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Temporal Trends in the Incidence of Hemophagocytic Lymphohistiocytosis: A Nationwide Cohort Study From England 2003–2018

Joe West[1,2,3], Peter Stilwell[2], Hanhua Liu[2], Lu Ban[4], Mary Bythell[2], Tim R. Card[1,3], Peter Lanyon[1,2,3], Vasanta Nanduri[5], Judith Rankin[2,6], Mark J. Bishton [2,3,7], Colin J. Crooks[2,3,7]

Correspondence: Joe West (joe.west@nottingham.ac.uk).

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is rare, results in high mortality, and is increasingly being diagnosed. We aimed to quantify the incidence of diagnosed HLH and examine temporal trends in relation to age and associated diseases. Using national linked electronic health data from hospital admissions and death certification cases of HLH that were diagnosed in England between January 1, 2003, and December 31, 2018. We calculated incidence rates of diagnosed HLH per million population by calendar year, age group, sex, and associated comorbidity (hematological malignancy, inflammatory rheumatological or bowel diseases [IBD]). We modeled trends in incidence and the interactions between calendar year, age, and associated comorbidity using Poisson regression. There were 1674 people with HLH diagnosed in England between 2003 and 2018. The incidence rate quadrupled (incidence rate ratio [IRR] 2018 compared to 2003: 3.88, 95% confidence interval [CI] 2.91 to 5.28), increasing 11% annually (adjusted IRR 1.11, 95% CI 1.09 to 1.12). There was a transition across age groups with greater increases in those aged 5–14 years of HLH associated with rheumatological disease/IBD compared with hematological malignancy, with similar increases in HLH associated with both comorbidities for those 15–54, and greater increases in HLH associated with hematological malignancies for those 55 years and older. The incidence of HLH in England has quadrupled between 2003 and 2018. Substantial variation in the incidence occurred with inflammatory rheumatological diseases/IBD-associated HLH increasing more among the younger age groups, whereas in older age groups, the largest increase was seen with hematological malignancy-associated HLH.

INTRODUCTION

Understanding the causes and burden of disease for the purposes of planning optimal health care requires contemporary population-level estimates of disease incidence.[1] Although attempts to do so have been made, improving our ability to quantify and describe the occurrence of rare diseases remains a worldwide challenge.[2] Precisely measuring the occurrence of a rare disease in a population is difficult as the population needs to be large enough to adequately quantify temporal trends in incidence and variation by important socicodemographic and clinical factors, while minimizing the bias inherent in case reports or small cohorts compiled in specialist centers.[3] Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical syndrome characterized by fever, hyperinflammation, organ dysfunction, cytopenias, and hemophagocytosis[4] and, as it can be an inherited or acquired disorder affecting all ages and has several risk factors, is an appropriate exemplar. HLH is associated with high mortality rates in all age groups,[4] particularly those with underlying malignancy.[5] However, the incidence of HLH on a population level has rarely been quantified[6–8] with only one previous report containing information on both children and adults from the same population.[9] That report indicated that the incidence of HLH appears to be increasing over time, but it was unable to explore the reasons why as despite being the largest incidence study in the literature it was still too small to examine how trends over time varied by age, sex, and the underlying diseases associated with HLH. A combination of the increasing incidence of non-Hodgkin lymphoma,[10] increasing use of biologic therapies or immune-suppressants in autoimmune inflammatory diseases,[11,12] increasing age of first exposure to the Epstein-Barr virus (EBV), or increasing clinical awareness could be contributing to the observed rise in HLH.[13]

[1]Population and Lifespan Sciences, University of Nottingham, UK
[2]National Disease Registration Service, NHS Digital, Leeds, UK
[3]NIHR Biomedical Research Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
[4]PPD, Beijing, China
[5]Watford General Hospital NHS Trust, Watford, UK
[6]Population Health Sciences Institute, Newcastle University, Newcastle, UK
[7]Translational Medical Sciences, University of Nottingham
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To examine the temporal trends in incidence of HLH and explore the relationships with demographic and clinical characteristics, we have carried out a nationwide study in England in partnership with the National Disease Registration Service (NDRS).

METHODS

Data sources

We used linked electronic health records from English Hospital Episode Statistics (HES),[14] the National Cancer Registration Dataset (NCRD),[15] and Office for National Statistics (ONS) death certification data. In brief, HES data are collected routinely for all National Health Service (NHS)-related hospital admissions in England and contain sociodemographic and clinical information, the latter coded with International Classification of Diseases, 10th revision (ICD-10) and Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS-4), NCRD contains all cancers registered in England and their associated histological and staging information and ONS death certification data contains the contents of the death certificate coded for underlying cause of death (with ICD-10), including any associated free text.

Study population and case identification

Patients diagnosed with HLH were identified using our previously validated approach.[16] They included HLH patients of all ages who were admitted to hospital or died between January 1, 2003, and December 31, 2018, in England. In brief, we included people who had an admission coded with ICD-10 codes for HLH–D76.1 or D76.2 (hemophagocytic syndrome) or a death coded with D76.1, D76.2, or D76.3 (other histiocytosis syndromes) as long as in the latter situation, and there was confirmatory free text on the death certificate indicating HLH. The date of diagnosis was taken as the first day of the hospital admission in which HLH was coded or, if identified only by death registration, the date of death.

HLH-associated characteristics and associated comorbidities

For all patients, we extracted information on age and sex at diagnosis and determined HLH-associated comorbidities. The presence or absence of comorbidities was identified from all available HES and NCRD records before the diagnosis of HLH and up to 3 months after diagnosis. We defined hematological cancer, nonhematological cancer (excluding nonmelanoma skin cancer), inflammatory rheumatological disease, inflammatory bowel disease (IBD), herpes viruses (cytomegalovirus [CMV], EBV, and varicella zoster virus [VZV]), and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) using ICD-10 codes (Suppl. Tables S1, S2, and S3). For inflammatory rheumatological diseases, we assigned subcategories of diagnosis (Suppl. data Table S1), that is, systemic juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), etc. If more than one subcategory of inflammatory rheumatological disease was identified, the patient was assigned to the diagnosis group that was recorded closest in time to the HLH diagnosis. For hematological malignancy, if 2 malignancies were recorded patients were assigned to both subcategories. For the purposes of later analyses where there was overlap of noninfectious-associated comorbidities, we classified patients with the following mutually exclusive hierarchy: hematological malignancy, rheumatological disease/IBD, nonhematological malignancy, and none of these recorded. For patients where more than one malignancy was recorded, a panel of authors (JW, CJC, MB, PS) considered the different diagnoses and temporal relationships to the diagnosis of HLH for each case. For the purposes of hierarchical coding, the malignancy assigned was the diagnosis that occurred within the period 3 years before HLH and up to 1 month after the HLH diagnosis. If the malignancies were prior to 3 years before the HLH diagnosis, the hematological malignancy was assigned. As there was not access to serological tests for the cohort, the type (acute, chronic, reactivation) of viral illness could not be ascertained and so we have not included these in the "associated diseases hierarchy."

Statistical analysis

Numbers and frequencies of the patient's characteristics were calculated, and an assessment of those cases with more than one HLH-associated comorbidity was carried out via cross tabulation and plotting a Venn diagram. The incidence rate (equivalent to the frequency of clinical diagnosis) of HLH was calculated by summing the number of cases (including those diagnosed via death certificate only) within age group, sex, and calendar year strata and dividing by the summed person years within each stratification variable based on the ONS mid-year population estimates. Incidence rates of HLH cases with associated comorbidities were calculated by including only the relevant cases (only for the chronic, noninfectious morbidities) over the whole population denominator. Incidence rates were then presented by calendar year, age group, sex, and associated comorbidity with 95% confidence intervals (CIs) around the estimates derived via a Poisson distribution. A Poisson regression model was fitted to estimate the age group and sex adjusted incidence rate ratios (IRRs) associated with calendar year (fitted as a categorical variable). To estimate the annual % change in incidence, a further model was fitted using calendar year as a linear term adjusted for age group and sex. This model was compared to the model with calendar year as a categorical variable with a likelihood ratio test to assess evidence of departure from a linear trend. To assess temporal trends in incidence within age group, by the various HLH-associated comorbidity groups and by age group and associated comorbidity, we plotted incidence rates over time within age groups, by each HLH-associated comorbidity group and both together. For ease of display in the latter case, we plotted the moving average of the incidence rate using a locally estimated scatterplot smoothing curve (LOESS). To quantify these time trends, we fitted a model containing a 2-way interaction between age group and calendar year as a linear term, and separately associated comorbidity and calendar year. We modeled changes in associated comorbidity within age groups by fitting a 2-way interaction within age stratified models. Finally, we computed stratum-specific adjusted IRRs and 95% CIs for each age group, associated comorbidity, and jointly to estimate the annual increase in incidence over the study period, with 2003 as the reference category.

No consent was obtained from individuals for this study as the data were collected and analyzed under the National Disease Registries Directions 2021, made in accordance with sections 254(1) and 254(6) of the 2012 Health and Social Care Act. Ethical approval for this study was therefore not required per the definition of research according to the UK Policy Framework for Health and Social Care Research. The data are available to those that have the legal basis to access it, either through the Data Access Request Service (https://digital.nhs.uk/services/data-access-request-service-dars) or partnership with NDRS. The protocol was approved by the joint NDRS project board reference PPF1920_027. Study findings are reported in accordance with the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) recommendations.[17] We used R (version 4.1.2)[18] for the data management and statistical analyses.

RESULTS

In the 16-year study period 2003 to 2018, we identified 1674 patients with an incident diagnosis of HLH (Suppl. Figure 1—study flow diagram) via our validated approach.[16] The majority,

1091 (65%), were identified through an admission to hospital coded with either ICD-10 D76.1 or D76.2 in HES, while a further 183 (11%) were identified at death using the same codes, or a D76.3 code with confirmatory free text, used anywhere on their death certificates. The remainder were identified in both HES and ONS mortality data. Of the whole cohort, 551 (33%) had a record in the NCRD indicating a registered cancer (excluding nonmelanoma skin cancer) prior to or up to 3 months after their HLH diagnosis. Of the whole cohort, 534 (32%) had a recorded associated nonmalignant comorbidity (inflammatory rheumatological disease/IBD/viral), and the majority of chronic autoimmune comorbidities were recorded in hospital admissions prior to the admission in which the HLH diagnosis occurred (92%). The characteristics of the cases are described in Table 1 and overlap of associated comorbidities in Figure 1. Almost 70% were aged ≥15 years, over half (56%) were male and just over half (51%) of people had at least one of the associated comorbidities recorded in their records. Of these diseases, the commonest single disease entities were lymphoma, leukemia, systemic juvenile idiopathic arthritis, IBD, vasculitis, and SLE. There was evidence of clinically diagnosed EBV, CMV, VZV infection or HIV/AIDS in 7.6%, 5.7%, 1.2%, and 0.6%, respectively. One hundred seven (6.4%) patients had a record of an allogeneic peripheral blood stem cell transplant and 27 (1.6%) had a record of an autologous peripheral blood stem cell transplant. The majority of these stem cell transplants in children occurred after the diagnosis of HLH (82%), whereas for adults, 50% occurred after the HLH diagnosis. In terms of associated comorbidities, less than 5% of cases had more than one recorded. The largest overlap in associated comorbidities was between hematological malignancies and rheumatological disease/IBD (Figure 1).

Reported crude incidence rates of HLH increased during the study period from around 1 per million person years in 2003 to around 4 per million in 2018 (Table 1) equating to an age and sex

Table 1

Characteristics of the HLH Cohort With Incidence Rates Per Million Population

Characteristic		n	%	Rate[a]	CI (95%)
Sex	Female	729	43.55	1.7	(1.57 to 1.82)
	Male	945	56.45	2.27	(2.13 to 2.42)
Calendar year	2003	53	3.17	1.06	(0.8 to 1.39)
	2004	42	2.51	0.84	(0.6 to 1.13)
	2005	44	2.63	0.87	(0.63 to 1.17)
	2006	55	3.29	1.08	(0.81 to 1.4)
	2007	63	3.76	1.23	(0.94 to 1.57)
	2008	63	3.76	1.22	(0.93 to 1.56)
	2009	77	4.6	1.48	(1.16 to 1.84)
	2010	86	5.14	1.63	(1.31 to 2.02)
	2011	95	5.68	1.79	(1.45 to 2.19)
	2012	120	7.17	2.24	(1.86 to 2.68)
	2013	122	7.29	2.26	(1.88 to 2.7)
	2014	141	8.42	2.6	(2.19 to 3.06)
	2015	142	8.48	2.59	(2.18 to 3.05)
	2016	141	8.42	2.55	(2.15 to 3.01)
	2017	194	11.59	3.49	(3.01 to 4.01)
	2018	236	14.1	4.22	(3.70 to 4.79)
Age, years	0–4	324	19.35	6.3	(5.63 to 7.02)
	5–14	196	11.71	1.96	(1.69 to 2.25)
	15–54	577	34.47	1.27	(1.17 to 1.38)
	55+	577	34.47	2.41	(2.22 to 2.62)
Chronic conditions	Inflammatory bowel disease	70	4.18	0.08	(0.06 to 0.1)
	Inflammatory rheumatological disease	322	19.24	0.38	(0.34 to 0.42)
	Systemic juvenile idiopathic arthritis	82	4.9	0.1	(0.08 to 0.12)
	Systemic lupus erythematosus	48	2.87	0.06	(0.04 to 0.08)
	Adult-onset Still's disease	31	1.85	0.04	(0.02 to 0.05)
	Rheumatoid arthritis	43	2.57	0.05	(0.04 to 0.07)
	Vasculitis	66	3.94	0.08	(0.06 to 0.10)
	Other inflammatory arthritis	10	0.6	0.01	(0.01 to 0.02)
	Other connective tissue diseases	42	2.51	0.05	(0.04 to 0.07)
Malignancies	Any lymphoma condition[b]	279	16.67	0.33	(0.29 to 0.37)
	T-cell lymphoma	84	5.02	0.1	(0.08 to 0.12)
	B-cell lymphoma	121	7.23	0.14	(0.12 to 0.17)
	Hodgkin lymphoma	45	2.69	0.05	(0.04 to 0.07)
	Lymphoma NOS	32	1.91	0.04	(0.03 to 0.05)
	Leukemia	131	7.83	0.15	(0.13 to 0.18)
	Other hematological histiocytic/myelodysplastic/malignancy/unspecified	74	4.42	0.09	(0.07 to 0.11)
	Nonhematological malignancy excluding nonmelonoma skin cancer	112	6.69	0.13	(0.11 to 0.16)
Hierarchical chronic conditions	Hematological malignancy	467	27.9	0.55	(0.50 to 0.60)
	Rheumatological disease/IBD	323	19.3	0.38	(0.34 to 0.43)
	Nonhematological malignancy excluding nonmelonoma skin cancer	75	4.48	0.09	(0.07 to 0.11)
	None of the above	809	48.33	0.96	(0.89 to 1.02)

[a]Rate per million population.

[b]Multiple lymphoma conditions allowed.

CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease; NOS = not otherwise specified.

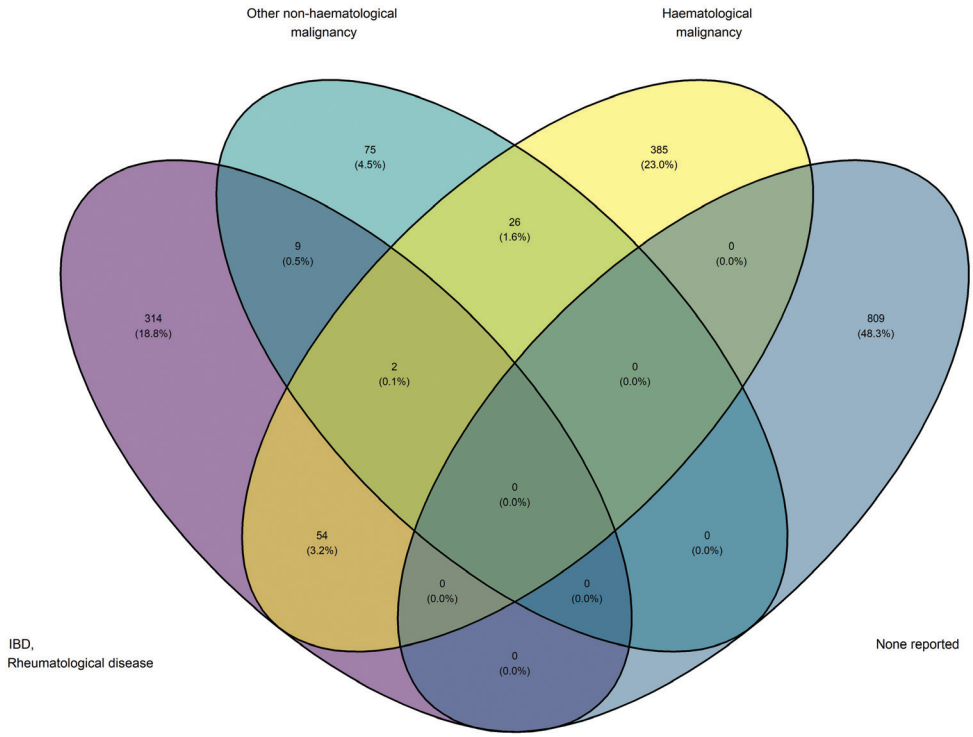

Figure 1. Venn diagram to show the overlap between of comorbidities within the whole HLH cohort. HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease.

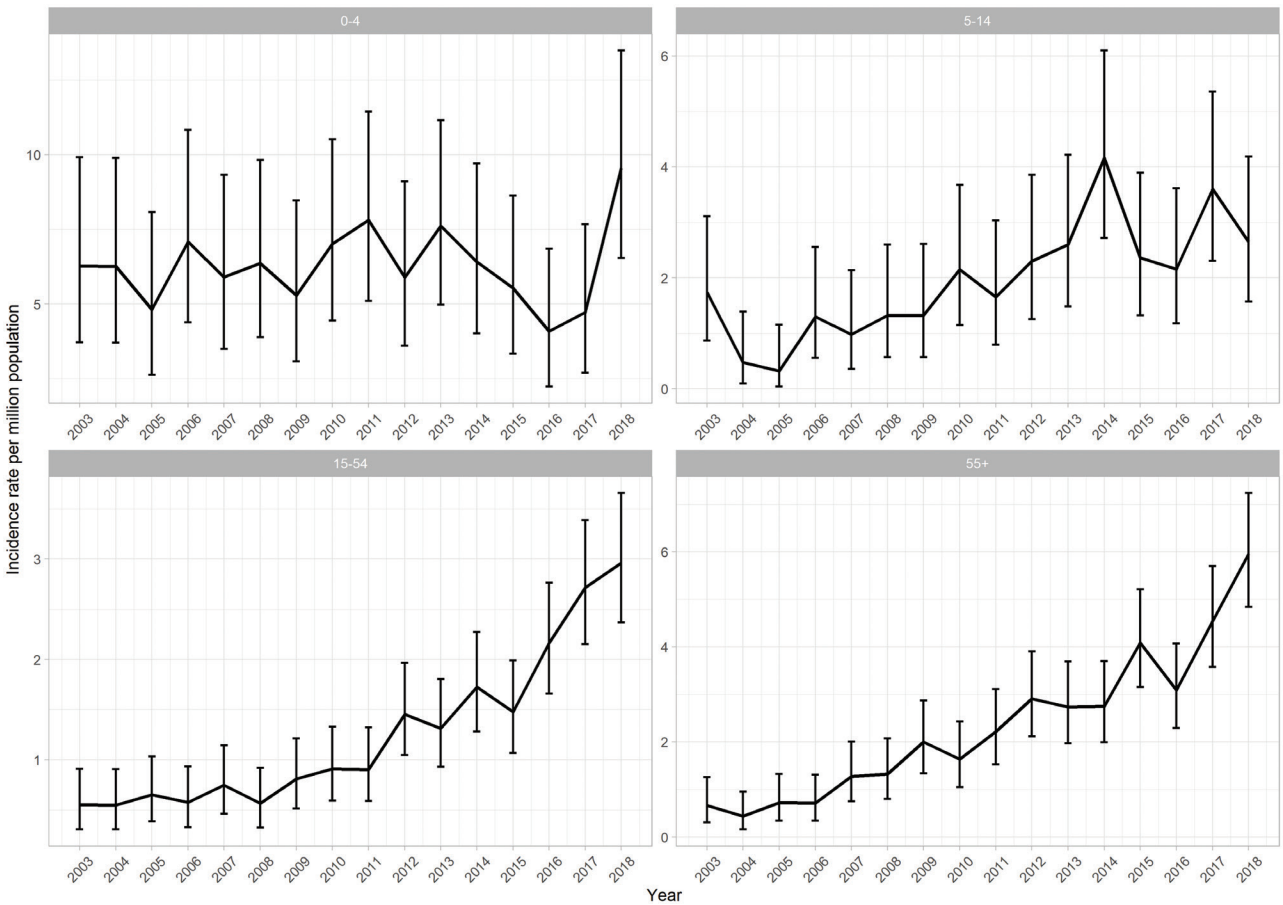

Figure 2. Incidence (95% CI) of HLH per million population over calendar time (2003–2018) and by age group. CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis.

Table 2

Incidence Rate Ratios Including the Interaction Between Age Group and Calendar Year

Age Group, y	IRR[a]	CI (95%)
0–4	1	(0.97 to 1.04)
5–14	1.09	(1.05 to 1.14)
15–54	1.14	(1.11 to 1.16)
55+	1.16	(1.13 to 1.19)

[a]This represents the relative annual change in incidence of HLH (1.00 represents no change) for each age group.

CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis; IRR = incidence rate ratio.

adjusted 4-fold (2018 compare to 2003: IRR 3.88, 95% CI 2.91 to 5.28) increase in the reported incidence of HLH over the whole study period (Suppl. Table S4). Across the whole study period, the estimated year-on-year relative increase (calendar year fitted as a continuous variable), assuming a linear trend, of HLH incidence was 11% (IRR 1.11, 95% CI 1.09 to 1.12). When compared to the model with calendar year as a categorical variable, there was no evidence of departure from a linear trend ($P = 0.32$). This trend over time varied substantially by age (Figure 2, P value for interaction <0.01) such that there was no change in incidence over the study period in the under 5-year olds (IRR per year 1.00, 95% CI 0.97 to 1.04), whereas there was an increasing rate in incidence over time in the 5–14, 15–54, and 55+ age groups (Table 2).

There was variation in the incidence rate of HLH over calendar time when stratified by the recorded presence of an associated comorbidity (Figure 3; Table 3; P value for interaction <0.01) such that it was apparent that diagnoses of HLH with either hematological malignancy (IRR per year 1.17, 95% CI 1.14 to 1.21), or rheumatological disease/IBD (IRR per year 1.20, 95% CI 1.15 to 1.24) increased almost 20% per year. By contrast, those with no recorded comorbidity (IRR per year 1.05, 95% CI 1.03 to 1.07) or cases associated with nonhematological malignancy (IRR per year 1.12, 95% CI 1.05 to 1.20) rose less markedly.

Finally, we examined the effect on the temporal trends of the interaction between age group and associated comorbidities (Figure 4; Table 4; Suppl. Figure S2). This showed that there was a transition across the age groups with increases in incidence in those aged 5–14 years of HLH associated with rheumatological disease/IBD (IRR per year 1.12, 95% CI 1.04 to 1.22) showing a 12% annual increase. When compared to HLH associated with hematological malignancy the 5–14 year olds had only a 4% annual increase (IRR per year 1.04, 95% CI 0.94 to 1.14). In the 15–54 year age group, there were similar annual increases in HLH associated with both hematological malignancy and rheumatological disease/IBD (17% and 20%, respectively), and for those 55 years and older, there were increases in associated hematological malignancies (~18% annual increase).

DISCUSSION

The incidence of diagnosed HLH in England increased 11% year on year between 2003 and 2018 resulting in a 4-fold increase over the 16-year study period. Substantial variation in the incidence occurred by age groups, with no increase over time in those under 5-year olds contrasting with a 9% annual

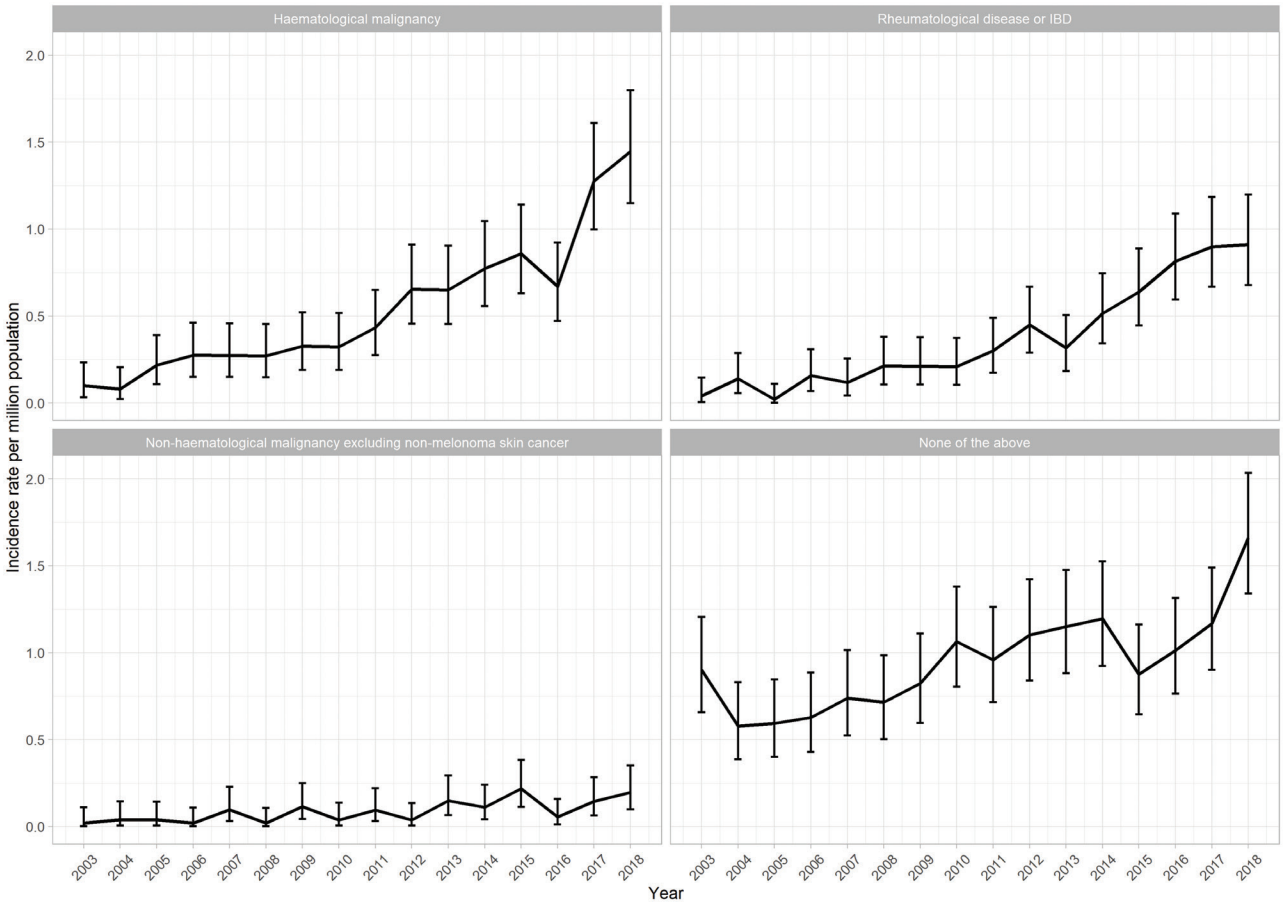

Figure 3. Incidence (95% CI) of HLH per million population over calendar time by associated comorbidity. CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis.

Table 3

Incidence Rate Ratios Including the Interaction Between Comorbidity Group and Calendar Year

Comorbidity Group	IRR[a]	CI (95%)
Rheumatological disease/IBD	1.2	(1.15 to 1.24)
Non-hematological malignancy excluding non-melonoma skin cancer	1.13	(1.05 to 1.2)
Hematological malignancy	1.17	(1.14 to 1.21)
None of the above	1.05	(1.03 to 1.07)

[a]This represents the relative annual change in incidence of HLH (1.00 represents no change) for each comorbidity group.
CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease; IRR = incidence rate ratio.

increase in 5–14 year olds, a 14% annual increase in 15–54 year olds and a 16% annual increase in those aged 55 and over. Furthermore, we observed increases in diagnoses of HLH associated with inflammatory rheumatological disease/IBD and hematological malignancy-associated HLH over time, which also varied by age. Among the young and middle age groups, there were increases in both rheumatological disease/IBD and hematological malignancy-associated HLH, whereas in older age groups, the increase was seen mainly with hematological malignancy-associated HLH. These findings imply that the temporal increase in HLH we have observed is being driven more in younger people by changes in autoimmune disease and its treatment, for example, biologics and immunosuppressants, and more in older people by the known increase in the incidence of hematological cancer, particularly non-Hodgkin lymphoma, during the study period.[10] Part of the increase in the rate of diagnosed HLH is likely to be due to the groups of clinicians involved in managing the associated comorbidities increasingly recognizing HLH during the study period.

Our case definition of HLH is based on a published validation exercise we carried out in five English NHS Trusts (hospitals) that showed a positive predictive value for a diagnosis of HLH of 89.0% (95% CI 80.2%–94.9%).[19] In a systematic review of validation studies of other diseases, HES recording has been shown to be accurate for the purposes of research in this manner.[20] Two other studies in France[21] and Chicago, The United States[22] have used a similar algorithm to identify cases of HLH and NHS Digital, who oversee coding within the NHS in England, confirmed that no changes have occurred in the procedural use of D76.1, D76.2, and D76.3 during the study period. We are therefore reasonably confident that the cases we have included represent true diagnoses of HLH, and that these diagnoses are underpinned by the clinical use of diagnostic scoring systems such as the "H-Score"[23] or the "HLH-2004 diagnostic criteria."[24,25] Our study design does mean that there will have been under-ascertainment of HLH as it is recognized to be a difficult disease to diagnose,[4] and therefore, our estimates of incidence are likely to be, in general, underestimates as cases of HLH that occurred but were not clinically diagnosed as such in the hospital setting would not have been included in our study.

The results in the current study confirm those found in our recent report that utilized a smaller sample of the English population (via the Clinical Practice Research Datalink[26] [CPRD]) over a similar time period[9]—a rising incidence rate and variation by age. The current report encompasses the whole of

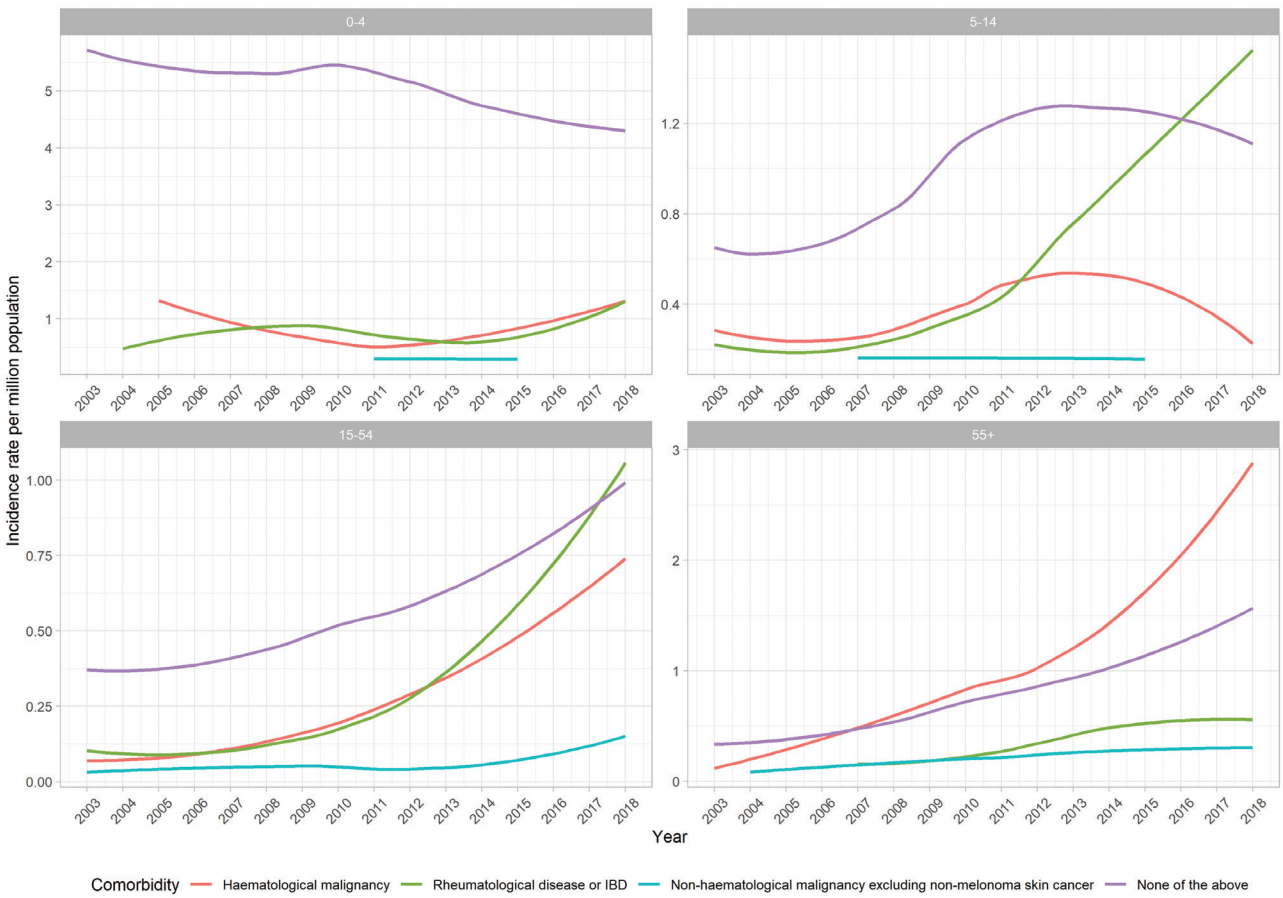

Figure 4. Incidence (LOESS) of HLH per million population over calendar time by age group and comorbidity. HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease.

Table 4

Incidence Rate Ratios Including the Interaction Between Age Group, Calendar Year, and Associated Comorbidity

Associated Comorbidity	Age Group, y	IRR[a]	CI (95%)	*P* Value for Interaction
Hematological malignancy	0–4	1	(0.90 to 1.11)	
	5–14	1.04	(0.94 to 1.14)	
	15–54	1.17	(1.11 to 1.24)	<0.01
	55+	1.18	(1.14 to 1.23)	
Rheumatological disease/IBD	0–4	1.01	(0.90 to 1.14)	
	5–14	1.12	(1.04 to 1.22)	
	15–54	1.2	(1.14 to 1.27)	0.01
	55+	1.13	(1.03 to 1.24)	
Non-hematological malignancy excluding non-melonoma skin cancer	0–4	0.84	(0.34 to 2.06)	
	5–14	1	(0.68 to 1.47)	
	15–54	1.05	(0.94 to 1.17)	0.9
	55+	1.05	(0.96 to 1.15)	
None of the above recorded	0–4	0.98	(0.95 to 1.02)	
	5–14	1.06	(1.01 to 1.12)	
	15–54	1.08	(1.04 to 1.11)	<0.01
	55+	1.11	(1.06 to 1.15)	

[a]This represents the relative annual change in incidence of HLH (1.00 represents no change) within each age group, for each comorbidity.
CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease; IRR = incidence rate ratio.

England and therefore is not subject to selection bias with a sample size eight times bigger than our original study. Due to this size, we were able to investigate temporal trends in incidence by age group and associated comorbidities, for all age groups, in a manner that no prior study of HLH has been able to do. Indeed, our use of a national population-based cohort means that the number of patients we report with HLH and hematological cancer—467—is far larger than any other single study in the literature to date.[4] The characteristics of our cohort are, as might be expected, similar to our CPRD study[9] but also to the most relevant, recent, comparable studies of HLH from France,[21] Germany,[27] China,[28,29] Sweden,[6] and the United States[30,31] in terms of age and sex distributions and also the proportions with hematological malignancy and rheumatological diseases.

Reasons why we have observed such a marked increase in the incidence rate of HLH in England over time and the variation by both age and associated comorbidities require some explanation. The increasing rates of diagnosis over time would, in part, be due to increasing frequency of recognition and diagnosis of HLH—essentially an increase in ascertainment. Notably, the rises in incidence over time were not observed in the under 5-year age group, which will be, in the majority, "primary HLH" due to inherited risk factors. If we accept that not all of the increase in the frequency of diagnosis in those aged 5 or older is due to ascertainment, then we can speculate on the alternative causes of the temporal trends. During the study period, there has been a steady increase in the incidence of hematological malignancy, particularly non-Hodgkin lymphoma,[10] and in the prevalence of some inflammatory rheumatic diseases[32–34] and IBD.[35] In addition, for all these diseases, there has been an increase in the use of immunomodulators or immunosuppressant therapies, for example, in some malignancies—checkpoint inhibitors[36–38] and CAR-T[39]; in inflammatory rheumatic diseases and IBD, biologics such as antitumor necrosis factor antibodies and thiopurines are recommended.[11,12] Another notable finding is the relatively high numbers of patients with HLH who had co-occurring vasculitis, which may reflect a risk associated with thiopurine exposure which is often used for maintenance therapy after initial remission induction.[40] Last, the age at which EBV is first acquired is rising.[41,42] If this infection is first contracted or reactivates during treatment for an HLH-associated comorbidity, this may precipitate HLH.[13] Taken together, it seems likely that some of the explanation for the increase in HLH among children over the age of 5 years and young, middle and older aged adults are due to the trends in the occurrence of associated comorbidities and changes in their treatment.

In conclusion, we have provided the first nationwide, population-based estimates of the incidence of HLH across all ages and demonstrated important temporal trends by both age and HLH-associated underlying diseases. These trends imply that some of the rise in frequency of the diagnosis of HLH may be due to either underlying diseases or their treatments and as such highlight areas in which early diagnosis or preventative measures could be developed.

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AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualization, acquisition of funding, drafting of the manuscript and approval of final draft for submission. PS, CJC, and JW had full access to the data in the study and carried out the design of and execution of the analysis. JW is the guarantor. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DISCLOSURES

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