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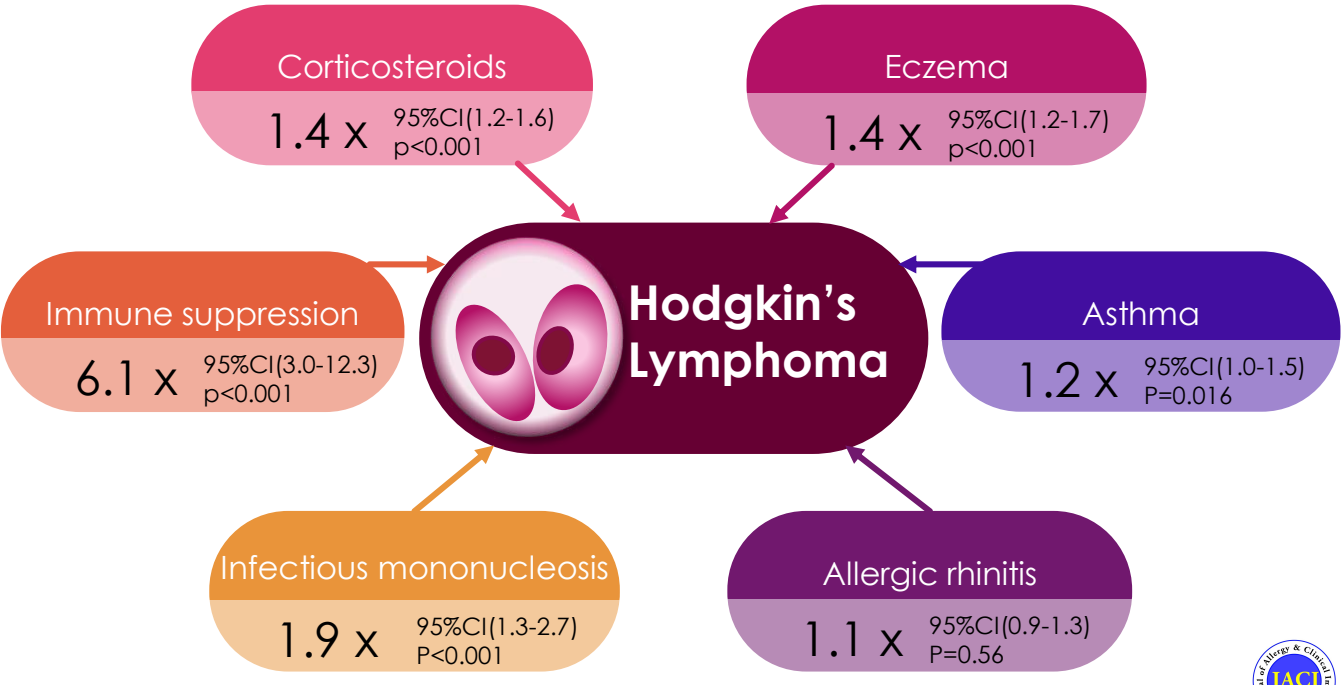
Risk of Hodgkin's Lymphoma in allergic disease



Allergic disease, corticosteroid use and risk of Hodgkin's lymphoma: A UK Nationwide case-control study

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ABSTRACT

Background

Immunodeficiency syndromes (acquired/congenital/iatrogenic) are known to increase Hodgkin's lymphoma (HL) risk, but the effect of allergic immune dysregulation and corticosteroids are poorly understood.

Objective

To assess the risk of HL associated with allergic disease (asthma, eczema and allergic rhinitis) and corticosteroid use.

Methods

We conducted a case-control study using the UK Clinical Practice Research Datalink (CPRD) linked to hospital data. Multivariable logistic regression investigated associations between allergic diseases and HL after adjusting for established risk factors. Potential confounding or effect modification by steroid treatment were examined.

Results

1,236 cases of HL were matched to 7,416 controls. Immunosuppression was associated with 6-fold greater odds of HL (Adjusted Odds Ratio (AOR), 6.18; 95%CI, 3.04–12.57), with minimal change after adjusting for steroids. Any prior allergic disease or eczema alone were associated with 1.4-fold increased odds of HL (AOR, 1.41; 95%CI, 1.24–1.60; AOR, 1.41; 95%CI, 1.20–1.65, respectively). These associations decreased but remained significant after adjustment for steroids (AOR, 1.25; 95%CI, 1.09–1.43; AOR, 1.27; 95%CI, 1.08–1.49, respectively). There was no effect modification by steroid use. Previous steroid treatment was associated with 1.4-fold greater HL odds (AOR, 1.38; 95%CI, 1.20–1.59).

Conclusions

In addition to established risk factors (immunosuppression and infectious mononucleosis), allergic disease and eczema are risk factors for developing HL. This association is only partially explained by steroids, which are associated with increased HL risk. These findings add to the growing evidence that immune system malfunction, following allergic disease or immunosuppression, is central to HL development.

KEY MESSAGES

- Allergic disease, especially eczema, is associated with increased risk of Hodgkin's lymphoma
- Corticosteroid treatment is associated with increased Hodgkin's lymphoma risk
- Immune system malfunction, following allergic disease or immunosuppression, is central to HL development

CAPSULE SUMMARY

Our data support that prior allergic disease, especially eczema, and corticosteroid treatment increase the risk of developing incident Hodgkin's lymphoma before the age of 50. Immune system malfunction is central to Hodgkin's lymphoma development.

KEYWORDS

Allergic disease; Hodgkin's lymphoma; corticosteroids; asthma; eczema; allergic rhinitis; risk; atopic dermatitis

ABBREVIATIONS

HL, Hodgkin's lymphoma; TYA, teenagers and young adults; IM, infectious mononucleosis; EBV, Epstein Barr virus; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation; SES, socioeconomic status; OR, odds ratio; AOR, adjusted odds ratio; PPV, positive predictive value; IV/IM, intravenous/intramuscular.

INTRODUCTION

Hodgkin's lymphoma (HL) is a cancer of the lymphatic system and is the most common cancer in teenagers and young adults (TYAs) worldwide (1, 2). A number of conditions with disordered immune regulation have been associated with an increased risk of developing HL in TYAs. These include infectious mononucleosis (IM) following Epstein Barr virus (EBV) infection (3-7), HIV infection (8-10), immunosuppressive therapy (11-17) and several autoimmune diseases such as multiple sclerosis (18), systemic lupus erythematosus (19) and rheumatoid arthritis (20, 21). Certain HLA genes that are responsible for the regulation of the immune system in humans have also been associated with increased risk of HL in genetic studies (22, 23). These findings together provide support for immune system malfunction playing a central role in development of HL.

The antigenic stimulation hypothesis has been suggested to explain the underlying mechanism for immune system malfunction in HL development. It proposes that conditions with chronic immune stimulation predispose individuals to developing haematological malignancies, such as multiple myeloma, non-Hodgkin's lymphoma and leukaemia, by promoting development of randomly occurring pro-oncogenic mutations in actively dividing immune cells (24-26). There is a growing body of evidence supporting this hypothesis and showing that a number of immune-related cancers, including leukaemia, occur as a consequence of immune system malfunction in early life (27-29).

Allergic diseases, including asthma, eczema and allergic rhinitis, are amongst the commonest perpetrators of chronic immune stimulation. Few studies have investigated the link between allergic diseases and HL and the results have been conflicting and inconclusive (24, 25, 30-35). Previous studies have been small scale or relied on small numbers of exposed individuals and therefore may not have had the power to detect associations. No studies have been conducted using electronic health records from primary care, where allergic disease is predominantly diagnosed and managed, or in the UK population which has one of the highest rates of both HL in TYAs and allergic disease worldwide (36, 37).

Corticosteroids are a mainstay in the treatment of allergic diseases. Their use is often reserved for more severe cases that have not responded to first-line conventional therapies and they primarily act through suppression of the immune response. Any association between allergic disease and HL could therefore be intertwined with the effect of steroids: Steroid use could modify any effect (as they are a marker of allergic disease severity); or confound it (as they are used in treatment of a range of immune-related diseases that may also be risk factors for HL). It is important to therefore consider this interplaying role in any study of allergic disease. Some studies have identified steroids as a risk factor for developing lymphoma (38-40), although others have found no increased risk (41, 42); more importantly, it is unclear whether steroid use is an independent risk factor, a marker of allergic disease severity, or a proxy for other immune-related diseases. Furthermore, many of the studies did not differentiate between the types of lymphoma or focused only on topical steroids, adding to the uncertainty surrounding the role of steroid treatment and HL risk.

In this study we used linked primary care electronic health records to determine if individuals with a history of allergic disease (asthma, eczema or allergic rhinitis) are at a greater risk of developing HL in earlier life and whether HL risk varied according to steroid exposure.

METHODS

Study design and setting:

We conducted a matched case-control study using data from the UK Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistic (HES) inpatient data and index of multiple deprivation (IMD) data. CPRD is an electronic health record database containing prospectively collected anonymised data from UK primary care consultations. It is the largest source of longitudinal primary care data, holding information on 22 million patients representing approximately 9% of the UK population (in 2013) (43). Data are available from 1987 onwards when CPRD was first established. It contains information on clinical symptoms, diagnoses (coded using Read codes), investigation results, medications and referrals to specialists. Practices contributing to CPRD are regularly audited to ensure high data quality and that 95% of prescribing and morbidity events are captured before practices are declared 'up-to-standard' (UTS) for research purposes (43). CPRD data used in this study were enhanced by pre-linkage to HES. The HES database contains records from every attendance at an NHS hospital in England (~125 million episodes per year). Each episode consists of clinical information on diagnoses, procedures and past medical history, coded in ICD10 (International Classification of Diseases, 10th revision). Data are available from April 1997 for patients in practices that have consented to data linkage (57% of all contributing CPRD practices in the UK) (44). CPRD data were additionally pre-linked to information on quintiles of IMD scores in practices that had consented to data linkage. These can be considered to represent a composite ecological (small-area based) measure of the socioeconomic status (SES) of a patient, based on the income, employment, disability, educational attainment and other attributes of the LSOA (Local Super Output Area) of a postcode. The latter typically comprise populations between 1,000 and 3,000 residents. All patients had an aggregate IMD score pertaining to the LSOA that their general practice is located. For this study, data were extracted from the July 2016 CPRD build and the Set 13 linked data.

Study population:

Hodgkin's lymphoma has a bimodal age-specific incidence pattern with the first peak occurring between 15-34 years (45). Individuals aged ≤50 years who were actively registered with a CPRD practice that had UTS data between January 1992 and July 2016 were eligible for inclusion in the study. Individuals were excluded if they had a HL diagnosis prior to entry into the study, to avoid inclusion of retrospectively recorded past/prevalent cases; if they had no recorded IMD status; and if they had follow-up of less than one year in CPRD.

Defining cases with HL

All individuals in the study population with a first diagnosis of HL aged ≤50 years in either CPRD or HES during the study period were included as potential cases (see Supplementary Tables S1 for Read and ICD-10 code lists). The earliest recorded date of diagnosis was taken as the index date. Cases were excluded if the diagnosis was made within 1 year of registering with a CPRD practice (in accordance with previous studies to ensure that only incident HL diagnoses were identified) (46) or if there was no event date for the HL diagnosis.

Defining matched controls

Six controls for each case were selected, using individual matching on age at index date (±1 year), sex and duration of active follow-up time (±2 years). A matched design was an efficient way to deal with the potential contributing effects of these variables. Concurrent sampling was used to match HL cases to controls who were HL-free at the index date of the case, while being under active follow up in an up-to-standard CPRD practice with a similar length of follow-up time prior to the index date. These individuals could not have a HL

diagnosis at the time of matching (index date), but could go on to develop HL in the future. This method allowed 'matching on time' with cases in this dynamic population (47). Each control was assigned an index date corresponding to the diagnosis date in their matched case.

Defining patients with allergic disease

A diagnosis of allergic disease was defined as a coded diagnosis of asthma, eczema or allergic rhinitis in CPRD or HES at any point before the index date. As we are interested in both incident and prevalent cases of allergic disease, individuals with a diagnosis at any point in their medical record before the index date, were classed as having an allergic disease (see Supplementary Table S2 for Read and ICD-10 code lists). The total number of allergic diseases (with a maximum of three) and the date and age of first reporting of allergic disease diagnosis were recorded (categorised as infant (<1 years), childhood (1-17 years) or adult (≥18 years) onset).

Defining corticosteroid use

Corticosteroid use was defined as coded use of any corticosteroid (sub classified as inhaled, topical, oral or intravenous/intramuscular (IV/IM)) in CPRD at any point more than 6 months before the index date (see Supplementary Table S3 for code list). A 'lag time' of 6 month prior to the index date was used in line with previous studies to reduce the possibility of reverse causality in the months immediately prior to HL diagnosis, as early symptoms of undiagnosed HL might lead to steroid treatment in the period leading up to the diagnosis (48). Steroid use was further classified by frequency of use during follow up (total number of coded issues prior to 6m before index date).

Covariates and mediators

We used a directed acyclic graph to inform the identification of potential covariates and mediators and to avoid collider bias (Figure 1). The covariates included the matched variables age, sex and follow-up time, and SES (using quintiles of 2010 IMD). A prior diagnosis of IM or immunosuppressive conditions were also included based on a recorded diagnosis in HES or CPRD before the index date, as these are established risk factors for HL. For IM, codes for EBV infection, positive laboratory tests and IM caused by other viruses were included (Supplementary Table S4). When classifying immunosuppression, congenital, acquired and iatrogenic causes were included (see Supplementary Table S5 for code lists).

Statistical analysis

Primary analyses

We initially described the baseline characteristics of cases and controls. Univariable conditional logistic regression (matched on age at index date, sex and follow-up duration) was used to generate odds ratios (OR) for the association between each of the exposure variables and HL, followed by multivariable conditional logistic regression adjusting for all other variables in the model. Interaction terms were subsequently introduced to investigate potential effect modification of the association between HL incidence and allergic disease by age, sex and SES. A further analysis was conducted on the final regression model, categorising allergic disease as a linear rather than binary variable to take into account the number of allergic diagnoses. We assessed for linear trend by number of allergic diagnosis, first by estimating the linear effect using likelihood ratio tests, and then investigating departure from linearity by comparing models in which allergic disease was added as a non-linear vs. a linear term. We used 95% confidence intervals (CI) and an implied 5% level of statistical significance to minimise the risk of a type 1 error.

We repeated the analyses with alternative exposure definitions where each allergic disease was considered separately. First we constructed a cross-tabulation comparing the frequency of combinations of allergic diseases in cases and controls. Then we repeated the conditional logistic regression analysis described above with asthma, eczema and allergic rhinitis included as separate variables to evaluate their independent effect on HL incidence after adjusting for each other and other variables in the model. Interaction terms were introduced to investigate for potential effect modification of the estimated risk associated with each allergic disease by age, sex and SES strata, and also other allergic disease. In supplementary analysis, for each of the three allergic diseases separately, using likelihood ratio tests we examined whether a model where they were categorized as infant / childhood / adult onset differed from a model where they were considered as yes-no variables independent of age of onset. Where there was evidence for heterogeneity, stratum-specific AORs were estimated.

Secondary analyses

A secondary analysis was conducted incorporating steroid use into the final model to assess for potential effect modification when stratifying by steroid use; and to investigate the extent to which the effect of variables may be confounded by steroid treatment, by comparing effect estimates before and after adjustment for steroid use. The effect of steroids was also assessed before and after adjustment for other variables, both collectively (any steroid use) and stratified by route of administration (inhaled, topical, oral or intravenous/intramuscular). We assessed for a potential dose-response relationship by estimating the linear effect of number of steroid prescriptions before the index date on HL risk and by route of administration (ordered according to strength/level of systemic absorption) using likelihood ratio tests as described above.

Sensitivity analysis

A sensitivity analysis was performed restricted to individuals with HES-linked data and effect estimates were compared to the estimates of the whole case-control population. Analyses were performed using Stata (version 15; StataCorp, College Station, TX, USA).

RESULTS

There were 1,236 incident cases of HL in this study individually matched to 7,416 controls. Table 1 shows the baseline characteristics of individuals in the case-control sample. Mean follow-up time was 6 years. Cases were more likely to be immunosuppressed (1% vs 0.2%), have a history of IM (4% vs 2%) and a diagnosis of at least one of the 3 allergic diseases (41% vs 33%) (Table 1). Treatment with steroids was more commonly seen in cases than in controls for all routes of administration, with significantly more cases having 2 or more steroid prescriptions during follow-up when compared to controls (43% vs 34%, p<0.001) (Table 1). Cross-tabulation of combinations of allergic diseases showed increased prevalence of asthma (19% vs 15%), eczema (21% vs 16%) and asthma and eczema combined (7% vs 4%) in cases compared to controls (Table 2). The distribution of all other exposure variables did not differ substantially between cases and controls (Table 1).

Immunosuppression

Immunosuppression was by far the strongest risk factor for HL incidence in this study. Immunosuppressed individuals had 6 times greater odds of developing HL on univariable analysis (p<0.001). There was very little change in OR after adjusting for other variables, indicating the effect was independent of SES, allergic disease and IM (Adjusted OR (AOR) 6.18, 95%CI 3.04–12.57, p<0.001). A slight attenuation in the OR was noted after adjusting for steroid use (AOR 6.05, 95%CI 2.97 – 12.33, p<0.001), indicating that part of the effect of immunosuppression on HL risk may be attributable to steroid use (Table 3).

Infectious Mononucleosis

IM was associated with double the odds of developing HL on univariable analysis (p<0.001). There was minimal attenuation of the effect in the mediation models after adjusting for immunosuppression, SES and allergic disease (AOR 1.89, 95%CI 1.33–2.68, p<0.001); and negligible change in the OR after adjusting for steroid use (Table 3). This indicates the effect of IM on HL is independent of these variables.

Allergic Disease

A previous diagnosis of one of more allergic diseases was associated with 1.4–fold greater odds of developing HL (p<0.001), with minimal change after adjusting for other variables (AOR 1.41, 95%CI 1.24–1.60), p<0.001) (Table 3). The risk of HL increased with increasing number of allergic diagnoses (p linear trend <0.001) (Table 4). When analysing by specific allergic disease type, eczema and asthma were associated with increased risk of developing HL (AOR 1.41, 95%CI 1.20–1.65, p<0.001; AOR 1.23, 95%CI 1.04–1.45, p=0.016, respectively) with no evidence of an association between allergic rhinitis and HL (Table 4).

In supplementary analysis comparing age of allergic disease onset, asthma and allergic rhinitis had similar average age of onset in cases and controls. However, for eczema the median age of onset was 15 years in controls and 20 years in cases (p=0.004). Relatedly, there were significantly more incidences of adult onset eczema among cases than controls (54% vs 44%, supplementary table S6), with strong evidence that the effect of eczema on HL risk differed according to age of eczema onset (p=0.006). Only adult onset eczema was associated with increased odds of HL (AOR 1.73, 95%CI 1.40 – 2.13, p<0.001, supplementary table S7). There was no evidence of heterogeneity of effect estimates by age of onset for asthma or allergic rhinitis (p=0.33 and 0.27, respectively, data not shown).

In the secondary analysis, after adjusting for steroid use, the associations between allergic disease and eczema with HL were attenuated, but still found to be significant (AOR 1.25, 95%CI 1.09–1.43, p=0.002; AOR 1.27, 95%CI 1.08–1.49, p=0.005, respectively) (Table 3 and 4). In asthmatics, after adjustment for steroids there was no increased risk of HL (Table 4). There was no difference in effect estimates when stratifying by steroid use (Table 5) and there was no evidence of effect modification by age at index date, sex or SES (test for interaction p=0.12, 0.063 and 0.41 respectively – additional analyses not shown in tables).

Corticosteroid use

Previous steroid use for any indication was associated with increased risk of HL. Individuals with a history of steroid use at any time prior to 6 months before the index date had 1.5–fold increased odds of developing HL (OR 1.51, 95%CI 1.33–1.72, p<0.001). All routes of administration were associated with increased risk, with the strongest associations seen for IV/IM, followed by oral, topical and then inhaled steroids (Table 4). After adjusting for other variables, including allergic disease and other immune conditions, steroid use remained a significant risk factor for HL development (AOR 1.38, 95%CI 1.20–1.59, p<0.001) and this was seen for all routes of administration except for inhaled steroids (Table 4).

Sensitivity analysis

Restricting the analysis to patients who had HES-linked data available (59.6% of all patients in this study) gave similar effect estimates for variables across all regression analyses.

DISCUSSION

This study shows that allergic disease and steroid use for any indication are associated with an increased risk of developing HL before the age of 50. A previous diagnosis of eczema, but not asthma or allergic rhinitis, is associated with development of HL, this effect being concentrated in patients with adult onset eczema. This effect does not differ by steroid exposure and persists after adjustment for steroid use. Previously established risk factors for HL involving immune dysfunction were also found in this study to be important risk factors for HL in early life. Immunosuppressed individuals had a 6-fold increased odds of developing HL and those with a history of IM had almost double the odds.

Comparison with the literature

The associations between allergic conditions and HL have been inconsistent and inconclusive in the literature (see supplementary table S8). Söderberg et al. conducted a Swedish population-based case-control study of 2,394 HL cases that found asthma was associated with a 40% reduced risk of HL (25). This study relied hospital discharge summary data, which are likely to include only severe asthma, and results were based on only 18 exposed cases. Vineis et al. conducted an Italian population-based case-control study that reported a 50% reduced risk of HL in individuals with allergic rhinitis, but no effect of asthma or eczema (30). This was a small study of 354 cases and relied on face-to-face interviews of adult cases, which may introduce recall bias of childhood exposures. Cozen et al. carried out a twin-study comparing 188 HL-discordant twin pairs in the USA using questionnaires (31). This found eczema was associated with a four-fold increased risk of HL, but was based on only 19 discordant pairs for the exposure. A number of further studies have concluded no association between allergic disease and HL risk (24, 32-35). These were small-scale case-control studies of up to 585 cases and relied on retrospectively collected exposure data from telephone interviews and questionnaires. Misclassification is therefore likely owing to

exposures being self-reported. Additionally, many of the studies included a diagnosis of HL at any age, which could produce misleading results as studies have shown HL in individuals aged <50 and >50 are likely to have different etiologies and may even be two separate disease entities (49-51).

Existing studies on steroid use and HL are also limited and have produced conflicting findings. One study found an increased risk of any lymphoma with oral steroid use, but no increased risk with topical steroids after adjusting for other factors (39). A second study focusing specifically on HL found no increased risk, even at considerable and cumulative doses of oral steroids, however this study focused on HL cases aged over 50 years (41). Some further studies of topical steroid use have shown increased HL risk in a dose-response fashion with increasing duration of exposure and potency (38, 40), but other have shown no increased risk even with moderate/highly potent topical steroids (42).

Strengths and limitations

We know of no previous studies assessing the association between allergic diseases with HL using prospectively collected population-based primary care electronic health records data and considering the potential interplay with steroid treatment. CPRD data are representative of the UK population across a number of demographic variables (43), which supports the external validity of the findings. Allergic conditions are predominantly diagnosed and treated in primary care, making GP electronic health records an ideal setting for examining them. Recording of asthma diagnosis in CPRD has high validity against gold standard diagnosis, with a positive predictive value (PPV) of 86.4% (52). HL diagnoses have high validity in CPRD when compared to gold standard national cancer registration (NCR) data (PPV for lymphoma 89.6%, sensitivity 97.3%) (53). The combined use of primary and secondary care HES-linked data further improved validity of exposures and outcomes by supplementing GP records with hospital data to improve capture of diagnoses. We used

detailed exploration of diagnostic codes, verified by two clinicians and crosschecking with existing code lists in the literature to further improve accuracy of diagnoses. Rates of allergic diseases and HL in the study population showed a similar distribution to that reported in the literature. The large study sample enabled the precise estimation of associations, providing adequate power to identify associations when the effect size is small. Prospectively collected data have low risk of recall bias, unlike other types of data used previous studies.

As for all observational studies based on routine data, there is potential for confounding, bias and missing data. However, the high degree of concordance of CPRD data with the NCR means misclassification of HL is likely to be low in this study with good capture of cases. CPRD data do not include staging information, which precluded us exploring possible variation in effect estimates by stage at diagnosis. A degree of misclassification and underreporting of allergic diagnoses is likely but this non-differential misclassification would potentially bias towards the null, meaning that the observed estimates of associations between allergic diseases and HL will be conservative. Some patients who will have contracted EBV will not experience any symptoms leading to consultation; and some who do, will be misdiagnosed. These mechanisms would both similarly result in potential underestimation of effect estimates, as the two comparator groups (cases / controls) become more similar artefactually, therefore the findings for IM are likely conservative. Route of steroid administration was used as a proxy for steroid strength as a marker of a dose-response relationship (it was not possible to directly estimate cumulative steroid exposure or exact doses).

Implications

We propose three potential explanations for the observed association between allergic disease and increased HL risk in early life identified in this study. The first is in support of the antigenic stimulation hypothesis for HL pathogenesis. Chronic over-activation of the immune response in individuals with allergic disease over time results in randomly occurring

mutations in rapidly dividing lymphocytes. These may be carcinogenic or cancer promoting, leading to HL development in predisposed individuals. The second explanation is that allergic disease and HL development in TYAs share a common immune pathway in their development and when regulation of this pathway is disrupted the risk of subsequently developing both conditions increases. Some studies have proposed the PD-1 (programmed death 1) receptor pathway and its ligands (PD-L1 and PDL2) as a potential culprit, as its components have been linked to both allergic diseases and HL pathogenesis (6, 54-58). Further studies are required to ascertain the presence and components of common underlying pathways, which if identified could present new targets for therapeutic intervention for these conditions (59). The third explanation is that therapeutic treatment for allergic diseases, such as steroids, which could themselves affect immunity may increase an individual's risk of developing HL either directly or by increasing the risk of contracting pro-oncogenic infections such as EBV. Disruption of the skin barrier in eczema may also act in this way by increasing access to other viral pathogens. However, we observed that allergic disease was associated with increased odds of developing HL even after adjusting for steroids and IM history. Further studies should explore the potential interplay between eczema, other viral infections and HL risk.

This study showed that steroid use for any indication is associated with increased risk of developing HL in this patient population. There was evidence of a possible dose-response effect by route of administration, with routes of higher systemic absorption associated with greater HL risk. Interestingly, although steroid use was more frequently observed in cases than controls, the effect of allergic disease on HL risk did not differ when stratifying by steroid use. This suggests the effects of steroids are not due to them being a marker of more severe allergic disease. Additionally, the association with steroids and HL persisted after adjusting for allergic diseases and other established risk factors included in the model, indicating their effect is not fully explained by these conditions. Possible explanations include that steroids may be an independent risk factor for HL and this is a genuine causal

association; it is more likely however that steroids are a proxy for other immune diseases, which are independent risk factors for HL and occur more commonly in allergic individuals in this patient population. Previous studies have demonstrated evidence for a link between allergic diseases and other immune conditions in support of this hypothesis (60). Further studies are required to examine the timing, duration and dose-response relationships between steroid exposure and HL development and the role of other immune diseases to establish their role in HL development more clearly.

Conclusions

This study has identified allergic diseases, specifically eczema, and steroid use for any indication as risk factors for developing HL in early life. This is in addition to the established risk factors of immunosuppression and IM, which also cause immune dysfunction. These findings add to the growing evidence that immune dysregulation is central to the development of HL in early life and allergic disease in childhood may increase the risk of developing haematological malignancies in the future.

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Ethics approval and consent to participate

The protocol for this project was approved by the London School of Hygiene and Tropical Medicine Ethics Committee (ref:11182) and the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number:16_237). Generic ethical approval for observational studies conducted using anonymised CPRD data with approval from ISAC has been granted from a National Research Ethics Service Committee (NRESC).The study was performed in accordance with the Declaration of Helsinki

Conflict of interest: The authors declare no potential conflicts of interest.

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608

609 **Figure legend:**

610 **Figure 1: Directed acyclic graph (DAG) for the study.** Solid lines indicate assumed associations
611 from previous studies, dashed lines indicate proposed associations examined in the current analysis.

612

613 **Tables:**

Characteristics	Cases of HL (n=1236)	Controls (n=7416)	P value[¥]
Mean years follow-up* (SD, range)	6.03 (5.00, 0.01-26.42)	6.01 (4.96, 0.00-26.87)	0.9
Male sex*	702 (56.8%)	4212 (56.8%)	1.00
Age at start of follow-up (years)			0.98
0–10	208 (16.8%)	1265 (17.1%)	
11–20	241 (19.5%)	1396 (18.8%)	
21–30	357 (28.9%)	2129 (28.7%)	
31–40	331 (26.8%)	2026 (27.3%)	
41–50	99 (8.0%)	600(8.1%)	
Age at index date* (years)			1.00
0–10	35 (2.8%)	210 (2.8%)	
11–20	239 (19.3%)	1434 (19.3%)	
21–30	337 (27.3%)	2002 (27.3%)	
31–40	355 (28.7%)	2129 (28.7%)	
41–50	270 (21.8%)	1621 (21.9%)	
IMD quintile			0.09
5 (most deprived)	251 (20.3%)	1598 (21.6%)	
4	277 (22.4%)	1641 (22.1%)	
3	246 (19.9%)	1442 (19.4%)	
2	221 (17.9%)	1325 (17.9%)	
1 (least deprived)	241 (19.5%)	1410 (19.0%)	
Immunosuppression	16 (1.3%)	15 (0.2%)	<0.001
Infectious mononucleosis	43 (3.5%)	131 (1.8%)	<0.001
Allergic disease[þ]	500 (40.5%)	2429 (32.8%)	<0.001
Steroid use	731 (59.1%)	3714 (50.1%)	<0.001
Inhaled	294 (23.8%)	1548 (20.9%)	0.02
Topical	604 (48.9%)	3011 (40.6%)	<0.001
Oral	110 (8.9%)	449 (6.1%)	<0.001
IV/IM	30 (2.4%)	112 (1.5%)	0.02
No. of steroids			<0.001
0	505 (40.9%)	3702 (49.9%)	
1	201 (16.3%)	1178 (15.9%)	
≥2	530 (42.9%)	2536 (34.2%)	

Median no. of steroids (IQR)	1 (0 – 4)	1 (0 – 3)	<0.001

Table 1: Baseline characteristics of cases with Hodgkin's Lymphoma and controls. HL, Hodgkin's Lymphoma; ¥ p value from chi-squared test or Mann-Whitney U-test for continuous variables; * matched variables; SD, standard deviation; ᵇDefined as diagnosis of asthma, and/or eczema and/or allergic rhinitis during follow-up period.

	Concurrent Allergic Diagnoses in Cases (n=1,236)			
	Asthma	**Eczema**	**Allergic Rhinitis**	**All three**
Asthma	**18.9% (233)**	6.6%(82)	4.6%(57)	
Eczema	6.6%(82)	**21.0% (260)**	4.4%(55)	
Hay fever	4.6%(57)	4.4%(55)	**13.9% (172)**	
All three				**2.4%(29)**
	Concurrent Allergic Diagnoses in Controls (n=7,416)			
Asthma	**15.2% (1129)**	4.4%(323)	4.2%(308)	
Eczema	4.4%(323)	**15.6%(1154)**	3.2%(241)	
Hay fever	4.2%(308)	3.2%(241)	**12.4%(918)**	
All three				**1.4%(100)**
P Value*	0.001	<0.001	0.13	

Table 2: Frequency of concurrent allergic diseases**:** Proportion of cases and controls with a diagnosis or one or more allergic conditions. n, number; * P value for chi-squared test comparing allergic disease in cases and controls.

Variable	Univariable OR (95% CI)	Adjusted OR[þ] (95%CI)	OR after adjustment for steroids (95% CI)
Immunosuppression	6.36(3.15-12.87)	6.18(3.04-12.57)	6.05(2.97-12.33)
p value	**<0.001**	**<0.001**	**<0.001**
Infectious mononucleosis	2.00(1.41-2.84)	1.89(1.33-2.68)	1.87(1.31-2.67)
p value	**<0.001**	**<0.001**	**0.001**
Allergic disease	1.42(1.25-1.62)	1.41(1.24-1.60)	1.25(1.09-1.43)
p value	**<0.001**	**<0.001**	**0.002**
Deprivation quintile			
5 (most deprived)	*ref*	*ref*	*ref*
4	1.08(0.89-1.29)	1.09(0.90-1.30)	1.08(0.90-1.30)
3	1.09(0.90-1.32)	1.08(0.89-1.31)	1.07(0.89-1.30)
2	1.06(0.87-1.29)	1.05(0.86-1.28)	1.04(0.86-1.27)
1 (least deprived)	1.09(0.90-1.32)	1.06(0.88-1.29)	1.05(0.87-1.28)
p value	**0.47***	**0.69***	**0.75***
Steroid use	1.51(1.33-1.72)	1.38(1.20-1.59)	–
p value	**<0.001**	**<0.001**	–

623 **Table 3:** Association between exposures and Hodgkin's Lymphoma incidence (≤50 years). OR, odds
624 ratio; CI, confidence interval; [þ] matched on age, sex and follow-up time and adjusted for other
625 variables in the model (region, deprivation, immunosuppression, atopy and infectious mononucleosis);
626 p value from Likelihood-ratio Test; *p value for test for linear trend.

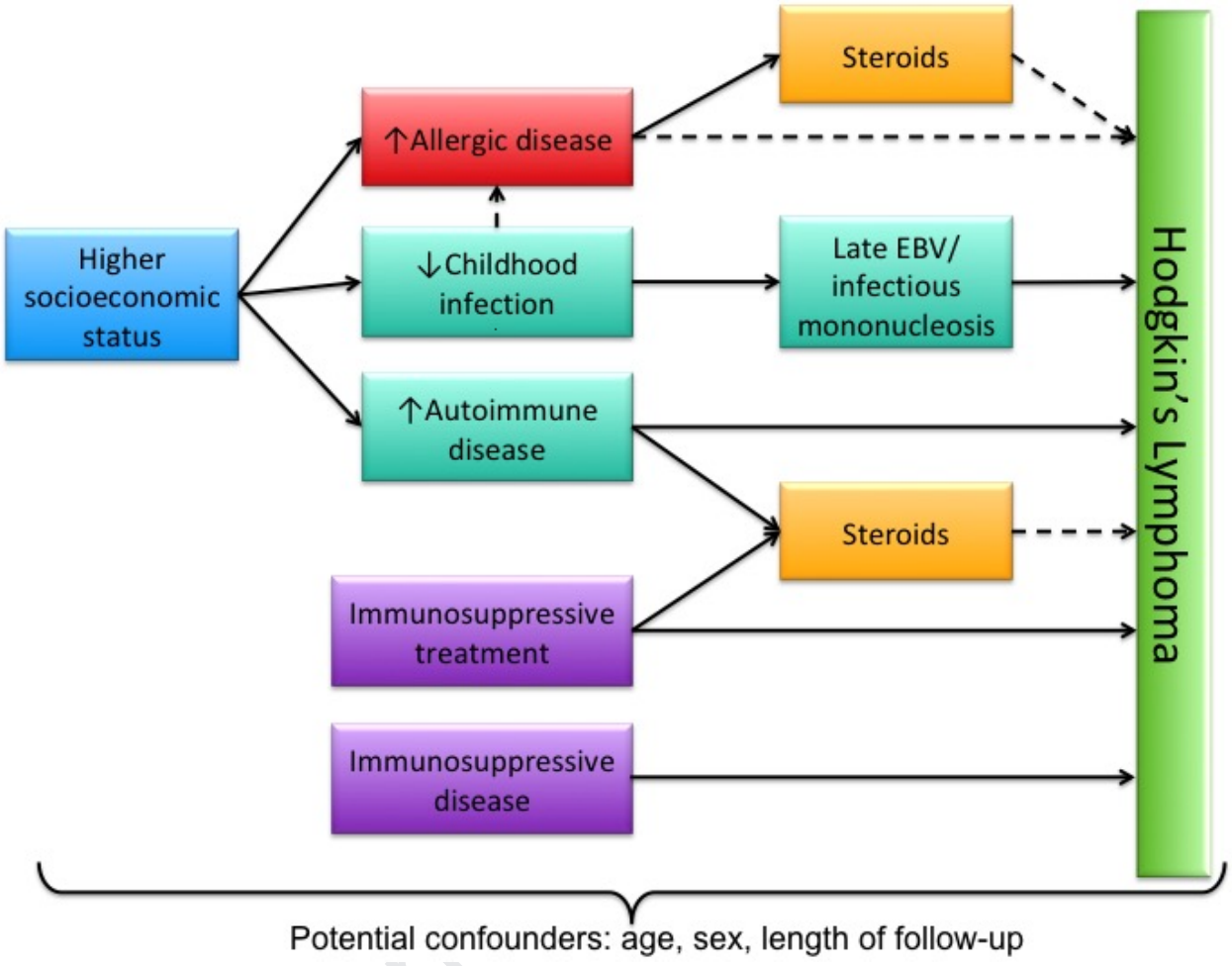
627

Variable	Univariable OR	Adjusted OR[♭]	OR after adjustment for steroids
Asthma	1.31(1.11-1.53)	1.23(1.04-1.45)	1.15(0.97-1.36)
p value	**0.001**	**0.016**	**0.11**
Eczema	1.47(1.26-1.72)	1.41(1.20-1.65)	1.27(1.08-1.49)
p value	**<0.001**	**<0.001**	**0.005**
Allergic rhinitis	1.15(0.96-1.37)	1.06(0.88-1.27)	0.99(0.83-1.19)
p value	**0.13**	**0.56**	**0.94**
Immunosuppression	6.36(3.15-12.87)	6.05(2.98-12.30)	5.94(2.91-12.10)
p value	**<0.001**	**<0.001**	**<0.001**
Infectious mononucleosis	2.00(1.41-2.84)	1.88(1.32-2.68)	1.87(1.31-2.66)
p value	**<0.001**	**<0.001**	**0.001**
Steroid use	1.51(1.33-1.72)	1.39(1.21-1.60)	–
p value	**<0.001**	**<0.001**	–
Topical steroid	1.46(1.28-1.66)	1.34(1.17-1.54)	–
p value	**<0.001**	**<0.001**	–
Inhaled steroid	1.20(1.03-1.39)	1.03(0.87-1.23)	–
p value	**0.017**	**0.73**	–
Oral steroid	1.54(1.23-1.92)	1.30(1.02-1.65)	–
p value	**<0.001**	**0.036**	–
IV/IM steroid	1.63(1.08-2.46)	1.55(1.03-2.35)	–
p value	**0.019**	**0.037**	–
Number of steroids	1.01(1.00-1.01)	1.00(1.00-1.01)	–
	0.003	**0.37**	–
No. of atopic diseases			
0	*ref*	*ref*	*ref*
1	1.43(1.24-1.64)	1.42(1.23-1.63)	1.27(1.09-1.47)
2	1.30(1.04-1.63)	1.27(1.01-1.60)	1.10(0.87-1.39)
3	2.05(1.34-3.13)	2.04(1.34-3.13)	1.75(1.14-2.68)
p value*	**<0.001**	**<0.001**	**0.005**

Table 4: Association between atopic diseases and Hodgkin's Lymphoma incidence (<50 years). OR, odds ratio; CI, confidence interval; p value from Likelihood-ratio Test; [♭] matched on age, sex and follow-up time and adjusted for other variables in the model (socioeconomic status, immunosuppression, atopic diseases and infectious mononucleosis); No., number; ref, reference group; *p value for test for linear trend.

Variable		Used steroid Adjusted OR♭ (95%CI)	Never used steroids Adjusted OR♭ (95%CI)	P value for effect modification
Allergic disease		1.17(0.99-1.37)	1.48(1.15-1.90)	
	p value	0.064	0.002	0.12
Asthma		1.00(0.83-1.21)	1.85(1.34-2.56)	
	p value	**0.99**	**<0.001**	0.002
Eczema		1.27(1.07-1.51)	1.27(0.81-1.99)	
	p value	**0.007**	**0.31**	0.99
Allergic rhinitis		0.96(0.78-1.18)	1.14(0.77-1.71)	
	p value	**0.69**	**0.51**	0.45
Immunosuppression		9.08(3.59-22.96)	2.67(0.71-10.10)	
	p value	**<0.001**	**0.15**	0.12
Infectious mononucleosis		1.82(1.17-2.83)	1.96(1.08-3.56)	
	p value	**0.008**	**0.028**	0.85

Table 5: Association between allergic diseases and Hodgkin's Lymphoma incidence stratified by steroid use. OR, odds ratio; CI, confidence interval; p value from Likelihood-ratio Test; ♭matched on age, sex and follow-up time and adjusted for other variables in the model (socioeconomic status, immunosuppression, atopic diseases and infectious mononucleosis).


Steroids
↑Allergic disease
Higher socioeconomic status
↓Childhood infection
Late EBV/ infectious mononucleosis
Hodgkin's Lymphoma
↑Autoimmune disease
Steroids
Immunosuppressive treatment
Immunosuppressive disease
Potential confounders: age, sex, length of follow-up