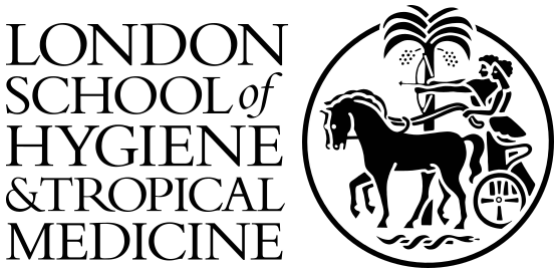

Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study

Yochai Schonmann MD MSc*[1-3], Kathryn E. Mansfield MBBS BSc MRes PhD*[1], Joseph F. Hayes MB.ChB MSc PhD[4,5], Katrina Abuabara MD MsCE MA[6], Amanda Roberts Bsc[8], Liam Smeeth MBChB FRCGP FFPH FRCP MSc PhD FMedSci[1], Sinéad M. Langan FRCP MSc PhD[1,7,9]

*Contributed equally

1. Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK.
2. Clalit Health Services; Department of Family Medicine, Rabin Medical Center, Petah Tikva, Israel
3. Department of Family medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
4. UCL Division of Psychiatry, University College London, UK.
5. Camden and Islington NHS Foundation Trust, London, UK.
6. Program for Clinical Research, Department of Dermatology, University of California San Francisco, San Francisco, CA, U.S.A.
7. St John's Institute of Dermatology, Guy's & St Thomas' Hospital NHS Foundation Trust and King's College London, London, U.K.
8. Nottingham Support Group for Carers of Children with Eczema, Nottingham, UK.
9. Health Data Research UK.

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Address for correspondence: Kathryn Mansfield, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK. +44 (0)20 7636 8636
kathryn.mansfield@lshtm.ac.uk

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ABSTRACT

Background

Atopic eczema is a common and debilitating condition associated with depression and anxiety, but the nature of this association remains unclear.

Objective

To explore the temporal relationship between atopic eczema and new depression/anxiety.

Methods

A matched cohort study using routinely-collected data from the UK Clinical Practice Research Datalink, linked to hospital admissions data. We identified adults with atopic eczema (1998-2016) using a validated algorithm, and up to five individuals without atopic eczema matched on date of diagnosis, age, sex and general practice. We estimated the hazard ratio (HR) for new depression/anxiety using stratified Cox regression to account for age, sex, calendar period, Index of Multiple Deprivation, glucocorticoid treatment, obesity, smoking and harmful alcohol use.

Results

We identified 526,808 adults with atopic eczema who were matched to 2,569,030 without. Atopic eczema was associated with increased incidence of new depression (HR 1.14; 99% confidence interval [CI] 1.12-1.16), and anxiety (HR 1.17; 99% CI 1.14-1.19). We observed a stronger effect of atopic eczema on depression with increasing atopic eczema severity (HR [99% CI] compared to no atopic eczema: mild 1.10 [1.08-1.13]; moderate 1.19 [1.15-1.23]; severe 1.26 [1.17-1.37]). A dose-response association, however, was less apparent for new anxiety diagnosis (HR [99% CI] compared to no atopic eczema: mild 1.14 [1.11-1.18]; moderate 1.21 [1.17-1.26]; severe 1.15; [1.05-1.25]).

Conclusions

Adults with atopic eczema are more likely to develop new depression and anxiety. For depression, we observed a dose-response relationship with atopic eczema severity.

KEYWORDS

atopic eczema; atopic dermatitis; anxiety; depression; population-based; severity

ABBREVIATIONS

CPRD	Clinical Practice Research Datalink
HR	Hazard ratio
BMI	Body mass index
IMD	Index of Multiple Deprivation
CI	Confidence interval
HES	Hospital Episode Statistics
IQR	Inter-quartile range
GP	General Practitioner
UK	United Kingdom
GAD	Generalised anxiety disorder
DAG	Directed acyclic graph
SD	Standard deviation
UTS	Up-to-standard

HIGHLIGHTS BOX

What is already known about this topic?

Atopic eczema is a common debilitating skin condition. An association between atopic eczema and common mental disorders is well-documented, but its nature and temporal direction remain unclear.

What does this article add to our knowledge?

Individuals affected with atopic eczema are more likely to develop new depression (14% increased incidence) and anxiety (17% increased incidence). The observed dose-response relationship between atopic eczema severity and depression supports a causal mechanism for the association.

How does this study impact current management guidelines?

Recent atopic eczema guidelines comment briefly on the influence of psychological and emotional factors on the clinical course of atopic eczema. Our findings suggest that depression and anxiety should be addressed explicitly in updated guidelines.

INTRODUCTION

Atopic eczema (eczema, atopic dermatitis) is a chronic relapsing inflammatory skin disease. It can cause intense itching and discomfort. Itch and disfiguring lesions result in sleeplessness and social embarrassment, impairing the quality of life of both sufferers and their families.[1,2] Atopic eczema is common (20% of children and up to 10% of adults in developed countries) and is a major cause of years lost due to disability.[2–4] Emerging evidence suggests that biologic agents, an effective treatment modality for severe atopic eczema,[2,5,6] may also reduce symptoms of depression and anxiety among people with atopic eczema.[7]

Mental health disorders are one of the leading causes of disability worldwide,[8] with depression and anxiety together accounting for over half of that burden.[9] Depression, manifesting as loss of interest and enjoyment in ordinary things and experiences, affects approximately 4.4% of the global population; anxiety disorders, characterised by excessive fear, anxiousness, or avoidance of perceived threats, affect approximately 3.6%.[10] Both depression and anxiety are associated with increased morbidity and mortality.[11–15] Atopic eczema has been shown to be associated with common mental disorders (depression and anxiety) and suicidality in cross-sectional studies that have frequently relied on self-reported exposures and outcomes.[16–25] Individuals with atopic eczema may be more likely to experience depression and anxiety through the effects of itch and discomfort, disfigurement, and perceived social-stigmatisation;[26–28] additionally, poor sleep related to atopic eczema may increase the risk of mental illness.[29,30] Inflammatory mediators in atopic eczema could also contribute to the development of depression.[22,31] However, those with depression and anxiety could also be more likely to consult for a physical condition

such as atopic eczema. As longitudinal evidence is scarce and conflicting, the temporality of any association between atopic eczema and depression and anxiety, and whether the relationship changes with increasing atopic eczema severity, remains unclear.[32–34]

Insight into the temporal relationship between atopic eczema and depression/anxiety could guide the clinical approach to this vulnerable group with visible and potentially stigmatising skin disease. Atopic eczema is common, so if people with atopic eczema are indeed at increased risk of new-onset depression or anxiety, then this would suggest: 1) a major population impact; 2) a potential role for targeted mental health screening for individuals with atopic eczema; and 3) the possibility of mental health modification through improved atopic eczema control (for example, using new biologic agents). Therefore, we aimed to investigate the association between atopic eczema and newly-diagnosed depression and anxiety, and whether any association increased with increasing atopic eczema severity through a longitudinal analysis of UK primary care electronic health record data.

METHODS

Study design and setting

We conducted a cohort study, using routinely-collected primary care electronic health record data from practices contributing to the UK Clinical Practice Research Datalink (CPRD), and linked hospital admissions data from the Hospital Episode Statistics (HES) database. The CPRD covers approximately 7% of the UK population, is broadly representative of the general population and includes demographic information, diagnoses, prescriptions and secondary care referrals.[35] Diagnoses are recorded in the CPRD using Read codes,[36] and have been demonstrated to be valid.[37,38] The CPRD assures high-quality data through algorithmic analysis of gaps in data entry and deaths recorded by each practice.[35] HES includes data on all the National Health Service funded inpatient hospital stays in England since 1997, including diagnoses recorded using the International Classification of Diseases, 10th revision coding system (ICD-10).[39] Linkage to HES data is available in approximately 80% of English CPRD practices. The study period was from 02/01/1998-31/03/2016.

Study population

Individuals with atopic eczema and disease severity

Atopic eczema diagnosis was based on a validated algorithm (positive predictive value of 82%) requiring a record of at least one diagnostic code for atopic eczema and at least two records for atopic eczema therapy.[40] Systemic glucocorticoids were not included in the validated algorithm to identify atopic eczema, and their use is generally discouraged.[41] (**Text E1**). Other inclusion criteria were: adults aged 18 years and over; eligible for HES linkage; registered with a CPRD practice meeting

CPRD patient- and practice-level quality control standards; and contribution of valid follow-up time during the study period (02/01/1998-31/03/2016).

To capture the progressive nature of atopic eczema and to avoid immortal-time bias, atopic eczema severity was modelled as a time-updated variable.[42] We categorised severity into three, mutually exclusive, progressive categories (mild, moderate and severe) according to recorded atopic eczema therapy.[5,43,44] By default, all individuals with atopic eczema were classified as having mild disease. They could be re-categorised as: 1) moderate atopic eczema if potent topical steroids or calcineurin inhibitors were prescribed; or 2) severe, if there was a record for a referral to a dermatologist, or a record for systemic treatment. Individuals with moderate/severe disease kept their severity category until the end of follow-up and could not be re-categorised as having milder disease (**Text E1**).

Comparison group of individuals without atopic eczema

Each atopic eczema-exposed individual was matched (without replacement) with up to five individuals without atopic eczema on sex, age, general practice and calendar time. Unexposed individuals had no record of a diagnostic code for atopic eczema (in CPRD or HES) but were required to have at least one year of follow-up in CPRD as well as meet all other inclusion criteria. To minimise selection bias due to the exclusion of unmatched individuals and closely adjust for its effects, age was matched in 15-year strata and used as the underlying time scale for all analysis. To avoid misclassifying unexposed person-time, individuals could contribute unexposed person-time until the date of their first record of a diagnostic code for atopic eczema, regardless of later therapies prescribed. (**Figure E1**)

Outcomes

We considered depression and anxiety as separate outcomes, with onset defined as the date of the first recorded diagnosis in either CPRD or HES (any inpatient hospital diagnosis). Codes for the depression outcome were those compatible with unipolar depression,[45] and for the anxiety outcome, included those consistent with generalised anxiety (GAD) and panic disorders. We considered broader definitions of depression and anxiety in pre-specified sensitivity analyses (**Text E2**).

Defining follow-up

Individuals entered the cohort at the latest of: practice registration date plus 12 months; the date their practice met CPRD quality control standards; the date an individual met our atopic eczema diagnosis definition; or the start of the study (02/01/1998). Individuals without atopic eczema entered the cohort on the same day as their matched atopic eczema-exposed case. We included a mandatory 'wash-in' period of 12 months prior to cohort entry to assure adequate time to capture true incident outcome diagnoses, as well as other baseline variables (e.g. body mass index [BMI], smoking).[46]

Cohort members were followed until the first of the following events: anxiety or depression diagnosis (depending on analysis); a diagnosis suggesting an alternative cause for each outcome (i.e. organic depression or dementia for depression analyses; obsessive-compulsive disorder or post-traumatic stress disorder anxiety analyses; and schizophrenia or bipolar disease for both depression and anxiety analyses); record of a morbidity code for an atopic eczema diagnosis (for the unexposed group); death date recorded in CPRD; end of registration with practice; last data collection from practice; or the end of the study (31/03/2016).

Covariates

Covariate selection was guided by a literature review and construction of a directed acyclic graph (DAG) to avoid collider bias.[47,48] (**Text E3, Figure E2, Tables E1 and E2**) Age, calendar period, sex, and level of deprivation (as quintiles of the Index of Multiple Deprivation score [IMD]), and ethnic group were deemed plausibly associated with both exposure and outcome, and not on the causal pathway (i.e. potential confounders). We considered BMI, smoking status, harmful alcohol use, and high-dose oral glucocorticoid as possible mediators of the association between atopic eczema and depression/anxiety. The data sources and definitions used to identify all covariates are detailed in **Texts E4 and E5** and morbidity code lists are available to download (https://doi.org/10.17037/DATA.00000941).

Statistical analysis

We assessed the effect of the atopic eczema exposure on each outcome (depression or anxiety) using Cox regression stratified by matched set. We included the covariates used for matching in an initial crude model (implicitly adjusted for sex and general practice by stratification on matched set, and for age through the underlying timescale). We then adjusted for the remaining pre-specified potential confounders (calendar period and IMD) in an adjusted model. Finally, we also further adjusted for potential mediators of the relationship between atopic eczema and depression/anxiety (BMI; smoking; harmful alcohol and high-dose oral glucocorticoid use) in a third model. To preserve matching, analyses only included valid matched sets; i.e. entire matched sets were excluded if the atopic eczema exposed individual was excluded (due to pre-existing outcome diagnosis at cohort entry, or due to missing BMI or smoking data in the models including possible mediators of the

relationship between atopic eczema and depression/anxiety), or if no individuals without atopic eczema remained in the set.

The absolute incidence rates of new depression and anxiety could be directly calculated among those with atopic eczema, but matching precluded a similar approach in those without atopic eczema (as this was not a representative sample of the general population). We, therefore, estimated incidence rates in those without atopic eczema by multiplying rates in those with atopic eczema by the corresponding estimated hazard ratio (after inverting it to compare unexposed with exposed).[49] We calculated attributable risks as the difference between the incidence rates in those with and without atopic eczema, and the population attributable risks by using the estimated hazard ratio and assuming the prevalence of atopic eczema to be 10%.[50]

We conducted a series of sensitivity analyses to explore possible sources of bias introduced by: strict definitions of the psychiatric diagnoses; use of a 'mixed' incident and prevalent cohort; differential practice attendance; or restrictive algorithm-based definitions of atopic eczema (**Table E3**).

In pre-specified secondary analyses, we: 1) redefined atopic eczema exposure using atopic eczema severity as a time-updated variable and compared incidence rates of depression and anxiety in those with mild, moderate or severe atopic eczema to those with no atopic eczema; and 2) explored possible effect modification of the relationship between atopic eczema and depression/anxiety by age, sex and calendar period.

We checked the proportional hazards assumption for the main analysis models through visual inspection of Schöenfeld residual plots. All p-values reported are

based on likelihood-ratio tests, with 99%.[51] Statistical analysis was performed using Stata, version 15.1 (StataCorp LP, College Station, Texas).

RESULTS

Baseline characteristics

We identified 3,095,838 adults aged 18 years or older, including 526,808 with atopic eczema, and matched them to 2,569,030 without (**Figure 1**). Further exclusions of individuals with relevant pre-existing psychiatric diagnoses on or before the start of follow up yielded 2,467,791 participants in the cohort for analyses with depression as the outcome, and 2,650,629 with anxiety as the outcome (all belonging to 'valid sets', i.e. matched sets with at least one exposed and one unexposed individual). Median follow-up was similar in both cohorts: 4.7 (interquartile range [IQR] 1.6-8.6) years for individuals with atopic eczema and 4.2 (IQR 1.9-9.1) for those without atopic eczema (**Table 1**). The mean age of the atopic eczema exposed individuals was 43.9 years (standard deviation [SD] ±21.7) in the depression cohort and 44.1 (SD±21.43) in the anxiety cohort.

Participants with atopic eczema were less likely to have missing BMI values or smoking status, compared to those without atopic eczema, and those with missing information were more likely to be young and male (**Tables E4 and E5**).

Main analysis

We explored diagnoses compatible with unipolar depression, GAD, and panic disorders as the primary outcomes. There was a 1.14-fold (99%CI 1.12-1.16) increase in the HR for depression in those with atopic eczema compared to those without, after adjusting for age, sex, general practice, current calendar period and

IMD at cohort entry (**Table 2**. Full model **Table E6**). Atopic eczema was also associated with a 1.17-fold (99%CI 1.14-1.19) increase in the risk of anxiety. Both estimates were attenuated after additionally adjusting for BMI, smoking status, harmful alcohol use, and high-dose corticosteroid use (variables that may mediate the relationship between atopic eczema and depression/anxiety) (depression: HR 1.10 [99%CI 1.10-1.12]; anxiety: HR 1.12 [99%CI 1.10-1.15]). The absolute excess risk of depression/anxiety among those with atopic eczema that could be considered due to atopic eczema (attributable risk) was 160 per 100,000 person-years with atopic eczema (99%CI 146-186) for depression, and 144 per 100,000 for anxiety (115-153). While the excess risk of depression/anxiety in the population that could be considered due to atopic eczema (population attributable risk) was 1.4% (95%CI 1.2-1.6) for depression, and 1.7% (1.4-1.9) for anxiety (**Table E7**) (these estimates were calculated assuming a 10% prevalence of atopic eczema and would increase if atopic eczema were more common).

Our sensitivity analyses showed broadly similar effect estimates-those from the main analysis (**Table E3**).

Secondary analyses

Atopic eczema severity

Regardless of atopic eczema severity level, we saw evidence for an association between atopic eczema and both depression and anxiety (**Figure 2**). Compared to those without atopic eczema, the risk of depression increased with increasing atopic eczema severity (P<0.0001 for linearity; P=0.3832 for departure from linearity in the adjusted model, and P=0.6983 for departure from linearity in the model additionally adjusted for potential mediators). However, the results of analyses exploring the

relationship between atopic eczema severity and anxiety did not demonstrate a similarly clear dose-response relationship; for mild and moderate atopic eczema there was some evidence of a similar dose-response increase, but there was strong statistical evidence for departure from linearity (P<0.0001) (**Table E8**).

Effect modification by sex, age and calendar period

We saw some evidence (P<0.0001) for sex modifying the effect of atopic eczema on depression; with a slightly higher risk of depression in those with atopic eczema compared to those without in men (1.19 [99%CI 1.16-1.23]) than in women (1.11 [99%CI 1.08-1.13]). We saw a similar pattern for risk of anxiety in those with and without atopic eczema after stratifying on sex (HR [99% CI): Men 1.22 [99%CI 1.17-1.27]; women 1.14 [99%CI 1.11-1.17]. P=0.0003 for interaction). We also saw evidence for effect modification by current age, with the HR comparing those with atopic eczema to those without for both depression (P<0.0001) and anxiety (P=0.0052) being higher in those aged 40-59, compared to younger and older age groups. There was no evidence of a change in the effect of atopic eczema on both depression (p=0.3229) and anxiety (p=0.287) in different calendar periods (**Table E9**).

DISCUSSION

Main findings

We found that (treated) atopic eczema was associated with a 14% increase in the risk of newly diagnosed depression (adjusted HR 99%CI 1.12-1.16), and a 17% increase in the risk of a subsequent anxiety diagnosis (adjusted HR 99%CI 1.14-1.19). These associations were only slightly attenuated after further adjusting for potential mediators of the association between atopic eczema and

anxiety/depression (BMI, smoking status, and alcohol and high-dose corticosteroid use) and were present at all levels of atopic eczema disease severity. Risk of a new depression diagnosis increased linearly with increasing atopic eczema severity, providing strong evidence for a dose-response association. The outcomes were diagnoses compatible with unipolar depression, GAD, and panic disorders, but we considered broader definitions of depression/anxiety in subsequent sensitivity analyses.

Strengths and limitations

We identified a large, nationally-representative sample of people, the largest reported to-date,[20,21] assuring precise effect estimations, and increased generalisability. We used a validated diagnostic algorithm to identify atopic eczema in primary care,[52] and relied on highly-specific physician-diagnoses rather than self-reported outcomes.[53–55] We chose the covariates included in the analysis based on *a priori* reasoning (**Text E3, Figure E2**).[48] While some chronic conditions may be associated with atopic eczema,[56] as well as with depression/anxiety,[57] in the context of this study, we did not consider these conditions fit the definition for confounding because the potential confounder (chronic comorbidity) could be considered to be either a consequence of the outcome (anxiety/depression), or to mediate the relationship between exposure and outcome (**Text E3**).

We deemed other factors (i.e. BMI, smoking, systemic glucocorticoids, harmful alcohol use) as likely mediators of the effect of atopic eczema on depression and anxiety, rather than confounders; we consequently adjusted for these variables separately. Atopic eczema may be associated with the later development of conditions such as cardiovascular disease and various malignancies,[49,56] but

exploring the potential mediating role of chronic comorbidity was beyond the scope of our analysis.

The study also has several limitations. The algorithm we used to define atopic eczema excluded untreated individuals, reducing its sensitivity to detect milder cases.[58] This limitation was mitigated by the availability of primary care data, as 97% of those with atopic eczema in the UK are managed in primary care,[59,60] and by including emollients, which are routinely prescribed for atopic eczema in the UK.[61] The results also remained robust in sensitivity analyses using less restrictive atopic eczema definitions. Analyses stratified by atopic eczema severity provided further reassuring evidence of an association between atopic eczema and anxiety/depression even among mild cases. However, our definition of atopic eczema severity might have misclassified individuals with severe atopic eczema as having less severe disease if they refused medical therapy.[62] Misclassification of disease status or severity may have over- or under-estimated the real association between severity of eczema and anxiety/depression, since early symptoms of depression/anxiety could influence diagnostic and treatment preferences. However, GPs recorded their depression/anxiety diagnoses independently and prospectively, so reverse causality likely affected all study participants equally regardless of atopic eczema status (i.e. non-differential misclassification, suggesting bias towards the null rather than a spurious association).

A further limitation of our eczema severity definition was that we were unable to capture symptom reduction or resolution (absence of a record for eczema does not necessarily mean absence in symptoms). Consequently, we considered individuals as having moderate or severe disease from the date they met the respective

definition, and may therefore have wrongly classified people as having moderate/severe eczema when their symptoms had reduced or resolved. The result of wrongly classifying individuals as having more severe disease when their symptoms had actually remitted would only be to dilute the effect of eczema severity on depression/anxiety and bias our effect estimate to null.

Follow-up began in adulthood, resulting in a mixed cohort of prevalent and incident (newly diagnosed) atopic eczema cases, introducing possible bias due to left truncation (i.e. the possibility of an outcome event occurring before cohort entry), with consequent under or overestimation of the effect of atopic eczema on depression and anxiety. However, following only incident cases when exploring predominantly adult-onset outcomes would have shortened follow-up and limited the study's power. Additionally, the exact onset date of a relapsing condition such as atopic eczema cannot be captured accurately in routinely-collected data; In such circumstances, a dynamic cohort including prevalent cases is preferred.[63] A sensitivity analysis offered evidence against bias introduced by including both 'incident' and prevalent atopic eczema cases in our cohort; as it showed broadly similar results in those with prevalent atopic eczema, and those more likely to have new-onset atopic eczema.

Smoking status and/or BMI were not recorded for some study participants, and it is likely that whether smoking status/BMI were recorded or not of was dependent on having atopic eczema or anxiety/depression (i.e. missing not-at-random). BMI and smoking status are often captured opportunistically and are therefore more likely to be recorded in those who consult their GP more frequently (due to health-seeking behaviour or chronic conditions).[64] While previous studies suggested no clear-cut

association between physical illness and detection of psychiatric diagnoses in primary-care,[65,66] the possibility of selection bias when applying complete case analysis (i.e. including only those with complete data) remains. In our study, this did not affect the main analysis, as the variables containing missing data were not included in the main adjusted analysis (they were considered as potential mediators). Comparable results from the model including smoking and BMI, also provide evidence against substantial bias introduced by missing data. Finally, GPs do not routinely record patients' quality of sleep, and we were not able to assess the extent to which itch-related sleep disturbances mediate the development of depression and anxiety among people with atopic eczema.[30]

Comparisons to existing literature

An association between atopic eczema, depression and anxiety has been described in cross-sectional and case-control studies, in which the temporal sequence (i.e. whether atopic eczema precedes depression or anxiety, or vice versa) could not be determined.[16–22] The few longitudinal studies that addressed this question had inconsistent results.[32–34] These studies were limited by short follow-up windows;[34] inclusion of selected, non-representative populations (e.g. male military conscripts,[34] or secondary-care diagnoses [32,33]); no account of atopic eczema disease severity;[32,34] low-quality or no individual-level information on lifestyle variables;[32,34] and reliance on disease-specific medication usage as a non-specific proxy measure to ascertain depression and anxiety.[33,34] Notably, a recent Danish cohort study demonstrated point-estimates that were in-line with the estimates reported in our study, but the association was not evident in the adjusted models that included healthcare consumption.[33]

Interpretation and clinical implications

Atopic eczema, like several other chronic conditions,[57] is associated with depression/anxiety. The link to chronic mental illness further supports the view of atopic eczema as a systemic disorder.[67] Our results suggest that the association between atopic eczema and depression/anxiety is not substantially mediated through glucocorticoid treatment, obesity, smoking, or harmful alcohol intake. Evidence against a dose-response association between atopic eczema severity and anxiety could imply different pathophysiological mechanisms, but could also reflect misclassification of outcome, as the anxiety outcome was more heterogeneously defined. Our findings suggest that atopic eczema was more strongly associated with depression and anxiety in those aged 40-59 (compared to younger and older age groups). However, it is unclear why; further research could investigate possible explanations for differences in the association between atopic eczema and depression/anxiety risk in those at different ages (for example, different age-specific coping strategies, or increased health care contacts due to active cardiovascular screening in that age group). Future research could also support our findings of a dose-response association between atopic eczema and depression/anxiety by including people with more severe forms of these conditions (e.g. identified using prescriptions for antidepressants and anxiolytic medications).

While our results apply directly to UK primary care, they are likely to be relevant in other settings, especially where there is primary care-oriented universal access to healthcare. Mental illness is underdiagnosed in people with skin or other chronic diseases,[68–70] but their detection and treatment might improve atopic eczema control by facilitating better adherence to skin disease treatment,[71] or through direct anti-

inflammatory actions of antidepressants.[72] Current UK guidelines address only the management of atopic eczema in children, emphasising the importance of assessing the psycho-social well-being and quality of life.[73] Recent guidelines from the European Academy of Dermatology and Venereology comment briefly on the influence of psychological and emotional factors on the clinical course of atopic eczema.[5] Neither of these guidelines mentions the long-term mental-health implications of atopic eczema. Our findings suggest that depression and anxiety should be addressed explicitly in future guideline updates. Further research is needed to explore and define possible mediators; to characterise subpopulations at increased risk (e.g. those with adult-onset atopic eczema, or those with more active variants of the disease); and to elucidate the feasibility and effectiveness of screening, early detection and prevention of depression and anxiety among those with atopic eczema.

Conclusions

Individuals affected with atopic eczema were more likely to develop depression and anxiety, regardless of atopic eczema severity. Strong evidence for a dose-response relationship between atopic eczema severity and depression supports a causal association. These results highlight the importance of a comprehensive bio-psycho-social approach to limit common mental disorders in those with atopic eczema and could guide recommendations for the management of atopic eczema.

DECLARATIONS

Contributions

SML had the original idea for the study. YS and KEM contributed equally to this paper. All authors were involved in the study design. KEM undertook the initial data management. YS undertook the statistical analysis, under the supervision of KEM and SML. YS wrote the first manuscript draft. All authors contributed to subsequent drafts and approved the final manuscript.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders.

Ethical approval

The study protocol was approved by the Independent Scientific Advisory Committee for the Clinical Practice Research Datalink (ISAC protocol number: 16_100RA) and the London School of Hygiene and Tropical Medicine (Reference: 15460).

Informed consent was not required, as the study used anonymised data.

Data sharing

No additional data are available.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

KA reports personal fees from TARGETDerm for guidance on the development of an atopic dermatitis registry outside the submitted work. The other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Patient involvement

The research questions, design, conduct, and initial results and interpretation of the findings of this study have been overseen by the Wellcome Senior Clinical Fellowship steering committee, which includes lay representation. A patient-representative, AR, was involved in this study as a co-author.

We are not able to disseminate the results of the research directly to study participants because the data used were anonymised.

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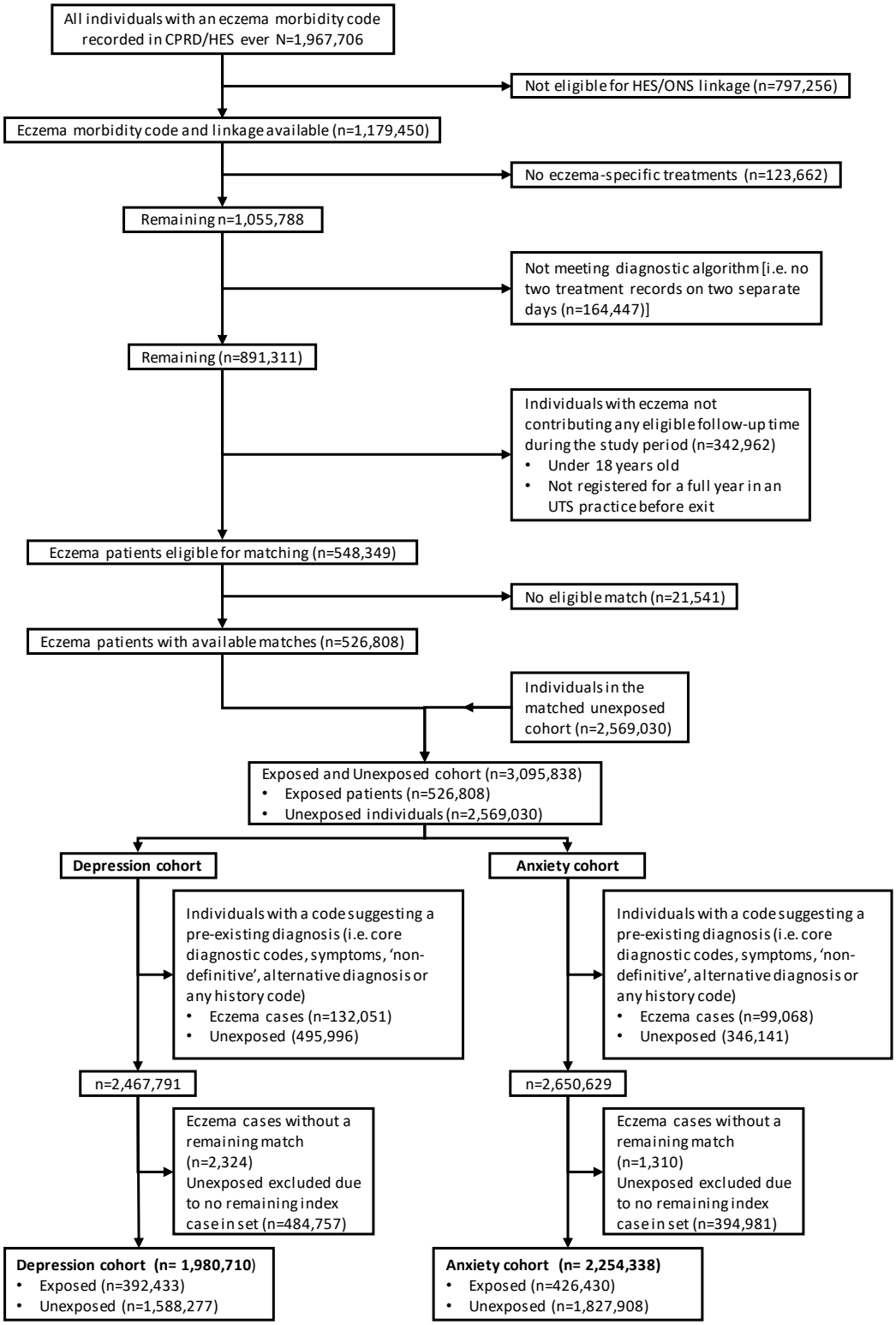
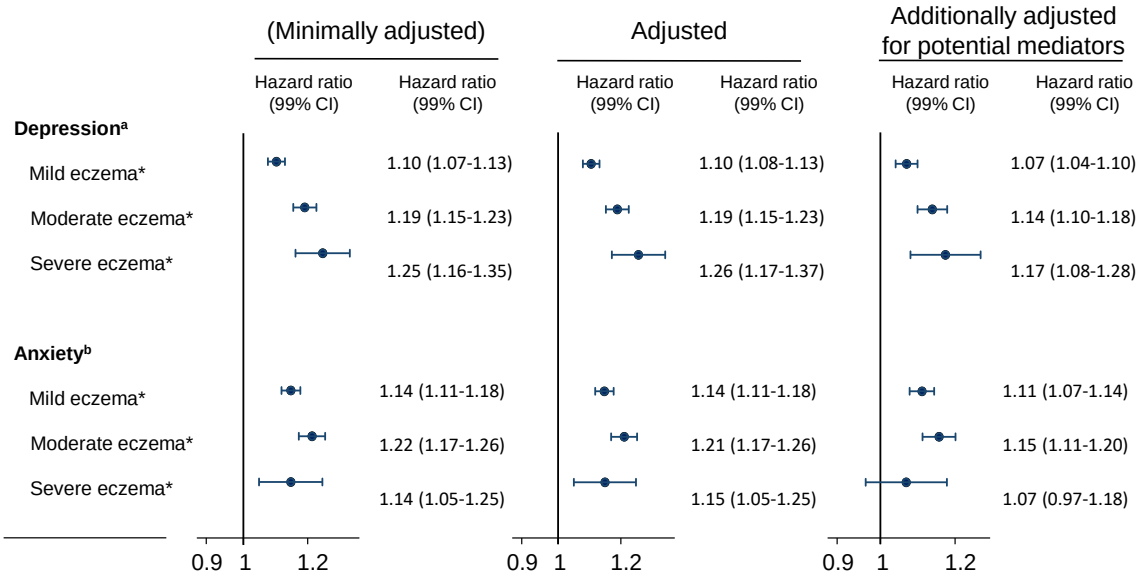
763 **FIGURES**

764 **Figure 1. Flow diagram showing the creation of the cohort and reasons for**
765 **exclusion (1998-2016)**



766
767 Abbreviations: CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics UTS, up-
768 to-standard

Figure 2. Hazard ratios (99%CI) for the association between eczema severity (time-updated) and depression and anxiety.



* compared to no atopic eczema

Abbreviations: BMI, body mass index; IMD, index of multiple deprivation.

All models were fitted to people with complete data for all included variables. Sets without at least one exposed and one unexposed were excluded. Hazard ratios were estimated from a Cox regression model with current age as the underlying time scale, stratified by matched set (sex, age and general practice).

A **minimally adjusted** model accounted for the matching variables (1,980,710 participants in the depression cohort [1,920,172 unique people], and 2,242,905 in the anxiety cohort [2,171,784 unique people]).

The **adjusted** model additionally included current calendar period (years: 1998-2001, 2002-06, 2007-11, 2012 16,) and quintiles of IMD at cohort entry (same participants as in the minimally adjusted).

A final model, **additionally adjusted for potential mediators** included also BMI (categorised as normal, 18.5-24 kg/m2; underweight, <18.5 kg/m2; overweight 25-29 kg/m2; obese ≥30 kg/m2) smoking status, and alcohol and high-dose corticosteroid use (≥20 mg/day prednisolone equivalent dose), both as time updated variables (1,371,005 participants in the depression cohort [1,322,284 unique people], and 1,583,390 in the anxiety cohort [1,583,390 unique people]).

a. Depression - P-values were <0.0001 for linearity in all models, and for departure from linearity were: minimally adjusted p=0.3810; adjusted p=0.3832; and additionally adjusted for potential mediators p=0.6983.

b. Anxiety - P-values were <0.0001 for linearity in all models, and <0.0001 for departure from linearity in all models.

TABLES

Table 1. Characteristics of people with and without atopic eczema at cohort entry for both depression and anxiety cohorts.

	Depression cohort		Anxiety cohort	
Characteristic*	Without atopic eczema n=1,588,277	With atopic eczema n=392,433	Without atopic eczema n=1,827,908	With atopic eczema n=426,430
Follow-up (years), median (IQR)	4.21 (1.63-8.62)	4.72 (1.86-9.12)	4.18 (1.62-8.6)	4.71 (1.85-9.13)
Female sex	802,909 (50.6%)	211,118 (53.8%)	981,824 (53.1%)	237,527 (55.7%)
Age (years)				
18-39	828,072 (52.1%)	195,455 (49.8%)	941,183 (51.5%)	210,764 (49.4%)
40-59	355,209 (22.4%)	89,126 (22.7%)	431,329 (23.6%)	100,592 (23.6%)
≥60	404,996 (25.5%)	107,852 (27.5%)	455,396 (24.9%)	115,074 (27.0%)
Index of multiple deprivation (quintiles)				
1 (least deprived)	395,025 (24.9%)	99,161 (25.3%)	443,389 (24.3%)	104,672 (24.6%)
2	368,687 (23.2%)	91,856 (23.4%)	419,555 (23.0%)	98,500 (23.1%)
3	311,975 (19.6%)	76,756 (19.6%)	360,901 (19.7%)	84,121 (19.7%)
4	295,103 (18.6%)	72,538 (18.5%)	346,152 (18.9%)	80,198 (18.8%)
5 (most deprived)	217,487 (13.7%)	52,122 (13.3%)	257,911 (14.1%)	58,939 (13.8%)
Body mass index (kg/m2), mean (SD)	25.74 (5.1)	26.01 (5.3)	25.87 (5.2)	26.18 (5.4)
Normal (18.5-24 kg/m^2)	574,056 (36.1%)	147,216 (37.5%)	663,955 (36.3%)	158,315 (37.1%)
Underweight (<18.5 kg/m^2)	40,118 (2.5%)	9,830 (2.5%)	46,346 (2.5%)	10,536 (2.5%)
Overweight (25-29 kg/m^2)	397,525 (25.0%)	105,468 (26.9%)	460,537 (25.2%)	114,921 (27.0%)
Obese (≥30 kg/m^2)	209,823 (13.2%)	60,643 (15.5%)	258,799 (14.2%)	70,714 (15.6%)
Missing	366,755 (23.1%)	69,276 (17.7%)	398,271 (21.8%)	71,944 (16.9%)
Smoking status				
Non-smoker	833,152 (52.5%)	211,240 (53.8%)	939,278 (51.4%)	222,529 (52.2%)
Current/ex-smoker	638,023 (40.2%)	168,778 (43.0%)	763,295 (41.8%)	191,066 (44.8%)
Missing	117,102 (7.4%)	12,415 (3.2%)	125,335 (6.9%)	12,835 (3.0%)
Harmful alcohol use	23,244 (1.5%)	7,114 (1.8%)	31,639 (1.7%)	9,119 (2.1%)
High-dose glucocorticoids (>=20 mg/day prednisolone equivalent dose)	65,155 (4.1%)	42,738 (10.9%)	78,579 (4.3%)	47,840 (11.2%)

Abbreviations: IQR, interquartile range; SD, standard deviation.

* See **Text E4** for details of variable definitions.

Table 2. Hazard ratios (99% CI) from Cox regression for the association between atopic eczema and anxiety and depression.

			Minimally adjusted*	Adjusted**	Additionally adjusted for potential mediators***		
	No.	Events/PYAR	Hazard Ratio (99% CI)	Hazard Ratio (99% CI)	No.	Events/PYAR	Hazard Ratio (99% CI)
Depression							
No atopic eczema	1,588,277	102,882/8,935,934	1.00 (ref)	1.00 (ref)	1,054,673	76,638/6,531,745	1.00 (ref)
Atopic eczema	392,433	31,322/2,354,118	1.14 (1.12-1.16)	1.14 (1.12-1.16)	316,332	27,405/2,042,715	1.10 (1.07-1.12)
Anxiety							
No atopic eczema	1,818,796	82,137/10,187,499	1.00 (ref)	1.00 (ref)	1,237,423	63,592/7,566,056	1.00 (ref)
Atopic eczema	424,109	24,283/2,543,384	1.17 (1.14-1.19)	1.17 (1.14-1.19)	345,967	21,666/2,223,508	1.12 (1.09-1.15)

Abbreviations: BMI, body mass index; IMD, index of multiple deprivation; CI, confidence interval; PYAR, person years at risk.
All models were fitted to people with complete data for all included variables. Matched sets without at least one individual with atopic eczema and one without were excluded. Hazard ratios were estimated from a Cox regression model with current age as the underlying time scale, stratified by matched set (sex, age and general practice).
*M**inimally-adjusted** model accounted for the matching variables (1,980,710 participants in the depression cohort [1,920,172 unique people], and 2,242,905 in the anxiety cohort [2,171,784 unique people]).
The **adjusted model additionally included current calendar period (years: 1998-2001, 2002-06, 2007-11, 2012-16) and quintiles of IMD at cohort entry (same participants as in the minimally adjusted).
***__Additionally adjusted for potential mediators:__ BMI (categorised as normal, 18.5-24 kg/m2; underweight, <18.5 kg/m2; overweight 25-29 kg/m2; obese ≥30 kg/m2) smoking status, and alcohol and high-dose corticosteroid use (≥20 mg/day prednisolone equivalent dose), both as time updated variables (1,371,005 participants in the depression cohort [1,322,284 unique people], and 1,583,390 in the anxiety cohort [1,583,390 unique people]).