Trends in mortality due to haemophagocytic lymphohistiocytosis across 29 European countries from 2011 to 2021: a retrospective, international, population-based study

Leher Gumber, Reza Omidvar, Francesca Gonnelli, Adam Taylor, Thomas Trimble, Mark Bishton, Matthew Collin, Richard Hubbard, Peter C Lanyon, Rachel S Tattersall, Jessica J Manson, Fiona A Pearce

Summary

Background Previous research has suggested that the incidence of haemophagocytic lymphohistiocytosis is increasing in Europe. We aimed to examine rates of mortality due to haemophagocytic lymphohistiocytosis across 29 European countries from 2011 to 2021.

Methods In this retrospective, population-based, descriptive study, we applied to EUROSTAT for publicly available death certificate data for mortality due to haemophagocytic lymphohistiocytosis in countries in Europe. We defined haemophagocytic lymphohistiocytosis mortality as any death recorded with ICD-10 codes of D76.1 or D76.2 as the underlying cause. We calculated age-specific and sex-specific death registration rates from Jan 1, 2011, to Dec 31, 2021, for each country and used Poisson regression to compare Europe-wide rates over time. We used direct standardisation to compare rates between countries. We also searched Scopus Analytics to establish the number of haemophagocytic lymphohistiocytosis publications for each country from Jan 1, 2000, to June 11, 2024, and analysed the correlation between mortality rates and research activity measured by the number of relevant publications.

Findings Of 34 European countries that provided data, five were excluded from the analysis because the data had been censored due to small numbers of deaths. Analysis of 3345 deaths from the remaining 29 countries showed that crude haemophagocytic lymphohistiocytosis mortality increased from 3·9 per 10 000 000 person-years in 2011, to 6·6 per 10 000 000 person-years population in 2021. The age–sex-standardised mortality rate across Europe was 4·7 (95% CI 3·0–6·4) per 10 000 000 person-years, with the highest recorded rate in France (10·1, 0·0–27·3) and the lowest in Romania (0·5, 0·0–13·6). Crude mortality rates were highest in infants aged 0–4 years (17·5, 95% CI 16·1–19·0) and adults aged 80–85 years (15·6, 13·7–17·6). Mortality was higher in male than in female individuals (adjusted rate ratio 1·5, 95% CI 1·4–1·6). Increased haemophagocytic lymphohistiocytosis-related research activity often occurred in countries with higher rates of mortality recorded due to haemophagocytic lymphohistiocytosis than countries with lower rates (Pearson's correlation coefficient 0·4968; p=0·012).

Interpretation Recorded rates of mortality due to haemophagocytic lymphohistiocytosis have nearly doubled over the past decade in Europe. Deaths were most common at the extremes of age and were more common in male than in female individuals. Age-standardised rates between countries differed substantially, suggesting potential under-recognition of the diagnosis of haemophagocytic lymphohistiocytosis. There is a need to increase awareness among clinicians together with implementation of evidence-based guidelines for diagnosis and urgent treatment.

Funding Medical Research Council Rare Disease Platform Node for Histiocytic Disorders.

Introduction

Haemophagocytic lymphohistiocytosis or macrophage activation syndrome is a rare disorder characterised by dysregulated immune activity resulting in systemic inflammation and multiorgan failure. It arises from inappropriate activation of natural killer cells, cytotoxic T cells, and macrophages. Primary haemophagocytic lymphohistiocytosis presents in early childhood and rarely later in life and is caused by genetic mutations affecting the typical functions of natural killer and cytotoxic T cells. Secondary haemophagocytic lymphohistiocytosis occurs in adults when their immune tolerance is breached with trigger factors, including infection, malignancy (especially haematological), drugs or medications, and autoimmune or autoinflammatory disorders.[1–4]

Haemophagocytic lymphohistiocytosis can have diverse clinical manifestations. Common symptoms and signs include fever, hepatosplenomegaly, raised ferritin of more than 2000 ng/mL, cytopenias, and presence of activated

Lancet Rheumatol 2025

Published Online November 28, 2025 https://doi.org/10.1016/S2665-9913(25)00292-9

See Online/Comment https://doi.org/10.1016/S2665-9913(25)00339-X

Translational and Clinical Research Institute, Newcastle University, Newcastle, UK (L Gumber MSc); **Department of Rheumatology, Gateshead Health National Health Service (NHS) Foundation Trust, Tyne and Wear, UK** (L Gumber); **Digital Research Service, University of Nottingham, Nottingham, UK** (R Omidvar MSc, A Taylor MEng, T Trimble BSc); **Biomedical Sciences and Public Health, Polytechnic University of Marche, Ancona, Italy** (F Gonnelli PhD); **Lifespan and Population Health, University of Nottingham, Nottingham, UK** (F Gonnelli, M Bishton PhD, Prof R Hubbard DM, P C Lanyon DM, F A Pearce PhD); **Department of Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK** (M Bishton); **Department of Haematology, Newcastle University, Newcastle, UK** (Prof M Collin PhD); **Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, UK** (P C Lanyon, F A Pearce); **Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK** (R S Tattersall PhD); **Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK** (J J Manson PhD)

Correspondence to: Dr Fiona A Pearce, Lifespan and Population Health, University of Nottingham, Nottingham, UK **fiona.pearce@nottingham.ac.uk**

Research in context

Evidence before this study

We did a literature search for population-level observational studies on the epidemiology of haemophagocytic lymphohistiocytosis. We searched PubMed for articles published from database inception to July 22, 2025, with no language restrictions, using the MESH term "Lymphohistiocytosis, Hemophagocytic " OR the terms "Hemophagocytic Lymphohistiocytosis" OR "Haemophagocytic Lymphohistiocytosis" OR "HLH" in the title or abstract AND the terms "epidemiology" OR "incidence" OR "prevalence" OR "mortality" OR "fatality" OR "trend*" OR "population-based" OR "registry". There were few population-based studies and these were restricted to a single nation (eg, England, Germany, Sweden, and the USA). There were no studies comparing the occurrence or rates of mortality due to haemophagocytic lymphohistiocytosis across Europe.

Added value of this study

This analysis of haemophagocytic lymphohistiocytosis as the underlying cause of death in 29 countries across Europe provides important insights into variation over time by age, sex, and country. We found that the recorded crude mortality rates of haemophagocytic lymphohistiocytosis have doubled over the past decade from 3·9 per 10 000 000 to 6·6 per 10 000 000. These results highlight age and sex differences with a trend towards higher recorded mortality at the extremes of ages and in male individuals compared with female individuals. We show substantial variation in deaths and research activity between countries.

Implications of all the available evidence

There are country-specific disparities in recorded mortality rates and this study could not explain whether these were due to differences in incidence of haemophagocytic lymphohistiocytosis and its underlying risk factors, differences in recognition of the diagnosis, or differences in case fatality. However, other evidence suggests that recorded incidence (influenced by recognition and true incidence) is increasing and case fatality rates are stable. Circumstantial evidence suggests underdiagnosis to some extent in all countries and this theory was supported by the association between research publications in haemophagocytic lymphohistiocytosis and increased recorded mortality due to haemophagocytic lymphohistiocytosis in this study. Increasing awareness among health-care professionals and development and implementation of guidelines at local and national levels is essential to respond to the high mortality associated with this disease.

macrophages in affected organs.[1] Patients can present with signs related to pulmonary, renal, or cardiac involvement.[1] For this reason, it is often mistaken for severe sepsis and there is evidence to suggest that haemophagocytic lymphohistiocytosis remains under-recognised.[5] 1-year survival rates vary substantially and can be as low as 30% in adults older than 75 years.[6] Therefore, early identification and aggressive treatment of hyperinflammation and triggers are needed in most cases.[6]

The annual incidence of haemophagocytic lymphohistiocytosis in England is approximately 2 per million people in the adult population, with mean age at presentation of 50 years,[6] although accurate estimates are difficult to obtain in such a rare disease. The overall 1-year survival rates for adults are approximately 50%, with lower rates observed in older adults than in infants and younger adults.[7] Similar rates have been reported in other studies, including the USA,[8] Germany,[9] and Sweden.[10] However, these studies focused on single nations and specific subpopulations, so there remains a paucity of epidemiological data on global incidence.

Understanding the epidemiology of haemophagocytic lymphohistiocytosis is key to improving outcomes through increased recognition and service provision. Previous estimates of mortality rates are scarce and usually based on a small sample size in a single nation. We therefore conducted a descriptive study using publicly available data from death registrations to examine the trends in mortality due to haemophagocytic lymphohistiocytosis across Europe between 2011 and 2021, and presented these data next to the research output about haemophagocytic lymphohistiocytosis from each country.

For **EUROSTAT** see https://ec.europa.eu/eurostat/web/main/home

Methods

Study design and data sources

This retrospective, international, population-based, descriptive study obtained data from 34 countries across Europe (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Türkiye, and the UK) to analyse mortality rates due to haemophagocytic lymphohistiocytosis.

The number of deaths recorded with haemophagocytic lymphohistiocytosis as the underlying cause was obtained from EUROSTAT, the statistical office of the EU, for the period Jan 1, 2011, to Dec 31, 2021. EUROSTAT compiles data across the EU in partnership with EU member states and states from the wider European Economic Area. We wrote the manuscript in accordance with the Reporting of Studies Conducted using Observational Routinely Collected Health Data statement.[11,12] EUROSTAT data include cause of mortality derived from death certificates and are publicly available by application. We received data stratified by 5-year age bands, sex, and country. EUROSTAT also provides

contemporary data on the total population of the country to act as the denominator. Because these data are publicly available, the Faculty of the Medicine and Health Sciences Research Ethics Committee of the University of Nottingham (Nottingham, UK) established that ethical approval was not required. Patient and public involvement undertaken through the Rare Disease Node for Histiocytic Disorders included engagement with haemophagocytic lymphohistiocytosis survivors and family members, who expressed a strong desire to contribute to research that improves understanding of the disease and helps prevent others from experiencing the severe illness and long-term effects that they have faced.

Procedures

We defined haemophagocytic lymphohistiocytosis mortality as any death recorded with ICD-10 codes of D76.1 (haemophagocytic lymphohistiocytosis) or D76.2 (haemophagocytic syndrome, infection-associated) as the underlying cause of death. All European countries follow WHO guidelines on assigning the underlying cause of death on the basis of the death certificate.[13] Identifying haemophagocytic lymphohistiocytosis from these codes on death certificates has been validated in a previous UK study with accuracy of 98·6% from 2014 onwards.[11]

We also examined how rates of mortality due to haemophagocytic lymphohistiocytosis correlate with published research in each country, for which we used the search terms "haemophagocytic AND lymphohistiocytosis" in Scopus Analytics (language restrictions were not available). The search was conducted on June 11, 2025. In the analysis, we included all publications conducted in each European country, excluding case reports, published between Jan 1, 2000, and the most recently indexed.

Statistical analysis

We pooled data from all years (2011–21) for each country included in the analysis, and calculated crude rates of mortality due to haemophagocytic lymphohistiocytosis using each country's annual population during the study period. Direct standardisation was then applied to the European Standard Population 2013 to calculate standardised mortality rates for each country.[14] Poisson confidence intervals were used for both crude and standardised rates. We pooled data from all countries, displayed the crude mortality rate for each year, and used Poisson regression (using log of population as offset) to calculate changes in mortality rates over time. We then presented the annual crude mortality rate for each country reporting more than 100 deaths due to haemophagocytic lymphohistiocytosis over the 10-year time period. Additionally, we pooled the data from all countries and all years and calculated the crude mortality rate stratified by 5-year age band (0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, and ≥90 years) and sex (male and female). We used Poisson regression to calculate mortality rate ratios by sex and age band. Regarding research activity, we present the number of publications per country and the rate of publications per country normalised to the population size using the 2013 European Standard Population as the reference population. We plotted the mortality rate against the publication rate for each country and calculated Pearson's correlation coefficient and its p-value to assess strength of correlation.

Some data were missing from some years for some countries; in those cases, the total number of deaths from that particular country was lower than if they had contributed data from all years, but the rates are unaffected because the years with no data were completely excluded. All statistical analyses were conducted using Python version 3.12 or Stata version 18.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Data were available for the period of interest for most European countries; however, data from Liechtenstein, Bulgaria, Malta, Cyprus, and Serbia were censored by EUROSTAT due to the small number of deaths in those countries, to prevent de-anonymisation. We analysed 3345 deaths due to haemophagocytic lymphohistiocytosis from the remaining 29 European countries from 2011 to 2021. The total death counts, crude mortality rates due to haemophagocytic lymphohistiocytosis, and standardised mortality rates due to haemophagocytic lymphohistiocytosis for each country are shown in the table. The following countries had missing data for some years: the UK (2019–21 due to leaving the EU), Greece (2011–13), and Türkiye (2020). Seven countries (Estonia, Iceland, Lithuania, Luxembourg, Latvia, Slovenia, and Slovakia) each recorded fewer than ten deaths due to haemophagocytic lymphohistiocytosis, and data from these countries should be interpreted with caution due to wide confidence intervals.

The crude mortality rate per 10 000 000 person-years across Europe was 5·3 (95% CI 5·2–5·5) and the age–sex-standardised mortality rate per 10 000 000 person-years across Europe was 4·7 (3·0–6·4). In the countries recording more than ten deaths due to haemophagocytic lymphohistiocytosis, which we consider to provide more reliable estimates, we observed the highest mortality rate in France (age–sex-standardised mortality rate 10·1 [95% CI 0·0–27·3]) and the lowest in Romania (0·5 [0·0–13·6]).

We observed increasing crude reported mortality rates for haemophagocytic lymphohistiocytosis in Europe during the 10-year period, from 3·9 per 10 000 000 person-years in 2011 to 6·6 per 10 000 000 person-years in

2021. The Poisson regression modelling of mortality rates found a 5% increase per year (mortality rate ratio 1·05 [95% CI 1·04–1·06]), equating to a 1·7 times increase in the reported mortality of haemophagocytic lymphohistiocytosis over the whole study period (figure 1). The exception was in 2020, whereby mortality rates declined rapidly and temporarily during the COVID-19 pandemic, as has been seen in other conditions. When we looked at mortality trends in different age groups from 2011 to 2021 (appendix p 3), we found a decrease in death rates due to haemophagocytic lymphohistiocytosis in those aged 0–19 years (mortality rate ratio of 0·94 [95% CI 0·92–0·96]; 6% decrease per year); an increase in death rates due to haemophagocytic lymphohistiocytosis in those aged 20–49 years (1·09 [1·06–1·12]; 9% increase per year); and an increase in mortality rates due to haemophagocytic lymphohistiocytosis in those aged 50 years and older (1·09 [1·07–1·10]; 9% increase per year).

See Online for appendix

Mortality rates of haemophagocytic lymphohistiocytosis varied across different age groups and by sex (figure 2). Mortality rates were highest in infants aged 0–4 years (17·5 [95% CI 16·1–19·0 per 10 000 000 person-years]) and adults aged 70 years and older (for all age bands ≥70 years, mortality was >10 per 10 000 000 person-years; appendix p 4). Large differences were observed between male and female individuals, with higher rates in males than in females (age-adjusted mortality rate ratio 1·51 [95% CI 1·41–1·62]; appendix p 4). The greatest differences in mortality rates were in males and females aged 60 years and older (figure 2).

Figure 3 provides an overview of the trends in haemophagocytic lymphohistiocytosis mortality between 2011 and 2021 in the seven European countries with more than 100 deaths due to haemophagocytic lymphohistiocytosis. The trend in most countries suggests a steady increase in the mortality rate of haemophagocytic lymphohistiocytosis across Europe over the 10-year period, although a large increase was observed in France between 2017 and 2019. Important differences in haemophagocytic lymphohistiocytosis mortality exist between countries. We observed increasing mortality rates over time across all countries except for Türkiye, in which mortality rates remained unchanged across the 10-year period.

There were notable age and sex differences in mortality rates between individual countries (appendix p 2). Germany, the UK, Italy, and Spain had similar trends, with the highest number of deaths in older age groups as well as in the youngest age group (children aged 0–4 years), and in older men (≥70 years) particularly. Mortality rates were highest in infants in Türkiye (children aged 0–4 years), with very few deaths in older age. Conversely, mortality rates in France were predominantly in people older than 65 years with very few deaths in infants, children, and young adults.

	Deaths	Crude mortality rate per 10 000 000 person-years	Standardised mortality rate per 10 000 000 person-years
Austria	39	4·1 (2·8–5·4)	4·1 (0·0–18·2)
Belgium	91	7·3 (5·9–8·8)	7·5 (0·0–22·7)
Croatia	13	2·9 (1·3–4·6)	2·8 (0·0–13·7)
Czechia	27	2·3 (1·5–3·3)	2·3 (0·0–13·6)
Denmark	49	7·8 (5·7–10·0)	7·9 (0·0–22·7)
Estonia	4	2·8 (0·7–6·2)	2·6 (0·0–13·6)
Finland	23	3·8 (2·3–5·5)	3·6 (0·0–18·2)
France	705	9·6 (8·9–10·4)	10·1 (0·0–27·3)
Germany	271	3·0 (2·7–3·4)	2·9 (0·0–18·2)
Greece	52	6·1 (4·4–7·8)	5·6 (0·0–25·0)
Hungary	17	1·6 (0·8–2·4)	1·6 (0·0–13·7)
Iceland	1	2·7 (0·01–0·7)	2·9 (0·0–18·2)
Ireland	39	7·4 (5·1–9·9)	9·3 (0·0–27·3)
Italy	265	4·0 (3·5–4·5)	3·9 (0·0–18·2)
Latvia	4	1·9 (0·5–4·2)	1·9 (0·0–13·6)
Lithuania	9	2·8 (1·3–5·1)	3·5 (0·0–18·2)
Luxembourg	6	9·4 (3·1–18·8)	11·3 (0·0–31·8)
Netherlands	111	5·9 (4·9–7·0)	6·2 (0·0–22·7)
Norway	19	3·3 (1·9–4·9)	4·1 (0·0–18·2)
Poland	61	1·5 (1·1–1·9)	1·5 (0·0–13·6)
Portugal	72	6·3 (4·9–7·8)	6·4 (0·0–22·7)
Romania	10	0·5 (0·2–0·8)	0·5 (0·0–13·6)
Slovakia	4	0·7 (0·2–1·5)	0·7 (0·0–13·6)
Slovenia	2	0·9 (0·0–2·6)	1·1 (0·0–13·6)
Spain	359	7·0 (6·3–7·7)	7·1 (0·0–22·7)
Sweden	81	7·4 (5·9–9·1)	7·8 (0·0–22·7)
Switzerland	31	3·4 (2·3–4·7)	3·7 (0·0–18·2)
Türkiye	612	7·0 (6·5–7·6)	5·6 (0·0–22·9)
UK	368	7·1 (6·4–7·8)	7·5 (0·0–25·0)
All Europe	3345	5·3 (5·2–5·5)	4·7 (3·0–6·4)

Data are n or mortality rate (95% CI).

Table 1: **Mortality rate for haemophagocytic lymphohistiocytosis between 2011 and 2021, by country**

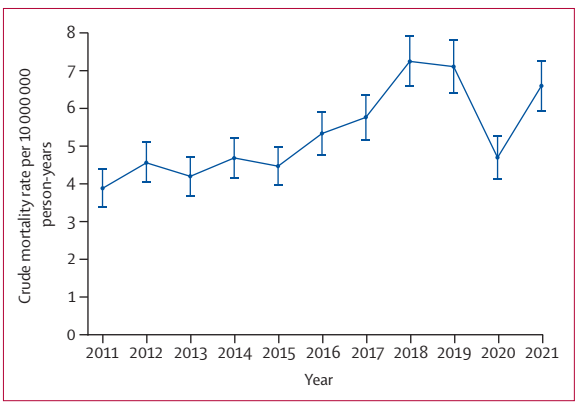

Figure 1: **Trends in crude mortality rates of haemophagocytic lymphohistiocytosis in Europe (2011–21)**
Bars are 95% CI.

A total of 2275 haemophagocytic lymphohistiocytosis research articles were identified as published across Europe from Jan 1, 2000, to June 11, 2024. The publication output for each country is depicted in figure 4, alongside the corresponding standardised mortality rate for haemophagocytic lymphohistiocytosis. Mortality rate and publication rate for each country showed moderate positive correlation (Pearson's correlation coefficient 0·4968; 23 degrees of freedom, p=0·012; appendix p 5). Most haemophagocytic lymphohistiocytosis research publications were in the UK, France, Germany, Italy, Sweden, Spain, and Türkiye. Generally, the volume of haemophagocytic lymphohistiocytosis research in each country reflected its mortality rate. However, some countries had substantially fewer research publications compared with their standardised mortality rate (Ireland 11 publications, standardised mortality rate 9·3 per 100 000 000 population; Denmark 30 publications, 7·9; and Portugal 35 publications, 6·4).

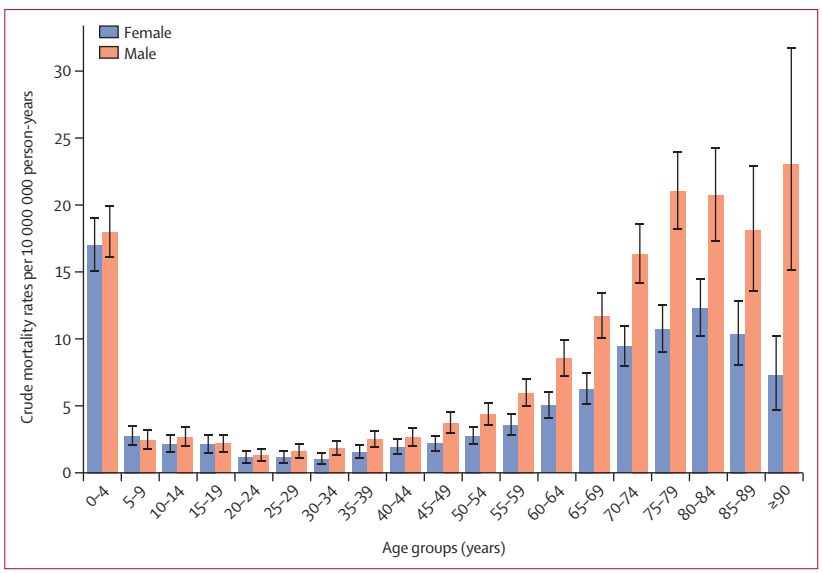

Figure 2: **Crude mortality rates of haemophagocytic lymphohistiocytosis by age and sex in Europe (2011–21)**
Bars are 95% CI.

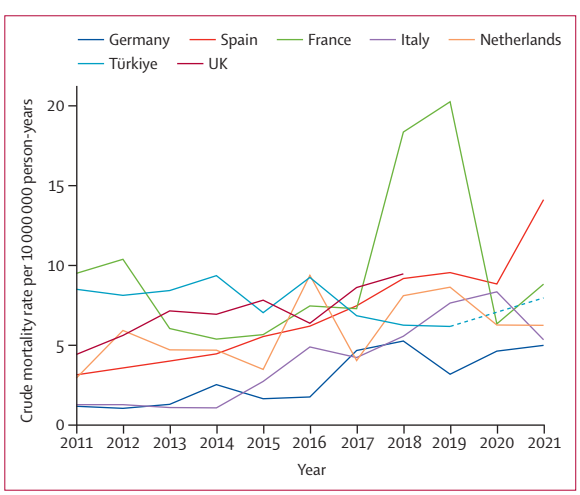

Figure 3: **Crude annual mortality rate for haemophagocytic lymphohistiocytosis in European countries with more than 100 deaths (2011–21)**
Türkiye has a dotted line between 2019 and 2021 because no data was submitted in 2020. No data were submitted by Greece in 2011–13 and no data were submitted by the UK after 2018.

Discussion

In this large, population-based study across 29 European countries over a 10-year period, we observed that mortality due to haemophagocytic lymphohistiocytosis being recorded as the underlying cause of death remained rare, but nearly doubled during the study period. Age-standardised mortality rates were higher in male than in female individuals, with the highest mortality in young children (aged 0–4 years) and adults aged 65 years and older. There was marked variation across countries, with France reporting the highest age-standardised mortality rates that were 20-times higher than Romania, which had the lowest rates. However, due to the small numbers of deaths in each country, the age-standardised rates were not significantly different (established by overlapping confidence intervals). To our knowledge, this study provides the most comprehensive description of haemophagocytic lymphohistiocytosis mortality patterns in Europe to date.

These findings are broadly consistent with previous studies showing that haemophagocytic lymphohistiocytosis, although uncommon, is increasingly being diagnosed.[6,8,9,15] Mortality is influenced by true incidence, diagnostic recognition, and case fatality. Few previous studies have reported mortality or compared rates across countries. Single-country incidence studies from England, Germany, and the USA have shown similar increasing trends over time and similar age and sex distributions to this study.[6,8,9,15] The case fatality rate has remained stable over time,[6,8,9] suggesting that the increasing mortality reported is likely driven by rising diagnosed incidence.

There is evidence that true incidence of haemophagocytic lymphohistiocytosis is increasing due to increasing incidence of malignancies and autoimmune diseases that can trigger it. The ageing population in Europe means a rising prevalence of haematological and other malignancies, as well as increased use of immunomodulatory therapies (eg, checkpoint inhibitors) that can trigger haemophagocytic lymphohistiocytosis.[16–18] There has also been an increase in the prevalence of autoimmune diseases, including rheumatological diseases.[19] However, improved rates of diagnosis by clinicians are also likely. Previous studies provide indirect evidence for historical underdiagnosis: in US inpatients between 2010 and 2014, 86% of patients with haemophagocytic lymphohistiocytosis were treated at teaching hospitals,[8] despite these hospitals treating only around 50% of common diagnoses, such as myocardial

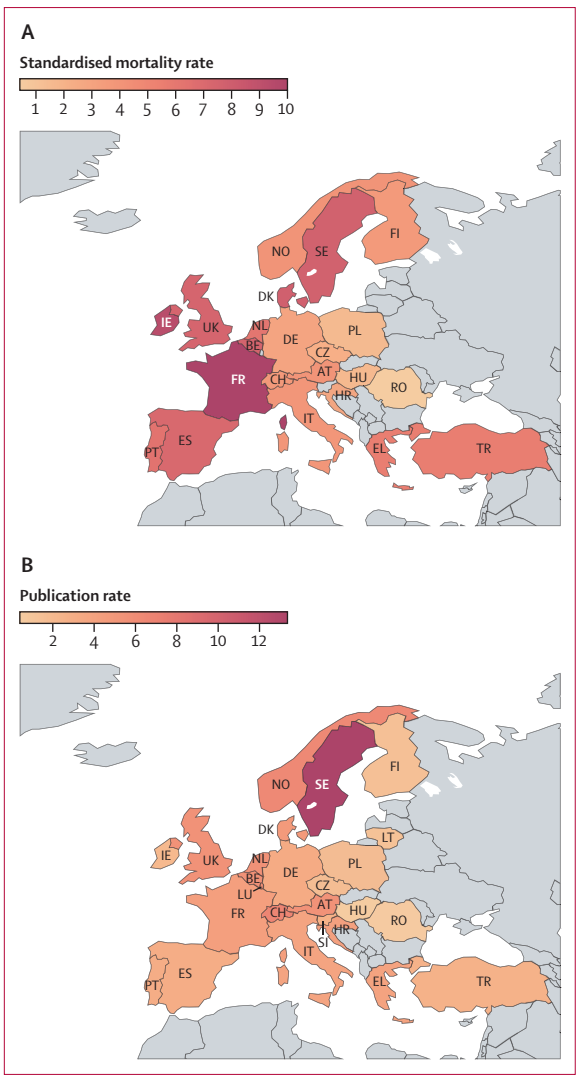

Figure 4: **Choropleth maps of haemophagocytic lymphohistiocytosis mortality and research publications across Europe**
(A) Standardised mortality rate of haemophagocytic lymphohistiocytosis per 10 000 000 person-years for each European country reporting ten or more deaths due to haemophagocytic lymphohistiocytosis from 2011 to 2021. (B) Number of publications in the 10-year period on haemophagocytic lymphohistiocytosis per 10 000 000 population for each European country. AT=Austria. BE=Belgium. CH=Switzerland. CZ=Czechia. DE=Germany. DK=Denmark. EL=Greece. ES=Spain. FI=Finland. FR=France. HR=Croatia. HU=Hungary. IE=Ireland. IT=Italy. LT=Lithuania. LU= Luxembourg. NL=Netherlands. NO=Norway. PL=Poland. PT=Portugal. RO=Romania. SE=Sweden. SI=Slovenia. TR=Türkiye.

infarction.[20] This disproportionate concentration of cases in teaching hospitals suggests that the condition might have been under-recognised and underdiagnosed in non-teaching hospitals, where specialist expertise and diagnostic resources are less widely available. In this study, countries with greater research activity, which is likely associated with higher clinician awareness, tended to have higher recorded mortality rates than those with less research activity.

The differences between countries were striking and are likely multifactorial. True variation in incidence could be a contributor, but differences in case ascertainment, coding practices, and treatment are also probable. The most pronounced contrasts were between France and Türkiye. France reported the highest mortality in adults and the lowest in infants, whereas Türkiye had the opposite pattern. Genetic factors likely explain some of the higher infant mortality rates in Türkiye, where haemophagocytic lymphohistiocytosis is often hereditary and consanguinity is more common.[21,22] France has had a strong focus on haemophagocytic lymphohistiocytosis research, including a prospective registry (2012–19) and the development of the widely used HScore.[23] These initiatives might have increased rates of diagnosis at all ages, but only increased the coding of adult deaths due to haemophagocytic lymphohistiocytosis. This is because, in France, bone marrow transplants are offered to all infants with primary haemophagocytic lymphohistiocytosis, and deaths after bone marrow transplantation are recorded with transplantation as the underlying cause of death (unpublished data).

A major strength of this study is the use of a large, harmonised mortality dataset covering almost the entire European population. The EUROSTAT database applies WHO rules for standardised ICD-10 coding of death certificates, enabling comparability between countries and over time. The inclusion of all certified deaths provides a population-level perspective and avoids the selection bias inherent to hospital-based or registry studies. ICD-10 coding is standardised through the WHO process: conditions listed on death certificates are coded and one is designated as the underlying cause of death.[13] Validation work in the UK found good positive predictive value for haemophagocytic lymphohistiocytosis diagnosis on death certificates (80·4% before and 98·6% after the introduction of the IRIS automated coding software in 2014),[11] and IRIS is now used in at least 13 European countries.[24]

Several limitations should be considered. Haemophagocytic lymphohistiocytosis is a challenging diagnosis, particularly in older adults with non-specific features, and under-recognition of the diagnosis is likely. Death certificate data only capture haemophagocytic lymphohistiocytosis when recorded as the underlying cause of death; we could not identify cases in which haemophagocytic lymphohistiocytosis was contributory but not coded as the primary cause. Coding practices differ between countries and over time, which might have affected the rates of death attributed to haemophagocytic lymphohistiocytosis. The ICD-10 system used for EUROSTAT mortality data does not distinguish between primary and secondary haemophagocytic lymphohistiocytosis and, because death certificate data do not capture the diagnostic criteria applied by certifying clinicians, we cannot establish whether standardised tools such as the HScore or HLH-2004 criteria were used.

Finally, the absence of clinical data prevented analyses of underlying triggers or treatment outcomes.

Despite the limitations, these findings highlight the need to increase awareness among clinicians of haemophagocytic lymphohistiocytosis, especially in older adults and in countries with low reported haemophagocytic lymphohistiocytosis mortality. Under-recognition of rare diseases is well documented[25,26] and affected individuals often have unmet health-care needs, such as delayed diagnosis, little access to specialist expertise, and restricted access to treatment. Improving awareness and infrastructure for rare diseases has been an EU priority for two decades.[27] International guidelines from the past 6 years[28–30] and national initiatives, such as the National Health Service England's Getting It Right First Time programme cross-specialty consensus pathway (2024),[31] aim to raise awareness and promote increased and earlier diagnosis. Standardising diagnostic criteria and death certification could strengthen surveillance and allow better understanding of international differences. Linking mortality data with clinical registries and hospital discharge data would further clarify the contribution of triggers, comorbidities, and treatment outcomes. Future research should explore whether observed mortality trends reflect true changes in incidence or improved recognition and reporting.

Contributors

FAP, FG, and RH conceptualised the study. MC, RST, and JJM acquired the funding. RO, AT, and FAP were involved in data curation and analysis. LG, FAP, PCL, MC, MB, RST and JJM were involved in clinical interpretation of results. LG drafted the initial manuscript and all authors contributed. FAP, AT, TT, and RO accessed the data, all authors were permitted to access the raw data, and the raw data were verified by FAP and AT. All authors were responsible for the decision to submit the manuscript. All authors have seen and approved the final text.

Declaration of interests

FG has received consultancy fees from Boehringer Ingelheim. FAP has received investigator-led research grant funding to her institution from CSL Vifor. MB has received payment to his institution from the Histio UK patient charity and Nottingham University Hospitals Charity. PCL declares that he is Joint National Clinical Lead for Rheumatology, Getting It Right First Time (GIRFT) programme and National Health Service England and that GIRFT has produced a consensus pathway and recommendations for the management of haemophagocytic lymphohistiocytosis. RT declares she is a trustee of HistioUK and co-chair of HiHASC and in these roles has produced patient and professional information and educational materials; All other authors declare no competing interests.

Data sharing

This study used publicly available data. All data and supporting information used in this study are available on request to EUROSTAT.

Acknowledgments

This study was funded by the Medical Research Council Rare Disease Platform Node for Histiocytic Disorders (MR/Y008189/1). FAP is funded by a National Institute for Health and Care Research Advanced Fellowship (NIHR300863). During the preparation of this work, we used ChatGPT (v3.5) to improve readability and to check the communication of our ideas. After using this tool, we reviewed and edited the content as needed and take full responsibility for the content of the publication.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps

References

1 Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. *Arch Pathol Lab Med* 2022; **146:** 507–19.
2 Al-Samkari H, Berliner N. Haemophagocytic lymphohistiocytosis. *Annu Rev Pathol* 2018; **13:** 27–49.
3 Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int* 2016; **58:** 817–25.
4 Schram AM, Comstock P, Campo M, et al. Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years. *Br J Haematol* 2016; **172:** 412–19.
5 Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383:** 1503–16.
6 West J, Card TR, Bishton MJ, et al. Incidence and survival of haemophagocytic lymphohistiocytosis: a population-based cohort study from England. *J Intern Med* 2022; **291:** 493–504.
7 West J, Stilwell P, Liu H, et al. 1-year survival in haemophagocytic lymphohistiocytosis: a nationwide cohort study from England 2003–2018. *J Hematol Oncol. J Hematol Oncol* 2023; **16:** 56.
8 Abdelhay A, Mahmoud AA, Al Ali O, Hashem A, Orakzai A, Jamshed S. Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006–19: a national, retrospective cohort study. *EClinicalMedicine* 2023; **62:** 102143.
9 Kuron D, Voran JC, von Samson-Himmelstjerna FA, et al. Epidemiology of haemophagocytic lymphohistiocytosis at the population level in Germany. *Br J Haematol* 2023; **201:** 285–89.
10 Meeths M, Horne A, Sabel M, Bryceson YT, Henter JI. Incidence and clinical presentation of primary hemophagocytic lymphohistiocytosis in Sweden. *Pediatr Blood Cancer* 2015; **62:** 346–52.
11 Bishton MJ, Stilwell P, Card TR, et al. A validation study of the identification of haemophagocytic lymphohistiocytosis in England using population-based health data. *Br J Haematol* 2021; **194:** 1039–44.
12 Benchimol EI, Smeeth L, Guttmann A, et al. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS* 2015; **12:** e1001885.
13 WHO. International Classification of Diseases: cause of death: mortality statistics are widely used for medical research, monitoring of public health, evaluating health interventions, and planning and follow-up of health care. World Health Organization. 2025. https://www.who.int/standards/classifications/classification-of-diseases/cause-of-death (accessed July 28, 2025).
14 EUROSTAT. Revision of the European Standard Population: report of EUROSTAT's task force: 2013 edition. Publications Office of the EU. 2013.
15 West J, Stilwell P, Liu H, et al. Temporal trends in the incidence of hemophagocytic lymphohistiocytosis: a nationwide cohort study from England 2003–2018. *HemaSphere* 2022; **6:** e797.
16 Kroll MH, Rojas-Hernandez C, Yee C. Hematologic complications of immune checkpoint inhibitors. *Blood* 2022; **139:** 3594–604.
17 Davis EJ, Salem JE, Young A, et al. Hematologic complications of immune checkpoint inhibitors. *Oncologist* 2019; **24:** 584–88.
18 Prathap R, Kirubha S, Rajan AT, Manoharan S, Elumalai K. The increasing prevalence of cancer in the elderly: an investigation of epidemiological trends. *Aging Med* 2024; **7:** 516–27.
19 Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet* 2023; **401:** 1878–90.
20 Gupta T, Patel K, Kolte D, et al. Relationship of hospital teaching status with in-hospital outcomes for st-segment elevation myocardial infarction. *Am J Med* 2018; **131:** 260–268.
21 Fışgın T, Patıroğlu T, Özdemir A, et al. Clinical and laboratory data of primary hemophagocytic lymphohistiocytosis: a retrospective review of the Turkish Histiocyte Study Group. *Turk J Haematol* 2010; **27:** 257–62.
22 Nepesov S, Yaman Y, Elli M, et al. Clinical, genetic, and outcome characteristics of pediatric patients with primary hemophagocytic lymphohistiocytosis. *Turk Arch Pediatr* 2022; **57:** 398–405.

23 Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014; **66:** 2613–20.

24 Federal Institute for Drugs and Medical Devices. Iris users. Federal Institute for Drugs and Medical Devices. 2025. https://www.bfarm.de/EN/Code-systems/Collaboration-and-projects/Iris-Institute/Iris-users/_node.html (accessed July 28, 2025).

25 Auvin S, Irwin J, Abi-Aad P, Battersby A. The problem of rarity: estimation of prevalence in rare disease. *Value Health* 2018; **21:** 501–07.

26 Tumiene B, Peters H, Melegh B, et al. Rare disease education in Europe and beyond: time to act. *Orphanet J Rare Dis* 2022; **17:** 441.

27 Commission of the European Communities. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: on Rare Diseases: Europe's Challenges. Commission of the European Communities. 2008. https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf (accessed July 8, 2025).

28 Hines MR, von Bahr Greenwood T, Beutel G, et al. Consensus-based guidelines for the recognition, diagnosis, and management of hemophagocytic lymphohistiocytosis in critically ill children and adults. *Crit Care Med* 2022; **50:** 860–72.

29 Shakoory B, Geerlinks A, Wilejto M, et al, and the HLH/MAS task force. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). *Ann Rheum Dis* 2023; **82:** 1271–85.

30 La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019; **133:** 2465–77.

31 Getting It Right First Time. Haemophagocytic lymphohistiocytosis (HLH): guidance on the diagnosis, treatment, management and governance. Getting It Right First Time. 2025. https://gettingitrightfirsttime.co.uk/wp-content/uploads/2025/06/HLH-Guide-final-version-v1.3-June-2025.pdf (accessed July 28, 2025).