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Schonmann, Yochai; Mansfield, Kathryn E; Hayes, Joseph F; Abuabara, Katrina; Roberts, Amanda; Smeeth, Liam; Langan, Sinéad M; (2019) Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study. *Journal of Allergy and Clinical Immunology: In Practice*. ISSN 2213-2198 DOI: <https://doi.org/10.1016/j.jaip.2019.08.030>

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

3 Yochai Schonmann MD MSc*¹⁻³, Kathryn E. Mansfield MBBS BSc MRes PhD*¹,
4 Joseph F. Hayes MB.ChB MSc PhD^{4,5}, Katrina Abuabara MD MsCE MA⁶, Amanda
5 Roberts Bsc⁸, Liam Smeeth MBChB FRCGP FFPH FRCP MSc PhD FMedSci¹,
6 Sinéad M. Langan FRCP MSc PhD^{1,7,9}

7 *Contributed equally

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

23 **Word count:** 3,917

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

27 **Funding:** This work was supported by a Wellcome Senior Research Fellowship in
28 Clinical Science (205039/Z/16/Z), and by Health Data Research UK (grant No.
29 LOND1), which is funded by the UK Medical Research Council, Engineering and
30 Physical Sciences Research Council, Economic and Social Research Council,
31 Department of Health and Social Care (England), Chief Scientist Office of the
32 Scottish Government Health and Social Care Directorates, Health and Social Care
33 Research and Development Division (Welsh Government), Public Health Agency
34 (Northern Ireland), British Heart Foundation and Wellcome Trust. The findings and
35 conclusions in this report are those of the authors and do not necessarily represent
36 the views of the funders.

37 **Conflicts of interest:** All authors have completed the ICMJE uniform disclosure
38 form at www.icmje.org/coi_disclosure.pdf (available on request from the
39 corresponding author).
40 KA reports personal fees from TARGETDerm for guidance on the development of an
41 atopic dermatitis registry outside the submitted work. The other authors declare no
42 support from any organisation for the submitted work; no financial relationships with
43 any organisations that might have an interest in the submitted work in the previous
44 three years, no other relationships or activities that could appear to have influenced
45 the submitted work.

46 **ABSTRACT**

47 **Background**

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

50 **Objective**

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

53 **Methods**

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

61 **Results**

62 We identified 526,808 adults with atopic eczema who were matched to 2,569,030
63 without. Atopic eczema was associated with increased incidence of new depression
64 (HR 1.14; 99% confidence interval [CI] 1.12-1.16), and anxiety (HR 1.17; 99% CI
65 1.14-1.19). We observed a stronger effect of atopic eczema on depression with
66 increasing atopic eczema severity (HR [99% CI] compared to no atopic eczema: mild
67 1.10 [1.08-1.13]; moderate 1.19 [1.15-1.23]; severe 1.26 [1.17-1.37]). A dose-
68 response association, however, was less apparent for new anxiety diagnosis (HR
69 [99% CI] compared to no atopic eczema: mild 1.14 [1.11-1.18]; moderate 1.21 [1.17-
70 1.26]; severe 1.15; [1.05-1.25]).

71 **Conclusions**

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

75 KEYWORDS

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

77 ABBREVIATIONS

78 CPRD Clinical Practice Research Datalink

79 HR Hazard ratio

80 BMI Body mass index

81 IMD Index of Multiple Deprivation

82 CI Confidence interval

83 HES Hospital Episode Statistics

84 IQR Inter-quartile range

85 GP General Practitioner

86 UK United Kingdom

87 GAD Generalised anxiety disorder

88 DAG Directed acyclic graph

89 SD Standard deviation

90 UTS Up-to-standard

91 **HIGHLIGHTS BOX**

92 **What is already known about this topic?**

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

96 **What does this article add to our knowledge?**

97 Individuals affected with atopic eczema are more likely to develop new depression
98 (14% increased incidence) and anxiety (17% increased incidence). The observed
99 dose-response relationship between atopic eczema severity and depression
100 supports a causal mechanism for the association.

101 **How does this study impact current management guidelines?**

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

105 INTRODUCTION

106 Atopic eczema (eczema, atopic dermatitis) is a chronic relapsing inflammatory skin
107 disease. It can cause intense itching and discomfort. Itch and disfiguring lesions
108 result in sleeplessness and social embarrassment, impairing the quality of life of both
109 sufferers and their families.^{1,2} Atopic eczema is common (20% of children and up to
110 10% of adults in developed countries) and is a major cause of years lost due to
111 disability.²⁻⁴ Emerging evidence suggests that biologic agents, an effective treatment
112 modality for severe atopic eczema,^{2,5,6} may also reduce symptoms of depression
113 and anxiety among people with atopic eczema.⁷

114 Mental health disorders are one of the leading causes of disability worldwide,⁸ with
115 depression and anxiety together accounting for over half of that burden.⁹

116 Depression, manifesting as loss of interest and enjoyment in ordinary things and
117 experiences, affects approximately 4.4% of the global population; anxiety disorders,
118 characterised by excessive fear, anxiousness, or avoidance of perceived threats,
119 affect approximately 3.6%.¹⁰ Both depression and anxiety are associated with
120 increased morbidity and mortality.¹¹⁻¹⁵ Atopic eczema has been shown to be
121 associated with common mental disorders (depression and anxiety) and suicidality in
122 cross-sectional studies that have frequently relied on self-reported exposures and
123 outcomes.¹⁶⁻²⁵ Individuals with atopic eczema may be more likely to experience
124 depression and anxiety through the effects of itch and discomfort, disfigurement, and
125 perceived social-stigmatisation;²⁶⁻²⁸ additionally, poor sleep related to atopic eczema
126 may increase the risk of mental illness.^{29,30} Inflammatory mediators in atopic eczema
127 could also contribute to the development of depression.^{22,31} However, those with
128 depression and anxiety could also be more likely to consult for a physical condition

129 such as atopic eczema. As longitudinal evidence is scarce and conflicting, the
130 temporality of any association between atopic eczema and depression and anxiety,
131 and whether the relationship changes with increasing atopic eczema severity,
132 remains unclear.³²⁻³⁴

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

144 **METHODS**

145 **Study design and setting**

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

160 **Study population**

161 *Individuals with atopic eczema and disease severity*

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

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

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

180 *Comparison group of individuals without atopic eczema*

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

191 **Outcomes**

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

198 **Defining follow-up**

199 Individuals entered the cohort at the latest of: practice registration date plus 12
200 months; the date their practice met CPRD quality control standards; the date an
201 individual met our atopic eczema diagnosis definition; or the start of the study
202 (02/01/1998). Individuals without atopic eczema entered the cohort on the same day
203 as their matched atopic eczema-exposed case. We included a mandatory 'wash-in'
204 period of 12 months prior to cohort entry to assure adequate time to capture true
205 incident outcome diagnoses, as well as other baseline variables (e.g. body mass
206 index [BMI], smoking).⁴⁶

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

215 **Covariates**

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

226 **Statistical analysis**

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

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

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

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

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

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

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

264 **RESULTS**

265 **Baseline characteristics**

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

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

280 **Main analysis**

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

285 IMD at cohort entry (**Table 2**. Full model **Table E6**). Atopic eczema was also
286 associated with a 1.17-fold (99%CI 1.14-1.19) increase in the risk of anxiety. Both
287 estimates were attenuated after additionally adjusting for BMI, smoking status,
288 harmful alcohol use, and high-dose corticosteroid use (variables that may mediate
289 the relationship between atopic eczema and depression/anxiety) (depression: HR
290 1.10 [99%CI 1.10-1.12]; anxiety: HR 1.12 [99%CI 1.10-1.15]). The absolute excess
291 risk of depression/anxiety among those with atopic eczema that could be considered
292 due to atopic eczema (attributable risk) was 160 per 100,000 person-years with
293 atopic eczema (99%CI 146-186) for depression, and 144 per 100,000 for anxiety
294 (115-153). While the excess risk of depression/anxiety in the population that could
295 be considered due to atopic eczema (population attributable risk) was 1.4% (95%CI
296 1.2-1.6) for depression, and 1.7% (1.4-1.9) for anxiety (**Table E7**) (these estimates
297 were calculated assuming a 10% prevalence of atopic eczema and would increase if
298 atopic eczema were more common).

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

301 **Secondary analyses**

302 *Atopic eczema severity*

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

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

313 *Effect modification by sex, age and calendar period*

314 We saw some evidence ($P < 0.0001$) for sex modifying the effect of atopic eczema on
315 depression; with a slightly higher risk of depression in those with atopic eczema
316 compared to those without in men (1.19 [99%CI 1.16-1.23]) than in women (1.11
317 [99%CI 1.08-1.13]). We saw a similar pattern for risk of anxiety in those with and
318 without atopic eczema after stratifying on sex (HR [99% CI): Men 1.22 [99%CI 1.17-
319 1.27]; women 1.14 [99%CI 1.11-1.17]. $P = 0.0003$ for interaction). We also saw
320 evidence for effect modification by current age, with the HR comparing those with
321 atopic eczema to those without for both depression ($P < 0.0001$) and anxiety
322 ($P = 0.0052$) being higher in those aged 40-59, compared to younger and older age
323 groups. There was no evidence of a change in the effect of atopic eczema on both
324 depression ($p = 0.3229$) and anxiety ($p = 0.287$) in different calendar periods (**Table**
325 **E9**).

326 **DISCUSSION**

327 **Main findings**

328 We found that (treated) atopic eczema was associated with a 14% increase in the
329 risk of newly diagnosed depression (adjusted HR 99%CI 1.12-1.16), and a 17%
330 increase in the risk of a subsequent anxiety diagnosis (adjusted HR 99%CI 1.14-
331 1.19). These associations were only slightly attenuated after further adjusting for
332 potential mediators of the association between atopic eczema and

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

340 **Strengths and limitations**

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

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

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

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

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

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

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

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

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

415 **Comparisons to existing literature**

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

429 **Interpretation and clinical implications**

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

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

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

466 **Conclusions**

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

473 **DECLARATIONS**

474 **Contributions**

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

480 **Funding**

481 This work was supported by a Wellcome Senior Research Fellowship in Clinical
482 Science (205039/Z/16/Z), and by Health Data Research UK (grant No. LOND1),
483 which is funded by the UK Medical Research Council, Engineering and Physical
484 Sciences Research Council, Economic and Social Research Council, Department of
485 Health and Social Care (England), Chief Scientist Office of the Scottish Government
486 Health and Social Care Directorates, Health and Social Care Research and
487 Development Division (Welsh Government), Public Health Agency (Northern
488 Ireland), British Heart Foundation and Wellcome Trust.

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

491 **Ethical approval**

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

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

496 **Data sharing**

497 No additional data are available.

498 **Competing interests**

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

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

508 **Patient involvement**

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

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

515 **Acknowledgements**

516 This work uses data provided by patients and collected by the UK National Health
517 Service as part of their care and support.

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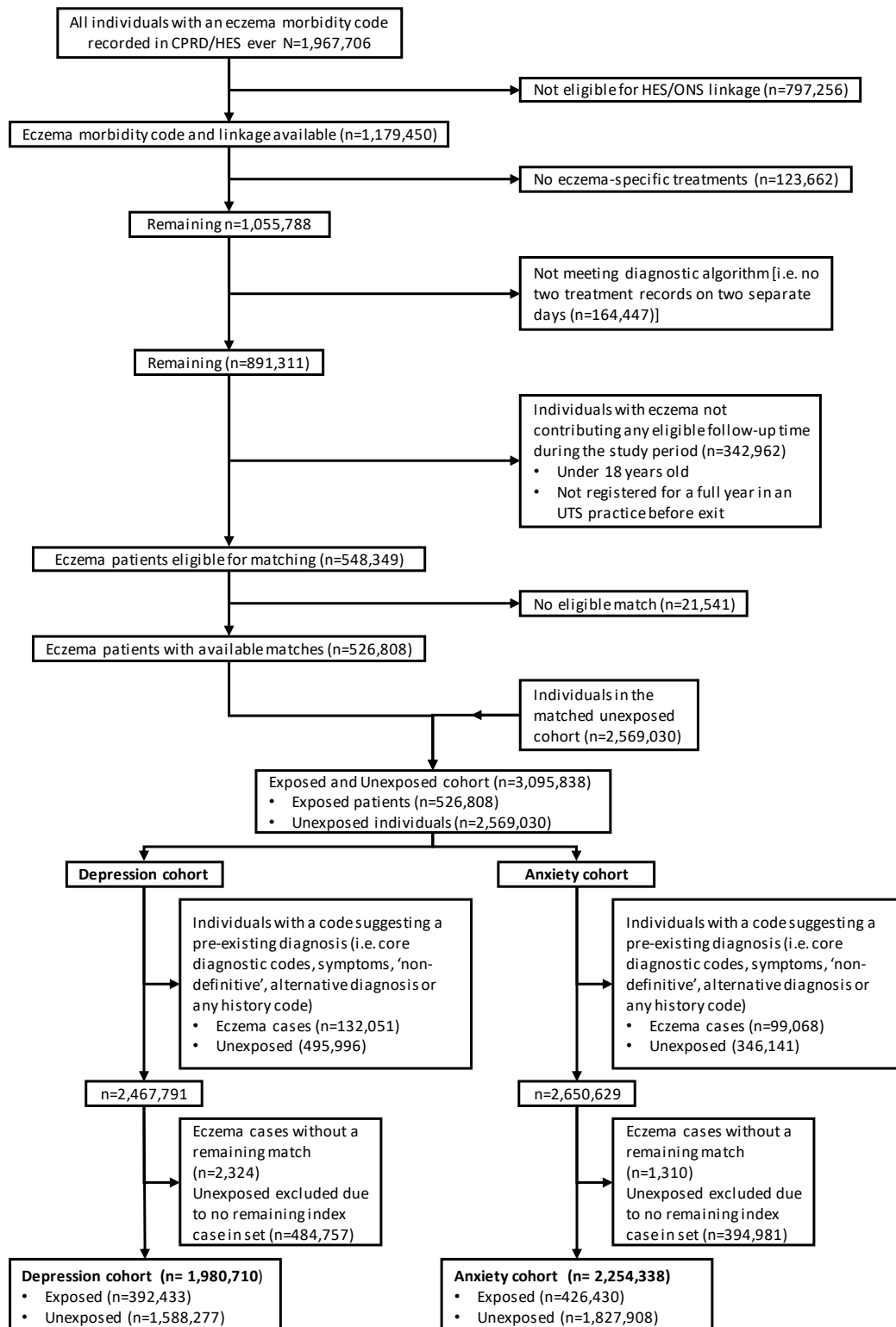
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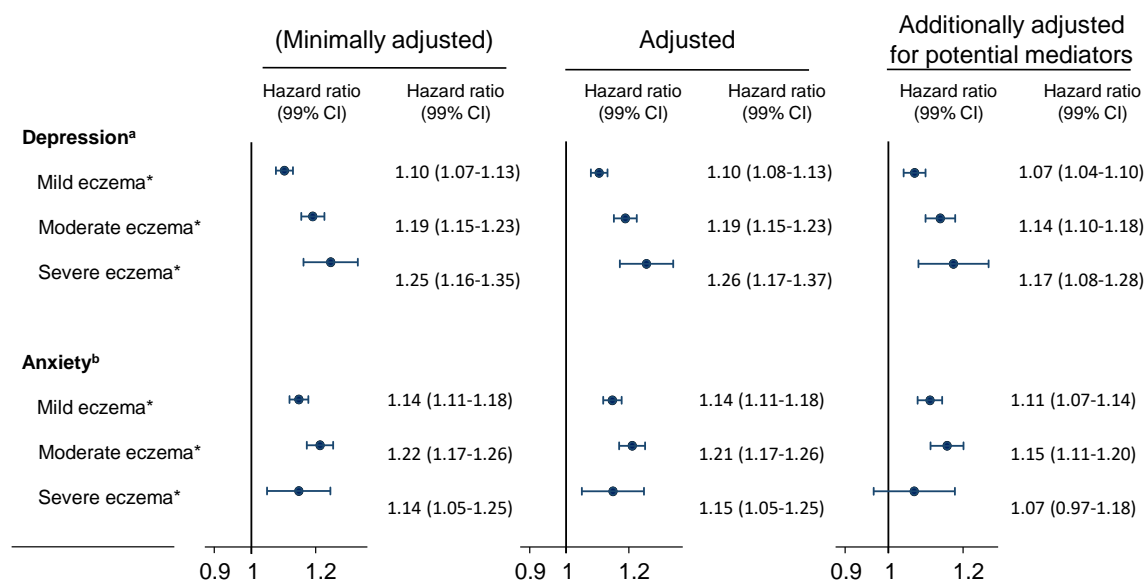
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- 762

763 FIGURES

764 Figure 1. Flow diagram showing the creation of the cohort and reasons for
765 exclusion (1998-2016)766
767
768

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

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



771 * compared to no atopic eczema

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

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

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

780 The **adjusted** model additionally included current calendar period (years: 1998-2001, 2002-06, 2007-
 781 11, 2012-16,) and quintiles of IMD at cohort entry (same participants as in the minimally adjusted).

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

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

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

792 TABLES

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

Characteristic*	Depression cohort		Anxiety cohort	
	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%)

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

796 * See Text E4 for details of variable definitions.

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

	No.	Events/PYAR	Minimally adjusted*	Adjusted**	Additionally adjusted for potential mediators***		
			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)

799 Abbreviations: BMI, body mass index; IMD, index of multiple deprivation; CI, confidence interval; PYAR, person years at risk.
 800 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
 801 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
 802 and general practice).
 803 ***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
 804 in the anxiety cohort [2,171,784 unique people]).
 805 **The **adjusted** model additionally included current calendar period (years: 1998-2001, 2002-06, 2007-11, 2012-16) and quintiles of IMD at cohort entry
 806 (same participants as in the minimally adjusted).
 807 *****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
 808 ≥30 kg/m²) smoking status, and alcohol and high-dose corticosteroid use (≥20 mg/day prednisolone equivalent dose), both as time updated variables
 809 (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]).