



# Steroid prescribing in primary care increases prior to Hodgkin lymphoma diagnosis: A UK nationwide case-control study

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## ABSTRACT

**Background:** Steroid use is associated with increased risk of Hodgkin lymphoma (HL). However, allergic symptoms commonly treated with steroids are also presenting features of HL in some patients, thereby introducing protopathic bias in estimates of aetiological associations. It is therefore important to examine steroid prescribing patterns pre-diagnosis to understand timing of associations and when healthcare use increases before cancer diagnosis to inform future epidemiological study design.

**Methods:** We analysed steroid prescribing in 1232 HL patients and 7392 matched controls using primary care electronic health records (Clinical Practice Research Datalink (CPRD), 1987–2016). Using Poisson regression, we calculated monthly steroid prescribing rates for the 24-months preceding HL diagnosis, identifying the inflection point when they start to increase from baseline in cases, comparing rates with synchronous controls, and stratifying by route-of-administration and allergic disease status.

**Results:** 46 % of HL patients had a steroid prescription in the 24-months preceding diagnosis compared to 26 % of controls (OR 2.55, 95 %CI 2.25–2.89,  $p < 0.001$ ). Odds of underlying HL were greatest in patients receiving multiple steroid prescriptions, oral steroids and in patients with a new allergic disease diagnosis. Among HL patients, steroid prescribing rates increased progressively from 7-months pre-diagnosis, doubling from 52 to 111 prescriptions/1000 patients/month.

**Conclusion:** Steroid prescribing increases during periods leading up to HL diagnosis, suggesting steroid-treated symptoms may be early presenting features of HL. A diagnostic window of appreciable length exists for potential earlier HL diagnosis in some patients; this 7-month ‘lag-period’ pre-diagnosis should be excluded in studies examining aetiological associations between steroids and HL.

## 1. Introduction

Hodgkin lymphoma (HL) is the most common cancer in teenagers and young adults (TYA) [1,2]. Advances are needed in both the understanding of its aetiology and in improving the timeliness of its diagnosis [3–5]. Studies have reported that history of allergic disease and chronic steroid use are associated with increased risk of subsequent HL diagnosis [6–11]. However, allergic symptoms (such as pruritus, rash, shortness of breath or cough) often treated by steroids also form part of the presenting features in one in four HL patients [12]. Therefore, associations between steroid use and risk of HL could at least partly reflect increased

prescribing in the lead up to HL diagnosis (a phenomenon known as reverse causality or ‘protopathic bias’ i.e. the as-yet-undiagnosed cancer is the cause of the prescribing, rather than the inverse [13,14]).

The concept of a ‘diagnostic time window’ has been proposed to indicate the earliest time at which changes from background rates of healthcare utilisation can be observed among symptomatic patients subsequently diagnosed with cancer [15–17]. Increased rates of drug prescribing have been observed 2, 4, 6 and 18-months, before the diagnosis of breast [18], lung [16,18], prostate [18] and colorectal [15, 18,19] cancer, respectively. These prescribing patterns reflect the treatment of presenting symptoms or complications of

*Abbreviations:* HL, Hodgkin lymphoma; TYA, teenagers and young adults; EHR, electronic health records; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; UTS, ‘up-to-standard’; IMD, Index of Multiple Deprivation; OR, odds ratio; RR, rate ratio.

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**Table 1**

Association between Hodgkin lymphoma and steroid prescribing or allergic disease diagnosis in the 24 months preceding diagnosis. HL, Hodgkin lymphoma; P value from Likelihood-ratio Test; m, months; Ref, reference category; † subcategories represent different models and patients can be in more than one category.

Characteristics	Cases of HL (n = 1232)	Controls (n = 7392)	Absolute risk difference	Crude Odds Ratio (95 % CI)	P value
Any steroid prescription in 24 m before diagnosis	571 (46.4 %)	1906 (25.8 %)	20.6 %	2.55 (2.25–2.89)	< 0.001
Any steroid prescription in 12 m before diagnosis	448 (36.4 %)	1308 (17.7 %)	18.7 %	2.71 (2.38–3.10)	< 0.001
No. of steroids prescriptions in 24 m before diagnosis					
0	661 (53.7 %)	5486 (74.2 %)	-20.5 %	Ref	
1	232 (18.8 %)	881 (11.9 %)	6.9 %	2.23 (1.89–2.63)	< 0.001
2	109 (8.9 %)	353 (4.8 %)	4.1 %	2.66 (2.11–3.36)	< 0.001
≥ 3	230 (18.7 %)	672 (9.1 %)	9.6 %	2.94 (2.47–3.49)	< 0.001
Route of steroid administration†					
Inhaled (Yes/No)	204 (16.5 %)	789 (10.7 %)	5.8 %	1.68 (1.42–1.99)	< 0.001
Topical (Yes/No)	416 (33.8 %)	1287 (17.4 %)	16.4 %	2.47 (2.16–2.83)	< 0.001
Oral (Yes/No)	91 (7.4 %)	157 (2.1 %)	5.3 %	3.68 (2.82–4.81)	< 0.001
Steroid prescription at‡					
12–9 months before index (Yes/No)	160 (13.0 %)	544 (7.4 %)	5.6 %	1.90 (1.57–2.30)	< 0.001
6–9 months before index (Yes/No)	184 (14.9 %)	569 (7.7 %)	7.2 %	2.11 (1.76–2.52)	< 0.001
3–6 months before index (Yes/No)	208 (16.9 %)	535 (7.2 %)	9.7 %	2.63 (2.21–3.13)	< 0.001
0–3 months before index (Yes/No)	239 (19.4 %)	536 (7.3 %)	12.1 %	3.12 (2.63–3.69)	< 0.001
Any Allergic disease					
None	732 (59.4 %)	4975 (67.3 %)	-7.9 %	Ref	
Pre-existing diagnosis only	425 (34.5 %)	2248 (30.4 %)	4.1 %	1.31 (1.14–1.49)	< 0.001
New diagnosis in 12 months before diagnosis	75 (6.1 %)	169 (2.3 %)	3.8 %	3.16 (2.36–4.23)	< 0.001
Eczema					
None	974 (79.1 %)	6247 (84.5 %)	-5.4 %	Ref	
Pre-existing		1077 (14.6 %)	2.9 %	1.30 (1.10–1.54)	0.002

**Table 1 (continued)**

Characteristics	Cases of HL (n = 1232)	Controls (n = 7392)	Absolute risk difference	Crude Odds Ratio (95 % CI)	P value
	216 (17.5 %)				
New	42 (3.4 %)	68 (0.9 %)	2.5 %	4.02 (2.71–5.96)	< 0.001
Asthma					
None	999 (81.1 %)	6269 (84.8 %)	-3.7 %	Ref	
Pre-existing	207 (16.8 %)	1080 (14.6 %)	2.2 %	1.21 (1.03–1.43)	0.023
New	26 (2.1 %)	43 (0.6 %)	1.5 %	3.92 (2.38–6.46)	< 0.001
Hay fever					
None	1060 (86.0 %)	6476 (87.6 %)	-1.6 %	Ref	
Pre-existing	160 (13.0 %)	854 (11.6 %)	1.4 %	1.15 (0.96–1.38)	0.14
New	12 (1.0 %)	62 (0.8 %)	0.2 %	1.18 (0.63–2.22)	0.60

as-yet-undiagnosed cancer, initially attributed to unrelated common conditions (e.g. prescribing laxatives for constipation in colorectal cancer or antibiotics for chest infections super-imposed on lung cancer). It is not known whether similar prescribing increases occur prior to HL diagnosis and, if so, the length of such diagnostic windows.

Given the above, we used linked primary care electronic health records (EHRs) to examine new allergic disease diagnoses and steroid prescribing patterns over time in patients subsequently diagnosed with HL to identify both the length of ‘diagnostic time windows’ for potential earlier diagnosis [15–17], and the length of the lag-time that should be applied in aetiological studies examining steroid use and HL to avoid protopathic bias.

## 2. Methods

### 2.1. Design and setting

We performed a matched case-control study using data from the UK Clinical Practice Research Datalink (CPRD) from 1st September 1987 to 1st July 2016 linked to Hospital Episode Statistics (HES, Set 13) inpatient data. CPRD is an electronic health records (EHR) database of anonymised data from UK primary care [20] containing coded data on symptoms, diagnoses, tests and prescriptions [23]. HES contains records from every English NHS hospital admission [21] from April 1997 for patients in practices that have consented to data linkage (57 % of CPRD practices are eligible for HES linkage) [22,23].

### 2.2. Study population

Individuals aged ≤ 50 years actively registered with a CPRD practice for more than 1 year with ‘up to standard’ (UTS) CPRD data during the study period were eligible for inclusion. This represents the age group where the majority of HL cases occur [24], and where diagnostic difficulty is greater due to the rarity of neoplastic disease in younger patients. Moreover, this is the age group where allergic symptoms at presentation are likely more frequent [25,26]. Patients were excluded if they had a HL diagnosis prior to entry into the study to avoid possible inclusion of retrospectively recorded past/prevalent diagnoses.

**Table 2**

Association between Hodgkin lymphoma and steroid prescribing by allergic disease status in the 24 months preceding diagnosis. HL, Hodgkin lymphoma; P value from Likelihood-ratio Test; m, months; Ref, reference category; †sub-categories represent different models and patients can be in more than one category.

Characteristics	No allergic diagnosis (n = 5707)				
	Cases of HL (n = 732)	Controls (n = 4975)	Absolute risk difference	Odds Ratio (95 %CI)	P value
Steroid use in 24 m before index	244 (33.3 %)	786 (15.8 %)	17.5 %	2.63 (2.19–3.17)	< 0.001
Steroid use in 12 m before index	177 (24.2 %)	468 (9.4 %)	14.8 %	3.09 (2.49–3.83)	< 0.001
Route of steroid administration <sup>†</sup>					
Inhaled (Yes/No)	43 (5.9 %)	176 (3.5 %)	2.4 %	1.72 (1.18–2.50)	0.005
Topical (Yes/No)	184 (25.1 %)	607 (12.2 %)	12.9 %	2.48 (2.02–3.05)	< 0.001
Oral (Yes/No)	41 (5.6 %)	39 (0.8 %)	4.8 %	6.31 (3.78–10.53)	< 0.001
Number of steroids prescriptions					
0	488 (66.7 %)	4189 (84.2 %)	-17.5 %	Ref	
1	141 (19.3 %)	494 (9.9 %)	9.4 %	2.29 (1.83–2.86)	< 0.001
2	48 (6.6 %)	131 (2.6 %)	4.0 %	3.41 (2.33–5.01)	< 0.001
≥ 3	55 (7.5 %)	161 (3.2 %)	4.3 %	3.33 (2.32–4.76)	< 0.001
Mean Rate (No. of steroids/person/24 m)	0.41 (0.38–0.45)	0.16 (0–0.51)	–	–	–
Characteristics	Pre-existing allergic diagnosis only (n = 2673)				
	Cases of HL (n = 425)	Controls (n = 2248)	Absolute risk difference	Odds Ratio (95 %CI)	P value
Steroid use in 24 m before index	264 (62.1 %)	999 (44.4 %)	17.7 %	2.15 (1.65–2.80)	< 0.001
Steroid use in 12 m before index	209 (49.2 %)	727 (32.3 %)	16.9 %	2.05 (1.59–2.66)	< 0.001
Route of steroid administration <sup>†</sup>					
Inhaled (Yes/No)	134 (31.5 %)	553 (24.6 %)	6.9 %	1.63 (1.23–2.15)	0.001
Topical (Yes/No)	185 (43.5 %)	599 (26.7 %)	16.8 %	2.13 (1.63–2.78)	< 0.001
Oral (Yes/No)	35 (8.2 %)	106 (4.7 %)	3.5 %	1.35 (0.81–2.23)	0.25
Number of steroids prescriptions					
0	161 (37.9 %)	1249 (55.6 %)	-17.7 %	Ref	
1	70 (16.5 %)	338 (15.0 %)	1.5 %	1.67 (1.14–2.44)	0.008

**Table 2 (continued)**

2	50 (11.8 %)	196 (8.7 %)	3.1 %	2.10 (1.35–3.26)	0.001
≥ 3	144 (33.9 %)	465 (20.7 %)	13.2 %	2.48 (1.83–3.37)	< 0.001
Mean Rate (No. of steroids/person/24 m)	3 (0–34)	2 (0–63)	–	–	–
Characteristics	New allergic diagnosis (n = 244)				
	Cases of HL (n = 75)	Controls (n = 169)	Absolute risk difference	Odds Ratio (95 %CI)	P value
Steroid use in 24 m before index	63 (84.0 %)	121 (71.6 %)	12.4 %	0.80 (0.21–3.01)	0.74
Steroid use in 12 m before index	62 (82.7 %)	113 (66.9 %)	15.8 %	0.80 (0.21–3.01)	0.74
Route of steroid administration <sup>†</sup>					
Inhaled (Yes/No)	27 (36.0 %)	60 (35.5 %)	0.5 %	1.35 (0.36–5.07)	0.66
Topical (Yes/No)	47 (62.7 %)	81 (47.9 %)	14.8 %	0.76 (0.21–2.72)	0.67
Oral (Yes/No)	15 (20.0 %)	12 (7.1 %)	12.9 %	2.56 (0.23–29.12)	0.45
Number of steroids prescriptions					
0	12 (16.0 %)	48 (28.4 %)	-12.4 %	Ref	
1	21 (28.0 %)	49 (29.0 %)	-1.0 %	0.43 (0.08–2.49)	0.35
2	11 (14.7 %)	26 (15.4 %)	-0.7 %	1.19 (0.19–7.50)	0.85
≥ 3	31 (41.3 %)	46 (27.2 %)	14.1 %	1.78 (0.24–13.10)	0.57
Mean Rate (No. of steroids/person/24 m)	3 (0–15)	2 (0–20)	–	–	–

**2.3. Definition of HL cases and controls**

Cases were patients with a new diagnosis of HL in either CPRD or HES (Supplementary Table S1 for code lists). Six controls were concurrently matched [27] to each case based on age at index date (± 1 year), sex and length of follow-up (± 2 years). The earliest recorded date of HL diagnosis was taken as the index date for cases and their matched controls. Data on practice socioeconomic status was collected using the Index of Multiple Deprivation (IMD) quintile.

**2.4. Defining steroid prescribing**

All steroid prescriptions issued by a General Practitioner (GP) in the 24-months preceding the index date were included (new and repeat prescriptions, Supplementary Table S2 for code list). Information was collected on date of issue (to calculate monthly prescribing rates); and route of administration (inhaled, topical or oral). Intravenous and intramuscular steroids were excluded as are rarely prescribed in primary care. The number of steroid prescriptions per patient in the 24-months before the index date (categorised as 0, 1, 2 or ≥ 3 prescriptions) was also calculated.

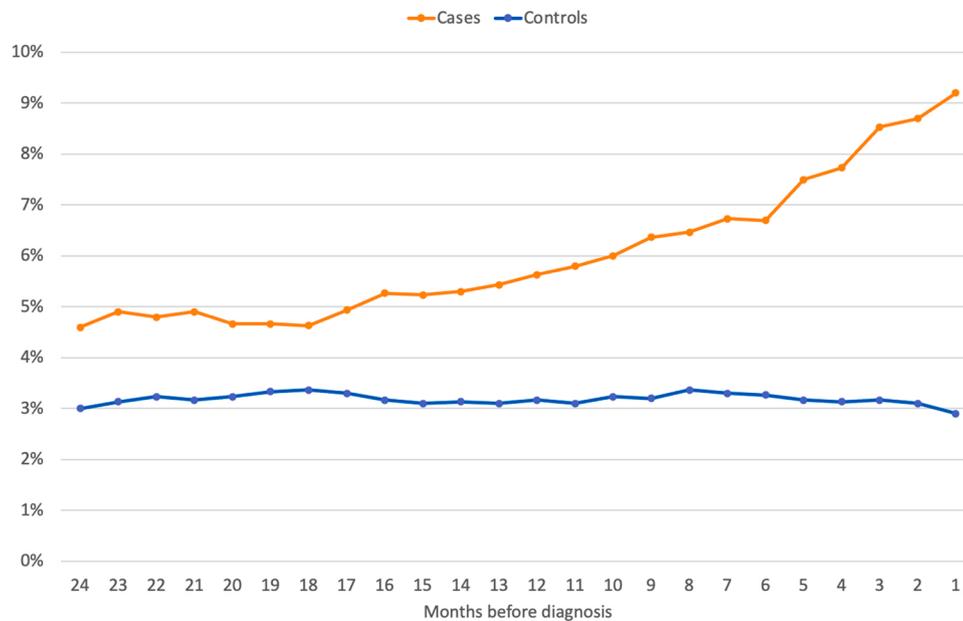


Fig. 1. Monthly proportion of patients receiving a steroid prescription over time in the 24-months before Hodgkin lymphoma diagnosis/index date (3-month moving average).

### 2.5. Defining allergic disease status

Data were collected from CPRD and HES on the first recorded date of allergic disease diagnosis (eczema, asthma, allergic rhinitis, [Supplementary Table S3](#) for code lists) in participants and used to categorise individuals as follows: pre-existing allergic disease (present at any point > 1 year before the index date), new allergic disease (first diagnosis in the year preceding index date without previous diagnosis of the same allergic disease), and no history of allergic disease at any point.

### 2.6. Statistical analysis

Our analysis had 3 main objectives.

To compare baseline characteristics between cases and controls, and examine associations between steroid prescribing, allergic disease and HL diagnosis in the following 24-months, conditional logistic regression models were used. Given evidence that classifying steroids by total number of prescriptions (in the 2 years before diagnosis), route of administration and timing of prescription; and classifying allergic disease by timing of diagnosis, type (asthma, eczema, and allergic rhinitis) and status (none/pre-existing/newly diagnosed) each improved model fit using likelihood ratio tests, odds ratios (ORs) based on each of these classifications were estimated.

To analyse time trends in steroid prescribing rates pre-diagnosis, mixed-effects Poisson regression was used. Monthly prescriptions counts in each of the 24-months preceding the index date in HL patients and controls were modelled including a random intercept for matching set given the study's case-control design. Monthly prescribing rates with 95 % confidence intervals were plotted separately for cases and controls. Rate ratios (RR) were estimated comparing prescribing rates in HL patients first to their baseline rate at 24-months pre-diagnosis and then to controls at synchronous time points. Following the method outlined in Moullet et al. [28], Poisson regression models were run with different inflection points (taking into account any background trend in cases) to identify the timing of inflection points when prescribing rates in HL patients first started to deviate from the background trend, and the model with the best fit was selected. Bootstrapping was used to provide confidence intervals for this inflection point (full details in [Supplementary Data](#)).

Further analyses examined whether associations between steroid

prescribing and HL differed by a.) route of steroid administration and b.) patient allergic disease status (none/pre-existing/newly diagnosed). Given evidence that interactions existed, RRs for steroid prescribing over time were estimated stratifying by route and allergic disease status. Analyses were performed using Stata (version 15; StataCorp, College Station, TX, USA).

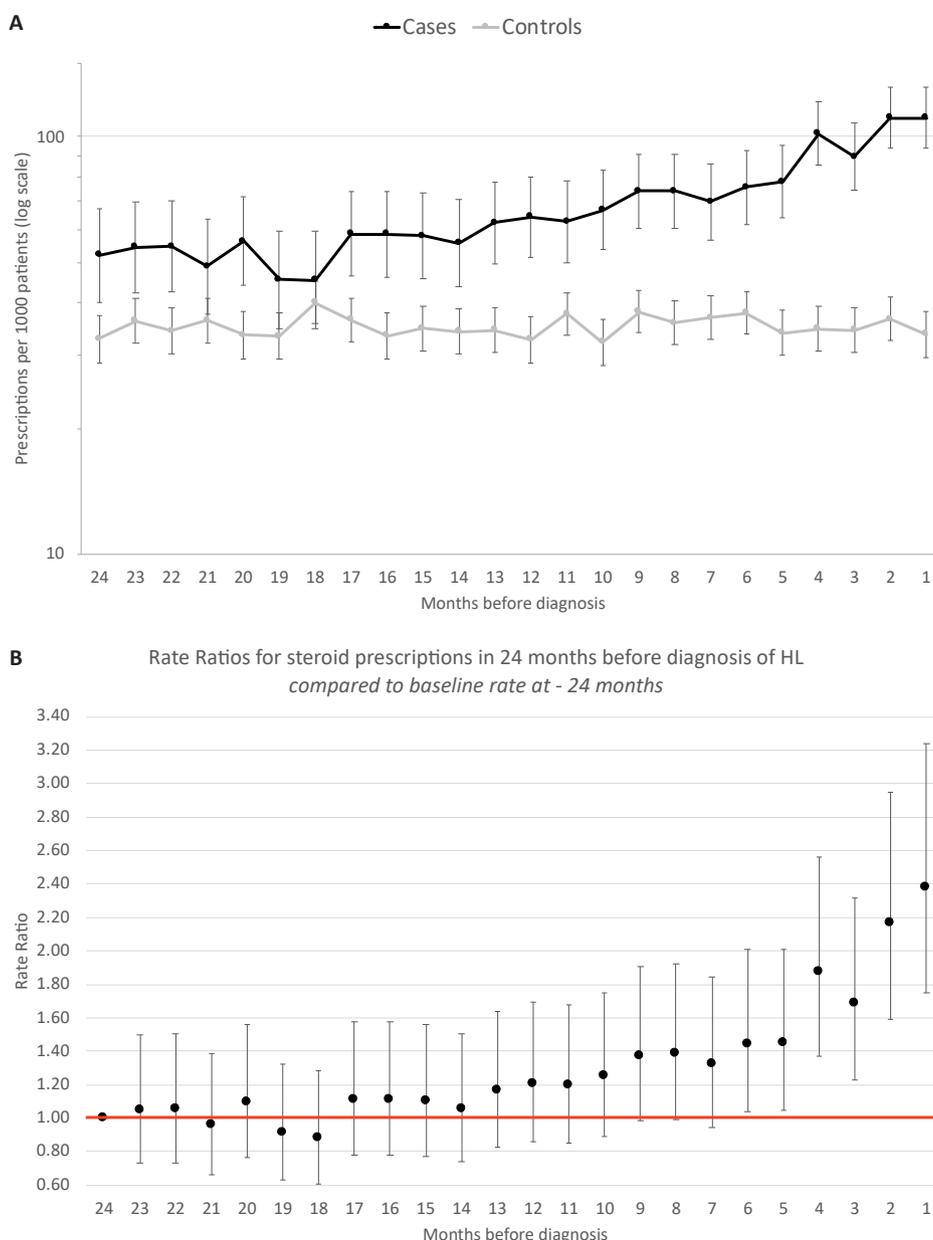
## 3. Results

1232 incident cases of HL were matched to 7392 controls. Cases and controls were similar with regards to the matched variables (age, sex, follow-up length, calendar time), socioeconomic status and UK region, with 57 % males, a mean age at diagnosis/index date of 31 years and no evidence of variation by IMD ( $p = 0.89$ ) or UK region ( $p = 0.49$ ) in both groups ([Supplementary Table S4](#)).

### 3.1. Steroid prescriptions pre-diagnosis

HL patients were 3-fold more likely to have been prescribed steroids in the 2 years preceding diagnosis compared to controls (46 % vs. 26 %, OR 2.55, 95 %CI 2.25–2.89,  $p < 0.001$ ). The odds of HL diagnosis increased with higher number of steroids prescriptions ( $p < 0.001$ ), with patients receiving 3 or more steroid prescriptions having 3-fold greater odds of HL (OR 2.94, 95 %CI 2.47–3.49,  $p < 0.001$ ). Further, when examining sequential time periods pre-diagnosis, the odds of HL increased the closer the prescription was issued to diagnosis and were greater with oral (4-fold increased odds) compared with topical or inhaled steroids ([Table 1](#) and [Supplementary table S5](#)).

Allergic disease was also associated with HL when examining each of the sequential 6-month time periods in the 2 years before HL diagnosis. The odds of HL increased the closer the new allergic diagnosis was made to HL detection, with HL patients significantly more likely to have a new allergic disease diagnosis in the year before their cancer diagnosis compared to controls, particularly new eczema and asthma diagnoses in the 6-months before HL detection (4-fold increased odds for both, corresponding to 3.4 % and 2.1 % for cases and 0.9 % and 0.6 % for controls in the year pre-diagnosis/index date, respectively) ([Table 1](#) and [Supplementary Table S5](#)). Additionally, the association between steroid prescribing and subsequent HL diagnosis differed by patient allergic disease status ( $P_{\text{interaction}} = 0.021$ ). Individuals with pre-existing or no



**Fig. 2.** Monthly GP steroid prescribing rates (total number of steroid prescriptions/1000 persons/month) in the 24-months before Hodgkin lymphoma diagnosis in cases (n = 1232) and controls (n = 7392) (Panel A) and monthly rate ratios comparing prescribing rates in cases to their baseline rate 24-months pre-diagnosis (Panel B) with 95 % CIs.

allergic disease and steroid use in the preceding 24-months had more than 2-fold greater odds of being diagnosed with HL, the strongest association being observed following oral steroid use in individuals without allergic disease (6-fold increase in odds) (Table 2).

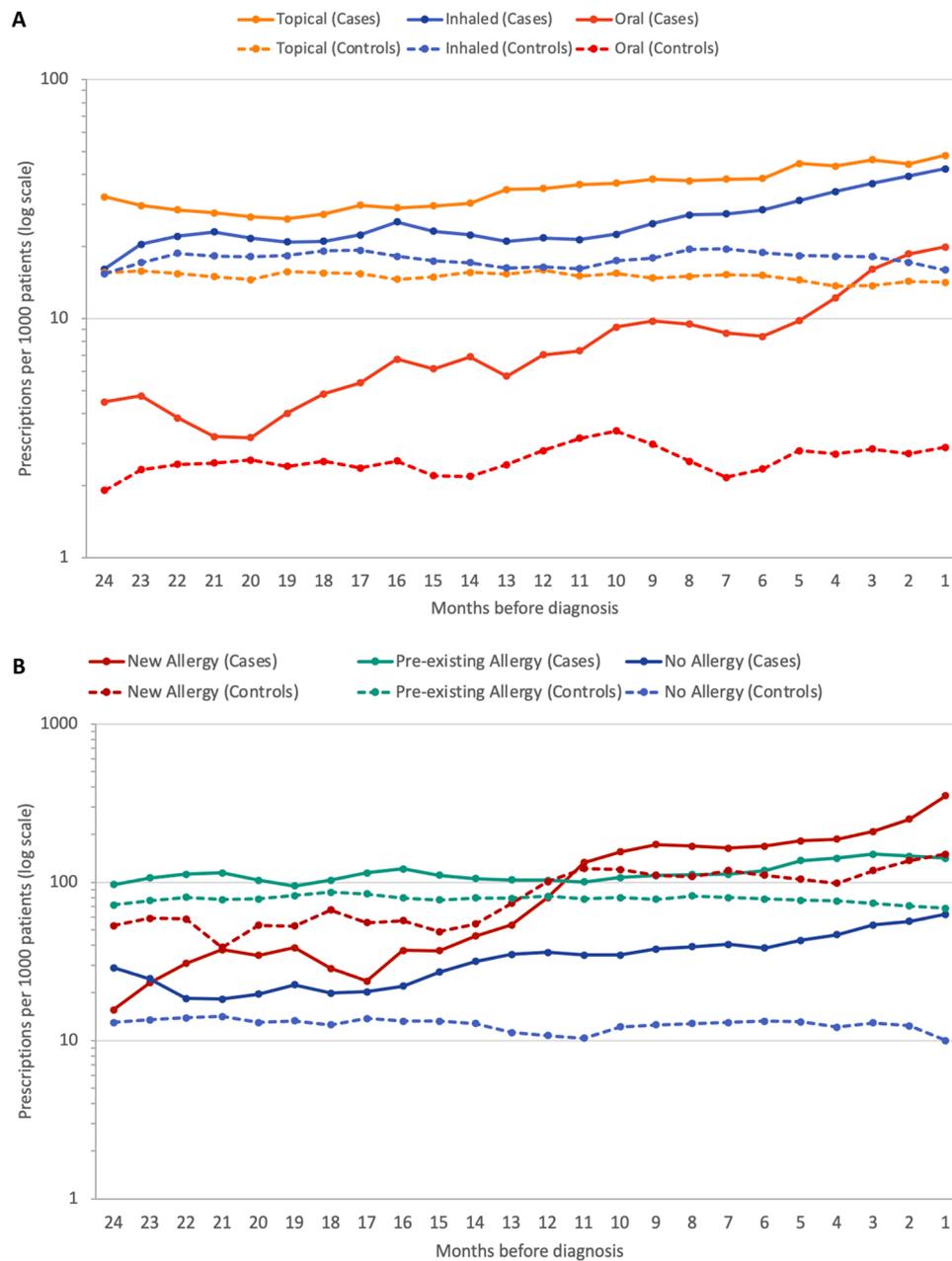
The proportion of HL patients receiving one or more steroid prescriptions each month was consistently higher compared to controls throughout the 24-months pre-diagnosis, increasing progressively from a baseline of 4–5 % up to 9 %, while remaining stable around 3 % in controls (Fig. 1).

### 3.2. Inflection points in steroid prescribing

Poisson modelling showed the inflection point in steroid prescribing rates in HL patients with the best fit to be at 7-months prior to diagnosis (95 %CI 3–20), with prescribing increasing progressively and doubling from a baseline of 52 prescriptions per 1000 persons/month to a peak of 111 prescriptions per 1000 persons/month in the month immediately

preceding HL diagnosis (RR 2.38, 95 %CI 1.71–3.24, P < 0.001), while remaining stable in controls (Fig. 2 and Supplementary Fig. S6). Across this 7-month period steroid prescribing rates were consistently significantly higher in HL cases compared to controls (Fig. 2, Supplementary Table S7). Similar patterns were observed for all routes of steroid administration (Fig. 3 panel A, Supplementary Table S8 and Supplementary Fig. S9).

Examining steroid prescribing over time by allergic disease status, the largest increase in steroid prescribing rates was seen in cases with a ‘new’ diagnosis of allergic disease, who experienced a 21-fold increase in steroid prescribing rates from a baseline of 16 prescriptions per 1000 persons/month to a peak of 352 prescriptions per 1000 persons/month in the month immediately preceding HL diagnosis (RR 20.68, 95 %CI 2.83–151.00, P = 0.003) (Fig. 3 panel B, Supplementary Table S10 and Supplementary Fig. S11).



**Fig. 3.** Monthly GP steroid prescribing rates (total number of steroid prescriptions/1000 persons/month) in the 24 months before Hodgkin lymphoma diagnosis in cases and controls using a 3 month moving average: by route of administration (panel A) and allergic disease status (panel B), ‘No allergy’ (cases n = 732, controls n = 4975), ‘Pre-existing allergy (cases n = 425, controls n = 2248) ‘New allergy diagnosis’ (cases) n = 75, controls n = 169).

**4. Discussion**

Newly diagnosed HL patients were 3-fold more likely to have been prescribed steroids in the 2 years before their cancer diagnosis, with 1 in 2 HL patients receiving a GP steroid prescription in this period. HL diagnosis was more likely in patients receiving multiple steroid prescriptions, oral steroid prescriptions and in patients with a new allergic disease diagnosis. Among patients subsequently diagnosed with HL, the rate of GP steroid prescribing progressively increases from 7-months pre-diagnosis compared to the baseline trend and is substantially elevated compared to controls throughout this period. The largest increases in steroid prescribing were observed for the oral route and in patients with a ‘new’ diagnosis of allergic disease.

**4.1. Comparison with the literature**

Pre-diagnostic prescribing patterns have been previously used to identify the maximum length of diagnostic windows for potential earlier cancer diagnosis [17]. Marked increases in new drug prescribing have been reported 6–18-months before cancer diagnosis, with increased proton-pump inhibitor, anti-haemorrhoidal, laxative and antibiotic prescribing observed before colorectal cancer diagnosis [15,18,19,29, 30]; and increased opioid, cough suppressant, antibiotic and inhaled beta-agonist use before lung cancer diagnosis [16,18], and increasing number of prescriptions associated with increased risk of cancer diagnosis [19]. This study for the first time demonstrates similar trends in increased prescribing of steroids up to 7-months before HL diagnosis.

Previous studies exploring aetiological association between steroid use and HL diagnosis have reported conflicting results, with some

finding evidence of an association and others none [6,9,10,31–35]. This may partly reflect methodological differences in separating out causal associations resulting from long-term exposure with the effects of HL symptoms, which can prompt steroid use to manage presenting symptoms [12]. For example, there is wide variation in the 'lag-time' periods applied pre-diagnosis to account for protopathic bias, with several studies including any steroid exposure up to HL diagnosis [10,32,34,35] and others excluding 6–12 months pre-diagnosis [6,9,31,33], selected a priori [18]. Pottegård and Hallas recommended that applying a 6-month lag-time should avoid protopathic bias in most drug-cancer associations in the context of breast, lung, colon and prostate cancer [18]. Our findings concord with their conclusion, examining patterns of drug prescribing prior to HL diagnosis, specifically steroids.

#### 4.2. Strengths and limitations

The study uses a large representative sample [20], enabling the examination of steroid prescribing over time by route of administration and allergic disease status and segments the time periods pre-diagnosis to examine temporal risk variation and the potential impact of reverse causality/protopathic bias [36]. Wide use of electronic prescription recording in the UK means records have high levels of completeness and accuracy. Recording of lymphoma diagnosis in CPRD has validity when compared to the English population-based cancer registration data (PPV for lymphoma 89.6 %, sensitivity 97.3 %) [37], and was supplemented in this study using hospital data, therefore misclassification of cases is likely to be minimal. Inflection points were estimated using a maximum likelihood based technique and, although confidence intervals were wide, findings were supported by comparison of monthly RR in cases compared to baseline (24 months pre-diagnosis) and plots of prescribing rates over time compared to synchronous controls. Although we were unable to determine the clinical indication for steroid prescriptions, our analysis took into account the background rate of prescribing in cases and examined concurrent new allergic diagnoses in participants over time, enabling us to distinguish between prescriptions for chronic disease/existing conditions associated with HL development [6–11,38–41] and new increases closer to diagnosis that are likely driven by the underlying cancer. Future research could explore the timing and duration of symptoms of incipient HL pre-diagnosis. Our study included HL patients younger than 50 years. Because HL subtypes differ by age, findings are not necessarily generalisable to the diagnostic pathway of older HL patients. Finally, our results represent population-level findings for primary care utilisation and do not necessarily relate to individual-level findings.

#### 4.3. Implications

The observed increase in primary care prescribing activity from 7-months before HL diagnosis suggests an appreciable diagnostic time window exists where some HL patients are presenting to their GP several months before diagnosis with symptoms that are being treated. These symptoms are likely early, non-specific presentations of HL masquerading as other conditions, such as allergic disease, and potentially represent opportunities for earlier diagnosis in some HL patients [17]. This finding concurs with evidence indicating that HL patients have higher odds of being diagnosed with a 'new allergic condition' in the previous year than controls in this study and frequently experience multiple primary care consultations before specialist referral [42,43].

However, as HL is rare and steroid prescribing is relatively common and non-specific for cancer, identifying patients with as-yet-undiagnosed HL based on steroid use alone would be impractical, resulting in over-investigation of large numbers of patients predominantly without disease. Therefore, substantial improvements in the diagnostic process should only be possible if new and more accurate diagnostic technologies become available in the future to identify other early signals of disease [17], potentially by combining information from

symptoms, prescriptions, lab tests and consultation patterns.

Additionally, the findings suggest that estimation of likely aetiological associations between steroid prescribing and HL risk could reflect reverse causality (protopathic bias) unless a lag-period of 7-months pre-diagnosis is excluded from the analysis.

## 5. Conclusion

Primary care steroid prescribing increases 7-months before diagnosis of HL, likely reflecting the syndromic management of allergic symptoms of (as-yet-unrecognised) HL in some patients. A diagnostic time window of appreciable length exists in many patients with HL, documenting the potential for improvements in the diagnostic process of at least some patients. Suitably long lag-time periods should be used in aetiological studies exploring aetiological associations between steroid use and HL risk.

### CRediT authorship contribution statement

**Meena Rafiq:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **Georgios Lyratzopoulos:** Supervision, Conceptualization, Methodology, Writing – original draft. **Gary Abel:** Methodology, Formal analysis, Writing – review & editing. **Cristina Renzi:** Conceptualization, Methodology, Writing – review & editing.

### Conflict of interest

The authors declare no potential conflicts of interest.

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This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

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### Ethics approval and consent to participate

The protocol for this project was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol no.: 16.237). Ethical approval for observational studies conducted using anonymised CPRD data with approval from ISAC has been granted from a National Research Ethics Service Committee (NRES). The study was performed in accordance with the Declaration of Helsinki.

### CRediT authorship contribution statement

M.R., and G.L. conceived of the presented idea. M.R. developed the methods. M.R. performed the statistical analysis assisted by G.A. who supervised this section. M.R., G.L., C.R. and G.A. were involved in interpretation of the results. M.R. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. G.L. supervised the project.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.canep.2022.102284](https://doi.org/10.1016/j.canep.2022.102284).

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