease with placebo had on mental illness in people with atopic eczema or psoriasis Other study types (ecological or case series studies, case reports, systematic reviews) and article types (letters, conference proceedings, editorials, opinion articles) were excluded as they were unlikely to report sufficient information to answer our research question. However, relevant summary reviews were flagged, and reference lists searched for eligible studies
Potential factors were any variable that was analysed for an association with the following outcomes: depression, anxiety or severe mental illness (i.e. schizophrenia, bipolar disorder or other psychoses) in people with atopic eczema or psoriasis, and an effect estimate (i.e. ratio or difference measures) was reported	Studies where effect estimates were not reported (i.e. studies where correlates were instead calculated) were not included, as correlations between variables simply show that there is a pattern in the data, while an effect estimate measures the strength of the association
Studies in any language and from any geographical setting were considered	To capture all eligible studies

This resulted in piloting the forms for six studies (three observational studies, three RCTs). Data from the remaining studies were extracted by a single reviewer (E.I.A.).

Risk of bias

We used the Quality in Prognosis Studies tool to assess risk of bias across the following six domains in the included studies: (i) study participation; (ii) study attrition; (iii) prognostic factor measurement; (iv) outcome measurement; (v) study confounding; and (vi) statistical analysis and reporting.[30] We assessed risk of bias as low, moderate, or high in each domain. We did not produce an overall risk of bias score for each study as summated scores are not recommended (owing to potentially inappropriately assigning equal weights to assessed domains).[30]

Data analysis

We synthesized our results narratively, describing results separately by skin disease (AE, psoriasis) and study type (observational study, RCT). If at least two studies were sufficiently homogeneous (in terms of study design, study population, factor assessed and outcome), we pooled effect estimates in a random effects meta-analysis using the DerSimonian and Laird method,[31] and assessed statistical heterogeneity using the I^2 and τ^2 statistics.[32] Prediction intervals (PIs) were used alongside confidence intervals (CIs) to illustrate the degree of heterogeneity in the forest plots of random effects meta-analysis by providing a 95% range for the possible associations between the factor and outcome.[33] We did not use funnel plots to assess publication bias as the number of studies included was below the recommended minimum of 10.[32] All analyses were conducted using STATA version 16 (StataCorp, College Station, TX, USA).

Results

Our search identified 17 539 articles. After deduplication and including articles from citation searching and reference lists, we screened 9053 titles and abstracts. We reviewed 40 full-text articles and included 21 (including one article in Mandarin, which was translated by a native speaker) (Figure 1, Appendix S3, Table S1; see Supporting Information). We included 11 observational studies in psoriasis (one cohort, 10 cross-sectional)[34–44] and 10 RCTs (five AE, five psoriasis) (Tables 2 and S2–S4; see Supporting Information).[45–54]

Risk of bias assessments

The percentage agreement for the risk of bias assessments conducted by two reviewers for six of the included studies was 91%. Of 11 observational studies included, one was at moderate risk of bias in one domain and low risk of bias in other domains,[41] and 10 studies[34–40,42–44] were at moderate or high risk of bias in 2 or more domains (Figure 2[55] and Table S5; see Supporting Information). All observational studies were judged to have at least moderate risk of bias owing to confounding. Bias as a result of study participation affected nine observational studies[34–37,39,40,42–44] owing to inadequately describing the sampling frame, source population, recruitment method, or characteristics of nonparticipants.

All five eczema trials and three psoriasis trials were considered to have a low risk of bias in all domains (Figure 2,[55] Table S5).[45–52] Two psoriasis trials had a moderate risk of bias in the statistical analysis and reporting domain,[53,54] and

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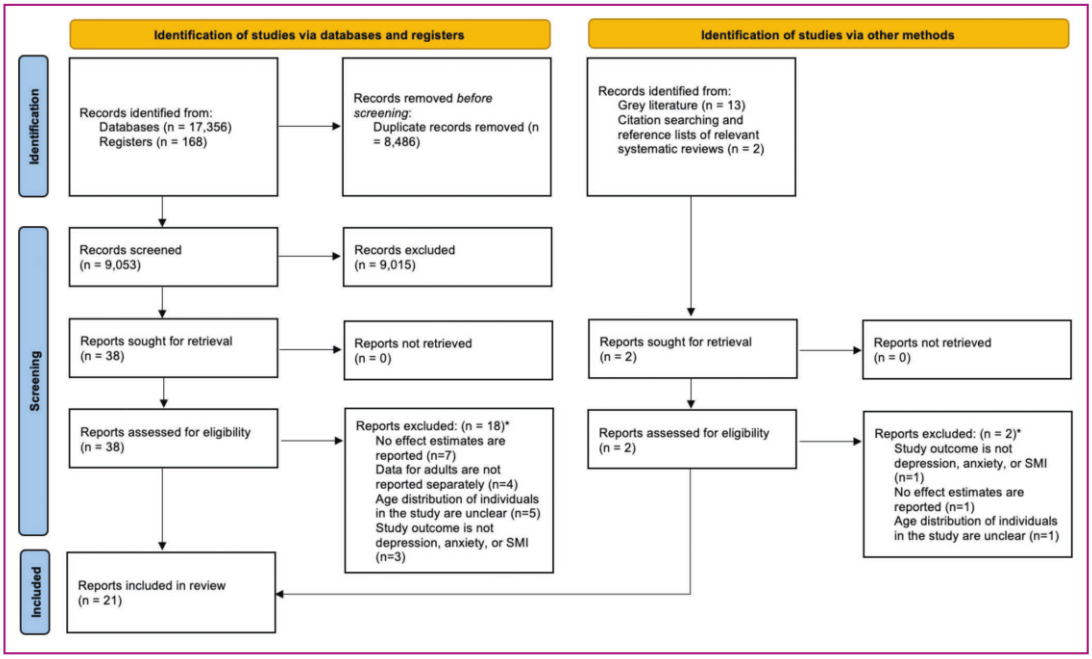

Figure 1 PRISMA flow diagram of the study selection.SMI, severe mental illness. *Some studies were excluded for more than one reason; the total number does not add up to number in brackets.

one psoriasis trial had a high risk of bias in the study attrition domain.[54]

Atopic eczema

We did not identify any eligible observational studies in AE. In the five RCTs included (Table S6; see Supporting Information), individuals with AE who were randomized to receive placebo had higher mean depression, anxiety, or combined anxiety and depression scores after 16 weeks than those receiving targeted treatment (dupilumab, abrocitinib).[45–49]

Psoriasis

All observational studies included were conducted in adults with psoriasis. We identified factors associated with depression (Table S7; see Supporting Information), anxiety (Table S8; see Supporting Information) and schizophrenia (Table S9; see Supporting Information). There were five included RCTs of psoriasis treatment (Table S10; see Supporting Information).[50–54]

Observational studies

Depression

Pooled effect estimates (Figure 3a) from two studies of moderate heterogeneity investigating age,[39,44] two studies of moderate heterogeneity investigating psoriasis severity,[39,40] and two studies of low heterogeneity investigating systemic therapy[35,44] found no evidence that age [odds ratio (OR) 1.00, 95% CI 0.97–1.02, $I^2 = 28.00\%$, $\tau^2 = 0.00$], moderate/severe psoriasis (OR 1.15, 95% CI 0.92–1.44, $I^2 = 26.70\%$, $\tau^2 = 0.01$), or systemic therapy (OR 0.62, 95% CI 0.30–1.26, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with depression.

However, pooled effect estimates from five eligible studies of moderate heterogeneity investigating sex[37,39,42–44] and three studies of low heterogeneity investigating psoriatic arthritis[35,36,44] reported that female sex (OR 1.62, 95% CI 1.09–2.40, 95% PI 0.62–4.23, $I^2 = 24.90\%$, $\tau^2 = 0.05$) and psoriatic arthritis (OR 2.26, 95% CI 1.56–3.25, 95% PI 0.21–24.23, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with increased depression, compared with male sex and no psoriatic arthritis, respectively.

Included studies conducted in people with psoriasis found no evidence of associations between depression and urban or rural living,[43] occupation,[43] instrumental social support (e.g. physical assistance),[42] motivational salience (i.e. attention to appearance),[42] facial or genital lesions,[42] psoriasis phenotype,[44] and comorbidities (bipolar disorder, cardiovascular disease, cerebrovascular disease, diabetes, ischaemic heart disease, schizophrenia).[35,38] Multiple studies in people with psoriasis reported conflicting results regarding associations between education,[37,38,43] ethnicity,[38,44] and age at psoriasis onset,[39,42] and depression (meta-analyses not possible owing to differences in definitions between the factors of interest and/or study design).

Evidence from single studies suggested increased associations with depression in people with psoriasis with high

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Table 2 Summary of studies included in the review

First author, publication year	Mental health condition			Study design	Study setting	Sample size	Factors investigated
	Depression	Anxiety	SMI				
Observational studies in psoriasis							
Bakar, 2021[34]	Yes	Yes	No	Cross-sectional study	Dermatology outpatient clinic	174	Lower limb lesions, dyslipidaemia, quality of life
Kwan, 2018[35]	Yes	Yes	No	Cross-sectional study	Dermatology outpatient clinic	102	Psoriasis severity, head involvement, use of systemic therapy, quality of life, diabetes, ischaemic heart disease, cerebrovascular disease, psoriatic arthropathy
Lada, 2022[36]	Yes	No	No	Cross-sectional study	Specialist psoriasis and psoriatic arthritis clinics	219	Comorbid psoriatic arthritis
Petraškienė, 2016[37]	Yes	Yes	No	Cross-sectional study	Inpatient and outpatient units of hospital dermatology department	385	Sex, age group, education
Strober, 2017[38]	Yes	No	No	Longitudinal cohort study	Data from PSOLAR registry	7490	Treatment with biologics or phototherapy, age, sex, ethnicity, years since psoriasis began, baseline PGA score, change in PGA score from baseline to depression, education, insurance, psoriatic arthritis, diabetes, schizophrenia, anxiety, bipolar disease, chronic obstructive pulmonary disease, CAD/MI/ACVD/stroke/TIA
Tian, 2019[39]	Yes	Yes	No	Cross-sectional study	Dermatology department in a hospital	208	Age, sex, stress reaction, psoriasis severity, psoriasis duration, age at psoriasis onset
Tribó, 2019[40]	Yes	Yes	No	Cross-sectional study	Dermatology department in a tertiary referral centre	300	Psoriasis severity
Tu, 2017[41]	No	No	Yes	Cross-sectional study	Electronic health records from the LHID	10 796	Age, gender, psoriasis duration, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatological disease, liver disease, diabetes, hemiplegia or paraplegia and renal disease
Wojtyna, 2017[42]	Yes	No	No	Cross-sectional study	Dermatology outpatient and inpatient clinics, and Polish psoriasis associations	219	Sex, age at onset of psoriasis, psoriasis severity, ASI-SES, ASI-MS, emotional and instrumental social support, facial lesions, genital lesions, and distress
Yu, 2015[43]	Yes	No	No	Cross-sectional study	Dermatology outpatient clinic	246	Sex, education, occupation, and address
Lamb, 2017[44]	Yes	Yes	No	Cross-sectional study	Single centre tertiary psoriasis service	607	Psoriasis severity (using PASI), age, gender, ethnicity, psoriasis phenotype, psoriasis treatment, psoriatic arthritis, previous depression, or anxiety
RCTs in atopic eczema							
de Bruin-Weller, 2018[45]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinics	325	Targeted atopic eczema treatment (dupilumab) plus TCS vs. placebo plus TCS
Simpson, 2016[46]	Yes	Yes	No	Phase IIb, double-blind, parallel dose-ranging trial	Dermatology outpatient clinics	380	Targeted atopic eczema treatment (dupilumab) vs. placebo
Simpson, 2016[47] and Cork, 2019[48a]	Yes	Yes	No	Phase III, double-blind, parallel trials	Dermatology outpatient clinics	1379	Targeted atopic eczema treatment (dupilumab) vs. placebo
Simpson, 2021[49]	Yes	Yes	No	Phase IIb, double-blind parallel trial	Dermatology outpatient clinics	267	Targeted atopic eczema treatment (abrocitinib) vs. placebo
RCTs in psoriasis							
Gordon, 2018[50]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	992	Targeted psoriasis treatment (guselkumab) vs. placebo or adalimumab
Griffiths, 2017[51]	Yes	No	No	Phase III, double-blind, parallel trials	Dermatology outpatient clinic	320	Targeted psoriasis treatment (ixekizumab) vs. placebo
Langley, 2010[52]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	1230	Targeted psoriasis treatment (ustekinumab) vs. placebo
Menter, 2010[53]	Yes	No	No	Phase II, double-blind, parallel trial	Dermatology outpatient clinic	96	Targeted psoriasis treatment (adalimumab) vs. placebo
Tyring, 2006[54]	Yes	No	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	620	Targeted psoriasis treatment (etanercept) vs. placebo

ACVD, acute cardiovascular disease; ASI-R, Appearance Schemas Inventory-Revised scale includes ASI-MS (motivational salience) and ASI-SES (self-evaluative salience); CAD, coronary artery disease; LHID, longitudinal health insurance database; MI, myocardial infarction; PSOLAR, Psoriasis Longitudinal Assessment and Registry; RCT, randomized controlled trial; SMI, severe mental illness (including schizophrenia, bipolar disorder and other psychoses); TCS, topical corticosteroid; TIA, transient ischaemic attack. [a]Simpson, 2016 is the original RCT. Cork, 2019 is a pooled analysis of the trials.

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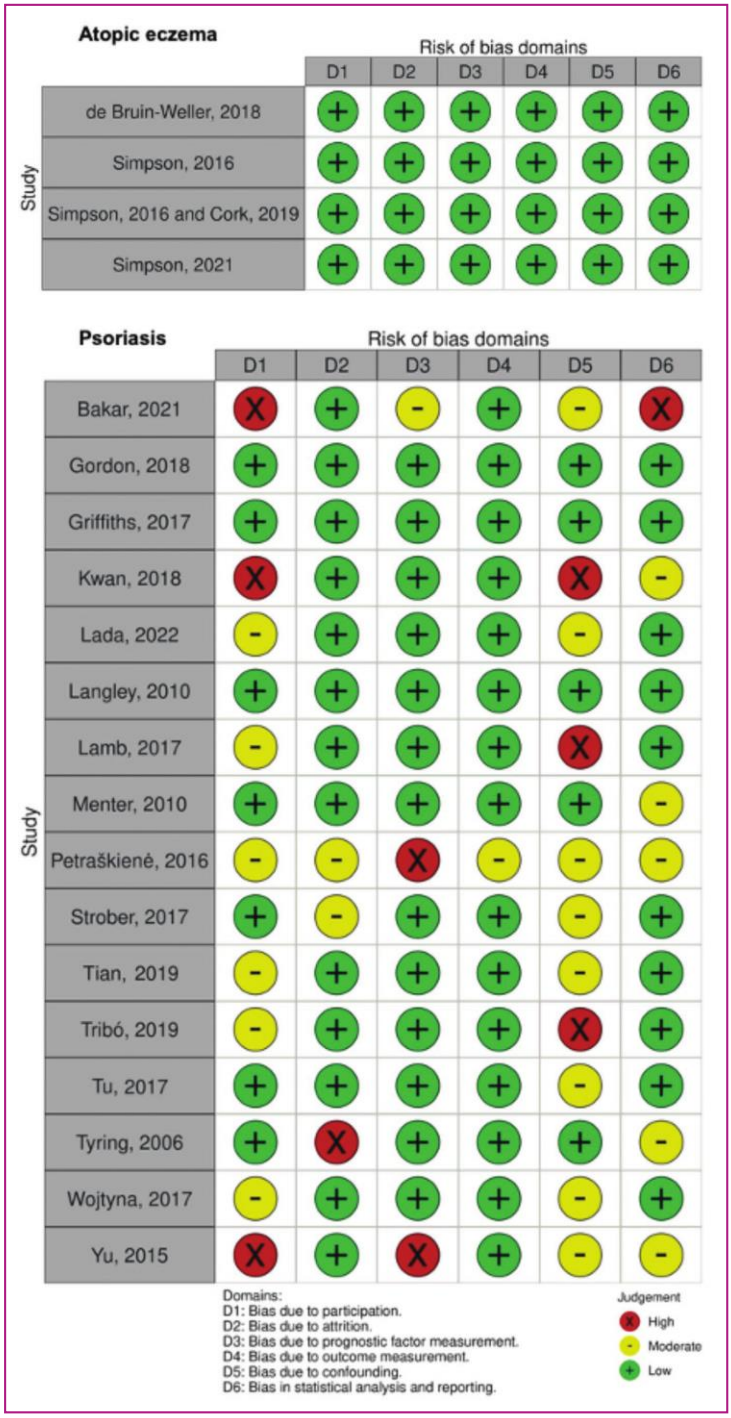

Figure 2 Risk of bias assessments of included studies using the Quality in Prognostic Studies tool.

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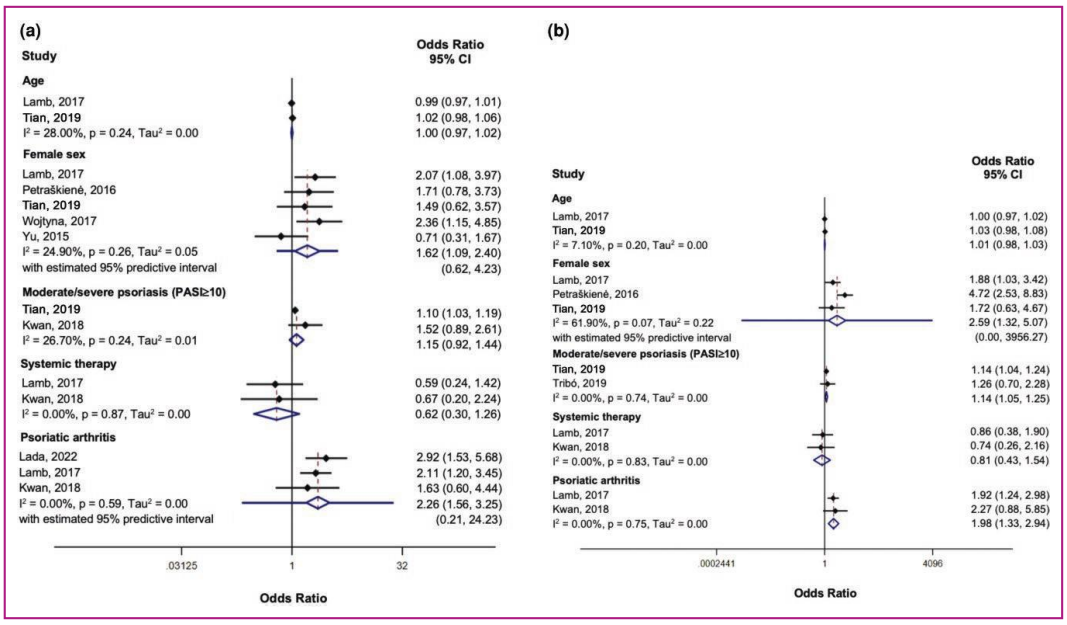

Figure 3 (a) Random effects meta-analyses of factors associated with depression among adults with psoriasis. (b) Random effects meta-analyses of factors associated with anxiety among adults with psoriasis.CI, confidence interval. PASI, Psoriasis Area and Severity Index.

baseline physician global assessment score[38] [Physician's Global Assessment (PGA), used to evaluate psoriasis severity and treatment response],[56] psoriatic head involvement,[35] lower limb lesions,[34] self-evaluative salience (e.g. physical appearance importance),[42] high psychological distress,[42] previous depression,[44] positive stress reaction,[39] and comorbid anxiety or chronic obstructive pulmonary disease.[38] Evidence from multiple studies suggested that impaired quality of life was associated with increased depression in people with psoriasis (meta-analysis not possible owing to differences in factor definition).[34,35] Evidence from single studies suggested associations between reduced depression with: emotional social support (e.g., having a confidant),[42] private health insurance,[38] longer psoriasis duration,[38,39] comorbid dyslipidaemia,[34] biologic therapy treatment (specifically adalimumab),[38] and a decrease in PGA score from baseline to depression diagnosis.[38]

Anxiety

Pooled effect estimates (Figure 3b) from two studies of low heterogeneity investigating age,[39,44] and two studies of low heterogeneity investigating systemic therapy[35,44] found no evidence that age (OR 1.01, 95% CI 0.98–1.03; $I^2 = 7.10\%$, $\tau^2 = 0.00$) or systemic therapy (OR 0.81, 95% CI 0.43–1.54, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with anxiety.

However, pooled effect estimates from three eligible studies of substantial heterogeneity investigating sex[37,39,44] two studies of minimal heterogeneity investigating psoriasis severity,[39,40] and two studies of low heterogeneity investigating psoriatic arthritis[35,44] reported that female sex (OR 2.59, 95% CI 1.32–5.07, 95% PI 0.00–3956.27, $I^2 = 61.90\%$, $\tau^2 = 0.22$), moderate/severe psoriasis (OR 1.14, 95% CI 1.05–1.25, $I^2 = 0.00\%$, $\tau^2 = 0.00$) and psoriatic arthritis (OR 1.98, 95% CI 1.33–2.94, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with increased anxiety, compared with male sex, mild psoriasis and no psoriatic arthritis, respectively.

Evidence from single studies found no evidence of associations with anxiety and psoriasis phenotype,[44] or comorbidities (cerebrovascular disease, diabetes, ischaemic heart disease).[35] Evidence from single studies suggested increased anxiety with primary education alone,[37] psoriatic head involvement,[35] positive stress reaction,[39] Asian ethnicity,[44] previous anxiety,[44] and severely impaired quality of life.[35] Evidence from a small cross-sectional study suggested that psoriasis presentation in patients aged $\geq$ 18 years, or longer psoriasis duration, is associated with reduced anxiety.[39]

Schizophrenia

A single cross-sectional study investigated factors associated with schizophrenia in people with psoriasis.[41] Individuals aged 40–59 years were associated with increased schizophrenia compared with those aged 20–39 years. Comorbid cerebrovascular disease or chronic pulmonary disease were also associated with increased schizophrenia. There was no evidence of associations with schizophrenia and sex, psoriasis duration, or comorbidities (congestive heart disease, diabetes, hemiplegia or paraplegia, liver disease, peripheral vascular disease, renal disease, rheumatological disease).

Randomized controlled trials

In all psoriasis trials, individuals with psoriasis randomized to receive placebo had higher depression/anxiety scores

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than those receiving targeted treatment (ixekizumab, adalimumab, etanercept, guselkumab, ustekinumab).[49–53] The maximum trial follow-up was 24 weeks.

Discussion

We identified evidence from 11 observational studies and 10 RCTs regarding factors associated with depression, anxiety and SMI in adults with AE or psoriasis. Among adults with psoriasis, pooled effect estimates suggested that female sex and psoriatic arthritis were associated with increased depression and anxiety, while moderate/severe psoriasis was associated with increased anxiety, but not depression. Evidence that related to other factors of interest were often from single studies only. Evidence for factors associated with SMI were limited, with one observational study investigating factors associated with schizophrenia in adults with psoriasis. Evidence from RCTs suggested that AE and psoriasis treated with placebo was associated with higher depression and anxiety scores compared with skin disease treated with targeted therapy; however, follow-up was limited to 24 weeks maximum. Therefore, the prolonged effects on mental health are unclear.

To our knowledge, this is the first study to systematically review literature on factors associated with depression, anxiety and SMI among adults with AE or psoriasis. We followed a prespecified protocol[32] and searched multiple databases, trial registries and grey literature. Language or geographical restrictions were not applied. We assessed risk of bias for individual studies. Despite the comprehensiveness of our search strategy, it may have missed relevant studies. Studies that did not find associations (between factors of interest and depression, anxiety or SMI in people with AE or psoriasis) may not have been published. We were unable to investigate nonpharmacological factors associated with depression, anxiety, and SMI in people with AE, because no eligible studies were found. Our review investigated associations between each factor and mental illness in isolation; however, the reality is likely to consist in a complex relationship between identified factors (e.g. AE or psoriasis severity, stigmatization, lifestyle factors).

Many observational studies included in our systematic review had small sample sizes, which limited their power to detect associations between factors of interest and mental illness. Additionally, most observational studies tested associations between multiple factors and mental illness, suggesting some observed associations occurred by chance owing to multiple testing. Most observational studies included were cross-sectional, so we cannot exclude bidirectional relationships between factors and mental illness. Variability in factor definitions and differences in study design prevented us calculating pooled effect estimates for some factor and outcome pairs. Owing to the limited number of studies, we were unable to conduct explorations of study heterogeneity. We were unable to have data from all included studies extracted by two independent reviewers, even though this is considered best practice. We deviated from our original protocol as we were unable to use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool to evaluate the quality of evidence for each mental illness outcome (depression, anxiety and SMI) and factor pair. This deviation was due to the paucity of specific guidelines for the application of GRADE to systematic reviews identifying variables associated with an outcome (rather than reviews identifying prognostic factors).[57]

Included RCTs investigated only short-term effects of treating skin disease with placebo on depression or anxiety in people with AE or psoriasis; maximum follow-up was 16 weeks for AE and 24 weeks for psoriasis. Consequently, it is difficult to draw conclusions about long-term effects of skin disease treatment on depression/anxiety in people with skin disease. Some included RCTs had strict eligibility criteria where individuals with multimorbidity[52,54] were excluded from participating, suggesting that trial study populations may be healthier and not represent broader patient populations.

Studies that use surveys to capture information on the factors of interest may be susceptible to recall bias and subsequent misclassification. They also have limited generalizability as survey responders are often systematically different to nonresponders.[58] All included observational studies were assessed to have at least moderate risk of bias in the confounding domain, suggesting that results of associations between factors of interest and depression, anxiety and SMI may be subject to residual confounding, and should be interpreted with caution.

Our review identified factors associated with mental illness consistent with those seen in the general population (e.g. female sex and lack of social support with depression and anxiety).[59,60] However, some factors associated with mental illness in the general population were not identified (e.g. female sex with schizophrenia, diabetes with depression),[59,61,62] potentially owing to bias and small sample sizes in the included studies. Our finding that individuals with AE or psoriasis treated with biologics have reduced depression or anxiety symptoms is consistent with two systematic reviews of the effect of biologic therapies in people with skin disease.[63,64] A review of psychiatric comorbidities associated with psoriasis identified correlations between facial or genital psoriatic lesions and depression;[65] however, our review found no evidence of these associations.

The variety of factors associated with anxiety and depression identified in people with psoriasis in this review reflects potential mechanisms described in the literature to explain the link between AE or psoriasis and mental illness, including (i) a bidirectional relationship owing to shared immunological changes in AE, psoriasis and mental illness leading to high proinflammatory cytokine levels[21,65,66] and (ii) stigmatization owing to visible skin conditions leading to low self-esteem and psychological burden.[63,65]

Our review included studies demonstrating associations between high baseline PGA (used to evaluate psoriasis severity and treatment response)[56] and depression, and moderate/severe psoriasis and anxiety, both of which support the theory that inflammation is associated with mental illness. Evidence from included RCTs showing that treatment of AE or psoriasis is associated with reduced symptoms of depression or anxiety also supports an inflammatory mechanism, as biologics treat skin disease by limiting overreaction of the immune system and reducing inflammation.[67,68] However, other explanations for the association between psoriasis severity and anxiety could include severe disease

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exacerbating problems with stigmatization and increasing mental illness risk.[65,69] The observed association between self-evaluative salience (i.e. importance of physical appearance) and increased depression in psoriasis is consistent with visible skin disease resulting in stigmatization and affecting mental health.[65,69]

We found limited evidence relating to factors associated with SMIs in people with AE or psoriasis. From observational studies, we identified that female sex, and psoriatic arthritis were associated with depression and anxiety, while moderate/severe psoriasis was associated with anxiety, suggesting that individuals with psoriasis and these characteristics may benefit from targeted prevention strategies such as mental health screening. However, this interpretation should be taken with caution owing to the limitations of the included studies. The large number of factors assessed in the included studies suggest that an accurate account of the relationships between AE or psoriasis and mental illness is complex and multifactorial. Including mental health screening in primary care as part of overall psoriasis and AE care may overcome limitations associated with identifying higher-risk individuals. In RCTs, we noted short-term benefits of biological therapies on depression and anxiety in people with both AE and psoriasis. Trials with longer follow-up and inclusive eligibility criteria are required to establish whether biological therapies have longer-term effects on depression or anxiety symptoms and improve the generalizability of findings.

Our review reveals a gap regarding known factors associated with depression, anxiety and SMI in people with AE or psoriasis. Evidence on factors associated with mental illness in psoriasis was often conflicting or from single studies; however, pooled effect estimates suggest that female sex and psoriatic arthritis are associated with increased depression and anxiety, while moderate/severe psoriasis is associated with increased anxiety. There was no corresponding observational evidence in AE. Critically, we found little evidence for factors associated with SMIs. Future research should focus on better understanding factors associated with mental illness – particularly SMIs – in people with AE or psoriasis and identifying high-risk groups to reduce mental illness burden on people with skin diseases.

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Conflicts of interest

J.F.H. has received consultancy fees from Wellcome Trust and juli Health. R.M. has received consultancy fees from AMGEN.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Ethics statement

Ethics approval was not required for this systematic review.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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3.4 Summary

- This systematic review synthesised and evaluated all available evidence on the risk factors for depression, anxiety, and SMI among adults with atopic eczema or psoriasis.
- 21 studies were included in the review – 11 observational studies and 10 RCTs. All observational studies in the review were in adults with psoriasis, no atopic eczema studies fulfilled the eligibility criteria. Five RCTs were in adults with atopic eczema, and five were in adults with psoriasis.
- Observational studies in adults with psoriasis included in the review mainly investigated factors for depression or anxiety (only a single cross-sectional study investigated factors for schizophrenia). Pooled effect estimates from observational studies indicated that being a woman and having comorbid psoriatic arthritis were associated with increased depression and anxiety. Moderate/severe psoriasis was associated with increased anxiety, but not depression. Evidence on other factors were often conflicting, or from single studies only.
- Included observational studies were limited by: (1) small sample sizes leading to a lack of statistical power to detect associations between factors and mental health outcomes; (2) residual confounding of effect estimates; and (3) differences in factor definitions.
- Included RCTs suggest that atopic eczema and psoriasis treated with standard treatment or placebo are associated with higher depressive and anxiety symptoms compared to skin disease treated with targeted therapy (e.g., biologics), however, follow-up of RCTs was limited, so long-term effects on mental health are unclear.
- This review highlights a gap regarding the factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis. Future research should focus on better understanding factors associated with mental health conditions in people with skin disease and identifying high-risk groups.

- In the following chapter, I will describe the data sources used in the population-based cohort studies included in this thesis. I used the results from this systematic review, alongside the literature, to identify key covariates that should be included in the analyses of the cohort studies included in this thesis.

4 Overview of data sources

4.1 Introduction

In the previous chapter, I reported the results of a systematic review conducted to investigate factors associated with depression, anxiety, and severe mental illness (SMI) among adults with atopic eczema or psoriasis. I used the results of this systematic review to identify potential confounders or mediators of associations between atopic eczema and depression, anxiety, or SMI and the association between psoriasis and SMI (**Chapters 7,8**). In this chapter, I will present an overview of the electronic health record (EHR) data sources used in the population-based cohort studies in this thesis.

4.2 Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) is an ongoing research service provided by the United Kingdom (UK) government, supported by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR).[208] CPRD collects pseudonymised primary care health records from participating UK primary care practices, and provides it to researchers worldwide to facilitate observational public health research.[208] In the UK, over 98% of the population are registered with a National Health Service (NHS) general practitioner (GP) providing care that is free at the point of use.[209] In the UK, GPs are the first point of contact in the NHS, providing treatment or referring individuals to secondary or tertiary care.[209] Consequently, with most individuals registered with a GP, and GPs acting as the gatekeeper to healthcare services, UK primary care is a rich resource for epidemiological research.

4.2.1 Database versions

Within UK primary care, there are several clinical software systems used to manage patient data. CPRD collects data from consenting primary care practices using two electronic health record software systems: Vision (used in 18% of English practices)

and EMIS systems (used in 55% of English practices).[210] Due to differences in the structure and coding methods used in different GP electronic health record management software, CPRD provides primary care data as two different formats (GOLD and Aurum).[211] CPRD GOLD contains data from practices using Vision Software, while Aurum contains data from practices using the EMIS system.

Although CPRD Aurum includes data from more patients than CPRD GOLD,[209,212] I used primary care data from CPRD GOLD for all the population-based cohort studies included in this thesis. The choice in database was made for several reasons. Firstly, the definitions used to identify atopic eczema and psoriasis in the population-based cohort studies (further described in **Chapter 5**) have been previously validated in The Health Improvement Network, an electronic health record primary care database which similarly to CPRD GOLD, collects data from GP practices using the Vision software system.[213–215] Secondly, CPRD GOLD data has been widely used in epidemiological research for over 30 years,[209] including studies investigating atopic eczema,[80,148,216] psoriasis,[217–219] and mental health conditions,[148,220] and has been reported to consist of high-quality data.[221] In contrast, CPRD Aurum was more recently established in October 2017 and has therefore not been utilised as often for skin disease research.[212] Finally, CPRD GOLD has UK wide coverage as the database includes data from all countries (England, Scotland, Wales, and Northern Ireland) in the UK.[209] On the other hand, at the time the population-based cohort studies included in the thesis began (January 2021 release), over 99% of practices contributing data to CPRD Aurum were in England.[222] However, it is likely that conducting the population-based cohort studies included in this thesis using CPRD Aurum instead of CPRD GOLD would yield results similar to those in this thesis. Previous studies of other conditions that have conducted the same research in both CPRD GOLD and Aurum have also shown similar results.[223,224]

4.2.2 Data recording practices

CPRD GOLD includes data on demographic characteristics, symptoms, diagnoses, prescriptions, tests, vaccinations, and referrals to hospital and specialist care.[209] Data are recorded electronically during consultations by general practice staff mainly

using Read coding, a comprehensive hierarchical clinical classification system of morbidity and symptom codes.[225] Prescriptions are recorded with the product name, British National Formulary Code, quantity and dosage instructions.[209] General practices also receive information about patients from secondary care that are entered manually into the patient record by practice staff.[209] General practices may also record observations as free text, however, this is not routinely included in CPRD data for research as it may contain identifiable information.[209]

There are certain aspects of how data is recorded in CPRD GOLD that may lead to limitations in the use of the data. Firstly, there may be variations between practices in how data are recorded. Clinicians may report some detail of diagnoses as free text rather than in Read codes,[226] which may mean that researchers miss vital information (e.g., someone without a Read code for a disease would be considered by a researcher to not have the disease). Secondly, the frequency of data recording may depend on the health of the individual. For example, someone with health issues, who are consequently consulting their GP more frequently, may be more likely to have their weight or blood pressure recorded than those without health issues. Thirdly, CPRD does not capture information on diet, physical activity, over the counter medication use, and other aspects of health that may be important for specific research questions. Finally, manual entry of information from secondary care may lead to incorrect or incomplete data.

4.2.3 Population coverage and representativeness

As of July 2022, CPRD GOLD holds data from 986 GP practices and over 21 million patients.[227] Active patients (individuals who are alive and currently registered to a practice that contributes data) include 4.6% of the UK population and have a median follow-up time of 13 years (Interquartile range [IQR] 4.74 – 26.10 years).[227] The large size of the CPRD GOLD database and the length of individual follow-up allows research into rare diseases and long-term outcomes.

A comparison of the July 2013 CPRD dataset to data from the 2011 UK census found that individuals registered with CPRD GOLD practices were broadly representative of the UK population in terms of age and sex, and comparable to the

UK census in terms of ethnicity.[209] However, it is likely that there has been a decline in the representativeness of the dataset over the years. Comparing the population of active individuals included in CPRD GOLD over time shows a clear pattern of reduction. Figures from July 2013 show that CPRD GOLD held information on 4.4 million active patients, representing 6.9% of the UK population.[209] This is larger than figures from July 2022 where the population of active patients was 3.1 million, representing 4.6% of the total UK population.[227] It is likely that the decrease in the number of active patients is due to more GP practices moving to the EMIS clinical software system,[210] however, reductions in the numbers of active patients may also have important implications for the representativeness of CPRD GOLD. CPRD GOLD may also not be representative of practices in the UK in terms of geography. Figures from July 2022 report that over 56% of currently contributing practices are in Scotland, 29% in Wales, 10% in Northern Ireland, and less than 5% in England.[227] CPRD GOLD also does not include individuals that are not registered with NHS practices. These may include those registered with private practices, individuals who are homeless, and prisoners.[209]

4.2.4 Data quality

Data entered by GPs during consultations are recorded for routine care, not for research, so data quality varies. CPRD GOLD has two broad data quality indicators – an ‘acceptability’ flag for patients and an up to standard date for practices.[209] Individuals are labelled as ‘acceptable’ by a process that identifies and excludes those with poor data recording (i.e., no valid age or sex, non-continuous follow-up).[209] The up to standard date is the date when data in the practice is considered to be of continuous high quality for use in research.[209] Both the ‘acceptability’ flag and the UTS date do not ensure data quality, but they are a good first step in identifying whether health record data are suitable for research.

4.2.5 Ethics

CPRD seeks annual ethics approval from the UK’s Health Research Authority (HRA) to support research using anonymised patient data.[212] Access to CPRD data by

researchers is subject to protocol approval by the CPRD's Research Data Governance (RDG) process.[228] The RDG process ensures that the proposed research is feasible, methodologically sound, and is for the benefit of public health.[228] Previously, access to CPRD data required approval from the Independent Scientific Advisory Committee (ISAC), however, this changed to the RDG in June 2021.[228]

4.2.6 Linkage to other databases

Data from consenting English practices in CPRD GOLD are linked through a third-party (NHS Digital) to other data sources to provide more comprehensive information for individuals included. The studies included in this thesis use linked data from: the Carstairs Index and Hospital Episode Statistics Admitted Patient Care. I also planned to use linked data from the Mental Health Dataset.

4.2.6.1 Carstairs Index

The Carstairs Index is a measure of socioeconomic deprivation that I used in both population-based cohort studies included in this thesis (**Chapters 7,8**). It is based on the sum of scores for four indicators judged to represent material deprivation from the 2011 census: male unemployment, lack of car ownership, overcrowded households, and low occupational social class.[229,230] In CPRD GOLD, practice postcode linkage is available for individuals registered to practices in England, Wales and Scotland (practice-level linkage) and individual postcode linkage is available for individuals registered in England (patient-level linkage).[229]

4.2.6.2 Hospital Episode Statistics Admitted Patient Care

The Hospital Episode Statistics Admitted Patient Care (HES APC) dataset contains details of NHS-funded hospital admissions in England. HES APC includes admission and discharge dates, diagnoses, procedures, and specialists seen.[231] Diagnoses are coded using the International Classification of Diseases, Version 10 (ICD-10) codes.[231] Only individuals registered with English CPRD GOLD practices are eligible for HES APC linkage. In the studies included on this thesis, I only use HES APC data once, as part of a sensitivity analysis for the study described in **Chapter 8** (investigating associations between atopic eczema and depression or anxiety in

white and minority ethnic groups). In this sensitivity analysis, I identify an alternative study population using individuals within CPRD GOLD that are eligible for HES APC linkage as previous work suggests that combining CPRD and HES APC increases the completeness of ethnicity data.[232]

4.2.6.3 Mental Health Dataset

The Mental Health Dataset (MHDS) includes data for individuals who are receiving specialist adult mental health care in an NHS-funded setting in England. The specialist secondary mental health care settings covered by the MHDS include services provided in hospital, community, or at outpatient settings. Information recorded in the MHDS includes the type and location of care received, the length of care received, and contacts with mental health and social care professionals.[233] Diagnostic recording is not mandatory in the MHDS, and knowledge of diagnoses is sometimes limited to data recorded within Health of the Nation Outcome Scales (HoNOS) scores, Patient Health Questionnaire (PHQ-9) scores, or specific event or episode types.[229,233] Individuals registered with an English practice in the CPRD GOLD database with a valid NHS identifier can be linked to MHDS, however the linkage only covers the period April 2007 to November 2015.[233] Due to changes in the structure of the dataset and variables recorded by mental health care professionals, the CPRD provides the MHDS in two different formats: Format 1 includes data collected between April 2007 and March 2011, while format 2 holds data collected between April 2011 and November 2015.

I planned to conduct a study using CPRD GOLD and linked MHDS data to investigate the agreement of severe mental illness (i.e., schizophrenia, bipolar disorder, and other psychoses) recording across English primary care and secondary mental health care. The protocol for the study had been developed and received approval from the CPRD RDG's process, however, in early 2022, CPRD removed the MHDS as one of their standard linkages and access to the data required an extra fee and was limited to only this project. The removal of the dataset as a standard linkage suggested that the research would have limited useful insight for future researchers, and unlikely to provide answers to the main questions of the study. Additionally follow up studies were limited by the restricted access to the

dataset. Consequently, I decided not to go ahead with the study. The approved protocol for the study can be found in **Appendix 3**.

4.3 Summary

- The population-based cohort studies included in this thesis (**Chapters 7,8**) used anonymised primary care EHR data from CPRD GOLD. Information recorded in CPRD GOLD includes demographic characteristics, symptoms, diagnoses, prescriptions, tests, and much more.
- CPRD GOLD can be linked to other data sources. The linkages used in the studies included in this thesis are the Carstairs Index and HES APC.
- Key strengths of CPRD GOLD include the size of the dataset, the length of follow-up available for individuals in the dataset, and the representativeness of the dataset in comparison to data from the 2011 UK Census.
- Weaknesses of CPRD GOLD include potential misclassification of exposures and outcomes due to missing data, potential mistakes in hospital admissions data due to manual entry, and the lack of recording of aspects of health that may be important for research (i.e., diet and physical activity).
- In the following chapter, I will describe how the variables (exposures, mental health outcomes, and covariates) used in the population-based cohort studies included in this thesis were defined using CPRD GOLD data and its linkages.

5 Overview of common variables used in included studies

5.1 Introduction

In the previous chapter, I introduced the UK's Clinical Practice Research Datalink (CPRD) GOLD database, the main data source used in the population-based cohort studies (**Chapters 7,8**) included in this thesis. In this chapter, I will describe how the variables (exposures, mental health outcomes, and covariates) used in the population-based cohort studies were defined using CPRD GOLD data and its linkages. I identified the covariates defined in this chapter using the results of the systematic review described in **Chapter 3**, as well as a search of the literature. The code lists used to capture the variables described in this chapter are available to download from online repositories specific to the population-based cohort studies included in the thesis.[234,235]

5.2 Exposures

5.2.1 Atopic eczema and psoriasis

I identified atopic eczema and psoriasis based on previously validated definitions.[213,214] The atopic eczema definition was based on a record of at least one diagnostic code for atopic eczema recorded in primary care, and at least two records of eczema therapy recorded on separate days.[213] Eczema therapy included: (1) records of phototherapy identified using Read codes in primary care; and (2) primary care prescription records for topical emollients, corticosteroids or calcineurin inhibitors, or oral glucocorticoids, azathioprine, methotrexate, ciclosporin or mycophenolate. The psoriasis definition was based on a record of at least one psoriasis diagnostic code recorded in primary care.[214]

I chose to use both atopic eczema and psoriasis definitions as they had both been validated for use in The Health Improvement Network, an electronic health record

(EHR) database that similarly to CPRD GOLD, collects data from participating primary care practices that use Vision software.[215] Both definitions have also been used extensively in other high-quality observational research of atopic eczema and psoriasis. [80,148,216–219] In addition, the Positive Predictive Value (PPV), also known as the probability that individuals identified by the definitions have the disease as determined by clinicians, was high for both definitions (86% for the atopic eczema definition, 90% for the psoriasis definition).[213,214]

The atopic eczema and psoriasis definitions are not without limitations. Firstly, both definitions may misclassify individuals with atopic eczema or psoriasis who do not have the relevant diagnostic Read codes (because they do not consult their general practitioner (GP) for their skin disease) as not having atopic eczema or psoriasis. Additionally, the atopic eczema definition may misclassify individuals with atopic eczema who do not receive treatment (either because their disease is mild, or they refuse treatment) as not having atopic eczema. However, an atopic eczema definition that includes only diagnostic codes may not identify individuals with chronic atopic eczema.[213]

5.2.2 Atopic eczema and psoriasis severity

In analyses examining atopic eczema or psoriasis severity, I classified individuals with atopic eczema as having mild, moderate, or severe disease, and individuals with psoriasis as having mild or moderate-to-severe disease using previously developed definitions that have been used in prior research.[216,217]

I considered individuals to have mild disease by default. I classified individuals as having moderate atopic eczema from the first of: (1) a second potent topical corticosteroid prescription within one year; or (2) a first prescription for a topical calcineurin inhibitor.[216] I classified individuals as having severe atopic eczema from the first of: (1) use of phototherapy or systemic treatment for atopic eczema (excluding systemic glucocorticoids, as they may have been prescribed for coexisting asthma); or (2) referral to a dermatologist.[216] I considered individuals to have moderate-to-severe psoriasis if they had any phototherapy records, or primary care prescriptions for systemic (acitretin, etretinate, ciclosporin, hydroxycarbamide,

methotrexate, and fumaric acid) or biologic (etanercept, adalimumab, infliximab, ustekinumab, and efalizumab) therapies.[217]

I updated severity over time. Once an individual was defined as having moderate or severe atopic eczema or moderate-to-severe psoriasis, they remained in this category for the rest of follow-up and could not be categorised as having milder disease as I was unable to capture symptom reduction that would suggest a reduction in atopic eczema or psoriasis severity. The inability to capture a reduction in severity may mean individuals were misclassified as having more severe disease when their conditions had improved, or their symptoms had reduced.

The atopic eczema and psoriasis severity definitions have limitations. A major limitation is the reliance on skin disease therapies to classify disease severity instead of validated scoring systems such as the Eczema Area and Severity Index for atopic eczema severity or the Static Physician's Global Assessment for psoriasis severity. However, to my knowledge, there are no validated measures to ascertain atopic eczema or psoriasis severity using EHR data. Additionally, the use of skin disease therapies as proxy for disease severity is well documented in previous observational research using EHR data.[9,217,236] A further limitation is that the atopic eczema and psoriasis severity definitions may misclassify individuals with severe disease as having milder disease if they refused skin disease therapies.

5.3 Mental health outcomes

In the population-based cohort studies included in this thesis, I investigated the following mental health outcomes: depression, anxiety, and severe mental illness (SMI). In all the cohort studies, I identified depression, anxiety, and SMI outcomes based on the earliest record of a diagnostic Read code recorded for the relevant outcome in CPRD GOLD.

I developed preliminary code lists of potentially relevant codes to identify each outcome in CPRD GOLD by searching the National Health Service (NHS) UK Read code browser using keywords from Medical Subject Headings (MeSH), a hierarchical and controlled vocabulary used to index and search health biomedical related

information. [237,238] I compared initial code lists to those provided in the Quality and Outcomes Framework (QOF) for depression and SMI,[239] as well as to other published code lists that were used in previous EHR studies to identify any missing codes.[148,220,240,241] Code lists for depression, anxiety and SMI were then reviewed by a psychiatrist (Joseph Hayes) and two individuals with experience of UK clinical practice and EHR research (Kathryn Mansfield, Sinéad Langan) to produce the final code lists. I classified codes for outcomes into two categories – definite and possible. Definite codes were used to define the primary outcomes in the main analysis of each study, while possible codes were used in sensitivity analyses.

For SMI, definite codes included only diagnostic Read codes that specifically identified schizophrenia, bipolar disorder, or other non-organic psychoses. Possible codes for SMI included broader 'symptom' codes that are not exclusive to the condition (e.g., delusions).

Definite codes for depression included diagnostic Read codes for depression (e.g., depressive disorder, dysthymia and other mood related depressive disorders) and Read symptom codes of depression (e.g., depressive symptoms, low mood, or dysphoric mood). Possible codes for depression included broader symptom codes that are not exclusive to the condition (e.g., tearfulness, or emotional upset).

Definite codes for anxiety included diagnostic Read codes for anxiety disorders (e.g., generalised anxiety disorder, panic disorder and obsessive-compulsive disorder) and Read symptom codes for anxiety (e.g., anxiousness). Possible codes for anxiety included broader symptom codes that are not exclusive to anxiety (e.g., nerves, tenseness). Mixed anxiety and depression codes were included in code lists for anxiety and depression.

There are several limitations associated with how I captured mental health outcomes. Firstly, none of the mental health outcome definitions used have been validated in CPRD GOLD, however, the lack of standardised and validated definitions for diagnoses is a common limitation of research using EHR data.[209] Some individuals with depression or anxiety may not consult their GP for their mental health condition and may therefore be misclassified as not having depression or anxiety. Using CPRD GOLD to capture SMI outcomes may miss individuals with SMI

as the condition is usually identified in secondary mental health care. However, it is likely numbers of missed individuals with SMI will be small as in the UK, GPs have a central role in the care of people with SMI. Since the introduction of the QOF, GPs receive renumeration for maintaining a register of individuals with an SMI diagnosis, developing, and maintaining comprehensive care plans, and conducting annual health checks in those with an SMI diagnosis.[142]

5.4 Covariates used across studies

5.4.1 Body mass index and smoking status

I defined body mass index (BMI) and smoking status based on primary care records for these measures. I used an algorithm that used primary care records to identify the status recorded closest to the index date. In the algorithm, records within -1 year to +1 month of the index date were regarded as the best, +1 month to +1 year from the index date as second best, the nearest before -1 year from the index date as the third best, and the nearest after +1 year from the index date as the worst. Read codes for BMI were not used as they are rarely recorded. Instead, BMI was calculated using height and weight measures recorded closest to the index date. I classified BMI according to the World Health Organisation categories: underweight (<18.5kg/m^2); normal weight (18.5-24.9 kg/m^2); pre-obesity/overweight (25.0-29.9 kg/m^2); obese (≥30.0 kg/m^2). Smoking status was identified using morbidity codes recorded closest to the index date. I classified smoking status as: (1) current/ex-smoker; or (2) non-smoker. In the cohort studies included in this thesis, I did not use smoking status or BMI recorded after the relevant mental health outcome had occurred as several studies have shown that individuals with depression, anxiety, or SMI have higher BMIs and a more likely to smoke,[162,167,198,242] and therefore any change in BMI or smoking status could be considered a consequence of the mental health outcomes under investigation.

It is likely that in the population-based cohort studies included in this thesis, BMI and smoking status will not be recorded for some individuals. This is mainly because recording of lifestyle data such as smoking status or height and weight

measurements required to calculate BMI is often opportunistic and is more likely to occur in people that consult their GP more frequently.[243] Therefore, in the context of this thesis, it is expected that individuals with atopic eczema, psoriasis, or the mental health outcomes under investigation may be less likely to have missing BMI or smoking status data.

5.4.2 Calendar period

I categorised the study period into calendar periods to account for changes in clinical, diagnostic, and administrative practices over the study period that may have influenced the measurement of exposures, mental health outcomes, and other covariates. For example, there may be changed in how mental health conditions are coded in EHR records due to the introduction of renumeration by the QOF.[111,128] The calendar periods used differed between the population-based cohort studies included in this thesis. Further detail can be found in the relevant chapters (**Chapters 7,8**).

5.4.3 Comorbid asthma

In one of the population-based cohort studies (**Chapter 8**), I also identified adults with comorbid asthma based on morbidity coding in primary care. I regarded individuals as having asthma from the earliest record of a relevant diagnostic code. However, the definition used to define asthma is not validated, and may misclassify individuals as not having asthma if they do not have a relevant diagnostic code.

5.4.4 Comorbidity burden

I used the Charlson Comorbidity Index (CCI) as a summary measure to capture the burden of comorbidities at cohort entry. The CCI was originally developed in 1987 as a method of categorising comorbid medical conditions of individuals that may predict short-term mortality risk for individuals in longitudinal studies.[244] Now, the CCI is a widely used measure to adjust for comorbidities in research.[245] The CCI initially included 19 conditions,[244] but has since been modified to contain 12 or 17 conditions. In this study, I used the CCI index that contained 17 conditions. Weights

are assigned to each of the 17 conditions included in the index, and the sum of the weights in each individual results in a single comorbidity summary score.[244,245] Each condition in the CCI is weighted from one to six, with a weight of six representing the most severe morbidity.[245] CCI scores were categorised into 3 groups: low (0 points), intermediate (1-2 points), and high (≥3 points).

However, there are limitations associated with the use of the CCI. The CCI may be affected by errors in the recording of diagnostic read codes in EHR data. Although the presence of a diagnostic code suggests an individual has a condition, and the absence of a code suggests the absence of a condition, errors in recording may mean individuals are misclassified. Another limitation is that the CCI was developed to categorise conditions that may predict mortality in the 80s, therefore the weights associated with the included conditions may not reflect current prognosis, and the conditions included in the index may not necessarily be relevant to the research question under investigation. However, in the context of this thesis, I used the CCI as a measure to generally capture comorbidity burden, and the limitations, although relevant, will not affect the interpretation of the results of the cohort studies included in the thesis.

5.4.5 Socioeconomic deprivation

I used patient-level quintiles of the Carstairs Index as a measure for socioeconomic deprivation where available.[229] Individuals in the first quintile were the least deprived, while individuals in the fifth quintile were the most deprived. Patient-level Carstairs data was only available for people in English practices that consented to participate in the linkage scheme, therefore when patient-level data was unavailable, I used practice-level Carstairs data. Although using practice-level data when patient-level data is unavailable is a common approach, may mean some individuals socioeconomic deprivation quintile may not match that of the GP that they are registered to, and this may lead to an underestimation of the confounding effect of socioeconomic deprivation on exposure-outcome relationships under investigation in this thesis. However, although limited, practice-level deprivation captures part of the relationship between deprivation and health outcomes.[246] Additionally, if I were to

categorise individuals without patient-level data as having missing deprivation data, this would exclude many individuals in the analysis of the cohort studies included in this thesis and affect the representativeness of the results.

5.4.6 Ethnicity

I identified the ethnicity of individuals in my studies by using a previously validated algorithm using Read morbidity coding in primary care electronic health records.[232] The algorithm classifies ethnicity into five high-level categories – White, South Asian, Black, Other or Mixed – based on ethnic groups in the 2011 census. The algorithm is also suggested for use in the CPRD dataset from 2006 onwards due to the incentivisation of ethnicity recording by the QOF between 2006 and 2012 improving the completeness of ethnicity data for individuals newly registered at GP practices. However, it is likely that for individuals registered with GP practices before 2006, ethnicity data will be largely incomplete.

5.4.7 Harmful alcohol use

I defined harmful alcohol use based on primary care morbidity codes suggesting harmful or heavy alcohol use (including alcohol dependency codes and codes related to physical/psychological harm linked to alcohol use) or a prescription for drugs used to maintain alcohol abstinence (acamprosate, disulfiram, or nalmefene) that have been used in previous studies.[148,216] I defined individuals as harmful alcohol users on the date of the first record of a relevant morbidity code or prescription. I decided to capture harmful alcohol users instead of generally capturing any codes relating to alcohol consumption because a previous study investigating the completeness of alcohol recording in UK primary care found that alcohol consumption data was only available for approximately half of all adults registered to CPRD GOLD practices.[247] Therefore, generally capturing alcohol consumption would lead to a large number of individuals with missing alcohol data. I instead captured harmful alcohol use so individuals who do not fulfil the definition will be classified as not consuming harmful amounts of alcohol rather than being classified as having missing data.

5.4.8 High-dose oral glucocorticoid use

I identified prescriptions for oral glucocorticoids (e.g., prednisolone, hydrocortisone) and converted the prescribed daily dose to the prednisolone equivalent dose (PED). High-dose oral glucocorticoid use was defined as a dose of 20 mg/day or higher PED. I captured high dose oral glucocorticoid use as a binary time-updated variable with status changing for a short period (90 days) on the date of the first record of a prescription for a dose of 20mg/day or more PED. I decided to time-update high-dose oral glucocorticoid use and change the status for a period of 90 days because treatment of severe atopic eczema with high-dose glucocorticoids is limited to certain circumstances, the length of treatment is usually short term, [52,53] and their effect is temporary.[171] It is likely that prescriptions for glucocorticoids are well recorded in EHR records since their use is discouraged,[52,53] and the National Institute for Health and Care Excellence (NICE) recommends regular monitoring for those prescribed the treatment,[248] therefore the definition used is unlikely to misidentify individuals.

5.4.9 Problems with sleep

I identified problems with sleep based on primary care morbidity codes suggesting sleep problems and prescriptions for drugs used to manage problems with sleep. I identified a preliminary code list of morbidity codes by searching the Read term browser using MeSH keywords. I also identified a list of prescription drugs used to manage sleep problems using the treatment summary for hypnotics and anxiolytics on the British National Formulary (BNF) and clinical expertise from supervisors.[249] Both the list of morbidity codes and prescription drugs were reviewed by three clinicians to produce the final lists.

I classified codes for problems with sleep into two categories using clinical knowledge and information from the BNF – definite and possible. Definite sleep problems included diagnostic and symptom Read codes (for insomnia, poor sleep pattern, or other sleep disturbances) and prescriptions for drugs that are only used to treat problems with sleep (zaleplon, zolpidem tartrate, zopiclone, hydroxyzine hydrochloride and promethazine hydrochloride when taken at night). Possible sleep problems additionally included prescriptions for drugs that may be prescribed for

sleep problems but can also be prescribed for other conditions (melatonin and benzodiazepines). The Read codes and prescription drugs in the definite category were used in main analyses, while the prescription drugs in the possible category were used in sensitivity analyses.

It is likely that my definition of problems with sleep will not identify some individuals with sleep problems. Individuals that use over-the-counter sleeping aids, or those that do not consult their GP for sleep problems may be misclassified as not having problems with sleep. Additionally, GPs do not routinely record quality of sleep, so it is likely that some individuals may be missed. However, by using both Read and prescription codes to capture problems with sleep, I will identify the most severely affected individuals even if I am unable to identify all individuals with sleep problems.

5.5 Summary

- In this chapter, I discussed how key variables used in the population-based cohort studies included in this thesis were defined using data from CPRD GOLD.
- Exposure variables were atopic eczema and psoriasis, and in secondary analyses, atopic eczema, and psoriasis severity.
- Mental health outcomes under investigation were depression, anxiety, and SMI.
- Covariates included calendar period, comorbidities (including comorbidity burden and comorbid asthma), socioeconomic deprivation, ethnicity, lifestyle factors (harmful alcohol use, BMI, and smoking status), high-dose oral glucocorticoid use, and problems with sleep.
- In the following chapter, I will discuss directed acyclic graphs (DAGs). I will also discuss how I used DAGs to illustrate and understand relationships between the key covariates defined in this chapter and their relationship to the exposures (atopic eczema or psoriasis) and the mental health outcomes (depression, anxiety, and SMI).

6 Directed acyclic graphs to guide covariate selection for associations between atopic eczema or psoriasis and depression, anxiety, and severe mental illness

6.1 Introduction

In the previous chapter, I described how the variables (exposures, mental health outcomes, and covariates) used in the population-based cohort studies included in this thesis were defined using Clinical Practice Research Datalink (CPRD) GOLD data. In this chapter, I will discuss the directed acyclic graphs (DAGs) I developed for the two cohort studies included in the thesis (**Chapters 7,8**), and explain how I used them to illustrate and consider the roles of key variables in associations between atopic eczema or psoriasis (exposures), and depression, anxiety, or severe mental illness (SMI) (mental health outcomes) that are investigated in the population-based cohort studies of this thesis (**Chapters 7,8**). Some of the variables included in the DAGs within this chapter are recorded in CPRD GOLD and their definitions have been described in the previous chapter.

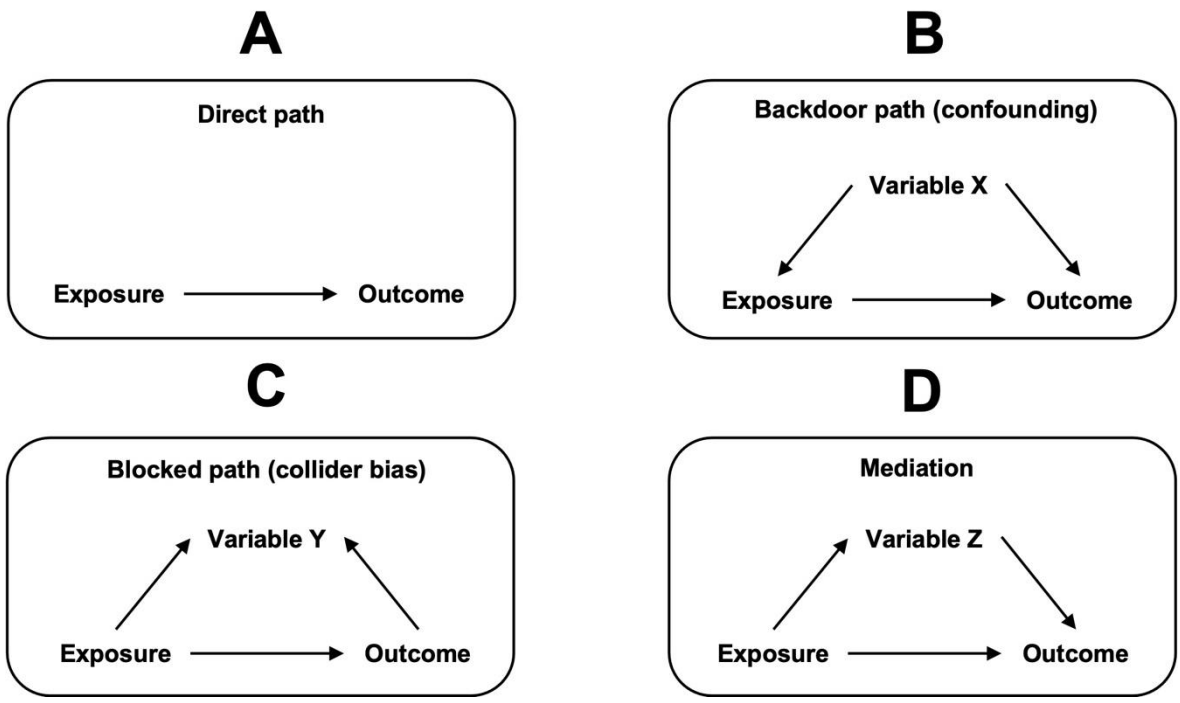
6.2 Directed acyclic graphs

When estimating the causal effect of an exposure on an outcome using data from observational studies, it is important to explicitly consider the roles that other variables may have in relation to the exposure and outcome. Directed acyclic graphs (DAGs) are causal diagrams commonly used as a visual representation of the assumptions made regarding the causal relationships between variables.[250] They are ‘directed’ as all variables in the graph are connected by unidirectional arrows representing a causal pathway, and ‘acyclic’ as the graph does not form a cycle (i.e., a variable in a DAG cannot cause itself).[250,251] Arrows in a DAG and their direction are based on prior knowledge,[250] usually in the form of a review of the literature, and causal assumptions.

6.2.1 Key components

In a DAG, a ‘path’ is a sequence of arrows in any direction that connects the exposure to the outcome.[250] There are three main types of path in a DAG – directed paths, backdoor paths, or blocked paths.[250] In a directed path, all arrows within a sequence point in the same direction, and the association between each of the variables within the directed path represents a causal relationship.[250] **Figure 6.1A** illustrates a direct path between the exposure and the outcome.

Figure 6.1: Illustration of the common paths in directed acyclic graphs



A backdoor path occurs when two variables in a DAG share the same cause (known as a common cause).[250] For example, the DAG in **Figure 6.1B** shows a backdoor path from exposure to outcome via a common cause ‘Variable X’. The presence of a common cause or a backdoor path in a DAG is equivalent to the presence of confounding.[250] Confounding can distort estimates of the effect of an exposure on an outcome and confounding variables should be adjusted for in analyses to remove their effects. However, when the confounding variable is unknown, unmeasured, or partially adjusted for in analysis, it is likely there will be residual confounding.[250,252]

A blocked path occurs when two variables in a DAG have the same effect (known as a common effect or a collider).[250] In **Figure 6.1C**, 'Variable Y' is a collider that blocks the path between the exposure and the outcome. Adjusting for a collider variable in analysis can introduce collider bias, a form of selection bias that can distort associations between an exposure and outcome.[250,253] For example, when investigating the association between shift work and sleep apnoea, adjusting for disturbed sleep would introduce collider bias as disturbed sleep can occur as a common consequence of both shift work and sleep apnoea.[254]

In a DAG, a mediator is a variable caused by the exposure that in turn causes the outcome.[250,251] In **Figure 6.1D**, 'Variable Z' is an example of a mediator as it lies on the causal pathway between exposure and outcome. Decisions on whether to adjust for mediating variables in analyses depend on the research questions being asked in a study. If the research question is focused on understanding the total effect of the exposure on the outcome, adjusting for mediators would lead to an underestimation of the effect of the exposure.[250] However, if the research question is to understand the direct effect of the exposure on the outcome, adjusting for mediators, or more complex mediation analyses, would occur.[255]

6.2.2 Limitations

The creation of a DAG is dependent on the prior knowledge and causal assumptions of researchers involved. Simplifying complex relationships between variables into DAGs can be difficult and may miss some nuances between associations. It is also possible that some assumptions are incorrect, or that different researchers may have different opinions on the relationships between variables in a DAG. Differing assumptions between researchers may lead to the creation of several DAGs for a single research question, with the correct DAG being unknown. Although the reliance on causal assumptions can be seen as a limitation, DAGs can encourage discussion between researchers as they provide explicit visual representation of the assumptions made.[250] In the case of several potential DAGs, the results of analyses guided by different DAGs can be reviewed to investigate the effect of different assumptions.[256] One clear limitation of standard DAGs is that they cannot be used to

convey information about effect modification – when the effect of an exposure on the outcome differs depending on the level of a third variable.[256] A different type of DAG, known as the interaction DAG (IDAG) can be constructed,[257] however, it's use is beyond the scope of the work presented in this thesis.

6.3 Key variables

Using the results of the systematic review described in **Chapter 3**, and existing literature, I identified key variables potentially involved in associations between atopic eczema, and depression, anxiety or SMI, and the association between psoriasis and SMI. In the following sections, I will describe how I considered each of the variables to be related to the exposures (atopic eczema or psoriasis) and the mental health outcomes (depression, anxiety, or SMI) under investigation. The variables that can be captured in CPRD GOLD are referred to as measured variables (see **Chapter 5** for how they were captured using CPRD data). Other variables are not well captured or are not recorded, in CPRD GOLD and are therefore referred to as unmeasured variables.

I used the information on the relationships between each of the variables and the exposures and outcomes to create DAGs. I drew simplified DAGs using an online application called DAGitty and used the DAGs to inform covariate selection for the population-based cohort studies included in this thesis (**Chapters 7,8**).[258] **Figure 6.2** shows a DAG of the relationships between atopic eczema and depression, anxiety, and SMI. **Figure 6.3** shows a DAG of the relationship between psoriasis and SMI. **Table 6.1** provides a summary of the variables included in the DAGs and their roles in the population-based cohort studies included in the thesis.

6.3.1 Measured variables

6.3.1.1 Age

Age can be considered a potential confounder of associations between atopic eczema, and depression, anxiety or SMI, and the association between psoriasis and SMI. Atopic eczema can occur at any age, however, the usual age of onset is in

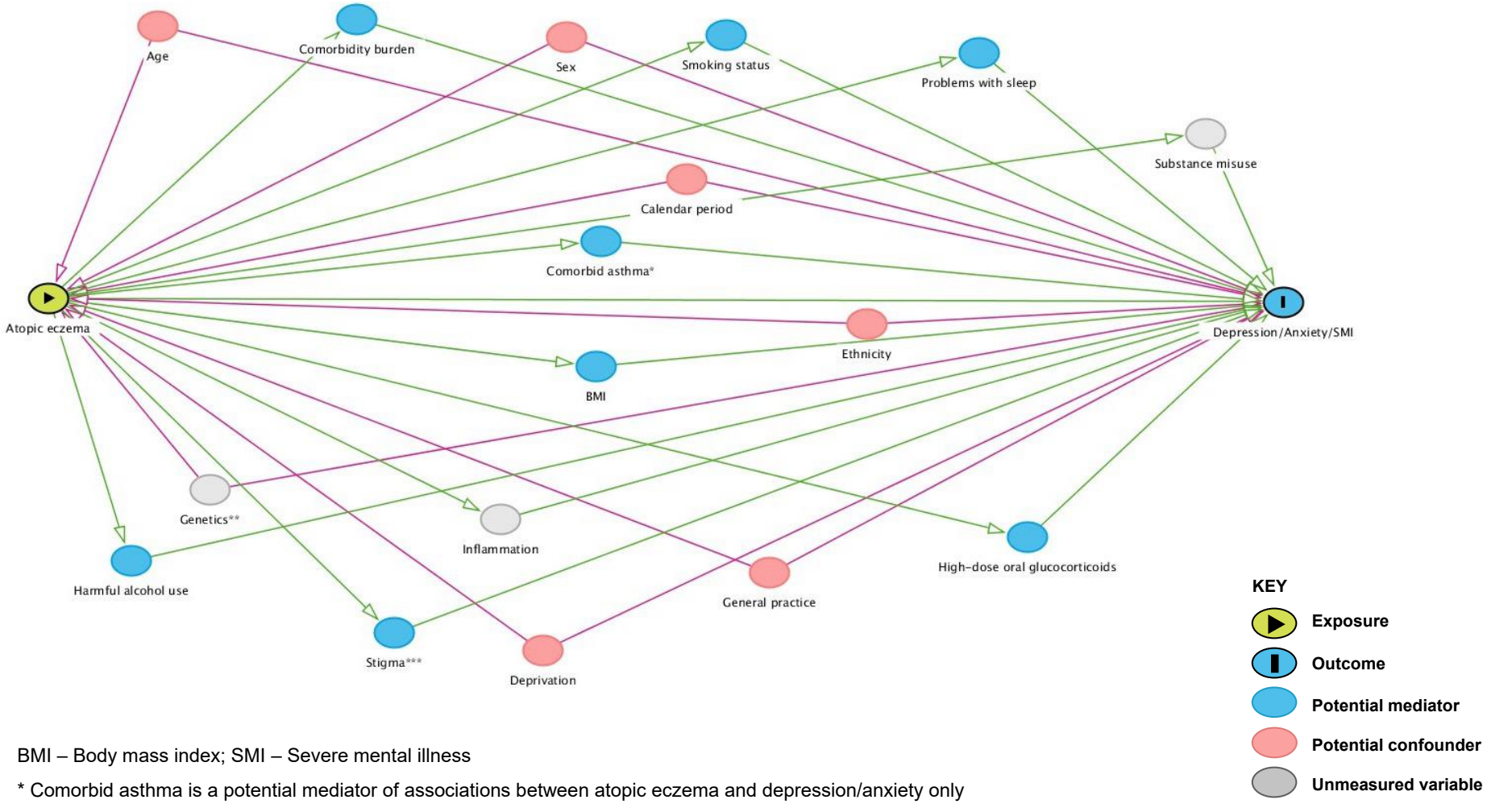
early childhood, with the highest incidence at age 3-6 months.[40] and 85% of cases occurring before 5 years of age.[41]The incidence of atopic eczema is lower in adulthood.[153] The prevalence of atopic eczema is highest among children aged 0-17 and older adults aged 75-99, with prevalence increasing with age among older adults, and decreasing with age among children.[152] Psoriasis can occur at any age, however, the mean age of onset for the first presentation of psoriasis is between 15-20 years of age, with a second peak between 55-60 years.[42] Additionally, most affected individuals present with psoriasis before 35 years of age.[2] Prevalence of psoriasis has also been shown to be highest among individuals aged between 55 and 75 years of age.[259] Depression and anxiety can affect people of all ages; however, prevalence rates by age vary between the two conditions. Prevalence of depression peaks in older adulthood (individuals aged between 55-74 years), but it can also occur at a lower level than adults in children and adolescents below the age of 15.[106] On the other hand, prevalence rates of anxiety do not differ considerably between age groups, however, prevalence tends to decrease among older age groups.[106] In England, prevalence of SMI is highest among people aged 35-74 compared to those aged 15-34.[7]

6.3.1.2 Sex

Sex can be considered a potential confounder of associations between atopic eczema, and depression, anxiety or SMI, and the association between psoriasis and SMI. Evidence from several studies suggest that atopic eczema is more common in women compared to men,[152,153] with a systematic review of population-based studies reporting a higher prevalence of atopic eczema in women compared to men.[260] In contrast, there is a lack of agreement on variations in psoriasis incidence or prevalence by sex. Some studies reported higher rates of psoriasis in women compared to men, while others reported contradictory results with higher rates in men.[2,154] Depression and anxiety are more common among women than men.[105,106,109] In 2014, the Adult Psychiatric Morbidity Survey (APMS) found that 22.5% of women aged 16 and older showed symptoms of anxiety and depression, a larger proportion compared to 16.8% in men.[156] The prevalence of SMI as a whole is higher in males compared to females.[7] In terms of specific SMI diagnoses, diagnosis

of schizophrenia and other psychoses is more common in men, while diagnoses of bipolar disorder is more common in women.[128]

Figure 6.2: Directed acyclic graph illustrating the implicitly assumed causal relationship between atopic eczema and depression, anxiety, or SMI



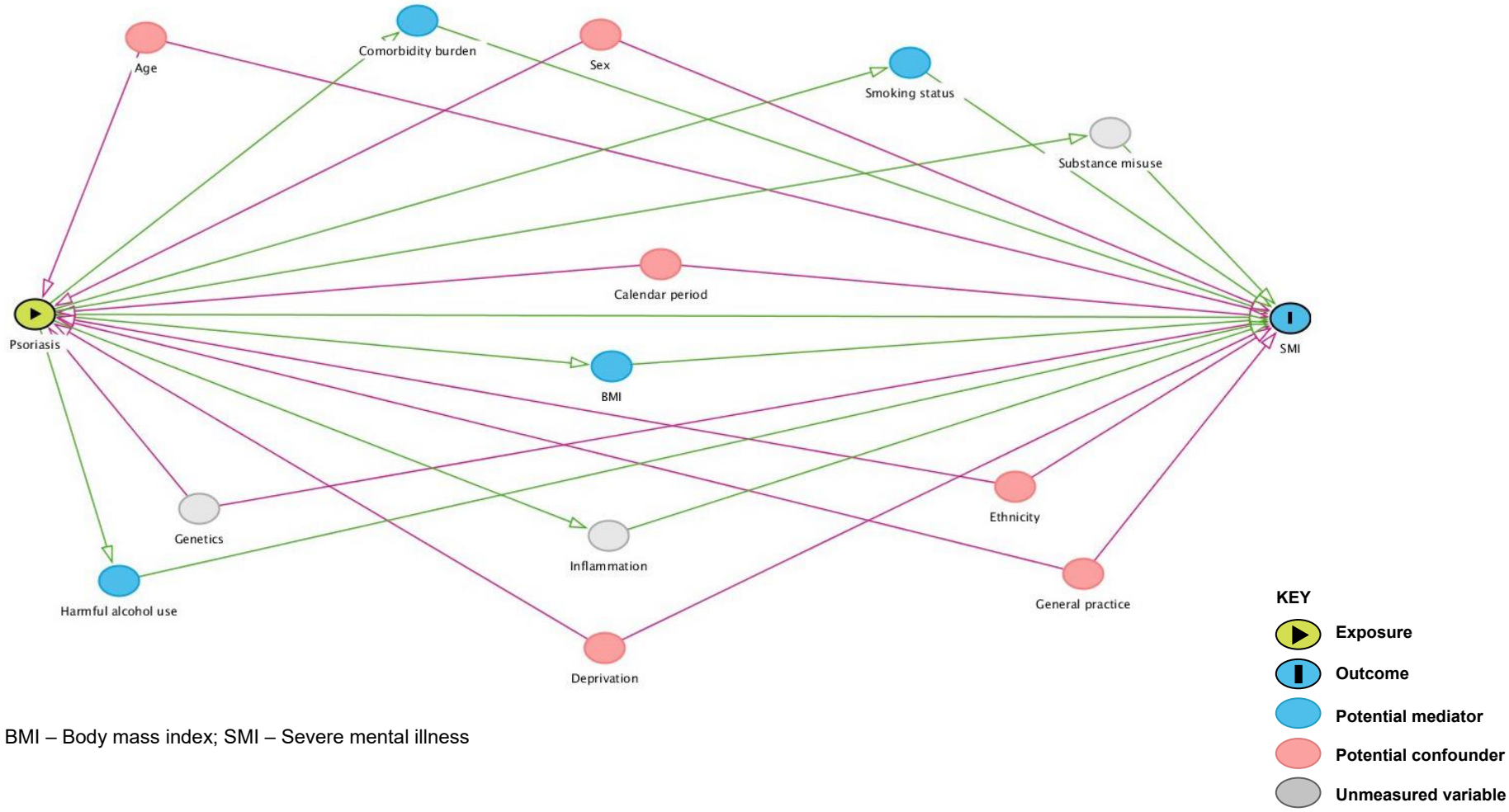
BMI – Body mass index; SMI – Severe mental illness

* Comorbid asthma is a potential mediator of associations between atopic eczema and depression/anxiety only

** Evidence of a genetic link between atopic eczema and depression only

*** Stigma is a potential mediator of associations between atopic eczema and depression/anxiety only

Figure 6.3: Directed acyclic graph illustrating the implicitly assumed causal relationship between psoriasis and SMI



BMI – Body mass index; SMI – Severe mental illness

Table 6.1: Summary of variables included in the DAGs and their roles in the population-based cohort studies included in this thesis

Variable	**Captured in CPRD GOLD?**	**Population-based cohort studies included in this thesis**			
		Associations between atopic eczema or psoriasis and SMI (Chapter 7)		**Associations between atopic eczema and depression or anxiety in white and minority ethnic groups (Chapter 8)**	
		Included	**Role**	**Included**	**Role**
Age	Yes	Yes	Confounder	Yes	Confounder
Sex	Yes	Yes	Confounder	Yes	Confounder
General practice	Yes	Yes	Confounder	Yes	Confounder
BMI	Yes	Yes	Mediator	Yes	Mediator
Calendar period	Yes	Yes	Confounder	Yes	Confounder
Comorbidity burden	Yes	Yes	Mediator	Yes	Mediator
Comorbid asthma	Yes	No	N/A	Yes	Mediator
Socioeconomic deprivation	Yes	Yes	Confounder	Yes	Confounder
Ethnicity	Yes	Yes	Confounder	Yes	Effect modifier
Genetics	No	No	N/A	No	N/A
Harmful alcohol use	Yes	Yes	Mediator	Yes	Mediator
High-dose oral glucocorticoid use [a]	Yes	Yes	Mediator	Yes	Mediator
Inflammation	No	No	N/A	No	N/A
Problems with sleep [a]	Yes	Yes	Mediator	Yes	Mediator
Smoking status	Yes	Yes	Mediator	Yes	Mediator
Stigma	No	No	N/A	No	N/A
Substance misuse	No	No	N/A	No	N/A

BMI – Body mass index; SMI – Severe mental illness

[a] Considered as a covariate in atopic eczema analyses only

6.3.1.3 General practice

There may be differences in clinical and administrative practices between general practitioners (GPs) that individuals are registered to that may confound associations between atopic eczema and depression, anxiety, or SMI and the association between psoriasis and SMI. These may include differences in the implementation and adherence of clinical practice guidelines,[261] differences in the recording of atopic eczema or psoriasis exposure and mental health outcomes,[128] or recording of covariates (i.e., body mass index).[262]

6.3.1.4 Body mass index

Body mass index (BMI) can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Evidence suggests that a high body mass index (BMI) is associated with atopic eczema and psoriasis. A population-based study in the UK using primary care data found that people with atopic eczema had 8% higher odds of being overweight or obese compared to those without atopic eczema.[75] A similar relationship is seen between psoriasis and BMI. A meta-analysis of 16 observational studies found that people with psoriasis had 66% higher odds of obesity compared to those without psoriasis.[157] A longitudinal study also found that the risk of new-onset obesity was 18% higher in individuals with psoriasis compared to those without.[158] Possible explanations for the association between skin disease and obesity may include people with skin disease avoiding physical exercise to prevent sweat agitating inflamed skin,[74] or the underlying systemic inflammation in the skin disease itself leading to weight gain.[75]

Higher BMI is also strongly associated with increased risk of depression and anxiety,[162,163] with evidence from Mendelian randomisation studies suggesting a causal mechanism.[164] A high BMI is also associated with SMI. Studies have found a high prevalence of obesity in people with SMI, with these individuals being up to three times more likely to be overweight or obese than the general population.[198] However, there is a lack of clarity on the direction of the relationship between BMI and SMI. There is some evidence to suggest that high BMI may occur as a consequence of SMI. Studies have found that people with SMI diagnoses lead

unhealthy lifestyles by consuming poor diets, smoking more and engaging in less physical activity than the general population,[263] all factors that contribute to obesity. Second generation antipsychotics such as Olanzapine and Clozapine have been found to result in rapid weight gain, with data suggesting an increase of up to 17kg in the first year of treatment.[264] On the other hand, genetics may play a role in the association between BMI and SMI. Genetic linkage studies have suggested that the 1q21– 42 region is of interest as this area is associated with an increased risk of obesity and the development of schizophrenia.[198] However, this hypothesis is speculative and not supported by empirical evidence.

This evidence suggests that the relationship between BMI and SMI is complex and includes several factors. Because of the limited studies investigating the direction of the relationship between BMI and SMI, and the evidence that suggests an increased BMI may occur as a result of SMI diagnosis, BMI can be considered as both a potential mediator or a collider variable of the associations between atopic eczema or psoriasis and SMI. However, to avoid potential collider bias in the population-based cohort studies, I considered BMI as a potential mediator of associations between atopic eczema and depression, anxiety, or SMI and the association between psoriasis and SMI, and excluded BMI measurements recorded after the mental health outcome had occurred from analyses.

6.3.1.5 Calendar period

The relationships between atopic eczema, and depression, anxiety, or SMI and between psoriasis and SMI may be confounded by various calendar-based factors that affect how well recognised and recorded variables are by clinicians in primary care electronic health records over time. There is some evidence that chronic diseases such as atopic eczema may be more poorly recorded over time in UK primary care as GPs are not required to enter codes each occasion a patient visits the GP,[213] however, capture of codes as consecutive visits has not been fully investigated. Studies have shown that over time, the incidence of diagnosed depression and anxiety fell, while the incidence of depressive and anxiety symptoms rose.[109,126] After the introduction of performance indicators for depression in the Quality and Outcomes Framework (QOF) in 2006, GP recording of depression or

anxiety has been further altered, and the use of symptom codes for both depression and anxiety have additionally increased.[111] Similarly, renumeration for SMI recording has been included in the QOF since 2004 which may possibly affect how well SMIs are recognised and recorded by GPs.[128]

6.3.1.6 Comorbid asthma

Atopic eczema has been found to be associated with, or predispose affected individuals to, numerous atopic comorbidities including asthma.[59–62] Early research suggests that atopic eczema precedes the development of asthma in what is known as the 'atopic march',[63] however, evidence from longitudinal research and studies using machine learning have challenged this concept. Although alternative trajectories of atopic disease progression to the atopic march have been proposed, evidence suggests that atopic eczema and asthma often develop alongside each other, either due to a common genetic predisposition, or through impaired immunity.[68,69] Asthma is also known to be associated with anxiety and depression, with the literature reporting a higher prevalence and incidence of depression and anxiety in people with asthma compared to the general population.[178] Comorbid asthma can therefore be considered a potential mediator of associations between atopic eczema and depression or anxiety.

6.3.1.7 Comorbidity burden

Comorbidity burden can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Atopic eczema has been found to be associated with several atopic comorbidities (e.g., asthma and allergic rhinitis),[59–62] cardiovascular outcomes (e.g., hypertension, coronary heart disease, heart failure) which may partly relate to lifestyle habits (i.e., sedentary lifestyle, diet, harmful alcohol consumption),[59,71–75] infections,[1,79] and fractures.[80] Psoriatic arthritis (PsA) is the most common comorbidity people with psoriasis are at increased risk of, with approximately 30% of psoriasis patients developing the condition within their lifetime.[81] Individuals with psoriasis are also at increased risk of metabolic syndrome (type 2 diabetes mellitus, hypertension, obesity, hyperlipaemia),[82] myocardial infarction,[83] stroke,[84] and cardiovascular mortality[85] compared to the general population.

The relationships between comorbidity burden and depression, anxiety and SMI are often complex and bidirectional. Long-term physical health problems such as cancer, diabetes, cardiovascular disease, and other chronic conditions can be distressing and lead to depression or other psychological problems in affected individuals. For example, anxiety is common in people with chronic respiratory diseases, while depression is more common in people with diabetes.[115] However, there is also evidence that mental health conditions can increase the risk of chronic conditions. Evidence from systematic reviews and meta-analyses suggest that depression and anxiety disorders are independent risk factors for diabetes and coronary heart disease.[115] There is compelling evidence that people with SMI experience poorer physical health than the general population and have a higher prevalence of chronic conditions such as cardiovascular disease, liver disease, respiratory disease and cancer.[7] Second-generation antipsychotic medications are well known to cause both obesity and diabetes,[264] however there is also limited evidence of a shared genetic link between diabetes and other cardiometabolic diseases and schizophrenia.[265,266]

Due to the complexity of the relationship between chronic conditions and mental illness, comorbidity burden can be considered a potential mediator or collider of the associations between atopic eczema or psoriasis and depression, anxiety, or SMI. To avoid potential collider bias in the population-based cohort studies, I considered comorbidity burden a potential mediator of associations between atopic eczema and depression, anxiety, or SMI and the association between psoriasis and SMI, and excluded comorbidities recorded after the mental health outcome had occurred from analyses.

6.3.1.8 Socioeconomic deprivation

Socioeconomic deprivation can be considered a potential confounder of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Multiple studies have found that a higher socioeconomic status (and thus lower levels of deprivation) in children is associated with an increased prevalence of atopic eczema,[35,152] while in adulthood, prevalence was either unaffected by socioeconomic status or higher in individuals with lower socioeconomic status.[152,153] On the other hand, lower socioeconomic status is

associated with increased atopic eczema severity.[35] Overall, studies suggest that atopic eczema prevalence estimates are plateauing over time in high-income countries, and increasing in low- middle-income countries with the largest increase occurring over the past 30 years.[1,41] Evidence suggests that psoriasis is more common in countries with a higher socioeconomic status (e.g., Australia and Norway),[2,267] however, individuals with psoriasis are more likely to be unemployed or have a lower income (low socioeconomic status).[155] There is also strong evidence that people of lower socioeconomic status (and high levels of deprivation) are more likely to develop and experience mental health problems such as depression, anxiety, or SMI.[7,109,156]

6.3.1.9 Ethnicity

Ethnicity can be considered a potential confounder of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. There is evidence that atopic eczema is more common in Black or Asian ethnic groups,[153,183,268] while psoriasis is more common in individuals of White ethnicity.[184] There are also ethnic differences in the risk of mental illness. According to data from the United States, African Americans, and people from a Hispanic background exhibit elevated rates of major depression compared to those of White ethnicity.[185] The prevalence of depression has also been shown to be higher in migrants and ethnic minorities in UK primary care.[187] In the UK, Black and minority ethnic groups (BME) have been shown to have higher rates of SMI, with the risk of psychosis in Black ethnic groups estimated to be nearly seven times higher than in the White population.[156] A systematic review and meta-analyses of the incidence of schizophrenia and other psychoses in England reported that rates of psychotic illness were elevated in Black and South Asian minority ethnic groups compared to the White population.[138]

There are also several mechanisms by which ethnicity can be considered a potential effect modifier of associations between atopic eczema and depression or anxiety including: (1) darker skin in individuals from minority ethnic groups affecting atopic eczema diagnosis and treatment, and subsequently impacting mental health;[183] (2) dyspigmentation in individuals with darker skin exacerbating feelings of discomfort

and stigmatisation, further contributing to development of depression or anxiety;[183] (3) the association of atopic eczema with various beliefs and taboos in different cultures leading to a profound effect on mental health;[190] and (4) individuals from minority ethnic groups being disproportionately affected by barriers to health services, deprivation, discrimination and racism, all of which can reinforce health inequalities and also have a negative impact on mental health.[195,196] Genetics may also play a role in the ethnic variation of associations between atopic eczema and depression or anxiety, however, this is likely to be a small part, and other previously described factors (underdiagnosis, dyspigmentation, cultural beliefs, healthcare barriers) are likely to play a more important role.[269]

6.3.1.10 Harmful alcohol use

Evidence shows that individuals with atopic eczema or psoriasis consume more alcohol than the general population and subsequently have a higher prevalence of alcohol use disorders compared to populations without skin disease.[74,159,160] Harmful alcohol use and alcohol dependence have been regularly associated with symptoms of depression and anxiety.[165,166] Similarly, a high prevalence of heavy drinking and alcohol use disorders has been identified in people with SMI.[199] Chronic alcohol consumption (consuming large amounts of alcohol for an extended period of time) or alcohol withdrawal in a formerly dependent individual can induce hallucinations or delusions, both of which are symptoms of psychosis.[201] Harmful alcohol use can therefore be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI.

6.3.1.11 High-dose oral glucocorticoid use

The use of high-dose oral glucocorticoids can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI. High dose oral glucocorticoids (≥20mg/day prednisolone equivalent dose) such as prednisolone, dexamethasone, and hydrocortisone may be used for short-term use in individuals where topical treatments or phototherapy have failed, or in people with severe atopic eczema flares.[1,29] During therapy, glucocorticoids can induce psychiatric side effects including symptoms of depression, anxiety, mania, and psychosis, however, their effect is temporary.[171]

6.3.1.12 Problems with sleep

In people with atopic eczema, sleep disturbances are a common and well-recognised consequence of severe itch. Chronic and intense itching is a major clinical manifestation of atopic eczema that continues throughout the day and gets worse at night, leading to sleep disturbance or deprivation.[41] Studies have found that people with atopic eczema are more likely to report fatigue, regular insomnia, shorter sleep duration, and daytime sleepiness when compared to the general population.[169] Dry, itchy skin is also a characteristic of psoriasis in affected individuals, however, understanding of sleep disturbance in psoriasis is limited.[270] Longitudinal evidence has identified sleep disturbances as risk factors for the development of depression and anxiety,[170] while high levels of sleep deprivation have been linked to SMI like symptoms such as hallucinations and distorted perceptions.[205,271,272] Problems with sleep can therefore be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI.

6.3.1.13 Smoking status

Smoking status can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Evidence suggests that both atopic eczema and psoriasis are associated with smoking. Adults with atopic eczema are 28% more likely to be current smokers compared to the general population,[74] while the prevalence of ever smoking was higher in adults with psoriasis compared to the general population.[161] Smoking rates are also high in individuals with depression, anxiety, or schizophrenia, with some longitudinal evidence suggesting that smoking leads to later development of depression or anxiety.[167] People with a psychiatric disorder are twice as likely to smoke compared to people without.[242] Results of meta-analysis from a large systematic review suggests that daily smokers are more than twice as likely to develop new psychotic disorders compared to non-smokers.[200] Specifically in individuals with atopic eczema, a relationship has been demonstrated between smoking status and an increased risk of depression.[168]

6.3.2 Unmeasured variables

6.3.2.1 Substance misuse

Substance misuse can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Substance misuse can be defined as the use of illegal psychoactive drugs, or the use of prescription or over-the-counter medication for purposes other than those they are meant for.[273] Evidence suggests that people with atopic eczema or psoriasis are more likely than people in the general population to misuse substances such as cannabis.[202,203] One potential reason for cannabis use is that cannabinoids have a powerful anti-itch effect that could potentially reduce the symptoms and appearance of atopic eczema or psoriasis.[274] Heavy and regular use of cannabis is also associated with an increased risk of depressive symptoms,[275] and evidence suggests that cannabis can trigger schizophrenia or psychosis in people who are at risk of SMI.[204] However, studies have reported that substance misuse is recorded in primary care at lower rates compared to national surveys,[276] and that GPs consider many factors (e.g., the potential adverse effect on GP-patient relationships) before deciding whether to ask patients about and/or record substance misuse in primary care records.[273] There are also stigmas associated with substance misuse,[273] so affected individuals may not feel comfortable discussing substance use with their GPs. Substance misuse is therefore incompletely captured in CPRD GOLD and has been considered an unmeasured variable.

6.3.2.2 Genetics

Limited studies have suggested a shared genetic link between atopic eczema and depression.[179] There is also evidence of a shared genetic aetiology from genome wide association studies (GWAS) between psoriasis and schizophrenia that may involve immune signalling pathways.[207] The evidence suggests that genetics may potentially confound the associations between atopic eczema and depression, or psoriasis and schizophrenia, however, studies investigating the role of genetics in the association between skin diseases and mental illness should be interpreted with caution due to limited evidence. Genetic links and biomarkers are not recorded in CPRD GOLD; therefore, genetics can be considered an unmeasured variable.

6.3.2.3 Inflammation

Inflammation can be considered a potential mediator of associations between atopic eczema, and depression, anxiety, or SMI, and the association between psoriasis and SMI. Both atopic eczema and psoriasis are chronic inflammatory skin diseases that are characterised by elevated levels of circulating pro-inflammatory cytokines.[29–31] Evidence also suggests that as atopic eczema or psoriasis severity increases, so do the levels of inflammatory markers.[173,174] Both depression and anxiety have been associated with increased inflammatory response of the immune system,[175] and clinical trials of biologics that target inflammatory cytokines in those with atopic eczema or psoriasis have found that these drugs may also be associated with a reduction in symptoms of depression and anxiety.[176,177] Inflammatory biomarkers seen in people with atopic eczema or psoriasis have also been identified in people with SMIs such as schizophrenia or bipolar disorder.[29–31,206] Inflammation is not recorded in CPRD GOLD; therefore, it is considered an unmeasured variable.

6.3.2.4 Stigma

Stigma can be considered a potential mediator of associations between atopic eczema, and depression or anxiety. Stigma plays a major role in the lives of individuals with visible skin disease. In a survey of adults with atopic eczema, respondents indicated perceiving stigma in social events, employment, romantic relationships and self-image.[172] Stigma can exacerbate negative emotions and impact the self-esteem of those affected, consequently leading to mental health outcomes.[172] Stigma has been found to be a predictor for depressive symptoms and psychological factors in people with atopic eczema and psoriasis.[91,172] Individuals with psoriasis have also reported experiencing both social stigmatisation (lack of acceptance from others) and self-stigmatisation (low self-esteem due to a lack of self-acceptance) which can result in impaired social functioning (e.g., social activities, personal relationships),[96,97] however, the effect this may have on associations with SMI is unclear. Stigma is not recorded in CPRD GOLD; therefore, it is considered an unmeasured variable.

6.4 Summary

- DAGs are causal diagrams often used in epidemiological studies as a visual representation of the assumptions made regarding the causal relationships between variables.
- In this chapter, I described how I considered key variables (identified from the results of the systematic review described in **Chapter 3**, and existing literature) to be related to exposures and outcomes in associations between: 1) atopic eczema, and depression, anxiety, or SMI: and 2) between psoriasis and SMI.
- I also described how I used this information on the role of key variables in relation to exposures and outcomes to draw DAGs that informed the study design and covariate selection for the population-based cohort studies included in the thesis (**Chapters 7,8**).
- In the following chapter, I will describe the population-based cohort studies conducted to investigate longitudinal associations between atopic eczema or psoriasis and incident SMI among adults. I used the DAGs shown in this chapter to inform the study design and covariate selection for statistical analysis in this study.

7 Severe mental illness among adults with atopic eczema or psoriasis: population-based matched cohort studies within UK primary care

7.1 Introduction

In the previous chapter, I described how I used the information about key variables to draw directed acyclic graphs (DAGs) about the associations between atopic eczema and depression, anxiety, and severe mental illness (SMI), and associations between psoriasis and SMI. In this chapter, I will describe the population-based cohort studies (considering atopic eczema and psoriasis in two separate cohorts) I conducted to address the second objective of this thesis – investigating associations between atopic eczema or psoriasis and incident SMI. These studies used data from the Clinical Practice Research Datalink and its linkages (**Chapter 4**). I used the results from the systematic review (**Chapter 3**) and the DAGs described in **Chapter 6** to inform covariate selection for these studies.

7.2 Ethical approvals

The protocol for these studies was approved by the CPRD's Research Data Governance (RDG) Process (Protocol number: 20_051) and the London School of Hygiene & Tropical Medicine Ethics Committee (Reference number: 17815).

7.3 Article

A manuscript for this study has been published in a peer reviewed scientific journal (Clinical Epidemiology) and is provided on the following pages. The supplementary material referred to in the manuscript is provided in **Appendix 4** of this thesis.

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Surname/Family Name	Adesanya		
Thesis Title	Depression, anxiety, and severe mental illness among adults with atopic eczema or psoriasis		
Primary Supervisor	Dr Kathryn Mansfield		

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Stage of publication	**In press**

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 carried out the statistical analysis of the study and wrote the first draft of the manuscript. All authors contributed to further drafts and approved the final manuscript.

SECTION E

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ORIGINAL RESEARCH

Severe Mental Illness Among Adults with Atopic Eczema or Psoriasis: Population-Based Matched Cohort Studies within UK Primary Care

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Background: Existing research exploring associations between atopic eczema (AE) or psoriasis, and severe mental illness (SMI – ie, schizophrenia, bipolar disorder, other psychoses) is limited, with longitudinal evidence particularly scarce. Therefore, temporal directions of associations are unclear. We aimed to investigate associations between AE or psoriasis and incident SMI among adults.

Methods: We conducted matched cohort studies using primary care electronic health records (January 1997 to January 2020) from the UK Clinical Practice Research Datalink GOLD. We identified two cohorts: 1) adults (≥18 years) with and without AE and 2) adults with and without psoriasis. We matched (on age, sex, general practice) adults with AE or psoriasis with up to five adults without. We used Cox regression, stratified by matched set, to estimate hazard ratios (HRs) comparing incident SMI among adults with and without AE or psoriasis.

Results: We identified 1,023,232 adults with AE and 4,908,059 without, and 363,210 with psoriasis and 1,801,875 without. After adjusting for matching variables (age, sex, general practice) and potential confounders (deprivation, calendar period) both AE and psoriasis were associated with at least a 17% increased hazard of SMI (AE: HR=1.17,95% CI=1.12–1.22; psoriasis: HR=1.26,95% CI=1.18–1.35). After additionally adjusting for potential mediators (comorbidity burden, harmful alcohol use, smoking status, body mass index, and, in AE only, sleep problems and high-dose glucocorticoids), associations with SMI did not persist for AE (HR=0.98,95% CI=0.93–1.04), and were attenuated for psoriasis (HR=1.14,95% CI=1.05–1.23).

Conclusion: Our findings suggest adults with AE or psoriasis are at increased risk of SMI compared to matched comparators. After adjusting for potential mediators, associations with SMI did not persist for AE, and were attenuated for psoriasis, suggesting that the increased risk may be explained by mediating factors (eg, sleep problems). Our research highlights the importance of monitoring mental health in adults with AE or psoriasis.

Keywords: epidemiology, dermatology, psychology

Introduction

Atopic eczema (AE) and psoriasis are common inflammatory skin diseases associated with substantial morbidity and impaired quality of life for both sufferers and their families.[1,2] Worldwide, AE affects 1–3% of adults, and psoriasis affects up to 2% of adults.[3,4]

Severe mental illnesses (SMIs, including schizophrenia, bipolar disorder, and other psychoses) are long-lasting psychological conditions affecting approximately 0.9% of the UK population.[5] People with SMI experience substantial health inequalities including a higher prevalence of chronic comorbidities (eg, respiratory, or cardiovascular disease), a shorter life expectancy (up to 20 years) and increased mortality than the general population.[5,6]

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Substantial evidence demonstrates associations between atopic eczema or psoriasis and several psychiatric comorbidities including depression,[7–10] anxiety,[7,10] and suicidality.[7–10] Limited evidence from cross-sectional[11–13] and case–control[14–17] studies suggest an association between AE or psoriasis and SMIs. Potential mechanisms for the relationships are unclear; however, proposed hypotheses include shared genetic susceptibility, immune dysregulation, unhealthy lifestyle choices (eg, harmful alcohol use), and chronic itch in AE leading to sleep deprivation and subsequent psychiatric symptoms.[13,14,18–22]

Longitudinal evidence for associations between AE or psoriasis and SMI in adults are particularly scarce, with only a few studies – with important limitations (including small study populations or focus on specific SMIs) – aiming to address temporal associations.[23–27] Temporality of associations between AE or psoriasis and SMI in adults are therefore unclear. Temporal associations between AE or psoriasis and SMI could substantially impact public health as AE and psoriasis are common, and there is considerable morbidity and mortality associated with SMI.

We undertook matched cohort studies using primary care electronic health record data to investigate longitudinal associations between AE or psoriasis, and incident SMI in adults. We also explored whether associations varied with AE or psoriasis severity.

Methods

Study Design and Setting

We conducted two matched cohort studies between January 2, 1997, and January 31, 2020, using primary care electronic health record data from the UK's Clinical Practice Research Datalink (CPRD GOLD). CPRD is an ongoing, nationwide primary care database of routinely collected and anonymised medical records that includes approximately 7% of the UK population.[28]

Study Population

All adults (≥18 years) with at least 1 year of registration with a general practice meeting CPRD quality-control standards during the study period were eligible for inclusion. We identified two matched cohorts: 1) people with and without AE and 2) people with and without psoriasis. We matched (without replacement) each adult with AE or psoriasis on age (within 5 years), sex, and general practice with up to five adults without AE (in the AE cohort) or psoriasis (in the psoriasis cohort) in calendar date order (Appendix S1). Adults with AE and psoriasis were identified using previously validated definitions.[29,30] The AE definition required records of at least one diagnostic code, and at least two skin disease therapies (eg, phototherapy or prescriptions for topical or oral drugs) recorded on separate days. Individuals were determined as having AE from the latest record of either their first AE diagnostic code, or the second record for AE therapy. The psoriasis definition required a record of at least one diagnostic code.

We followed individuals with AE or psoriasis from the latest of (index date): study start (January 2, 1997); date they met AE or psoriasis definitions; 1 year after the date of registration with their practice; date their practice met CPRD quality-control standards; or their 18th birthday. Follow-up for individuals without AE or psoriasis began on the same date as matched individual with AE or psoriasis. Follow-up ended at the earliest of SMI diagnosis; study end (January 31, 2020); end of registration with practice; practice no longer contributing data to CPRD; AE or psoriasis diagnosis (for adults without) or death (Figure 1).

Outcome

We identified SMI based on the earliest primary care record of an SMI diagnostic Read code (schizophrenia, bipolar disorder, other non-organic psychoses). We considered broader definitions of SMI (including "symptom" codes, eg, delusions) in sensitivity analyses (Table S1). We excluded adults with a diagnosis of any SMI before follow-up began. Individuals with prior depression or anxiety were not excluded as they may represent early symptoms of SMI or be present in individuals later develop SMI.

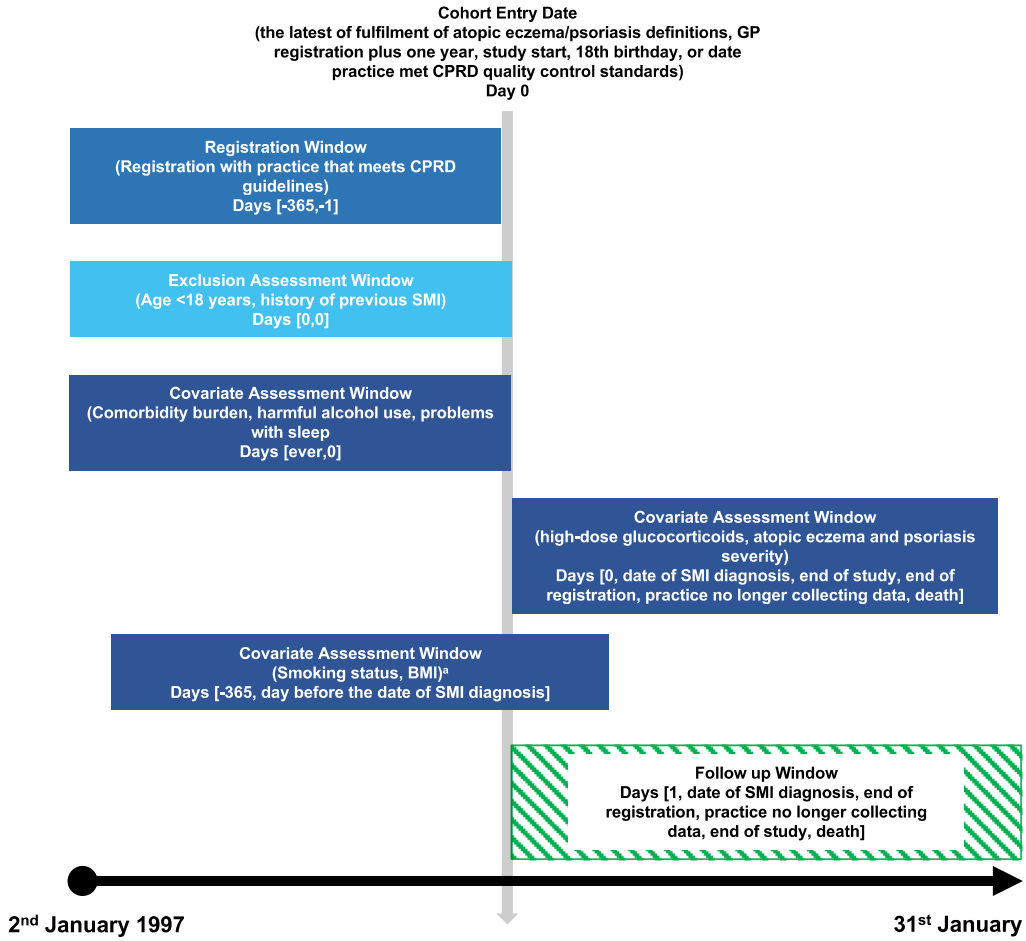

Figure 1 Diagram of cohort study design, describing the dates of cohort entry, covariate assessment, follow-up, and study exit. [a]Identified using an algorithm where records identified within −1 year to +1 month of the index date are regarded as the best, +1 month to +1 year from the index date as second best, the nearest before −1 year from the index date as the third best, and the nearest after +1 year from the index date as the worst. Smoking status or body mass index recorded after severe mental illness diagnosis were not used.
Abbreviations: BMI, body mass index; CPRD, Clinical Practice Research Datalink; SMI, severe mental illness.

Covariates

We used directed acyclic graphs (DAGs) and a systematic review to inform covariate selection (Appendix S2).[31,32] We matched on age, sex, and general practice, and considered calendar time (1997–2003, 2004–2009, 2010–2015, 2016–2020) and deprivation (quintiles of patient-level Carstairs Index used when available, otherwise practice-level Carstairs Index used) as potential confounders.[33] We considered the following variables as potential mediators: comorbidity burden (using the Charlson Comorbidity Index),[34] body mass index (BMI), smoking status, harmful alcohol use, and in AE only, sleep problems and high-dose glucocorticoid use. We considered age, sex, and calendar period as potential effect modifiers as associations between AE or psoriasis and SMI may be modified by age and sex differences in SMI prevalence,[5] and changes in clinical, diagnostic, and administrative practices over time. Further details on covariate definitions are available in Appendix S3. Justifications of variable roles are available in Appendix S2.

Statistical Analyses

Main Analysis

We initially described characteristics of adults with and without AE or psoriasis. We used Cox regression, stratified by matched set,[35] with current age as the underlying timescale to estimate hazard ratios (HRs) and 95% confidence intervals for associations between AE or psoriasis, and SMI.

We initially constructed minimally adjusted models including only the main exposure variable (AE or psoriasis) and implicitly adjusting for age (through underlying timescale) and matching variables (age, sex, general practice) by stratifying on matched set, followed by sequential models further adjusting for other potential explanatory variables. In sequential models, we 1) adjusted for potential confounders (deprivation and calendar period) and 2) further adjusted for factors potentially on the causal pathway that mediate associations between AE or psoriasis and SMI (comorbidity burden, harmful alcohol use, smoking status, and BMI, and, in AE only, sleep problems and high-dose glucocorticoid use). Using sequential models allowed us to differentiate between the direct (eg, inflammatory effect of AE or psoriasis) and total effect through the skin disease and other potential mediating variables (eg, lifestyle factors) of AE or psoriasis on SMI. We assessed proportional hazards assumptions using Schoenfeld residuals (Appendix S4). All data were managed and analysed using Stata V16 (StataCorp, Texas, USA). Code lists for covariates and analysis code are available to download from an online repository.[36]

We estimated absolute incidence rates and rate differences for incident SMI in both AE and psoriasis cohorts. We repeated our analysis in a series of sensitivity analyses to assess the robustness of our findings (details in Table S1).

Secondary Analyses

We investigated associations between AE or psoriasis severity and by classifying individuals with AE as having mild, moderate, or severe disease, and individuals with psoriasis as having mild or moderate-to-severe disease using previously developed definitions.[37,38] We updated severity over time, and compared SMI risk at each severity level with risk in those without AE or psoriasis using stratified Cox regression. We stratified analyses separately by age, sex, and calendar period to investigate whether they modified associations between AE or psoriasis and SMI. We used likelihood ratio tests to test for statistical evidence of effect modification. We individually tested effects of potential mediators on confounder-adjusted associations between AE or psoriasis and SMI in a post hoc analysis.[39] Each potential mediator was added in a separate model. Further details on secondary analyses are available in Appendix S5.

Results

Baseline Characteristics

We initially identified 1,032,782 adults with AE matched to 4,990,125 without, and 366,884 with psoriasis matched to 1,834,330 without who were eligible for study inclusion (Figure 2). After excluding those with SMI diagnosed on or before follow-up began, and those who were not in valid matched sets (including at least one exposed and one unexposed individual), 1,023,232 adults with AE matched to 4,908,059 without, and 363,210 adults with psoriasis matched to 1,801,875 without remained.

In the AE cohort, median follow-up was 5.5 years (IQR:2.2–10.4) in those with AE, and 4.8 years (IQR:1.8–9.6) in those without. In the psoriasis cohort, median follow-up was 5.9 years (IQR:2.3–11.5) in those with psoriasis, and 5.9 years (IQR:2.4–11.4) in those without. People with and without AE or psoriasis had broadly similar age, sex, and deprivation (Table 1 and Table S2). More than half of individuals in both cohorts had missing ethnicity data, therefore ethnicity was only considered in sensitivity analyses. Fewer adults with AE or psoriasis had missing BMI and smoking data. Those with missing BMI or smoking status were more likely to be young and male compared to those with complete data (Tables S3 and S4).

Main Analysis

After adjusting for matching variables (age, sex, general practice) and potential confounders (calendar period, deprivation), both AE and psoriasis were associated with at least a 17% increased hazard of SMI (AE: HR=1.17, 95% CI:1.12–1.22; psoriasis: HR=1.26, 95% CI:1.18–1.35) (Table 2). Small differences in absolute SMI risk were seen between

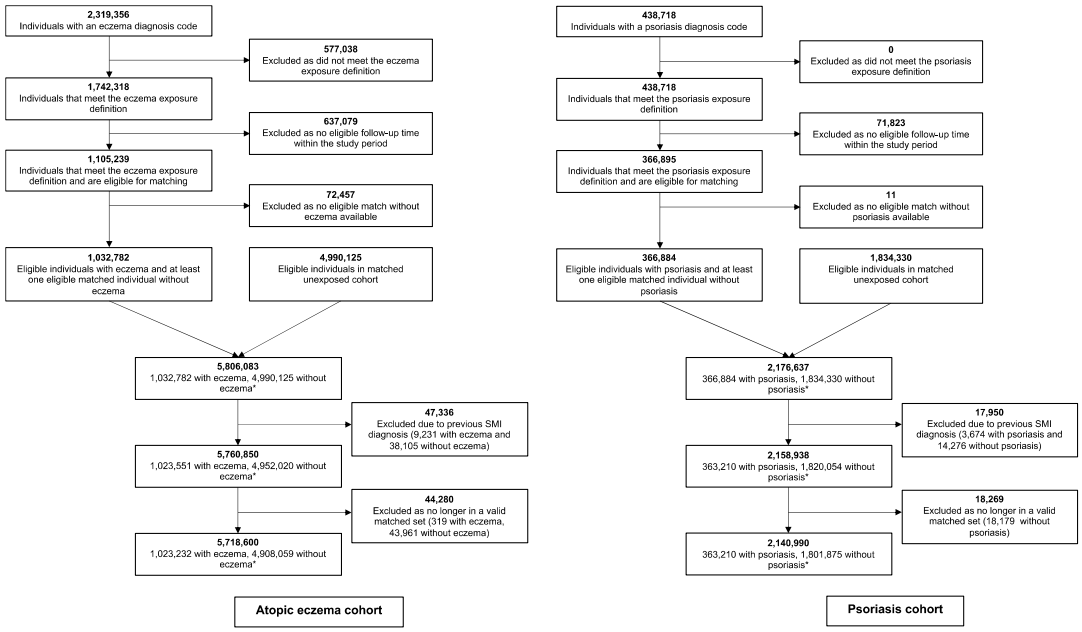

Figure 2 Flowchart illustrating identification of participants in atopic eczema and psoriasis cohorts. *Numbers of people with and without atopic eczema or psoriasis do not sum to the total number of individuals included in each cohort. Individuals with atopic eczema or psoriasis could be included in the matched comparison cohort up until the date of their first atopic eczema or psoriasis diagnosis.

individuals with and without AE or psoriasis (Table S5). After additionally adjusting for potential mediators (comorbidity burden, harmful alcohol use, smoking status, and BMI, and, in AE only, sleep problems and high-dose glucocorticoid use), associations with SMI did not persist in adults with AE (HR=0.98, 95% CI:0.93–1.04) and were attenuated in adults with psoriasis (HR=1.14, 95% CI:1.05–1.23). In sensitivity analyses, we saw similar results to the main analyses, however, additionally adjusting for ethnicity attenuated associations between AE or psoriasis and SMI (Table S1).

Secondary Analysis

Skin Disease Severity

In adults with severe AE and moderate-to-severe psoriasis, there were only a small number of SMI events (severe AE: 89 events; moderate-to-severe psoriasis: 43 events). We saw evidence that, compared to individuals without AE, individuals with moderate or severe AE had increased hazard of SMI (confounder-adjusted HRs: moderate AE: HR=1.61, 95% CI:1.50–1.73; severe AE: HR=1.56, 95% CI: 1.21–2.01) (Table S6, Figure 3). Compared to adults without psoriasis, individuals with mild psoriasis had increased hazard of SMIs (confounder-adjusted HR=1.28, 95% CI:1.19–1.37), while there was no evidence individuals with moderate-to-severe psoriasis were at increased risk of SMI (confounder-adjusted HR=0.97, 95% CI:0.69–1.35).

Effect Modification

We found no evidence the relationship between AE and SMI varied by sex or calendar period, but we found evidence of effect modification by age group ($p<0.01$). Adults aged 30–39 (HR=1.23, 95% CI:1.11–1.35) or 40–59 (HR=1.37, 95% CI:1.26–1.48) had the highest HRs for associations between AE and SMI (Table S7). In adults with psoriasis, we found no evidence associations with SMI varied by sex. However, we saw evidence ($p=0.01$) psoriasis was associated with increased SMI in all age groups apart from adults aged 30–39 (Table S7). We also saw evidence ($p=0.01$) of effect modification by calendar time, with HRs for associations between psoriasis and SMI higher in 2004–2009, 2010–2015, and 2016–2020 than in 1997–2003.

Table 1 Characteristics of Atopic Eczema and Psoriasis Cohorts at Cohort Entry

	Atopic Eczema Cohort		Psoriasis Cohort	
	With Atopic Eczema n=1,023,232	**Without Atopic Eczema n=4,908,059**	**With Psoriasis n=363,210**	**Without Psoriasis n=1,801,875**
Follow-up[a]				
Total person-years	6,995,892	30,935,170	2,680,394	13,246,255
Median (IQR) duration of follow-up (years)	5.5 (2.2–10.4)	4.8 (1.8–9.6)	5.9 (2.3–11.5)	5.9 (2.4–11.4)
Sex				
Female (%)	596,388 (58.3%)	2,842,125 (57.9%)	189,511 (52.2%)	940,489 (52.2%)
Age (years)[b]				
18–29	326,309 (31.9%)	1,566,148 (31.9%)	78,207 (21.5%)	389,718 (21.6%)
30–39	159,606 (15.6%)	796,251 (16.2%)	70,325 (19.4%)	349,056 (19.4%)
40–59	261,153 (25.5%)	1,274,882 (26.0%)	119,899 (33.0%)	593,805 (33.0%)
60+	276,164 (27.0%)	1,270,778 (25.9%)	94,779 (26.1%)	469,296 (26.0%)
Quintiles of Carstairs deprivation index[c]				
1 (least deprived)	128,266 (12.5%)	612,978 (12.5%)	43,233 (11.9%)	214,804 (11.9%)
2	202,153 (19.8%)	969,896 (19.8%)	68,391 (18.8%)	339,661 (18.9%)
3	211,882 (20.7%)	1,021,847 (20.8%)	76,487 (21.1%)	379,580 (21.1%)
4	247,290 (24.2%)	1,185,082 (24.1%)	88,207 (24.3%)	437,347 (24.3%)
5 (most deprived)	199,370 (19.5%)	954,675 (19.5%)	70,341 (19.4%)	348,450 (19.3%)
Missing	34,271 (3.3%)	163,581 (3.3%)	16,551 (4.6%)	82,033 (4.6%)
Body mass index (kg/m^2)[d]				
Underweight (<18.5)	25,486 (2.5%)	122,658 (2.5%)	6,767 (1.9%)	37,208 (2.1%)
Normal (18.5–24.9)	368,313 (36.0%)	1,680,277 (34.2%)	118,438 (32.6%)	610,457 (33.9%)
Overweight (25–29.9)	274,062 (26.8%)	1,219,689 (24.9%)	106,417 (29.3%)	497,192 (27.6%)
Obese (30+)	181,183 (17.7%)	773,562 (15.8%)	77,511 (21.3%)	312,832 (17.4%)
Missing	174,188 (17.0%)	1,111,873 (22.7%)	54,077 (14.9%)	344,186 (19.1%)
Smoking status[d]				
Non-smoker	529,881 (51.8%)	2,433,856 (49.6%)	149,937 (41.3%)	866,540 (48.1%)
Current or ex-smoker	446,798 (43.7%)	2,006,409 (40.9%)	196,330 (54.1%)	788,823 (43.8%)
Missing	46,553 (4.5%)	467,794 (9.5%)	16,943 (4.7%)	146,512 (8.1%)
Harmful alcohol use (%)[d]	73,353 (7.2%)	294,033 (6.0%)	22,822 (6.3%)	89,889 (5.0%)
Sleep problems (%)[d]	278,516 (27.2%)	877,318 (17.9%)	n/a	n/a
Ethnicity				
White	387,082 (37.8%)	1,783,293 (36.3%)	150,087 (41.3%)	608,246 (33.8%)
South Asian	25,119 (2.5%)	97,603 (2.0%)	4799 (1.3%)	24,687 (1.4%)
Black	10,964 (1.1%)	54,725 (1.1%)	1071 (0.3%)	13,520 (0.8%)
Other	7797 (0.8%)	44,126 (0.9%)	1811 (0.5%)	11,397 (0.6%)
Mixed	4013 (0.4%)	18,864 (0.4%)	816 (0.2%)	4398 (0.2%)
Not stated or missing	588,257 (57.5%)	2,909,448 (59.3%)	204,626 (56.3%)	1,139,627 (63.2%)
Charlson comorbidity index[d]				
Low (0)	636,704 (62.2%)	3,605,319 (73.5%)	252,430 (69.5%)	1,308,427 (72.6%)
Moderate (1–2)	340,946 (33.3%)	1,103,589 (22.5%)	94,223 (25.9%)	421,230 (23.4%)
Severe (3 or more)	45,582 (4.5%)	199,151 (4.1%)	16,557 (4.6%)	72,218 (4.0%)

Notes: Values are numbers (percentages) unless otherwise stated. Individuals can contribute data as both atopic eczema or psoriasis exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column. [a]Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or severe mental illness diagnosis. [b]Age at index date. [c]Carstairs deprivation index based on practice-level data (from 2011). [d]Based on records closest to index date.
Abbreviation: IQR, interquartile range.

Individual Effects of Potential Mediators

Including sleep problems in our confounder-adjusted model reduced the HR for associations between AE and SMI from 1.17 (95% CI:1.12–1.22) to 0.98 (95% CI:0.94–1.02) (Table S8). Individual effects of other potential mediators on associations between AE or psoriasis and SMI were minimal.

Table 2 HRs (95% CI) for the Association Between Atopic Eczema or Psoriasis and Severe Mental Illness. Fitted to Adults with Complete Data for All Variables Included in Each Model and from Valid Matched Sets[a]

Cohort	Minimally Adjusted			Confounder Adjusted[b]			Additionally Adjusted for Potential Mediators[c]		
	Number	Events/PYAR	HR (95% CI)[d]	Number	Events/PYAR	HR (95% CI)[d]	Number	Events/PYAR	HR (95% CI)[d]
Atopic eczema									
Unexposed	4,908,059	11,999/30,935,170	1 (reference)	4,744,478	11,428/29,565,265	1 (reference)	3,117,531	8,131/21,282,283	1 (reference)
Exposed	1,023,232	3,150/6,995,891	1.16 (1.12, 1.21)	988,961	3,012/6,686,453	1.17 (1.12, 1.22)	793,030	2,632/5,789,012	0.98 (0.93, 1.04)
Psoriasis									
Unexposed	1,801,875	4,598/13,246,255	1 (reference)	1,719,842	4,319/12,491,309	1 (reference)	1,179,789	3,252/9,176,327	1 (reference)
Exposed	363,210	1,191/2,680,394	1.27 (1.19, 1.36)	346,659	1,107/2,523,477	1.26 (1.18, 1.35)	286,396	990/2,218,106	1.14 (1.05, 1.23)

Notes: [a]Matched sets including one exposed patient and at least one unexposed patient. [b]Adjusted for calendar period and quintiles of Carstairs deprivation index (using 2011 census data). [c]AE cohort is further adjusted for comorbidity burden (using the Charlson comorbidity index), sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index. Psoriasis cohort is further adjusted for comorbidity burden (using the Charlson comorbidity index), smoking status, harmful alcohol use and body mass index. [d]Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry).
Abbreviations: CI, confidence interval; HR, hazard ratio; PYAR, person-years at risk.

Discussion

After adjusting for confounders, AE and psoriasis were associated with a 17% and 26% increase respectively in the hazard of incident SMI compared to matched comparators. After further adjusting for potential mediators, associations with SMI did not persist in adults with AE and were attenuated in adults with psoriasis. SMI risk was highest in adults with moderate or severe AE and mild psoriasis, compared to those without AE or psoriasis.

Strengths and Limitations

To our knowledge, this is the largest study to investigate temporal associations between AE or psoriasis and incident SMI in adults. The CPRD dataset used is broadly representative of the UK population,[28] suggesting our results are generalisable to the UK population with AE or psoriasis. We identified adults with AE or psoriasis in primary care using validated definitions.[29,30] We used DAGs to inform covariate selection.

However, our study has several limitations. Firstly, the definition used to identify AE (a validated definition requiring records of at least one diagnostic code, and at least two skin disease therapies)[29] may introduce selection bias as it excludes untreated adults who may have milder disease. Additionally, not all adults will consult their general practitioner about their AE or psoriasis, meaning they could be incorrectly classified as not having AE or psoriasis. Misclassification of AE or psoriasis exposure in this study may be independent of SMI, biasing our estimates of associations between AE

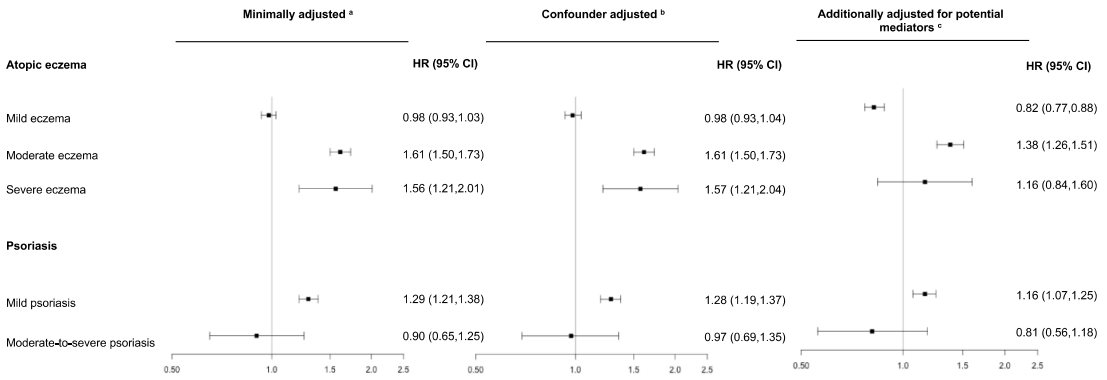

Figure 3 HRs (95% CI) for the association between atopic eczema or psoriasis severity and severe mental illness. Models fitted to adults with complete data for all variables included in each model and from valid matched sets. [a]Model implicitly adjusted for matching variables. [b]Model further adjusted for potential confounders (socioeconomic deprivation – using Carstairs index – and calendar time. [c]Confounder adjusted model additionally adjusted for potential mediators (comorbidity burden [using Charlson comorbidity index], smoking status, harmful alcohol use, body mass index, and in atopic eczema analyses only, problems with sleep and high-dose glucocorticoid use).

or psoriasis and SMI towards the null. Conversely, SMI ascertainment may be more likely in adults with AE or psoriasis due to increased contact with primary care because of their skin disease, leading to a potential overestimate of associations between AE or psoriasis and SMI. However, our sensitivity analysis restricting study inclusion to adults with at least one consultation in the year prior to cohort entry produced results like the main analyses of increased SMI in adults with AE and psoriasis.

Using CPRD data to capture SMI outcomes may miss individuals with SMI as the condition is usually identified in secondary mental health care. However, it is likely numbers of missed individuals with SMI will be small as in the UK, GPs have a central role in the care of people with SMI. Since the introduction of the Quality and Outcomes Framework (QOF) in 2004, GPs receive renumeration for the care of people with SMIs and maintaining a register of individuals with an SMI diagnosis.[40]

Our definition of AE or psoriasis severity may have misclassified adults with severe disease as having milder disease if they refused skin disease therapies, reducing numbers of individuals classified as having severe disease, and under-powering our analyses of associations between AE or psoriasis severity and SMI.

We may have introduced selection bias in our mediator-adjusted estimates, as we conducted complete case analyses. BMI and smoking data were more likely to be missing in adults without AE or psoriasis, and those with missing BMI or smoking data were more likely to be young and male. However, percentages of individuals excluded from analyses due to missing data are relatively low compared to the overall size of the cohorts; therefore, effects on our study are likely to be small.

We were unable to robustly capture all information on some potential confounders of associations between AE or psoriasis and SMI. For example, individual-level Carstairs deprivation data were only available for individuals in England, and practice-level data may not accurately represent individual-level deprivation. Additionally, information on potential mediators (eg, self and social stigmatisation due to visible skin disease, high levels of stress, substance misuse) of associations between AE or psoriasis and SMI were unavailable because they are either not captured, or captured incompletely, in routinely collected primary care data. Our estimates of associations between AE or psoriasis and SMI may therefore include residual effects of incompletely captured confounders and mediators.

Our cohorts included prevalent and incident AE or psoriasis, which is appropriate for chronic relapsing conditions like AE and psoriasis where exact onset date cannot be captured accurately using electronic health records.[41] We captured some potential mediators (eg, comorbidity burden) on or before index date, and consequently some mediators may have occurred before eczema or psoriasis diagnosis (ie, not on the causal pathway after exposure as our analysis strategy assumes). However, given that approximately one-third of people with AE or psoriasis (31% AE and 37% psoriasis) entered cohorts on the date of first AE or psoriasis record, and eczema often starts in childhood,[1] the timing of our capture of mediators in relation to AE or psoriasis onset may have limited effect on our mediator-adjusted estimates.

Comparisons to Existing Literature

Our findings of increased risk of SMI in those with atopic eczema or psoriasis are consistent with limited longitudinal studies aiming to address temporal associations between atopic disorders or psoriasis and specific SMI outcomes.[23–27] However, those studies were limited by 1) inclusion of children and adolescents in skin disease cohorts (due to known differences in psychiatric diagnostic practices between adults and children); 2) investigating atopic diseases in general, with a lack of focus on AE; 3) investigating specific SMIs such as schizophrenia, rather than SMI all together; () smaller study populations; and 5) inability to explore reasons for associations between AE or psoriasis and SMI due to adjustment for limited confounders and/or mediators. Additionally, previous longitudinal studies in the US used data from administrative health insurance databases, further limiting their ability to adjust for key covariates and may introduce selection bias (people with health insurance in the US may be different to people without).

Our study addresses some limitations of existing studies and adjusts for key confounders and mediators to investigate reasons for associations between AE or psoriasis and SMI. We found that associations between AE and SMI were strongly mediated by sleep problems. This finding is consistent with evidence from previous studies where AE disturbs sleep due to persistent itching,[42] and disturbed sleep is linked to schizophrenia-like symptoms (eg, hallucinations and distorted perception) and can precede the onset of SMI.[19,43]

Implications for Research and Clinical Practice

Our study, along with previous studies establishing temporal relationships between AE or psoriasis and other mental health conditions (ie, depression, anxiety),[10,44] highlights the importance of monitoring mental health in adults with AE or psoriasis. Evidence suggests a large burden of psychological distress in adults with AE or psoriasis, and a lack of focus on mental health may negatively impact health of affected individuals. Unrecognised mental illness may reduce treatment adherence for skin conditions,[45] lessening skin treatment benefits, potentially worsening the skin condition, and subsequently contributing to potentially worsening mental health. Recent UK guidelines suggest clinicians assess the impact of AE or psoriasis on the psychological wellbeing of those affected and use validated tools to objectively assess quality of life.[46,47] However, evidence suggests individuals that present with physical symptoms (eg, AE or psoriasis) are less likely to have their mental health conditions detected.[48] Introducing targeted mental health screening in UK primary care of adults with AE or psoriasis may allow early detection and intervention of mental health conditions. Improved identification of clinically significant depression and anxiety in people with psoriasis has been seen after introduction of mental health screening in specialist dermatology clinics.[49]

Our study also highlights the importance of identifying modifiable risk factors as they offer an opportunity to intervene and provide treatments that may reduce SMI risk. We found that associations between AE and SMI were largely mediated by sleep problems. Enhanced treatment of underlying skin disease using highly effective targeted therapies (ie, dupilumab) may have an additional effect of reducing sleep problems;[50] however, additional strategies addressing insomnia with evidence-based therapies may also have a key role.[51] Additional research should further investigate the mediating factors of associations between psoriasis and SMI.

Conclusions

Adults with AE or psoriasis appear to be at increased risk of SMI compared to adults without AE or psoriasis. In adults with AE, and to a lesser extent in adults with psoriasis, increased risk may be explained by mediating factors (eg, sleep problems or lifestyle factors). Adults with mild psoriasis and more severe AE were at greater risk of SMI. Prevention strategies including targeted mental health screening and modifying mediating factors should be considered to reduce SMI burden in adults with AE or psoriasis.

Abbreviations

AE, atopic eczema; BMI, body mass index; CI, confidence interval; CPRD, Clinical Practice Research Datalink, HR, hazard ratio; SMI, severe mental illness.

Declarations

This paper was presented at the Society for Academic Primary Care (SAPC) Annual Scientific Meeting (ASM) 2022 as a short oral presentation. The abstract for the talk can be found on the SAPC ASM 2022 website (doi: https://sapc.ac.uk/doi/10.37361/asm.2022.1.1). This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Data Sharing Statement

Data may be obtained from a third party and are not publicly available. Data from this study were obtained from the Clinical Practice Research Datalink (CPRD) and to guarantee patient data confidentiality, only the authors have access to the data during the study, and the data cannot be distributed to other parties. Data are available directly from CPRD subject to independent approval.

Ethics Approvals and Patient Consent

This study was approved by the United Kingdom Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (protocol 20_051) and London School of Hygiene and Tropical Medicine (LSHTM) Research Ethics Committee. This study was performed in line with the principles of the Declaration of Helsinki. Consent is given by GP practices that contribute to CPRD. Individual patient consent is implied. However, patients are offered the right to opt out from the use of their de-identified data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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7.4 Summary

- In this chapter, I described the population-based cohort studies (one investigating the association between atopic eczema and SMI, and the other psoriasis and SMI) I conducted to investigate associations between atopic eczema or psoriasis, and incident SMI among adults.
- I found that after implicitly adjusting for matching variables and underlying timescale (age, sex, primary care practice) and adjusting for potential confounders (calendar period, socioeconomic deprivation) adults with atopic eczema or psoriasis were at increased risk of SMI compared to matched comparators without atopic eczema or psoriasis.
- After further adjusting for potential mediators (problems with sleep in atopic eczema analyses, and BMI, smoking status, harmful alcohol use, and comorbidity burden in psoriasis analyses) associations between atopic eczema and SMI no longer persisted, while associations between psoriasis and SMI were attenuated.
- Evidence from these studies suggests a burden of severe mental illness among adults with atopic eczema or psoriasis and highlights the importance of monitoring mental health among individuals with skin disease.
- In the following chapter I will describe the population-based cohort studies I conducted to investigate whether associations between atopic eczema and depression or anxiety differed between individuals from white and minority ethnic groups. I used the results from the systematic review (**Chapter 3**) and the directed acyclic graphs described in **Chapter 6** to inform covariate selection for these studies.

8 Ethnic differences in depression and anxiety among adults with atopic eczema: population-based matched cohort studies within UK primary care

8.1 Introduction

In the previous chapter, I described the population-based cohort studies (considering atopic eczema and psoriasis separately) I conducted to investigate longitudinal associations between atopic eczema or psoriasis and incident SMI among adults. In this chapter, I will describe the population-based cohort studies I performed to address the third objective of this thesis – whether associations between atopic eczema and incident depression or anxiety differs between adults from white and minority ethnic groups. In these studies (looking at depression and anxiety outcomes separately), I stratified the associations between atopic eczema and depression or anxiety by ethnicity to investigate ethnicity as an effect modifier of the associations. These studies used data from the Clinical Practice Research Datalink (CPRD) GOLD database and linked data which are described in **Chapter 4** of this thesis. I was unable to investigate ethnic differences in associations between atopic eczema and SMI, or psoriasis, and depression, anxiety, or SMI due to limited statistical power.

8.2 Ethical approvals

The protocol for these studies was approved by the CPRD's Research Data Governance (RDG) Process (Protocol number: 22_001916) and the London School of Hygiene & Tropical Medicine Ethics Committee (Reference number: 28060).

8.3 Article

A manuscript for these studies is currently being prepared for submission to a peer reviewed scientific journal (Clinical and Translational Allergy) and the current draft is

provided on the following pages. The supplementary material referred to in the manuscript is provided in **Appendix 5** of this thesis.

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Primary Supervisor	Dr Kathryn Mansfield		

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Stage of publication	**Not yet 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, along with my supervisors Kathryn Mansfield, Sinéad Langan and Alasdair Henderson had the original idea for the study and designed the study. I obtained aprovals to access the data. I carried out the statistical analysis of the study and wrote the first draft of the manuscript.

SECTION E

Student Signature	E.Adesanya
Date	8th December 2022

Supervisor Signature	K. Mansfield
Date	12th December 2022

Ethnic differences in depression and anxiety among adults with atopic eczema: population-based matched cohort studies within UK primary care

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ABSTRACT

Background

Evidence demonstrates individuals with atopic eczema (eczema) have increased depression and anxiety, however, the role of ethnicity in associations is poorly understood. We aimed to investigate whether associations between eczema and depression or anxiety differed between adults from white and minority ethnic groups in the UK.

Methods

We used UK Clinical Practice Research Datalink GOLD to conduct matched cohort studies of adults (≥18 years) with ethnicity recorded in primary care electronic health records (April 2006-January 2020). We matched (age, sex, practice) adults with eczema to up to five adults without. We used stratified Cox regression with an interaction between eczema and ethnicity, to estimate hazard ratios (HRs) for associations between eczema and incident depression and anxiety in individuals from white ethnic groups and a pooled minority ethnic group (adults from Black, South Asian, Mixed and Other groups).

Results

We identified separate cohorts for depression (215,073 with eczema matched to 646,539 without) and anxiety (242,598 with eczema matched to 774,113 without). After adjusting for matching variables and potential confounders (age, sex, practice, deprivation, calendar period), we found strong evidence (p<0.01) of ethnic differences in associations between eczema and depression (minority ethnic groups: HR=1.33,95%CI=1.22,1.45; white ethnic groups: HR=1.15, 95%CI=1.12,1.17) and anxiety (minority ethnic groups: HR=1.41, 95%CI=1.28,1.55; white ethnic groups: HR=1.17,95%CI=1.14,1.19).

Conclusions

Adults with eczema from minority ethnic groups appear to be at increased depression and anxiety risk compared to their white counterparts. Culturally adapted mental health promotion and prevention strategies should be considered in individuals with eczema from minority ethnic groups.

INTRODUCTION

Atopic eczema (referred to as eczema throughout) is a common inflammatory skin disease (affecting up to 10% of adults) associated with substantial morbidity and impaired quality of life.[1] Depression and anxiety are common mental disorders associated with increased morbidity,[2,3] which can worsen prognosis and increase mortality in people with another medical condition.[2] Worldwide, depressive disorders are the second, and anxiety disorders the eighth, leading causes of years lived with disability.[4] In the UK, 17% of adults experienced depression or anxiety in the past week.[5]

Considerable evidence demonstrates that people with eczema are at increased risk of depression and anxiety,[6–12] including temporal evidence suggesting that eczema precedes depression and anxiety diagnosis.[10–12] Reasons for associations between eczema and depression or anxiety are likely to be multifactorial and may include lifestyle factors (e.g., smoking, harmful alcohol use),[13–17] disturbed sleep due to itch,[18,19] stigma due to visible skin disease,[20,21] and the inflammatory process itself.[22]

Ethnicity is a potentially important factor in associations between eczema and depression or anxiety, which has not been fully explored. Evidence suggests individuals from minority ethnic groups experience greater prevalence and incidence of eczema, depression, and anxiety compared to people from white ethnic groups.[23–25] There are also potential mechanisms by which ethnicity affects associations between eczema and depression or anxiety including: (1) darker skin in individuals from minority ethnic groups delaying eczema diagnosis and treatment, and subsequently impacting mental health;[23] (2) dyspigmentation in individuals with darker skin exacerbating feelings of stigmatisation, further contributing to development of depression or anxiety;[23] (3) various beliefs in different cultures associated with skin diseases that can profoundly affect mental health;[26] and (4) barriers to health service access, deprivation, discrimination and racism, all of which disproportionately affect individuals from minority ethnic groups and can reinforce health inequalities and also negatively impact mental health.[27,28] Genetics may also partially explain ethnic differences in associations between eczema and depression

or anxiety, however, other mechanisms described are likely to play a more substantial role.[29]

Previous longitudinal studies have either not investigated the role of ethnicity in the associations between eczema and depression or anxiety, or only done so in sensitivity analyses.[7,10–12] It is therefore unknown whether depression or anxiety risk in people with eczema varies by ethnic group. Given the paucity of previous research, and the health inequalities experienced by those from minority ethnic groups, it is important to identify whether associations between eczema and depression or anxiety differ between ethnic groups.

We undertook two matched cohort studies using primary care electronic health record data to investigate whether associations between eczema and incident depression or anxiety differed between adults from white ethnic groups and a pooled minority ethnic group (including individuals from Black, South Asian, Mixed, and Other ethnicities) groups. We also explored whether there were differences in eczema severity between individuals from white and minority ethnic groups, and whether associations varied with eczema severity.

METHODS

Study design and setting

We conducted matched cohort studies (April 1, 2006, to January 31, 2020), using primary care electronic health record data from the UK's Clinical Practice Research Datalink (CPRD GOLD). CPRD is an ongoing, nationwide database of routinely collected primary care records including information on demographics, diagnoses, symptoms, and prescriptions.[30] Morbidity code lists and all analytic code used in this study are available for download.[31]

Study population

All adults (≥18 years) with complete ethnicity data and at least one year of registration with a general practice meeting CPRD quality-control standards during the study period were eligible for inclusion. We matched (without replacement) each adult with eczema (on age [±5 years], sex, and practice) with up to five adults without eczema in calendar date order **(Appendix S1)**. Adults with eczema were identified using a previously validated definition requiring records of at least one eczema diagnostic code, and at least two eczema therapies (e.g., phototherapy, prescriptions for topical or oral drugs) recorded on separate days.[32] We identified two matched cohorts – one to investigate depression (depression cohort) and the other to investigate anxiety (anxiety cohort) (although individuals included in the cohorts only varied based on exclusion due to previous anxiety/depression/SMI diagnosis). In both cohorts, we excluded individuals with relevant mental health conditions prior to cohort entry (e.g., exclusion of those with previous depression in the depression cohort; and previous anxiety in the anxiety cohort; severe mental illness – i.e., schizophrenia, bipolar disorder, and other psychoses – in both depression and anxiety cohorts).

We followed individuals with eczema from the latest of (index date): study start (April 1, 2006); date they met our eczema definition; one year after the date of registration with their practice; date their practice met CPRD quality-control standards; or their 18th birthday. Follow-up for individuals without eczema began on the same date as their matched individual with eczema. Follow-up ended at the earliest of: depression

or anxiety diagnosis or symptom recording (depending on the outcome under investigation); diagnosis of severe mental illness (suggests an alternative cause for the depression or anxiety); study end (January 31, 2020); end of registration with practice; practice no longer contributing data to CPRD; eczema diagnosis (for adults without); or death. Individuals without eczema with an eczema diagnostic code during follow-up were censored from the comparison cohort and become eligible for inclusion in the eczema cohort.

Outcomes

We considered depression and anxiety as separate outcomes. We identified depression and anxiety based on the earliest record of a diagnostic or symptom morbidity code recorded in primary care as evidence suggests that GPs record depression and anxiety symptoms as well as diagnoses.[33–35] We considered broader definitions of depression and anxiety in sensitivity analyses (**Table 1**).

Covariates

We identified ethnicity using a previously validated algorithm using primary care records to classify individuals into five ethnic groups: White, Black, South Asian, Mixed, and Other.[36] Due to limited statistical power, we pooled individuals from Black, South Asian, Mixed and Other ethnic groups into a 'minority ethnic' group. We used this grouping to investigate whether associations between eczema and depression or anxiety differed between individuals from white and minority ethnic groups.

We used a directed acyclic graph (DAG) and a systematic review to inform covariate selection **(Appendix S2)**.[37,38] We matched on age, sex, and practice (as an indirect means of accounting for differences in coding practice, rural/urban location, and socioeconomic deprivation). We considered age, sex, calendar period (2006-2010, 2011-2015, 2016-2020) and deprivation (quintiles of individual-level Carstairs Index used when available, and practice-level Carstairs if not) as potential confounders.[39] We considered the following variables as potential mediators (captured on or before index date): comorbidity burden (captured using Charlson Comorbidity Index [CCI]),[40] comorbid asthma (identified using primary care morbidity coding), body

mass index (BMI), smoking status, harmful alcohol use, sleep problems and high-dose glucocorticoid use (**Appendix S3** includes details of covariate definitions).

Statistical analyses

Main analysis

We initially described characteristics of adults with and without eczema. We used Cox regression, stratified by matched set with current age as the underlying timescale, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between eczema and depression or anxiety in individuals from white and minority ethnic groups.

We initially constructed minimally-adjusted models including an interaction term between eczema and ethnicity, implicitly adjusting for age (through underlying timescale) and matching variables (age, sex, practice) by stratifying on matched set. We then followed with sequential models: 1) additionally adjusted for potential confounders (deprivation, calendar period) to investigate the total associations through eczema and other potential mediating variables of eczema on depression/anxiety in white and minority ethnic groups; and 2) further adjusted for factors potentially on the causal pathway that may mediate associations between eczema and depression/anxiety (comorbidity burden, comorbid asthma, BMI, smoking status, harmful alcohol use, sleep problems, high-dose glucocorticoid use). We performed likelihood ratio tests to assess whether there is interaction between eczema and ethnicity. We assessed proportional hazards assumptions using Schoenfeld residuals **(Appendix S4)**. All data were managed and analysed using Stata V17 (StataCorp, Texas, USA).

We repeated our main analysis in a series of sensitivity analyses to assess the robustness of our findings (**Tables 1, S1-S4, Appendix S5)**.

Secondary analyses

We classified adults with eczema as having mild, moderate, or severe disease using a previously developed, time-updated definition based on primary care morbidity coding and prescriptions (**Appendix S6**).[41] To explore whether there were differences in eczema severity (based on primary care recording) between

individuals from white and minority ethnic groups, we described the proportions of total follow-up adults with eczema in each ethnic group (white or minority ethnic) spent at each level of eczema severity. We also estimated HRs and 95% Cis for associations between eczema severity and depression or anxiety in individuals from white and minority ethnic groups.

RESULTS

We identified 597,117 adults with eczema matched to 2,844,120 adults without (**Figure 1**). After excluding individuals with missing ethnicity data, those with the outcome of interest or severe mental illness on or before start of follow-up, and those who no longer remained in valid matched sets (i.e., matched set including at least one exposed and one unexposed individual): the depression cohort included 215,073 adults with eczema matched to 646,539 without; and the anxiety cohort included 242,598 with eczema matched to 774,113 without. Individuals with missing ethnicity data were more likely to be younger, male, and have missing BMI and smoking status (**Table S5**).

In those with eczema, median follow-up was between 3.2 and 3.3 years (depression cohort 3.2 [IQR:1.3-5.9], anxiety cohort 3.3 [IQR:1.4-6.0]), and in those without eczema between 2.8 and 2.9 years (depression cohort 2.8 [IQR:1.2-5.5], anxiety cohort 2.9 [IQR:1.2-5.6]). In both cohorts, people with and without eczema had broadly similar age, sex, deprivation, and ethnicity (**Tables 2, S6**). Fewer adults with eczema had missing BMI and smoking status, and those with missing data were more likely to be younger and male compared to those with complete data (**Tables S7, S8**).

Main analyses

We found strong evidence ($p<0.01$) that associations between eczema and depression or anxiety varied by ethnic group (**Table 3**). After implicitly adjusting for matching variables (age, sex, practice) and adjusting for potential confounders (calendar period, deprivation), we found that people with eczema had increased hazards for depression (HR=1.17, 95% CI=1.14,1.19) and anxiety (HR=1.19, 95% CI=1.16,1.21) compared to matched comparators (**Table S9**). When stratified by ethnicity, hazards for depression (minority ethnic groups: HR=1.33, 95% CI=1.22,1.45; white ethnic groups: HR=1.15, 95% CI=1.12,1.17) and anxiety (minority ethnic groups: HR=1.41, 95% CI=1.28,1.55; white ethnic groups: HR=1.17, 95% CI=1.14,1.19) were higher in adults from minority ethnic groups than adults from white ethnic groups.

After additionally adjusting for potential mediators (CCI, comorbid asthma, harmful alcohol use, smoking status, BMI, sleep problems, high-dose glucocorticoid use), estimates of associations between eczema and depression (minority ethnic groups: HR=1.14, 95% CI=1.02,1.26; white ethnic groups: HR=1.05, 95% CI=1.03,1.08) and anxiety (minority ethnic groups: HR=1.22, 95% CI=1.09,1.37; white ethnic groups: HR=1.07, 95% CI=1.04,1.09) remained higher among adults from minority ethnic groups.

In all sensitivity analyses **(Tables S1–S4, Appendix 5)**, we saw broadly similar results to the main analysis with more elevated hazards of depression and anxiety among adults from minority ethnic groups compared to adults from white ethnic groups.

Secondary analyses

Individuals from white and minority ethnic groups spent similar proportions of total follow-up at each level of eczema severity (**Table S10**). We saw evidence that at the same level of eczema severity, individuals from minority ethnic groups had higher hazards of depression and anxiety than adults from white ethnic groups (**Table S11, Figure 2**). This observation was particularly clear in associations between moderate eczema severity and depression (confounder adjusted HRs: minority ethnic groups: HR=1.90, 95% CI=1.58,2.29; white ethnic groups: HR=1.38, 95% CI=1.33,1.45) and anxiety (confounder adjusted HRs: minority ethnic groups: HR=1.83, 95% CI=1.49,2.25; white ethnic groups: HR=1.43, 95% CI=1.36,1.50), which were higher in minority ethnic groups compared to white ethnic groups.

DISCUSSION

We found that associations between eczema and depression or anxiety were more pronounced in adults from minority ethnic groups compared to adults from white ethnic groups (after implicitly adjusting for matching variables and adjusting for potential confounders (calendar period, deprivation). Estimated hazard ratios remained higher in adults from minority ethnic groups even after further adjusting for potential mediators (CCI, comorbid asthma, harmful alcohol use, smoking status, BMI, sleep problems, high-dose glucocorticoid use). There were no clear differences in eczema severity between individuals from white and minority ethnic groups. At the same level of eczema severity, individuals from minority ethnic groups had higher hazards of depression and anxiety than adults from white ethnic groups.

Strengths and limitations

To our knowledge, this is the first study to investigate whether associations between eczema and incident depression or anxiety differ between adults from white and minority ethnic groups. We identified adults with eczema in primary care and their ethnic groups using validated definitions.[32,36] CPRD GOLD is broadly representative of the UK population,[30] suggesting our results are broadly generalisable to the UK population with eczema.

However, our study has limitations. The definition used to identify eczema (a combination of at least one diagnostic code, and at least two records of skin disease therapies) may introduce selection bias as it excludes untreated adults who may have milder disease. Further, our eczema definition required the presence of a diagnostic code, however, not all individuals with eczema will consult their general practitioner, meaning that they could be incorrectly classified as not having eczema. Misclassification of eczema in this study is likely to be related to the ascertainment of depression and anxiety, as individuals who do not consult their general practitioners for eczema may also not consult for depression or anxiety.

Both the misclassification of eczema, and ascertainment of depression and anxiety are also likely to be different in individuals from white and minority ethnic groups. eczema appears different in skin of colour,[23] and this visual difference can lead to misdiagnosis and subsequent misclassification of eczema exposure in individuals

with skin of colour from minority ethnic groups. Additionally, evidence suggests that individuals from minority ethnic groups are more likely to have their depression and anxiety missed in primary care,[42–44] either because health seeking behaviour is affected (by stigma or beliefs associated with mental health conditions),[45] due to greater uncertainty by clinicians in diagnosing depression and anxiety,[46] or because of a focus on physical health conditions despite the presence of mental health symptoms.[46] In the context of this study, misclassification of eczema exposure and reduced ascertainment of depression and anxiety in individuals from minority ethnic groups may have biased our estimates of associations between eczema and depression or anxiety in individuals from minority ethnic groups towards the null, and true estimates of associations may be higher.

It could be argued that ascertainment of depression and anxiety may be more likely in adults with diagnosed eczema due to increased contact with primary care because of their skin disease, and this may lead to potential overestimates of associations between eczema and depression or anxiety in white and minority ethnic groups. However, our sensitivity analyses restricting study participation to adults with at least one primary care consultation in the year before cohort entry produced similar results to the main analysis, suggesting a minimal effect to our results.

Our eczema severity definition may have misclassified adults with severe disease as having milder disease if they did not receive treatment. Additionally, individuals with more severe disease from minority ethnic groups may have been misclassified as having less severe disease as redness, a key identifier of disease severity, is difficult to see in people with darker skin.[23] Misclassification of eczema severity is likely to lead to underestimates of associations eczema severity and depression or anxiety in white and minority ethnic groups. Misclassification of eczema severity may have also reduced the numbers of individuals classified as having severe disease, underpowering our analyses and affecting the precision of estimates of associations between severe eczema and depression or anxiety in minority ethnic groups.

We excluded individuals with missing ethnicity data from both our depression and anxiety cohorts, however, individuals with missing ethnicity were more likely to be younger, male, and have missing BMI and smoking status. However, it is unlikely

that excluding these individuals affected our results as multiple imputation of missing ethnicity data (**Appendix S5**) produced broadly similar results to those in the main analysis.

We pooled individuals from Black, South Asian, Mixed and Other ethnic groups into a minority ethnic group due to limited power. Pooling individuals meaning that we were unable to investigate associations between eczema and incident depression and anxiety in the specific ethnic groups. Grouping individuals from several ethnic groups into one group and using an umbrella term such as ‘minority ethnic’ implies that they reflect a singular homogenous ethnic identity even though there is significant diversity between them. The white ethnic group in this study includes individuals from white minority groups (Gypsy, Roma, and Irish Traveller groups) who may also experience inequalities that may lead to differences in associations between eczema and depression or anxiety compared to individuals of White British ethnicity. However, investigating the inequalities experienced by white minority groups was limited by low statistical power.

Our mediator-adjusted estimates of associations between eczema and depression or anxiety may include residual effects of incompletely captured and uncaptured mediators. For example, sleep problems are likely to be imperfectly captured in routinely collected primary care data, because individuals do not always consult their general practitioner for sleep problems. Additionally, cultural beliefs about skin disease, discrimination and inequalities experienced by individuals from minority ethnic groups are important factors that could potentially mediate associations, however they cannot be captured using CPRD data. Further, we captured some potential mediators on or before index date, and consequently some mediators may have been captured before eczema diagnosis,[47] meaning they cannot be on the causal pathway after exposure as our analysis strategy assumes. However, given that eczema frequently starts in childhood and most individuals with eczema did not enter the cohorts on the date of the first eczema diagnosis, and it is unlikely that the measurement of most included mediators (e.g., BMI, smoking status) change over time, the timing of capture of our mediators may have a limited effect on our mediator-adjusted estimates.

Comparisons to existing literature

There is limited existing evidence on the role of ethnicity in associations between eczema and depression or anxiety. Our study addresses the limitation of previous research by specifically estimating HRs for associations between eczema and depression or anxiety in white and minority ethnic groups. Our finding that adults from minority ethnic groups are at increased risk of depression or anxiety compared to those from white ethnic groups is consistent with studies conducted in the general population where rates of depression, anxiety, and other mental health conditions are much higher in minority ethnic communities.[24,25,48,49]

One possible explanation for differences in associations with depression or anxiety may be due to potential differences in how eczema is diagnosed and managed in different ethnic groups. Eczema appears different in skin of colour, which may lead to delayed diagnosis, underestimation of disease severity, or even misdiagnosis among people with darker skin from minority ethnic groups.[23] Our eczema and severity definitions are also based on skin disease therapies, and differences in eczema diagnoses in skin of colour may subsequently lead to undertreatment or delayed treatment and an increased risk of mental health conditions. We did not observe a clear difference in eczema severity between adults of white and minority ethnic groups, a finding that is inconsistent with studies reporting greater eczema severity in individuals from minority ethnic groups.[50,51] The difference in findings may be explained by differences in the eczema severity definitions used across studies. Our severity definition was based on treatment with skin disease therapies, while in other studies,[50,51] severity was assessed through surveys or clinical scoring tools. Additionally, the study populations of previous studies included only children and adolescents, potentially indicated ethnic differences in eczema severity may be different in adulthood.

Implications for research and clinical practice

Our findings suggest individuals with eczema from minority ethnic groups are at higher risk of depression and anxiety and highlights the importance of monitoring mental health in this vulnerable population. Monitoring mental health and wellbeing in individuals from minority ethnic groups with eczema is vital, since individuals from

these communities in the general population are already at comparatively higher risk of depression and anxiety than people from white communities,[24,25,48,49] and an eczema diagnosis may further increase the risk.

Unrecognised depression or anxiety in people with eczema from minority ethnic groups may reduce skin disease treatment adherence,[52] therefore reducing treatment benefits, potentially worsening skin disease, and subsequently contributing to worsening mental health. Introducing mental health promotion strategies as targeted mental health screening in primary care of adults with eczema from minority ethnic groups may avoid the development of depression and anxiety, or in individuals already affected, may allow early detection and intervention. Ensuring mental health promotion and assessment is ethnically and culturally appropriate (i.e., sensitive to the beliefs and the expression of symptoms in individuals from minority ethnic groups) may lead to improved recognition of depression and anxiety. Several systematic reviews have reported that the use of culturally sensitive mental health assessments and interventions effectively improve health outcomes.[53,54]

CONCLUSIONS

Adults with eczema from minority ethnic groups appear to be at increased risk of depression or anxiety compared to their white counterparts. Mental health promotion and prevention strategies that are culturally adapted should be considered to prevent the development or reduce the burden of mental health conditions in individuals with eczema from minority ethnic groups.

Contributor statement

EA, AH, SL and KM had the original idea for the study. EA carried out the statistical analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript.

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Conflicts of interest

JFH has received consultancy fees from Wellcome Trust and juli Health. RM and KM have received consultancy fees from AMGEN.

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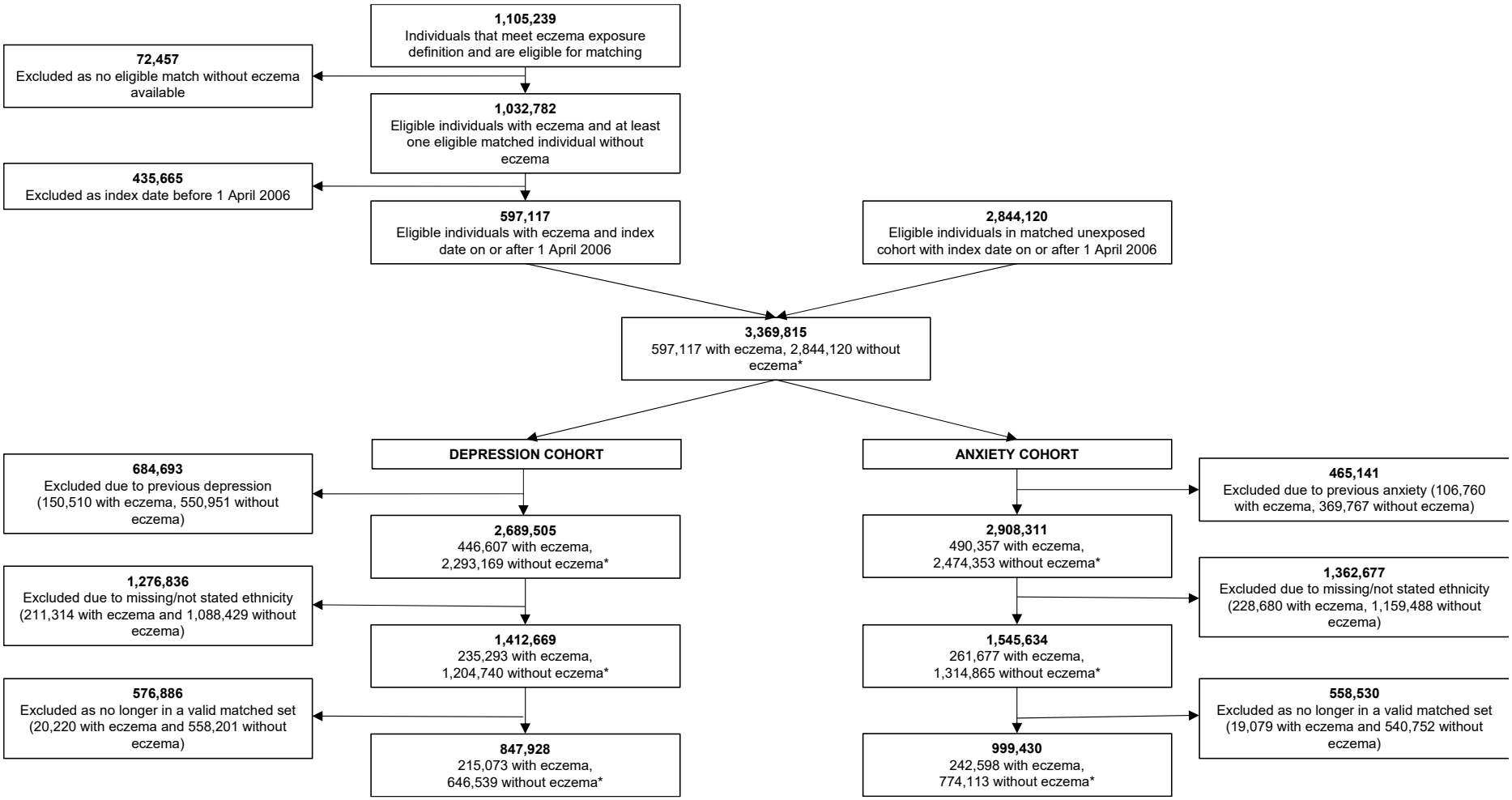
Figure 1: Flowchart illustrating identification of participants in depression and anxiety cohorts



* Numbers of people with and without atopic eczema do not sum to the total number of individuals included in each cohort. Individuals with atopic eczema could be included in the matched comparison cohort up until the date of their first atopic eczema diagnosis.

Table 1: Description and rationale of sensitivity analyses

Description of sensitivity analyses	**Rationale**
Repeating the main analysis using alternative code lists to identify depression and anxiety outcomes (including broader codes and symptom codes)	To explore the sensitivity of the results due to the definitions of the depression and anxiety outcomes
Restricting cohort entry to individuals with at least one consultation with their GP in the year before cohort entry.	To exclude individuals who are practice non-attenders. There may be differential recording of exposure, covariates and outcomes among practice attenders and non-attenders. For example, practice non-attenders may be more likely to have missing smoking or BMI data.
Repeating the main analysis after removing censoring at the time of an alternative diagnoses that may also represent the outcome of interest (i.e., severe mental illness).	To avoid potentially informative censoring of outcomes by severe mental illness.
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006 that are eligible for linkage with HES and have complete ethnicity data.	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias. The main study population included only individuals with complete ethnicity data who are likely to be different from those with missing ethnicity data, which may introduce selection bias. Previous work has shown that combining CPRD and HES increases the completeness of ethnicity data.
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006. Missing ethnicity data was imputed using multiple imputation. [b]	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias.
Repeating the main analysis using less strict definitions for sleep problems (main analysis code list includes Zolpidem and Zopiclone which are only prescribed for sleep problems, sensitivity analysis code list expanded to include prescriptions for benzodiazepines, melatonin, and other drugs).	To explore whether including broader drugs that are prescribed for conditions other than sleep disturbances further mediates the association between atopic eczema and severe mental illness.

Table 2: Characteristics of depression and anxiety cohorts at cohort entry. Values are numbers (percentages) unless otherwise stated

	Depression cohort		Anxiety cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=215,073	n=646,539	n=242,598	n=774,113
Follow-up [a]				
Total person-years	845,534	2,381,779	970,230	2,898,227
Median (IQR) duration of follow-up (years)	3.2 (1.3-5.9)	2.8 (1.2-5.5)	3.3 (1.4-6.0)	2.9 (1.2-5.6)
Sex				
Female (%)	119,149 (55.4%)	354,208 (54.8%)	138,964 (57.3%)	446,169 (57.6%)
Age (years) [b]				
18-29	83,066 (38.6%)	267,060 (41.3%)	88,755 (36.6%)	297,014 (38.4%)
30-39	36,715 (17.1%)	113,881 (17.6%)	42,298 (17.4%)	140,665 (18.2%)
40-49	25,545 (11.9%)	70,699 (10.9%)	31,182 (12.9%)	94,977 (12.3%)
50-59	21,605 (10.0%)	59,361 (9.2%)	26,090 (10.8%)	78,533 (10.1%)
60-69	21,999 (10.2%)	63,035 (9.7%)	25,257 (10.4%)	77,543 (10.0%)
70+	26,143 (12.2%)	72,503 (11.2%)	29,016 (12.0%)	85,381 (11.0%)
Ethnicity				
White	183,612 (85.4%)	548,100 (84.8%)	208,462 (85.9%)	661,005 (85.4%)
Minority ethnic	31,461 (14.6%)	98,439 (15.2%)	34,136 (14.1%)	113,108 (14.6%)
Quintiles of Carstairs deprivation index [c]				
1 - Least deprived	40,005 (18.6%)	112,671 (17.4%)	44,123 (18.2%)	132,325 (17.1%)
2	42,331 (19.7%)	127,095 (19.7%)	46,993 (19.4%)	149,716 (19.3%)
3	44,016 (20.5%)	129,585 (20.0%)	49,443 (20.4%)	154,764 (20.0%)
4	45,293 (21.1%)	138,247 (21.4%)	52,153 (21.5%)	168,516 (21.8%)
5 - Most deprived	40,855 (19.0%)	131,872 (20.4%)	47,062 (19.4%)	160,670 (20.8%)

	Depression cohort		Anxiety cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=215,073	n=646,539	n=242,598	n=774,113
Missing	2,573 (1.2%)	7,069 (1.1%)	2,824 (1.2%)	8,122 (1.0%)
Body mass index (kg/m^2) [d]				
Underweight (<18.5)	5,583 (2.6%)	18,965 (2.9%)	6,156 (2.5%)	22,161 (2.9%)
Normal (18.5-24.9)	78,647 (36.6%)	233,286 (36.1%)	87,042 (35.9%)	276,952 (35.8%)
Overweight (25-29.9)	57,766 (26.9%)	163,116 (25.2%)	65,734 (27.1%)	198,662 (25.7%)
Obese (30+)	38,849 (18.1%)	105,050 (16.2%)	47,546 (19.6%)	136,952 (17.7%)
Missing	34,228 (15.9%)	126,122 (19.5%)	36,120 (14.9%)	139,386 (18.0%)
Smoking status [d]				
Non-smoker	115,457 (53.7%)	346,669 (53.6%)	124,789 (51.4%)	399,346 (51.6%)
Current or ex-smoker	95,696 (44.5%)	278,407 (43.1%)	113,859 (46.9%)	352,189 (45.5%)
Missing	3,920 (1.8%)	21,463 (3.3%)	3,950 (1.6%)	22,578 (2.9%)
Charlson Comorbidity Index [d]				
Low (0)	134,391 (62.5%)	479,693 (74.2%)	149,031 (61.4%)	565,797 (73.1%)
Moderate (1-2)	71,488 (33.2%)	139,122 (21.5%)	82,401 (34.0%)	172,496 (22.3%)
Severe (3 or more)	9,194 (4.3%)	27,724 (4.3%)	11,166 (4.6%)	35,820 (4.6%)
Asthma (%) [d]	54,774 (25.5%)	82,629 (12.8%)	63,142 (26.0%)	102,633 (13.3%)
Harmful alcohol use (%) [d]	15,943 (7.4%)	40,279 (6.2%)	19,740 (8.1%)	53,118 (6.9%)
Problems with sleep (%) [d]	37,355 (17.4%)	66,682 (10.3%)	47,582 (19.6%)	93,110 (12.0%)

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table 3: HRs (95% CI) [a] for the association between atopic eczema and depression or anxiety. Fitted to adults with complete data for all variables included in each model and from valid matched sets [b]

Cohort	Minimally adjusted [c]			Further adjusted for potential confounders [d]			Additionally adjusted for potential mediators [e]		
	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)
Depression									
White									
Without atopic eczema	548,100	42,656/2,083,588	1 (reference)	541,478	41,994/2,054,242	1 (reference)	385,813	31,151/1,542,760	1 (reference)
With atopic eczema	183,612	17,555/735,495	1.15 (1.12,1.17)	181,173	17,246/724,343	1.15 (1.12,1.17)	145,302	14,436/604,767	1.05 (1.03,1.08)
Minority ethnic									
Without atopic eczema	98,439	3,847/298,191	1 (reference)	97,992	3,839/296,708	1 (reference)	69,137	2,989/222,425	1 (reference)
With atopic eczema	31,461	1,926/110,039	1.32 (1.21,1.44)	31,327	1,919/109,442	1.33 (1.22, 1.45)	25,478	1,665/93,033	1.14 (1.02,1.26)
Anxiety									
White									
Without atopic eczema	661,005	38,443/2,550,372	1 (reference)	653,373	37,781/2,515,225	1 (reference)	478,957	29,019/1,934,703	1 (reference)
With atopic eczema	208,462	15,384/848,896	1.17 (1.14,1.19)	205,779	15,080/836,483	1.17 (1.14,1.19)	168,344	12,849/710,076	1.07 (1.04,1.09)
Minority ethnic									
Without atopic	113,108	3,227/347,855	1 (reference)	112,618	3,215/346,231	1 (reference)	81,361	2,469/265,107	1 (reference)

P values for interaction by ethnicity is p<0.01 for all models and outcomes. Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

[a] Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry)

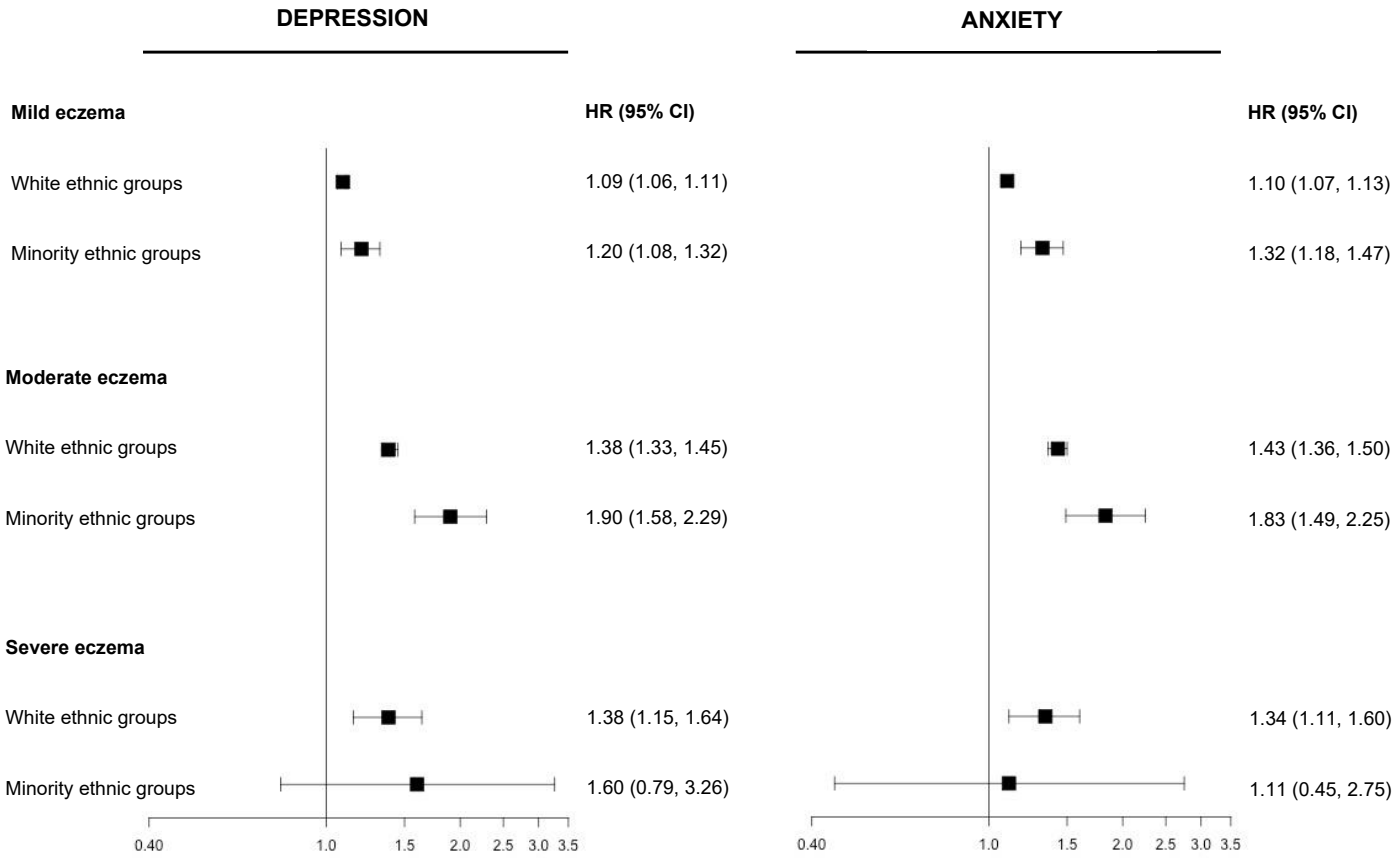
[b] Matched sets including one individual with atopic eczema and at least one matched comparator without.

[c] Adjusted for matching variables (age, sex, practice)

[d] Minimally adjusted model further adjusted for calendar period and deprivation (using quintiles of Carstairs deprivation index [using 2011 census data)])

[e] Cohort is further adjusted for comorbidity burden (using the Charlson comorbidity index), comorbid asthma, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index

Figure 2: Associations (adjusted for deprivation and calendar period) between atopic eczema severity and incident depression and anxiety among adults in white and minority ethnic groups and adults in minority ethnic groups



8.4 Additional information about methods used

8.4.1 Power calculations

I initially planned to investigate whether associations between atopic eczema or psoriasis and incident depression or anxiety differed between adults from five ethnic groups (White, Black, South Asian, Mixed, and Other). However, performing power calculations led to the discovery that analyses using CPRD GOLD to investigate associations within each of the five ethnic groups, and associations between psoriasis and depression and anxiety in different ethnic groups in general would be statistically underpowered. I therefore decided to adapt the studies by removing the investigation on whether associations between psoriasis and depression or anxiety differed between adults from different ethnic groups. I also decided to pool individuals from Black, South Asian, Mixed and Other ethnic groups into a 'minority ethnic' group to ensure that analyses were sufficiently powered, although there are limitations associated with this.

8.4.2 Exposures, outcomes, and covariates

Further information on the definitions of the exposure (atopic eczema), outcomes (depression and anxiety), covariates (ethnicity, age, sex, calendar period, socioeconomic deprivation, comorbidity burden, comorbid asthma, body mass index [BMI], smoking status, harmful alcohol use, problems with sleep, and high-dose oral glucocorticoid use) used in these studies are described in **Chapter 5** of this thesis. I used the results of the systematic review (**Chapter 3**) and the directed acyclic graph (DAG) in **Figure 6.1** of **Chapter 6** to inform covariate selection for these studies.

8.4.3 Sensitivity analyses using redefined study populations

As stated in the manuscript, I repeated the main analyses of these studies in a series of sensitivity analyses to assess the robustness of my findings. One of the sensitivity analyses included exploring the sensitivity of the results to the definition of the study population. The study population for these studies includes adults entering from 1st

April 2006 onwards with complete ethnicity data. However, previous studies have shown that large amounts of ethnicity data are missing in CPRD GOLD,[148,216,232] and adults with complete ethnicity data are likely to be different from those with missing ethnicity data, which may introduce selection bias. I therefore repeated the main analyses in two redefined study populations – one identified using multiple imputation and the other using Hospital Episode Statistics (HES) linkage – and compared the characteristics of the cohorts used in the main analyses to the cohorts from the redefined study populations in the sensitivity analysis.

8.4.3.1 Multiple imputation study population

In this study population, adults entering from 1st April 2006 onwards were eligible for inclusion. I used multiple imputation to impute missing ethnicity data and then identified adults with and without atopic eczema. Multiple imputation is a statistical technique used to handle missing data. During the imputation process, several datasets are generated and the missing values are replaced with imputed values within each dataset, allowing for uncertainty about the missing data.[277] The desired statistical analysis is then performed in each imputation, and the results of the analysis from each imputation are combined to produce a single result.[277] Twenty imputed datasets are recommended to reduce sampling error during the imputation process,[277] and this was what was used in these studies.

8.4.3.2 HES linkage study population

In this study population, adults entering from 1st April 2006 onwards that were eligible for linkage with HES Admitted Patient Care (APC) and had complete ethnicity data were eligible for inclusion. Previous work has shown that combining CPRD and HES APC increases the completeness of ethnicity data although it may reduce the overall size of the study population due to only English practices being eligible for this linkage.[232]

8.5 Summary

- In this chapter, I described a study I conducted to investigate whether associations between atopic eczema and depression or anxiety differed between adults from white and minority ethnic groups.
- After implicitly adjusting for matching variables (age, sex, GP) and adjusting for potential confounders (calendar time, socioeconomic deprivation), I found that adults with atopic eczema from both white and minority ethnic groups were at increased risk of depression and anxiety compared to matched comparators without atopic eczema.
- However, the risk of depression and anxiety was higher in adults with atopic eczema from minority ethnic groups, compared with individuals from white ethnic groups, even after adjusting for potential mediators (comorbidity burden, comorbid asthma, high-dose oral glucocorticoids, problems with sleep, BMI, and smoking status) and at the same level of atopic eczema severity.
- The results of this study suggest a large burden of depression and anxiety among individuals with atopic eczema from minority ethnic groups and highlights the importance of monitoring mental health in this vulnerable population.

9 Discussion

9.1 Introduction

The preceding chapters of this thesis investigated associations between the common inflammatory skin diseases atopic eczema and psoriasis, and depression, anxiety, and severe mental illness (SMI). In this concluding chapter, I will present a discussion compiling the key points across the included studies. Initially I will present an overview of the studies included in this thesis, summarise their findings, and compare them with those of previously published studies. I will then outline the overall strengths and limitations of the work. Finally, I will discuss the implications of my work for clinical practice and policy and suggest potential avenues for future research.

9.2 Overview of studies

The initial systematic review of the literature synthesised and evaluated all available evidence on factors associated with depression, anxiety, and SMI among adults with atopic eczema or psoriasis (**Chapter 3**). Given the paucity of longitudinal evidence regarding the relationship between inflammatory skin diseases and SMI revealed by the systematic review and a search of the literature, I undertook matched cohort studies using primary care electronic health record (EHR) data to investigate associations between atopic eczema or psoriasis, and incident SMI in adults, exploring whether associations varied with severity of atopic eczema or psoriasis (**Chapter 7**). As the potential role of ethnicity in the relationships between atopic eczema and depression or anxiety had not been fully explored, I conducted matched cohort studies to investigate whether associations between atopic eczema and incident depression or anxiety varied between adults from white and minority ethnic groups (**Chapter 8**). Informed by the results of the systematic review (**Chapter 3**), and using directed acyclic graphs (**Chapter 6**), I adjusted the effect estimates from the population-based matched cohort studies for other potential explanatory

variables to produce confounder-adjusted and mediator-adjusted estimates. Key findings from all the studies included in the thesis are presented in **Table 9.1**.

Table 9.1: Key findings of studies included in the thesis

Longitudinal associations
• Evidence of temporal relationships between **atopic eczema or psoriasis, and SMI**: after adjusting for matching variables (age, sex, general practice) and potential confounders (socioeconomic deprivation, calendar period), adults with atopic eczema had a 17% increase and psoriasis a 26% increase in hazards of new SMI diagnosis compared to matched comparators (atopic eczema: HR=1.17, 95%CI=1.12,1.22; psoriasis: HR=1.26, 95%CI=1.18,1.35) • **Absolute incidence rate differences were small**, with an estimated additional 6 per 100,000 cases of SMI in those with atopic eczema, and 9 per 100,000 cases of SMI in those with psoriasis • Evidence of temporal relationships between **atopic eczema and depression or anxiety**: Compared to matched comparators adults with atopic eczema from both **white and minority ethnic** groups had increased hazards of incident depression (minority ethnic: HR=1.33, 95%CI=1.22,1.45; white : HR=1.15, 95%CI=1.12,1.17) and anxiety (minority ethnic: HR=1.41, 95%CI=1.28,1.55; white : HR=1.17, 95%CI=1.14,1.19)
The role of ethnicity
• **Systematic review – psoriasis and depression:** Conflicting evidence from two studies included in the systematic review regarding whether the risk of depression varied by ethnic group in people with psoriasis: 1) one cohort study found that people with psoriasis from non-white ethnic groups were at increased risk compared to those from white ethnic groups (HR=1.72, 95% CI=1.39,2.13); while 2) a cross-sectional study found no evidence of any difference in depression between different ethnic groups. • **Systematic review – psoriasis and anxiety:** Evidence from a single cross-sectional study included in the systematic review reported that, compared to individuals of White British ethnicity with psoriasis, adults of Asian ethnicity with psoriasis were at increased odds of anxiety (OR=3.42, 95% CI=1.63,7.20) • **Atopic eczema/psoriasis and SMI:** Additionally adjusting for ethnicity as a potential confounder in **sensitivity analyses** attenuated effect estimates of associations between atopic eczema (main analysis: HR=1.17, 95% CI=1.12,1.22; sensitivity analysis: HR=1.09, 95% CI=1.01,1.17) or psoriasis (main analysis: HR=1.26, 95% CI=1.18,1.35; sensitivity analysis: HR=1.17, 95% CI=1.04,1.32) and SMI, suggesting that ethnicity has an important role in temporal associations between atopic eczema or psoriasis and SMI • **Atopic eczema and depression/anxiety:** Compared to adults from white ethnic groups, and even after adjusting for potential mediators and at the same level of atopic eczema severity, adults with atopic eczema from minority ethnic groups had higher hazards of depression (minority ethnic groups: HR=1.33, 95%CI=1.22,1.45; white ethnic groups: HR=1.15, 95%CI=1.12,1.17) and anxiety (minority ethnic groups: HR=1.41, 95%CI=1.28,1.55; white ethnic groups: HR=1.17, 95%CI=1.14,1.19). • **Atopic eczema severity in white and minority ethnic groups:** According to primary care recording of skin disease therapies, adults from white and minority ethnic groups spent similar proportions of total follow-up at each level of atopic eczema severity.
Atopic eczema or psoriasis severity, and depression, anxiety, or SMI
• **Systematic review:** Pooled effect estimates from studies included in the systematic review suggest **moderate-to-severe psoriasis** is associated with increased **anxiety** (OR=1.14, 95%CI=1.05,1.25, I^2=0.00%, Tau^2=0.00), but **not depression** (OR=1.15, 95%CI=0.92,1.44, I^2=26.70%, Tau^2=0.01) among adults with psoriasis • All **RCTs** included in the **systematic review** found that individuals with moderate-to-severe atopic eczema or psoriasis randomised to receive **placebo had higher mean depression, anxiety**, **or combined anxiety and depression** scores after the trial period than those receiving **targeted biologic treatments** (e.g., dupilumab in atopic eczema, adalimumab in psoriasis) that help reduce inflammation • **Atopic eczema severity and SMI:** Compared to people without atopic eczema, individuals with moderate or severe atopic eczema had increased hazards of SMI (confounder-adjusted HRs: moderate: HR=1.61, 95%CI=1.50,1.73; severe: HR=1.56, 95% CI=1.21,2.01). However, there was no evidence of an

association between mild atopic eczema and SMI (confounder-adjusted HRs: mild: HR=0.98, 95%CI=0.93,1.04)

- **Atopic eczema severity and depression/anxiety:** Compared to people without atopic eczema, moderate atopic eczema was associated with the highest hazards of depression and anxiety in adults from white (depression: HR=1.38, 95% CI=1.33,1.45; anxiety: HR=1.43, 95% CI=1.36,1.50) and minority ethnic groups (depression: HR=1.90, 95% CI=1.58,2.29; anxiety: HR=1.83, 95% CI=1.49,2.25).

Factors potentially explaining associations between atopic eczema or psoriasis and depression, anxiety, or SMI

- **Systematic review:** Pooled effect estimates from studies included in the systematic review suggest that in individuals with psoriasis:
  - being a **woman** is associated with **increased depression** (OR=1.62, 95%CI=1.09,2.40, 95%PI=0.62,4.23, I^2=24.90%, Tau^2=0.05) **and anxiety** (OR=2.59, 95%CI=1.32,5.07, 95%PI=0.00,3956.27, I^2=61.90%, Tau^2=0.22);
  - comorbid **psoriatic arthritis** is associated with **increased depression** (OR=2.26, 95%CI=1.56,3.25, 95%PI=0.21,24.23, I^2=0.00%, Tau^2=0.00) **and anxiety** (OR=1.98,95%CI=1.33,2.94, I^2=0.00%, Tau^2=0.00).
- **Systematic review:** All RCTs found that adults with atopic eczema or psoriasis randomised to receive **placebo** had **higher mean depression and anxiety scores** compared to those randomised to receive **targeted biologic therapies**
- **Atopic eczema and SMI:** A post hoc analysis showed that further adjusting for the potential mediating effect of problems with **sleep**, led to **associations between atopic eczema and SMI not persisting** (confounder-adjusted: HR=1.17, 95%CI=1.12,1.22; additionally adjusted for sleep problems: HR=0.98, 95%CI=0.93,1.04)
- **Psoriasis and SMI:** Further adjusting **potential mediators** (comorbidity burden, harmful alcohol use, smoking status, and BMI) **attenuated associations** between psoriasis and SMI (confounder-adjusted: HR=1.26, 95%CI=1.18,1.35; mediator adjusted: HR=1.14, 95%CI=1.05,1.23)

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; OR – Odds Ratio; RCT – Randomised controlled trial; SMI – Severe mental illness

9.3 Discussion of findings

9.3.1 Longitudinal associations

9.3.1.1 Atopic eczema or psoriasis, and SMI

Clear evidence of temporal associations between atopic eczema or psoriasis, and SMI were reported in this thesis. In the cohort study described in **Chapter 7**, after implicitly adjusting for matching variables (age, sex, general practice) and adjusting for potential confounders (calendar period, socioeconomic deprivation), compared with matched comparators, atopic eczema was associated with a 17% increased hazard of incident SMI (hazard ratio [HR]=1.17, 95% CI=1.12,1.22), while psoriasis was associated with a 26% increased hazard of incident SMI (HR=1.26, 95% CI=1.18,1.35). Higher hazards corresponded to small absolute incident rate differences, with an estimated additional 6 per 100,000 cases of SMI in those with atopic eczema, and 9 per 100,000 cases of SMI in those with psoriasis.

Associations between atopic eczema or psoriasis and SMI identified in this thesis are consistent with the findings of previous smaller longitudinal studies in children and adolescents showing an increased risk of SMI in those with atopic diseases, autoimmune disorders, or psoriasis.[25–28] Associations between atopic eczema or psoriasis and SMI may be explained by several mechanisms. Both atopic eczema and psoriasis are chronic inflammatory skin conditions characterised by elevated levels of circulating pro-inflammatory cytokines (specifically IL-4, IL-5, IL-13 and IL-18 in atopic eczema,[29,278] and IL-12, IL-13, IL-17, IL-22, IL-23, TNF-alpha in psoriasis).[30] Increasing evidence suggests inflammation is involved in multiple psychiatric disorders, with some studies suggesting that inflammation may have a causal effect in the development of mental health conditions.[206,279,280] Furthermore, inflammatory biomarkers identified in people with atopic eczema or psoriasis have also been implicated in people with SMIs.[206,207] For example, studies of inflammation-related biomarkers in major psychiatric disorders have reported that TNF-alpha, sIL-6R, sIL-2R, IL-4 are elevated in bipolar disorder, while levels of CRP, sIL-2R, IL-6, IL-1RA, IL-12 are increased in schizophrenia.[206] Genetics may also play

a role, as limited evidence suggests a shared genetic susceptibility between psoriasis and schizophrenia involving immune signalling pathways.[207]

Evidence regarding the impact of impaired psychosocial functioning in atopic eczema or psoriasis, and potential associations with SMI are limited. Although both skin conditions are associated with embarrassment, low self-esteem, stigma, and social withdrawal due to visible skin disease,[281,282] the effect this may have on temporal associations with SMI are unclear. However, it has been suggested that stressful situations or life-events (that may result from stigma and discrimination due to skin disease) may trigger SMI symptoms in susceptible individuals.[136] Atopic eczema and psoriasis treatments may also contribute to temporal associations. The use of high-dose systemic oral corticosteroids used to treat moderate-to-severe forms of atopic eczema and psoriasis is associated with adverse psychiatric effects including symptoms of hypomania, mania, depression and psychosis which are characteristic of SMI.[171] However, these symptoms are temporary, with evidence suggesting symptoms resolve up to a few weeks following cessation of corticosteroid therapy.[283] Another explanation that may account for some of the association is surveillance bias. People with atopic eczema or psoriasis may be more likely to visit their GPs to manage their condition, meaning that it may be more likely for other additional illnesses – like SMI – to be detected.

Reasons for higher effect estimates of associations between psoriasis and SMI compared to those between atopic eczema and SMI reported in the cohort study are unclear. However, potential reasons for an increased risk of SMI in individuals with psoriasis compared to individuals with atopic eczema may include: (1) different pathological mechanisms between atopic eczema or psoriasis; (2) genetic factors; or (3) different behavioural or psychological responses to atopic eczema or psoriasis, however, further investigation is required.

9.3.1.2 Atopic eczema and depression or anxiety

Consistent with other longitudinal studies of with increased depression and anxiety in people with atopic eczema,[9,25,147,148] I found evidence of temporal associations between atopic eczema and depression or anxiety. In the cohort study described in **Chapter 8**, adults with atopic eczema from both white and minority ethnic groups

had increased hazards of incident depression (minority ethnic groups: HR=1.33, 95%CI=1.22,1.45; white ethnic groups: HR=1.15, 95%CI=1.12,1.17) and anxiety (minority ethnic groups: HR=1.41, 95%CI=1.28,1.55; white ethnic groups: HR=1.17, 95%CI=1.14,1.19) compared to matched comparators without eczema.

Several mechanisms may explain temporal associations between atopic eczema and depression or anxiety. Firstly, atopic eczema is a chronic inflammatory skin condition, and inflammation has been associated with numerous psychiatric disorders.[206,279,280] More specifically, the pathogenesis of atopic eczema shares elevated levels of several inflammation-related factors, which have also been implicated in the pathogenesis of depression and anxiety (including IL-12, IL-13 and IL-18).[29,206,278,279] Secondly, atopic eczema can have a significant psychosocial impact.[281] Atopic eczema can cause physical discomfort due to chronic itch,[41] and can limit physical activity (as affected individuals may avoid physical activity to prevent sweating that may exacerbate itch), which will both affect mood.[284] Additionally, low self-esteem, embarrassment and stigma are common consequences of atopic eczema potentially leading to social isolation.[172,281] Physical discomfort, limited physical activity and stigma can lead to emotional and psychological distress,[172,284] and may explain associations seen between atopic eczema and depression or anxiety. Finally, high-dose systemic oral corticosteroids used to treat unresponsive and severe atopic eczema are associated with depressive symptoms, however, their effect is temporary and guidelines recommend they should only be prescribed in short courses.[1,29,171]

9.3.2 The role of ethnicity

9.3.2.1 Atopic eczema or psoriasis, and depression or anxiety

In the systematic review (**Chapter 3**), two included studies reported conflicting findings regarding whether the risk of depression in adults with psoriasis differed by ethnic group. The first study – a large (n=7,490) longitudinal cohort study investigating factors predicting depressive symptoms in adults with psoriasis – reported that compared to adults from white ethnic groups, adults from non-white ethnic groups had 72% higher hazards of depressive symptoms (HR=1.72, 95%

CI=1.39,2.13). In contrast, the second study – a small (n=607) cross-sectional study investigating characteristics associated with depression and anxiety in adults with psoriasis – found no evidence of a difference in depression risk between ethnic groups. However, the same study reported that compared to individuals of White British ethnicity with psoriasis, adults of Asian ethnicity with psoriasis had more than three times the odds of anxiety (OR=3.42, 95% CI=1.63,7.20).

The systematic review included in this thesis did not identify any observational studies in adults with atopic eczema investigating the risk of mental health conditions in people from different ethnic groups. In the cohort study described in **Chapter 8**, after implicitly adjusting for matching variables (age, sex, general practice), and adjusting for potential confounders (calendar period, socioeconomic deprivation), there was strong evidence ($p<0.01$) that adults with atopic eczema from minority ethnic groups had increased hazards of incident depression (minority ethnic groups: HR=1.33, 95% CI=1.22,1.45; white ethnic groups: HR=1.15, 95% CI=1.12,1.17) and anxiety (minority ethnic groups: HR=1.41, 95% CI=1.28,1.55; white ethnic groups: HR=1.17, 95% CI=1.14,1.19) compared to adults with atopic eczema from white ethnic groups, and at the same level of atopic eczema severity. Due to limited statistical power, I was unable to investigate whether associations between psoriasis and incident depression or anxiety differed between white, and minority ethnic groups (as suggested by findings from of the systematic review).

Findings from the cohort study of ethnic differences in associations between atopic eczema and depression or anxiety (**Chapter 8**), as well as the findings from two studies included in the systematic review (**Chapter 3**), suggest that individuals from minority ethnic groups with skin disease are at increased risk of depression or anxiety compared to their white counterparts. Although there is limited existing evidence investigating ethnic differences in the risk of mental health conditions in people with skin disease, evidence from studies conducted in the general population where individuals from minority ethnic groups are at comparatively higher risk of depression and anxiety than people from white ethnic groups support my findings.[185,187,285,286] Studies conducted in population groups with other chronic diseases also support what I saw in people with atopic eczema. A large US study

found that Black individuals with cardiovascular disease had more than twice the odds of major depressive disorder compared to White individuals with cardiovascular disease (OR=2.11, 95% CI=1.21,3.70).[287] Another large US study found that Hispanic individuals with diabetes had 69% greater prevalence of anxiety compared to their white counterparts (prevalence ratio=1.69, 95% CI=1.33,2.15).[288]

Explanations for why individuals with atopic eczema or psoriasis from minority ethnic groups are at increased risk of depression or anxiety are unclear, however, there are several potential mechanisms. Cultural taboos and stigma associated with skin disease in individuals from minority ethnic groups may be partially responsible for the increased risk.[190,191] Associations may also be explained by the diagnosis and management of skin diseases in individuals from minority ethnic groups. For example, both atopic eczema and psoriasis appear different in skin of colour, and in people with darker skin, this may lead to delayed diagnosis, underestimation of disease severity, and even misdiagnosis for other skin diseases, which may subsequently delay treatment.[183,184] Individuals with darker skin are also at increased risk of developing post-inflammatory dyspigmentation following atopic eczema or psoriasis diagnosis.[183,184] Dyspigmentation is more noticeable in darker skin due to increased contrast, and this may be distressing for those affected, and further exacerbate feelings of stigma which can contribute to an increased risk of depression and anxiety. Additionally, in skin of colour, phototherapy is more effective at higher doses as melanin can act as a ultraviolet filter, so lower doses may be ineffective[289] Delayed or ineffective treatment of skin diseases may be associated with an increased risk of mental health conditions.

There may also be differences in how mental health conditions are diagnosed and managed in different ethnic groups that may explain increased associations. Studies investigating primary health care visits reported that clinicians may be more uncertain when diagnosing depression or anxiety in individuals from minority ethnic groups,[290,291] and this may lead to delayed diagnosis when the mental health condition is more debilitating or severe in affected individuals. Individuals from minority ethnic groups are also more likely to receive counselling or cognitive behavioural therapy to treat depression and anxiety instead of pharmacological

interventions, mainly due to negative beliefs associated with the use of medication to treat mental health conditions.[291,292] Counselling alone may be less effective than counselling in combination with medication,[293] especially when depression and anxiety are more severe, and this may be associated with more depression and anxiety within minority ethnic groups.

9.3.2.2 Atopic eczema or psoriasis, and SMI

Ethnicity may also be important in associations between atopic eczema or psoriasis and SMI. In the cohort study investigating associations between atopic eczema or psoriasis and SMI (**Chapter 7**), additionally adjusting for ethnicity as a potential confounder in sensitivity analyses attenuated effect estimates of associations between atopic eczema (main analysis: HR=1.17, 95% CI=1.12,1.22; sensitivity analysis: HR=1.09, 95% CI=1.01,1.17) or psoriasis (main analysis: HR=1.26, 95% CI=1.18,1.35; sensitivity analysis: HR=1.17, 95% CI=1.04,1.32) and SMI. While the attenuation of effect estimates may suggest ethnicity is a potential confounder of associations between atopic eczema or psoriasis and SMI, it is possible that (similar to the differing associations between atopic eczema and depression or anxiety seen in white and minority ethnic groups, seen in **Chapter 8**) SMI risk differs by ethnic group. Although there is limited existing evidence investigating ethnic differences in SMI risk in people with skin disease, studies in the UK general population suggest that individuals from Black and minority ethnic groups (BME) have higher rates of SMI, with the risk of psychosis in Black ethnic groups estimated to be nearly seven times higher than in the White population.[138,156] Further research, specifically estimating HRs, is required to assess whether there are similar patterns to those seen in the general population for associations between atopic eczema or psoriasis, and SMI in white and minority ethnic groups.

9.3.2.3 Differences in atopic eczema and psoriasis severity between ethnic groups

In the cohort study investigating ethnic differences in the association between atopic eczema and depression or anxiety (**Chapter 8**), I did not detect clear differences in atopic eczema severity between individuals from white and minority ethnic groups. These findings suggest that individuals with atopic eczema from white and minority

ethnic groups experience similar levels of atopic eczema severity, and contrasts with results from previous studies in children and adolescents that reported greater atopic eczema severity in individuals from minority ethnic groups.[188,294] However, the atopic eczema severity definition I used in the cohort study is based on prescriptions for skin disease therapies recorded in primary care EHR, and therefore measures level of recorded treatment for atopic eczema. This contrasts with the atopic eczema severity definitions in previous studies which used validated clinical scoring tools and may therefore measure true atopic eczema severity. Therefore, my finding of no clear differences in atopic eczema severity between individuals from white and minority ethnic groups may instead suggest that individuals from white and minority ethnic groups have similar levels of recorded skin disease treatment, which does not necessarily mean that they have the same level of atopic eczema severity. Additionally, the definition of atopic eczema severity used is susceptible to errors in recording and misclassification, particularly if individuals from ethnic groups are undertreated.

I was unable to investigate any differences in psoriasis severity between adults from white and minority ethnic groups due to limited statistical power. However, a previous cross-sectional study in US psoriasis patients reported that the presenting severity of psoriasis was higher in individuals of Asian and Hispanic ethnicity compared to those of White ethnicity.[189]

9.3.3 Atopic eczema or psoriasis severity, and depression, anxiety, or SMI

The findings of this thesis suggest skin disease severity may be an important factor in associations between atopic eczema or psoriasis, and mental health conditions. In secondary analyses of the cohort study investigating associations between atopic eczema or psoriasis and SMI (**Chapter 7**), adults with moderate (confounder-adjusted HR=1.61, 95% CI=1.50,1.73) or severe (confounder-adjusted HR=1.56, 95% CI=1.21,2.01) atopic eczema had increased hazards of SMI compared to matched comparators. However, there was no evidence of an association with mild eczema (confounder-adjusted HR=0.98, 95%CI=0.93,1.04). In terms of depression

and anxiety, in secondary analyses of the cohort study of ethnic differences in associations between atopic eczema and depression or anxiety (**Chapter 8**), although adults with mild atopic eczema from both white and minority ethnic groups had increased hazards of depression and anxiety compared to matched comparators, moderate atopic eczema was associated with the highest hazards of depression and anxiety in adults from white (depression: HR=1.38, 95% CI=1.33,1.45; anxiety: HR=1.43, 95% CI=1.36,1.50) and minority ethnic groups (depression: HR=1.90, 95% CI=1.58,2.29; anxiety: HR=1.83, 95% CI=1.49,2.25). Adults from white ethnic groups with severe disease also had increased hazards of depression and anxiety, however, there were small numbers of depression and anxiety events in minority ethnic groups with severe eczema (n=30 depression events, n=30 anxiety events) precluding a robust of assessment of the association in this group.

The association between increasing atopic eczema severity and an increased risk of depression, anxiety, and SMI demonstrated in the cohort studies included in this thesis (**Chapters 7,8**) is consistent with the findings of previous research. A UK population-based longitudinal cohort study identified a dose-response gradient between atopic eczema severity and incident depression, and increased hazards of incident anxiety in moderate and severe atopic eczema.[148] Another study reported that the risk of antidepressant and anxiolytic medication use in individuals with moderate-to-severe atopic eczema was approximately twice the risk in those with mild eczema.[9]

In the secondary analysis of the cohort studies investigating associations between atopic eczema or psoriasis and SMI (**Chapter 7**), there was no evidence that moderate-to-severe psoriasis was associated with increased hazards of SMI. However, it is likely that this finding was due to the small number of SMI events (n=43) in those with psoriasis. The lack of an association between moderate-to-severe psoriasis and SMI may also be due to the use of skin disease therapies as a surrogate to define psoriasis severity. Individuals with moderate-to-severe psoriasis were those on the most potent therapies (i.e., phototherapy or systemic therapies) known to be effective in the treatment of psoriasis.[217] Individuals receiving these

treatments are likely to have well-controlled psoriasis with minimal disease activity, therefore associations between psoriasis severity and mental health conditions may be under-estimated based on the severity definition I used.

The possibility of my electronic-health-record-based psoriasis severity definition under-estimating a potential link between more severe psoriasis and mental health conditions is supported by the contrasting findings of my systematic review (**Chapter 3**). Pooled effect estimates from the systematic review suggested that moderate-to-severe psoriasis was associated with increased anxiety (OR=1.14, 95%CI=1.05,1.25, I^2=0.00%, Tau^2=0.00), although the systematic review did not reveal a similar association with depression (OR=1.15, 95%CI=0.92,1.44, I^2=26.70%, Tau^2=0.01). These findings are consistent with other longitudinal studies from the UK, Denmark, and South Korea reporting that individuals with severe psoriasis were at increased risk of depression and anxiety compared to matched comparators, and have higher hazards of mental health conditions than those with mild psoriasis.[149–151] The lack of association between moderate-to-severe psoriasis and depression in pooled estimates in the systematic review (**Chapter 3**) may be due to imprecision in the effect estimates because of high sampling variability and small sample sizes of the pooled studies.

Associations between atopic eczema or psoriasis severity, and mental health conditions may be explained by stigma. As skin disease becomes more severe, it may also be more visible, further exacerbating feelings of stigma and contributing to the development of depression or anxiety.[91,172] Associations between skin disease severity and mental health conditions could also support an inflammatory mechanism. As already discussed, atopic eczema and psoriasis are characterised by elevated levels of circulating pro-inflammatory cytokines,[29–31] which have also been linked to depression, anxiety, and SMI,[29–31,175,206] suggesting an inflammatory mechanism that could link atopic eczema or psoriasis, and mental health conditions.

Evidence from the randomised controlled trials (RCTs) included in my systematic review (**Chapter 3**) also potentially supports an inflammatory mechanism. Short-term evidence from included RCTs found that moderate-to-severe atopic eczema or psoriasis treated with placebo was associated with higher depression and anxiety

scores compared to atopic eczema or psoriasis treated using targeted biologic therapies. Biologic therapies target immune pathways and prevent excess immune system activation.[1,31]

9.3.4 Factors potentially explaining associations between atopic eczema or psoriasis and depression, anxiety, or SMI

Pooled estimates from the systematic review (**Chapter 3**) found that, among adults with psoriasis, being female and comorbid psoriatic arthritis were associated with increased depression (female sex: OR=1.62, 95%CI=1.09,2.40, 95%PI=0.62,4.23, I^2=24.90%, Tau^2=0.05; psoriatic arthritis: OR=2.26, 95%CI=1.56,3.25, 95%PI=0.21,24.23, I^2=0.00%, Tau^2=0.00) and anxiety (female sex: OR=2.59, 95%CI=1.32,5.07, 95%PI=0.00,3956.27, I^2=61.90%, Tau^2=0.22; psoriatic arthritis: OR=1.98,95%CI=1.33,2.94, I^2=0.00%, Tau^2=0.00). These findings are consistent with another study (not included in the systematic review as they did not meet eligibility criteria) investigating correlates of psychiatric comorbidities among people with psoriasis, which reported that being female and comorbid conditions were strongly associated with mental health outcomes. [295] General population studies have also identified being a woman as a factor associated with depression and anxiety.[296,297]

My systematic review (**Chapter 3**) did not identify any eligible observational studies investigating factors associated with depression, anxiety, or SMI in adults with atopic eczema. It is possible the review did not identify observational studies in adults with atopic eczema because the condition frequently has an early onset and previous studies may have been limited to younger study populations, while my review was restricted to studies in adults (≥18 years). However, factors found to be associated with mental health conditions in people with psoriasis may also be associated with mental health conditions in people with atopic eczema due to the similarities (some common features in their pathogenesis, associations with significant morbidity, stigma, and impaired quality of life) between the conditions.

Evidence from RCTs included in my systematic review (**Chapter 3**) found that individuals with atopic eczema or psoriasis randomised to receive placebo had

higher mean depression and anxiety scores after the trial period compared to those randomised to receive targeted biologic treatments (e.g., dupilumab in atopic eczema, adalimumab in psoriasis). This finding of worse depression/anxiety scores in those receiving the placebo suggests that targeted biologic therapies may improve symptoms of depression and anxiety. There are two potential mechanisms by which biologic therapies may improve mental health outcomes. Firstly, targeted biologic therapies are effective treatments for atopic eczema and psoriasis, reducing body surface area involvement and other clinical signs of disease severity.[298] By improving skin disease, targeted biologics may indirectly improve symptoms of depression and anxiety as individuals with less severe disease may experience improved sleep and quality of life, better psychosocial function, and reduced stigma and embarrassment due to visible skin disease. Secondly, targeted biologic treatments may also directly affect mental health outcomes through their action on inflammation. Biologic agents target specific cytokines that are elevated in atopic eczema and psoriasis.[1,31] Several of the cytokines elevated in skin disease have also been associated with mental health outcomes (IL-12, IL-13 and IL-18 in atopic eczema, IL-1, IL-6, IL-17, and TNF-alpha in psoriasis),[29,30,206,278,279] therefore decreasing their levels may reduce any effects of these cytokines on mental health outcomes.

However, targeted biologic therapies have also been linked to psychiatric adverse events in the treatment of skin disease. In 2017, depression, anxiety, and suicidal ideation and behaviour were identified as potential risks in Phase three trials of brodalumab (a monoclonal antibody against the IL-17 receptor used in the treatment of moderate-to-severe psoriasis).[299,300] The therapy was eventually authorised for use due to a lack of causal evidence;[300] however, a warning was given that the risks and benefits of the treatment should be carefully weighed among individuals with history of depression or suicidal ideation.[299] Depression and other adverse psychiatric events have also been reported in clinical trials of other biological therapies for psoriasis (adalimumab) and other conditions (e.g., systemic lupus erythematous).[301,302] However, a biological mechanism through which these therapies may cause psychiatric events has not been demonstrated.[300] Additionally, it is difficult to differentiate between the psychiatric risk potentially linked to the underlying skin disease, and the direct effect of the biologic therapy.[299]

In the cohort study investigating associations between psoriasis and SMI (**Chapter 7**), adjusting for potential mediators (comorbidity burden, harmful alcohol use, smoking status, body mass index [BMI]) reduced the effect estimate of the association between psoriasis and SMI from 1.26 (95% CI=1.18,1.35) to 1.13 (95% CI=1.04-1.22). The reduction in effect estimates after adjustment of potential mediators, and the multiple factors identified as potentially associated with mental health conditions among adults with psoriasis in my systematic review (**Chapter 3**), suggests that the factors associated with depression, anxiety, and SMI in people with psoriasis are complex and multifactorial.

A post hoc secondary analysis of individual factors that may potentially mediate associations between atopic eczema and SMI (**Chapter 7**) also found that adjusting for problems with sleep alone shifted the effect estimate of the association between atopic eczema and SMI towards the null from 1.17 (95% CI=1.12,1.22) to 1.01 (95% CI=0.97,1.06), meaning that associations between atopic eczema and SMI no longer persisted. This finding suggests that problems with sleep may potentially mediate associations between atopic eczema and SMI, although the sleep problems may also be a proxy for eczema severity or a result of the mental health condition itself.

To my knowledge, this is the first study to investigate the role of sleep problems in associations between atopic eczema and SMI. However, previous studies have found associations between sleep disturbance and mental health conditions. In the general population, studies have reported that chronic sleep problems are linked to depression and anxiety,[170] and SMI.[205,271,272] So, it is perhaps not surprising, given that atopic eczema is known to disrupt sleep,[41,169] that I found evidence to support sleep problems as a mediator of the relationship between atopic eczema and SMI.

9.4 Strengths and limitations

9.4.1 Sample size

A key strength of this thesis is the large size and long-term follow up available in the CPRD GOLD dataset used for the population-based cohort studies (**Chapters 7,8**). The characteristics of CPRD GOLD meant that I was able to conduct well powered

main analyses investigating associations between atopic eczema or psoriasis, and incident SMI (**Chapter 7**) and associations between atopic eczema and incident depression or anxiety in white and minority ethnic groups (**Chapter 8**) in detail and with a level of statistical precision that would not be possible using a smaller data source. Unfortunately, secondary analyses of associations between severe atopic eczema or psoriasis and SMI (**Chapter 7**), and associations between severe atopic eczema and depression or anxiety in white and minority ethnic groups (**Chapter 8**) were underpowered due to small numbers of individuals with severe disease. Additionally, I was unable to replicate the cohort studies investigating associations between atopic eczema and incident depression or anxiety in white and minority ethnic groups in individuals with psoriasis as prior power calculations suggested the analyses would be underpowered.

9.4.2 Study design

A key strength of this thesis are the study designs I used. The systematic review (**Chapter 3**) was comprehensive with multiple scientific databases, trial registries and grey literature databases searched without applying language or geographical restrictions. The population-based cohort studies (**Chapters 7,8**) used a longitudinal design (allowing investigation of temporality of associations) and excluded people with the outcome of interest prior to cohort entry (ensuring that all mental health outcome events were incident cases). The ability to investigate temporal associations is an important advantage of the cohort studies in this thesis in contrast to previously published cross-sectional studies.[8,9,24,10–14,21–23] Previous cross-sectional studies investigating associations between skin disease and mental health conditions have been limited by potential reverse causality.

9.4.3 Generalisability

The studies included in this thesis have limitations that that may affect their generalisability. In the systematic review (**Chapter 3**), nine observational studies were likely to have some selection bias,[24,303–311] and included RCTs had strict eligibility criteria. The select study populations in these studies mean that their

results may not be generalisable to all populations with atopic eczema or psoriasis. However, factors identified as potentially associated with mental health conditions in the review reflected potential explanations described in the literature (e.g., being female, comorbid psoriatic arthritis, psoriasis severity, inflammatory mechanisms),[9,148,314,315,149–151,295–297,312,313] suggesting that these studies remained internally valid even if their effect estimates were not generalisable to all individuals with atopic eczema or psoriasis.

As discussed in **Chapter 4.2.3**, the CPRD GOLD dataset is broadly representative of the 2011 UK population in terms of age, sex, and ethnicity,[209] but may be geographically unrepresentative.[227] Additionally, confounder- and mediator-adjusted estimates from the cohort studies (**Chapters 7,8**) excluded individuals from Northern Ireland due to missing Carstairs deprivation data. The population coverage and representativeness of the CPRD GOLD dataset suggest that the findings of the population-based cohort studies are generalisable to individuals with atopic eczema or psoriasis within regions of the UK covered by the dataset. However, as the number of active patients registered with CPRD GOLD has decreased over time,[210,227] and to my knowledge, there have been no formal comparisons between CPRD GOLD and more recent census data, it is difficult to conclude whether the representativeness, and therefore generalisability of the population-based cohort studies are affected.

9.4.4 Identification of exposure status

There are both strengths and limitations associated with how exposure status was identified in the studies included in this thesis.

In the systematic review (**Chapter 3**), factors from observational studies investigated as potentially associated with depression, anxiety, and SMI among adults with psoriasis can be considered exposures. In five out of ten cross-sectional studies included in the review,[303,304,307,308,310] some exposures were identified using surveys, which could be susceptible to recall bias and subsequent misclassification. For example, individuals with psoriasis and one of the mental health conditions under investigation may be more likely to report stress or impaired quality of life than those

without mental health conditions, suggesting that these effect estimates may be inaccurate measures of true associations between factors of interest and mental health conditions. However, most factors investigated in the studies included in the systematic review (e.g., psoriasis severity, comorbidities) were verified using clinical records, suggesting a low potential for misclassification.

A key strength of this thesis is the use of validated definitions (described in **Chapter 5**) with high positive predictive values to accurately identify adults with atopic eczema and psoriasis in the cohort studies included in this thesis (**Chapters 7,8**).[213,214] However, the atopic eczema definition excludes individuals with only an atopic eczema diagnostic code, which may introduce selection bias as it excludes individuals with milder disease, or lead to misclassification of exposure status whereby people with mild or inactive eczema are classified as having no atopic eczema. Similarly, the previously developed atopic eczema and psoriasis severity definitions (described in **Chapter 5**) may have misclassified adults with severe disease as having less severe disease if they did not receive treatment, or for those whose condition had improved, they might continue to be characterised as having more severe disease. Wrongly identifying people with atopic eczema or psoriasis as not having atopic eczema or psoriasis and selection bias may mean that estimates of longitudinal associations between atopic eczema or psoriasis and SMI described in **Chapter 7**, or atopic eczema and depression or anxiety in white and minority ethnic groups described in **Chapter 8** are underestimates of true associations.

9.4.5 Identification of outcome status

A limitation of this thesis is the lack of validation of code lists used to define and identify depression, anxiety, and SMI in the cohort studies included (**Chapters 7,8**). This contrasts with the studies included in the systematic review, where clinical diagnoses or validated tools (e.g., the Hospital Anxiety and Depression Scale) were used to capture depression, anxiety, and SMI outcomes. However, to limit any potential effects of not using validated definitions, I compared the code lists I generated with codes provided in the Quality and Outcomes Framework (QOF) and other published code lists used in previous EHR studies to identify any missing

codes.[148,220,239–241] The code lists were also reviewed by a psychiatrist and two individuals with experience in UK clinical practice and EHR research. Furthermore, I undertook sensitivity analyses using broader definitions of depression, anxiety, and SMI outcomes to explore the sensitivity of the results to definitions of the mental health conditions used, and these sensitivity analyses produced similar findings to the main results. Additionally, it is likely that if an individual has a code for a mental health condition in CPRD GOLD, then they have that mental health condition. However, it is also possible that CPRD GOLD does not capture all individuals with mental health conditions in primary care, either because they do not consult with their GP, or they are not registered with a GP.

9.4.6 Confounders and mediators

A key limitation of my systematic review (**Chapter 3**) is that all observational studies included had at least moderate risk of bias in the confounding domain, suggesting that associations between factors of interest and mental health conditions identified from these studies may be subject to residual confounding, and should be interpreted with caution. However, I conducted the review to inform the selection of covariates for the cohort studies (**Chapters 7,8**) included in the thesis, and the primary aim of many of the studies included in the review was not to investigate associations between the factor of interest and a mental health condition, therefore, issues with the control of confounding in included studies are understandable.

There are both strengths and limitations regarding the adjustment for potential confounders and mediators in the cohort studies included in this thesis (**Chapters 7,8**). A major strength is the breadth of data available in the CPRD GOLD allowed me to adjust for potential confounders and mediators that had not been considered in previous work investigating associations between atopic eczema or psoriasis and mental health conditions.

However, it is important to acknowledge that there are key limitations of the cohort studies (**Chapters 7,8**). Firstly, the effectiveness of adjustment for key confounders and mediators depended on if they were recorded at all in primary care electronic health records, how well they were recorded, and when the variables were recorded.

Some key confounders and mediators (described in **Chapters 5,6**) are incompletely captured, or not recorded at all in CPRD GOLD, suggesting that estimates from the cohort studies may include residual effects of incompletely captured confounders and mediators (e.g., stigmatisation, substance misuse). The timing of the capture of some potential mediators in both cohort studies may have occurred before atopic eczema or psoriasis diagnosis, and hence may not be on the causal pathway as my analysis strategy assumes. However, given that both atopic eczema and psoriasis are chronic relapsing conditions, with onset often early in life, the timing of the capture of mediators may have had limited effect on the mediator-adjusted estimates.

Finally, although based on the literature, causal assumptions in directed acyclic graphs (DAGs) of associations between atopic eczema or psoriasis and depression, anxiety, and SMI (described in **Chapter 6**) that were used to inform covariate selection may be incorrect, or there may be different opinions on the relationships between variables in a DAG. The uncertainty associated with DAGs may mean that in the cohort studies included in the thesis (**Chapters 7,8**) some variables may have been inappropriately adjusted for as key confounders or mediators.

9.5 Implications

The results of this thesis highlight the importance of monitoring mental health conditions in adults with atopic eczema or psoriasis. Evidence from this thesis reports a large burden of depression, anxiety, and SMI among adults with atopic eczema and psoriasis. and identifies subgroups of individuals with atopic eczema or psoriasis who may be at increased risk of mental health conditions, including individuals from minority ethnic groups, those with more severe skin disease, women, and people with comorbidities.

9.5.1 Clinical practice

Evidence suggests that dermatologists frequently underestimate detection of depression and anxiety among individuals with skin disease.[316] Within primary care, individuals who present with physical conditions (such as atopic eczema or

psoriasis) may be less likely to have their mental health conditions detected.[317–319] The reduction in identification of mental health conditions may particularly occur among individuals from minority ethnic groups,[291] either due to decreased health seeking behaviour,[193,194,320] or greater uncertainty in diagnosing mental health conditions in minority ethnic groups by clinicians.[290] Given the under recognition of mental health conditions in people with skin disease, an improved awareness of associations between atopic eczema or psoriasis and depression, anxiety, and SMI is required in clinical practice. This may involve specific training of general practitioners (GPs) and dermatologists on identifying depressive and anxiety disorders in the presence of other chronic conditions,[321] in individuals of different ethnic groups, and highlighting the importance and benefits of identifying comorbid mental health conditions in improving treatment outcomes for skin disease.[114]

Once there is an improved awareness of the mental health burden associated with skin disease, strategies can be implemented to reduce risk or improve identification of mental health conditions – particularly depression and anxiety – in the care of individuals with atopic eczema or psoriasis. Firstly, primary prevention strategies that aim to stop mental health conditions before onset can be utilised within primary care. These strategies have been reported to reduce the risk of mental health conditions or lead to less debilitating mental health conditions.[322–324] An important aspect of primary prevention is educating individuals with atopic eczema or psoriasis on potential associated mental health burdens. This may involve community-based mental health promotion to help individuals develop healthy behaviours (e.g., encouraging individuals to practice mindfulness and develop a supportive network of friends or family).[323,324] As the findings from this thesis suggest that adults from minority ethnic groups with skin disease are at higher risk of mental health conditions, it is important mental health promotion strategies are accessible, non-stigmatising and culturally sensitive to individuals from minority ethnic groups with skin disease to ensure their effectiveness in the population.[325] The iCOPE Psychological Services Programme administered by the Camden and Islington NHS Trust is an example of a mental health programme that provides culturally specific resources and therapy for individuals from minority ethnic groups.[326] The programme offers clinics in different languages, runs educational workshops within community

settings and creates resources specifically for individuals from minority ethnic groups (i.e., audio recordings of relaxation exercises available in different languages, translated materials, community groups in different languages).[326]

Primary prevention may also involve targeting modifiable factors associated with mental health conditions in the general population (e.g., substance misuse, harmful alcohol use)[165,166,199,201,204,275] in adults with atopic eczema or psoriasis. Additionally, in adults with atopic eczema, primary prevention strategies could target problems with sleep – either through enhanced treatment of underlying skin disease or treating the sleep problem itself –[176,327] as evidence from this thesis reported that sleep strongly mediated associations between atopic eczema and SMI (**Chapter 7**).

Secondary mental health prevention strategies could also be included in care of individuals with atopic eczema or psoriasis, including mental health screening to increase early detection and prompt intervention on mental health conditions.[328] Screening methods used should depend on the specific mental health condition, however, validated tools such as the Hospital Anxiety and Depression Scale (HADS) should be used when feasible.[329]

However, before either primary and secondary mental health prevention strategies are implemented in the care of individuals with atopic eczema or psoriasis, it is important that their effectiveness and cost-effectiveness is demonstrated (particularly for public health decision makers).[330,331] Effectiveness of interventions can be ascertained by quantifying the reduction in diagnoses of mental health conditions attributable to the intervention among individuals with atopic eczema or psoriasis. Cost-effectiveness can be estimated by comparing the costs of implementing the intervention to the medical and productivity costs averted by the intervention, and the quality-adjusted life-years gained by the intervention.[331]

9.5.2 Public health and policy

Recent UK guidelines by the National Institute for Health and Care Excellence (NICE), suggest that clinicians should assess the psychological impact of atopic eczema or psoriasis by asking affected individuals about the effect of skin disease on daily activities (i.e., school, work, social life), sleep, and mood, and use validated

tools (e.g., Dermatology Life Quality Index [DLQI]) to assess the impact on quality of life.[332,333] However, guidelines do not mention the potential implications of atopic eczema or psoriasis on the mental health of affected individuals long-term. In addition, evidence suggests that validated quality of life questionnaires may miss clinically important psychiatric disorders. A small (n=607) cross-sectional study investigating the integration of mental health screening into routine care as part of the Integrating Mental and Physical Healthcare: Research Training Services (IMPARTS) programme in a specialist dermatology clinic reported that one in three cases of depression and anxiety would be missed using validated quality of life questionnaires (e.g., DLQI) alone without the use of additional mental health screening tools;[306] this is unsurprising given that they aim to capture different domains.

Updates to future guidelines could explicitly address the associations between atopic eczema or psoriasis, and depression, anxiety, and SMI among adults. Future guidelines could also consider implementing targeted mental health screening for depression and anxiety among adults with atopic eczema or psoriasis using validated screening tools such as the Hospital Anxiety and Depression Scale (HADS). Introducing targeted mental health screening in the care of individuals with atopic eczema or psoriasis would provide opportunities to improve health outcomes and potentially reduce psychological burdens in affected individuals. It is likely that targeted screening of depression and anxiety among adults with atopic eczema or psoriasis should not be limited to specialist dermatology clinics, as in the UK, skin diseases are the most common new reason people present to their GP with a new health problem,[334] and most individuals with skin conditions are managed exclusively within primary care.[335] Using mobile health technology may allow for easier mental health screening of individuals with atopic eczema or psoriasis within primary care settings,[336] and may also lead to the identification of cases that may usually be missed. Mobile health strategies may include giving individuals with skin disease tablets with validated mental health questionnaires in GP waiting rooms or asking individuals with skin disease to download an app to their mobile device that allows remote completion of mental health questionnaires.

9.6 Future research

9.6.1 Investigating associations in different ethnic groups

In the cohort studies investigating ethnic differences in associations between atopic eczema and depression or anxiety (**Chapter 8**), I pragmatically decided to: (1) pool individuals from Black, South Asian, Mixed and Other ethnic groups into a 'minority ethnic' group and investigate associations between atopic eczema and depression or anxiety in white and the minority ethnic group; and (2) not investigate associations between psoriasis and depression or anxiety due to limited statistical power. Future studies should address these limitations by investigating associations between atopic eczema and depression or anxiety in all five of the ethnic groups used to categorise ethnicity in the UK (White, Asian, Black, Mixed, and Other) as individuals in these ethnic groups do not reflect a singular homogenous ethnic identity, and there may also be significant diversity in the associations between the ethnic groups (for example, there may be different cultural beliefs about skin disease in different ethnic groups influencing psychological responses to the experience of skin disease with subsequent mental health implications). Associations between psoriasis, and depression or anxiety should also be studied. These objectives could be achieved by using other data sources. CPRD Aurum (which includes electronic health records from UK primary care practices captured using different software to CPRD GOLD) is larger than CPRD GOLD and contains more active patients,[212] potentially improving statistical power. Alternatively, the use of datasets with higher proportions of individuals from minority ethnic groups (e.g., the South London and Maudsley NHS Foundation Trust Biomedical Research Centre Case Register, a EHR dataset a large mental healthcare provider) [337] may allow more detailed explorations of associations between atopic eczema or psoriasis and mental health conditions in different ethnic groups.

9.6.2 Improving understanding of potential mediators

An important avenue for future research is identifying factors that may mediate, relationships between atopic eczema or psoriasis, and depression, anxiety, or SMI.

While some of these factors may have been identified by the studies included in this thesis (e.g., problems with sleep in associations between atopic eczema and SMI), a more detailed exploration of the role these factors play is vital. Additionally, further study may identify other modifiable factors or opportunities to intervene that may moderate risk or even prevent the development of mental health conditions.

Future research using alternative data sources that include information on factors that could not be reliably captured in EHR (e.g., inflammatory markers, psychosocial factors, sleep, exercise) may lead to a better understanding of factors potentially mediating associations between atopic eczema or psoriasis, and mental health conditions. Examples of alternative data sources that could be used include: (1) UK Biobank, a large (n=500,000) population-based prospective study where data on a range of potential mediators that are difficult to capture in EHR data have been collected;[180,181] (2) the 1970 British Cohort Study (BCS70), a continuing longitudinal survey monitoring the development of over 17,000 people born in the UK within a single week of 1970;[338] and (3) the Avon Longitudinal Study of Parents and Children (ALSPAC), an observational study of over 13,000 mothers and their children investigating characteristics that influence health and development.[339,340] These datasets contain a wealth of information including data on physical activity, diet, social support, and other psychosocial factors which could be used to adjust for the impact of some aspects of impaired psychosocial function among individuals with atopic eczema or psoriasis on associations with mental health conditions.[180,181,338–340]UK Biobank and ALSPAC also capture biomarker data on C-reactive protein,[180,340] a protein that is elevated during inflammatory conditions,[341] which could be used to begin investigating the role of inflammation in associations between atopic eczema or psoriasis and mental health conditions. Additionally, UK Biobank and ALSPAC include genetic data, allowing for Mendelian randomisation studies using genetic indicators of potential mediators to identify causal associations.[342] However, a limitation associated with UK Biobank is the inability to investigate the role of ethnicity in associations between skin disease and mental health conditions as approximately 95% of participants within the cohort are of white ethnicity.[343]

Additionally, using alternative data sources such as may also: (1) allow for more detailed information to be used to fully capture potentially mediating variables, for example, UK Biobank contains self-reported information on smoking habits (e.g., number of cigarettes per day, and the duration of smoking) that may more effectively capture smoking;[344] and (2) allow triangulation of findings through study replication to increase the validity of findings within the thesis.[345]

Future research should also consider utilising formal statistical mediation analysis methods to quantify potential mechanisms by which atopic eczema or psoriasis are linked with mental health conditions. Although the findings in this thesis suggest that problems with sleep mediated associations between atopic eczema and SMI, I was unable to estimate the proportion of the association that was mediated by problems with sleep as I did not use formal mediation analysis approaches. Statistical mediation analyses allow the total effect of an exposure on an outcome to be separated into indirect effects (the effect of the exposure acting through mediators) and direct effects (the effect of the exposure without the action of mediators) and provides estimates of the proportion of the association mediated. However, mediation analyses are challenging in longitudinal study designs using stratified Cox regression, incorporating time updated covariates, and including multiple potential mediating variables.[255] Further research may be able to quantify potential mediators by using alternative statistical methods.[346,347]

9.6.3 Identifying additional high-risk groups

This thesis identified groups with atopic eczema or psoriasis that may potentially be at higher risk of mental health conditions (e.g., women, those with more severe skin disease, individuals from minority ethnic groups). Further research is required to identify additional high-risk groups with atopic eczema or psoriasis who may experience inequalities in depression or anxiety risk. For example, in adults, low socioeconomic status (and high levels of deprivation) is associated with a high prevalence of atopic eczema,[152,153] psoriasis,[155] and mental health conditions,[7,109,156] however, it is unclear whether associations between atopic eczema or psoriasis and mental health conditions differ by socioeconomic deprivation level.

9.6.4 Investigating associations in different settings

While the population-based cohort studies included in this thesis used UK primary care data their broad findings of increased mental health conditions in people with atopic eczema and psoriasis are likely to be generalisable to other countries and healthcare settings. Nevertheless, future research should investigate mental health condition burden in individuals with atopic eczema or psoriasis using data from other countries as there may be regional differences in the factors explaining associations or the magnitude of associations (offering insights into potential mechanisms explaining the associations). For example, in countries with constantly high temperatures, atopic eczema,[348] and a subset of psoriasis cases,[349] may be aggravated or poorly controlled, leading to flare ups and potentially subsequent greater risk of mental health conditions. There may also be different cultural responses to skin disease in different settings that may affect associations with mental health conditions (e.g., greater stigma associated with having visible skin disease). Additionally, investigating associations between skin disease and mental health conditions in different settings, and/or using data other than routine-collected electronic health record data, will offer opportunities to create a more complete picture of the underlying truth (using different data sources – with differing strengths and limitations – to answer the same research question allows a more robust picture through triangulation of findings).

9.7 Conclusions

In conclusion, the studies included in this thesis identified a high burden of anxiety, depression, and SMI among adults with atopic eczema or psoriasis. Adults with atopic eczema or psoriasis appeared to be at increased risk of SMI compared to matched comparators, and in adults with atopic eczema, this increased risk seemed to be largely mediated by problems with sleep. Adults with atopic eczema from both white and minority ethnic groups were at increased risk of developing depression and anxiety compared to matched comparators, however, the risk was particularly elevated in individuals from minority ethnic groups compared to those from white ethnic groups. Being a woman, having more severe skin disease, and comorbid

psoriatic arthritis may be associated with increased depression and anxiety among adults with psoriasis. It is important to increase awareness among patients, clinicians, and policy makers regarding the mental health burden experienced by those with atopic eczema or psoriasis. Raising awareness may lead to the implementation of mental health promotion and prevention strategies (e.g., targeted mental health screening) that improve mental health outcomes among individual with atopic eczema or psoriasis.

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Appendices

Appendix 1: Supplementary material for systematic review protocol

Supplementary Table 1: Search strategy in MEDLINE database

Item number	Searches
Risk factor terms	
1	risk OR risk factor* OR protective factor OR predict* OR correlat* OR associate* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR caus* OR path*
2	exp Risk/
3	1 OR 2
Atopic eczema terms	
4	atopic dermatitis OR atopic eczema OR atopy
5	Dermatitis, Atopic/
6	exp Eczema/
7	4 OR 5 OR 6
Psoriasis terms	
8	psoriasis OR psoria*
9	pustulo* AND (palmopl* OR palmari* OR palmar)
10	exp Psoriasis/
11	8 OR 9 OR 10
Combining atopic eczema and psoriasis terms with 'OR'	
12	7 OR 11
Mental illness terms	
13	mental health OR mental* ill* OR mental disorder* OR affective OR anxi* OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
14	psychiatr* AND (ill* OR disorder OR disease*)
15	psychological* AND (ill* OR disorder OR disease* OR distress)
16	Mental Health/
17	Exp Mental Disorders/
18	13 OR 14 OR 15 OR 16 OR 17
Combining key concepts with 'AND'	
19	3 AND 12 AND 18

Appendix 2: Supplementary material for systematic review

Appendix – Factors associated with depression, anxiety, and severe mental illness among adults with atopic eczema and psoriasis: a systematic review and meta-analysis

Authors: Elizabeth I Adesanya, Julian Matthewman, Yochai Schonmann, Joseph F Hayes, Alasdair Henderson, Rohini Mathur, Amy R Mulick, Catherine H Smith, Sinéad M Langan, Kathryn E Mansfield

Appendix S1: Search strategy

Appendix S2: Numbers of records identified from each database searched

Appendix S3: Data extraction forms

Table S1: Papers excluded after full text review and reasons for exclusion

References

Table S2: Characteristics of observational studies for factors associated with mental illness among people with psoriasis included in the review

Table S3: Characteristics of randomised controlled trials for the association between atopic eczema treatment and mental illness among people with atopic eczema included in the review

Table S4: Characteristics of randomised controlled trials for the association between atopic eczema treatment and mental illness among people with psoriasis included in the review

Table S5: Justification for risk of bias assessments of studies included in the review using the Quality in Prognostic Studies (QUIPS) tool

Table S6: Association between atopic eczema treatment and mental illness, stratified by mental illness outcome identified from randomised controlled trials

Table S7: Factors associated with depression in people with psoriasis identified from observational studies

Table S8: Factors associated with anxiety in people with psoriasis identified from observational studies

Table S9: Factors associated with schizophrenia in people with psoriasis identified from observational studies

Table S10: Association between psoriasis treatment and mental illness, stratified by mental illness outcome identified from randomised controlled trials

Appendix S1: Search strategy

Our search strategy included terms relating to three key concepts – 'association' terms, 'atopic eczema or psoriasis' and 'mental illness' – combined using the Boolean logic operator 'AND' (table below). We used our search strategy to identify relevant database-specific subject headings. We searched databases by for each search term using our search strategy to search abstracts, keywords and titles, and the relevant subject headings. Our search strategy was developed in Medline and reviewed by a librarian, and then adapted for use in other databases.

Search term	Keywords
Association terms	risk OR risk factor* OR prognostic factor OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR caus* OR path*
Atopic eczema or psoriasis terms	atopic dermatitis OR eczema OR atopy OR psoriasis OR psoria* OR (pustulo* AND palmopl* OR palmari* OR palmar)
Mental illness terms	mental health OR mental* ill* OR mental disorder* OR psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease* OR psychological* ill* OR psychological* disorder* OR psychological* disease* OR affective* OR anxi* OR depress* OR phobi* OR panic OR bipolar* OR schizophrenia OR schizo* OR delusion* OR psychotic* OR psychos#s OR psychological* distress

Search strategy in MEDLINE

Item number	Searches
Association terms	
1	risk OR risk factor* OR protective factor OR prognostic factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
2	exp Risk/
3	1 OR 2
Atopic eczema terms	
4	atopic dermatitis OR atopic eczema OR eczema OR atopy
5	Dermatitis, Atopic/
6	exp Eczema/
7	4 OR 5 OR 6
Psoriasis terms	
8	psoriasis OR psoria*
9	pustulo* AND (palmopl* OR palmari* OR palmar)
10	exp Psoriasis/
11	8 OR 9 OR 10
Combining atopic eczema and psoriasis terms with 'OR'	
12	7 OR 11
Mental illness terms	
13	mental health OR mental* ill* OR mental disorder* OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
14	psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease
15	psychological* ill* OR psychological* disorder OR psychological* disease* OR psychological* distress
16	Mental Health/
17	Exp Mental Disorders/
18	13 OR 14 OR 15 OR 16 OR 17
Combining key concepts with 'AND'	
19	3 AND 12 AND 18

Search strategy in EMBASE

Item number	Searches
Association terms	
1	risk OR risk factor* OR prognostic factor OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
2	exp risk factor/
3	exp etiology/
4	exp association/
5	exp causality/
6	1 OR 2 OR 3 OR 4 OR 5
Atopic eczema terms	
7	atopic dermatitis OR atopic eczema OR eczema OR atopy
8	exp eczema/
9	exp atopic dermatitis/
10	exp atopy/
11	7 OR 8 OR 9 OR 10
Psoriasis terms	
12	psoriasis OR psoria*
13	pustulo* AND (palmopl* OR palmari* OR palmar)
14	exp psoriasis/
15	12 OR 13 OR 14
Combining atopic eczema and psoriasis terms with 'OR'	
16	11 OR 15
Mental illness terms	
17	mental health OR mental* ill* OR mental disorder* OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
18	psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease
19	psychological* ill* OR psychological* disorder OR psychological* disease* OR psychological* distress
20	exp mental Health/
21	exp mental disease/
22	exp depression/
23	exp anxiety/
24	exp psychosis/
25	exp mood disorder/
26	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
Combining key concepts with 'AND'	
27	6 AND 16 AND 26

Search strategy in Global Health

Item number	Searches
Association terms	
1	risk OR risk factor* OR prognostic factor OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
2	exp risk factors/
3	exp aetiology/
4	1 OR 2 OR 3
Atopic eczema terms	
5	atopic dermatitis OR atopic eczema OR eczema OR atopy
6	Exp eczema/
7	exp atopy/
8	Exp atopic dermatitis/
9	5 OR 6 OR 7 OR 8
Psoriasis terms	
10	psoriasis OR psoria*
11	pustulo* AND (palmopl* OR palmari* OR palmar)
12	exp Psoriasis/
13	10 OR 11 OR 12
Combining atopic eczema and psoriasis terms with 'OR'	
14	9 OR 13
Mental illness terms	
15	mental health OR mental* ill* OR mental disorder* OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
16	psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease
17	psychological* ill* OR psychological* disorder OR psychological* disease* OR psychological* distress
18	Exp Mental Health/
19	Exp Mental Disorders/
20	15 OR 16 OR 17 OR 18 OR 19
Combining key concepts with 'AND'	
21	4 AND 14 AND 20

Search strategy in SCOPUS

Item number	Searches
Association terms	
1	risk OR “risk factor*” OR “prognostic factor” OR “protective factor” OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
Atopic eczema terms	
2	“atopic dermatitis” OR “atopic eczema” OR eczema OR atopy
Psoriasis terms	
3	psoriasis OR psoria*
4	pustulo* AND (palmopl* OR palmari* OR palmar)
5	#3 OR #4
Combining atopic eczema and psoriasis terms with ‘OR’	
6	#2 OR #5
Mental illness terms	
7	“mental health” OR “mental* ill*” OR “mental disorder*” OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
8	“psychiatr* ill*” OR “psychiatr* disorder” OR “psychiatr* disease”
9	“psychological* ill*” OR “psychological* disorder” OR “psychological* disease*” OR “psychological* distress”
10	#7 OR #8 OR #9
Combining key concepts with ‘AND’	
21	#1 AND #6 AND #10

Search strategy in Cochrane library

Item number	Searches
Association terms	
1	risk OR “risk factor*” OR “prognostic factor” OR “protective factor” OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
2	exp Risk/
3	#1 OR #2
Atopic eczema terms	
4	“atopic dermatitis” OR “atopic eczema” OR eczema OR atopy
5	Dermatitis, Atopic/
6	Eczema/
7	#4 OR #5 OR #6
Psoriasis terms	
8	psoriasis OR psoria*
9	pustulo* AND (palmopl* OR palmari* OR palmar)
10	Psoriasis/
11	#8 OR #9 OR #10
Combining atopic eczema and psoriasis terms with ‘OR’	
12	#7 OR #11
Mental illness terms	
13	“mental health” OR “mental* ill*” OR “mental disorder*” OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
14	“psychiatr* ill*” OR “psychiatr* disorder” OR “psychiatr* disease”
15	“psychological* ill*” OR “psychological* disorder” OR “psychological* disease*” OR “psychological* distress”
16	Mental Health/
17	Exp Mental Disorders/
18	#13 OR #14 OR #15 OR #16 OR #17
Combining key concepts with ‘AND’	
19	#3 AND #12 AND #18

Search strategy in Web of Science

Item number	Searches
Association terms	
1	risk OR “risk factor*” OR “prognostic factor” OR “protective factor” OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
Atopic eczema terms	
2	“atopic dermatitis” OR “atopic eczema” OR eczema OR atopy
Psoriasis terms	
3	psoriasis OR psoria*
4	pustulo* AND (palmopl* OR palmari* OR palmar)
5	#3 OR #4
Combining atopic eczema and psoriasis terms with ‘OR’	
6	#2 OR #5
Mental illness terms	
7	“mental health” OR “mental* ill*” OR “mental disorder*” OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos?s
8	“psychiatr* ill*” OR “psychiatr* disorder” OR “psychiatr* disease”
9	“psychological* ill*” OR “psychological* disorder” OR “psychological* disease*” OR “psychological* distress”
10	#7 OR #8 OR #9
Combining key concepts with ‘AND’	
21	#1 AND #6 AND #10

Search strategy in PsycInfo & PsycExtra

Item number	Searches
Association terms	
1	risk OR risk factor* OR prognostic factor OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*
Atopic eczema terms	
2	atopic dermatitis OR atopic eczema OR eczema OR atopy
Psoriasis terms	
3	psoriasis OR psoria*
4	pustulo* AND (palmopl* OR palmari* OR palmar)
5	3 or 4
Combining atopic eczema and psoriasis terms with 'OR'	
6	2 OR 5
Mental illness terms	
7	mental health OR mental* ill* OR mental disorder* OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychos#s
8	psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease
9	psychological* ill* OR psychological* disorder OR psychological* disease* OR psychological* distress
10	Exp Mental Health/
11	Exp Mental Disorders/
12	Exp Anxiety/
13	Exp Major Depression/
14	Exp Schizophrenia/
15	Exp Psychosis/
16	Exp Bipolar Disorder/
17	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
Combining key concepts with 'AND'	
13	1 AND 6 AND 17

Search strategy in GREAT

risk OR risk factor* OR prognostic factor OR protective factor OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*

AND

atopic dermatitis OR atopic eczema OR eczema

AND

mental health OR mental* ill* OR mental disorder* OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychoses OR psychosis OR psychiatr* ill* OR psychiatr* disorder OR psychiatr* disease OR psychological* ill* OR psychological* disorder OR psychological* disease* OR psychological* distress

Search strategy in BASE

(risk "risk factor*" "prognostic factor" "protective factor" predict* correlat* associat* aetiol* etiol* relationship mediat* mechanism* cause* causal* causation* causative* pathway*) AND ("atopic dermatitis" "atopic eczema" eczema atopy psoriasis psoria*) AND ("mental health" "mental* ill*" "mental disorder*" affective anxiety anxi* depression depress* phobi* panic bipolar* schizo* schizophrenia delusion* psychotic* psychoses psychosis "psychiatr* ill*" "psychiatr* disorder" "psychiatr* disease" "psychological* ill*" "psychological* disorder" "psychological* disease*" "psychological* distress")

Search strategy in OpenGrey

(risk OR “risk factor*” OR “prognostic factor” “protective factor” OR predict* OR correlat* OR associat* OR aetiol* OR etiol* OR relationship OR mediat* OR mechanism* OR cause* OR causal* OR causation* OR causative* OR pathway*) AND (“atopic dermatitis” OR “atopic eczema” OR eczema OR psoria* OR psoriasis) AND (“mental health” OR “mental* ill*” OR “mental disorder*” OR affective OR anxiety OR anxi* OR depression OR depress* OR phobi* OR panic OR bipolar* OR schizo* OR schizophrenia OR delusion* OR psychotic* OR psychosis OR psychoses OR “psychiatr* ill*” OR “psychiatr* disorder” OR “psychiatr* disease” OR “psychological* ill*” OR “psychological* disorder” OR “psychological* disease*” OR “psychological* distress”)

Search Strategy in New York Academy of Medicine Grey Literature Report

You can only search by keywords which are automatically combined using AND. This means that I searched for just eczema (and associated terms e.g. atopy, dermatitis, atopic eczema, atopic dermatitis) and psoriasis separately and got 0 results

Search strategy in ClinicalTrials.gov

Condition or disease

“Atopic dermatitis” OR “Atopic eczema” OR eczema OR psoriasis

Other terms

(risk OR "risk factor" OR correlation OR association OR relationship OR cause) AND (mental health OR mental illness OR anxiety OR depression OR schizophrenia OR bipolar OR psychosis OR psychoses)

Search strategy in EU Clinical trials register

(“Atopic dermatitis” OR “Atopic eczema” OR eczema OR psoriasis) AND (risk OR "risk factor" OR correlation OR association OR relationship OR cause) AND (mental health OR

mental illness OR anxiety OR depression OR schizophrenia OR bipolar OR psychosis OR psychoses)

Search strategy in ISRCTN

(“Atopic dermatitis” OR “Atopic eczema” OR eczema OR psoriasis) AND (risk OR "risk factor" OR correlation OR association OR relationship OR cause) AND (mental health OR mental illness OR anxiety OR depression OR schizophrenia OR bipolar OR psychosis OR psychoses)

Search strategy in ANZCTR

(eczema OR psoriasis) AND (relationship OR "risk factor") AND ("mental health" OR "mental illness")

Different iterations of this term using different synonyms (this registry has a 100 character limit

Appendix S2: Numbers of records identified from each database searched

Databases

Medline (n = 2,472)

Embase (n = 6,056)

Global Health (n = 373)

PsycInfo (n = 445)

Scopus (n = 4,491)

Cochrane Library (n = 455)

Web of Science (n = 1,908)

BASE – Bielefeld Academic Search Engine (n = 1,156)

Trial registries

ClinicalTrials.gov (n = 162)

EU Clinical Trials Register (n = 5)

Japan Primary Registries Network (n = 0)

ISRCTN (International Standard Randomised Controlled Trial Number) registry (n = 1)

ANZCTR – Australian New Zealand Clinical Trials Registry (n = 0)

Grey literature

PsycExtra (n = 5)

OpenGrey (n = 8)

New York Academy of Grey Literature (n = 0)

Other

Citation searching and reference lists of relevant systematic reviews (n = 2)

Appendix S3: Data extraction form (observational studies)

1. Your initials *

2. First author and year of publication *
   Last name/ family name of first author (e.g. Ang 2012)

3. Publication title *

Study characteristics

4. Year(s) study was conducted *

5. Country where study took place *

6. Setting study was conducted *

7. Study funding source *

   Check all that apply.

   - [ ] Industry funded
   - [ ] Government/charity funded
   - [ ] Not stated

8. Aims and objectives of study *

9. Study participant inclusion criteria *

10. Study participant exclusion criteria *

11. Skin disease under investigation *

Mark only one oval.

- ◯ Atopic Eczema
- ◯ Psoriasis
- ◯ Both

12. Total number of people in the study with skin disease

13. Age of participants in the study *

Report as median (with IQR - interquartile range); mean (with SD - standard deviation) OR % distributions in different age bands - depends on how it is written in the study

14. Number (and percentage) of males in the study

15. Number (and percentage) of females in the study

16. Ethnicity of participants included in the study

Select one or more

Check all that apply.

- ☐ White
- ☐ Mixed/Multiple ethnic groups
- ☐ Asian
- ☐ Black/African/Caribbean
- ☐ Not stated
- Other: ☐

17. Additional notes

Exposure, outcome and results - complete this section for each exposure (risk factor) and outcome pair (1)

18. What is the risk factor of interest?

19. What are people with the risk factor/exposure of interest being compared to?

20. How were individuals with the risk factor of interest identified?

E.g. the diagnostic criteria used

21. Which mental illness outcome is under investigation?

Mark only one oval.

- Depression
- Anxiety
- Combined depression and anxiety
- Schizophrenia
- Bipolar disorder
- Other psychoses

22. How were individuals with the outcome identified?

23. Describe the results of the effect of the risk factor on the outcome

Include the results for both the risk factor group and the comparison group in detail. Include the analysis method, which measures of effect were used (ratio or difference measure), the effect estimates (including confidence intervals and p-values) as well as if any confounders were adjusted for and what these were.

24. Were some participants excluded from analysis?

Mark only one oval.

- Yes
- No

25. If the previous answer is YES, state the reasons given

26. Additional notes

Include information on relevant additional results given (e.g. effect modification)

27. Have any additional risk factors or outcomes been investigated in this study? *

Mark only one oval.

- ◯ Yes *Skip to question 28*
- ◯ No *Skip to section 18 (Risk of Bias Assessment)*

Risk of Bias Assessment

Some studies/papers may have looked at more than one risk/prognostic factor and outcome. Therefore, for each domain, assessors should judge the risk of bias for the overall quality of the paper. However, after you have answered questions for each domain, there will be room for notes to write down key issues regarding the different prognostic factors and outcomes.

Domain 1 - Study Participation

This domain addresses the representativeness of the study sample to the source population (risk of selection bias). It helps the assessor judge whether the study's reported association is a valid estimate of the true relationship between the prognostic factors and the outcome of interest in the source population. Some items in the domain may not be relevant to the specific study. Please write your reasoning/answers for each of the signalling questions in the comments section under each question

168. Is there adequate participation in the study be eligible individuals? *

Here, consider the proportion of eligible people that participated in the study.

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

169. Comments

170. Has the source population/population of interest been adequately described according to key characteristics? *

Mark only one oval.

- ( ) Yes
- ( ) Partial
- ( ) No
- ( ) Unsure
- ( ) Not relevant for study

171. Comments

172. Has the baseline study sample (individuals entering the study) been adequately described according to key characteristics? *

Mark only one oval.

- ( ) Yes
- ( ) Partial
- ( ) No
- ( ) Unsure
- ( ) Not relevant for study

173. Comments

174. Has the sampling frame and method of recruitment for participants in the study been adequately described? *

Mark only one oval.

- ( ) Yes
- ( ) Partial
- ( ) No
- ( ) Unsure
- ( ) Not relevant for study

175. Comments

176. Has the period and place of recruitment (setting and geographic location) been adequately described? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

177. Comments

178. Have the inclusion and exclusion criteria been adequately described? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

179. Comments

180. Using the above prompting items and the risk of bias ratings document provided, how would you assess the risk of bias for the study participation domain? *

Mark only one oval.

- ◯ Low risk of bias
- ◯ Moderate risk of bias
- ◯ High risk of bias

181. Comments

182. Additional notes

Domain 2 - Study Attrition

This domain addresses whether participants with follow-up data represent persons enrolled in the study. It helps the assessor judge whether the reported association between the prognostic factor and outcome is biased by the assessment of outcomes in a selected group of participants who completed the study. Please write your reasoning/answers for each of the signalling questions in the comments section under each question

183. Is there an adequate response rate for study participants (i.e. the proportion of the study sample that complete the study and provide outcome data is adequate and many participants did not withdraw)? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

184. Comments

185. Have attempts to collect information on participants who dropped out of the study been described? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

186. Comments

187. Have reasons for loss to follow-up been provided? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

188. Comments

189. Have participants who are lost to follow-up adequately described according to key characteristics? *

Mark only one oval.

- ◯ Yes
- ◯ Partial
- ◯ No
- ◯ Unsure
- ◯ Not relevant for study

190. Comments

191. Are there important differences between key characteristics and outcomes in participants who completed the study and those who did not? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

192. Comments

193. Using the above prompting items and the risk of bias ratings document provided, how would you assess the risk of bias for the study attrition domain? *

Mark only one oval.

- Low risk of bias
- Moderate risk of bias
- High risk of bias

194. Comments

195. Additional notes

Domain 3 - Prognostic Factor Measurement

This domain addresses adequacy of prognostic factor measurement. It helps the assessor judge whether the study measured the prognostic factor in a similar, valid, and reliable way for all participants.Please write your reasoning/answers for each of the signalling questions in the comments section under each question

196. Has a clear definition or description of the prognostic factor been provided? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

197. Comments

198. Is the method of prognostic factor measurement adequately valid and reliable? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

199. Comments

200. Are continuous variables reported or have appropriate cut off points been used? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

201. Comments

202. Is the method and setting of measurement of the prognostic factors the same for all study participants? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

210. Additional notes

Domain 4 - Outcome Measurement

This domain addresses the adequacy of outcome measurement. It helps the assessor judge whether the study measured the outcome in a similar, reliable, and valid way for all participants.Please write your reasoning/answers for each of the signalling questions in the comments section under each question

211. Has a clear definition of the outcome been provided? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

212. Comments

213. Is the method of outcome measurement used adequately valid and reliable? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

214. Comments

215. Is the method and setting of outcome measurement the same for all study participants? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

216. Comments

217. Using the above prompting items and the risk of bias ratings document

224. Is the measurement of all important confounders adequately valid and reliable? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

225. Comments

226. Is the method and setting of confounding measurement the same for all study participants? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

2

227. Comments

228. Have appropriate methods for imputation been used for missing confounder data? *

2

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

2

229. Comments

230. Are important potential confounders accounted for in the study design? *

2

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

231. Comments

232. Are important potential confounders accounted for in the analysis? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

233. Comments

234. Using the above prompting items and the risk of bias ratings document provided, how would you assess the risk of bias for the study confounding domain? *

Mark only one oval.

- Low risk of bias
- Moderate risk of bias
- High risk of bias

235. Comments

236. Additional notes

Domain 6 - Statistical Analysis and Reporting

This domain addresses the appropriateness of the study's statistical analysis and completeness of reporting. It helps the assessor judge whether results are likely to be spurious or biased because of analysis or reporting. Please write your reasoning/answers for each of the signalling questions in the comments section under each question

237. Is there sufficient presentation of data to assess the adequacy of the analytic strategy? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

238. Comments

239. Is the strategy for model building appropriate and based on a conceptual framework or model? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

240. Comments

241. Is the selected statistical model adequate for the design of the study? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

242. Comments

243. Is there selective reporting of results? *

Mark only one oval.

- Yes
- Partial
- No
- Unsure
- Not relevant for study

244. Comments

245. Using the above prompting items and the risk of bias ratings document provided, how would you assess the risk of bias for the statistical analysis and reporting domain? *

Mark only one oval.

- Low risk of bias
- Moderate risk of bias
- High risk of bias

246. Comments

247. Additional notes

Appendix S3: Data extraction form (randomised controlled trials)

1. Your initials *

2. First author and year of publication *
   Last name/ family name of first author (e.g. Ang 2012)

3. Publication title *

Study characteristics

4. Country where trial took place *

5. Setting trial was conducted *

6. Trial funding source *

   Check all that apply.

   - [ ] Industry funded
   - [ ] Government/charity funded
   - [ ] Not stated

7. Were there any possible conflicts of interest for the study authors? If yes, please describe *

8. Start date of trial

9. End date of trial

10. Design of trial *

Check all that apply.

- [ ] Parallel design
- [ ] Crossover design
- [ ] Factorial design
- [ ] Other: _____

11. Unit of randomisation allocation *

Check all that apply.

- [ ] Individual
- [ ] Group/cluster
- [ ] Other: _____

12. Was ethical approval obtained for the trial? *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] Unclear
- [ ] Ethical approval not required

13. Aim of the trial *

14. Additional notes

Study participants

Include information for both the intervention and comparison group(s). If not stated in the paper, write not stated in the relevant answer box

15. Description of study population (include skin disease under investigation) *

16. Inclusion criteria *

17. Exclusion criteria *

18. Method of participant recruitment *

19. Was informed consent obtained? *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] Unclear

20. Total number of people randomised *

21. Were there any imbalances between the intervention and comparison group at baseline? If so, please describe *

22. Were there any withdrawals or exclusions in the intervention or comparison group? If so, please describe *

23. Age of participants in the trial *

24. Sex of participants in the trial *

25. Ethnicity of participants in the trial *

26. Other relevant characteristics of participants in the trial *

27. Additional notes

Intervention and comparison (1)

Complete this section for each intervention and comparison group pair

29. Number randomised to the intervention group *

30. Number randomised to the comparison/control group *

31. Description of intervention given *

Include timing, duration of treatment, dose

32. Describe the comparison/control group - what were the intervention groups compared to? *

33. Was there compliance with the intervention? If no, please describe *

34. Additional notes

35. Was there more than one intervention group in this trial? *

Mark only one oval.

- Yes *Skip to question 36*
- No *Skip to question 60*

Outcome and results (1)

Complete this section for each mental illness outcome investigated in the trial

60. What was the outcome of interest? *

Check all that apply.

- Depression
- Anxiety
- Schizophrenia
- Bipolar disorder
- Other

61. Type of outcome *

Check all that apply.

- [ ] Primary outcome
- [ ] Secondary outcome
- [ ] Unclear

62. How was the outcome of interest ascertained? *

For example, if a questionnaire was given, provide details about the questionnaire

63. Was the tool used to measure the outcome of interest validated? *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] Unclear
- [ ] Not relevant

64. When was the outcome of interest measured? *

For example, was it measured a certain number of months after the intervention? or as a change from baseline? Include all the timepoints if the outcome was measured at more than one timepoint

65. Is the outcome of interest dichotomous (having only two possible values) or continuous (on a numerical scale)? *

Check all that apply.

- [ ] Dichotomous
- [ ] Continuous

66. Give a brief summary of the intervention and comparison *

COMPLETE ONLY IF CONTINUOUS OUTCOME

67. Describe the results in the intervention group

Include the mean, standard deviation as well as the number of participants in this group. Include confidence intervals and p-values if given. Include unadjusted and adjusted values if given, including which variables were adjusted for.Include all the results if the outcome is measured at more than one timepoint

68. Describe the results in the comparison group

Include the mean, standard deviation as well as the number of participants in this group. Include confidence intervals and p-values if given. Include unadjusted and adjusted values if given, including which variables were adjusted forInclude all the results if the outcome is measured at more than one timepoint

69. Number of missing participants and reasons missing

If none missing, write none

70. Number of participants moved between groups and reasons they were moved

If none moved, write none

71. Which statistical methods were used, and were these methods appropriate?

COMPLETE ONLY IF DICHOTOMOUS OUTCOME

72. Describe the results in the intervention group

Include the total number of people in the intervention group, the number of people with the outcome of interest and the measure of effect (e.g. the ratio). Include confidence intervals and p-values if given. Include unadjusted and adjusted ratios if given, including which variables were adjusted for. Include all the results if the outcome is measured at more than one timepoint.

73. Describe the results in the comparison group

Include the total number of people in the comparison group, the number of people with the outcome of interest and the measure of effect (e.g. the ratio). Include confidence intervals and p-values if given. Include unadjusted and adjusted ratios if given, including which variables were adjusted for.Include all the results if the outcome is measured at more than one timepoint.

74. Number of missing participants and reasons missing

If none missing, write none

75. Number of participants moved between groups and reasons they were moved

If none moved, write none

76. Which statistical methods were used, and were these methods appropriate?

77. Additional notes

78. Was more than one mental illness outcome investigated in this trial? *

Mark only one oval.

- ◯ Yes *Skip to question 79*
- ◯ No *Skip to section 11 (Risk of Bias Assessment)*

Table S1: Papers excluded after full text review and reasons for exclusion

Study	Reason(s) for exclusion
Aguayo-Carreras, 2019[1]	Study outcome is not depression, anxiety, or SMI
Gelfand, 2008[2]	Intervention under investigation is the method of treating skin disease (patients receive either continous or interrupted treatment of the same drug, there is no placebo group) and cannot be classified as 'untreated skin disease'.
Guerra-Tapia, 2007[3]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
	Age distribution of individuals in the study are unclear, cannot be sure if individuals under 18 are included in the study
Hu, 2019[4]	Study includes both adults and children, however, data for adults are not reported separately
Jensen, 2016[5]	Study population includes individuals without skin disease as individuals with mild or severe psoriasis are compared to those with no psoriasis
Lakuta, 2017[6]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
Lakuta, 2018[7]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
Luca, 2020[8]	Study outcome is not depression, anxiety, or SMI
Margolis, 2019[9]	Age distribution of individuals included in the study are unclear, cannot be sure if individuals under 18 are included in the study
McDonough, 2014[10]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
	Age distribution of individuals included in the study are unclear, cannot be sure if individuals under 18 are included in the study
Quintana, 2017[11]	Study includes both adults and children, however, data for adults are not reported separately
Schuster, 2021[12]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
Singh, 2016[13]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
	Age distribution of individuals included in the study are unclear, cannot be sure if individuals under 18 are included in the study
Singh, 2017[14]	No factors of interest – intervention is psychiatry based therefore, it cannot be classified as untreated skin disease
	Study includes both adults and children, however, data for adults are not reported separately
Talamonti, 2021[15]	Study outcome is not depression, anxiety, or SMI
Vasilakis-Scaramozza, 2020[16]	Age distribution of individuals included in the study are unclear, cannot be sure if individuals under 18 are included in the stud
Wu, 2016[17]	Study outcome is not depression, anxiety, or SMI, it is a combined outcome of depression or insomnia
	Study includes both adults and children, however, data for adults are not reported separately
Yang, 2010[18]	No effect estimates of factors associated with depression, anxiety, or SMI are reported
Yang, 2019[19]	No effect estimates of factors associated with depression, anxiety, or SMI are reported

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Table S2: Characteristics of *observational studies* for factors associated with mental illness among people with *psoriasis* included in the review

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
Bakar, 2021	Malaysia, 2019	Cross-sectional study	Dermatology outpatient clinic	People with psoriasis, aged ≥18 years.	Not reported	174	56.40 (15.14)	Lower limb lesions, dyslipidaemia, quality of life (DLQI score)	DLQI identified by questionnaire. Participants were asked to state whether they had dyslipidaemia or lesions on lower limbs. Some information was counter-checked with clinical records (unclear which)	Depression and Anxiety. Both outcomes identified using the HADS questionnaire.
Kwan, 2018	Malaysia, 2013-2015	Cross-sectional study	Dermatology outpatient clinic.	People with chronic plaque psoriasis (and its associated subtypes)	Not reported.	102	50.90 (17.70)	Psoriasis severity, head involvement, use of systemic therapy, quality of life, diabetes, ischaemic heart disease,	Comorbidities identified using medical records. All other factors collected using questionnaires.	Depression and Anxiety. Both outcomes identified using the DASS-42 questionnaire.

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
				attending the dermatology clinic for regular follow-up, aged ≥18 years.				cerebrovascular disease, psoriatic arthropathy.	Psoriasis severity assessed using the PASI. Quality of life assessed using the DLQI.	
Lada, 2022	United Kingdom, 2019-2021	Cross-sectional study	Specialist psoriasis and psoriatic arthritis clinics	People with psoriasis, aged 18-65 years	Dermatologist	219	45.40 (11.70)	Comorbid psoriatic arthritis	Medical records	Depression. Identified using the HADS questionnaire.
Petraškienė, 2016	Lithuania, 2012-2014	Cross-sectional study	Inpatient and outpatient units of the Department of Skin and Venereal Diseases, Hospital of the	People with psoriasis who were treated at the inpatient and outpatient units of the Department of Skin and	Medical documentation.	385	Age range 18-85, (15.83)	Sex, age group, education	Collected using a questionnaire.	Depression and Anxiety. Both outcomes identified using the HADS questionnaire.

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
			Lithuanian University of Health Sciences.	Venereal Diseases, aged ≥18 years.						
Strober, 2017[a]	United States, Argentina, Australia, Austria, Belgium, Canada, Chile, Colombia, Czech Republic, Greece, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, Portugal, Slovakia,	Longitudinal cohort study	Data from PSOLAR registry.	People with moderate-to-severe psoriasis who are receiving or are eligible to receive conventional systemic or biological therapies, aged ≥18 years.	Identified using the PSOLAR registry.	7,490	48.00 (13.80)	Treatment with biologics or phototherapy, age, sex, ethnicity, years since psoriasis began, baseline PGA score, change in PGA score from baseline to depression, education, insurance, psoriatic arthritis, diabetes, schizophrenia, anxiety, bipolar disease, chronic obstructive pulmonary disease, and CAD/MI/ACVD/stroke/TIA.	Collected using information from the PSOLAR registry.	Depression. Identified using the HADS-D questionnaire.

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
	Slovenia, Spain, Sweden, Taiwan, Ukraine, 2007-2015									
Tian, 2018	China, 2016-2017	Cross-sectional study	Department of Dermatology in a tertiary hospital in Shanghai.	Chinese people with psoriasis, aged at least 18 years.	Dermatologist after clinical examination.	208	40.79 (14.19)	Age, sex, stress reaction, psoriasis severity, psoriasis duration, age at psoriasis onset.	Collected using a standardised form. Psoriasis severity assessed using the PASI.	Depression and Anxiety. Depression was identified using the PHQ-9. Anxiety was identified using GAD-7.
Tribó, 2019	Spain, year of study not reported	Cross-sectional study	Department of Dermatology in a tertiary referral centre in Barcelona.	Outpatients with psoriasis, aged 18-89 years.	Not reported.	300	49.70 (SD not reported)	Psoriasis severity.	Two dermatologists used the PASI, BSA and PDI to evaluate the severity of psoriasis.	Depression and Anxiety. HADS-A and HADS-D were used as a self-report measure for anxiety and depression respectively. The HRSD and MADRS

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
										were used as a clinician administered measure for depression. STAI was administered to measure state and trait anxiety.
Tu, 2016	Taiwan, 2010	Cross-sectional study	Electronic health records from the LHID.	People diagnosed with psoriasis in the LHID during the period from January 1, 1997, to December 31, 2010, aged 20-100 years.	The presence of ICD-9-CM codes for psoriasis (696.0, 696.1 or 696.8) in the LHID one or more times during the study period.	10,796	50.50 (17.80)	Age, gender, psoriasis duration, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, liver disease, diabetes, hemiplegia or paraplegia and renal disease.	Age, gender, and psoriasis duration were collected using the demographic information within the LHID. Each comorbidity was ascertained by ICD-9-CM codes documented over three times during	Schizophrenia. Individuals with an ICD-9-CM code for schizophrenia (295) in the LHID one or more times and a catastrophic illness certificate due to schizophrenia during the study period.

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
									the study period.	
Wojtyna, 2017	Poland, year of study not reported	Cross-sectional study	Dermatology outpatient and inpatient clinics, and Polish psoriasis associations	People diagnosed with psoriasis for at least one year, aged ≥18 years.	Dermatologist.	219	38.15 (13.30)	Sex, age at onset of psoriasis, psoriasis severity, ASI-SES, ASI-MS, emotional and instrumental social support, facial lesions, genital lesions, and distress.	All data was collected using surveys. Psoriasis severity was assessed using BSA. ASI-SES and ASI-MS were identified using the ASI-R, an instrument that assesses body image investment. Emotional and instrumental social support were assessed using BSSS. The level of distress was	Depression. Identified using the BDI questionnaire.

First author, publication year	Country, year of study	Study design	Study setting	Study population	Method of psoriasis ascertainment	Number of people with psoriasis	Mean (SD) age in years at baseline	Factors assessed	Method of identifying factors	Outcome, method of ascertainment
									assessed using the DT.	
Yu, 2015	China, 2012-2015	Cross-sectional study	Dermatology clinics of three hospitals in Nanjing.	Outpatients with psoriasis that has been treated at one of the three dermatology clinics, aged ≥18 years.	Not reported.	246	Males: 31.90 Females: 35.90. SD for both males and females not reported.	Sex, education, occupation, and address	Unclear	Depression. The CES-D questionnaire was used.
Lamb, 2017	United Kingdom, 2013-2014	Cross-sectional study	Single centre tertiary psoriasis service	Patients (new and return) with a clinical diagnosis of psoriasis	Clinical diagnosis	607	47.00 (13.90)	Psoriasis severity (using PASI), age, gender, ethnicity, psoriasis phenotype, psoriasis treatment, psoriatic arthritis, previous depression, or anxiety	Extracted from electronic patient records.	Depression and Anxiety. Ascertained due to participants completing self-report questionnaires. PHQ-9 was used to measure depression and the GAD-7 was used to measure anxiety.

Abbreviations: ACVD – Acute Cardiovascular Disease; ASI-R – Appearance Schemas Inventory-Revised scale includes ASI-MS (Motivational Salience) and ASI-SES (Self-Evaluative Salience); BDI – Beck Depression Inventory; BSA – Body Surface Area; BSSS – Berlin Social Support Scales; CAD – Coronary Artery Disease; CES-D – Center for Epidemiologic Studies Depression Scale; DASS-42 – Depression and Anxiety Stress Scales-42; DLQI – Dermatology Life Quality Index; DT – Distress Thermometer; GAD-7 – Generalised Anxiety Disorder-7; HADS – Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale; HRSD – Hamilton Depression Rating Scale; ICD-9-CM – International Classification of Diseases, Ninth Revision, Clinical Modification; LHID – Longitudinal Health Insurance Database; MADRS – Montgomery-Asberg Depression Rating Scale; MI – Myocardial Infarction; PASI – Psoriasis Area and Severity Index; PDI – Psoriasis Disability Index; PGA – Physician Global Assessment; PHQ-9 – Patient Health Questionnaire-9; PSOLAR – Psoriasis Longitudinal Assessment and Registry; SD – Standard Deviation; STAI – State-Trait Anxiety Inventory; TIA – Transient Ischaemic Attack

[a] Individuals with a medical history of depression or a clinically relevant Hospital Anxiety and Depression Scale (HADS) depression score were excluded from the cohort.

Table S3: Characteristics of *randomised controlled trials* for the association between *atopic eczema treatment* and mental illness among people with *atopic eczema* included in the review

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
de Bruin-Weller, 2018	Austria, Germany, Belgium, Ireland, Netherlands, Poland, Russia, Slovakia, Spain, United Kingdom, 2016 – 2017	Phase 3, double-blind, parallel trial.	A central interactive voice-/web-response randomisation system was utilised, stratified by baseline IGA score and prior CsA exposure.	Adult patients (aged ≥18 years) with atopic dermatitis and a history of inadequate response or intolerance to CsA, or CsA naïve patients for whom CsA treatment was medically inadvisable.	325	16 weeks	Dupilumab (300mg) subcutaneously weekly plus TCS or dupilumab (300mg) every 2 weeks plus TCS for 16 weeks.	Dupilumab weekly – 110 Dupilumab every 2 weeks – 107	Weekly subcutaneous injection of placebo plus TCS.	108	Placebo + TCS: 37.50 (29.00-49.00) Dupilumab weekly + TCS: 38.00 (29.00-48.00) Dupilumab every 2 weeks + TCS: 38.00 (25.00-47.00)	Combined depression and anxiety. Measured at baseline and week 16 using the HADS questionnaire.
Simpson, 2016	Canada, Czech Republic, Germany, Hungary, Japan, Poland, United States, 2013 – 2014	Phase 2b, double-blind, parallel dose-ranging trial.	A central randomisation scheme, provided by an interactive voice response system to the designated study pharmacist or qualified designee.	Adult patients (aged ≥18 years) with moderate to severe atopic dermatitis, with disease not adequately controlled by topical medications	380	16 weeks	Dupilumab (100mg) subcutaneously every 4 weeks, dupilumab (300mg) every 4 weeks, dupilumab (200mg) every 2 weeks, dupilumab (300mg) every 2 weeks, or	Dupilumab (100mg) every 4 weeks – 65 Dupilumab (300mg) every 4 weeks – 65 Dupilumab (200mg)	Weekly subcutaneous injection of placebo for 16 weeks.	61	Placebo: 37.20 (13.10) Dupilumab (100mg) every 4 weeks: 36.60 (11.60) Dupilumab (300mg) every 4	Combined and individual depression and anxiety. Measured at baseline and week 16 using the HADS questionnaire.

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
				or for whom topical treatment was inadvisable.			dupilumab 300mg every week for 16 weeks.	every 2 weeks – 61 Dupilumab (300mg) every 2 weeks – 64 Dupilumab 300mg every week – 63			weeks: 36.80 (10.80) Dupilumab (200mg) every 2 weeks: 35.80 (14.90) Dupilumab (300mg) every 2 weeks: 39.40 (12.10) Dupilumab 300mg every week: 36.20 (10.70)	
Simpson, 2016 and Cork, 2019[b]	Bulgaria, Canada, Denmark, Estonia, Finland, Germany, Japan, Singapore, Spain, United States, France, Hong Kong,	Phase 3, double-blind, parallel trials.	A central interactive voice response system. Randomisation was stratified according to disease severity and region.	Two independent trials (SOLO 1 and SOLO 2) were conducted. Adults with moderate to severe atopic dermatitis whose disease was inadequately	SOLO 1 671 SOLO 2 708 POOLED DATA 1,379	16 weeks	Dupilumab (300mg) subcutaneously every week or every other week for 16 weeks.	SOLO 1 Dupilumab every other week – 224 Dupilumab every week – 223 SOLO 2 Dupilumab every other	Weekly subcutaneous injection of placebo for 16 weeks.	SOLO 1 224 SOLO 2 236 POOLED DATA 460	SOLO 1 Placebo group: 39.00 (27.00 - 50.50) Dupilumab every other week: 38.00	Combined depression and anxiety. Measured at baseline and week 16 using the HADS questionnaire.

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
	Italy, Lithuania, Republic of Korea, United Kingdom, 2014-2015			controlled by topical treatment or for whom topical treatment is medically inadvisable, aged ≥18 years.				week – 233 Dupilumab every week – 239 POOLED DATA Dupilumab every other week – 457 Dupilumab every week – 462			(27.50 - 48.00) Dupilumab every week: 39.00 (27.00 - 51.00) SOLO 2 Placebo group: 35.00 (25.00-47.00) Dupilumab every other week: 34.00 (25.00-46.00) Dupilumab every week: 35.00 (25.00-46.00) POOLED DATA Placebo group:	

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
											38.40 (14.00) Dupilumab every other week: 38.30 (14.40) Dupilumab every week: 38.20 (14.50)	
Simpson, 2021	United States, Australia, Canada, Germany, Hungary, 2016-2017	Phase 2b, double-blind, parallel trial.	Not stated	Patients aged 18-75 years with moderate-to-severe atopic dermatitis.	267	16 weeks	Abrocitinib (10mg, 30mg, 100mg, or 200mg) once daily for 12 weeks	Abrocitinib 10mg – 49 Abrocitinib 30mg – 51 Abrocitinib 100mg – 56 Abrocitinib 200mg – 55	Placebo once daily for 12 weeks	56	Placebo: 42.60 (15.10) Abrocitinib 10mg: 44.30 (15.90) Abrocitinib 30mg: 37.60 (15.90) Abrocitinib 100mg: 41.10 (15.60) Abrocitinib 200mg:	Depression and Anxiety. Measured at baseline and weeks 1, 2, 4, 6, 8, 12, 14, and 16 using the HADS questionnaire.

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
											38.70 (17.60)	

[a] The length of follow up reported is the total length of follow-up that occurred prior to the final measurement of the outcome of interest.
[b] The paper Cork, 2019 is a pooled analysis of an original study (Simpson, 2016). Specific study characteristics for Cork, 2019 are under the subheading Pooled Data.
Abbreviations: CsA – Ciclosporin-A; HADS – Hospital Anxiety and Depression Scale; IGA – Investigators Global Assessment; TCS – Topical corticosteroids

Table S4: Characteristics of *randomised controlled trials* for the association between *psoriasis treatment* and mental illness among people with *psoriasis* included in the review

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
Gordon, 2018	United States, Australia, Canada, Czech Republic, Germany, Republic of Korea, Poland, Russia, Spain, 2014 – 2016	Phase 3, double-blind, parallel trial.	Not reported	Adult outpatients (aged ≥18 years) with moderate to severe plaque-type psoriasis.	992	24 weeks	Guselkumab (100mg) at weeks 0,4, 12 and 20.	496	Placebo at weeks 0, 4, and 12 followed by guselkumab (100mg) at weeks 16 and 20. Adalimumab (80mg) at week 0, adalimumab (40mg) at week 1 and then adalimumab (40mg) every 2 weeks through week 23.	Placebo – 248 Adalimumab - 248	43.50 (12.20)	Depression and anxiety. Measured at baseline, week 8, 16 and 24 using the HADS questionnaire.
Griffiths, 2017	United States, Germany, Poland, Romania, Denmark, Italy, United Kingdom, Australia, Hungary, Canada, Japan,	Phase 3, double-blind, parallel trials.	Not reported	Data were integrated from three identical phase 3 trials (UNCOVER 1, 2, and 3). Adult outpatients (aged ≥18 years) who had been	320	12 weeks	Ixekizumab (80mg) every 2 weeks, or every 4 weeks for a 12 week period.	Ixekizumab every 2 weeks – 107 Ixekizumab every 4 weeks – 120	Placebo was given to match all active treatment dosing regimens.	93	Placebo 46.80 (13.10) Ixekizumab every 2 weeks 45.5 (12.40) Ixekizumab every 4 weeks 44.2 (13.30)	Depression. Measured at baseline and 12 weeks using the QIDS-SR16 questionnaire.

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
	2011 – 2014			diagnosed with psoriasis for at least 6 months and met the following severity criteria: BSA≥10%, PASI score ≥12, and static PSA score ≥3 (at least moderate severity).							Total 45.4 (13.00)	
Langley, 2010	Austria, Canada, France, Germany, Switzerland, United Kingdom, United States, 2006 – 2007	Phase 3, double-blind, parallel trial.	Not reported	Adult patients (aged ≥18 years) with a diagnosis of plaque psoriasis that is moderate to severe	1,230	24 weeks	Ustekinumab 45mg or 90mg at weeks 0, 4 and every 12 weeks thereafter.	Ustekinumab 45mg – 409 Ustekinumab 90mg – 411	Placebo at weeks 0 and 4, with half randomised to crossover to receive ustekinumab 45mg and the other half to ustekinumab 90mg at weeks 12, 16, and every 12 weeks thereafter.	410. At week 12, 197 crossed over to ustekinumab 45mg and 195 to ustekinumab 90mg	Placebo 47.00 (12.50) Ustekinumab 45mg 45.10 (12.10) Ustekinumab 90mg 46.60 (12.10)	Depression and anxiety. Measured at baseline and weeks 12 and 24 using the HADS questionnaire.
Menter, 2010	United States, Canada, years of	Phase 2, double-	Not reported	Anti-TNF naïve patients with	96	12 weeks	Adalimumab (40mg) every other	44	Placebo every other week for 12 weeks.	52	Placebo 43.30 (13.10)	Depression. Measured at baseline and

First author, publication year	Country, year(s) of study	Type of randomised controlled trial	Method of randomisation	Study population	Total study size (N)	Length of follow up [a]	Intervention group(s)		Comparison group(s)		Age at baseline (mean [SD] or median [IQR])	Outcome, method of ascertainment
							Definition	Number	Definition	Number		
	study not reported	blind, parallel trial.		moderate to severe psoriasis (BSA ≥5%) that could not be controlled by topical therapy, aged ≥18 years.			week for 12 weeks.				Adalimumab 45.60 (11.70)	week 12 using the ZDS.
Tyring, 2006	United States, Canada, 2003 – 2004	Phase 3, double-blind, parallel trial.	Randomisation code lists were generated by a designated person with no other association to the study. Randomisation was stratified by those who had received systemic/phototherapy or those that had not.	People (aged ≥18 years) with active, clinically stable plaque psoriasis involving 10% or more of the total body surface area, a minimum PASI of 10 and have received phototherapy or systemic therapy at least once.	620	12 weeks	Etanercept (50mg) injected subcutaneously twice weekly for 12 weeks.	311	Placebo injected subcutaneously twice weekly for 12 weeks.	309	Placebo 45.60 (12.10) Etanercept 45.80 (12.80)	Depression. Measured at baseline, week 4, 8 and 12 using the HAM-D and the BDI questionnaires.

[a] The length of follow up reported is the total length of follow-up that occurred prior to the final measurement of the outcome of interest.
Abbreviations: BDI – Beck's Depression Inventory; BSA – Body Surface Area; HADS – Hospital Anxiety and Depression Scale; HAM-D – Hamilton Depression Rating Scale; PASI – Psoriasis Area and Severity Index; PSA – Physician Global Assessment; TNF – Tumor Necrosis Factor; QIDS-SR16 – Quick Inventory of Depressive Symptomatology Self-report-16; ZDS – Zung Depression Scale

Table S5: Justification for risk of bias assessments of studies included in the review using the Quality in Prognostic Studies (QUIPS) tool

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Bakar, 2021	High A selective method was used to sample the population (convenience sampling). It is unclear/unlikely that the sample is representative of the source population.	Low There is an adequate response rate for study participants. None of the participants dropped out of the study.	Moderate Participants were asked to recall their status and some of these were checked with medical records. It is unclear how many of the participants had their records checked so we cannot be sure that factor measurement was the same for all participants.	Low A clear definition of the outcome was provided, and the method used is validated. The method and setting of outcome measurement are also the same for all study participants.	Moderate Independent variables collected at baseline were all adjusted for each other; however, it is unlikely that all important confounders were adjusted for.	High Study looked at factors for both depression and anxiety, however, only results for depression were presented.
de Bruin-Weller, 2018	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.
Gordon, 2018	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
				interventions that were received by study participants.	known and unknown confounders are equally distributed between the comparison groups.	
Griffiths, 2017	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.
Kwan, 2018	High A selective method is used to sample the population (convenience sampling) rather than a consecutive sample of eligible patients. Additionally, the sampling frame isn't described, and neither are the characteristics of the source population. Therefore, it is unclear whether this sample is representative of the source population.	Low There is an adequate response rate for study participants. None of the participants dropped out of the study.	Low Clear definitions of the factors have been provided, and all were measured similarly for all people in the study.	Low A clear definition of the outcome was provided, and the method used is validated. The method and setting of outcome measurement are also the same for all study participants.	High Results from univariate analysis has been reported. No confounders have been adjusted for.	Moderate More data could have been presented to assess the adequacy of the analysis strategy. Some parts of the method used to build the multivariate models are unclear, for example, why certain variables were included and why some were not.
Lada, 2022	Moderate	Low	Low	Low	Moderate	Low

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
	It is unclear how many people were eligible for the study, so it is difficult to know if there is adequate participation. Additionally, the source population was not described, and the baseline sample was only partially described according to key characteristics. Therefore, it is difficult to say whether the sample is representative of the source population.	There was an adequate response rate for this study, the participants that were lost to follow-up provided reasons, and there were no differences between the participants lost to follow-up and those that remained in the study.	A clear definition of the factors of interest were provided, and it was measured in the same way for all participants in the study.	A clear definition of the outcome was provided, and the method used is validated. The outcome was also measured in the same way for all study participants.	Although some confounders have been adjusted for, it is likely that these are not all the important confounders that could have been adjusted for.	The analysis method used is appropriate for the study and there is no selective reporting of results.
Langley, 2010	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.
Lamb, 2017	Moderate Of the 636 patients that completed screening, a large proportion (607) were eligible for inclusion. However, the source population for the study	Low Some elements of this domain are not relevant to this study as it was a cross-sectional study and information on the factors of interest was obtained	Low Clear definitions of the factors of interest were provided and they were measured/captured in the same way for all	Low Clear definitions of the outcomes of interest were provided and they were measured/captured in the	High This study did not adjust any of the effect estimates for factors that may confound	Low The analysis method used is appropriate for the study and there is no selective reporting of results.

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
	was not described, and neither was the sampling frame or method of recruitment.	from electronic patient records. All included participants contributed data.	participants included in the study.	same way for all study participants.	associations with depression or anxiety.	
Menter, 2010	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Moderate There is no information on whether the trial was analysed in accordance with a pre-specified analysis plan.
Petraškienė, 2016	Moderate It is unclear how many people were eligible for the study, so it is difficult to know if there is adequate participation. Additionally, the source population was not described, and the baseline sample was only partially described according to key characteristics. Therefore, it is difficult to say whether the sample is representative of the source population.	Moderate The paper states that there was a 100% response rate for the 385 people randomised to the study. However, only 241/385 people given the questionnaire were included in the analysis. This gives a response rate of 62.6% which is slightly lower than an adequate response rate of 70%.	High Different approaches were used to measure the factors of interest. Inpatient participants were interviewed while outpatients were given a questionnaire. As there was a 62.6% response rate, some participants also had missing data.	Moderate Different approaches were used to ascertain outcomes in different participants. Inpatient participants were interviewed while outpatients were given a questionnaire. However, the method of outcome measurement (HADS) is a validated and reliable measure.	Moderate Important confounders were defined and adjusted for. However, different approaches were used to ascertain confounders in different participants. Inpatient participants were interviewed while outpatients were given a questionnaire. This may introduce some bias.	Moderate More data could have been presented to assess the adequacy of the analysis strategy. Additionally, there is no mention of a conceptual framework or prespecified analysis plan.

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Simpson, 2016	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.
Simpson, 2016 and Cork, 2019	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements or multiple analyses of the data.
Simpson, 2021	Low Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and	Low None of the participants dropped out of the trial or were lost to follow up.	Low Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	Low The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups.	Low Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and	Low The trial was analysed in accordance with a pre-specified plan. Additionally, results were not selected from multiple outcome measurements

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
	were recruited consecutively.			The outcome assessors were also unaware of the interventions that were received by study participants.	comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	or multiple analyses of the data.
Strober, 2017	Low The population of interest has been adequately described according to key characteristics and the baseline study sample have also been described according to key characteristics. Other aspects of this domain (participation, sampling frame and method of recruitment) are not relevant as the study uses registry data.	Moderate There does not seem to be any information about the proportion of people with the outcome that responded at each time point, so the response rate and the level of study attrition is unclear.	Low Clear definitions were given for all the factors that were looked at in the study. The method of measuring the factors is also valid and reliable. The method and setting of measurement of the factors are also the same for all the study participants. Appropriate methods of imputation were also used for people with missing data.	Low A clear definition of the outcome was provided, and the method used is validated. The method and setting of outcome measurement are also the same for all study participants.	Moderate A lot of potentially important confounders have been adjusted for in the analysis, and the methods used to measure these confounders are adequately valid and reliable. However, as registry data was used, we cannot say for certain that all study participants had their confounder data measured in the same way.	Low There is no selective reporting of results – all analysis in the statistical analysis plan were reported as part of the main paper or in the supplementary material. The analysis method used also seems adequate for the data.
Tian, 2018	Moderate While there is adequate participation in this study, the source population as well as the method of recruitment used is unclear.	Low There was an adequate response rate in this study, and in the participants that dropped out, phone calls were used to try and capture those with missing information.	Low Clear definitions of the factors of interest have been provided, and all were measured similarly for all people in the study.	Low A clear definition of the outcome was provided, and the method used is validated. The method and setting of outcome measurement are also the same for all study participants.	Moderate Although confounders have been adjusted for through multivariate logistic regression, it is likely that these are not all the important confounders that could have been adjusted for.	Low The analysis method used is appropriate for the study and there is no selective reporting of results.
Tribó, 2019	Moderate The study has high participation. Although the source population wasn't described in any	Low All participants in the study have been included in the analysis. It is unlikely that the	Low All participants had their factors of interest measured using the same methods. There may however be an	Low There does not seem to be a different level of outcome measurement based on the exposure. All participants	High Several confounders were included in the analysis, however, there are some other important	Low There is no selective reporting of results – all analysis in the statistical analysis plan were

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
	detail, the characteristics of the sample population in terms of the distribution of certain characteristics are even. However, there is a larger proportion of people with moderate-severe psoriasis compared to mild (61% to 39%) which may be because almost all patients with moderate to severe psoriasis in the area go to the centre where the study was conducted. People in the sample have also not been fully described according to characteristics. Additionally, it is unclear how people were recruited into this study.	association between the factors and the outcome is biased by the assessment of the outcome in a selected group of participants.	element of recall bias in those whose severity is measured using the DLQI, however, this is probably not much of an issue as the DLQI is a validated questionnaire and 2 other methods (PASI and BSA) were used to classify severity which involved dermatologists.	have their outcome measured in the same way using the HADS, HRSD and MADRS scales that are validated.	confounders that were not adjusted for and may mask or explain the associations that were seen. It is also unclear whether the confounders adjusted for where prespecified in the analysis plan or chosen during analysis. Additionally, the methods used to measure the confounders were not stated, so it is difficult to conclude other the confounders were measured the same for people with different levels of skin disease severity.	reported as part of the main paper or in the supplementary material. The analysis method used also seems adequate for the data.
Tu, 2016	Low	Low	Low	Low	Moderate	Low
	All the participants identified using the electronic health records were included in the study. Other factors related to study participation have also been adequately described.	Many aspects of this domain (e.g., response rate, and loss to follow-up) are not relevant as the study uses electronic health records.	Clear definitions were given for all the factors that were investigated in the study. The method of measurement is also valid and reliable (electronic health records and using ICD-9-CM codes to identify comorbidities). The method and setting of measurement of the factors are also the same for all the study participants.	A clear definition of the outcome was provided, and the method used is validated. The method and setting of outcome measurement are also the same for all study participants.	Some confounders have been adjusted for in the analysis. However, both psoriasis and schizophrenia are complex diseases, so, it is likely that some potentially important confounding factors have not been included in the analysis (e.g., medication or other lifestyle variables).	The analysis method used is appropriate for the study and there is no selective reporting of results.

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Tyring, 2006	Low	High	Low	Low	Low	Moderate
	Although some elements of this domain are not relevant to trials, participants that took part are likely to be representative of the source population and were recruited consecutively.	Not all individuals completed the questionnaire for mental illness at the end of the trial. More people in the intervention group responded which may be because they are healthier and therefore more likely to respond, suggesting a high risk of bias in this domain	Skin disease treatment provided to individuals in each arm of the trial is the same dose and administered in the same way.	The method of measuring the outcome was appropriate, and the measurement/ascertainment of the outcome did not differ between the intervention and comparison groups. The outcome assessors were also unaware of the interventions that were received by study participants.	Randomisation was used to assign individuals to intervention and to receive placebo. There were no baseline differences between the intervention and comparison groups, suggesting that both known and unknown confounders are equally distributed between the comparison groups.	There is no information on whether the trial was analysed in accordance with a pre-specified analysis plan.
Wojtyna, 2017	Moderate	Low	Low	Low	Moderate	Low
	While the population distribution in this study may not be vastly different to those who would usually have psoriasis, there is an inherent bias associated with studies where data is collected using surveys (those that respond are likely to be different to those who do not).	There is an adequate response rate for study participants. None of the participants dropped out of the study.	Clear definitions of the factors of interest have been provided, and all were measured similarly for all people in the study.	The method used to measure the outcome is a valid method of evaluating depression and all the participants in the study have had this outcome measured in the same way.	Although confounders have been adjusted for through multivariate logistic regression, it is likely that these are not all the important confounders that could have been adjusted for.	The analysis method used is appropriate for the study and there is no selective reporting of results.
Yu, 2015	High	Low	High	Low	Moderate	Moderate
	It is unclear how people were recruited into the study and if there is adequate participation. It is also unclear what the sampling frame used in the study was, therefore, it is difficult to conclude	All participants in the study were included in the analysis. No participants dropped out or were lost to follow up.	While clear definitions of the factors have been provided, it is unclear how or when the factors were measured, therefore we can't be sure if the method is adequately valid or reliable, and if the	A clear definition of the outcome has been provided, and the method of outcome measurement used is valid, reliable, and is the same for all participants in the study.	Although confounders have been adjusted for through multivariate logistic regression, it is likely that these are not all the important confounders that could have been adjusted for.	The analysis strategy is adequate for the data, however, the strategy used to build models is unclear. There also does not seem to be selective reporting of results.

Study	Bias Domains					
	Study participation	**Study attrition**	**Prognostic factor measurement/Measurement of factors of interest**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
	whether the study sample represents the source population.		method was the same for all study participants.			

Table S6: Association between *atopic eczema* treatment and mental illness, stratified by mental illness outcome identified from randomised controlled trials

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group	
					Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)		Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)
Anxiety	Simpson, 2016	380	Baseline and week 16	Dupilumab 100mg every 4 weeks	7.40 (4.20)	-1.40 (0.40), p=0.08	Weekly placebo	6.70 (3.80)	-0.40 (0.40)
				Dupilumab 300mg every 4 weeks	6.50 (4.30)	-1.30 (0.40), p=0.08			
				Dupilumab 200mg every 2 weeks	7.60 (5.10)	-1.90 (0.40), p=0.01			
				Dupilumab 300mg every 2 weeks	7.90 (4.40)	-2.20 (0.40), p=0.00			
				Dupilumab 300mg every week	6.80 (3.60)	-2.20 (0.40), p=0.00			
	Simpson, 2021	267	Baseline and weeks 1, 2, 4, 6, 8, 12, 14, and 16	Abrocitinib (10mg, 30mg, 100mg, or 200mg) once daily for 12 weeks	Abrocitinib 200mg 6.20 (4.30)	Abrocitinib 200mg Week 2: -2.50, p<0.05 Week 8: -2.70, p<0.05	Daily placebo	8.20 (4.10)	Week 2: -1.30 Week 8: -1.20
Depression	Simpson, 2016	380	Baseline and week 16	Dupilumab 100mg every 4 weeks	6.50 (4.80)	-1.00 (0.50), p=0.03	Weekly placebo	5.40 (4.30)	-0.40 (0.50)
				Dupilumab 300mg every 4 weeks	5.30 (4.30)	-1.40 (0.40), p=0.00			
				Dupilumab 200mg every 2 weeks	6.00 (4.40)	-2.00 (0.50), p<0.01			
				Dupilumab 300mg every 2 weeks	6.00 (4.10)	-2.00 (0.40), p<0.01			
				Dupilumab 300mg every week	5.80 (4.20)	-2.40 (0.40), p<0.01			
	Simpson, 2021	267	Baseline and weeks 1, 2, 4, 6, 8, 12, 14, and 16	Abrocitinib (10mg, 30mg, 100mg, or 200mg) once daily for 12 weeks	Abrocitinib 200mg 4.50 (4.00)	Abrocitinib 200mg Week 2: -1.90, p<0.01 Week 4: -2.20, p<0.01 Week 8: -1.90, p<0.01	Daily placebo	5.30 (4.20)	Week 2: -0.40 Week 4: -0.40 Week 8: -0.60

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group	
					Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)		Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)
Combined depression and anxiety	de Bruin-Weller, 2018	325	Baseline and week 16	Dupilumab 300mg + TCS every week Dupilumab 300mg + TCS every two weeks	Not reported	-5.20 (0.53), p<0.01 -6.10 (0.54), p<0.01	Weekly placebo + TCS	Not reported	-2.30 (0.56)
	Simpson, 2016	380	Baseline and week 16	Dupilumab 100mg every 4 weeks Dupilumab 300mg every 4 weeks Dupilumab 200mg every 2 weeks Dupilumab 300mg every 2 weeks Dupilumab 300mg every week	13.90 (7.80) 11.70 (7.70) 13.60 (8.70) 14.00 (7.80) 12.60 (7.10)	-2.4 (0.8), p=0.03 -2.7 (0.8), p=0.01 -4.0 (0.8), p=0.00 -4.3 (0.8), p<0.01 -4.6 (0.8), p<0.01	Weekly placebo	12.10 (7.50)	-0.00 (0.80)
	Simpson 2016 and Cork, 2019[a]	SOLO 1 671 SOLO 2 708 POOLED DATA 1,379	Baseline and week 16	Dupilumab 300mg every week (QW) Dupilumab 300mg every other week (Q2W)	POOLED DATA QW:13.70 (8.20) Q2W: 13.00 (7.40)	SOLO 1 QW: -5.20 (0.50) Q2W: -5.20 (0.50) SOLO 2 QW: -5.80 (0.40) Q2W: -5.10 (0.40) POOLED DATA QW: -5.00 (0.28), p<0.01 Q2W: -4.70 (0.28), p<0.01	Weekly placebo	POOLED DATA 13.20 (8.30)	SOLO 1 -3.00 (SE=0.70) SOLO 2 -0.80 (SE=0.40) POOLED DATA -0.80 (0.23)

[a] The paper Cork, 2019 is a pooled analysis of an original study (Simpson, 2016). Specific results for Cork, 2019 are under the subheading pooled data.
Only results reported in the papers are presented in this table. p-values reported in this table are compared to the placebo/comparison group unless stated otherwise
Abbreviations: SD – Standard Deviation; SE – Standard Error; TCS – Topical corticosteroids

Table S7: Factors associated with *depression* in people with *psoriasis* identified from *observational studies*

First author, publication year	Factor	Definition of factor	OR/HR, 95% CI, p-value	Adjusted/Unadjusted
Age, ethnicity, and sex				
Lamb, 2017	Age	Range 18-86 years	OR=0.99, 95% CI (0.97-1.01), p=0.46	Unadjusted
Petraškienė, 2016	Age	<35 (reference), 35-44, 45-54, 55-64, or ≥65 years	35-44: OR=1.72, 95% CI (0.47-6.33), p=0.41 45-54: OR=3.02, 95% CI (0.87-10.55), p=0.08 55-64: OR=7.28, 95% CI (2.10-25.16), p=0.00 ≥65: OR=5.52, 95% CI (1.16-26.27), p=0.03	Adjusted [a]
Strober, 2017	Age	Per 10-year increase	HR=1.12, 95% CI (1.05-1.21), p=0.00	Adjusted [b]
Tian, 2018	Age	Not reported	OR=1.02, 95% CI (0.98-1.06), p=0.41	Unadjusted
Lamb, 2017	Ethnicity	White British (reference), White other, Asian, Black, Mixed, Other, Unknown	White other: OR=1.06, 95% CI (0.35-3.26), p=0.92 Asian: OR=1.96, 95% CI (0.85-4.53), p=0.12 Black: OR=1.48, 95% CI (0.17-12.88), p=0.72 Mixed: OR=1.78, 95% CI (0.17-19.15), p=0.63 Other: OR=1.38, 95% CI (0.19-9.10), p=0.75 Unknown: OR=0.56, 95% CI (0.11-3.00), p=0.50	Unadjusted
Strober, 2017	Ethnicity	Non-white or white (reference)	Non-white: HR=1.72, 95% CI (1.39-2.13), p<0.01	Adjusted [b]
Lamb, 2017	Sex	Male (reference) or female	Female: OR=2.07, 05% CI (1.08-3.97), P=0.03	Unadjusted
Petraškienė, 2016	Sex	Male (reference) or female	Female: OR=1.71, 95% CI (0.78-3.73), p=0.17	Adjusted [a]
Strober, 2017	Sex	Male or female (reference)	Male: HR=1.09, 95% CI (0.91-1.30), p=0.36	Adjusted [b]
Tian, 2018	Sex	Male (reference) or female	Female: OR=1.49, 95% CI (0.62-3.57), p=0.37	Unadjusted
Wojtyna, 2017	Sex	Male (reference) or female	Female: OR=2.36, 95% CI (1.15- 4.85), p=0.02	Adjusted [c]
Yu, 2015	Sex	Male or female (reference)	Male: OR=1.40, 95% CI (0.60-3.23), p=0.43	Adjusted [c]
Social factors				
Yu, 2015	Urban or rural living	Urban (reference) or rural	Rural: OR=0.77, 95% CI (0.33-1.83), p=0.56	Adjusted [c]
Petraškienė, 2016	Education	Higher (reference), primary, secondary, or continuing education	Primary: OR=1.26, 95% CI (0.25-6.28), p=0.78 Secondary: OR=0.59, 95% CI (0.22-1.60), p=0.31 Continuing: OR=0.74, 95% CI (0.28-1.94), p=0.55	Adjusted [a]
Strober, 2017	Education	≥College/university or <High school (reference)	≥College/university: HR=0.79, 95% CI (0.66-0.95), p=0.01	Adjusted [b]

First author, publication year	Factor	Definition of factor	OR/HR, 95% CI, p-value	Adjusted/Unadjusted
Yu, 2015	Education	≤ High school or university education (reference)	≤High school: OR=0.88, 95% CI (0.36-2.11), p=0.77	Adjusted [c]
Wojtyna, 2017	Emotional social support	Not reported	OR=0.20, 95% CI (0.07-0.59), p=0.00	Adjusted [c]
Wojtyna, 2017	Instrumental social support	Not reported	OR=0.35, 95% CI (0.12-1.04), p=0.06	Adjusted [c]
Strober, 2017	Insurance	None (reference), public or private	Public: HR=1.29, 95% CI (0.92-1.81), p=0.15 Private: HR=0.62, 95% CI (0.45-0.85), p=0.00 Both public and private: HR=0.94 95% CI (0.60-1.46), p=0.78	Adjusted [b]
Yu, 2015	Occupation	Retired (reference), unemployed, student or currently employed	Unemployed: OR=0.28, 95% CI (0.05-1.52), p=0.14 Student: OR=1.48, 95% CI (0.37-5.86), p=0.58 Currently employed: OR=1.13, 95% CI (0.40-3.18), p=0.83	Adjusted [c]
Psoriasis related factors				
Tian, 2018	Age at onset of psoriasis	<18 (reference) or ≥18	≥18: OR=0.33, 95% CI (0.13-0.87), p=0.02	Adjusted [d]
Wojtyna, 2017	Age at onset of psoriasis	Younger or older (reference)	Younger: OR=1.16, 95% CI (0.57-2.38), p=0.68	Adjusted [c]
Strober, 2017	Baseline PGA	2-3 or 4-5	2-3: HR=1.45, 95% CI (1.17-1.79), p=0.00 4-5: HR=2.36, 95% CI (1.62-3.43), p<0.01	Adjusted [b]
Strober, 2017	Change in PGA from baseline to depression	-2 or lower, -1, 1 or ≥2	-2 or lower: HR=0.44, 95% CI (0.33-0.59), p<0.01 -1: HR=0.66, 95% CI (0.52-0.84), p=0.00 1: HR=0.69, 95% CI (0.52-0.91), p=0.10 ≥2: HR=1.01, 95% CI (0.70-1.44), p=0.97	Adjusted [b]
Wojtyna, 2017	Facial lesions	Yes or no (reference)	Yes: OR=0.57, 95% CI (0.20-1.63), p=0.29	Adjusted [c]
Wojtyna, 2017	Genital lesions	Yes or no (reference)	Yes: OR=1.24, 95% CI (0.43-3.57), p=0.68	Adjusted [c]
Kwan, 2018	Head involvement	Yes or no (reference)	Yes: OR=8.51, 95% CI (1.08-67.23), p=0.02	Unadjusted
Bakar, 2021	Lower limb lesions	Yes or no (reference)	Yes: OR=4.11, 95% CI (1.13-14.90), p=0.03	Adjusted [e]
Lamb, 2017	Psoriasis phenotype	Chronic plaque (reference), Generalized pustular, Localized pustular, and Nonpustular acral	Generalized pustular: OR=2.10, 95% CI (0.23-18.98), p=0.51 Localized pustular: OR=0.24, 95% CI (0.00-28.58), p=0.56 Nonpustular acral: OR=4.98, 95% CI (0.39-63.60), p=0.22	Unadjusted
Kwan, 2018	Psoriasis severity	Mild (reference – PASI <7), moderate (PASI 7-12) or severe psoriasis (PASI >12)	Moderate: OR=1.89, 95% CI (0.61-5.87), p=0.27 Severe: OR=2.23, 95% CI (0.77-6.43), p=0.14	Unadjusted
Lamb, 2017	Psoriasis severity	PASI range 0-50	OR=1.10, 95% CI (1.05-1.15), p<0.01	Unadjusted

First author, publication year	Factor	Definition of factor	OR/HR, 95% CI, p-value	Adjusted/Unadjusted
Tian, 2018	Psoriasis severity	Mild (reference – PASI <10) or moderate/severe psoriasis (PASI ≥10)	OR=1.09, 95% CI (1.02-1.17), p=0.01	Adjusted [d]
Tribó, 2019	Psoriasis severity	Mild (PASI, BSA or DLQI <10, reference) vs moderate/severe psoriasis (PASI, BSA or DLQI ≥10)	Depression measured using HADS: PASI Mild: reference Moderate/severe: OR=1.52, 95% CI (0.89-2.61) BSA Mild: reference Moderate/severe: OR=1.12, 95% CI (0.67-1.88) DLQI Mild: reference Moderate/severe: OR=2.70, 95% CI (1.21-6.03) Depression measured using HRSD: PASI Mild: reference Moderate/severe: OR= 1.26, 95% CI (0.72-2.21) BSA Mild: reference Moderate/severe: OR=1.33, 95% CI (0.77-2.28) DLQI Mild: reference Moderate/severe: OR=1.14, 95% CI (0.53-2.48) Depression measured using MADRS PASI Mild: reference Moderate/severe: OR=1.51, 95% CI (0.86-2.63) BSA Mild: reference Moderate/severe: OR=1.00, 95% CI (0.59-1.72) DLQI Mild: reference Moderate/severe: OR=1.84, 95% CI (0.83-4.06)	Adjusted [f]
Wojtyna, 2017	Psoriasis severity	Mild (reference – BSA≤10) or moderate/severe psoriasis (BSA>10)	Moderate/severe: OR=2.47, 95% CI (0.73-8.37), p=0.15	Adjusted [c]

First author, publication year	Factor	Definition of factor	OR/HR, 95% CI, p-value	Adjusted/Unadjusted
Lamb, 2017	Psoriasis treatment	Biologics (reference), Systemic, Phototherapy, Topical, and None	Systemic: OR=0.59, 95% CI (0.24-1.42), p=0.24 Phototherapy: no patients in this group Topical: OR=1.51, 95% CI (0.64-3.58), p=0.34 None: OR=0.90, 95% CI (0.24-3.33), p=0.87	Unadjusted
Kwan, 2018	Psoriasis treatment – systemic therapy	Use of systemic therapy (Yes or no – reference)	Yes: OR=0.67, 95% CI (0.20, 2.24), p=0.52	Unadjusted
Strober, 2017	Psoriasis treatment – biologic agents	Biologic agents (including ustekinumab, infliximab, etanercept, adalimumab), phototherapy or conventional systemic agents (reference)	Biologic agents: HR=0.76, 95% CI (0.59-0.98), p=0.04 Ustekinumab: HR=0.80, 95% CI (0.60-1.06), p=0.12 Infliximab: HR=0.70, 95% CI (0.47-1.03), p=0.07 Etanercept: HR=0.91, 95% CI (0.67-1.23), p=0.52 Adalimumab: HR=0.63, 95% CI (0.46-0.86), p=0.00 Phototherapy: HR=1.05, 95% CI (0.71-1.54), p=0.82	Adjusted [b]
Strober, 2017	Increasing years since psoriasis began	Not reported	HR=0.99, 95% CI (0.98-1.00), p=0.00	Adjusted [b]
Tian, 2018	Psoriasis duration	Longer vs shorter duration (reference)	Longer duration: OR=0.94, 95% CI (0.90-0.99), p=0.02	Adjusted [d]
Comorbidities				
Strober, 2017	Anxiety	Yes or no (reference)	Yes: HR=1.64, 95% CI (1.19-2.25), p=0.00	Adjusted [b]
Strober, 2017	Bipolar disorder	Yes or no (reference)	Yes: HR=2.01, 95% CI (0.99-4.09), p=0.05	Adjusted [b]
Strober, 2017	Cardiovascular disease (CAD/MI/ACVD/stroke/TIA)	Yes or no (reference)	Yes: HR=0.81, 95% CI (0.57-1.15), p=0.24	Adjusted [b]
Kwan, 2018	Cerebrovascular disease	Yes or no (reference)	Yes: OR=0.66, 95% CI (0.07-6.22), p=1.00	Unadjusted
Strober, 2017	Chronic obstructive pulmonary disease	Yes or no (reference)	Yes: HR=2.10, 95% CI (1.19-3.71), p=0.01	Adjusted [b]
Kwan, 2018	Diabetes	Yes or no (reference)	Yes: OR=1.12, 95% CI (0.42-2.95), p=0.83	Unadjusted
Strober, 2017	Diabetes	Yes or no (reference)	Yes: HR=1.15, 95% CI (0.90-1.48), p=0.27	Adjusted [b]
Bakar, 2021	Dyslipidaemia	Yes or no (reference)	Yes: OR=0.19 (0.05-0.76), p=0.02	Adjusted [e]
Kwan, 2018	Ischaemic heart disease	Yes or no (reference)	Yes: OR=0.66, 95% CI (0.07-6.22), p=1.00	Unadjusted
Lada, 2022	Psoriatic arthritis	Yes or no (reference)	HADS-D ≥8 Yes: OR=2.92, 95% CI (1.53-5.68), p=0.01 HADS-D ≥11 Yes: OR=4.08, 95% CI (1.92-9.06), p=0.00	Adjusted [g]

First author, publication year	Factor	Definition of factor	OR/HR, 95% CI, p-value	Adjusted/Unadjusted
Lamb, 2017	Psoriatic arthritis	Yes or no (reference)	Yes: OR=2.11, 95% CI (1.29-3.45), p=0.00	Unadjusted
Kwan, 2018	Psoriatic arthritis	Yes or no (reference)	Yes: OR=1.63, 95% CI (0.60-4.44), p=0.34	Unadjusted
Strober, 2017	Psoriatic arthritis	Yes or no (reference)	Yes: HR=1.58, 95% CI (1.32-1.88), p<0.01	Adjusted [b]
Lamb, 2017	Previous depression	Yes or no (reference)	Yes: OR=6.86, 95% CI (3.24-14.56), p<0.01	Unadjusted
Strober, 2017	Schizophrenia	Yes or no (reference)	Yes: HR=2.16, 95% CI (0.53-8.79), p=0.28	Adjusted [b]
Other factors				
Wojtyna, 2017	Self-evaluative salience	The importance of physical appearance in personal life and its salience to the sense of self and esteem.	OR=4.46, 95% CI (1.40-14.20), p=0.01	Adjusted [c]
Wojtyna, 2017	Motivational salience	Attention to appearance, and performance of appearance-management behaviours.	OR=2.00, 95% CI (0.72-5.55), p=0.18	Adjusted [c]
Wojtyna, 2017	Psychological distress	None to low distress (reference –DT <4) or high distress (DT ≥4)	High distress: OR=4.17, 95% CI (1.79, 9.71), p<0.01	Adjusted [c]
Kwan, 2018	Quality of life	None to low impairment (reference – DLQI<10) or severely impaired (DLQI ≥10)	Severely impaired: OR=7.16, 95% CI (2.70-18.98), p<0.01	Unadjusted
Bakar, 2021	Quality of life	DLQI score (specific score used not reported)	OR=1.22, 95% CI (1.11-1.35), p<0.01	Adjusted [e]
Tian, 2018	Stress reaction	Negative (reference) or positive stress reaction	Positive: OR=2.61, 95% CI (1.06-6.45), p=0.04	Adjusted [d]

Abbreviations: ACVD – Acute Cardiovascular Disease; ASI-R – Appearance Schemas Inventory-Revised scale includes ASI-MS (Motivational Salience) and ASI-SES (Self-Evaluative Salience); BSA – Body Surface Area; CAD – Coronary Artery Disease; CI – Confidence Interval; DLQI – Dermatology Life Quality Index; DT – Distress Thermometer; HADS – Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale; HRSD – Hamilton Depression Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; MI – Myocardial Infarction; OR – Odds Ratio; PASI – Psoriasis Area and Severity Index; PDI – Psoriasis Disability Index; PGA – Physician Global Assessment; TIA – Transient Ischaemic Attack

[a] Adjusted for age group, sex, education, marital status, body mass index and alcohol consumption

[b] Adjusted variables presented. Potential covariates were included in a multivariate cox regression model. Potential covariates included age, sex, ethnicity, educational status, psychiatric history, type of insurance, body mass index, duration of psoriasis, historic peak PGA, baseline PGA, change in disease severity (defined as change in PGA from peak or baseline to time of event or last available PGA score), comorbidities (including psoriatic arthritis, diabetes, chronic obstructive pulmonary disease, and cardiovascular disease [defined as CAD, MI, ACVD, stroke, and TIA]), and smoking status. All covariates with an overall univariate P value less than 0.2 were included in the Cox model.

[c] Adjusted variables presented. All factors were included in a multivariable logistic regression model. Adjusted variables not specified

[d] Adjustment done using stepwise multiple regression, unclear which specific variables have been adjusted for

[e] Adjusted for variables that met the initial screening criterion of $p<0.25$ in univariate logistic regression, does not specifically state what these variables are but we know that they could be sociodemographic data (such as age, gender, race, education level, income, and marital status) and clinical characteristics (type of psoriasis, presence of psoriasis arthropathy, anatomical site of psoriatic lesions, and comorbidities)

[f] Adjusted for age, sex, education, alcohol, smoking, systemic treatment/phototherapy, current psychological/psychiatric treatment.

[g] HADS-D $\geq$8 adjusted for age, body mass index (BMI), presence of potentially confounding physical comorbidities (history of hypertension, ischemic heart disease or stroke, cancer, diabetes, inflammatory bowel disease, other musculoskeletal, severe systemic or central nervous system disease, and severe chronic infections), psoriasis severity, and time of completion (before/during COVID-19 pandemic). HADS-D $\geq$11 adjusted only for age, time of completion, and physical comorbidities due to lower prevalence of the outcome.

Table S8: Factors associated with *anxiety* in people with *psoriasis* identified from observational studies

First author, publication year	Factor	Definition of factor	OR, 95% CI, p-value	Adjusted/Unadjusted
Age, ethnicity, and sex				
Lamb, 2017	Age	Age range 18-86	OR=1.00, 95% CI (0.97-1.02), p=0.69	Unadjusted
Petraškienė, 2016	Age	<35 (reference), 35-44, 45-54, 55-64, or ≥65 years	35-44: OR=0.85, 95% CI (0.33-2.20), p=0.75 45-54: OR=1.04, 95% CI (0.42-2.57), p=0.93 55-64: OR=1.22, 95% CI (0.47-3.15), p=0.68 ≥65: OR=0.40, 95% CI (0.08-1.76), p=0.22	Adjusted [a]
Tian, 2018	Age	Not reported	OR=1.03, 95% CI (0.98-1.09), p=0.24	Unadjusted
Lamb, 2017	Sex	Male (reference) or female	Female: OR=1.88, 95% CI (1.03-3.42), p=0.04	Unadjusted
Petraškienė, 2016	Sex	Male (reference) or female	Female: OR=4.72, 95% CI (2.53-8.83), p<0.01	Adjusted [a]
Tian, 2018	Sex	Male (reference) or female	Female: OR=1.72, 95% CI (0.63-4.67), p=0.29	Unadjusted
Lamb, 2017	Ethnicity	White British (reference), White other, Asian, Black, Mixed, Other, Unknown	White other: OR=1.82, 95% CI (0.69-4.81), p=0.23 Asian: OR=3.42, 95% CI (1.63-7.20), p=0.00 Black: OR=1.49, 95% CI (0.17-12.97), p=0.72 Mixed: OR=1.19, 95% CI (0.11-12.88), p=0.89 Other: OR=1.66, 95% CI (0.23-12.04), p=0.62 Unknown: OR=0.48, 95% CI (0.09-2.49), p=0.38	Unadjusted
Social factors				
Petraškienė, 2016	Education	Higher (reference), primary, secondary, or continuing education	Primary: OR=4.42, 95% CI (1.12-17.42), p=0.03 Secondary: OR=0.94, 95% CI (0.42-2.12), p=0.90 Continuing: OR=1.05, 95% CI (0.47-2.34), p=0.90	Adjusted [a]
Psoriasis related factors				
Tian, 2018	Age at onset of psoriasis	<18 (reference) or ≥18	≥18: OR=0.23, 95% CI (0.07-0.7), p=0.01	Adjusted [b]
Kwan, 2018	Head involvement	Yes or no (reference)	Yes: OR=6.47, 95% CI (1.40-29.86), p=0.01	Unadjusted
Tian, 2018	Psoriasis duration	Longer vs shorter duration (reference)	Longer duration: OR=0.90, 95% CI (0.83-0.96), p=0.00	Adjusted [b]
Lamb, 2017	Psoriasis phenotype	Chronic plaque (reference), Generalized pustular, Localized pustular, and Nonpustular acral	Generalized pustular: OR=1.72, 95% CI (0.19-15.91), p=0.63 Localized pustular: OR=3.20, 95% CI (0.30-33.80), p=0.13 Nonpustular acral: OR=1.13, 95% CI (0.31-4.15), p=0.86	Unadjusted

First author, publication year	Factor	Definition of factor	OR, 95% CI, p-value	Adjusted/Unadjusted
Kwan, 2018	Psoriasis severity	Mild (reference – PASI <7), moderate (PASI 7-12) or severe psoriasis (PASI >12)	Moderate: OR=1.39, 95% CI (0.50-3.89), p=0.53 Severe: OR=1.74, 95% CI (0.64-4.52), p=0.26	Unadjusted
Lamb, 2017	Psoriasis severity	PASI range 0-50	OR=1.07, 95% CI (1.02-1.12), p=0.01	Unadjusted
Tian, 2018	Psoriasis severity	Mild (reference – PASI <10) or moderate/severe psoriasis (PASI ≥10)	OR=1.12, 95% CI (1.03-1.22), p=0.01	Adjusted [b]
Tribó, 2019	Psoriasis severity	Mild (reference – PASI, BSA or DLQI <10, reference) vs moderate/severe psoriasis (PASI, BSA or DLQI ≥10)	Anxiety measured using HADS: PASI Moderate/severe: OR=1.26, 95% CI (0.70-2.28) BSA Moderate/severe: OR=0.97, 95% CI (0.55-1.70) DLQI Moderate/severe: OR=1.68, 95% CI (0.74-3.83) Anxiety measured using SAI: PASI Moderate/severe: OR=1.18, 95% CI (0.68-2.06) BSA Moderate/severe: OR=1.22, 95% CI (0.72-2.06) DLQI Moderate/severe: OR=2.52, 95% CI (1.16-5.50) Anxiety measured using TAI: PASI Moderate/severe: OR=1.01, 95% CI (0.58-1.77) BSA Moderate/severe: OR=0.77, 95% CI (0.44-1.32) DLQI Moderate/severe: OR=1.87, 95% CI (0.87-4.00)	Adjusted [c]
Lamb, 2017	Psoriasis treatment	Biologics (reference), Systemic, Phototherapy, Topical, and None	Systemic: OR=0.86, 95% CI (0.38-1.90), p=0.70 Phototherapy: OR=7.03, 95% CI (0.58-85.20), p=0.13 Topical: OR=3.66, 95% CI (1.65-8.10), p=0.00 None: OR=1.13, 95% CI (0.31-4.15), p=0.86	Unadjusted
Kwan, 2018	Psoriasis treatment	Use of systemic therapy (Yes or no – reference)	Yes: OR=0.74, 95% CI (0.26-2.16), p=0.59	Unadjusted

First author, publication year	Factor	Definition of factor	OR, 95% CI, p-value	Adjusted/Unadjusted
Comorbidities				
Kwan, 2018	Cerebrovascular disease	Yes or no (reference)	Yes: OR=0.41, 95% CI (0.04-3.81), p=0.65	Unadjusted
Kwan, 2018	Diabetes	Yes or no (reference)	Yes: OR=0.59, 95% CI (0.23-1.53), p=0.28	Unadjusted
Kwan, 2018	Ischaemic heart disease	Yes or no (reference)	Yes: OR=1.64, 95% CI (1.40-1.92), p=0.15	Unadjusted
Lamb, 2017	Psoriatic arthritis	Yes or no (reference)	Yes: OR=1.92, 95% CI (1.24-2.98), p=0.00	Unadjusted
Kwan, 2018	Psoriatic arthritis	Yes or no (reference)	Yes: OR=2.27, 95% CI (0.88-5.85), p=0.09	Unadjusted
Lamb, 2017	Previous anxiety	Yes or no (reference)	Yes: OR=8.70, 95% CI (4.14-18.27), p<0.01	Unadjusted
Other factors				
Kwan, 2018	Quality of life	None to low impairment (reference – DLQI<10) or severely impaired (DLQI ≥10)	Severely impaired: OR=8.80, 95% CI (3.36-23.07), p<0.01	Unadjusted
Tian, 2018	Stress reaction	Negative (reference) or positive stress reaction	Positive: OR=2.77, 95% CI (1.07-7.93), p=0.04	Adjusted [b]

Abbreviations: BSA – Body Surface Area; CI – Confidence Interval; DLQI – Dermatology Life Quality Index; HADS – Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale; HRSD – Hamilton Depression Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; OR – Odds Ratio; PASI – Psoriasis Area and Severity Index; PGA – Physician Global Assessment; SAI – State Anxiety Inventory; TAI – Trait Anxiety Inventory

[a] Adjusted for age group, sex, education, marital status, body mass index and alcohol consumption

[b] Adjustment done using stepwise multiple regression, unclear which specific variables have been adjusted for

[c] Adjusted for age, sex, education, alcohol, smoking, systemic treatment/phototherapy, current psychological/psychiatric treatment.

Table S9: Factors associated with *schizophrenia* in people with *psoriasis* identified from *an observational study*

First author, publication year	Factor	Definition of factor	OR, 95% CI, p-value	Adjusted/Unadjusted
Age, ethnicity, and sex				
Tu, 2016	Age	20-39 (reference), 40-59 or ≥60 years	40-59: OR=2.49, 95% CI (1.55-4.00), p=0.00 ≥60: OR=0.79, 95% CI (0.41-1.51), p=0.47	Adjusted
	Sex	Male (reference) or female	Female: OR=1.26, 95% CI (0.87-1.81), p=0.22	Adjusted
Psoriasis related factors				
	Psoriasis duration	≤5 (reference), 5-10 or >10 years	5-10 years: OR=0.74, 95% CI (0.50-1.12), p=0.15 >10 years: OR=0.87, 95% CI (0.54-1.41), p=0.57	Adjusted
Comorbidities				
	Cerebrovascular disease	Yes or no (reference)	Yes: OR=2.01, 95% CI (1.11-3.65), p=0.02	Adjusted
	Chronic pulmonary disease	Yes or no (reference)	Yes: OR=1.64, 95% CI (1.07-2.49), p=0.02	Adjusted
	Congestive heart failure	Yes or no (reference)	Yes: OR=0.42, 95% CI (0.13-1.37), p=0.15	Adjusted
	Diabetes	Yes or no (reference)	Yes: OR=1.33, 95% CI (0.82-2.18) p=0.25	Adjusted
	Hemiplegia or paraplegia	Yes or no (reference)	Yes: OR=1.62, 95% CI (0.63-4.19) p=0.32	Adjusted
	Liver disease	Yes or no (reference)	Yes: OR=1.08, 95% CI (0.71-1.65) p=0.72	Adjusted
	Peripheral vascular disease	Yes or no (reference)	Yes: OR=0.39, 95% CI (0.09-1.63), p=0.20	Adjusted
	Renal disease	Yes or no (reference)	Yes: OR=0.97, 95% CI (0.38-2.47) p=0.95	Adjusted
	Rheumatologic disease	Yes or no (reference)	Yes: OR=0.64, 95% CI (0.23-1.77) p=0.39	Adjusted

All odds ratios reported in this table are adjusted for age, sex, and comorbidities
Abbreviations: CI – Confidence Interval; OR – Odds Ratio

Table S10: Association between *psoriasis treatment* and mental illness, stratified by mental illness outcome identified from *randomised controlled trials*

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group		Mean difference between intervention and comparison group
					Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)		Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)	
Anxiety	Gordon, 2018	992	Baseline, week 8, week 16 and week 24	Guselkumab 100mg at weeks 0,4, 12 and 20.	6.9 (4.1)	Week 8 -1.60 (SD=3.10), p<0.01 Week 16 -1.70 (SD=3.40), p<0.01 Week 24 -2.00 (SD=3.60), p<0.01 (versus adalimumab)	Placebo at weeks 0, 4, and 12 followed by guselkumab 100mg at weeks 16 and 20 Adalimumab 80mg at week 0, adalimumab 40mg at week 1 and then adalimumab 40mg every 2 weeks through week 23	Placebo 6.50 (4.10) Adalimumab 6.90 (4.50)	Placebo Week 8 -0.20 (SD=2.90) Week 16 -0.20 (SD=2.90) Adalimumab Week 8 -1.00 (SD=3.20), p=0.00 Week 16 -1.10 (SD=3.40), p=0.00 Week 24 -1.00 (SD=3.60)	Not reported
	Langley, 2010	1,230	Baseline, week 12 and week 24	Ustekinumab 45mg at weeks 0, 4 and every 12 weeks thereafter	6.80 (4.40)	Week 12 -1.60 (SD=3.60), p<0.01 Week 24 -1.80 (SD=3.70)	Placebo at weeks 0 and 4, with half randomised to crossover to receive ustekinumab 45mg and the other half to ustekinumab 90mg at weeks 12, 16, and every 12	7.00 (4.20)	Week 12 Placebo: -0.11 (SD=2.70) Week 24 Placebo to ustekinumab 45mg: -1.50 (SD=3.10) Placebo to ustekinumab 90mg: -1.80 (SD=3.20)	Not reported
				Ustekinumab 90mg at weeks 0, 4 and every 12 weeks thereafter	6.90 (4.30)	Week 12 -1.60 (SD=3.40), p<0.01 Week 24 -2.00 (SD=3.50)				

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group		Mean difference between intervention and comparison group
					Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)		Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)	
							weeks thereafter			
Depression	Gordon, 2018	992	Baseline, week 8, week 16 and week 24	Guselkumab 100mg at weeks 0,4, 12 and 20.	5.30 (4.20)	Week 8 -1.30 (SD=3.30), p<0.01 Week 16 -1.60 (SD=3.60), p<0.01 Week 24 -1.70 (SD=3.80), p=0.06 (versus adalimumab)	Placebo at weeks 0, 4, and 12 followed by guselkumab 100mg at weeks 16 and 20 Adalimumab 80mg at week 0, adalimumab 40mg at week 1 and then adalimumab 40mg every 2 weeks through week 23	Placebo 5.10 (4.30) Adalimumab 5.30 (4.30)	Placebo Week 8 0.00 (SD=2.90) Week 16 -0.10 (SD=2.90) Adalimumab Week 8 -1.20 (SD=3.00), p<0.01 Week 16 -1.20 (SD=3.40), p<0.01 Week 24 -1.10 (SD=3.50)	Not reported
	Griffiths, 2017	320	Baseline and week 12	Ixekizumab 80mg every 2 weeks Ixekizumab 80mg every 4 weeks	13.80 (2.60) 14.20 (2.60)	-7.10 (0.44), p<0.01 -6.10 (0.41), p<0.01	Placebo given to match all active treatment dosing regimens	14.00 (3.10)	-3.40 (0.48)	Not reported
	Langley, 2010	1,230	Baseline, week 12 and week 24	Ustekinumab 45mg at weeks 0, 4 and every 12 weeks thereafter	4.90 (3.80)	Week 12 -1.70 (SD=3.10), p<0.01 Week 24	Placebo at weeks 0 and 4, with half randomised to	4.90 (3.70)	Week 12 Placebo: -0.21 (SD=2.80) Week 24	Not reported

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group		Mean difference between intervention and comparison group
					Mean (SD) at baseline	**Mean difference (SE) from baseline to timepoint(s)**		**Mean (SD) at baseline**	**Mean difference (SE) from baseline to timepoint(s)**	
						-1.80 (SD=3.40)	crossover to receive ustekinumab 45mg and the other half to ustekinumab 90mg at weeks 12, 16, and every 12 weeks thereafter		Placebo to ustekinumab 45mg: -1.70 (SD=3.20) Placebo to ustekinumab 90mg: -1.40 (SD=3.00)	
				Ustekinumab 90mg at weeks 0, 4 and every 12 weeks thereafter	5.40 (4.20)	Week 12 -2.10 (SD=3.40), p<0.01 Week 24 -2.30 (SD=3.50)				
	Menter, 2010	96	Baseline and week 12	Adalimumab 40mg every other week	42.90 (12.40)	-6.70, 95% CI (-10.10, -3.30), p=0.00	Placebo every other week	45.80 (14.00)	-1.50, 95% CI (-4.00, 1.00), p=0.23	Adalimumab reduced mean score by 6 points more than placebo, 95% CI (-9.50, -2.50), p<0.01
	Tyring, 2006	620	Baseline, week 4, week 8 and week 12	Etanercept 50mg twice weekly	Depression measured using HAM-D 4.50 (4.60) Depression measured using BDI 8.10 (7.70)	Week 12 Depression measured using HAM-D Mean total score improvement is 1.50	Placebo twice weekly	Depression measured using HAM-D 4.50 (5.10) Depression measured using BDI 8.40 (8.50)	Week 12 Depression measured using HAM-D Mean total score improvement is 0.40	Week 12 Depression measured using HAM-D Difference between etanercept and placebo groups was 1.20, 95% CI (0.40-1.90), p=0.00, effect size of 0.25 Week 12

Mental illness outcome	Author, publication year	Total study size	Timepoint(s) outcome was measured	Intervention(s)	Results in intervention group		Comparison	Results in comparison group		Mean difference between intervention and comparison group
					Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)		Mean (SD) at baseline	Mean difference (SE) from baseline to timepoint(s)	
										Depression measured using BDI Difference between etanercept and placebo is 1.80, 95% CI (0.60-2.90), p=0.00, effect size of 0.22

[a] Mean differences and standard errors are reported unless stated otherwise
p-values reported in this table are compared to the placebo/comparison group unless stated otherwise
Abbreviations: BDI – Beck's Depression Inventory; CI – Confidence Interval; HAM-D – Hamilton Depression Rating Scale; SD – Standard Deviation; SE – Standard Error; TCS – Topical corticosteroids

Appendix 3: Protocol of stopped study investigating the agreement of severe mental illness recording across English primary care and secondary mental health care

1

General information

Protocol reference Id

22_001838

Study title

Agreement of severe mental illness recording across English primary care and secondary mental health care.

Research Area

Disease Epidemiology

Methodological

Does this protocol describe an observational study using purely CPRD data?

Yes

Does this protocol involve requesting any additional information from GPs, or contact with patients?

No

2 Research team

Role	Chief Investigator
Title	Assistant Professor
Full name	Kathryn Mansfield
Affiliation/organisation	London School of Hygiene & Tropical Medicine (LSHTM)
Email	kathryn.mansfield@lshtm.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Corresponding Applicant
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Status	Confirmed

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Will this person be analysing the data?	No
Status	Confirmed

3

Access to data

Sponsor

London School of Hygiene & Tropical Medicine (LSHTM)

Funding source for the study

Is the funding source for the study the same as Chief Investigator's affiliation?

No

Funding source for the study

National Institute for Health Research (NIHR)

Institution conducting the research

Is the institution conducting the research the same as Chief Investigator's affiliation?

Yes

Institution conducting the research

London School of Hygiene & Tropical Medicine (LSHTM)

Method to access the data

Indicate the method that will be used to access the data

Institutional multi-study licence

Is the institution the same as Chief Investigator's affiliation?

Yes

Institution name

London School of Hygiene & Tropical Medicine (LSHTM)

Extraction by CPRD

Will the dataset be extracted by CPRD

No

Multiple data delivery

This study requires multiple data extractions over its lifespan

No

Data processors

Data processor is	Same as the chief investigator's affiliation
Processing	Yes
Accessing	Yes
Storing	Yes
Processing area	UK

4 Information on data

Primary care data

CPRD GOLD

Do you require data linkages

Yes

Patient level data

Mental Health Services Data Set (MHSDS)

NCRAS data

Covid 19 linkages

Area level data

Do you require area level data?

Yes

Practice level (UK)

Practice Level Rural-Urban Classification

Patient level (England only)

Patient Level Index of Multiple Deprivation

Withheld concepts

Are withheld concepts required?
No

Linkage to a dataset not listed

Are you requesting a linkage to a dataset not listed?
No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?
No

5

Protocol information

Lay Summary

Routine information is recorded when someone contacts their general practitioner (GP), making medical records a large and powerful resource for research. Common mental health conditions like depression, are often diagnosed by GPs and therefore recorded in GP records. However severe mental illnesses like schizophrenia are often diagnosed in specialist mental healthcare, and it is unclear how well they are recorded across different health care records. GPs play an important role in the care of people with severe mental illnesses, so it is important that their diagnoses are in GP records.

Our study will describe the proportion of people with their severe mental illness recorded in GP or mental health records alone, or in both GP and mental health care records. We will also explore whether there are differences in the type of people whose severe mental illness is, or is not, recorded in GP or mental health records. For example, people who have their severe mental illness recorded in GP records alone might be a different age, sex, or ethnicity, live in different regions, be less deprived, or seek medical help more often. We will also investigate whether specific types of severe mental illnesses are better recorded.

Our study will help us understand how to use electronic health records for severe mental illness research and allow us to recognise whether certain people are more likely to have their severe mental illnesses recorded in GP records, and therefore highlight whether some people may not receive optimal holistic care.

Technical Summary

Electronic health records are often used to study mental illness in epidemiological research. Common mental disorders (i.e., depression, anxiety) are diagnosed and managed in primary care. Severe mental illnesses (SMI: schizophrenia, bipolar disorder, other psychoses) are diagnosed in secondary mental healthcare, with management across both primary and secondary care. How well SMIs are recorded in primary or secondary mental healthcare records is unclear. GPs are integral in care of individuals with SMIs, so recording in secondary care alone may suggest individuals are not receiving holistic care. Conversely, SMI recorded in primary care alone may suggest SMI is well managed in primary care.

We will investigate the agreement of SMI recording across English primary care and secondary mental healthcare. Adults (18years+) registered with English practices for at least one year, eligible for Mental Health Dataset (MHDS) linkage, with an SMI record in primary care or MHDS between April 2007-November 2015 are eligible for inclusion.

We will estimate proportions and describe characteristics of individuals with SMI recorded in primary or secondary mental health care alone, or in both. We will describe which specific SMI diagnoses (e.g., schizophrenia, bipolar disorder, other psychoses) are more completely recorded. We will use logistic regression to explore characteristics associated with SMI recording in both primary and secondary care. We will repeat our main analyses in sensitivity analyses including: (1) using alternative codelists to identify SMI outcomes; and (2) describing smoking status of individuals using records identified before and after the most recent SMI diagnosis. In secondary analyses, we will: (1) stratify our results by calendar periods covered by the two MHDS formats (Format 1: April 2007-March 2011, Format 2: April 2011-November 2015); and (2) describe timing between secondary care diagnosis and primary care recording for individuals whose SMI was recorded first in secondary mental healthcare.

Outcomes to be measured

Recording of severe mental illness (i.e., schizophrenia, bipolar disorder, and other psychoses) in primary or secondary mental health care alone, or in both primary and secondary mental health care.

Objectives, specific aims & rationale

The overall aim of our study is to investigate the agreement of severe mental illness (i.e., schizophrenia, bipolar disorder, and other psychoses) recording across English primary care and secondary mental health care.

Specific research objectives for the main analyses are:
1) To identify the proportion of individuals whose severe mental illness has been recorded in primary or secondary mental health care alone, or in both primary and secondary mental health care.
2) To describe the characteristics of individuals whose severe mental illness is recorded in both primary and secondary mental health care, or in primary or secondary mental health care alone.
3) To estimate the association between individual characteristics (e.g., age, sex, ethnicity) and severe mental illness recording in both primary and secondary mental health care records.
4) To describe whether specific severe mental illnesses are more likely to be recorded in both primary and secondary mental health care records by stratifying results based on specific severe mental illness diagnoses: schizophrenia, bipolar disorder, and other severe mental illness diagnoses.

Specific research objectives for the secondary analyses are:
1) To assess severe mental illness recording in primary care and secondary mental health care by stratifying our results based on the different calendar periods covered by the two MHDS formats. Format 1 covers April 2007 – March 2011, while format 2 covers April 2011 – November 2015.
2) To describe the timing between secondary care diagnosis and primary care coding for individuals whose severe mental illness was recorded first in secondary mental health care

Rationale:

The objectives of the main analyses will allow us to:
1) Ascertain how well secondary mental health care severe mental illness diagnoses are recorded in primary care records and improve our understanding of the quality of primary care and MHDS data for use in future epidemiological studies of severe mental illness outcomes (Objective 1 of main analysis).
2) Understand the characteristics of people with severe mental illness recording in primary or secondary mental health care alone, and therefore highlight potential inequalities in access to holistic care (Objectives 2 and 3 of main analysis).
3) Assess whether clearly defined severe mental illness diagnoses, such as schizophrenia and bipolar disorder, are more likely to be recorded in both primary and secondary mental health care compared to other severe mental illness diagnoses (Objective 4 of main analysis).

The objectives of the secondary analyses will allow us to:
1) Assess whether recording of severe mental illness diagnoses in primary care and secondary mental health care changes over time (Secondary Objective 1).
2) Understand how long it takes for severe mental illness diagnoses initially recorded in secondary mental health care to be recorded in primary care (Secondary Objective 2)

Study background

Primary care electronic health record databases such as the CPRD have been widely used to capture mental health conditions for epidemiological research.(1-3) Common mental disorders (CMDs – depression or anxiety) are mainly diagnosed and managed in primary care (4,5), while severe mental illnesses (SMIs – schizophrenia, bipolar disorder, and other psychoses) are more often diagnosed in specialised secondary mental healthcare (6,7), with management taking place across both primary and secondary mental health care settings.(8) As SMIs are more often diagnosed in secondary mental health care settings, it is unclear how well their diagnoses are recorded in the primary care records of affected individuals.

The absence of an SMI diagnosis in primary care records, with the implication that a GP might not be aware of the diagnosis, may have a detrimental effect on the care of affected individuals. In the UK, GPs and primary care have a central role in the holistic care of people with SMIs.(8) The Quality and Outcomes Framework (QOF) has offered financial incentives to GPs since its inception in 2004 for the care of people with SMIs. Currently, GPs receive renumeration for maintaining a register of individuals with an SMI diagnosis, developing, and maintaining comprehensive care plans, and conducting annual health checks (where BMI, blood pressure and smoking status are monitored) in those with an SMI diagnosis. (9) GPs also facilitate referrals to secondary care for those with suspected SMI, act in conjunction with secondary care services by prescribing medication, and, in those who have been discharged from secondary care settings, may be fully responsible for their care. (8) Additionally, people with an SMI diagnosis have been found to be of poorer physical health compared to the general population, and to be at increased risk of conditions such as cancer, liver disease and cardiovascular disease.(10) Therefore, if an individual with an SMI diagnosis only has their SMI diagnosis recorded in secondary mental health care, it may mean that their GP is unaware of their diagnosis and will therefore be unable to manage their mental health condition or assess their physical health to provide holistic care.

The recording of SMI diagnoses in secondary mental health care records is also unclear. Previous research has found that one-third of people with SMI are seen only in primary care.(11) This means that a lack of SMI diagnosis recording in secondary mental health care records may suggest that an individual's SMI is well managed in primary care without the need for secondary mental health intervention, or that the individual is not open to secondary care services. However, it may also suggest possible inequalities in access to secondary mental health care services. A previous study in people with depression and/or anxiety found that individuals in more deprived areas were less likely to use planned secondary mental health care.(12) It is unknown whether this pattern is seen in people with SMI.

There has been limited research into the agreement of SMI recording across primary care and secondary mental health care. Previous studies have focused on exploring the rate of SMI recording by GPs in primary care,(13) or investigating the sensitivity of SMI recording within general hospitals.(14) This study therefore aims to investigate the agreement of SMI recording across primary care and secondary mental health care by identifying the proportion and describing the characteristics of individuals whose SMI diagnoses are recorded in primary or secondary mental health care alone, or in both primary and secondary mental health care.

This study may have methodological implications for future epidemiological studies by clarifying whether primary care databases alone are enough to fully capture information on SMI diagnoses. This study may also allow the identification of potential inequalities that may be present in the recording of SMI outcomes in primary care.

Study type

Objectives 1, 2 and 4 are descriptive. Objective 3 will be hypothesis testing (people with SMI recorded in primary and secondary mental health care have different characteristics compared to people with SMI recorded in primary or secondary care alone).

Study design

We will undertake a cross-sectional study using data from the Clinical Practice Research Datalink (CPRD GOLD) along with linked data from the Mental Health Data Set (MHDS). Individuals eligible for study inclusion will be identified between April 2007 to November 2015 (period of MHDS data availability).

Feasibility counts

A feasibility count of individuals registered with CPRD practices for at least one year who were eligible for MHDS linkage identified 25,263 adults with a severe mental illness diagnosis during the study period (April 2007 to November 2015).

Sample size considerations

Objectives 1, 2 and 4 are descriptive, therefore a formal power calculation for is unnecessary. Objective 3 involves hypothesis testing, so we have completed a formal power calculation. From our feasibility counts, we expect to identify at least 25,263 people with an SMI diagnosis registered with a CPRD practice eligible for MHDS linkage between April 2007 and November 2015. We chose to use drug misuse in our power calculations as it is likely to be the least common characteristic that we will use to identify characteristics associated with SMI recording in both primary care and secondary mental health care records. We cannot be sure at this stage how many individuals with SMI will be categorised as misusing drugs, however, a previous study estimated that 12.5% of people with SMI misuse drugs.(15) Using this figure, we estimate that 3,158 individuals with SMI will misuse drugs and 22,105 will not. We also cannot be sure how the proportion of individuals with SMI recorded in both primary and secondary mental health care will differ between those who do or do not misuse drugs. We have therefore estimated power based on a range of plausible odds ratios (1.1, 1.15, 1.2, 1.25, 1.3) and a conservative range of proportions of individuals with SMI recording in both primary and secondary care records (10%, 20%, 30%, 40%, 50%). Assuming that 3,158 individuals in our study are identified as misusing drugs, and of these individuals, 20% had their SMI diagnoses recorded in both primary care and secondary mental health care records, we would have over 90% power, at the 5% significance level, to detect differences in odds of SMI recording in both primary and secondary care of 1.20 or more. If the proportion of individuals with SMI diagnoses recorded in both primary care and secondary mental health care records is higher than our cautious estimate of 20%, then we will require a smaller sample size to detect the same effect. Equally, if the characteristic that we are analysing is more prevalent than 12.5% (assumed for drug misuse) the sample size required to detect the same effect will also decrease. Our power calculation suggests that our study will be adequately powered. We will not report results of our analyses including a small number of individuals (i.e., cell counts <5) to reduce the risk of potential individual and/or practice re-identification.

Planned use of linked data and benefit to patients in England and Wales

We intend to use the Mental Health Data Set (MHDS) to identify individuals with a SMI diagnosis in secondary mental health care records.

We intend to use quintiles of the 2010 patient-level Index of Multiple Deprivation (IMD) as a measure of socioeconomic deprivation in our analyses. We will also use practice-level Rural-Urban classification to classify whether an individuals' GP practice is in a rural or urban area to establish whether ease of access to services affects SMI recording in primary and secondary care.

In the context of this study, we believe that individual-level IMD and rural-urban practice location capture distinct measures. It is likely that there are differences in severe mental illness health provision between rural and urban areas, potentially due to differences in geographical access to specialist services. We believe that the differences in access to mental health services are not necessarily a reflection of deprivation measured by patient-level IMD.

The use of the linked MHDS data in this study may have methodological implications for future epidemiological studies (with consequent indirect impact on patient care through more robust future studies) by clarifying whether primary care databases alone are enough to fully capture information on SMI diagnoses. The use of linked patient-level IMD data and practice-level Rural-Urban data in this study may highlight potential inequalities in care associated with recording of SMI outcomes in primary care, and subsequent access to holistic care (with potential for direct impact on clinical practice guidelines by highlighting those who may be less likely to receive holistic care).

Definition of the study population

Individuals registered with CPRD GOLD practices will be eligible for study inclusion if they meet the following criteria: Adults (aged 18 years and over); At least one year of registration with a CPRD practice in England that meets CPRD quality control standards; Eligible for MHDS linkage; Have a record of a severe mental illness diagnosis in either CPRD Gold or MHDS between April 2007 and November 2015 (period of MHDS data availability).

Selection of comparison groups/controls

Our initial results will be descriptive. However, for Objectives 2 and 3, we will compare individuals whose SMI diagnosis are recorded in both primary care and secondary mental health care to: 1) individuals whose SMI diagnosis have been recorded in primary care alone; and 2) individuals whose SMI diagnosis have been recorded in secondary care alone.

Exposures, outcomes and covariates

Exposures

In Objectives 2 and 3, exposure variables will be characteristics that may differ between individuals whose severe mental illness diagnoses are and are not recorded in primary care, including: age, sex, ethnicity, deprivation, geographical region, urban/rural living, harmful alcohol use, smoking status, drug misuse, and healthcare utilisation.

Ethnicity will be identified based on a previously validated algorithm based on primary care coding.(16) Individuals will be classified into one of five ethnic groups: White, Black, South Asian, Mixed, and Other.

We will use quintiles of the 2010 patient-level index of multiple deprivation (IMD) as a proxy for socioeconomic deprivation. We have chosen to use the 2010 patient level IMD as this measure is closest to the midpoint of our study period (April 2007 and November 2015) allowing us to minimise misclassification of deprivation status.

Geographical region will be based on recording in CPRD and categorised into one of ten English regions: Northeast, Northwest, Yorkshire & The Humber, East Midlands, West Midlands, East of England, Southwest, South Central, London, and Southeast Coast.

We will use the 2011 practice-level rural urban classification to categorise individuals into rural or urban regions.

We will define smoking status using an algorithm that uses primary care morbidity code records to identify smoking status that is closest to the date of the most recent severe mental illness diagnosis in either the CPRD or MHDS databases. (17) In the algorithm, records within -1 year to +1 month of the date of SMI diagnosis are regarded as the best, +1 month to +1 year from the date of SMI diagnosis as second best, the nearest prior to the year before the date of SMI diagnosis as the third best, and within +1 year from the date of SMI diagnosis as the worst. Smoking status will be classified as: (1) current smoker; (2) ex-smoker; or (3) non-smoker. In main analyses, we will use records of smoking status identified before the date of the most recent severe mental illness diagnosis to describe the characteristics of individuals whose severe mental illness is recorded in both primary and secondary mental health care, or in primary or secondary mental health care alone. In sensitivity analyses, we will use smoking status records identified either before or after the date of the most recent severe mental illness diagnosis to describe individuals.

We will identify individuals as harmful alcohol users based on previously defined primary care morbidity codes suggesting harmful or heavy alcohol use (including codes related to alcohol dependency or harm related to alcohol use), or a prescription for drugs used to maintain alcohol abstinence (acamprosate, disulfiram, or nalmefene).(18)

We will identify individuals as misusing drugs based on previously defined primary care morbidity codes suggesting dependence, abuse, or addiction of drugs other than alcohol. A list of Read codes that will be used is provided in the appendix.

We will define healthcare utilisation as the number of non-mental health related GP consultations in the year preceding the date of the most recent severe mental illness diagnosis. This method will allow us to quantify health seeking behaviours unrelated to mental health prior to a confirmed diagnosis of severe mental illness. We will be able to assess whether individuals who have higher numbers of consultations with the GP for non-mental health related concerns are more or less likely to have their severe mental illness diagnoses recorded in primary care records.

Outcomes
In Objectives 1 and 2, the outcome under investigation will be the recording of severe mental illness. We will identify severe mental illness in CPRD using the earliest record of a diagnostic Read code. We will identify severe mental illness outcomes in the MHDS data using International Classification of Diseases version 10 (ICD-10) codes.

In Objective 3, the outcome will be severe mental illness recording in both primary and secondary mental health care records (compared to recording in only primary care or only secondary mental health care).

In Objective 4, the outcomes will be specific subtypes of the severe mental illness outcome: schizophrenia, bipolar disorder, and other psychoses. These outcomes will be identified in the CPRD dataset using Read codes and in the MHDS using ICD-10 codes.

A list of Read codes and ICD-10 codes used to identify severe mental illness is provided in the appendix.

Covariates
Variables identified as exposures (see above) will be considered as covariates.

Data/statistical analysis

We will initially describe the characteristics (including age, sex, socioeconomic deprivation, geographical region) of individuals in the study. Numbers and percentages will be used for categorical data, and the median (interquartile range) or the mean (standard deviation) will be used for continuous data.

Main analyses

Objective 1 – Identify the proportion of individuals whose severe mental illness outcomes have been recorded in primary or secondary mental health care alone, or in both primary and secondary care.

We will calculate the proportion of the study population whose severe mental illness outcomes have been recorded in primary or secondary mental health care alone or in both primary and secondary care electronic health record data sources. We will consider the most recent severe mental illness diagnosis recorded in either the CPRD or MHDS dataset during an individual's study period as the index episode. Using the most recent SMI diagnostic code recorded during the study period is likely to be more accurate due to diagnostic practices.
Individuals will stay in the SMI subgroup of their most recent diagnosis (index episode). Any other SMI recorded before the index episode will not be included in the analysis (ensuring that individuals appear only once in the study).

Objective 2 - Describe the characteristics of individuals whose severe mental illness outcomes are recorded in both primary and secondary care, or in primary or secondary care alone.

We will describe the characteristics of individuals whose severe mental illness outcomes are recorded in both primary and secondary care, or in primary or secondary care alone. We will use the variables listed under the 'exposures' to describe these individuals.

Objective 3 – To estimate the association between individual characteristics and severe mental illness outcome recording in both primary and secondary mental health care records.

If there is sufficient statistical power, we will use univariable logistic regression (with robust standard errors to account for clustering by GP practice) to estimate odds ratios for the association between each of the exposures (i.e., characteristics that may differ between people with and without a primary care record of their severe mental illness, see exposures, outcomes and covariates section) and recording of severe mental illness outcomes in both primary and secondary mental health care records. Univariable regression analyses will be followed by sequential models adjusting for the other exposure variables. In sequential models, we will: 1) initially adjust for age and sex; 2) adjust for exposure variables without missing data or collinearity between the variables; and 3) adjust for the remaining exposure variables with missing data (i.e., ethnicity or smoking status) or collinearity between variables. This will allow us to identify which of the variables are associated with the recording of severe mental illness outcomes in both primary and secondary care records.

Objective 4 – Describe whether specific severe mental illness outcomes are more likely to recorded in both primary and secondary mental health care records by stratifying results based on specific SMI diagnoses: schizophrenia, bipolar disorder, and other severe mental illness diagnoses.

Individuals will be classified according to the subgroup of their most recent SMI diagnosis. For each SMI diagnosis subgroup (schizophrenia, bipolar disorder, and other psychoses), we will identify the number of individuals whose outcomes are recorded in both primary and secondary

care. This will allow us to see if there is a difference in the recording between specific severe mental illness outcomes (i.e., schizophrenia and bipolar disorder) or less specific severe mental illness outcomes (i.e., other psychoses).

Sensitivity analyses
We will repeat our main analyses by:
1) We will use alternative code lists (containing less sensitive symptom codes and history of codes) to identify severe mental illness outcomes.
2) We will use records of smoking status identified either before or after the date of the most recent severe mental illness diagnosis to describe the characteristics of individuals whose severe mental illness is recorded in both primary and secondary mental health care, or in primary or secondary mental health care alone.

Secondary analyses
1) We will assess severe mental illness recording in primary care and secondary mental health care by stratifying our results based on the different calendar periods covered by the two MHDS formats. Format 1 covers April 2007 – March 2011, while format 2 covers April 2011 – November

2015.
2) For individuals whose severe mental illness was recorded first in secondary mental health care, we will look at the timing delay between secondary care diagnosis and primary care coding.

Plan for addressing confounding

Our study is mainly exploratory, and we will not interpret our findings causally, therefore confounding is less of an issue. However, we will assume that all individual characteristic variables (that may explain complete SMI recording) are possible confounders between the other exposure variables and the outcome of complete recording in CPRD and MHDS. In our logistic regression analyses, we will adjust each exposure variable by other exposure variables in sequential models as described in the data/statistical analysis section.

Plans for addressing missing data

While it is likely that there will be more complete ethnicity and smoking data in people with an SMI diagnosis due incentivisation of physical health checks for people with SMI by the QOF, some individuals may not have these variables recorded in our study. Records for ethnicity have become more complete following the introduction of renumeration for recording ethnicity in the QOF in 2006, but there may still be a proportion of the study population without this information. It is likely that the amount of missing data is not substantial relative to the sample size of the study. We will describe the proportion of people with and without primary care severe mental illness diagnoses with missing ethnicity or smoking data. During logistic regression analyses, we will adjust for ethnicity and smoking status in a separate model. If missing ethnicity or smoking data is greater than 30%, we will conduct a quantitative bias analysis to assess the effect that the missing data will have on our results.

Patient or user group involvement

As this is a largely a study that will inform future research, we have not included patients in our study design. However, if our results reveal findings that are likely to be interesting to individuals with SMI, or their carers, we will discuss our findings with a patient and public involvement group.

Plans for disseminating & communicating

We will publish the study finding in peer-reviewed journals and present at relevant academic conferences.

Conflict of interest statement

None

Limitations of study design

Recording of mental illness diagnoses is not mandatory in the MHDS dataset. Therefore, it is likely that the number of people with severe mental illness recorded in the MHDS dataset will be low and will underestimate the number of people with severe mental illness seen in specialist secondary mental healthcare during the study period. It is also possible that there will be individuals with severe mental illness recorded in primary care, but not in MHDS. We will identify the number of these individuals and describe their characteristics to understand the usefulness of the MHDS dataset to capture severe mental illness outcomes in future studies.

It is likely that the number of people whose SMI outcomes are recorded in secondary mental healthcare records alone will be low as SMI recording has been incentivised by the Quality and Outcomes Framework since 2004 (GPs receive remuneration for maintaining an SMI register).(19) It is unclear to what degree incentivisation has improved primary care SMI recording, and we will be unable to assess this in our study because we will not have access to data before 2004 (our study period is April 2007 to November 2015).

Some individuals with severe mental illness may not be candid about their lifestyle behaviours (i.e., smoking status, drug misuse, harmful alcohol use), meaning the accuracy of these measures may not be reliable.

This study aims to look at the severe mental illness recording between April 2007 and November 2015. Severe mental illness recording in primary and secondary care during this period may not be representative of SMI recording as a whole.

The MHDS dataset is provided in two different formats covering two different calendar periods (due to structural changes in the way data was collected over different time periods). We will therefore conduct a secondary analysis to explore recording separately for the two formats.

Using the MHDS dataset linked to the CPRD means that we may possibly miss individuals treated in secondary care that are not registered with a GP practice. These individuals may potentially live chaotic lives due to their mental illness and only go to secondary care mental health services to receive treatment, or they may be long-term residents in secondary mental health care settings.(20) These individuals may still be receiving holistic care, however, they will not be included in our study, so our results must be interpreted with this in mind.

Data on drug misuse is likely to be poorly recorded in the CPRD dataset, however, we will still be able to describe whether individuals with recorded drug misuse are more or less likely to have their severe mental illness diagnoses recorded in both primary and secondary mental health care records.

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Appendices

drug_misuse.txt

icd10codes-smi.txt

readcodes-smi.txt

Grant ID

Appendix 4: Supplementary material of population-based cohort studies investigating associations between atopic eczema or psoriasis and incident severe mental illness among adults

Appendix S1: Explanation of matching without replacement in calendar date order

Appendix S2: Directed acyclic graphs (DAGs) of the implicitly assumed causal relationships between atopic eczema/psoriasis and severe mental illness, and explanation of the variables included in the DAGs.

Appendix S3: Variable definitions

Appendix S4: Testing the proportional hazards assumption using Schoenfeld residual plots

Appendix S5: Secondary analyses

References

Table S1: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses

Table S2: Person-time under follow-up in atopic eczema and psoriasis cohorts broken down by individual-level characteristics and atopic eczema or psoriasis exposure status.

Table S3: Characteristics of the atopic eczema study population at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status.

Table S4: Characteristics of the psoriasis study population at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status.

Table S5: Absolute incidence rates and rate differences of severe mental illness in atopic eczema and psoriasis cohorts

Table S6: HRs (95% CI) for the association between atopic eczema or psoriasis severity and severe mental illness.

Table S7: Adjusted hazard ratios (95% CIs) for the association between atopic eczema or psoriasis and severe mental illness, stratified by sex, age, and calendar period (adjusted for calendar period and Carstairs deprivation).

Table S8: Effects of individual mediators on the associations between atopic eczema or psoriasis and severe mental illness

Table S9: Characteristics of the psoriasis study population at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status.

Appendix S1 – Explanation of matching without replacement in calendar date order

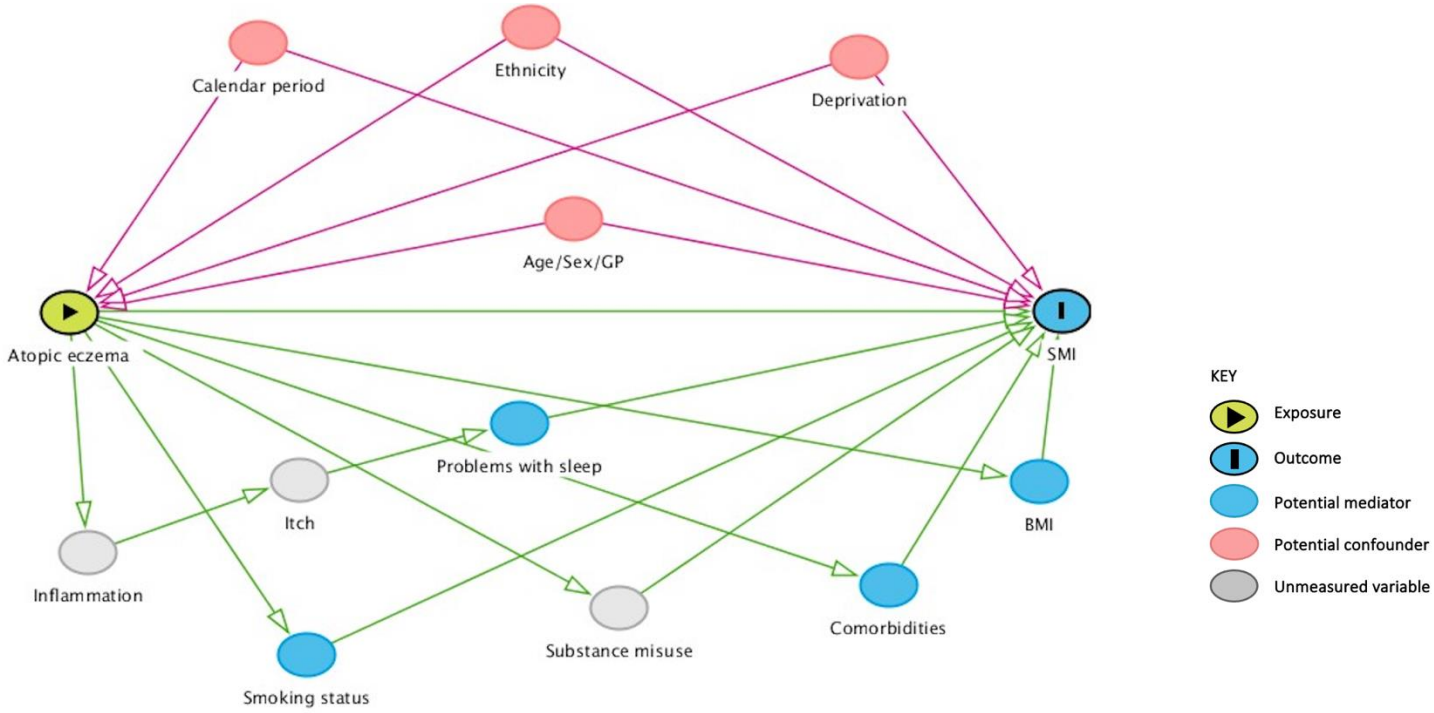
In this study, we matched adults with atopic eczema or psoriasis (on age, sex, and general practice) with up to five adults without atopic eczema or psoriasis without replacement and in calendar date order.

Matching without replacement means that each of the up to five adults without atopic eczema or psoriasis were matched to only one adult with atopic eczema or psoriasis. This contrasts to matching with replacement, where the matched comparators (i.e., those without atopic eczema or psoriasis) could be matched to multiple individuals with atopic eczema or psoriasis. Matching with replacement allows sample size to be maximised as fewer exposed people (those with atopic eczema or psoriasis) are excluded because of lack of comparators and a high matching ratio can be ensured. However, as we had a large pool of eligible comparators (and were consequently not limited by sample size considerations, and able to preserve our matching ratio), we were not limited to matching with replacement. We chose to match without replacement as matching with replacement can result in substantial reuse of comparators meaning that standard errors become too optimistic and confidence intervals artificially narrow.

By ‘matching in calendar date order’ we mean that unexposed individuals (those without atopic eczema or psoriasis) in the matched cohort were assigned first to exposed individuals with the earliest cohort entry. Matching in calendar date order avoids some time-related bias.

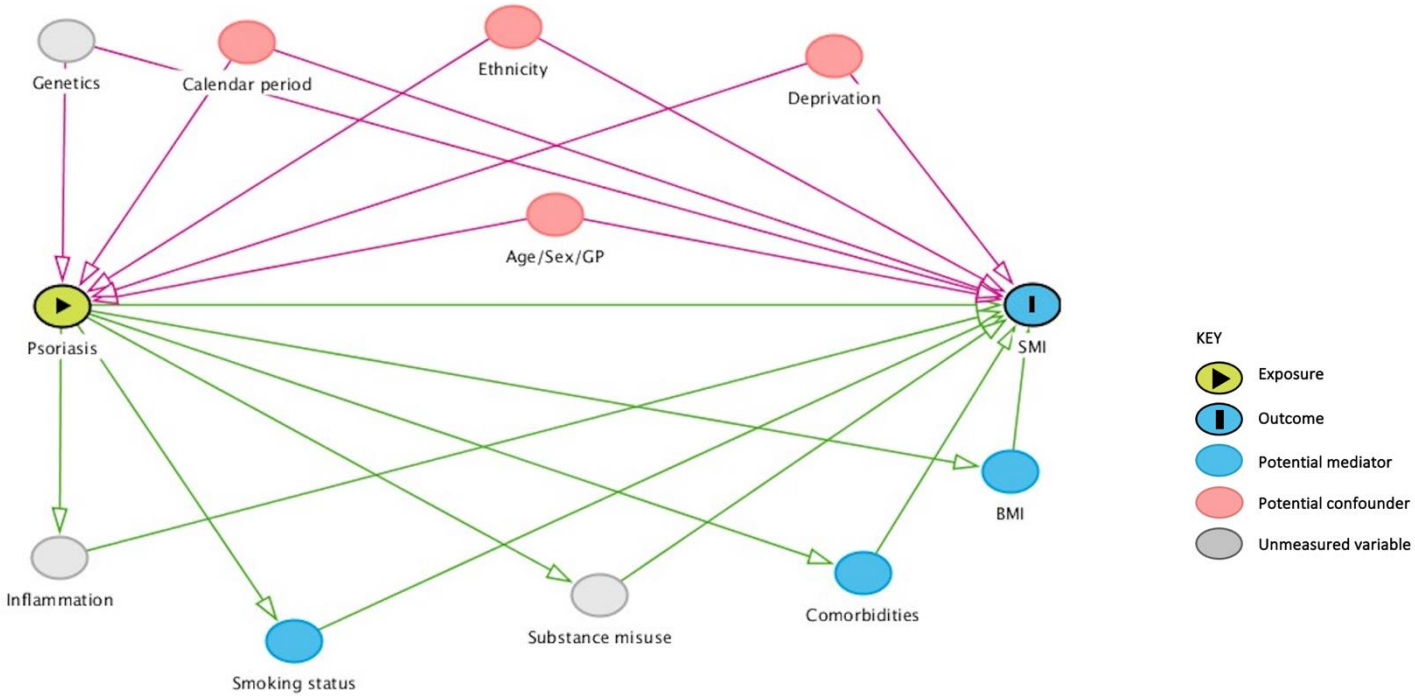
Appendix S2 – Directed acyclic graphs (DAGs) of the implicitly assumed causal relationships between atopic eczema/psoriasis and severe mental illness, and explanation of the variables included in the DAGs

Simplified directed acyclic graph of the implicitly assumed causal relationship between atopic eczema and severe mental illness, true relationships between variables are likely to be more complex



Abbreviations – BMI: Body mass index; GP: General practice; SMI: Severe mental illness

Simplified directed acyclic graph of the implicitly assumed causal relationship between psoriasis and severe mental illness, true relationships between variables are likely to be more complex



Abbreviations – BMI: Body mass index; GP: General practice; SMI: Severe mental illness

Explanation of variables included in directed acyclic graphs of the relationships between atopic eczema/psoriasis and severe mental illness

Variable(s)	Type	Measured/Unmeasured	Justification
Age/Sex/General practice	Confounder (matching variables)	Measured	There is evidence that atopic eczema is more prevalent in younger people and in women,[1] while the prevalence of psoriasis is higher in males and older individuals.[2,3] Age and sex are also associated with SMI. The literature suggests that SMI, particularly schizophrenia, tends to occur between the ages of 15-35,[4] with a higher incidence in males.[5] As these variables were not on the causal pathway in the association between atopic eczema/psoriasis and SMI, they were considered as potential confounders and used to match individuals in the study. We also matched on general practice to control for clinical and administrative practices that may differ between general practitioners.
Body mass index (BMI)	Mediator	Measured	Evidence suggests that a high BMI is associated with atopic eczema and psoriasis. A population-based study in the UK using primary care data found that people with atopic eczema had 8% higher odds of being overweight or obese compared to those without atopic eczema.[6] A similar relationship is seen between psoriasis and BMI. A meta-analysis of 16 observational studies found that people with psoriasis had 66% higher odds of obesity compared to those without psoriasis.[7] A longitudinal study also found that the risk of new-onset obesity was 18% higher in individuals with psoriasis compared to those without.[8] Possible explanations for the association between skin disease and obesity may include people with skin disease avoiding physical exercise to prevent sweat agitating inflamed skin,[9] or the underlying systemic inflammation in the skin disease itself leading to weight gain.[6] Increased BMI is also associated with SMI. Studies have found a high prevalence of obesity in people with SMI, with these individuals being up to three times more likely to be overweight or obese than the general population.[10] However, studies investigating the direction of the relationship between BMI and SMI are limited. There is some evidence to suggest that high BMI may occur as a consequence of SMI. Studies have found that people with SMI diagnoses lead unhealthy lifestyles by consuming poor diets, smoking more and engaging in less physical activity than the general population,[11] all factors that contribute to obesity. Second generation antipsychotics such as Olanzapine and Clozapine have been found to result in rapid weight gain, with data suggesting an increase of up to 17kg in the first year of treatment.[12] On the other hand, genetics may play a role in the association between BMI and SMI. Genetic linkage studies have suggested that the 1q21–42 region is of interest as this area is associated with an increased risk of obesity and the development of schizophrenia.[10] However, this hypothesis is speculative and not supported by empirical evidence. What we can conclude is that the relationship between BMI and SMI is complex and includes a number of factors.

			In the context of this study, we considered BMI as a mediator of the relationship between atopic eczema/psoriasis and SMI. As there is some evidence that increased BMI may occur as a result of SMI diagnosis, we excluded BMI measurements taken after the SMI outcome. Including BMI measurements taken after SMI diagnosis may introduce collider bias in our analysis, attenuating our effect estimates towards the null.
Calendar period	Confounder	Measured	The relationship between atopic eczema/psoriasis and SMI may be influenced by various calendar-based factors such as changes in clinical and administrative practices in atopic eczema/psoriasis and SMI over time. Adjusting for calendar period as a confounder in our analysis will allow us to remove any possible calendar variation and effectively assess the true association between atopic eczema/psoriasis and SMI.
Comorbidities	Mediator	Measured	Skin diseases are associated with an increased risk of some chronic conditions. For example, individuals with atopic eczema are at increased risk of asthma[13] while people with psoriasis are at increased risk of psoriatic arthritis.[14] Both atopic eczema and psoriasis are also associated with an increased risk of diabetes and cardiovascular disease.[13,15,16] There is compelling evidence that people with SMI experience poorer physical health than the general population, leading to increased morbidity and mortality and a reduction in life expectancy by up to 20 years.[17] The prevalence of conditions such as cardiovascular disease, liver disease, respiratory disease and cancer is higher in people with SMI, however, the direction that the relationship occurs is not well established. In other words, it is unknown whether the presence of SMI leads to development of the health issues, or whether the conditions play a mediating role in the development of SMI. There is evidence for both theories. For example, conditions such as cardiovascular disease and diabetes that occur more in people diagnosed with SMI are associated with obesity and metabolic syndrome,[18] both of which are known effects of second-generation antipsychotic medication.[12] On the other hand, several studies have found evidence of shared genetic mechanisms between physical health conditions and SMI.[19,20] In terms of comorbidities mediating the association between skin disease and SMI, there is evidence that people with skin disease are more likely to smoke.[9,21] Smoking is a risk factor for cardiovascular disease and some respiratory disease,[22] and is also associated with an increased risk of psychosis.[23] What we can see from the evidence is that long term physical health conditions and severe mental illness often co-occur, and the direction of the relationship between both conditions is complex and difficult to understand. In the context of this study, we considered comorbidities as mediators of the association between skin disease and SMI. We used the Charlson Comorbidity Index (CCI) as a summary measure to capture the burden of comorbidities at index date.

Deprivation	Confounder	Measured	Evidence suggests that the prevalence of atopic eczema or psoriasis is higher in countries or individuals with higher socioeconomic status.[24,25] Low socioeconomic status is associated with an increased risk of severe mental health problems.[26] Therefore, in this study, we considered deprivation as a potential confounder of the association between atopic eczema/psoriasis and SMI.
Ethnicity (sensitivity analyses only)	Confounder	Measured	Atopic eczema has been found to occur more frequently in Asian and Black individuals compared to White individuals,[27] while psoriasis is more prevalent in White individuals.[28] There are also important ethnic differences in the visual appearance of skin disease, making it likely that skin disease is diagnosed differentially between those of different ethnicities.[27,28] There are also ethnic differences in the risk of SMI. In the UK, Black and minority ethnic groups (BME) have been shown to have higher rates of SMI, with the risk of psychosis in Black ethnic groups estimated to be nearly seven times higher than in the White population.[29] Due to its association with atopic eczema/psoriasis and SMI, we will consider ethnicity as a potential confounding variable in our analysis. However, ethnicity is not well recorded in the CPRD GOLD dataset prior to the introduction of renumeration for ethnicity recording by the Quality and Outcomes Framework in 2006.[30] Therefore, we considered ethnicity as a potential confounder in sensitivity analyses only, restricting cohort entry to adults registered from 2006 onwards.
Genetics (psoriasis and SMI only)	Confounder	Unmeasured	Studies have provided evidence for a shared genetic aetiology between schizophrenia and psoriasis,[31] and bipolar disorder and psoriasis[32] that may involve immune signalling pathways. This relationship is not on the causal pathway, suggesting that genetics are a potential confounder of the association between psoriasis and SMI, or that a shared genetic aetiology is the reason for any observed association. However, genetic information is not routinely recorded in primary care records, therefore this variable is unmeasured. A genetic association between atopic eczema and SMI has not been established.
Harmful alcohol use	Mediator	Measured	Evidence shows that individuals with atopic eczema or psoriasis consume more alcohol than the general population and subsequently have a higher prevalence of alcohol use disorders compared to populations without skin disease.[9,33,34] Harmful alcohol use is also linked to SMI. A high prevalence of heavy drinking and alcohol use disorders has been identified in people with SMI.[35] Chronic alcohol consumption (consuming large amounts of alcohol for an extended period of time) or alcohol withdrawal in a formerly dependent individual can induce hallucinations or delusions, both of which are symptoms of psychosis.[36] Due to this evidence, we considered harmful alcohol use as a potential mediator of the association between atopic eczema/psoriasis and SMI.

High dose oral glucocorticoids (atopic eczema and SMI only)	Mediator	Measured	High dose oral glucocorticoids (≥20mg/day prednisolone equivalent dose) are prescribed to individuals with moderate-to-severe atopic eczema.[37] During therapy, glucocorticoids can induce symptoms of hypomania, mania, and psychosis, however, their effect is temporary.[38] Because of this, we investigated the role of high dose oral glucocorticoids as potential mediators of the association between atopic eczema and SMI.
Inflammation	Mediator	Unmeasured	Evidence suggests that atopic eczema and psoriasis result in elevated levels of circulatory pro-inflammatory cytokines. Evidence also suggests that changes in inflammation play an important role in the brain and central nervous system that is associated with SMI.[39,40] Inflammation can therefore be considered a potential confounder of the relationship between atopic eczema/psoriasis and SMI. However, inflammation is not recorded in CPRD GOLD, so it is an unmeasured variable. However, in people with atopic eczema, inflammation can lead to itch and cause sleep problems in those affected.
Itch and sleep problems (atopic eczema and SMI only)	Mediator	Measured	Evidence suggests that itch is an important consequence of atopic eczema.[41] Frequent itching can affect sleep quality.[42] High levels of sleep deprivation have been linked to SMI like symptoms such as hallucinations and distorted perceptions.[43] Itch and sleep problems can therefore be considered as a potential mediator of the association between atopic eczema and SMI. However, itch is not recorded in CPRD GOLD, so it is an unmeasured variable. On the other hand, sleep problems and sleep quality can be captured in CPRD GOLD, although they are likely to be an underestimate of sleep problems.
Smoking status	Mediator	Measured	There is evidence that both atopic eczema and psoriasis are associated with smoking. Adults with atopic eczema are 28% more likely to be current smokers compared to the general population,[9] while the prevalence of ever smoking was higher in adults with psoriasis compared to the general population.[21] Smoking is also associated with SMI. People with severe mental illnesses such as schizophrenia are up to three times more likely to smoke, and to smoke heavily compared to the general population.[44] The reasons why individuals with SMI are more likely to smoke are unclear, however, results of meta-analysis from a large systematic review suggests that daily smokers are more than twice as likely to develop new psychotic disorders compared to non-smokers.[23] Daily smokers also developed psychotic illness a an earlier age than non-smokers.[23] In this study, we considered smoking status as a potential mediator of the relationship between atopic eczema/psoriasis and SMI.
Substance misuse	Mediator	Unmeasured	Evidence suggests that people with atopic eczema or psoriasis are more likely to misuse substances (e.g., cannabis),[45,46] and substance misuse is associated with an increased risk of SMI.[47] Substance misuse can therefore be considered a potential mediator of the association between atopic eczema/psoriasis and SMI. However, substance misuse is not well recorded in CPRD GOLD, so it has been classified as an unmeasured variable.

BMI – Body mass index; CPRD – Clinical Practice Research Datalink; SMI – Severe mental illness

Appendix S3 – Variable definitions

Atopic eczema and psoriasis

We identified atopic eczema and psoriasis using previously validated algorithms.[48,49] The atopic eczema algorithm was based on a record of at least one diagnostic code recorded in primary care and at least two records of eczema therapy recorded (in primary care using Read codes or prescription data) on separate days. Eczema therapy included: (1) records of phototherapy identified using Read codes in primary care and (2) primary care prescription records for topical emollients, corticosteroids or calcineurin inhibitors, or oral glucocorticoids, azathioprine, methotrexate, ciclosporin or mycophenolate. The psoriasis algorithm was based on a record of at least one diagnostic code recorded in primary care.

Severe mental illness

We identified severe mental illness based on the earliest record of a diagnostic Read code for severe mental illness (schizophrenia, bipolar disorder, other non-organic psychoses) recorded in primary care. We considered broader definitions of the severe mental illness outcome (including 'symptom' codes such as delusions) that are not exclusive to the condition in sensitivity analyses.

General practice

We matched on general practice as an indirect method to capture and adjust for general practice location (i.e., rural, or urban locations) and socioeconomic deprivation. Matching individuals on general practice also allowed us to account for differences in coding practices between GPs.

Calendar period

Calendar period was categorised as 1997 – 2003, 2004 – 2009, 2010 – 2015, and 2016 – 2020 to account for changes in clinical, diagnostic, and administrative practices over the study period that may have influenced the measurement of exposure, outcomes, and other covariates.

Comorbidities

We used the Charlson Comorbidity Index (CCI) as a summary measure to capture the burden of comorbidities recorded on or before index date. The CCI is a method of categorising comorbidities of individuals that assigns weights to each of the 17 conditions included in the index, and then sums the weights of those conditions present in the individual.[50,51] Each condition in the CCI is weighted from one to six, with a weight of six representing the most severe morbidity.[50] The sum of the weights in each individual results in a single comorbidity summary score. We categorised CCI scores into 3 groups: low (0 points), intermediate (1-2 points), and high (≥3 points).

Deprivation

We used the Carstairs Index (CI) as a proxy for socioeconomic deprivation. The Carstairs Index was measured using quintiles of the individual-level Carstairs scores from 2011 census data linked via the individual postal code. Patient level Carstairs data was only available for people in English practices that consented to participate in the linkage scheme. When individual-level data was unavailable, we used practice-level Carstairs data.

Ethnicity

We identified ethnicity using a previously validated algorithm that identifies ethnicity using primary care electronic health records.[30] The algorithm classifies ethnicity into five categories – White, South Asian, Black, Other or Mixed – and is suggested for use with the CPRD dataset from 2006 onwards to maximise completeness and comparability of data.

Harmful alcohol use

We defined harmful alcohol use based on primary care morbidity codes suggesting harmful or heavy alcohol use (including alcohol dependency codes and codes related to physical/psychological harm related to alcohol use) or a prescription for drugs used to maintain abstinence (acamprosate, disulfiram, or nalmefene). Individuals were defined as harmful alcohol users on the date of the first record of a relevant morbidity code or prescription.

High-dose oral glucocorticoid use

We identified prescriptions for oral glucocorticoids (prednisolone, betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone, and cortisone) and converted the prescribed daily dose to the prednisolone-equivalent dose (PED). High-dose oral glucocorticoid use was defined as a dose of 20 mg/day or higher PED. We captured high-dose oral glucocorticoid use as a binary time-updated variable with status changing for a short period (90 days) on the date of the first record of a prescription for a dose of 20mg/day or more PED.

Sleep problems

We identified sleep problems based on primary care morbidity codes suggesting sleep problems and prescriptions for drugs used to manage sleep problems. In our main analysis, this included diagnostic Read codes (for insomnia, sleep disorders, poor sleep pattern, or other sleep disturbances) and prescriptions for drugs that are only used to treat sleep problems (zaleplon, zolpidem tartrate, zopiclone, hydroxyzine hydrochloride and promethazine hydrochloride when taken at night). In our sensitivity analysis, we used alternative code lists including prescriptions for drugs that may be prescribed for sleep problems but can also be prescribed for other conditions (melatonin and benzodiazepines).

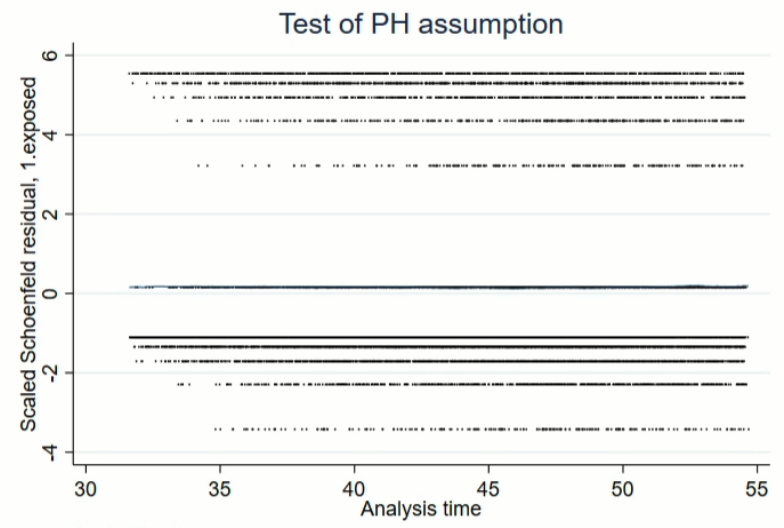
Smoking status and body mass index (BMI)

We defined BMI and smoking status using an algorithm using primary care records to identify the status recorded closest to the cohort entry date. The algorithm regarded records identified within -1 year to +1 month of the index date as the best, +1 month to +1 year from the index date as second best, the nearest before -1 year from the index date as the third best, and the nearest after +1 year from the index date as the worst. We did not include smoking status or BMI recorded after the outcome had occurred. Smoking status was classified as: (1) current/ex-smoker; or (2) non-smoker. BMI was classified according to the World Health Organisation categories: underweight (<18.5kg/m2); normal weight (18.5-24.9 kg/m2); pre-obesity (25.0-29.9 kg/m2); obese (≥30.0 kg/m2). Smoking status or BMI recorded after SMI diagnosis were not used

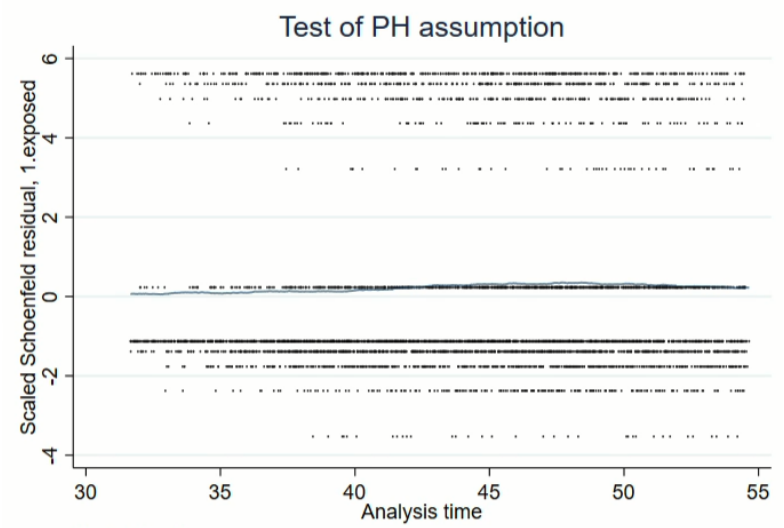
Appendix S4 – Testing proportional hazards assumption using Schoenfeld residual plots

We tested the proportional hazards assumption of our confounder-adjusted Cox regression models (adjusted for socioeconomic deprivation and calendar period) using Schoenfeld residual plots. In the confounder-adjusted models in the atopic eczema and psoriasis cohorts, there was no evidence that the proportional hazards assumption was violated.

Confounder-adjusted model in the atopic eczema cohort: p=0.9998



Confounder-adjusted model in the psoriasis cohort: p=0.2514



Appendix S5 – Secondary analyses

In secondary analyses, we investigated whether the association between atopic eczema or psoriasis and severe mental illness was: (1) affected by atopic eczema or psoriasis severity; and (2) modified by age, sex, or calendar period. We also individually tested the effects of potential mediators on the confounder-adjusted associations between atopic eczema or psoriasis and severe mental illness in separate models in a post-hoc analysis.

Atopic eczema and psoriasis severity definitions

In analyses examining atopic eczema or psoriasis severity, we classified individuals with atopic eczema as having mild, moderate, or severe disease, and individuals with psoriasis as having mild or moderate-to-severe disease using previously developed definitions.[52,53] We considered individuals to have mild disease by default. We classified individuals as having moderate atopic eczema from the first of: (1) a second potent topical corticosteroid prescription within one year; or (2) a first prescription for a topical calcineurin inhibitor. We classified adults as having severe atopic eczema from the first of: (1) use of phototherapy or systemic treatment for atopic eczema (excluding systemic glucocorticoids, as they may have been prescribed for coexisting asthma); or (2) referral to a dermatologist. We classified adults as having moderate-to-severe psoriasis if they had any records of phototherapy or prescription records for systemic (acitretin, etretinate, ciclosporin, hydroxycarbamide, methotrexate, and fumaric acid) or biologic (etanercept, adalimumab, infliximab, ustekinumab, and efalizumab) therapies. We updated severity over time, and once an individual was defined as having severe atopic eczema or moderate-to-severe psoriasis, they remained in this category for the rest of follow-up and could not be categorised as having milder disease.

Statistical analysis

Atopic eczema and psoriasis severity

We redefined atopic eczema or psoriasis exposure using atopic eczema or psoriasis severity. Using the same methods as the main analyses, we constructed stratified Cox regression models implicitly adjusted for matching variables (age, sex, general practice) and then sequentially adjusted for potential confounders (deprivation and calendar period) and potential mediators (comorbidities, harmful alcohol use, smoking status, and body mass index, and, in atopic eczema only, sleep problems and high-dose glucocorticoid use).

Effect modification by age, sex, or calendar period

We tested effect modification by constructing stratified Cox regression models with and without an interaction term between the exposure variable (atopic eczema or psoriasis) and the potential effect modifier (age, sex, or calendar period) and conducting likelihood ratio tests.

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Table S1: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses

Description	Justification	Atopic eczema cohort				Psoriasis cohort			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
Main analysis		**988,961**	**6,686,453**	**3,012**	**1.17 (1.12, 1.22)**	**346,659**	**2,523,477**	**1,107**	**1.26 (1.18, 1.35)**
Repeating the main analysis using broader definitions of severe mental illness (main analysis code list includes definite diagnostic codes only, sensitivity analysis code list expanded to include symptom codes).	To explore the sensitivity of the results due to the definition of the severe mental illness outcome.	988,558	6,683,082	3,382	1.17 (1.12, 1.22)	225,751	1,863,129	876	1.23 (1.13, 1.33)
Additionally adjusting for ethnicity (White, South Asian, Black, Other, or Mixed, identified from CPRD) in the main analysis	To examine whether the omission of ethnicity as a covariate in the main analysis induced bias.	398,892	2,613,527	1,134	1.09 (1.01, 1.17)	141,363	987,918	425	1.17 (1.04, 1.32)
Restricting cohort entry to a subset of individuals registered from 2006 onwards and additionally adjusting for ethnicity (White, South Asian, Black, Other, or Mixed, identified from CPRD) in the main analysis.	Records for ethnicity became more complete following the introduction of renumeration for including ethnicity data in the Quality and Outcomes Framework in 2006.	302,479	1,300,586	656	1.09 (1.00, 1.20)	101,145	424,831	221	1.23 (1.04, 1.45)

Description	Justification	Atopic eczema cohort				Psoriasis cohort			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
Restricting cohort entry to individuals with at least one consultation with their GP in the year before cohort entry.	To exclude individuals who are practice non-attenders. There may be differential recording of exposure, covariates and outcomes among practice attenders and non-attenders. For example, practice non-attenders may be more likely to have missing smoking or BMI data.	713,400	4,903,938	2,344	1.09 (1.04, 1.15)	294,096	2,118,249	956	1.15 (1.06, 1.24)
Restricting cohort entry to individuals entering from 2004 onwards.	To account for changes in diagnostic and coding practices over time – specifically those introduced by the Quality and Outcomes Framework in 2004. This is likely to be more important for severe mental illness outcomes and some covariates. However, as there are no specific dermatology indicators in the Quality and Outcomes Framework, it is unlikely that eczema/psoriasis coding was affected.	672,037	3,379,069	1,586	1.15 (1.08, 1.22)	214,940	1,080,332	551	1.41 (1.28, 1.56)
Main analysis adjusted for potential mediators		793,030	5,789,012	2,632	0.98 (0.93, 1.04)	n/a	n/a	n/a	n/a
Repeating the main analysis using less strict definitions for	To explore whether including broader drugs that are prescribed for	793,030	5,789,012	2,632	0.99 (0.93, 1.04)	n/a	n/a	n/a	n/a

Description	Justification	Atopic eczema cohort				Psoriasis cohort			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
sleep problems (main analysis code list includes Zolpidem and Zopiclone which are only prescribed for sleep problems, sensitivity analysis code list expanded to include prescriptions for benzodiazepines, melatonin, and other drugs).	conditions other than sleep disturbances further mediates the association between atopic eczema and severe mental illness.								

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

Table S2: Person-time under follow-up in atopic eczema and psoriasis cohorts broken down by individual-level characteristics and atopic eczema or psoriasis exposure status. Values are person-years-at-risk (percentages) unless stated otherwise

	Atopic eczema cohort		Psoriasis cohort	
	With atopic eczema	**Without atopic eczema**	**With psoriasis**	**Without psoriasis**
Total person-years	6,995,892	30,935,170	2,680,394	13,246,255
Median (IQR) duration of follow-up (years) [a]	5.5 (2.2-10.4)	4.8 (1.8-9.6)	5.9 (2.3-11.5)	5.9 (2.4-11.4)
Sex				
Female (%)	4,142,744 (59.2%)	17,896,266 (57.9%)	1,389,969 (51.9%)	6,882,671 (52.0%)
Age (years)				
18-29	1,821,306 (26.0%)	7,906,322 (25.6%)	480,020 (17.9%)	2,376,484 (17.9%)
30-39	1,194,264 (17.1%)	5,357,387 (17.3%)	533,158 (19.9%)	2,607,097 (19.7%)
40-59	2,133,928 (30.5%)	9,668,584 (31.3%)	1,007,482 (37.6%)	4,980,894 (37.6%)
60+	1,846,393 (26.4%)	8,002,878 (25.9%)	659,734 (24.6%)	3,281,779 (24.8%)
Quintiles of Carstairs deprivation index [b]				
1(least deprived)	883,375 (12.6%)	3,886,119 (12.6%)	320,447 (12.0%)	1,589,287 (12.0%)
2	1,339,495 (19.1%)	5,927,456 (19.2%)	477,698 (17.8%)	2,375,948 (17.9%)
3	1,406,243 (20.1%)	6,250,620 (20.2%)	555,215 (20.7%)	2,753,249 (20.8%)
4	1,667,207 (23.8%)	7,397,501 (23.9%)	639,720 (23.9%)	3,162,484 (23.9%)
5(most deprived)	1,390,133 (19.9%)	6,103,569 (19.7%)	530,397 (19.8%)	2,610,341 (19.7%)
Missing	309,438 (4.4%)	1,369,906 (4.4%)	156,916 (5.9%)	754,946 (5.7%)

Body mass index (kg/m^2) [c]				
Underweight (<18.5)	158,610 (2.3%)	677,371 (2.2%)	44,123 (1.6%)	243,402 (1.8%)
Normal (18.5-24.9)	2,669,225 (38.2%)	11,172,418 (36.1%)	916,940 (34.2%)	4,716,013 (35.6%)
Overweight (25-29.9)	2,062,211 (29.5%)	8,599,887 (27.8%)	853,808 (31.9%)	3,991,258 (30.1%)
Obese (30+)	1,293,157 (18.5%)	5,181,420 (16.7%)	579,219 (21.6%)	2,370,550 (17.9%)
Missing	812,690 (11.6%)	5,304,074 (17.1%)	286,304 (10.7%)	1,925,031 (14.5%)
Smoking [c]				
Non-smoker	3,800,397 (54.3%)	16,306,983 (52.7%)	1,187,908 (44.3%)	6,845,726 (51.7%)
Current or ex-smoker	3,063,083 (43.8%)	12,773,438 (41.3%)	1,435,864 (53.6%)	5,750,191 (43.4%)
Missing	132,412 (1.9%)	1,854,750 (6.0%)	56,622 (2.1%)	650,338 (4.9%)
Harmful alcohol use (%) [c]	565,890 (8.1%)	2,175,554 (7.0%)	209,626 (7.8%)	824,001 (6.2%)
Sleep problems (%) [c]	2,176,362 (31.1%)	6,583,496 (21.3%)	n/a	n/a
Ethnicity				
White	2,678,104 (38.3%)	11,206,208 (36.2%)	1,082,735 (40.4%)	4,647,093 (35.1%)
South Asian	133,986 (1.9%)	408,814 (1.3%)	24,294 (0.9%)	122,941 (0.9%)
Black	53,792 (0.8%)	217,837 (0.7%)	5,246 (0.2%)	62,052 (0.5%)
Other	39,107 (0.6%)	162,749 (0.5%)	9,062 (0.3%)	54,187 (0.4%)
Mixed	18,108 (0.3%)	69,767 (0.2%)	3,665 (0.1%)	19,613 (0.1%)
Not stated or missing	4,072,794 (58.2%)	18,869,795 (61.0%)	1,555,391 (58.0%)	8,340,370 (63.0%)
Charlson comorbidity index [c]				

Low (0)	4,557,168 (65.1%)	23527501 (76.1%)	1,960,454 (73.1%)	10,023,005 (75.7%)
Moderate (1-2)	2,215,747 (31.7%)	6,555,345 (21.2%)	640,230 (23.9%)	2,879,902 (21.7%)
Severe (3 or more)	222,976 (3.2%)	852,325 (2.8%)	79,711 (3.0%)	343,348 (2.6%)
Calendar period				
1997-2003	1,161,675 (16.6%)	5,411,017 (17.5%)	472,670 (17.6%)	2,308,729 (17.4%)
2004-2009	2,087,878 (29.8%)	9,259,211 (29.9%)	836,276 (31.2%)	4,083,446 (30.8%)
2010-2015	2,587,796 (37.0%)	11,213,477 (36.2%)	942,558 (35.2%)	4,681,819 (35.3%)
2016-2020	1,158,542 (16.6%)	5,051,465 (16.3%)	428,889 (16.0%)	2,172,262 (16.4%)
High-dose oral glucocorticoids (20mg+ prednisolone equivalent dose)	695,906 (9.9%)	2,567,956 (8.3%)	n/a	n/a

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both eczema or psoriasis exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or severe mental illness diagnosis
[b] Carstairs deprivation index based on practice-level data (from 2011).
[c] Based on records closest to index date.

Table S3: Characteristics of the atopic eczema study population at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
Number	1,023,232	4,908,059	988,961	4,744,478	34,271	163,581	793,030	3,117,531	174,188	1,111,873	46,553	467,794
Follow-up [a]												
Total person-years	6,995,892	30,935,170	6,686,453	29,565,265	309,438	1,369,906	5,789,012	21,282,283	812,690	5,304,074	132,412	1,854,750
Median (IQR) duration of follow-up (years)	5.5 (2.2-10.4)	4.8 (1.8-9.6)	5.4 (2.2-10.3)	4.8 (1.8-9.5)	8.0 (3.4-13.9)	7.1 (2.9-13.0)	6.1 (2.6-11.0)	5.5 (2.2-10.4)	3.3 (1.3-6.8)	3.3 (1.2-7.1)	1.8 (0.7-3.9)	2.5 (1.0-5.6)
Sex												
Female (%)	596,388 (58.3%)	2,842,125 (57.9%)	576,743 (58.3%)	2,749,167 (57.9%)	19,645 (57.3%)	92,958 (56.8%)	492,472 (62.1%)	1,980,741 (63.5%)	73,146 (42.0%)	489,237 (44.0%)	20,518 (44.1%)	212,283 (45.4%)
Age (years) [b]												
18-29	326,309 (31.9%)	1,566,148 (31.9%)	313,707 (31.7%)	1,506,029 (31.7%)	12,602 (36.8%)	60,119 (36.8%)	190,200 (24.0%)	643,243 (20.6%)	112,854 (64.8%)	624,017 (56.1%)	29,104 (62.5%)	241,219 (51.6%)
30-39	159,606 (15.6%)	796,251 (16.2%)	154,316 (15.6%)	769,784 (16.2%)	5,290 (15.4%)	26,467 (16.2%)	134,412 (16.9%)	546,806 (17.5%)	17,030 (9.8%)	141,294 (12.7%)	4,870 (10.5%)	69,052 (14.8%)
40-59	261,153 (25.5%)	1,274,882 (26.0%)	252,675 (25.5%)	1,234,046 (26.0%)	8,478 (24.7%)	40,836 (25.0%)	231,693 (29.2%)	977,432 (31.4%)	18,475 (10.6%)	164,788 (14.8%)	4,385 (9.4%)	74,294 (15.9%)
60+	276,164 (27.0%)	1,270,778 (25.9%)	268,263 (27.1%)	1,234,619 (26.0%)	7,901 (23.1%)	36,159 (22.1%)	236,725 (29.9%)	950,050 (30.5%)	25,829 (14.8%)	181,774 (16.3%)	8,194 (17.6%)	83,229 (17.8%)
Quintiles of Carstairs deprivation index [c]												
1 (least deprived)	128,266 (12.5%)	612,978 (12.5%)	128,266 (13.0%)	612,978 (12.9%)	n/a	n/a	102,526 (12.9%)	398,132 (12.8%)	22,230 (12.8%)	145,675 (13.1%)	5,603 (12.0%)	61,009 (13.0%)
2	202,153 (19.8%)	969,896 (19.8%)	202,153 (20.4%)	969,896 (20.4%)	n/a	n/a	161,206 (20.3%)	635,201 (20.4%)	35,344 (20.3%)	219,724 (19.8%)	9,738 (20.9%)	93,899 (20.1%)
3	211,882 (20.7%)	1,021,847 (20.8%)	211,882 (21.4%)	1,021,847 (21.5%)	n/a	n/a	170,160 (21.5%)	674,894 (21.6%)	36,022 (20.7%)	228,723 (20.6%)	9,693 (20.8%)	94,576 (20.2%)
4	247,290 (24.2%)	1,185,082 (24.1%)	247,290 (25.0%)	1,185,082 (25.0%)	n/a	n/a	199,480 (25.2%)	787,666 (25.3%)	41,258 (23.7%)	261,566 (23.5%)	11,278 (24.2%)	110,275 (23.6%)
5 (most deprived)	199,370 (19.5%)	954,675 (19.5%)	199,370 (20.2%)	954,675 (20.1%)	n/a	n/a	159,658 (20.1%)	621,638 (19.9%)	34,268 (19.7%)	222,369 (20.0%)	9,358 (20.1%)	95,731 (20.5%)
Missing	34,271 (3.3%)	163,581 (3.3%)	n/a	n/a	n/a	n/a	n/a	n/a	5,066 (2.9%)	33,816 (3.0%)	883 (1.9%)	12,304 (2.6%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
Body mass index (kg/m2) [d]												
Underweight (<18.5)	25,486 (2.5%)	122,658 (2.5%)	24,560 (2.5%)	118,484 (2.5%)	926 (2.7%)	4,174 (2.6%)	22,842 (2.9%)	89,668 (2.9%)	n/a	n/a	802 (1.7%)	5,834 (1.2%)
Normal (18.5-24.9)	368,313 (36.0%)	1,680,277 (34.2%)	355,350 (35.9%)	1,622,355 (34.2%)	12,963 (37.8%)	57,922 (35.4%)	341,639 (43.1%)	1,346,622 (43.2%)	n/a	n/a	7,290 (15.7%)	52,851 (11.3%)
Overweight (25-29.9)	274,062 (26.8%)	1,219,689 (24.9%)	264,786 (26.8%)	1,178,048 (24.8%)	9,276 (27.1%)	41,641 (25.5%)	257,644 (32.5%)	1,023,867 (32.8%)	n/a	n/a	3,570 (7.7%)	24,432 (5.2%)
Obese (30+)	181,183 (17.7%)	773,562 (15.8%)	175,143 (17.7%)	747,534 (15.8%)	6,040 (17.6%)	26,028 (15.9%)	170,905 (21.6%)	657,374 (21.1%)	n/a	n/a	1,855 (4.0%)	11,588 (2.5%)
Missing	174,188 (17.0%)	1,111,873 (22.7%)	169,122 (17.1%)	1,078,057 (22.7%)	5,066 (14.8%)	33,816 (20.7%)	n/a	n/a	n/a	n/a	33,036 (71.0%)	373,089 (79.8%)
Smoking status[d]												
Non-smoker	529,881 (51.8%)	2,433,856 (49.6%)	511,040 (51.7%)	2,348,215 (49.5%)	18,841 (55.0%)	85,641 (52.4%)	414,960 (52.3%)	1,640,634 (52.6%)	90,716 (52.1%)	460,418 (41.4%)	n/a	n/a
Current or ex-smoker	446,798 (43.7%)	2,006,409 (40.9%)	432,251 (43.7%)	1,940,773 (40.9%)	14,547 (42.4%)	65,636 (40.1%)	378,070 (47.7%)	1,476,897 (47.4%)	50,436 (29.0%)	278,366 (25.0%)	n/a	n/a
Missing	46,553 (4.5%)	467,794 (9.5%)	45,670 (4.6%)	455,490 (9.6%)	883 (2.6%)	12,304 (7.5%)	n/a	n/a	33,036 (19.0%)	373,089 (33.6%)	n/a	n/a
Harmful alcohol use (%) [d]	73,353 (7.2%)	294,033 (6.0%)	70,678 (7.1%)	283,467 (6.0%)	2,675 (7.8%)	10,566 (6.5%)	64,307 (8.1%)	229,582 (7.4%)	5,508 (3.2%)	27,657 (2.5%)	882 (1.9%)	5,232 (1.1%)
Sleep problems (%) [d]	278,516 (27.2%)	877,318 (17.9%)	264,911 (26.8%)	831,318 (17.5%)	13,605 (39.7%)	46,000 (28.1%)	227,009 (28.6%)	631,574 (20.3%)	33,158 (19.0%)	113,444 (10.2%)	7,093 (15.2%)	28,343 (6.1%)
Ethnicity												
White	387,082 (37.8%)	1,783,293 (36.3%)	382,415 (38.7%)	1,757,101 (37.0%)	4,667 (13.6%)	26,192 (16.0%)	333,321 (42.0%)	1,330,439 (42.7%)	43,974 (25.2%)	254,056 (22.8%)	4,393 (9.4%)	38,767 (8.3%)
South Asian	25,119 (2.5%)	97,603 (2.0%)	25,062 (2.5%)	97,204 (2.0%)	57 (0.2%)	399 (0.2%)	21,805 (2.7%)	71,128 (2.3%)	2,922 (1.7%)	16,309 (1.5%)	343 (0.7%)	3,142 (0.7%)
Black	10,964 (1.1%)	54,725 (1.1%)	10,951 (1.1%)	54,564 (1.2%)	13 (0.0%)	161 (0.1%)	9,133 (1.2%)	39,237 (1.3%)	1,666 (1.0%)	9,895 (0.9%)	268 (0.6%)	2,237 (0.5%)
Other	7,797 (0.8%)	44,126 (0.9%)	7,690 (0.8%)	43,435 (0.9%)	107 (0.3%)	691 (0.4%)	6,606 (0.8%)	29,367 (0.9%)	1,006 (0.6%)	9,404 (0.8%)	115 (0.2%)	2,258 (0.5%)
Mixed	4,013 (0.4%)	18,864 (0.4%)	3,998 (0.4%)	18,739 (0.4%)	15 (0.0%)	125 (0.1%)	3,232 (0.4%)	12,290 (0.4%)	690 (0.4%)	4,163 (0.4%)	78 (0.2%)	804 (0.2%)
Not stated or missing	588,257 (57.5%)	2,909,448 (59.3%)	558,845 (56.5%)	2,773,435 (58.5%)	29,412 (85.8%)	136,013 (83.1%)	418,933 (52.8%)	1,635,070 (52.4%)	123,930 (71.1%)	818,046 (73.6%)	41,356 (88.8%)	420,586 (89.9%)
Charlson comorbidity index [d]												
Low (0)	636,704 (62.2%)	3,605,319 (73.5%)	614,489 (62.1%)	3,484,377 (73.4%)	22,215 (64.8%)	120,942 (73.9%)	486,457 (61.3%)	2,197,116 (70.5%)	115,578 (66.4%)	908,292 (81.7%)	33,569 (72.1%)	409,417 (87.5%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
Moderate (1-2)	340,946 (33.3%)	1,103,589 (22.5%)	330,211 (33.4%)	1,067,282 (22.5%)	10,735 (31.3%)	36,307 (22.2%)	268,063 (33.8%)	766,598 (24.6%)	53,849 (30.9%)	181,078 (16.3%)	11,552 (24.8%)	51,716 (11.1%)
Severe (3 or more)	45,582 (4.5%)	199,151 (4.1%)	44,261 (4.5%)	192,819 (4.1%)	1,321 (3.9%)	6,332 (3.9%)	38,510 (4.9%)	153,817 (4.9%)	4,761 (2.7%)	22,503 (2.0%)	1,432 (3.1%)	6,661 (1.4%)

Abbreviations: IQR – Interquartile range

Individuals can contribute data as both eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.

[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or severe mental illness diagnosis

[b] Age at index date

[c] Carstairs deprivation index based on practice-level data (from 2011).

[d] Based on records closest to index date.

Table S4: Characteristics of the psoriasis study population at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With psoriasis	Without psoriasis	With psoriasis	Without psoriasis	With psoriasis	Without psoriasis	With psoriasis	Without psoriasis	With psoriasis	Without psoriasis	With psoriasis	Without psoriasis
Number	363,210	1,801,875	346,659	1,719,842	16,551	82,033	286,396	1,179,789	54,077	344,186	16,943	146,512
Follow-up [a]												
Total person-years	2,680,394	13,246,255	2,523,477	12,491,309	156,916	754,946	2,218,106	9,176,327	286,304	1,925,031	56,622	650,338
Median (IQR) duration of follow-up (years)	5.9 (2.3-11.5)	5.9 (2.4-11.4)	5.8 (2.3-11.4)	5.8 (2.4-11.3)	8.6 (3.7-15.1)	8.2 (3.5-14.7)	6.4 (2.6-12.1)	6.5 (2.7-12.0)	3.6 (1.4-7.8)	4.1 (1.6-8.4)	2.2 (0.9-4.5)	3.0 (1.2-6.3)
Sex												
Female (%)	189,511 (52.2%)	940,489 (52.2%)	180,662 (52.1%)	896,606 (52.1%)	8,849 (53.5%)	43,883 (53.5%)	156,320 (54.6%)	671,945 (57.0%)	21,687 (40.1%)	131,202 (38.1%)	6,983 (41.2%)	55,516 (37.9%)
Age (years) [b]												
18-29	78,207 (21.5%)	389,718 (21.6%)	73,595 (21.2%)	366,735 (21.3%)	4,612 (27.9%)	22,983 (28.0%)	48,570 (17.0%)	171,588 (14.5%)	22,735 (42.0%)	140,011 (40.7%)	6,585 (38.9%)	52,013 (35.5%)
30-39	70,325 (19.4%)	349,056 (19.4%)	67,057 (19.3%)	332,830 (19.4%)	3,268 (19.7%)	16,226 (19.8%)	55,244 (19.3%)	220,466 (18.7%)	10,347 (19.1%)	68,175 (19.8%)	3,546 (20.9%)	31,992 (21.8%)
40-59	119,899 (33.0%)	593,805 (33.0%)	114,764 (33.1%)	568,432 (33.1%)	5,135 (31.0%)	25,373 (30.9%)	101,938 (35.6%)	435,073 (36.9%)	11,423 (21.1%)	79,002 (23.0%)	3,536 (20.9%)	36,022 (24.6%)
60+	94,779 (26.1%)	469,296 (26.0%)	91,243 (26.3%)	451,845 (26.3%)	3,536 (21.4%)	17,451 (21.3%)	80,644 (28.2%)	352,662 (29.9%)	9,572 (17.7%)	56,998 (16.6%)	3,276 (19.3%)	26,485 (18.1%)
Quintiles of Carstairs deprivation index [c]												
1 (least deprived)	43,233 (11.9%)	214,804 (11.9%)	43,233 (12.5%)	214,804 (12.5%)	n/a	n/a	35,515 (12.4%)	145,639 (12.3%)	6,720 (12.4%)	42,483 (12.3%)	2,012 (11.9%)	17,709 (12.1%)
2	68,391 (18.8%)	339,661 (18.9%)	68,391 (19.7%)	339,661 (19.7%)	n/a	n/a	56,581 (19.8%)	233,092 (19.8%)	10,095 (18.7%)	64,768 (18.8%)	3,244 (19.1%)	27,599 (18.8%)
3	76,487 (21.1%)	379,580 (21.1%)	76,487 (22.1%)	379,580 (22.1%)	n/a	n/a	63,150 (22.0%)	260,685 (22.1%)	11,544 (21.3%)	71,673 (20.8%)	3,692 (21.8%)	30,587 (20.9%)
4	88,207 (24.3%)	437,347 (24.3%)	88,207 (25.4%)	437,347 (25.4%)	n/a	n/a	73,043 (25.5%)	302,865 (25.7%)	13,160 (24.3%)	82,119 (23.9%)	4,154 (24.5%)	34,993 (23.9%)
5 (most deprived)	70,341 (19.4%)	348,450 (19.3%)	70,341 (20.3%)	348,450 (20.3%)	n/a	n/a	58,107 (20.3%)	237,508 (20.1%)	10,598 (19.6%)	69,546 (20.2%)	3,396 (20.0%)	30,318 (20.7%)
Missing	16,551 (4.6%)	82,033 (4.6%)	0 (0.0%)	0 (0.0%)	n/a	n/a	n/a	n/a	1,960 (3.6%)	13,597 (4.0%)	445 (2.6%)	5,306 (3.6%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With psoriasis	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**
Body mass index (kg/m2) [d]												
Underweight (<18.5)	6,767 (1.9%)	37,208 (2.1%)	6,432 (1.9%)	35,342 (2.1%)	335 (2.0%)	1,866 (2.3%)	6,078 (2.1%)	27,771 (2.4%)	n/a	n/a	248 (1.5%)	1,510 (1.0%)
Normal (18.5-24.9)	118,438 (32.6%)	610,457 (33.9%)	112,761 (32.5%)	581,614 (33.8%)	5,677 (34.3%)	28,843 (35.2%)	108,684 (37.9%)	484,831 (41.1%)	n/a	n/a	3,186 (18.8%)	16,466 (11.2%)
Overweight (25-29.9)	106,417 (29.3%)	497,192 (27.6%)	101,454 (29.3%)	473,882 (27.6%)	4,963 (30.0%)	23,310 (28.4%)	99,097 (34.6%)	407,332 (34.5%)	n/a	n/a	1,917 (11.3%)	8,644 (5.9%)
Obese (30+)	77,511 (21.3%)	312,832 (17.4%)	73,895 (21.3%)	298,415 (17.4%)	3,616 (21.8%)	14,417 (17.6%)	72,537 (25.3%)	259,855 (22.0%)	n/a	n/a	1,006 (5.9%)	3,829 (2.6%)
Missing	54,077 (14.9%)	344,186 (19.1%)	52,117 (15.0%)	330,589 (19.2%)	1,960 (11.8%)	13,597 (16.6%)	n/a	n/a	n/a	n/a	10,586 (62.5%)	116,063 (79.2%)
Smoking status[d]												
Non-smoker	149,937 (41.3%)	866,540 (48.1%)	142,505 (41.1%)	826,134 (48.0%)	7,432 (44.9%)	40,406 (49.3%)	121,192 (42.3%)	602,251 (51.0%)	21,254 (39.3%)	131,380 (38.2%)	n/a	n/a
Current or ex-smoker	196,330 (54.1%)	788,823 (43.8%)	187,656 (54.1%)	752,502 (43.8%)	8,674 (52.4%)	36,321 (44.3%)	165,204 (57.7%)	577,538 (49.0%)	22,237 (41.1%)	96,743 (28.1%)	n/a	n/a
Missing	16,943 (4.7%)	146,512 (8.1%)	16,498 (4.8%)	141,206 (8.2%)	445 (2.7%)	5,306 (6.5%)	n/a	n/a	10,586 (19.6%)	116,063 (33.7%)	n/a	n/a
Harmful alcohol use (%) [d]	22,822 (6.3%)	89,889 (5.0%)	21,655 (6.2%)	85,572 (5.0%)	1,167 (7.1%)	4,317 (5.3%)	19,881 (6.9%)	69,793 (5.9%)	1,632 (3.0%)	6,774 (2.0%)	276 (1.6%)	1,123 (0.8%)
Ethnicity												
White	150,087 (41.3%)	608,246 (33.8%)	147,209 (42.5%)	598,758 (34.8%)	2,878 (17.4%)	9,488 (11.6%)	130,767 (45.7%)	471,495 (40.0%)	15,558 (28.8%)	65,016 (18.9%)	1,369 (8.1%)	7,744 (5.3%)
South Asian	4,799 (1.3%)	24,687 (1.4%)	4,779 (1.4%)	24,582 (1.4%)	20 (0.1%)	105 (0.1%)	4,235 (1.5%)	18,851 (1.6%)	506 (0.9%)	3,220 (0.9%)	51 (0.3%)	565 (0.4%)
Black	1,071 (0.3%)	13,520 (0.8%)	1,065 (0.3%)	13,477 (0.8%)	6 (0.0%)	43 (0.1%)	919 (0.3%)	10,388 (0.9%)	131 (0.2%)	1,782 (0.5%)	20 (0.1%)	348 (0.2%)
Other	1,811 (0.5%)	11,397 (0.6%)	1,778 (0.5%)	11,210 (0.7%)	33 (0.2%)	187 (0.2%)	1,536 (0.5%)	8,225 (0.7%)	223 (0.4%)	1,832 (0.5%)	32 (0.2%)	352 (0.2%)
Mixed	816 (0.2%)	4,398 (0.2%)	813 (0.2%)	4,359 (0.3%)	3 (0.0%)	39 (0.0%)	696 (0.2%)	3,220 (0.3%)	109 (0.2%)	659 (0.2%)	9 (0.1%)	106 (0.1%)
Not stated or missing	204,626 (56.3%)	1,139,627 (63.2%)	191,015 (55.1%)	1,067,456 (62.1%)	13,611 (82.2%)	72,171 (88.0%)	148,243 (51.8%)	667,610 (56.6%)	37,550 (69.4%)	271,677 (78.9%)	15,462 (91.3%)	137,397 (93.8%)
Charlson comorbidity index [d]												
Low (0)	252,430 (69.5%)	1,308,427 (72.6%)	240,662 (69.4%)	1,248,116 (72.6%)	11,768 (71.1%)	60,311 (73.5%)	194,985 (68.1%)	822,626 (69.7%)	41,021 (75.9%)	284,310 (82.6%)	13,329 (78.7%)	129,301 (88.3%)
Moderate (1-2)	94,223 (25.9%)	421,230 (23.4%)	90,148 (26.0%)	402,585 (23.4%)	4,075 (24.6%)	18,645 (22.7%)	77,446 (27.0%)	300,906 (25.5%)	11,326 (20.9%)	54,069 (15.7%)	3,101 (18.3%)	15,334 (10.5%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With psoriasis	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**	**With psoriasis**	**Without psoriasis**
Severe (3 or more)	16,557 (4.6%)	72,218 (4.0%)	15,849 (4.6%)	69,141 (4.0%)	708 (4.3%)	3,077 (3.8%)	13,965 (4.9%)	56,257 (4.8%)	1,730 (3.2%)	5,807 (1.7%)	513 (3.0%)	1,877 (1.3%)

Abbreviations: IQR – Interquartile range
Individuals can contribute data as both psoriasis exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or severe mental illness diagnosis
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table S5: Absolute incidence rates and rate differences of severe mental illness in atopic eczema and psoriasis cohorts

Model	Cohort	HR (95% CI) in exposed [c]	Number of SMI events in exposed	Absolute rate in exposed (per 100,000 PYAR)	Estimated absolute rate in unexposed (per 100,000 PYAR)	Absolute rate difference (per 100,000 PYAR)
Minimally adjusted	Atopic eczema	1.16 (1.12, 1.21)	3,150	45	39	6
	Psoriasis	1.27 (1.1.9, 1.36)	1,191	44	35	9
Confounder-adjusted [a]	Atopic eczema	1.17 (1.12, 1.22)	3,012	45	39	6
	Psoriasis	1.26 (1.18, 1.35)	1,107	44	35	9
Mediator-adjusted [b]	Atopic eczema	1.01 (0.96, 1.07)	2,632	45	45	0
	Psoriasis	1.13 (1.04, 1.22)	990	45	40	5

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk
[a] Adjusted for calendar period and quintiles of Carstairs deprivation index (using 2011 census data)
[b] Atopic eczema cohort is further adjusted for comorbidities (using the Charlson comorbidity index), sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index. Psoriasis cohort is further adjusted for comorbidities (using the Charlson comorbidity index), smoking status, harmful alcohol use and body mass index.
[c] Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry)

Table S6: HRs (95% CI) for the association between atopic eczema or psoriasis severity and severe mental illness. Fitted to adults with complete data for all variables included in each model and from valid matched sets [a]

Cohort	Minimally adjusted				Confounder adjusted [b]				Additionally adjusted for potential mediators [c]			
	Number	PYAR	Events	HR (95% CI) [d]	Number	PYAR	Events	HR (95% CI) [d]	Number	PYAR	Events	HR (95% CI) [d]
Atopic eczema												
Unexposed	4,908,059	30,935,170	11,999	1 (reference)	4,744,478	29,565,265	11,428	1 (reference)	3,117,531	21,282,283	8,131	1 (reference)
Mild eczema	791,317	4,799,119	1,875	0.98 (0.93, 1.03)	765,883	4,595,659	1,796	0.98 (0.93, 1.04)	597,830	3,887,048	1,542	0.82 (0.77, 0.88)
Moderate eczema	246,592	2,034,775	1,181	1.61 (1.50, 1.73)	237,363	1,939,343	1,127	1.61 (1.50, 1.73)	209,075	1,764,883	1,008	1.38 (1.26, 1.51)
Severe eczema	18,724	161,998	94	1.56 (1.21, 2.01)	17,788	151,451	89	1.57 (1.21, 2.04)	15,473	137,082	82	1.16 (0.84, 1.60)
Psoriasis												
Unexposed	1,801,875	13,246,255	4,598	1 (reference)	1,719,842	12,491,309	4,319	1 (reference)	1,179,789	9,176,327	3,252	1 (reference)
Mild psoriasis	349,649	2,529,032	1,147	1.29 (1.21, 1.38)	334,121	2,385,265	1,064	1.28 (1.19, 1.37)	274,959	2,089,482	953	1.16 (1.07, 1.25)
Moderate-to-severe psoriasis	13,976	151,362	44	0.90 (0.65, 1.25)	12,922	138,213	43	0.97 (0.69, 1.35)	11,802	128,625	37	0.81 (0.56, 1.18)

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

[a] Matched sets including one exposed patient and at least one unexposed patient.

[b] Adjusted for calendar period and quintiles of Carstairs deprivation index (using 2011 census data)

[c] Atopic eczema cohort is further adjusted for comorbidities (using the Charlson comorbidity index), sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index. Adjusted for comorbidities, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and BMI. Psoriasis cohort is further adjusted for comorbidities (using the Charlson comorbidity index), smoking status, harmful alcohol use and body mass index.

[d] Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry)

Table S7: Adjusted hazard ratios (95% CIs) for the association between atopic eczema or psoriasis and severe mental illness, stratified by sex, age, and calendar period (adjusted for calendar period and Carstairs deprivation).

Variable	Atopic eczema cohort					Psoriasis cohort				
	Number of individuals	PYAR	Events	HR (95% CI)	P value	Number of individuals	PYAR	Events	HR (95% CI)	P value
Sex					0.26					0.26
Males										
Unexposed	1,995,311	12,458,113	4,653	1 (ref)		823,236	6,011,033	1,948	1 (ref)	
Exposed	412,218	2,726,164	1,128	1.13 (1.06, 1.21)		165,997	1,217,725	513	1.32 (1.19, 1.46)	
Females										
Exposed	2,749,167	17,107,152	6,775	1 (ref)		896,606	6,480,277	2,371	1 (ref)	
Unexposed	576,743	3,960,289	1,884	1.19 (1.13, 1.25)		180,662	1,305,753	594	1.21 (1.11, 1.33)	
Age					<0.01					0.01
18-29										
Unexposed	1,506,029	7,474,646	3,965	1 (ref)		366,735	2,188,125	1,031	1 (ref)	
Exposed	313,707	1,723,120	965	1.05 (0.98, 1.13)		73,595	439,890	286	1.46 (1.27, 1.68)	
30-39										
Unexposed	769,784	5,105,659	2,009	1 (ref)		332,830	2,447,829	983	1 (ref)	
Exposed	154,316	1,137,985	557	1.23 (1.11, 1.35)		67,057	499,914	221	1.10 (0.95, 1.28)	
40-59										
Unexposed	1,234,046	9,261,761	2,721	1 (ref)		568,432	4,716,350	1,329	1 (ref)	
Exposed	252,675	2,043,721	818	1.37 (1.26, 1.48)		114,764	952,963	356	1.30 (1.15, 1.47)	
60+										
Unexposed	1,234,619	7,723,198	2,733	1 (ref)		451,845	3,139,006	976	1 (ref)	
Exposed	268,263	1,781,627	672	1.05 (0.96, 1.15)		91,243	630,710	244	1.17 (1.01, 1.36)	
Calendar period					0.86					
1997-2003										
Unexposed	1,556,548	5,226,532	2,214	1 (ref)		654,477	2,213,622	854	1 (ref)	0.01
Exposed	321,591	1,122,582	550	1.17 (1.06, 1.29)		131,819	453,126	188	1.04 (0.89, 1.23)	
2004-2009										
Unexposed	2,516,467	8,911,202	3,248	1 (ref)		996,336	3,881,467	1,290	1 (ref)	
Exposed	538,913	2,009,886	863	1.19 (1.10, 1.29)		202,899	793,958	320	1.19 (1.05, 1.35)	
2010-2015										
Unexposed	3,096,454	10,714,880	4,086	1 (ref)		1,166,319	4,410,754	1,494	1 (ref)	
Exposed	682,304	2,473,959	1,083	1.14 (1.06, 1.22)		236,097	886,218	421	1.45 (1.29, 1.63)	
2016-2020										
Unexposed	1,892,797	4,712,650	1,880	1 (ref)		751,484	1,985,466	681	1 (ref)	

Exposed	426,765	1,080,026	516	1.18 (1.06, 1.31)	149,555	390,176	178	1.30 (1.09, 1.55)

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

Table S8: Effects of individual mediators on the associations between atopic eczema or psoriasis and severe mental illness

	Atopic eczema cohort				Psoriasis cohort			
	Number of individuals	**PYAR**	**Events**	**HR (95% CI)**	**Number of individuals**	**PYAR**	**Events**	**HR (95% CI)**
Confounder adjusted model	**988,961**	**6,686,453**	**3,012**	**1.17 (1.12, 1.22)**	**346,659**	**2,523,477**	**1,107**	**1.26 (1.18, 1.35)**
Further adjusted for:								
Comorbidities	988,961	6,686,453	3,012	1.14 (1.09, 1.19)	346,659	2,523,477	1,107	1.25 (1.17, 1.34)
Sleep problems	988,961	6,686,453	3,012	0.98 (0.94, 1.02)	n/a	n/a	n/a	n/a
Harmful alcohol use	988,961	6,686,453	3,012	1.16 (1.11, 1.21)	346,659	2,523,477	1,107	1.24 (1.15, 1.33)
High dose glucocorticoids	988,961	6,686,453	3,012	1.19 (1.14, 1.24)	n/a	n/a	n/a	n/a
BMI	807,637	5,839,813	2,671	1.13 (1.08, 1.19)	292,881	2,240,474	1,003	1.20 (1.12, 1.30)
Smoking status	940,567	6,542,904	2,935	1.13 (1.08, 1.18)	329,959	2,467,245	1,085	1.17 (1.09, 1.26)
Fully adjusted model (all mediators)	**793,030**	**5,789,012**	**2,632**	**1.01 (0.96, 1.07)**	**286,396**	**2,218,106**	**990**	**1.13 (1.04, 1.22)**

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

Appendix 5 – Supplementary material of population-based cohort studies investigating associations between atopic eczema and depression or anxiety in white or minority ethnic groups

Appendix S1: Explanation of matching without replacement in calendar date order

Appendix S2: Directed acyclic graph (DAG) of the implicitly assumed causal relationships between atopic eczema and depression/anxiety, and explanation of the variables included in the DAG

Appendix S3: Variable definitions

Appendix S4: Testing the proportional hazards assumption using Schoenfeld residual plots

Appendix S5: Multiple imputation of missing ethnicity data

Appendix S6: Secondary analyses

References

Table S1: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses in depression cohort

Table S2: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses in anxiety cohort

Table S3: Characteristics of main analysis cohort, HES-enriched sensitivity cohort, and multiple imputation of missing ethnicity cohort used to investigate associations between atopic eczema and depression in white and minority ethnic groups

Table S4: Characteristics of main analysis cohort, HES-enriched sensitivity cohort, and multiple imputation of missing ethnicity cohort used to investigate associations between atopic eczema and anxiety in white and minority ethnic groups

Table S5: Comparison of baseline characteristics of individuals with recorded and without recorded ethnicity in depression and anxiety cohorts

Table S6: Person-time under follow-up in depression and anxiety cohorts broken down by individual-level characteristics and atopic eczema exposure status

Table S7: Characteristics of the depression cohort at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

Table S8: Characteristics of the anxiety cohort at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

Table S9: HRs (95% CI) for the association between atopic eczema and depression or anxiety. Fitted to adults with complete data for all variables included in each model and from valid matched sets

Table S10: Proportions of total follow up each ethnic group (white or minority ethnic) spends at each level of atopic eczema (mild, moderate, or severe) severity during follow up. Data are n (%)

Table S11: HRs (95% CI) for the association between atopic eczema severity and depression or anxiety in white and minority ethnic groups

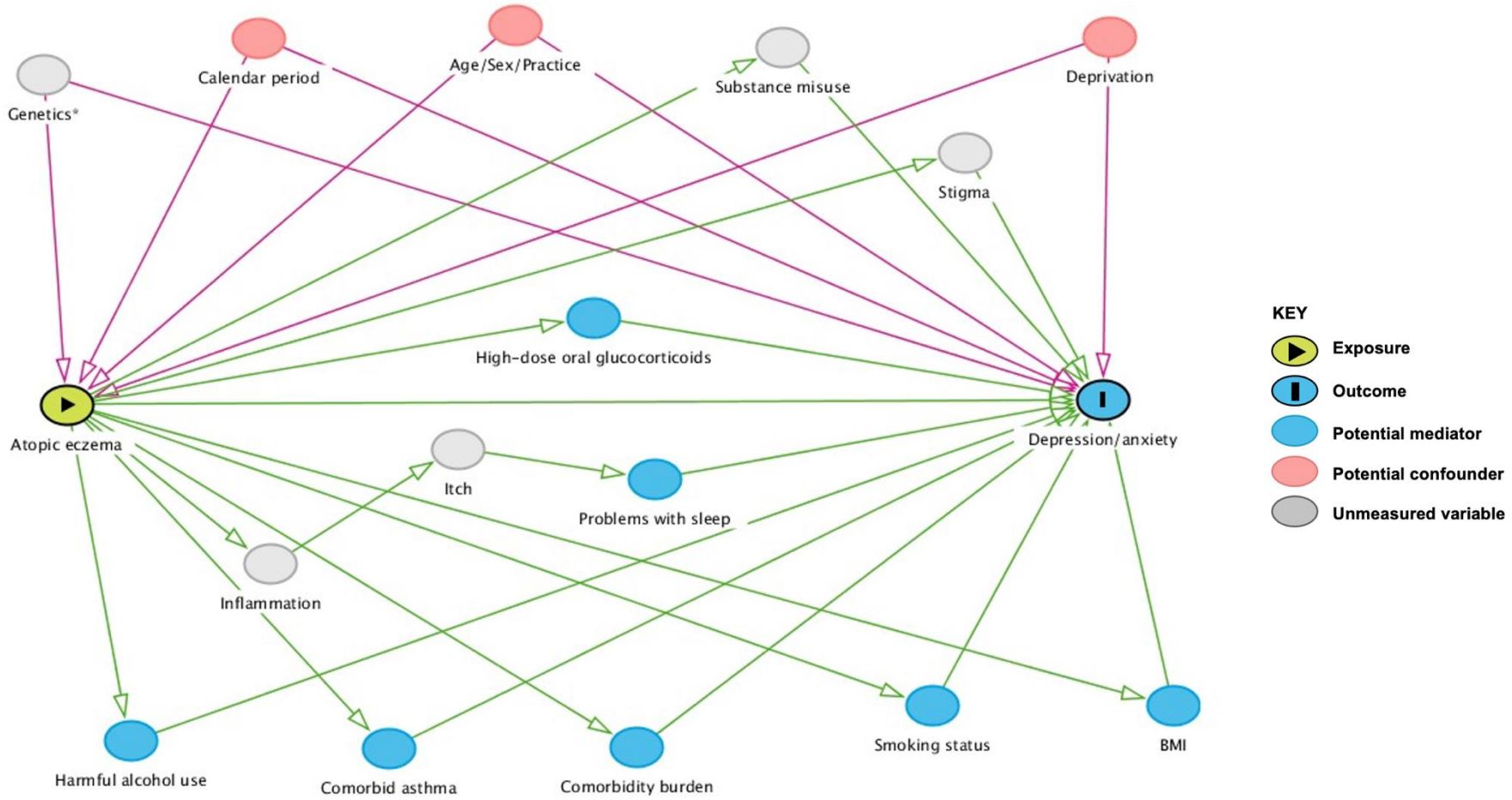
Appendix S1 – Explanation of matching without replacement in calendar date order

In this study, we matched adults with atopic eczema (on age, sex, and practice) with up to five adults without atopic eczema without replacement and in calendar date order. We matched one individual with atopic eczema with up to five without to increase the precision of estimates of effect. Beyond five matched comparators, there is little gain in efficiency.

Matching without replacement means that each of the up to five adults without atopic eczema were matched to only one adult with atopic eczema. This contrasts to matching with replacement, where the matched comparators (i.e., those without atopic eczema) could be matched to multiple individuals with atopic eczema. Matching with replacement allows sample size to be maximised as fewer exposed people (those with atopic eczema) are excluded because of lack of comparators and a high matching ratio can be ensured. However, as we had a large pool of eligible comparators (and were consequently not limited by sample size considerations, and able to preserve our matching ratio), we were not limited to matching with replacement. We chose to match without replacement as matching with replacement can result in substantial reuse of comparators meaning that standard errors become too optimistic and confidence intervals artificially narrow.

By ‘matching in calendar date order’ we mean that unexposed individuals (those without atopic eczema) in the matched cohort were assigned first to exposed individuals with the earliest cohort entry. Matching in calendar date order avoids some time-related bias.

Appendix S2: Directed acyclic graph (DAG) of the implicitly assumed causal relationships between atopic eczema and depression or anxiety, and explanation of the variables included in the DAG



Explanation of variables included in directed acyclic graphs of the relationships between atopic eczema and depression or anxiety

Variables	Type	Measured/Unmeasured	Justification
Age/Sex/Practice	Potential confounder (matching variables)	Measured	Atopic eczema can occur at any age, however, it is more prevalent in younger people (the usual age of onset is in early childhood), [1,2] and women compared to men.[3,4] The prevalence of depression peaks in older adulthood (individuals aged between 55-74 years), but it can also occur at a lower level than adults in children and adolescents below the age of 15.[5] On the other hand, prevalence rates of anxiety do not differ considerably between age groups, however, prevalence tends to decrease among older age groups.[5] Depression and anxiety are more common among women than men.[5–7] As these variables were not on the causal pathway in the association between atopic eczema and depression or anxiety, they were considered as potential confounders and used to match individuals in the study. We also matched on practice to control for clinical and administrative practices that may differ between general practitioners.
BMI	Potential mediator	Measured	Evidence suggests that a BMI is associated with atopic eczema. A population-based study in the UK using primary care data found that people with atopic eczema had 8% higher odds of being overweight or obese compared to those without atopic eczema.[8] Higher BMI is also strongly associated with increased risk of depression and anxiety,[9,10] with evidence from Mendelian randomisation studies suggesting a causal mechanism.[11] Due to this evidence, we considered BMI a potential mediator of associations between atopic eczema and depression or anxiety.
Calendar period	Potential confounder	Measured	The relationship between atopic eczema and depression or anxiety may be influenced by various calendar-based factors such as changes in clinical and administrative practices in atopic eczema, depression, and anxiety over time. For example, after the introduction of performance indicators for depression in the Quality and Outcomes Framework (QOF) in 2006, GP recording of depression or anxiety have been altered, and the use of symptom codes for both depression and anxiety have increased.[12] Adjusting for calendar period as a confounder in our analysis will allow us to remove any possible calendar variation and effectively assess the true association between atopic eczema and depression or anxiety.

Comorbid asthma	Potential mediator	Measured	Atopic eczema has been found to be associated with, or predispose affected individuals to, numerous atopic comorbidities including asthma.[13–16] Asthma is also known to be associated with anxiety and depression, with the literature reporting a higher prevalence and incidence of depression and anxiety in people with asthma compared to the general population.[17] Due to this evidence, we considered comorbid asthma a potential mediator of associations between atopic eczema and depression or anxiety.
Comorbidity burden	Potential mediator	Measured	Atopic eczema has been found to be associated with several atopic comorbidities (e.g., asthma and allergic rhinitis),[13–16] cardiovascular outcomes (e.g., hypertension, coronary heart disease, heart failure) which may partly relate to lifestyle habits (i.e., sedentary lifestyle, diet, harmful alcohol consumption),[8,13,18–21] infections,[22,23] and fractures.[24] The relationships between comorbidity burden and depression or anxiety are often complex and bidirectional. Long-term physical health problems such as cancer, diabetes, cardiovascular disease, and other chronic conditions can be distressing and lead to depression or other psychological problems in affected individuals. For example, anxiety is common in people with chronic respiratory diseases, while depression is more common in people with diabetes.[25] However, there is also evidence that mental health conditions can increase the risk of chronic conditions. Evidence from systematic reviews and meta-analyses suggest that depression and anxiety disorders are independent risk factors for diabetes and coronary heart disease.[25] What we can see from the evidence is that long term physical health conditions and depression or anxiety often co-occur, and the direction of the relationship between both conditions is complex and difficult to understand. In the context of this study, we considered comorbidity burden as a potential mediator of associations between atopic eczema and depression or anxiety, and excluded comorbidities recorded after the mental health outcome had occurred from analyses.
Deprivation	Potential confounder	Measured	Multiple studies have found that a higher socioeconomic status (and thus lower levels of deprivation) in children is associated with an increased prevalence of atopic eczema,[3,26] while in adulthood, prevalence was either unaffected by socioeconomic status or higher in individuals with lower socioeconomic status.[3,4] There is also strong evidence that people of lower socioeconomic status (and high levels of deprivation) are more likely to develop and experience mental health

			problems such as depression and anxiety.[7,27] Therefore, in this study, we considered deprivation a potential confounder of associations between atopic eczema and depression or anxiety.
Genetics (atopic eczema and depression only)	Potential confounder	Unmeasured	Limited studies have suggested a shared genetic link between atopic eczema and depression.[28] This relationship is not on the causal pathway, suggesting that genetics are a potential confounder of the association between atopic eczema and depression, or that a shared genetic aetiology is the reason for any observed association. However, genetic information is not routinely recorded in primary care records, therefore this variable is unmeasured. To my knowledge, a genetic association between atopic eczema and anxiety has not been established.
Harmful alcohol use	Potential mediator	Measured	Evidence shows that individuals with atopic eczema consume more alcohol than the general population and subsequently have a higher prevalence of alcohol use disorders compared to populations without skin disease.[21,29] Harmful alcohol use and alcohol dependence have been regularly associated with symptoms of depression and anxiety.[30,31] Due to this evidence, we considered harmful alcohol use a potential mediator of associations between atopic eczema and depression or anxiety.
High-dose oral glucocorticoids	Potential mediator	Measured	High dose oral glucocorticoids (≥20mg/day prednisolone equivalent dose) such as prednisolone, dexamethasone, and hydrocortisone may be used for short-term use in individuals where topical treatments or phototherapy have failed, or in people with severe atopic eczema flares.[22,32] During therapy, glucocorticoids can induce psychiatric side effects including symptoms of depression, anxiety, mania, and psychosis, however, their effect is temporary.[33] Due to this evidence, we considered high-dose oral glucocorticoid use a potential mediator of associations between atopic eczema and depression or anxiety.
Inflammation	Potential mediator	Unmeasured	Atopic eczema is a chronic inflammatory skin disease characterised by elevated levels of circulating pro-inflammatory cytokines.[32] Evidence also suggests that as atopic eczema severity increases, so do the levels of inflammatory markers.[34] Both depression and anxiety have been associated with increased inflammatory response of the immune system,[35] and clinical trials of biologics that target inflammatory cytokines in those with atopic eczema have found that these drugs may also be associated with a reduction in symptoms of depression

			and anxiety.[36] Inflammation can therefore be considered a potential confounder of the relationship between atopic and depression or anxiety. However, inflammation is not recorded in CPRD GOLD, so it is an unmeasured variable. However, in people with atopic eczema, inflammation can lead to itch and cause sleep problems in those affected
Itch and problems with sleep	Potential mediator	Measured	In people with atopic eczema, sleep disturbances are a common and well-recognised consequence of severe itch. Chronic and intense itching is a major clinical manifestation of atopic eczema that continues throughout the day and gets worse at night, leading to sleep disturbance or deprivation.[2] Studies have found that people with atopic eczema are more likely to report fatigue, regular insomnia, shorter sleep duration, and daytime sleepiness when compared to the general population.[37] Longitudinal evidence has identified sleep disturbances as risk factors for the development of depression and anxiety.[38] However, itch is not recorded in CPRD GOLD, so it is an unmeasured variable. On the other hand, problems with sleep can be captured in CPRD GOLD, although they are likely to be an underestimate of sleep problems. Due to this evidence, we considered problems with sleep a potential mediator of associations between atopic eczema and depression or anxiety.
Smoking status	Potential mediator	Measured	Evidence suggests that atopic eczema is associated with smoking. Adults with atopic eczema are 28% more likely to be current smokers compared to the general population.[21] Smoking rates are also high in individuals with depression and anxiety, with some longitudinal evidence suggesting that smoking leads to later development of depression or anxiety.[39] Specifically in individuals with atopic eczema, a relationship has been demonstrated between smoking status and an increased risk of depression.[40] Due to this evidence, we considered smoking status a potential mediator of associations between atopic eczema and depression or anxiety.
Stigma	Potential mediator	Unmeasured	In a survey of adults with atopic eczema, respondents indicated perceiving stigma in social events, employment, romantic relationships and self-image.[41] Stigma can exacerbate negative emotions and impact the self-esteem of those affected, consequently leading to mental health outcomes.[41] Stigma has been found to be a predictor for depressive symptoms and psychological factors in people with atopic eczema.[41,42] Stigma can therefore be considered a potential mediator

			of associations between atopic eczema and depression or anxiety, however, it is not recorded in CPRD GOLD; therefore, it is considered an unmeasured variable.
Substance misuse	Potential mediator	Unmeasured	Substance misuse can be defined as the use of illegal psychoactive drugs, or the use of prescription or over-the-counter medication for purposes other than those they are meant for.[43] Evidence suggests that people with atopic eczema are more likely than people in the general population to misuse substances such as cannabis,[44] potentially due to the powerful anti-itch effect of cannabinoids that could potentially reduce the symptoms and appearance of atopic eczema.[44] Heavy and regular use of cannabis is also associated with an increased risk of depressive symptoms.[45] Substance misuse can therefore be considered a potential mediator of associations between atopic eczema and depression or anxiety. However, studies have reported that substance misuse is recorded in primary care at lower rates compared to national surveys.[46] There are also stigmas associated with substance misuse,[43] so affected individuals may not feel comfortable discussing substance use with their GPs. Substance misuse is therefore incompletely captured in CPRD GOLD and has been considered an unmeasured variable.

BMI – Body mass index; CPRD – Clinical Practice Research Datalink

Appendix S3 – Variable definitions

Atopic eczema

We identified atopic eczema using a previously validated definition based on a record of at least one diagnostic code recorded in primary care and at least two records of eczema therapy recorded (in primary care using Read codes or prescription data) on separate days.[47] Eczema therapy included: (1) records of phototherapy identified using Read codes in primary care and (2) primary care prescription records for topical emollients, corticosteroids or calcineurin inhibitors, or oral glucocorticoids, azathioprine, methotrexate, ciclosporin or mycophenolate.

Depression and anxiety

We identified depression and anxiety based on the earliest record of a diagnostic or symptom Read code recorded in primary care. We considered broader definitions of depression and anxiety in sensitivity analyses.

Ethnicity

We identified ethnicity using a previously validated algorithm that identifies ethnicity using primary care electronic health records.[48] The algorithm classifies ethnicity into five categories – White, South Asian, Black, Other or Mixed – and is suggested for use with the CPRD dataset from 2006 onwards to maximise completeness and comparability of data. We pooled individuals from Black, South Asian, Mixed and Other ethnic groups into a 'minority ethnic' group. We used this grouping to investigate whether associations between atopic eczema and depression/anxiety differed between individuals from white and minority ethnic groups.

General practice

We matched on general practice as an indirect method to capture and adjust for general practice location (i.e., rural, or urban locations) and socioeconomic deprivation. Matching individuals on general practice also allowed us to account for differences in coding practices between GPs.

Calendar period

Calendar period was categorised as 2006-2010, 2011-2015, and 2016-2020 to account for changes in clinical, diagnostic, and administrative practices over the study period that may have influenced the measurement of exposure, outcomes, and other covariates.

Comorbidity burden

We used the Charlson Comorbidity Index (CCI) as a summary measure to capture the burden of comorbidities recorded on or before index date. The CCI is a method of categorising comorbidities of individuals that assigns weights to each of the 17 conditions included in the index, and then sums the weights of those conditions present in the individual.[49–51] Each condition in the CCI is weighted from one to six, with a weight of six representing the most severe morbidity.[49,51] The sum of the weights in each individual results in a single comorbidity summary score. We categorised CCI scores into 3 groups: low (0 points), intermediate (1-2 points), and high ($\geq$3 points).

Comorbid asthma

We identified adults with comorbid asthma based on morbidity coding in primary care. Individuals were regarded as having asthma from the earliest record of a relevant diagnostic code.

Deprivation

We used the Carstairs Index (CI) as a proxy for socioeconomic deprivation. The Carstairs Index was measured using quintiles of the individual-level Carstairs scores from 2011 census data linked via the individual postal code. Patient level Carstairs data was only available for people in English practices that consented to participate in the linkage scheme. When individual-level data was unavailable, we used practice-level data.

Harmful alcohol use

We defined harmful alcohol use based on primary care morbidity codes suggesting harmful or heavy alcohol use (including alcohol dependency codes and codes related to physical/psychological harm related to alcohol use) or a prescription for drugs used to maintain abstinence (acamprosate, disulfiram, or nalmefene). Individuals were defined as harmful alcohol users on the date of the first record of a relevant morbidity code or prescription.

High-dose oral glucocorticoid use

We identified prescriptions for oral glucocorticoids (prednisolone, betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone, and cortisone) and converted the prescribed daily dose to the prednisolone-equivalent dose (PED). High-dose oral glucocorticoid use was defined as a dose of 20 mg/day or higher PED. We captured high-dose oral glucocorticoid use as a binary time-updated variable with status changing for a short period (90 days) on the date of the first record of a prescription for a dose of 20mg/day or more PED.

Sleep problems

We identified sleep problems based on primary care morbidity codes suggesting sleep problems and prescriptions for drugs used to manage sleep problems. In our main analysis, this included diagnostic Read codes (for insomnia, sleep disorders, poor sleep pattern, or other sleep disturbances) and prescriptions for drugs that are only used to treat sleep problems (zaleplon, zolpidem tartrate, zopiclone, hydroxyzine hydrochloride and promethazine hydrochloride when taken at night). In our sensitivity analysis, we used alternative code lists including prescriptions for drugs that may be prescribed for sleep problems but can also be prescribed for other conditions (melatonin and benzodiazepines).

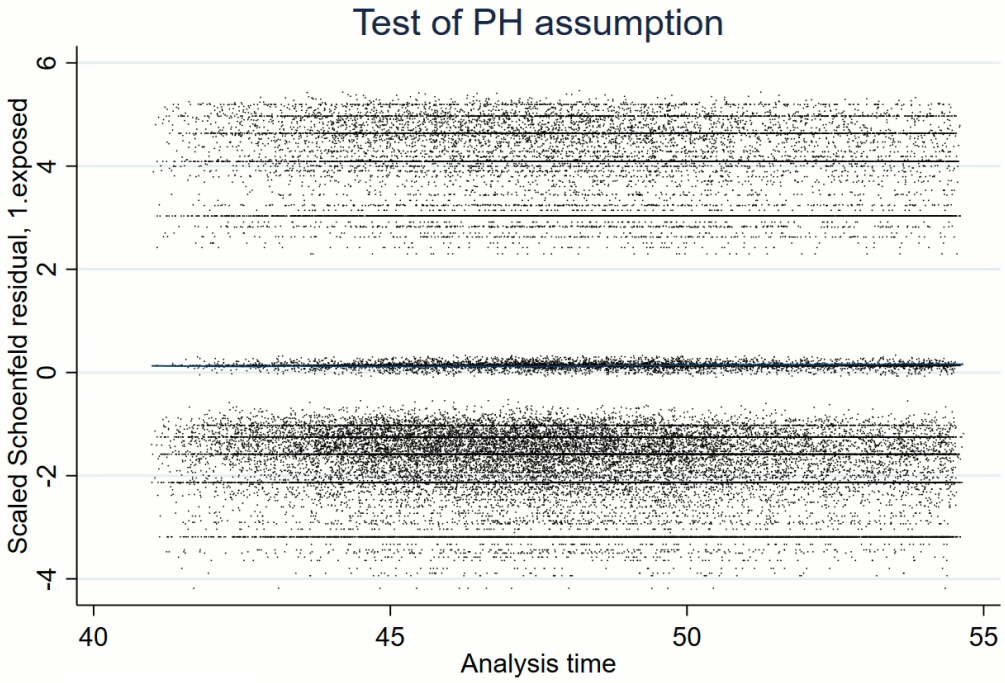
Smoking status and body mass index (BMI)

We defined BMI and smoking status using an algorithm using primary care records to identify the status recorded closest to the cohort entry date. The algorithm regarded records identified within -1 year to +1 month of the index date as the best, +1 month to +1 year from the index date as second best, the nearest before -1 year from the index date as the third best, and the nearest after +1 year from the index date as the worst. We did not include smoking status or BMI recorded after the outcome had occurred. Smoking status was classified as: (1) current/ex-smoker; or (2) non-smoker. BMI was classified according to the World Health Organisation categories: underweight (<18.5kg/m2); normal weight (18.5-24.9 kg/m2); pre-obesity (25.0-29.9 kg/m2); obese (≥30.0 kg/m2). Smoking status or BMI recorded after depression or anxiety diagnoses were not used.

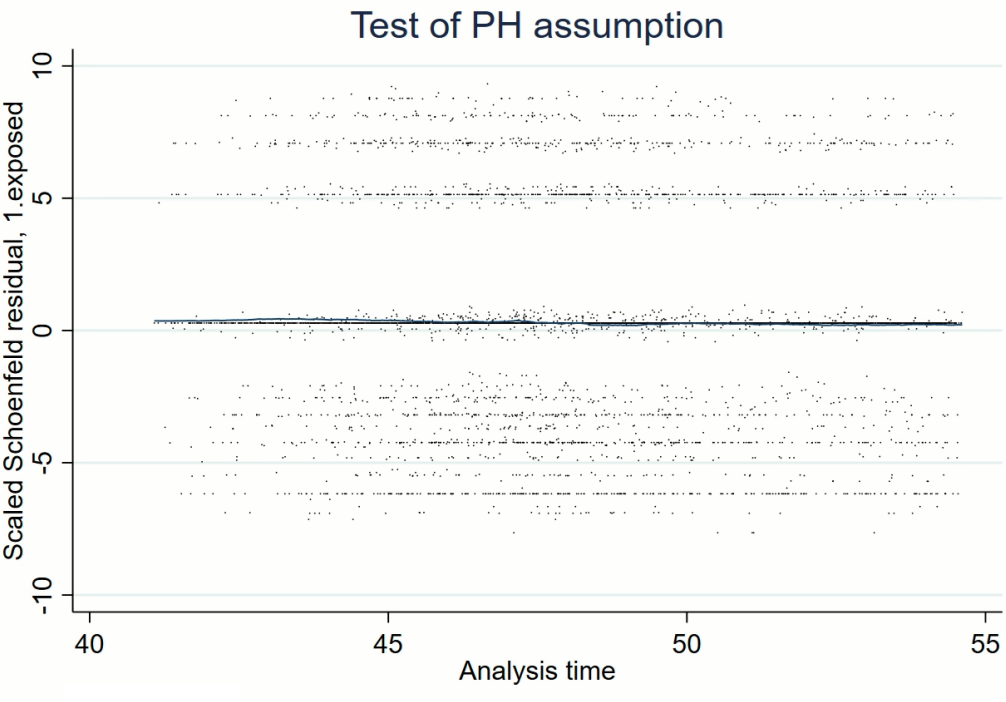
Appendix S4 – Testing proportional hazards assumption using Schoenfeld residual plots

We tested the proportional hazards assumption of our confounder-adjusted Cox regression models (adjusted for deprivation and calendar time) using Schoenfeld residual plots. In the confounder-adjusted models for white and minority ethnic groups in the depression and anxiety cohorts, there was no evidence that the proportional hazards assumption was violated.

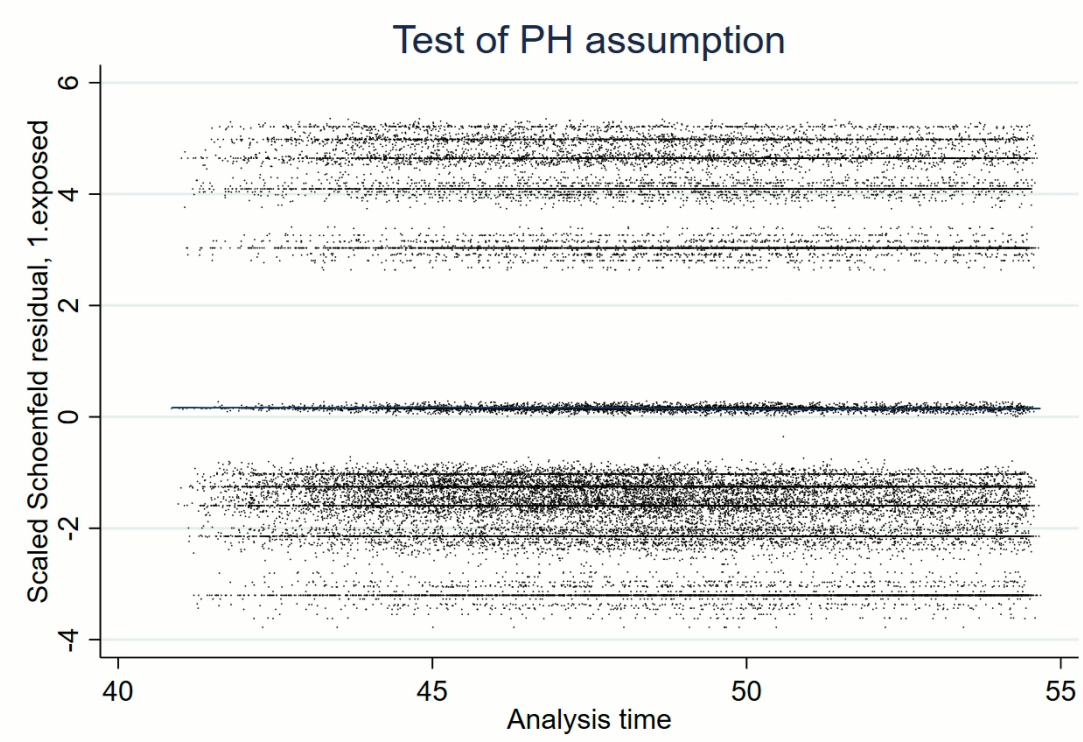
Confounder-adjusted model in the depression cohort (white ethnic group): p = 0.6832



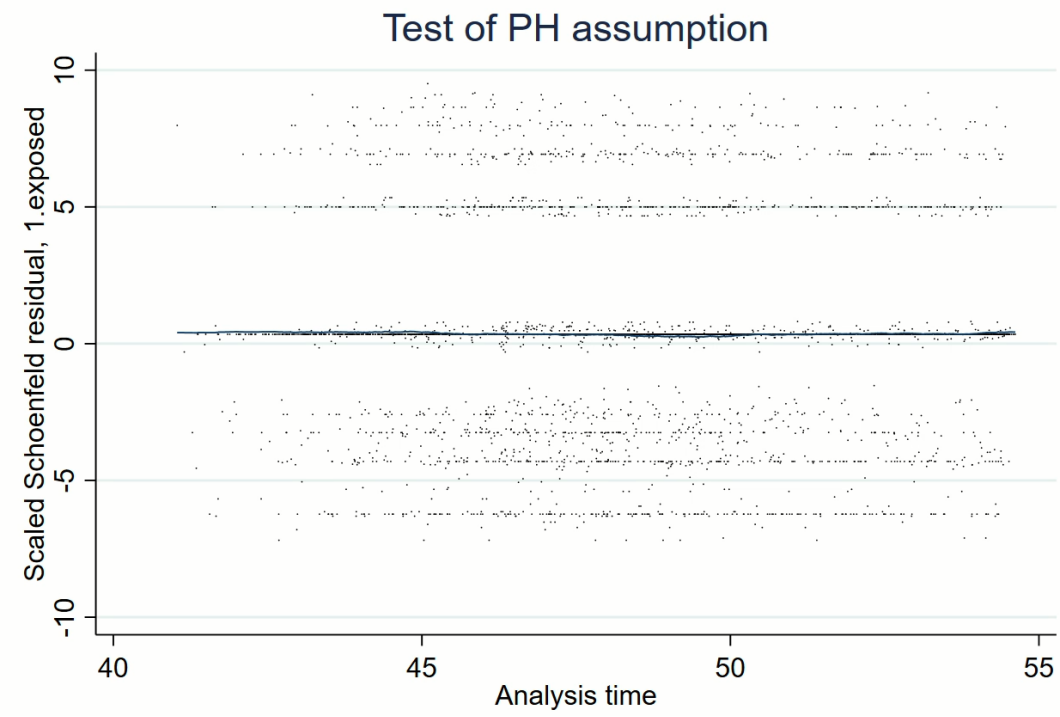
Confounder-adjusted model in the depression cohort (minority ethnic group): p = 0.2689



Confounder-adjusted model in the anxiety cohort (white ethnic group): p = 0.9953



Confounder-adjusted model in the anxiety cohort (minority ethnic group): p = 0.9381



Appendix S5 – Multiple imputation of missing ethnicity data

Imputation method

We used a logistic regression imputation method to fill in missing values of the binary ethnicity variable (white ethnic group, minority ethnic groups). We created 10 imputations of the missing ethnicity variable, including potential confounders (deprivation and calendar period) in our imputation model. Although at least 20 imputations are recommended, we conducted 10 as more imputations above this were computationally intensive.

Results of multiple imputation

The table below shows the distribution of ethnicity across imputations in the depression and anxiety cohorts. Although numbers of individuals in each ethnic group varied across imputations, sample sizes vastly increased with on average over 430,000 adults with atopic eczema matched to over 1,700,000 adults without atopic eczema in the depression cohort, and over 480,000 adults with atopic eczema matched with over 2,000,000 without atopic eczema in the anxiety cohort.

Imputation	Depression cohort		Anxiety cohort	
	Number	Events	Number	Events
IMPUTATION 1				
White				
Without atopic eczema	1,471,472	113,915	1,738,109	97,533
With atopic eczema	374,169	36,246	415,726	30,140
Minority ethnic				
Without atopic eczema	243,800	9,764	273,242	7,932
With atopic eczema	62,384	3,449	66,475	2,633
IMPUTATION 2				
White				
Without atopic eczema	1,471,750	113,922	1,737,526	97,648
With atopic eczema	374,160	36,241	415,749	30,075
Minority ethnic				
Without atopic eczema	243,430	9,757	273,799	7,817
With atopic eczema	62,180	3,454	66,535	2,698
IMPUTATION 3				
White				
Without atopic eczema	1,471,377	113,958	1,738,170	97,574
With atopic eczema	374,364	36,263	415,882	30,146
Minority ethnic				
Without atopic eczema	243,835	9,721	273,174	7,891
With atopic eczema	62,182	3,432	66,187	2,627
IMPUTATION 4				
White				
Without atopic eczema	1,471,974	114,043	1,738,383	97,562

With atopic eczema	373,650	36,225	415,807	30,189
Minority ethnic				
Without atopic eczema	243,322	9,636	272,899	7,903
With atopic eczema	62,817	3,470	66,308	2,584
IMPUTATION 5				
White				
Without atopic eczema	1,471,731	113,810	1,737,441	97,524
With atopic eczema	373,950	36,269	415,784	30,155
Minority ethnic				
Without atopic eczema	243,416	9,869	273,812	7,941
With atopic eczema	62,514	3,426	66,330	2,618
IMPUTATION 6				
White				
Without atopic eczema	1,471,273	113,849	1,737,982	97,623
With atopic eczema	374,508	36,288	415,337	30,144
Minority ethnic				
Without atopic eczema	243,825	9,830	273,296	7,842
With atopic eczema	61,900	3,407	66,883	2,629
IMPUTATION 7				
White				
Without atopic eczema	1,471,801	113,916	1,737,328	97,648
With atopic eczema	373,882	36,223	415,694	30,163
Minority ethnic				
Without atopic eczema	243,321	9,763	273,903	7,817
With atopic eczema	62,729	3,472	66,372	2,610
IMPUTATION 8				
White				
Without atopic eczema	1,471,555	113,886	1,737,502	97,626
With atopic eczema	374,208	36,312	415,760	30,128
Minority ethnic				
Without atopic eczema	243,596	9,793	273,787	7,839
With atopic eczema	62,125	3,383	66,397	2,645
IMPUTATION 9				
White				
Without atopic eczema	1,471,486	113,813	1,737,916	97,637
With atopic eczema	374,182	36,315	415,955	30,213
Minority ethnic				
Without atopic eczema	243,794	9,866	273,243	7,828
With atopic eczema	62,309	3,380	66,097	2,560

IMPUTATION 10				
White				
Without atopic eczema	1,471,653	113,955	1,737,253	97,613
With atopic eczema	374,027	36,271	415,775	30,191
Minority ethnic				
Without atopic eczema	243,645	9,724	274,028	7,852
With atopic eczema	62,445	3,424	66,276	2,582

Limitations

One problem that arose when we tried to estimate the hazard ratio for the association between atopic eczema and depression in individuals from minority ethnic groups using imputed data was that omitted variables varied across imputations. In one imputation, no variables were omitted, yet in another, one or more variables were omitted. It is possible that this occurred because in some of the variable groups included in the imputation, no individuals were observed, therefore corresponding coefficients could not be estimated. Therefore, the multiple imputation of missing ethnicity data was too uncertain to carry out the Cox regression to estimate the association between atopic eczema and depression in adults from minority ethnic groups.

Appendix S5 – Secondary analyses

In secondary analyses, we described the proportions of total follow-up adults with atopic eczema in white and minority ethnic groups spent at each level of atopic eczema severity during follow-up and investigated whether associations between atopic eczema severity and depression or anxiety differed between individuals of white and minority ethnic groups.

Atopic eczema severity definition

In analyses examining atopic eczema severity, we classified individuals with atopic eczema as having mild, moderate, or severe disease using a previously developed definition.[52] We considered individuals to have mild disease by default. We classified individuals as having moderate atopic eczema from the first of: (1) a second potent topical corticosteroid prescription within one year; or (2) a first prescription for a topical calcineurin inhibitor. We classified adults as having severe atopic eczema from the first of: (1) use of phototherapy or systemic treatment for atopic eczema (excluding systemic glucocorticoids, as they may have been prescribed for coexisting asthma); or (2) referral to a dermatologist. We updated severity over time, and once an individual was defined as having severe atopic eczema, they remained in this category for the rest of follow-up and could not be categorised as having milder disease.

Statistical analysis

We redefined atopic eczema exposure using atopic eczema severity. We described the proportions of total follow-up adults with atopic eczema in white and minority ethnic groups spent at each level of atopic eczema severity during follow-up. Using the same methods as the main analyses, we constructed stratified Cox regression models implicitly adjusted for matching variables (age, sex, general practice) and then sequentially adjusted for potential confounders (deprivation and calendar period) and potential mediators (comorbidity burden, comorbid asthma, harmful alcohol use, smoking status, body mass index, sleep problems and high-dose glucocorticoid use).

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Table S1: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses in depression cohort

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
Main analysis [a]		**181,173**	**724,343**	**17,246**	**1.15 (1.12, 1.17)**	**31,327**	**109,442**	**1,919**	**1.33 (1.22, 1.45)**
Repeating the main analysis using alternative code lists to identify depression outcome (including broader codes and symptom codes)	To explore the sensitivity of the results due to the definitions of the depression outcome	180,499	721,162	17,282	1.14 (1.12, 1.17)	31,263	109,158	1,942	1.35 (1.23, 1.47)
Restricting cohort entry to individuals with at least one consultation with their GP in the year before cohort entry.	To exclude individuals who are practice non-attenders. There may be differential recording of exposure, covariates and outcomes among practice attenders and non-attenders. For example, practice non-attenders may be more likely to have missing smoking or BMI data.	123,501	477,160	12,192	1.08 (1.06, 1.11)	22,453	77,253	1,431	1.22 (1.10, 1.36)
Repeating the main analysis after removing censoring at the time of an alternative diagnoses that may also represent the outcome of interest	To avoid potentially informative censoring of outcomes by severe mental illness.	181,173	724,343	17,246	1.15 (1.12, 1.17)	31,327	109,442	1,919	1.33 (1.22, 1.45)

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
(i.e., severe mental illness).									
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006 that are eligible for linkage with HES and have complete ethnicity data.	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias. The main study population included only individuals with complete ethnicity data who are likely to be different from those with missing ethnicity data, which may introduce selection bias. Previous work has shown that combining CPRD and HES increases the completeness of ethnicity data.	97,565	371,235	8,850	1.13 (1.10, 1.16)	20,821	71,221	1,271	1.33 (1.20, 1.47)
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006. Missing ethnicity data was imputed using multiple imputation. [b]	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias.	n/a	n/a	n/a	1.20 (1.19,1.22)	n/a	n/a	n/a	n/a
Main analysis further adjusted for potential mediators [c]		**145,302**	**604,767**	**14,436**	**1.05 (1.03, 1.08)**	**25,478**	**93,033**	**1,665**	**1.14 (1.02, 1.26)**

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
Repeating the main analysis using less strict definitions for sleep problems (main analysis code list includes Zolpidem and Zopiclone which are only prescribed for sleep problems, sensitivity analysis code list expanded to include prescriptions for benzodiazepines, melatonin, and other drugs).	To explore whether including broader drugs that are prescribed for conditions other than sleep disturbances further mediates the association between atopic eczema and severe mental illness.	145,302	604,767	14,436	1.04 (1.02, 1.07)	25,478	93,033	1,665	1.12 (1.01, 1.25)

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

[a] Adjusted for calendar time and quintiles of Carstairs deprivation index (using 2011 census data)

[b] Effect estimate from cohort of 427,366 people with atopic eczema matched to 1,699,374 without. 1,099,210 individuals in the cohort had complete ethnicity data (939,135 from the white ethnic group, 160,075 from the minority ethnic group) and 990,980 had missing ethnicity data which was imputed. During follow-up, there were 101,538 depression events. The number of observations among the subpopulations of people from white and minority ethnic groups varied across imputations, therefore numbers of individuals, PYARs and numbers of events could not be obtained. Producing an effect estimate for the minority ethnic group was not feasible as omitted variables varied across imputations.

[c] Cohorts are further adjusted for comorbidity burden (using the Charlson comorbidity index), comorbid asthma, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index

Table S2: Description of sensitivity analyses, and HR (95% CI) of sensitivity analyses in anxiety cohort

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
Main analysis [a]		**205,779**	**836,483**	**15,080**	**1.17 (1.14,1.19)**	**33,995**	**120,072**	**1,501**	**1.41 (1.28,1.55)**
Repeating the main analysis using alternative code lists to identify depression and anxiety outcomes (including broader codes and symptom codes)	To explore the sensitivity of the results due to the definitions of the depression and anxiety outcomes	201,012	814,678	15,883	1.17 (1.15,1.20)	33,266	117,406	1,735	1.41 (1.29, 1.54)
Restricting cohort entry to individuals with at least one consultation with their GP in the year before cohort entry.	To exclude individuals who are practice non-attenders. There may be differential recording of exposure, covariates and outcomes among practice attenders and non-attenders. For example, practice non-attenders may be more likely to have missing smoking or BMI data.	141,768	556,742	10,809	1.11 (1.08, 1.14)	24,529	85,617	1,085	1.31 (1.16, 1.48)
Repeating the main analysis after removing censoring at the time of an alternative diagnoses that may also represent the outcome of interest	To avoid potentially informative censoring of outcomes by severe mental illness.	205,779	836,483	15,080	1.17 (1.14, 1.19)	33,995	120,702	1,501	1.41 (1.28, 1.55)

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
(i.e., severe mental illness).									
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006 that are eligible for linkage with HES and have complete ethnicity data.	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias. The main study population included only individuals with complete ethnicity data who are likely to be different from those with missing ethnicity data, which may introduce selection bias. Previous work has shown that combining CPRD and HES increases the completeness of ethnicity data.	111,237	429,021	7,645	1.17 (1.13, 1.20)	22,780	79,030	1,037	1.42 (1.27, 1.59)
Repeating the main analysis using a redefined cohort of adults entering from 1 April 2006. Missing ethnicity data was imputed using multiple imputation. [b]	To explore the sensitivity of our results to the definition of our study population and examine whether the study population of the main analysis is susceptible to selection bias.	n/a	n/a	n/a	1.22 (1.20, 1.23)	n/a	n/a	n/a	1.38 (1.25, 1.52)
Main analysis further adjusted for mediators [d]		**168,344**	**710,076**	**12,849**	**1.07 (1.04, 1.09)**	**27,963**	**103,522**	**1,322**	**1.22 (1.09, 1.37)**
Repeating the main analysis using less	To explore whether including broader drugs that are	168,344	710,076	12,849	1.03 (1.01, 1.06)	27,963	103,522	1,322	1.15 (1.03, 1.30)

Description	Justification	White ethnic group				Minority ethnic group			
		Number of individuals	PYAR	Events	HR (95% CI)	Number of individuals	PYAR	Events	HR (95% CI)
strict definitions for sleep problems (main analysis code list includes Zolpidem and Zopiclone which are only prescribed for sleep problems, sensitivity analysis code list expanded to include prescriptions for benzodiazepines, melatonin, and other drugs).	prescribed for conditions other than sleep disturbances further mediates the association between atopic eczema and severe mental illness.								

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

[a] Adjusted for calendar time and quintiles of Carstairs deprivation index (using 2011 census data)

[b] Effect estimates from cohort of 471,860 people with atopic eczema matched to 1,991,567 without. 1,292,737 individuals in the cohort had complete ethnicity data (1,112,495 from the white ethnic group, 180,242 from the minority ethnic group) and 1,125,489 had missing ethnicity data which was imputed. During follow-up, there were 82,367 anxiety events. The number of observations among the subpopulations of people from white and minority ethnic groups varied across imputations, therefore numbers of individuals, PYARs and numbers of events could not be obtained.

[c] Cohorts are further adjusted for comorbidity burden (using the Charlson comorbidity index), comorbid asthma, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index

Table S3: Characteristics of main analysis (confounder-adjusted) cohort, HES-enriched sensitivity cohort, and multiple imputation of missing ethnicity cohort used to investigate associations between atopic eczema and depression in white and minority ethnic groups

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=212,500	n=639,470	n=118,386	n=339,243	n=427,366	n=1,699,374
Follow-up [a]						
Total person-years	833,785	2,350,951	442,456	1,206,507	1,757,814	6,724,293
Median (IQR) duration of follow-up (years)	3.2 (1.3-5.9)	2.8 (1.2-5.5)	3.0 (1.3-5.6)	2.8 (1.2-5.3)	3.3 (1.3-6.3)	3.1 (1.2-6.1)
Sex						
Female (%)	117,663 (55.4%)	350,103 (54.7%)	66,540 (56.2%)	191,075 (56.3%)	226,360 (53.0%)	850,026 (50.0%)
Age (years) [b]						
18-29	82,012 (38.6%)	264,086 (41.3%)	43,693 (36.9%)	136,920 (40.4%)	179,947 (42.1%)	769,430 (45.3%)
30-39	36,122 (17.0%)	112,161 (17.5%)	19,612 (16.6%)	55,633 (16.4%)	59,297 (13.9%)	239,124 (14.1%)
40-49	25,234 (11.9%)	69,899 (10.9%)	14,157 (12.0%)	35,749 (10.5%)	47,022 (11.0%)	176,046 (10.4%)
50-59	21,397 (10.1%)	58,833 (9.2%)	12,189 (10.3%)	31,767 (9.4%)	42,192 (9.9%)	156,222 (9.2%)
60-69	21,837 (10.3%)	62,606 (9.8%)	13,077 (11.0%)	36,359 (10.7%)	43,054 (10.1%)	162,543 (9.6%)
70+	25,898 (12.2%)	71,885 (11.2%)	15,658 (13.2%)	42,815 (12.6%)	55,854 (13.1%)	196,009 (11.5%)
Ethnicity						
White	181,173 (85.3%)	541,478 (84.7%)	97,565 (82.4%)	279,304 (82.3%)	196,927 (46.1%)	758,847 (44.7%)
Minority ethnic	31,327 (14.7%)	97,992 (15.3%)	20,821 (17.6%)	59,939 (17.7%)	32,872 (7.7%)	130,373 (7.7%)
Missing	n/a	n/a	n/a	n/a	197,567 (46.2%)	810,154 (47.7%)
Quintiles of Carstairs deprivation index [c]						
1 - Least deprived	40,005 (18.8%)	112,671 (17.6%)	28,286 (23.9%)	76,485 (22.5%)	84,902 (19.9%)	327,853 (19.3%)

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=212,500	n=639,470	n=118,386	n=339,243	n=427,366	n=1,699,374
2	42,331 (19.9%)	127,095 (19.9%)	25,821 (21.8%)	72,202 (21.3%)	84,163 (19.7%)	330,950 (19.5%)
3	44,016 (20.7%)	129,585 (20.3%)	23,394 (19.8%)	65,002 (19.2%)	92,188 (21.6%)	364,776 (21.5%)
4	45,293 (21.3%)	138,247 (21.6%)	21,710 (18.3%)	64,214 (18.9%)	94,856 (22.2%)	380,465 (22.4%)
5 - Most deprived	40,855 (19.2%)	131,872 (20.6%)	19,175 (16.2%)	61,340 (18.1%)	71,257 (16.7%)	295,330 (17.4%)
Missing	n/a	n/a	n/a	n/a	n/a	n/a
Body mass index (kg/m^2) [d]						
Underweight (<18.5)	5,525 (2.6%)	18,766 (2.9%)	3,187 (2.7%)	10,223 (3.0%)	10,901 (2.6%)	44,914 (2.6%)
Normal (18.5-24.9)	77,544 (36.5%)	230,252 (36.0%)	45,059 (38.1%)	125,858 (37.1%)	144,072 (33.7%)	530,546 (31.2%)
Overweight (25-29.9)	57,035 (26.8%)	161,216 (25.2%)	32,544 (27.5%)	86,966 (25.6%)	106,064 (24.8%)	376,390 (22.1%)
Obese (30+)	38,378 (18.1%)	103,913 (16.2%)	20,715 (17.5%)	55,011 (16.2%)	71,336 (16.7%)	242,370 (14.3%)
Missing	34,018 (16.0%)	125,323 (19.6%)	16,881 (14.3%)	61,185 (18.0%)	94,993 (22.2%)	505,154 (29.7%)
Smoking status [d]						
Non-smoker	114,066 (53.7%)	342,819 (53.6%)	63,445 (53.6%)	181,253 (53.4%)	232,869 (54.5%)	876,966 (51.6%)
Current or ex-smoker	94,525 (44.5%)	275,352 (43.1%)	53,184 (44.9%)	148,145 (43.7%)	178,971 (41.9%)	666,808 (39.2%)
Missing	3,909 (1.8%)	21,299 (3.3%)	1,757 (1.5%)	9,845 (2.9%)	15,526 (3.6%)	155,600 (9.2%)
Charlson Comorbidity Index [d]						
Low (0)	132,686 (62.4%)	474,241 (74.2%)	74,310 (62.8%)	248,889 (73.4%)	269,200 (63.0%)	1,270,184 (74.7%)
Moderate (1-2)	70,731 (33.3%)	137,779 (21.5%)	38,977 (32.9%)	74,532 (22.0%)	140,414 (32.9%)	360,088 (21.2%)
Severe (3 or more)	9,083 (4.3%)	27,450 (4.3%)	5,099 (4.3%)	15,822 (4.7%)	17,752 (4.2%)	69,102 (4.1%)
Asthma (%) [d]	54,194 (25.5%)	81,832 (12.8%)	29,654 (25.0%)	43,618 (12.9%)	108,226 (25.3%)	221,362 (13.0%)
Harmful alcohol use (%) [d]	15,733 (7.4%)	39,803 (6.2%)	8,088 (6.8%)	19,180 (5.7%)	27,200 (6.4%)	88,970 (5.2%)

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=212,500	n=639,470	n=118,386	n=339,243	n=427,366	n=1,699,374
Problems with sleep (%) [d]	36,757 (17.3%)	65,742 (10.3%)	20,381 (17.2%)	35,326 (10.4%)	73,874 (17.3%)	169,342 (10.0%)

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table S4: Characteristics of main analysis (confounder-adjusted) cohort, HES-enriched sensitivity cohort, and multiple imputation of missing ethnicity cohort used to investigate associations between atopic eczema and anxiety in white and minority ethnic groups

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=239,774	n=765,991	n=134,017	n=407,680	n=471,860	n=1,991,567
Follow-up [a]						
Total person-years	957,185	2,861,456	508,051	1,471,796	1,977,734	8,013,905
Median (IQR) duration of follow-up (years)	3.2 (1.4-6.0)	2.9 (1.2-5.6)	3.1 (1.3-5.7)	2.9 (1.2-5.4)	3.4 (1.4-6.4)	3.2 (1.3-6.2)
Sex						
Female (%)	137,304 (57.3%)	441,348 (57.6%)	78,014 (58.2%)	242,305 (59.4%)	258,395 (54.8%)	1,052,359 (52.8%)
Age (years) [b]						
18-29	87,674 (36.6%)	293,892 (38.4%)	46,913 (35.0%)	152,832 (37.5%)	188,677 (40.0%)	833,089 (41.8%)
30-39	41,633 (17.4%)	138,644 (18.1%)	22,673 (16.9%)	69,111 (17.0%)	67,674 (14.3%)	295,620 (14.8%)
40-49	30,814 (12.9%)	93,953 (12.3%)	17,254 (12.9%)	48,076 (11.8%)	55,897 (11.8%)	232,047 (11.7%)
50-59	25,845 (10.8%)	77,856 (10.2%)	14,692 (11.0%)	41,871 (10.3%)	49,745 (10.5%)	203,296 (10.2%)
60-69	25,056 (10.4%)	76,975 (10.0%)	15,017 (11.2%)	44,918 (11.0%)	48,490 (10.3%)	198,155 (9.9%)
70+	28,752 (12.0%)	84,671 (11.1%)	17,468 (13.0%)	50,872 (12.5%)	61,377 (13.0%)	229,360 (11.5%)
Ethnicity						
White	205,779 (85.8%)	653,373 (85.3%)	111,237 (83.0%)	338,617 (83.1%)	221,343 (46.9%)	912,119 (45.8%)
Minority ethnic	33,995 (14.2%)	112,618 (14.7%)	22,780 (17.0%)	69,063 (16.9%)	35,391 (7.5%)	148,682 (7.5%)
Missing	n/a	n/a	n/a	n/a	215,126 (45.6%)	930,766 (46.7%)
Quintiles of Carstairs deprivation index [c]						

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=239,774	n=765,991	n=134,017	n=407,680	n=471,860	n=1,991,567
1 - Least deprived	44,123 (18.4%)	132,325 (17.3%)	31,175 (23.3%)	90,160 (22.1%)	91,748 (19.4%)	376,606 (18.9%)
2	46,993 (19.6%)	149,716 (19.5%)	28,860 (21.5%)	85,926 (21.1%)	91,895 (19.5%)	384,119 (19.3%)
3	49,443 (20.6%)	154,764 (20.2%)	26,606 (19.9%)	79,015 (19.4%)	101,479 (21.5%)	425,502 (21.4%)
4	52,153 (21.8%)	168,516 (22.0%)	25,108 (18.7%)	78,421 (19.2%)	106,617 (22.6%)	455,574 (22.9%)
5 - Most deprived	47,062 (19.6%)	160,670 (21.0%)	22,268 (16.6%)	74,158 (18.2%)	80,121 (17.0%)	349,766 (17.6%)
Missing	n/a	n/a	n/a	n/a	n/a	n/a
Body mass index (kg/m^2) [d]						
Underweight (<18.5)	6,093 (2.5%)	21,951 (2.9%)	3,513 (2.6%)	11,991 (2.9%)	11,874 (2.5%)	52,060 (2.6%)
Normal (18.5-24.9)	85,862 (35.8%)	273,573 (35.7%)	50,059 (37.4%)	150,246 (36.9%)	157,296 (33.3%)	625,197 (31.4%)
Overweight (25-29.9)	64,917 (27.1%)	196,450 (25.6%)	37,138 (27.7%)	106,273 (26.1%)	118,764 (25.2%)	454,555 (22.8%)
Obese (30+)	47,000 (19.6%)	135,493 (17.7%)	25,463 (19.0%)	71,842 (17.6%)	85,491 (18.1%)	312,146 (15.7%)
Missing	35,902 (15.0%)	138,524 (18.1%)	17,844 (13.3%)	67,328 (16.5%)	98,435 (20.9%)	547,609 (27.5%)
Smoking status [d]						
Non-smoker	123,333 (51.4%)	395,175 (51.6%)	68,824 (51.4%)	210,325 (51.6%)	247,432 (52.4%)	996,610 (50.0%)
Current or ex-smoker	112,504 (46.9%)	348,409 (45.5%)	63,430 (47.3%)	186,955 (45.9%)	208,804 (44.3%)	830,528 (41.7%)
Missing	3,937 (1.6%)	22,407 (2.9%)	1,763 (1.3%)	10,400 (2.6%)	15,624 (3.3%)	164,429 (8.3%)
Charlson Comorbidity Index [d]						
Low (0)	147,185 (61.4%)	559,610 (73.1%)	82,611 (61.6%)	294,593 (72.3%)	292,987 (62.1%)	1,467,740 (73.7%)
Moderate (1-2)	81,550 (34.0%)	170,920 (22.3%)	45,130 (33.7%)	92,684 (22.7%)	157,614 (33.4%)	435,448 (21.9%)
Severe (3 or more)	11,039 (4.6%)	35,461 (4.6%)	6,276 (4.7%)	20,403 (5.0%)	21,259 (4.5%)	88,379 (4.4%)
Asthma (%) [d]	62,501 (26.1%)	101,698 (13.3%)	34,389 (25.7%)	54,533 (13.4%)	121,442 (25.7%)	265,742 (13.3%)

	Main analysis cohort		HES-enriched cohort		Multiple imputation of missing ethnicity cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=239,774	n=765,991	n=134,017	n=407,680	n=471,860	n=1,991,567
Harmful alcohol use (%) [d]	19,484 (8.1%)	52,503 (6.9%)	9,980 (7.4%)	25,231 (6.2%)	32,870 (7.0%)	115,723 (5.8%)
Problems with sleep (%) [d]	46,876 (19.6%)	91,862 (12.0%)	26,193 (19.5%)	49,507 (12.1%)	91,154 (19.3%)	228,679 (11.5%)

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table S5: Comparison of baseline characteristics of individuals with recorded and without recorded ethnicity in depression and anxiety cohorts

	Depression cohort		Anxiety cohort	
	With recorded ethnicity	**Without recorded ethnicity**	**With recorded ethnicity**	**Without recorded ethnicity**
	n=1,117,355	n=1,046,043	n=1,313,076	n=1,185,642
Follow-up [a]				
Total person-years	4,262,859	4,600,242	5,100,510	5,318,617
Median (IQR) duration of follow-up (years)	3.0 (1.2-5.8)	3.5 (1.4-6.8)	3.1 (1.2-5.9)	3.6 (1.4-7.0)
Sex				
Female (%)	601,991 (53.9%)	489,905 (46.8%)	742,074 (56.5%)	582,216 (49.1%)
Age (years) [b]				
18-29	471,845 (42.2%)	505,950 (48.4%)	517,033 (39.4%)	532,712 (44.9%)
30-39	184,357 (16.5%)	120,211 (11.5%)	224,371 (17.1%)	145,522 (12.3%)
40-49	122,802 (11.0%)	104,533 (10.0%)	160,302 (12.2%)	132,388 (11.2%)
50-59	104,636 (9.4%)	97,270 (9.3%)	135,206 (10.3%)	121,945 (10.3%)
60-69	110,258 (9.9%)	97,271 (9.3%)	133,469 (10.2%)	115,292 (9.7%)
70+	127,737 (11.4%)	124,285 (11.9%)	148,280 (11.3%)	142,295 (12.0%)
Quintiles of Carstairs deprivation index [c]				
1 - Least deprived	204,505 (18.3%)	200,770 (19.2%)	235,498 (17.9%)	223,927 (18.9%)
2	215,813 (19.3%)	192,460 (18.4%)	250,294 (19.1%)	217,285 (18.3%)
3	225,897 (20.2%)	223,174 (21.3%)	264,902 (20.2%)	252,475 (21.3%)
4	239,325 (21.4%)	227,728 (21.8%)	286,912 (21.9%)	264,733 (22.3%)
5 - Most deprived	213,670 (19.1%)	146,848 (14.0%)	255,131 (19.4%)	167,069 (14.1%)
Missing	18,145 (1.6%)	55,063 (5.3%)	20,339 (1.5%)	60,153 (5.1%)
Body mass index (kg/m^2) [d]				
Underweight (<18.5)	32,106 (2.9%)	24,896 (2.4%)	36,922 (2.8%)	28,049 (2.4%)

	Depression cohort		Anxiety cohort	
	With recorded ethnicity	**Without recorded ethnicity**	**With recorded ethnicity**	**Without recorded ethnicity**
	n=1,117,355	n=1,046,043	n=1,313,076	n=1,185,642
Normal (18.5-24.9)	399,001 (35.7%)	287,409 (27.5%)	463,892 (35.3%)	329,822 (27.8%)
Overweight (25-29.9)	281,072 (25.2%)	207,016 (19.8%)	335,834 (25.6%)	242,919 (20.5%)
Obese (30+)	182,403 (16.3%)	134,097 (12.8%)	233,195 (17.8%)	166,751 (14.1%)
Missing	222,773 (19.9%)	392,625 (37.5%)	243,233 (18.5%)	418,101 (35.3%)
Smoking status [d]				
Non-smoker	599,716 (53.7%)	532,612 (50.9%)	677,967 (51.6%)	587,371 (49.5%)
Current or ex-smoker	479,678 (42.9%)	376,239 (36.0%)	595,641 (45.4%)	453,501 (38.2%)
Missing	37,961 (3.4%)	137,192 (13.1%)	39,468 (3.0%)	144,770 (12.2%)
Charlson Comorbidity Index [d]				
Low (0)	800,837 (71.7%)	768,267 (73.4%)	928,109 (70.7%)	861,811 (72.7%)
Moderate (1-2)	268,616 (24.0%)	238,568 (22.8%)	324,002 (24.7%)	274,957 (23.2%)
Severe (3 or more)	47,902 (4.3%)	39,208 (3.7%)	60,965 (4.6%)	48,874 (4.1%)
Asthma (%) [d]	173,385 (15.5%)	161,288 (15.4%)	208,214 (15.9%)	183,239 (15.5%)
Harmful alcohol use (%) [d]	72,132 (6.5%)	44,755 (4.3%)	93,286 (7.1%)	56,014 (4.7%)
Problems with sleep (%) [d]	129,887 (11.6%)	119,421 (11.4%)	175,080 (13.3%)	150,706 (12.7%)

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table S6: Person-time under follow-up in depression and anxiety cohorts broken down by individual-level characteristics and atopic eczema exposure status

	Depression cohort		Anxiety cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=215,073	n=646,539	n=242,598	n=774,113
Follow-up [a]				
Total person-years	845,534	2,381,779	970,230	2,898,227
Median (IQR) duration of follow-up (years)	3.2 (1.3-5.9)	2.8 (1.2-5.5)	3.3 (1.4-6.0)	2.9 (1.2-5.6)
Sex				
Female (%)	459,129 (54.3%)	1,260,967 (52.9%)	547,861 (56.5%)	1,628,566 (56.2%)
Age (years) [b]				
18-29	281,931 (33.3%)	842,812 (35.4%)	308,702 (31.8%)	956,354 (33.0%)
30-39	142,008 (16.8%)	403,118 (16.9%)	167,164 (17.2%)	509,384 (17.6%)
40-49	113,254 (13.4%)	298,536 (12.5%)	140,056 (14.4%)	405,274 (14.0%)
50-59	98,913 (11.7%)	264,508 (11.1%)	119,707 (12.3%)	347,775 (12.0%)
60-69	105,224 (12.4%)	292,866 (12.3%)	119,819 (12.3%)	353,903 (12.2%)
70+	104,204 (12.3%)	279,939 (11.8%)	114,783 (11.8%)	325,536 (11.2%)
Ethnicity				
White	735,495 (87.0%)	2,083,588 (87.5%)	848,896 (87.5%)	2,550,372 (88.0%)
Minority ethnic	110,039 (13.0%)	298,191 (12.5%)	121,334 (12.5%)	347,855 (12.0%)
Quintiles of Carstairs deprivation index [c]				
1 - Least deprived	156,862 (18.6%)	420,347 (17.6%)	174,640 (18.0%)	498,743 (17.2%)
2	160,296 (19.0%)	451,953 (19.0%)	180,086 (18.6%)	539,198 (18.6%)
3	174,334 (20.6%)	473,431 (19.9%)	198,407 (20.4%)	573,725 (19.8%)
4	181,471 (21.5%)	522,120 (21.9%)	213,193 (22.0%)	645,682 (22.3%)
5 - Most deprived	160,821 (19.0%)	483,100 (20.3%)	190,859 (19.7%)	604,108 (20.8%)

	Depression cohort		Anxiety cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=215,073	n=646,539	n=242,598	n=774,113
Missing	11,749 (1.4%)	30,828 (1.3%)	13,045 (1.3%)	36,771 (1.3%)
Body mass index (kg/m^2) [d]				
Underweight (<18.5)	19,656 (2.3%)	60,532 (2.5%)	22,108 (2.3%)	72,028 (2.5%)
Normal (18.5-24.9)	309,831 (36.6%)	845,639 (35.5%)	347,158 (35.8%)	1,020,088 (35.2%)
Overweight (25-29.9)	244,152 (28.9%)	657,207 (27.6%)	280,832 (28.9%)	807,041 (27.8%)
Obese (30+)	162,093 (19.2%)	425,212 (17.9%)	202,625 (20.9%)	561,062 (19.4%)
Missing	109,802 (13.0%)	393,189 (16.5%)	117,508 (12.1%)	438,008 (15.1%)
Smoking status [d]				
Non-smoker	460,175 (54.4%)	1,287,472 (54.1%)	504,246 (52.0%)	1,503,145 (51.9%)
Current or ex-smoker	378,148 (44.7%)	1,046,599 (43.9%)	458,665 (47.3%)	1,344,154 (46.4%)
Missing	7,212 (0.9%)	47,707 (2.0%)	7,320 (0.8%)	50,928 (1.8%)
Charlson Comorbidity Index [d]				
Low (0)	537,885 (63.6%)	1,760,084 (73.9%)	606,702 (62.5%)	2,113,349 (72.9%)
Moderate (1-2)	274,688 (32.5%)	527,027 (22.1%)	323,575 (33.4%)	661,722 (22.8%)
Severe (3 or more)	32,961 (3.9%)	94,667 (4.0%)	39,953 (4.1%)	123,156 (4.2%)
Calendar time				
2006-2010	150,033 (17.7%)	423,453 (17.8%)	169,427 (17.5%)	504,116 (17.4%)
2011-2015	425,043 (50.3%)	1,207,024 (50.7%)	489,255 (50.4%)	1,475,157 (50.9%)
2016-2020	270,459 (32.0%)	751,301 (31.5%)	311,548 (32.1%)	918,955 (31.7%)
Asthma (%) [d]	210,868 (24.9%)	313,723 (13.2%)	249,392 (25.7%)	398,170 (13.7%)
Harmful alcohol use (%) [d]	70,167 (8.3%)	173,203 (7.3%)	88,514 (9.1%)	231,232 (8.0%)
Problems with sleep (%) [d]	157,538 (18.6%)	273,866 (11.5%)	206,138 (21.2%)	393,992 (13.6%)

	Depression cohort		Anxiety cohort	
	With atopic eczema	**Without atopic eczema**	**With atopic eczema**	**Without atopic eczema**
	n=215,073	n=646,539	n=242,598	n=774,113
High-dose oral glucocorticoids (20mg+ prednisolone equivalent dose)	58,946 (7.0%)	125,768 (5.3%)	72,272 (7.4%)	165,533 (5.7%)

Abbreviations: IQR: Interquartile range
Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.
[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)
[b] Age at index date
[c] Carstairs deprivation index based on practice-level data (from 2011).
[d] Based on records closest to index date.

Table S7: Characteristics of the depression cohort at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
Number	215,073	646,539	212,500	639,470	2,573	7,069	170,780	454,950	34,228	126,122	3,920	21,463
Follow-up [a]												
Total person-years	845,534	2,381,779	833,785	2,350,950	11,749	30,828	697,799	1,765,185	109,802	393,188	7,211	47,706
Median (IQR) duration of follow-up (years)	3.2 (1.3-5.9)	2.8 (1.2-5.5)	3.2 (1.3-5.9)	2.8 (1.2-5.5)	4.0 (1.6-7.0)	3.6 (1.5-6.6)	3.3 (1.4-6.2)	3.1 (1.3-5.8)	2.4 (1.0-4.7)	2.3 (0.9-4.6)	1.4 (0.5-2.5)	1.5 (0.5-3.1)
Sex												
Female (%)	119,149 (55.4%)	354,208 (54.8%)	117,663 (55.4%)	350,103 (54.7%)	1,486 (57.8%)	4,105 (58.1%)	100,514 (58.9%)	269,245 (59.2%)	13,709 (40.1%)	52,617 (41.7%)	1,319 (33.6%)	7,385 (34.4%)
Age (years) [b]												
18-29	83,066 (38.6%)	267,060 (41.3%)	82,012 (38.6%)	264,086 (41.3%)	1,054 (41.0%)	2,974 (42.1%)	51,974 (30.4%)	136,698 (30.0%)	25,495 (74.5%)	89,354 (70.8%)	3,539 (90.3%)	17,269 (80.5%)
30-39	36,715 (17.1%)	113,881 (17.6%)	36,122 (17.0%)	112,161 (17.5%)	593 (23.0%)	1,720 (24.3%)	31,578 (18.5%)	88,340 (19.4%)	3,589 (10.5%)	15,735 (12.5%)	164 (4.2%)	1,888 (8.8%)
40-49	25,545 (11.9%)	70,699 (10.9%)	25,234 (11.9%)	69,899 (10.9%)	311 (12.1%)	800 (11.3%)	22,945 (13.4%)	58,979 (13.0%)	1,705 (5.0%)	7,052 (5.6%)	70 (1.8%)	890 (4.1%)
50-59	21,605 (10.0%)	59,361 (9.2%)	21,397 (10.1%)	58,833 (9.2%)	208 (8.1%)	528 (7.5%)	19,957 (11.7%)	51,726 (11.4%)	1,023 (3.0%)	4,505 (3.6%)	48 (1.2%)	620 (2.9%)
60-69	21,999 (10.2%)	63,035 (9.7%)	21,837 (10.3%)	62,606 (9.8%)	162 (6.3%)	429 (6.1%)	20,680 (12.1%)	56,724 (12.5%)	867 (2.5%)	3,509 (2.8%)	42 (1.1%)	397 (1.8%)
70+	26,143 (12.2%)	72,503 (11.2%)	25,898 (12.2%)	71,885 (11.2%)	245 (9.5%)	618 (8.7%)	23,646 (13.8%)	62,483 (13.7%)	1,549 (4.5%)	5,967 (4.7%)	57 (1.5%)	399 (1.9%)
Ethnicity												
White	183,612 (85.4%)	548,100 (84.8%)	181,173 (85.3%)	541,478 (84.7%)	2,439 (94.8%)	6,622 (93.7%)	145,302 (85.1%)	385,813 (84.8%)	29,239 (85.4%)	106,394 (84.4%)	3,300 (84.2%)	17,453 (81.3%)
Minority ethnic	31,461 (14.6%)	98,439 (15.2%)	31,327 (14.7%)	97,992 (15.3%)	134 (5.2%)	447 (6.3%)	25,478 (14.9%)	69,137 (15.2%)	4,989 (14.6%)	19,728 (15.6%)	620 (15.8%)	4,010 (18.7%)
Quintiles of Carstairs deprivation index [c]												
1 - Least deprived	40,005 (18.6%)	112,671 (17.4%)	40,005 (18.8%)	112,671 (17.6%)	n/a	n/a	32,831 (19.2%)	82,441 (18.1%)	5,801 (16.9%)	20,552 (16.3%)	681 (17.4%)	3,460 (16.1%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
2	42,331 (19.7%)	127,095 (19.7%)	42,331 (19.9%)	127,095 (19.9%)	n/a	n/a	34,246 (20.1%)	92,434 (20.3%)	6,540 (19.1%)	23,280 (18.5%)	772 (19.7%)	3,783 (17.6%)
3	44,016 (20.5%)	129,585 (20.0%)	44,016 (20.7%)	129,585 (20.3%)	n/a	n/a	35,662 (20.9%)	93,125 (20.5%)	6,755 (19.7%)	24,451 (19.4%)	800 (20.4%)	4,325 (20.2%)
4	45,293 (21.1%)	138,247 (21.4%)	45,293 (21.3%)	138,247 (21.6%)	n/a	n/a	35,968 (21.1%)	96,804 (21.3%)	7,626 (22.3%)	28,298 (22.4%)	814 (20.8%)	4,633 (21.6%)
5 - Most deprived	40,855 (19.0%)	131,872 (20.4%)	40,855 (19.2%)	131,872 (20.6%)	n/a	n/a	32,073 (18.8%)	90,146 (19.8%)	7,296 (21.3%)	28,742 (22.8%)	842 (21.5%)	5,098 (23.8%)
Missing	2,573 (1.2%)	7,069 (1.1%)	n/a	n/a	n/a	n/a	n/a	n/a	210 (0.6%)	799 (0.6%)	11 (0.3%)	164 (0.8%)
Body mass index (kg/m^2) [d]												
Underweight (<18.5)	5,583 (2.6%)	18,965 (2.9%)	5,525 (2.6%)	18,766 (2.9%)	58 (2.3%)	199 (2.8%)	5,040 (3.0%)	14,997 (3.3%)	n/a	n/a	52 (1.3%)	260 (1.2%)
Normal (18.5-24.9)	78,647 (36.6%)	233,286 (36.1%)	77,544 (36.5%)	230,252 (36.0%)	1,103 (42.9%)	3,034 (42.9%)	73,849 (43.2%)	199,864 (43.9%)	n/a	n/a	276 (7.0%)	1,377 (6.4%)
Overweight (25-29.9)	57,766 (26.9%)	163,116 (25.2%)	57,035 (26.8%)	161,216 (25.2%)	731 (28.4%)	1,900 (26.9%)	54,961 (32.2%)	145,942 (32.1%)	n/a	n/a	110 (2.8%)	604 (2.8%)
Obese (30+)	38,849 (18.1%)	105,050 (16.2%)	38,378 (18.1%)	103,913 (16.2%)	471 (18.3%)	1,137 (16.1%)	36,930 (21.6%)	94,147 (20.7%)	n/a	n/a	98 (2.5%)	380 (1.8%)
Missing	34,228 (15.9%)	126,122 (19.5%)	34,018 (16.0%)	125,323 (19.6%)	210 (8.2%)	799 (11.3%)	n/a	n/a	n/a	n/a	3,384 (86.3%)	18,842 (87.8%)
Smoking status [d]												
Non-smoker	115,457 (53.7%)	346,669 (53.6%)	114,066 (53.7%)	342,819 (53.6%)	1,391 (54.1%)	3,850 (54.5%)	89,109 (52.2%)	239,210 (52.6%)	20,810 (60.8%)	70,632 (56.0%)	n/a	n/a
Current or ex-smoker	95,696 (44.5%)	278,407 (43.1%)	94,525 (44.5%)	275,352 (43.1%)	1,171 (45.5%)	3,055 (43.2%)	81,671 (47.8%)	215,740 (47.4%)	10,034 (29.3%)	36,648 (29.1%)	n/a	n/a
Missing	3,920 (1.8%)	21,463 (3.3%)	3,909 (1.8%)	21,299 (3.3%)	11 (0.4%)	164 (2.3%)	n/a	n/a	3,384 (9.9%)	18,842 (14.9%)	n/a	n/a
Charlson Comorbidity Index [d]												
Low (0)	134,391 (62.5%)	479,693 (74.2%)	132,686 (62.4%)	474,241 (74.2%)	1,705 (66.3%)	5,452 (77.1%)	105,375 (61.7%)	326,174 (71.7%)	23,165 (67.7%)	103,962 (82.4%)	3,277 (83.6%)	19,614 (91.4%)
Moderate (1-2)	71,488 (33.2%)	139,122 (21.5%)	70,731 (33.3%)	137,779 (21.5%)	757 (29.4%)	1,343 (19.0%)	57,128 (33.5%)	104,644 (23.0%)	10,506 (30.7%)	20,305 (16.1%)	617 (15.7%)	1,764 (8.2%)
Severe (3 or more)	9,194 (4.3%)	27,724 (4.3%)	9,083 (4.3%)	27,450 (4.3%)	111 (4.3%)	274 (3.9%)	8,277 (4.8%)	24,132 (5.3%)	557 (1.6%)	1,855 (1.5%)	26 (0.7%)	85 (0.4%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
	54,774	82,629	54,194	81,832	580	797	42,587	57,705	8,921	14,688	458	1,208
Asthma (%) [d]	(25.5%)	(12.8%)	(25.5%)	(12.8%)	(22.5%)	(11.3%)	(24.9%)	(12.7%)	(26.1%)	(11.6%)	(11.7%)	(5.6%)
Harmful alcohol use	15,943	40,279	15,733	39,803	210	476	14,377	33,805	930	2,962	53	215
(%) [d]	(7.4%)	(6.2%)	(7.4%)	(6.2%)	(8.2%)	(6.7%)	(8.4%)	(7.4%)	(2.7%)	(2.3%)	(1.4%)	1.0%)
Problems with sleep	37,355	66,682	36,757	65,742	598	940	30,521	50,775	4,939	9,191	365	793
(%) [d]	(17.4%)	(10.3%)	(17.3%)	(10.3%)	(23.2%)	(13.3%)	(17.9%)	(11.2%)	(14.4%)	(7.3%)	(9.3%)	(3.7%)

Abbreviations: IQR: Interquartile range

Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.

[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)

[b] Age at index date

[c] Carstairs deprivation index based on practice-level data (from 2011).

[d] Based on records closest to index date.

Table S8: Characteristics of the anxiety cohort at cohort entry, for: the overall cohort, individuals included in the model additionally adjusting for potential confounders (i.e., individuals with no missing Carstairs deprivation data), individuals with missing Carstairs data, individuals included in the model additionally adjusting for potential mediators (i.e., individuals with no missing BMI or smoking status data), and for individuals with missing BMI or smoking status

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
Number	242,598	774,113	239,774	765,991	2,824	8,122	196,307	560,318	36,120	139,386	3,950	22,578
Follow-up [a]												
Total person-years	970,230	2,898,227	957,184	2,861,456	13,045	36,771	813,597	2,199,809	117,507	438,007	7,319	50,928
Median (IQR) duration of follow-up (years)	3.3 (1.4-6.0)	2.9 (1.2-5.6)	3.2 (1.4-6.0)	2.9 (1.2-5.6)	4.0 (1.7-7.1)	3.8 (1.5-6.9)	3.4 (1.5-6.2)	3.1 (1.3-5.9)	2.4 (1.0-4.8)	2.3 (0.9-4.6)	1.4 (0.5-2.5)	1.5 (0.5-3.2)
Sex												
Female (%)	138,964 (57.3%)	446,169 (57.6%)	137,304 (57.3%)	441,348 (57.6%)	1,660 (58.8%)	4,821 (59.4%)	118,986 (60.6%)	346,307 (61.8%)	14,990 (41.5%)	61,391 (44.0%)	1,330 (33.7%)	8,046 (35.6%)
Age (years) [b]												
18-29	88,755 (36.6%)	297,014 (38.4%)	87,674 (36.6%)	293,892 (38.4%)	1,081 (38.3%)	3,122 (38.4%)	57,191 (29.1%)	159,020 (28.4%)	26,035 (72.1%)	94,057 (67.5%)	3,524 (89.2%)	17,633 (78.1%)
30-39	42,298 (17.4%)	140,665 (18.2%)	41,633 (17.4%)	138,644 (18.1%)	665 (23.5%)	2,021 (24.9%)	36,638 (18.7%)	109,720 (19.6%)	4,086 (11.3%)	18,977 (13.6%)	178 (4.5%)	2,164 (9.6%)
40-49	31,182 (12.9%)	94,977 (12.3%)	30,814 (12.9%)	93,953 (12.3%)	368 (13.0%)	1,024 (12.6%)	28,250 (14.4%)	79,652 (14.2%)	2,021 (5.6%)	9,170 (6.6%)	75 (1.9%)	1,104 (4.9%)
50-59	26,090 (10.8%)	78,533 (10.1%)	25,845 (10.8%)	77,856 (10.2%)	245 (8.7%)	677 (8.3%)	24,276 (12.4%)	68,924 (12.3%)	1,185 (3.3%)	5,650 (4.1%)	54 (1.4%)	720 (3.2%)
60-69	25,257 (10.4%)	77,543 (10.0%)	25,056 (10.4%)	76,975 (10.0%)	201 (7.1%)	568 (7.0%)	23,775 (12.1%)	69,848 (12.5%)	987 (2.7%)	4,238 (3.0%)	46 (1.2%)	482 (2.1%)
70+	29,016 (12.0%)	85,381 (11.0%)	28,752 (12.0%)	84,671 (11.1%)	264 (9.3%)	710 (8.7%)	26,177 (13.3%)	73,154 (13.1%)	1,806 (5.0%)	7,294 (5.2%)	73 (1.8%)	475 (2.1%)
Ethnicity												
White	208,462 (85.9%)	661,005 (85.4%)	205,779 (85.8%)	653,373 (85.3%)	2,683 (95.0%)	7,632 (94.0%)	168,344 (85.8%)	478,957 (85.5%)	30,933 (85.6%)	118,010 (84.7%)	3,326 (84.2%)	18,384 (81.4%)
Minority ethnic	34,136 (14.1%)	113,108 (14.6%)	33,995 (14.2%)	112,618 (14.7%)	141 (5.0%)	490 (6.0%)	27,963 (14.2%)	81,361 (14.5%)	5,187 (14.4%)	21,376 (15.3%)	624 (15.8%)	4,194 (18.6%)
Quintiles of Carstairs deprivation index [c]												
1 - Least deprived	44,123 (18.2%)	132,325 (17.1%)	44,123 (18.4%)	132,325 (17.3%)	n/a	n/a	36,642 (18.7%)	99,085 (17.7%)	6,105 (16.9%)	22,487 (16.1%)	684 (17.3%)	3,629 (16.1%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
2	46,993 (19.4%)	149,716 (19.3%)	46,993 (19.6%)	149,716 (19.5%)	n/a	n/a	38,685 (19.7%)	111,359 (19.9%)	6,850 (19.0%)	25,543 (18.3%)	774 (19.6%)	3,932 (17.4%)
3	49,443 (20.4%)	154,764 (20.0%)	49,443 (20.6%)	154,764 (20.2%)	n/a	n/a	40,768 (20.8%)	114,151 (20.4%)	7,092 (19.6%)	27,004 (19.4%)	807 (20.4%)	4,586 (20.3%)
4	52,153 (21.5%)	168,516 (21.8%)	52,153 (21.8%)	168,516 (22.0%)	n/a	n/a	42,403 (21.6%)	121,913 (21.8%)	8,091 (22.4%)	31,517 (22.6%)	842 (21.3%)	4,918 (21.8%)
5 - Most deprived	47,062 (19.4%)	160,670 (20.8%)	47,062 (19.6%)	160,670 (21.0%)	n/a	n/a	37,809 (19.3%)	113,810 (20.3%)	7,764 (21.5%)	31,973 (22.9%)	830 (21.0%)	5,342 (23.7%)
Missing	2,824 (1.2%)	8,122 (1.0%)	n/a	n/a	n/a	n/a	n/a	n/a	218 (0.6%)	862 (0.6%)	13 (0.3%)	171 (0.8%)
Body mass index (kg/m^2) [d]												
Underweight (<18.5)	6,156 (2.5%)	22,161 (2.9%)	6,093 (2.5%)	21,951 (2.9%)	63 (2.2%)	210 (2.6%)	5,628 (2.9%)	17,890 (3.2%)	n/a	n/a	56 (1.4%)	274 (1.2%)
Normal (18.5-24.9)	87,042 (35.9%)	276,952 (35.8%)	85,862 (35.8%)	273,573 (35.7%)	1,180 (41.8%)	3,379 (41.6%)	82,353 (42.0%)	239,901 (42.8%)	n/a	n/a	285 (7.2%)	1,509 (6.7%)
Overweight (25-29.9)	65,734 (27.1%)	198,662 (25.7%)	64,917 (27.1%)	196,450 (25.6%)	817 (28.9%)	2,212 (27.2%)	62,869 (32.0%)	178,900 (31.9%)	n/a	n/a	119 (3.0%)	691 (3.1%)
Obese (30+)	47,546 (19.6%)	136,952 (17.7%)	47,000 (19.6%)	135,493 (17.7%)	546 (19.3%)	1,459 (18.0%)	45,457 (23.2%)	123,627 (22.1%)	n/a	n/a	112 (2.8%)	422 (1.9%)
Missing	36,120 (14.9%)	139,386 (18.0%)	35,902 (15.0%)	138,524 (18.1%)	218 (7.7%)	862 (10.6%)	n/a	n/a	n/a	n/a	3,378 (85.5%)	19,682 (87.2%)
Smoking status [d]												
Non-smoker	124,789 (51.4%)	399,346 (51.6%)	123,333 (51.4%)	395,175 (51.6%)	1,456 (51.6%)	4,171 (51.4%)	97,963 (49.9%)	283,095 (50.5%)	21,427 (59.3%)	76,157 (54.6%)	n/a	n/a
Current or ex-smoker	113,859 (46.9%)	352,189 (45.5%)	112,504 (46.9%)	348,409 (45.5%)	1,355 (48.0%)	3,780 (46.5%)	98,344 (50.1%)	277,223 (49.5%)	11,315 (31.3%)	43,547 (31.2%)	n/a	n/a
Missing	3,950 (1.6%)	22,578 (2.9%)	3,937 (1.6%)	22,407 (2.9%)	13 (0.5%)	171 (2.1%)	n/a	n/a	3,378 (9.4%)	19,682 (14.1%)	n/a	n/a
Charlson Comorbidity Index [d]												
Low (0)	149,031 (61.4%)	565,797 (73.1%)	147,185 (61.4%)	559,610 (73.1%)	1,846 (65.4%)	6,187 (76.2%)	118,905 (60.6%)	396,247 (70.7%)	24,252 (67.1%)	113,953 (81.8%)	3,290 (83.3%)	20,613 (91.3%)
Moderate (1-2)	82,401 (34.0%)	172,496 (22.3%)	81,550 (34.0%)	170,920 (22.3%)	851 (30.1%)	1,576 (19.4%)	67,329 (34.3%)	132,995 (23.7%)	11,186 (31.0%)	22,941 (16.5%)	626 (15.8%)	1,871 (8.3%)
Severe (3 or more)	11,166 (4.6%)	35,820 (4.6%)	11,039 (4.6%)	35,461 (4.6%)	127 (4.5%)	359 (4.4%)	10,073 (5.1%)	31,076 (5.5%)	682 (1.9%)	2,492 (1.8%)	34 (0.9%)	94 (0.4%)

	Overall cohort		Sample included in model adjusting for potential confounders		Individuals with missing Carstairs data		Sample included in model adjusting for potential mediators		Individuals with missing BMI data		Individuals with missing smoking data	
	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema	With atopic eczema	Without atopic eczema
	63,142	102,633	62,501	101,698	641	935	50,437	74,744	9,442	16,158	467	1,234
Asthma (%) [d]	(26.0%)	(13.3%)	(26.1%)	(13.3%)	(22.7%)	(11.5%)	(25.7%)	(13.3%)	(26.1%)	(11.6%)	(11.8%)	(5.5%)
Harmful alcohol use	19,740	53,118	19,484	52,503	256	615	17,890	44,882	1,150	3,854	62	271
(%) [d]	(8.1%)	(6.9%)	(8.1%)	(6.9%)	(9.1%)	(7.6%)	(9.1%)	(8.0%)	(3.2%)	(2.8%)	(1.6%)	(1.2%)
Problems with sleep	47,582	93,110	46,876	91,862	706	1,248	39,944	73,060	5,531	11,278	389	850
(%) [d]	(19.6%)	(12.0%)	(19.6%)	(12.0%)	(25.0%)	(15.4%)	(20.3%)	(13.0%)	(15.3%)	(8.1%)	(9.8%)	(3.8%)

Abbreviations: IQR: Interquartile range

Individuals can contribute data as both atopic eczema exposed and unexposed. Therefore, numbers of exposed/unexposed do not total the whole cohort, as individuals may be included in more than one column.

[a] Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or depression or anxiety diagnosis, diagnosis that suggests an alternative cause of the depression or anxiety outcome (severe mental illness)

[b] Age at index date

[c] Carstairs deprivation index based on practice-level data (from 2011).

[d] Based on records closest to index date.

Table S9: HRs (95% CI) [a] for the association between atopic eczema and depression or anxiety. Fitted to adults with complete data for all variables included in each model and from valid matched sets [b]

Cohort	Minimally adjusted [c]			Further adjusted for potential confounders [d]			Additionally adjusted for potential mediators [e]		
	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)
Depression									
Without atopic eczema	646,539	46,503/2,381,779	1 (reference)	639,470	45,833/2,350,951	1 (reference)	454,950	34,140/1,765,185	1 (reference)
With atopic eczema	215,073	19,481/845,534	1.17 (1.14,1.19)	212,500	19,165/833,785	1.17 (1.14,1.19)	170,780	16,101/697,8900	1.06 (1.03,1.08)
Anxiety									
Without atopic eczema	774,113	41,670/2,898,227	1 (reference)	765,991	40,996/2,861,456	1 (reference)	560,318	31,488/2,199,809	1 (reference)
With atopic eczema	242,598	16,893/970,230	1.19 (1.17,1.21)	239,774	16,581/957,185	1.19 (1.16,1.21)	196,307	14,171/813,598	1.08 (1.06,1.11)

Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk

[a] Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry)

[b] Matched sets including one individual with atopic eczema and at least one matched comparator without.

[c] Adjusted for matching variables (age, sex, practice)

[d] Minimally adjusted model further adjusted for calendar period and deprivation (using quintiles of Carstairs deprivation index [using 2011 census data)])

[e] Cohort is further adjusted for comorbidity burden (using the Charlson comorbidity index), comorbid asthma, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index

Table S10: Proportions of total follow up each ethnic group (white or minority ethnic) spends at each level of atopic eczema (mild, moderate, or severe) severity during follow up. Data are n (%)

Cohort	Total PYAR at each level of atopic eczema severity			Total follow-up
	Mild eczema	Moderate eczema	Severe eczema	
Depression				
White	570,467 (77.6)	155,585 (21.2)	9,443 (1.2)	735,495
Minority ethnic	85,437 (77.7)	22,938 (20.8)	1,664 (1.5)	110,039
Anxiety				
White	655,936 (77.2)	182,098 (21.5)	10,862 (1.3)	848,896
Minority ethnic	93681 (77.2)	25819 (21.3)	1834 (1.5)	121,334

Abbreviations: PYAR – Person years at risk

Table S11: HRs (95% CI) for the association between atopic eczema severity and depression or anxiety in white and minority ethnic groups

Cohort	Minimally adjusted			Confounder adjusted			Mediator adjusted		
	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)	Number	Events/PYAR	HR (95% CI)
Depression									
White									
Unexposed	548,100	42,656/2,083,588	1 (reference)	541,478	41,994/2,054,242	1 (reference)	385,813	31,151/1,542,760	1 (reference)
Mild	152,503	13,208/570,467	1.09 (1.06, 1.11)	150,521	12,996/562,033	1.09 (1.06, 1.11)	118,859	10,760/462,020	1.01 (0.98, 1.03)
Moderate	32,616	4,095/155,585	1.39 (1.33, 1.45)	32,131	4,001/153,088	1.38 (1.33, 1.45)	27,841	3,461/134,754	1.22 (1.16, 1.28)
Severe	2,076	252/9,443	1.31 (1.10, 1.55)	2,042	249/9,221	1.38 (1.15, 1.64)	1,743	215/7,993	1.27 (1.04, 1.56)
Minority ethnic									
Unexposed	98,439	3,847/298,191	1 (reference)	97,992	3,839/296,708	1 (reference)	69,137	2,989/222,425	1 (reference)
Mild	26,426	1,400/85,437	1.19 (1.07, 1.31)	26,317	1,395/84,974	1.20 (1.08, 1.32)	21,098	1,202/71,247	1.01 (0.90, 1.14)
Moderate	5,092	496/22,938	1.91 (1.59, 2.30)	5,068	494/22,811	1.90 (1.58, 2.29)	4,450	438/20,367	1.71 (1.37, 2.14)
Severe	386	30/1,665	1.55 (0.76, 3.15)	385	30/1,657	1.60 (0.79, 3.26)	326	25/1,419	1.40 (0.61, 3.21)
Anxiety									
White									
Unexposed	661,005	38,443/2,550,372	1 (reference)	653,373	37,781/2,515,225	1 (reference)	478,957	29,019/1,934,703	1 (reference)
Mild	172,887	11,569/655,937	1.10 (1.08, 1.13)	170,721	11,359/646,642	1.10 (1.07, 1.13)	137,741	9,606/541,356	1.02 (0.99, 1.05)
Moderate	37,552	3,593/182,098	1.43 (1.37, 1.50)	36,998	3,503/179,234	1.43 (1.36, 1.50)	32,444	3,050/159,473	1.25 (1.18, 1.32)
Severe	2,350	222/10,862	1.34 (1.12, 1.61)	2,312	218/10,608	1.34 (1.11, 1.60)	1,992	193/9,248	1.21 (0.98, 1.50)
Minority ethnic									
Unexposed	113,108	3,227/347,855	1 (reference)	112,618	3,215/346,231	1 (reference)	81,361	2,469/265,107	1 (reference)
Mild	28,591	1,096/93,681	1.30 (1.17, 1.46)	28,476	1,090/93,193	1.32 (1.18, 1.47)	23,113	955/78,907	1.16 (1.02, 1.33)
Moderate	5,632	383/25,819	1.83 (1.49, 2.25)	5,607	381/25,683	1.83 (1.49, 2.25)	4,948	344/23,064	1.49 (1.18, 1.89)
Severe	420	30/1,834	1.15 (0.47, 2.84)	419	30/1,826	1.11 (0.45, 2.75)	356	23/1,551	0.45 (0.14, 1.51)

P values for interaction by ethnicity is p<0.01 for all models and outcomes. Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; PYAR – Person years at risk
[a] Matched sets including one exposed patient and at least one unexposed patient.
[b] Adjusted for calendar time and quintiles of Carstairs deprivation index (using 2011 census data)
[c] Cohort is further adjusted for comorbidity burden (using the Charlson comorbidity index), comorbid asthma, sleep problems, smoking status, high dose glucocorticoid use, harmful alcohol use and body mass index
[d] Estimated hazard ratios from Cox regression with current age as underlying timescale, stratified by matched set (matched on age at cohort entry, sex, general practice, and date at cohort entry)