Hollestein Loes Maria (Orcid ID: 0000-0001-8922-6791)

The association between atopic eczema and lymphopenia: results from a UK cohort study with replication in US survey data

Loes M Hollestein[1,2], Morgan Ya Fang Ye[3], Ang Ky-Leigh[4], Harriet Forbes[5], Kathryn E Mansfield[4], Katrina Abuabara[3], Liam Smeeth[4], Sinéad M Langan[4,6]

ORCID
Loes M Hollestein: 0000-0001-8922-6791
Morgan Ya Fang Ye: 0000-0002-0023-8946
Ang Ky-Leigh:
Harriet Forbes: 0000-0001-6888-2212
Kathryn E Mansfield: 0000-0002-2551-410X
Katrina Abuabara: 0000-0002-7736-6946
Liam Smeeth: 0000-0002-9168-6022
Sinéad M Langan: 0000-0002-7022-7441

[1] Department of Dermatology, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands.
[3] Department of Dermatology, University of California San Francisco, 1701 Divisadero Street, San Francisco, CA, 9411, United States of America
[4] Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
[5] Department of Population Health Sciences, University of Bristol, Bristol, United Kingdom
[6] Health Data Research UK, Gibbs Building, 215 Euston Road, London, NW1 2BE

Conflict of interest statement
The author report no conflict of interests.

Counts
JEADV: Abstract: 298 (max 300)
Words: 3007 (max 3000)
Tables + Figures: 1 Tables, 3 Figures
Supplementary files: 10 Tables, 2 Figures

Corresponding author:
Sinéad M Langan, sinead.langan@lshtm.ac.uk

Data availability statement: The data that support the findings of this study are available from Clinical Practice Research Datalink (CPRD) and National Health and Nutrition Examination Survey (NHANES). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from CPRD and NHANES on a licensed basis.

Abstract (max 300 words)

Background: Lymphocyte skin homing in atopic eczema (AE) may induce lymphopenia.

Objective: To determine if AE is associated with lymphopenia.

Methods: We used UK primary care electronic health records (Clinical Practice Research Datalink GOLD) for a matched cohort study in adults (18yrs+) (1997-2015) with at least 1 recorded lymphocyte count. We matched people with AE to up to 5 people without. We used multivariable logistic regression to estimate the association between AE and lymphopenia (two low lymphocyte counts within 3 months) and linear mixed effects regression to estimate the association with absolute lymphocyte counts using all available counts. Cox proportional hazard models were used to investigate the effect of lymphopenia on common infections. We replicated the study using US survey data (National Health and Nutrition Examination Survey [NHANES]).

Results: Amongst 71,731 adults with AE and 126,349 adults without AE, we found an adjusted odds ratio (OR) for lymphopenia of 1.16 (95%CI: 1.09-1.23), the strength of association increased with increasing eczema severity.
When comparing all recorded lymphocyte counts from adults with AE(n=1,497,306) to those of people without AE(n=4,035,870) we saw a lower mean lymphocyte (adjusted mean difference -0.047*10^9/L (95%CI:- 0.051- -0.043)) in those with AE. The difference was larger for men, increasing age, increasing AE severity and was present among people with AE not treated with immunosuppressive drugs. In NHANES (n=22,624), the adjusted OR for lymphopenia in adults with AE was 1.30 (95% CI 0.80-2.11), and the adjusted mean lymphocyte count difference was -0.03*10^9/L (95%CI -0.07-0.02). **Despite having a lower lymphocyte count,** adjusting for time with lymphopenia, did not alter risk estimates of infections.

Conclusion: AE, including increasing AE severity, is associated with a decreasing lymphocyte count, regardless of immunosuppressive drug use.. Whether the decreasing lymphocyte count has wider health implications for people with severe eczema warrants further investigation.

Introduction

Atopic eczema (AE) is a chronic inflammatory condition affecting up to 20% of children and 10% of the adult population [1]. AE has the highest global burden in terms of disability adjusted life years of all skin conditions, yet quantitative markers of disease activity and severity are lacking [2].

AE etiology involves both skin barrier dysfunction and immune dysregulation, for which lymphocytes play a key role [1]. The immunology literature describes skin homing of lymphocytes (i.e., movement of white blood cells out of the circulating volume to the skin) as a major feature of AE [3-5]. The degree of skin homing may be sufficient to induce detectable lymphopenia on laboratory testing as is evidenced by case reports of lymphopenia in severe AE [6, 7]. Lymphopenia may be a marker of increased infection risk and it complicates initiation and monitoring of currently available broad immunosuppressive systemic therapies to manage AE [8].

People with AE are known to have increased rates of cutaneous and non-cutaneous infections [9, 10]. As AE is common and infections can be associated with serious health consequences including morbidity and mortality, understanding whether at a population level, AE is associated with lymphopenia and whether this might lead to increased risk of infection is important. Therefore, we conducted a cohort study to investigate whether adults with AE were more likely to have lymphopenia when compared to people without AE. We undertook exploratory analyses to determine if lymphopenia might be a mediator of increased infection risks and we then externally replicated our findings by repeating the analyses in a separate cohort.

Methods

We conducted a matched cohort study comparing the odds of lymphopenia in people with AE to a matched (age, sex, practice) cohort without AE using UK primary care data from Clinical Practice Research Datalink (CPRD GOLD). We then repeated our analysis using US survey data from the National Health and Nutrition Examination Survey (NHANES). Here, we describe the main CPRD study in CPRD in detail and briefly describe the replication in NHANES (Details can be found in the supplementary methods).

Setting

We used routinely collected UK primary care electronic health record data from CPRD GOLD (9% of the UK population), and linked hospital admissions data from Hospital Episode Statistics (HES), Office for National Statistics mortality data, and Index of Multiple Deprivation (IMD) data based on the individual's postcode [11]. IMD consists of seven components (i.e. income, employment, education, health, crime, barriers to housing and services and living environment) which are weighted and compiled into a single score of deprivation. Data include diagnoses (coded using Read morbidity codes), prescriptions, and referrals to specialists. Approximately 80% of CPRD practices have consented to their records being linked to other data sources. HES data includes all NHS-funded hospital admissions coded using ICD-10 (international classification of diseases, 10th revision) codes.

Study population

Adults (≥18 years) registered with a CPRD practice between 1st April 1997 and 31st March 2015, who were eligible for HES linkage were eligible for inclusion.

Atopic eczema

We defined AE based on at least 3 medical record codes including a diagnosis code and at least two AE therapy codes (recorded on separate dates), consistent with a validation study showing a positive predictive value in adults of 82% [12]. AE diagnostic codes were identified in CPRD (using Read codes) and HES (using ICD-10 codes recorded in the primary diagnosis field of any episode). AE therapies included AE-related primary care prescriptions: emollients, topical and oral corticosteroids, tacrolimus and systemic immunosuppressants, and phototherapy records from primary (CPRD) or secondary (Office of Population Censuses and Surveys [OPCS] Classification of Interventions and Procedures codes in HES) care. Severity of AE was defined as a time-updated variable (Supplementary methods).

Matched individuals without AE

For each individual with AE, we randomly matched, without replacement, up to five individuals by age (within 15 years), sex, and general practice in calendar date order. People without AE were required to have at least one year of follow-up in CPRD and no history of AE when matched. Any individuals with a diagnosis of AE were included in the pool of eligible people without AE until the date of their AE diagnosis.

Exclusions

We excluded individuals without a valid lymphocyte count recorded in the primary care records. We also excluded matched sets if either the person with AE or all matched persons without AE did not have any lymphocyte counts.

Follow-up

Follow-up for people with AE began on the latest of: 1 April 1997 (study start), 18th birthday, date they fulfilled our AE diagnosis algorithm, or one year after registration with a CPRD practice. Individuals without AE entered the cohort on the same date as the individual with AE whom they were matched to. Follow-up ended at the earliest of study end date (31 March 2015), death, no longer registered with practice, or practice no longer contributing to CPRD. We included all those contributing at least one day of follow-up.

Outcome: blood cell counts

We identified lymphocyte counts from CPRD using established methodology [13, 14]. We also included lymphocyte count values without a Read term for lymphocyte count. If multiple lymphocyte counts were recorded for an individual on the same day, we took the mean value. We only used absolute lymphocyte counts and excluded any relative counts (2 out of 12 million lymphocyte counts). We considered lymphocyte counts between $1*10^9$ and $4.8*10^9$/L as within normal range and $<1*10^9$/L as lymphopenia. Total white blood cell count, neutrophil count, and platelet count were identified as negative controls, as we hypothesized no associations with AE. As immunosuppressive drug use may influence total white blood cell count, total white blood cell count and neutrophil count were performed within patients without any immunosuppressive drug use.

Covariates

People with and without AE were matched on 15-year age category and sex. Other covariates included ethnicity, deprivation (quintiles of 2015 IMD), smoking, comorbidities and immunosuppressive drug use, which were taken into account in a relevant time window (Supplementary methods).The effect of all covariates on the outcome was assessed statistically. All covariates that influenced the effect estimate by 10% or more were included in the final model. The final models included smoking (lymphopenia and absolute lymphocyte count model) and oral glucocorticoid use (lymphopenia model only) in addition to age and sex (matching variables). All codes used to define outcomes, exposures and covariates are available for download (Supplementary excelfile 1).

Statistical analysis

Primary outcome: Lymphopenia

In order to avoid misclassification of lymphopenia based on one accidental finding, we defined lymphopenia as having two low lymphocyte counts (<1*109/L) within 3 months. We used logistic regression to compare the odds of lymphopenia in people with AE to people without (Supplementary Figure 1a). The date of the first low lymphocyte count was considered the date of lymphopenia and was used to define the relevant time window for measuring each covariate.

Secondary outcome: Absolute lymphocyte count

In order to take all recorded lymphocyte counts from all individuals into account , we applied a linear mixed effects model (LMM) (Supplementary Figure 1b). Data were clustered within individuals (all lymphocyte counts for each individual) and within matched sets (people with AE matched to individuals without). Due to the large sample size, a random intercept for each individual, or matched set, was not feasible. Therefore, we included a random intercept for General Practitioner (GP) practice and included the other matching variables (age, sex, and calendar time) as fixed covariables in the model. To model the correlation between multiple lymphocyte counts per person during follow-up, we applied a compound symmetry covariance structure (i.e., all lymphocyte counts for the same individual were equally correlated, regardless of time between the lymphocyte counts), which resulted in the best fitting model based on Akaike's Information Criterion (AIC). Models included time-varying covariates as described above.

Secondary analyses

We stratified models on AE severity and immunosuppressive drug use, regardless of statistical interaction, because we hypothesized that the lymphocyte count would decrease with increasing AE severity and that the association would also be present among people with AE who did not use immunosuppressive drugs. As severe AE is likely to be associated with immunosuppressive drug use, we also applied stratification on immunosuppressive drug use within categories of AE severity. We also investigated whether the effect of AE on lymphopenia was modified by age, sex, smoking and ethnicity (see supplementary methods). Based on the p-value for interaction, the logistic regression model for lymphopenia did not require any further stratification, but the LMM for absolute lymphocyte count was also stratified on age and sex.

Having demonstrated that AE was associated with lymphopenia, we undertook a further *post hoc* cohort study in CPRD GOLD to investigate whether people with AE were more likely to experience common infections (cellulitis, varicella zoster, gastroenteritis, urinary tract infection) compared to a comparator cohort matched on age, sex, and primary care practice, and whether lymphopenia mediated the relationship (Supplementary methods).

External replication

We replicated our analyses in another population-based setting, using publicly available data from NHANES, a US population-based survey. NHANES uses a multistage probability design to select a nationally-representative sample of the non-institutionalized, civilian US population [15]. Details on AE definition, data on blood samples and analyses can be found in the Supplementary Methods.

Results

Primary outcome: Lymphopenia

In the primary analyses 71,731 adults with AE and 126,349 adults without AE were included (Figure 1, Table 1). Of all people with AE, 4.1% (2,909) had lymphopenia compared to 3.7% (4,700) without AE and the prevalence of lymphopenia increased with AE severity (Supplementary table 1).

The adjusted OR for lymphopenia in people with AE compared to people without AE was 1.16 (95% CI: 1.09-1.23), and increased with increasing AE severity (e.g., OR severe AE: 1.89, 95%CI: 1.54-2.32) (Figure 2, Supplementary Table 2). Immunosuppressive drugs use was also associated with lymphopenia (OR: 1.15, 95%CI: 1.06-1.24). Patients who had severe eczema, but did not use any immunosuppressive drugs, also had an increased OR for lymphopenia (Supplementary Table 3). Negative controls (platelet, total white blood cell and neutrophil count) were not associated with AE (Supplementary Table 4).

Secondary outcome: Lymphocyte count

The lymphocyte count analyses (LMM) included 1,497,306 lymphocyte counts of 286,906 people with AE and 4,035,870 lymphocyte counts of 866,319 matched individuals without AE (Supplementary Figure 2, Supplementary Table 5). The median lymphocyte count of people with AE was $1.80*10^9$/L (interquartile range [IQR]: 1.40-2.30) compared to $1.88*10^9$/L (IQR: 1.45-2.35) for people without AE. Lymphocyte counts of people with AE were lower than lymphocyte counts of people without AE (adjusted mean difference $-0.047*10^9$/L, 95%CI: 0.051-0.043) (Figure 3, Supplementary Table 6). The difference was larger for men and older people (Figure 3, Supplementary Table 6). The lymphocyte count decreased with increasing AE severity. AE regardless of immunosuppressive drug use was associated with decreased lymphocyte count compared to people without AE (Supplementary Table 6 and 7).

None of the negative controls (platelet, total white blood cell and neutrophil count) were associated with AE (Supplementary table 8).

Secondary analysis: infection risks

Using CPRD data (Supplementary Results), we estimate the adjusted hazard ratios (HR) comparing rate of common infections in individuals with AE to those without: cellulitis 1.58 (95% CI 1.57-1.60), varicella zoster (VZ) 1.11 (95% CI 1.06-1.16), gastroenteritis 1.33 (95% CI 1.31-1.34), and UTI 1.18 (95% CI 1.17-1.19). HR estimates for all four infections were unchanged after further adjusting for time with lymphopenia.

The absolute excess rate of infection that could be due to AE (attributable risk) was: cellulitis 44.10 per 10,000 person-years at risk (PYAR) (95%CI 43.25-44.93), VZ 0.65 per 10,000 PYAR (95%CI 0.47-0.82), gastroenteritis 25.39 per 10,000 PYAR (95%CI 24.41-25.87), and UTI 54.73 per 10,000 PYAR (95%CI 54.73-56.75). Sensitivity analyses showed broadly similar effect estimates to those from the main analysis.

External replication

We included 22,624 participants from NHANES between 1999-2006, in which 5,563 participants were part of the 2005-2006 survey wave of which 7-8% had AE in the past year (Supplementary Table 9). In the pooled analysis for NHANES 1999-2006, there was a trend towards an inverse association between AE in the past year and lymphocyte count (adjusted mean difference -0.03, 95% CI -0.07, 0.02). There was also a trend towards an increased odds of lymphopenia (adjusted OR 1.30, 95% CI 0.80, 2.11) (Figure 2, Figure 3, Supplementary Table 10).

Discussion

Using data from UK primary care, we have shown that adult AE is associated with both lymphopenia and lower mean lymphocyte counts. We found that the association was larger among individuals with more severe AE, men, and older adults, and did not appear to be influenced by immunosuppressive drug use. In a replication study using survey data from the US, we found similar estimates, but with wider confidence intervals that spanned the null. We identified in secondary analyses that adults with AE had increased risks of common infections. In order to address whether or not a reduced lymphocyte count resulted in increased risk of common infections, we adjusting for time with lymphopenia, but this did not result in attenuation of the associations between AE and specific infections.

Most studies investigating blood counts in AE have focused on rates of eosinophilia or anaemia; ours is one of the first to examine lymphopenia in a population-based setting [6, 16, 17], and it is the largest to examine infections in the UK [10, 18]. Lymphopenia has been recognized in other chronic immune mediated inflammatory disorders, including inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Like our findings, a study of IBD found that lymphopenia did not explain higher rates of common infections [19], though lymphopenia has been associated with both common and severe infections in RA [20, 21].

Strengths of our study include the use of a routinely collected dataset that is representative of the general population of the UK [22, 23]. A validated algorithm [24] for use in primary care records was used to identify individuals with AE, based on physician diagnosis. A large proportion (97%) of individuals with AE in the UK are treated by their GP [25, 26], suggesting that most individuals with AE will be identified from their GP records and the probability of selection bias is low. Hence, results of this study are likely to be generalisable to the UK population. We used negative control outcomes comprising other haematological parameters and repeated our lymphopenia analyses in an independent dataset.

The study also has several limitations. Due to the use of routinely collected data, all variables rely on the individual consulting for their condition and their clinician's recording in their health records. Many individuals with lymphopenia may not be tested or have no records in primary care. This is unlikely to differ by exposure status, although surveillance bias may have occurred, as blood tests are likely to vary with immunosuppressive use. This will result in a non-differential misclassification and an underestimation of time with lymphopenia. An increased rate of infections (indirect cause) may have caused lower lymphocyte counts among AE patients, rather than the AE (direct cause) itself. Although we addressed the temporality of infection and lymphopenia to reduce the possibility of reverse causality we were not able to assess temporality of lymphopenia with AE diagnosis or treatments.

Additionally, time with lymphopenia only accounted for a very small proportion of total follow-up time, resulting in a lack of power. The infection analyses were powered to detect moderate effect sizes (minimum detectable HR ranging from 1.21 to 2.45 depending on the incidence rate of the infection), however our results were smaller than the minimum detectable HRs. This could explain why the HR and 95%CI of all infections remained the same in the model accounting for potential mediators and the model accounting for lymphopenia. Finally, severity levels were based on

therapeutic prescriptions rather than a direct measure of severity, which is a common approach in the dermatologic literature [27-30].

Gastroenteritis and UTI are common in the population [31-33]. Individuals may consequently experience mild gastroenteritis or UTI and not report their symptoms to their GP. However, this is unlikely to be differential by AE status and therefore unlikely to affect the hazard ratio. The increased rates of cutaneous and non-cutaneous infection among individuals with AE could be explained by ascertainment bias. Individuals with AE are more likely to have regular skin checks and report to their GPs for medical attention. Hence, GPs would be more likely to pick up infections among individuals with AE, biasing the HR of infection away from the null.

Our findings may have several important implications for the clinical management of and study of AE. A major limitation to population-based research is the lack of reliable markers of AE disease activity and severity in routinely collected data, and it is possible that data on lymphocyte counts could help to fill this gap. Moreover, lymphocyte counts may be useful to clinicians to monitor disease activity, severity, and course. For example, the lymphopenia-to-neutrophil ratio has been proposed as a cost-effective and readily available biomarker to track disease activity in RA and ankylosing spondylitis [34]. Additionally, clinicians may consider testing prior to commencement of immunosuppressive treatment known to reduce lymphocyte counts to establish baseline values.

Although the period of this study pre-dates the coronavirus pandemic, it is important to note that lymphopenia has been consistently associated with more severe disease and worse outcomes in COVID-19 [35]. Although current consensus does not indicate that AE patients are at increased risk of SARS-CoV-2 infection or poor outcomes overall [36], clinicians may consider checking lymphocyte levels in higher risk subsets of patients. Lymphopenia has been associated with mortality in the general population [37]. Thus, additional research is needed to understand the long-term clinical implications in AE.

In summary, we found higher rates of lymphopenia and common infections in adults with AE, though lymphocyte counts were not predictive of increased infection risk. Additional research on the implications of lymphopenia and clinical utility of blood counts is warranted. Knowing that individuals with AE have higher rates of infection can help in the development of a more comprehensive approach to decrease morbidity in individuals with AE and may help guide more targeted vaccination and/or treatment strategies in the future.

Figure Headings and Footnotes

Figure 1: Flow diagram of the lymphopenia analyses (Primary outcome).

Figure 2: Odds Ratios (95% CI) for lymphopenia in people with atopic eczema compared to individuals without atopic eczema (Primary outcome).

Larger squares indicate a larger sample size. Lines indicate the 95% confidence intervals. Associated numbers included in the analyses and exact effect estimates, 95% CI and p-values are reported in Supplement Table 2 and 10. All covariates are described in the methods and were assessed in the analyses. Final adjusted models included smoking and oral glucocorticoid use in addition to age and sex (matching variables). External validation in NHANES were adjusted for the same variables as the adjusted model in CPRD. Stratified models were adjusted as well.

Figure 3: Difference in absolute lymphocyte count (95% CI) in people with atopic eczema patients compared to people without atopic eczema (Secondary outcome).

Footnote: Larger squares indicate a larger sample size. Lines indicate the 95% confidence intervals. Associated numbers included in the analyses and exact effect estimates, 95% CI and p-values are reported in Supplement Table 6 and 10. All covariates are described in the methods and were assessed in the analyses. Final adjusted models included smoking in addition to age and sex (matching variables). External validation in NHANES were adjusted for the same variables as the adjusted model in CPRD. Stratified models were adjusted as well.

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020; 396:345-60.
2. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. Br J Dermatol 2021; 184:304-9.
3. Gaspar K, Barath S, Nagy G, Mocsai G, Gyimesi E, Szodoray P, et al. Regulatory T-cell subsets with acquired functional impairment: important indicators of disease severity in atopic dermatitis. Acta Derm Venereol 2015; 95:151-5.
4. Ferran M, Santamaria-Babi LF. Pathological mechanisms of skin homing T cells in atopic dermatitis. World Allergy Organ J 2010; 3:44-7.
5. Czarnowicki T, Malajian D, Shemer A, Fuentes-Duculan J, Gonzalez J, Suarez-Farinas M, et al. Skin-homing and systemic T-cell subsets show higher activation in atopic dermatitis versus psoriasis. J Allergy Clin Immunol 2015; 136:208-11.
6. Bakker DS, Garritsen FM, Leavis HL, van der Schaft J, Bruijnzeel-Koomen C, van den Broek MPH, et al. Lymphopenia in atopic dermatitis patients treated with oral immunosuppressive drugs. J Dermatolog Treat 2018; 29:682-7.
7. Chan G, Wee CP, Ong PY. Complete blood count profiles in children with eczema herpeticum. Pediatr Allergy Immunol 2022; 33:e13648.
8. Schmitt J, Schakel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. Acta Derm Venereol 2007; 87:100-11.
9. Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis DJ. Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis-A Cohort Study. J Invest Dermatol 2017.
10. Serrano L, Patel KR, Silverberg JI. Association between atopic dermatitis and extracutaneous bacterial and mycobacterial infections: A systematic review and meta-analysis. J Am Acad Dermatol 2019; 80:904-12.
11. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015; 44:827-36.
12. Abuabara K, Magyari AM, Hoffstad O, Jabbar-Lopez ZK, Smeeth L, Williams HC, et al. Development and validation of an algorithm to accurately identify atopic dermatitis patients in primary care electronic health records from the UK. Journal of Investigative Dermatology 2017; Accepted for publication.
13. Shah A. Using electronic health records to investigate blood biomarkers and onset of cardiovascular diseases: example of differential white cell count. School of Life and Medical Sciences, Faculty of Population Health Sciences, Institute of Cardiovascular Science: University College London, 2015:269.
14. CALIBER Lymphocyte counts phenotype.] Available from https://www.caliberresearch.org/portal/phenotypes/lymphocytes.
15. Curtin LR, Mohadjer LK, Dohrmann SM, Montaquila JM, Kruszan-Moran D, Mirel LB, et al. The National Health and Nutrition Examination Survey: Sample Design, 1999-2006. Vital Health Stat 2 2012:1-39.
16. Simon D, Braathen LR, Simon HU. Eosinophils and atopic dermatitis. Allergy 2004; 59:561-70.
17. Drury KE, Schaeffer M, Silverberg JI. Association Between Atopic Disease and Anemia in US Children. JAMA Pediatr 2016; 170:29-34.
18. Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis DJ. Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis-A Cohort Study. J Invest Dermatol 2017; 137:1375-7.
19. Irving PM, de Lusignan S, Tang D, Nijher M, Barrett K. Risk of common infections in people with inflammatory bowel disease in primary care: a population-based cohort study. BMJ Open Gastroenterol 2021; 8.

20. Nikiphorou E, de Lusignan S, Mallen C, Khavandi K, Roberts J, Buckley CD, et al. Haematological abnormalities in new-onset rheumatoid arthritis and risk of common infections: a population-based study. Rheumatology (Oxford) 2020; 59:997-1005.

21. Subesinghe S, Kleymann A, Rutherford AI, Bechman K, Norton S, Benjamin Galloway J. The association between lymphopenia and serious infection risk in rheumatoid arthritis. Rheumatology (Oxford) 2020; 59:762-6.

22. Data. 2021.] Available from https://cprd.com/Data.

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

24. Abuabara K, Magyari AM, Hoffstad O, Jabbar-Lopez ZK, Smeeth L, Williams HC, et al. Development and validation of an algorithm to accurately identify atopic eczema patients in primary care electronic health records from the UK. J Invest Dermatol 2017; 137:1655-62.

25. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. Br J Dermatol 1998; 139:73-6.

26. Schofield J, Grindlay D, Williams H. Skin conditions in the UK : a health care needs assessment. 2009.

27. Ascott A, Mansfield KE, Schonmann Y, Mulick A, Abuabara K, Roberts A, et al. Atopic eczema and obesity: a population-based study. Br J Dermatol 2021; 184:871-9.

28. Schonmann Y, Mansfield KE, Hayes JF, Abuabara K, Roberts A, Smeeth L, et al. Atopic Eczema in Adulthood and Risk of Depression and Anxiety: A Population-Based Cohort Study. The journal of allergy and clinical immunology. In practice 2020; 8:248-57.e16.

29. Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ 2018; 361:k1786.

30. Mansfield KE, Schmidt SAJ, Darvalics B, Mulick A, Abuabara K, Wong AYS, et al. Association Between Atopic Eczema and Cancer in England and Denmark. JAMA Dermatology 2020; 156:1086-97.

31. Tam CC, Rodrigues LC, Viviani L, Dodds JP, Evans MR, Hunter PR, et al. Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. Gut 2012; 61:69-77.

32. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int 2010; 107:361-7.

33. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993; 329:1328-34.

34. Mercan R, Bitik B, Tufan A, Bozbulut UB, Atas N, Ozturk MA, et al. The Association Between Neutrophil/Lymphocyte Ratio and Disease Activity in Rheumatoid Arthritis and Ankylosing Spondylitis. J Clin Lab Anal 2016; 30:597-601.

35. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis 2020; 96:131-5.

36. Wollenberg A, Flohr C, Simon D, Cork MJ, Thyssen JP, Bieber T, et al. European Task Force on Atopic Dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and atopic dermatitis. J Eur Acad Dermatol Venereol 2020; 34:e241-e2.

37. Zidar DA, Al-Kindi SG, Liu Y, Krieger NI, Perzynski AT, Osnard M, et al. Association of Lymphopenia With Risk of Mortality Among Adults in the US General Population. JAMA Netw Open 2019; 2:e1916526.

Table 1: Individual characteristics of the study population in the lymphopenia analysis (Primary outcome).

	Adults with Atopic Eczema		Adults without Atopic Eczema	
	N	%	N	%
Total	71,731		126,349	
Follow-up in years (median, IQR)	9.0 (5.5-13.0)		8.8 (5.4-12.8)	
Age in years (median, IQR)[2]	68 (50-78)		70 (55-79)	
Sex				
Men	24,459	34%	44,447	35%
Women	47,272	66%	81,902	65%
Smoking[1]				
No smoker	25,383	35%	46,968	37%
Current smoker	18,406	26%	32,553	26%
Ex-smoker	17,085	24%	27,861	22%
Missing information	10,857	15%	18,967	15%
Ethnicity				
White	36,123	50%	64,677	51%
Other	2,859	4%	3,922	3%
Missing information	32,749	46%	57,750	46%
Socioeconomic deprivation[1]				
1 (low)	17,511	24%	30,998	25%
2	15,711	22%	27,921	22%
3	15,147	21%	27,432	22%
4	12,675	18%	22,026	17%
5 (high)	10,632	15%	17,829	14%
Missing information	55	0%	143	0%
Eczema Severity[3]				
Mild	39,269	55%		
Moderate	27,829	39%		
Severe	4,633	6%		
Comorbidities				
Asthma[5]	16,549	23%	19,033	15%
Autoimmune disorders[5]	2,564	4%	4231	3%
Cardiac failure[5]	4,667	7%	7785	6%
Chronic Kidney Disease[5]	8,539	12%	15594	12%
Hemopoeitic Stem Cell Transplantation[4]	6	0%	11	0%
Infections[6]	129	0%	191	0%
Lymphoproliferative Malignancy[4]	190	0%	335	0%
Sarcoidosis[4]	52	0%	11	0%
Solid organ cancer[4]	4.070	6%	7.748	6%
Stress-related symptoms[3]	288	0%	383	0%

Immunosuppresive drug use[4]				
Oral glucocorticoids	11,042	15.4%	14,514	11.5%
Other immunosuppressive drugs	2,666	3.7%	4,097	3.2%

Numbers indicate the timepoint or window of covariate assessment. The time window refers to the time before the 1st lymphocyte count + time between 1st and 2nd lymphocyte count, see supplementary figure 1a.

[1] Cohort entry

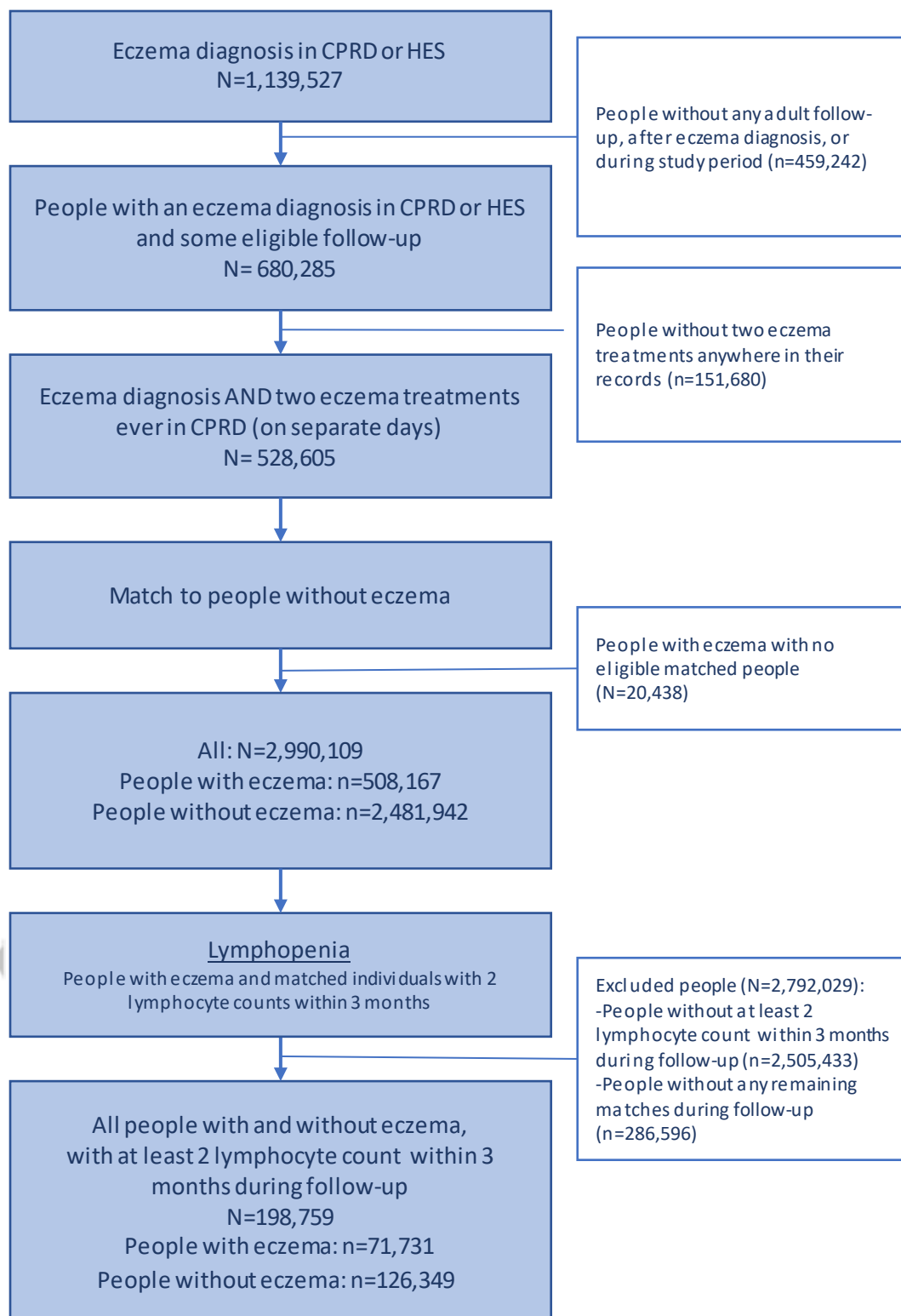[2] Lymphopenia assessment (second lymphocyte count)
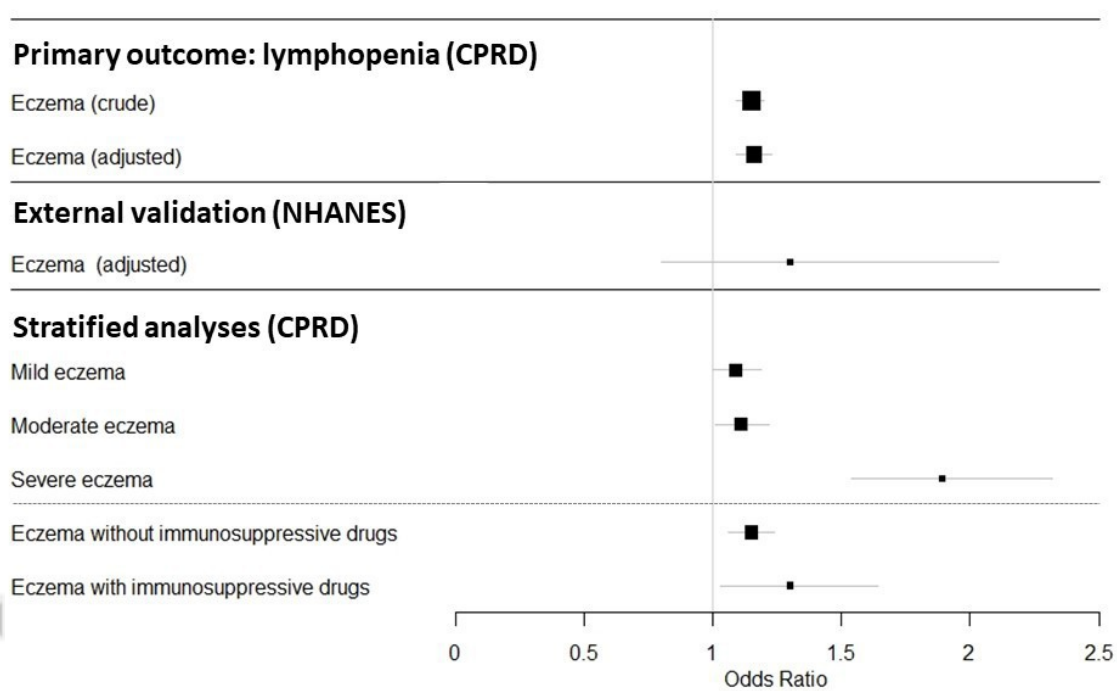
[3] Time window: 1 year

[4] Time window: 2 years

[5] Time window: ever

[6] Time windows: 3 months for acute infections (influenza) and 2 years for chronic infections (HIV, TBC, viral hepatitis)

Unless, indicated otherwise, there were no missing values.

Eczema diagnosis in CPRD or HES
N=1,139,527

People without any adult follow-up, after eczema diagnosis, or during study period (n=459,242)

People with an eczema diagnosis in CPRD or HES and some eligible follow-up
N= 680,285

People without two eczema treatments anywhere in their records (n=151,680)

Eczema diagnosis AND two eczema treatments ever in CPRD (on separate days)
N= 528,605

Match to people without eczema

People with eczema with no eligible matched people (N=20,438)

All: N=2,990,109
People with eczema: n=508,167
People without eczema: n=2,481,942

Lymphopenia
People with eczema and matched individuals with 2 lymphocyte counts within 3 months

Excluded people (N=2,792,029):
-People without at least 2 lymphocyte count within 3 months during follow-up (n=2,505,433)
-People without any remaining matches during follow-up (n=286,596)

All people with and without eczema, with at least 2 lymphocyte count within 3 months during follow-up
N=198,759
People with eczema: n=71,731
People without eczema: n=126,349

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Secondary outcome: absolute lymphocyte count (CPRD)
Eczema (crude)
Eczema (adjusted)

External validation (NHANES)
Eczema (adjusted)

Stratified analyses (CPRD)
Males with eczema
Females with eczema

Eczema at age 18-56
Eczema at age 57-74
Eczema at age 74 or older

Mild eczema
Moderate eczema
Severe eczema

Eczema without immunosuppressive drug use
Eczema with Immunosuppresive drug use

-0.2   -0.15   -0.1   -0.05   0 0.025
Mean difference of lyphocyte count (*10^9)

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